EDUCATIONAL COMMENTARY – SMUDGE CELLS: USELESS ARTIFACT OR PROGNOSTIC INDICATOR?

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Learning Objectives

On completion of this exercise, the participant should be able to

- identify smudge cells on a peripheral blood smear;
- explain the potential significance of reporting smudge cells;
- discuss reasons for not reporting smudge cells; and
- describe when and how to count smudge cells.

Introduction

Smudge cells are traditionally associated with chronic lymphocytic leukemia (CLL), but can occur in many other situations. For more than a hundred years they were thought to be a simple artifact from the slide-making process, but in the past ten years, a growing number of research studies have linked increased smudge cells in patients who have already been diagnosed with CLL to a longer overall survival rate. This approach is not yet widely embraced in the medical laboratory community. Many pathologists consider the presence of smudge cells to be a nonspecific finding and that it is not necessary to include them on the patient report.

What Is a Smudge Cell?

Smudge cells, sometimes referred to as “basket cells”, are remnants of leukocytes without cytoplasmic structure; sometimes only bare nuclei are seen. They are literally smashed, or “smudged,” by the physical glass-on-glass action of making a routine differential slide in the laboratory, either with an automated slide maker or a manual push smear. The degree of smudging can be reduced by preparing a 1:5 or 1:10 mixture of blood with bovine albumin before making the smear. The albumin acts as a cellular cushion for fragile leukocytes and improves accuracy in counting a white blood cell differential. Increased numbers of smudge cells are most often associated with lymphoproliferative disorders, especially chronic lymphocytic leukemia (CLL), because the lymphocytes are more fragile in these diseases. Smudge cells in patients with CLL are ruptured B-cell lymphocytes, but are indistinguishable morphologically from other disintegrated lymphocytes.
A variety of diseases and other factors such as infectious mononucleosis, T-cell leukemias and other small-cell lymphoproliferative disorders, or even old blood and improper handling can produce smudge cells on a complete blood cell count (CBC) smear. Leukocytes begin to disintegrate after 4 hours at ambient temperature, or 24 hours in EDTA at 4°- 8° Celsius. Stability is affected by storage at temperatures that are too warm or too cold, or by overly vigorous mixing. Even routine smears on hospital patients can have smudge cells due to rapid cellular turnover. Some smudged cells can still be recognized as neutrophils, monocytes, eosinophils, and if positive identification can be made, they can be included in a differential, according to individual laboratory policy. However, they are not reported as “smudge cells” if they are counted as their individual cell type, such as eosinophil. Bare nuclei cannot be identified as anything other than a smudge cell.
Infectious mononucleosis. Clockwise from top: smudge cells (2), reactive lymphocyte, neutrophil.

In the context of old blood, reporting the presence of smudge cells will have no clinical significance to the physician. It could even lead to an erroneous supposition of CLL, in particular if the neutrophils have markedly disintegrated because of specimen age, leading to a relative, false lymphocytosis. In such instances, the overall white blood cell count is usually normal.

Chronic lymphocytic leukemia typically presents with an increased number of small mature lymphocytes, along with the presence of smudge cells. Some refer to these CLL lymphocytes as “soccer-ball” lymphocytes because the nucleus is very mature, dark, and can have a “cracked” appearance.⁹
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Many different scenarios can lead to smudge cells on a slide, but because the presence of smudge cells traditionally implies CLL, it is not currently standard practice in the United States to report smudge cells in any context other than CLL, and then usually only as “present,” without quantitation or grading. Smudge cell reporting requires the agreement and understanding of the community’s hematology oncologists.

Staging and Treatment of Chronic Lymphocytic Leukemia (CLL)

Chronic lymphocytic leukemia is the most common type of adult leukemia in the US and the UK, and rare in Asian countries. Most people are diagnosed during routine CBC testing before developing any symptoms. CLL is diagnosed by demonstrated lymphocytosis (>5000 lymphocytes per microliter of blood) and confirmed by flow cytometry or genetic testing of the blood or bone marrow, where available. As the disease progresses, the B-cell lymphocytes grow uncontrolled in the bone marrow where they crowd out normal cells, leading to anemia and infections.

Staging by the Rai or Binet classification systems to determine the extent of the disease is based on blood counts and physical manifestation of lymphocyte involvement, such as enlarged spleen, liver, or lymph nodes. The higher the staging classification, the poorer the prognosis, and the sooner treatment is required to manage symptoms. CLL is generally considered an incurable disease.

CLL is often so slow to progress that treatment is not initiated until the disease stage indicates the patient’s quality of life is being affected. Some patients can live normal lives for decades before treatment is required, but approximately 30-40% have a rapidly progressing form, requiring aggressive treatment to control it.

Individual Studies on Significance of Reporting Smudge Cells in CLL


The Mayo Clinic conducted two similar studies that suggested that the number of smudge cells on smears for patients with CLL may be more significant than the customary assumption of smear artifact. Their studies focused on vimentin, a cytoskeletal protein that is integral in lymphocyte cellular rigidity. Vimentin has separately been associated with poor prognosis in breast and colon cancer, as well as in leukemia. Patients with CLL with low vimentin expression have a high percentage of smudge cells (i.e., increased cell fragility). The percentage of smudge cells out of the overall lymphocyte total was determined, and a threshold of 30% smudge cells confirmed the risk for aggressive disease. Patients with less than 30% smudge cells showed shorter time to requiring treatment for symptom management and shorter overall survival. Patients with more than 30% smudge cells demonstrated much longer overall survival. The percentage of smudge cells is directly proportional to survival time and timetable for
needing to begin treatment. Smudge cell percentage is almost universally available, even in basic laboratories, and does not require expensive, high-tech equipment or specialized staff.1,7

Brazil, 2009.

This study considered whether the presence of smudge cells was diagnostic for CLL. Analysis of 125 patients with chronic B-cell lymphoproliferative diseases found that there were definitively more smudge cells in CLL than in the other diseases, but specificity was not high enough to make the diagnosis of CLL from the presence of smudge cells.11


This flow cytometry study showed that low CD45 expression was an indicator of increased cell fragility in CLL. Because increased cell fragility also correlates with increased smudge cells on the smear, the researchers were making a parallel point about monitoring cell fragility as a prognostic indicator. The study found that CLL cells from patients with more than 36% smudge cells had very low levels of CD45, correlating with the cutoff of 30% used in the studies from the United States, India, and Senegal. Low levels of CD45 and increased CLL cell fragility are associated with longer time until treatment is necessary.2

India, 2014.

This study states CLL is a common disease in the West, but relatively rare in India. The authors reviewed records covering 12 years, from 2000 to 2011, and analyzed the percentage of smudge cells in 222 patients previously diagnosed as having CLL by flow cytometry. This study came to a similar conclusion as the American studies; patients with 30% or fewer smudge cells had much more advanced disease and lower overall survival. The authors also concluded that smudge cell percentage could be useful in following CLL patients in situations with limited resources.12

Senegal, 2015.

Chronic lymphocytic leukemia can present either as an aggressive leukemia or as an indolent form that will not require treatment for many years. Flow cytometry and cytogenetic analysis can provide very specific markers for staging and treatment of disease, but many laboratories in developing countries do not have the equipment available for such tests. This study of 42 patients diagnosed as having CLL found a strong correlation between low numbers of smudge cells (< 30%) and advanced-stage disease. The authors propose using smudge cell percentage as a less expensive prognostic indicator in patients with CLL living in developing countries.13
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Laboratory Methods of Counting and Reporting Smudge Cells

Although recent research has suggested that smudge cell percentage is useful as a prognostic indicator for patients with CLL, there remains much debate on the value of reporting this figure on routine CBC smears. Most laboratories do not report smudge cells at all, and those that do are limited to reporting this finding only in CLL. The smudge cells are not quantitated. Consultation with leading reference laboratories\(^4\)\(^,\)\(^5\) and a prominent cancer center\(^3\) during the writing of this commentary agree that smudge cells are non-specific; their pathologists differ on whether they should be reported.

If, in the future, hematologist-oncologists and laboratory scientists agree to begin tracking smudge cell percentage for CLL patients, the 2009 Mayo study suggested a 200-cell count of lymphocytes, intact and smudged, to determine the percentage of smudge cells, without adding albumin to the slide preparation. The smudge cell percentage would be reported as a percentage of the lymphocyte total, as a separate count performed in addition to the traditional white blood cell differential.\(^1\)

Conclusion

The presence and percentage of smudge cells shows good correlation with the overall survival rate in patients with chronic lymphocytic leukemia, but it is a nonspecific finding. The practice of enumerating smudge cells is not yet established or standardized for laboratory practice except in populations of patients with CLL. There are other prognostic indicators with greater specificity to guide treatment for CLL, but these tests require more expensive equipment and are not universally available, especially in developing countries.

References


3. Hirsch-Ginsberg, Cheryl. Univeristy of Texas MD Anderson Cancer Center, Houston Texas. "Smudge cell reporting on differentials." E-mail message to the author. 5 February 2017.


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