An Unusual Case of Leukemic Mantle Cell Lymphoma With a Blastoid Component Showing Loss of CD5 and Aberrant Expression of CD10

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Abstract

Characteristically, mantle cell lymphoma (MCL) expresses surface immunoglobulin (sIg), CD19, CD20, and CD5 and lacks CD10 and CD23. Rare CD5– MCL variants have been described. This report describes a case of leukemic MCL with morphologically and immunophenotypically distinct classic MCL and blastoid-variant MCL (BV-MCL) components. The classic MCL had typical morphologic features and immunophenotype (κ sIg light chain–restricted and CD5+; CD10– and CD23–). The BV-MCL had larger nuclei and open chromatin; these cells also were κ sIg light chain–restricted; however, they were CD10+ and CD5–. Fluorescence in situ hybridization studies demonstrated cyclin D1–immunoglobulin heavy chain gene fusion in both components; the bone marrow biopsy cellularity was replaced by CD10+ and cyclin D1+ and CD5– BV-MCL. This case illustrates the phenotypic heterogeneity of MCL and underscores the need for histopathologic correlation and, in some instances, ancillary genetic studies to accurately classify B-cell lymphomas.

Characteristically, the neoplastic cells of mantle cell lymphoma (MCL) express surface immunoglobulin (sIg), CD19, CD20, and CD5 and lack expression of both CD10 and CD23. These cells usually have relatively high levels of sIg and surface CD20 expression and, therefore, stain brightly with antibodies to these antigens. This disease-associated immunophenotype frequently is used to screen for potential MCL cases. The diagnosis typically is confirmed through the demonstration of the t(11;14)(q13;q32) involving the cyclin D1 (CCND1) and immunoglobulin heavy chain (IgH) genes or the resultant aberrant cyclin D1 protein expression. The blastoid variant of MCL (BV-MCL) typically arises as a de novo neoplasm and is both immunophenotypically and genetically similar to classic MCL. In the relatively uncommon circumstance in which BV-MCL arises from a previously documented classic MCL, the immunophenotype of the transformed disease usually is similar to its predecessor.

Recently, cases of CD5– classic MCL and BV-MCL have been reported. This absence of CD5 expression might occur in up to 10% of MCL cases. However, to our knowledge, no MCL cases that showed conversion from a CD5+ to a CD5– phenotype or that contained both CD5+ and CD5– subsets have been described. In this article we report a case of leukemic MCL containing both classic and blastoid components. This case was of particular interest because while the classic component had a typical MCL phenotype, the blastoid component was CD5– and furthermore showed aberrant expression of CD10.

Materials and Methods

Flow cytometric immunophenotyping analysis was performed according to previously described methods.
Following isotonic lysis, nucleated cells were stained with fluorochrome-conjugated antibodies to the following antigens: CD3, CD5, CD10, CD11c, CD14, CD16, CD19, CD20, CD22, CD23, CD38, CD45, and κ and λ immunoglobulin light chains. All antibody conjugates were obtained from Becton Dickinson Biosciences, San Jose, CA. Analysis was performed on a FACSCalibur instrument (Becton Dickinson), and the data were processed using CellQuest software (Becton Dickinson). Immunoperoxidase stains were performed on the B-5–fixed, decalcified, paraffin-embedded bone marrow biopsy specimen using previously described techniques. The antibodies to CD3 (polyclonal), CD20 (L26), bcl-2 (124), bcl-6 (PB-B6p), and cyclin D1 (DCS-6) were obtained from DAKO, Carpinteria, CA. The antibodies to CD5 (4C7) and CD10 (56C6) were from Novocastra, Burlingame, CA.

Fluorescence in situ hybridization (FISH) studies for "CCND1-IgH" gene fusion were performed on the peripheral blood specimen using different colored, directly labeled, gene-specific probes (Vysis, Downers Grove, IL) according to previously described methods.

Case Report

A 64-year-old woman with a 29-month history of “chronic lymphocytic leukemia” sought care because of new-onset fatigue and lassitude. The previous diagnosis of chronic lymphocytic leukemia was based on persistent peripheral blood lymphocytosis; immunophenotyping studies reportedly were not performed. The physical examination revealed marked splenomegaly without appreciable lymphadenopathy. Peripheral blood CBC analysis showed a marked leukocytosis (WBC count, 378,000/µL [378.0 × 10^9/L]) associated with anemia (hemoglobin, 7.7 g/dL [77 g/L]) and thrombocytopenia (platelet count, 72 × 10^3/µL [72 × 10^9/L]). An initial manual differential count was performed, and 80% (0.80) of the WBCs were thought to represent lymphocytes and 10% “blasts.” Based on these findings, the possibility of acute leukemia was raised, and peripheral blood and bone marrow biopsy specimens were submitted for analysis.

On review of the peripheral blood smear, 2 morphologically distinct groups of lymphocytes were identified. One was composed of cells having small nuclei with condensed chromatin and irregular nuclear contours and the other of cells having larger nuclei with delicately reticulated chromatin, multiple nucleoli, and densely basophilic, vacuolated cytoplasm. These cell populations were present in relatively equivalent proportions.

Flow cytometric analysis revealed the peripheral blood leukocytes to be largely composed of CD19+ B cells with bright, monoclonal, κ slg light chain expression. However, despite the relatively uniform staining intensity for CD19 and κ light chain, it was evident that 2 immunophenotypically distinct monoclonal B-cell populations were present. One cell population, located primarily in the small lymphocyte gate (forward scatter and side scatter gating), stained brightly with antibodies to CD20 and CD45 and expressed CD5; these cells did not coexpress CD10 or CD23 and showed partial, dim staining with antibodies to CD38. The second cell population, found in the large lymphocyte gate, expressed CD10 and CD38 and was CD5– and CD23–. In comparison with the CD5+ cells, this second cell population showed slightly diminished staining intensity for CD45.

A diagnosis of MCL was considered based on the presence of clonal, CD5+ B cells; however, it was unclear whether the CD10+CD5– B-cell clone was a related or second, distinct process. FISH studies performed on the peripheral blood specimen demonstrated "CCND1-IgH" gene fusion in 93% of 500 analyzed nuclei, confirming a diagnosis of MCL. The percentage of FISH-positive cells was approximately equal to the percentage of peripheral blood lymphocytes by manual differential (95% [0.95]), indicating that "CCND1-IgH" fusion was present in both the CD5+ and CD10+ lymphocyte subsets.

The bone marrow biopsy specimen was infiltrated densely by neoplastic lymphocytes having blastoid cytologic features with intermediate-sized nuclei, speckled chromatin, and open chromatin, and dense, basophilic cytoplasm (Wright-Giemsa, ×1,000).
Peripheral blood flow cytometric immunophenotyping results. **A**, Flow cytometric immunophenotyping revealed the presence of κ surface immunoglobulin (sIg) light chain–restricted B cells, some of which express CD5 and lack CD10 and some of which conversely express CD10 and lack CD5. Both cell populations lack CD23 expression. **B** and **C**, Selective gating revealed that the CD5+, κ sIg light chain–restricted B cells are primarily in the small lymphocyte gate (B) (forward scatter [FSC] and side scatter [SSC]), whereas the CD10+ clonal B cells that strongly express CD10 and are CD5− are found in the large lymphocyte gate (C).
multiple small nucleoli, and numerous mitotic figures \( \text{Image 3A} \). Immunoperoxidase stains demonstrated the neoplastic cells to be CD20+ B cells \( \text{Image 3B} \) that coexpressed CD10 \( \text{Image 3C} \) and lacked expression of CD5 \( \text{Image 3D} \), bcl-2, bcl-6, and the blast-associated antigen CD34 (data not shown). These cells showed uniform nuclear positivity with antibodies to cyclin D1 \( \text{Image 3E} \), confirming a diagnosis of a BV-MCL with an unusual immunophenotype.

Peripheral blood and bone marrow specimens submitted 6 weeks after diagnosis and the initiation of treatment revealed neither morphologic nor immunophenotypic evidence of residual disease. However, a cerebrospinal fluid specimen submitted 5 months after diagnosis was involved by recurrent CD5–CD10+ BV-MCL.

**Discussion**

The generally accepted CD5+CD23– MCL-associated immunophenotype frequently is used as a tool to identify potential MCL cases and, thereby, permit the selective use of confirmatory molecular genetic and immunohistochemical studies.\(^1\),\(^13\) The reliance on immunophenotypic screening for MCL is greatest in fluidic specimens (peripheral blood and bone marrow aspirate) and small needle biopsy specimens in which the morphologic clues to the diagnosis might be lacking. Whereas this approach permits the more judicious use of ancillary laboratory studies, the underlying rationale has been challenged by descriptions of varying patterns of antigen expression in MCL. A number of reports have documented MCL cases that lack CD5 expression when assessed by immunoperoxidase or flow cytometric methods.\(^10\),\(^14\),\(^15\) MCL cases with coexpression of CD5 and CD10 also have been reported, although this seems to occur infrequently.\(^16\),\(^17\) None of these immunophenotypic subgroups have been associated specifically with BV-MCL. The potential immunophenotypic heterogeneity of MCL is highlighted further by this case, which represents an extreme example having a blastoid component showing both loss of CD5 and aberrant expression of CD10. Indeed, if a component of the disease had not retained immunophenotypic features typical of MCL, it is improbable that this diagnosis would have been considered.

The advent of complex multicolor flow cytometric instruments with the ability to analyze numerous fluorescence channels has enhanced our ability to assess antigen expression by neoplastic cell populations. This, in turn, has led to increased efforts to identify disease-defining immunophenotypic characteristics in hematolymphoid...
Bone marrow biopsy findings. **A**, Dense marrow infiltration by malignant cells having blastoid cytologic features with open chromatin, multiple small nucleoli, and numerous mitotic figures (H&E, ×1,000). **B** and **C**, These neoplastic cells showed strong immunoperoxidase positivity for CD20 (**B**, ×400) and also stained with antibodies to CD10 (**C**, ×400) with distinct staining of the atypical lymphoid cells (**C**, inset, ×1,000). **D**, The neoplastic cells failed to stain distinctly with antibodies to CD5 (×400). Scattered small CD5+ cells were present and likely represented interspersed T cells because their distribution was similar to CD3+ cells (data not shown). **E**, Immunoperoxidase staining with antibodies to cyclin D1 demonstrated uniform nuclear positivity in the neoplastic cells, supporting a diagnosis of blastoid variant mantle cell lymphoma (×400).
malignant neoplasms. The case described herein illustrates the potential pitfalls in attempting to subclassify B-cell neoplasms based exclusively on patterns of surface antigen expression. These patterns have been useful in generally categorizing different types of B-cell lymphoproliferative disorders and in helping to identify the physiologic counterparts from which these disorders likely arise. However, although there is ever-expanding knowledge of the disease-specific genetic abnormalities associated with these disorders, no direct link between these abnormalities and the cell-surface expression of antigens such as CD5 has been elucidated. In contrast, our understanding of these genetic abnormalities has permitted the identification of cases that challenge accepted paradigms of antigen expression in B-cell lymphomas. For this reason, accurate diagnosis and classification of B-cell malignant neoplasms such as MCL require correlation of the immunophenotype with adequate histopathologic material and, when appropriate, genetic findings. Overreliance on the results of immunophenotyping studies can lead to potential misdiagnosis, particularly when there is little or no evaluable histologic material to help narrow the diagnostic considerations.

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References
