

CD5-positive, Small B-Cell Lymphoproliferative Disorders: Aberrant Findings of CLL/SLL and MCL

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Abstract

Most common CD5-positive, small B cell lymphoproliferative disorders include chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) and mantle cell lymphoma (MCL). Among these cases, atypical morphology, immunophenotype, and/or cytogenetic abnormalities are not uncommon. As an aberrant marker, CD5 expression is not limited to the cells of CLL/SLL or MCL and has been found in other B cell lymphomas (both low grade and more aggressive types). CD5-negative CLL/SLL and MCL also are well documented, as are reports of other aberrant immunophenotypes of CLL/SLL and MCL. In addition, monoclonal B-cell lymphocytosis (MBL) of unknown significance has recently been reported in otherwise healthy individuals. We review here the findings that do not fulfill the current definitions of CLL/SLL or MCL. It is imperative that a pathologist should be familiar with these aberrant findings when considering CLL/SLL or MCL as a possible diagnosis. Furthermore, these aberrant findings may be clues to further understanding these entities.

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Introduction

CD5 is a membrane glycoprotein. It is, in addition to being a pan-T cell marker, expressed in a subset of long lived B cells named B1 B-cells that are found mostly at the mantle zone of lymphoid follicles in mice.¹ In humans, CD5 may promote B-cell survival through stimulation of autocrine interleukin10 (IL-10) production.² CD5-positive, small B cell lymphoproliferative disorders include a couple of pathologically and clinically well defined entities: chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) and mantle cell lymphoma (MCL).³ They both are the result of dysregulated proliferation of mature-appearing, small, CD5-positive B lymphocytes which show somewhat subtle morphological, but critical phenotypic and cytogenetic differences between the two. Diagnosis of either entity is often straight forward with the current multimodality diagnostic approach available in many laboratories, provided there is sufficient tissue material and relevant clinical history. On the other hand, a morphologic diagnosis of CLL/SLL or MCL may be very difficult based on a needle core biopsy due to lack of adequate material for evaluation of lymph node architecture and/or additional immunophenotyping workup. Partial involvement of a lymph node by SLL and/or MCL can also be so subtle as to be overlooked during morphological evaluation of lymph nodes for other disease processes such as metastatic carcinoma. The distinction between large proliferation centers and large cell transformation (Richter's transformation) of SLL may be at times subjective or controversial. In addition, morphologic, phenotypic, and /or cytogenetic, atypical forms of both entities are not uncommon and have been reported intermittently.

Furthermore, both CLL/SLL and MCL, well-defined as they are, are still biologically and clinically heterogeneous. While many CLL/SLL show an indolent, slowly progressive clinical course and watchful waiting has been the standard of care for patients of early stage disease for decades, a subset of patients will progress more aggressively.⁴ On the other hand, generally considered a clinically more aggressive lymphoma, MCL patients with a more indolent clinical course have been observed.⁵ Prognostic stratification of both CLL and MCL patients has been a challenge for both pathologists and oncologists. Given the fact that the pathogenesis of malignant lymphoma including both CLL/SLL and MCL remains poorly understood, it is quite conceivable that further study at the molecular level will better characterize subtypes

of CLL/SLL and MCL and provide prognostic insight into the disease entities. In this article, we review the reported, but less well characterized, atypical (morphologic, phenotypic, or cytogenetic) forms of CLL/SLL and MCL, with the emphasis on the pathologic differential diagnoses.

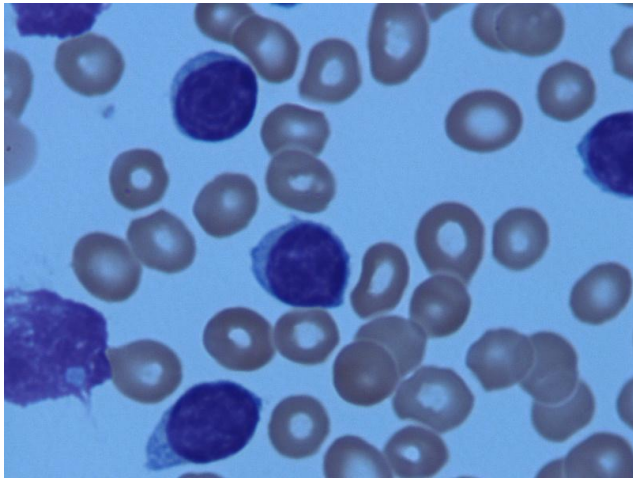


Figure 1a. CLL in peripheral blood showing lymphocytes with smooth nuclear contour and smudge cells (100x magnification).

Typical CLL/SLL

According to the recent WHO definition, CLL/SLL is a neoplasm composed of monomorphic, small, round to slightly irregular B lymphocytes that involve peripheral blood, bone marrow, spleen, and lymph nodes ³ (**Figure 1a**). The number of larger lymphocytes with prominent, centrally located nucleoli, termed prolymphocytes, varies depending on the case, but usually are less than 2% in peripheral blood. An increased percentage of larger cells are often associated

with a more aggressive clinical behavior. As mentioned earlier, Richter’s transformation to large cell lymphoma may occur. Phenotypically, the CLL/SLL cells co-express CD5 and CD23. CD20. Surface immunoglobulin staining is usually of low intensity (**Figure 1b**), the latter being a feature that is thought to be related to the mutations in the associated CD79b.⁶ The International Workshop on Chronic Lymphocytic Leukemia (IWCLL) defines SLL as lymphadenopathy with no cytopenia due to bone marrow infiltration by CLL/SLL cells and $< 5 \times 10^9/L$ B-cells in peripheral blood.⁷

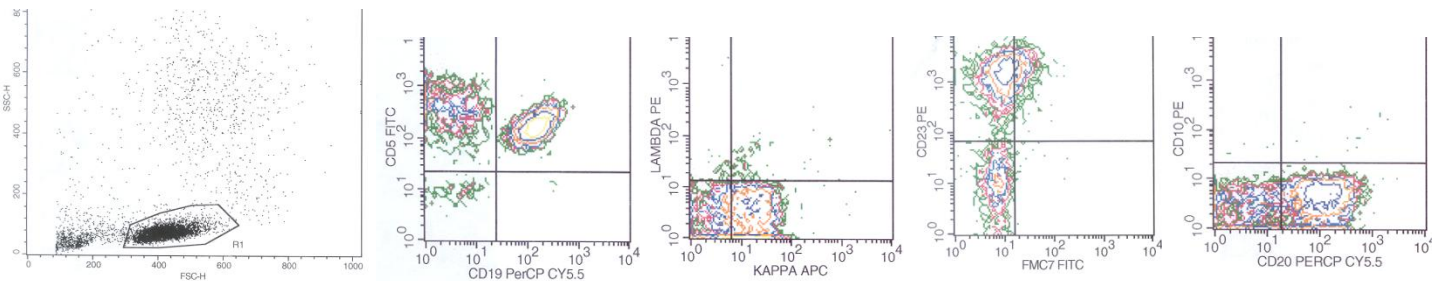


Figure 1b. CLL in peripheral blood showing low intensity CD20 and kappa light chain expression, positive CD23 and negative FMC7.

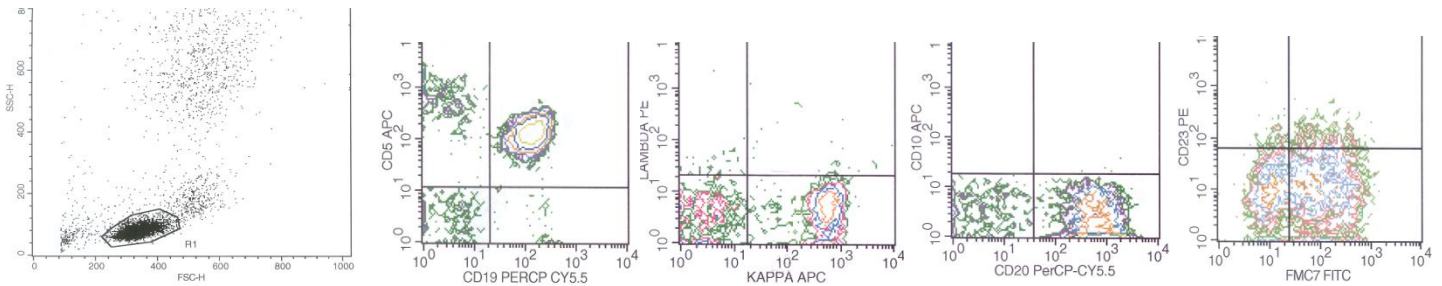


Figure 2b. Mantle cell in peripheral blood showing higher intensity CD20 and kappa light chain expression, negative CD23 and positive FMC7.

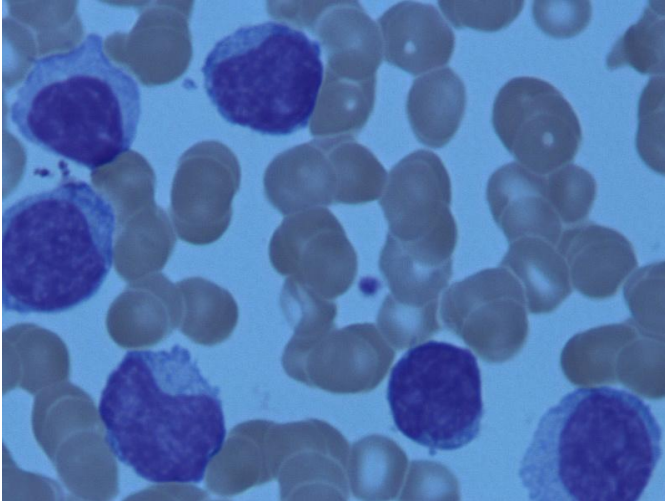


Figure 2a. MCL in peripheral blood showing lymphocytes with irregular nuclear contour (100 x magnification).

Typical MCL

MCL is a B-cell neoplasm composed of monomorphous, small to medium sized lymphoid cells with distinct morphologic, immunophenotypic and cytogenetic features that are close to, but different from, CLL/SLL. It was initially described as an entity different from CLL/SLL based solely on its more irregular nuclear morphology.⁸ Subsequent immunophenotypic studies show MCL cells to be also CD5 positive. However, in contrast to CLL/SLL, MCL cells demonstrate bright CD20, high intensity cell surface Ig, positive FMC7 and negative CD23 by flow cytometric study (**Figure 2b**). Additionally, MCL cells were later found to be positive for cyclinD1 by immunohistochemical staining, which also correlates well with over-expression of cyclinD1 mRNA and the cytogenetic finding of t(11;14)(q13;q32) translocation between IgH and cyclinD1 genes.⁹⁻¹⁰ The unique cytogenetic abnormality of t(11;14) translocation and positive immunostaining for cyclinD1, while not specific for MCL, in the appropriate setting, are very powerful diagnostic findings in establishing a diagnosis of MCL. Clinically, MCL is usually not an indolent lymphoma like most CLL/SLL and requires more aggressive chemotherapy. A spectrum of morphologic variants of MCL has been described. One of them is a blastoid variant which is defined based on the immature chromatin pattern and high mitotic rate of the lymphoma cells. These cells are not true lymphoblasts since they are negative for blast markers such as terminal deoxynucleotidyl transferase (TdT) and CD34. This variant is also clinically more aggressive. Recently, there have been reports of partial or limited lymph node involvement by the lymphoma: *MCL In Situ*, as a diagnostic pitfall when evaluating a lymph node biopsy.¹¹ A unique clinical presentation of MCL is multiple lymphomatous polyposis of the gastrointestinal tract.¹²

Atypical Forms and Differential Diagnoses

Mostly CLL related:

In the last few years, one of the important progresses in the study of CLL is the flow cytometric documentation of monoclonal B cells in a small number of healthy individuals. This has been called monoclonal B-cell lymphocytosis (MBL). Often the cells in MBL are CD5 positive (termed CLL-like cells). In addition to the reported 3.5% prevalence of the presence of CLL-like cells in a study of 910 outpatients over 40 years old on this seminal paper,¹³ different prevalence rates of MBL and non-CLL-like clones have been reported.¹⁴ Elderly patients are more likely to be positive for the CLL-like cells. Monoclonality of the CLL-like cells is determined by immunoglobulin light chain restriction and has been confirmed in a subset of the cases by consensus-primer IgH PCR study. These individuals are asymptomatic and a diagnosis of CLL cannot be made based on the current diagnostic criteria.⁷ The significance of these findings is not certain at this point and whether MBL is considered an example of atypical CLL/SLL is controversial. However, it is expected a few of them will progress to frank CLL/SLL, probably analogous to the relationship between monoclonal gammopathy of unknown significance (MGUS) and myeloma. In fact, in a study of 77,469 healthy adults enrolled in a cancer screening study, 44 of 45 patients who developed CLL (up to 6.4 years later) had pre-diagnostic B-cell clones in their initial stored blood specimens.¹⁵

One category of atypical CLL are cases with increased number of larger cells in peripheral blood or bone marrow aspirate, often over 10%. The larger cells may be prolymphocyte-like or plasmacytoid. The atypical forms also appear more likely to be positive for CD38, CD43 and FMC7 by flow cytometric analysis. An earlier study of 544 CLL cases, consisting of both usual and atypical morphologic forms, defined five chromosome groups including trisomy 12.¹⁶ The study showed that the atypical forms of CLL were more likely to be related to trisomy 12. The association is even more frequent when trisomy 12 occurred together with other chromosomal abnormalities. Trisomy 12 is also found to be associated with increased expression of CD11a by flow cytometric study.¹⁷ A comparative genomic hybridization (CGH) study indicated additional gains on chromosome 12p and 12q outside the common amplified region of 12q21 in the atypical CLL cases.¹⁸ Recently, a study of a small series of CLL cases with t(2;14)(p16;q32) translocation indicated a correlation between atypical morphology and unmutated immunoglobulin variable region heavy chain (IgVH) genes.¹⁹ The reported six cases also expressed ZAP70, a surrogate marker for unmutated IgVH in CLL/SLL. These cases also showed more aggressive clinical course. The atypical morphology includes both plasmacytoid differentiation and increased prolymphocytes. It would be interesting to see in future studies whether a firm relationship can be established amongst the three variables, i.e., atypical morphology, unmutated IgVH, and aggressive clinical course.

CD5-negative B-cell CLL cases have been well recognized with the available flow cytometry studies and immunohistochemical stains. However, the clinical significance of the finding, other than in avoiding a misdiagnosis in the laboratory, is not clear. A French study of 42 CD5-negative cases indicated more frequently isolated splenomegaly to be the initial clinical presentation and higher level of surface Ig by flow cytometry, in contrast to the usual CD5-positive CLL cases.²⁰ In this study, MCL, marginal zone lymphoma, prolymphocytic leukemia, and hairy cell leukemia were ruled out based on the combined morphologic and immunophenotypic review. The study demonstrated a similar prognosis between the CD5-negative and CD5-positive CLL cases. To echo these findings, there have been reports indicating CD5-negative CLL, similar to CD5-positive CLL cases, have been successfully treated or controlled with rituximab.²¹⁻²²

While familial and sporadic CLL may be indistinguishable based on morphologic review, a recent flow cytometric study of 24 familial CLL cases and 104 sporadic CLL cases indicates that aberrant expression of CD2 or CD13 are more commonly seen in familial CLL.²³ Furthermore, CD38 expression in familial CLL does not seem to carry the negative prognosis observed in sporadic CLL.

As was acknowledged in the 2008 WHO classification of hematopoietic neoplasm, CLL and SLL are currently considered different manifestations of the same disease entity.³ While SLL usually shows partial or complete replacement of a lymph node by the lymphoma, more subtle or unusual patterns of involvement such as perifollicular, interfollicular, or marginal zone involvement only may occasionally be encountered in clinical practice.²⁴ Increased awareness of clinical history and appropriate use of CD5, CD23 and cyclinD1 antibodies for immunohistochemical stain may help avoid a misdiagnosis. In fact, finding partial lymph node involvement by lymphoma does not necessarily mean the disease is in its early stage. The above mentioned study indicated most had disseminated disease (stage III or IV) in the 12 cases with adequate clinical data.

One of the major immunophenotypic differences between CLL and MCL is the CD23 status. Before anti-cyclinD1 antibody was widely available as a powerful tool to help distinguish MCL from CLL, CD23 status by flow cytometry had been considered very useful in separating CLL from MCL, especially when CD23 is either moderately to brightly positive or completely negative by flow cytometry.²⁵ However, if the CD23 expression is in the low intensity range, it would be much less helpful in differentiating between CLL/SLL and MCL.²⁶ Additional studies of cyclinD1 expression by immunohistochemical stain or chromosomal translocation by fluorescent in situ hybridization (FISH) then becomes the confirmatory test. In a study of 350 CLL/SLL cases and 90 MCL cases, CD11c expression was reported in up to 90% of CLL cases and was rarely positive in MCL.²⁷ The study indicated that, like

CD23, CD11c may aid in the differential diagnosis of CD5+ B cell neoplasms and should be included in the antibody panel used in the workup of potential CLL or MCL cases.

Mostly MCL related:

As noted earlier, on the peripheral blood smear and marrow aspirate smear, morphologic differences between CLL and MCL can be very subtle. Fortunately for a diagnostic pathologist, immunophenotypic differences between the two are often quite apparent: typical MCL cases are CD20+, CD5+, FMC7+, CD23- and show much higher surface Ig intensity than CLL. Nevertheless, not surprisingly, like CLL, aberrant immunophenotypes have been reported in MCL. In a study of 50 cases of MCL, lack of CD5 expression was seen in 5 cases which were all positive for cyclinD1.²⁸ Aberrant CD5-/CD10+ immunophenotype has been reported in lymphomas with otherwise typical MCL morphology, positive t(11;14) translocation and cyclinD1 protein expression.²⁹⁻³⁰ This phenotype may mimic that of follicular lymphoma. In fact, one of the above reported cases was initially diagnosed as a follicular lymphoma. Therefore, if the level of suspicion for MCL is not high, cyclinD1 study may not be included in the workup of a case and a MCL diagnosis may be missed. Histologically, MCL may also mimic marginal zone B cell lymphoma, a type of low grade lymphoma.³¹ The blastoid variant of MCL can be readily differentiated from diffuse large B-cell lymphoma and/or lymphoblastic lymphoma based on the cyclinD1 status and other immuno markers. To underscore the importance of cytogenetic studies in an even seemingly immunophenotypically characteristic CLL or MCL case, Ho, et.al. looked at the cytogenetic status of 28 cases of CD5-positive small B cell neoplasms with typical MCL immunophenotype as assessed by flow cytometry.³² They found only 57% (16/28) had t(11;14), consistent with MCL. 32% (9/28) lacked t(11;14) but harbored other cytogenetic abnormalities commonly found in CLL. No significant morphologic or flow cytometric immunophenotypic differences were found between the t(11;14)-positive and t(11;14)-negative cases. Therefore, the overlapping CD5 positive feature as well as the similar morphology makes it mandatory to confirm the presence of cyclin D1 expression by immunohistochemistry, or perform FISH studies for t(11;14) on the tissue sections or cytogenetic evaluation on the peripheral blood or marrow aspirate. Analysis of cyclin D1 by real-time RT-PCR may now be performed on the formalin fixed paraffin tissue sections.³³ CyclinD1 analysis by flow cytometry has been done but is currently not clinically standardized.

A plasma cell component or differentiation has been noted in MCL, and is almost always non-neoplastic. However, two cases reported by Young et al showed plasma cell differentiation that was monoclonal in an otherwise typical MCL.³⁴ The plasma cells were found to be derived from the same B-cell clone as the MCL cells.

Most MCL show chromosomal translocation t(11;14)(q13;q32) which results in cyclinD1 over-expression. Additional cytogenetic abnormalities are rare. Translocations involving chromosome 3q27 was found in 4 of 5 MCL cases that showed aberrant BCL6 protein expression.³⁵ A search of the lymphoma cases during a 10-year period at one cancer institute found 5 cases with complex karyotype including t(11;14) and 8q24 chromosomal abnormalities, all with blastoid features.³⁶

Other atypical forms

CD5 positivity has been seen in various types of B-cell lymphoma/leukemia other than CLL/SLL, MCL, or MBL. In a study of 42 cases of B-cell lymphoma with co-expression of CD5 and CD10,³ there were 14 (33%) cases of large B-cell lymphoma, 10 (24%) cases of follicular lymphoma, 9 cases (21%) of MCL, 4 cases (10%) of CLL, 2 cases (5%) of acute lymphoblastic leukemia and 3 cases (7%) of other low-grade B-cell lymphoma. In a recent report of 229 cases of atypical CD5+ chronic B-cell lymphoproliferative disorders that do not fit into the typical CLL/SLL, MCL, or MBL based on flow cytometry study of peripheral blood and/or bone marrow, further study of non-BM tissue biopsy (lymph node, spleen, mesentery, bowel, mediastinal mass, etc) in 75 cases (33% of total) was performed.³⁸ A definitive diagnosis could be made in 61 cases (81% of 75), in which, the biopsy samples were adequate for a comprehensive histopathologic analysis. CLL/SLL was the most frequent (44% of 61) diagnosis made. The rest of the diagnoses were leukemic phases of marginal zone B-cell lymphoma, lymphoplasmacytic lymphoma, diffuse large B cell lymphoma and high grade B-cell lymphoma, not otherwise specified. Inadequate tissue quantity or suboptimal tissue condition was the reason for the 14 cases in which a definitive diagnosis could not be made. On the other hand, in 86% of the patients who did not go through a non-BM tissue biopsy, the lymphoproliferative disorders could not be further classified and remained "unclassified". In the patients who had at least one BM biopsy and/or aspiration, a definitive diagnosis was made in 24% of the cases, the most common diagnosis being lymphoplasmacytic lymphoma. The study highlights the importance of non-BM tissue biopsy in CD5-positive, chronic lymphoproliferative disorders. CD5-positive MALT lymphoma limited to the ocular adnexal origin was reported in two cases.³⁹ In a study of 24 cases of splenic marginal zone lymphoma with CD5-positive B-cells in peripheral blood, the patients tended to show higher peripheral lymphocytosis and more frequent diffuse marrow infiltration.⁴⁰ However, no significant differences in clinical outcome were found in relation to the CD5 expression.

Summary and Discussion

As noted earlier, even though CLL/SLL and MCL appear quite well defined pathologically, patients of either of the two show heterogeneous clinical behavior and vastly different outcome. The role of CD5 positivity in the disease

development of either CLL/SLL or MCL, other than being a categorical marker in aiding the classification, is very much unclear as of now. Therefore, while CD5 is currently extremely useful as a surrogate marker for CLL/SLL and MCL, in the future, how clinically relevant it is remains to be seen. As more is learned about both entities and lymphoma as a whole at the molecular level, it is expected that more subtypes will be defined. The exceptions or the atypical cases that we encounter in the diagnosis of CLL/SLL and MCL now may become easy for us to understand.

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