blood advances

Diagnosing TMAs by automated red cell morphology analyses

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In this issue of *Blood Advances*, Foy et al used a hematology autoanalyzer available in many routine laboratories to develop an automated morphological red blood cell (RBC) differential generated using machine learning techniques.[1] Although many newer hematology autoanalyzers have image functionality and will offer morphological diagnoses, this functionality is usually limited and more effective for leukocyte imaging than for RBC abnormalities, even for erythrocyte pathologies such as malaria.[2] Smears from healthy individuals that frequently contain some abnormal cells and show the ability to distinguish normal from abnormal cells, particularly schistocytes, are important.[3] Several organizations have recognized this difficulty and raised the need for morphology standardization.[4,5] The Cellavision analyzer, already considered quite good at detecting schistocytes, often requires a manual review for accurate diagnoses.[6]

Using a group of 10 geometric features in tandem with the usual Cellavision RBC sorting, the investigators constructed an algorithm using a support vector machine learning model that better differentiates cell types, concentrating the use of algorithms that will detect and enumerate healthy RBCs, elliptocytes, microcytes, macrocytes, schistocytes, sickle cells, spiculated cells, teardrop cells, and other abnormal RBCs. In addition to evaluating whole-cell populations, their algorithms allow for single-cell classification. Unlike flow cytometry and manual smear review, these are rapid quantitative assessments that allow for quick diagnoses. Although other groups have demonstrated the ability to quantitate schistocytes from peripheral smears using combined imaging flow cytometry and machine learning, this group has significantly advanced the collective field and provided image sets as publicly available data in the hope of increasing collaboration.

Notably, Foy et al assessed their algorithms within the clinical disease context and confirmed the ability of their RBC-differentiating algorithm to make specific diagnoses. Using predominant cell types to arrive at a gestalt assessment of the smear pathology, the authors analyzed the RBC-differentiation ability of smears using the peripheral blood from patients with thrombotic thrombocytopenia purpura (TTP) and hemolytic uremic syndrome and could distinguish these from other thrombotic microangiopathies (TMA). Importantly, they went on to demonstrate that schistocyte counts are associated with prognosis. The authors further found that they could correlate schistocyte counts from patients without TMA with all-cause mortality, similar to what had been shown previously for parameters such as red cell distribution width.[7]

There are limitations. As expected, the sensitivity of the classification appears to vary for different cell types, and each will require validation. This system does not account for cells that might change shape within circulation, such as sickle cell anemia. This machine learning algorithm relies heavily on the use of black-white boundary detection to identify different RBC shapes but does not detect or differentiate between RBC inclusions.

Assessing peripheral blood smears requires expertise and is a time-consuming and costly exercise. Although the authors clarify that their RBC-differentiation algorithm is not intended to replace manual review, the idea that an automated, high-level, accurate RBC differential would be useful in a resource-limited setting is very appealing. Even in the United States, there is pressure on hematology laboratories to minimize the number of smears that require review. The intriguing possibility of diagnosing iron deficiency, thalassemia, sickle cell, or immune-hemolytic pathologies via smear further extends the potential utility of RBC-differentiation algorithm. This also paves the way to encourage more scientific research: why do schistocytes correlate with mortality? What causes schistocyte formation in those with nonhematological acute illnesses?

The future is very likely to include some type of accurate RBC differential that will not only be able to make the diagnosis but will also monitor disease progression and treatment efficacy. Classical hematology has frequently been regarded as too difficult and the problems as too emergent.[8] One of the remaining reasons for a hematologist to visit the hospital in the middle of the night is the possibility of seeing schistocytes on a smear, which will help diagnose a TMA, particularly TTP.[9] This could also be a boon to the idea of a better work-life balance for classical hematologists.

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