

Learning Morphology in Hematology



“Morphology is 5% knowledge and 95% squinting”

(AI has been used to generate the image.)



Muddy Points

- Role of morphology in the era of automation
- Why does morphology appear difficult?
- Key to learning morphology
- How does Artificial Intelligence (AI) link to morphology?

Role of Morphology in the Era of Automation

Since the introduction of automated CBC analyzers in the 1950s, there has been enormous progress in technology. Modern-day analyzers generate many novel parameters, flags, and graphical data (histograms and scatterplots) which have revolutionized CBC assessment. Automation provides rapid, precise, and accurate results. However, morphology still plays a pivotal role in many hematological conditions.

Morphological examination of blood cells in the peripheral smear is a vital part of CBC evaluation. Since automation has taken care of the mundane normal cases, the morphologist can spend more time on the difficult cases for more in-depth interpretation. CBC analyzers,

with flagging and abnormal histograms or scatterplots, assist in earmarking cases that require a detailed peripheral smear review.

Some abnormalities always require peripheral blood smear evaluation for their detection. Examples include: differentiating reactive lymphocytes from blasts, identifying dysplastic cells in myelodysplastic neoplasms (MDS), Auer rods, hemoparasites like malaria, microfilaria, fragmented cells (schistocytes), sickle cells, toxic granulation, and various RBC inclusions.

Potentially actionable abnormalities indicated by automated analyzers include: Atypical lymphocyte or blast flag, immature granulocyte flag, platelet clumps, thrombocytopenia, schistocytes, nucleated RBCs, malarial parasite, and giant platelet flag. These will always require a visual confirmation.

With increasing automation, there is also increasing awareness of numerous artifactual results that may be generated even with the most advanced analyzers. Peripheral blood smear examination is extremely important in this setting to reach the right diagnosis.

Why does Morphology Appear Difficult?

“A picture is worth a thousand words.” Morphology in hematology underscores this oft-repeated saying well. Hematology is an exciting blend of visual art and science. Understanding morphology well demands patience, focus, and willingness to learn, all three casualties of our hyper connected world full of distractions.

“Blood cells do not read textbooks.” Cell morphology in real life is never classical as taught in medical schools and given in standard textbooks. That spectacle shaped nucleus of an eosinophil, a typical myeloblast that checks all the boxes of the WHO description, or a monocyte with a book-picture kidney-shaped nucleus, its “lacy” chromatin are not always readily apparent. In daily hematology practice, blood cells come with many variations, and mastering morphology is an outcome of learning these nuanced differences among cells.

Real-life slides often show glimpses of a cell that looks like a lymphoblast one moment and lymphocyte at the other, an Auer rod-like structure that excites you but doesn’t convince you enough, an eosinophil with four lobes, RBCs that look small one moment and normal-sized the next. Many such dilemmas challenge trainee students each day.

Added to this is the potpourri of variation in staining, different stains used across laboratories, multiple technical hands that stain slides, artifactual distortion of cells, abnormal or atypical cells that have overlapping features, and not to forget multiple opinions from peers and seniors trained in different institutions.

This disconnect between what is taught and seen in textbooks, and what the students encounter in real life, causes much confusion and uncertainty. Some simple questions that bother young trainees are:

- “What is mild, moderate, or severe anisopoikilocytosis in RBCs?”
- “Why do I always undercount platelets, reticulocytes, and monocytes?”
- “How much of a left shift is significant?”

These are valid queries that are hardly discussed or have consistent answers. Even with criteria available for some of these questions, applying them to actual cases appears challenging at times.

These “more than 50 shades of grey” are not given sufficient attention during the training period. Hence, students finish their courses with these doubts “carried on”, never to be solved again, as they are suddenly catapulted to being consultants who, one fine day, are supposed to magically know it all. These “real” questions then get a slow burial till another young trainee raises them in the future.

There is also a human tendency to ignore those occasional cells that one cannot identify confidently on morphology. I feel we must make that extra effort (read, ask, think) to identify these cells to prepare for that one day when all or most cells in a peripheral smear will look like it

“Picking the wrong end of the stick.” During the training period, the habit of students to use automated data to “construct” peripheral smear reports is their worst enemy. The bias introduced at this early stage of learning seems to make their lives easier. However, it gradually erodes their confidence to report smears without the support of automated data.

Awareness about the advantages and limitations of both automated and manual methods is lacking among trainees as well as some teachers, leading to misinterpretation or undermining one of the methods. It is never technology “*versus*” morphology but rather technology and morphology.

For example: An MCV of 78 fL is unlikely to show microcytosis consistently for the morphologist. Early microcytosis with minimal anisocytosis in iron deficiency may be detected by automated analyzers by a high RDW, much before poikilocytosis being visible on microscopy.

A focused approach to peripheral blood smear interpretation is often lacking during the training period. With increasing automation, blood smear review rates have reduced in laboratories, leading to less exposure to smear viewing for students. This has a very easy solution; make smears anyway and learn from these living glass teachers.

Bone marrow morphology appears still more difficult than the peripheral blood smear due to different stains used, vast number and variety of cells (most of them immature), along with the presence of stromal elements and some cells like osteoblasts, osteoclasts, mast cells, and plasma cells not usually seen in the peripheral blood.

Key to Learning Morphology

“Normal is Boring.” Most trainee students dismiss normal blood smears as mundane and hence pay the least attention to them. This is the gravest mistake one could make and is one of the key reasons for a lack of confidence in cell identification.

“Familiarity” Getting familiar with subtle variations of normal cells seen in daily routine is the key to confidently identifying abnormal cell populations. *For example*, monocytes and lymphocytes, in their stages of activation, show myriad morphological variations. If one spends enough time on normal smears trying to identify these variations, the common morphological threads that bind their identity become apparent gradually.

“Visual Reference Library” The study of normal blood or bone marrow smears gradually creates a visual reference library in the brain, which helps to differentiate normal harmless variations from real pathology. This helps to avoid overcalling abnormalities when none

exist. Repeated visual exposure to normal smears trains the brain to detect subtle deviations from normal and to flag early signs of disease.

“Expertise” Gaining expertise in morphology has a learning curve like any other subject or skill. Working at it consistently with patience and sincerity will one day give that “enlightenment” when cells become your allies and not foes. You start getting that vision that this one appears odd, and that odd one is only a variation of a normal monocyte or a neutrophil. Pattern recognition, the key to learning any subject, then comes easily.

“Learning Morphology,” is much like the time when we learnt cycling as children. We never gave up, even after falling repeatedly. What kept us going was the excitement of being on our own sometime in the future. We can look at learning blood cell morphology similarly. Inquisitiveness and passion about “sorting” these blood cells are important to be a good morphologist.

“Self-blinding can make you see.” A preferred method to learn morphology would be to form one’s independent opinion of the smear: RBC morphology, TLC, DLC, platelet count, and only then verify with the automated report. The discrepancies seen, discussed, and the smear re-visited complete a learning cycle that teaches like none other.

How does Artificial Intelligence (AI) Link to Morphology?

- Artificial intelligence methods used in hematology (cell classification, peripheral blood reporting) familiarize the system with numerous images of variable cell morphologies of blood cells. This trains the system to identify various blood cells, even though they may be different from the classically taught morphology.
- When assessing many normal and abnormal blood smears, humans also subconsciously train their minds to correctly “call out” cells with affirmation from their mental library. Much like AI, the more we see, the more we learn.
- Human intelligence can never be replaced by artificial intelligence. Rather than considering them as two opposite poles, we must use artificial intelligence to judiciously augment human intelligence.

Suggested Reading

1. Bain BJ. Morphology in the diagnosis of red cell disorders. *Hematology*. 2005;10(Suppl 1):178-181.
2. Tyrrell L, Scruggs M, Kerwin A, Kahwash SB. The role of peripheral blood smear examination in the evaluation of suspected platelet-related disorders in children: a practical approach and an illustrated review. *Malays J Pathol*. 2022;44(3):397-413.
3. Trotta GE, Santinelli E, Mariani S, Paciaroni K, Caravita di Toritto T, Cenfra N, *et al*. The role of morphology in diagnosing MDS with non-clonal cytopenias. *Leuk Res*. 2025;153:107703.
4. McArthur JR, Miwa S, Catovsky D. Morphology in hematology. *Rev Invest Clin*. 1994;46(Suppl):115-117, 81-82.
5. Panozzo B, Ramnarain J, Chen S, Yuen HLA, Tatarczuch M, Vilcassim S, *et al*. A critical analysis of CellaVision systems in the modern hematology laboratory. *Am J Clin Pathol*. 2025;164(2):163-173.
6. Yang WH, Yang YJ, Chen TJ. ChatGPT’s innovative application in blood morphology recognition. *J Chin Med Assoc*. 2024;87(4):428-433.

AUTHOR'S CORNER

- One must understand the magic as well as the limitations of both automation and morphology. These complementary techniques must be used optimally for decision-making that is beneficial to clinicians for patient management. Over-reliance on automation in areas that cry out for morphological evaluation can lead to missed or inappropriate diagnoses.
- Good knowledge of the “Normal” is the key to understanding the “Abnormal”.
- “I don’t know” are three words that should always stay in a pathologist’s dictionary, irrespective of the level of experience. It is good to honestly admit when one is not confident with morphology of a cell. This avoids overdiagnosis and keeps the window for learning open.
- An orderly approach to peripheral blood smear examination must be followed. An initial scanner screen, low power, high power, and finally examination under oil immersion magnification is important so as not to miss key findings.
- Honesty can never be overemphasized in learning and reporting morphology. I am reminded of a postgraduate student some years back who identified microfilariae in about 10 blood smears in which screening was not requested by the clinician. This is an example of following recommended teaching to the hilt. The slide screen on the scanner and low-power views done diligently are the only measures that would have made the diagnosis possible.
- Most of us at some time during our student life remember that expert teacher who would make that fascinating diagnosis from the blood smear fairly quickly. However, there are very few teachers who, after basking in the glory, would take time out to teach the “approach” of their thinking process of reaching that diagnosis. Without teaching this vital element, students are left in turmoil once the blood cells surround them.
- Even the doyens of morphology in hematology accept real-life morphological dilemmas and have suggested ways to solve them. When struggling with a decision between two cells with overlapping morphological features, one can safely place it in the category that it resembles the most, although it might not fulfill all standard criteria.
- There is a rare, almost extinct species of students or faculty who continue asking questions on morphology all their life with a quest to be friends with as many cells as possible. This species may be much better at cell identification than even some senior faculty.
- Automation, a huge boon in hematology laboratory practice, has often been blamed for the reduction in emphasis on morphology. I sometimes “feel” for these immensely loyal instruments which have made the life of pathologists much easier. It is how we use them that determines how automation marries morphology. Sometimes trainee students see a fancy automated CBC printout and then “manufacture” the peripheral smear report. This is a sure-shot way of blocking any useful morphology learning. Being dependent on technology becomes so commonplace that one gets jitters when handed a peripheral smear for evaluation without the CBC printout.
- In the early training period, it is important to allow trainee students to commit mistakes, even blunders, as they walk through the maze of so many cells trying to grab their attention. In a fear-free environment, the grooves in our neurons dig deeper, and knowledge retention is more meaningful.

8 Practical Laboratory Hematology: A Survival Guide for Trainees and Pathologists

- Appreciation, even when students get simple morphology right, goes a long way in getting them to be friends with the cells. The constant anxiety about missing an important diagnostic cell is what makes morphology scary for trainees. This should be addressed early on.
- If a trainee student has brought a case with a TLC of $22 \times 10^9/L$ and DLC showing 81% neutrophils, the senior correcting the neutrophils to 85% is not warranted. It will only undermine the student's confidence needlessly over an absolute neutrophil count change that is not clinically relevant. Similarly, it is good practice not to significantly change opinion statements prepared by students/younger faculty if the words or opinion you would have preferred do not alter their meaning much (quite often we are in love with our own style). Accepting such opinions is taken by the student as their own acceptance. This can do their confidence a world of good. Of course, this does not mean that if the meaning or clinical implication is significantly altered, the senior should not point it out and rectify it. In such cases, once the change is made, the reason for the same must be clearly explained to the student. This scenario, if not handled well, can make the student feel undermined, or if dealt sensitively, can be an excellent learning exercise.
- Expertise in morphology has been dwindling over the years with over-reliance on automation. Morphology is a great skill to acquire and will never go out of fashion. Its contribution to clinical care with critical information provided is always valued by clinicians and provides immense job satisfaction.
- Learning morphology is a continuous process. Patience is the key. There will always be challenging days when some cells trouble the best of morphologists. This day should not be feared. Probably, another "teacher" has arrived!