



Saint Luke's Regional Laboratories Clinical Laboratory Letter

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SOX11: A Valuable Biomarker for Mantle Cell Lymphoma

Diagnosis and separation of mantle cell lymphoma (MCL) from other small cell non-Hodgkin lymphomas is important because it is considered one of the most aggressive lymphomas which often requires high-dose chemotherapy and potential autologous stem cell transplant, especially in younger patients. MCL accounts for 3 to 10% of non-Hodgkin lymphomas. The characteristic lesion defining MCL is a *IGH/CCND1* translocation, resulting in up-regulation of cyclin d1 protein. Detection of cyclin d1 by immunohistochemistry and/or demonstration of *IGH/CCND1* gene fusion by fluorescence in situ hybridization (FISH) is imperative for diagnosis.

Unfortunately, 10% of cases are negative for cyclin d1 and/or *IGH/CCND1* translocation, in spite of being morphologically and immunophenotypically indistinguishable from conventional MCL. This discrepancy poses a diagnostic dilemma. Global gene expression profiling studies have revealed similar expression profiles in both cyclin d1 positive and negative MCL cases. Overexpression of other cyclin d proteins including d2 and d3 have been reported in cyclin d1 negative MCL, but testing for such overexpression is not widely available and is fraught with interpretive problems.

SOX11 is a transcriptional factor normally expressed in embryonic central nervous system but not in adult tissues. Overexpression of *SOX11*, has been demonstrated in certain malignancies including ovarian cancer, medulloblastoma, and malignant glioma. Recent studies have shown that both *SOX11* mRNA and protein are also up-regulated in lymphoblastic lymphoma, Burkitt's lymphoma, and MCL independent of cyclin d1 status. The first two types of lymphoma are easily distinguished from MCL by morphology and immunophenotype,

which makes *SOX11* a very useful biomarker for diagnosis of cyclin d1 negative MCL.

Several studies have validated its utility in diagnosis of cyclin d1 negative MCL. Recently, Saint Luke's hematopathologist used a *SOX11* immunostain to confirm the diagnosis of MCL in a case that showed partial positivity for cyclin d1 in neoplastic B cells and negative *IGH/CCND1* fusion FISH studies.

Significance of Schistocytes

Schistocytes or schizocytes are defined as circulating red blood cell fragments. Detection of schistocytes is an important clue for the diagnosis of thrombotic microangiopathy (TMA), which includes both thrombotic thrombocytopenic purpura (TTP) and hemolytic-uremic syndrome (HUS). Other causes of schistocyte formation include structural abnormalities of heart and great vessels, malfunctioning prosthetic valve, HELLP syndrome, malignant hypertension, and metastatic carcinoma. A more recent indication for schistocyte counting is monitoring bone marrow transplant patients for the onset of TMA, which is a frequent and severe complication. Non-TMA causes of red blood cell fragmentation include red blood cell membrane defects, thalassemia, megaloblastic anemia, primary myelofibrosis, and thermal injury. The red blood cell fragments in these cases show high variability in shapes and marked aniso-poikilocytosis which are not specific for the diagnosis of TMA.

Poorly defined morphological criteria for identification and enumeration of schistocytes have adversely affected treatment and clinical outcome of TMA in the past. In 2008, the Schistocyte Working Group (SWG) of the Internal Council for Standardization in Hematology undertook the task of preparing scientific recommendations to standardize schistocyte identification, enumeration, and reporting. The overall final recommendations of SWG were

published in 2011 and are available at www.ISLH.org. Briefly the recommendations are:

1. The morphological criteria required for identification of schistocytes includes cells smaller than intact red blood cells and have shapes with sharp angles and straight borders, small crescents, helmet cells, keratocytes, and microspherocytes.
2. A schistocyte count should be considered clinically meaningful if schistocytes represent the main morphological red blood cell abnormality in the smear.
3. In adults, a schistocyte percentage above 1% should be considered as a robust cytomorphological indication favoring TMA. In cases where the clinical suspicion of TMA is high but schistocytes are absent, blood smear screening for schistocytes should be repeated daily because their appearance may be delayed for several days.
4. For diagnosis of transplant associated TMA, schistocyte threshold of 4% is recommended together with thrombocytopenia, increased lactate dehydrogenase, decreased hemoglobin concentration, and decreased haptoglobin.
5. Automated hematology analyzers flag for fragmented red cells (FRC) and some of these analyzers can also provide an automated FRC count which can be used for screening test and follow-up. Unfortunately, the current hematology analyzers in Saint Luke's laboratories do not include this parameter.

The following flow chart is a practical guide for the use of the schistocyte count in the diagnosis of TMA.

