Section

1

DISEASES OF CONJUNCTIVA AND OCULAR SURFACE

1. Embryology and Developmental Anomalies of Conjunctiva
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Chapter

1

Embryology and Developmental Anomalies of Conjunctiva

Chapter Outline

EMBRYOLOGY OF CONJUNCTIVA
- General considerations
- Development of conjunctiva

CONGENITAL DISORDERS OF CONJUNCTIVA
- Conjunctival choristoma
- Congenital pigmented lesions of conjunctiva
- Congenital epitarsus
- Conjunctival telangiectasia
- Congenital anomalies of caruncle

EMBRYOLOGY OF CONJUNCTIVA

GENERAL CONSIDERATIONS

Eyelids are formed by reduplication of surface ectoderm above and below the cornea during 2nd month of gestation (Fig. 1.1). The folds enlarge and their margins meet and fuse with each other. The lids cut off a space called conjunctival sac.

DEVELOPMENT OF CONJUNCTIVA

Conjunctiva develops from the ectoderm lining of the lids and covering the globe (Fig. 1.1).

Conjunctival glands develop as growth of the basal cells of upper conjunctival fornix. Fewer glands develop from the lower fornix.

CONGENITAL DISORDERS OF CONJUNCTIVA

A few of the congenital disorders of conjunctiva worth mentioning include:

- Conjunctival choristoma
- Congenital pigmented lesions of conjunctiva
- Congenital epitarsus
- Conjunctival telangiectasia
- Cavernoma of conjunctiva
- Developmental anomalies of caruncle

CONJUNCTIVAL CHORISTOMA

Choristoma refers to benign tumour consisting of microscopically normal tissue derived from germ cell layers foreign to that body site. Conjunctival choristoma possess little growth potential and contain both dermal and epithelial elements that are not normally found in the conjunctiva.

Types of conjunctival choristomas

There are four types of conjunctival choristoma:

- Solid epibulbar dermoid
- Diffuse dermolipoma
- Complex choristomas, and
- Single-tissue choristoma

SOLID EPIBULBAR DERMOID

Demography

- *Frequency.* The estimated worldwide incidence of limbal dermoids ranges from 1 case per 10,000 population to 3 cases per 10,000 population.
- *Race.* No racial predisposition exists.
- *Sex.* Limbal dermoids occur with equal frequency in males and in females.
- *Age.* Limbal dermoids are present at birth but may not be recognized until the first or second decade of life. They may also appear to enlarge as the body matures.

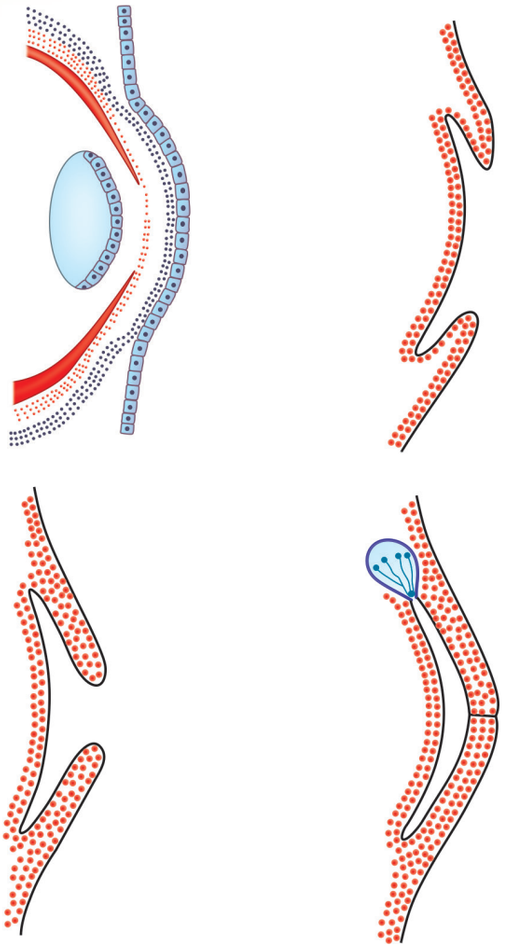

Fig. 1.1: Development of eyelids and conjunctiva.

- *Inheritance.* Limbal dermoids generally are not inherited, although some exceptions have been reported. Familial presentation of limbal dermoids in association with systemic disorders, such as Goldenhar syndrome, is well recognized and follows a multifactorial pattern of inheritance. Two rare forms of epibulbar dermoid (i.e. the annular limbal form, the corneal dystrophy form) presenting in multiple family members have been reported.

Pathophysiology

Several theories have been proposed to explain the development of limbal dermoids. Two important ones are:

1. *Theory of metaplastic transformation of the mesoblast.* According to this theory there occurs an early developmental error in between the rim of the optic nerve and the surface ectoderm.
2. *Theory of sequestration of the pluripotential cells* during embryonic development of the surrounding ocular structures, has also been suggested in pathophysiology.

Note. The exact pathogenesis probably varies from case to case.

Clinical features

Solid epibulbar dermoids are compact, pale yellow growths that typically occur unilaterally at the inferotemporal limbus (Fig. 1.2). Most limbal dermoids are superficial and only minimally involve the cornea and sclera. However, some tumours can penetrate deeply into the cornea, sclera, and conjunctiva.

Types. Based on the location, there are three broad categories of epibulbar dermoids:

- *First type of epibulbar dermoid is the limbal dermoid* which is the most common type, in which the tumour straddles the limbus. Limbal dermoids are usually superficial lesions but rarely may involve deeper ocular structures.
- *Second type of epibulbar dermoid* involves only the superficial cornea, sparing the limbus, the Descemet membrane, and the endothelium.
- *Third type of epibulbar dermoid* involves the entire anterior segment, replacing the cornea with a dermolipoma that may involve the iris, the ciliary body, and the lens.

Associations. Limbal dermoids may be associated with Goldenhar syndrome, linear naevus sebaceous syndrome, and encephalocraniocutaneous lipomatosis. Eyelid colobomas may also occur in association with limbal dermoids, which suggest the postulate that both anomalies may result from incomplete fusion of the lids with displacement of skin elements into the dermoid tumour.

Histological features

Histological examination reveals a thick, collagenous lesion that may contain hair, sweat glands, fat, sebaceous glands, or teeth (Fig. 1.3).

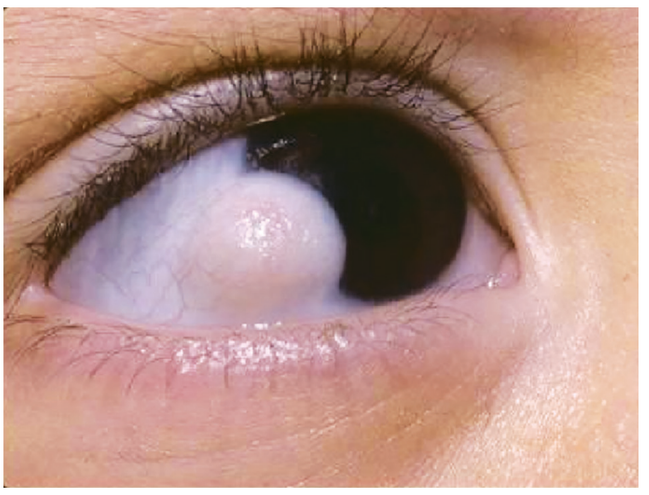

Fig. 1.2: Limbal dermoid.

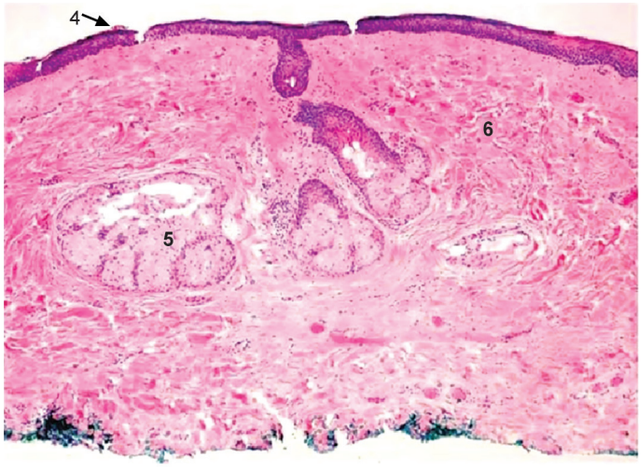

Fig. 1.3: Histological structure of limbal dermoid.

Treatment

Treatment of limbal dermoids may consist of:

Periodic removal of irritating cilia, and ***topical lubrication*** to prevent foreign body sensation.

Or

Excision of the dermoid if it is causing significant cosmetic disfigurement or interfering with vision. Surgical treatment should be instituted only when the risk of subsequent scar formation or surgical complications are outweighed by the likelihood of improving the patient's vision or cosmetic appearance.

Surgical excision usually involves:

- *A superficial sclerokeratectomy*, cutting flush with the surface of the globe (shaving the lesion off the cornea and sclera) is the procedure of choice for removal of the dermoid. Excised tissue always should be sent to the pathologist for examination.
- *Exposed sclera should be covered* by relaxing the adjacent conjunctiva and sewing it into the scleral defect.
- *Lamellar keratoplasty* can be performed to reinforce the site of excision, when a deep excision is necessary.
- *Amniotic membrane graft*. Large patches of bare sclera can be treated with application of single or multilayered amniotic membrane graft tissue. The amniotic membrane can be secured to underlying sclera using sutures and/or fibrin-glue adhesive.

DIFFUSE DERMOLIPOMA

Dermolipomas are less dense than solid epibulbar dermoids and contain more adipose tissue. These are true choristomas, because fatty tissue is usually not found anterior to the orbital septum. They are typically found on the superior temporal bulbar conjunctiva. These masses can extend from the limbus anteriorly to the posterior aspect of the globe and in the orbit between the superior and lateral rectus. It presents in adulthood and appears as soft, yellowish white, movable subconjunctival mass most frequently at outer canthus (Fig. 1.4). It consists of fatty tissue and the surrounding dermis-like connective tissue, hence the name lipodermoid.

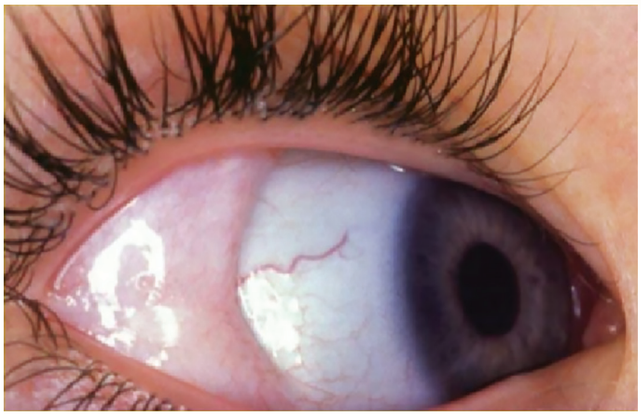

Fig. 1.4: Lipodermoid.

Treatment

Surgical excision is required only in the presence of significant cosmetic disfigurement. Usually, surgery is restricted to partial resection of the anterior portion of the tumour. Complete removal is usually not possible. Care must be taken during surgical removal not to damage the extraocular muscles, levator muscle, or lacrimal gland.

COMPLEX CHORISTOMAS

Complex choristomas consist of variable combinations of ectopic tissues such as cartilage, adipose tissue, smooth muscle, and acinar glands.

Clinical features

Clinically, these lesions resemble dermoids and lipodermoids. When acinar elements compose the majority of the tumour, complex choristomas may assume a fleshier, vascularized appearance with raised translucent nodules. These raised nodules have been referred to as ectopic lacrimal glands. Although mild growth may occur, especially during puberty, malignant transformation is rare.

Treatment

As these tumours also tend to invade deeply into the globe, excision is usually avoided. For cosmetic reasons, partial resection of the anterior portion of the tumour may be done.

SINGLE-TISSUE CHORISTOMA

Single-tissue choristomas include choristomas of lacrimal gland, respiratory tissue, and osseous choristomas.

Epibulbar osseous choristoma is the rarest type of choristoma of the eye. These are composed of firm deposits of bone and are most commonly found in the supero-

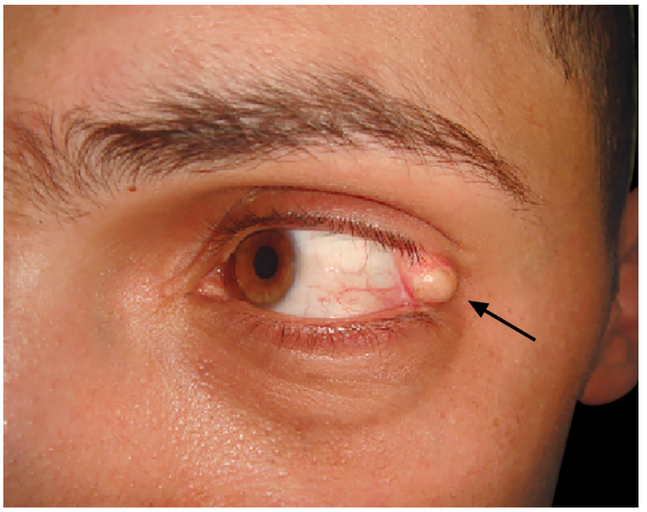

Fig. 1.5: Epibulbar osseous choristoma.

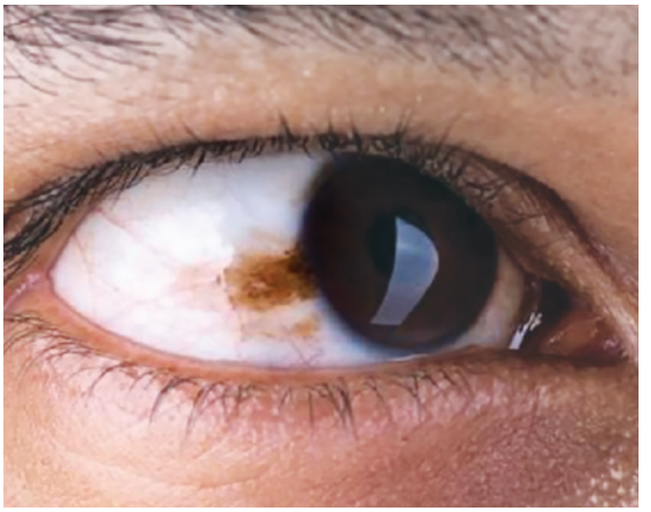

Fig. 1.6: Conjunctival naevus.

temporal conjunctiva (Fig. 1.5) occasionally, the mass is firmly attached to the sclera. As with all choristomas, osseous choristomas are believed to be congenital. Due to its location underneath the eyelid, the mass is usually detected once the child becomes old enough to palpate it. Osseous choristomas are solitary nodules that resemble dermoids. However, they can be differentiated from dermoids clinically because of their location about 5–10 mm posterior to the limbus and their more discrete borders.

Treatment. Usually, excision is performed for cosmetic reasons only.

CONGENITAL PIGMENTED LESIONS OF CONJUNCTIVA

Congenital melanocytic pigmented lesions of conjunctiva include:

- Conjunctival naevi
- Conjunctival epithelial melanosis
- Conjunctival subepithelial melanosis.

CONJUNCTIVAL NAEVI

Clinical features

Naevi or congenital moles are common pigmented lesions, usually presenting as grey gelatinous, brown or black, flat or slightly raised nodules on the bulbar conjunctiva, mostly near the limbus (Fig. 1.6). Melanocytic naevi are the most common tumours of the conjunctiva, accounting for 28% of all tumours. These lesions most commonly arise in the bulbar conjunctiva can also occur on caruncle, or plica semilunaris. They usually appear during early childhood and may increase in size at puberty or during pregnancy.

- Naevi present clinically as circumscribed, flat to slightly raised macules or papules.
- Naevi in children often lack pigmentation, but usually acquire pigmentation after puberty. However, up to 30% of naevi remain amelanotic.
- Naevi on the bulbar conjunctiva move freely over the sclera and appear well circumscribed without extension into the cornea. A common and characteristic feature of conjunctival naevi is the presence of intralesional cysts.
- Malignant melanoma will develop in less than 1% of conjunctival naevi. Clinical features particularly suggestive of evolving melanoma include extension into the cornea, attachment to the sclera, and development of multiple "feeder vessels" seen by slit-lamp examination. There are no specific clinical signs that can accurately predict malignant transformation in a conjunctival naevus.

Histopathology

Biopsy is indicated when a pigmented naevus shows clinical characteristics of possible malignancy such as rapid growth, change in shape and/or colour, recurrence after prior biopsy, and unusual location such as the palpebral conjunctiva or the fornix. Histologically, conjunctival melanocytic naevi are classified similarly as in the skin, including junctional, compound, and subepithelial naevi.

- *Junctional naevi.* About 5% of conjunctival naevi are junctional, characterized by nested but sometimes also lentiginous proliferations of type A or type B cells confined to the epithelium. They may show occasional mitotic activity. Most junctional naevi are found in patients in the younger age groups. Therefore, they are believed to be at an early stage in the evolution of compound naevi.

- *Compound naevi* are the most common type of conjunctival naevus, comprising about 70–78% of all naevi. A very characteristic and diagnostically useful feature of conjunctival naevi is induction of epithelial protrusions into the lamina propria and formation of intralesional epithelial cysts lined by conjunctival epithelium and goblet cells. These cysts are present in 50% of cases. It seems that cyst formation is a function of time, as they are less frequent in early lesions.
- *Subepithelial naevi* are the conjunctival counterpart of the dermal naevus and represent about 9% of all naevi. These are more prevalent in the older age groups and have predominantly type B or C nevomelanocytes in the substantia propria, without an intraepithelial component.

Treatment

Conjunctival naevi do not require treatment if clinically stable.

- *Excision or rebiopsy* is recommended in lesions that change in size or colour, recur, or show other clinical features of possible malignancy, or for cosmetic indications.
- Excision should be complete, whatever may be the indication.
- Reexcising of conjunctival naevi showing focal cytologic atypia is of no clinical benefit.

CONJUNCTIVAL EPITHELIAL MELANOSIS

Conjunctival epithelial melanosis (Fig. 1.7) develops in early childhood, and then remains stationary. It is found in 90% of the blacks. The pigmented spot freely moves with the movement of conjunctiva. It has got no malignant potential and hence no treatment is required.

CONJUNCTIVAL SUBEPITHELIAL MELANOSIS

Subepithelial melanosis may occur as:

- An isolated anomaly of conjunctiva (congenital melanosis oculi, Fig. 1.8) or

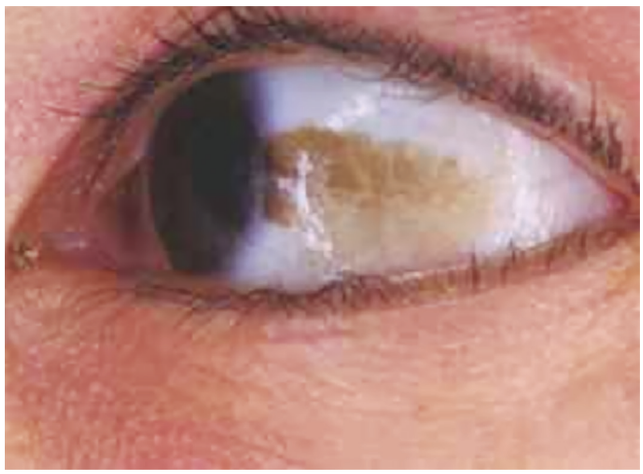

Fig. 1.7: Conjunctival epithelial melanosis.

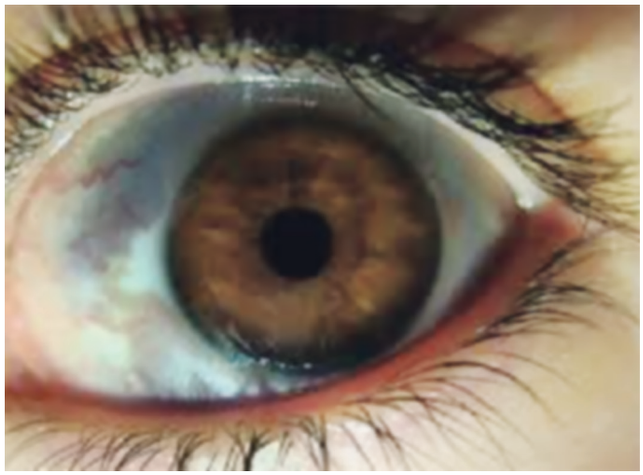

Fig. 1.8: Congenital melanosis oculi.

- In association with the ipsilateral hyperpigmentation of the face (oculodermal melanosis or naevus of Ota).

NAEVUS OF OTA

Melanosis bulbi associated with ipsilateral hyperpigmentation of the face, is also known as naevus of Ota or oculomucodermal melanocytosis. This condition was first described by Dr Ota, a Japanese physician, in 1939, and hence the term naevus of Ota. Naevus of Ota should not be confused with Mongolian spots. Unlike Mongolian spots, naevus of Ota does not disappear with time.

Demography

- *Age.* Naevus of Ota is a skin condition that is normally present at birth, but can occur during adolescence too.
- *Sex.* Both males and females are affected, but females are affected much more than males in a 5:1 ratio.
- *Race.* All racial and ethnic groups are at risk, though naevus of Ota is more frequent among the Japanese population and other Asian races compared to Europeans, Americans, or Africans.

Etiology

- Exact cause of naevus of Ota formation is not known.
- Some researchers believe that it may be formed due to abnormal accumulation of melanocytes (cells producing melanin) in the fetal development stage.
- Even though a congenital presentation is noted, but naevus of Ota is not a hereditary condition.

Clinical features

Naevus of Ota may not present any major signs and symptoms in most cases. The general features of the skin condition include:

- *Skin pigmentation*. It is a benign skin lesion that occurs as a hyperpigmented skin patch. The skin patch may be bluish to bluish-brown in colour.

- *Head and neck region* is mostly affected, especially the face; either one side, or both sides of the face may be involved.
- *Ocular melanosis* is seen in two-thirds of the cases, the sclera of the eye is affected. The condition may be unilateral or bilateral, meaning that either one eye or both eyes may be affected.

Complications

Complications from naevus of Ota may include:

- *Cosmetic concerns* and stress may occur in some cases.
- *Glaucoma* risk is higher if along with skin lesion is present in the eye(s).
- *Malignant melanoma* is known to develop rarely from the site of the lesion, and hence, close follow-up is important and necessary.

Treatment measures for naevus of Ota include:

- *No treatment* is generally required in mild cases. A regularly observation is all that may be required, i.e. a "wait and watch" approach may be followed.
- *Laser surgery* is found to be beneficial in case of cosmetic reasons.
- *Surgical excision.* Naevus of Ota can also be excised through electrocautery surgical procedure.

Prognosis of naevus of Ota is excellent even if no treatment is provided and only periodic observation maintained, since typically it is a benign skin condition.

EPITARSUS

Epitarsus is a peculiar condition which typically occurs as an apron-like fold of conjunctiva attached to the inner surface of the upper lid but occasionally as a bridge of tissue under which a probe may be passed.

Types: Etiologically epitarsus is of two types:

1. *Primary epitarsus*, occurring purely as a congenital anomaly; and
2. *Secondary epitarsus*, following neglected cases of conjunctivitis.

Congenital epitarsus

Epitarsus occurring as a congenital anomaly is rare. The deformity is almost invariably seen in the upper lid, though its bilateral occurrence in the lower lids has also been reported.

Four clinical varieties of epitarsus depending on the extent of the deformity reported are:

- Intrafornix
- Fornix-tarsal
- Fornix-limbal, and
- Interfornix (Fig. 1.9A)

Histopathological examination following resection of the fold shows moderately dense fibrovascular connective tissue covered by stratified squamous epithelium on both the sides (Fig. 1.10).

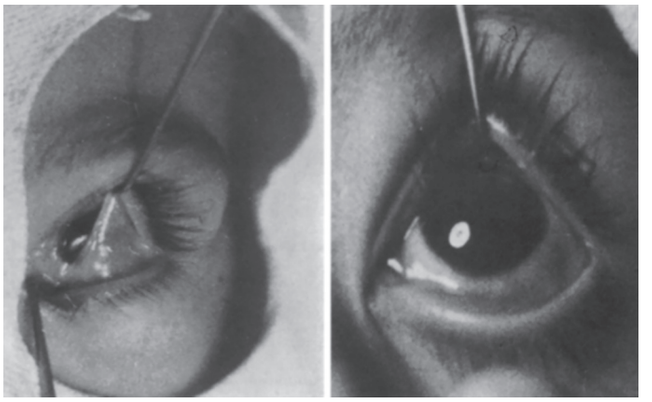

Fig. 1.9: A, Interfornix epitarsus—the membrane extending from upper fornix to lower fornix; B, After excision of the membrane, underlying eyeball is normal.

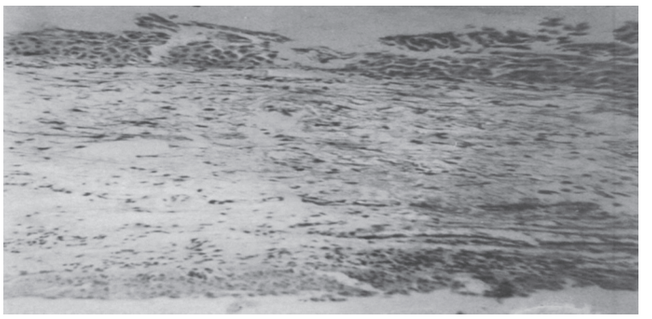

Fig. 1.10: The mucosa on either side comprises stratified squamous epithelium. Subepithelial soft tissue contains few mononuclear cells. (Haematoxylin and eosin ×120).

Treatment. Simple excision gives good cosmetic and functional results (Fig. 1.9B).

CONJUNCTIVAL TELANGIECTASIA

Conjunctival telangiectasia refers to abnormal, dilated conjunctival capillary formation, which usually develop between 3 and 5 years of age.

Clinical features

Conjunctival telangiectasia appears as dot-like, corkscrew, irregular vessels near the limbus (Fig. 1.11).

- Subconjunctival haemorrhage may occur from the telangiectatic vessels.
- Patients usually have no symptoms except the asymptomatic red spots on eye.

Associations include epistaxis and gastrointestinal bleeding.

Evaluation should include:

- *Complete ophthalmic history and eye examination* with attention to conjunctiva, cornea, lens, and ophthalmoscopy.
- *CT scan* may need to be considered for multisystem disorders.
- *Medical consultation* to rule out systemic disease.

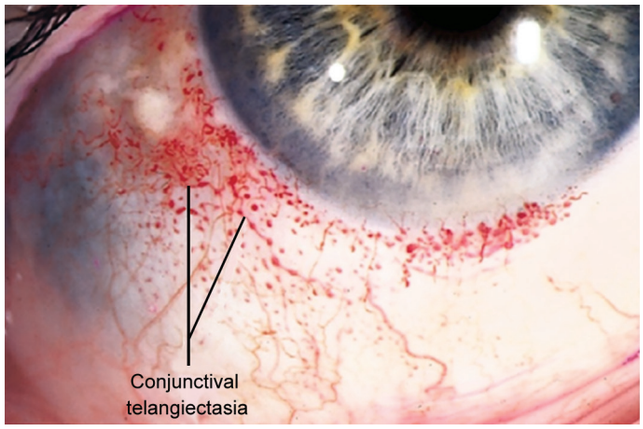

Fig. 1.11: Conjunctival telangiectasia appearing as dot-like, corkscrew, irregular vessels near the limbus.

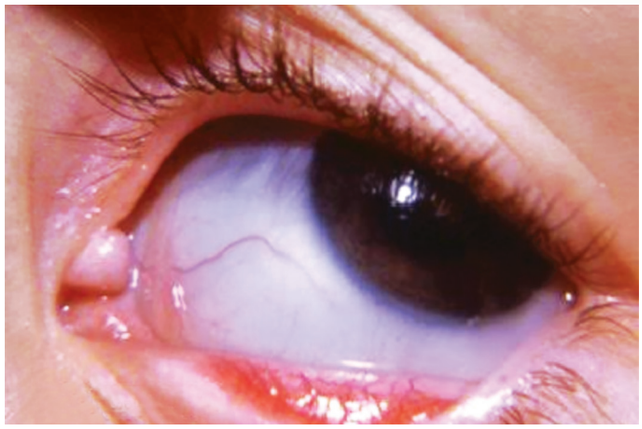

Fig. 1.12: Congenital bifurcated caruncle.

Differential diagnosis

Differential diagnosis consists of an idiopathic lesion, Osler-Weber-Rendu syndrome, ataxia-telangiectasia, Fabry's disease, and Sturge-Weber syndrome.

Management. No treatment is recommended.

Prognosis. Usually benign; may bleed; depends on etiology.

CONGENITAL ANOMALIES OF CARUNCLE

CONGENITAL BIFURCATED CARUNCLE

It is a rare anomaly which can be seen in the presence of normal plica semilunaris (Fig. 1.12).

OTHER CONGENITAL ANOMALIES OF CARUNCLE

Congenital anomalies of caruncle are in general rare. The rare case reports in the literature are on:

- *Dysplastic caruncle*, which may occur isolated or as part of Goldenhar syndrome.
- *Ectopic caruncle*
- *Congenital megacaruncle*
- *Supernumerary caruncles* are always unilateral and un-associated with other ocular abnormalities or Goldenhar syndrome.
- Caruncular dermoid has also been reported in the literature. Histopathology of caruncular dermoid shows a keratinizing epidermis-like surface and dense, thick collagen in place of substantia propria.

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Chapter

2

Conjunctivitis

Chapter Outline

DEFINITION AND CLASSIFICATION
- Definition
- Classification

INFECTIVE CONJUNCTIVITIS
- Bacterial conjunctivitis
- Chlamydial conjunctivitis
- Viral conjunctivitis
- Ophthalmia neonatorum
- Granulomatous conjunctival inflammations

ALLERGIC CONJUNCTIVITIS
- Acute allergic conjunctivitis
- Vernal keratoconjunctivitis or spring catarrh
- Atopic keratoconjunctivitis
- Giant papillary conjunctivitis
- Phlyctenular keratoconjunctivitis

CICATRICIAL CONJUNCTIVITIS

Immunologic Conjunctivitis
- Ocular mucous membrane pemphigoid (OMMP)
- Stevens-Johnson syndrome and toxic epidermal necrolysis

Secondary Cicatricial Conjunctivitis

TOXIC CONJUNCTIVITIS
- Toxic conjunctivitis—secondary to molluscum contagiosum
- Chemical toxic conjunctivitis

DEFINITION AND CLASSIFICATION

DEFINITION

Inflammation of the conjunctiva (conjunctivitis) is classically defined as conjunctival hyperaemia associated with a discharge which may be watery, mucoid, mucopurulent or purulent.

CLASSIFICATION

Etiologically conjunctivitis can be classified as below:

A. Infective conjunctivitis

1. Bacterial conjunctivitis
- Acute bacterial conjunctivitis
- Hyperacute bacterial conjunctivitis
- Chronic bacterial conjunctivitis
- Angular bacterial conjunctivitis

Chlamydial conjunctivitis
- Trachoma
- Adult inclusion conjunctivitis
- Neonatal chlamydial conjunctivitis

2. Viral conjunctivitis
- Adenovirus conjunctivitis
  - Epidemic keratoconjunctivitis
  - Pharyngoconjunctival fever
- Enterovirus conjunctivitis
- Molluscum contagiosum conjunctivitis
- Herpes simplex conjunctivitis

3. Ophthalmia neonatorum (a separate entity)

4. Granulomatous conjunctivitis
- Parinaud oculoglandular syndrome.

B. Allergic conjunctivitis

1. Simple allergic conjunctivitis
- Hay fever conjunctivitis (rhinoconjunctivitis)
- Seasonal allergic conjunctivitis (SAC)
- Perennial allergic conjunctivitis (PAC)

2. Vernal keratoconjunctivitis (VKC)

3. Atopic keratoconjunctivitis (AKC)

4. Giant papillary conjunctivitis (GPC)

5. Phlyctenular conjunctivitis (PKC)

6. Contact dermoconjunctivitis (drop conjunctivitis).

C. Cicatricial conjunctivitis

- Ocular mucous membrane pemphigoid (OMMP),
- Stevens-Johnson syndrome (SJS),
- Toxic epidermal necrolysis (TeN), and
- Secondary cicatricial conjunctivitis.

D. Toxic conjunctivitis

- Toxic conjunctivitis secondary to molluscum contagiosum
- Chemical toxic conjunctivitis

INFECTIVE CONJUNCTIVITIS

Infective conjunctivitis, i.e. inflammation of the conjunctiva caused by micro-organisms is the commonest variety. This is in spite of the fact that the conjunctiva has been provided with *natural protective mechanisms* in the form of:

- Low temperature due to exposure to air,
- Physical protection by lids,
- Flushing action of tears,
- Antibacterial activity of lysozymes, and
- Humoral protection by the tear immunoglobulins.

BACTERIAL CONJUNCTIVITIS

There has occurred a relative decrease in the incidence of bacterial conjunctivitis in general and those caused by gonococcus and *Corynebacterium diphtheriae* in particular. However, in developing countries, it still continues to be the commonest type of conjunctivitis. It can occur as sporadic and epidemic cases. Outbreaks of bacterial conjunctivitis, epidemics are quite frequent during monsoon season.

Etiology

A. Predisposing factors for bacterial conjunctivitis, especially epidemic forms, are flies, poor hygienic conditions, hot dry climate, poor sanitation and dirty habits. These factors help the infection to establish, as the disease is highly contagious.

B. Causative organisms. It may be caused by a wide range of organisms in the following approximate order of frequency:

- *Staphylococcus aureus* is the most common cause of bacterial conjunctivitis and blepharoconjunctivitis.
- *Staphylococcus epidermidis* is an innocuous flora of lid and conjunctiva. It can also produce blepharoconjunctivitis.
- *Streptococcus pneumoniae* (Pneumococcus) produces acute conjunctivitis usually associated with petechial subconjunctival haemorrhages. The disease has a self-limiting course of 9–10 days.
- *Streptococcus pyogenes* (haemolyticus) is virulent and usually produces pseudomembranous conjunctivitis.
- *Haemophilus influenzae* (aegyptius, Koch-Weeks bacillus). It classically causes epidemics of mucopurulent conjunctivitis, known as 'red-eye' especially in semitropical countries.
- *Moraxella lacunata* (Morax-Axenfeld bacillus) is most common cause of angular conjunctivitis and angular blepharoconjunctivitis.
- *Pseudomonas pyocyanea* is a virulent organism, which readily invades the cornea.
- *Neisseria gonorrhoeae* typically produces acute purulent conjunctivitis in adults and ophthalmia neonatorum in newborn. It is capable of invading intact corneal epithelium.
- *Neisseria meningitidis* (Meningococcus) may produce mucopurulent conjunctivitis.
- *Corynebacterium diphtheriae* causes acute membranous conjunctivitis. Such infections are not known nowadays.

C. Mode of infection. Conjunctiva may get infected from three sources, viz. exogenous, local surrounding structures and endogenous, by following modes:

1. *Exogenous infections* are the commonest and may spread:
   - *Directly* through close contact, as airborne infections or as waterborne infections.
   - *Vector transmission* (e.g. flies)
   - *Material transfer* such as infected fingers of doctors, nurses, common towels, handkerchiefs, and infected tonometers.
2. *Local spread* may occur sometimes from neighbouring structures such as infected lacrimal sac, lids, and nasopharynx. In addition to these, a change in the character of relatively innocuous organisms present in the conjunctival sac itself may cause infections.
3. *Endogenous infections* may occur very rarely through blood, e.g. gonococcal and meningococcal infections.

PATHOLOGY

Pathological changes of bacterial conjunctivitis consist of:

1. ***Vascular response.*** It is characterised by congestion and increased permeability of the conjunctival vessels associated with proliferation of capillaries.
2. ***Cellular response.*** It is in the form of exudation of polymorphonuclear cells and other inflammatory cells into the substantia propria of conjunctiva as well as in the conjunctival sac.
3. ***Conjunctival tissue response.*** Conjunctiva becomes oedematous. The superficial epithelial cells degenerate, become loose and even desquamate. There occurs proliferation of basal layers of conjunctival epithelium and increase in the number of mucin-secreting goblet cells.
4. ***Conjunctival discharge.*** It consists of tears, mucus, inflammatory cells, desquamated epithelial cells, fibrin and bacteria. If the inflammation is very severe, diapedesis of red blood cells may occur and discharge may become blood stained.

Severity of pathological changes varies depending upon the severity of inflammation and the causative organism. The changes are thus more marked in purulent conjunctivitis than mucopurulent conjunctivitis.

CLINICAL TYPES OF BACTERIAL CONJUNCTIVITIS

Depending upon the causative bacteria and the severity of infection, bacterial conjunctivitis may present in following clinical forms:

- Acute bacterial conjunctivitis,
- Hyperacute bacterial conjunctivitis,
- Chronic bacterial conjunctivitis, and
- Angular bacterial conjunctivitis.

ACUTE BACTERIAL CONJUNCTIVITIS

Acute bacterial conjunctivitis is characterised by marked conjunctival hyperaemia and mucopurulent discharge from the eye. So, clinically, it is called acute mucopurulent conjunctivitis. It is the most common type of bacterial conjunctivitis.

Common causative bacteria are: *Staphylococcus aureus*, Koch-Weeks bacillus, *Streptococcus pneumoniae*, *Haemophilus influenzae* (Table 2.1). Mucopurulent conjunctivitis generally accompanies exanthemata such as measles and scarlet fever.

CLINICAL FEATURES

Symptoms

- *Discomfort, foreign body, grittiness, blurring and redness* of sudden onset (due to engorgement of vessels) are the usual presenting symptoms.
- *Mild to moderate pain* is often experienced by the patients.
- *Mild photophobia*, i.e. difficulty to tolerate light.
- *Mucopurulent discharge* from the eyes.
- *Sticking together of lid margins* with discharge during sleep.
- *Slight blurring* of vision due to mucous flakes in front of cornea.
- *Coloured halos*, may be complained by some patients due to prismatic effect of mucus present on cornea.

Signs (Fig. 2.1)

- *Flakes of mucopus* seen in the fornices, canthi and lid margins is a critical sign.
- *Conjunctival congestion*, which is more marked in palpebral conjunctiva, fornices and peripheral part of bulbar conjunctiva, giving the appearance of 'fiery red eye'. The congestion is typically less marked in circumcorneal zone.

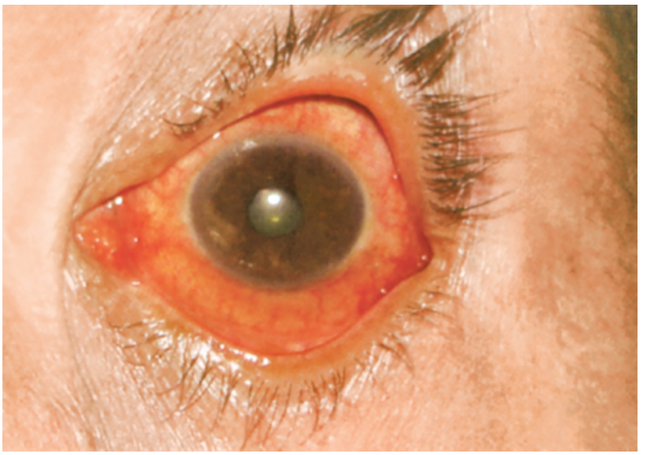


Fig. 2.1: Signs of acute mucopurulent conjunctivitis.

- *Chemosis*, i.e. swelling of conjunctiva.
- *Papillae* of fine type may be seen.
- *Petechial haemorrhages* are seen when the causative organism is *Streptococcus pneumoniae*.
- *Cilia are usually matted* together with yellow crusts.
- *Eyelids* may be slightly oedematous.

Clinical course

Acute mucopurulent conjunctivitis is usually bilateral, although one eye may become affected 1–2 days before the other. The disease usually reaches its height in three to four days. If untreated, in mild cases the infection may be overcome and the condition is cured in 10–15 days; or it may pass to less intense form, the 'chronic catarrhal conjunctivitis'.

Complications

Occasionally, the disease may be complicated by superficial punctate corneal epitheliopathy, marginal corneal ulceration, superficial keratitis, blepharitis, or dacryocystitis.

DIFFERENTIAL DIAGNOSIS

1. *From other causes of acute red eye* (Table 2.2).
2. *From other types of conjunctivitis.* It is made out from the typical clinical feature of disease and is confirmed by conjunctival cytology and bacteriological examination of secretions and scrapings (Table 2.3).

TABLE 2.1: Common pathogens causing acute, hyperacute and chronic bacterial conjunctivitis

Acute conjunctivitis	*Hyperacute conjunctivitis*	*Chronic conjunctivitis*
Staphylococcus aureus	*Neisseria gonorrhoeae*	*Staphylococcus aureus*
Streptococcus pneumoniae	*Neisseria meningitidis*	*Moraxella lacunata*
Koch-Weeks bacillus		*Proteus mirabilis*
Haemophilus influenzae		*Klebsiella pneumoniae*
		Escherichia coli

TABLE 2.2: Distinguishing features between acute conjunctitis, acute iridocyclitis and acute congestive glaucoma

Features	*Acute conjunctivitis*	*Acute iridocyclitis*	*Acute congestive glaucoma*
1. Onset	Gradual	Usually gradual	Sudden
2. Pain	Mild discomfort	Moderate in eye and along the first division of trigeminal nerve	Severe in eye and the entire trigeminal area
3. Discharge	Mucopurulent	Watery	Watery
4. Coloured halos	May be present	Absent	Present
5. Vision	Good	Slightly impaired	Markedly impaired
6. Congestion	Superficial con junctival	Deep ciliary	Deep ciliary
7. Tenderness	Absent	Marked	Marked
8. Pupil	Normal	Small and irregular	Large and vertically oval
9. Media	Clear	Hazy due to KPs, aqueous flare and pupillary exudates	Hazy due to oedematous cornea
10. Anterior chamber	Normal	May be deep	Very shallow
11. Iris	Normal	Muddy	Oedematous
12. Intraocular pressure	Normal	Usually normal	Raised
13. Constitutional symptoms	Absent	Little	Prostration and vomiting

TABLE 2.3: Differentiating features of common types of conjunctivitis

	Bacterial	*Viral*	*Allergic*	*Chlamydial (TRIC)*
(A) Clinical signs				
1. Congestion	Marked	Moderate	Mild to moderate	Moderate
2. Chemosis	++	±	++	±
3. Subconjunctival haemorrhages	±	±	–	–
4. Discharge	Purulent or mucopurulent	Watery	Ropy/watery	Mucopurulent
5. Papillae	±	–	++	±
6. Follicles	–	+	–	++
7. Pseudomembrane	±	±	–	–
8. Pannus	–	–	– (Except vernal)	+
9. Preauricular lymph nodes	+	++	–	±
(B) Cytological features				
1. Neutrophils	+	+ (Early)	–	+
2. Eosinophils	–	–	+	–
3. Lymphocytes	–	+	–	+
4. Plasma cells	–	–	–	+
5. Multinuclear cells	–	+	–	–
6. Inclusion bodies:				
Cytoplasmic	–	+ (Pox)	–	+
Nuclear	–	+ (Herpes)	–	–
7. Micro-organisms	+	–	–	–

TREATMENT

1. Topical antibiotics to control the infection constitute the main treatment of acute bacterial conjunctivitis. Ideally, the antibiotic should be selected after culture and sensitivity tests but in practice, it is difficult. However, in routine, most of the patients respond well to broad spectrum antibiotics. Therefore, treatment may be started with chloramphenicol (1%), or gentamicin (0.3%), or tobramycin 0.3% or framycetin 0.3% eye drops 3–4 hourly in day and ointment used at night will not only provide antibiotic cover but also help to reduce the early morning stickiness. If the patient does not respond to these antibiotics, then the quinolone antibiotic drops such as ciprofloxacin (0.3%), ofloxacin (0.3%), gatifloxacin (0.3%) or moxifloxacin (0.5%) may be used.

2. Irrigation of conjunctival sac with sterile lukewarm saline once or twice a day will help by removing the deleterious material. Frequent eyewash (as advocated earlier) is, however, contraindicated as it will wash away the lysozyme and other protective proteins present in the tears.

3. Dark goggles should be used to prevent photophobia.

4. No bandage should be applied in patients with mucopurulent conjunctivitis. Exposure to air keeps the temperature of conjunctival cul-de-sac low which inhibits the bacterial growth; while after bandaging, conjunctival sac is converted into an incubator, and thus infection flares to a severe degree within 24 hours. Further, bandaging of eye will also prevent the escape of discharge.

5. No steroids should be applied, otherwise infection will flare up and bacterial corneal ulcer may develop.

6. Anti-inflammatory and analgesic drugs (e.g. ibuprofen and paracetamol) may be given orally for 2–3 days to provide symptomatic relief from mild pain especially in sensitive patients.

Preventive measures to reduce risk of transmission to the close contacts

- Frequent handwashing, and
- Avoidance of sharing towel, handkerchief and pillow with others.

HYPERACUTE BACTERIAL CONJUNCTIVITIS

Hyperacute bacterial conjunctivitis also known as acute purulent conjunctivitis or *acute blennorrhoea* is characterised by a violent inflammatory response.

It occurs in two forms:

1. Adult purulent conjunctivitis
2. Ophthalmia neonatorum in newborn (*see* page 27).

HYPERACUTE CONJUNCTIVITIS OF ADULTS (GONOCOCCAL CONJUNCTIVITIS)

ETIOLOGY

The disease affects adults, predominantly males.

- *Gonococcal infection* directly spreads from genitals to eye. Presently, incidence of gonococcal conjunctivitis has markedly decreased.
- *Other pathogen* causing hyperacute conjunctivitis is *Neisseria meningitidis* (Table 2.1).

CLINICAL FEATURES

Gonococcal conjunctivitis

Onset is hyperacute (12 to 24 hours).

Symptoms include:

- *Pain* which is moderate to severe.
- *Purulent discharge*, which is usually copious.
- *Swelling of eyelids*, which is usually marked.
- *Mild photophobia*, i.e. difficulty to tolerate light.
- *Sticking together of lid margins* with discharge during sleep.
- *Slight blurring* of vision due to mucous flakes in front of cornea.

Signs are as follows (Fig. 2.2):

- *Eyelids* are tense and swollen.
- *Tenderness* is marked.
- *Discharge* is thick purulent, copious trickling down the cheeks.
- *Conjunctiva shows* marked chemosis, congestion and papillae, giving bright red velvety appearance. Frequently, a pseudomembrane may be seen on the conjunctival surface (Fig. 2.3).
- *Preauricular lymph nodes* are usually enlarged and tender.

Associations. Gonococcal conjunctivitis is usually associated with urethritis and arthritis.

COMPLICATIONS

1. *Corneal involvement* is quite frequent as the gonococcus can invade the normal cornea through an intact epithelium. It may occur in the form of diffuse haze and oedema, central necrosis, corneal ulceration or even perforation.

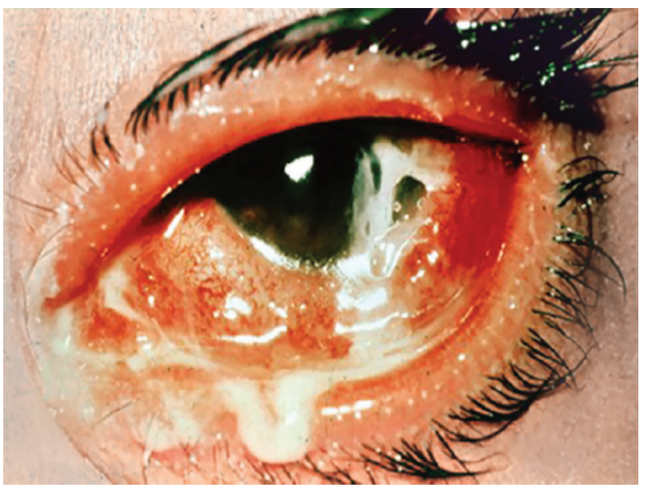


Fig. 2.2: Hyperacute conjunctivitis.

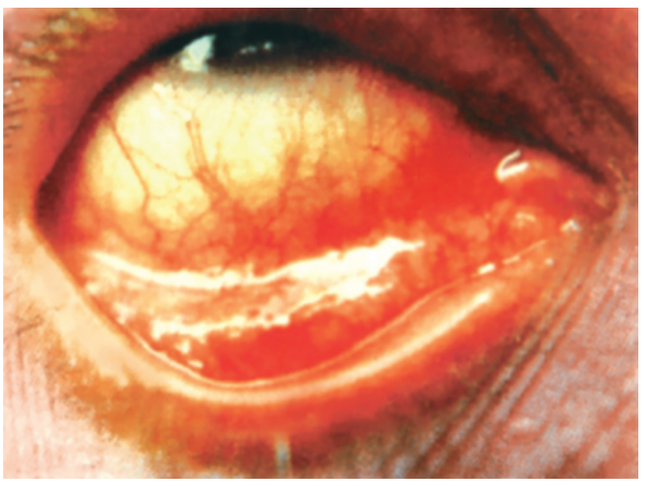


Fig. 2.3: Pseudomembranous conjunctivitis.

2. *Iridocyclitis* may also occur, but is not as common as corneal involvement.
3. *Systemic complications*, though rare, include gonorrhoea arthritis, endocarditis and septicaemia.

TREATMENT

1. Systemic therapy is far more critical than the topical therapy for the infections caused by *N. gonorrhoeae*. Any of the following regimes can be adopted:

- *Third generation cephalosporin* such as cefoxitin 1.0 g or cefotaxime 500 mg IV qid or ceftriaxone 1.0 g IM qid, all for 5 days; should be preferred treatment.
- *Quinolones* such as norfloxacin 1.2 g orally qid for 5 days, or
- *Spectinomycin* 2.0 g IM for 3 days, may be used alternatively.

All of the above regimes should then be followed by a one week course of either doxycycline 100 mg bid or erythromycin 250–500 mg orally qid.

2. Topical antibiotic therapy, presently recommended includes ofloxacin, ciprofloxacin or tobramycin eye drops or bacitracin or erythromycin eye ointment every 2 hours for the first 2–3 days and then 5 times daily for 7 days.

3. Irrigation of the eyes frequently with sterile saline is very therapeutic in washing away infected debris.

4. Other general measures are similar to acute mucopurulent conjunctivitis.

5. Topical atropine 1% eye drops should be instilled once or twice a day if cornea is involved.

Note. Sexual partner should also be treated with systemic antibiotics. Further, both the patient and the sexual partner should be referred for evaluation of other sexually transmitted diseases.

Meningococcal conjunctivitis

Hyperacute conjunctivitis caused by *Neisseria meningitidis* is comparatively milder than gonococcal conjunctivitis. It may be of two types: Primary and secondary.

Primary meningococcal conjunctivitis is extremely rare in adults and can be:

- *Invasive disease*, which is followed by systemic meningococcal disease.
- *Non-invasive disease*, i.e. isolated conjunctival infection.

Treatment of meningococcal conjunctivitis

- *Topical treatment* in similar to gonococcal conjunctivitis.
- *Systemic treatment* includes intravenous penicillin or intravenous cefotaxime or ceftriaxone (in penicillin-resistant cases).

Note. *Close contacts* of invasive meningococcal conjunctivitis should receive prophylaxis with a single dose of ciprofloxacin 500 mg or rifampin 600 mg twice daily for two days.

CHRONIC BACTERIAL CONJUNCTIVITIS

Chronic bacterial conjunctivitis also known as *'Chronic catarrhal conjunctivitis'* or *'simple chronic conjunctivitis'* is characterised by mild catarrhal inflammation of the conjunctiva. Chronic bacterial conjunctivitis lasts more than 3 weeks and is often associated with blepharitis.

ETIOLOGY

A. Predisposing factors

1. *Chronic exposure* to dust, smoke, and chemical irritants.
2. *Local cause of irritation* such as trichiasis, concretions, foreign body and seborrhoeic scales.
3. *Eye strain* due to refractive errors, phorias or convergence insufficiency.
4. *Abuse of alcohol,* insomnia and metabolic disorders.

B. Causative organisms (Table 2.1)

- *Staphylococcus aureus* is the commonest cause of chronic bacterial conjunctivitis. It colourizes the eyelid margin and then causes direct infection of conjunctiva or conjunctival inflammation through the exotoxins released.
- *Gram-negative rods* such as *Proteus mirabilis, Klebsiella pneumoniae, Escherichia coli, Moraxella lacunata, Serratia marcescens*, and *Branhamella catarrhalis* are other rare causes.

C. Source and mode of infection. Chronic conjunctivitis may occur:

1. *As continuation of acute mucopurulent conjunctivitis* when untreated or partially treated.
2. *As chronic infection* from associated chronic dacryocystitis, chronic rhinitis or chronic upper respiratory catarrh.
3. *As a mild exogenous infection* which results from direct contact, airborne or material transfer of infection.

CLINICAL FEATURES

Symptoms of simple chronic conjunctivitis include:

- *Burning and grittiness* in the eyes, especially in the evening.
- *Mild chronic redness* in the eyes. Feeling of heat and dryness on the lid margins.
- *Difficulty in keeping the eyes open.*
- *Mild mucoid discharge* especially in the canthi.
- *Watering*, off and on is often a complaint.
- *Feeling of sleepiness* and tiredness in the eyes.

Signs. Grossly the eyes look normal but careful examination may reveal following signs:

- *Congestion* of posterior conjunctival vessels which is mild and diffuse.
- *Mild papillary hypertrophy* of the palpebral conjunctiva.
- *Follicles,* may also occur
- *Conjunctival* thickening
- *Sticky look* of surface of the conjunctiva.

- *Lid margins* may show congestion, telangiectasis, loss of lashes and blepharitis.
- *Cornea* may develop marginal corneal ulcer.

TREATMENT

1. *Eliminate predisposing factors* when associated.
2. *Topical antibiotics* such as chloramphenicol, tobramycin or gentamicin should be instilled 3–4 times a day for about 2 weeks to eliminate the mild chronic infection.
3. *Astringent eye drops* such as zinc–boric acid drops provide symptomatic relief.
4. *Treatment of blepharitis*, which is usually associated needs to be done by good lid hygiene with warm compresses, and eyelid scrubs followed by rubbing of combination of antibiotic and corticosteroid eye ointment.
   - Systemic therapy with oral tetracycline 250 mg 4 times a day, or doxycycline 100 mg 1–2 times a day, may be needed for severe cases of blepharitis.

ANGULAR BACTERIAL CONJUNCTIVITIS

It is a type of chronic conjunctivitis characterised by mild grade inflammation confined to the conjunctiva and lid margins near the angles (hence the name) associated with maceration of the surrounding skin.

ETIOLOGY

1. *Predisposing factors* are same as for 'simple chronic conjunctivitis'.
2. *Causative organisms. Moraxella-Axenfeld* (MA) is the commonest causative organism. MA bacilli are placed end to end, so the disease is also called 'diplobacillary conjunctivitis'. Rarely, staphylococci may also cause angular conjunctivitis.
3. *Source of infection* is usually nasal cavity.
4. *Mode of infection.* Infection is transmitted from nasal cavity to the eyes by contaminated fingers or handkerchief.

PATHOLOGY

The causative organism, i.e. MA bacillus produces a proteolytic enzyme which acts by macerating the epithelium. This proteolytic enzyme collects at the angles by the action of tears and thus macerates the epithelium of the conjunctiva, lid margin and the skin, the surrounding angles of eye. The maceration is followed by vascular and cellular responses in the form of mild grade chronic inflammation. Skin may show eczematous changes.

CLINICAL FEATURES

Symptoms include:

- Irritation, burning sensation and feeling of discomfort in the eyes.
- History of collection of dirty-white foamy discharge at the angles.
- Redness in the angles of eyes.

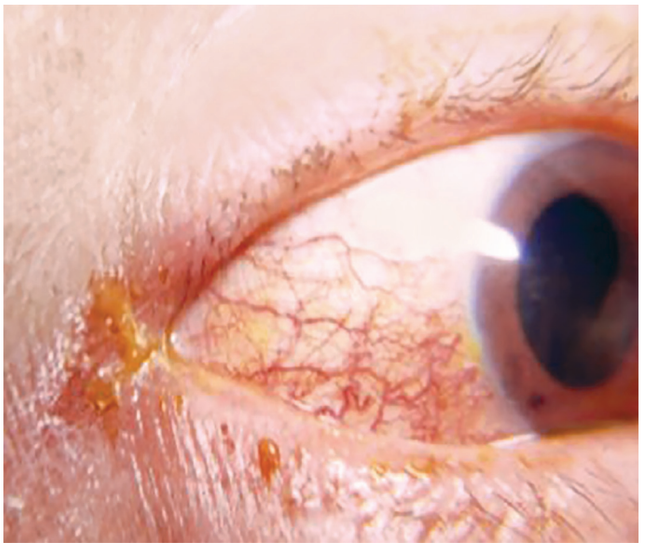


Fig. 2.4: Signs of angular conjunctivitis.

Signs include (Fig. 2.4):

- *Hyperaemia of bulbar conjunctiva* near the canthi.
- *Hyperaemia of lid margins* near the angles.
- *Excoriation of the skin* around the angles.
- *Foamy mucopurulent discharge* at the angles is usually present.

Complications include blepharitis and shallow marginal catarrhal corneal ulceration.

TREATMENT

A. Prophylaxis includes treatment of associated nasal infection and good personal hygiene.

B. Curative treatment consists of:

1. *Oxytetracycline* (1%) eye ointment, 2–3 times a day for 9–14 days will eradicate the infection.
2. *Zinc lotion* instilled in daytime and zinc oxide ointment at bed time inhibits the proteolytic ferment and thus helps in reducing the maceration.

CHLAMYDIAL CONJUNCTIVITIS

Chlamydia, earlier classified as a separate organism in between bacteria and viruses, has now been classified as bacterium belonging to the family Chlamydiaceae having two genera: Chlamydia and Chlamydophila.

Characteristics of Chlamydia

- Small, obligate intracellular, Gram-negative bacteria.
- Possess both RNA and DNA, ribosomes and cell wall similar to that of Gram-negative bacteria.
- Differ from most true bacteria is not having peptidoglycan.
- Lack the ability to produce their own ATP, therefore, use host's ATP (energy parasites).
- Multiply by binary fission.
- Inclusion bodies are basophilic in nature.

- Multiply in the cytoplasm of the host cell forming microcolonies or inclusion bodies which drape around the nucleus like a cloak or mantle (*chlamys* means mantle).
- Possess a genus-specific lipopolysaccharide-protein complex antigen.
- Exist in two morphologically distinct forms, namely elementary body (EB) and reticulate body (RB).

Life cycle of Chlamydia

Chlamydia exists in two morphological forms: The elementary body (EB) and reticulate body (RB). Life cycle of Chlamydia is shown in Figure 2.5:

- *Elementary bodies* (EBs) are extracellular infectious particles (Fig. 2.5A). These initiate infection by attaching to the susceptible host cells (Fig. 2.5B). After attachment, the EB enters the cytoplasm of the host cells within a vesicle (Fig. 2.5C), where it increases in size and differentiates into reticulate body (RB) (Fig. 2.5D).
- *Reticulate body* (RB) is thus intracellular, metabolically active form that divides by binary fission (Fig. 2.5E). Soon there occurs condensation of DNA within the RBs, disulphide bonds are formed in the outer membrane proteins and new EBs develop within the enlarging vesicle. The developing chlamydiaceal microcolony within the vesicle is termed inclusion body which is typically perinuclear and may contain 100–500 EBs (Fig. 2.5F).
- *Release of new* EBs into the extracellular space occurs following rupture of the inclusion body (Fig. 2.5G). The liberated EBs then infect the new cells where the whole cycle is repeated (Fig. 2.5G).

Ocular infections produced by Chlamydia

Ocular infections produced by Chlamydia in human beings are summarised in Table 2.4.

TRACHOMA

Trachoma (previously known as *Egyptian ophthalmia*) is a chronic keratoconjunctivitis, primarily affecting the superficial epithelium of conjunctiva and cornea simultaneously. It is characterised by a mixed follicular and papillary response of conjunctival tissue, pannus formation and in late stages cicatrization giving rough appearance. The word 'trachoma' comes from the Greek word for 'rough' which describes the surface appearance of the conjunctiva in chronic trachoma. It is still one of the leading causes of preventable blindness in the world.

ETIOLOGY

A. Causative organism. Trachoma is caused by the bacterium *Chlamydia trachomatis*, biovar TRIC. The organism is epitheliotropic and produces intracytoplasmic inclusion bodies called *HP bodies* (*Halberstaedter-Prowazek bodies*). Presently, 12 serovars of *Chlamydia trachomatis* biovar TRIC (A, B, Ba, C, D, E, F, G, H, I, J and K) have been identified using microimmunofluorescence techniques.

- *Serovars A, B, Ba and C* are associated with hyperendemic (blinding) trachoma.
- *Serovars D to K* are associated with inclusion conjunctivitis (oculogenital chlamydial disease).

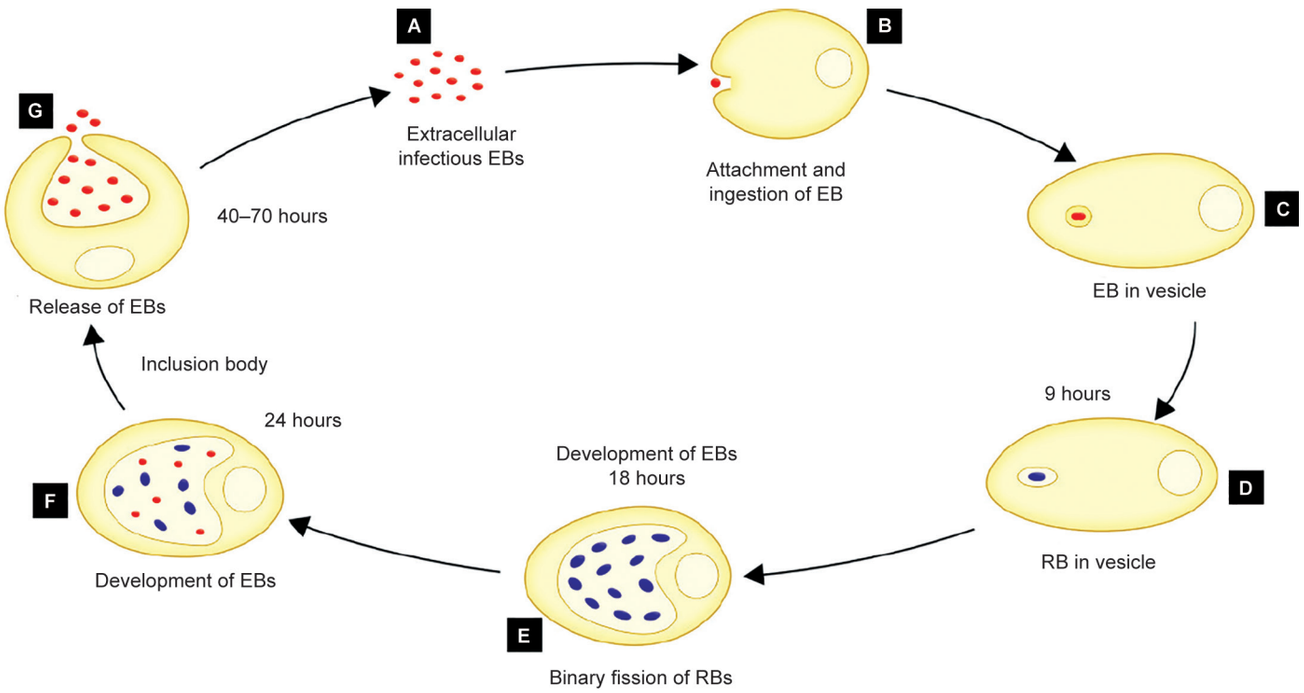


Fig. 2.5A to G: Life cycle of Chlamydia.

TABLE 2.4: Summary of ocular infections caused by Chlamydia

Family	*Chlamydiaceae*				
Genra	Chlamydia			Chlamydophila	
Biovar	*C. trachomatis* (TRIC agent) (humans)		*C. lymphogranulomatis* (humans)	*C. psittacosis* (animals)	*C. pneumoniae* (humans)
Serovar	A, B, Ba, C	D to K	L1, L2, L3	–	–
				–	–
Ocular disease	Hyperendemic trachoma	Paratrachoma (neonatal and adult inclusion conjunctivitis)	Lymphogranuloma venereum conjunctivitis		
Transmission	Eye to eye	Genitals to eye	Genitals to eye	–	–

B. Predisposing factors include:

- *Age.* The infection is usually contracted during infancy and early childhood. Otherwise, there is no age bar.
- *Sex.* As far as sex is concerned, there is general agreement that preponderance exists in the females both in number and in severity of disease.
- *Race.* No race is immune to trachoma, but the disease is very common in Jews and comparatively less common among Negroes.
- *Climate.* Trachoma is more common in areas with dry and dusty weather.
- *Socioeconomic status.* The disease is more common in poor classes owing to unhygienic living conditions, overcrowding, unsanitary conditions, abundant fly population, paucity of water, lack of materials like separate towels and handkerchiefs, and lack of education and understanding about spread of contagious diseases.
- *Environmental factors* like exposure to dust, smoke, irritants, sunlight, etc. increase the risk of contracting disease. Therefore, outdoor workers are more affected in comparison to office workers.

C. Source of infection. In trachoma endemic zones, the main source of infection is the conjunctival discharge of the affected person. Therefore, superimposed other bacterial infections help in transmission of the disease by increasing the conjunctival secretions.

D. Modes of infection. Infection may spread from eye to eye by any of the following modes:

1. *Direct spread* of infection may occur through contact by airborne or waterborne modes.
2. *Vector transmission* of trachoma is common through flies.
3. *Material transfer* plays an important role in the spread of trachoma. Material transfer can occur through contaminated fingers of doctors, nurses and contaminated tonometers. Other sources of material transfer of infection are use of common towel, handkerchief, bedding and surma-rods.

PREVALENCE

Trachoma is a worldwide disease, but it is highly prevalent in North Africa, Middle East and certain regions of South-East Asia. It is believed to affect some 500 million people in the world. There are about 150 million cases with active trachoma and about 30 million having trichiasis, needing lid surgery. Trachoma is responsible for 15–20% of the world's blindness, being second only to cataract.

CLINICAL AND PATHOLOGICAL FEATURES

Clinical features of trachoma can be described into two phases.

I. *Phase of active trachoma*

Phase of active trachoma usually occurs during childhood due to active chlamydial infection.

- *Incubation period* of active trachoma varies from 7 to 14 days.
- *Onset of disease* is usually insidious (subacute), however, rarely it may present in acute form.

Symptoms

Symptoms of active trachoma are determined by the absence or presence of secondary other bacterial infection (a very common situation).

▪ *In the absence of secondary infection*, a pure trachoma is characterized by following symptoms:

- Mild foreign body sensation
- Occasional lacrimation

- Slight stickiness of the lids
- Scanty mucoid discharge.

Note. The above symptoms are so mild that the disease is usually neglected so, the term trachoma dubium was suggested.

▪ *In the presence of secondary other bacterial infection*, typical symptoms of acute mucopurulent conjunctivitis develop (*see* page 12).

Signs

A. Conjunctival signs

1. *Congestion* of upper tarsal and forniceal conjunctiva.
2. *Conjunctival follicles.* Follicles (Figs 2.6A and B) look like boiled sago-grains and are commonly seen on upper tarsal conjunctiva and fornix; but may also be present in the lower fornix, plica semilunaris and caruncle. Sometimes, follicles may be seen on the bulbar conjunctiva (pathognomonic of trachoma).

▪ *Pathological structure of follicle.* Follicles are formed due to scattered aggregation of lymphocytes and other cells in the adenoid layer. Central part of each follicle is made up of mononuclear histiocytes, few lymphocytes and large multinucleated cells called Leber cells. The cortical part is made up of a zone of lymphocytes showing active proliferation. Blood vessels are present in the most peripheral part. In later stages, signs of necrosis are also seen. Presence of Leber cells and signs of necrosis differentiate trachoma follicles from follicles of other forms of follicular conjunctivitis.

3. *Papillary hyperplasia.* Papillae are reddish, flat topped raised areas which give red and velvety appearance to the tarsal conjunctiva (Fig. 2.7).

▪ *Pathologically* each papilla consists of central core of numerous dilated blood vessels surrounded by lymphocytes and covered by hypertrophic epithelium.

B. Corneal signs

1. *Superficial keratitis* may be present in the upper part.
2. *Herbert follicles* refer to typical follicles present in the limbal area. *Histologically* these are similar to conjunctival follicles.
3. *Progressive pannus*, i.e. infiltration of the cornea associated with vascularisation is seen in upper part (Fig. 2.8). The vessels are superficial and lie between epithelium and Bowman's membrane. Later on, Bowman's membrane is also destroyed. Pannus in active trachoma is progressive in which infiltration of cornea is ahead of vascularisation (Fig. 2.8A).
4. *Corneal ulcer* may sometime develop at the advancing edge of pannus. Such ulcers are usually shallow which may become chronic and indolent.

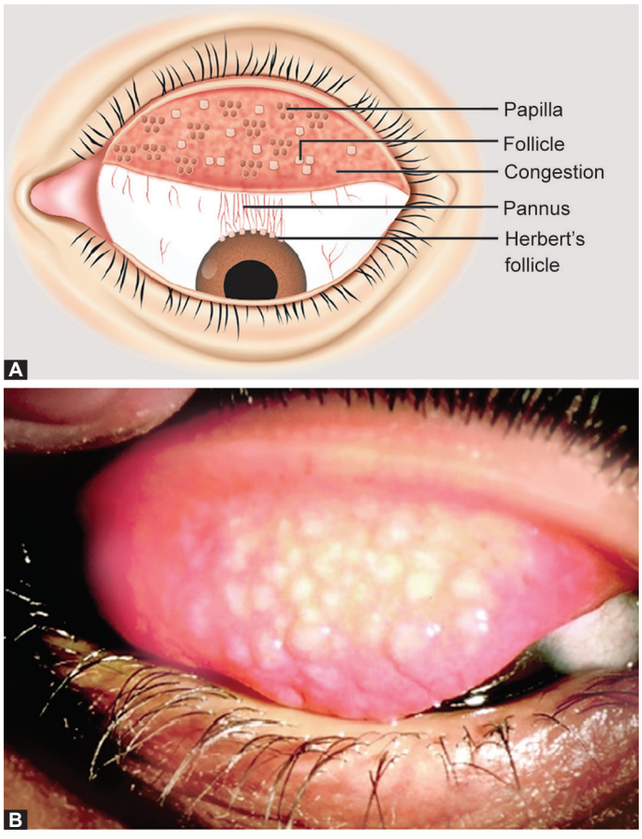


Fig. 2.6: Signs of active trachoma. A, Diagrammatic; B, Clinical photograph of trachomatous inflammation (TF) follicular.

II. *Phase of cicatricial trachoma*

Cicatricial phase of trachoma manifests in middle age. It results due to continued mild grade chronic inflammation. In fact recurrent infection elicits chronic immune response consisting of cell-mediated delayed hypersensitivity (type IV) reaction to the intermittent presence of chlamydial antigen, which is responsible for cicatricial phase of trachoma. The end stage of cicatricial trachoma is also referred to as sequelae of trachoma. This phase is characterized by following clinical features.

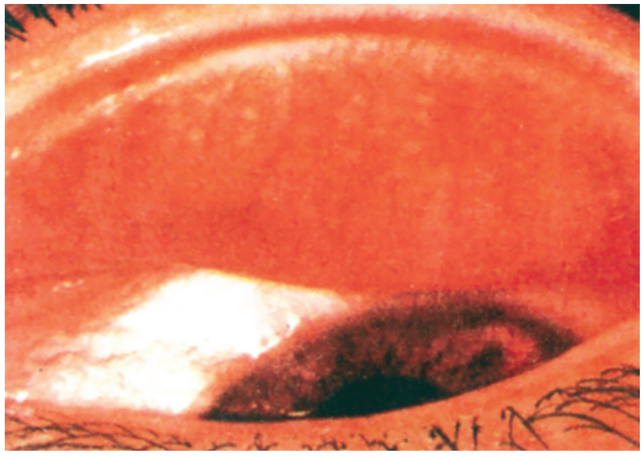


Fig. 2.7: Trachomatous inflammation (TI) intense.

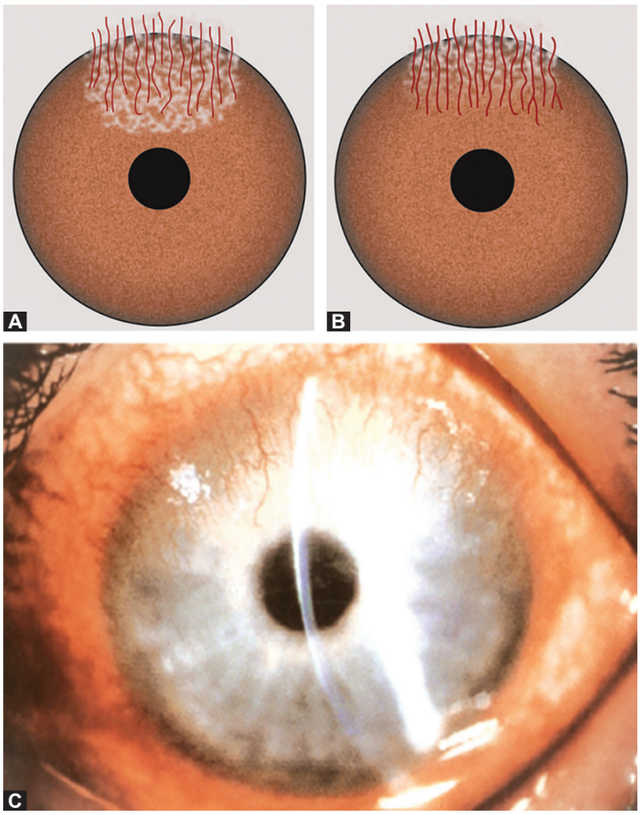


Fig. 2.8: Trachomatous pannus. A, Progressive; B, Regressive (diagrammatic); C, Clinical photograph.

A. Conjunctival signs

i. *Conjunctival scarring* (Fig. 2.9), which may be irregular, star-shaped or linear. Linear scar present in the sulcus subtarsalis is called *Arlt's line*.

ii. *Concretions* are hard looking whitish deposits varying from pinpoint to 2 mm in size (Fig. 2.10). These are not calcareous deposits, but are formed due to accumulation of dead epithelial cells and inspissated mucus in the depressions called *glands of Henle*. Hence, the name is misnomer.

iii. *Other conjunctival sequelae* include *concretions, pseudocyst, xerosis* and *symblepharon*.

B. Corneal sign

i. *Regressive pannus* (pannus siccus) in which (Fig. 2.8B) vessels extend a short distance beyond the area of infiltration.

ii. *Herbert pits* are the oval or circular pitted scars, left after healing of Herbert follicles in the limbal area (Fig. 2.11).

iii. *Corneal opacity* (Fig. 2.12) may be present in the upper part. It may even extend down and involve the papillary area. It is the end result of trachomatous corneal lesions.

iv. *Other corneal sequelae* may be corneal ectasia, corneal xerosis and total corneal pannus (blinding sequelae).

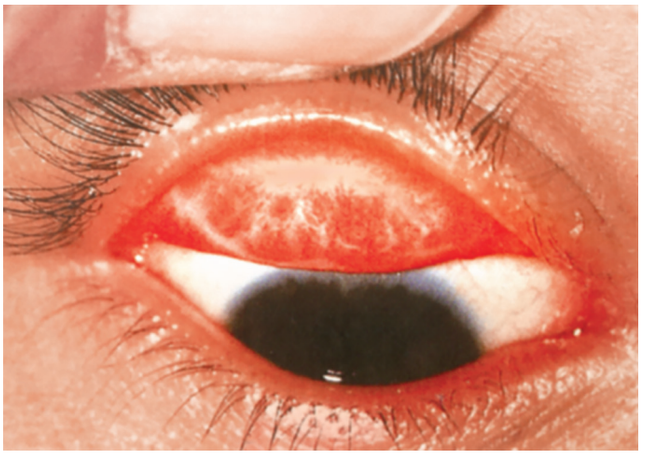


Fig. 2.9: Trachomatous scarring (TS).

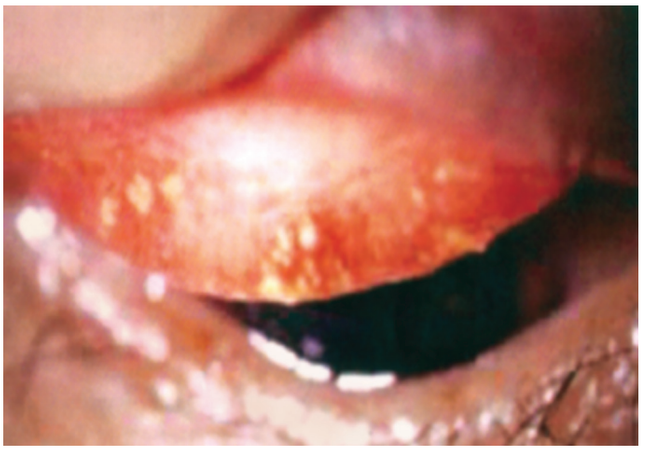


Fig. 2.10: Concretions in upper palpebral conjunctiva.

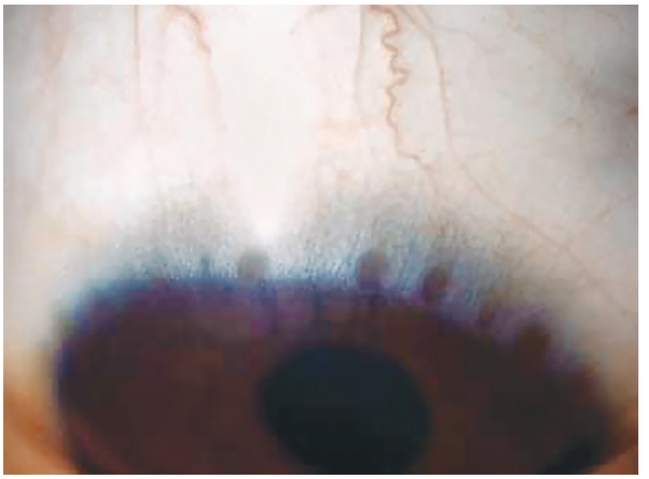


Fig. 2.11: Trachomatous Herbert's pits.

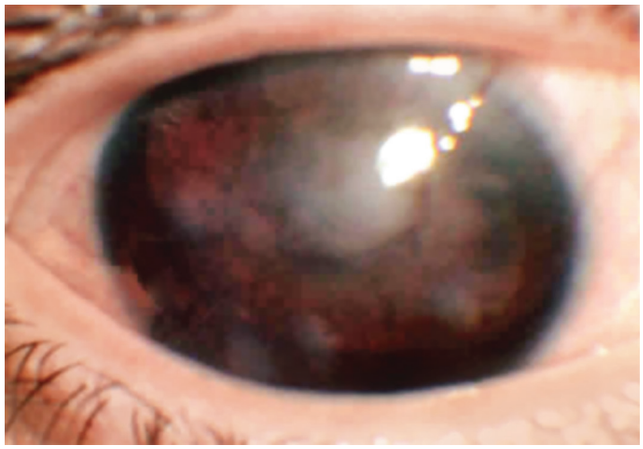


Fig. 2.12: Trachomatous corneal opacity (CO).

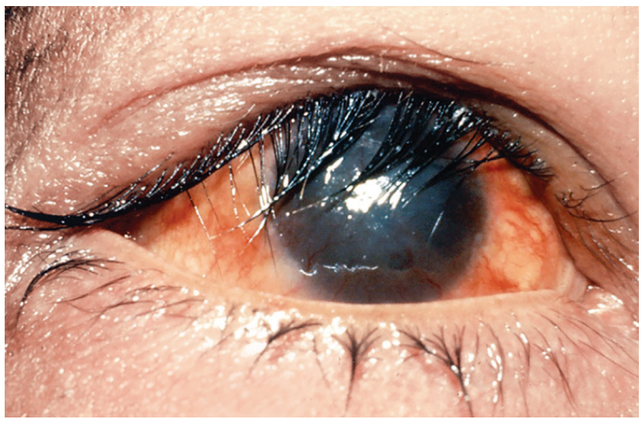


Fig. 2.13: Trachomatous trichiasis (TT).

C. Lid signs. Sequelae in the lids may be trichiasis (Fig. 2.13), entropion, tylosis (thickening of lid margin), ptosis, madarosis and ankyloblepharon.

D. Lacrimal apparatus sequelae may be chronic dacryocystitis, and chronic dacryoadenitis.

GRADING OF TRACHOMA

McCallan's classification

McCallan, in 1908, divided the clinical course of the trachoma into four stages:

1. *Stage I* (incipient trachoma or stage of infiltration). It is characterized by hyperaemia of palpebral conjunctiva and immature follicles.
2. *Stage II* (established trachoma or stage of florid infiltration). It is characterized by appearance of mature follicles, papillae and progressive corneal pannus.
3. *Stage III* (cicatrising trachoma or stage of scarring). It includes obvious scarring of palpebral conjunctiva.
4. *Stage IV* (healed trachoma or stage of sequelae). The disease is quiet and cured but sequelae due to cicatrisation, give rise to symptoms.

WHO classification

The latest simplified classification suggested by WHO in 1987 is as follows (FISTO):

1. *TF: Trachomatous inflammation-follicular.* It is the stage of active trachoma with predominantly follicular inflammation. To diagnose this stage at least five or more follicles (each 0.5 mm or more in diameter) must be present on the upper tarsal conjunctiva (*see* Fig. 2.6). Further, the deep tarsal vessels should be visible through the follicles and papillae.
2. *TI: Trachomatous inflammation intense.* This stage is diagnosed when pronounced inflammatory thickening of the upper tarsal conjunctiva obscures more than half of the normal deep tarsal vessels (*see* Fig. 2.7).
3. *TS: Trachomatous scarring.* This stage is diagnosed by the presence of scarring in the tarsal conjunctiva. These scars are easily visible as white, bands or sheets (fibrosis) in the tarsal conjunctiva (*see* Fig. 2.9).
4. *TT: Trachomatous trichiasis.* TT is labelled when at least one eyelash rubs the eyeball. Evidence of recent removal of inturned eyelashes should also be graded as trachomatous trichiasis (Fig. 2.13).
5. *CO: Corneal opacity.* This stage is labelled when easily visible corneal opacity is present over the pupil (Fig. 2.12). This sign refers to corneal scarring that is so dense that at least part of pupil margin is blurred when seen through the opacity. The definition is intended to detect corneal opacities that cause significant visual impairment (less than 6/18).

COMPLICATIONS

The only complication of trachoma is corneal ulcer which may occur due to rubbing by concretions, or trichiasis with superimposed bacterial infection.

DIAGNOSIS

A. Clinical diagnosis of trachoma is made from its typical signs. Clinical grading of each case should be done as per WHO classification into TF, TI, TS, TT or CO.

B. Laboratory diagnosis. Advanced laboratory tests are employed for research purposes only. Laboratory diagnosis of trachoma includes:

1. *Conjunctival cytology.* Giemsa-stained smears showing a predominantly polymorphonuclear reaction with presence of plasma cells and Leber cells is suggestive of trachoma.
2. *Detection of inclusion bodies* in conjunctival smear may be possible by Giemsa stain, iodine stain or immunofluorescent staining, especially in cases with active trachoma.
3. *Enzyme-linked immunosorbent assay* (ELISA) for chlamydial antigens.
4. *Polymerase chain reaction* (PCR) is also useful.
5. *Isolation of Chlamydia* is possible by yolk sac inoculation method and tissue culture technique. Standard single-passage McCoy cell culture requires at least 3 days.

6. *Serotyping of TRIC agents* is done by detecting specific antibodies using microimmunofluorescence (micro-IF) method. *Direct monoclonal fluorescent antibody microscopy* of conjunctival smear is rapid and inexpensive.

DIFFERENTIAL DIAGNOSIS

1. Active trachoma with follicular hypertrophy must be differentiated from acute adenoviral follicular conjunctivitis (epidemic keratoconjunctivitis) as follows:

- *Distribution of follicles* in trachoma is mainly on upper palpebral conjunctiva and upper fornix, while in EKC lower palpebral conjunctiva and lower fornix is predominantly involved.
- *Associated signs* such as papillae and pannus are characteristic of trachoma.
- *Laboratory diagnosis* of trachoma helps in differentiation of clinically indistinguishable cases.

2. Active trachoma with predominant papillary hypertrophy needs to be differentiated from palpebral form of spring catarrh as follows:

- *Papillae* are large in size and usually there is typical cobble-stone arrangement in spring catarrh.
- *pH of tears* is usually alkaline in spring catarrh, while in trachoma it is acidic.
- *Discharge* is ropy in spring catarrh.
- *Follicles and pannus* may also be present in trachoma.
- *Conjunctival cytology* and other laboratory tests for trachoma usually help in diagnosis in clinically indistinguishable cases.

MANAGEMENT

Management of trachoma includes curative as well as prophylactic measures.

A. Treatment of trachoma

I. Treatment of active trachoma

Stage TF and TI of WHO classification constitute active trachoma in which acute infection is present, and therefore, treatment is directed at eliminating the Chlamydia organism.

Antibiotics, thus constitute the mainstay of treatment of active trachoma. These can be given topically or systemically or in combination.

1. *Topical therapy regimes* are best for individual cases and consist of:

- *Tetracycline* (1%) or erythromycin (1%) eye ointment twice daily for 6 weeks, or
- *Sulfacetamide* (20%) eye drops three times a day along with 1% tetracycline eye ointment at bed time for 6 weeks.

2. *Systemic antibiotic therapy regimes* include:

- *Tetracycline* or *erythromycin* 250 mg orally, four times a day for 3–4 weeks, or
- *Doxycycline* 100 mg orally twice daily for 3–4 weeks, constitute the traditional standard systemic therapy.
- *Azithromycin* 20 mg/kg body weight up to maximum 1 g as single oral dose is as effective as 6 weeks of topical therapy and so is presently considered the first drug of choice. It is not used in pregnancy and children below 6 years of age.

3. *Combined topical and systemic therapy regime.* It is preferred when the ocular infection is severe (TI) or when there is associated genital infection. It includes:

- *Tetracycline* (1%) or *erythromycin* eye ointment 2 times a day for 6 weeks; and
- *Azithromycin* single oral dose (first choice) or tetracycline or erythromycin 250 mg orally 4 times a day for 2 weeks.

II. Treatment of cicatricial (inactive) trachoma

Stages TS, TI and CO of WHO classification constitute the inactive trachoma during which infection is no longer present, i.e. only trachoma sequelae are present, and therefore, treatment is directed towards these sequelae as below:

Stage TS measures include:

- *Concretions* should be removed with a hypodermic needle.
- *Conjunctival xerosis* should be treated by artificial tears (lubricating drops).

Stage TI includes trichiasis and cicatricial entropion.

- *Trichiasis*, a few misdirected cilia, should be treated with permanent lash removal measures such as electrolysis, cryolysis, and radiofrequency epilation.
- *Bilamellar tarsal resection* is the surgical procedure of choice for multiple misdirected lashes.
- *Cicatricial entropion* should be corrected surgically.

Stage CO (corneal opacification) constitutes stage of marked visual disability or blindness. After treating other trachoma sequelae, following measures must be taken:

- *Penetrating keratoplasty (PK)* is indicated for significant corneal scarring. However, the outcome is less than optimum, as these patients have extensive corneal vascularisation.
- *Keratoprosthesis (KP)* is indicated in bilateral blind cases with extensive corneal scarring and ocular surface problems.
- *Punctal occlusion and lateral tarsorrhaphy,* which takes care of the coexistent ocular surface problems, may be useful adjuncts for increasing the success of the above surgeries.

B. Prophylaxis for trachoma infection and blindness

Since immunity is very poor and short lived, so reinfections and recurrences are likely to occur. So, prophylactic measures are essential.

WHO defines blinding trachoma elimination as:

- TF prevalence, 5% in 1–9 years children, and
- TI prevalence, 1 per 1000 in total population.

SAFE strategy

The WHO's GET 2020 program (Global Elimination of Trachoma by 2020), has adopted the so-called SAFE strategy for prophylaxis against trachoma infection and prevention of blindness.

SAFE strategy includes:

S : Surgery (tertiary prevention)
A : Antibiotic use (secondary prevention)
F : Facial hygiene (primary prevention)
E : Environmental changes (primordial prevention).

1. Environmental changes (primordial prevention). Flies and other fomites are the common causes of spread of trachoma. So, environmental sanitation will constitute the primordial prevention for trachoma. Recommended environmental sanitation measures include:

- Provision of water latrines and good water supply to reduce flies and improve washing habits,
- Refuse dumps,
- Sprays to control flies,
- Animal pens away from human household, and
- Health education to improve personal and environmental hygiene.

2. Facial hygiene (primary prevention). Facial hygiene is critical measure for primary prevention of trachoma and should include:

- *Frequent face wash* with clean water to eliminate the potentially infectious ocular secretions.
- *Avoidance of common use* of towel, handkerchief, surmarods, etc. are important facial hygienic measures to prevent spread of trachoma infections.

3. Antibiotics for prevention against trachoma (secondary prevention). Use of antibiotics constitutes the secondary prevention against trachoma. Current WHO recommendations for community-based mass antibiotic therapy in endemic areas are as follows:

i. *In areas with 10% or more prevalence of active trachoma (TF in children 1–9 years) recommendation are as below:*

- *Oral azithromycin* (single dose of 20 mg/kg up to 1 g), should be administered to all community members.
- *Tetracycline eye ointment* twice daily for 6 weeks is recommended for all pregnant women, children, 6 months and those allergic to macrolides.

Note. The mass antibiotic therapy should be given once in a year for continuous three years, after which reassessment of prevalence should be made. The annual treatment should be continued till the TF prevalence in 1–9 years children of that area becomes less than 5%.

ii. *In areas with prevalence between more than 5% and less than 10%,* the targeted antibiotic therapy is recommended only among family members and close contacts of the patients.

iii. *In areas with prevalence less than 5%,* treatment of the patients only is recommended.

4. Surgery (tertiary prevention). Surgery for trichiasis and entropion constitutes tertiary prevention for trachomatous corneal blindness. WHO recommends bilamellar tarsal rotation surgery at community level for the affected persons.

ADULT INCLUSION CONJUNCTIVITIS

It is a type of acute follicular conjunctivitis associated with mucopurulent discharge. It usually affects the sexually active young adults.

ETIOLOGY

- *Serotypes D to K of Chlamydia trachomatis* are associated with adult inclusion conjunctivitis.
- *Primary source of infection* is urethritis in males and cervicitis in females.
- *Transmission of infection* may occur to eyes either through contaminated genital-hand-eye or genital-eye contact.
- *Spread of infection may also occur* through contaminated water of swimming pools (hence the name swimming pool conjunctivitis).

CLINICAL FEATURES

Incubation period of the disease is 5–14 days.

Symptoms are similar to acute mucopurulent conjunctivitis and include:

- *Ocular discomfort, foreign body sensation,*
- *Mild photophobia,* and
- *Mucopurulent discharge* from the eyes.

Signs of inclusion conjunctivitis are (Fig. 2.14):

- *Conjunctival hyperaemia*, more marked in the lower palpebral conjunctiva and fornix.
- *Acute follicular hypertrophy* predominantly of lower palpebral conjunctiva and fornix.
- *Superficial keratitis* in upper half of cornea. Sometimes, superior micropannus may also occur.
- *Pre-auricular lymphadenopathy* (non-tender) is a usual finding on the ipsilateral side.

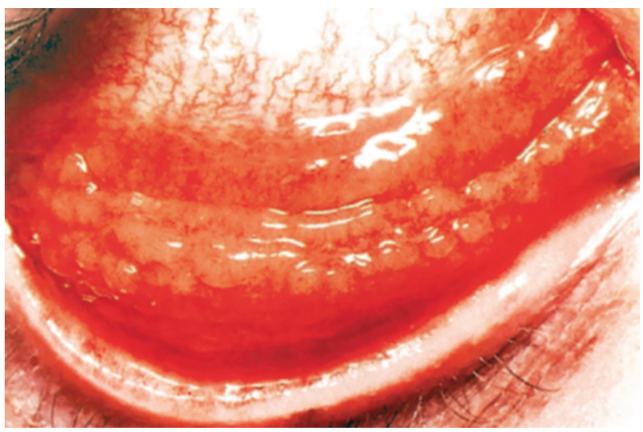


Fig. 2.14: Signs of acute follicular conjunctivitis.

Clinical course. The disease runs a benign course and often evolves into the chronic follicular conjunctivitis.

Investigations required, their role and status is same as described above for trachoma.

Differential diagnosis must be made from other causes of acute follicular conjunctivitis.

MANAGEMENT

Treatment

1. Topical therapy. It consists of tetracycline (1%) eye ointment 4 times a day for 6 weeks.

2. Systemic therapy is very important, since the condition is often associated with an asymptomatic venereal infection. Commonly employed antibiotics are:

- *Azithromycin* 1 g as a single dose repeated after one week is currently drug of choice, a 3rd dose is required in 30% of cases.
- *Tetracycline* 250 mg four times a day for 3–4 weeks, or
- *Erythromycin* 250 mg four times a day for 3–4 weeks (only when the tetracycline is contraindicated, e.g. in pregnant and lactating females), or
- *Doxycycline* 100 mg twice a day for 3 weeks.

3. Referral to genitourinary specialist is mandatory. Sexual partners should be treated simultaneously. Attention should also be given to other sexually transmitted diseases, contact tracing and pregnancy testing.

Prophylaxis

- Improvement in personal hygiene.
- Regular chlorination of swimming pool water will definitely decrease the spread of disease.
- Patient's sexual partner should be examined and treated. Abstinence of sexual contact until completion of treatment.

VIRAL CONJUNCTIVITIS

Most of the viral infections tend to affect the epithelium, both of the conjunctiva and cornea; so, the typical viral lesion is a 'keratoconjunctivitis'. In some viral infections, conjunctival involvement is more prominent (e.g. pharyngoconjunctival fever), while in others cornea is more involved (e.g. herpes simplex).

Viral infections of conjunctiva include:

- Adenovirus conjunctivitis
- Herpes simplex keratoconjunctivitis
- Herpes zoster conjunctivitis
- Molluscum contagiosum conjunctivitis
- Poxvirus conjunctivitis
- Myxovirus conjunctivitis
- Paramyxovirus conjunctivitis
- Arbor virus conjunctivitis.

Clinical presentations of acute viral conjunctivitis include:

- Acute follicular conjunctivitis
- Acute haemorrhagic conjunctivitis.

ADENOVIRAL CONJUNCTIVITIS

Adenoviruses are the commonest causes of viral conjunctivitis. These are non-enveloped, double-stranded DNA viruses, which replicate within the nucleus of host cells. General reservoir of adenoviruses is only human. Fifty-one distinct human adenoviral serotypes have been described and are classified into six subgenera (A–F). More than half of all adenoviral subtypes (32) belong to subgenus D. With a few exceptions, most adenoviral conjunctivitis is caused by this genus.

Clinical types of adenoviral conjunctivitis include:

- Epidemic keratoconjunctivitis (EKC)
- Nonspecific acute follicular conjunctivitis
- Pharyngoconjunctival fever (PCF)
- Chronic relapsing adenoviral conjunctivitis.

EPIDEMIC KERATOCONJUNCTIVITIS (EKC)

It is a type of acute follicular conjunctivitis mostly associated with superficial punctate keratitis and usually occurs in epidemics, hence the name epidemic keratoconjunctivitis (EKC).

Etiology

EKC is mostly caused by adenoviruses type 8, 19 and 37 with type 8 being the classic cause. The condition is markedly contagious and spreads through contact with contaminated fingers, solutions and tonometers.

Clinical features

Incubation period after infection is about 8 days and virus is shed from the inflamed eye for 2–3 weeks.

Symptoms

Symptoms are similar to severe form of acute catarrhal conjunctivitis and include:

- *Redness* of sudden onset associated with watering, usually profuse, with mild mucoid discharge.
- *Ocular discomfort* and foreign body sensation.
- *Photophobia*, usually mild, becomes marked when cornea is involved.

Signs

I. Eyelids are swollen causing narrowing of palpebral aperture.

II. Conjunctival signs are:

- *Hyperaemia* is usually marked and prominent.
- *Chemosis* of conjunctiva is often present.
- *Follicles* of small to moderate size typically involving the lower fornix and palpebral conjunctiva form the characteristic feature (Fig. 2.15).

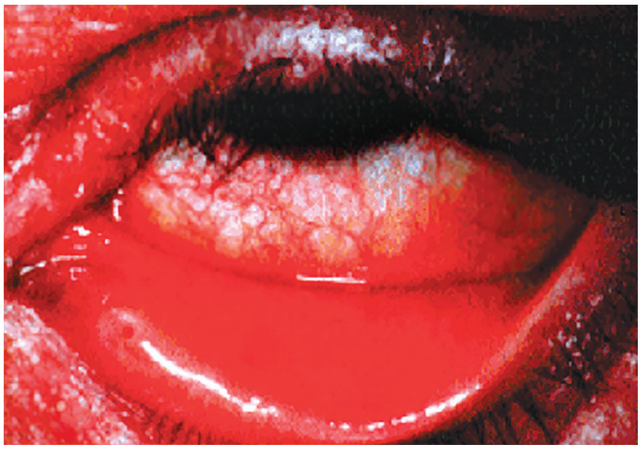


Fig. 2.15: Acute follicular adenoviral conjunctivitis.

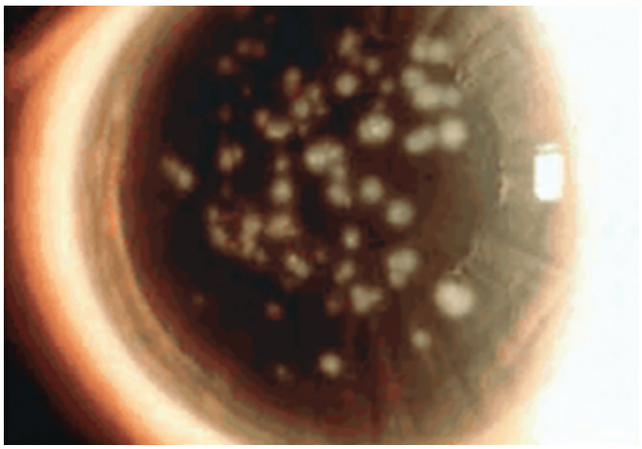


Fig. 2.17: Superficial punctate keratitis in EKC.

- *Papillary reaction* may also be seen in many cases.
- *Petechial subconjunctival haemorrhages* may be seen in severe adenoviral conjunctivitis (Fig. 2.16).
- *Pseudomembrane* lining the lower fornix and palpebral conjunctiva (Fig. 2.16) may be formed in about 3% patients with severe inflammation.

III. Corneal involvement occurs in about 80% of cases and is characterized by following lesions:

- *Epithelial microcystic* diffuse fine non-staining lesions are common during the early stage.
- *Superficial punctate keratitis* (SPK), a typical feature of EKC (Fig. 2.17), usually occurs after 10 days of onset of symptoms and lasts for 3 weeks even after subsidence of conjunctival inflammation.
- *Subepithelial infiltrates* may develop under the focal epithelial lesions in 20–50% of cases. These opacities may be initially disabling and may persist for months to years.

IV. Pre-auricular lymphadenopathy is associated in almost all cases of EKC.

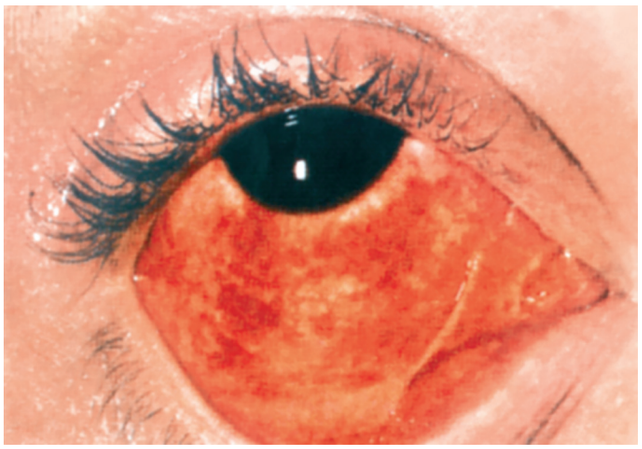


Fig. 2.16: Pseudomembrane and petechial subconjunctival haemorrhage in acute epidemic keratoconjunctivitis (EKC).

Differential diagnosis

EKC needs to be differentiated from *other causes of acute follicular conjunctivitis* which include:

- *Other types of adenoviral keratoconjunctivitis* such as:
- Nonspecific acute follicular conjunctivitis, and
- Pharyngoconjunctival fever.
- *Acute haemorrhagic conjunctivitis*
- *Herpes simplex virus conjunctivitis*
- *Systemic viral infections* such as herpes zoster conjunctivitis, measles, mumps and chikungunya virus conjunctivitis
- *Adult inclusion conjunctivitis.*

Differentiation is made from:

- *Typical clinical features* of each entity described.
- *Investigations* are required mainly for research purposes and in some nonresolving cases, and include:
  - *Conjunctival cytology* with Giemsa stain shows predominantly mononuclear cells in adenoviral conjunctivitis and multinucleated gaint cells in herpetic conjunctivitis.
  - *Polymerase chain reaction (PCR) test* is sensitive and specific for viral DNA.
  - *Point-of-care immunochromatography test* takes only 10 minutes to detect adenoviral antigens in tears and have excellent sensitivity and specificity.
  - *Viral cultures* are tedious and time consuming with variable sensitivity but 100% specificity.

Treatment

1. *Supportive treatment* for amelioration of symptoms is the only treatment required and includes:
   - Cold compresses, and sun glasses to decrease glare.
   - Decongestant and lubricant tear drops to decrease discomfort.
2. *Topical antibiotics* help to prevent superadded bacterial infections.

3. *Topical antiviral drugs* are not beneficial in adenoviral conjunctivitis. Recently promising results are reported with adenine arabinosides (Ara-A) and cidofovir.

4. *Topical steroids should not be used during active inflammation* as these may enhance viral replication and extend the period of infectivity. Weak steroids such as fluorometholone or loteprednol (0.5%) are indicated in patients with subepithelial infiltrates, and in those with membrane formation.

Prevention of spread of infection to the contacts

It is very important as the adenoviral conjunctivitis is highly contagious and patients may be infectious for up to 11 days after onset.

Transmission usually occurs

- From eye to fingers to eyes.
- Tonometers, contact lenses and eye drops are other routes of transmission.

Preventive measures include:

- Frequent handwashing and use of hand sanitizers,
- Relative isolation of infected individual,
- Avoiding eye rubbing and common use of towel or handkerchief sharing, and
- Disinfection of ophthalmic instruments and clinical surfaces after examination of a patient is essential.

NONSPECIFIC ACUTE FOLLICULAR CONJUNCTIVITIS

- *Most common* form of acute follicular conjunctivitis.
- *Caused by* adenovirus serotypes 1 to 11 and 19.
- *Clinical features* are of milder form of acute follicular conjunctivitis. Corneal involvement is not known.
- *Treatment and preventive measures* are similar to as described for EKC.

PHARYNGOCONJUNCTIVAL FEVER

Etiology. It is a highly infectious adenoviral infection commonly associated with subtypes 3, 4 and 7. *Transmitted* by three routes: Personal contact, fomites or through swimming pools or ponds.

Clinical features. Pharyngoconjunctival fever (PCF) primarily affects children and appears in epidemic form. It is characterised by an:

- Acute follicular conjunctivitis, associated with pharyngitis.
- Fever and pre-auricular lymphadenopathy.
- Corneal involvement in the form of superficial punctate keratitis is seen only in 30% of cases.

Treatment is usually supportive as described for EKC.

NEWCASTLE CONJUNCTIVITIS

Etiology. It is a rare type of acute follicular conjunctivitis caused by Newcastle virus. The infection is derived from contact with diseased owls; and thus the condition mainly affects poultry workers.

Clinically, the condition is similar to pharyngoconjunctival fever.

ACUTE HERPETIC CONJUNCTIVITIS

Acute herpetic follicular conjunctivitis is always an accompaniment of the 'primary herpetic infection', which mainly occurs in small children and in adolescents.

Etiology

The disease is commonly caused by herpes simplex virus type 1 and spreads by kissing or other close personal contacts. HSV type 2 associated with genital infections, may also involve the eyes in adults as well as children, though rarely.

Clinical features

Acute herpetic follicular conjunctivitis is usually a unilateral affection with an incubation period of 5–14 days. It may occur in two clinical forms—typical and atypical.

- In *typical form*, the follicular conjunctivitis is usually associated with other lesions of primary infection such as vesicular lesions of face and lids.
- In *atypical form*, the follicular conjunctivitis occurs without lesions of the face, eyelid and the condition then resembles epidemic keratoconjunctivitis. The condition may evolve through phases of no-specific hyperaemia, follicular hyperplasia and pseudomembrane formation.
- *Corneal involvement*, though rare, is not uncommon in primary herpes. It may be in the form of fine or coarse epithelial keratitis or typical dendritic keratitis.
- *Preauricular lymphadenopathy* occurs almost always.

Treatment

Primary herpetic infection is usually self-limiting.

- The topical antiviral drugs control the infection effectively and prevent recurrences.
- Supportive measures are similar to EKC.

ACUTE HAEMORRHAGIC CONJUNCTIVITIS

It is an acute inflammation of conjunctiva characterised by multiple conjunctival haemorrhages, conjunctival hyperaemia and mild follicular hyperplasia.

Etiology

The disease is caused by picornaviruses (enterovirus type 70) which are RNA viruses of small (pico) size. The disease is very contagious and is transmitted by direct hand-to-eye contact.

Clinical features

The disease has occurred in an epidemic form in the far East, Africa and England and hence the name 'epidemic

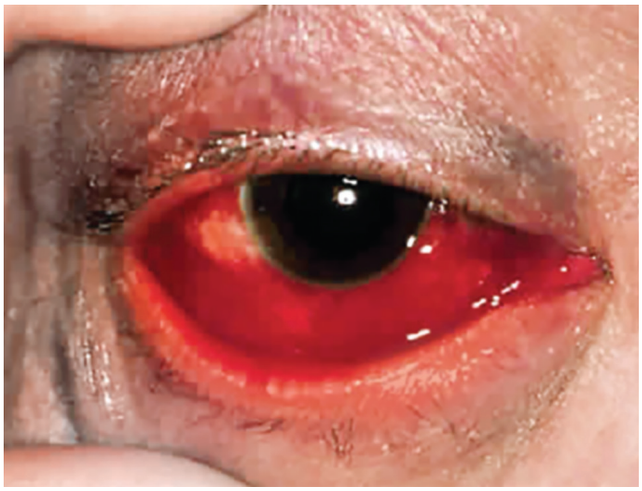


Fig. 2.18: Acute haemorrhagic conjunctivitis.

haemorrhagic conjunctivitis (EHC)' has been suggested. An epidemic of the disease was first recognized in Ghana in 1969 at the time when Apollo XI spacecraft was launched, hence the name '*Apollo conjunctivitis*'.

- *Incubation period* of EHC is very short (1–2 days).
- *Symptoms* include pain, redness, watering, mild photophobia, transient blurring of vision and lid swelling.
- *Signs* of EHC are conjunctival congestion, chemosis, multiple haemorrhages in bulbar conjunctiva, mild follicular hyperplasia, lid oedema and pre-auricular lymphadenopathy (Fig. 2.18).
- *Corneal involvement* may occur in the form of fine epithelial keratitis.

Treatment

EHC is very infectious and poses major potential problems of cross-infection.

- *Prophylactic measures* are very important and are same as described for EKC.
- *No specific effective curative treatment* is known. However, broad-spectrum antibiotic eye drops may be used to prevent secondary bacterial infections.
- Usually the disease has a *self-limiting course* of 7 days.
- *Supportive measures* are same as EKC.

OPHTHALMIA NEONATORUM

Ophthalmia neonatorum, or neonatal conjunctivitis is the name given to bilateral inflammation of the conjunctiva occurring in an infant, less than 30 days old. It is a preventable disease usually occurring as a result of carelessness at the time of birth. As a matter of fact any discharge or even watering from the eyes in the first week of life should arouse suspicion of ophthalmia neonatorum, as tears are not formed till then.

ETIOLOGY

Source and mode of infection

Infection may occur in three ways: Before birth, during birth and after birth.

1. *Before birth* infection is very rare through infected liquor amnii in mothers with ruptured membranes.
2. *During birth.* In vaginally delivered infants, the most common mode of infection is from the infected birth canal especially when the child is born with face presentation or with forceps.
3. *After birth.* Infection may occur during first bath of newborn or from soiled clothes or fingers with infected lochia.

Causative agents

1. Chemical neonatal conjunctivitis. It is caused by (in older days silver nitrate was the common cause) or antibiotics used for prophylaxis.

2. Gonococcal infection was considered a serious disease in the past, as it used to be responsible for 50% of blindness in children. But, the decline in the incidence of gonorrhoea as well as effective methods of prophylaxis and treatment have almost eliminated it in developed countries. However, in many developing countries, it still continues to be a problem.

3. Other bacterial infections, responsible for ophthalmia neonatorum are *Staphylococcus aureus, Haemophilus species, Streptococcus haemolyticus*, and *Streptococcus pneumoniae*.

4. Neonatal inclusion conjunctivitis caused by serotypes D to K of Chlamydia trachomatis is at present the commonest cause of ophthalmia neonatorum in developed countries.

5. Herpes simplex ophthalmia neonatorum is a rare condition caused by herpes simplex II virus from the infected birth canal.

CLINICAL FEATURES

Incubation period

It varies depending on the type of the causative agent as shown below:

Causative agent	*Incubation period*
• Chemical	6 hours
• Gonococcal	2–5 days
• Other bacterial	5–8 days
• Neonatal inclusion conjunctivitis	5–14 days
• Herpes simplex	6–15 days

Symptoms and signs

1. *Pain* and *tenderness* in the eyeball.
2. *Conjunctival discharge*. It is purulent in gonococcal ophthalmia neonatorum (Fig. 2.19) and mucoid or muco-purulent in other bacterial cases and neonatal inclusion conjunctivitis.

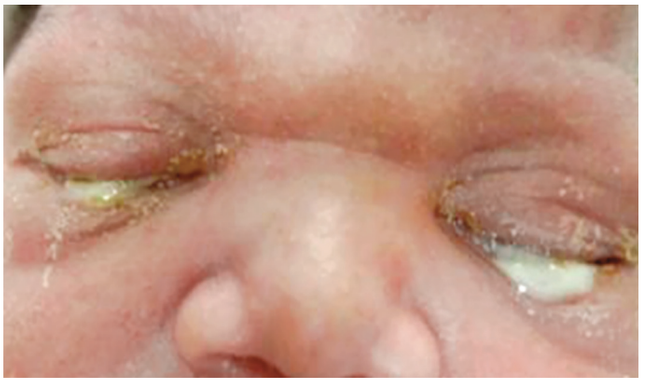


Fig. 2.19: Gonococcal ophthalmic neonatorum.

3. *Lids* are usually swollen in infective cases. Eyelids and periocular vesicles may occur in HSV infection.
4. *Conjunctiva* may show hyperaemia and chemosis. There might be mild papillary response in neonatal inclusion conjunctivitis and herpes simplex ophthalmia neonatorum. Follicular response is typically absent in infants because of immaturity of lymphoid system up to 6–8 weeks of life.
5. *Corneal involvement*, though rare, may occur in the form of superficial punctate keratitis especially in herpes simplex ophthalmia neonatorum.

Complications

Untreated cases, especially of gonococcal ophthalmia neonatorum, may develop corneal ulceration, which may perforate rapidly resulting in corneal opacification or staphyloma formation.

MANAGEMENT

Prophylaxis

Prophylactic treatment is always better than curative. Prophylaxis needs antenatal, natal and postnatal care.

1. Antenatal measures include thorough care of mother and treatment of genital infections when suspected. Surveillance of women during the third trimester of pregnancy for evidence of chlamydial, herpetic or gonococcal infection is critical in prevention of neonatal conjunctivitis.

2. Natal measures are of utmost importance, as mostly infection occurs during childbirth.

- Deliveries should be conducted under hygienic conditions taking all aseptic measures.
- The newborn baby's closed lids should be thoroughly cleansed and dried.

3. Postnatal measures include:

- *Povidone-iodine* 2.5% solution is effective against the common pathogens, and is widely used.
- *Use of either 1% tetracycline ointment* or 0.5% erythromycin ointment into the eyes of the babies immediately after birth are useful for preventing bacterial and chlamydial ophthalmia neonatorum.
- *Single injection of ceftriaxone* 50 mg/kg IM or IV (not to exceed 125 mg) should be given to infants born to mothers with untreated gonococcal infection.

Note. In the past, 1% silver nitrate solution was put in the eyes of babies immediately after birth (Crede's method). It is mentioned here just for the historical value.

Treatment

As a rule, conjunctival cytology samples and culture sensitivity swabs should be taken before starting the treatment.

1. Chemical ophthalmia neonatorum is a self-limiting condition, and does not require any treatment.

2. Gonococcal ophthalmia neonatorum needs prompt treatment to prevent complications.

- *Topical therapy* should include:
  - *Saline lavage* hourly till the discharge is eliminated.
  - *Bacitracin eye ointment* 4 times/day. Because of resistant strains topical penicillin therapy is not reliable. However, in cases with proved penicillin susceptibility, penicillin drops 5000 to 10000 units per millilitre should be instilled every minute for half an hour, every 5 minutes for next half an hour and then half hourly till the infection is controlled.
  - *If cornea is involved* then atropine sulphate ointment should be applied.
- *Systemic therapy.* Neonates with gonococcal ophthalmia should be treated for 7 days with one of the following regimes:
  - Ceftriaxone 75–100 mg/kg/day IV or IM, qid, or
  - Cefotaxime 100–150 mg/kg/day IV or IM, 12 hourly, or
  - Ciprofloxacin 10–20 mg/kg/day or norfloxacin 10 mg/kg/day, or
  - If the gonococcal isolate is proved to be susceptible to penicillin, crystalline benzyl penicillin G 50,000 units to full term, normal weight babies and 20,000 units to premature or low weight babies should be given intramuscularly twice daily for 3 days.

3. Other bacterial ophthalmia neonatorum should be treated for 2 weeks by broad-spectrum antibiotic drops and ointments such as neomycin-bacitracin or tobramycin.

4. Neonatal inclusion conjunctivitis responds well to topical tetracycline 1% or erythromycin 0.5% eye ointment qid for 3 weeks. However, systemic erythromycin 50 mg/kg/day in 3 or 4 divided days for 2 to 3 weeks should also be given since the presence of Chlamydia agents in the conjunctiva implies colonization of upper respiratory tract as well. Alternatively azithromycin suspension 20 mg/kg either as a single dose or once daily for 3 days should be administered. Both parents should also be treated with systemic erythromycin.

5. Herpes simplex conjunctivitis is usually a self-limiting disease. However, topical antiviral drugs control the infection more effectively and may prevent the recurrence.

High dose intravenous acyclovir is indicated in cases suspected of systemic herpes infection.

GRANULOMATOUS CONJUNCTIVAL INFLAMMATIONS

Granulomatous inflammations of the conjunctiva are characterised by proliferative lesions which usually tend to remain localised to one eye and are mostly associated with regional lymphadenitis.

Common granulomatous conjunctival inflammations are:

- Tuberculosis of conjunctiva
- Sarcoidosis of conjunctiva
- Syphilitic conjunctivitis
- Leprotic conjunctivitis
- Conjunctivitis in tularaemia
- Ophthalmia nodosa.

PARINAUD'S OCULOGLANDULAR SYNDROME

Clinical features: It is the name given to a group of conditions characterised by:

- Unilateral granulomatous conjunctivitis (nodular elevations surrounded by follicles),
- Pre-auricular lymphadenopathy, and
- Fever.

Common causes are tularaemia, cat-scratch disease (Bartonella henselae infection), tuberculosis, syphilis, sporotrichosis, lymphogranuloma venereum, etc.

Note. This term (Parinaud's oculoglandular syndrome) is largely obsolete, since the infecting agents can now be usually determined.

OPHTHALMIA NODOSA (CATERPILLAR HAIR CONJUNCTIVITIS)

It is a granulomatous inflammation of the conjunctiva characterized by:

- *Formation of a nodule* on the bulbar conjunctiva in response to irritation caused by the retained *hair of caterpillar*. The disease is, therefore, common in summers.
- The condition may be often mistaken for a tubercular nodule. Histopathological examination reveals hair surrounded by giant cells and lymphocyte.

Treatment consists of excision biopsy of the nodule.

ALLERGIC CONJUNCTIVITIS

It is the inflammation of conjunctiva due to allergic or hypersensitivity reactions which may be immediate (humoral) or delayed (cellular). The conjunctiva is ten times more sensitive than the skin to allergens.

Types

1. Acute allergic conjunctivitis
   - Seasonal allergic conjunctivitis (SAC)
   - Perennial allergic conjunctivitis (PAC)
2. Vernal keratoconjunctivitis (VKC)
3. Atopic keratoconjunctivitis (AKC)
4. Giant papillary conjunctivitis (GPC)
5. Phlyctenular keratoconjunctivitis (PKC)
6. Allergic dermatoconjunctivitis (ADC)

ACUTE ALLERGIC CONJUNCTIVITIS

It is a non-specific allergic conjunctivitis characterised by itching, hyperaemia and mild papillary response. Basically, it is an acute or subacute urticarial reaction.

ETIOLOGY

Acute allergic conjunctivitis, is a type I immediate hypersensitivity reaction mediated by IgE and subsequent mast cell activation, following exposure of ocular surface to airborne allergens. Family history of atopy might be present. Acute allergic conjunctivitis is known to occur in two forms:

1. Seasonal allergic conjunctivitis (SAC). SAC is a response to seasonal allergens such as tree and grass pollens. It is of very common occurrence and may be associated with hay fever (allergic rhinitis) and also known as *hay fever conjunctivitis*. It manifests as acute allergic conjunctivitis.

2. Perennial allergic conjunctivitis (PAC) is a response to perennial allergens such as house dust, animal dander and mite. It is not so common. The onset is subacute, the condition is chronic in nature and occurring all through the year.

PATHOLOGY

Pathological features of simple allergic conjunctivitis comprise vascular, cellular and conjunctival responses.

1. *Vascular response* is characterised by sudden and extreme vasodilation and increased permeability of conjunctival vessels leading to exudation.
2. *Cellular response* is in the form of conjunctival infiltration and exudation in the discharge of eosinophils, plasma cells and mast cells producing histamine and histamine-like substances.
3. *Conjunctival response* is in the form of boggy swelling of conjunctiva followed by increased connective tissue formation and mild papillary hyperplasia.

CLINICAL FEATURES

Clinical features are typically bilateral, i.e. both eyes are simultaneously involved.

Symptoms

- *Intense itching* and burning sensation in the eyes associated with
- *Watery, mucus, stringy discharge*, and
- *Mild photophobia*.

Signs

- *Hyperaemia and chemosis* which give a swollen juicy appearance to the conjunctiva.

- *Mild papillary reaction* may be seen on palpebral conjunctiva.
- *Oedema of lids* is often present.

DIAGNOSIS

Diagnosis is made from:
- Typical symptoms and signs,
- Normal conjunctival flora, and
- Cytological examination of conjunctival scrapings shows eosinophilic infiltration.
- Tear film shows elevated levels of IgE and histamine.

TREATMENT

1. *Avoiding known allergen triggers* is critical. Possible strategies for avoiding allergens include:
- *SAC patients* may benefit from staying indoor during times of high pollen counts, using room and car air conditioners, and keeping windows closed.
- *PAC patients* may benefit from covering beddings with plastic covers, removing carpets and avoiding pets.

2. *Cold compresses* may reduce swelling and may provide some additional relief.
3. *Artificial tears* like carboxymethyl cellulose provide soothing effect.
4. *Topical vasoconstrictors* like naphazoline, antazoline and tetrahydrozoline provide immediate decongestion.
5. *Mast cell stabilizers* such as sodium cromoglycate and nedocromil sodium are very effective in preventing recurrences in atopic cases.
6. *Dual action antihistamines and mast cell stabilizers* such as azelastine, olopatadine and ketotifen are very effective for exacerbations.
7. *Non-steroidal anti-inflammatory drugs (NSAIDs)* like ketorolac tromethamine and diclofenac help by decreasing the activity of cyclo-oxygenase an enzyme responsible for arachidonic acid metabolism which in turn reduce prostaglandin production.
8. *Steroid eye drops* should preferably be avoided. However, these may be prescribed for short duration in severe and non-responsive patients. These help by blocking most allergic inflammatory cascade.
9. *Systemic antihistaminic drugs* are useful in acute cases with marked itching.

VERNAL KERATOCONJUNCTIVITIS (VKC) OR SPRING CATARRH

VKC is a recurrent, bilateral, interstitial, self-limiting, allergic inflammation of the conjunctiva having a periodic seasonal incidence.

ETIOPATHOGENESIS

VKC is found in individuals with predisposed atopic background. It has been considered classically an atopic disorder, mainly type I IgE-mediated hypersensitivity reaction to pollen allergens. However, few studies have reported that pathogenesis of VKC is characterised by Th2 lymphocyte alteration and that the exaggerated IgE response to common allergens is a secondary event.

Predisposing factors

1. *Age and sex.* 4–20 years with a peace incidence between 11 and 13 years; more common in boys than girls.
2. *Season.* More common in summer; hence the name spring catarrh seems to be a misnomer. Recently, it is being labelled as *'warm weather conjunctivitis'*. Seasonal exacerbation, is common, but patients may have symptoms year-round.
3. *Climate.* More prevalent in tropics, less in temperate zones and almost non-existent in cold climate.
4. *Other atopic manifestations,* such as eczema or asthma, are associated in 40–75% patients with VKC.
5. *Family history of atopy* is found in 40–60% of patients.

PATHOLOGY

The typical lesions seen in VKC are palpebral papillae, limbal papillae and Florence-Trantas' spots.

Palpebral papillae are characterised by following histopathological changes:
- *Conjunctival epithelium* contains large number of mast cells, eosinophils and in the area of papilla formation undergoes hyperplasia and sends downward projections into the subepithelial tissue.
- *Adenoid layer* shows marked cellular infiltration by mast cells eosinophils, plasma cells, lymphocytes and histiocytes.
- *Fibrous layer* shows proliferation which later on undergoes hyaline changes.
- *Conjunctival vessels* also show proliferation, increased permeability and vasodilation.

All these pathological changes lead to formation of multiple papillae in the upper tarsal conjunctiva.

Limbal papillae, arranged as confluent lumps around the limbus, histopathologically are characterised by:
- Hyperplasia of limbal epithelial cells infiltrated with lymphocytes, plasma cells, macrophages, basophils, many eosinophils and an increased number of conjunctival goblet cells.

Horner-Trantas' spots, which grossly appear as white chalk-like gelatinous nodules are composed of eosinophils and epithelial debris located at the limbus.

CLINICAL FEATURES

Symptoms

Spring catarrh is characterised by:
- *Marked burning and itching sensation* which is usually intolerable and accentuated when patient comes in a warm humid atmosphere. Itching is more marked with palpebral form of disease.

- *Other associated symptoms* include: Mild photophobia, lacrimation, stringy (ropy) discharge and heaviness of lids.

Signs

Signs of vernal keratoconjunctivitis can be described in following three clinical forms:

1. Palpebral form. Usually upper tarsal conjunctiva of both eyes is involved. The typical lesion is the presence of hard, flat topped, papillae arranged in a *'cobble-stone'* or *'pavement stone'*, fashion along with conjunctival hyperaemia (Fig. 2.20). Tiny twigs of vessels are found in the centres of the papillae, which help to differentiate these from large follicles such as seen in trachoma. In severe cases, papillae may hypertrophy to produce cauliflower-like excrescences of 'giant papillae'. Conjunctival changes are associated with white ropy discharge.

2. Bulbar limbal form. It is characterised by:

- *Dusky red triangular congestion* of bulbar conjunctiva in palpebral area.
- *Limbal papillae occur as gelatinous, thickened* accumulation of tissue around the limbus as confluent rounded lumps (Fig. 2.21A). Tiny twig-like vessel arising in the centre of each lump differentiate it from limbal follicles. The gelatinous opacification around the limbus may override the cornea.
- *Presence of discrete whitish raised dots* along the limbus (Horner-Trantas' spots) (Fig. 2.21B).

3. Mixed form. It shows combined features of both palpebral and bulbar forms (Fig. 2.22).

Vernal keratopathy

Corneal involvement in VKC may be primary or secondary due to extension of limbal lesions. Vernal keratopathy is more frequent with palpebral form and includes following types of lesions:

1. *Punctate epithelial keratitis,* involving upper cornea, is usually associated with palpebral form of disease and is caused by:

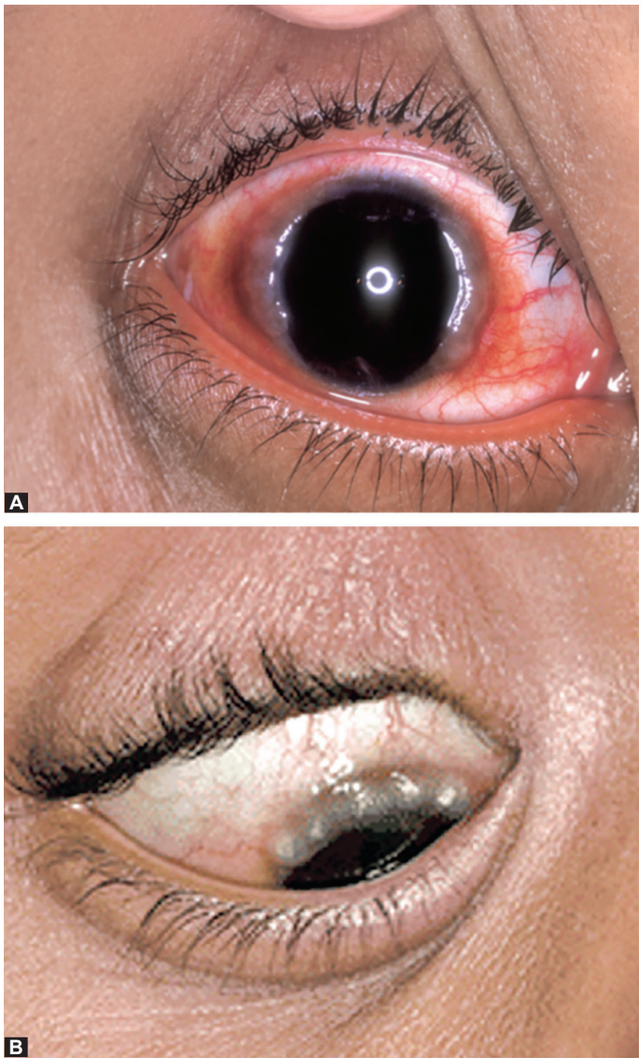


Fig. 2.21: Bulbar form of VKC depicting. A, Gelatinous membrane around limbus; B, Trantas' spots at limbus.

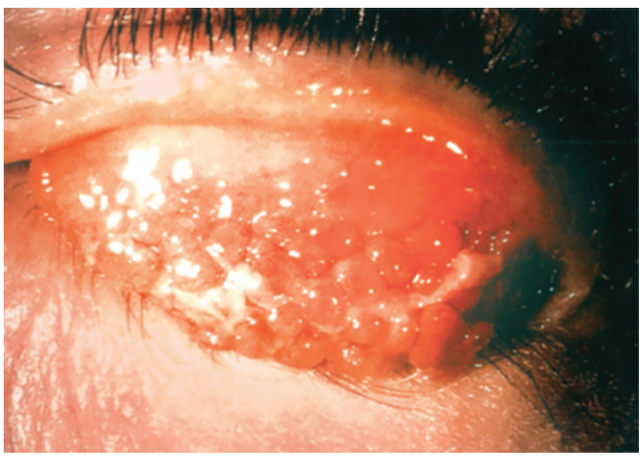


Fig. 2.20: Palpebral form of vernal keratoconjunctivitis.

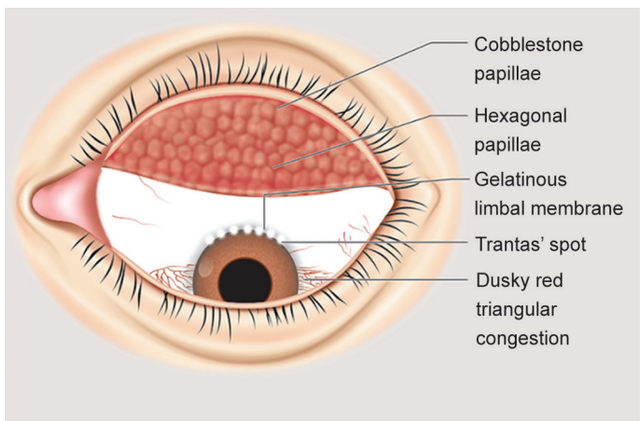


Fig. 2.22: Artist's diagram of mixed form of vernal kerato-conjunctivitis.

- Direct mechanical effect of raised palpebral papillae on the corneal epithelium, and
- Toxic effect of inflammatory mediators released from the inflamed tarsal conjunctiva.

The lesions always stain with rose bengal and invariably with fluorescein dye.

2. *Frank epithelial erosions*, leaving Bowman's membrane intact, result due to coalescence of punctate epithelial lesions.

3. *Vernal corneal plaques* result due to coating of bare areas of epithelial macroerosions with a layer of mucus and calcium phosphate (Fig. 2.23A).

4. *Ulcerative vernal keratitis (shield ulceration)* presents as a shallow transverse ulcer in upper part of cornea (Fig. 2.23B). The ulceration results due to epithelial macroerosions. It is a serious problem which may be complicated by bacterial keratitis.

5. *Subepithelial scarring* occurs in the form of a grey and oval ring scar.

6. *Pseudogerontoxon* can develop in recurrent limbal disease and is characterised by a classical 'cupid's bow' outline.

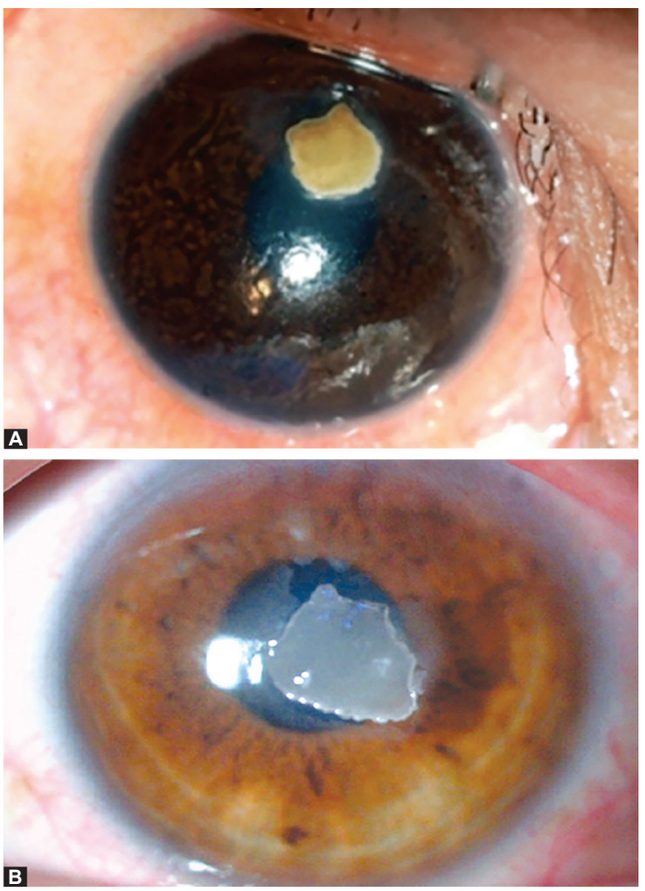


Fig. 2.23: Vernal keratopathy. A, Vernal corneal plaque; B, Shield ulcer.

7. *Keratoconus* and other corneal ectasis, seen in patients with long-standing disease are thought, at least partly, to occur because of the affect of eye rubbing.

Vernal eyelid disease

In long-standing care allergic dermatitis of eyelid skin may occur and is usually mild in contrast to atopic keratoconjunctivitis.

Clinical course of disease is often self-limiting and usually burns out spontaneously after 5–10 years.

Differential diagnosis. *Palpebral form of VKC needs to be differentiated from trachoma* with predominant papillary hypertrophy (*see* page 22).

Atopic keratoconjunctivitis (AKC) forms the principal differential diagnostic entity. Table 2.5 summarises the comparison and contrast between VKC and AKC.

TREATMENT

A. *Topical anti-inflammatory therapy*

Topical anti-inflammatory therapy with combined steroids, mast cell stabilisers, antihistamines, and NSAIDs forms the mainstay of treatment of VKC.

1. Topical steroids. These are effective in all forms of spring catarrh. However, their use should be minimised, as they frequently cause steroid-induced glaucoma. Therefore, monitoring of intraocular pressure is very important during steroid therapy. Frequent instillation (2 hourly) to start with (7 days) should be followed by maintenance therapy for 4 times a day for 2 weeks.

Commonly used steroid solutions are of fluorometholone, medrysone, betamethasone or dexamethasone. Medrysone and fluorometholone are safest of all these.

2. Mast cell stabilisers such as sodium cromoglycate (2%) drops 5 times a day are quite effective in controlling VKC, especially atopic cases.

TABLE 2.5: Comparison of VKC and AKC

	VKC	*AKC*
Age	Younger	Older
Sex	Male > female	No predilection
Duration of disease	Limited; resolves at puberty	Chronic
Time of year	Spring	Perennial
Conjunctival involvement	Upper tarsus	Lower tarsus
Cornea	Shield ulcer	Persistent epithelial defects
Corneal scar	Comon; not vision threatening	Common; vision threatening
Conjunctival vascularisation	Rare	Common

3. Dual action antihistamines and mast cell stabilisers such as azelastine, olopatadine and ketotifen are very effective for control and prevention of exacerbations.

4. NSAIDs eye drops such as ketorolac and diclofenac give added benefits.

5. Topical cyclosporine (0.5 to 1%), the immune modulator, is indicated when steroids are ineffective, inadequate, or poorly tolerated, or when given as a steroid-sparing agent in patients with severe disease.

6. Tacrolimus (0.03% ointment) is another immunomodulator, which can be useful in refractory cases.

B. *Topical lubricating and mucolytics*

1. *Artificial tears*, such as carboxymethyl cellulose, provide soothing effect.

2. *Acetylcysteine* (0.5%) used topically has mucolytic properties and is useful in the treatment of early plaque formation.

C. *Systemic therapy*

1. *Oral antihistaminics* may provide some relief from itching in severe cases.

2. *Oral steroids* for a short duration have been recommended for advanced, very severe, non-responsive cases.

D. *Treatment of large papillae*

Very large (giant) papillae can be tackled either by:

- Supratarsal injection of long acting steroid, or
- Cryo application, or
- Surgical excision is recommended for extraordinarily large papillae.

E. *Supportive measures* include:

- Dark goggles to prevent photophobia.
- Cold compresses and ice packs have soothing effects.
- Maintenance of air conditioned atmosphere.
- Change of place from hot to cold area is recommended for recalcitrant cases.

F. *Desensitization*

Desensitization has also been tried without much rewarding results.

G. *Treatment of vernal keratopathy*

- *Punctate epithelial keratitis* requires no extra treatment except that instillation of steroids should be increased.
- *A large vernal plaque* requires surgical excision by superficial keratectomy.
- *Severe shield ulcer* resistant to medical therapy may need surgical treatment in the form of debridement, superficial keratectomy, excimer laser therapeutic keratectomy as well as amniotic membrane transplantation to enhance re-epithelialization.

ATOPIC KERATOCONJUNCTIVITIS (AKC)

It can be thought of as an adult equivalent of vernal keratoconjunctivitis and is often associated with atopic dermatitis. Most of the patients are young atopic adults, with male predominance.

PATHOGENESIS

In AKC, both IgE and cell-mediated immune mechanisms play role, i.e. type I as well as type IV hypersensitivity reactions are responsible for the inflammatory changes of conjunctiva, cornea, lid margin and skin of eyelids. Mast cells and eosinophils are found in the conjunctival epithelium of AKC patients. Furthermore, a complex immune cell profile implicates more than the mast cells alone, but the details of those cellular interaction remain speculative.

CLINICAL FEATURES

Symptoms

- Itching, soreness, dry sensation.
- Mucoid discharge.
- Photophobia or blurred vision.

Signs

1. Eyelid signs

- *Lid margins* are chronically inflamed with rounded posterior borders.
- *Extra lid folds* (Dennie-Morgan fold) may occur due to chronic eyelid rubbing.
- *Loss of lateral eyebrows* (Hertoghe's sign) may be seen.
- Blepharitis, meibomianitis, and tarsal margin keratinization are also reported.
- *Trichiasis, madarosis, punctal ectropion, ectropion* and entropion may occur as sequelae of inflammation.

2. Conjunctival signs

- *Tarsal conjunctiva* has a milky appearance. There are very fine papillae, hyperaemia and scarring with shrinkage. Inferior palpebral conjunctiva is more severly involved in contrast to VKC, where superior palpebral conjunctiva is predominantly involved.
- *Bulbar conjunctiva* is chemosed and congested.
- *Limbal conjunctiva* may show gelatinous deposits and Tranta's dots as seen in VKC.
- *Subepithelial fibrosis,* fornix shortening and symblepharon are also noticed.

3. Corneal signs

- *Punctate epithelial erosions*, often more severe in the lower half of cornea, may be seen.
- *Persistent epithelial defects*, sometimes associated with focal thinning, can also occur.
- *Filamentary keratitis may also occur.*
- *Plaque formation* may occur similar to VKC.
- *Peripheral vascularisation* and stromal scarring are more common than VKC.

4. Associations

- *Keratoconus* is associated in about 15% of cases.

- *Atopic cataract*, in the form of anterior or posterior subcapsular opacities, may be associated.
- *Retinal detachment*, incidence is more higher than in general public.

Clinical course. Like the atopic dermatitis eczema with which it is associated, AKC has a protracted course with exacerbations and remissions. Like vernal keratoconjunctivitis, it tends to become inactive when patient reaches the fifth decade.

Differential diagnosis of AKC needs to be made from VKC in many patients (*see* Table 2.5).

TREATMENT

- *Treatment of AKC* is exactly on the same lines as described for VKC (*see* page 32), except that the AKC is generally less responsive and requires more intensive and prolonged therapy.
- *Lid margin inflammation and facial eczema* should be treated by oral NSAIDs, oral antibiotics (doxycycline or azithromycin) and local application of steroids and antibiotic eye ointment.

GIANT PAPILLARY CONJUNCTIVITIS (GPC)

GPC is the inflammation of conjunctiva with formation of very large-sized papillae greater than 1 mm in size (currently defined as papillae greater than 0.3 mm in diameter).

ETIOPATHOGENESIS

GPC, also known as mechanically-induced papillary conjunctivitis, is a localised allergic response to a physically rough or deposited surface (contact lens, prosthesis, exposed nylon sutures and scleral buckle). Exact pathogenesis of GPC is not clear, but is most frequently attributed to the combined effect of mechanical trauma and the subsequent immune response to antigens in the form of surface deposits or environmental factors. It has been postulated that the antigens from surface coating of contact lens or other materials are first processed by the membrane antigen processing cells (M cells) in the area of conjunctival-associated lymphoid tissue (CALT) before being presented to B lymphocytes, which then mediate the subsequent immune response.

CLINICAL FEATURES

Symptoms include mild irritation and itching, stringy discharge and reduced wearing time of contact lens or prosthetic shell.

Signs. Papillary hypertrophy (often ranging between 0.6 mm and 1.75 mm in diameter) of the upper tarsal conjunctiva, similar to that seen in palpebral form of VKC with hyperaemia are the main signs (Fig. 2.24). Size and pattern of papillae vary with the offending cause.

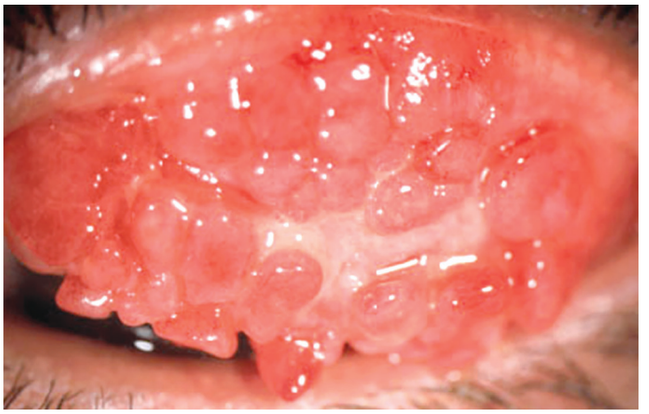


Fig. 2.24: Giant papillary conjunctivitis (GPC).

TREATMENT

1. *Offending cause should be removed.* After discontinuation of contact lens or artificial eye or removal of nylon sutures, the papillae resolve over a period of one month.
2. *Mast cell stabilizer* such as sodium cromoglycate and nedocromil are known to relieve the symptoms and enhance the rate of resolution.
3. *Combined antihistamines and mast cell stabilizers* like azelastine and olopatadine are very effective.
4. *Steroids* may be required in resistant cases.

MICROBIALLERGIC CONJUNCTIVITIS

Microbiallergic conjunctivitis refers to type IV hypersensitivity response to the bacterial toxic protein breakdown products.

Types. Two types of microbiallergic conjunctivitis are known:

- Chronic staphylococcal allergic blepharoconjunctivitis, and
- Phlyctenular keratoconjunctivitis.

CHRONIC STAPHYLOCOCCAL ALLERGIC BLEPHAROCONJUNCTIVITIS

This is a chronic type of blepharoconjunctivitis occurring as type IV hypersensitivity response to the staphylococcal bacterial breakdown products. It is the most common form of microbiallergic conjunctivitis. The staphylococcal bacterial breakdown products cause an allergic response in the conjunctiva as well as cornea.

Clinical features and treatment. It is similar to chronic blepharoconjunctivitis (*see* page 16). It is pertinent to note that:

- Typically such patients do not have history of atopy.
- Marginal corneal infiltrates are commonly associated with chronic blepharoconjunctivitis.

PHLYCTENULAR KERATOCONJUNCTIVITIS

Phlyctenular keratoconjunctivitis is a characteristic nodular affection (phlycten) occurring as an allergic

response of the conjunctival and corneal epithelium to some endogenous allergens to which they have become sensitized. Phlyctenular conjunctivitis is of worldwide distribution. However, its incidence is higher in developing countries.

Etiology

It is believed to be a delayed hypersensitivity (type IV cell mediated) response to endogenous microbial proteins so-called as *microbial allergic conjunctivitis*.

I. *Causative allergens*

1. *Tuberculous proteins* were considered, previously, a common cause.
2. *Staphylococcus proteins* are now thought to account for most of the cases.
3. *Other allergens* may be proteins of Moraxella-Axenfeld bacillus, certain parasites (worm infestation). *Candida albicans*, *Coccidioides immitis*, Chlamydia and lymphogranuloma venereum.

II. *Predisposing factors*

1. *Age.* Peak age group is 3–15 years.
2. *Sex.* Incidence is higher in girls than boys.
3. *Undernourishment*. Disease is more common in undernourished children.
4. *Living conditions.* Overcrowded and unhygienic.
5. *Season.* It occurs in all climates but incidence is high in spring and summer seasons.

PATHOLOGY

1. Stage of nodule formation. In this stage, there occurs exudation and infiltration of leucocytes into the deeper layers of conjunctiva leading to a nodule formation. The central cells are polymorphonuclear and peripheral cells are lymphocytes. The neighbouring blood vessels dilate and their endothelium proliferates.

2. Stage of ulceration. Later on necrosis occurs at the apex of the nodule and an ulcer is formed. Leucocytic infiltration increases with plasma cells and mast cells.

3. Stage of granulation. Eventually, floor of the ulcer becomes covered by granulation tissue.

4. Stage of healing. Healing occurs usually with minimal scarring.

CLINICAL FEATURES

Disease is usually unilateral (in contrast to vernal kerato-conjunctivitis which is bilateral).

Symptoms in simple phlyctenular conjunctivitis are few, like mild discomfort in the eye, irritation and reflex watering. However, usually there is associated mucopurulent conjunctivitis due to secondary bacterial infection.

Signs. The phlyctenular conjunctivitis can present in three forms: Simple, necrotizing and miliary.

1. Simple phlyctenular conjunctivitis. It is the most commonly seen variety. It is characterised by the presence of a typical pinkish white nodule surrounded by hyperaemia on the bulbar conjunctiva, usually near the limbus. Most of the times, there is solitary nodule but at times, there may be two nodules (Fig. 2.25). In a few days, the nodule ulcerates at apex which later on gets epithelised. Rest of the conjunctiva is normal.

2. Necrotizing phlyctenular conjunctivitis is characterised by the presence of a very large phlycten with necrosis and ulceration leading to a severe pustular conjunctivitis.

3. Miliary phlyctenular conjunctivitis is characterised by the presence of multiple phlyctens which may be arranged haphazardly or in the form of a ring around the limbus and may even form a ring ulcer.

Phlyctenular keratitis. Corneal involvement may occur secondarily from extension of conjunctival phlycten; or rarely as a primary disease. It may present in two forms: The 'ulcerative phlyctenular keratitis' or 'diffuse infiltrative keratitis'.

A. *Ulcerative phlyctenular keratitis* may occur in the following three forms:

1. *Scrofulous ulcer* is a shallow marginal ulcer formed due to breakdown of small limbal phlycten. It differs from the catarrhal ulcer in that there is no clear space between the ulcer and the limbus and its long axis is frequently perpendicular to limbus. Such an ulcer usually clears up without leaving any opacity.
2. *Fascicular ulcer* has a prominent parallel leash of blood vessels (Fig. 2.26). This ulcer usually remains superficial but leaves behind a band-shaped superficial opacity after healing.
3. *Miliary ulcer.* In this form multiple small ulcers are scattered over a portion of or whole of the cornea.

B. *Diffuse infiltrative phlyctenular keratitis* may appear in the form of central infiltration of cornea with characteristic rich vascularisation from the periphery, all around the limbus. It may be superficial or deep.

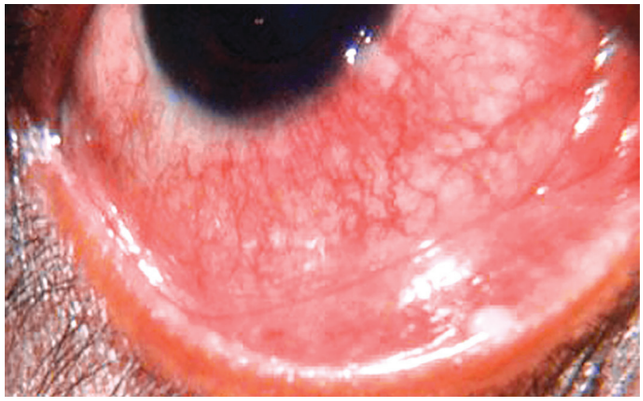
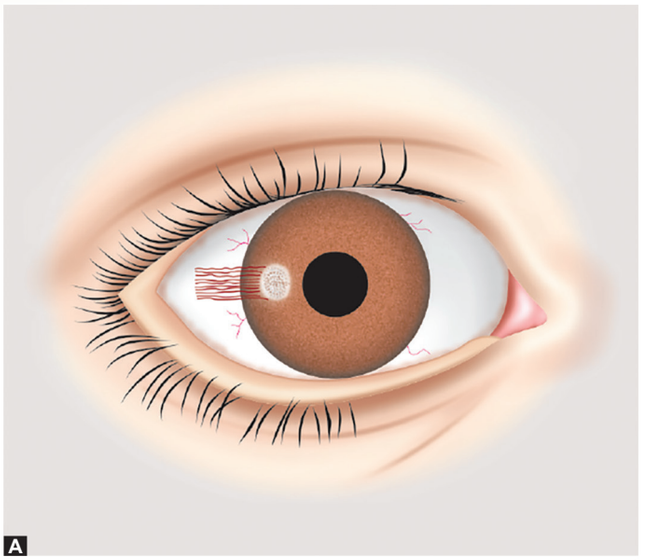


Fig. 2.25: Phlyctenular conjunctivitis.



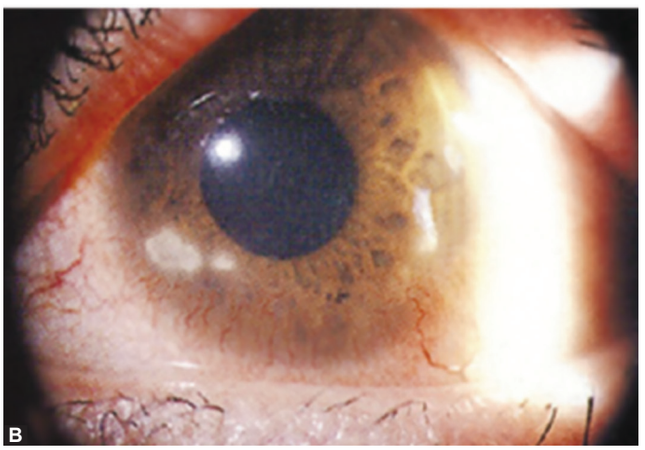


Fig. 2.26: Fascicular corneal ulcer. A, Diagrammatic; B, Clinical photograph.

Clinical course is usually self-limiting and phlycten disappears in 8–10 days leaving no trace. However, recurrences are very common.

DIFFERENTIAL DIAGNOSIS

Phlyctenular conjunctivitis needs to be differentiated from the *episcleritis, scleritis*, and *conjunctival foreign body granuloma.*

Presence of one or more whitish raised nodules on the bulbar conjunctiva near the limbus, with hyperaemia usually of the surrounding conjunctiva, in a child living in bad hygienic conditions (most of the times) are the diagnostic features of the phlyctenular conjunctivitis.

MANAGEMENT

It includes treatment of phlyctenular conjunctivitis by local therapy, investigations and specific therapy aimed at eliminating the causative allergen and general measures to improve the health of the child.

1. Local therapy

i. *Topical steroids,* in the form of eye drops or ointment (dexamethasone or betamethasone) produce dramatic effect in phlyctenular keratoconjunctivitis.

ii. *Antibiotic drops and ointment* should be added to take care of the associated secondary infection (mucopurulent conjunctivitis).

iii. *Atropine (1%) eye ointment* should be applied once daily when cornea is involved.

2. Specific therapy

Attempts must be made to search and eradicate the following causative conditions:

i. Tuberculous infection should be excluded by X-rays chest, Mantoux test, TLC, DLC and ESR. In case, a tubercular focus is discovered, antitubercular treatment should be started to combat the infection.

ii. Septic focus, in the form of tonsillitis, adenoiditis, or caries teeth, when present should be adequately treated by systemic antibiotics and necessary surgical measures.

iii. Parasitic infestation should be ruled out by repeated stool examination and when discovered should be adequately treated for complete eradication.

3. General measures

General measures aimed to improve the health of child are equally important. Attempts should be made to provide high protein diet supplemented with vitamins A, C and D.

ALLERGIC DERMATOCONJUNCTIVITIS

Allergic dermatoconjunctivitis, also known as 'contact allergic blepharoconjunctivitis', is an allergic disorder, involving conjunctiva and skin of lids along with surrounding area of face, occurring as a reaction to the eye drops, eye ointment and contact lenses solution.

Etiology

It is in fact a delayed hypersensitivity (type IV) response to prolonged contact with chemicals and drugs. A few common topical ophthalmic medications known to produce contact dermatoconjunctivitis are atropine, penicillin, neomycin, soframycin, gentamicin and contact lens solutions.

Clinical features

Clinically, it is the most common form of allergic reaction seen by the ophthalmologists and contact lenses practitioners (optometes). Its features include:

1. *Cutaneous involvement* is in the form of weeping eczematous reaction, involving all areas with which medication comes in contact
2. *Conjunctival response* is in the form of hyperaemia with a generalised papillary response affecting the lower fornix and lower palpebral conjunctiva more than the upper.
3. *Cornea* may show punctate epithelial keratitis and erosions.

Diagnosis

- *Clinical features* are usually typical.
- *Conjunctival cytology* shows a lymphocytic response with masses of eosinophils.
- *Skin test* to the causative allergen is positive in most of the cases.

Treatment

1. Discontinuation of the causative medication
2. Topical steroid eye drops to relieve symptoms
3. Application of steroid ointment on the involved skin.

NON-ALLERGIC EOSINOPHILIC CONJUNCTIVITIS

The term non-allergic eosinophilic conjunctivitis (NAEC) has recently been proposed to denote a chronic non-atopic conjunctivitis predominantly occurring in women, most of whom also have associated dry eye. The condition is relatively common but under diagnosed.

Pathogenesis is similar to non-allergic eosinophilic rhinitis.

Symptoms are similar to allergic conjunctivitis and include itching, redness foreign body sensation and mild watery discharge.

Conjunctival scrapings show eosinophilia without significant IgE levels in serum and tear film.

Treatment includes:

- *Topical steroids* for 1–2 weeks
- *Topical mast cell stabilisers* and topical NSAIDs are required as maintenance therapy for 3–4 weeks.

CICATRICIAL CONJUNCTIVITIS

Cicatricial conjunctivitis may be devided into two groups: Primary (immunologic) and secondary.

Primary (immunologic) cicatricial conjunctivitis

Primary cicatricial conjunctivitis is basically immunologic conjunctivitis seen in the following ***immunological disorders of ocular surface*:**

- Ocular mucous membrane pemphigoid (OMMP)
- Stenvens-Johnson syndrome (SJS)
- Toxic epidermal necrosis

Note. For details, *see* Chapter 4, page 60.

Secondary cicatricial conjunctivitis

Cicatricial conjunctivitis may occur secondary to:

- *Injuries to conjunctiva* (such as thermal, radiational or chemical burns), and
- *Infective conjunctivitis* (such as trachoma and viral pseudomembranous conjunctivitis).

TOXIC CONJUNCTIVITIS

TOXIC CONJUNCTIVITIS: SECONDARY TO MOLLUSCUM CONTAGIOSUM

It is a type of chronic follicular conjunctivitis that occurs as a response to toxic cellular debris desquamated into the conjunctival sac from the molluscum contagiosum nodules present on the lid margin (the primary lesion).

CHEMICAL TOXIC CONJUNCTIVITIS

Also known as toxic keratoconjunctivitis related to topical medication is an irritative follicular conjunctival response which occurs after prolonged administration of topical medication.

Common topical preparations associated with chronic follicular conjunctivitis are: Idoxuridine (IDU), eserine, pilocarpine, DFP, adrenaline, topical beta-adrenergic blocker dorzolamide, prostaglandin group of glaucoma medication, neomycin, preservatives including contact lens solutions and topical anaesthetics.

Other causes of toxic keratoconjunctivitis include:

- Cosmetics and skin care products,
- Hair care products, and
- Tear gas weapons and lacrimating agents.

Treatment

- Cessation of use of offending agent
- Lubricating drops and ointments provide symptomatic relief.
- Measures for persistent corneal epithelial defects depending upon the severity, include: Bandage contact lens, tarsorrhaphy and amniotic membrane transplants.

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Chapter

3

Tear Film and Dry Eye Disease

Chapter Outline

TEAR FILM

Functions, Structure, Properties and Composition

- Functions of tear film
- Structure of tear film
- Physical properties of tear film
- Chemical composition of tears

Tear Film Dynamics

- Secretion of tears
- Formation of periocular tear film
- Retention and redistribution of tear film
- Displacement phenomenon
- Evaporation of tear film
- Stability drying and rupture of tear film
- Dynamic events during blinking
- Elimination of tears

DRY EYE DISEASE

Definition, Classification and Causes

- Definition
- Classification
- Causes

Pathogenesis

Clinical Features

- Symptoms
- Signs
- Sjögren's syndrome

Tests for Tear Film Adequacy

- Schirmer test
- Tear film break up time
- Vital staining
- Other tear film tests

Grading of Dry Eye Severity

- DEWS system of grading

Treatment of Dry Eye Disease

- Step-ladder treatment based on the severity

TEAR FILM

The value of tear fluid in preserving a clear cornea has been understood since ages. The fact that the blinking action of lids was essential for spreading the tears and maintaining a moist surface on anterior portion of globe was obvious even in olden age. That is why in the ancient times, as a crueler form of punishment eyelids used to be excised, invariably leading to blindness due to desiccation and opacification of cornea. Hence, the knowledge of the precorneal liquid is of long-standing and so is the knowledge that the cornea will dry up, if the blinking is prevented.

The presence of precorneal layer of liquid was first demonstrated by Fischer in 1928, by using light reflected from the corneal surface on a photographic plate (reflectography). Further studies showed it to be an important part of cornea and Rollet even described it as the most superficial, sixth layer of cornea.

FUNCTIONS, STRUCTURE, PROPERTIES AND COMPOSITION OF TEAR FILM

FUNCTIONS OF TEAR FILM

1. The most important function of the tear film is *to form an almost perfectly smooth optical surface on the cornea* by filling in and smoothening out small surface irregularities in the corneal epithelium.
2. *It serves to keep the surface of cornea and conjunctiva moist.* It is unlikely that the sensitive epithelial cells could survive, if the surfaces were dry.
3. *It serves as a lubricant for the preocular surface and lids,* thereby decreasing the frictional forces that are generated during the constant blinking movements of the eyelids and rotational movements of the eyeball.
4. *It transfers oxygen* from the ambient air to the cornea.

5. *It prevents infection* due to the presence of antibacterial substances such as lysozyme, betalysin, lactoferrin, immunoglobulins and other proteins.
6. *It washes away debris* and noxious irritants.
7. *It provides a pathway for white blood cells* in case of injury.

STRUCTURE OF TEAR FILM

Wolff (1946) was the first to describe in detail the structure of tear film. He gave a clinical description of the fluid in the conjunctival sac with special reference to the lid margin. He coined the term "precorneal film" and assumed that it consisted of three layers, viz. an outer oily layer, an intermediate aqueous layer and an inner mucoid layer (Fig. 3.1A). This description still holds good in understanding tear film and its various abnormalities. Another model with six layers has also been proposed by Tiffany, which included the original three layers proposed by Wolff, along with air–lipid, lipid–aqueous and aqueous–mucin interfaces.

Further, it has also been suggested that there are dissolved mucins in the aqueous layer which decrease in concentration towards the lipid layer. The most current concept is that the tear film is a bilayer structure consisting of an aqueous–mucinous phase, with a overlying superficial lipid phase (Figs 3.1B and C). However, for understanding, the description given below is as per classical concept.

Lipid layer

Outermost superficial oily layer of tear film derived from the secretions of Meibomian, Zeiss and Moll glands covers the entire free surface of the tear fluid.

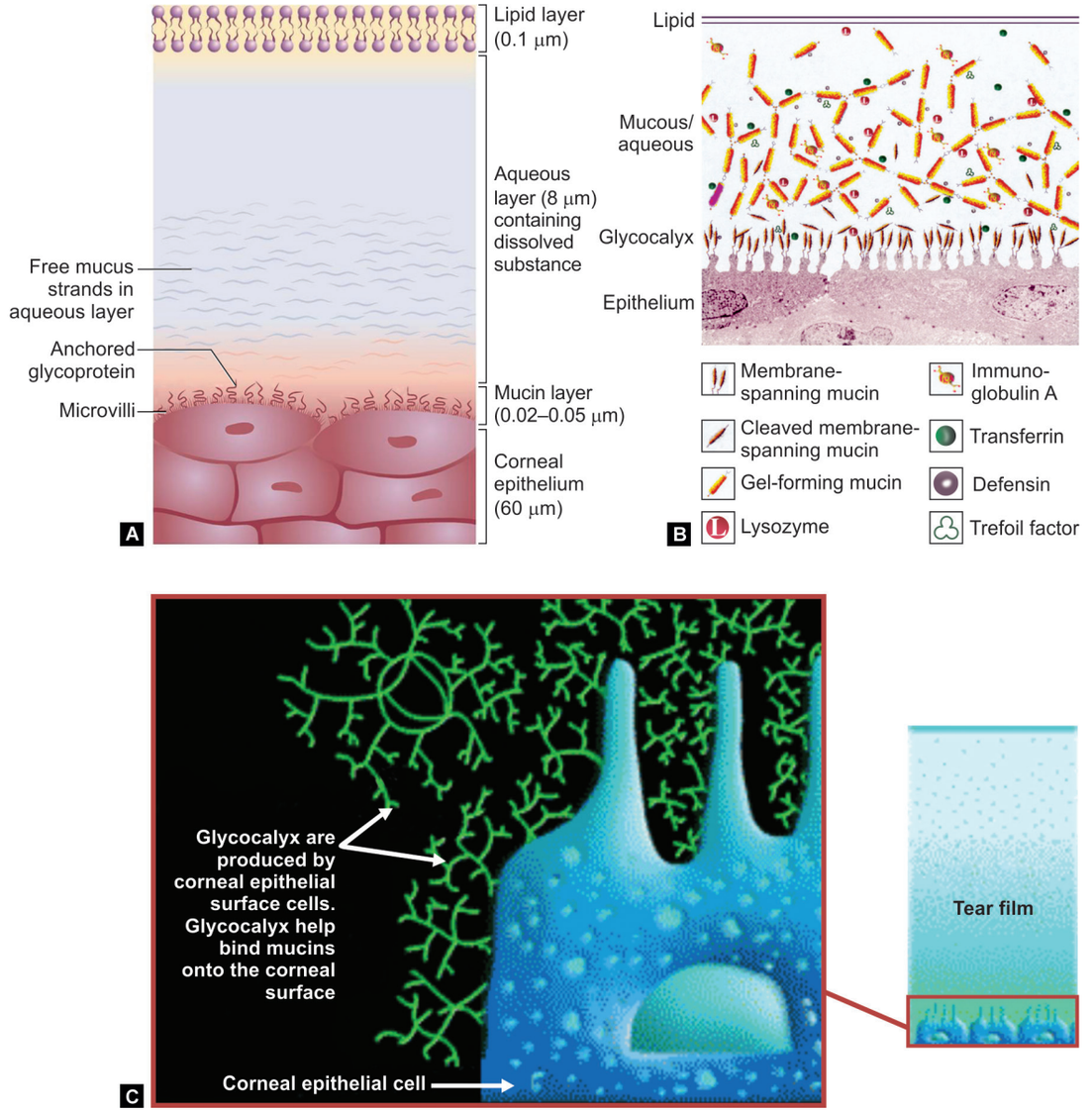

Fig. 3.1A to C: Structure of tear film.

Marginal tear strip. Wolff found that this layer on the lid margins forms a strip which extends to the posterior margin of the openings of the meibomian glands and limits the anterior end of the tear fluid reservoirs. He called it marginal tear strips.

Physical integrity of lipid layer. Thickness of lipid layer is about 0.1–0.2 mm and depends on the palpebral fissure width, i.e. it increases when the lids are partially closed.

Brauninger *et al* demonstrated the existence and physical integrity of oily layer by simple physical method of bombarding the tear film with microdroplets of oil and water, and then observing their behaviour upon striking the surface. The water particles rolled off the tear film surface, while the oily particles were immediately absorbed into the anterior surface of the tear film, indicating that the anterior surface of the tear film is an oily layer.

Chemically, this layer consists of lipids having low polarity, such as wax and cholesterol esters. These lipids are fluid at body temperature despite their considerable cholesterol contents and high average molecular weight. Lipid layer is formed from polar and neutral lipids. The polar lipids face the aqueous component of the tear film and non-polar lipids face the air. There are a number of different types of lipid secreted. High polarity lipids such as triglycerides, free fatty acids and phospholipids are present in negligible amounts.

Control of lipid secretion is neuroendocrinal:

- *Androgen sex hormones* regulate lipid synthesis and secretion.
- *Neurotransmitters* from the nerves surrounding the acini can alter lipid synthesis or alveolar cell rupture.

Functions of lipid layer include:

- *Oily layer of tear film prevents the overflow of tears and retards their evaporation.* The latter fact accrues from the observation that cauterization of the orifices of meibomian glands increases the evaporation by more than 10 times and results in absence of oily layer.
- *It prevents migration of skin lipids* onto the ocular surface.
- *It provides a clear ocular medium* and smooth surface for refraction of light.
- *Acts as a barrier for preventing contamination* of tear film.
- *It acts as a surfactant layer* which makes an effective bridge between the non-polar lipid phase and aqueous–mucinous phase.
- *It acts as a lubricant* to facilitate smooth movement of eyelids during blinking.

Aqueous layer

Middle aqueous layer of tear film is secreted by the lacrimal gland and the accessory glands of Krause and Wolfring as depicted in Figure 3.2. Main bulk of thickness of tear film

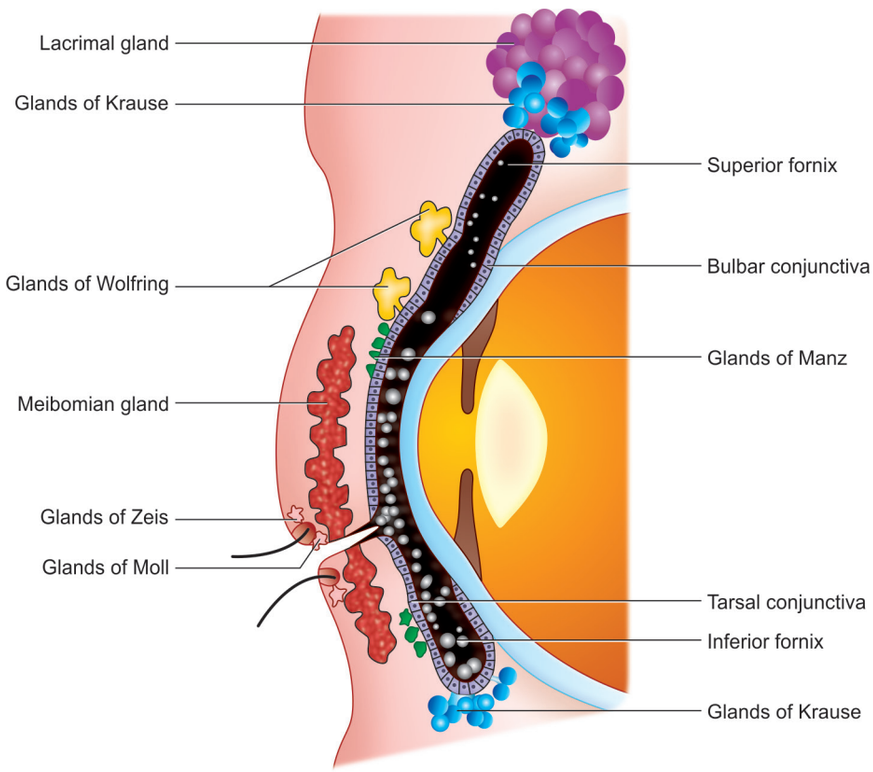

Fig. 3.2: Parts of conjunctiva and conjunctiva glands.

is constituted by this layer. Aqueous layer comprises 60% of the tear film. Thickness of aqueous layer of precorneal tear film is uniform over the cornea and is about 7 µm. The film covering the cornea is considerably thinner than over the conjunctiva. Recently, it has also been suggested that there are dissolved mucins in the aqueous layer which decrease in concentration towards the lipid layer and form the so-called aqueous–mucinous phase.

Composition. This layer is an aqueous solution of low viscosity, containing ions of inorganic salts, glucose, urea and various biopolymers such as enzymes, proteins and glycoproteins. Lysozyme, lactoferrin, tear specific prealbumin and secretory immunoglobulin A are the main constituents of protein fraction. Because some bicarbonate ions as well as proteins are present, the tear fluid has some buffering capacity. It has been observed that only the macromolecular solutes of the tears have surface activity. The electrolyte concentration of aqueous layer varies with flow rate. At low flow rates, the fluid is hypertonic, whereas at high flow rates it becomes isotonic.

Surface tension of normal aqueous tears varies between 40 and 42 dyn/cm. All the surface active substances in the aqueous tear that determine its surface tension are macromolecular and believed to be mucous glycoproteins.

Functions. It serves to provide atmospheric oxygen to the epithelium, washes away debris and noxious irritants and contains antibacterial substances like lysozyme and betalysin. Thus, the aqueous layer has antibacterial, antiadhesive and lubricant properties.

Mucus layer

Deepest stratum of the precorneal tear film is the mucus coat. Being in a highly hydrated, semisolid state, the mucus layer is not strictly a part of fluid film. It plays a vital role in the stability of the tear film. That is why Holly and Lemp found it reasonable to consider it as the third layer of tear film. They also observed that in healthy eyes the mucus layer is rather thin (only 0.02–0.04 µm), so its morphology usually resembles the microvillous, ridged appearance of superficial epithelial cell walls. However, it has been suggested that tear mucins are of two types, i.e. aqueous soluble mucins and membrane adherent mucins, and as per recent concepts the mucins dissolved in the aqueous forms the so-called aqueous–mucinous phase of tear film.

Mucin layer is mainly secreted by conjunctival goblet cells, crypts of Henle and the glands of Manz. But mucus has also been identified both histochemically and biochemically in the secretions of the main lacrimal gland. Mucus layer is made from the epithelial cell *glycocalyx* and a layer of tear mucins (*glycoprotein*). MUC5AC is the main tear mucin which is produced along with the trefoil protein TFF1 and 3.

Clear corneal epithelium is a relatively hydrophobic surface. In order for tears to completely cover the cornea, the surface must be converted from its natural hydrophobic state to a hydrophilic state that allows complete wetting. Mucin converts the hydrophobic corneal surface to a hydrophilic surface by adhering to the glycocalyx on the corneal microvilli.

- *Glycocalyx* are long chain molecules that help hold mucin to the corneal surface. Formed by corneal cells, glycocalyx migrate out from the surface of the corneal microvilli to form a hydrophilic network that holds mucin on the ocular surface (Fig. 3.1C).
- Holding mucin to the ocular surface creates a water attraction, as well as protection against bacterial pathogens. Mucin (a glycoprotein) produced by goblet cells, mixed and spread by action of lids, gets adsorbed on the cell membrane of epithelial cells and anchored by their microvilli forming a new hydrophilic surface on which aqueous and lipid layers spread spontaneously. It thus plays a vital role in the stability of preocular tear film, as the latter depends upon the constant supply of mucin to maintain proper hydration of ocular surface tissues.

Thickness. Electron micrographs of epithelial sections stained with Mowry's colloidal iron stain revealed that mucous layer has a thickness ranging from 200 to 500 Å (0.02 to 0.04 µm).

Functions of mucus are as below:

- Mucin lubricates the ocular and palpebral surfaces, so that minimal energy is lost as friction during blinking and eye movements.
- It also provides a slippery coating over the foreign bodies, thereby protecting the cornea and conjunctiva against abrasive effects of such particles as they move about with blinking.

PHYSICAL PROPERTIES OF TEAR FILM

Tear fluid is clear, salty, slightly alkaline and watery. It varies somewhat in its appearance and composition, depending on whether it is collected from the ducts of gland or from the conjunctival sac. Some of the important physical characteristics of the tear film are described in Table 3.1:

1. *Thickness of tear film.* The average thickness of tear film varies from 7 to 8 µm. The film is thickest after a blink, measuring about 9 µm. The thickness then decreases in a linear manner until at 30 seconds it has decreased to its minimal thickness of 4 µm. However, recent confocal microscopy has shown that tear film is about 40 µm thick.

2. *Volume of tear film.* The average volume of tear film has been reported to be 7 µl with a range from 4 to 13 µl (one to two drops) during basal conditions. The volume is highest in youth and then begins to decline in a linear manner until it reaches a value of 10% the youthful value by the age of 70 years. This constant slow decrease in tear film volume is accompanied by signs and symptoms of dryness.

TABLE 3.1: Physical properties of tear film	
1. Thickness	7–8 mm
2. Volume	4–13 ml
3. Rate of tear secretion	1.2 ml/min
4. Turnover rate	18% per min
5. Refractive index	1.357
6. pH	7.3–7.7
7. Osmotic pressure	0.90–0.95% NaCl soln
8. Temperature	35°C at the limbus; 30°C at the centre
9. O_2 tension (PO_2)	40–160 mm Hg

3. *Rate of tear secretion.* In the non-stimulated subjects, the average rate of tear secretion is 1.2 µl per min, with a total 24-hour secreting volume of about 10 cu ml.

4. *Turnover rate.* The tear turnover rate is 18% per minute. This high turnover rate with low volume of conjunctival sac (20 ml) is responsible for poor retention of instilled medication.

5. *Refractive index.* Refractive index of tear film is about 1.357.

6. *pH of tears.* The pH of tears is nearly 7.4 and approximates that of blood plasma. Although, wide variations have been found in normal individuals (between 5.2 and 8.35), the usual range is from 7.3 to 7.7. Reflex tears are somewhat more consistent with pH values ranging between 7.5 and 8. Tear pH is the lowest on awakening due to acid byproducts associated with relatively anaerobic conditions in prolonged lid closure and increases due to loss of carbon dioxide as eyes are open. Tear pH is maintained at constant level during waking hours by the normal buffering mechanism. When solutions having a pH lower than 6.6 and above 7.8 are instilled into the conjunctival sac, subjective discomfort occurs. Corneal injuries tend to produce an alkaline reaction in the tears.

Age, sex, time of examination, the presence of pterygium or pinguecula seem to have a little effect on pH of tears. Inflammatory conditions of conjunctiva and cornea tend to produce a shift towards a more acid tear film.

7. *Osmotic pressure.* The osmotic pressure of the tear film in normal eyes is equivalent to 0.90 to 0.95% sodium chloride solution. The optical integrity of the cornea is significantly influenced by the tonicity of tears. Variation in osmotic pressure between 0.6% and 1.3% sodium chloride equivalent is well tolerated by the eye, but beyond these limits discomfort is experienced. Total osmotic pressure is proportional to the dissolved crystalloids. The osmotic pressure of tears is slightly below that of the blood. There is no difference in osmotic pressure between tears and the aqueous humour. Osmotic pressure is significantly changed with reflex stimulation of tears. Corneal oedema often seen in early stages of contact lens adaptation occurs due to relative hypotonicity of tears resulting from a reflex stimulation.

8. *Temperature of tear film.* Under basal conditions with a normal blink rate, temperature of the tear film and anterior cornea with eyelids open ranges from 35°C at the limbus to a low of 30°C at the centre of cornea. It varies with extremely cold or hot environment, under windy conditions, and with the eyelids tightly closed or held open for prolonged period of time.

9. *Oxygen tension (PO_2).* In the normal tear film under basal conditions, PO_2 varies from 40 to 160 mm Hg. Under a tightly fitting contact lens it may drop to a value as low as 20 mm Hg. With a well fitted contact lens a more normal PO_2 is retained during blinking as the tidal flow of tears changes beneath the lens.

CHEMICAL COMPOSITION OF TEARS

Regarding composition of tear film, there seems a general agreement that it mainly consists of water with a certain content of salts and low molecular weight substances. The continuous evaporation of water from the tears makes defining a "tear composition" very difficult. A second confusing factor is the sensitivity of the tear-producing processes to stimulation while the tears are being collected for analysis. Table 3.2 depicts the chemical composition of tears. The data includes consensus values from different studies. The constituent of the tears is as follows.

Water

The aqueous phase of tear film is a dilute watery solution of salts and dissolved organic materials. The water forms the largest part of tear liquid; 98.2% with 1.8% dissolved solids.

Proteins

The total tear protein content strongly depends on the method of collection of tears. Small unstimulated tears show levels of about 2 g% while stimulated tears show much

TABLE 3.2: Chemical composition of human tears and plasma		
	Tears	*Plasma*
Water	98.2 g%	94 g/100 ml
Solids, total	1.8%	6 g/100 ml
Na^+	142 mEq/L	137–142 mEq/L
K^+	15–29 mEq/L	5 mEq/L
Cl^-	120–135 mEq/L	102 mEq/L
HCO_3^-	26 mEq/L	24.3 mEq/L
Ca^{++}	2.29 mg/100 ml	
Total proteins	0.6–2 g/100 ml	6.78 g/100 ml
Amino acids	8 mg/100 ml	
Urea	0.04 mg/100 ml	20–40 mg/100 ml
Glucose	3–10 mg/100 ml	80–90 mg/100 ml

lower values in the range of 0.3 to 0.7 g% reflecting the level of lacrimal gland fluid. As in practice, reflex tearing is difficult to avoid; a mixture of stimulated and unstimulated tears can be obtained giving normal values in the range from 0.6 to 2.0 g%. A number of protein components have been isolated from human tears. The major fractions include, specific tear protein (STP) or prealbumin, albumin, immunoglobulin, metal carrying protein, lysozyme and other enzymes. These proteins can be divided into two groups as follows:

Group A. The components of this group are similar to serum proteins. They are in a low concentration representing less than 15% of all tear proteins. Immunoglobulin G, albumin, transferrin, alpha-1 antitrypsin, alpha-1 antichymotrypsin and beta-2-microglobulins are always present. Others which occur sporadically are ceruloplasmin, haptoglobulins and zinc alpha-2-glucoproteins.

Group B. These are specific proteins, synthesized by tear glands, also known as "rapid migrating proteins". They are also present in other external secretions. Electrophoretically, they correspond to three main peaks. Protein migrating to cathode is lysozyme and the one migrating to anode is lactoferrin and third peak of immunoglobulin A.

Albumin

The albumin represents 58.2% of total protein in basic tears and 20.2% of total protein in reflex tears (Table 3.3).

Tear specific protein (prealbumin)

It is an acidic protein constituting most of the albumin content of tears. Albumin identical with serum albumin forms only a minor component of continuous tears but rises markedly in reflex tearing. While the total albumin content decreases in reflex tearing as compared with that present in continuous tears (Table 3.3), the amount of serum albumin increases relative to specific tear albumin. The exact function of albumin in the tears is not known; perhaps aids the oily meibomian secretion in stabilizing the thin tear film.

Immunoglobulins

Approximate levels of tear immunoglobulin *vis-à-vis* plasma immunoglobulin are given in Table 3.4. IgA is the most prominent tear immunoglobulin as compared to IgA in the serum. Tear IgA is a secretory immunoglobulin produced locally by plasma cells located in adenoid layer of the conjunctiva. It differs from the circulating IgA in having an additional secretory piece. While the circulating immunoglobulins function in blocking systemic infection, locally produced antibody provides a more effective defence against externally invasive viral or bacterial antigens. Tear IgM and IgE are also produced locally in the conjunctiva. In general, tear immunoglobulins are found in higher concentration in reflex tears than in continuous tears.

TABLE 3.3: Proteins found in human tears

Protein	*Normal undisturbed state (%)*	*Reflex tears (%)*
Albumin	58.2	20.2
Globulin	23.9	56.9
Lysozyme	17.9	22.9

From Iwata S (1973): Chemical composition of aqueous phase. In Holly and Kemp (eds): The preocular tear film and dry eye syndrome. International ophthalmic clinics. Boston, Little Brown.

TABLE 3.4: Levels of tear and serum immunoglobulins

Class	*Tear*	*Plasma*
IgA	14–24 mg/100 ml	170–200 mg/100 ml
IgG	17 mg/100 ml	1000 mg/100 ml
IgM	<1 mg/100 ml	125 mg/100 ml
IgD	<1 mg/100 ml	3 mg/100 ml
IgE	250 mg/ml	2000 mg/100 ml

Lysozyme

Lysozyme also termed muramidase is a proteolytic enzyme, first discovered by Fleming in 1922. Tear lysozyme concentration is highest amongst all the body fluids, forming nearly 20% of the tear proteins. In fact, lysozyme is one of the most important protein contents of the human tear film.

Lysozyme, probably produced by the acinar cells of the lacrimal gland, is a strongly basic protein of molecular weight 14000–25000 with an isoelectric point 10.5 to 11. It has a net positive charge at physiological pH so that it migrates to the cathode, in contrast with the other proteins which have a net negative charge.

Lysozyme acts as a protective agent against bacterial infections. It causes lysis by hydrolysis of the polymer N-glucosamine-N-acetyl muramic acid present in the bacterial cell wall. In addition to its bactericidal activity it has also been reported to facilitate secretory IgA-mediated bacteriolysis in the presence of complement and to promote contact inhibition of cells. Perhaps, it also helps in determining the role of lysis in an IgM antibody complement system.

The total antibacterial activity of human tears is some 200 times greater than that could be ascribed to lysozyme; depicting thereby an important role of non-lysozomal fraction. It has been reported that the non-lysozomal fraction is active against many Gram-negative organisms while lysozyme is active only against certain Gram-positive organisms.

Other enzymes

Glycolytic enzymes and the enzymes of tricyclic citric acid cycle can be detected in high levels, only in tear samples collected in paper strips or in small volumes

of unstimulated tears. The source of these enzymes is conjunctiva, where they are secreted in small amounts. *Lactate dehydrogenase* (LDH) is the enzyme in highest concentration in tears. Electrophoretically, it can be separated into its fine isoenzymes. Tear LDH originates from the corneal epithelium. In patients suffering from various corneal diseases, the distribution of the LDH isoenzymes in tears can differ from those found in healthy individuals. *Betalysin* is an antibacterial agent presents in higher concentration in tears than in human serum, but its activity is found to be poor as compared to lysozyme.

Various workers have demonstrated the presence of amylase and peroxidase in normal tears and collagenases in tears from patients of corneal ulceration due to infection, chemical burns, trauma or desiccation.

Mucopolysaccharides

Mucopolysaccharides are found in tear fluid as indicated by electrophoretic and histochemical studies. The surface of corneal epithelium can also be stained with Alcian blue or with Mowry's modification of the colloidal iron reaction, both methods indicating the presence of mucopolysaccharides.

Glycoproteins

Glycoproteins are found in the mucoid layer as well as in the tear fluid, since they are highly soluble in water. Iwata and Kabasawa fractionated three types of glycoproteins by gel filtration from tear mucoid clots collected from the conjunctival surface of rabbit eye.

Amino acids

Some 17-amino acids have been isolated from human tears. Whether all or part of the amino acid component of tears is due to secretion, filtration, local synthesis or local degradation of proteins and polypeptides is unknown. Also not much is known about the role of amino acids in conjunctival and corneal diseases.

Amino acids are present in small amount (8 mg per 100 ml) in the tears.

Lipids

Lipids are present in small amount in tears as they are contained only in very thin superficial oily layer of the tear film. Tiffany (1978) found out all possible lipids in meibomian gland secretions, namely hydrocarbon, wax esters, cholesterol ester, triglycerides and less amounts of—diglycerides, monoglycerides, free fatty acids, free cholesterol and phospholipids. The profile of free fatty acids and the proportion of lipid classes varies considerably between individuals, and may be a factor that predisposes to the development of chronic blepharitis. The composition of lipid after release is altered by the action of lipolytic lid margin bacteria and is invariably different from that of the lipid originally produced by the meibomian glands.

Metabolites

- ***Glucose*** is present in minimum amounts, about 3 to 10 mg/ml, in tear fluid collected in capillary tubes during stimulation in normoglycemic persons. This concentration is one-tenth of the concentration in the blood. Tokyda found a corresponding rise in tear glucose with elevation of plasma glucose above 100 mg% while other workers found no significant elevation in the tear glucose level in diabetics with blood glucose levels of more than 20 mmol/L.
- ***Lactate*** levels of 1–5 mmol/L in tears are far higher than the normal blood levels of 0.5–0.8 mmol/L.
- ***Pyruvate*** level is about the same as is normal for blood.
- ***Urea*** concentration in tear fluid is about 0.04 mg per 100 ml.

Electrolytes

Sodium and potassium are the main positively charged electrolytes while chlorides and bicarbonates are main negatively charged electrolytes in tears. An equal concentration of Na^+ in tears and plasma suggests its passive diffusion in tears. In fact, the primary secretion from the acinar region of lacrimal gland is essentially an ultrafiltrate of plasma, it is later modified by ductal secretion of potassium chloride. A much higher concentration of K^+ (3.5 times) than the corresponding plasma concentration explains this active secretion of K^+ in the tears. Ca^{++} is independent of the tear production and is lower than the free fraction in plasma.

TEAR FILM DYNAMICS

The main role of the lacrimal system is to establish and maintain a continuous tear film over the preocular surface. The primary role of tear film is to establish a refractive surface of high quality for the cornea and to ensure the well-being of the cornea and conjunctival epithelium.

Tear film accomplishes its functions by the highly specialized and well-organized dynamic activities which starting from the secretion to the elimination of tears in a chronological order include the following:

- Secretion of tears
- Formation of preocular tear film
- Retention and redistribution of tear film
- Displacement phenomenon
- Evaporation of tear film
- Stability drying and rupture of tear film
- Dynamic events during blinking
- Elimination of tears

SECRETION OF TEARS

Tears are continuously secreted throughout the day by accessory (basal secretion) and main (reflex secretion) lacrimal glands. This concept of 'basal tear secretion' is

presently thought to be redundant one; as even minimal tear production in the undisturbed eye is thought to be secondary to light or temperature stimulation or both. (Proprioceptors in the lids may also play a part.)

- *Reflex secretion* occurs in response to sensations from the cornea and conjunctiva, probably produced by evaporation and break-up of tear film.
- *Hyperlacrimation* occurs due to irritative sensations from the cornea and conjunctiva.
- *Afferent pathway of this secretion* is formed by fifth nerve and efferent by parasympathetic (secretomotor) supply of lacrimal gland.

Normal rate of tear production is about 1.2 µl/min, the tear volume in the eye at any time is about 7 µl and the turnover rate is about 5 to 7 min. Abnormal lacrimation brought about by ocular surface irritation or emotion can increase the production rate several hundred folds.

Most (82%) of the full term newborn babies secrete tear within 24 hours and 95% of all full term infants have normal tear secretory rate within the first week of life. However, it is of interest to note that abnormal tearing starts only after an infant is 4 months old. A newborn baby produces no excess tear fluid even when crying loudly. The absence of excess tearing in very young infants may be connected with the low innervation of the cornea. A newborn can tolerate large particles on the cornea without being uncomfortable.

It is generally accepted that the main lacrimal gland secretes water and electrolytes only during reflex tearing and that its contribution to the normal tear film is negligible. However, occasional reports indicate that, following excision of the main gland, a dry eye syndrome may follow. Conversely blocking the lacrimal puncta or excision of the lacrimal sac, i.e. dacryocystectomy results in an appropriate decrease in lacrimal secretion on the ipsilateral side, so that tears do not overflow the lid margin. The exact mechanism of these fluids and electrolyte secretory changes is unknown.

Continuous preocular tear film is formed by the secretions of the main lacrimal gland, accessory lacrimal gland, meibomian gland and mucous glands of the conjunctiva, which flows over the ocular surface.

FORMATION OF PREOCULAR TEAR FILM

Wettability of a surface is characterised by the tendency of liquids to spread on it. A drop of liquid placed on a solid surface will either spread completely or form a certain boundary line beyond which it will not spread. At this boundary, a positive angle (contact angle, theta) is formed between the liquid and solid surfaces. A solid surface, on which a liquid forms such a positive contact angle is said to be only partially wetted (non-wetted) by the liquid. In contrast, liquids that wet (spread on) a solid surface completely show a contact angle of zero.

With respect to water, surfaces on which water forms the angle θ greater than 90° are said to be hydrophobic; those with angle q between zero and 90° are relatively hydrophobic; and those with zero angle q are hydrophilic.

Corneal epithelium is a relatively hydrophobic surface. Experiments conducted by Lemp and Holly have indicated that principal constituent of tears, responsible for the wetting of corneal surface, is conjunctival mucus which spreads on to the cornea by the action of lids and converts its surface to a hydrophilic one.

Doane in 1980 studied the interaction of eyelids and tears in corneal wetting and held the blinking process responsible for distributing tear fluid over the ocular surface or wiping away the excess fluid.

Sequence of events in the formation of a continuous precorneal tear film can be summarized as follows:

- *Lids surfacing cornea* with a thin layer of mucus.
- *On this new surface, the aqueous component* of tears now spreads spontaneously.
- *Then the superficial lipid layer spreads over the aqueous film,* probably contributing to its stability and retarding evaporation between blinks.

Tear film thus formed has three distinctive phases layered one above the other. The mucin adsorbed onto the corneal epithelium, together with any excess mucin not yet dissolved and coating the adsorbed mucin layer, forms the bottom layer. The outermost layer is superficial lipid layer.

RETENTION AND REDISTRIBUTION OF TEAR FILM

The tear film is retained at a uniform thickness over the corneal surface against a gravitational force, since it is normally positioned almost vertically. The absence of downward flow of the precorneal tear film was suggested by Wolff in 1954. Further, studies indicated that the outermost layer of corneal epithelium, along with mucopolysaccharides play an important role in retaining the fluid layer on the corneal surface.

The fluid in the precorneal tear film is stagnant, unless it is mixed by blinking and eye movements with the tear fluid in the marginal strip. Redistribution occurs in the form of bringing of new tear fluid by way of marginal strip where there is constant flow of tears.

DISPLACEMENT PHENOMENON

If with a finger the lower eyelid is carefully displaced upwards over the eyeball, the particles in the film are seen to move up the cornea as an integral whole all particles on the surface including those lying far away from the margin of the eyelid, moving upward.

Based on this phenomenon, it has been concluded that surface of cornea is covered by a film possessing a certain stability, compressibility and elasticity and that it is more or less unaffected by gravity. It has been postulated that the displacement phenomenon is possible due to thin monomolecular layer on the surface of cornea that is displaced in the aforesaid manner and not the whole of the precorneal film.

EVAPORATION OF TEAR FILM

It has been shown that almost all lipid films including those of wax esters and cholesterol esters retard the evaporation of water. With proper type of measurement technique, specific resistance to evaporation due to lipid layer can be determined. Using such an approach, evaporation retarding effect has been demonstrated both *in vivo* and *in vitro.*

Such a retarding effect of superficial lipid layer is important, especially under conditions of low humidity and turbulent air flow near the cornea such as exists in a windy and arid climate.

Evaporation from the tear film is estimated to be about 10% of the production rate. That makes the evaporation 0.12 µl/min since the tear production rate is 1.2 µl/min. There is a little effect of air motion on the evaporation rate because most of the resistance to evaporation is the oily layer on the tear film.

STABILITY DRYING AND RUPTURE OF TEAR FILM

The tears can function properly only if the tear film covers the entire preocular surface and is re-established quickly and completely after a blink. In the normal human eye, the precorneal tear film has a short-lived stability. When blinking is prevented, after a brief time interval of 15–40 seconds, the tear film ruptures and dry spots appear on various parts of cornea. The drying of the corneal surface cannot be a result of evaporation of water alone, because at least ten minutes would be required to eliminate the whole tear film by drying only according to evaporation rates observed *in vivo* with the oily layer in place. It is interesting to note that among the lower animals, the tear film can remain complete for as long as 600 seconds between blinks. Following mechanisms have been put forward to explain the break-up of tear film in humans.

Mechanism of tear film break up

Holly (1973) has described a mechanism of tear film rupture (Fig. 3.3). The steps involved in the break-up of tear film as per Holly (also known as Holly and Lemp's mechanisms) are as follows:

- First of all the tear film thins uniformly by evaporation (Fig. 3.3A).

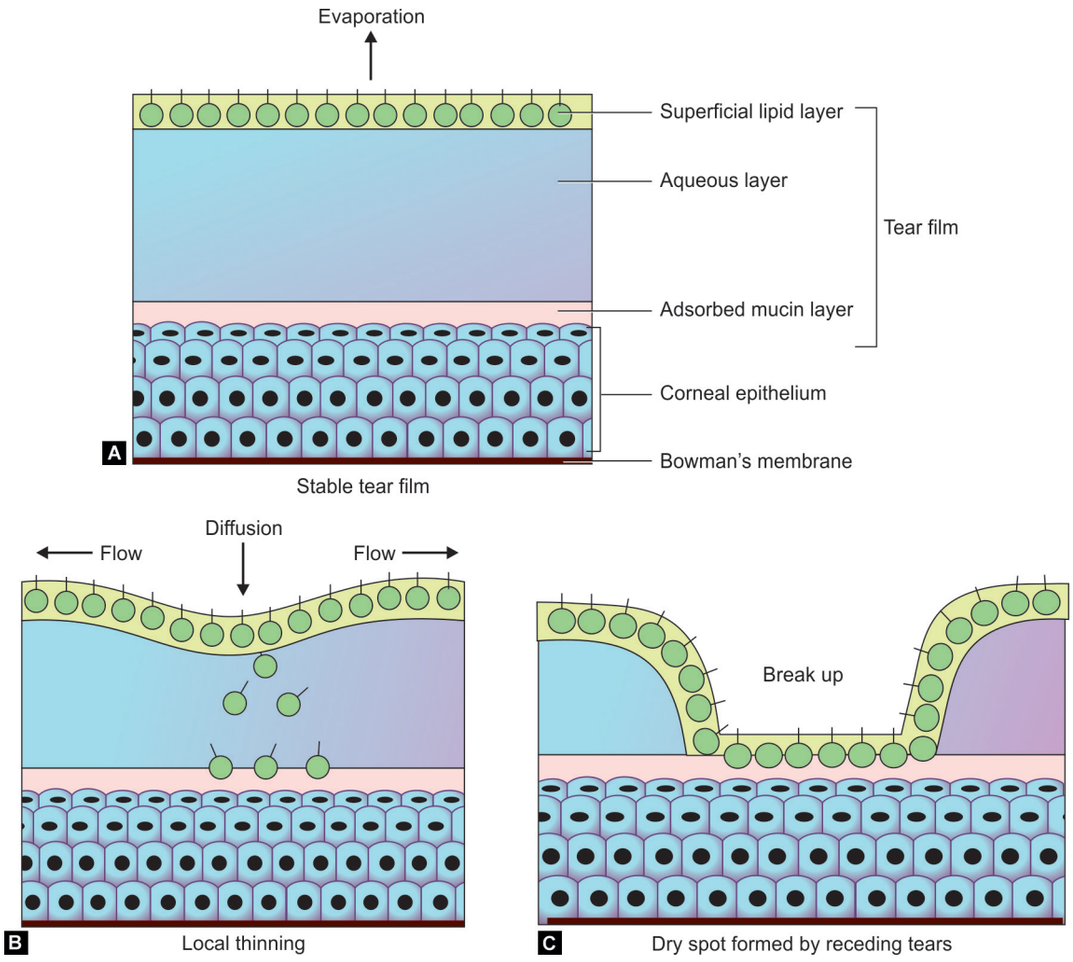

Fig. 3.3A to C: Mechanism of rupture of tears.

- When the tear film is thinned out to some critical thickness, a significant number of lipid molecules begin to be attracted by the mucin layer and migrate down to this layer. This migration process is enhanced, if there is any spontaneous local thinning (Fig. 3.3B).
- When the mucin layer on the epithelium is sufficiently contaminated by lipid migrating down from the top surface of the tear film, the mucin becomes hydrophobic and the tear film ruptures (Fig. 3.3C).

Of course, the blinking can supposedly repair the rupture by removing the lipid contaminant from the mucin layer and restoring a thick aqueous layer.

Thus, the dry spot formation is essentially localised non-wetting, and not localised drying caused by discontinuities in the superficial lipid layer. As regards the location of these dry spots, it has been noticed that these occur twice more in temporal quadrant as compared to nasal one. The suggested reason for these differences is that nasal areas are more protected against air currents and have comparatively higher temperature.

DYNAMIC EVENTS DURING BLINKING

Holly (1980) has given a brief account of events during blinking. A complex series of events take place (Fig. 3.4). As the upper lid moves downwards, the superficial layer is compressed. As it thickens, it begins to exhibit interference colours. The whole lipid layer together with the associated biopolymers is compressed between the lid edges. Lipid

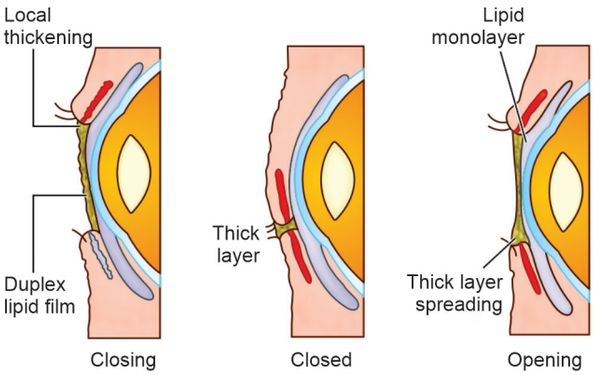

Fig. 3.4: Dynamic events during blinking.

epiphora almost never occurs as the compressed lipid layer between closed eyelids has a thickness only of the order of 0.1 μm.

This lipid contaminated mucus according to Norn is rolled up in a thread-like shape and dragged into lower fornix (Fig. 3.5).

When the eye opens, at first the lipid spreads in the form of a monolayer against the upper eyelid. In this spreading process, the limiting factor is the motion of eyelid. The spreading of the excess lipid follows and in about 1 sec. multimolecular layer of lipid is formed. The spreading lipid drags some aqueous tears with it, thereby thickening the tear film. The magnitude of this effect is controlled by

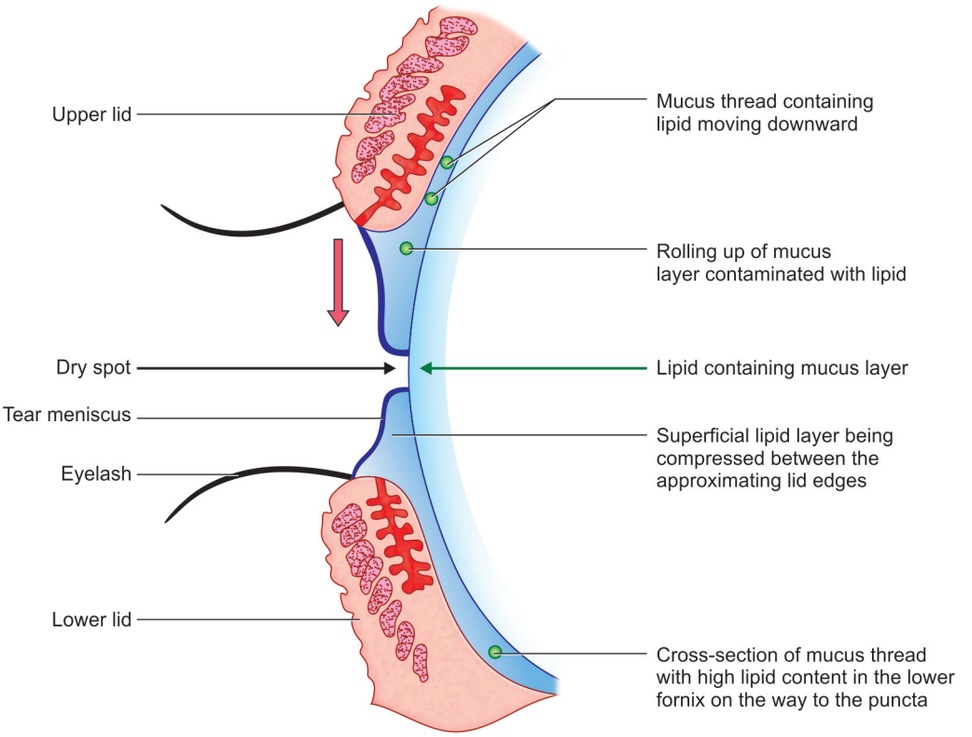

Fig. 3.5: Mechanism of removal of lipid contaminated mucus.

the size and shape of tear meniscus adjacent to lid edges. As soon as there are insufficient tears to form a saturated meniscus, a local thinning adjacent to the meniscus, takes place which effectively prevents further fluid flow from the meniscus to the tear film.

ELIMINATION OF TEARS

Drainage of lacrimal fluid from lacus lacrimalis into the nasolacrimal duct

The lacrimal fluid flows over the preocular surface and reaches the marginal tear strip running along the ciliary margin of each eyelid and collects as lacus lacrimalis in the inner canthus. 25% of tears are lost by evaporation. From the lacus lacrimalis and along the marginal tear strip, the lacrimal fluid is then drained by the lacrimal passages into the nasal cavity (Fig. 3.6). Capillary action plays an important role in conducting the tears into the punctum and vertical limb of canaliculus. Flow along the lacrimal passages is brought about by an *active lacrimal pump mechanism* constituted by fibres of the preseptal portion of the orbicularis which arise from the lacrimal fascia and posterior lacrimal crest (Horner's muscle). This lacrimal pump operates with the blinking movements of the eyelids as follows:

A. *On eyelid closing movement,* following three events occur concomitantly (Fig. 3.7A):

1. *Contraction of pretarsal fibres* of the orbicularis compresses the ampulla and shortens the canaliculi. This movement propels the tear fluid present in the ampulla and horizontal part of the canaliculi toward the lacrimal sac.
2. *Contraction of preseptal fibres of orbicularis pulls* the lacrimal fascia and lateral wall of the lacrimal sac laterally, thereby opening the normally closed lacrimal sac. This produces a relative negative pressure and draws the tears from the canaliculi into lacrimal sac.
3. *Along with the increased tension on the lacrimal fascia* (which opens the lacrimal sac), the inferior portion closes more tightly, thereby preventing aspiration of air from the nose.

B. *When the eyelids open,* tone in the orbicularis muscle is decreased and following events occur concomitantly (Fig. 3.7B):

1. *Relaxation of pretarsal fibres* of the orbicular allows the canaliculi to expand and reopen. The expansion of the canaliculi and ampullae draws in the lacrimal fluid through the puncti from the lacrimal lake.
2. *Relaxation of the portion of the preseptal fibres* (Horner's muscle) allows the lacrimal sac to collapse. The collapse of the lacrimal sac expels the fluid therein downwards into the now open nasolacrimal duct. Therefore, in atony of the sac tears is not drained rough the lacrimal passages, in spite of anatomical patency, resulting in epiphora.

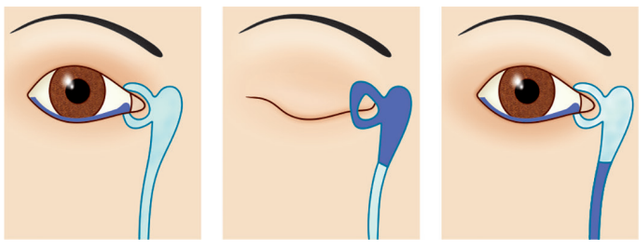

Fig. 3.6: Elimination of tears by lacrimal pump mechanism.

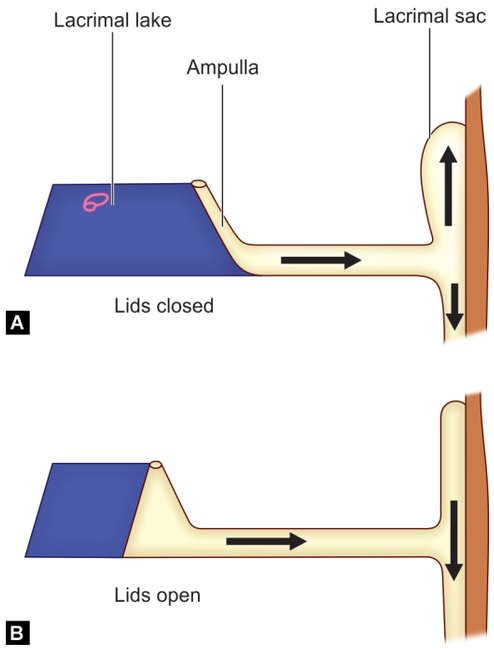

Fig. 3.7: Lacrimal pump mechanism. A, When lids close; B, When lids open (see text for explanation).

Drainage of lacrimal fluid from nasolacrimal duct (NLD) into the nasal cavity

Once the lacrimal fluid enters the upper end of the NLD, the influence of eyelid movements on its further downward flow ends.

Factors which influence the flow of tears along the NLD are as follows:

- *Gravity* helps in downward flow.
- *Air current movement within the nose:* The opening of NLD in the nasal cavity is so placed that air currents passing either inward or outward, induce a negative pressure within the NLD and thus draw the fluid down the potential lumen of the duct into the nose.
- *Hasner's valve* present at the lower end of NLD remains open as long as the pressure within the nose is less than the NLD and thus allows the tears to flow from the NLD into the nose. However, when the intranasal pressure increases (as on blowing the nose), the Hasner's valve closes, thereby preventing the reflux upward.

From the nose, the tears pass posteriorly with the nasal mucus secretions.

DRY EYE DISEASE

DEFINITION, CLASSIFICATION AND CAUSES

DEFINITION

TFOS International Dry Eye Workshop (DEWS) II, new definition of dry eye disease (DED) is as follows: "Dry eye is a multifactorial disease of the ocular surface characterised by a loss of homeostasis of the tear film, and accompanied by ocular symptoms, in which tear film instability and hyperosmolarity, ocular surface inflammation and damage, and neurosensory abnormalities play etiological roles".

CLASSIFICATION AND CAUSES OF DED

According to International Dry Eye Workshop report (DEWS report 2007), the causes of dry eye can be classified as below.

I. AQUEOUS DEFICIENCY DRY EYE

Aqueous deficiency dry eye (ADDE) also known as keratoconjunctivitis sicca (KCS). Its causes include:

a. *Sjögren's syndrome* (primary keratoconjunctivitis sicca).

b. *Non-Sjögren's keratoconjunctivitis sicca.* Causes can be grouped as below:

1. *Primary age-related hyposecretion* is the most common cause.
2. *Lacrimal gland deficiencies* as seen in congenital alacrima, infiltrations of lacrimal gland, e.g. in sarcoidosis, tumours, post-radiation fibrosis of lacrimal gland and surgical removal.
3. *Lacrimal gland duct obstruction* as seen in old trachoma, chemical burns, cicatricial pemphigoid and Stevens-Johnson syndrome.
4. *Reflex hyposecretion* (neurogenic causes) as seen in familial dysautonomia (Riley-Day syndrome), Parkinson disease, reflex sensory block, reflex motor blade, 7th cranial nerve damage, reduced corneal sensations after refractive surgery and corneal lens wear.

II. EVAPORATIVE DRY EYE

It is caused by the conditions which decrease tear film stability and thus increase evaporation.

Causes can be grouped as:

1. *Meibomian gland dysfunction* as seen in chronic posterior blepharitis, rosacea, and congenital absence of meibomian glands.
2. *Lagophthalmos* as seen in facial nerve palsy, severe proptosis, symblepharon and eyelid scarring.
3. *Defective blinking* such as low blink rate as seen in prolonged computer users and other causes.
4. *Vitamin A deficiency and other factors* affecting ocular surface, e.g. topical drugs, preservatives, contact lens wear, ocular surface allergic disease and scarring disorders.

PATHOGENESIS

Dry eye disease (DED) is a chronic inflammatory condition that can be initiated by numerous extrinsic or intrinsic factors that promote an unstable and hyperosmolar tear film.

Core mechanism of DED is evaporation-induced tear hyperosmolarity, which is the hallmark of the disease, as concluded by the TFOS DEWS II pathophysiology subcommittee. It damages the ocular surface both directly as well as by initiating inflammation. The broad outlines of cycle of events, described as the *vicious circle of DED* is shown in Figure 3.8 and details are shown in Figure 3.9.

Two forms of DED are recognized. Aqueous deficiency dry eye (ADDE) and evaporative dry eye (EDE).

- *In ADDE*, tear hyperosmolarity results when lacrimal secretion is reduced, in conditions of normal evaporation from the eye.
- *In EDE*, tear hyperosmolarity is caused by excessive evaporation from the exposed tear film in the presence of a normally functioning lacrimal gland.

Since tear osmolarity is a function of tear evaporation in either ADDE or EDE, tear hyperosmolarity arises due to evaporation from the ocular surface and, in that sense, all forms of DED are evaporative. In other words, EDE is more accurately considered a hyper-evaporative state. EDE is associated with meibomian gland dysfunction (MGD) (*see* page 76 for pathogenesis of MGD).

Tear hyperosmolarity activates stress signalling pathways in the ocular surface epithelium as well as resident immune cells and triggers production of innate inflammatory molecules that initiate a vicious self-perpetuating cycle (Figs 3.8 and 3.9) that may lead to further decline in tear function and worsen the symptoms. The numerous extrinsic factors (e.g. desiccating environment, exposure) and intrinsic (e.g. ageing, autoimmunity, drying medications) factors that can contribute to this inflammatory cycle demonstrate why it is often difficult to ascribe a single cause for most cases of dry eye disease and the importance of addressing all modifiable risk factors.

Hyperosmolar stress has a direct pro-inflammatory effect on the ocular surface epithelium. It has been shown to activate mitogen-activated protein kinases (MAPKs), stimulate secretion of pro-inflammatory cytokines (e.g. IL-1β, TNF-α, and IL-6), chemokines and matrix metalloproteinases such as MMP-3 and MMP-9 and induce apoptosis. The interaction of these inflammatory mediators is complex and they have been shown to upregulate each other; thus amplifying the inflammatory cascade. For example, IL-1β stimulates the production of TNF-α and MMP-3, among other factors. In turn, TNF-α stimulates MMP-9 and MMP-3 which is a physiological activator of MMP-9. MMP-9 contributes to corneal barrier disruption by lysing tight junctions in the superficial epithelium. Increased tear MMP-9 has also been

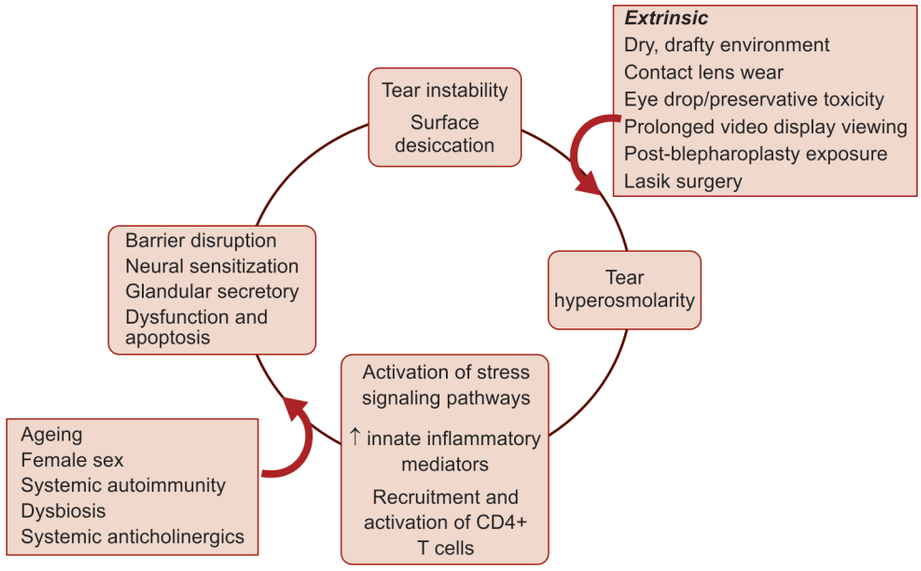

Fig. 3.8: Broad outlines of vicious cycle of events involved in pathogenesis of dry eye.

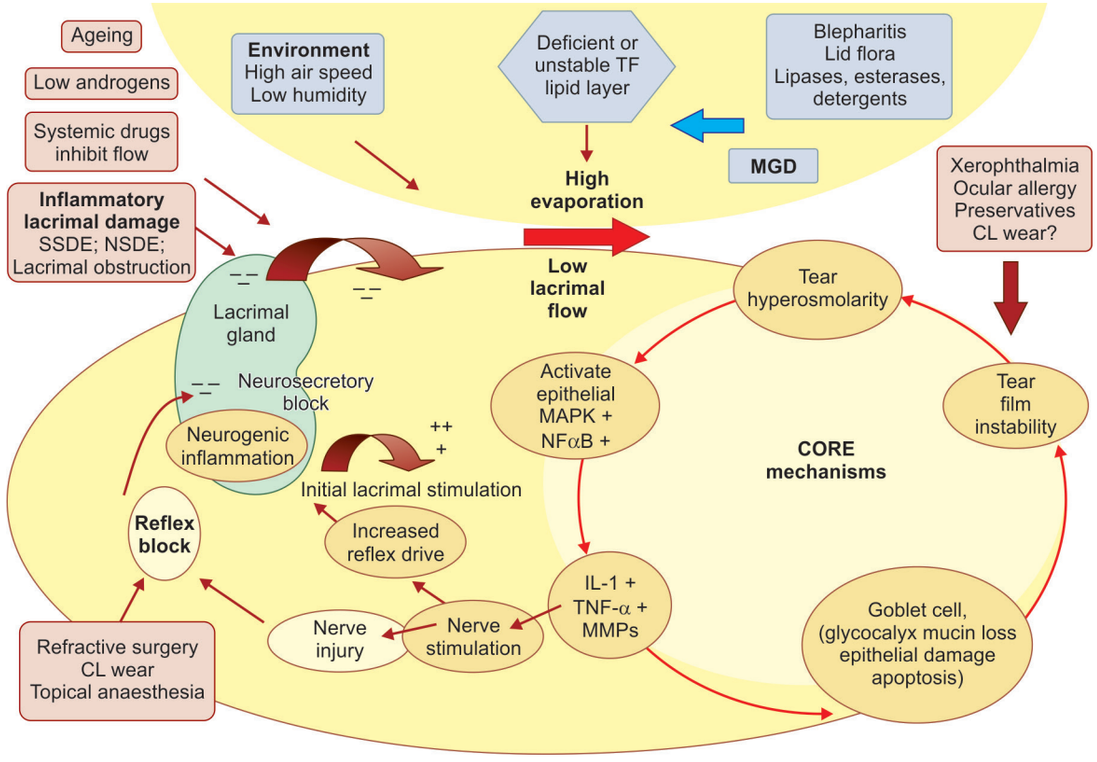

Fig. 3.9: Detailed outlines of vicious cycle of events involved in pathogenesis of dry eye.

detected in other ocular surface diseases, such as atopic and vernal keratoconjunctivitis, corneal ulceration, recurrent corneal erosions and ocular burns that also have corneal barrier disruption. *Detection of elevated tear MMP-9 provides a rationale for use of anti-inflammatory/protease therapies in these conditions.*

Ocular surface epithelial cells also secrete chemokines that attract inflammatory cells. Increased levels of chemokines CCL20 (MIP-3α), CXCL9 (MIG), CXCL10 (IP-10) and CXCL11 (I-TAC) and their receptors were noted in ocular surface cells and/or tears of dry eye patients.

Another effect of desiccation is upregulation of innate inflammatory pathways in the epithelium, including the nucleotide-binding domain, leucine-rich-containing family, pyrin domain-containing 3 (NLRP3), toll-like receptor and oxidative stress pathways.

Metaplasia and goblet cell loss in the conjunctival epithelium is a well-recognized feature of aqueous tear deficiency. The most severe ocular surface disease, such as Stevens-Johnson syndrome, mucous membrane pemphigoid, graft-*vs*-host disease and severe alkali burns involving the conjunctiva often have complete loss of conjunctival goblet cells. T helper cytokines have been found to modulate conjunctival goblet cell differentiation. In addition to producing tear-stabilizing mucins, goblet cells also produce immunoregulatory factors, such as TGF-β and retinoic acid. Crosstalk between goblet cells and dendritic cells is critical to maintaining immune tolerance in mucosal tissues. Studies indicate a critical role of goblet cell products in conditioning tolerogenic properties in conjunctival dendritic cells and maintaining ocular surface immune tolerance.

Evidence indicates that the initial innate immune response to dryness is followed by an adaptive CD4+ T cell autoimmune response in mice exposed to desiccating stress and in patients with Sjögren syndrome (SS) and non-SS associated aqueous tear deficiency. While the target autoantigen(s) in this autoimmune reaction have not been identified, members of the kallikrein family have been implicated as putative antigens in some studies.

In addition to producing tear-stabilizing mucins, goblet cells also produce immunoregulatory factors, such as TGF-β and retinoic acid. Crosstalk between goblet cells and dendritic cells is critical to maintaining immune tolerance in mucosal tissues. Goblet cell associated passages that deliver surface antigens to the underlying dendritic cells and promote tolerance have been identified in both intestine and conjunctiva. Mice with deletion of the SAM pointed domain containing ETS transcription factor gene (Spdef knockout) are devoid of goblet cells, develop conjunctival inflammation and lose immune tolerance to topically applied antigens, as has been found in other mouse dry eye models that are accompanied by goblet cell loss. These studies indicate a critical role of goblet cell products in conditioning tolerogenic properties in conjunctival dendritic cells and maintaining ocular surface immune tolerance.

Lacrimal gland (LG) inflammation and dysfunction develop with age and in the autoimmune disease Sjögren syndrome (SS). The hallmarks of SS are lymphocytic infiltration of the lacrimal and salivary glands, serum autoantibodies, keratoconjunctivitis sicca and dry mouth. Mouse models of SS and aging have identified a pathogenic role for CD4+ T and B cells. These studies suggest that similar to the ocular surface, a vicious cycle of inflammation and apoptosis involving infiltrating cells and glandular acinar cells perpetuates LG inflammation leading to glandular dysfunction in SS and age-related dry eye.

There is evidence demonstrating that the microbiome, the microbial community that inhabits the human body, has immunoregulatory functions. The presence of an ocular microbiome has long been suspected; however, traditional swab cultures of the conjunctiva are often negative. Studies using 16S genomic sequencing have demonstrated an ocular surface microbiome that may have the lowest biomass of any tissue in the mice that had an antibiotic-induced depletion of the microbiome with a cocktail of five oral antibiotics prior to experimental desiccating stress developed significantly worse dry eye than control mice that did not receive antibiotics.

CLINICAL FEATURES

Symptoms suggestive of dry eye include irritation, foreign body (sandy) sensation, feeling of dryness, itching, nonspecific ocular discomfort and chronically sore eyes not responding to a variety of drops instilled earlier.

Signs of dry eye are as below:

- *Tear film signs.* It may show presence of stingy mucous and particulate matter. Marginal tear strip is reduced or absent (normal height is 1 mm).
- *Conjunctival sign.* It becomes lustureless, mildly congested, conjunctival xerosis and keratinization may occur. Rose bengal or lissamine green staining may be positive (details given in tear film tests).
- *Corneal sign.* It may show punctate epithelial erosions, filaments and mucus plaques. Cornea may loose lusture. Vital stains, fluorescein, rose bengal or lissamine green may delineate the above lesions.
- *Signs of causative disease* such as posterior blepharitis, conjunctival scarring diseases (trachoma, Stevens-Johnson syndrome, chemical burns, ocular pemphigoid) and lagophthalmos may be depicted.

Sjögren syndrome (SjS, SS) is a *long-term autoimmune disease* that affects the body's moisture-producing *glands*. Primary symptoms are a *dry mouth* and *dry eyes*. Other symptoms can include *dry skin*, vaginal dryness, a *chronic*

cough, numbness in the arms and legs, *feeling tired, muscle and joint pains*, and *thyroid problems*. Those affected are at an increased risk (5%) of *lymphoma.*

- While the exact cause is unclear, it is believed to involve a combination of *genetics* and an *environmental trigger* such as exposure to a *virus* or *bacteria*. It can occur independently of other health problems (primary Sjögren syndrome) or as a result of another *connective tissue disorder* (secondary Sjögren syndrome). The *inflammation* that results progressively damages the glands. Diagnosis is by biopsy of moisture-producing glands and *blood tests* looking for specific *antibodies*. On *biopsy* there are typically *lymphocytes* within the glands
- Treatment is directed at the person's *symptoms*. For dry eyes *artificial tears*, medications to reduce inflammation, *punctal plugs*, or surgery to shut the *tear ducts*, may be tried. For a dry mouth, *chewing gum* (preferably *sugar free*), sipping water, or a *saliva substitute* may be used. In those with joint or muscle pain, *ibuprofen* may be used. Medications that can cause dryness, such as *antihistamines*, may also be stopped.

TESTS FOR TEAR FILM ADEQUACY

A number of tests of tear function have been developed to aid in the diagnosis of dry eye conditions.

SCHIRMER TEST

It is the test for tear quantity. Schirmer investigated the extent of wetting of a 5 × 35 mm blotting paper strip after folding 5 mm from one end and placing it in the lower fornix, at the junction of outer one-third and inner two-thirds for 5 minutes (Fig. 3.10). He found that normal secretion varied from 0.50 to 0.67 ml of tears per day and more than 15 mm of wetting in 5 minutes, measured from the folded end, was normal. Later, Whatman filter paper number 41 was standardised for this test. This test became popular as ***Schirmer I*** (or simply Schirmer) ***test*** and gives the value for both basic and reflex secretions of tears. It involves an open eye technique as closure of eyes during the test is believed to give false positive results.

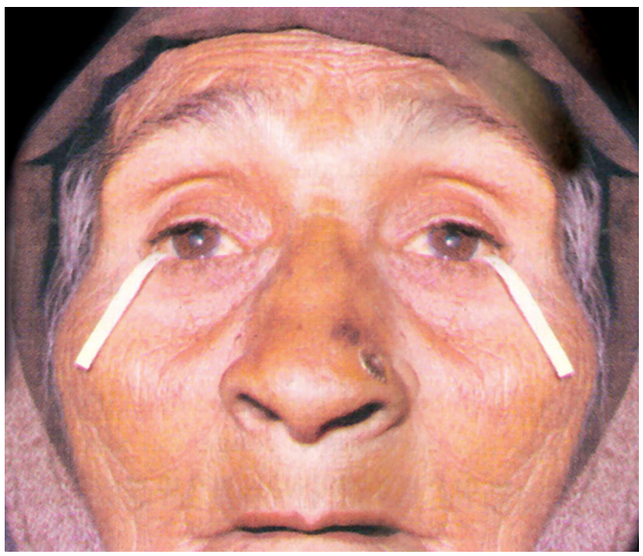

Fig. 3.10: Technique of Schirmer I test.

A basal secretion test has been described in which the conjunctiva is anaesthetised before performing the test in a similar manner as above. The difference between Schirmer I test and this test is a measure of basal secretion of tears. No statistical data supports this test as it is believed that conjunctiva is not fully anaesthetised to block reflex secretion.

Schirmer II test. To know the reflex secretion of tears, Schirmer II test was described. It is performed in the same way, after rubbing the unanaesthetised nasal mucosa with a dry cotton and noting the wetting after 2 minutes. But, since reflex secretion is not of major clinical sequence, this test is seldom used and Schirmer testing without anaesthesia or stimulation usually gives most useful and reproducible clinical information.

Schirmer III test. Schirmer extended his observations to know the reflex secretion and described a Schirmer III test, which required the patient to look directly in the sun. It has no diagnostic value and is potentially dangerous.

The Schirmer values were found to be age dependent, decreasing beyond age 60. One-third of persons above the age of 40 years were observed to have a wetting of 15 mm or less, the cut-off line suggested by Schirmer. Young women were reported to have more active lacrimation than young men while older women produced lesser amount of tears than older men.

Different cut-off values have been suggested for Schirmer test. Beetham, later on supported by Jones, suggested that wetting of less than 10 mm/5 minutes would indicate a diminished lacrimal secretion, whereas in another study, the safest cut-off value was reported to be 5 mm/5 minutes.

Modifications of Schirmer test have been described in an attempt to make it more appropriate and reproducible. Jones multiplied the distance of wetting of a standard strip placed for one minute by a factor of three and found it to correlate with a 5-minute reading.

A modified Schirmer test, in which the standard strip intended to be placed for 5 minutes was moved to a different place if there was no wetting after first 2 minutes, has been reported to obviate false positive results.

Thread test is claimed to measure tear component more efficiently than the filter paper.

Kinetic tear flow test has also been devised in which capillary tear flow in a Schirmer strip is prevented from evaporating by plastic cuff around the filter paper.

TEAR FILM BREAK-UP TIME

Break-up time (BUT) has been defined as the interval between a complete blink and the appearance of the first randomly distributed dry spot on the cornea. It is noted after instilling a drop of fluorescein and examining in the cobalt-blue light of a slit-lamp.

In the literature, there has been a wide fluctuation in the normal duration of BUT as studies by various workers. No significant relation between age, sex or corneal sensation and BUT has been observed. In other studies, however, females and older people were reported to have a shorter BUT. Similarly, no correlation of palpebral fissure width, intraocular pressure, humidity or temperature with BUT has been observed. A significant decrease in BUT on holding the lids apart has, however, been reported.

A BUT of 10 seconds has been recommended as a cut-off point for normal individuals by both Western and Indian authors. Values less than this are reported to indicate an abnormal, unstable tear film suggestive of mucin deficiency. One study showed, a definite correlation between goblet cell population and BUT.

BUT was found to be decreased significantly after use of benzalkonium chloride and topical beta-blockers. Exposure to cigarette smoke also resulted in substantial (30–40%) fall in BUT.

VITAL STAINING

Normally, the corneal surface is regular, smooth and shiny, and the tear film covering the epithelium is not directly seen. The histological principle of making transparent structures visible by admixing dyes has been applied to ocular tissues as well. The literature on vital staining of the eye is comprehensive and dates back to the end of last century. It became more popular with the introduction of slit-lamp biomicroscopy.

Many dyes, like fluorescein, rose bengal, lissamine green, Alcian blue, scarlet red, etc., have been used for vital staining of the cornea and conjunctiva.

Fluorescein staining

It was synthesized by Baeyer in 1871. Chemically, fluorescein is resorcinolphthalein with molecular weight 376.27 and formula $C_{20}H_6Na_2$. Sodium salt of fluorescein is an orange red hygroscopic powder producing an intense green fluorescent colour in alkaline (pH above 5.0) solution. It was used in nineteenth century to delineate abrasions or minute ulcerations.

The intact corneal epithelium because of its high lipid content resists penetration of water soluble fluorescein and is not stained by it. Any break in the epithelial barrier permits rapid fluorescein penetration and staining of areas denuded of epithelium. Due to slight acidic reaction of normal tear film, staining appears yellow or orange; the more alkaline aqueous humour colours fluorescein brilliant green in denuded areas. Fluorescein staining of the eye is transient and disappears within 30 minutes. Fluorescein staining is considered a sensitive test for detection of KCS and a positive staining was found in 96% cases of Sjögren's syndrome in a clinical study.

Rose bengal staining

It is a dark red powder soluble in water. It is employed as 1% aqueous solution which is very irritating especially in tear deficient eyes. Unlike fluorescein, rose bengal selectively stains the mucus, debris and devitalised cells of corneal and conjunctival epithelium as readily visible red colour.

Bijsterveld found the dye to be very useful in diagnosis of KCS. He suggested a grading system of rose bengal staining in such patients. The palpebral aperture was divided into three areas, nasal and temporal conjunctiva and the cornea. A score of 0 for absent, 1 for just present, 2 for moderate staining, and 3 for gross staining was suggested in each of these areas; a total score was used for interpretation and a score of 3.5 out of 9 was considered abnormal.

The staining patterns have also been classified as A, B and C according to severity of KCS. 'C' pattern represents mild or early cases with fine punctate stains in the interpalpebral area 'B' the moderate cases with extensive staining of entire exposed area; and in 'A' pattern there is confluent rose bengal staining on the exposed bulbar conjunctiva and blotchy and confluent on the cornea.

The staining pattern has been quantified by a point system. The number of stained dots on cornea, medial and lateral bulbar conjunctiva were estimated on a slit-lamp and were given points from 1 to 5 for <30, <100, <1000, <10,000 and >10,000 stained dots, respectively. Points more than 6 (out of a total of 15) were considered pathological.

Lissamine green staining

It is a dark green, water-soluble substance used for colouring articles of food. It is an acidic, synthetically produced organic dye with a molecular weight of 576.6.

Norn first employed this dye for vital staining of the cornea and conjunctiva. He investigated 171 eyes and 99 specimens of mucus threads, epithelial scrapings, and conjunctival fluid using 1% lissamine green solution, subjected to biomicroscopy. He concluded that lissamine green has vital staining properties almost identical with those of rose bengal and it stains degenerated and dead cells and mucus. It was further noted that lissamine green is far less irritating as compared to rose bengal.

OTHER TEAR FILM TESTS

Marginal tear strip characteristics

Marginal tear strip or tear meniscus is a continuous, full and slightly concave meniscus formed by tears between the eyelid margin and the inferior bulbar conjunctiva where the lid touches the globe. A height of 0.5 mm of tear strip

on slit-lamp examination considered normal. A scanty, discontinuous or absent tear meniscus is an important sign of dry eye and suggests tear deficiency.

pH (hydrogen ion concentration)

Normal pH is necessary for buffering action of tears. A wide difference in normal values tear pH is reported in the literature. In the early literature, the value reported was about 7.4 while the more modern it is about 7.0. The results depend upon the method of its determination, viz. vital staining, glass electrode, indicator paper or microcombination glass pH probe technique and sources of error, most common being due to CO_2 evaporation.

Abelson et al suggested that tear pH measured by pH indicator paper, if adjusted by a correction factor of +0.70 pH units, would yield an equivalent pH as measured by an electrode. Indicator paper, however, was not found to be reliable for measuring tear pH.

Tear pH is known to change in many ocular conditions. A little has been reported in the literature about tear pH studies in dry eye syndrome. Recently, KCS patients were found to exhibit slight alkaline shift which, however, was statistically insignificant.

Tear lysozyme levels

It is a bacteriolytic enzyme produced by tubuloacinar epithelial cells of main and accessory lacrimal glands. It presents 20% of protein contents of tear.

It can be determined qualitatively and quantitatively. Tear lysozyme levels are decreased in early stages of dry eye and is thus an important test for early diagnosis of dry eye.

Tear lactoferrin levels

Recently, the role of tear lactoferrin in the diagnosis of dry eye has been identified. Lactoferrin levels were observed to correlate closely to tear lysozyme assay. It may form a useful clinical tool in diagnosing dry eye syndrome, either singly or in combination with other tests.

Tear evaporation

Rolando and Refojo devised a tear evaporimeter and measured tear film evaporation in normal and dry eye patients. They reported a significant increased rate of evaporation in certain conditions like KCS, Stevens-Johnson syndrome, ocular pemphigoid and meibomitis. The instrument, though complex for routine diagnosis, serves as a non-invasive diagnostic and research tool.

Tear film osmolarity

Osmolarity of tear film has been reported to be isotonic (3.02 + 6.3 mOsm/L) in normal subjects and hypertonic (330 to 340 mOsm/L) in KCS. Though unsuitable for routine use, it is believed to be a very specific diagnostic test for KCS.

Conjunctival biopsy and scrapings

Conjunctival biopsy and scrapings have been advocated to detect the histological changes in dry eye. After staining the material, goblet cell densities and their morphology, and keratinisation of epithelial cells, which is very specific in dry eye, can be seen microscopically.

Conjunctival impression cytology

Recently, a non-invasive technique of impression cytology, where conjunctival impressions are taken to examine cellular structure, has been used for the diagnosis of dry eye. Ocular surface cells are obtained by using cellulose acetate filter material to make an impression.

Squamous metaplasia involves three major steps, namely loss of goblet cells, increase in cellular stratification and keratinization. On the basis of cellular changes occurring in course of squamous metaplasia, the findings on conjunctival impression cytology have been graded according to the severity of dry eye state from 0 to 5 as follows:

Stage 0: Normal cellular structure.
Stage 1: Early loss of goblet cells without keratinization.
Stage 2: Total loss of goblet cells with slight enlargement of epithelial cells.
Stage 3: Early and mild keratinization.
Stage 4: Moderate keratinization.
Stage 5: Advanced keratinization.

Fluorophotometry

Fluorescein dilution test or fluorophotometry is used to estimate tear flow, tear film thickness and various subvolumes of the total volume by measuring the dilution of an initial concentration of fluorescein in tear. The test is limited because of unavailability of fluorophotometer attachment with a slit-lamp routinely.

OCULAR SURFACE ANALYSIS

Ocular surface analysers are now commercially available on sophisticated gadgets for comprehensive analysis of ocular surface.

Ocular surface disease index (OSDI) is determined with the help of a symptoms questionnaire.

STEPS IN DIAGNOSIS OF DRY EYE DISEASE

Step 1: ***DED confirmation with 'Positive symptom score*** using:

1. Dry eye questionnaire 5 (DEQ 5), and/or
2. Ocular surface disease index (OSDI).

Step 2: ***DED confirmation with 'Positive homeostasis markers*** using:

1. Reduced non-invasive break-up time
2. Elevated or a large interocular disparity in tear osmolarity
3. Ocular surface staining

Step 3: ***DED subtype (ADDE or EDE) classification tests***

1. Tear volume measurement
2. Meibography
3. Lipid interferometry.

GRADING OF DRY EYE SEVERITY

Various criteria have been proposed to grade severity of dry eye. Recently accepted system based on severity of signs and tear film tests recommended by Dry Eye Workshop (DEWS) Report (2007) grades the severity of dry eye into 4 levels:

- Level 1 (mild dry eye),
- Level 2 (moderate dry eye),
- Level 3 (severe dry eye), and
- Level 4 (very severe dry eye).

DEWS system of grading of severity of dry eye is summarized in Table 3.5.

TREATMENT OF DRY EYE DISEASE

Treatment of dry eye disease can be described as ***step-ladder treatment*** based on the severity level of dry eye.

STEP I: FOR LEVEL 1 (MILD) DRY EYE DISEASE

1. Patient education and supportive measures

- About dry eye disease, its management, and prognosis.
- Regarding lifestyle changes especially the importance of blinding while reading, watching television or using a computer screen.
- Potential dietary modification. Environmental review and modification.

2. Managing the potential affecting topical and systemic drugs being used by the patients. Tables 3.6 and 3.7 shows the topical and systemic drugs associated with dry eye. These drugs showed be eliminated or changed with those having lesser side effects.

3. Supplementation with tear substitutes. Artificial tears remain the mainstay in the treatment of dry eye. These are available as drops, ointments and slow-release inserts. Mostly available artificial tear drops contain either cellulose derivatives (e.g. 0.25 to 0.7% methylcellulose and 0.3% hypromellose) or polyvinyl alcohol (1.4%).

4. Treatment of the causative disease of dry eye when discovered is very useful, e.g.:

- *Systemic tetracycline*, lid hygiene and warm compressor in patients with chronic posterior blepharitis (meibomitis).
- *Vitamin A supplement* for the deficiency.
- Treat the cause of lagophthalmos, entropion, ectropion, etc. when present.

STEP II: FOR LEVEL 2 (MODERATE SEVERITY) DRY EYE DISEASE

In patients with level 2 dry eye or when step I measures are inadequate following measures are recommended:

1. ***Preservative-free artificial tear*** to minimize preservative-induced toxicity.

TABLE 3.5: Dry eye severity grading scheme

Symptoms, signs and tear film test	*Dry eye severity level*			
	1	*2*	*3*	*4**
Discomfort, severity	Mild and/or episodic; occurs under environmental stress	Moderate episodic or chronic, stress or no stress	Severe frequent or constant without stress	Severe and/or disabling and constant
Visual symptoms	None or episodic mild fatigue	Annoying and/or activity-limiting	Annoying, chronic and/or constant, limiting activity	Constant and/ or possibly disabling
Conjunctival injection	None to mild	None to mild	+/–	+/++
Conjunctival staining	None to mild	Variable	Moderate to marked	Marked
Conjunctival staining	None to mild punctate erosions	Variable (severity/location)	Marked central	Severe
Corneal/tear signs	None to mild	Mild debris, ↓ meniscus	Filamentary keratitis, mucus clumping, ↓ tear debris	Filamentary keratitis, mucus clumping, ↓ tear debris, ulceration
Lid/meibomian	MGD variably present	MGD variably present	Frequent	Trichiasis, keratinization, symblepharon
TFBUT (sec)	Variable	≤10	≤5	Immediate
Schirmer score (mm/5 min)	Variable	≤10	≤5	≤2

*Must have signs and symptoms. TBUT: Fluorescein tear break-up time. MGD: Meibomian gland disease.

Reprinted from Behrens A, Doyle JJ, Stem L, et al. Dysfunctional tear syndrome. A Delphi approach to treatment recommendations. Cornea 2006; 25: 90–7.

TABLE 3.6: Topical ocular drugs that may cause or aggravate dry eye	
Class	*Examples*
Agents used to treat glaucoma	
• Beta-blocking agents	Betaxolol, carteolol, levobunolol, metipranolol, timolol
• Adrenergic agonist drugs	Apraclonidine, brimonidine
• Carbonic anhydrase inhibitors	Brinzolamide, dorzolamide
• Cholinergic agents	Pilocarpine
• Prostaglandins	Bimatoprost, latanoprost, travoprost, dipivefrine, unoprostone
Agents used to treat allergies	Emedastine, olopatadine
Antiviral agents	Aciclovir, idoxuridine, trifluridine
Decongestants	Naphazoline, tetryzoline
Miotics	Dapiprazole
Mydriatics and cycloplegics	Cyclopentolate, tropicamide, hydroxyamfetamine
Preservatives	Benzalkonium chloride
Topical local anaesthetics	Cocaine, proxymetacaine, tetracaine
Topical ocular NSAIDs	Bromfenac, diclofenac, ketorolac, nepafenac

TABLE 3.7: Systemic drugs probably causing or aggravating dry eyes	
Class	*Examples*
Antihypertensive agents (beta-agonists)	Acebutolol
Antihypertensive agents (alpha-agonists)	Atenolol
Antiarrhythmic agents (beta-blockers)	Carvedilol, labetalol, metoprolol, nadolol, pindolol, clonidine, prazosin, oxprenolol, propranolol
Antipsychotic agents	Chlorpromazine, fluphenazine, lithium carbonate, perphenazine, prochlorperazine, promethazine, quetiapine, thiethylperazine, thioridazine, brompheniramine, carbinoxamine, chlorphenamine (chlorpheniramine), clemastine, cyproheptadine, dexchlorpheniramine
Bronchodilators	Diphenhydramine
Antispasmodics/antimuscarinic	Doxylamine
Antiarrhythmic agents	Ipratropium, atropine, homatropine, tolterodine, hyoscine (scopolamine), hyoscine methobromide (methscopolamine), disopyramide
Antineoplastic agents	Busulfan, cyclophosphamide, interferon (alpha, beta, gamma or PEG), vinblastine, cetuximab, erlotinib, gefitinib
Antihistamines	Cetirizine, desloratadine, fexofenadine, loratadine, olopatadine, tripelennamine
Antidepressants	Citalopram, fluoxetine, fluvoxamine, paroxetine, sertraline
Antileprosy agents	Clofazimine
Antirheumatic agents/analgesics	Aspirin, ibuprofen
Sedatives and hypnotics	Primidone
Drugs secreted in tears	Aspirin, chloroquine, clofazimine, docetaxel, ethyl alcohol, hydroxychloroquine, ibuprofen, isotretinoin
Antiandrogens	Tamsulosin, terazosin, doxazosin, alfuzosin
Neurotoxins	Botulinum A or B toxin
Antimalarial agents	Chloroquine, hydroxychloroquine
Retinoids	Isotretinoin
Antiviral	Aciclovir
Thiazides	Bendroflumethiazide, chlorothiazide, chlortalidone, hydrochlorothiazide, hydroflumethiazide, indapamide, methyclothiazide, metolazone, polythiazide, trichlormethiazide
Cannabinoids	Dronabinol, hashish, marijuana
Chelating agents	Methoxsalen
Strong analgesics	Morphine, opium/opioids
Antipsychotic agents	Pimozide

2. ***Anti-inflammatory drugs*** to control the ocular surface inflammation should be added. These include:
   - *Topical cyclosporine* (0.05%, 0.1%) is reported to be very effective drug for dry eye
   - *Topical steroids* used for limited duration are effective
   - *Oral omega fatty acids* were also reported useful. However, recently the DREAM study has concluded that omega fatty acids play not much role in the treatment of dry eye diseases.
3. ***Secretogogues*** such as pilocarpine, cevimeline, and rebamipide.
4. ***Tear conservation*** by use of:
   - *Punctal occlusion* with temporary measures
   - *Moist chamber* spectacles and spectacle with side shields.
5. ***Measure for MGD,*** associated dry eye, includes:
   - *Oral macrolide* or tetracycline antibiotic
   - *Topical antibiotics* or antibiotic–steroid combination eye ointment to be rubbed at lid margin.
   - *Physical heating* and expression of the meibomian glands (including device-assisted therapies such as lipi-flow.
   - *In-office intense pulsed* light therapy for MGD.

   Note: For detailed management of MGD, *see* Chapter 6, page 83.
6. ***Demodex,*** when present, should be treated with tea tree oil.

STEP III: FOR LEVEL 3 (SEVERE) DRY EYE DISEASE

Following additional measures over those described in step II include:

1. ***Serum eye drops,*** autologous or allogenic
2. ***Oral secretogogues***
3. ***Therapeutic contact lens options*** are:
   - Soft bandage lenses,
   - Rigid scleral lenses.

STEP IV: FOR LEVEL 4 (VERY SEVERE) DRY EYE DISEASE

The additional measures include:

1. ***Topical steroids*** for longer duration
2. ***Systemic anti-inflammatory agents***
3. ***Surgical measures***
   - *Permanent punctal occlusion,* surgically, for preserving the tear
   - *Tarsorrhaphy* is useful for ocular surface recovery
   - *Mucous membrane or amniotic membrane transplantation* for corneal complications
   - *Salivary gland* autotransplantation may be required in very severe cases.

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Chapter

4

Immunological Disorders of Ocular Surface

Chapter Outline

INTRODUCTION

IMMUNOLOGICAL DISORDERS OF OCULAR SURFACE

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- Etiopathogenesis
- Clinical features
- Diagnosis
- Treatment

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- Etiology
- Pathophysiology
- Clinical features
- Diagnosis
- Treatment

Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis
- Subdivisions
- Etiopathogenesis
- Clinical features
- Differential diagnosis
- Treatment

INTRODUCTION

The eye is a common target of inflammatory responses induced by local and systemic immunologic hypersensitivity reactions. Inflammatory ocular conditions resulting from immune responses are highly prominent because of the eye's considerable vascularization and the sensitivity of the vessels in the conjunctiva, which are embedded in a transparent medium. The eye and its surrounding tissues are also involved in a variety of other immunologically mediated disorders (Table 4.1).

When such reactions occur, they are not infrequently seen first by the clinical allergist/immunologist, who then

TABLE 4.1: Immunologic involvement of the eye

Ocular structures	*Lesions*
Lids	Blepharitis, contact dermatitis
Conjunctiva	Allergic conjunctivitis, atopic conjunctivitis, vernal conjunctivitis, GPC pemphigus/pemphigoid, Stevens-Johnson syndrome
Sclera	Episcleritis, scleritis
Cornea	Corneal allograft rejection, amyloid deposition
Iris	Iritis, cyclitis, pars planitis
Vitreous	Vitreitis
Retina	Retinitis
Choroid	Choroiditis
Optic nerve	Optic neuritis, vasculitis (e.g. temporal arteritis)
Extraocular muscles	Myasthenia gravis, orbital pseudotumour vasculitis

is in a position to correlate ocular and systemic findings and to coordinate therapy so as to treat underlying disease (if present) rather than only local eye symptoms.

While all the above conditions have been discussed in detail in respective chapters, few are being discussed here.

COMMON IMMUNOLOGICAL DISORDERS OF OCULAR SURFACE

PEMPHIGUS

Ocular pemphigus has been established as a clinical entity since 1858, when White Cooper, in the first volume of the Royal London Ophthalmic Hospital Reports, described a case. The term "pemphigus" comes from the Greek word pemphis, meaning blisters. It is certain that prior to this date the disease occurred, but was confused with the various conjunctival degenerations known at that time, notably as conjunctival xerosis. Subsequent to this date the exact pathological differentiation of the condition occasioned dispute amongst dermatologists and ophthalmologists, a controversy which was engendered by the rarity of the disease, until von Graefe, in 1879, identified pemphigus with what had hitherto been called "essential shrinking of the conjunctiva". Various authors (Pergens and others) have testified to the rarity of the condition; the average for eye cases is about 1 case per 20,000 and for skin cases 1 per 300 (Pusey).

ETIOPATHOGENESIS

Etiology is still uncertain for both pemphigus and ocular pemphigus but the isolation of a virus from pemphigus vulgaris has been claimed, current reports however suggest an autoimmune aetiology.

Autoimmune bullous diseases are associated with autoimmunity against structural components that maintain cell-cell and cell-matrix adhesion in the skin and mucous membranes. They include those where the skin blisters at the basement membrane zone and those where the skin blisters within the epidermis.

Clinical subtypes

The variants of pemphigus are determined according to the level of intraepidermal split formation.

- Pemphigus vulgaris (most common)
- Pemphigus foliaceus
- Pemphigus erythematosus
- Drug-induced pemphigus
- Paraneoplastic pemphigus

Pathophysiology

Pemphigus vulgaris (PV) is caused by autoantibodies against desmoglein 3 (Dsg 3), a glycoprotein that localizes to the core of desmosomes. These autoantibodies cause acantholysis in the deeper suprabasal epidermis which is where Dsg 3 is mainly located. Dsg 3 is also located throughout the oral and other mucous membranes including the conjunctiva where blisters also occur in PV. ELISA tests for autoantibodies against desmoglein 1 (Dsg 1) and Dsg 3 are recently available that differentiate pemphigus vulgaris (anti-Dsg 3 IgG detected) from pemphigus foliaceus (only anti-Dsg 1 IgG detected), and the clinical subtypes of PV, i.e. mucosal dominant (anti-Dsg 3 IgG detected) and mucocutaneous (anti-Dsg 3 IgG and anti-Dsg 1 IgG detected).

In general, binding of autoantibodies results in loss of cell cohesion due to compromised function of specific cell-cell contact structures, the desmosomes. Autoantibody-induced interference with Dsg interaction and subsequently altered intracellular signaling seem to be required for full loss of cell cohesion and blister formation.

CLINICAL FEATURES

Pemphigus vulgaris is a rare, acute or chronic, usually fatal disease, characterized by a generalised eruption of bullae, containing, serous, haemorrhagic or purulent material on a previously normal skin (Fig. 4.1). Mucous membrane complications may occur simultaneously with the skin eruption in the mouth and throat (Fig. 4.2) which often interfere with mastication and swallowing and in late

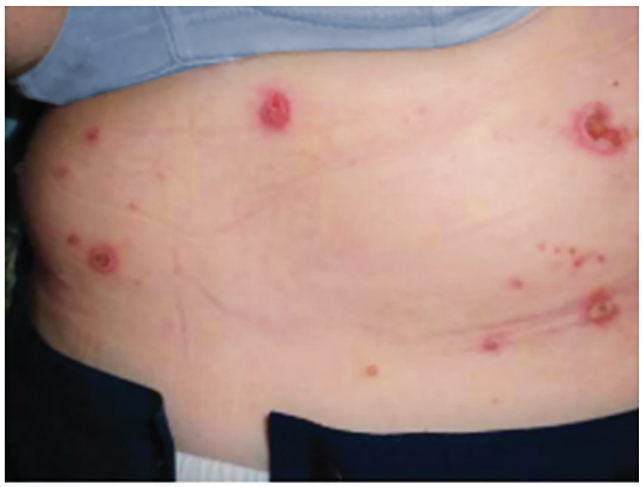

Fig. 4.1: Ulcerated skin lesions.

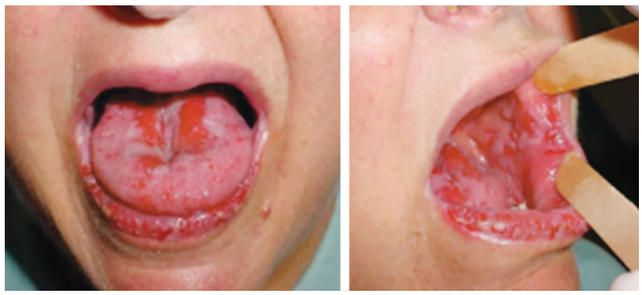

Fig. 4.2: Ulcerated lesions on the buccal mucosa, the lip and the back of the tongue.

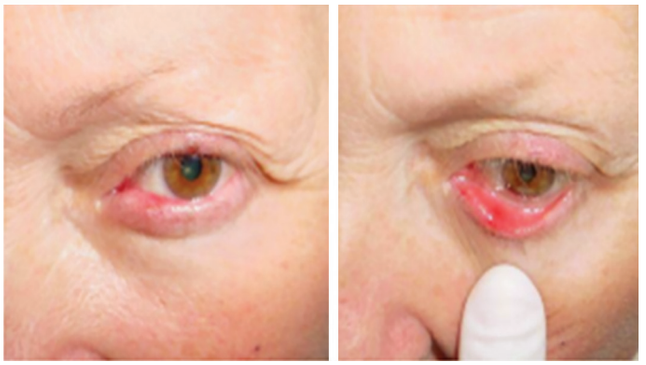

Fig. 4.3: Vesicular lesion on the mucosa of the eyelid.

state the mucous membrane of the eyes (Fig. 4.3) may be involved. Death usually ensues in a matter of weeks from sepsis or bronchopneumonia.

Ocular manifestations

The conjunctiva is nearly always involved and the lesions in both acute and chronic types are similar. Non-cicatricial conjunctivitis is the most frequent, and ulcerated lesions on the eyelid and ocular mucosa are uncommon. Occlusion of the tear duct, subepithelial fibrosis, formation of the symblepharon and perforation of the cornea are also described in the literature.

Acute ocular pemphigus consists of bullae which rupture rapidly leaving ulcerated base. The bullae are transient. It is often difficult to find a case with an intact bullae. In acute cases death supervenes before cicatricial changes can develop.

Chronic ocular pemphigus (benign mucous membrane pemphigoid) may occur either with or without associated mucous membrane lesions of the nose, and throat and in the absence of skin changes. When there are no mouth changes the diagnosis is difficult but it can be made on the basis of bullous lesions on the conjunctiva with progressive cicatrization which is most marked in the lower fornix over a period of month. The low grade conjunctival eosinophilia of pemphigus is usual in differentiating it from erythema multiforme bullosum.

Prognosis is poor in acute case and death results in a matter of weeks (in some cases steriod gives temporary effect). Chronic cases are characterised by long remissions and exacerbation until death finally ensues. Death may not occur however until vision has been greatly diminished or lost through cicatrization of the conjunctiva and cornea. Loss of tear function due to cicatrization in the upper fornix results in keratinization of the corneal epithelium and contributes to loss of vision.

DIAGNOSIS

Diagnosis of PV is made by a characteristic clinical presentation, histological suprabasilar intraepithelial acantholysis, IgG autoantibodies on the cell surface by direct immunofluorescence testing of a biopsied lesion and the presence of circulating antiepithelial autoantibodies.

Differential Diagnosis

PV is a differential diagnosis of several pathologies of autoimmune and vesicle-bullous origin, such as

- Benign mucosal pemphigoid,
- Systemic lupus erythematosus,
- Epidermolysis bullosa,
- Erosive lichen planus,
- Erythema multiforme, and
- Herpes simplex and zoster.

TREATMENT

The treatment should have a multidisciplinary approach, involving a dermatologist, ophthalmologist and immunologist.

Systemic treatment

The recommended therapeutic regimen for PV and being a systemic autoimmune disease should first be treated with systemic corticosteroid therapy, and this procedure may be associated or in combination with other immunosuppressants such as azathioprine and other alternatives include cyclosporine, cyclophosphamide, prostaglandin, chlorambucil, levamisole and immunoglobulins. The expected outcome of the isolated or combined use of these drugs is the reduction of the production of autoantibodies. These therapies should be prescribed by a physician experienced in immunosuppressive therapy.

Currently, low-power laser therapy combined with immunosuppressants becomes an effective and recommended alternative therapeutic option, providing improvements in the health and quality of life of patients.

Ocular treatment

Adequate eye care is required in particular in infection prevention, scar development and corneal perforation. Surgical treatment of trichiasis, poor eyelid position and perforation of the cornea are performed in the more severe cases of pemphigus vulgaris.

OCULAR MUCOUS MEMBRANE PEMPHIGOID

Mucous membrane pemphigoid (ocular mucous membrane pemphigoid/cicatricial pemphigoid/ocular cicatricial pemphigoid/benign mucous membrane pemphigoid) is an autoimmune disease in which binding of anticonjunctival basement membrane antibodies results in conjunctival inflammation. It is unrelated to bullous pemphigoid.

Ocular cicatricial pemphigoid (OCP) or ocular mucous membrane pemphigoid (OMMP) is considered a subtype of mucous membrane pemphigoid (abbreviated MMP), and thus these terms are sometimes used interchangeably.

OCP is a type of autoimmune conjunctivitis that leads to cicatrization (i.e. scarring) of the conjunctiva. If OCP is left untreated, it can lead to blindness.

ETIOLOGY

The exact pathogenesis of OMMP remains to be elucidated but the existing evidence supports a Type II hypersensitivity response caused by an autoantibody to a cell surface antigen in the basement membrane of the conjunctival epithelium and other similar squamous epithelia.

Studies of HLA (human leukocyte antigen) typing have found an increased susceptibility to the disease in patients with HLA-DR4. The **HLA-DQB1*0301** allele in particular shows a strong association with OCP and other forms of pemphigoid disease. HLA-DQB1*0301 is thought to bind to the beta-4 subunit of the alpha-6 beta-4 integrin (the suspected autoantigen in OCP).

PATHOPHYSIOLOGY

Although the exact mechanism remains to be elucidated, the existing evidence supports the production of an autoantibody in susceptible individuals to the beta-4 subunit of the alpha-6 beta-4 integrin of hemidesmosomes in the lamina lucida of the conjunctival basement membrane.

Binding of the autoantibody to the autoantigen activates complement, resulting in the cytotoxic destruction of the conjunctival membrane. Disruption of the conjunctival basement membrane subsequently leads to bullae formation.

The associated cellular inflammatory infiltrate of the epithelium and substantia propria manifests as chronic conjunctivitis that is the hallmark of this disease. Eosinophils and neutrophils mediate inflammation in the early and acute phases of the disease, similar to what is observed in the skin. Chronic disease has largely lymphocytic infiltration. Fibroblast activation leads to subepithelial fibrosis, which in early disease appears as fine white striae most easily seen in the inferior fornix. A scar in the upper palpebral conjunctiva may also be seen. Over time, the fibrotic striae contract, leading to conjunctival shrinkage, symblepharon formation, and forniceal shortening. In severe cases of conjunctival fibrosis, entropion, trichiasis and symblepharon may develop, leading to associated keratopathy and corneal vascularization, scarring, ulceration, and epidermalization.

The clinical course and severity is variable. Recurrent inflammation causes loss of goblet cells and obstruction of lacrimal gland ductules, leading to aqueous and mucous tear deficiency. The resulting xerosis is severe, and along with progressive subepithelial fibrosis and destruction of limbal stem cells leads to limbal stem cell deficiency and ocular keratinization.

Several pro-inflammatory cytokines are found to be elevated in the conjunctival tissues of patients with OCP. Levels of interleukin-1 (IL-1), tumour necrosis factor-α (TNF-α), migration inhibition factor, and macrophage colony-stimulating factor, and IL-13 have been found to be elevated. IL-13 has been found to have a pro-fibrotic and pro-inflammatory effect on conjunctival fibroblasts, and may be implicated in the progressive conjunctival fibrosis that can occur despite clinical quiescence.

Additionally, testing of the tears of patients with OCP found elevated levels of IL-8, matrix metalloproteinase 8 (MMP-8), MMP-9, and myeloperoxidase (MPO), which are thought to result from neutrophilic infiltrate in patients with OCP.

CLINICAL FEATURES

In patients with MMP, oral involvement is most common (in 90% of cases), followed by ocular involvement (in 61% of cases). Ocular involvement of MMP is considered high risk and carries a poorer prognosis (despite treatment) than when oral mucosa and/or skin alone are affected. Up to one-third of patients with oral disease progress to ocular involvement.

Additional sites of involvement include the oropharynx, nasopharynx, esophagus, larynx, genitalia, and anus. The skin is involved in approximately 15% of cases. Dysphagia may be a presenting symptom.

Ocular features

Foster's classification system has 4 stages as well and is based on specific clinical signs:

Stage I: Early stage

May include nonspecific symptoms and minimal findings which lead to under-recognition of the disease. Commonly presents as chronic conjunctivitis, tear dysfunction, and subepithelial fibrosis. Subepithelial fibrosis manifests as fine grey-white striae in the inferior fornix. Signs and symptoms are usually bilateral, and may be asymmetric.

Stage II: Shortening of the fornices

A normal inferior forniceal depth is approximately 11 mm. A reduced inferior forniceal depth is abnormal and should prompt further investigations.

Stage III: Symblepharon formation

Can be detected by pulling the lower eyelid down while the patient looks up and vice versa (Fig. 4.4).

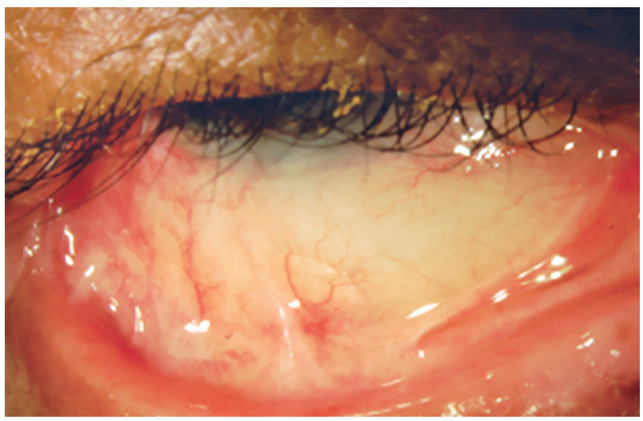

Fig. 4.4: Symblepharon formation in the inferior fornix of a patient with OCP.

Stage IV: Ankyloblepharon

Represents end-stage disease, with surface keratinization, and extensive adhesions between the eyelid and the globe, resulting in restricted motility (Figs 4.5 and 4.6).

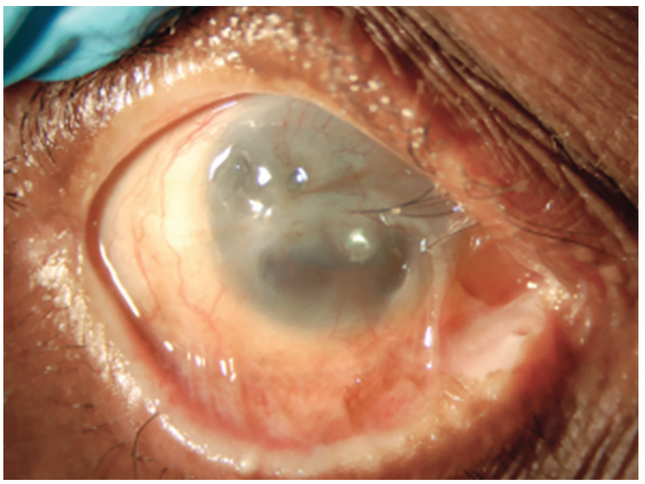

Fig. 4.5: Patient with advanced, end-stage disease. Note the extensive surface keratinization and symblepharon.

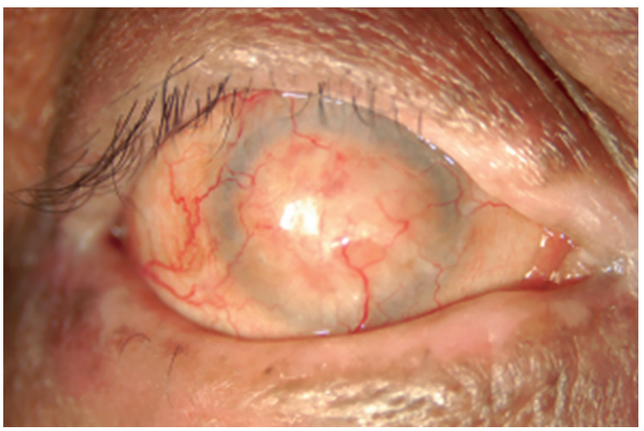

Fig. 4.6: Complete keratinization of the ocular surface in a patient with end-stage OCP.

Patients with OCP vary significantly in disease severity and rate of progression, but untreated disease often progresses in up to 75% of patients. Additionally, the subepithelial fibrosis in OCP can progress even despite clinical quiescence. A study conducted in the UK found that 42% of patients had disease progression in the absence of clinical inflammation.

Histological analysis of these patients has found significant inflammatory cellular infiltrate despite the white and quiet appearance of the conjunctiva clinically, and this has been termed "white inflammation". This is particularly important as 30% of patients with advanced conjunctival fibrosis become blind and represent a clinical challenge to treatment of disease.

Differences between pemphigus and pemphigoid are summarised in Table 4.2.

DIAGNOSIS

Diagnosis is based on clinical signs and positive direct immunofluorescence testing of the conjunctiva.

Conjunctival biopsy of an actively involved area is needed and the conjunctival tissue must be submitted unfixed for analysis. If involvement is diffuse, biopsy of the inferior conjunctival fornix is recommended. Judicious biopsy is advisable as OCP is an obliterating disease of the conjunctiva and only the minimal amount of tissue necessary should be removed. Alternatively, biopsy of an active oral mucosa lesion can be diagnostic as well.

Immunofluorescence reveals linear staining of the epithelial basement membrane zone. The sensitivity of immunofluorescence may be as low as 50%, especially for long-standing/severe cicatrization because of the loss of immunoreactants and the destruction of basement membrane in long-standing disease.

Serological testing is not routinely used in diagnosis.

Sequential photographs are useful to monitor clinical progression.

TABLE 4.2: Differences between pemphigus vulgaris and bullous pemphigoid

Characteristics	*Pemphigus vulgaris*	*Bullous pemphigoid*
Age	Middle-aged people	Elderly people
Clinical features	Monomorphic	Polymorphic
Blisters	Rupture easily, flaccid	Tense, firm
Content of blisters	Fluid-filled	Often haemorrhagic
Oral lesions	Common	Rare
Nikolsky's sign	Positive	Negative
Tzanck smear	Acantholysis	No acantholysis
Direct immunofluorescence	Intraepidermal deposits	Deposits at the epidermal basement membrane
Zone	Target antigen	Desmoglein 1 and 3 BPAG2 (type 17 collagen)

Differential diagnosis

Differential diagnosis of OCP is broad as it encompasses the differential for cicatricial conjunctivitis. The differential includes:

- Infectious etiologies such as trachoma,
- Inflammatory etiologies such as rosacea,
- Autoimmune etiologies such as linear IgA disease, graft-versus-host disease (GVHD), and Stevens-Johnson syndrome (SJS), and
- Allergic etiologies such as atopy, conjunctival trauma, chemical burns, medicamentosa, radiation, and neoplasia.

TREATMENT

Without treatment, the disease progresses in up to 75% of patients. While systemic treatment stops progression of cicatrization in most patients, it fails in approximately 10% of them.

1. ***Topical treatment*** comprises:

- Tear substitutes, to be used frequently.
- Antibiotics for secondary infection.
- Steroids may help in reducing inflammation (caution for corneal melting).

2. ***Systemic immunosuppression:*** Systemic therapy is necessary in OCP as ocular involvement comprises a high risk subset of MMP and is insufficiently treated with topical therapy alone. Systemic treatment is best managed by a physician trained in the management of anti-inflammatory and immunomodulatory treatment given the significant risk of systemic complications necessitating frequent blood test monitoring. Several drugs are effective in treating OCP and a stepwise approach of escalation of therapy when there is insufficient response, is recommended:

- Mild disease—use dapsone (1 mg/kg).
- Moderate disease—use antimetabolite such as methotrexate or azathioprine.
- Severe disease—use intravenous methylprednisolone with or without cyclophosphamide for 4 days, followed by oral prednisolone.

3. ***Surgical intervention*** required in late stage (depending upon the condition) may be:

- Punctal occlusion for dry eye.
- Silicon hydrogel contact lens use.
- Correction of trichiasis and entropion.
- Ocular surface reconstruction for advanced scarring.
- Corneal transplantation.
- Keratoprosthesis in extensive corneal and ocular surface scarring.

Note. Seemingly trivial surgical intervention and conjunctival trauma can lead to serious exacerbation of disease. Surgical intervention, such as treatment of trichiasis, entropion and cataract should be deferred if possible until control of active disease is achieved. In some situations this may not be possible and a multi-disciplinary approach is best.

Inferior eyelid retractor plication for trichiasis avoids surgery on the conjunctiva and has been shown to be safe and effective when undertaken in the setting of clinically quiescent OCP. Cryotherapy for the treatment of trichiasis has also been shown to be safe and moderately effective when undertaken in the setting of clinically quiescent OCP.

STEVENS-JOHNSON SYNDROME AND TOXIC EPIDERMAL NECROLYSIS

Stevens-Johnson syndrome and toxic epidermal necrolysis (SJS/TEN) are on a spectrum of a rare immune-mediated mucocutaneous disease usually associated with severe ocular complications.

SJS/TEN is a severe immune-mediated disease which can lead to blindness. Seemingly mild disease in the acute or subacute stage can lead to end-stage blindness if left unaddressed. Attentive examination and management in the acute stage provides the best opportunity to prevent or mitigate chronic disease. There are changes in the ocular surface at every stage of the disease, which if left unaddressed, can become irreversible, and a lost opportunity to improve the visual function and quality of life of these patients.

SUBDIVISIONS OF STEVENS-JOHNSON SYNDROME AND TOXIC EPIDERMAL NECROLYSIS

- Stevens-Johnson syndrome (SJS)
- SJS/TEN overlap
- Toxic epidermal necrolysis (TEN)

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) represent opposite ends of a spectrum of disease that results from an adverse reaction, most often to certain medications. SJS is the less severe end, but still represents a serious condition and potential medical emergency. TEN is a severe, life-threatening disorder. These disorders are differentiated by the degree of skin detachment.

SJS affects less than 10% of the body surface area; TEN affects more than 30% of the body surface area. The term SJS/TEN overlap syndrome is used to describe cases in which 10–30% of the body surface area is detached.

The reaction may start with a persistent fever and nonspecific, flu-like symptoms followed by appearance of erythematous macules (red spots) that may cover a large part of the body, and painful blistering of the skin and mucous membranes. The eyes are often involved.

ETIOPATHOGENESIS

The exact pathogenesis of SJS/TEN is unknown but appears to involve cell-mediated keratinocyte apoptosis via the Fas signaling cascade and granulysin release. The syndrome can result from exposure to certain medications, infections,

or malignancy, though almost a quarter of cases have no known trigger.

Numerous drugs have been reported to cause SJS and TEN and the following have shown an increased risk in larger studies (Table 4.3):

- Anti-bacterial sulfonamides
- Non-steroidal anti-inflammatory drugs of the oxicam type
- Certain anti-seizure drugs (anti-epileptics)
- Allopurinol
- Nevirapine

However, approximately one quarter (25%) of cases are not caused by drugs, but potentially by infections or have to be considered as idiopathic (of unknown cause).

CLINICAL FEATURES

Systemic features

Most cases involve the development of general, nonspecific symptoms including a persistent fever, burning or stinging eyes, body aches, and discomfort or difficulty swallowing.

Additional nonspecific symptoms include headaches, chills, joint paint, and a general feeling of poor health (malaise).

A pus-producing (purulent) cough that also brings up mucous, phlegm and saliva (sputum) may also occur. Such symptoms may precede the development of skin involvement by a few days.

Skin lesions include often the development of a superficial reddening of the skin (erythema) or reddish spots on the skins (macules) that rapidly spread and come together (coalesce) to form a rash. In some cases, these lesions may resemble a target or bull's eye, so-called "target" lesions. A rash often first develops on the upper chest, face, and the palms and soles. The rash may remain limited to these areas or it may spread, within a few hours or days, to cover a significant portion of the body. The rash may be itchy (pruritic) or painful. Blisters appear on the confluent eruption leading to detachment of the skin and leaving erosions.

Ocular features

Ocular involvement begins with oedema, erythema and crusting of the eyelids.

TABLE 4.3: Most common causes of SJS/TEN

Pharmacologic	*Infectious*
• Allopurinol • Anticonvulsants – Carbamazepine – Phenytoin – Lamotrigine • Barbiturates • Sulfonamides • NSAIDs	• Bacterial – Mycoplasma pneumoniae – Group A β-hemolytic *Streptococcus* • Viral – Cytomegalovirus – Herpes simplex virus – HIV

Palpebral conjunctiva becomes hyperaemic and distinct vesicles or bullae may occur (Fig. 4.7).

- In many instances, a concomitant conjunctivitis appears that is characterised by watery discharge with mucoid strands.
- Secondary infection, most commonly with *Staphylococcus species*, may develop.
- In severe cases, a membranous or pseudomembranous conjunctivitis may result from coalescence of fibrin and necrotic cellular debris (Fig. 4.8).
- ***Symblepharon formation*** (Fig. 4.9) may occur with severe pseudomembranous conjunctivitis.
- Primary corneal involvement and iritis are rare ocular manifestations of disease.

Late ocular complications occur in approximately 20% of patients, and include:

- *Structural anomalies of lid* position (ectropion and entropion), trichiasis and symblepharon.
- *Dry eye syndrome* may also result from deficiencies in the tear film—either in the aqueous layer, from scarring of lacrimal duct orifice, or more commonly, in the mucin layer, from destruction of the conjunctival goblet cells.

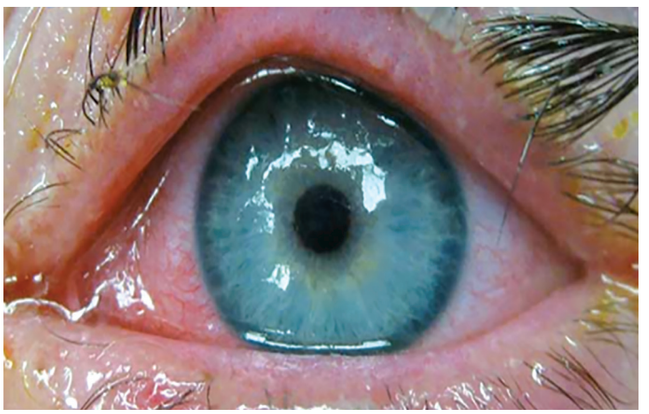

Fig. 4.7: External photograph of the left eye showing a corneal epithelial defect and diffuse conjunctival injection.

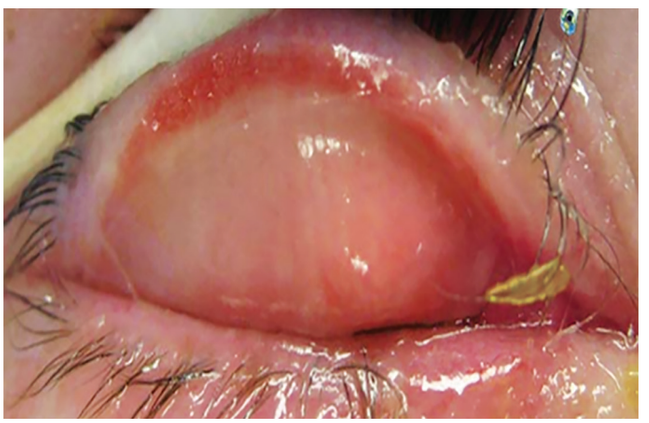

Fig. 4.8: Eversion of the right upper eyelid shows a conjunctival membrane.

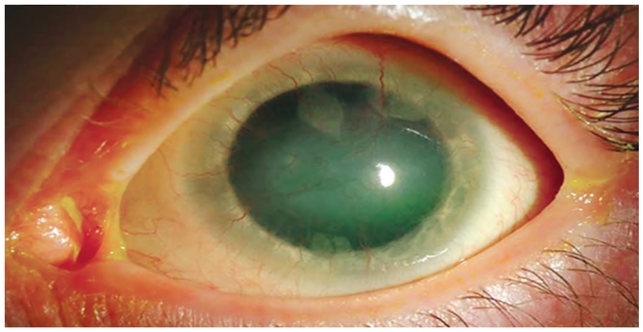

Fig. 4.9: Slit-lamp photograph showing the long-term consequences of SJS/TEN, which can include limbal stem cell deficiency and symblepharon.

DIFFERENTIAL DIAGNOSIS

- Erythema multiforme
- Cicatricial pemphigoid
- Paraneoplastic pemphigus
- Epidermolysis bullosa acquisita
- Graft-versus-host disease
- Atopic keratoconjunctivitis
- Infectious conjunctivitis—adenovirus, trachoma, *C. diphtheriae.*

TREATMENT

Systemic treatment in acute phase includes: Removal (e.g. causative drugs) or treatment (e.g. of causative infection) of the inciting factor:

- Intravenous immunoglobulin,
- Role of systemic steroids is controversial,
- Maintenance of hydration, and
- Debridement and replacement of sloughing skin.

Ocular treatment during acute phase includes:

- *Topical tear drops* and prevention of exposure,
- *Topical antibiotics* and steroid eye drops, and
- *Pseudomembrane peel* and symblepharon lysis with glass rod or moistened cotton swab should be done daily.
- *Amniotic membrane transplantation:* It may be used as either a temporary bandage or permanent graft. Not every case of SJS/TEN is suitable for AMT. This technique is generally reserved for patients with moderate or severe conjunctival involvement, as these are the patients at greatest risk of visual loss from ocular surface scarring. Patients with minimal epithelial sloughing may instead be treated medically.

Ocular treatment during chronic SJS/TEN includes:

- *Patients with cicatrizing diseases, including SJS/TEN, are poor candidates for traditional penetrating keratoplasty* (PKP) due to the development of lid abnormalities and severe surface dryness.
- *End-stage corneal blindness that is unresponsive to the above measures* may necessitate a keratoprosthesis. Keratoprostheses can restore vision almost immediately after surgery but not indefinitely, and postoperative complications are higher in these patients than in those who receive keratoprostheses for other indications.
- *Keratoprosthesis and limbal allografting:* Rarely match the success of early surgical treatment, but these methods can provide some visual recovery despite limbal stem cell loss and corneal conjunctivalization.
- *Keratolimbal allografting (KLAL)* is a technique that transplants cadaveric keratolimbal tissue to correct limbal stem cell deficiency.

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Chapter

5

Chemical Burns of Ocular Surface

Chapter Outline

ETIOPATHOGENESIS
- Source of common chemical agents
- Modes of chemical injuries
- Pathogenesis

GRADING OF CHEMICAL BURNS
- Roper-Hall classification
- Dua classification

CLINICAL COURSE
- Acute stage
- Early reparative stage
- Late reparative stage and sequelae

MANAGEMENT

General Principles and Goals of Treatment

Management Protocol
- Immediate treatment
- Early reparative stage management
- Treatment of sequelae

ETIOPATHOGENESIS

Chemical injuries form a large chunk of 'Ophthalmic emergencies'. Ranging from just a mild discomfort and minimal tissue damage; to severe, irreversible tissue damage; the manifestations could be varied. Depending upon access of the patient to prompt and adequate management, the prognosis could change from 'good' to 'grim'.

SOURCE OF COMMON CHEMICAL AGENTS

Source of common chemical agents implicated in chemical injuries of eyes are summarised in Table 5.1.

General comments about chemical agents causing ocular injuries are:

- *Alkali injuries* are more common, compared to acid injuries, because of their more frequent household use.
- *Ammonia*, that is found in fertilisers, refrigerants and cleaning solutions, is the most common cause of chemical eye injuries.
- *Other chemicals*, besides ammonia, such as hydroxides of sodium, potassium and magnesium are also important etiological agents.
- *Most common acid* implicated in ocular trauma is sulphuric acid, which is commonly used in invertor batteries, car batteries, fertilisers, manufacturing of dyes, explosives and refining petroleum.

TABLE 5.1: Source of chemical agents implicated in eye injuries

Chemical agent	*Source*
Calcium hydroxide	Cement, mortar, white-wash
Potassium hydroxide	Caustic potash
Magnesium hydroxide	Sparklers
Ammonia	Fertilizers, refrigerants
Sulphuric acid	Battery, industrial cleaner
Acetic acid	Vinegar, glacial acetic acid
Sulphurous acid	Bleach, refrigerants, food preservative
Hydrofluoric acid	Glass polishing, gasoline alkylation, silicone production
Hydrochloric acid	Chemical laboratories

- *Other acids* such as nitric acid, chromic acid and hydrofluoric acid also contribute to ocular trauma.

MODES OF CHEMICAL INJURIES

Chemical injuries usually occur due to external contact with chemicals under following circumstances:

- *Domestic accidents*, with ammonia, solvents, detergents and cosmetics.
- *Agricultural accidents*, due to fertilisers, insecticides, toxins of vegetable and animal origin.

- *Chemical laboratory accidents*, with acids and alkalies.
- *Deliberate chemical attacks*, especially with acids to disfigure the face.
- *Chemical warfare injuries*.
- *Self-inflicted chemical injuries* are seen in malingerers and psychopaths.

PATHOGENESIS

Pathogenesis of alkali burns

Alkalis cause damage to the cornea and ocular surface by causing pH change, proteolysis and collagen synthesis defects.

Rise in pH leads to saponification of fatty acids of cell membranes, leading to cell destruction thus allowing the alkalis to enter the anterior chamber. This in turn leads to damage to all anterior segment structures.

Proteolysis. The damaged tissue and inflammatory cells secrete proteolytic enzymes, the response which leads to further tissue damage.

Collagen synthesis defect. Alkalis also damage ciliary body to reduce aqueous ascorbate levels that is necessary for conversion of proline and lysine to hydroxyproline and hydroxylysine, respectively, which is an important step of collagen synthesis.

Pathogenesis of acid burns

Acids damage the ocular surface by lowering the pH thereby precipitating tissue proteins, thus creating a barrier to further ocular penetration. Due to this, acid injuries are less severe than alkali injuries.

GRADING (CLASSIFICATION) OF CHEMICAL BURNS

Depending upon the severity of damage caused to the limbus and cornea, the extent of chemical burns may be graded as in Roper-Hall classification (Table 5.2) and Dua's classification (Table 5.3).

CLINICAL COURSE OF CHEMICAL BURNS

The clinical course following an acute chemical injury can be divided in three stages (Fig. 5.1).

1. ACUTE STAGE (IMMEDIATE TO ONE WEEK)

This stage is characterized by (Fig. 5.1):

- *Conjunctiva* shows marked oedema, congestion, widespread necrosis and a copious purulent discharge.

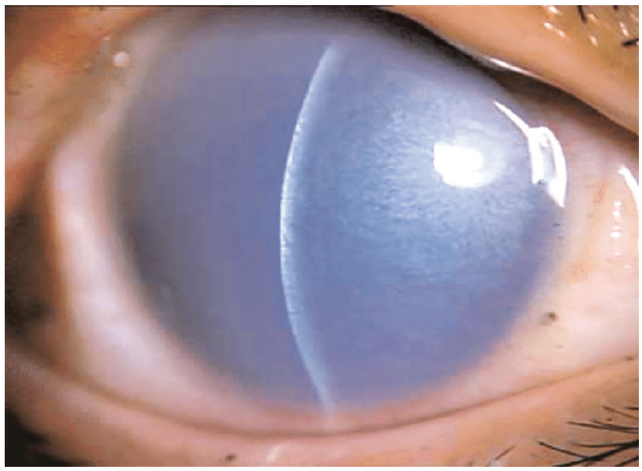

Fig. 5.1: Limbal ischaemia in a case of chemical burn.

TABLE 5.2: Roper-Hall classification (1965)

Grade	*Prognosis*	*Cornea*	*Conjunctiva/limbus*
I	Good	Corneal epithelial damage	No limbal ischaemia
II	Good	Corneal haze, iris details visible	<1/3 limbal ischaemia
III	Guarded	Total epithelial loss, stromal haze, iris details obscured	1/3–1/2 limbal ischaemia
IV	Poor	Cornea opaque, iris and pupil obscured	>1/2 limbal ischaemia

TABLE 5.3: Dua classification of ocular surface burns (2001)

Grade	*Prognosis*	*Clinical findings*	*Conjunctival involvement*	*Analogue scale*
I	Very good	0 clock hours limbal involvement	0%	0/0%
II	Good	≤3 clock hours limbal involvement	≤30%	0.1–3/1–29.9%
III	Good	>3–6 clock hours limbal involvement	>30–50%	3.1–6/31–50%
IV	Good to guarded	>6–9 clock hours limbal involvement	>50–75%	6.1–9/51–75%
V	Guarded to poor	>9–< 12 clock hours limbal involvement	>75–< 100%	9.1–11.9/75.1–99.9%
VI	Very poor	Total (12 clock hours) limbal involvement	100%	12/100%

- *Limbal ischaemia* (Fig. 5.2) may or may not be present depending upon the grade of chemical burn (Tables 5.2 and 5.3).
- *Cornea* develops widespread sloughing of the epithelium, oedema and opalescence of the stroma.
- *Iris* becomes violently inflamed and in severe cases both iris and ciliary body are replaced by granulation tissue.
- *Rise in intraocular pressure* due to compression of globe because of shortening of collagen fibrils and impedance of aqueous humor outflow.

2. EARLY REPARATIVE STAGE (ONE TO THREE WEEKS)

During this period there is clearing off of necrotic tissue and regeneration of the denuded area. ***Clinical findings*** depending on the grade of burns are as below:

- *Grade I/II burns*. Epithelium regeneration brings along clearing of stromal haze and synthesis of stromal collagen.
- *Grade III/IV burns*. Epithelium regeneration is difficult. Stroma remains hazy and stromal ulceration takes place due to action of digestive enzymes such as collagenases, matrix metalloproteinases (MMP), and other proteases released due to inflammation.

3. LATE REPARATIVE STAGE AND SEQUELAE (≥THREE WEEKS)

- *Grade I/II burns*. In such cases complete healing may occur without much sequelae.
- *Grade III/IV burns*. Sequelae occur in such cases and include corneal scarring, xerosis, symblepharon (Figs 5.2C and 5.3), ankyloblepharon, secondary glaucoma, uveitis, complicated cataract, lagophthalmos, cicatricial entropion or ectropion, trichiasis and dry eye disease.

MANAGEMENT

GENERAL PRINCIPLES AND GOALS OF TREATMENT

General principles and goals of management in a case of chemical burns are:

- Thorough removal of the chemical agent and necrotic debris from the eyes.
- Restoration of intact ocular surface.
- Control of acute inflammation.
- Prevention of superadded infection.
- Support of reparative process.
- Prevention and management of sequelae.

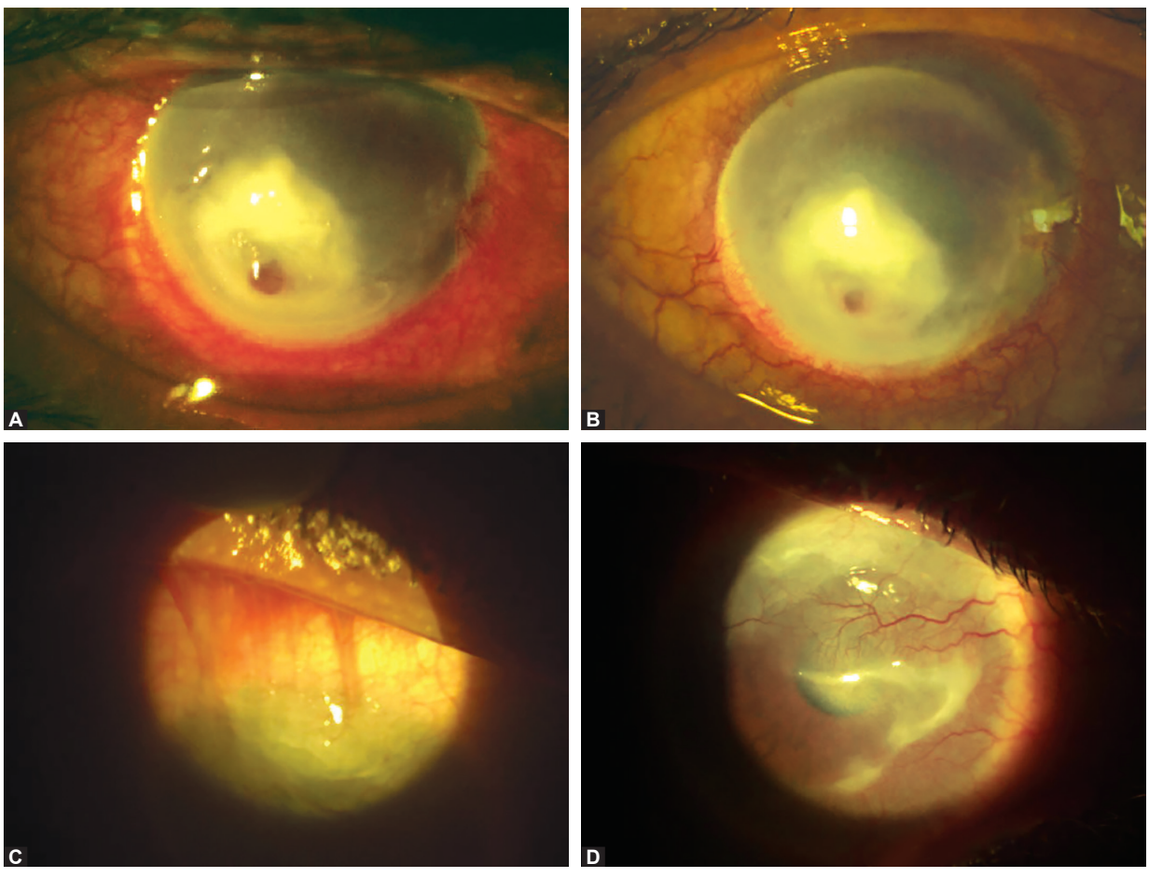

Fig. 5.2: A, Acute phase; B, Sequelae developed 3 months after mild chemical injury with a liquid cleansing agent; C, Symblepharon formation due to lime injury; D, Result after symblepharon release and amniotic membrane grafting.

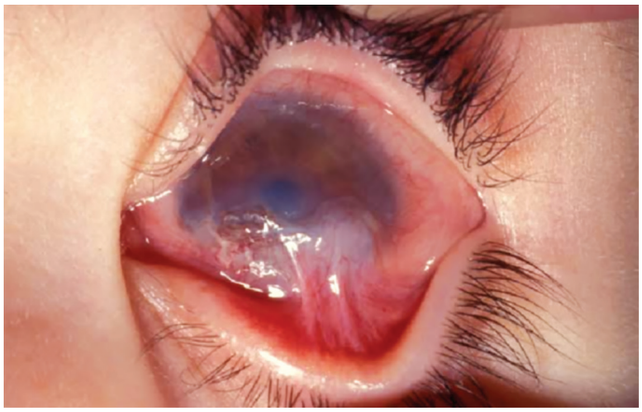

Fig. 5.3: Post-chemical burn symblepharon.

MANAGEMENT PROTOCOL

A. Immediate treatment

Aim of immediate treatment is to minimise tissue damage due to the chemical agent. ***Emergency kit***, should preferably, be maintained by the treating ophthalmologists for management of acute burns (Table 5.4).

Treatment protocol includes:

1. *Irrigation of the cul-de-sac.* Immediate copious irrigation of the eye must be initiated without wasting time on history and examination.

- *Irrigating solution* includes normal saline, Ringer's lactate, balanced salt solution, tap water, borate buffer solution or diphoterine (high buffer capacity amphoteric hypertonic polyvalent compound depending upon the availability).
- *Use of acidic solution* to neutralise alkali is dangerous and NOT recommended.
- *Duration of irrigation* may vary with the severity of injury:
  - 15–20 min in Grade 1 and 2 burns
  - 30–35 min in Grade 3 and 4 burns
  - 45–50 min in Grade 5 and 6 burns.

TABLE 5.4: Emergency kit for the management of acute chemical injuries

Constituents of the kit	*Purpose*
Bottles of Ringer's lactate/ normal saline and IV drip sets	Copious irrigation
Litmus paper strips	See the change in pH
Topical anaesthetic	Anaesthetize the eye to facilitate ocular examination
Swab stick	Clean the ocular surface
Desmarres retractor	Retract the eyelids to allow thorough ocular examination
26 gauge needle	Remove embedded chemical particles
Fluorescein strips	Extent of epithelial defects
Topical medication	Promote healing

- *pH of conjunctival cul-de-sac should be measured* after completion of irrigation, and further irrigation should be done till pH approaches normal level.

2. *Examination with everted lids* should always be done after thorough irrigation. The fornices along with the ocular surface should be examined after topical anaesthesia, by double eversion of eyelids or with Desmarres retractor. Often this is very difficult in the inflamed eye, but it is a very important step. Efforts should be made to note for presence of any particulate matter.

3. *Mechanical removal of contaminant.* If any particles are left behind, particularly in the case of lime, these should be removed carefully with a swab stick.

4. *Removal of contaminated and necrotic tissue.* Necrosed conjunctiva should be excised. Contaminated and necrosed corneal epithelium should be removed with a cotton swab stick.

B. Early reparative stage management

During this stage, intent of the treatment is to control inflammation-mediated damage, promote healing and prevent symblepharon formation.

I. **Controlling inflammation mediated damage.** This approach incorporates use of drugs such as anti-inflammatory drugs, enzyme inhibitors, and cycloplegics.

a. ***Topical anti-inflammatory drugs***

- *Topical steroids* used in the initial seven to ten days after injury to reduce inflammatory cells infiltrating the corneal stroma. Steroids should be rapidly tapered after this period if the epithelium is not intact, as it slows the repair process.
- *Topical nonsteroidal anti-inflammatory drugs (NSAIDs)* should be used cautiously due to their known ocular surface toxicity. Corneal melting is known to occur due to some NSAIDs.

b. ***Enzyme inhibitory drugs*** which help in controlling inflammation include:

- *Tetracycline eye ointment*, to be used two to three times a day.
- *Systemic tetracycline*. Doxycycline (100 mg BD) helps by inhibiting gene expression of neutrophil collagenase and epithelial gelatinase.
- *Collagenase inhibitors*. These include 10% sodium citrate drops made in artificial tears, cysteine, acetylcysteine, EDTA and penicillamine.

c. ***Cycloplegics***, e.g. atropine, may improve the comfort.

II. **Promoting healing.** This can be achieved by use of:

a. ***Medications promoting healing*** include:

- *Tear substitutes*. Most important medication, because adequate lubrication and prevention of symblepharon formation is one of the prime concerns. Preservative-free artificial tears help in stabilising tear film thereby hastening epithelial regeneration.

- *Autologous serum eye drops* (20–40%) contain growth factors.
- *Ascorbate*. Oral ascorbate 500 mg QID or topical 10% solution in artificial tears administered hourly promotes epithelial healing by replenishing ascorbic acid to fibroblasts of cornea.
- *Epidermal growth factor*. May be of help as it promotes epithelial migration.
- *Retinoic acid*. Promotes goblet cell recovery and tear film stabilisation.
- *Fibronectin*. It is still in experimental phase.

b. ***Mechanical methods which help in healing***, depending upon the prevailing situation, include:

- *Debridement*. Excision of necrotic tissues hastens the re-epithelialisation as necrotic tissue acts as a source of inflammatory mediators.
- *Bandage contact lens*. Prevents the ocular surface from windshield-wiper effect prouced by movement of the eyelids.
- *Conjunctival/tenon advancement (tenoplasty)*. It involves excision of the necrotic conjunctiva and cornea, followed by the advancement of Tenon's over the cornea.
- *Tissue adhesives* such as cyanoacrylate glue may be used along with a bandage contact lens, in the presence of a small corneal perforation.
- *Tectonic penetrating keratoplasty or patch graft* may be required.
- *Amniotic membrane transplantation*. May be of use in grade II–III chemical burns as amniotic membrane facilitates epithelialisation and prevents symblepharon formation, vascularisation and scarring.

III. **Prevention of symblepharon formation** can be done by using a glass shell or sweeping a glass rod in the fornices twice daily.

C. Treatment of sequelae

1. *Ocular surface rehabilitation* measures needed include symblepharon lysis, fornix formation, entropion surgery, and ectropion surgery. Keratoplasty, which provides corneal tissue for tectonic support, may be needed, in some cases.

2. *Limbal stem cell deficiency* can be treated by limbal stem cell transplantation using either conjunctival limbal autografts, or graft from living related or cadaveric donors or cultured limbal epithelium. This is especially useful in high grade chemical injuries with extensive perilimbal ischaemia.

3. *Secondary glaucoma* should be treated by topical 0.5% timolol, instilled twice a day along with oral acetazolamide 250 mg 3–4 times a day.

4. *Pseudopterygium*, when formed, should be excised together with conjunctival autograft (if adequate host conjunctiva) or amniotic membrane facilitated by antimitotic drugs (e.g. mitomycin C).

5. *Visual rehabilitation in the presence of corneal opacity* is done with:

- *Penetrating keratoplasty* may be performed after acute inflammatory stage has subsided.
- *Keratoprosthesis* remains a surgical option in severely damaged eyes where keratoplasty is not possible.

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Chapter 6

Blepharitis and Meibomian Gland Dysfunction

Chapter Outline

BLEPHARITIS

Definition and Classification

Anterior Blepharitis

- Bacterial blepharitis
- Seborrhoeic or squamous blepharitis

Posterior Blepharitis

- Chronic meibomitis
- Acute meibomitis
- Parasitic blepharitis

MEIBOMIAN GLAND DYSFUNCTION

Anatomy and Physiology of Meibomian Glands

Definition and Classification

- Definition of MGD
- Classification of MGD

Pathophysiology of MGD

- Low delivery MGD
- High delivery MGD
- Risk factors for MGD

Clinical Presentation of MGD

- Symptoms
- Morphological changes in MGD

Diagnostic Tests

- Routine tests
- Specialised tests

Management of MGD

- Principles of MGD management
- Management measures

BLEPHARITIS

DEFINITION AND CLASSIFICATION

The term 'blepharitis', means inflammation of the eyelid margin. Blepharitis is divided into an anterior and a posterior variety.

Anterior blepharitis refers to inflammation of the lid margin anterior to the grey line, i.e. of the skin, eyelashes, and lash follicles.

Posterior blepharitis means the inflammation of structures posterior to the grey line; that includes the meibomian duct orifices, meibomian glands, tarsal plate, and the blepharo-conjunctival junction.

Mixed variety of blepharitis may be seen frequently as the inflammatory process spreads from one structure to the next.

ANTERIOR BLEPHARITIS

Blepharitis is a subacute or chronic inflammation of the lid margins. It is an extremely common disease which can be divided into following clinical types:

- Bacterial blepharitis,
- Seborrhoeic or squamous blepharitis,
- Mixed staphylococcal with seborrhoeic blepharitis,
- Posterior blepharitis or meibomitis, and
- Parasitic blepharitis.

Bacterial Blepharitis

Bacterial blepharitis, also known as chronic anterior blepharitis, or staphylococcal blepharitis or ulcerative blepharitis, is a chronic infection of the anterior part of the lid margin. It is a common cause of ocular discomfort and irritation. The disorder usually starts in childhood and may continue throughout life.

Etiology

Causative organisms, most commonly involved, are coagulase positive Staphylococci. Rarely, Streptococci, *Propionibacterium acnes,* and Moraxella may be involved.

Predisposing factors, usually none, may rarely include chronic conjunctivitis and dacryocystitis.

Clinical features

Symptoms include chronic irritation, itching, mild lacrimation, gluing of cilia, and mild photophobia. The symptoms are characteristically worse in the morning. Remissions and exacerbations in symptoms are quite common.

Signs (Fig. 6.1) are as below:

- *Yellow crusts* are seen at the root of cilia which glue them together.
- *Small ulcers,* which bleed easily, are seen on removing the crusts.
- *Red, thickened lid margins* are seen with dilated blood vessels (rosettes).
- *Mild papillary conjunctivitis* and conjunctival hyperaemia are common associations.

Complications and sequelae of long-standing bacterial blepharitis include:

- *Lash abnormalities* such as madarosis (sparseness or absence of cilia), trichiasis (misdirected cilia), and poliosis (graying of lashes).
- *Tylosis*, i.e. thickening and scarring of lid margin.
- *Eversion of punctum* leading to epiphora.
- *Eczema of skin and ectropion* may develop due to prolonged watering.
- *Recurrent styes* (external hordeola) are a common complication.
- *Marginal keratitis,* and occasionally phlyctenulosis may develop.
- *Tear film instability,* and dry eye may result.
- *Secondary inflammatory and mechanical changes in the conjunctiva and cornea* are common because of intimate relationship between the lid margins and ocular surface.

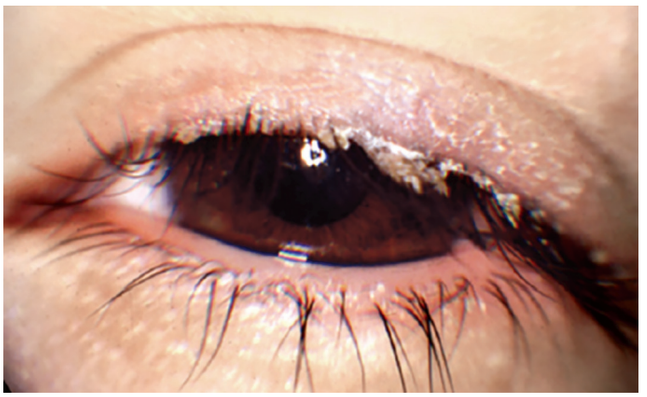

Fig. 6.1: Bacterial blepharitis.

Treatment

Bacterial blepharitis should be treated promptly, as below, to avoid complications and sequelae:

1. Lid hygiene is essential at least twice daily and should include:

- *Warm compresses* for 5–10 minutes to soften the crusts.
- *Crust removal and lid margin cleaning* with the help of cotton buds dipped in the dilute baby shampoo or solution of 3% sodium bicarbonate.
- *Avoid rubbing of the eyes* or fingering of the lids.

2. Antibiotics should be used as below:

- *Eye ointment* should be applied at the lid margin, immediately after removal of the crusts.
- *Antibiotic eye drops* should be used 3–4 times a day.
- *Oral antibiotics* such as erythromycin or doxycycline may be useful in unresponsive patients and those complicated by external hordeola and abscess of lash follicle.

3. Topical steroids (low potency) such as fluorometholone may be required in patients with papillary conjunctivitis, marginal keratitis and phlyctenulosis.

4. Ocular lubricants, i.e. artificial tear drops, are required for associated tear film instability and dry eye.

Seborrhoeic or squamous blepharitis

Seborrhoeic blepharitis is primarily anterior blepharitis with some spillover posteriorly. It is of common occurrence.

Etiology. It is usually associated with seborrhoea of scalp (dandruff). Some constitutional and metabolic factors play a part in its etiology. In it, glands of Zeis secrete abnormal excessive neutral lipids which are split by *Corynebacterium acne* into irritating free fatty acids.

Symptoms. Patients usually complain of deposition of whitish material (soft scales) at the lid margin associated with mild discomfort, irritation, occasional watering and a history of falling of eyelashes.

Signs include:

- *Accumulation of white dandruff-like scales* is seen on the lid margin, among the lashes (Fig. 6.2). On removing these scales underlying surface is found to be hyperaemic and greasy (no ulcers).
- *The lashes fall out easily* but are usually replaced quickly without distortion.
- *Lid margin* is thickened and the sharp posterior border tends to be rounded leading to epiphora, in long-standing cases.
- *Signs of bacterial blepharitis,* as described above, may be superadded in patients with mixed seborrhoeic and bacterial blepharitis.

Complications are similar to bacterial blepharitis with comparatively lesser frequency (*see* page 74).

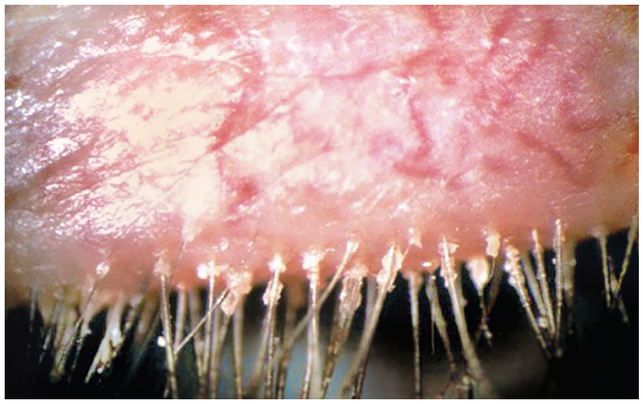

Fig. 6.2: Seborrhoeic blepharitis.

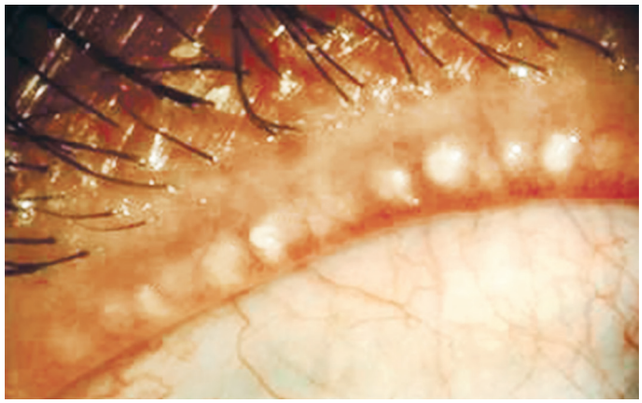

Fig. 6.3: Chronic meibomitis.

Treatment includes:

- *General measures* include improvement of health and balanced diet.
- Associated *seborrhoea of the scalp* should be adequately treated.
- *Local measures* include removal of scales from the lid margin with the help of lukewarm solution of 3% soda bicarb or baby shampoo and frequent application of combined antibiotic and steroid eye ointment at the lid margin.
- *Antibiotics,* as described above in bacterial blepharitis, may be required in patients with mixed seborrhoeic and bacterial blepharitis.

POSTERIOR BLEPHARITIS (MEIBOMITIS)

Meibomitis, i.e. inflammation of meibomian glands occurs in chronic and acute forms.

1. Chronic meibomitis

Chronic meibomitis is a commonly occurring meibomian gland dysfunction, seen more commonly in middle-aged persons, especially those with acne rosacea and/or seborrhoeic dermatitis. Bacterial lipases are being blamed to play main role in the pathogenesis of chronic meibomitis.

Clinical features

Symptoms include chronic irritation, burning, itching, grittiness, mild lacrimation with remissions and exacerbations intermittently. Symptoms are characteristically worse in the morning.

Signs include (Fig. 6.3):

- *White frothy (foam-like) secretions* are frequently seen on the eyelid margins and canthi (meibomian seborrhoea).
- *Opening of meibomian glands* become prominent with thick secretions which can be expressed out by pressure on the lids giving toothpaste appearance. Meibomian gland orifices may also show capping with oil globules, pouting, recession, or plugging.
- *Vertical yellowish streaks shining* through conjunctiva can be seen on eversion of the lids. These represent the meibomian ducts filled with thick secretion.
- *Hyperaemia and telangiectasia* of posterior lid margin around the orifices of meibomian glands can be seen frequently.
- *Oily and foamy tear film* with accumulation of froth on the lid margins or inner canthus.
- *Secondary changes* in the form of papillary conjunctivitis, and inferior corneal punctate epithelial erosions may be seen.

2. Acute meibomitis

Acute meibomitis occurs due to staphylococcal infection. It is characterised by painful swelling around the involved gland. Pressure on it results in expression of pus bead followed by serosanguineous discharge.

Treatment of meibomitis

1. *Lid hygiene* is essential at least once a day and should include:

- *Warm compresses* for several minutes.
- *Expression* of accumulated secretions by repeated vertical massage of lids in the form of milking.

2. *Topical antibiotics* in the form of eye ointment should be rubbed at the lid margin immediately after massage.

- Eye drops may be used 3–4 times a day.

3. *Systemic tetracyclines,* e.g. doxycycline 100 mg b.d. for 1 week and then o.d. for 6–12 weeks, remain the mainstay of treatment of posterior blepharitis because of their ability to block staphylococcal lipase production. Erythromycin may be used where tetracyclines are contraindicated.

4. *Ocular lubricants,* i.e. artificial tear drops are required for associated tear film instability and dry eye disease.

5. *Topical steroids* (weak) such as fluorometholone may be required in patients with papillary conjunctivitis.

Parasitic blepharitis (lash infestation)

Etiology

Blepharitis associated with infestation of lashes by lice is not uncommon in persons living in poor hygienic conditions. The lice infestations include the following:

- *Phthiriasis palpebrarum* refers to the infestation by *phthirus pubis* (crab louse). It is most commonly seen in adults in whom it is usually acquired as a sexually transmitted infection.
- *Pediculosis* refers to the infestation by *pediculus humanus corporis* or *capitis* (head louse). If heavily infested the lice may spread to involve lashes.
- *Demodex blepharitis* is caused by two distinct species: Demodex folliculorum which causes anterior blepharitis and demodex brevis which causes posterior blepharitis.

Clinical features

Infestation of lashes with lice causes chronic blepharitis and chronic follicular conjunctivitis.

Symptoms include chronic irritation, itching, burning, and mild lacrimation.

Signs are as below (Fig. 6.4):

- *Lid margins* are red and inflamed.
- *Lice* anchoring the lashes with their claws may be seen on slit-lamp examination.
- *Nits (eggs)* may be seen as opalescent pearls adherent to the base of cilia.
- *Conjunctival congestion* and follicles may be seen in long-standing cases.

Treatment

- *Mechanical removal* of the lices and nits with forceps.
- *Application of antibiotic ointment* and yellow mercuric oxide 1% to the lid margins and lashes.
- *Delousing* of the patient, family members, clothing and bedding is important to prevent recurrences.

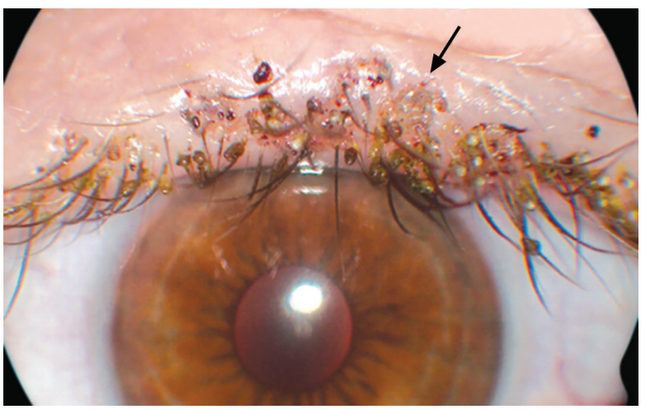

Fig. 6.4: Phthiriasis palpebrarum.

MEIBOMIAN GLAND DYSFUNCTION

ANATOMY AND PHYSIOLOGY OF MEIBOMIAN GLANDS

The meibomian glands were first described in detail by Heinrich Meibom in 1666. These are modified sebaceous glands with a tubuloacinar structure. Each gland consists of clusters of 10–15 secretory acini, arranged circularly around a long central duct and connected to it by short ductules. There are 30–40 glands in the upper tarsal plate and 25 in the lower; the glands in the upper tarsus are 5.5 mm long while the lower ones are 2 mm long.

Innervation. Meibomian glands are densely innervated by the sympathetic and parasympathetic nerve fibres via the V nerve which also supplies the lacrimal and accessory lacrimal glands, thereby ensuring an optimal composition of the tear film.

Hormonal control. Meibomian glands are also under a strong hormonal control mediated by androgens, oestrogens, progestins, retinoic acid, growth factors and neurotransmitters.

Secretion of meibomian glands is called meibum which is made up of mostly non-polar lipids (>90%: primarily wax and, sterol esters and triacylglycerols), while less than 10% are polar lipids [(O-acyl)-ω-hydroxy fatty acids (OAHFA)], and a small amount of proteins and electrolytes. The tear film lipid layer is a multilayered structure formed of a thin, monomolecular layer of polar lipids present at the aqueous–lipid interface and act as a surfactant. This is essential in the uniform spreading and stability of the tear film. It is covered over by a thick layer of non-polar lipids, which form the outermost eye–air interface that resists the evaporation of the aqueous component of the tear film.

Mode of secretion of meibum is holocrine, which means that the secretion is produced in the cytoplasm of an acinar cell; the cell membrane ruptures, releases its secretions into the gland's lumen while the cell itself is destroyed in the process. The secretion from multiple acini are poured via tiny ductules into the central duct that opens at the grey line of the lid margin. The terminal part of the central duct and the terminal acini close to the lid margin are encircled by a thin strip of orbicularis muscle fibres (Riolan's muscle). During a blink, the pre-tarsal orbicularis muscle produces uniform compression of the tarsal plate and of the enclosed meibomian glands, and promotes the flow of secretion towards the duct opening by a milking action. Meibum is squirted out of the duct openings by the contraction of Riolan muscle at the end of a blink.

Meibum is in a liquid/fluid state at the body temperature; this allows it to coat the lid margins, thus making their movement smooth over the ocular surface, and to be delivered to the tear meniscus. From there, it is picked up by the upper lid margin (as it comes down during a blink up picks up the tear meniscus) and is spread uniformly over the aqueous layer of the tear film. This prevents the

excess evaporation and thinning in-between the blinks, thus making the tear film stable.

If a person fails to blink for a long time, e.g. staring at a computer screen, or during sleep, meibum accumulates within the ducts and is delivered in increased amounts when the person blinks on waking up in the morning. This excess amount of oil in the precorneal tear film makes the vision misty and blurred in the morning, and explains the diurnal variation in meibum secretion.

Functions of a healthy meibomian secretion (in particular the lipids) are:

- To provide a smooth optical surface at the air–lipid interface for the cornea.
- To reduce excess evaporation of the tear film in-between blinks.
- To enhance the stability of the pre-corneal tear film.
- To enhance a uniform spreading of tear film over the cornea.
- To prevent spillover of tears from the lid margin.
- To prevent contamination of tear film by the sebum.
- To seal the apposing lid margins during sleep.

DEFINITION AND CLASSIFICATION

DEFINITION

The term meibomian gland dysfunction (MGD) was first described by Korb and Henriquez in the early 1980s, previously, there was no firmly established definition in the literature. MGD is generally considered by the clinicians as a *posterior blepharitis*. In 2011, the International Workshop on MGD conducted by the Tear Film and Ocular Surface Society (TFOS) defined it as *"A chronic, diffuse abnormality of the meibomian glands, characterised by the terminal duct obstruction and/or qualitative/quantitative changes in the glandular secretion. It may result in an alteration of the tear film, symptoms of ocular irritation, clinically apparent inflammation, and ocular surface disease"*. It is a very common condition, with a prevalence of more than 60% in Asian populations; while in Caucasians, it spans from 3.5 to 19.9%. It is *considered as the leading cause of dry eye disease throughout the world.*

Dry eye disease had been classically considered an aqueous deficiency problem, but after the report by TFOS, there has been a paradigm shift towards "not producing enough lipids to retain the tears that are being produced". This has led to a huge impact on the treatment protocols which are now targeting MGD as the primary underlying cause, rather than being focused on a symptomatic treatment of dry eyes. It has now been accepted worldwide that dry eye occurs when the ocular surface system cannot adequately protect itself from the desiccating stress due to the lack of healthy meibomian gland secretion.

CLASSIFICATION OF MGD

Etiological types of MGD

I. Primary MGD

In primary MGD only meibomian glands are affected. With age, there is an increase in meibomian gland dropout, particularly after the age of 50 years, which correlates with the appearance of primary MGD. A fall in bioavailable androgens may contribute to these events.

II. Secondary MGD

Secondary MGD is associated with either some other ocular pathology or systemic pathology (Fig. 6.5).

Classification of MGD proposed by the International Workshop on MGD

A new classification system proposed by the International Workshop on MGD is shown in Figure 6.5.

PATHOPHYSIOLOGY OF MGD

MGD is a highly complex disease that is caused by a variety of hormonal, microbial, metabolic and environmental factors. Pathophysiology of various types of MGD is summarised below (Fig. 6.5).

A. LOW DELIVERY MGD

Low delivery MGD may be hyposecretory or obstructive. It may be primary or secondary.

I. Hyposecretory MGD

Secondary hyposecretory MGD (meibomian sicca) occurs in seborrhoeic dermatitis, acne rosacea, and as a side effect of certain medications (hormone replacement therapy, antihistamines, antidepressants, isotretinoin for acne).

II. Obstructive MGD

Obstructive MGD may be cicatricial or non-cicatricial.

Non-cicatricial MGD

A key event in non-cicatricial MGD is hyperkeratinisation of the terminal ducts. Due to *hyperkeratinisation* of the terminal ducts and lid margin; the desquamated cells clump together to form plaques which block the duct openings. Obstruction may be exacerbated by changes in oil composition that increase meibum viscosity. Obstruction of duct opening results in stasis of meibum within the duct; the back pressure produces a cystic dilation of the glands and finally pressure/disuse atrophy of acini and gland dropout. The loss of acini further results in meibum hyposecretion.

In addition, stasis of meibum inside the ducts promotes the growth of commensal bacteria; the bacterial lipases cause degradation of lipids in the meibum and release of toxic mediators. All these factors aggravate the primary hyperkeratinisation and compositional disturbance of

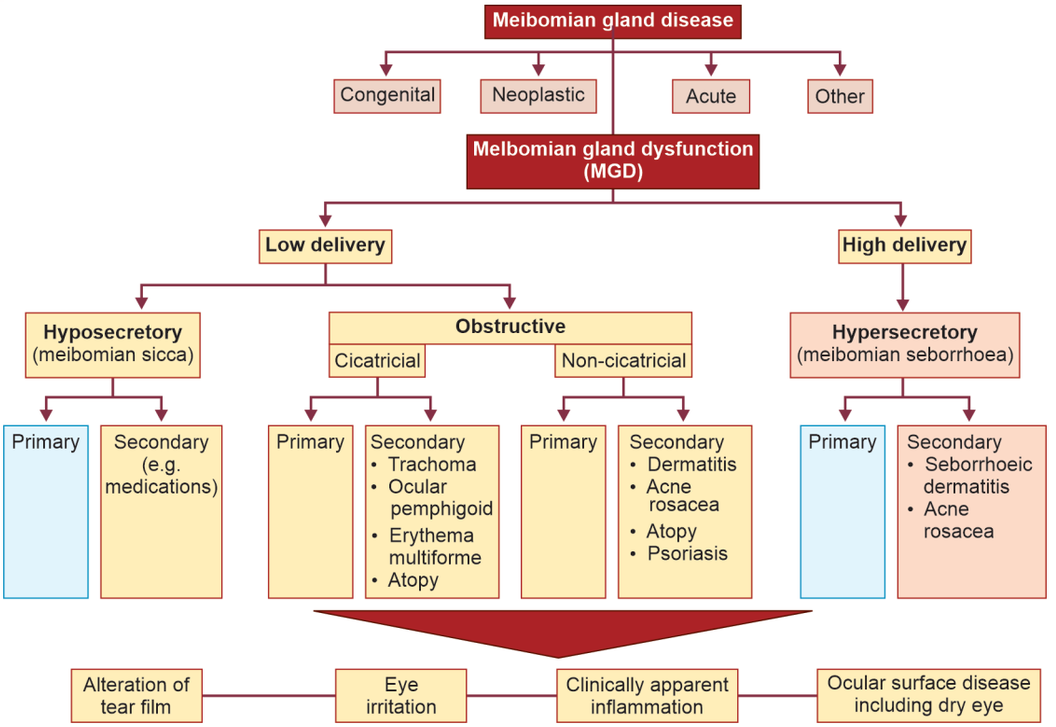

Fig. 6.5: The new classification system proposed by the International Workshop on MGD.

meibum, consequently, the MGD becomes a progressive and a chronic inflammatory disease. The degree to which inflammatory changes are found around affected glands varies in different reports, but signs of inflammation are common at the lid margin. Chronic obstruction leads to degeneration of the secretory gland tissue, and even if the primary obstruction is later resolved by therapeutic approaches, the damage is permanent.

Primary non-cicatricial MGD. Hyperkeratinisation is commonly due to hormonal imbalance as a part of the ageing process. With age, there is an increase in meibomian gland dropout, particularly after the age of 50 years, which correlates with the appearance of primary MGD. A fall in bioavailable androgens may contribute to these events.

Secondary non-cicatricial MGD is seen in the following conditions:

- *Skin disorders*, such as acne rosacea, atopic dermatitis, seborrhoeic dermatitis, and psoriasis.
- *Topical medications* which can promote MGD are:
  - Antiglaucoma drugs such as pilocarpine, timolol, carbonic anhydrase inhibitor
  - Retinoic acid
- Blink abnormality
- Prolonged contact lens wear
- Antiandrogen medications
- Decreased expression of androgen receptors as a result of anti-androgen therapy.

Polychlorinated biphenyls are also reported to cause MGD.

Cicatricial MGD

In cicatricial MGD, submucosal conjunctival scarring drags the meibomian orifices, terminal ducts and mucocutaneous junction posteriorly, across the posterior lid border and onto the tarsal plate, where the narrowed and displaced ducts can no longer deliver meibum effectively to the tear film lipid layer. Low meibum delivery and changes in oil composition can lead to tear film instability, increased tear evaporation and ultimately to EDE. Cicatricial MGD can also be primary or secondary.

Causes of secondary cicatricial MGD include:

- Trachoma,
- Chronic ocular surface inflammation,
- Chemical injuries,
- Stevens-Johnson syndrome,
- Erythema multiforme, and
- Ocular pemphigoid.

B. HIGH DELIVERY MGD

Hypersecretory MGD (meibomian seborrhoea)

Hypersecretion of meibum occurs in meibomitis (meibomian gland inflammation); excessive amount of meibum with an altered chemical composition is produced that is toxic to the ocular surface.

Primary hypersecretory MGD occurs due to abnormalities of meibum-secreting cells seen as a result of ageing.

Secondary hypersecretory MGD occurs due to *Staphylococcus aureus* or *Demodex folliculorum* infection, environmental factors (hot, dry climate) and nutritional disorders such as generalised malnutrition, a diet low in omega-3 fatty acids, protein deficiency, vitamin A deficiency. All these conditions have been associated with the production of a poor quality meibum.

RISK FACTORS FOR MGD

1. Ageing and hormonal imbalance. This is the most common cause of MGD. Oestrogen and androgen and receptors are present within the meibomian glands. Meibocytes contain enzymes which are necessary for the intracrine synthesis and metabolism of sex steroids. Androgens stimulate meibum secretion, promote the synthesis of proteins and lipids, suppress inflammation within the glands and prevent keratinisation of ductules, while oestrogens have all the opposite effects.

With increasing age, there is a decline in the total androgen pool in both genders, but the effects of androgen deficiency are more pronounced in post-menopausal women. In autoimmune diseases, like rheumatoid arthritis, Sjögren's syndrome and systemic lupus erythematosus, total androgen production in the body is reduced. The aged meibomian glands exhibit decreased meibocyte differentiation, cell renewal, gland size, and an increased inflammatory cell infiltration. These changes lead to gland atrophy and a hyposecretory state.

Similar changes in meibomian glands occur in individuals on anti-androgen therapy for benign prostatic hypertrophy or prostate cancer.

2. Gender. More common in women particularly with oily skin conditions, post-menopausal state and hormonal imbalance due to polycystic ovaries.

The key ingredient of many anti-ageing cosmetics for use around the eye is retinoid acid. It suppresses the action of androgens on meibomian glands, leading to their atrophy.

3. Environment. Hot and dry environment with a low humidity results in an alteration of meibocyte structure and function; there is an increase in basal acinar cell proliferation, a high meibum protein/lipid ratio that increases the viscosity of meibum, with a negative impact on the tear film stability. Increased production of meibum causes ductal dilation as well as depletion in the number of functioning meibocytes (as it is a holocrine secretion), with subsequent gland atrophy and hyposecretion. Exhaustion of the basal cells leads to the loss of acinar meibocytes and meibomian gland dropout.

4. Topical medications. Anti-glaucoma medications, like beta-blockers, prostaglandin analogs, carbonic anhydrase inhibitors, are associated with changes in meibomian gland morphology, including decreased acinar area and cell density. Chemical formulations, which contain adrenaline or phenylephrine, promote keratinisation of the lid margin and blocking of meibomian ducts. Retinoic acid reduces meibum production and alters its quality.

Topical medications contain preservatives to enhance their shelf life. The most commonly used preservative is benzalkonium chloride, which is most toxic to the ocular surface.

5. Dietary factors. Malnutrition (explained above) alters the quality of meibum. The use of oral fatty acids improves the quality and expressibility of meibum, especially the omega-3 fatty acids which alter the polar lipid profile and a decrease in the saturated fatty acid content of meibum. This helps in reducing ocular surface inflammation (by reduced production of pro-inflammatory mediators—prostaglandins, thromboxane and leukotriens). Foods rich in omega-3 fatty acids include flaxseed oil, fish oil, and olive oil. Taking 2 capsules of fish oil provide a daily dose of eicosapentaenoic acid 2 g and docosahexaenoic acid 1 g.

6. Microbial infection. Cholesterol esters present in meibum stimulate the proliferation of commensal organisms, in particular *Staphylococcus aureus*, on the eyelid margin. Bacterial lipases, in turn, breakdown the neutral fats and esters of meibum, releasing glycerides and free fatty acids into the tear film, destroy the mucin layer and make the cornea hydrophobic. This causes the tear film to become unstable. The free fatty acids also stimulate hyperkeratinisation of the lid margins, with keratin plugs adding to the blockage of meibomian ducts.

7. Infestation with the Demodex mite. It is a microscopic ectoparasite of the human skin and constitutes a part of the normal flora. It produces disease when its cell population increases, and is associated with MGD in about 46.8% of such patients. It is of two distinct varieties: *Demodex folliculorum* that infests the eyelash follicles, and *Demodex brevis* that burrows deep into sebaceous and meibomian glands. It causes a direct mechanical damage to the epithelial cells of eyelash follicles (by feeding on them), and by laying eggs at the base of eyelashes, causing follicular distension and misdirected lashes. *D. brevis* mechanically blocks the orifice of meibomian glands and results in a granuloma formation in the infected gland (chlazion). Therefore, it should be considered in the differential diagnosis of a chronic ocular surface disease not responding to the usual therapy.

Diagnosis can be made by random epilation of non-adjacent eyelashes placed on a glass slide, mounted to a coverslip with the addition of a droplet of oil, sodium fluorescein, peanut oil, or 75% alcohol which helps release embedded *Demodex* in the hair follicles.

8. Contact lens wear. Contact lens wear can result in the following harmful effects on the ocular surface:

i. *Thinning of tear film:* The thickness of a pre-corneal tear film is 3 m (approximately), while the average central thickness of a contact lens is 30 m. When the contact lens is worn, it splits the tear film both above and below the lens, the altered thickness results in an excessive evaporation and further thinning of the tear film.

ii. *Contact lenses cause a direct mechanical trauma to the lid margin:* By constant rubbing, it desquamates the surface epithelium, pluggs the meibomian duct orifices, resulting in the gland atrophy.

iii. *It causes a chronic ocular surface inflammation* which further affects the gland morphology and function, secretion of an altered meibum that adds to the ocular surface inflammation. All these changes are positively correlated with the duration of contact lens wear.

9. Congenital anomalies of meibomian glands. The number of meibomian glands can be decreased or they may be totally absent at birth, as seen in Turner syndrome, ectodermal dysplasia and cleft-lip and palate (ECC syndrome), and in anhidronic ectodermal dysplastic syndrome. Stub-like rudiments may be visible as yellow streaks on the tarsal conjunctival surface or the glands may be totally absent.

Primary distichiasis (aberrant row of eyelashes) may be present at birth in which meibomian glands are replaced by an extra row of eyelashes at the grey line. This results in meibum deficiency and ocular surface trauma due to the misdirected eyelashes. Secondary distichiasis can also occur as a result of metaplastic reaction caused by repeated rubbing of eyelids (in VKC or chronic allergic conjunctivitis or due to the autosomal dominant lymphoedema).

CLINICAL PRESENTATION OF MGD

MGD is asymptomatic and may remain undiagnosed in its early stages. It only becomes symptomatic when it has worsened enough to cause the tear film instability or eyelid inflammation. Its symptoms and signs vary, and include changes due to (Table 6.1):

- Altered morphology of the lid margin, altered meibum secretion, bacterial overgrowth and gland dropout,
- Tear film instability, and
- Ocular surface inflammation.

SYMPTOMS

I. Symptoms due to tear film instability include:

- *Fluctuation in vision* that occurs during the tasks associated with decreased blinking, such as reading, driving, staring at a computer screen or watching television is the most common symptom of MGD.
- *Blurred vision*. The thinning of pre-corneal tear film and reduced central corneal thickness, reduce the overall refractive power of the eye, this results in blurring of vision, reduced focusing ability, and sometimes even diplopia.
- *Epiphora*. Despite the presence of a dry eye, a foreign body sensation a paradoxical reflex watering may occur (as the lacrimal gland function is normal and dry spots on cornea stimulate the reflex), particularly when patient is exposed to low environmental humidity and blowing air (in air-conditioned rooms, under a fan).

II. Symptoms related to chronic lid margin inflammation include chronic lid discomfort, pain, redness and irritation.

III. Symptoms related to ocular surface inflammation are burning, itching, frequent blinking and photophobia that gradually worsen to produce severe blepharospasm.

- *Symptoms of ocular irritation* tend to be worse in the morning due to a prolonged exposure of the ocular surface to toxic meibum and hyperosmolar tears (due to poor clearance of the tear film) during sleep.

TABLE 6.1: Summary of MGD clinical features

Symptoms	*Clinical signs*
A. Due to tear film instability • Visual fluctuation • Blurred vision • Visual 'fatigue' and 'trouble focusing' • Monocular diplopia • Epiphora • Foreign body sensation • All worse under evaporative conditions	• Reduce visual acuity • Mteibomian gland obstruction • Meibomian gland inspissated secretions • Rapid tear film break-up time • Punctate epithelial erosions
B. Due to ocular surface inflammation • Itching (especially if atopic) • Burning • Photophobia • Tend to be worse upon awakening	• Conjunctival injection • Conjunctival chemosis • Conjunctivochalasis • Fornix foreshortening • Symblepharon • Inferior punctate epithelial erosions • Sterile keratitis (marginal)
C. Due to bacterial overgrowth • Morning discharge • History of recurrent conjunctivitis • History of recurrent hordeolum	• Eyelid seborrhoea, crusting, and loss of lashes • Conjunctival discharge • Papillary conjunctivitis • Microbial keratitis

- *Symptoms get worsened after the insertion of punctal plugs* due to reduced clearance of toxic tears.
- *Most troublesome symptom is a chronic burning sensation* in the eyes which is presumably attributable to the presence of inflammatory mediators or an increased tear osmolarity of the pre-corneal tear film.
- *Itching of eyelids* is more commonly present in atopic patients.

SIGNS (MORPHOLOGICAL CHANGES) IN MGD

Morphological changes in MGD should be assessed, systematically, on a slit-lamp examination and documented. These include:

1. *Lid margin changes.* These include thickening, hyperaemia, discharge, crusts, loss of eyelashes, distichiasis, telangiectasia, keratinisation, foaminess or frothing at the canthal angles and along the lid margin. The presence of scales along eyelash follicles should be noted (keeping in mind seborrhoeic dermatitis and Demodex infestation).

2. *Meibomian duct orifice changes.* These include changes in the orifice position with respect to the mucocutaneous junction, plugging with thick meibum (Fig. 6.3), and notching (indicating lost/atrophic glands).

3. *Meibum quality* is assessed by applying pressure on the eyelid margin with your finger or a cotton-tipped applicator, and noting the ease with which meibum is expressed and its texture.

4. *Ocular surface signs.* Ocular surface inflammation is manifested as conjunctival injection, chemosis, oedema, inferior limbal punctate epithelial erosions, peripheral/marginal keratitis, perilimbal neovascularisation, symblepharon formation, keratinisation of conjunctiva and cornea.

DIAGNOSTIC TESTS

Clinical diagnosis of MGD is evident from typical clinical features. Diagnostic tests are required for objectively evaluation of various parameters for instituting and monitory of treatment and also for research purposes.

Routine tests, should preferably be performed in the following sequence to minimise the extent to which one test may influence the other:

- Symptom questionnaire
- Measurement of blink rate, blink interval and blink dynamics
- Measurement of lower tear meniscus height
- Measurement of tear osmolarity
- Tear film break-up time (TBUT) and ocular protection index (OPI)
- Ocular surface fluorescein staining pattern
- Schirmer's test or alternative (phenol red thread test)
- Meibomian gland expressibility (MGE)

Specialised tests, particularly required for research purposes include:

- Interferometry—LipiView
- *In vivo* confocal microscopy (IVCM)
- Meibography

ROUTINE TESTS

1. Ocular surface disease index (OSDI)

Ocular surface disease index (OSDI) is determined with the help of a symptoms questionnaire. This questionnaire is a quick assessment of the symptoms of ocular irritation and how they are affecting the visual functions (photophobia, ocular/eyelid pain, blurring of vision, problems with reading/driving/watching TV) and quality of life of patients. The OSDI assesses the quality of life measures in such patients.

It is a 12-item questionnaire with 3 sub-scales: Ocular symptoms, vision-related function, and environmental triggers. Patients rate their responses on a 0–4 scale with 0 indicating 'none of the time' and 4 indicating 'all the time.' A final score is calculated, ranging from 0 to 100 with scores of 0–12 representing normal, 13–22 representing a mild dry eye disease, 23–32 representing a moderate dry eye disease, and greater than 33 representing a severe dry eye disease.

2. Measurement of blink rate, blink interval and blink dynamics

Normal blink rate is 15–20 times/minute and once every 3–4 seconds in most people. During reading or staring at a computer/cellphone screen, the blink rate reduces to 4.5 per minute, and the blink interval increases to 13.5 seconds. The examiner evaluates, by inspection on a slit-lamp, whether the upper lid closes onto the lower lid with a blink, notes the frequency of partial and complete blinks, the area of ocular surface (cornea and conjunctiva) that remains exposed with each complete blink. If the blink rate reduces and the *blinks are incomplete,* meibum will build up at the lid margin and inside the meibomian ducts, and meibomian glands will be used less over time. This could lead to meibomian gland atrophy, if unidentified.

3. Measurement of lower tear meniscus height

Measure lower tear meniscus height and its clarity. Normal lower tear meniscus is 1.00–2.00 mm. It can simply be measured by narrowing the vertical beam of a slit-lamp or by meniscometry (measurement of tear meniscus height, radius and cross-sectional area). A rotatable projection system with a target comprising black and white stripes is projected onto the lower central tear film meniscus. Images are recorded and then transferred to a computer for calculation of the radius of curvature.

4. Measurement of tear osmolarity

This measures the concentration of solutes/salts in the tear film. As the aqueous component of the tear film evaporates, the concentration of solutes (mainly salts) increases. This test has become a critical part of dry eye management. It requires

only a microlitre sample of tears (≤0.2 µl) which is collected by a micro-pen from the lateral canthal tear meniscus. It is placed in an instrument, called the osmometer, which gives the reading in a minute. The disadvantages are the need for an expensive equipment and its constant maintenance.

The osmolarity of both eyes is measured simultaneously; a difference of 8 mOsm/L or more between the two eyes is considered abnormal.

The osmolarity score of 300 mOsm/L or greater in the higher scoring eye is considered abnormal. From 300–320 mOsm/L, is graded as mild; from 320 to 340 mOsm/L, is graded as moderate; and greater than 340 mOsm/L, is graded as a severe dry eye disease.

5. Tear film break-up time (TFBUT)

It is assessed by applying a fluorescein strip to the conjunctiva and using a slit-lamp with cobalt blue illumination. Time is noted between the last blink and the appearance of a black island in the normal green fluorescence of the tear film, or the first dry spot on the cornea. The test is performed prior to the instillation of anaesthetic eye drops (as they are toxic to the corneal epithelium and produce dry spots). Normal TFBUT is 15–45 seconds. If it is >5 seconds, the patient is usually asymptomatic, but when it becomes less than 2 seconds, the patients are almost invariably symptomatic.

6. Ocular surface staining by fluorescein

It stains the corneal stroma under the desquamated epithelium but does not stain a dry spot (it becomes hydrophobic after losing its mucin coating), and appears as a blue spot in the uniform green fluorescence of the tear film. Fluorescein pools in the areas of epithelial erosions/thinning. The area of ocular surface stained should be noted as an interpalpebral staining is due to excess evaporation of aqueous while an inferior limbal staining is due to a toxic meibum production.

Early or mild cases of dry eye disease can be detected more easily with rose bengal or lissamine staining than with fluorescein as they stain dead/devitalised epithelial cells, healthy cells that have lost their mucin coating and the conjunctiva more intensely than the cornea.

7. Schirmer's test

It is of two types: Schirmer I and Schirmer II test. *Schirmer I test can be performed without the anaesthesia* in which it measures the basal tear secretion (which is from the accessory lacrimal glands) as well as the reflex secretion from the main lacrimal gland whose secretory activity is stimulated by the irritating nature of the filter paper. Less than 10 mm of wetting after 5 minutes is diagnostic of ATD. The test is relatively specific, but it is poorly sensitive.

Schirmer I test performed *after topical anaesthesia* measures only the basal lacrimal secretion. *It is highly specific and sensitive for a dry eye disease due to aqueous deficiency.* After instilling a topical anaesthetic, a thin strip of filter paper (5 × 35 mm) is placed in the inferior cul-de-sac in the lateral canthus. The excess tears should be wiped off prior to measuring the basal aqueous production. This distinguishes a dry eye due to less aqueous production from the one due to excess aqueous evaporation (due to MGD).

8. Meibomian gland expressibility score

Meibomian gland expressibility (MGE) is a clinical score that helps in assessing the severity of disease at initial presentation, and its improvement with treatment. The number of glands that can be expressed with mild pressure are counted (either with a cotton-tipped swab or a commercially available device). Five glands in the nasal, middle, and lateral thirds of the lower eyelid (total 15 glands) are expressed and scored at each visit. A score of 15 indicates almost all glands are expressible throughout the lower eyelid. A score of zero indicates a complete blockage of ducts and total absence of meibum. Patients with MGE score 0–5 are always symptomatic, while those with a score of 7 or more are usually asymptomatic. The quality of secretion expressed is also noted whether it is clear, opaque, vivid or cheesy.

Grading of MGD

Grade 0 MGD: Normal, clear meibum seen squirting out of the duct orifices with each blink, and can be easily expressed by lightly touching the lid margin.

Grade 1 MGD: Meibum looking opaque, viscous and needs pressure on the lid margin to be expressed. Patient is asymptomatic at this stage and has no corneal staining. MGE score is more than 7.

Grade 2 MGD: Meibum becomes very thick, cheese-like and expressed with difficulty; frothing may be noted at the lid margins (indicating lipid breakdown by bacterial lipases). Patient may be asymptomatic or may have slight discomfort of lid margins, mild conjunctival hyperaemia, mild corneal staining detected by fluorescein at the inferior limbus and an MGE score of 7.

Grade 3 MGD: Most of the ducts are plugged with thick meibum that cannot be expressed by pressure. MGE score is 3–7. Excessive frothing at the canthal angles or along the lid margins. Patient is moderately symptomatic with irritable lid margins, injected, watery eyes with inferior corneal and conjunctival staining.

Grade 4 MGD: Meibomian gland dropout is detected by the presence of notching at the grey line and by transillumination with a pen-light through everted eyelids or by infrared photography. MGE score is 0–3. At this stage, patient presents with severe dry eye symptoms and corneal staining.

SPECIALISED TESTS

1. Meibography

Meibography documents morphology and meibomian gland count in upper and lower lids by infrared camera

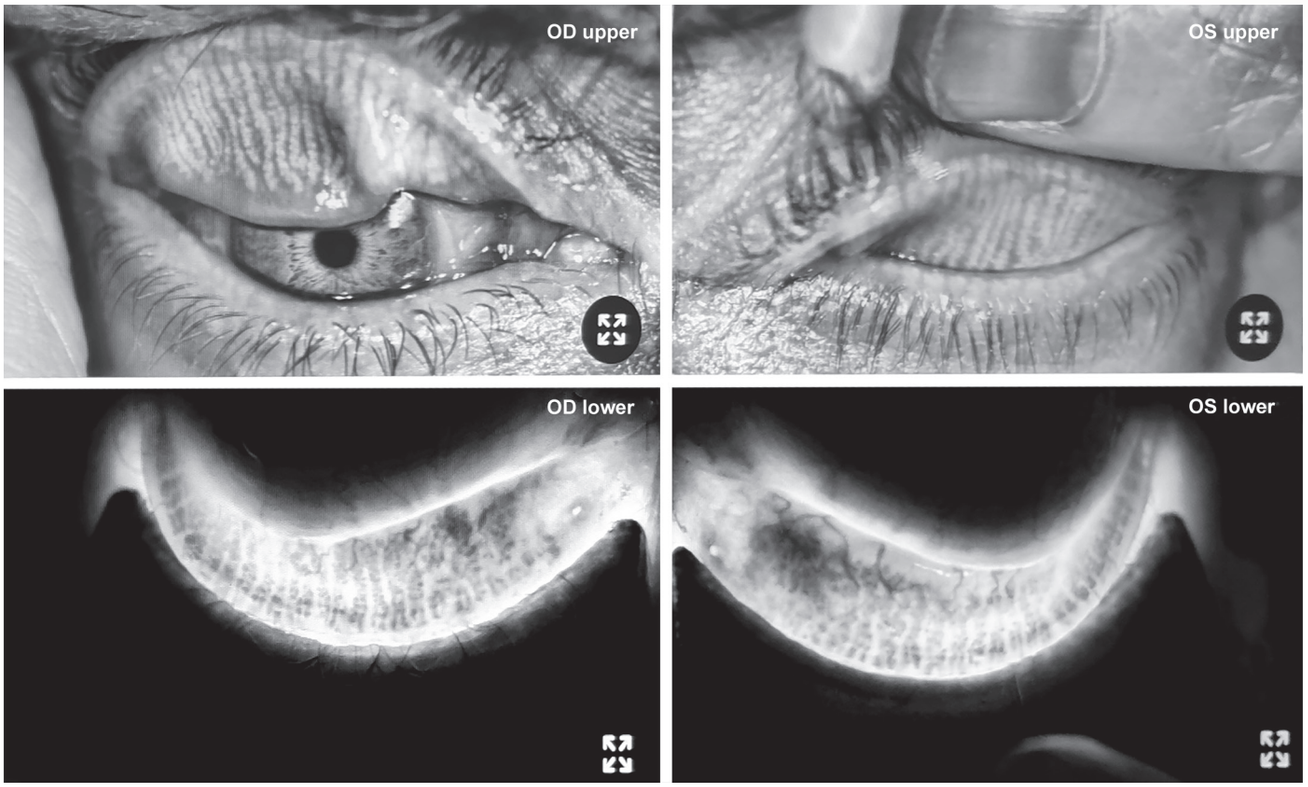

Fig. 6.6: Infrared camera (LipiView) meibography depicting normal meibomian glands in upper eyelids and some gland dropouts in lower eyelids.

(LipiView, Fig. 6.6), confocal microscopy, spectral-domain optical coherence tomography. Normal meibomian glands are long, vertical, extending from the lid margin to the end of tarsal plate. They become dilated and tortuous in early/mild disease. In disease of intermediate duration/moderate severity, the gland dropout increases with loss of identifiable gland architecture. In prolonged/severe disease, all glands are markedly shortened or absent.

2. Interferometry

Interferometry is required to analyse the lipid layer of tear film. Following techniques have been recommended over the period:

- ***Gearscope*** (Keeler Ltd, Windsor, UK) was the first device used for this purpose. It projects a cylindrical white fluorescent light on the tear film lipid layer (TFLL) and the interference images generated are used to evaluate the tear film.
- ***DR-1 Camera*** (Kowa, Nagoya, Japan) has also been derised to capture the tear film lipid layer and grade the severity of disease according to the *Yokoi dry eye grading system.*
- ***LipiView interferometer*** (Tear Science, Inc., Morrisville, NC, USA) is the most recent device, which uses white-light interferometry to form a pattern termed *interferogram*. This technique is used for:
  - *Lipid layer thickness measurement*, which is decreased in MGD.
  - *Dynamic lipid layer interference pattern (DLIP) test*. It measures the interference pattern of lipid layer on the control layer of tear film in between the blinks and provides a quantitative analysis of tear film lipid layer (TFLL).

3. *In vivo* confocal laser microscopy

In vivo confocal laser microscopy (IVCM) allows direct visualisation of the meibomian glands. It provides information about acinar density and diameter, secretion reflectivity and periglandular inflammation in patients with MGD. It can also be used to image the resident Demodex mites in the meibomian gland orifices.

MANAGEMENT OF MGD

PRINCIPLES OF MGD MANAGEMENT

MGD is an extremely common clinical entity and is the leading cause of an evaporative dry eye. It should be specifically looked for, and treated in its early stages even in an asymptomatic patient; if untreated, it progresses to meibomian gland atrophy and drop out which is an irreversible stage. The goal of therapy is to improve the

flow and the quality of meibum so as to restore the stability of the tear film. Since the therapy has to be continued for 2–3 months, patient education is mandatory to ensure compliance.

A. *Restore tear film stability*

1. *Relieve meibomian gland obstruction*
   - Hot compresses (>108.5°F)
   - Expression
     - Digital massage (patient)
     - Manual (eye care provider)
     - LipiFlow Thermal Pulsation System or equivalent
2. *Improve meibomian gland oils*
   - Fish oil supplementation
   - Systemic tetracycline or macrolide antibiotics
3. *Prevent desiccation*
   - Environmental manipulation
   - Blink exercises
   - Control atopy
   - Lipid layer supplementation
   - Aqueous layer supplementation
   - Correct eyelid and orbicularis muscle abnormalities

B. *Control ocular surface inflammation*

- Topical steroids
- Topical cyclosporine

C. *Reduce bacterial overgrowth*

- Eyelid hygiene
- Topical/systemic antibiotics

MANAGEMENT MEASURES

1. *Patient education.* As MGD is a chronic disease, in order to ensure compliance to the therapy, this is the most important part of treatment. Patients need to be educated regarding the nature of their disease, its prolonged therapy, the beneficial effects of diet containing omega-3 fatty acids (flaxseed oil, fish oil, and olive oil), how to combat environmental dryness/low humidity (by humidifiers in an air-conditioned rooms) and the drying effects of topical or systemic medications.

2. *Lid hygiene.* Lids should be scrubbed gently with a diluted baby shampoo, applied on cotton-tipped applicator, and rinsed with lukewarm water. This removes the toxic, foamy meibum and reduces the microbial load.

3. *Warm compresses* or application of heat is the mainstay of therapy. Normal meibum is liquid at body temperature, but denatured meibum becomes thick and hard. It blocks the duct openings as well as their entire lumen. Heat therapy helps in liquifying the thick meibum, but to be effective, the glands have to be consistently heated to at least 45°C (113°F). This can be done with application of warm wet towel or cotton pads, soaked in hot (not boiling) water; with the eyes closed, the hot towel is held onto the eyelids for 2 minutes. It is made wet again with hot water and the process repeated five times, so that total heat application is for 10 minutes. This needs to be done daily for at least a month. Heat masks are available commercially, or devices (LipiFlow, Thermal Pulsation System, MiBo Thermaflow) that can be applied to the lid margin and the emitted heat helps liquefy the meibum and massages it upwards towards the duct openings, from where it can easily be expressed.

4. *Gentle lid massage.* After the application of heat, upper eyelid should be massaged downwards with the fingers, while the lower lid massaged upwards to establish meibum flow out of the glands.

5. *Blinking exercises.* They help improve meibum flow and spread of the tear film over the ocular surface by contraction of pre-tarsal orbicularis and Riolan muscle. Patients should be advised to do 10 good blinks at a time; the eyes should be fully closed for 2 seconds, squeezed for another 2 seconds. This should be done for every hour of digital device use.

6. *Topical lubricants.* To relieve the symptoms, reduce tear film evaporation, stabilise lipids in the tear film and prevent aqueous evaporation; preservative-free preparations should be preferred.

7. *Topical or systemic antibiotics* to control infections: Low-dose oral doxycycline (50–100 mg/day for 6 weeks) helps to reduce inflammation in the eyelid tissue, it is anti-angiogenic and reduces lid swelling and hyperaemia, and helps in restoring healthy meibum secretion.

Topical tetracycline, erythromycin or azithromycin eye ointments have similar but more enhanced effects.

Topical cyclosporin eye drops and tacrolimus ointment are specific immunomodulators that affect primarily T lymphocytes. They are found to be highly effective in reducing inflammation of the meibomian glands and reduce their plugging and dysfunction.

8. *Treating Demodex mite infestation.* The aim of therapy is to reduce the number of Demodex mites; total eradication is not required as it is a part of the normal flora of the skin. This can be achieved by a combination of lid scrubs (scrubbing the eyelids twice daily with a baby shampoo diluted with water to yield a 50% dilution and applying an antibiotic ointment at night until resolution of symptoms) and removal of the eyelash collarettes with the use of a cotton-tipped applicator and lid foam. Demodex mites are resistant to a wide range of antiseptic agents including 10% povidone-iodine, 75% alcohol and erythromycin. The most effective and commonly used treatment is tea tree oil. Chemically, it is Terpinen-4-ol—a terpene that has an antimicrobial, antifungal, and antiseptic properties. Many commercially available products contain tea tree oil like shampoos, soaps, ointment, skin creams. Hypochlorous acid and mercury oxide 1% ointment are also effective. Patients should be instructed to avoid oil-based facial cleansers and greasy makeup as they can provide further 'food' for the mites. They should discard the previously used make-up, use hot water to wash clothes, and a hot dryer to dry them.

9. *Intraductal probing.* This can clear the obstruction of ducts and allows the meibum to flow, thereby reducing the intraductal pressure (IDP), inflammation, lid congestion and improvement of symptoms.

10. *Intense pulsed light (IPL) therapy.* This also liquifies the meibum and improves its drainage by delivering a combination of heat and gentle pressure to the eyelids. It is an in-office therapy and requires 1–2 sessions.

Staged treatment algorithm

The International Workshop on MGD recommended a Staged Treatment Algorithm, depending upon the grade of MGD:

Grade 1

i. Patient education regarding MGD, diet, environment.
ii. Lid hygiene
iii. Warm compresses

Grade 2

i. Advise patient to improve humidity and increase dietary intake of omega-3 fatty acids, or dietary supplements containing conjugated linoleic acid (vegetables, fruits, nuts, grains and seeds; linseed oil) or docosahexaenoic acid (DHA) 1000 mg daily.
ii. Warm compresses followed by firm lid massage
iii. Blinking exercises
iv. Topical lubricants
v. Topical tetracycline/azithromycin eye ointment massaged to lid margin.
vi. Oral tetracycline, 50–100 mg or azithromycin, 250 mg daily for a month.

Grade 3: All in Grade 2 plus:

i. Add anti-inflammatory therapy for dry eyes (topical cyclosporin, tacrolimus)
ii. Ductal probing.

Grade 4: All of Grade 3 therapy.

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Chapter

7

Xerophthalmia

Chapter Outline

GENERAL CONSIDERATIONS
- Definition
- Prevalence

ETIOPATHOGENESIS
- Vitamin A and its metabolism

CLINICAL MANIFESTATIONS AND CLASSIFICATION
- WHO classification

DIAGNOSIS
- Clinical diagnosis
- Laboratory investigations

TREATMENT AND PREVENTION

Treatment
- Vitamin A therapy
- Treatment of underlying conditions
- Local ocular therapy

Prevention
- Prolongation of breast-feeding and early food supplementation
- Food fortification with vitamin A
- Prophylactic vitamin A supplementation

GENERAL CONSIDERATIONS

DEFINITION

"Xerophthalmia" (Greek word for dry eyes) refers to an array of ocular manifestations caused due to vitamin A deficiency. As there is depletion of vitamin A stores in the body, manifestations occur with increasing severity in the form of night blindness, conjunctival xerosis, Bitot's spot, corneal xerosis, and corneal ulceration/keratomalacia. All of them usually respond rapidly to vitamin A therapy, the milder ones often clearing without sequelae while corneal scarring and opacification occurs when there is loss of deep corneal tissue from ulceration.

PREVALENCE

Xerophthalmia although can occur in any age group, it is especially prevalent in preschool-age children, adolescents and pregnant women owing to their greater vitamin A requirements for growth. Children are also at higher risk of intestinal infestations and infections, which may impair the absorption of vitamin A thereby causing deficiency. In India, prevalence of subclinical vitamin "A" deficiency (VAD) ranges from 31 to 57% among preschool children and a further 1 to 2% of children suffer from clinical VAD.

ETIOPATHOGENESIS

- Xerophthalmia is primarily caused by depletion of vitamin A in the body, it is especially prevalent in infants suffering from protein energy malnutrition (PEM).
- In addition, it is seen in association with certain systemic diseases such as Sjögren's syndrome, SLE, rheumatoid arthritis, scleroderma, sarcoidosis, amyloidosis and hypothyroidism.
- Certain medications such as antihistamines, nasal decongestants, tranquillizers and anti-depressants are associated with milder forms of xerophthalmia.

VITAMIN A AND ITS METABOLISM

Vitamin A, or retinol, is a fat-soluble vitamin required for gene expression, epithelial cell differentiation, normal growth, photopic vision and immunity. It is found in liver (particularly fish liver), egg yolk and dairy products. Carotenoids and potential provitamin A precursors that can be converted to retinol in the wall of the gut, are present in green leafy vegetables, red palm oil and yellow fruits. The relative biological values of these various substances were formerly expressed in international units (IU) of vitamin A activity, 1 IU being equivalent to 0. 3 µg of retinol,

0.55 µg of retinyl palmitate, 0.6 µg of 13-carotene, and 1.2 µg of other provitamin A carotenoids. 90% of ingested retinol is absorbed in the small intestine and transported, in association with chylomicrons, to the liver, where it is stored as retinyl palmitate. When needed, it is released into the bloodstream as retinol in combination with retinol-binding protein (RBP), a specific carrier protein elaborated by the liver. In the serum RBP—retinol complex combines with transthyretin, a large protein also synthesized in the liver. The retinol is then removed from the serum and utilized by target cells, such as retinal photoreceptors and epithelial linings throughout the body. Specific receptors exist on the cell surface and nucleus for the vitamin A complex or its active metabolites, particularly retinoic acid. Liver stores form an important buffer against variations in the intake of vitamin A and provitamin A carotenoids. When intake surpasses requirements, the excess is stored in the liver. If intake is less than this amount, liver stores are drained to maintain serum retinol at a normal level (well above 0.7 µmol/litre or 200 µg/litre). If intake remains low for prolonged periods there is depletion of liver stores followed by decrease in serum retinol levels resulting in impaired cellular function, abnormal differentiation (e.g. xerophthalmia) and other physiological consequences and clinical manifestations of deficiency (e.g. anaemia, impaired resistance to infection).

CLINICAL MANIFESTATIONS AND CLASSIFICATION

The first symptom of vitamin A deficiency is characterised by impaired adaptation to the dark, which can begin when serum retinol concentrations fall below 1.0 µmol/L, but occurs more often when they fall below 0.7 µmol/L. Xerophthalmia occurs when serum retinol concentrations fall below 0.35 µmol/L. Night blindness generally responds rapidly to vitamin A therapy, within 1–2 days, and prompt treatment of xerophthalmia generally results in the full preservation of eyesight up to the stage of corneal xerosis.

WHO CLASSIFICATION

Xerophthalmia manifestations have been classified by WHO (1982) into various categories as per Table 7.1.

TABLE 7.1: WHO classification of xerophthalmia signs

Classification	*Ocular signs*
XN	Night blindness
X1A	Conjunctival xerosis
X1B	Bitot's spots
X2	Corneal xerosis
X3A	Corneal ulceration/keratomalacia involving one-third or less of cornea
X3B	Corneal ulceration/keratomalacia involving one-half or more of cornea
XS	Corneal scar
XF	Xerophthalmic fundus

XN: Night blindness

Retinol is essential for the elaboration of rhodopsin (visual purple) by the rods, the sensory receptors of the retina responsible for vision under low levels of illumination. Vitamin A deficiency can interfere with rhodopsin production, impair rod function, and result in night blindness. Night blindness is generally the earliest manifestation of vitamin A deficiency. When mild, it may become apparent only after a photic stress, such as flying a kite on a sunny day. It takes some time for the eyes to adjust from brightly lit areas to dim ones. It is also associated with decrease in contrast vision. Night blindness responds rapidly, usually within 24–48 hours, to vitamin A therapy. In some instances term 'chicken eyes' has been used to describe night blindness as chicken lack rods and hence are night blind.

X1A, X1B: Conjunctival xerosis and Bitot's spot

Vitamin A deficiency causes alterations in epithelial architecture termed "keratinizing metaplasia". The columnar epithelium of the conjunctiva is transformed to the stratified squamous type, with a resultant loss of goblet cells, formation of a granular cell layer and keratinization of the surface. The distended squamous cells have large, open nuclei with prominent nucleoli. Clinically, this causes marked dryness of the conjunctiva which appears roughened with fine droplets or bubbles on the surface. These changes may not be seen in the presence of tears but as the tears drain off the affected area will emerge like "sandbanks at receding tide" which is best detected with an oblique illumination. Conjunctival xerosis first appears in the temporal quadrant, as an oval or triangular patch adjacent to the limbus in the interpalpebral fissure, usually in both eyes. In some individuals keratin and saprophytic bacilli accumulate on the xerotic surface, giving it a foamy or cheesy appearance. Such lesions are known as Bitot's spots. The overlying material can be easily wiped off and the amount can vary from day to day. With increase in deficiency of vitamin A, similar, though less prominent lesions are seen in the nasal quadrant.

Generalized conjunctival xerosis, involving the inferior and/or superior quadrants, suggests advanced vitamin A deficiency. The entire conjunctiva appears dry, roughened, and corrugated, sometimes skin like. There may be prominent conjunctival thickening and folds (Fig. 7.1). This is an advanced lesion, almost always accompanied by gross corneal involvement. Isolated, usually temporal, patches of conjunctival xerosis or Bitot's spot are sometimes encountered in the absence of active vitamin A deficiency. The affected individuals are usually of school-age or older and may have a history of previous bouts of night blindness or xerophthalmia. In most instances, these patches represent

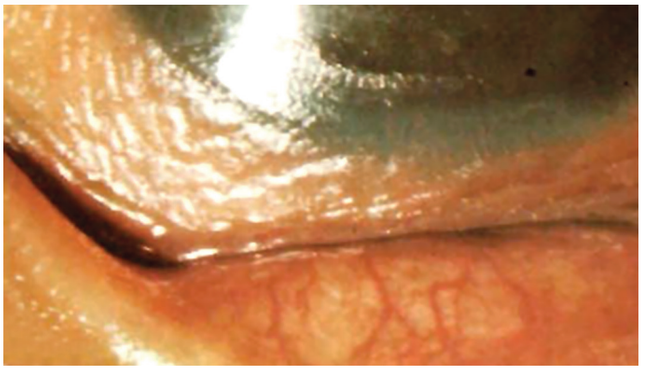

Fig. 7.1: Conjunctival xerosis (X1A).

persistent areas of squamous metaplasia-induced during a prior episode of vitamin A deficiency. The only certain means of distinguishing active from inactive lesions is to observe their response to vitamin A therapy. Active conjunctival xerosis and Bitot's spot begin to resolve within 2–5 days. Most will disappear within 2 weeks, though a significant proportion of temporal lesions may persist for months in shrunken form.

X2: Corneal xerosis

Corneal changes begin early in vitamin A deficiency, long before they can be seen with the naked eye. Many children with night blindness (without clinically evident conjunctival xerosis) have superficial punctate lesions over inferior nasal aspects of cornea that stain brightly with fluorescein. With more severe disease the punctate lesions become more numerous and spread upwards over the central cornea, and the corneal stroma becomes edematous (Fig. 7.2). Clinically, the cornea develops classical xerosis, a hazy, lustreless, dry appearance, first apparent near the inferior limbus. Thick, keratinized plaques resembling Bitot's spot may form, on the corneal surface. These are often dense in the interpalpebral zone. With treatment, these corneal plaques peel off, sometimes leaving a superficial erosion which quickly heals. Corneal xerosis responds within 2–5 days to vitamin A therapy, the cornea regaining its normal appearance in 1–2 weeks.

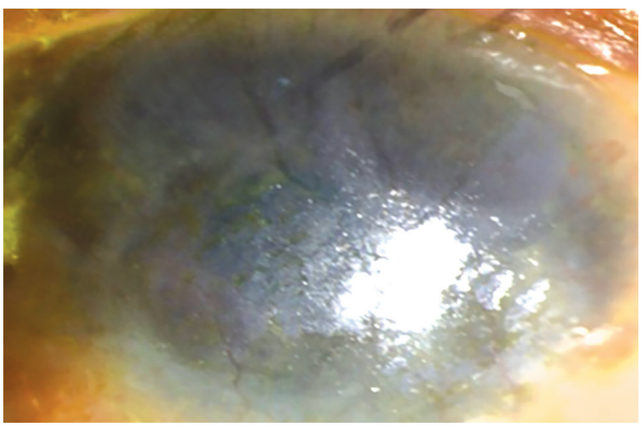

Fig. 7.2: Corneal xerosis (X2).

X3A, X3B: Corneal ulceration/keratomalacia

Ulceration/keratomalacia indicates permanent destruction of part or all of the corneal stroma, resulting in permanent structural alteration. Ulcers are classically round to oval "punched-out" defects, as if a trephine or cork-borer had been applied to the eye (Fig. 7.3). The surrounding cornea is generally xerotic but otherwise clear, and typically lacks the grey, infiltrated appearance of ulcers of bacterial origin. There may be more than one ulcer. Small ulcers are almost invariably confined to the periphery of the cornea, especially its inferior and nasal aspects. The ulceration may be shallow, but is commonly deep. Perforations become plugged with iris, thereby preserving the anterior chamber. Histologically, the sharply demarcated area of stromal necrosis is covered by keratinized epithelium.

With therapy, superficial ulcers often heal with surprisingly little scarring; deeper ulcers, especially perforations, form dense peripheral adherent leukomas. Localized keratomalacia is a rapidly progressive condition affecting the full thickness of the cornea. It first appears as an opaque, grey to yellow mound or outpouching of the corneal surface. In more advanced disease the necrotic stroma sloughs, leaving a large ulcer or descemetocele. As with smaller ulcers, these are usually peripheral and heal as dense, white, adherent leukomas. Ulceration/keratomalacia involving less than one-third of the corneal surface (X3A) generally spares the central pupillary zone; prompt therapy ordinarily preserves useful vision. More widespread involvement (Fig. 7.4) (X3B), especially generalized liquefactive necrosis, usually results in perforation, extrusion of intraocular contents, and loss of the globe. Prompt therapy may still save the other eye and the child's life. It is not always possible to distinguish cases

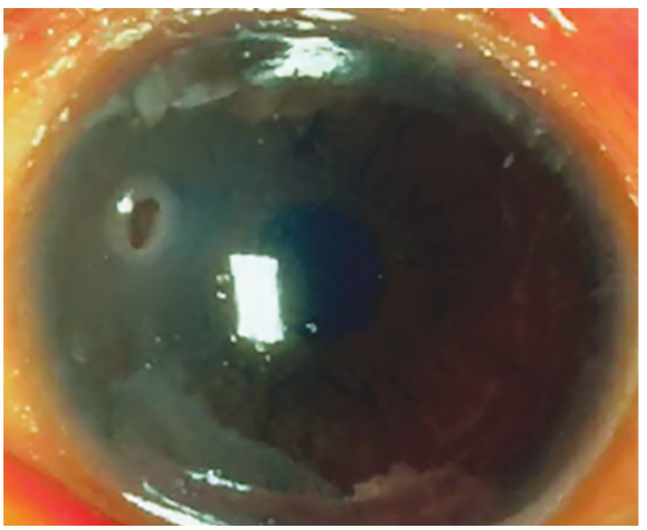

Fig. 7.3: Corneal ulceration (X3A).

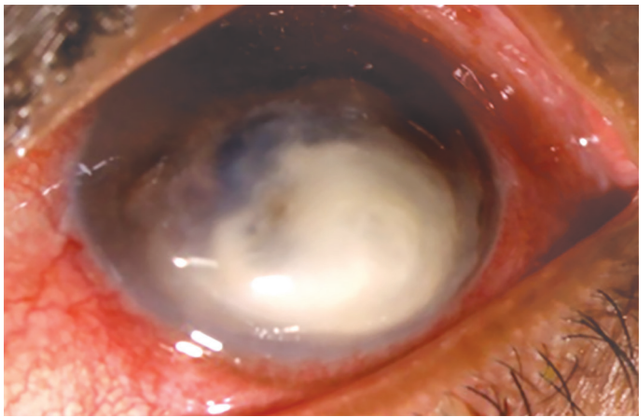

Fig. 7.4: Corneal ulceration (X3B).

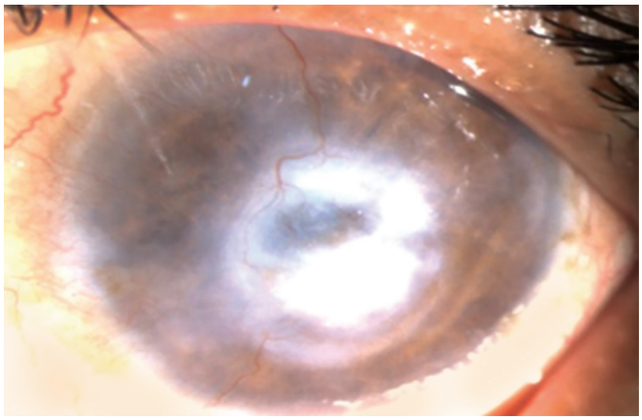

Fig. 7.5: Corneal scar (XS).

of ulceration/necrosis due to vitamin A deficiency from those due to bacterial or fungal infections. The most obvious reason is that vitamin A-related lesions can become secondarily infected. In addition, however, once ulceration/keratomalacia occurs, the conjunctiva usually becomes inflamed, and for reasons that are not well understood, inflammation commonly masks or reverses conjunctival xerosis. Examination of the other, unulcerated eye, may then reveal the true nature of the problem although not always. When vitamin A status deteriorates precipitously, as occurs with measles, severe gastroenteritis, or kwashiorkor in children previously in borderline vitamin A balance-corneal necrosis can precede the appearance of night blindness or conjunctival xerosis. In such instances it is safest to assume that both vitamin A deficiency and infection are present and the child should be treated accordingly.

Children suffering from forms of the disease destructive to the cornea are usually younger (often less than 1 year of age), more severely malnourished, and more deficient in vitamin A. History of a recent precipitating event (pneumonia, measles, gastroenteritis, tuberculosis, etc.) is common, and the mortality is often quite high (20–50%).

XS: Scars

Healed sequelae of prior corneal disease related to vitamin A deficiency include opacities or scars of varying density (nebula, macula, leukoma) (Fig. 7.5), weakening and outpouching of the remaining corneal layers (staphyloma, and descemetocele) and, where loss of intraocular contents had occurred, phthisis bulbi, a scarred shrunken globe. Such end-stage lesions are not specific for xerophthalmia and may arise from numerous other conditions, notably trauma and infection.

XF: Xerophthalmic fundus

It is characterized by small white retinal lesions which may be accompanied by constriction of the visual fields and will largely disappear within 2–4 months of vitamin A therapy.

DIAGNOSIS

Clinical diagnosis of xerophthalmia is based on clinical manifestations.

Laboratory investigations are rarely required but may be useful in few instances when there is doubt.

Serum retinol study is an expensive but direct measure to assess vitamin A deficiency. A value of <1.0 mg/dl indicates gross deficiency and >2.0 mg/dl indicates adequate vitamin A in the body. A value of <0.7 mg/L in children younger than 12 years is considered low.

Total retinol binding protein (RBP) is a less costly and easier to perform immunologic assay. Although it is a more stable compound than retinol, its measure is less accurate as it is affected by serum protein concentration and also zinc deficiency interferes with production of RBP.

TREATMENT AND PREVENTION

TREATMENT

1. Vitamin A therapy: Xerophthalmia is a medical emergency, requiring prompt administration of massive amounts of vitamin A. Oral administration is just as effective as parenteral administration.

i. ***All patients above the age of 1 year (except woman of reproductive age should be*** administered 110 mg oil- or water-miscible retinol palmitate or 66 mg retinol acetate (200,000 IU vitamin A) by mouth immediately upon diagnosis and repeat the dose of the following days.

- *An additional dose* should be given 1–2 weeks later to boost liver reserves.
- Because children with severe protein-energy deficiency handle a massive dose poorly, they should receive an additional dose, every 2 weeks, until protein status improves.
- *For children unable to swallow, or suffering from repeated vomiting or profuse diarrhoea*, an intramuscular injection of 55 mg *water-miscible* retinol palmitate (l00,000 IU) should be substituted for the first oral dose. Oil-miscible

preparations should never be given by injection because they are poorly absorbed from the injection site.

ii. ***For children less than 12 months*** of age the doses should be reduced by half.

iii. ***Women of reproductive age*** (pregnant or otherwise). Special attention is required while providing vitamin A supplementation to women of reproductive age because of the potential teratogenic effects of very high dose retinol if given early in pregnancy. Women of reproductive age with night blindness or Bitot's spots should be treated with a daily oral dose of 5,000–10,000 IU of vitamin A for at least 4 weeks. Such a daily dose should never exceed 10,000 IU, although a weekly dose not exceeding 25,000 IU may be substituted. All women of reproductive age, whether or not pregnant, who exhibit severe signs of xerophthalmia (i.e. acute corneal lesions) should be treated with three-dose treatment.

2. Treatment of underlying conditions: Malnutrition to be corrected by including plenty of milk, butter, dark green leafy vegetables, carrots, orange, cod-liver oil in the diet.

3. Local ocular therapy: Topical lubrication and antibiotics to be used as adjunctive measures.

Note: Vitamin A supplementation in excess can result in toxicity which is characterised by dermatitis with xanthosis cutis, hepatosplenomegaly, bone pain and increased risk of fracture and pseudotumour cerebri.

PREVENTION

I. Prolongation of breast-feeding and early food supplementation (preferably by 6 months of age) with tasty, easily digested provitamin A-rich fruits (e.g. mango and papaya) or appropriately prepared dark-green leafy vegetables are likely to have a significant impact. Dark-green leafy vegetables are often the least expensive and most widely and consistently available source of vitamin A activity. The same amount of vitamin A is obtained from 68 g of spinach as from 63 g of liver, 227 g of hens' eggs, 1.7 litres of whole cow's milk, or 6 kg of beef or mutton. The recommended dietary allowance (RDA) for children, adults and lactating women is 400 µg, 900 µg and 1200 µg respectively. *This is the best long-term approach.*

II. Food fortification with vitamin A serves as *medium term approach* for preventing vitamin A deficiency, where people cannot afford vitamin A-rich foodstuffs. Foodstuffs commonly used by poor and middle class population which can be fortified are:

- Vanaspati ghee or oil used to cook food.

III. Prophylactic vitamin A supplementation periodically serves as *short-term approach* for preventing vitamin A deficiency, especially in poor economic strata/population. This approach is mostly in vogue in Asian and African countries.

WHO recommended universal distribution of schedule of prophylactic vitamin A supplementation is as follows (Table 7.2):

1. *Newborn:* 27.5 mg retinol palmitate at birth (50,000 IU)
2. *Infant 6–12 month and older children who weigh less than 8 kg:* 100,000 IU orally every 4–6 months
3. *Children over 2 years and under 6 years of age:* 200,000 IU orally every 4–6 months.
4. *Women of childbearing age:* 165 mg retinol palmitate in 1 month (300,000 IU) of giving birth.
5. *Pregnant and lactating women:* 2.75 mg retinol palmitate every day (5000 IU) or 11 mg retinol palmitate once every week (20,000 IU).

Table 7.2 summarises prophylaxis schedule of vitamin A to prevent debilitating effects of xerophthalmia.

TABLE 7.2: Vitamin A prophylaxis schedule

Newborn	27.5 mg retinol palmitate at birth (50,000 IU)
Children <12 months	55 mg retinol palmitate once every 4–6 (100,000 IU) months
Children >12 months	110 mg retinol palmitate once every 4–6 (200,000 IU) months
Women of child-bearing age	165 mg retinol palmitate within 1 month (300,000 IU) of giving birth
Pregnant and lactating women	2.75 mg retinol palmitate every day (5000 IU) or 11 mg retinol palmitate once every week (20,000 IU)

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Chapter

8

Pterygium and Conjunctival Degenerations

Chapter Outline

PINGUECULA
- Etiology
- Pathology
- Clinical features
- Complications
- Treatment

PTERYGIUM
- Etiology
- Pathology
- Clinical features
- Treatment

Concretions
- Etiology
- Clinical features
- Treatment

AMYLOID DEGENERATION OF CONJUNCTIVA
- Etiology
- Clinical features
- Treatment

PINGUECULA

Pinguecula is an extremely common degenerative condition of the conjunctiva. It is characterised by formation of a yellowish white patch on the bulbar conjunctiva near the limbus. This condition is termed pinguecula, because of its resemblance to fat, which means pinguis.

Etiology of pinguecula is not known exactly. It has been considered as *an age-change*, occurring more commonly in persons chronically exposed to strong sunlight, dust and wind. Its predominant nasal location has been presumed to be due to reflection of light by the nose to the nasal conjunctiva. It has been suggested that the effect of ultraviolet light may be mediated by mutations in the *p53* gene. Earlier it was considered a precursor of pterygium. However, currently it is suggested that pinguecula does not progress to pterygium and that the two are distinct disorders.

Pathology

There is an elastotic degeneration of collagen fibres of the substantia propria of conjunctiva, coupled with deposition of basophilic elastotic fibres and granular deposits in the substance of conjunctiva. Cornea is never involved.

Clinical features

Pinguecula is a bilateral, usually stationary condition, presenting as yellowish white triangular patch near the limbus (Fig. 8.1). Apex of the triangle is away from the cornea. It affects the nasal side more commonly than the temporal side. When conjunctiva is congested, it stands out as an avascular prominence.

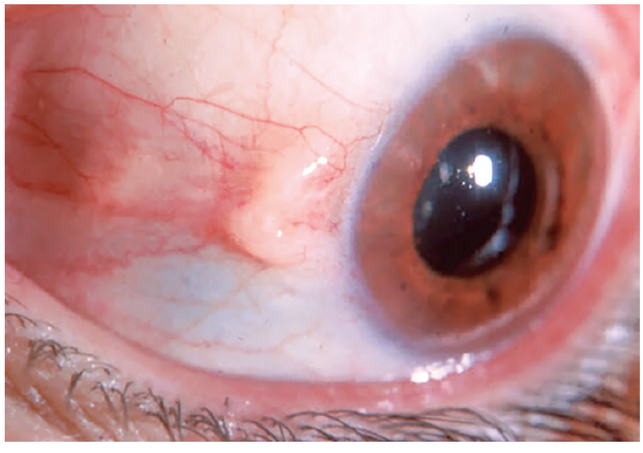

Fig. 8.1: Pinguecula.

Complications

Complications of pinguecula include its inflammation, intraepithelial abscess formation and rarely calcification and doubtful conversion into pterygium.

Differential diagnosis

Pinguecula is usually differentiated from:

- Diagnosis is obvious due to its typical appearance
- However, it needs to be differentiated from *conjunctival intraepithelial neoplasia*
- Gaucher's disease type I.

Treatment

In routine no treatment is required for pinguecula. However, when cosmetically unaccepted and if so desired, it may be excised. When inflamed it is treated with topical steroids.

PTERYGIUM

Pterygium (L. Pterygion = a wing) is a wing-shaped fold of conjunctiva encroaching upon the cornea from either side within the interpalpebral fissure. Recent evidence suggest that pterygium is a proliferative lesion rather than a degenerative condition characterised by proliferation of fibrovascular tissues, inflammatory infilteration, fibrosis, angiogenesis and breakdown of extracellular matrix.

ETIOLOGY

Etiology of pterygium is not definitely known. But the disease is more common in people living in hot climates. Therefore, the most accepted view is that it is a response to prolonged effect of environmental factors such as exposure to sun (ultraviolet rays), dry heat, high wind and abundance of dust.

Ultraviolet-induced damage to limbal stem cells and activation of matrix metalloproteinase is considered the basic mechanism for causation of pterygium.

Hereditary factors have been implicated for prediction. Molecular genetic alterations reported include loss of heterozygosity (LOH), and point mutations of proto-oncogeners.

Ocular surface markers, such as overexpression of defensins, phospholipases D3 and upregulation of growth factors, have also been implicated in pathogenesis of pterygium.

PATHOLOGY

Pathologically pterygium is a degenerative and hyperplastic condition of conjunctiva. The subconjunctival tissue undergoes elastotic degeneration and proliferates as vascularised granulation tissue under the epithelium, which ultimately encroaches the cornea. The corneal epithelium, Bowman's layer and superficial stroma are often destroyed.

- *Abnormal elastic fibres* form the significant part of pterygium tissue. These are called elastotic fibres, as they do not degrade with elastase.
- *Fibroblasts* are also seen in abundance in the vicinity of elastodysplasia, indicating probably an actinic-induced damage.

CLINICAL FEATURES

Demography

- *Age*: Usually seen in old age.
- *Sex*: More common in males doing outdoor work than females.

  More common nasal occurrence has been postulated to be due to reflection of ultraviolet rays from the nose in this region.
- *Laterality*: It may be unilateral or bilateral. Usually present on the nasal side but may also occur on the temporal side.
- *Region:* Occur more frequently and most severely in hot and dry climatic region, i.e. in tropical areas near the equator and to a lesser and milder degrees in cooler climates.
- *Profession:* Outdoor workers are exposed to sunlight, especially those working in the setting of highly reflective surfaces are more prone. Both blue and ultraviolet rays/radiation have been implicated to cause it.

Symptoms

- *Cosmetic intolerance* may be the only issue in otherwise asymptomatic condition in early stages.
- *Foreign body* sensation, irritation and mild watering may be experienced by many patients.
- *Defective vision* occurs when it encroaches the pupillary area or due to corneal astigmatism induced by fibrosis in the regressive stage.
- *Diplopia* may occur occasionally due to limitation of ocular movements.

Signs

Pterygium presents as a triangular fold of conjunctiva encroaching on the cornea in the area of palpebral aperture usually on the nasal side (Fig. 8.2) but may also occur on the temporal side. Very rarely, both nasal and temporal sides are involved (*primary double pterygium*).

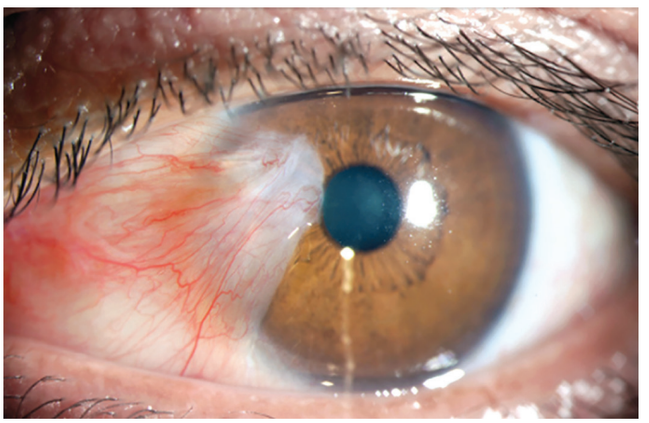

Fig. 8.2: Pterygium.

Parts of a fully-developed pterygium are as follows (Fig. 8.2):

- *Head:* Apical part present on the cornea, as elevated whitish mass.
- *Neck:* Constricted part present in the limbal area.
- *Body:* Scleral part, extending between limbus and the canthus.
- *Cap:* Semilunar whitish infiltrate present just in front of the head.

Types. Depending upon the progression it may be progressive or regressive pterygium.

- *Progressive pterygium* is thick, fleshy and vascular with a few whitish infiltrates in the cornea, in front of the head of the pterygium known as *Fuch's spots* or *islets of Vogt* also called cap of pterygium.
- *Regressive pterygium* is thin, atrophic, attenuated with very little vascularity. There is no cap, but deposition of iron (*Stocker's line*) may be seen sometimes, just anterior to the head of pterygium. Ultimately, it becomes membranous but never disappears.
- *Corneal astigmatism* is an important sign of pterygium and varies depending upon its extent and severity, usually with-the-rule astigmatism is induced. However, obliquely against-the-rule and irregular astigmatism may also occur.
- *Anterior segment optical coherence tomography (ASOCT)* examination reveals pterygium as a wedge-shaped mass of tissue separating the corneal epithelium from the Bowman's membrane. The Bowman's membrane is often seen as wavy, interspersed and destroyed. ASOCT also reveals stellate mass of subepithelial pterygium tissue beyond the clinically seen margin.

COMPLICATIONS

- *Cystic degeneration and infection* are of infrequent occurrence.
- *Neoplastic change* to epithelioma, fibrosarcoma or malignant melanoma, may occur rarely.

DIFFERENTIAL DIAGNOSIS

Pterygium must be differentiated from pseudopterygium. Pseudopterygium is a fold of bulbar conjunctiva attached to the cornea. It is formed due to adhesions of chemosed bulbar conjunctiva to the marginal corneal ulcer. It usually occurs following chemical burns of the eye. Differences between pterygium and pseudopterygium are given in Table 8.1.

TREATMENT

Surgical excision is the only satisfactory treatment.

Indications of pterygium surgery are:

- *Cosmetic disfigurement* is the common indication
- *Visual impairment* due to significant regular or irregular astigmatism.
- *Continued progression* threatening to encroach onto the pupillary area (once the pterygium has encroached pupillary area, wait till it crosses on the other side).
- *Diplopia* due to interference in ocular movements.
- *Atypical appearance* such as possible dysplasia.

Recurrence of the pterygium after surgical excision is the main problem (30–50%). Therefore, primary goal of treatment is to excise the pterygium and prevent recurrence. Following measures are recommended to reduce recurrences:

- *Surgical excision with free conjunctival limbal autograft* (CLAU) taken from the same eye or other eye is presently the preferred technique.
- *Surgical excision with amniotic membrane graft and mitomycin C* (MMC) (0.02%) application may be required in recurrent pterygium or when dealing with a very large pterygium.
- *Surgical excision with lamellar keratectomy and lamellar keratoplasty* may be required in deeply infiltrating recurrent recalcitrant pterygia.
- *Old methods to prevent recurrence* (not preferred now) included transplantation of pterygium in the lower fornix (McRaynold's operation) and postoperative use of beta-irradiations.

Surgical technique of pterygium excision

1. *After topical anaesthesia*, eye is cleansed, draped and exposed using universal eye speculum.
2. *Head of the pterygium is lifted* and dissected off the cornea very meticulously (Fig. 8.3A).
3. *Main mass of pterygium is then separated* from the sclera underneath and the conjunctiva superficially.
4. *Pterygium tissue is then excised* taking care not to damage the underlying medial rectus muscle (Fig. 8.3B).

TABLE 8.1: Differences between pterygium and pseudopterygium

	Pterygium	*Pseudopterygium*
1. Etiology	Degenerative process	Inflammatory process
2. Age	Usually occurs in elder persons	Can occur at any age
3. Sex	More common in male	Equally common
4. Site	Always situated in the palpebral aperture	Can occur at any site
5. Stages	Either progressive, regressive or stationary	Always stationary
6. Probe test	Probe cannot be passed underneath	A probe can be passed under the neck

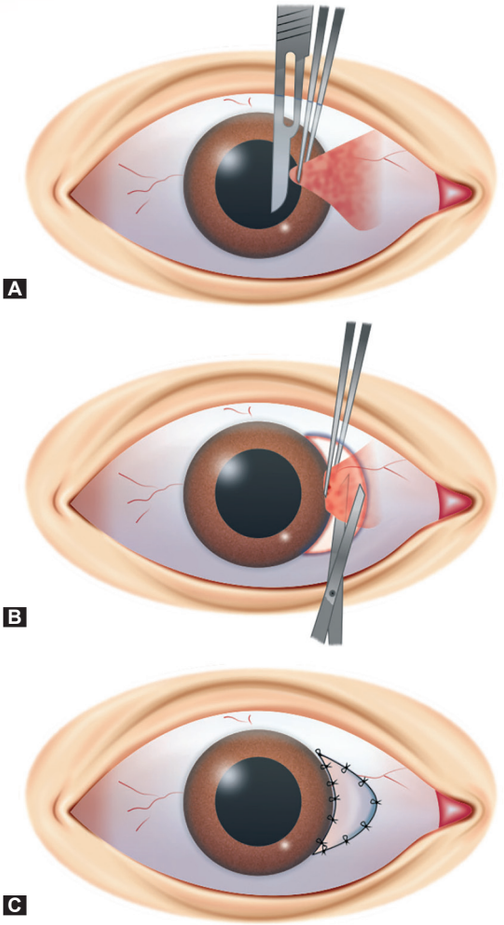

Fig. 8.3: Surgical technique of pterygium excision. A, Dissection of head from the cornea; B, Excision of pterygium tissue under the conjunctiva; C, Conjunctival limbal autograft after excising the pterygium.

5. *Haemostasis* is achieved and the episcleral tissue exposed is cauterised thoroughly.
6. *Conjunctival limbal autograft (CLAU)* transplantation to cover the defect after pterygium excision (Fig. 8.3C). It is the latest and most effective technique in the management of pterygium. Use of fibrin glue to stick the autograft in place reduces operating time as well as discomfort associated with the sutures.

Note: For further details, *see* Chapter 8.

CONCRETIONS

Etiology. Concretions are formed due to accumulation of inspissated mucus and dead epithelial cell debris into the conjunctival depressions called *loops of Henle*. They are commonly seen in elderly people in a degenerative condition and also in patients with scarring stage of trachoma. The name concretion is a misnomer, as they are not calcareous deposits.

Clinical features

- *Locations.* Concretions are seen on palpebral conjunctiva, more commonly on upper than the lower. They may also be seen in lower fornix.
- *Appearance.* These are yellowish white, hard looking, raised areas, varying in size from pin point to pin head (Fig. 8.4).
- *Symptoms.* Being hard, they may produce foreign body sensations and lacrimation by rubbing the corneal surface. Occasionally, they may even cause corneal abrasions.

Treatment. It consists of their removal with the help of a hypodermic needle under topical anaesthesia.

AMYLOID DEGENERATION OF CONJUNCTIVA

Etiology

Conjunctival amyloid, though rare, is reported to occur in two forms:

- *Primary conjunctival amyloid* is associated with deposition of light-chain immunoglobulin by the monoclonal B cells and plasma cells.
- *Secondary conjunctival amyloid* may occur secondary to systemic diseases or secondary to chronic conjunctival inflammations.

CLINICAL FEATURES

- Deposition of yellowish, well-demarcated, irregular amyloid material in the conjunctiva with superior fornix and tarsal conjunctiva being more commonly involved areas.
- Subconjunctival haemorrhages, recurrent may be associated with amyloid deposition in blood vessels.
- Amyloid involving stain of eyelid may be associated in patients with conjunctival amyloid secondary to systemic diseases.

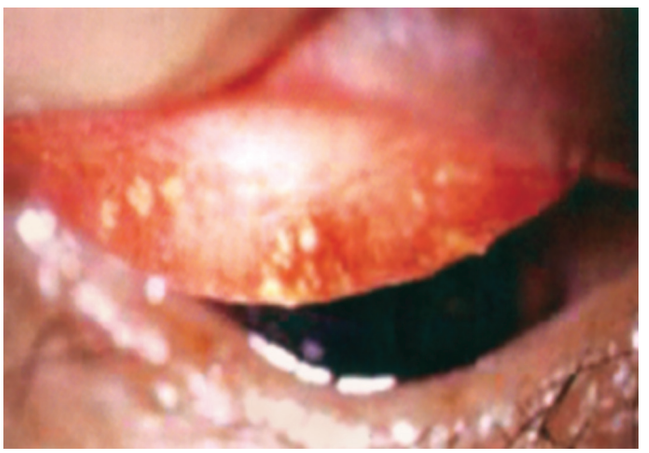

Fig. 8.4: Concretions in upper palpebral conjunctiva.

TREATMENT

- *Lubricating drops* are sufficient for mild symptoms.
- *Excision biopsy* can be performed in patients with marked irritation due to raised lesions. Surgical excision may not cause full regression of the deposited amyloid.
- *Radiotherapy* may be tried in recurrent cases to present progression.

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Chapter

9

Symptomatic Conditions of Conjunctiva

Chapter Outline

COMMON SYMPTOMATIC CONDITIONS OF CONJUNCTIVA
Introduction
Simple Hyperaemia of Conjunctiva
Chemosis of Conjunctiva
Ecchymosis of Conjunctiva
Xerosis of Conjunctiva
Discolouration of Conjunctiva
Conjunctival Lacerations
Conjunctival Foreign Body
CONJUNCTIVAL BLEB

COMMON SYMPTOMATIC CONDITIONS OF CONJUNCTIVA

INTRODUCTION

Conjunctival lesions are frequently seen in the eye clinic, because the conjunctiva is readily seen and patients notice some change in their ocular appearance. This discussion does not attempt to classify lesions, but only highlights some of the more common lesions that are seen.

Always obtain a full medical and ocular history. In the consulting room the conjunctiva can be examined with a bright light and magnifying glass. Examine what you can see and evert the upper lid to look at the tarsal conjunctiva. Always test the visual acuity, look at the cornea and feel for pre-auricular and submandibular lymph nodes.

Common symptomatic conditions

Common symptomatic conditions of conjunctiva include:

- Hyperaemia of conjunctiva
- Chemosis of conjunctiva
- Ecchymosis of conjunctiva
- Xerosis of conjunctiva
- Discolouration of conjunctiva
- Conjunctival lacerations
- Conjunctival foreign body
- Conjunctival bleb

SIMPLE HYPERAEMIA OF CONJUNCTIVA

Simple hyperaemia of conjunctiva means congestion of the conjunctival vessels due to acute exposure to some minor irritants without being associated with any of the established eye disease. The pattern of hyperaemia often appears with the greatest redness at the fornices and fades moving toward the limbus.

Etiology

It may be acute and transient, or recurrent and chronic.

1. *Acute transient hyperaemia.* It results due to temporary irritation caused by: (i) *Direct irritants* such as a foreign body, misdirected cilia, concretions, dust, chemical fumes, smoke, stormy wind, bright light, extreme cold, extreme heat and simple rubbing of eyes with hands. (ii) *Reflex hyperaemia* due to eye strain, from inflammations of nasal cavity, lacrimal passages and lids. (iii) *Hyperaemia associated with systemic febrile conditions*. (iv) *Nonspecific inflammation* of conjunctiva.

2. *Recurrent or chronic hyperaemia.* It often occurs due to chronic exposure to irritant as in chronic smokers, chronic alcoholics, people residing in dusty, ill-ventilated rooms, workers exposed to prolonged heat, in patients suffering from rosacea and insomnia or otherwise having less sleep.

Clinical features

- Feeling of discomfort, heaviness, grittiness, tiredness and tightness in the eyes are common complaints of patients with conjunctival hyperaemia.

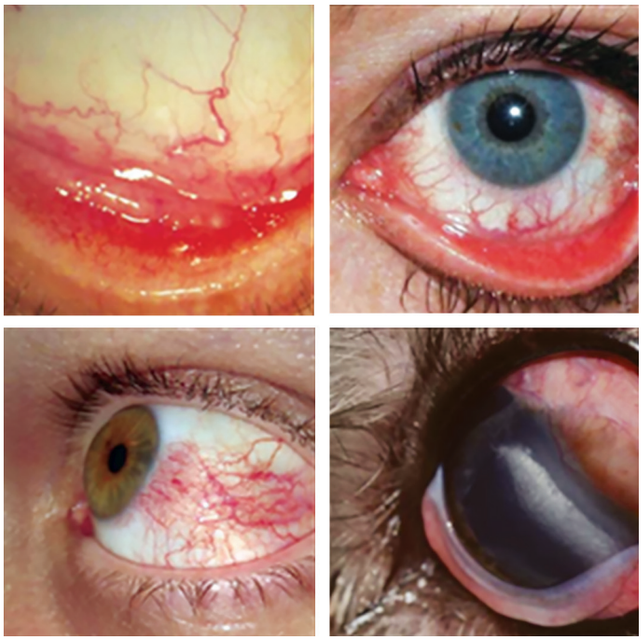

Fig. 9.1: Hyperaemia of conjunctiva.

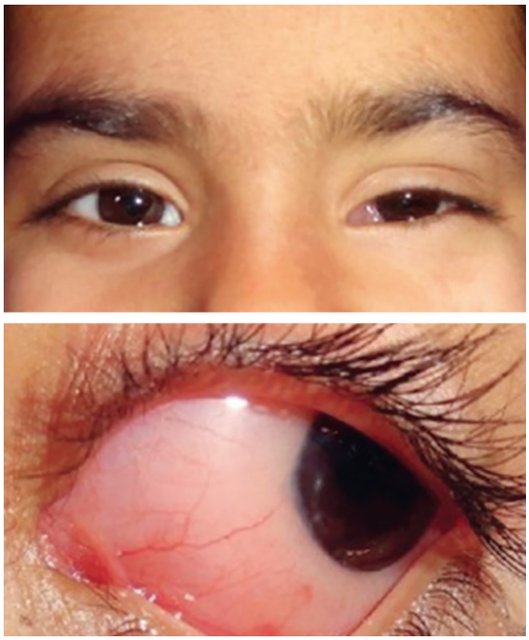

Fig. 9.2: Chemosis of conjunctiva.

- Mild lacrimation and minimal mucoid discharge, may occur.
- On cursory examination, the conjunctiva often looks normal. However, eversion of the lids may reveal mild to moderate congestion being more marked in fornices (Fig. 9.1).

Treatment

- *Removal of the cause of hyperaemia*, e.g. in acute transient hyperaemia the removal of irritants (e.g. misdirected cilia) gives prompt relief.
- *Symptomatic relief* may be achieved by use of topical decongestants (e.g. 1:10000 adrenaline drops) or naphazoline drops.

CHEMOSIS OF CONJUNCTIVA

Chemosis or oedema of the conjunctiva is of frequent occurrence owing to laxity of the tissue. The conjunctiva also serves as a defense against potential microbes from entering the eye that may potentially cause harm. When the defenses of the conjunctiva are active, it can become swollen, increasing the production of fluid leakage from abnormally permeable capillaries. This leads to the commonly seen presentation of chemosis, watery eyes (Fig. 9.2).

CAUSES

There are a variety of causes of chemosis, with the most usual one being allergies, viral and bacterial infections, and constant rubbing of the eyes themselves. Any factor that can lead to eye irritation can lead to the development of chemosis.

Common causes of chemosis

Allergies: Seasonal changes, pet dander, pollen, and virtually anything else you may be allergic to has a high chance of making your eyes water and become itchy.

Infections: Commonly caused by bacterial or viral infections leading to a condition called conjunctivitis. While these types of infection can be contagious, leading the eyes to become red, itchy, and watery, the specific symptom of chemosis cannot be transmitted alone. Some other conditions like corneal ulcers, fulminating iridocyclitis, endophthalmitis, panophthalmitis, styes, acute meibomitis, orbital cellulitis, acute dacryoadenitis, acute dacryocystitis, tendonitis and so on may also lead to chemosis.

Eye surgeries: Performing any type of surgery to the eye or eyelid frequently leads to the development of chemosis. Fortunately, these symptoms usually only last a couple of days with appropriate treatment using eye drops, cold compresses, or temporary eye patching.

Hyperthyroidism: A disorder of the thyroid gland leading to the overproduction of thyroid hormone. This condition can lead to several types of eye problems such as bulging of the eyes, eye puffiness, and retraction of the eyelids.

Excessive rubbing: Constantly touching, rubbing, or scratching the eyes is a common cause of chemosis. Rubbing the eyes is never recommended as this will induce more irritation and possibly even cause eye damage.

Systemic causes: These include severe anaemia and hypoproteinaemia, congestive heart failure, nephrotic syndrome, urticaria, and angioneurotic oedema.

Local obstruction to flow of blood and/or lymph: It may occur in patients with orbital tumours, cysts, endocrine exophthalmos, orbital pseudotumours, cavernous sinus thrombosis, caroticocavernous fistula, blockage of orbital lymphatics following orbital surgery, acute congestive glaucoma, etc.

Less common causes of chemosis

- Orbital cellulitis
- Acute glaucoma
- Obstruction of the superior vena cava
- Cluster headaches
- Urticaria
- Rhabdomyosarcoma of the orbit
- Parasitic infections
- Systemic lupus erythematosus
- Angioedema
- Dacryocystitis
- Carotid cavernous fistula

SYMPTOMS OF CHEMOSIS

Symptoms of chemosis often include:

- Watery eyes
- Excessive tearing
- Eye itchiness
- Double or blurred vision
- Chemosis sufferers may also have trouble closing the affected eye completely due to the swelling.

It is recommended to seek medical attention if one begins to experience eye pain of any kind in combination with watery eyes as it may signal a more severe underlying eye condition.

TREATMENT AND PREVENTION OF CHEMOSIS

Treatment methodologies generally depend on the underlying cause of particular case of chemosis. The following are examples of various treatments

Lubricating eye drops: Help combat dryness and irritation of the eye and is commonly prescribed in case of mild swelling.

Cold compress: Can provide immediate relief to reduce the intensity of chemosis, but only for mild cases.

Patching: Commonly done for patients who have difficulty closing the eye. Patching helps to prevent the eye from becoming excessively irritated and drying out.

Corticosteroids: Commonly given in the form of eyedrops to aid in reducing the eye's inflammatory response and subsequently reduce eye swelling.

Anti-inflammatory medication: Can be topical or oral medication to aid in the reduction of inflammation and pain.

Anti-histamines: A common treatment for allergic reactions to suppress the release of histamine, a substance produced by the body when exposed to allergens.

Adrenaline or epinephrine: Standard emergency treatment for life-threatening anaphylactic reactions. An absolute must in cases where the patient is having difficulty breathing or swallowing.

Antibiotics: May be prescribed for bacterial infections that result in chemosis or post-surgical to reduce the risk of a secondary infection. This may come in the form of medicated eye drops or ointments. Unfortunately, antibiotics are not effective against viruses.

Conjunctivoplasty: A minor surgery that involves performing a small incision into the conjunctiva and the removal of the excess membrane. This may be required in cases of prolonged swelling.

By avoiding potential allergic triggers, one can help reduce the occurrence of chemosis. It is also recommended to maintain a high level of personal hygiene, to limit the sharing of personal items that may come into contact with the eyes, such as towels or cosmetic products. However, it is important to keep in mind that chemosis may not be preventable in some cases.

ECCHYMOSIS OF CONJUNCTIVA

Ecchymosis or subconjunctival haemorrhage is a benign condition and is of very common occurrence. It is characterised by painless acute redness due to bleeding underneath conjunctiva in the absence of discharge or inflammation. It may vary in extent from small petechial haemorrhage to an extensive one spreading under the whole of the bulbar conjunctiva and thus making the white sclera of the eye invisible (Fig. 9.3). The condition though draws the attention of the patients immediately as an emergency but is most of the time trivial.

Whereas a bruise typically appears black or blue underneath the skin, a subconjunctival bleeding initially appears bright-red underneath the transparent conjunctiva. Later, the haemorrhage may spread and become green or yellow, like a bruise. Usually this disappears within 2 weeks.

The vision is usually unaffected by the haemorrhage. An extensive subconjunctival haemorrhage may track into the eyelids.

Recurrent or persistent subconjunctival haemorrhage needs to be investigated for systemic hypertension, ocular or systemic malignancies, bleeding disorders and any side effects of drugs.

Etiology

Subconjunctival haemorrhage may be associated with the following conditions:

1. *Trauma.* It is the most common cause of subconjunctival haemorrhage. It may be in the form of (i) local trauma to the conjunctiva including that due to surgery and subconjunctival injections, (ii) retrobulbar haemorrhage which almost immediately spreads below the bulbar conjunctiva. Mostly, it results from a retrobulbar injection and from trauma involving various walls of the orbit.

2. *Inflammations of the conjunctiva.* Petechial subconjunctival haemorrhages are usually associated with

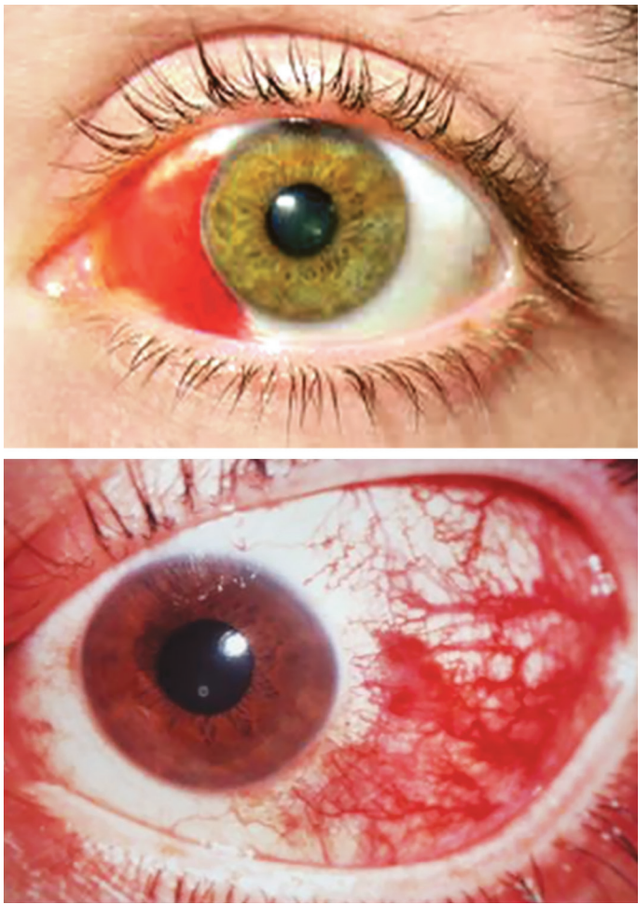

Fig. 9.3: Subconjunctival haemorrhage.

acute haemorrhagic conjunctivitis caused by picornaviruses, pneumococcal conjunctivitis and leptospirosis, icterohaemorrhagica conjunctivitis.

3. *Sudden venous congestion of head.* The subconjunctival haemorrhages may occur owing to rupture of conjunctival capillaries due to sudden rise in pressure. Common conditions are whooping cough, epileptic fits, strangulation or compression of jugular veins and violent compression of thorax and abdomen as seen in crush injuries.

4. *Spontaneous rupture of fragile capillaries* may occur in vascular diseases such as arteriosclerosis, hypertension and diabetes mellitus.

5. *Local vascular anomalies* like telangiectasia, varicosities, aneurysm or angiomatous tumour.

6. *Blood dyscrasias* like anaemias, leukaemias and dysproteinaemias.

7. *Bleeding disorders* like purpura, haemophilia and scurvy.

8. *Acute febrile systemic infections* such as malaria, typhoid, diphtheria, meningococcal septicaemia, measles and scarlet fever.

9. *Vicarious bleeding* associated with menstruation is an extremely rare cause of subconjunctival haemorrhage.

Clinical features

Symptoms. Subconjunctival haemorrhage per se is symptomless. Except for red discolouration noted by patients as a serious symptom. However, there may be symptoms of associated causative disease.

Signs. On examination, subconjunctival haemorrhage looks as a flat sheet of homogeneous bright red colour with well-defined limits (Fig. 9.3).

Natural course. In traumatic subconjunctival haemorrhage, posterior limit is visible when it is due to local trauma to eyeball, and not visible when it is due to head injury or injury to the orbit. Most of the time it is absorbed completely within 7 to 21 days. During absorption, colour changes are noted from bright red to orange and then yellow. In severe cases, some pigmentation may be left behind after absorption.

Treatment

- *Treat the cause* when discovered.
- *Cold compresses* to check the bleeding in the initial stage and hot compresses may help in absorption of blood in late stages.
- *Placebo therapy* with astringent and lubricant eye drops.
- *Psychotherapy and assurance* to the patient is most important part of treatment.

XEROSIS OF CONJUNCTIVA

Xerosis of the conjunctiva is a symptomatic condition in which conjunctiva becomes dry and lustreless (Fig. 9.4). Normal conjunctiva is kept moist by its own secretions, mucin from goblet cells and aqueous solution from accessory lacrimal glands. Therefore, even if the main lacrimal gland is removed, xerosis does not occur.

Etiology

Depending upon the aetiology, conjunctival xerosis can be divided into two groups, parenchymatous and epithelial xerosis.

1. *Parenchymatous xerosis.* It occurs following cicatricial disorganization of the conjunctiva due to local causes which can be in the form of:

- *Destructive interstitial conjunctivitis* as seen in trachoma, diphtheric membranous conjunctivitis, Stevens-Johnson syndrome, pemphigus or pemphigoid conjunctivitis, thermal, chemical or radiational burns of conjunctiva.
- *Exposure of conjunctiva to air* as seen in marked degree of proptosis, facial palsy, ectropion, lack of blinking (as in coma), and lagophthalmos due to symblepharon.

2. *Epithelial xerosis.* It occurs due to *hypovitaminosis A*. Epithelial xerosis may be seen in association with night blindness or as a part and parcel of the xerophthalmia (the term which is applied to all ocular manifestations of vitamin A deficiency) which range from night blindness to keratomalacia (*see* page 86).

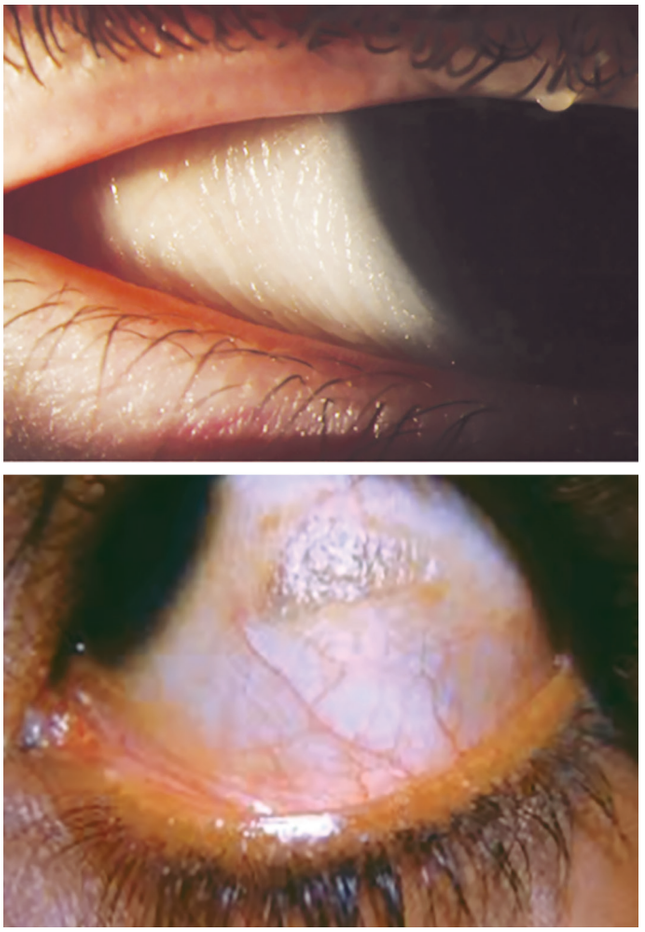

Fig. 9.4: Xerosis of conjunctiva.

Clinical features

Parenchymatous xerosis is characterised by marked dryness, thickening, scarring and even keratinization associated with features and complication of the causative disease.

Epithelial xerosis typically occurs in children and is characterised by varying degree of conjunctival dryness, thickening, wrinkling and pigmentation.

Treatment

Treatment of conjunctival xerosis consists of:

- *Treatment of the cause*, and their complications
- *Symptomatic local treatment* with artificial tear preparations (0.7% methylcellulose or 0.3% hypromellose or polyvinyl alcohol), which should be instilled frequently.

DISCOLOURATION OF CONJUNCTIVA

Normal conjunctiva is a thin transparent structure. In the bulbar region, underlying sclera and a fine network of episcleral and conjunctival vessels can be easily visualised. In the palpebral region and fornices, it looks pinkish because of underlying fibrovascular tissue.

Causes

Conjunctiva may show discolouration in various local and systemic diseases given below:

1. *Red discolouration*. A bright red homogeneous discolouration suggests subconjunctival haemorrhage (*see* Fig. 9.3).

2. *Yellow discolouration*. It may occur due to: (i) Bile pigments in jaundice, (ii) blood pigments in malaria and yellow fever, (iii) conjunctival fat in elder and Negro patients.

3. *Greyish discolouration*. It may occur due to application of kajal (surma or soot) and mascara in females.

4. *Brownish grey discolouration*. It is typically seen in argyrosis, following prolonged application of silver nitrate for treatment of chronic conjunctival inflammations. The discolouration is most marked in lower fornix.

5. *Blue discolouration*. It is usually due to ink tattoo from pens or effects of manganese dust. Blue discolouration may also be due to pseudopigmentation as occurs in patients with blue sclera and scleromalacia perforans.

6. *Brown pigmentation*. Its common causes can be grouped as under:

a. *Non-melanocytic pigmentation*

i. *Endogenous pigmentation.* It is seen in patients with Addison's disease and ochronosis.

ii. *Exogenous pigmentation.* It may follow long-term use of adrenaline for glaucoma. Argyrosis may also present as dark brown pigmentation.

b. *Melanocytic pigmentation*

i. *Conjunctival epithelial melanosis* (Fig. 9.5). It develops in early childhood, and then remains stationary. It is found in 90% of the blacks. The pigmented spot freely moves with the movement of conjunctiva. It has got no malignant potential and hence no treatment is required.

ii. *Subepithelial melanosis.* It may occur as an isolated anomaly of conjunctiva (congenital melanosis oculi,

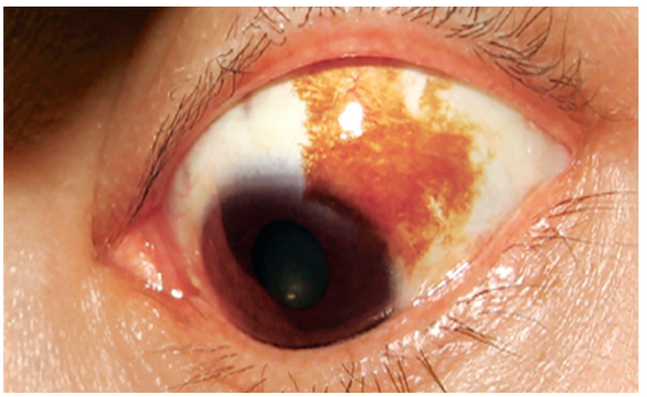

Fig. 9.5: Conjunctival epithelial melanosis.

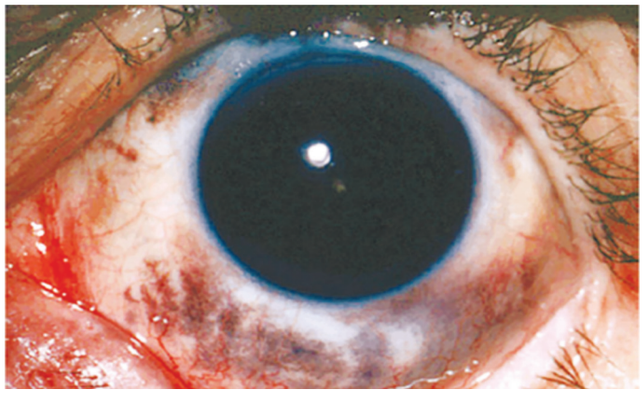

Fig. 9.6: Congenital melanosis oculi.

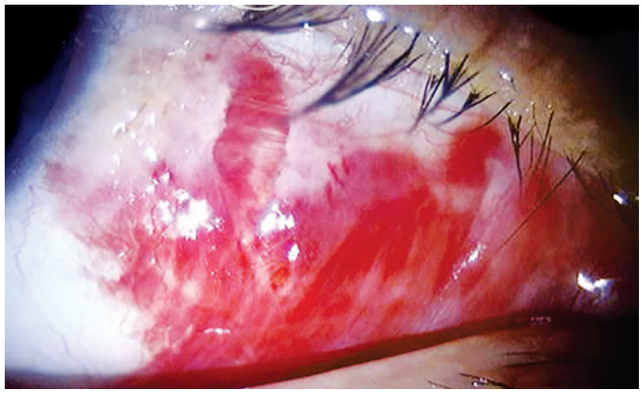

Fig. 9.7: Conjunctival laceration with subconjunctival haemorrhage.

Fig. 9.6) or in association with the ipsilateral hyperpigmentation of the face (oculodermal melanosis or naevus of Ota).

iii. *Pigmented tumours.* These can be benign naevi, precancerous melanosis or malignant melanoma (refer to melanocytic tumours of conjunctiva).

CONJUNCTIVAL LACERATIONS

Due to its exposed position, thinness, and mobility, the conjunctiva is susceptible to lacerations, which are usually associated with sub-conjunctival haemorrhage.

Etiology

Conjunctival lacerations most commonly occur as a result of penetrating wounds (such as from bending over a spiked-leaf palm tree or from a branch that snaps back onto the eye).

Clinical features

The patient experiences a foreign body sensation. Usually this will be rather mild. Examination will reveal circumscribed conjunctival reddening or subconjunctival haemorrhage in the injured area (Fig. 9.7). Chemosis may also be present. Occasionally only application of fluorescein dye to the injury will reveal the size of the conjunctival gap.

In such cases, it is important to rule out underlying scleral perforation. The fundus should be examined for any retinal tear or intraocular foreign body. An ultrasound may be done for the posterior segment evaluation. Seidel test should be done to rule out open globe injury and CT scan to rule out intraocular foreign body.

Treatment

Such cases are managed with observation and topical antibiotics in mild cases and in large lacerations, surgical repair may be needed using 8–0 vicryl suture.

CONJUNCTIVAL FOREIGN BODY

Foreign bodies can lodge in the inferior cul-de-sac or can be located on the conjunctival surface under the upper eyelid (Fig. 9.8). The most common foreign bodies in the conjunctiva include the following:

- Dust
- Dirt
- Contact lenses
- Sand
- Cosmetics

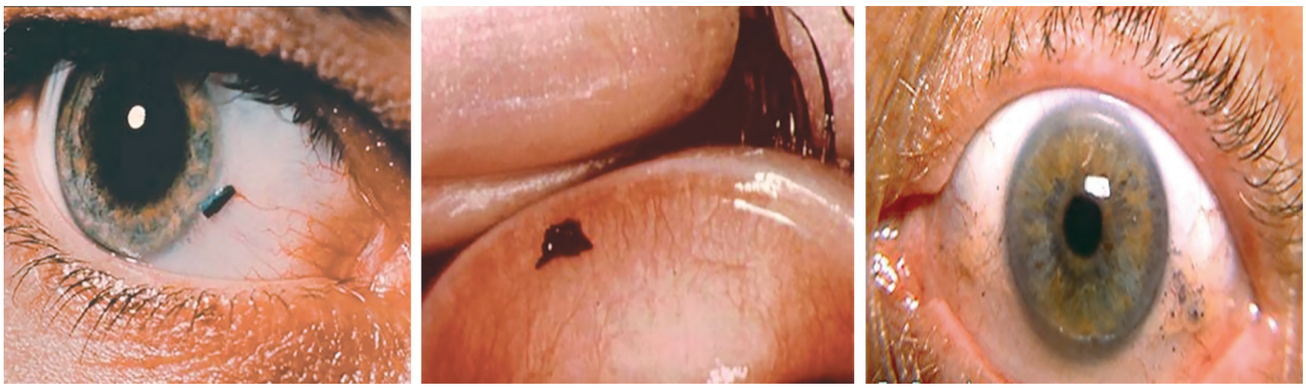

Fig. 9.8: Conjunctival foreign bodies.

Clinical features

Symptoms include ocular irritation, pain, foreign body sensation, tearing or red eye.

Examination

It is imperative to evert the upper eyelid to examine the superior tarsal plate and eyelid margin in all patients with a history that suggests a foreign body. If several foreign bodies are suspected or particulate matter is present, double eversion of the eyelid with a Desmarres retractor or a bent paperclip is advised to allow the examiner to effectively search the entire arc of the superior cul-de-sac. Foreign bodies on the conjunctival surface are best recognized with slit-lamp examination.

Following eversion of the upper eyelid, copious irrigation should be used to cleanse the fornix. This procedure should then be repeated using a Desmarres retractor for the upper and lower eyelids. Glass particles, cactus spines, and insect hairs are often difficult to see, but a careful search of the cul-de-sac with high magnification aids in identification and removal. With slit-lamp magnification, the clinician can gently use a moistened cotton-tipped applicator to remove superficial foreign material. Occasionally, saline lavage of the cornea or cul-de-sac washes out debris that is not embedded in tissue.

When a patient complains of foreign body sensation, topical fluorescein should be instilled to check for the fine, linear, vertical corneal abrasions that are characteristic of retained foreign bodies on the eyelid margin or superior tarsal plate. Foreign matter embedded in tissue is removed with a sterile, disposable hypodermic needle. Glass or particulate matter may be removed with a fine-tipped jeweler's forceps or blunt spatula. If a foreign body is suspected but not seen, the cul-de-sac should be irrigated and wiped with a moistened cotton-tipped applicator.

Treatment

- Careful examination of the entire eye is mandatory to rule out intraocular foreign bodies including a thorough slit-lamp and dilated retinal examination.
- B scan ultrasonography, X-ray film or CT scanning is sometimes indicated to rule out intraocular foreign body.
- MRI is contraindicated, since intraocular foreign body may be metallic.
- Multiple small fragments or debris can be removed with saline irrigation.
- Localized/embedded foreign body can be removed under topical anaesthesia at the slit-lamp using cotton-tipped applicator or forceps.
- Short course of topical antibiotic after foreign body removal may be given to prevent secondary infection.

CONJUNCTIVAL BLEB

A conjunctival bleb is formed when there is a direct connection of the aqueous in the anterior chamber to the subconjunctival space (Fig. 9.9). This bleb can be formed deliberately, e.g. in glaucoma surgery or after corneoscleral laceration repair. Ask the patient about any ocular trauma or surgery. It is extremely important never to try to puncture or deflate these cysts as it may lead to hypotonia of the eye or even endophthalmitis.

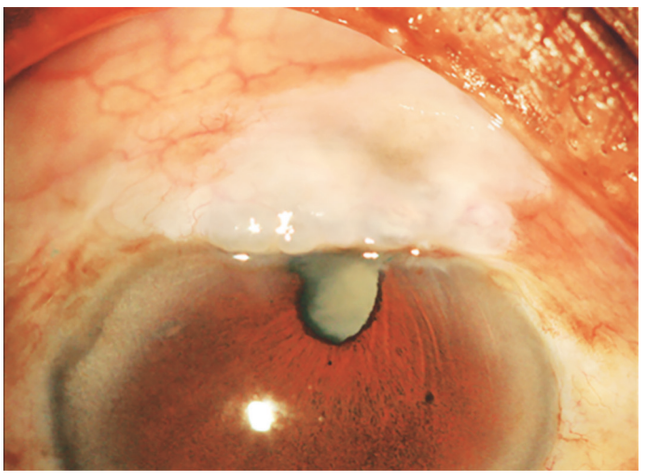

Fig. 9.9: Conjunctival bleb after trauma.

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Chapter

10

Cysts and Tumours of Conjunctiva

Chapter Outline

CYSTS OF CONJUNCTIVA
- Congenital cystic lesions
- Lymphatic cysts
- Retention cysts
- Epithelial cysts
  - Epithelial implantation cyst
  - Epithelial cysts due to downgrowth of epithelium
- Aqueous cyst
- Parasitic cysts
- Pigmented epithelial cysts

OCULAR SURFACE TUMOURS

Primary Tumours

Epithelial tumours

Classification
- Nonmelanocytic
- Melanocytic

Stromal tumours
- Vascular
- Fibrous
- Neural
- Histiocytic
- Myogenic
- Lipomatous
- Lymphoproliferative
- Choristoma

Caruncular Tumours

Metastasis and Secondary Tumours

CYSTS OF CONJUNCTIVA

Conjunctival cysts are mostly thin walled and slowly progressive. They are fluid-filled sacs, but can sometimes look more like a solid mass. These lesions are most common during first three decades of life. They are usually symptomless but can cause cosmetic disfigurement, reduced motility, foreign body sensation, dry eye due to unstable tear film and proptosis when they increase in size.

CLASSIFICATION

- Congenital cystic lesions
  - Congenital corneoscleral cysts
  - Cystic epibulbar dermoid
- Epithelial implantation cysts
- Epithelial cysts due to downgrowth of epithelium
- Lymphatic cysts
  - Lymphangiectasia
  - Lymphangioma
- Retention cysts
- Aqueous cysts
- Parasitic cysts
  - Hydatid cyst
  - Cysticercus
  - Filarial cyst
- Pigmented epithelial cysts: Prolonged topical use of cocaine/epinephrine.

CONGENITAL CYSTIC LESIONS

These are of rare occurrence and include congenital corneoscleral cyst and cystic form of epibulbar dermoid.

Conjunctival dermoids (Fig. 10.1) are usually noticed in adulthood, are located nasally or superonasally, lack an associated osseous defect and are lined by a non-keratinizing epithelium with goblet cells. The cut surface of the cyst contains cheesy material and hair shafts, sweat and sebaceous glands. The lumen contains granular keratin material.

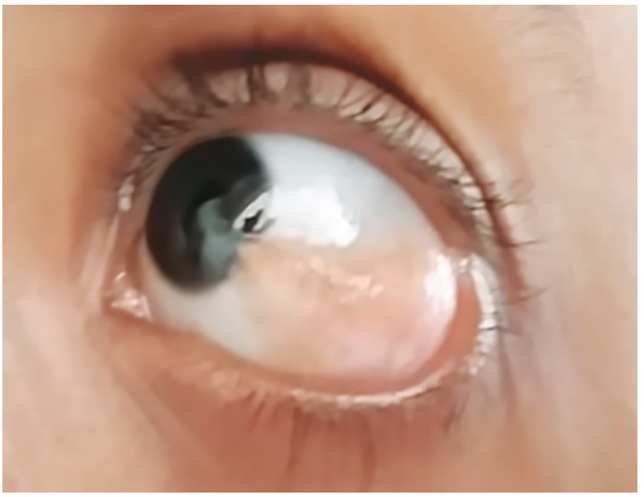


Fig. 10.1: Conjunctival dermoid.

EPITHELIAL CYSTS

Epithelial implantation cysts

Implantation cysts are benign cysts filled with clear serous fluid containing shed cells or gelatinous mucous material. Cyst wall consists of several layers of non-keratinised lining epithelium and connective tissue. The implantation cysts are the commonest cystic lesions of conjunctiva, 80% of the entire cystic lesions of conjunctiva being implantation cysts. These can be primary and secondary.

Primary implantation cyst

Pathogenesis of primary implantation cyst is due to excessive invagination of the caruncular epithelium or the fornix during embryonic development.

Age of presentation of these cysts range from birth to 70 years.

Typically located. These are in the superonasal part of the orbit and less commonly temporally (Fig. 10.2).

Typical clinical features. These consist of painless cystic masses of small to moderate size having thin walls and low pressure which generally do not induce significant mechanical alterations, however they can rarely erode adjacent bony structures and cause visual symptoms.

Secondary implantation cysts

Secondary implantation cysts are more common, they occur either naturally or under inflammatory conditions of the conjunctiva. In most cases these developed by detachment of a portion of conjunctival epithelium by surgery or trauma and even subtenon anaesthesia. Following implantation into the conjunctival epithelium, conjunctiva is especially vulnerable to injuries because of its presence on our outer eye. Any type of blow to the eye or vigrous rubbing can cause a conjunctival cyst to develop. Epithelial inclusion cysts occupy the major bulk.

In normal conjunctiva a mild degree of trauma may not lead to embedding of conjunctival epithelium into the deeper tissues. However, once there is conjunctival inflammation, the epithelium becomes loose and the deeper tissues get oedematous and even with mildest trauma the epithelial cells may get exfoliated and buried into the deeper tissues where mild fibrosis, shallowing of fornices and adhesions may progress slowly. Proliferation of these cells results in the formation of cysts. Hence, simultaneous occurrence of inflammation and trauma may contribute to its genesis.

Implantation cysts following small incision cataract surgery have also been reported (Fig. 10.3). This complication occurs due to implantation of conjunctival tissue during construction of tunnel or dragging of conjunctiva during IOL implantation. Chief differential diagnosis is the filtering bleb. This can be prevented by careful reflection of the conjunctiva during surgery. Inclusion cysts have also been reported in conditions of chronic inflammation like VKC.

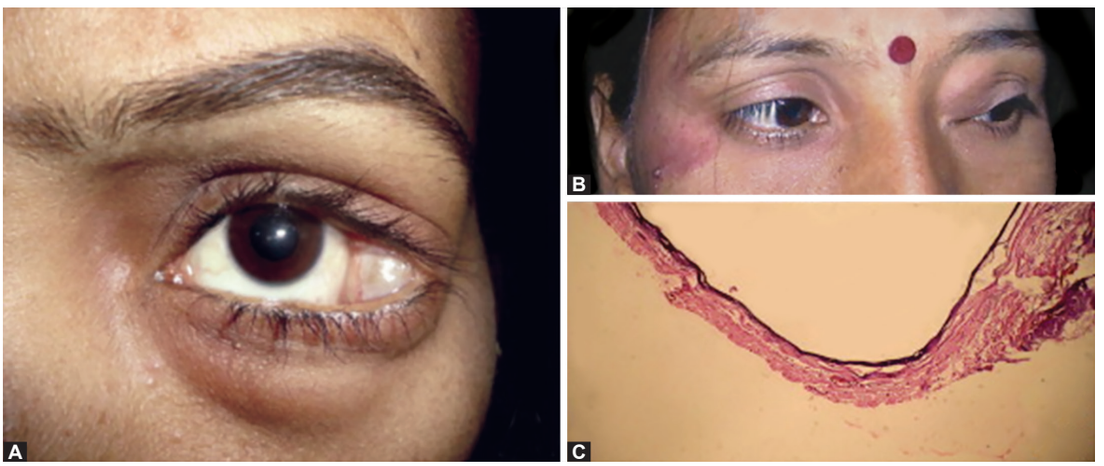


Fig. 10.2: Primary conjunctival cyst. A, On temporal side; B, On nasal side; and C, Histopathology—cyst lined with single layer of stratified squamous epithelium containing amorphous material.

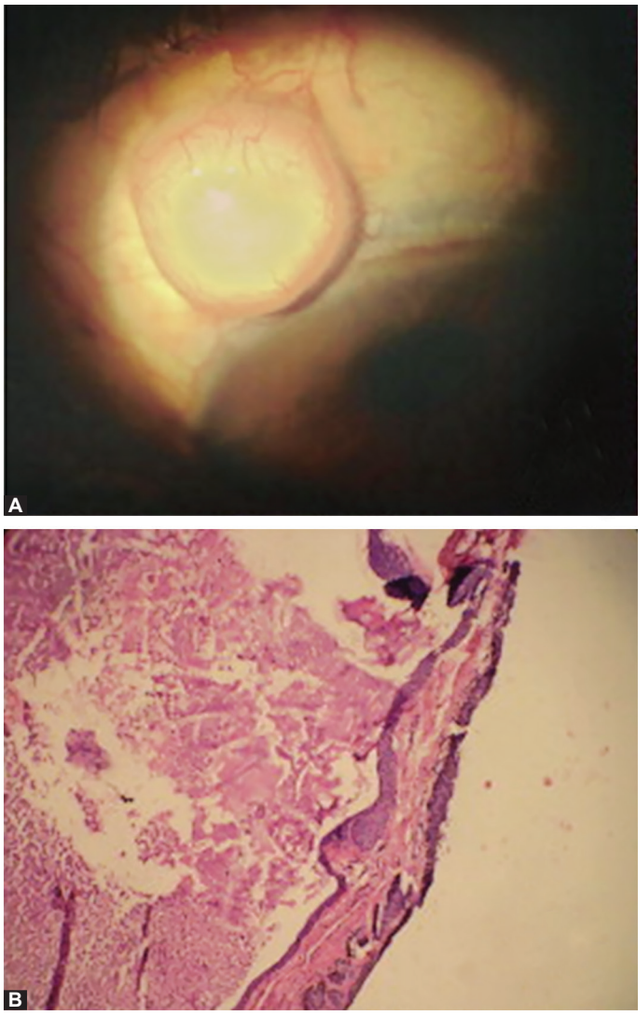


Fig. 10.3: Post-SICS cyst. A, Clinical photograph; B, HPE: Cyst lined by stratified squamous epithelium filled with amorphous material inside.

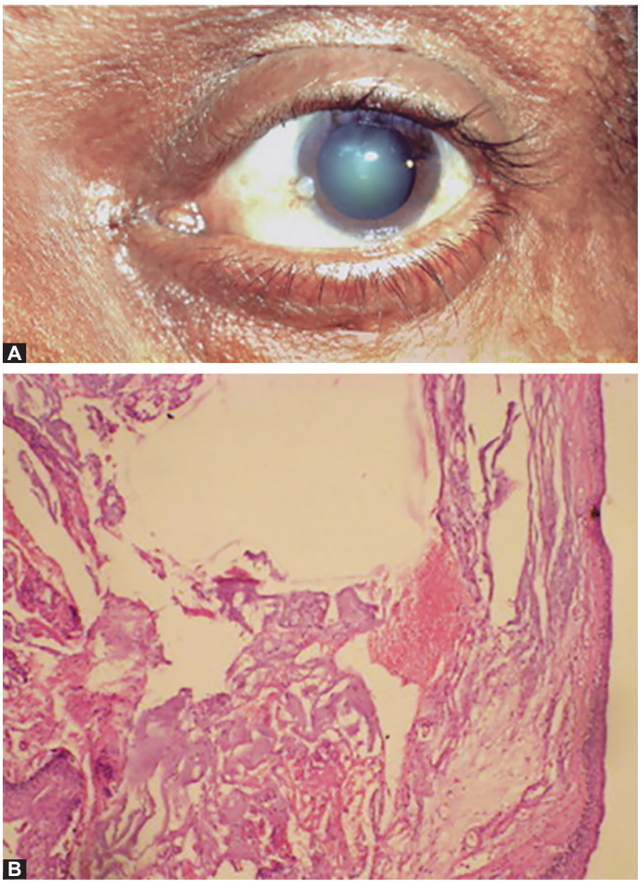


Fig. 10.4: Cystic change in pterygium. A, Clinical photograph with cyst; B, HPE: Pterygium with stratified squamous epithelium with cystic changes and mild chronic inflammatory reaction around the cyst.

Epithelial cysts due to downgrowth of epithelium

These are rarely seen in chronic inflammatory or degenerative conditions, e.g. cystic change in pterygium.

In such cases cyst may commonly be located at the head of the pterygium or embedded in the body (Fig. 10.4). There is no adherence of the cyst to the underlying structures. These cases are managed by excision of the cyst along with the reverse peeling of pterygium. Histopathology shows pterygium with stratified squamous epithelium lining with cystic changes, mild chronic inflammatory reaction can be seen around the cyst.

LYMPHATIC CYSTS

These are common and present under the bulbar conjunctiva and upper fornix (Fig. 10.5). Usually occur due to dilatation of lymph spaces in the bulbar conjunctiva. They are transparent, multilocular and filled with clear fluid.

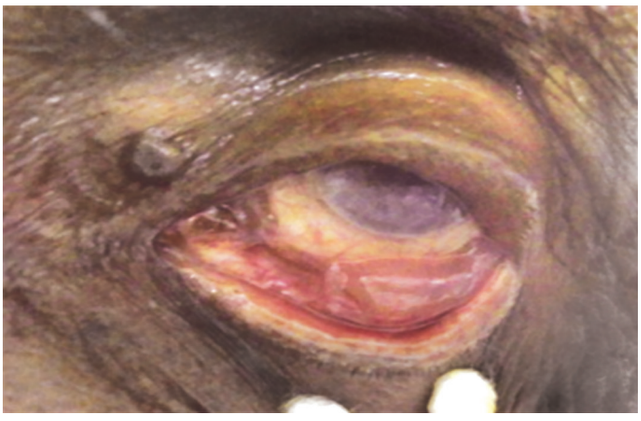


Fig. 10.5: Lymphatic cyst.

Rarely the cyst can be pedunculated. Histopathological examination shows dilated lymphatic spaces lined with endothelium. The dilated lymphatics which cannot be emptied are considered to develop into lymphatic cysts.

Lymphangiectasis is characterized by a row of small cysts. They can present either as cystic lesions of the conjunctiva which mimic allergic chemosis or as beaded dilatation of lymphatic vessels with a string of pearl appearance. Treatment modalities for conjunctival lymphangiectasia are surgical resection, marsupialization and obliteration of abnormal lymphatics by liquid nitrogen cryotherapy. Rarely, lymphangioma may occur as a single multilocular cyst.

RETENTION CYSTS

These occur occasionally due to blockage of ducts of accessory lacrimal glands of Krause in chronic inflammatory conditions, viz. trachoma and pemphigus. Retention cysts are more common in upper fornix.

AQUEOUS CYST

It may be due to healing by cystoid cicatrix formation, following surgical or non-surgical perforating limbal wounds.

PARASITIC CYSTS

Parasitic cysts such as subconjunctival cysticercosis, hydatid cyst and filarial cyst are not infrequent in developing countries.

Conjunctival cysticercosis

Parasitic conjunctival cysts due to cysticercus appear to be most common. The size of the parasitic cysts may vary and their shape may be circular or oval. These look whitish with a chalky white spot in the cavity representing the scolex of the parasite (Fig. 10.6A). Histopathological examination of these cysts (Fig. 10.6B) showed the body canal of cysticercus cellulosae lined by the epithelium (Fig. 10.6C). The left eye seems to be involved more with a predisposition to nasal side. This may be explained on the basis of anatomical reasons, i.e. the course of ophthalmic artery.

At times, the cyst may prolapse from the subconjunctival tissue. No obvious cause for the spontaneous expulsions could be elicited. However, mechanical stretching due to the presence of the cyst and weak conjunctiva (due to associated inflammation) could possibly explain the spontaneous expulsion.

Hydatid cyst

Hydatid cysts mostly occur in young people between 10 and 30 years. They most frequently present as exophthalmos, chemosis, lid oedema, visual impairment and restriction of extraocular movement. Sudden exacerbation of pain, increase in proptosis, and local inflammatory reaction in eye is an important diagnostic clue to the hydatid cyst. Definitive treatment is surgical excision.

PIGMENTED EPITHELIAL CYST

It may be formed sometimes following prolonged topical use of cocaine or epinephrine. Histopathological examination reveals the presence of aggregates of melanocytes under epithelium with a tendency to form adenomatous arrangement.

TREATMENT OF CONJUNCTIVAL CYSTS

Conjunctival cysts do not always require treatment, especially if they are small and are not causing any symptoms. In some cases, they go away on their own over time.

Conservative treatment in the form of lubricating eye drops may help with any dryness or discomfort. Steroid eye drops

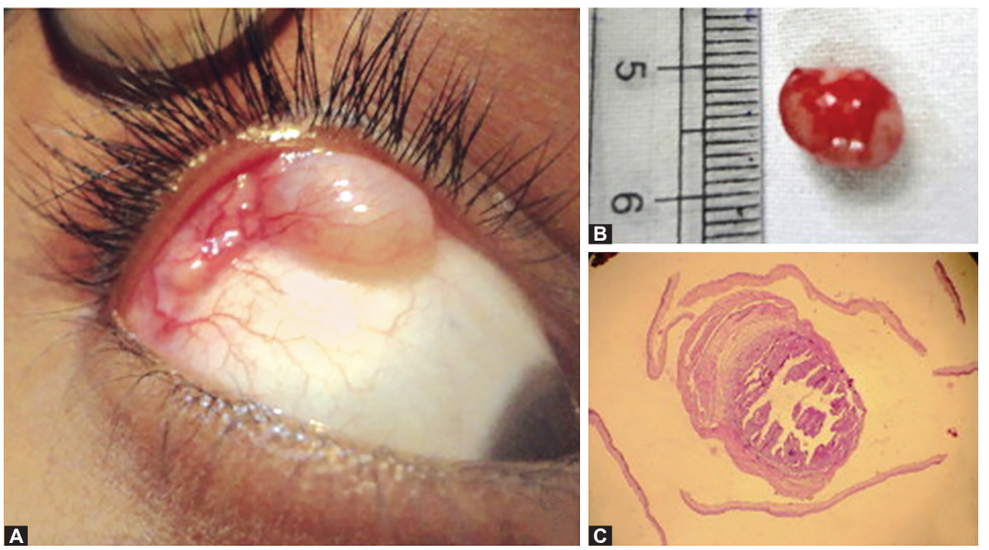


Fig. 10.6: Conjunctival cysticercosis cyst: A, Clinical photograph; B, Excised cysticercosis cyst; C, HPE: Cyst with embedded parasite, with chronic inflammatory cell infiltrate with lymphocytes, eosinophils and giant cells in the cyst wall.

can also help to reduce inflammation and prevent the cyst from getting bigger. This is especially helpful if the cyst is due to an allergic reaction to something.

Surgical excision is required in cases of large and symptomatic conjunctival cysts. As the cysts are thin walled, rupture is common during excision. Recurrence is the main postoperative concern. B scan USG and MRI of cyst can be done whenever required to see the posterior extent. Careful and intact removal of conjunctival cyst is important to prevent recurrence. Minor modifications in surgical technique according to the size, site and nature of cyst help in intact removal and prevent recurrence. The excised cyst should always be subjected to histopathological examination.

OCULAR SURFACE TUMOURS

Ocular surface tumours are rare but potentially deadly diseases of the conjunctiva and/or cornea. These tumours are grouped into two major categories of congenital and acquired lesions. The acquired lesions are further subdivided based on origin of the mass into surface epithelial, mucoepidermoid, melanocytic, vascular, fibrous, neural, histiocytic, myxoid, myogenic, lipomatous, lymphoid, leukaemic, metastatic and secondary tumours. It is important for ophthalmologists to recognise the characteristics of ocular surface tumours and to have an understanding of their management. Some common ocular surface tumours are described in this chapter.

Classification of ocular surface tumours

Primary tumours

Epithelial tumours

- Nonmelanocytic
- Melanocytic

Stromal tumours

- Vascular
- Fibrous
- Neural
- Histiocytic
- Myogenic
- Lipomatous
- Lymphoproliferative
- Choristoma

Caruncular tumours

Metastasis and secondary tumours

PRIMARY TUMOURS

EPITHELIAL TUMOURS

CONJUNCTIVAL NONMELANOCYTIC EPITHELIAL TUMOURS

CLASSIFICATION

A simplified classification of conjunctival nonmelanocytic tumours is given in Table 10.1.

CONJUNCTIVAL BENIGN NONMELANOCYTIC EPITHELIAL TUMOURS

1. Conjunctival papilloma

Etiology

Conjunctival papillomas occur in both children and adults with variable presentation.

In children, it results from infection of the conjunctival epithelium with human papilloma- virus (HPV) 6, 11 or 16.

In adults, clinically, it may resemble squamous cell carcinoma (SCC). It may be associated with HPV infection and immunocompromised status.

Prevalence

Prevalence of conjunctival papillomas ranges from 4 to 12%.

TABLE 10.1: A simplified classification of conjunctival nonmelanocytic tumour

	Child	*Adult*
Benign	• Conjunctival papilloma • Conjunctival hereditary benign intraepithelial dyskeratosis	• Conjunctival papilloma • Papilloma of caruncle • Conjunctival pseudoepitheliomatous hyperplasia • Keratoacanthoma • Conjunctival hereditary benign intraepithelial dyskeratosis • Conjunctival dacryoadenoma • Epithelial inclusion cyst
Premalignant	Conjunctival intraepithelial neoplasia	• Conjunctival keratotic plaque • Actinic keratosis • Conjunctival intraepithelial neoplasia
Malignant	Conjunctival invasive squamous cell carcinoma	• Conjunctival invasive squamous cell carcinoma • Mucoepidermoid carcinoma • Spindle cells carcinoma

Types of conjunctival papilloma

Conjunctival papillomas are categorized based on appearance, location, patient's age, propensity to recur after excision, and histopathology into:

- Squamous cell papilloma (infectious papilloma),
- Limbal papilloma, and
- Inverted papilloma.

They demonstrate an exophytic growth pattern. Interestingly, inverted papillomas exhibit exophytic and endophytic growth patterns.

Conjunctival papilloma also can be classified based on gross clinical appearance, as either pedunculated or sessile.

- *Pedunculated type* is synonymous with infectious conjunctival papilloma and squamous cell papilloma.
- *Sessile papilloma.* The limbal conjunctival papilloma often is referred to as noninfectious conjunctival papilloma because it is believed that limbal papillomas arise from UV radiation exposure. Because of its gross appearance, limbal papillomas are typed as sessile.

Clinical features

Squamous cell papilloma (infectious papilloma)

- This lesion is benign and self-limiting.
- It is seen commonly in children and young adults.
- Most lesions are asymptomatic without associated conjunctivitis or folliculitis.
- Anatomically, it is commonly located in the inferior fornix, but it also may arise in the limbus, caruncle, and palpebral regions.
- The lesion may be bilateral and multiple. It becomes confluent in extreme cases to form massive papillomatosis.
- Grossly, squamous cell papilloma appears as a greyish red, fleshy, soft, pedunculated mass with an irregular surface (cauliflower-like) (Fig. 10.7A).

Limbal papilloma

Characteristic features of limbal papilloma are (Fig. 10.7B):

- This lesion is typically benign.
- It is seen commonly in older adults.
- Anatomically, the lesion commonly occurs at the limbus or the bulbar conjunctiva.
- These lesions may spread centrally toward the cornea or laterally toward the conjunctiva.
- Visual acuity may be affected if the lesion grows centrally.
- These lesions almost always are unilateral and single.
- It has a lighter pink colour than the childhood variety.
- They tend to have variable proliferation potential with a tendency to slowly enlarge in size.

Inverted conjunctival papilloma

- This lesion (Fig. 10.7C) is slow growing and is seen commonly in the nose, paranasal sinuses, or both. The lacrimal sac and the conjunctiva are uncommon sites.
- The papilloma may invaginate inward into the underlying conjunctiva and substantia propria to present as a mixed inverted exophytic papilloma.
- Rarely, it appears as solid or cystic solitary nodule at the limbus, plica semilunaris, and tarsal conjunctiva.
- The lesion is unilateral and unifocal and does not recur after surgical excision.

Histopathology

Squamous cell papillomas (e.g. infectious papilloma, viral conjunctival papilloma) are composed of multiple branching fronds emanating from a narrow pedunculated base. Individual fronds are surrounded by connective tissue, each having a central vascularized core. Acute and chronic inflammatory cells are found within these fronds. The epithelium is acanthotic, nonkeratinized stratified squamous epithelium without atypia. Numerous goblet cells are seen along with acute inflammatory cells. Koilocytosis is exhibited. The basement membrane is intact (Fig. 10.8).

Squamous papilloma is reported to have low malignant potential. Occasionally, as a variant, it can assume an inverted growth pattern, which has a greater tendency

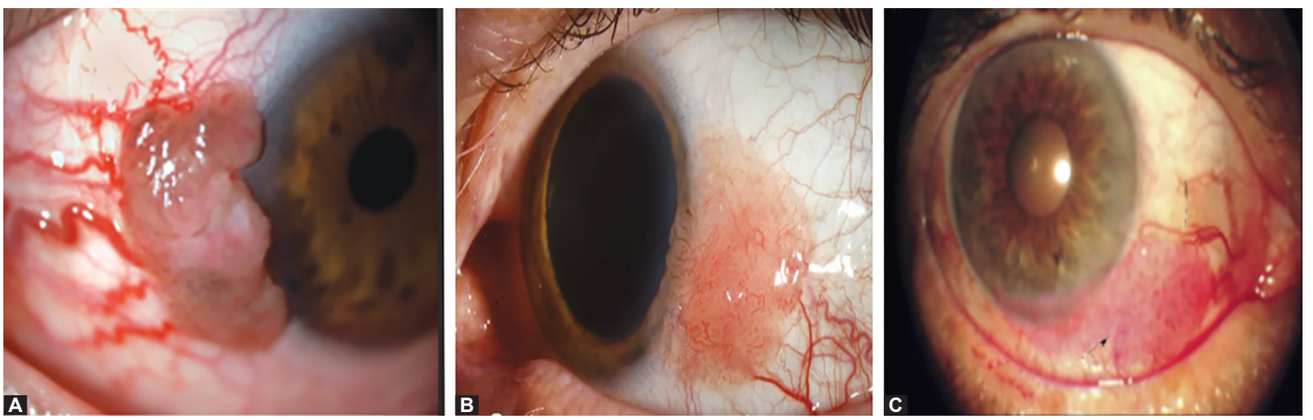


Fig. 10.7: Conjunctival papilloma. A, Squamous papilloma; B, Limbal papilloma; C, Inverted papilloma.

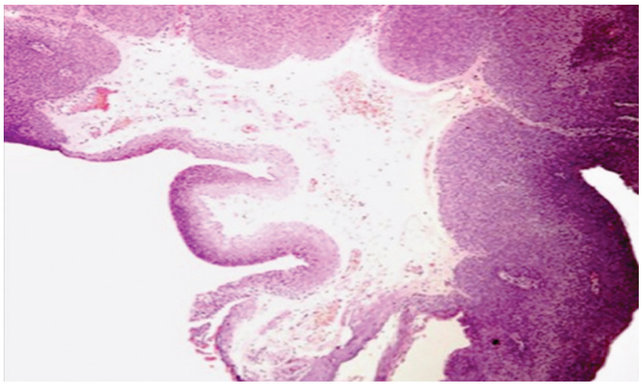


Fig. 10.8: Microphotograph of squamous papilloma. The lesion shows numerous vascularized papillary fronds lined by acanthotic epithelium.

towards malignant transformation into transitional cell carcinoma, SCC, or mucoepidermoid carcinoma.

Limbal papillomas are sessile lesions arising from a broad base with a gelatinous appearance. Corkscrew vascular loops and feeder vessels are seen. The epithelium is acanthotic, displaying varying degrees of pleomorphism and dysplasia. The epithelium surface may be keratinized with foci of parakeratosis within the papillary folds. The basement membrane is intact.

Inverted papillomas exhibit exophytic and endophytic growth patterns. Those arising from the conjunctiva tend to be less aggressive in malignant transformation, than those present in nose and paranasal sinuses. The lesions are composed of lobules of epithelial cells extending down into the stroma. The lesion may be elevated or umbilicated. Epithelial cells do not demonstrate atypia, and dysplastic changes are uncommon for conjunctival inverted papillomas. The cytoplasm is vacuolated in some cells. They may resemble squamous papilloma or pyogenic granuloma. Numerous goblet cells are intermixed with the epithelium. Cystic lesions may be seen secondary to the confluence of goblet cells. The lesion may contain melanin granules and/or melanocytes.

Differential diagnosis

- Ichthyosis
- Sebaceous gland carcinoma
- Conjunctival squamous cell carcinoma

Treatment

Observation and patient reassurance are indicated for squamous cell papillomas. These lesions may regress spontaneously over time. Seeding may follow excision, resulting in multiple new lesions.

Surgical excision by the "no-touch technique" followed by cryotherapy is the treatment of choice. For limbal papillomas, excision is indicated to rule out neoplastic changes.

Other reported treatment modalities include:

- Laser
- Dinitrochlorobenzene immunotherapy
- Interferon alpha 2b (IFN-α-2b)
- Topical mitomycin C (MMC) drops
- Recent reports show significant role of oral cimetidine in treating recalcitrant and recurrent conjunctival papillomatosis. It enhances the immune system by inhibiting certain T-cell functions.

2. Papilloma of caruncle

Santos-Gómez Leal et al reported in their series that this lesion has a prevalence of 25.66% of the tumours of the caruncle, with a mean age of 27 years (3–65 years old). It was more common in women 1.2:1. The characteristics are the same of the papilloma of conjunctiva in adults, with the same treatment.

3. Conjunctival pseudoepitheliomatous hyperplasia

Etiology

Pseudoepitheliomatous hyperplasia (PEH) is a benign reactive inflammatory proliferation of the epithelial cells, which simulates carcinoma clinically and histopathologically. It occurs as a conjunctival lesion secondary to irritation by concurrent or preexisting stromal inflammation such as pterygium, pinguecula, allergic conjunctivitis, and foreign body. It can be a result of various conditions such as infections, inflammation, trauma, and malignancy and is also referred to as pseudocarcinomatous hyperplasia.

Clinical features

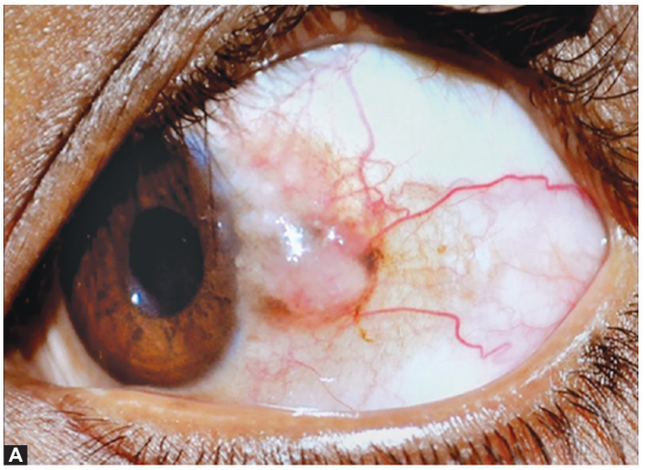
It appears as an elevated leukoplakic pink lesion in the limbal area. Usually, PEH appears as a well-demarcated plaque or nodule with scaling and crusting. Papules or nodules may range from <1 cm to several centimetres in size. The colour of the lesion may be as that of the mucosa or pigmented as in case of melanoma (Fig. 10.9A).

Histopathology

Histopathologically, it is characterised by massive acanthosis, hyperkeratosis, and parakeratosis of the conjunctival epithelium (Fig. 10.9B).

Differential diagnosis

The differential diagnosis of PEH is SCC, keratoacanthoma, granular cell tumour, necrotizing sialometaplasia, malignant melanoma, and verrucous carcinoma. The presence of a nodular lesion with feeder vessels and intrinsic vascularity should raise a suspicion of invasive SCC and hence, the word "diagnostic dilemma" is one of the most appropriate words for this lesion.



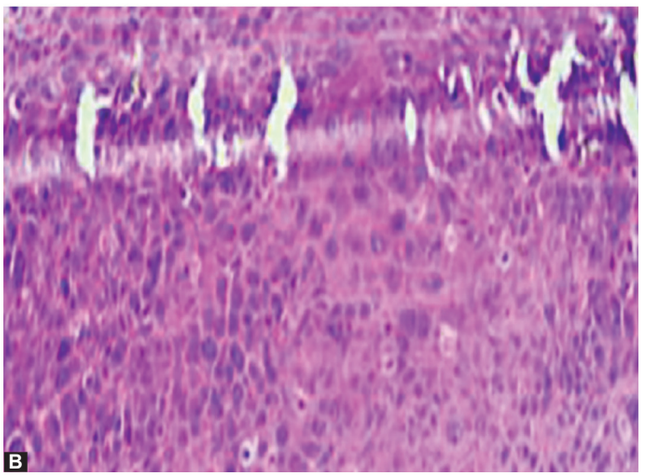


Fig. 10.9: A, Pseudoepitheliomatous hyperplasia. Elevated leukoplakic pink lesion in the temporal limbal area with apparent feeder vessels and pigmentation. Resembles a nodular OSSN; B, HPE shows hyperplasia, acanthosis, elongation of rete ridges.

Treatment

- ***Complete excision and additional cryotherapy*** would constitute optimal management, as difficulty prevails in clinically and histologically differentiating the lesion from low-grade SCC.
- ***Use of photodynamic therapy and microdebrider shaver*** in its treatment has also been reported.

4. Keratoacanthoma

Etiology

Keratoacanthoma, a benign epithelial tumour that grows rapidly and shows spontaneous regression, has a characteristic central crater filled with keratin. Keratoacanthomas arise most commonly in sun-exposed skin and only rarely in mucosa. The few reported cases of conjunctival keratoacanthoma have occurred mostly in whites. It is a variant of conjunctival pseudoepitheliomatous hyperplasia. Though it is a benign lesion, some believe that it may represent an abortive malignancy that rarely progresses to SCC.

Clinical features

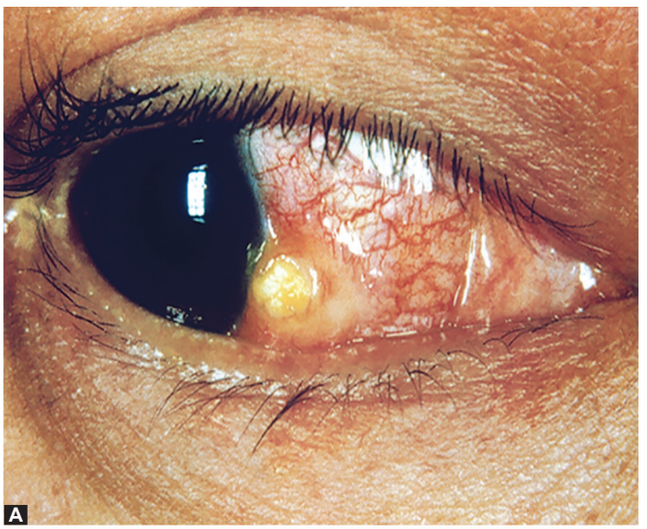
Appearance of keratoacanthoma is that of a nodule with rounded edges and a central keratin filled crater in its mature form approximately 1–2 cm in diameter in size.

Presenting symptoms include a sudden onset of conjunctival injection or irritation or a rapidly enlarging mass.

Onset as well as the progression is rapid (Fig. 10.10A).

Histopathology

It shows a central crater containing a keratotic plug surrounded by acanthotic conjunctival epithelium that includes horn pearls. The tumour cells have abundant, glassy, eosinophilic cytoplasm and small nuclei. In the deeper regions, tumour cells show cellular atypia and infiltrative growth associated with an inflammatory reaction (Fig. 10.10B).



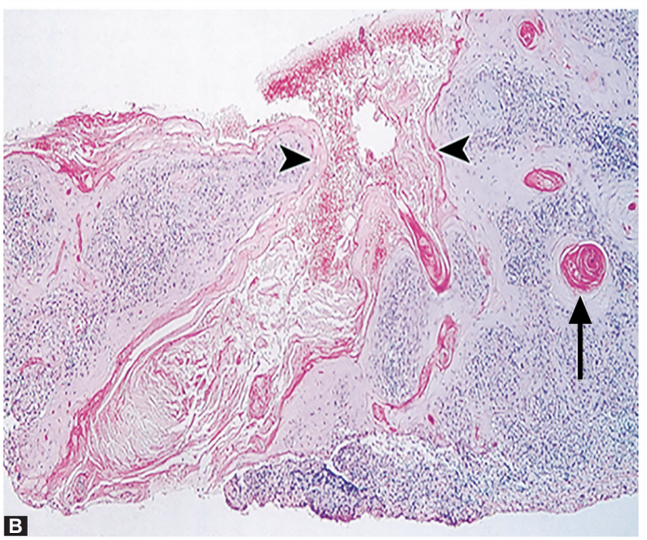


Fig. 10.10: Keratoacanthoma of conjunctiva: A, White, dome-shaped mass with a central crater filled with white material; B, HPE showing a central crater containing a keratotic plug (arrowheads), surrounded by acanthotic conjunctival epithelium including horn pearls (arrow).

Differential diagnosis

The main differential diagnosis of keratoacanthoma is squamous cell carcinoma which develops more slowly than keratoacanthoma, is less well demarcated, and is not usually characterised by the central keratin filled crater. Although it remains controversial whether squamous cell carcinoma can arise from keratoacanthoma, it is more likely that such tumours are well differentiated squamous cell carcinoma mimicking closely the histological features of keratoacanthoma. Such cases underline the importance of close follow-up of all patients with diagnosed conjunctival keratoacanthoma.

Treatment

Complete excision of the tumour and cryotherapy is the treatment of choice.

5. Dacryoadenoma

Etiology

Dacryoadenoma is a rare condition affecting children and young adults. It is not known if it is congenital or acquired. It originates from the surface epithelium by the downward invagination of tubular formations that undergo secondary and tertiary ramifications and develop glandular lobules similar to those seen in normal lacrimal glands but with abundant goblet cells.

Clinical features

It appears as a translucent and fleshy pink lesion in the bulbar, forniceal or palpebral conjunctiva (Fig. 10.11A).

Histopathology

The surface epithelium overlying the mass is not normal conjunctival squamous epithelium, but it is a modification in the form of a superficial layer of columnar to cuboidal cells surmounting several nuclei similar to the cells lining the subepithelial lumen-forming units. Scattered myoepithelial cells were associated with the acinar-type epithelium of the tumour, and there were goblet cells intermixed. Neither light nor electron microscopy disclosed the presence of true ducts (Fig. 10.11B).

Differential diagnosis

Differential diagnosis includes lymphoma and other pink- or salmon-coloured masses in the conjunctiva.

Treatment

Because of the benign nature of this disease, it can be followed with careful monitoring and photography. However, because of the rarity of this condition and the concern for other more serious problems, an excisional biopsy can help to differentiate this from other possible diseases.

6. Hereditary benign intraepithelial dyskeratosis

Etiology

This is a rare autosomal dominant condition of the conjunctiva and other mucous membranes. It is specifically

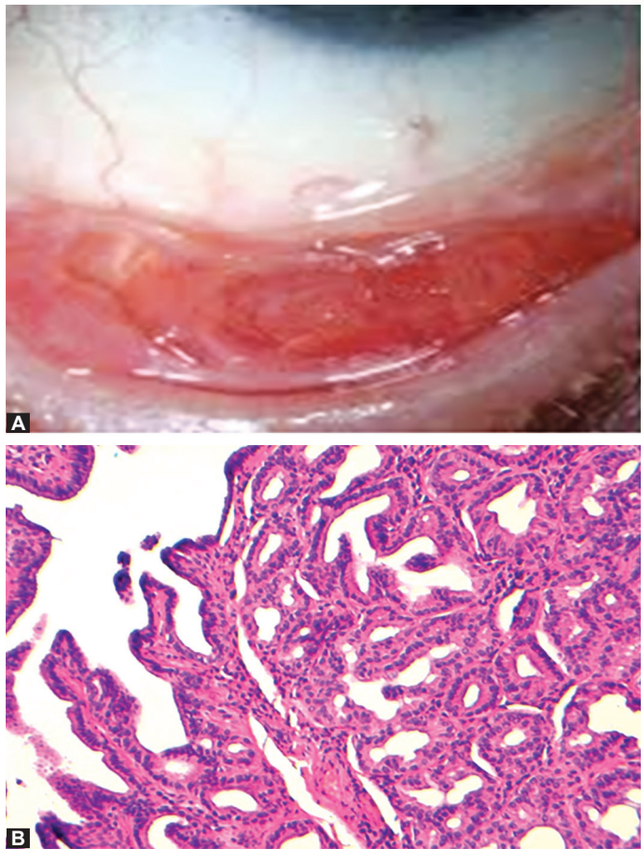


Fig. 10.11: A, Conjunctival dacryoadenoma; B, HPE showing acinar type of epithelium.

seen among the inbred Caucasians, African-Americans, and Native Americans known as Haliwa Indians but, is also seen in the population of other descent. Due to the classic sign of marked, bilateral conjunctival hyperaemia, this disease is sometimes referred to as the **"red eye"** disease.

Clinical features

Hereditary benign intraepithelial dyskeratosis (HBID) has a distinct clinical picture. Diagnosis can be made by slit lamp biomicroscopy alone. Affected patients may have ocular involvement, oral involvement, or both.

Oral manifestations of the disease include white, spongy plaques of the buccal mucosa, tongue, or lips.

Ocular manifestations of the disease are characterised by:

- *Bilateral, conjunctival injection* with whitish-grey, elevated, gelatinous corneal plaques located in the perilimbal area, most often nasally or temporally.
- *Corneal plaques* may become visually significant with extension into the central visual axis, disruption of the normal ocular surface, or induction of astigmatism.
- *Corneal neovascularization* can occur around areas of plaque formation. Most commonly, neovascularization

develops superficially, but involvement of the mid to deep stroma has been reported (Fig. 10.12A).

Although originally thought to be congenital, HBID is not present at birth. Symptoms begin in early childhood and follow a waxing and waning pattern throughout life. Few reports have suggested that plaques spontaneously shed, however, there has never been photographic documentation of this phenomenon. Excision of plaques leads to recurrence and further exacerbation in most cases.

Histopathology

In addition to clinical diagnosis, HBID can also be diagnosed histopathologically. Ocular and oral plaques are distinctively characterised by acanthosis, dyskeratosis, and parakeratosis within the stratified squamous epithelium. The hallmark dyskeratotic cells in hereditary benign intraepithelial dyskeratosis have a dense cytoplasm and pyknotic nuclei. Beneath the epithelium in the stroma lies a chronic, mild to moderate lymphocytic inflammatory response. The adjacent stratified squamous epithelium of the conjunctiva can be normal or acanthotic (Fig. 10.12B).

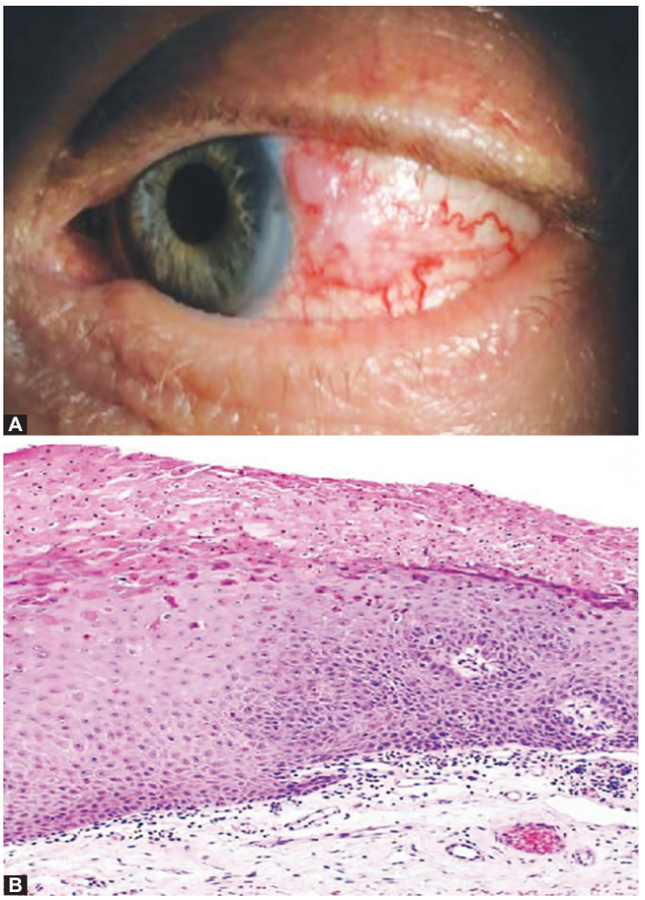


Fig. 10.12: A, Hereditary benign intraepithelial dyskeratosis; B, Acanthosis and underlying chronic lymphocytic infiltrate in HBID.

Treatment

Treatment of HBID has proven to be very difficult and there is no cure to date.

- *Medical management* with ATTs, topical corticosteroids, and systemic immunosuppression only minimally improves the symptoms.
- *Topical management* alone has not shown to reduce plaque size in the majority of cases.

Smaller symptomatic lesions are treated conservatively with lubricants and topical steroids while ***larger lesions*** require ***local resection*** with ocular surface reconstruction. It carries no risk of malignancy, but recurrence is common. Hence, complete excision with clear margins is warranted.

7. Epithelial inclusion cyst

The epithelial inclusion cyst could be spontaneous or occur after inflammation, surgery or trauma. It has round form lined by conjunctival epithelium with clear fluid inside. If the fluid has epithelial cells, they can go to the bottom of the cyst and form a pseudohypopyon. If they are asymptomatic they can be observed, but if it is too large it can be excised completely with primary closure of the conjunctiva.

This entity has been covered in detail in chapter (cysts of conjunctiva, page 104).

CONJUNCTIVAL PREMALIGNANT NONMELANOCYTIC EPITHELIAL NEOPLASMS

1. Conjunctival keratotic plaque and actinic keratosis

The conjunctival keratotic plaque and actinic keratosis are two lesions that cannot be clinically differentiated from each other. Shields et al in their clinical series of 1663 conjunctival tumours had four conjunctival keratotic plaques and four actinic keratoses, each representing less than 1% of the entire conjunctival tumour.

Clinical features

The two lesions develop on the limbal or the bulbar conjunctiva in the interpalpebral region. They are a flat and white plaque that appear gradually. They are a lot similar to the conjunctival intraepithelial neoplasia (CIN).

Keratotic plaque denotes local hyperplasia and cornification of the conjunctival and the corneal epithelium. It is a rare pathologic lesion when affecting the eye. Many other names have been used in the literature for these lesions, such as tyloma (Gallenga), cornification of the conjunctiva (Best), keratosis (Mohr and Schein) and conjunctival callosities (Saemisch).

Actinic keratosis is seen commonly as a focal leukoplakic lesion occurring at the interpalpebral area presenting as flat, white plaque sometimes with a frothy covering. Actinic keratosis progresses very gradually and shows no tendency towards aggressive growth. Clinically, it may often be indistinguishable from conjunctival intraepithelial

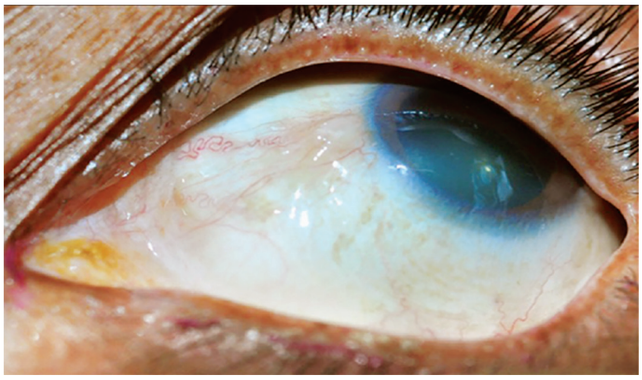


Fig. 10.13: Actinic keratosis, a focal leukoplakic lesion seen in the interpalpebral area. It can easily be misdiagnosed as pinguecula.

neoplasia (CIN). Rose bengal staining of the surface of the lesion tips the clinical suspicion in favour of CIN (Fig. 10.13).

Histopathology

The histopathology of the keratotic plaque shows acanthosis of the epithelium and keratinization of the conjunctival epithelium and parakeratosis.

The actinic keratosis also called senile keratosis shows a similar histopathologic aspect with prominent keratosis and usually appears over a chronic inflammation like a pingueculum or pterygium.

Treatment

- *Document and observe:* Some ophthalmologists prefer to document the lesion and follow it, particularly in elderly patients, because the prognosis is excellent.
- *Excision and supplementary cryotherapy:* Because of the clinical similarity with CIN, the finding of leukoplakia in the conjunctiva is a relative indication of excision and cryotherapy.

2. Conjunctival intraepithelial neoplasia

The conjunctival intraepithelial neoplasia is a squamous neoplasia confined to the conjunctival epithelium that sometimes transgresses the basement membrane but strictly do not have the potential to metastasize, unlike the invasive squamous carcinoma. Some authors are talking about an entire spectrum of epithelial neoplasia called "ocular surface squamous neoplasia", that includes dysplasia, CIN and invasive squamous cell carcinoma.

Etiology

CIN is more common in elderly and immunosuppressed patients with considerable sunlight exposure, but children can develop it.

The human papillomavirus (HPV) and sunlight are considered the main predisposing factors for the conjunctival intraepithelial neoplasia. But nevertheless, in some CIN there is not to be found the HPV with the polymerase chain reaction.

Shields et al found in their series that the CIN corresponded to 39% of all premalignant and malignant lesions and to 4% of all the conjunctival lesions.

Clinical features

Conjunctival intraepithelial neoplasia could be a fleshy, sessile or minimally elevated lesion that frequently appears perilimbal in the interpalpebral zone or less commonly begins in the inferior fornix or palpebral conjunctiva.

CIN can extend into the adjacent corneal epithelium. It appears like a grey superficial opacity that can be avascular or it can have fine vascularization (Fig. 10.14).

Histopathology

The histopathology of mild CIN shows a partial replacement of the surface epithelium by abnormal epithelial cells that do not have a normal maturation. In severe CIN, the histopathology is characterised by a total replacement of epithelium by abnormal epithelial cells with no maturation.

Treatment

- *Excision with adequate margins* is the recommended approach. Incomplete removal increases the recurrences.
- *Growth removal with alcohol corneal epitheliectomy,* partial lamellar sclerokeratoconjunctivectomy and double freeze thaw cryotherapy: This is for more localised lesions.
- *Low dose irradiation* with strontium-90
- *Chemotherapy with topical mitomycin C* for recurrent or persistent cases. Also interferon alpha 2b and 5-fluorouracil are used.
- *Cidofovir*.

CONJUNCTIVAL MALIGNANT NONMELANOCYTIC EPITHELIAL NEOPLASMS

1. Conjunctival invasive squamous cell carcinoma

Etiology

Conjunctival invasive squamous cell carcinoma is when CIN breaks the basement membrane of the conjunctival epithelium and invades the stroma and the underlying tissues.

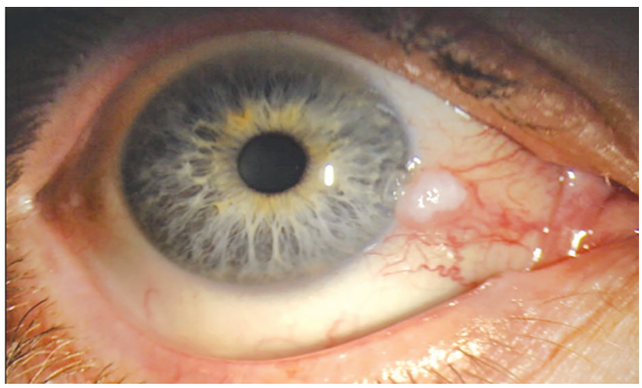


Fig. 10.14: Conjunctival intraepithelial neoplasia. Moderate dysplasia: Limbal leukoplakic appearing lesion with feeder vessels.

Conjunctival invasive squamous cell carcinoma. It tends to occur in patients with xeroderma pigmentosum and atopic eczema. It is associated to the dysfunction of T lymphocytes and the HPV type 16.

Incidence of the conjunctival invasive squamous cell carcinoma varies from 0.02 to 3.5 per 100,000, it is less frequent than the CIN, with a frequency of 60% of all conjunctival malignant epithelial tumours and 7% of all the conjunctival neoplasms. It is more common in men (75%) and elderly patients (75% >60 years old).

Clinical features

It occurs frequently in the interpalpebral region of Caucasian elderly or immunosuppressed patients. Most commonly it begins at the limbus (75%). The lesion can be a sessile, gelatinous, circumscribed or papillomatous mass with leukoplakia. Some lesions are diffuse, flat and poorly delineated that can be confused with a chronic conjunctivitis, scleritis or pagetoid invasion of sebaceous carcinoma.

The lesion is invasive to the local structures (orbit, cornea and the globe), but with a low range of metastasis (1–2%). If the invasion causes glaucoma, and the intraocular pressure is uncontrollable, that may necessitate an enucleation.

Diagnosis

Conjunctival invasive squamous cell carcinoma cannot be differentiated clinically from CIN.

- *Excisional biopsy:* If the lesion is localised and small.
- *Impression cytology:* If the lesion is diffuse.
- *Ultrasound biomicroscopy:* To determine the limbal invasion.

Histopathology

The histopathology of conjunctival invasive squamous cell shows well-differentiated neoplasm with abnormal epithelial cells that have mitotic activity and keratinic production. Some lesions can be poorly differentiated with pleomorphic cells, giant cells and a lot of mitotic figures with acanthosis and dyskeratosis.

Treatment

- *Excision with adequate margins and double freeze thaw cryotherapy:* This is the first approach. Incomplete removal increases the recurrences. If the lesion is large, adjuvant amniotic membrane grafting can be used.
- *Growth removal with alcohol corneal epitheliectomy,* partial lamellar sclerokeratoconjunctivectomy and double freeze thaw cryotherapy.
- *Chemotherapy with topical mitomycin C* for recurrent or persistent cases. Also interferon alpha 2b and 5-fluorouracil are used.
- Cidofovir
- Enucleation
- Eyelid-sparing exenteration

Note. As conjunctival invasive squamous cell carcinoma or OSSN is an extremely important topic, it has been described in detail in Chapter 11.

2. Mucoepidermoid carcinoma

Mucoepidermoid carcinoma is an aggressive variation of the conjunctival invasive squamous cell carcinoma, that is less than 5% of this lesion.

Clinical features

Mucoepidermoid carcinoma is more frequent in elderly men (>70 years old). It can be in the bulbar conjunctiva but can also be presented in the caruncle and then it can invade the orbit and paranasal sinuses. It can have a yellow, globular and cystic appearance. This neoplasm tends to invade the globe or the orbit. In the intraocular space, the mucoepidermoid carcinoma can produce a mucinous cyst in the suprauveal space. The mucin production is more frequent in the intraocular space than in the bulbar conjunctiva.

Histopathology

The histopathology of mucoepidermoid carcinoma shows an epidermoid component, mucin and goblet cells with signet cells. The pseudoadenomatous hyperplasia also have goblet cells and mucin that is why this is a differential diagnosis of the mucoepidermoid carcinoma. Other differential diagnosis is a primary mucoepidermoid carcinoma of the paranasal sinuses.

3. Spindle cell carcinoma

The spindle cell carcinoma is a more aggressive type of conjunctival invasive squamous cell carcinoma that is very rare with only 20 cases reported in the literature. It has a worst prognosis because of the tendency for intraocular invasion and metastasis to the lung and bone.

Histopathology

The histopathology of spindle cell carcinoma shows pleomorphic spindle cells that look like fibroblasts. This can be misdiagnosed as fibrosarcoma, therefore the diagnosis must be confirmed with immunohistochemistry and electron microscopy.

MELANOCYTIC EPITHELIAL TUMOURS

CLASSIFICATION

Benign

- Conjunctival melanocytic naevi
- Congenital ocular melanosis
- Racial melanosis
- Primary acquired melanosis

Premalignant

Primary acquired melanosis.

Malignant
Conjunctival melanoma.

BENIGN MELANOCYTIC EPITHELIAL TUMOURS

Conjunctival melanocytic naevus

Etiology

Melanocytic tumours of the conjunctiva have a wide spectrum. Conjunctival naevus usually becomes apparent in the first to the second decade of life as a group of small nests of pigmented epithelial cells in the basal layer of the epithelium. As the cells migrate into the underlying stroma in the second to third decade, the naevus progresses to become the compound naevus. Further migration occurs, and cells reside in the stroma as subepithelial naevus during the third and fourth decades. Naevus is more commonly seen in Caucasians (89%) than Africans (6%) and Asians (5%). Although most conjunctival naevi are pigmented (84%), some may be amelanotic or partially pigmented (16%).

Clinical features

Conjunctival naevi are mostly located near the limbus in the interpalpebral area (72%) (Fig. 10.15A). Other locations are the caruncle, semilunar folds, fornix, tarsus, and cornea. Characteristic clear cysts strongly support the diagnosis. They may also clinically demonstrate feeder vessels (64%) and intrinsic vascularity (77%). It can vary in size, colour, and location. Conjunctival naevus can increase in size in growing young children, during puberty, pregnancy, and sun exposure.

Malignant transformation was estimated to be <1%. Sudden increase in size, alteration in colour, and increased thickness with prominent feeder vessels indicates malignant transformation.

Histopathology

Histopathologically, a conjunctival naevus is composed of nests of benign melanocytes in the stroma near the basal layers of the epithelium (Fig. 10.15B). Positive immunostaining for HMB-45 and Ki-67 are useful adjuncts in differentiating benign melanocytic lesion from suspected malignant entities.

Differential diagnosis

Irregular and diffuse growth pattern poses a diagnostic confusion with primary acquired melanosis (PAM), melanoma, lymphoma, and pigmented OSSN.

Treatment

Periodic (annual) observation with slit-lamp measurements and serial photographs is the management of choice. If excision is performed for cosmesis or suspected growth, it is preferable not to leave any residual lesion.

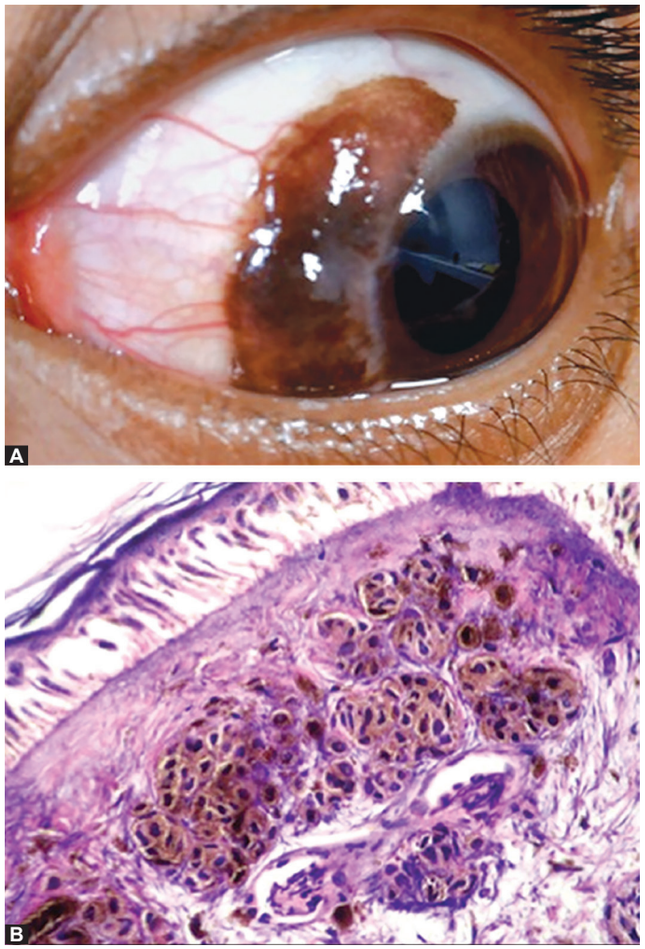


Fig. 10.15: A, Conjunctival naevus with intralesional cysts and feeder vessels; B, Microphotograph of a subepithelial naevus showing clumps of melanocytes with no cellular atypia (OM ×40).

Indications for excision of conjunctival naevus

- Distinct onset in middle age or later life
- Location in the fornix or palpebral conjunctiva
- Lesions more than 10 mm in diameter
- Exuberant feeder blood vessels
- Exuberant intrinsic vascularity and haemorrhage
- Lesions with no cysts
- Lesions with dark uniform pigmentation
- Corneal epithelial invasion >3 clock hours and 3 mm from limbus
- Episcleral fixity
- Cosmetic concern

Congenital ocular melanosis

Ocular melanocytosis is a congenital pigmentary condition of the periocular skin, sclera, orbit, meninges, and soft palate. It appears as irregular patches of scleral and episcleral pigmentation varying in colour from brown to

grey. Typically, there is no conjunctival pigment. It can involve the underlying uveal tract. Since it has an episcleral involvement, it does not move with manipulation of the conjunctiva. This condition imparts a 1 in 400 risk for the development of uveal melanoma.

The scleral pigmentation of congenital ocular melanocytosis has typical features and location (Fig. 10.16). It must be differentiated from other diffuse epibulbar pigmentary conditions like primary acquired melanosis and complexion related pigmentation. Unlike these other conditions it is attached to the sclera and does not move with manipulation of conjunctiva.

If associated with the dermal component, it is known as oculodermal melanocytosis or naevus of Ota. It is mandatory that all patients with oculodermal melanocytosis undergo fundus examination to exclude uveal melanocytosis or melanoma. Associated hairline pigmentation predisposes them for meningeal melanoma and palate pigmentation to esophageal melanoma, therefore, these signs should be elicited with appropriate referrals when needed.

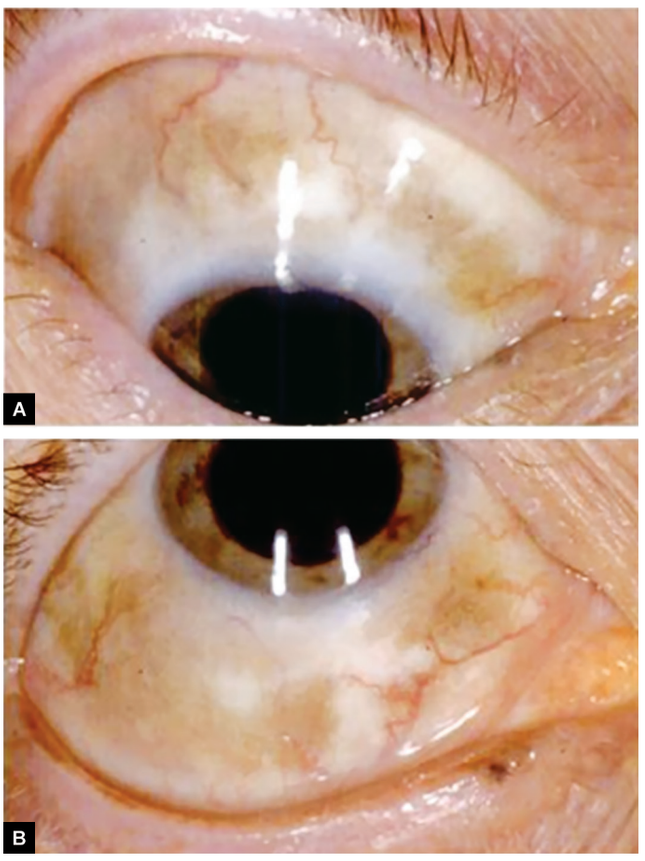


Fig. 10.16: A, Scleral melanocytosis showing diffuse patchy brown pigment in superior aspect of the right eye; B, Same patient shown in Fig. 10.16A demonstrating pigment in the inferior aspect of the right eye.

Racial melanosis or complexion-related conjunctival pigmentation

Etiology

The most common benign conjunctival lesions are due to racial (secondary) melanosis. Racial melanosis is present in 92.5% of African Americans, 35.7% of Asians, 28% of Hispanics, and 4.9% of Caucasians. This benign entity is the result of epithelial melanocytes producing excessive melanin which is transferred into surrounding keratinocytes. Typically racial melanosis is bilateral, asymmetric, occurs in the interpalpebral fissures, and does not contain cysts.

Clinical features

Complexion-related conjunctival pigmentation is a relatively common bilateral, flat, diffuse conjunctival pigmentation (Fig. 10.17). It is more concentrated in the limbus, often for 360°, with variable pigmentation at the perilimbal bulbar conjunctiva and cornea. Uncommonly, it may also involve the fornix and rarely the palpebral conjunctiva. Periodic observation is recommended.

PREMALIGNANT MELANOCYTIC EPITHELIAL TUMOURS

Primary acquired melanosis

Reese noted the tendency of a certain type of acquired conjunctival pigmentation to evolve into melanoma and named it precancerous melanosis. Zimmerman replaced the term with benign acquired melanosis, which was further modified by WHO as Primary Acquired Melanosis (PAM) in 1980.

Primary acquired melanosis (PAM) can either be regarded as benign (PAM without atypia) or represent a precancerous lesion (PAM with atypia).

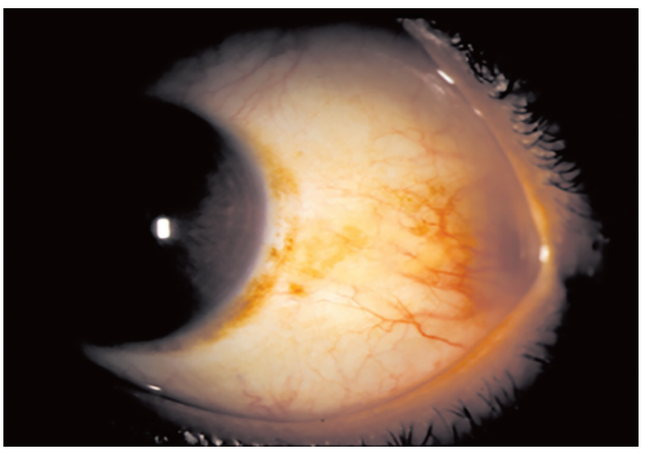


Fig. 10.17: Physiologic (racial) melanosis. Flat conjunctival pigmentation present bilaterally starting at the limbus and most prominent in the interpalpebral zone is likely to be racial melanosis in a darkly pigmented patient.

Etiology

Sunlight exposure may play a role in the development of PAM. It has also been seen in patients with neurofibromatosis raising suspicion that it may have a developmental relationship to the neural crest.

Clinical features

Primary acquired melanosis usually manifests in the middle age as unilateral, superficial, solitary, patchy, diffuse or multifocal pigmentation of the bulbar, forniceal and palpebral conjunctiva, and cornea (Figs 10.18 and 10.19).

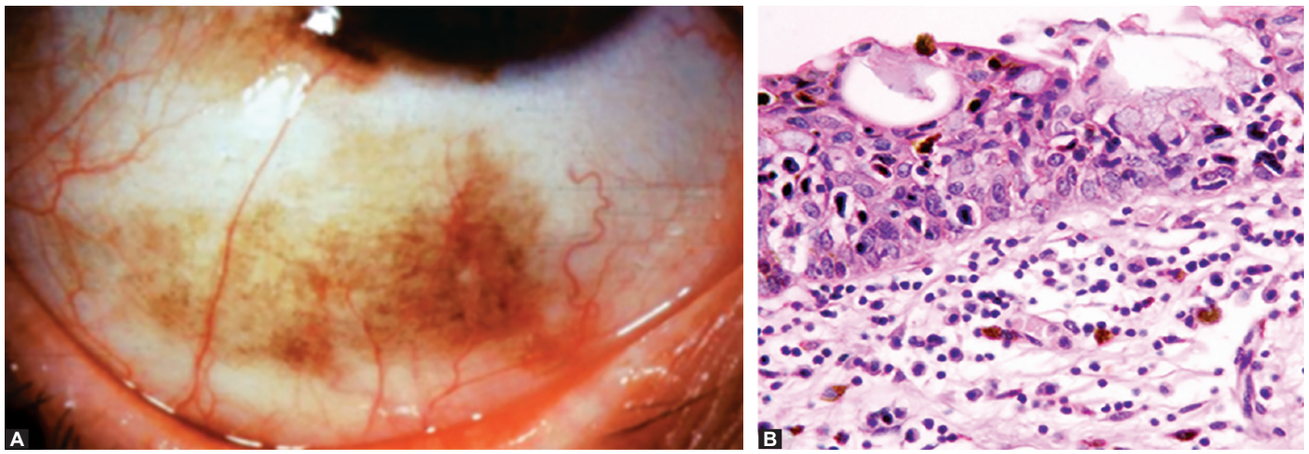


Fig. 10.18: Primary acquired melanosis: A, Diffuse pigmentation of bulbar conjunctiva in an elderly male; B, HPE of PAM with cellular atypia.

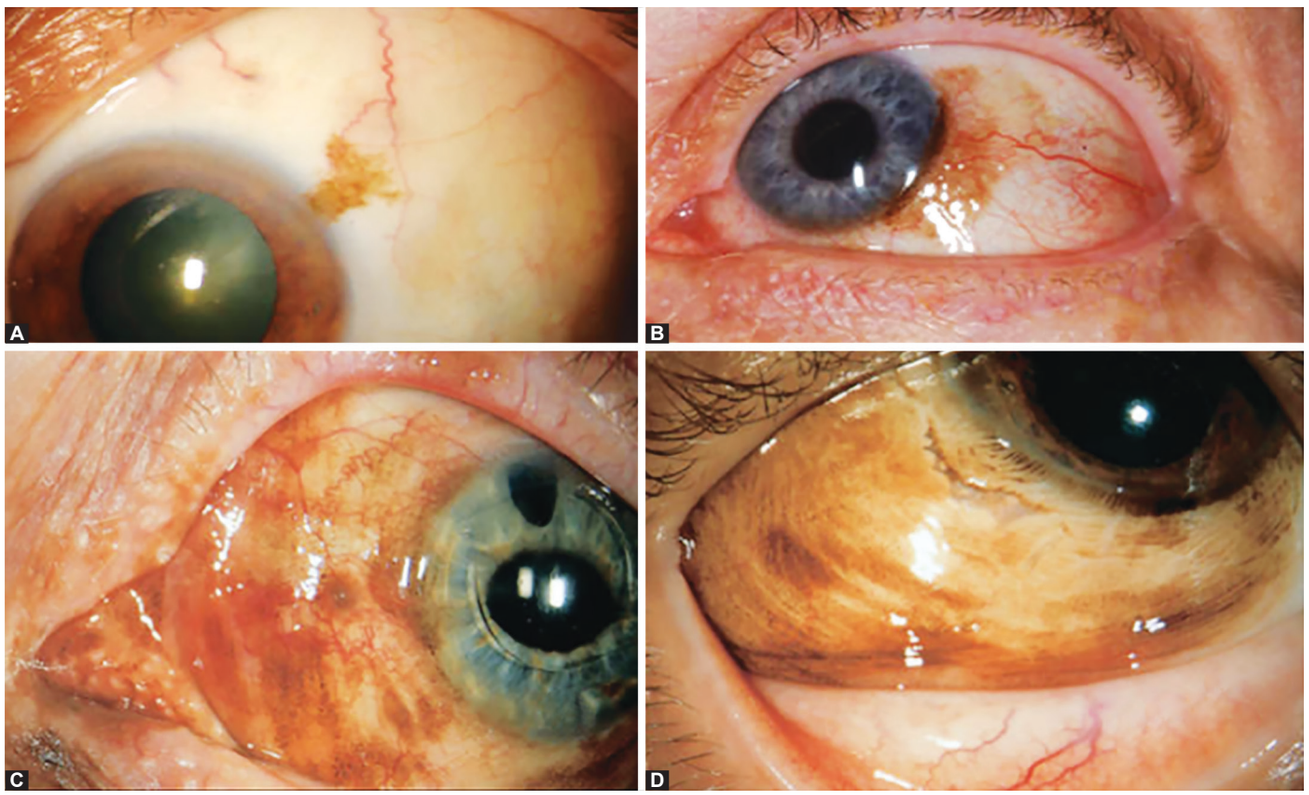


Fig. 10.19: Primary acquired melanosis (PAM) with varying extent of involvement. A, PAM involving less than 1 clock hour of bulbar conjunctiva; B, PAM involving 4 clock hours of conjunctiva with slight corneal extension; C, PAM involving more than 6 clock hours of bulbar conjunctiva with extension into the cornea; D, PAM involving entire bulbar conjunctiva (12 clock hours).

Occasionally, PAM can be amelanotic. In PAM without atypia, there occurs melanin pigmentation of the basal epithelium with or without hyperplasia of cytological benign melanocytes. This may progress to cytological atypical melanocytes to form PAM with atypia, where there is an increased risk of developing melanoma.

Malignant transformation. Clinically, larger the extent of PAM, greater the risk of malignant transformation. The PAM risk factors are summarised in Table 10.2.

Indications for biopsy of PAM

- Lesion diameter >5 mm
- Documented progression
- Thickening of involved conjunctiva
- Distant nodule arising within the lesion
- Nutrient vessels
- Involvement of the cornea
- Involvement of the palpebral conjunctiva
- Personal history of cutaneous/uveal melanoma
- Dysplastic naevus syndrome in patient or close relative.

A simple biopsy can determine whether a pigmented conjunctival tumour is a naevus, primary acquired melanosis, or conjunctival melanoma. As seen below, primary acquired melanosis typically affects one eye, in middle-aged, fair-skinned people.

Histopathology

A PAM without atypia is best characterised by minimal melanocytic hyperplasia along the basal epithelial layer of the conjunctiva. PAM with atypia shows usually isolated or confluent nests of atypical melanocytes. Pagetoid spread can also be observed. The melanocytes exhibit varying signs of atypia as large abnormal cells, prominent nucleoli, a high nuclear-cytoplasmic ratio, and mitotic figures.

It can be differentiated histologically by the degree of atypia of melanocytes. Without atypia, PAM is a benign melanocytic proliferation. With atypia, PAM may progress to malignant melanoma. Progression to melanoma occurred in 0% of PAM without atypia, 0% of PAM with mild atypia, and 13% of PAM with severe atypia. Multivariable analysis revealed that the most significant factor for both PAM recurrence and progression to melanoma was extent of PAM in clock hours.

Differential diagnosis

- *Racial melanosis*—almost always bilateral.
- *Conjunctival naevus*—does not extend into cornea or fornices, may have very little pigmentation, and can have cysts.
- *Secondary acquired melanosis*, e.g. foreign body, ciliary body melanoma, blood filled cysts.
- *Oculodermal melanocytosis* (naevus of Ota)— mostly in Blacks and Asians, unilateral, blue/grey colour, and does not move with the conjunctival epithelium.
- *Malignant melanoma*—growth and biopsy makes the diagnosis.
- *Congenital melanocytosis*—present at birth.
- *Conjunctival foreign body*
- *Exogenous pigmentation* (e.g. mascara)

Treatment

Management strategies are:

- *Observation* for PAM without atypia
- *Cryotherapy* for PAM with atypia <3 clock hours
- *Excision with excision edge cryotherapy* for PAM >3 clock hours
- *Topical MMC* for diffuse PAM with atypia.

MALIGNANT MELANOCYTIC EPITHELIAL TUMOURS

Conjunctival melanoma

Etiology

Conjunctival melanomas (CM) comprise approximately 2% of all ocular surface malignancies and 0.25% of all melanomas. Non-Hispanic Caucasians are most commonly affected, with an incidence of 0.2–0.8 per million. Conjunctival melanoma is most common in light-skinned individuals. Non-Whites are rarely affected.

Age and sex. Studies have failed to show consistent predilection for sex. It usually presents in the middle-aged or elderly. The median age of presentation is approximately 60 years.

TABLE 10.2: Primary acquired melanosis (PAM) risk factors

Higher risk	*Lower risk*
>3 clock hours involvement of conjunctiva	Small, circumscribed without extensive involvement of conjunctiva
Extension onto cornea	Confinement to the conjunctiva
Nodular	Flat
Multifocal	One lesion
Highly vascular	Minimal vasculature
History of skin or conjunctival melanoma	No history of skin or conjunctival melanoma
Older age	Young age

Risk factors have been difficult to ascertain due to the low incidence of disease. However, studies have reported risk for those with fair skin and hair, a family history, certain genetic syndromes (familial melanoma syndromes, xeroderma pigmentosum), and significant ultraviolet (UV) light exposure. Sunlight exposure is also suggested as a cause, but that fails to explain the occurrence of melanoma in the fornices and palpebral conjunctiva.

The surveillance, epidemiology, and end results (SEER) study reported an increased incidence of conjunctival melanoma in White males. The mechanism is hypothesized to be secondary to increased UV light exposure. There is also a strong association between primary acquired melanosis (PAM) and conjunctival naevi with CM. In particular, PAM with severe atypia transforms into CM in 13% of cases, with greater risk associated with more extensive circumferential spread of PAM. PAM without atypia or with mild atypia does not demonstrate a predisposition for progression to melanoma. Conjunctival melanomas arise from three sources: PAM (75%), *de novo* (20%), and naevus (5%); with PAM being most common and naevus being least common. Other risk factors are dysplastic naevus syndrome, neurofibromatosis, and xeroderma pigmentosum.

Conjunctival melanoma may rarely develop secondary to continuous touch from an eyelid margin melanoma (implantation melanoma).

Clinical features

Conjunctival melanoma appears (Fig. 10.20A) as a pigmented fleshy mass located in the bulbar, forniceal or palpebral conjunctiva. As a variant, it may appear as diffuse or multifocal with ill-defined margins particularly if arising from PAM. It occasionally originates in the forniceal and palpebral conjunctivae. It may extend to cover the cornea or even arise as a primary corneal tumour. Melanoma can be sparsely pigmented or amelanotic. It is typically amelanotic, fleshy, and vascular when it recurs after prior excision.

Classification. Conjunctival melanoma is classified according to the AJCC-TNM classification (Table 10.3).

Regional metastasis involves preauricular and submandibular lymph nodes. Sentinel lymphangiography makes it possible to accurately remove lymph nodes and is indicated in tumours more than 2 mm in thickness. Distant metastasis occurs in the brain, liver, skin, and bone.

Histopathology

Histopathologically (Fig. 10.20B), conjunctival melanoma is composed of variably pigmented malignant melanocytes. The cells may range from relatively low grade spindle cells to more anaplastic epithelioid cells. It initially affects the basal area of the epithelium but readily invades the stroma where it has access to conjunctival lymphatic channels.

Immunophenotype studies have shown that these cells are positive for S-100 protein, tyrosinase, melan-A, HMB-45, HMB-50, and microphthalmia conscription factor at high levels, suggesting that these are good diagnostic markers for these tumours.

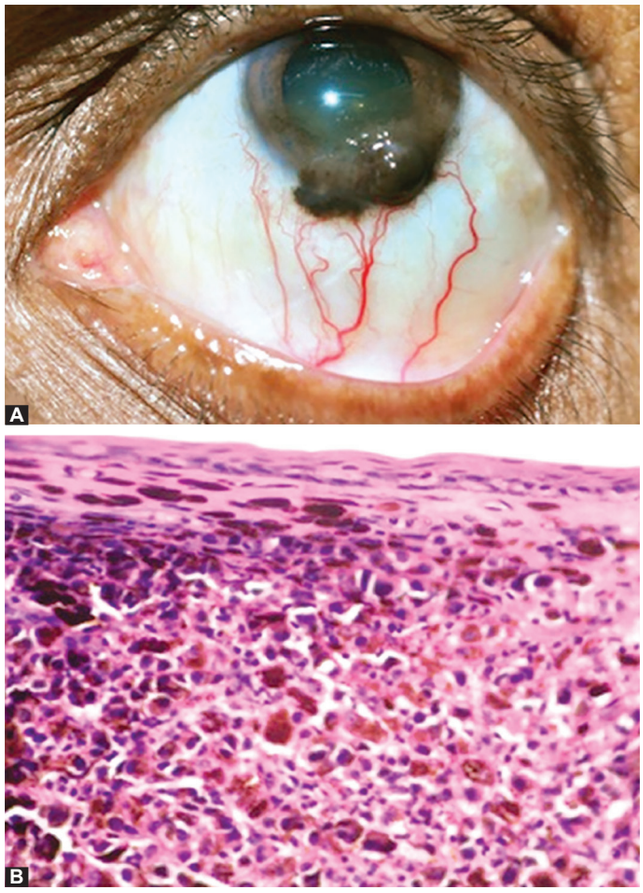


Fig. 10.20: Conjunctival melanoma. A, Elevated, nodular, pigmented mass at the inferior limbus with extension into the peripheral cornea. Feeder vessels and intrinsic vessels present; B, HPE of CM showing variably pigmented melanocytes with mitotic activity.

Differential diagnosis

Differential diagnoses are the same as for PAM (*see* page 118).

Treatment

Treatment of conjunctival melanoma is based on certain established principles:

- *Complete excision* in the episcleral plane with 4 mm clinically clear margins.
- *Alcohol keratoepitheliectomy* of the corneal epithelial component.
- *Partial lamellar sclerokeratectomy* if sclera and corneal stroma are involved.
- *Double freeze-thaw cryotherapy* to the excision edge, excision base cryotherapy if sclera is involved and the extent of involvement is <3 clock hours.

TABLE 10.3: AJCC–TNM classification of conjunctival melanoma

Stage	*Clinical*	*Stage*	*Pathological*
Primary tumour (T)			
Tx	Primary tumour cannot be assessed	Tx	Primary tumour cannot be assessed
T0	No evidence of primary tumour	T0	No evidence of primary tumour
T (is)	Malignant melanoma confined to conjunctival epithelium	T (is)	Malignant melanoma confined to conjunctival epithelium
T1	Malignant melanoma of the bulbar conjunctiva	pT1	Malignant melanoma of the bulbar conjunctiva
T1a	<1 quadrant	pT1a	<0.5 mm thick with invasion of substantia propria
T1b	>1 but <2 quadrant		
T1c	>2 but <3 quadrant	pT1b	>0.5–1.5 mm thick, with invasion of substantia propria
T1d	>3 quadrant		
		pT1c	>1.5 mm thick, with invasion of substantia propria
T2	Malignant melanoma of palpebral conjunctiva, forniceal conjunctiva, and/or caruncule	pT2	Malignant melanoma of palpebral conjunctiva, forniceal conjunctiva, and/or caruncule
T2a	<1 quadrant	pT2a	≤0.5 mm thick, with invasion of substantia propria
T2b	>1 quadrant but not involving caruncle	pT2b	>0.5–1.5 mm thick, with invasion of substantia propria
T2c	<1 quadrant and involving caruncle	pT2c	>1.5 mm thick, with invasion of substantia propria
T2d	>1 quadrant and involving caruncle		
T3	Malignant melanoma with local invasion	pT3	Malignant melanoma invading the eye, eyelid, nasolacrimal system, sinuses or orbit
T3a	Globe		
T3b	Eyelid		
T3c	Orbit		
T3d	Paranasal sinus		
T4	Malignant melanoma with local invasion	pT4	Malignant melanoma with intracranial extension
Regional lymph node (N)			
Nx	Regional lymph node cannot be assessed		
N0a	No regional lymph node metastasis, biopsy done		
N0b	No regional lymph node metastasis, no biopsy done		
N1	Regional lymph node metastasis		
Distant metastasis (M)			
M0	No distant metastasis		
M1	Distant metastasis		

Source: Edge SB, Byrd DR. Complon CC, et al. (Eds). Carcinoma of the conjunctiva. In: AJCC Cancer Staging Manual. 7th ed., New York. Springer, 2010.
AJCC: American Joint Committee on Cancer. TNM: Tumour, node and metastasis

- *Postoperative adjuvant plaque brachytherapy* if excision base is clinically detected to have been involved >3 clock hours and if the excision base is positive for tumour cells on histopathology. Since conjunctival melanoma is not radiosensitive, brachytherapy is not used as a sole treatment.
- *Extended enucleation with en bloc excision* if the tumour has deep corneal or scleral invasion or intraocular extension.
- *Eyelid sparing exenteration* if the tumour extends into the orbit. Proton beam radiotherapy may be used as an alternative and/or adjunct to exenteration.
- *Systemic chemotherapy* is administered with combination of IFN and interleukin-2 in disseminated melanoma.

Prognosis

- *Local recurrence* after therapy is as high as 50–70% at 10 years.
- *Overall mortality* rate is 25% in 10 years and more than 30% in 15 years.

TABLE 10.4: Prognostic indicators for conjunctival melanoma	
Higher risk	*Lower risk*
Tarsus, caruncle, forniceal involvement	Localised
Deeper extension into tissue	Limbal or bulbar
Thickness >1.8 mm	Thin
Lymphadenopathy	
Lid margin involvement	

- *Critical thickness* that may serve as a prognostic factor, according to various studies implies a value between 0.8 mm and 4 mm.
- *Conjunctival melanoma.* AJCC-TNM staging predicts the prognosis and outcome.
- *Prognostic risk factors* are summarised in Table 10.4.

STROMAL TUMOURS OF THE OCULAR SURFACE

VASCULAR STROMAL TUMOURS

1. Pyogenic granuloma

Etiology

Pyogenic granuloma is a misnomer; it is neither pyogenic nor a granuloma, but exuberant granulation tissue. It is a fibrovascular response to a tissue insult such as surgical or nonsurgical trauma or inflammation.

Clinical features

Pyogenic granuloma (Fig. 10.21) has rapid onset and progression and presents as fleshy, elevated, red, richly vascular mass. It can be round to ovoid, typically pedunculated, rarely broad-based, and even mushroom shaped. It may be seen in any part of the conjunctiva, limbus, and the cornea.

Histopathologically, it is composed of granulation tissue with lymphocytes, plasma cells, scattered neutrophils, and numerous small caliber vessels.

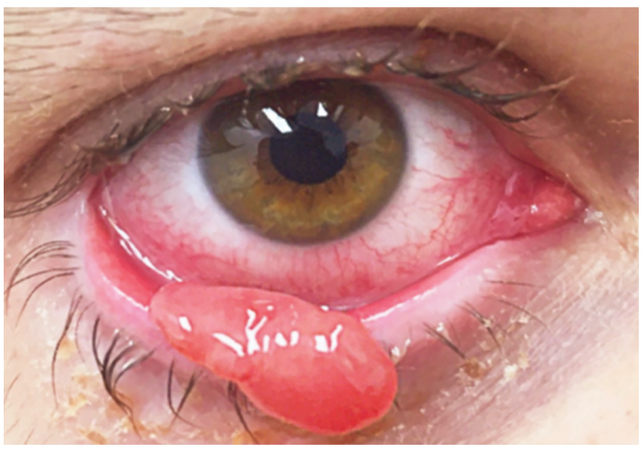


Fig. 10.21: Pyogenic granuloma of conjunctiva.

Treatment

- *Topical steroids,* when diagnosed early, are effective
- *Excision at the base followed by cauterization or cryotherapy* to the excision base is the treatment of choice for larger, unsightly, symptomatic or bleeding pyogenic granuloma.
- *Care of the inciting factor,* if found to minimize the risk of recurrence is important along with excision. It is usual to find a suture knot or a foreign body at the base if the cause is prior surgery or trauma.
- Low dose plaque brachytherapy can be employed for exuberant recurrence.

2. Capillary haemangioma

Etiology

Capillary haemangioma is common in the eyelids but is less common in the orbit and uncommon in the conjunctiva. It is present in 1–4% of all births and is more common in premature infants and often following chorionic villus sampling. The periocular lesion appears within the first few weeks after birth and usually has superficial or deep components. Primary conjunctival capillary haemangiomas are rarely reported. Seen as diffuse red elevated lesion, it may present as a small conjunctival component of a predominant eyelid lesion in a neonate. It may uncommonly develop as an acquired lesion in adults.

Clinical features

Capillary haemangioma (Fig. 10.22A) is usually a cutaneous, subcutaneous, or deep orbital lesion and commonly presents a few weeks after birth. The usual clinical course of infantile cutaneous or subcutaneous haemangiomas includes an initial engorgement (age 6–12 months) followed by regression (age 1–7 years). It usually regresses spontaneously and hence is kept under close observation. Spontaneous regression is often complete by 4–5 years of age.

Histopathology

Histologically, it is composed of lobules of proliferating endothelial cells separated by thin fibrous septa (Fig. 10.22B).

Differential diagnosis

The differential diagnosis for capillary haemangioma includes rhabdomyosarcoma, lymphangioma, chloroma, neuroblastoma, orbital cysts, and cellulitis.

Treatment

Management generally is observation until spontaneous regression. Active intervention is performed only if the lesion is very extensive and causes amblyopia, mechanical ptosis, exposure keratopathy, or optic neuropathy. Intervention is also considered if the lesion is unsightly, ulcerates and bleeds and relentlessly progresses.

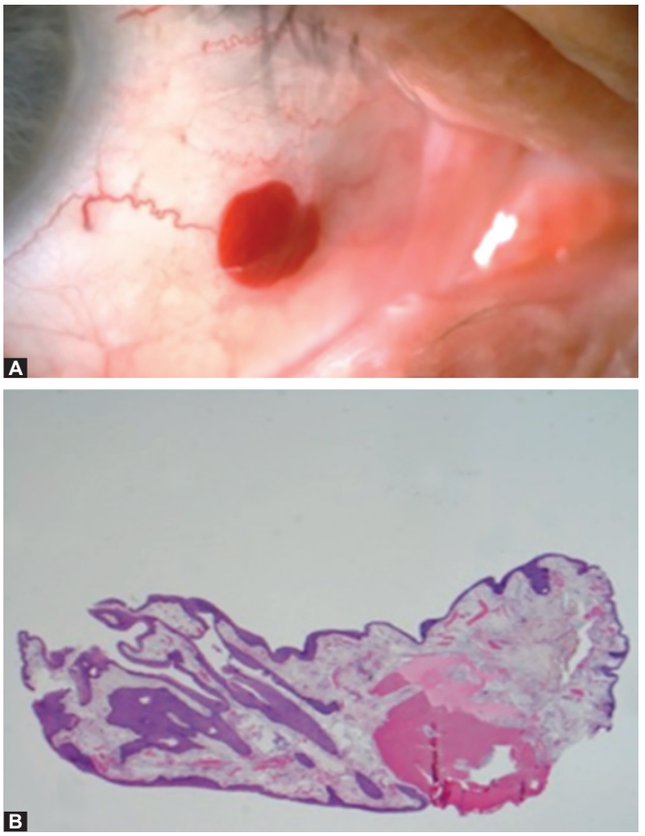


Fig. 10.22: A, Conjunctival capillary haemangioma; B, HPE showing thin walled vascular channels filled with blood.

Typical primary intervention is intralesional steroid injection. Triamcinolone is used in the maximum dose of 6 mg/kg body weight. In general, one injection results in significant involution of the lesion. Injection may be repeated at 6–8 weeks interval if there is a suboptimal response. Dermatologists favour using high-dose oral steroids over 4–6 weeks. Systemic propranolol 2 mg/kg body weight is being tried as an alternative therapy with encouraging results. If the tumour does not respond to these measures or if there is an indication for an emergent management (as in ulcerated and bleeding lesions), controlled surgical excision or debulking may help.

3. Cavernous haemangioma

Etiology

Cavernous haemangioma is a common orbital tumour, but relatively uncommon in the conjunctiva. It arises often from the conjunctival vessels and rarely from the scleral, muscular or orbital vessels. It appears as red blue lesion in the deep conjunctival stroma.

Clinical features

Conjunctival cavernous haemangioma appears at any age as a red or blue lesion (Fig. 10.23A), usually in the stroma. It can be solitary or it can occur in association with other cavernous haemangiomas such as Sturge-Weber syndrome, or diffuse neonatal haemangiomatosis. The literature is not entirely clear as to whether such lesions are a pure cavernous haemangioma or a combination of types.

It consists of multiplicity of venous channels of varying calibre, shows no tendency to involution and may become larger and trouble-some by bleeding sometimes giving rise to bloody tears after remaining stationary for years.

Histopathology

Histology shows dilated congested veins separated by connective tissue with smooth muscles in the walls of the blood vessels (Fig. 10.23B).

Treatment

The tumour is radiosensitive but can be treated well by surgical excision.

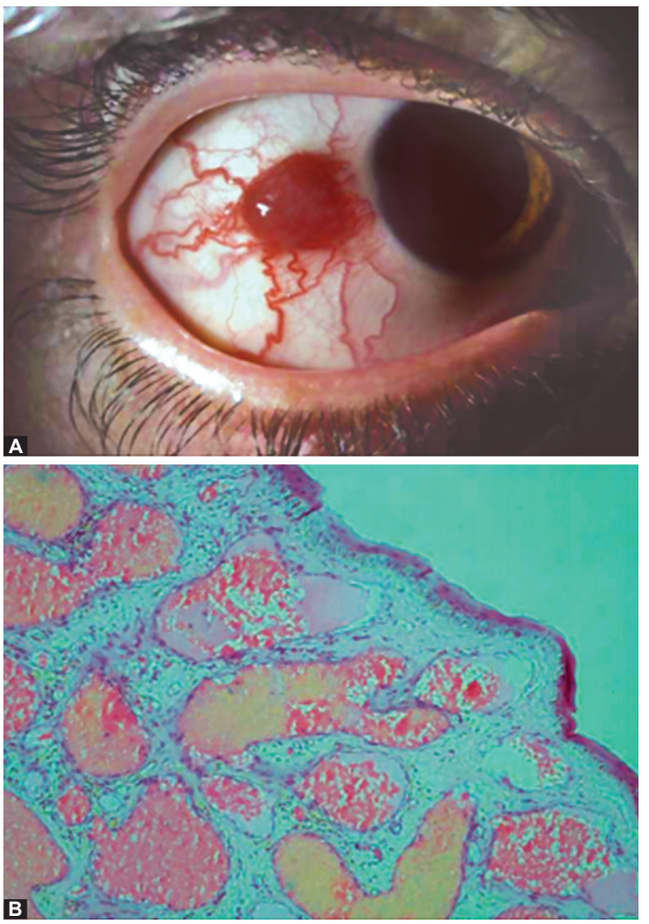


Fig. 10.23: A, A smooth, oval, dark red, lobular surface mass in the temporal side of bulbar conjunctiva with engorged episcleral and conjunctival vessels around the lesion; B, Histopathologic examination showed multiple, endothelium-lined cavernous spaces surrounded by fibromyxoid tissue (haematoxylin and eosin, magnification × 100).

4. Conjunctival varix

Etiology

Varix refers to venous malformation of the conjunctiva that may range from an isolated single channel to dilated complex venous channels. Often, it is the anterior extension of an orbital varix.

Clinical features

Conjunctival varix (Fig. 10.24) usually is an anterior extension of an orbital varix. It may be directly visible as large, distinct blood vessels or it may be deeper and have a diffuse faint blue black colour. It is generally movable and not fixed to sclera.

Histopathology

Histopathologically, varix is composed of venous channels, ranging from one dilated vessel to more complex channels. Thrombosis and hyalinization are frequent.

Differential diagnosis

Lymphangioma and cavernous haemangioma as their features can overlap.

Treatment

Management is generally conservative by observation and symptomatic treatment. They can be excised for cosmetic reasons, but one should be aware that they may have orbital extensions.

5. Racemose haemangioma

Racemose haemangioma involves loops of dilated arteries and veins communicating directly without the interface of a capillary bed. The lesion is clinically seen as loops of dilated vessels in the conjunctival stroma with no evidence of a stimulus for such vascularization or planned direction.

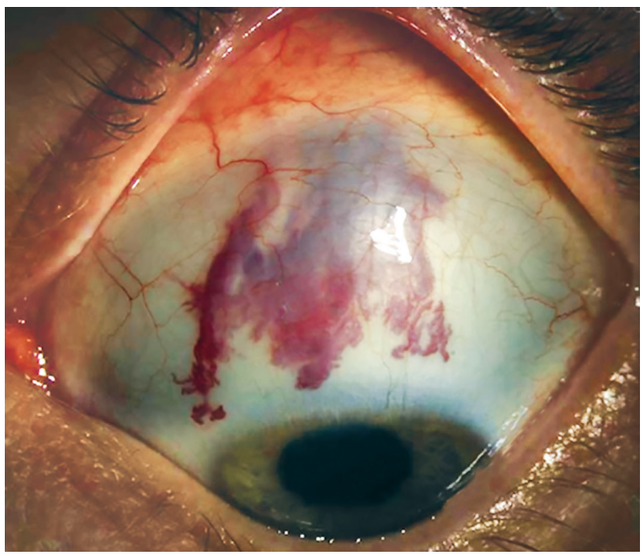


Fig. 10.24: Conjunctival varix.

It may be associated with Wyburn-Mason syndrome. It is generally observed unless symptomatic or a cosmetic blemish.

6. Haemangiopericytoma

Etiology

Haemangiopericytoma is known to be derived from the vascular pericytes but is recently considered to be a vascular entity of the solitary fibrous tumour. It is a very rare conjunctival tumour.

Clinical features

Haemangiopericytoma (Fig. 10.25A) presents as an elevated or pedunculated reddish pink mass, that has no distinct clinical features. It shows slow progressive growth and often is continuous with a more posterior orbital component.

Histopathology

It is a tumour composed of an abnormal proliferation of pericytes that surround blood vessels. With routine light microscopy, a characteristic feature is the 'staghorn' branching of blood vessels in the tumour (Fig. 10.25B).

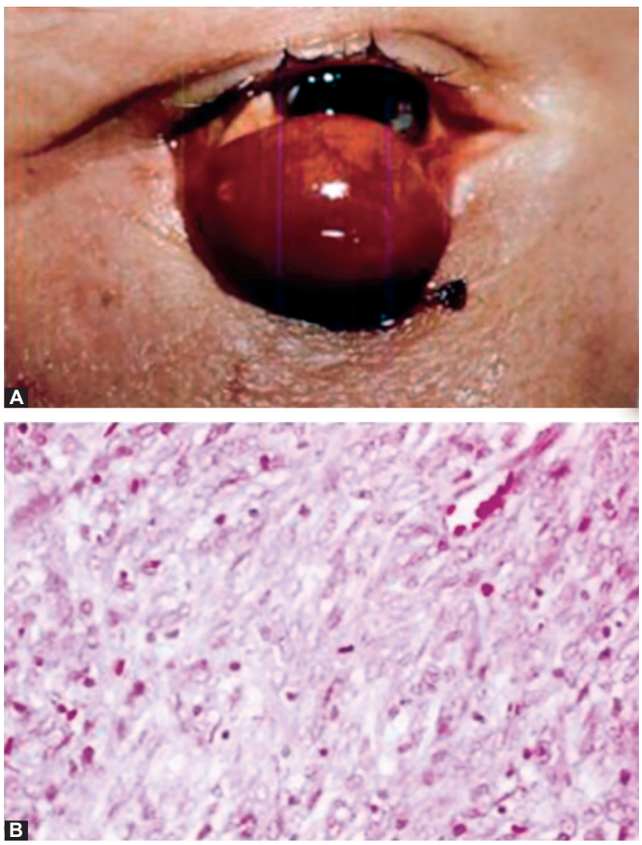


Fig. 10.25: A, Haemangiopericytoma arising from the inferior fornix in a 40-year-old woman (*Courtesy:* Hans Frossnikiaus, MD); B, Histopathology of lesion in Fig. 10.25A showing solid tumour composed of spindle-shaped cells and blood vessels (haematoxylin and eosin × 63).

Treatment

The diagnosis is rarely made clinically. A wide surgical resection with tumour-free margins is advocated.

7. Kaposi sarcoma

Etiology

Kaposi sarcoma was a rare tumour before the AIDS era. It is a malignant tumour seen more frequently in immunocompromised individuals, specifically with HIV, caused by the human herpesvirus 8. Sometimes the conjunctival Kaposi sarcoma is the first sign of immunocompromised status.

Clinical features

Kaposi's sarcoma (Fig. 10.26) clinically appears as single or multifocal vascular red conjunctival lesion, which may become confluent and resemble haemorrhagic conjunctivitis. May also appear as a bright red fleshy to violaceous nodular mass, commonly seen in the fornix.

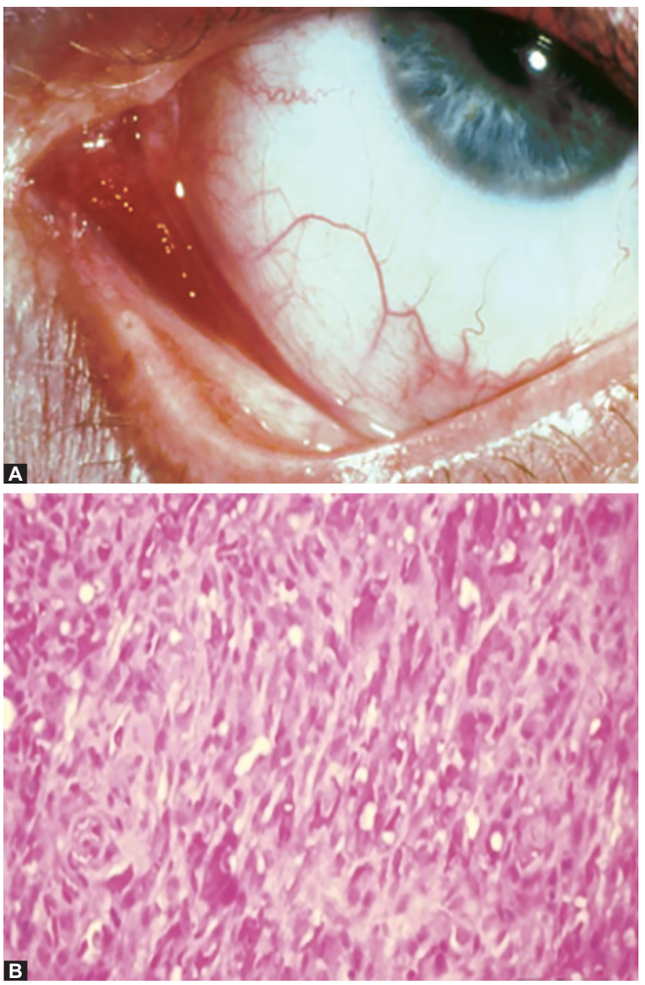


Fig. 10.26: A, Kaposi sarcoma affecting medial aspect of conjunctiva into the fornix; B, HPE reveals myriads of vascular channels.

Differential diagnosis

The differential diagnosis includes granuloma pyogenicum, cavernous haemangioma, foreign body granuloma, malignant melanoma, metastatic tumour, and chronic subconjunctival haemorrhage.

Treatment

- It is moderately responsive to IFN-α-2b and chemotherapy and markedly responsive to low dose radiotherapy (800–2000 cGy).
- The current thinking is in favour of the immediate institution of highly active antiretroviral therapy. The tumour is known to involute with improved immune status.
- Surgical excision: In extensive, large tumours, loosely connected with healthy tissue.

8. Lymphangiectasia

Etiology

When lymphatic channels in the conjunctiva are dilated and prominent, the condition is called lymphangiectasia. There exists a communication with conjunctival veins, and hence these dilated channels may often be filled with blood, termed haemorrhagic lymphangiectasia. It can occur spontaneously or after trauma or inflammation.

Clinical features

Lymphangiectasia can lead to irritation and redness from desiccation of the overlying conjunctival epithelium, epiphora, if the lacrimal puncta become functionally occluded by overhanging conjunctiva, blurred vision, and pain.

Surrounding conjunctiva appears edematous and is occasionally associated with sub-conjunctival haemorrhage (Fig. 10.27). It is intermittent with a resolution between episodes.

Treatment

No treatment is required unless it is a cosmetic blemish. Liquid nitrogen cryotherapy is effective in treating conjunctival lymphangiectasia probably by collapsing the lymph vessel walls onto each other with a cryogenic burn and also by scarring down the conjunctiva to the underlying globe.

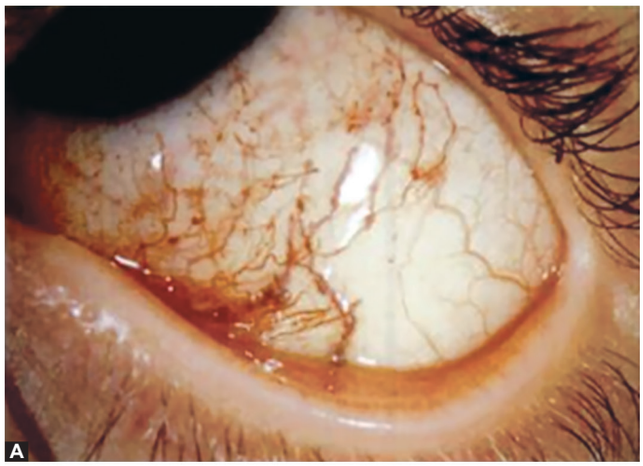
9. Lymphangioma

Etiology

Lymphangioma is a benign tumour of the lymphatic vessels that usually manifests in the first decade of life. It can occur as an isolated conjunctival lesion, but often represents a superficial component of an orbital lymphangioma.

Clinical features

Conjunctival lymphangiomas (Fig. 10.28A) generally appear as a visible mass without affecting vision, or the globe. These are multiloculated lesions with dilated cystic spaces. Those that contain blood are called chocolate cysts.



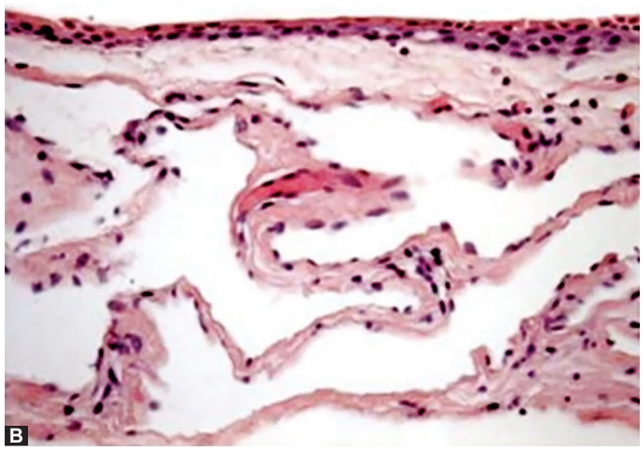
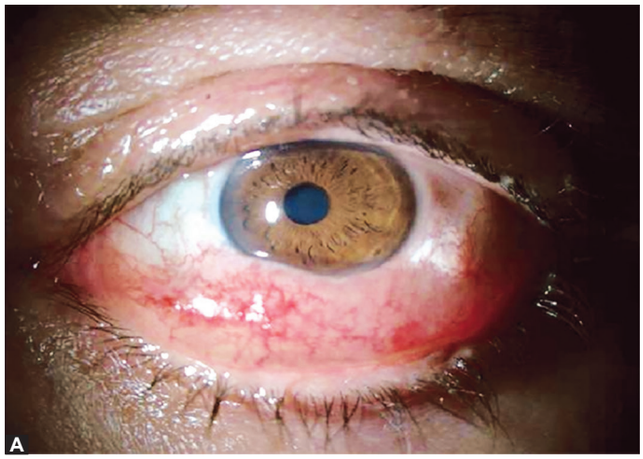


Fig. 10.27: A, Conjunctival haemorrhagic lymphangiectasia in a 10-year-old boy; B, Histopathology of conjunctival lymphangiectasia, showing bloodless ectatic vascular channels lined by thin endothelial cells.



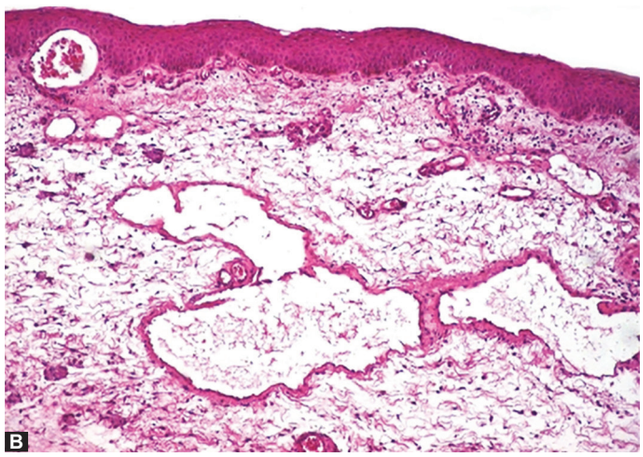


Fig. 10.28: A, Conjunctival lymphangioma; B, Histology showing a lymphatic proliferation and ectasia with a network of empty bloodless channels lined by flattened endothelium with the presence of some blood vessels and inflammatory infiltrate.

Histopathology

It histopathologically (Fig. 10.28B) appears as nonencapsulated, irregular mass composed of numerous cyst-like channels that contain clear fluid, blood, or a combination of the two. The ectatic channels are lined by somewhat attenuated endothelial cells. These channels are separated by loose connective tissue that contains aggregates of small lymphocytes, sometimes forming lymph follicle.

Treatment

- Surgical debulking
- CO_2 laser-assisted debulking
- β-irradiation using strontium-90 applicator
- Brachytherapy is used with partial success.

FIBROUS TUMOURS

Fibrous tumours manifest generally as slowly progressive acquired white stromal tumours in adults. These could be a well-circumscribed lesion or multi-nodular. Common fibrous tumours affecting the ocular surface are fibrous histiocytoma and nodular fasciitis.

1. Fibrous histiocytoma

Etiology

Fibrous histiocytomas (FHs) are soft tissue tumours usually found on the extremities, but can occur in any part of the body, including orbital tissues. They are classified as:

- Benign fibrous histiocytoma
- Malignant fibrous histiocytoma

Case reports have described the occurrence of conjunctival FHs after trauma and radiation and in the immunosuppressed.

Clinical features

Benign fibrous histiocytomas have been reported in the orbit, eyelid, and episclera, corneoscleral limbus. Conjunctival FHs usually present as painless masses and can develop at any age, but most commonly between the

ages of 20 and 40 years. Their gross appearance is of a circumscribed yellow or white mass (Fig. 10.29A), and they may have focal areas of haemorrhage, which can make them appear brown or black in colour. Symptoms and signs depend on the site, but may include decreased vision, pain, restricted eye movements, diplopia, and disc swelling. Ultrasound biomicroscopy discloses a dome-shaped lesion with peripheral corneal and scleral involvement with reduced echogenicity (Fig. 10.29B).

In contrast, malignant **fibrous histiocytomas** of the corneoscleral limbus characteristically appear in later life, between the ages of 50 and 70 years, with an equal distribution of males to females. They are highly aggressive tumours, and have been reported to have a local recurrence rate of 100% if a limited excision is performed. Recurrence can occur within a few months of excision.

Histopathology

The histopathological appearance of a **benign fibrous histiocytoma** includes a mixture of fibroblastic and histiocytic cells that are often arranged in a cartwheel or storiform pattern, and accompanied by varying numbers of inflammatory cells, including foam cells and siderophages. No atypical nuclei or mitotic figures are present. Although some authors regard these tumours as reactive proliferations of fibroblasts, others do not accept this view because the lesions tend not to regress spontaneously. Recurrence is rare.

Malignant fibrous histiocytomas have a broad range of histological appearances; storiform-pleomorphic, myxoid, giant cell, and inflammatory. The storiform-pleomorphic type is the most common. The cells are predominantly plump pleomorphic spindle-shaped with occasional large, ovoid histiocyte-like cells. Modest amounts of inflammatory cells, such as lymphocytes and plasma cells may be present (Fig. 10.29C).

Differential diagnosis

Clearly, the diagnosis of FH is challenging. Other neoplasms (sarcomas, melanoma, sarcomatous carcinoma, and neural tumours) and reactive lesions (nodular fasciitis) must be excluded. In addition to routine histopathological evaluation, immunohistochemical analysis is extremely helpful in differentiating an FH from above mentioned lesions. Fibrous histiocytoma typically displays strong immunoreactivity for vimentin; focal immunoreactivity for factor XIIIA, smooth muscle actin, and CD68; and occasional mild immunoreactivity for CD34 and lacks immunoreactivity for cytokeratins, the neural and melanocytic marker S-100, and the melanocytic marker HMB-45.

Treatment

For those limbal fibrous histiocytomas with a benign histopathological appearance, the management should be local surgical excision. The most appropriate management of FH at any site, particularly the conjunctiva, is complete surgical excision with tumour-free margins. The lesion should be managed by resecting it with a 4 to 5 mm wide margin, planar base clearance, excision edge cryotherapy, excision base cryotherapy for planar invasion, and appropriate ocular surface reconstruction. A pathologist should be consulted before and after surgery to ensure that appropriate measures are taken to care for the specimen. In the event of positive margins, adjuvant treatment such as brachytherapy is recommended. In order to exclude disease recurrence, patients require close, lifelong follow-up.

Malignant fibrous histiocytomas need to be managed cautiously, preferably by wide local excision and cryotherapy at the earliest opportunity. If necessary, enucleation should be considered to fully excise a limbal malignant fibrous histiocytoma.

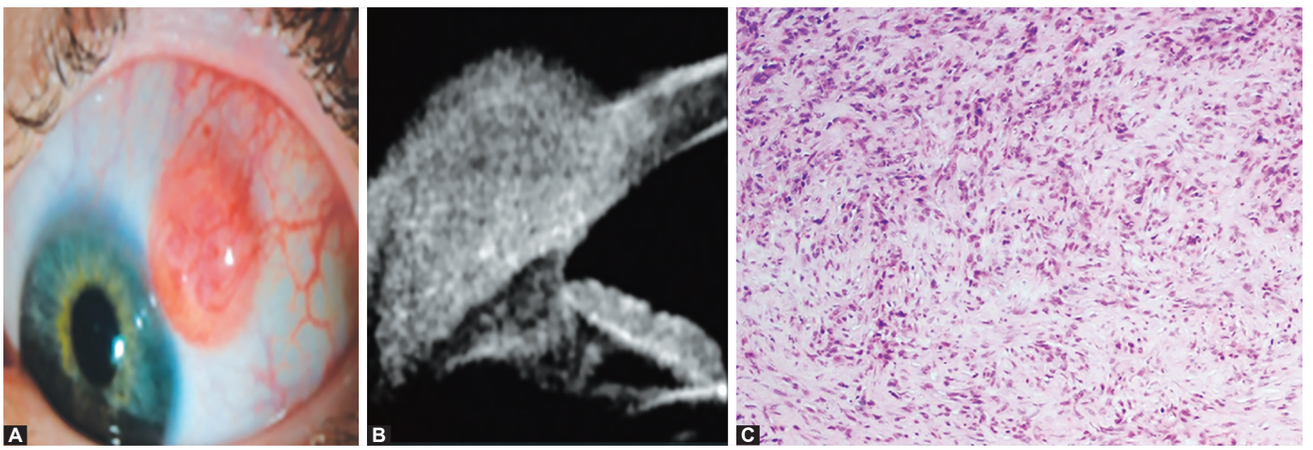


Fig. 10.29: A, Elevated, vascularized, and fleshy-pink lesion of the left superotemporal conjunctiva extending into the peripheral cornea; B, Ultrasound biomicroscopy discloses a dome-shaped lesion with peripheral corneal and scleral involvement with reduced echogenicity; C, Microscopic high power showing spindle cells with focal storiform arrangement and lymphocytic infiltrate.

2. Nodular fasciitis (pseudosarcomatous fasciitis)

Etiology

Nodular fasciitis is a benign nodular reactive proliferation of fibroblasts and vascular tissue usually arising within the fascia. It occurs in a variety of anatomical locations in both adult and pediatric populations, without gender predilection. In the eye, it usually manifests in the orbit, eyelid, or episclera and rarely conjunctiva. Although trauma has been suggested as a possible cause, there is no clear etiology.

Clinical features

Nodular fasciitis (Fig. 10.30) presents in the varied age group ranging from 3 to 81 years as a solitary white episcleral enlarging nodule at the limbus or over the sclera anterior to the insertion of one of the rectus muscles. The nodule may grow quickly and show signs of inflammation. Grossly, the lesions tend to be between 0.5 and 1.5 cm in diameter and tend to be round or oval. The specimen is not encapsulated. While benign, the tumour can be mistaken for malignancy. Proper identification is essential in helping direct appropriate treatment.

Histopathology

A histopathologic specimen is required for definitive diagnosis. The specimens tend to be sparsely cellular, with scant infiltration of lymphocytes and mononuclear cells. Gross samples are mostly made of spindle fibroblasts (non-atypical), myxoid ground substance, and vasculature. Mitotic figures may be identified, and it is important not to confuse this with a sarcoma.

Differential diagnosis

Nodular fasciitis may mimic episcleritis which is a benign recurring condition that often presents as hyperaemia, oedema, and infiltration, which are all limited to the episcleral tissue.

General considerations in the differentiation of nodular fasciitis and episcleritis are as follows: (1) Episcleritis tends to be a more lymphocytic reaction, whereas nodular fasciitis tends to be more of a fibrocytic reaction, (2) presence of a myxoid background points more towards nodular fasciitis, and (3) clinical history is important in making a diagnosis, i.e. the presence of systemic inflammatory illness increases the likelihood of nodular episcleritis.

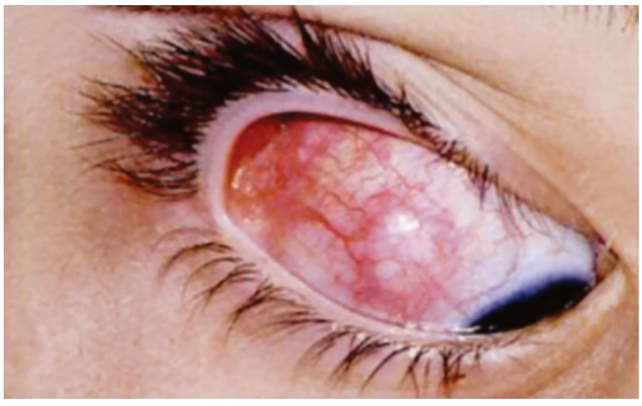


Fig. 10.30: Nodular fasciitis in epibulbar tissues superotemporally in an 11-year-old boy.

Treatment

Differentiating between nodular fasciitis and episcleritis is important because the treatments differ.

For nodular fasciitis, conservative steroid treatment may be attempted first to shrink the growth. Ultimately, the standard of care treatment for nodular fasciitis is surgical excision.

In contrast, episcleritis is often managed conservatively. As it is not typically sight-threatening and is often self-limited, symptomatic relief is the goal of therapy. For example, topical lubricants and oral NSAIDs can alleviate the discomfort.

NEURAL TUMOURS

1. Simple neuroma and neurofibroma

Simple neuromas are soft mucosal neural tumours that appear in the conjunctiva and other mucous membrane in patients with multiple endocrine neoplasia. All such patients have prominent corneal nerves in 100% of cases.

Neurofibroma is a peripheral nerve sheath tumour that can occur in the conjunctiva as a solitary mass or as a diffuse or plexiform variety associated with von Recklinghausen's neurofibromatosis 1 (NF-1). Conjunctival neurofibromas can be divided into solitary, diffuse and plexiform types. The solitary type is not usually associated with NF-1, the diffuse type is sometimes associated with NF-1, and the plexiform type is generally considered to be almost pathognomic of NF-1.

Clinical features

Clinically, simple neuroma appears as pink-yellow and grows over time. There is significant association with medullary carcinoma of the thyroid and so ophthalmologists should be familiar with these conjunctival lesions.

Solitary conjunctival neurofibroma appears as a yellow-grey sessile or dome-shaped mass located in the conjunctival stroma. The sessile variant can have poorly defined margins. The plexiform variant is an ill-defined, firm, irregular mass that has been likened to a bag of worms. The conjunctival plexiform neurofibroma is often in continuity with the same lesion of eyelid and orbit (Fig. 10.31).

Histopathology

Histopathologically, diffuse and plexiform neurofibromas are composed of bundles of enlarged nerves with proliferation of Schwann cells and endoneural fibroblasts in a mucoid matrix. A distinct perineural sheath defines the individual tumour cores. The localised neurofibroma lacks a perineural sheath and is encapsulated. It can sometimes be difficult to differentiate from other spindle cell tumours and special stains for axons may help make the diagnosis in such cases.

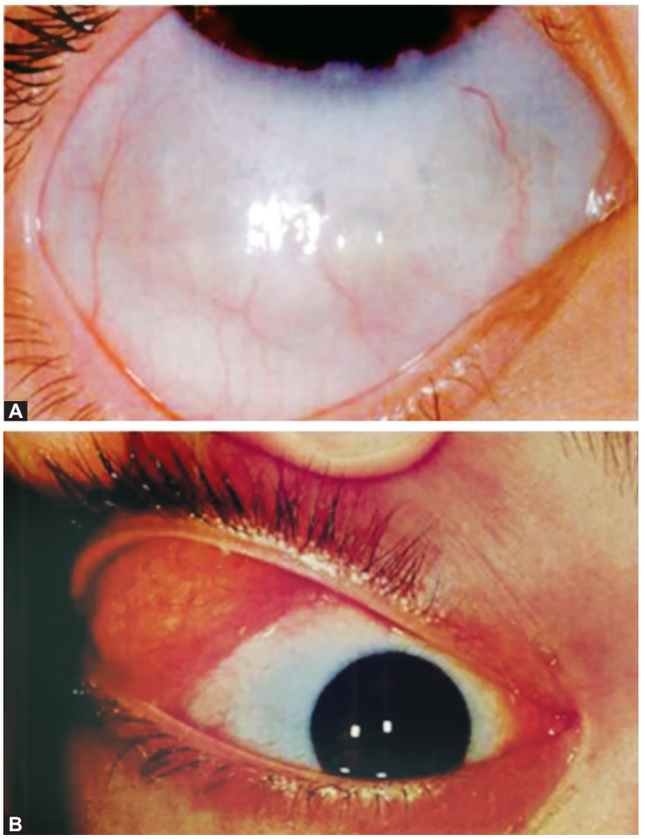


Fig. 10.31: A, Very subtle diffuse neurofibroma of the inferior bulbar conjunctiva in a young girl with NF-1; B, Involvement of superior aspect of conjunctiva with plexiform neurofibroma in a 4-year-old girl with NF-1 (*Courtesy:* Frederick Blodi, MD).

Treatment

These benign neural tumours are generally asymptomatic and usually require no treatment. Occasionally, solitary tumours appear as slowly enlarging elevated stromal masses that can be managed by complete surgical resection. The plexiform type can be extremely difficult to remove intact and debulking procedures are often necessary. This can result in extensive scarring. The systemic prognosis is good, malignant transformation is extremely rare.

2. Schwannoma

Etiology

Schwannoma is the proper name for tumours developing from the Schwann cells of the neural sheath in preference to the older terms, neurilemmoma and neurinoma, since the latter designate tumours containing connective tissue elements (i.e. neurofibromata).

Schwannomas are slow-growing, encapsulated, peripheral nerve sheath tumours that may be found in isolation or in association with von Recklinghausen neurofibromatosis. It has been proposed that these conjunctival schwannomas might arise from either the nasociliary nerves supplying the conjunctiva or the subconjunctivally lying autonomic nerve fibres. Overall, schwannomas typically appear in the third to fifth decades of life and demonstrate no sex predilection.

Clinical features

Conjunctival schwannomas have an indolent clinical course. They usually present as a slow- growing painless nodule on the conjunctiva/epibulbar surface (Fig. 10.32A). Since the bulbar conjunctiva is the most common site of this tumour, "epibulbar schwannoma" is probably the most apt description. In the conjunctiva, they present as a light pink-yellow, elevated mass that generally lies in the stroma of the bulbar conjunctiva or episcleral tissues. It is a slow-growing lesion that may have mildly dilated conjunctival or episcleral nutrient vessels.

Histopathology

Schwannomas are composed of a pure proliferation of Schwann cells. Two distinct, intermingling histologic patterns are seen (Fig. 10.32B): An Antoni A pattern of

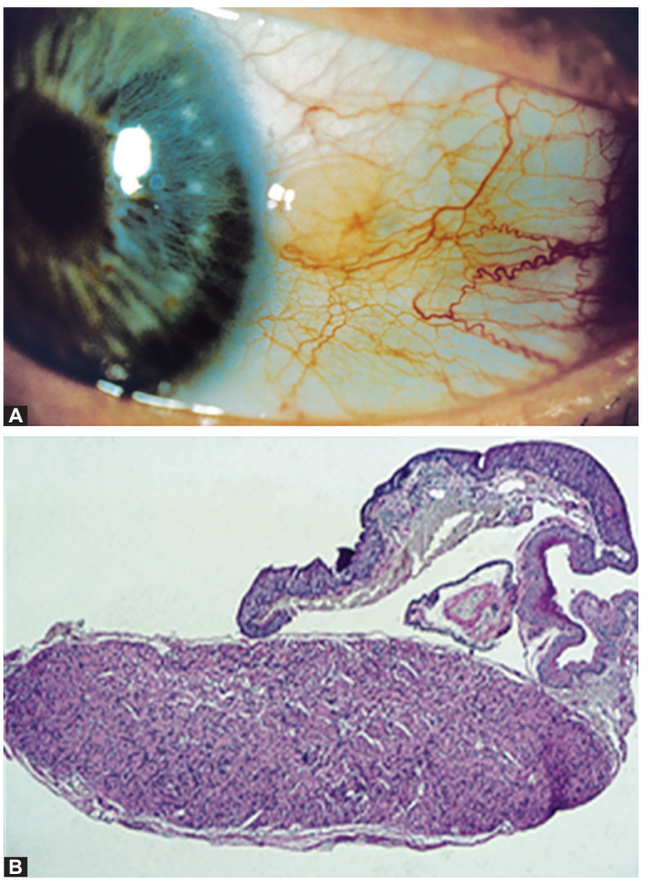


Fig. 10.32: A, An elevated, well-circumscribed, mobile, yellow, perilimbal conjunctival lesion at the 3 o'clock position; B, HPE showing spindle cell morphologic characteristics which are suggestive of Antoni A and B patterns.

sheets of palisading spindle cells with spindle-shaped nuclei forming Verocay bodies, and an Antoni B pattern of haphazardly arranged elongated cells in a myxoid stroma. Light-microscopic features of schwannoma are usually characteristic, but immunohistochemistry may be required in some cases.

Differential diagnosis

Schwannoma is not frequently included in the differential diagnosis of nonpigmented conjunctival masses, which consists of pingueculum, naevus, foreign body, neurofibroma, leiomyoma, fibrous histiocytoma, dermoid, squamous and sebaceous cell carcinomas, and amelanotic malignant melanoma.

Treatment

The treatment of epibulbar schwannomas is complete excision. While excising, one must be careful to excise it in-toto and prevent damage to the underlying sclera. Additional double freeze cryotherapy to the base, namely the underlying scleral bed if the mass is found to be adherent to underlying sclera peroperatively. However, it is unlikely that cryotherapy has any role in preventing recurrence, given the benign pathology of the tumour. Furthermore, no malignant transformation is noted. Epibulbar or conjunctival schwannoma can be best described as a common tumour at an uncommon site.

3. Granular cell tumour

Etiology

Granular cell tumour (GCT), also known as myoblastoma, is extremely rare. It is an uncommon neoplasm for which the pathogenesis is uncertain and disputed. Originally thought of having a striated muscle origin, recent suggestions are that it is of neural derivative, Schwann cell origin.

Clinical features

It is seen as a pink elevated smooth mass of the conjunctival stroma. It is clinically indistinguishable from most other well circumscribed, nonpigmented conjunctival neoplasms (Fig. 10.33A).

Histopathology

Microscopically, GCT consists of (Fig. 10.33B) cords and lobules of round, benign cells with a pronounced granular cytoplasm. Pseudoepitheliomatous hyperplasia of the overlying conjunctival epithelium is a recognized feature of this tumour. Based on electromicroscopic studies, it has been suggested that the cells may be modified Schwann cells, although the precise histogenesis of the tumour is still disputed. A malignant variant of this tumour may be indistinguishable from alveolar soft part sarcoma. Granular cell tumour is rarely diagnosed clinically.

Treatment

Treatment is by complete excision.

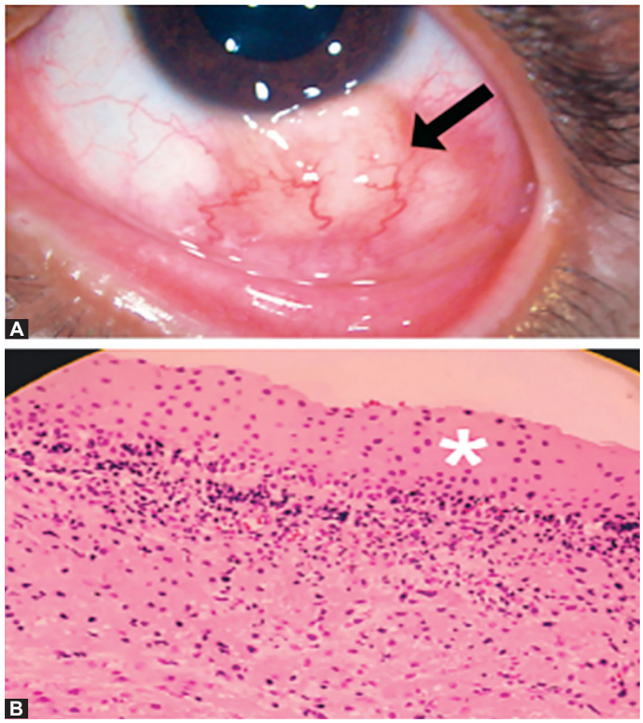


Fig. 10.33: A clinical aspect. A, Yellowish mass in the temporal area from the bulbar conjunctiva (arrow); B, Microphotography. At lower magnification, tumour cells can be identified under a normal conjunctival epithelium (asterisk).

HISTIOCYTIC TUMOURS

1. Xanthoma

Etiology

Xanthomas are nodular masses of lipid-laden histiocytes which may contain scattered Touton giant cells and are usually a manifestation of a group of diseases which are collectively referred to as the xanthomatoses. They occur in the systemic lipoidoses, in patients with increased serum lipids, and in apparently normal individuals.

Clinical features

Xanthoma presents as a yellow subepithelial mass on the epibulbar surface (Fig. 10.34A). These lesions may be solitary or may be seen as multiple plaques or papules with a characteristic distribution. In xanthoma disseminatum, multiple limbal lesions are found in both the eyes.

Histopathology

Microscopic examination revealed dense infiltration of the corneal stroma by macrophages containing foamy cytoplasm. A few lymphocytes were scattered in each field. The pathological diagnosis was "xanthoma" (Fig. 10.34B).

Treatment

Treatment is by complete excision.

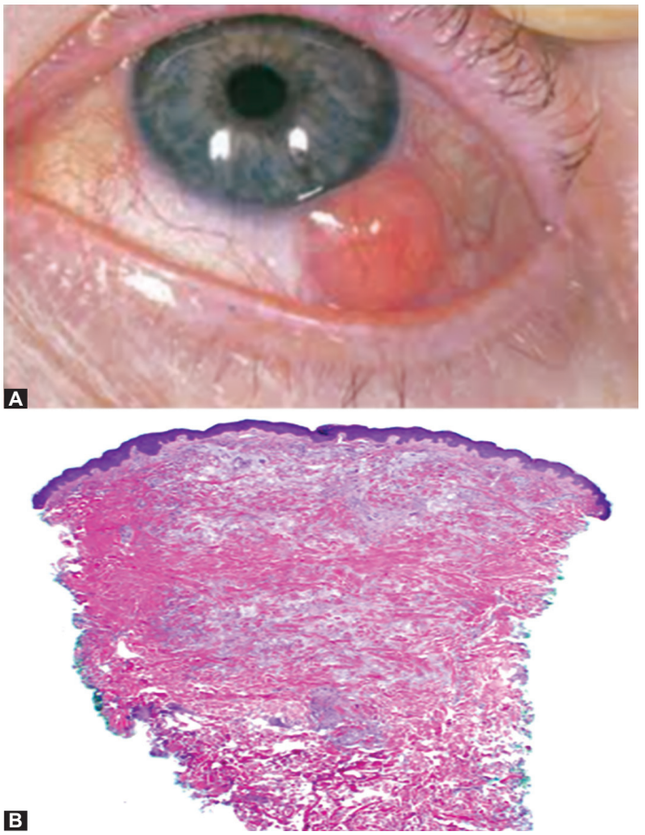


Fig. 10.34: A, Conjunctival xanthoma; B, HPE: Dermal foamy histiocytes with admixed neutrophils and extravascular lipid.

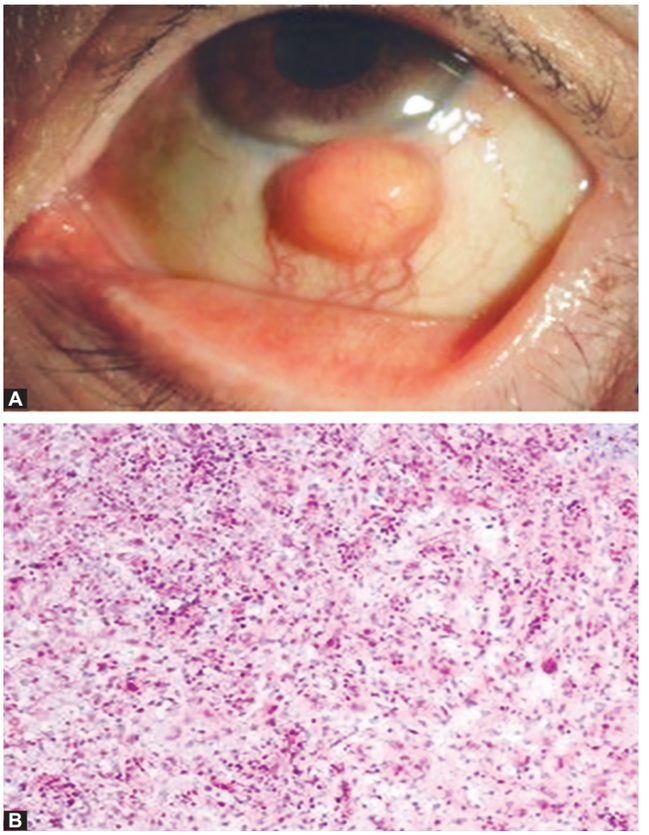


Fig. 10.35: A, Yellow-orange subconjunctival mass with feeding vessels at the limbus. The overlying conjunctiva was intact; B, HPE showing a mixed inflammatory lesion composed of dense infiltrates of epithelioid histiocytes with foamy cytoplasm, lymphocytes, plasma cells, and multinucleate giant cells.

2. Juvenile xanthogranuloma

Etiology

Juvenile xanthogranuloma (JXG) is an idiopathic cutaneous eruption of childhood characterised by solitary or multiple, yellow red, transient papules. In ocular region it is best known for causing an iris mass that can produce a spontaneous hyphaema. It can also affect the eyelid, conjunctiva and orbital tisssues. There are isolated case reports of juvenile xanthogranuloma of the conjunctiva in children.

Clinical features

Conjunctival involvement usually occurs as a solitary lesion unassociated with the skin eruption. It appears as a yellow elevated lesion, usually near the corneoscleral limbus in any quadrant. Although cutaneous and iris JXG classically appear in infancy or childhood, JXG on the conjunctiva often appears as a solitary mass and often has its onset in adulthood. This adult-onset xanthogranuloma seems to be identical clinically and histopathologically to the infantile or juvenile form (Fig. 10.35A).

Histopathology

Histopathologically, JXG is a mass composed of lipid histiocytes, chronic inflammatory cells and Touton giant cells, which typically have a ring of lipid around a focus of granulomatous inflammation. Fine blood vessels ramify through the lesion (Fig. 10.35B).

Differential diagnosis

The differential diagnosis of a yellowish conjunctival mass, with or without limbal involvement, includes epibulbar dermoid, dermolipoma, and, less frequently, phlyctenular keratoconjunctivitis, neurofibroma, fibrous histiocytoma, pterygium, pyogenic granuloma, and foreign body granuloma, as well as other primary and secondary inflammatory lesions such as JXG and Langerhans cell histiocytosis.

Treatment

Most conjunctival JXG lesions have been excised because the diagnosis was uncertain clinically. However, if the diagnosis is suspected clinically, a period of observation is justified, the lesion is said to resolve without treatment. Topical or oral corticosteroids can be employed for cases that do not resolve. Recurrence after complete excision is rare.

3. Reticulohistiocytoma

Etiology

Reticulohistiocytoma (RH) is a rare benign histiocytic lesion that is often a part of a systemic disorder known as multicentric reticulohistiocytosis.

Clinical features

Although multiple lesions can occur on the eyelid in association with multicentric histiocytosis, cases reported in the conjunctiva have been in adults and appeared as localised masses at the corneoscleral limbus without systemic evidence of multicentric reticulohistiocytosis (Fig. 10.36A).

Histopathology

RH is composed of large mononuclear or multinucleated cells with fine granular 'ground glass' cytoplasm and large nuclei with prominent nucleoli (Fig. 10.36B). It differs from juvenile xanthogranuloma in that it occurs in adults and lacks Touton giant cells histopathologically.

Treatment

RH should be included in the differential diagnosis of epibulbar benign histiocytic lesions. Management is complete surgical resection. The role of corticosteroids is unknown.

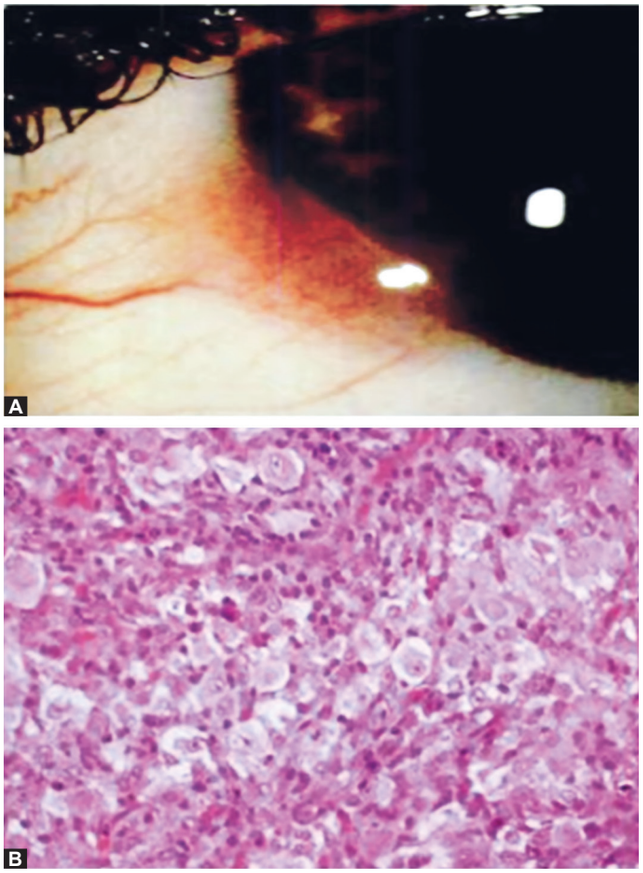


Fig. 10.36: A, Localised reticulohistiocytosis at the limbus; B, HPE showing large histiocytes with granular cytoplasm.

MYXOID TUMOURS

1. Conjunctival myxoma

Etiology

Conjunctival myxoma is a benign neoplasm presumably derived from primitive mesenchyme. It is a condition of adulthood with no predisposition for gender.

Clinical features

Myxoid tumours are rare benign stromal tumours, manifesting as slowly growing, asymptomatic freely movable unilateral, soft, pink white lesions usually seen in the temporal bulbar conjunctiva (Fig. 10.37A). Unlike naevus and lymphangioma which may appear similar, myxoma characteristically does not have cysts. However, the clear lesion can sometimes resemble a conjunctival cyst.

Carney complex

Conjunctival and eyelid myxoma can occur in association with an autosomal dominant condition called Carney complex, characterised by myxomas, spotty pigmentation of skin and mucous membranes, endocrine overactivity, and schwannomas. Most conjunctival myxomas have been solitary, without systemic evidence of Carney complex. However, any myxoma of the eyelid or conjunctiva should prompt evaluation for cardiac myxoma, a life-threatening condition. Eyelid and conjunctival myxomas can become apparent long before cardiac myxoma is recognised.

Histopathology

Histologically, they are hypocellular and are composed of stellate and spindle-shaped cells interspersed in the loose stroma. Cytoplasmic vacuoles are often present. Scattered mast cells may be present (Fig. 10.37B). Special stains and electron microscopy may help to differentiate myxoma from similar lesions like myxoid liposarcoma, spindle cell lipoma, myxoid neurofibroma, and rhabdomyosarcoma.

Treatment

Management is generally surgical resection, most excised lesions do not recur. If the diagnosis is suspected and the lesion is small and asymptomatic, observation only may be appropriate.

MYOGENIC TUMOURS

1. Rhabdomyosarcoma

Etiology

Malignant tumours of the conjunctiva in children are rare, accounting for only 3% of conjunctival tumours. Rhabdomyosarcoma (RMS), while more commonly a primary orbital tumour, can present as a primary

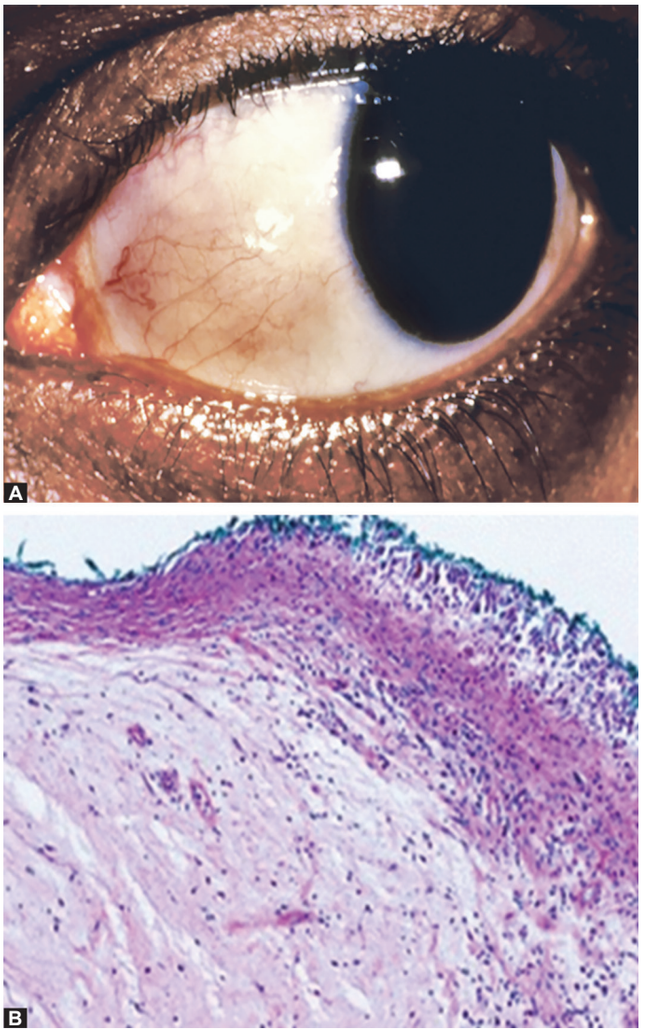


Fig. 10.37: A, Conjunctival myxoma. Anterior segment of the left eye showing a well-circumscribed, yellow-pink, translucent mass with a solid basal part and a cystic apical part on the nasal bulbar conjunctiva; B, HPE showing relatively paucicellular nature of lesion and abundant mucoid material.

conjunctival lesion. The occurrence of rhabdomyosarcoma in the conjunctiva alone is rare, it generally has an orbital component. Most commonly the embryonal type manifests with a conjunctival component. Botryoid rhabdomyosarcoma may be seen in the conjunctival fornices.

Clinical features

Rhabdomyosarcoma presents as a pink, rapidly growing vascular conjunctival mass (Fig. 10.38A). It may appear as a pedunculated soft tissue mass but occasionally swelling and erythema precede the visible tumour.

Histopathology

The most common ophthalmic RMS subtype is embryonal, which typically manifests with elongated spindle or strap-like cells and scattered rhabdomyoblasts with eosinophilic cytoplasm. Although cross striations are a characteristic feature, they are absent in many cases. The botryoid variant of embryonal RMS is named for its grape-like appearance and is usually found in the mucous membrane of the urogenital tract or conjunctiva (Fig. 10.38B).

Differential diagnosis

The clinical differential diagnosis includes progressive rapidly developing masses and inflammatory conditions of childhood, such as neuroblastoma, chloroma, lymphangioma, infantile haemangioma, cellulitis, and nonspecific inflammatory diseases.

Treatment

Complete surgical excision with protocol-based adjuvant chemotherapy and radiotherapy is the treatment of choice for rhabdomyosarcoma localised to the conjunctiva. The prognosis for ophthalmic RMS has drastically improved during the past 40 years to a >90% survival rate based on a combination of surgery, radiotherapy, and chemotherapy.

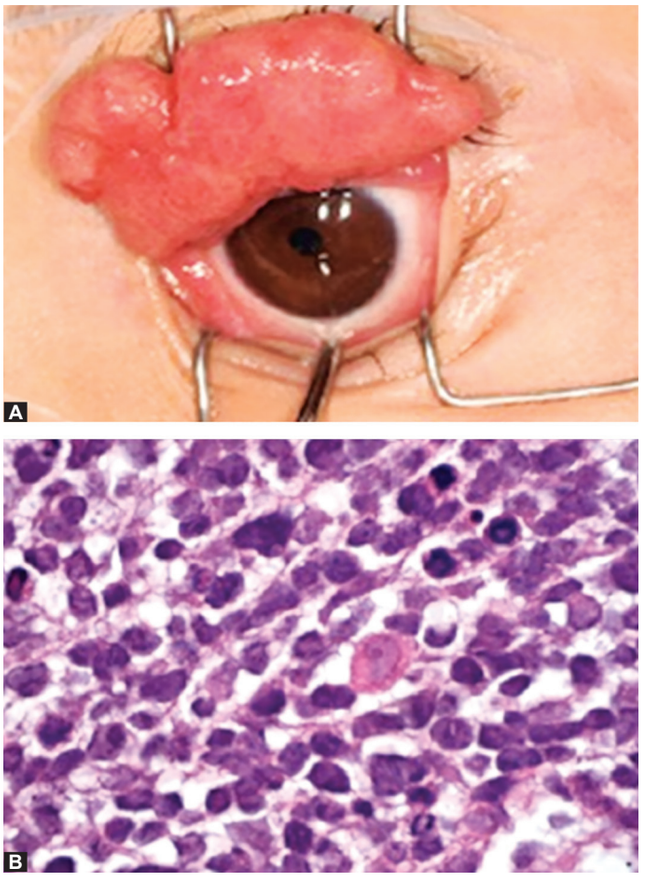


Fig. 10.38: A, Conjunctival rhabdomyosarcoma. Eversion of the left upper eyelid revealing a large multilobulated forniceal mass; B, HPE: The conjunctival substantia propria contained scattered strap cells and rhabdomyoblasts.

LIPOMATOUS TUMOURS

1. Lipoma and liposarcoma

Etiology

Although lipomas, benign tumours of mature adipose tissue cells represent by far, the most common mesenchymal neoplasms, conjunctival lipomas are a very rare occurrence. Most lipomas reported at this anatomic location have been of the pleomorphic lipoma types or dermolipoma. It may exist as a hereditary condition and as a congenital anomaly.

Clinical features

It appears as a localised, circumscribed, elevated, freely mobile, non-pigmented, yellowish growth in the bulbar conjunctiva. The mass is easily compressible and does not significantly increase in size on pressing the eyeball (Fig. 10.39A).

Histopathology

Lipoma shows loose myxoid connective tissue with pleomorphic lipocytes, often with a spindle cell configuration.

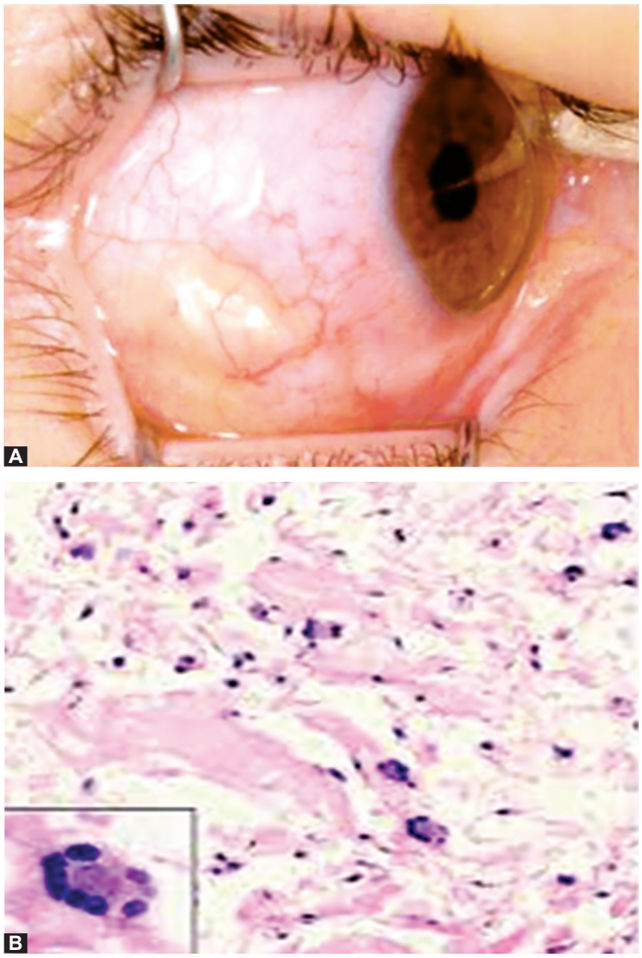


Fig. 10.39: A, Conjunctival lipoma; B, HPE showing lobules of mature adipocytes with a delicate fibrovascular connective tissue stroma, a characteristic morphology of lipoma.

Floret giant cells and nuclear pyknosis, and characteristic bubbly nuclear vacuolations are also seen (Fig. 10.39B). There is an absence of mitotic activity. Liposarcoma is clinically similar to lipoma but on histopathology neoplastic stellate lipid cells and signet ring cells have been observed.

Differential diagnosis

The differential diagnoses include dermoid cyst, vaso-formative and melanocytic lesions and both benign and malignant forms of epithelial and mesenchymal conjunctival tumours such as neurofibroma, dermatofibroma and a narrow range of carcinomata.

Treatment

It can be managed by surgical resection. Recurrence after complete surgical resection is unlikely.

2. Dermoid

Etiology

Conjunctival dermoid cysts are believed to result from embryonic sequestration of conjunctiva. Uncommon and small, conjunctival dermoid cysts are found anteriorly in the orbit, sometimes in the fornices or eyelids. These cysts typically involve soft tissue and do not erode bone.

Clinical features

Epibulbar dermoid is a well-circumscribed yellow white solid lesion involving the corneoscleral limbus. It most commonly occurs at the inferotemporal limbus and has fine white hairs that are best seen with slit-lamp biomicroscopy (Fig. 10.40). It is not uncommon to see them associated with Goldenhar syndrome. Rarely, it can extend to the central cornea or be located in the other quadrants. In addition to becoming a cosmetic blemish, can cause severe astigmatism and amblyopia in some cases.

Histopathology

Histopathologically, epibulbar dermoid is a simple choristomatous malformation that consists of dense fibrous

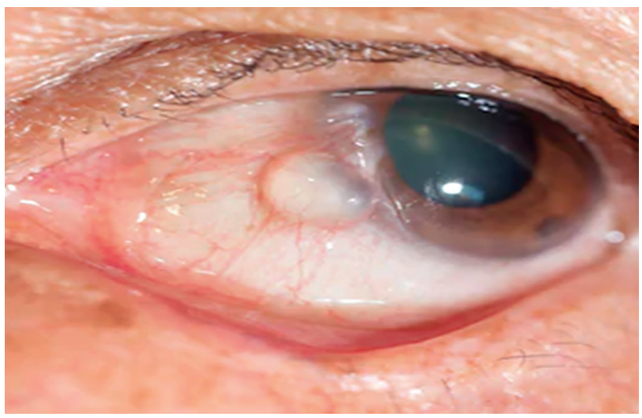


Fig. 10.40: Conjunctival dermoid.

tissue lined by conjunctival epithelium with deeper dermal elements including hair follicles and sebaceous glands.

Treatment

Observation alone is preferred if the dermoid is small and does not cause visual symptoms. Larger dermoids can be excised by lamellar keratosclerectomy with amniotic membrane grafting if the defect is superficial or closure using lamellar or full thickness corneal or sclerocorneal graft if the defect is deep or full thickness. While the cosmetic appearance does improve with surgery, the astigmatic error and visual acuity may not change significantly unless the child is treated early. It may have oncocytic differentiation.

3. Dermolipoma

Etiology

Dermolipoma is an uncommon benign tumour. It constitutes 4.2% of all conjunctival lesions. Although dermolipoma is congenital and present at birth, it typically remains asymptomatic for years and may not be detected until adulthood.

Clinical features

The lesion presents as a pale yellow, soft, fluctuant, mass protruding from the orbit through the conjunctival fornix superotemporally (Fig. 10.41A). Unlike herniated orbital fat, dermolipoma may show the fine white hair on its surface.

Histopathology

Histopathologically, it is lined by conjunctival epithelium on its surface, and subepithelial tissue has variable quantities of collagenous connective tissue and adipose elements (Fig. 10.41B). Pilosebaceous units and lacrimal gland tissue may occasionally be present.

Differential diagnosis

The appearance of dermolipoma closely resembles orbital fat prolapse and limbal dermoid and therefore, it is necessary to take this into account in diagnosis.

Treatment

No treatment is required unless for cosmetic considerations or in symptomatic patients with exuberant hair growth over the lesion. Visible portion of the dermolipoma may be debulked, and the ocular surface reconstructed with amniotic membrane graft.

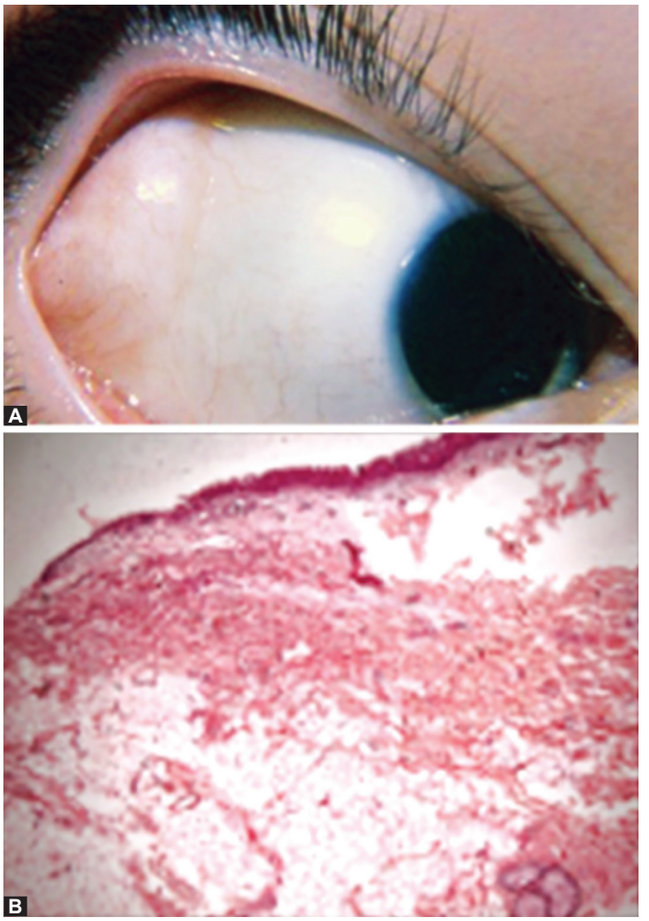


Fig. 10.41: A, Dermolipoma; B, Conjunctival epithelium underneath which are mild mononuclear inflammatory cells and dense collagen beneath which are abundant adipose tissue containing few sebaceous glands and eccrine duct.

LYMPHOPROLIFERATIVE TUMOURS

There are three major types of conjunctival lymphoproliferative lesions, varying from benign to malignant and present as a spectrum, but may appear identical clinically:

- Reactive lymphoid hyperplasia
- Atypical lymphoid hyperplasia
- Conjunctival lymphoma.

There is increasing emphasis that many conjunctival lymphomas may be low-grade B cell lymphomas of the mucosa-associated lymphoid tissue type (MALT). In one-third of patients, conjunctival lymphoma manifests with coexisting systemic lymphoma. Patients usually present with a conjunctival mass. They may also present with nonspecific irritation, ptosis, epiphora, blurred vision, proptosis, and diplopia.

Clinical features

Conjunctival lymphoproliferative lesions appear as diffuse, slightly elevated pink mass, resembling smoked salmon, seen mostly in the bulbar conjunctiva and fornix (Figs 10.42A and 10.43A). Some appear in the caruncle and plica, but very rarely in the palpebral conjunctiva. In the unilateral cases, chance of systemic lymphoma is 17%, and if bilateral cases, the chance is 47%. Systemic lymphoma occurs in 15% of patients at 5 years and 28% in 10 years.

Histopathology

Histopathologically, conjunctival lymphoproliferative tumours are composed of solid sheets of lymphocytes, with overlap between benign reactive lymphoid hyperplasia, atypical lymphoid hyperplasia, and malignant lymphoma. Benign reactive lymphoid hyperplasia is generally polymorphic, with well-differentiated lymphocytes and plasma cells, while lymphoma tends to be more monomorphic and poorly differentiated (Figs 10.42B and 10.43B). Most are non-Hodgkin's B cell lymphomas, whereas Hodgkin's and T cell lymphomas affect the conjunctiva rarely. Immunohistochemistry may be helpful in determining the cell types.

Prognostic factors for developing systemic lymphoma are forniceal or mid-bulbar location, multifocality, and bilaterality. There are several treatment options.

Treatment

- Excision biopsy
- Cryotherapy
- Low-dose external beam radiotherapy

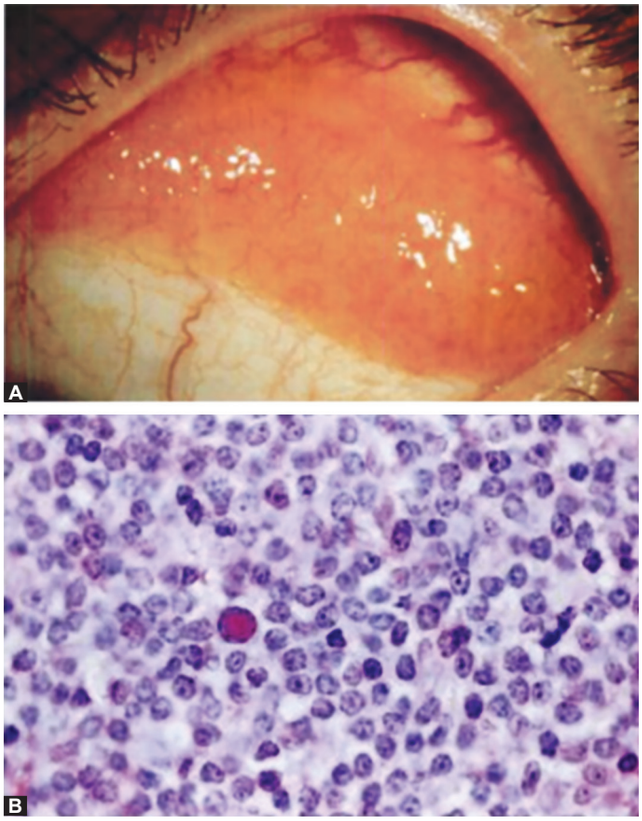


Fig. 10.42: A, Conjunctival benign reactive lymphoid hyperplasia presenting as a diffuse elevated mass in the superior bulbar conjunctiva in a 38-year-old man; B, Histopathology of reactive lymphoid hyperplasia showing well-differentiated uniform lymphocytes. Near the centre of the field, not the cell with the large intranuclear inclusion body; referred to as a Dutcher body (hematoxyline and eosin × 200).

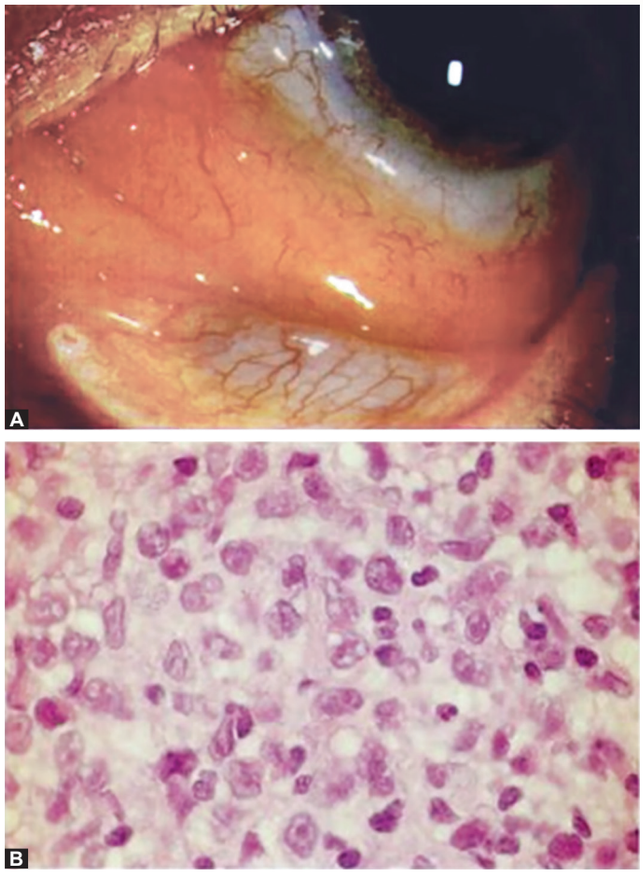


Fig. 10.43: A, Diffuse lymphoma affecting wide area of inferior conjunctiva in a 62-year-old woman; B, Histopathology of malignant lymphoma showing more anaplastic lymphoid cells (hematoxylin and eosin × 200).

- Local injection of IFN-α
- Brachytherapy
- Chemotherapy if associated with systemic involvement.

CHORISTOMA

Etiology

Choristoma is derived from a Greek word *choristos* meaning "separated" and is defined as the presence of normal tissue in an abnormal location. It differs from hamartoma which is an excessive proliferation of normal tissue at the normal site and from teratoma which is a neoplasm comprising tissues from all three germ layers. Choristoma makes up about 3% of all conjunctival and corneal tumours. It is considered a simple choristoma when composed of one type of tissue and a complex choristoma when a combination of displaced tissue is involved.

Although choristomas can be seen in any age, these are common in children and are the most common epibulbar and orbital tumours among them. A variety of choristomatous lesions have been reported previously

such as dermoid, dermolipoma, osseous choristoma, and lacrimal choristoma in different components of eye.

Clinical features

Ocular choristomas are most frequently epibulbar and located in the superotemporal quadrant near the superior and lateral rectus muscles (Fig. 10.44A). Epibulbar choristomas can be associated with eyelid and uveal coloboma, Goldenhar syndrome or organoid naevus syndrome.

Histopathology

Epipalpebral location is rare. Ocular choristomas contain a variable proportion of epithelium, dermal adnexa such as pilosebaceous or eccrine glands, adipose tissue, fibrous tissue, cartilage, bone, smooth muscle, and neural tissue (Fig. 10.44B).

However, complex choristoma is a very rare entity which contains a variety of tissues derived from more than one germ cell layer.

Differential diagnosis

The differential diagnosis of a pediatric conjunctival mass includes the following entities: Limbal dermoid, myxoma, scleral melanocytosis, melanoma, Kaposi's sarcoma, sebaceous carcinoma, extraocular retinoblastoma extension, and intraorbital foreign body, among others.

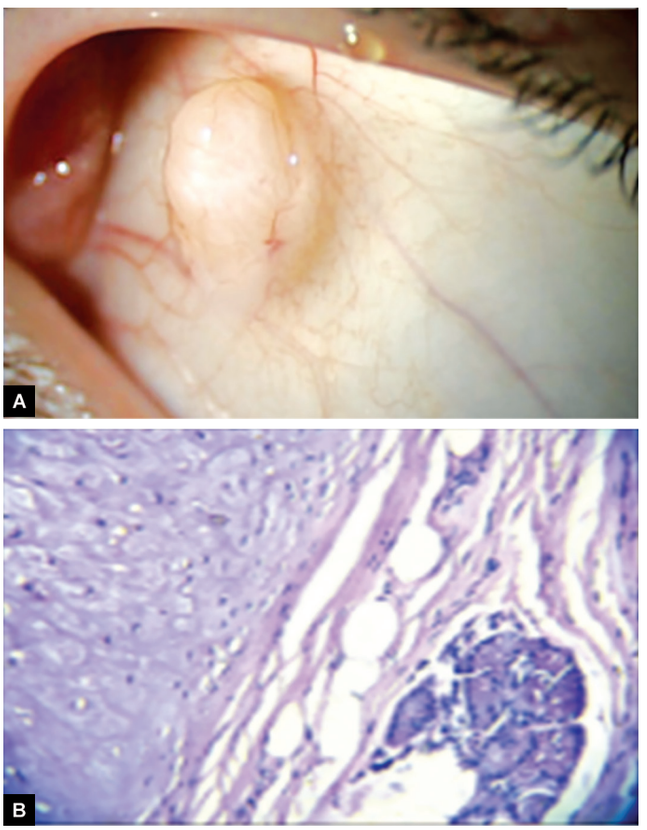


Fig. 10.44: A, Epibulbar choristoma; B, HPE showing mature cartilage and well-differentiated acinar structure.

Treatment

Treatment of complex choristoma depends on the size, location, and mechanical effect of the lesion. In general, wide excision of the lesion with closure is the treatment of choice. Sometimes, keratoplasty (when cornea is involved) and repair with amniotic membrane may be necessary.

CARUNCULAR TUMOURS AND CYSTS

Etiology

The caruncle lies at the inner canthus nasal to plica semilunaris, a unique anatomic structure containing elements of both conjunctiva and skin. The lesions occurring in the caruncle are similar to those that occur in mucous membranes and cutaneous structures. By histopathological analysis, 95% of the caruncular lesions are benign with the majority being either papilloma and melanocytic naevus, and 5% are malignant. Other lesions of caruncle include pyogenic granuloma, inclusion cysts, sebaceous hyperplasia, sebaceous adenoma, and oncocytoma.

Clinical features

Clinically, a caruncular tumour presents as an enlargement of the caruncle as a distinct mass arising from or displacing the caruncle. The clinical appearance varies with the type of tumour.

Papilloma generally appears as a frond-like mass with fine vascular tufts visible clinically in the central core of each frond.

Caruncular naevus usually appearing at about puberty is variably pigmented and may show slight change in size or colour with time. It generally contains clear cysts best seen with slit lamp biomicroscopy (Fig. 10.45A). Caruncular melanoma appears as a variably pigmented, usually noncystic solid mass.

Oncocytoma is a benign tumour that is believed to originate from transformed glandular epithelial cells particularly in the lacrimal gland, salivary glands and other organs. When it occurs in the caruncle, it appears as an asymptomatic slowly growing reddish blue solid or cystic mass (Fig. 10.46A).

Histopathology

It most often occurs in older individuals. It is composed of benign epithelial cells with abundant eosinophilic granular cytoplasm (Fig. 10.45B). Electron microscopy shows large number of abnormal mitochondria.

Several sebaceous gland tumours and cysts can arise from the caruncle. Sebaceous gland hyperplasia and sebaceous adenoma may resemble each other clinically appearing as a smooth or multinodular yellow mass. Sebaceous gland carcinoma may also arise from sebaceous gland of caruncle.

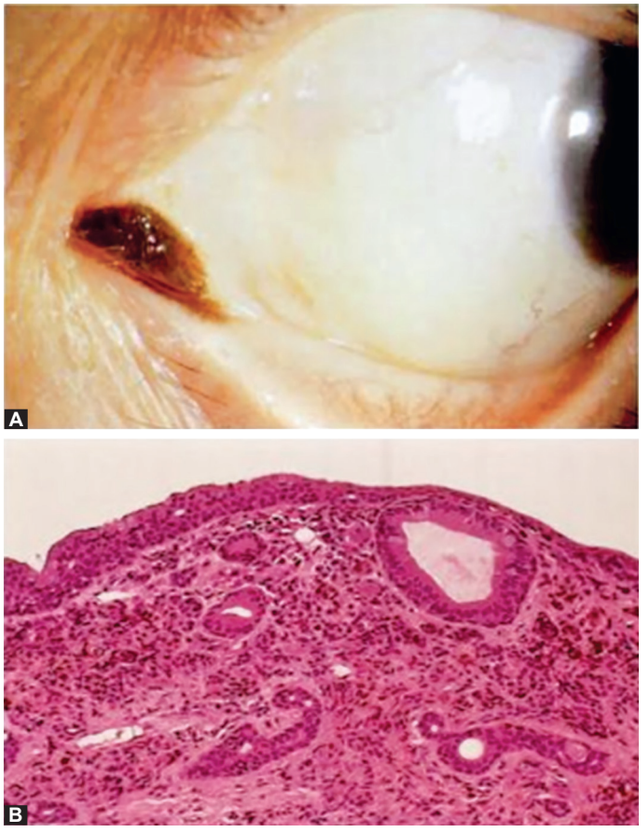


Fig. 10.45: A, Cystic caruncular naevus in a 47-year-old woman; B, Histopathology of lesion shown in Fig. 10.45A depicting cystic structures and naevus cells in stroma of the caruncle (hematoxylin and eosin × 100).

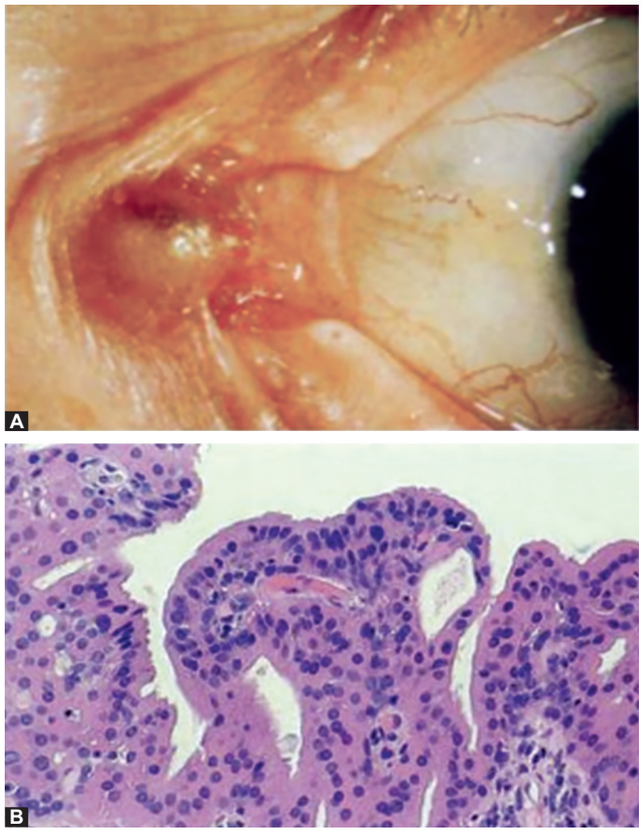


Fig. 10.46: A, Caruncular oncocytoma in a 75-year-old man; B, Histopathology of lesion in Fig. 10.46A showing lining of cystic area with epithelial cells with granular cytoplasm (hematoxylin and eosin × 75).

It can be aggressive and can metastasize. Histopathology of caruncular oncocystoma is shown in Fig. 10.46B.

Other lesions that can occasionally arise in the caruncle include metastatic carcinoid neoplasms, cavernous haemangioma, Kaposi sarcoma, lymphoma, adenosquamous carcinoma, dacryops and dermoid tumour.

Treatment

Management of a caruncular tumour is complete surgical excision when possible. We generally perform a circular incision through the conjunctiva and hook the medial rectus to prevent severing it. The tumour is then removed intact using a minimal manipulation or "no touch" method. We generally use supplemental cryotherapy. Squamous papilloma requires special precautions because like that in the caruncle disruption of the lesion can lead to shedding of viral particles into the surrounding tissue. Pedunculated papilloma is sometimes managed by clamping the base of mass with a haemostat and cutting beneath the haemostat removing the tumour intact. Another alternative is to freeze the lesion using the cryoprobe and cutting the base. Malignant tumour-like melanoma and sebaceous carcinoma may require wider excision and heavy cryotherapy because they have a greater capacity to invade into the deeper tissue. We often use punctual plugs in cases of primary acquired melanosis and melanoma to prevent seeding of tumour cells into the lacrimal drainage system.

METASTATIC AND SECONDARY TUMOURS

METASTATIC TUMOURS

Etiology

Most metastatic cancers to the ocular region involve the uveal tract and orbit. Eyelid and conjunctival metastasis are less common and individual cases are often reported. Conjunctival metastasis can occur from breast carcinoma, cutaneous melanoma, or other primary tumours. Most patients have a history of a primary malignancy but sometimes the conjunctival metastasis is the initial manifestation of a systemic cancer.

Clinical features

Clinically conjunctival metastasis appears as a rapidly growing sessile or nodular mass that has a yellow or fleshy

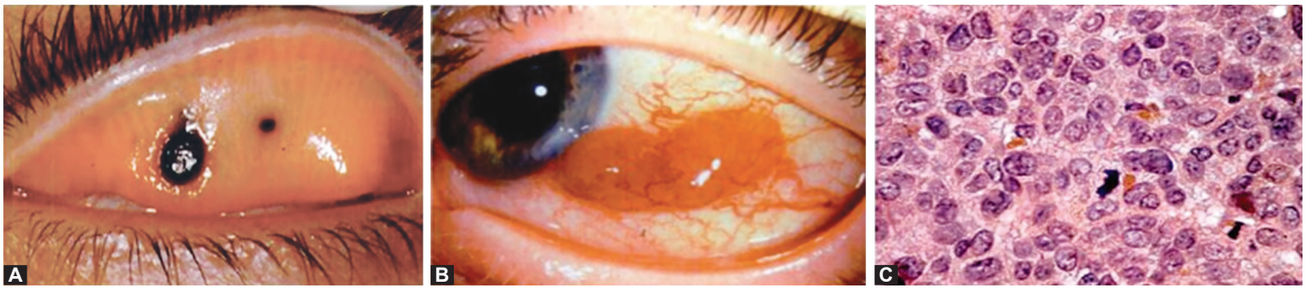


Fig. 10.47: A, Everted left upper eyelid showing multiple foci of metastatic melanoma on the tarsal conjunctiva; B, Tan-coloured mass in bulbar conjunctiva of a 48-year-old woman with a history of cutaneous melanoma. She had no known metastasis at time of ocular presentation, but was subsequently found to have widespread metastases; C, Higher magnification of lesion in Fig. 10.47B showing the epithelioid melanoma cells. Note the mitotic figures (hematoxylin and eosin).

colour. They may also appear as one or more fleshy pink vascularized conjunctival stromal tumours. The lesion can be diffuse or multifocal. Melanoma metastatic to the conjunctiva is usually pigmented (Fig. 10.47A) but can be nonpigmented (Fig. 10.47B).

Histopathology

Histopathologically, conjunctival metastasis varies with the primary tumour and degree of differentiation of the metastatic focus. Some lesions like melanoma (Fig. 10.47C), breast cancer or renal cell carcinoma have characteristic features. Poorly differentiated tumours may require immunohistochemistry to assist in confirming the primary site of involvement.

Treatment

In addition to the management of the primary neoplasm, the conjunctival metastasis may require specific management. A small lesion may be removed by local excision. Larger lesions may require an incisional biopsy to confirm the diagnosis. Needle biopsy can be performed, but it generally yields less tissue thus making the diagnosis more difficult. If the patient is receiving specific chemotherapy for the primary lesion a conjunctival metastasis can be observed for a period of time to assess the response to chemotherapy. If conjunctival metastasis does not respond to chemotherapy it can be treated with irradiation. Plaque brachytherapy is another option in selected cases.

LEUKAEMIC INFILTRATE

Etiology

Leukaemia is a complex disease with continually changing classification.Virtually all types of leukaemia can affect the ocular structures, specially acute myeloid leukaemia. It usually involves the orbit and less commonly extends to involve the eyelid and conjunctiva. Conjunctival involvement in patients with leukaemia usually takes the form of subconjunctival heamorrhage rather than direct infiltration of tissues with leukaemic cells. Conjunctival involvement can take place at any age depending on the type of leukaemia. It is often an early sign of relapse of previously treated disease.

Clinical features

In most instances, leukaemic infiltration of the conjunctiva has a similar appearance to lymphoma. It may be unilateral or bilateral with focal or diffuse lesions in the bulbar or palpebral conjunctiva. It has a spectrum of presentation, ranging from subconjunctival haemorrhage to direct infiltration of the tissue with leukaemic cells but often manifests as a firm, nontender, pink smooth mass (Fig. 10.48A) associated with haemorrhage. It has the tendency to appear in the perilimbal tissue near the cornea.

Histopathology

It is characterised by an infiltration of conjunctival stroma by leukaemic cells (Fig. 10.48B). The characteristics of the cell vary with the type of leukaemia. Special stains and immunohistochemistry may assist in characterising the nature of leukaemia.

Treatment

The management involves treatment of the systemic disease first. For cases that do not respond to such treatment, low dose radiotherapy can be very effective.

SECONDARY TUMOURS

Etiology

Some neoplasm can reach the conjunctiva and episcleral tissue by direct spread from an adjacent structure, such as the eyelid, orbit or sinuses. We can call such contiguous spread a "secondary conjunctival tumour" rather than a true metastasis.

The conjunctiva can be secondarily involved by tumours of adjacent structures, particularly by direct extension from the tumour of the eyelid. Intraocular and orbital tumours may also extend into the conjunctiva. Most important is the sebaceous gland carcinoma of the eyelid which can exhibit pagetoid invasion and direct invasion into the conjunctival epithelium. Uveal melanoma can extend extrasclerally into

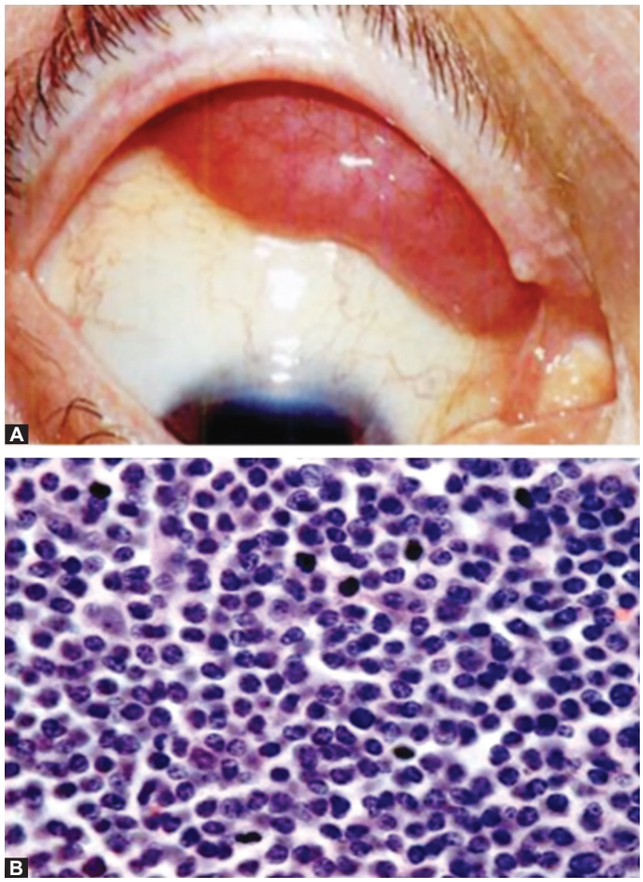


Fig. 10.48: A, Infiltration of the superior conjunctival tissues with chronic lymphocytic leukaemia in an 87-year-old man; B, Histopathology of lesion in Fig. 10.48A, showing sheets of mononuclear cells with round to oval uniform nuclei (haematoxylin and eosin × 200).

the subconjunctival tissues. Rhabdomyosarcoma of the orbit in children occasionally presents first with its conjunctival component.

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Chapter

11

Ocular Surface Squamous Neoplasia (OSSN)

Chapter Outline

GENERAL CONSIDERATIONS
- Introduction
- Incidence

ETIOPATHOGENESIS

CLINICAL FEATURES
- Morphological classification

DIAGNOSTIC TESTS
- Impression and exfoliative cytology
- Dye staining
- Histopathology
- Ultrasound biomicroscopy
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- Confocal microscopy

TREATMENT
- Surgical treatment
- Cryotherapy
- Radiotherapy
- Chemotherapy
- Immunotherapy
- Recurrence
- Recommended therapeutic strategy and current therapeutic practice

GENERAL CONSIDERATIONS

INTRODUCTION

Ocular surface squamous neoplasia (OSSN) refers to a broad spectrum of dysplastic changes involving the epithelia of the conjunctiva, cornea, and limbus.

Histological subtypes that comprise OSSN are squamous dysplasia, conjunctival/corneal intraepithelial neoplasia, and squamous cell carcinoma (SCC). They represent the most common primary tumours of the eye among adults. Also, OSSN is the most common non- pigmented malignant disease of the surface of the eye, comprising 7% of all conjunctival tumours. Although uncommon, they can cause ocular and at times systemic morbidity, hence their significance. The first case was described in 1860 by von Graefe, subsequently it has been extensively studied and reported, as a result, a range of management options are now available depending on the stage of the disease.

Earlier various terms like epithelial plaque, intraepithelial epithelioma, Bowen's disease, Bowenoid epithelioma, and precancerous epithelioma were used for non-invasive forms of squamous neoplasms. Pizzarello and Jakobiec classified conjunctival intraepithelial neoplasms as mild, moderate and severe dysplasia based on the extent of involvement on histopathology. Lesions that involved the basal one-third of the conjunctiva were classified as mild, those involving the inner two-thirds were classified as moderate, and lesions that were full thickness were termed severe dysplasia. Waring et al. extended the term to include the cornea, and Erie et al. further extended it to include invasive neoplasia.

The term ocular surface squamous neoplasia (OSSN) was given by Lee and Hirst and it has been classified into three grades: (i) Benign dysplasia, (ii) preinvasive OSSN; and (iii) invasive OSSN. Papilloma, pseudotheliomatous hyperplasia and benign hereditary intraepithelial dyskeratosis represent benign dysplastic changes. Conjunctival/corneal carcinoma *in situ* comprise preinvasive OSSN. Invasive OSSN consists of squamous carcinoma and mucoepidermoid carcinoma.

INCIDENCE

The overall estimated prevalence of OSSN is 1.9 per 100,000 per year. Its incidence is between 0.02 to 3.5 per 100,000; it is relatively common in Australia and African/tropical countries. In the last few decades, an increase in the

incidence of OSSN has been observed in these countries, and reported to be associated with sun exposure, human immunodeficiency virus (HIV), and human papillomavirus (HPV) infection. It is predominantly seen in males, although reported to be predominant in females in sub-Saharan Africa. This may be related to Africa having the highest prevalence of both HIV and HPV, which may increase the risk of OSSN in women and gender differences in mortality of HIV infected adults.

Ocular surface squamous neoplasia is mostly unilateral and is seen in middle-aged and older patients. Rarely, it is bilateral in immunosuppressed patients. The average age of occurrence has been noted to be 60 years, ranging from 20 to 88 years. Patients of xeroderma pigmentosum and human immunodeficiency virus (HIV) develop OSSN at a younger age. Young patients of HIV are more prone to develop aggressive OSSN.

ETIOPATHOGENESIS

OSSN is associated with certain risk factors which include sunlight exposure, human papillomavirus infection, history of actinic skin lesions (xeroderma pigmentosum), increased p53 expression, HIV seropositivity, chemical exposure (trifluridine, beryllium, arsenicals, petroleum products), heavy cigarette smoking, light pigmentation of the hair and eyes, ocular pigmentation, ocular surface injury, vitamin A deficiency, mechanical trauma (e.g. ocular prosthesis) and contact lens users. Other conditions in which OSSN has been reported are ocular cicatricial pemphigoid, non-Hodgkin's lymphoma, epidermodysplasia verruciformis and hepatitis C virus infection. Chronic inflammation associated with atopic keratoconjunctivitis may be a risk factor for the development of bilateral, diffuse, invasive, and recurrent OSSN. OSSN has also been reported in association with Papillon Lefèvre syndrome.

1. Ultraviolet B light (UV B). Higher incidence of OSSN seen in residents of lower latitudes near to the equator, in males (predominant outdoor activity), in fair skinned individuals and in individuals with actinic skin lesions (xeroderma pigmentosum), strongly suggest sunlight exposure as a major etiological factor. UV B causes pyrimidine dimer formation and damage to nucleotide excision repair which is responsible for the repair of DNA. In addition, it has also been seen to cause p53 mutation which is reported in OSSN. Xeroderma pigmentosum (XP) is an autosomal recessive disorder with defective DNA repair mechanism which predisposes to OSSN with aggressive clinical presentation at a younger age. OSSN has been reported as early as 3 years of age in a patient of XP. Scholz et al. identified telomerase reverse transcriptase (TERT) gene promoter mutations in 44% of 48 samples of conjunctival OSSN. They found that the TERT mutational profile supported ultraviolet light induction as the major source of the malignancy. However, there was no relationship with tumour recurrence comparing those with versus without TERT mutation.

2. Human papillomavirus. HPV genotypes 6 and 11 have been demonstrated in a large number of papillomas as well as dysplastic and malignant lesions of the cornea and conjunctiva. Deoxyribonucleic acid (DNA) and messenger ribonucleic acid (mRNA) of HPV 16 and 18 have been shown in conjunctival intraepithelial neoplasia (CIN) cases proving a causal relationship. Further, it has been demonstrated that the protein coded by the E6 region of HPV 16 and 18 forms a complex with the protein coded by the p53 tumor suppressor gene in the host.

3. Human immunodeficiency virus. In the HIV-positive population, there is a 12-fold increase in risk of OSSN. Few studies have shown OSSN in young may be a marker for HIV infection. OSSN in HIV-positive patients is more aggressive with larger and thicker tumours, higher incidence of deep invasion, and poorer prognosis, requiring enucleation or exenteration, than in the more common demographic of older, fair-skinned patients.

4. Stem cell theory. OSSN may represent the abnormal maturation of corneal and conjunctival epithelium as a result of a combination of damaging factors to the limbal transition zone such as UV B irradiation and HPV.

5. Role of ATP-binding cassette subfamily B member 5 (ABCB5). ABCB5 is a new member of the ATP-binding cassette super-family and has been identified as an important factor in regulating progenitor cell fusion, multi-drug sensitivity and cellular melanogenesis. The expression of ABCB5 is upregulated in OSSN and that elevated expression of ABCB5 may be involved in the pathogenesis of OSSN.

CLINICAL FEATURES

OSSN typically presents as a growth on the ocular surface and gives rise to symptoms like foreign body sensation, redness or irritation and rarely, diminution of vision due to high astigmatism or involvement of visual axis. OSSN lesions are usually located within the interpalpebral fissure at the limbus in the nasal quadrant, which receives the highest intensity of sunlight (Fig. 11.1A). They are slightly elevated lesions, pearly grey in appearance, with or without well-defined borders. The tumor appears as fleshy or nodular, sessile minimally elevated lesion with surface keratin, feeder vessels (sentinel vessels), and secondary inflammation (Figs 11.2A and 11.3A).

Rose bengal staining is helpful in the diagnosis and delineation of the tumor extent. Sometimes, these lesions have pigmentation (Fig. 11.3A) when it becomes difficult to distinguish it from melanoma. The tumor may extend for a variable distance into the adjacent corneal epithelium and appear as a subtle wavy, advancing, grey, superficial opacity that may be relatively avascular or may have fine

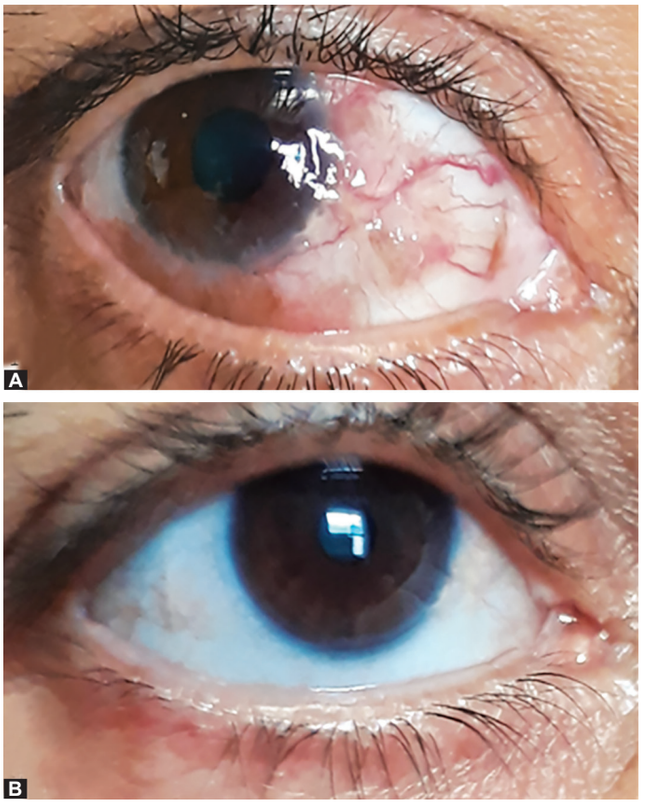

Fig. 11.1: A, Clinical picture showing diffuse gelatinous ocular surface squamous neoplasia right eye; B, Complete resolution post-treatment with topical interferon at 3 months.

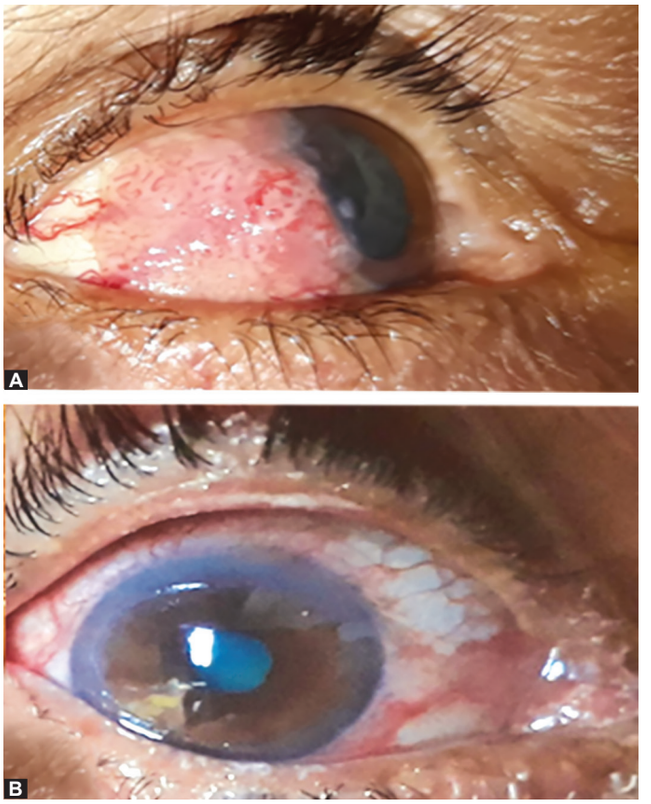

Fig. 11.2: A, OSSN post-treatment failure with MMC drops; B, Treated with interferon eye drops.

blood vessels. The presence of feeder vessels and intrinsic vascularity favours SCC. Although greater thickness is believed to be a sign of malignant transformation, there are thick tumors that remain within the epithelium. It is also important to examine the tarsal conjunctiva after everting the eyelid of patients with OSSN to detect contiguous or multifocal involvement of the tarsal conjunctiva.

MORPHOLOGICAL CLASSIFICATION

Conjunctival lesions

1. Gelatinous: Circumscribed gelatinous lesions are the most common OSSN lesions. The nodular lesion causes suspicion of invasive SCC. The nodular type is rapidly growing with a high incidence of metastasis to adjacent lymph nodes. The diffuse type is the least common and in the early stages presents as persistent redness of the conjunctiva, is slow growing and mimics chronic conjunctivitis.

2. Leukoplakic: These are usually preinvasive. Leukoplakia is usually absent or minimal in CIN; extensive leukoplakia raises the suspicion of malignancy.

3. Papilliform: These are typically exophytic, strawberry like, with a stippled red appearance corresponding to its fibrovascular core. They are clinically benign.

Corneal lesions

Corneal OSSN lesions are preinvasive, with a mottled ground glass sheet appearance which is opalescent. They have sharply defined fimbriated borders, the convex leading edge spreads in an arc away from the limbus and often white dots are present over the grey epithelium. They are usually avascular. These lesions are typically indolent, slow growing and prone to recurrence.

Advanced cases can infiltrate the cornea and sclera to have the intraocular extension. Noduloulcerative lesions are associated with high-risk of intraocular invasion. Rarely, the tumour may extend into the orbit causing proptosis. The tumour can metastasize to the regional lymph nodes and rarely distant metastasis may occur. Aggressive variants include spindle cell squamous carcinoma, mucoepidermoid carcinoma, and adenoid SCC. According to the American Joint Committee on Cancer (AJCC)—tumour, node, and metastasis (TNM) classification, SCC is classified depending on the size, tumour location, and extent of involvement (Table 11.1).

OSSN can mimic various conditions, it could present or be misdiagnosed as pannus, corneal ulcer, pinguecula, pterygium, pyogenic granuloma, keratoacanthoma, pseudoepitheliomatous hyperplasia, actinic keratosis,

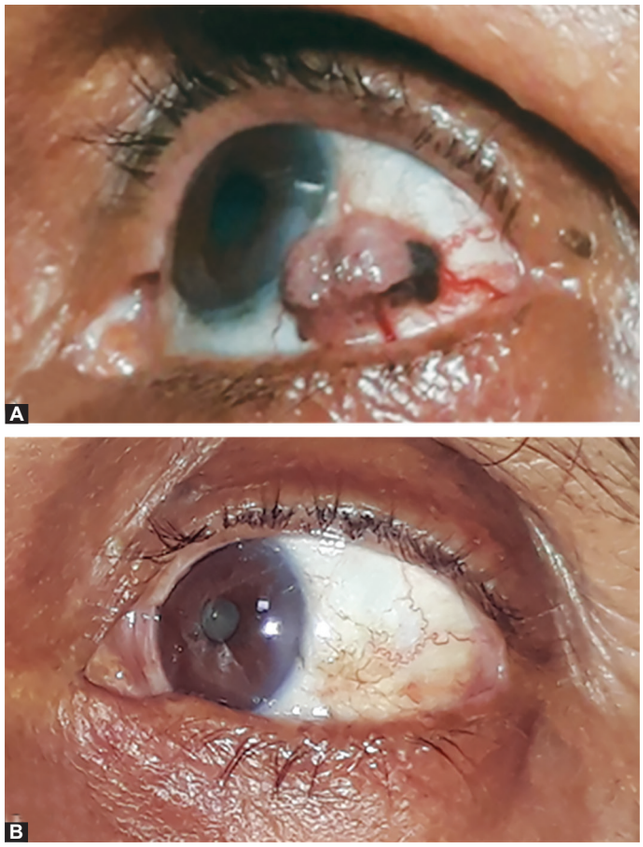

Fig. 11.3: A, Pigmented OSSN; B, Treated with perilesional injection of interferon alpha 2b.

sclerokeratitis, blepharoconjunctivitis, nodular scleritis, hereditary benign intraepithelial dyskeratosis, vitamin A deficiency, naevi, malignant melanoma and PUK.

DIAGNOSTIC TESTS

IMPRESSION AND EXFOLIATIVE CYTOLOGY

Impression cytology (IC): In this superficial epithelial cells are collected by applying collecting devices [either cellulose acetate filter paper (CAP) or Biopore membrane device (Millipore Corp, Bedford, MA)] such that the cells adhere to the surface and are removed from the eye to be fixed, stained, and then mounted on a slide for analysis. It has the advantage of maintained cell-to-cell relationship as compared to exfoliative cytology. However, these specimens require immediate processing. Using CAP for specimen collection, an 80% correlation was found between impression cytology, diagnosis and histopathology specimens obtained from incisional biopsy. Biopore membrane has better cell adherence and can be stored for subsequent analysis making it the procedure of choice. Nolan et al. found that 55% of intraepithelial OSSN cases diagnosed by IC had keratinized dysplastic cells often accompanied by hyperkeratosis, 35% had large syncytial-like groups, and 10% had non-keratinized dysplastic cells as a predominant feature. However, it is not possible to differentiate intraepithelial lesions from invasive squamous cell carcinoma given the superficial sampling of cells.

Exfoliative cytology (EC): This technique uses a cytobrush which is particularly suited as malignant cells have poor cell to cell adherence and tend to desquamate when located on the mucosal surface. After instillation of anaesthetic eye drops, samples for cytology are collected with the help of a specific brush with plastic bristles and a blepharostat. The material is then smeared onto a slide and fixed with 90% alcohol spray, and subsequently sent for analysis by the cytopathologist after staining with the Papanicolaou method.

Both IC and EC may also be used to monitor regression of lesion and response of the lesion to chemotherapeutic modulators. There are pitfalls using these modalities as

TABLE 11.1: AJCC 8th edition classification of conjunctival carcinoma (OSNN)

Definition of primary tumour (T)
TX Primary tumour cannot be assessed
T0 No evidence of primary tumour
Tis Carcinoma in situ
T1 Tumour (≤5 mm in greatest dimension) invades through the conjunctival basement membrane without invasion of adjacent structures
T2 Tumour (>5 mm in greatest dimension) invades through the conjunctival basement membrane without invasion of adjacent structures
T3 Tumour invades adjacent structures* excluding the orbit
T4 Tumour invades the orbit with or without further extension
T4a Tumour invades orbital soft tissues, without bone invasion
T4b Tumour invades bone
T4c Tumour invades adjacent paranasal sinuses
T4d Tumour invades brain
Definition of regional lymph nodes (N)
NX Regional lymph nodes cannot be assessed
N0 Regional lymph node metastasis absent
N1 Regional lymph node metastasis present
Definition of distant metastasis (M)
M0 Distant metastasis absent
M1 Distant metastasis present
Definition of histopathologic grade (G)
GX Grade cannot be assessed
G1 Well differentiated
G2 Moderately differentiated
G3 Poorly differentiated
G4 Undifferentiated

*Adjacent structures include cornea, forniceal conjunctiva, palpebral conjunctiva, tarsal conjunctiva, lacrimal punctum and canaliculi, plica, caruncle, anterior or posterior eyelid lamellae, eyelid margin, and/or intraocular compartments. (Data adapted from AJCC Cancer Staging Manual. 8th ed. Switzerland: Springer. 2017; 787793).

the only diagnostic tool. Keratinizing malignancies offer the highest chance of false negatives because of paucity of cells in the specimen and should be kept in mind in such cases. Cytological features that reliably differentiate carcinoma *in situ* (CIS) from invasive carcinoma are yet to be identified. Several patients may have histological CIN or partial thickness epithelial atypia adjacent to the invasive disease, which would not necessarily yield sheets of atypical cells if sampled by impression cytology. Endophytic lesions and orbital invasion cannot be identified with impression cytology, limiting its use as a diagnostic aid.

DYE STAINING

It is another diagnostic test that is inexpensive and helpful in identifying OSSN. Diagnostic dyes like lissamine green and rose bengal are used to stain and delineate the extent of OSSN lesions but since these dyes are nonspecific and stain many other ocular surface conditions, it is not possible to diagnose OSSN with the use of these dyes alone. Other vital dyes that have been studied in the diagnosis of OSSN include toluidine blue (ToB) and methylene blue. ToB and methylene blue are acidophilic dyes that stain abnormal tissue dark royal blue. They have an affinity for nucleic acids, and given the increased nuclear material from high rates of mitoses and poor cell-to-cell adhesion in malignancy, these tissues stain more frequently than benign tissues. Several studies have shown that ToB and methylene blue staining have a high sensitivity but low to moderate specificity in diagnosing OSSN compared to histopathology.

HISTOPATHOLOGY

The gold standard for confirming diagnosis of OSSN is excisional biopsy for histopathology. The specimens may be obtained from excision biopsies in small lesions which can be removed in toto or incisional biopsies in cases of large infiltrating lesions. Papillomas demonstrate papillary fibrovascular fronds covered by acanthotic epithelium. This epithelium may show varying degrees of dysplasia, however, the cells have normal polarity and the basal layers are often unremarkable. Preinvasive OSSN are classified as mild, moderate or severe depending on the degree of involvement of the dysplastic epithelium. In mild (CIN grade I), dysplasia is confined to lower third of the epithelium. In moderate (CIN grade II), dysplasia extends into the middle third and full thickness dysplasia is termed severe (CIN grade III).

In conjunctival and corneal intraepithelial neoplasia (CCIN), epithelial cells are thickened, dysplastic, and irregular with increased cell proliferation. These changes affect less than the full thickness of the epithelium. When the abnormal cellular proliferation involves only partial thickness of the epithelium it is classified as mild CIN, a condition also called mild or moderate dysplasia. When it affects full thickness epithelium it is called severe CIN, a condition also called severe dysplasia. In these cases, there may be an intact surface layer of cells. Where there are no longer normal surface cells, that is the entire epithelium is involved but tumor cells have not yet invaded the substantia propria, the lesion is categorized as carcinoma *in situ*. Invasive squamous cell carcinoma is defined as when the lesion has affected the epithelial basement membrane and substantia propria. CIN accounts for 39% of all premalignant and malignant lesions of the conjunctiva and for 4% of all conjunctival lesions. Unlike CIN, incidence of invasive SCC is of much lesser frequency, varying from 0.02 to 3.5/100,000 population. About 75% occur in men, 75% are diagnosed in older patients and over 75% occur at the limbus. It can locally invade the sclera, uvea, eyelids, and orbit and has the ability to metastasize to distant sites thus potentially becoming life-threatening.

In low-grade dysplasia cells show enlarged nuclei, hyperchromasia and irregular contour of the nuclear membrane with increased nuclear/cytoplasmic ratio. In high-grade dysplasia, there is pleomorphism of the nucleus with dyskeratotic cells. The presence of syncytial sheath, nucleoli and infiltration of inflammatory cells is suggestive of invasive SCC. Invasive OSSN show nests of infiltrating cells that have penetrated the epithelial basement membrane and spread into the conjunctival stroma. These cells can either be well differentiated and easily recognized as squamous, or poorly differentiated and difficult to distinguish. The latter are more uncommon and more aggressive. Two types of cells may be seen interspersed with squamous cells in these tumours: Spindle cells and mucoepidermoid cells.

Electron microscopy: In cases of OSSN electron microscopy reveals excessive mitochondria, tonofilaments and endoplasmic reticulum; decreased desmosomes, alteration/absence of basement membrane and deposition of fibrillogranular material between the basement membrane and Bowman's layer.

ULTRASOUND BIOMICROSCOPY (UBM)

UBM provides cross-sectional visualization of the anterior segment in an intact globe at microscopic resolution. In the 50 MHz mode, images to a depth of 5 to 6 mm at a resolution of 25 microns can be produced. Studies on the use of UBM in diagnosing OSSN have shown that UBM is most useful in assessing intraocular tumor extension. On UBM, the tumor surface is found to be hyperechoic while the tumor stroma is generally hypoechoic. Features suggestive of ocular tumour extension are blunting of the anterior chamber angle and uveal thickening, which correlated with histopathology findings. In patients with orbital extension, it has been reported that the relatively hypoechoic tumour can be differentiated from the more hyperechoic orbital tissues using UBM while 50 MHz images had better resolution, 20 MHz ultrasonography provided a deeper and wider field of view.

ANTERIOR SEGMENT OPTICAL COHERENCE TOMOGRAPHY (ASOCT)

ASOCT provides noncontact, non-invasive, and high axial resolution cross-sectional imaging of various anterior segment conditions. The technology has undergone refinements, with transition from time-domain to spectral-domain OCT providing a better axial resolution and increasing scanning speed, leading to improved diagnostic imaging. A novel custom-built, ultra high-resolution, spectral-domain anterior segment OCT (UHR-OCT) has been developed with an axial resolution of approximately 2 µm for evaluation of corneal pathologic features. UHR-OCT in ocular surface squamous neoplasia reveals epithelial thickening and increased reflectivity of the epithelium, and an abrupt demarcation from normal to abnormal tissue. Typically, there is sharp disparity in reflectivity of normal and diseased epithelium, allowing for exact localisation of the tumour margins.

Using UHR-OCT, Kieval et al. showed that an epithelial thickness value greater than 140 µm provided 94% sensitivity and 100% specificity for differentiating CCIN from pterygia. In contrast, using HR-OCT with a resolution of 5–7 µm, Nanji et al. demonstrated that an epithelial thickness cuts at greater than 120 µm provided 100% sensitivity and specificity for differentiating OSSN from pterygia. Normal epithelium overlying subepithelial lesion effectively rules out OSSN. UHR-OCT can also be used to diagnose pigmented CCIN, as demonstrated in the study by Shousha et al. where UHR-OCT demonstrated thickened and hyperreflective epithelium in a pigmented conjunctival lesion that had been referred for conjunctival melanoma. Histopathology confirmed the diagnosis of pigmented CCIN. UHR-OCT scan also be used to monitor disease resolution and detect residual subclinical disease. For lesions treated successfully with topical agents, post-treatment UHR-OCT showed normalisation of epithelial architecture at the site of the treated lesions. However, in lesions resistant to medical treatment, UHR-OCT will show persistently thickened epithelium with retained abrupt transition between normal and diseased epithelium. UHR-OCT is also useful to rule out OSSN in the setting of complex ocular pathology and in clinically indeterminate lesions. It has been used to show foci of OSSN in pterygia, Salzmann's nodular degeneration, HSV keratopathy, and atypical peripheral corneal infiltrates when the clinical diagnosis was unclear.

CONFOCAL MICROSCOPY

In vivo confocal microscopy (IVCM) is a simple, safe, and relatively non-invasive diagnostic tool that can provide with the initial clinical diagnosis of OSSN, estimation of recurrence, management of treatment, and evaluation of response to topical chemotherapeutic agents in patients with conjunctival and corneal squamous lesions. When compared with a subsequent biopsy, cytological evaluation with *in vivo* confocal microscopy was capable to distinguish different stages of OSSN in all the cases. The new generations of confocal scanning laser microscopes have an axial resolution of approximately 4 µm; however, the only disadvantage compared to UHR-OCT is that they provide a transverse view without reference to neighbouring corneal layers. The accuracy of diagnosis with cytological *in vivo* confocal microscopy could be improved by the implementation of automated image analysis which has been widely used in the interpretation of conjunctival and corneal exfoliative cytological analysis, and the acquired characteristics of cells were similar to those obtained from biopsies of OSSN. In addition, *in vivo* confocal microscopy sampling from various ocular surface regions can offer a real-time monitoring of the extent and condition of tumor, and guide further managements.

In conjunctival and corneal intraepithelial neoplasia, IVCM shows regular conjunctival epithelium interspersed with complexes of enlarged, irregular cells with bright hyper-reflective and polymorphic nuclei. Bright prominent nucleoli producing a starry night sky pattern has also been reported in these lesions. Further, the authors have reported absence of sub-basal corneal nerves in areas of CCIN. Larger case series also demonstrated correlation between IVCM and histopathology findings. Parrozzani et al. in their series of 10 cases of OSSN reported that IVCM demonstrated dysplastic cells in each case and morphologic agreement with *ex vivo* scraping cytology and histology in 100% of cases. A larger study conducted by Nguena et al. showed a statistically significant difference between the normal controls and cases (benign and OSSN combined) but there was no difference between the benign and OSSN cases. Therefore, there are limitations to the use of IVCM, it cannot reliably differentiate benign from OSSN lesions because of an overlap in IVCM features in the various ocular lesions, it provides only *en face* images in contrast to cross-sectional images obtained in tissue histology. Also as it provides images at a cellular level, IVCM cannot provide a comprehensive scan of the entire ocular surface. Despite the limitations, IVCM can reliably predict the grade of dysplasia that is based on cellular morphology, nuclear atypia, and nuclear to cytoplasmic ratio, it can differentiate between invasive and *in situ* tumors, helpful in initial evaluation of subtypes of OSSN and could also be valuable in the setting of suspected recurrent tumours and in the follow-up evaluation of patients on topical chemotherapeutic agents.

TREATMENT

SURGICAL TREATMENT

Surgery has been the treatment of choice as tissue diagnosis is considered essential before initiation of adjunctive therapy. Excision or incisional biopsy is an important initial step in the management as it is not possible to

exclude invasive disease clinically or with impression cytology. Excision allows an immediate histopathological diagnosis, debulking, and excludes invasive carcinoma. The only disadvantage of primary excision alone is the high recurrence rate which ranges from 15 to 52%. Enucleation, and rarely exenteration may be required in cases of intraocular or intraorbital spread. In all cases a no-touch technique is used, and direct manipulation of the tumour is avoided to prevent tumour seeding.

'No-touch' surgical technique tumor resection is done under peribulbar anaesthesia. Phenylephrine 2.5% drops are used to induce vasoconstriction, thus reducing perioperative bleeding and allowing better visualisation of the corneal advancement of the tumor. A wide surgical excision with a margin of 3–4 mm on conjunctival side is done to maximize the chances of complete removal. Rose bengal/lissamine green staining is helpful to delineate the margins of the lesion. A 'no-touch' technique avoiding direct manipulation of the lesion, by holding the tissue at the healthy conjunctival borders is employed to prevent tumour seeding into new area. If the tumour is adherent to the sclera, a partial thickness sclerectomy is performed with crescent knife. The use of absolute alcohol on the corneal side of the lesion to facilitate epithelial removal as one sheet, i.e. alcohol epitheliectomy, is recommended. Once the lesion is removed *en bloc*, the specimen is marked in the proper orientation with sutures and then transferred to a piece of pencil-marked paper or the excised conjunctival specimen is placed on an absorbent paper and air-dried to prevent loss of orientation, and sent for histopathology in formalin.

Conjunctival defect so created can be closed primarily if less than three clock hours in diameter. Larger defects require either transpositonal conjunctival flaps, free conjunctival flaps from the other eye, or amniotic membrane grafts. Fibrin sealant tissue adhesive can be used to shorten the surgical time, mitigate inflammation postoperatively and improve patient discomfort. Frozen section can be used to assess the adequacy of excision, and is accurate in delineating horizontal tumour spread. Bunns modification of Moh's technique of tumour margin surveillance may also be used. In this the free conjunctival edges are excised by 2 mm if residual tumour is evident even after excision of a 2 mm surgical margin.

CRYOTHERAPY

Intraoperative cryotherapy is commonly used as an adjunctive therapy during excision of the lesion as it is known to decrease the recurrence rate by destruction of any residual tumour tissue beyond the horizontal or deep surgical margin of the wound. It lowers the temperature and also causes ischemic necrosis, thereby destroying the tumour cells. It has the advantage of reaching both tumour cell islands and deeply infiltrated cells, thus obviating the need for radical surgery. A nitrous oxide cryoprobe tip (2.5 or 5 mm) is used to form an ice ball extending 2 mm for conjunctiva, 1 mm for episcleral tissue and 0.5 mm for the cornea. A slow duration freeze with a slow thaw, repeated two times (freeze-thaw-refreeze) is recommended. It is important to include the limbal region during cryotherapy, and not apply the cryoprobe for more than three seconds. Both extensive surgical excision and cryotherapy can cause limbal stem cell insufficiency.

RADIOTHERAPY

Radiation as an adjuvant treatment after surgery has been used for OSSN. The various forms which have been described are external radiotherapy with protons,[76,77] electrons, brachytherapy using strontium-90 (beta irradiation), orthovoltage external radiation, and stereotactic radiotherapy. For incompletely excised tumours Sr-90 brachytherapy with a concave 18 mm plaque size is an effective sole adjuvant treatment. It can be given as 1 week schedule of 10 Gy daily for 5 days or a single fraction of 30 Gy as single dose treatment to facilitate compliance.

External radiotherapy using electrons is an effective treatment option for invasive orbital OSSN. It helps to preserve the eye and vision while providing good disease control and cosmesis. Electrons are the special particulate type of radiation which deliver high dose of ionizing radiation to the tumor. Electrons have the inherent capacity of treating the surface with no exit dose avoiding the collateral damage. Proton radiation delivers more three-dimensional conformal dose than electrons, especially sparing lens and posterior eye structures. Long-term studies involving larger number of patients are required to look into the efficacy and side effect profile in detail. Electron radiotherapy is inexpensive and more widely available, as compared to stereotactic radiotherapy or protons.

CHEMOTHERAPY

Topical chemotherapy is inexpensive, simple and reduces the risk of limbal stem cell deficiency, and obviates the need for clear tumour margins by treating the entire ocular surface, including the potentially dysplastic cells. However, the drawback is the limited drug penetration in larger tumours, and a possibly deleterious effect on the ocular surface and nasopharyngeal epithelium on prolonged use.

1. Mitomycin C: It is an antimetabolite made from *Streptomyces caespitosus* and converted into an alkylating agent in tissues. It preferentially inhibits DNA synthesis in the G1 and S phases. As the hypoxia required for the intracellular reduction of MMC is greater in tumour tissue, it exhibits a certain degree of selectivity. MMC appears to produce cell death in OSSN by apoptosis and necrosis. It is used in the concentration of 0.02–0.04% four times a day with one week on and one week off in alternating cycles for a maximum of 8 weeks. The one week on, one week off regimen prevents damage to more slowly dividing epithelial cells and limbal stem cells, allowing them to repair their DNA. Allowing time for complete epithelial healing before application of MMC is

important in avoiding the more serious complications such as corneal epitheliopathy, scleral ulceration, uveitis, cataract, and glaucoma. MMC related changes may persist in ocular surface epithelium for at least 8 months following MMC therapy. The other side effects include contact dermatitis, limbal stem cell deficiency and punctal stenosis.

2. 5-Fluorouracil (5-FU): It is an antimetabolite that acts specifically during the S phase of the cell cycle. It is converted to 5-F DUMP, which inhibits thymydilate kinase thus preventing DNA and RNA synthesis. In contrast to MMC which acts on cells in all phases of the cell cycle, 5-FU inhibits cells that are in the S phase of the cell cycle, whereas dormant cells, such as part of the normal corneal and conjunctival cell population, can proliferate once treatment is completed. It is used as 1% in aqueous solution, four times a day over 4 weeks. Both MMC and 5-FU are currently being used four times daily for 1–2 weeks in a pulsed fashion, the treatment being repeated after every 1–2 weeks. This one week on and one week off drug regimen has the added advantage of good efficacy and better tolerance. Other regimens reported for topical 5-FU are 30 days on and 30 days off cycles, 2–6 courses of 2–4 days, with 30–45 days without any treatment. For nodular/thick lesions with limited superficial diffusion, surgical removal plus adjuvant topical chemotherapy remains the best option.

IMMUNOTHERAPY

Recently immunotherapy has become a very popular modality of treatment in view of fewer side effects, better tolerability as compared to chemotherapeutic agents and high efficacy. It is being increasingly used as first line monotherapy for OSSN lesions.

Interferon alpha 2b (IFN-α2b): It is a naturally occurring glycoprotein which binds to cell surface receptors affecting intracellular events resulting in antitumor and antiviral properties. Its efficacy in treatment of OSSN may be explained by the oncogenic link between HPV and OSSN. Topical drops and subconjunctival injections of IFN-α2b have been used as off-label therapy to treat OSSN. It has been used for extensive, multifocal or diffuse (Fig. 11.1B), residual (Fig. 11.2B), recalcitrant, recurrent lesions and for those that involve the visual axis where surgery is not the treatment of choice. Topical IFN-α2b is used as 1 million international unit/ml (IU/ml) four times a day until resolution, and a month thereafter. The main drawback of topical interferon is its requirement of storage in refrigeration. Perilesional injections (3 million IU/ml) are being increasingly given to shorten the duration for complete resolution (Fig. 11.3B). Median time for resolution has been reported as 54 days (range 28–188 days), with a mean follow-up ranging from 2.9 to 18 months. Experience from our centre shows a median time to complete resolution of 8 weeks with eye drops (n = 17) and 6 weeks in eyes with injections (n = 9). There seems to be no significant difference between 1 million IU/ml and 3 million IU/ml for perilesional injections. Medical therapy with interferons has the advantage of treating microscopic disease that may be present throughout the entire ocular surface. Perilesional injections have been associated with flu-like symptoms which lasted for 2 to 3 days, however, no adverse effects have been reported with topical interferons.

Pegylated interferon alpha 2b: Pegylation of therapeutic proteins is a well-established method for delaying clearance and reducing immunogenicity. Pegylated interferon alpha 2b (PEGIFN-α2b), polyethylene glycol (PEG) intron, Schering-Plough, Kenilworth, NJ) is a derivative of recombinant interferon alpha 2b and was developed to reduce the clearance of traditional recombinant interferon alpha 2b. Attachment of a single straight-chain polyethylene glycol (PEG; molecular weight of 12,000 Da) moiety to interferon alpha 2b significantly decreases renal clearance, increasing plasma half-life tenfold compared to non-pegylated interferon without altering the volume of distribution or spectrum of activity. This has potential advantage of significantly decreasing the dosing of the pegylated interferon. It was found in a small pilot study that PEGIFN-α2b was effective in treating OSSN with complete clinical resolution of the lesion in all patients. A mean of 3 injections were needed for tumour resolution in a case series using PEGIFN-α2b. In comparison, a previous case series using subconjunctival and topical recombinant interferon for the treatment of CIN reported that a mean of 5 injections were needed for tumour resolution. Pegylated interferon costs approximately 3 times as much as recombinant interferon.

Other agents

Topical bevacizumab: It is effective as a neoadjuvant therapy combined with surgical excision for the treatment of OSSN. It may be used before surgery to decrease the size of the excision. In a case series of six eyes with OSSN, topical 5 mg/ml bevacizumab in the dosage of 4 times daily for a period of 8 weeks was reported to be effective as a primary and sole therapy in two cases and as neoadjuvant therapy in four cases that required surgical excision at the end of the topical treatment period.

Topical cidofovir: It may provide an additional option for managing treatment-unresponsive lesions owing to potential HPV presence. Topical cidofovir use has been reported as 2.5 mg/ml drops 3 times each day for 6 weeks.

RECURRENCE

Recurrence rates of OSSN ranges from 15 to 52%, average reported being 30%. Recurrences are higher in case of inadequate excision margins, and occur usually within two years of surgery. These typically exhibit a more aggressive behaviour because of the tissue disruption associated with the primary excision theoretically enhancing the ability of the tumour cells to enter the eye. The main predictors for recurrence include age, histological grade of the lesion,

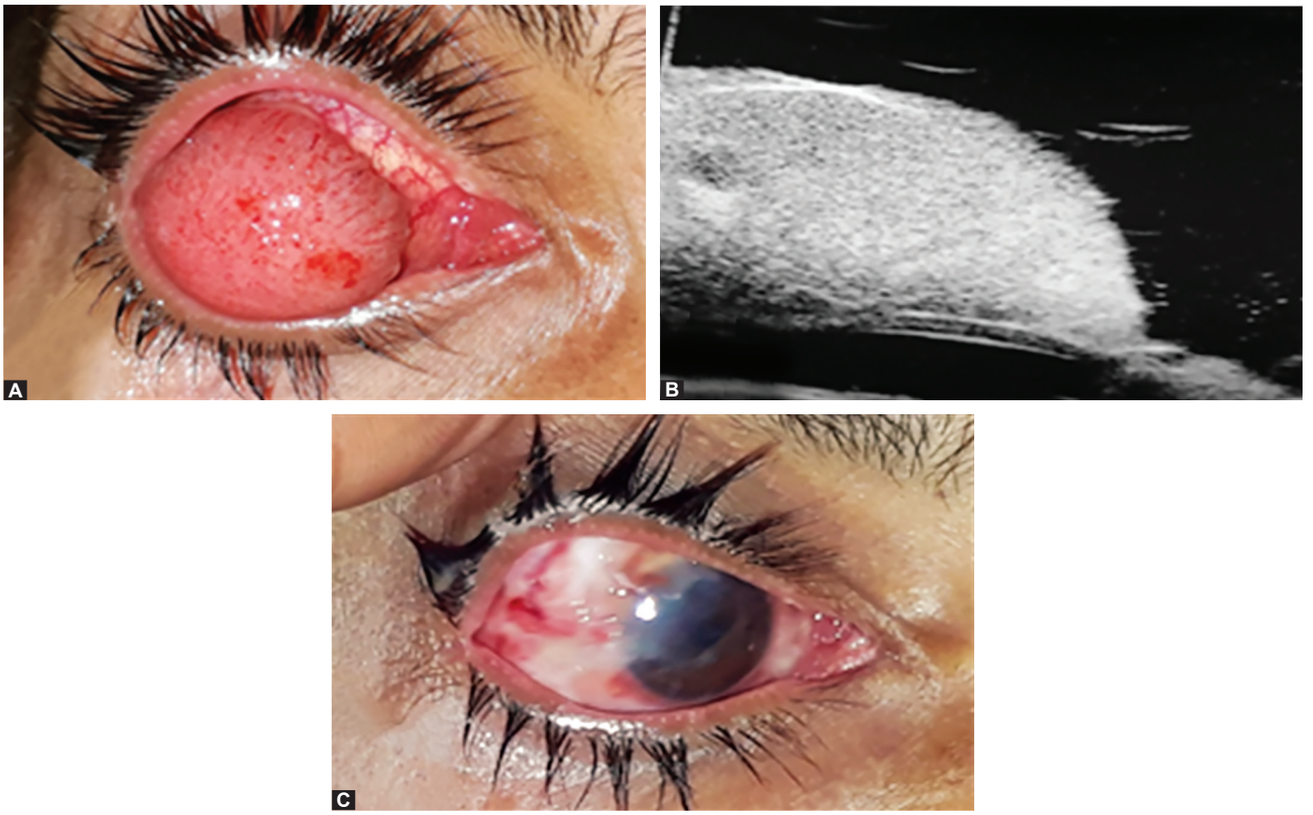

Fig. 11.4: A and B, Invasive OSSN; C, Treated with wide local excision.

adequacy of margins at initial excision, corneal location, larger size (>2 mm), and a high proliferation index. Immunostaining with antibody to Ki-67, a nuclear antigen expressed in proliferating cells, allows evaluation of the growth fraction of normal and neoplastic cells yielding the proliferation index.

RECOMMENDED THERAPEUTIC STRATEGY AND CURRENT THERAPEUTIC PRACTICE

According to recommendations made by Viani GA et al. incision biopsy may be done to rule out invasive lesions before starting on topical therapy in tumours of more than

TABLE 11.2: Drug classification, mechanism of action, administration and adverse effects

Drug	*Mechanism of action*	*Administration*	*Adverse effects*
MMC Alkylating agent	Generates free radicals under aerobic conditions ↓ Inhibition of DNA and protein synthesis. Inhibition of cell migration and production of extracellular matrix	Topical 0.02–0.04% 0.04% (0.4 mg/ml) 4 times a day 4 days a week 4 weeks Treatment-free interval of 2 weeks	Conjunctival hyperaemia Blepharospasm Corneal punctate erosion Punctal stenosis Limbal stem cell deficiency
5-FU Pyrimidine analog	Inhibits thymidylate synthetase ↓ Inhibits production and incorporation of thymidine into DNA Inhibits RNA synthesis	Topical 1% 5-FU. 1% is used 3–4 times a day continuously for 3–4 weeks or 3–4 times daily for 4–7 days with 30–45 days off and cycles repeated	Eyelid erythema Conjunctival hyperaemia Corneal punctate erosion
IFN-α2b Type 1 IFN	Immune-mediated suppression of IL-10, stimulates IL-2 and IFN-γ mRNA Anti-proliferative Anti-viral	Topical 1 million IU/ml four times daily or intralesional 3 million IU/ml	Superficial punctate keratopathy Follicular conjunctivitis Systemic flu-like syndrome Fever/myalgia

(Data adapted from Viani GA, Fendi LI. Adjuvant treatment or primary topical monotherapy for ocular surface squamous neoplasia: a systematic review. Arq Bras Oftalmol. 2017 Mar-Apr; 80(2): 131–136)

one quadrant size. However, incision biopsy may not be representative of the whole tumour and increases the risk of tumour progression and spread. Therefore, most centres avoid incision biopsy except in cases of OSSN requiring enucleation or exenteration. Most of the studies on topical treatment have used only clinical criteria for diagnosis and assessment of tumour grade with use of UBM to rule out invasion. With 70–80% tumours responding to immune or chemotherapy, most oncologists use them as primary treatment in non-invasive cases. Excision biopsy may be planned for invasive tumours, AJCC grade T1 tumours and cases with partial resolution to topical therapy. Due to absence of significant side effects, immunotherapy is emerging as primary management for immunotreatment or immuno-reduction for most cases with no invasion on imaging (UBM).

CONCLUSION

Squamous lesions of the cornea and conjunctiva are uncommon but demand appropriate attention due to the potential for visual loss and systemic morbidity and mortality. Newer modalities of diagnosis allow non-invasive evaluation which correlates well with histopathological tissue diagnosis. With the advent of interferons which have minimal side effects and comparable efficacy, more conservative approach is being followed for treatment of non-invasive lesions. Table 11.2 summarizes the commonly used drugs for treatment of OSSN.

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