**Case Report**

# A Case of CD5-/Cyclin D1+/SOX11- Mantle Cell Lymphoma with an Aberrant Immunophenotype and Indolent Clinical Course

Lei Zhang, MD, PhD; Nan Zhang, MD, PhD*

*Department of Pathology and Anatomical Sciences, Jacob School of Medicine and Biomedical Sciences, University at Buffalo, SUNY, NY*
*Kaleida Health System, 100 High Street, Buffalo, NY*

**Mantle cell lymphoma (MCL) is a clinically aggressive B-cell lymphoma associated with 11q13 translocation, which leads to cyclin D1 overexpression in almost all cases. Although CD5 expression is characteristic in MCL, rare CD5 negative cases with variable expression of CD10 and CD23 have been reported. Over the recent years, a subgroup of MCL with a relatively indolent clinical course started to be recognized. Herein, we report a case of CD5-/Cyclin D1+/SOX11- MCL in a 75-year-old female with diffuse and persistent lymphoma involving multiple lymph nodes, spleen, bone marrow, and lacrimal ducts over the course of nine years. Despite multiple chemotherapy regimens, the MCL had slowly progressed while her baseline health condition remained stable. The neoplastic lymphocytes from different time points during her clinical course showed similar histological features, genetic abnormality, and immunophenotypes. In particular, the lymphoma cells were CD5-, with overexpression of cyclin D1, aberrant expression of CD10 and BCL-6, absence of SOX11 expression, and presence of t(11; 14) (q13; q32) translocation. The indolent clinical course and unusual immunophenotype suggest this particular type of MCL may be considered a unique subentity under MCL.**

## INTRODUCTION

Mantle cell lymphoma (MCL) is an aggressive and untreatable B-cell neoplasm that occurs in middle-aged to older individuals with a male predominance. It was first distinguished in the 1990s from other lymphomas with similar morphologies, such as small lymphocytic lymphoma/chronic lymphocytic leukemia (SLL/CLL) and follicular lymphoma (FL). Commonly involved sites include lymph nodes, the spleen and bone marrow with or without peripheral blood involvement. Other extranodal sites are frequently involved, including the gastrointestinal tract, lung, and Waldeyer's ring. Most cases show monomorphic small to medium-sized lymphoid proliferation with a vaguely nodular, diffuse, mantle zone growth pattern. The neoplastic cells resemble centrocytes with irregular nuclear contours, slightly dispersed chromatin, and inconspicuous nucleoli.[1-3] Loss of a mantle zone growth pattern, an increase in nuclear size, pleomorphism and chromatin dispersal, and increase in mitotic activity can be seen in the blastoid and pleomorphic variants, which usually occurs at relapse and are considered to be of important clinical significance.[4] The neoplastic cells are typically CD5 positive, CD10 negative, BCL6 negative, and CD23 negative with strong surface IgM and IgD expression.[5,6] Although CD5 expression is characteristic in MCL, CD5 negative cases with variable expression of CD10, and CD23 have been reported.[7] These cases must be distinguished from other low grade B-cell lymphomas including SLL/CLL, nodal marginal zone B-cell lymphoma, splenic marginal zone lymphoma, FL, and hairy cell leukemia, which all have a relatively more indolent clinical course.[8-11] The molecular pathogenesis of MCL involves t(11; 14)(q13; q32) translocation, which results in rearrangement of the IGH and cyclin D1 (CCND1) gene and overexpression of cyclin D1.[12-14] Such t(11; 14) translocation has been detected in virtually all MCLs by the fluorescence in situ hybridization (FISH) technique.[15,16] Although not specific for MCL, the presence of cyclin D1overexpression and the t(11;14)(q13; q32) translocation, usually confirm the diagnosis of MCL. However, MCL cases with the similar morphological and phenotypic characteristics as conventional MCL but lacking the t(11;14) translocation and cyclin D1expression have been reported. Some have translocations involving cyclin D2 (CCND2) and either the immunoglobulin heavy chain or kappa light chain locus.[17,18] Recently, SOX11 (sex-determining region-Y-box11) has drawn considerable attention due to its essential role in

regulating normal B-cell features and the growth of MCLs through the SOX11-PAX5-PRDM1/BLIMP1 regulatory axis.[19-21] Specific and high level of SOX11 expression can be detected in 98% of all MCL cases at the RNA level and 93% at the protein level by immunohistochemistry,[22,23] which makes it a highly specific marker for both conventional and Cyclin D1-negative MCL.

Unlike most low-grade B-cell lymphoma subtypes, MCL has an overall poor prognosis with a median survival time of 3 years. No current therapy is curative. It is of particular importance to distinguish MCL from other low-grade B-cell lymphoma subtypes. Here we report a case of MCL with aberrant expression of various markers and a rather indolent clinical course.

**Table 1.** Immunophenotypical and genetic markers of the lymphoma cells from different body sites at various time points of the clinical course.

| Specimen | Timeline | CD5 | CD20 | CD23 | CD43 | PAX5 | CD10 | BCL-6 | BCL-2 | Cyclin D1 | ICH.CCN D1 FISH | MIB1 | Additional markers tested |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Retroperitoneal lymph nodes | Initial | - | + | n/a | - | n/a | + | n/a | + | n/a | n/a | ~5% | CD19+, CD45+, CD79a+, ƙ+. |
| Bone marrow | Initial | - | + | - | - | n/a | + | - | n/a | + | n/a | n/a | CD19 +, HLA-DR+, ƙ+, CD38+, CD103-, |
| Spleen | 3 month post-chemo | - | + | - | - | + | - | - | + | + | + | ~10% | CD45 +, HLA-DR+, CD19+, ƙ+, CD22+, CD52+, CD80+, CD34-, CD38-. IgD-, |
| Left axillary lymph nodes | 2 years later | - | + | n/a | n/a | n/a | - | - | + | + | n/a | n/a | n/a |
| Right lacrimal duct | 8 years later | - | + | - | - | + | + | + | + | + | + | ~10% | CD5 -, CD23 -, CD25 -, CD138 -, Annexin-, Sox11- |

## CASE REPORT

A 75-year-old Caucasian female who had been in her usual state of health until nine years ago presented with stomach fullness, intermittent gastric pain, and increased fatigue. An abdominal CT scan revealed massive splenomegaly of 24 cm with mass effect and periaortic lymphadenopathy. Biopsy of the retroperitoneal lymph nodes and bone marrow at the time showed infiltrating CD20 + lymphoproliferative neoplasm (**Table 1**). The patient was initially treated with RCHOP and Neulasta support and subsequently opted for a splenectomy due to persisted splenomegaly and lymphadenopathy.

Evaluation of spleen sections confirmed the diagnosis of CD5-negative MCL with cyclin D1 overexpression and the presence of t(11;14) (q13; q32) IgH/CCND1 translocation (**Table 1**). Despite additional chemotherapy with Velcade regimen, her MCL persisted and slowly progressed involving left axillary lymph nodes and bilateral inguinal lymph nodes two years later, and right lacrimal duct eight years later while her baseline health condition has remained stable since her initial diagnosis. In addition, no peripheral blood involvement is noted.
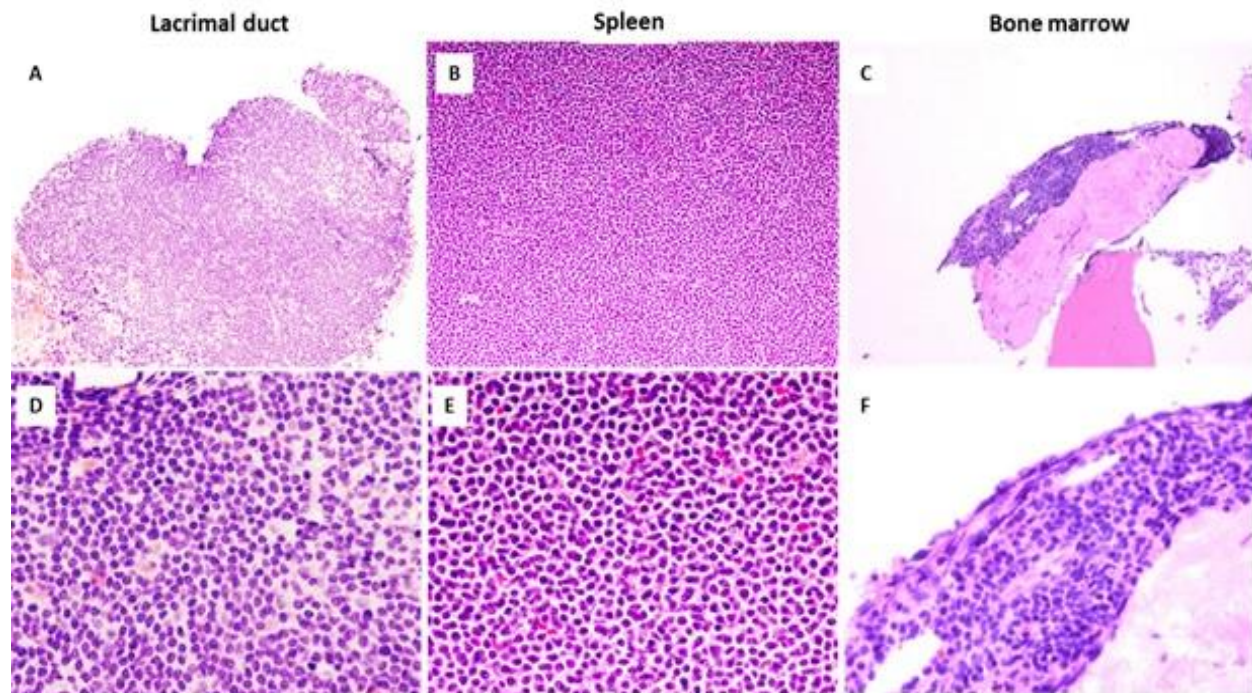


**Figure 1.** Top row, low power views of the lymphoma cells (hematoxylin-eosin stain, original magnification ×10) from lacrimal duct (**A**), spleen (**B**), and bone marrow (**C**). Bottom row, high-power views of the lymphoma cells (hematoxylin-eosin stain, original magnification ×40) from lacrimal duct (**D**) , spleen (**E**), and bone marrow (**F**).
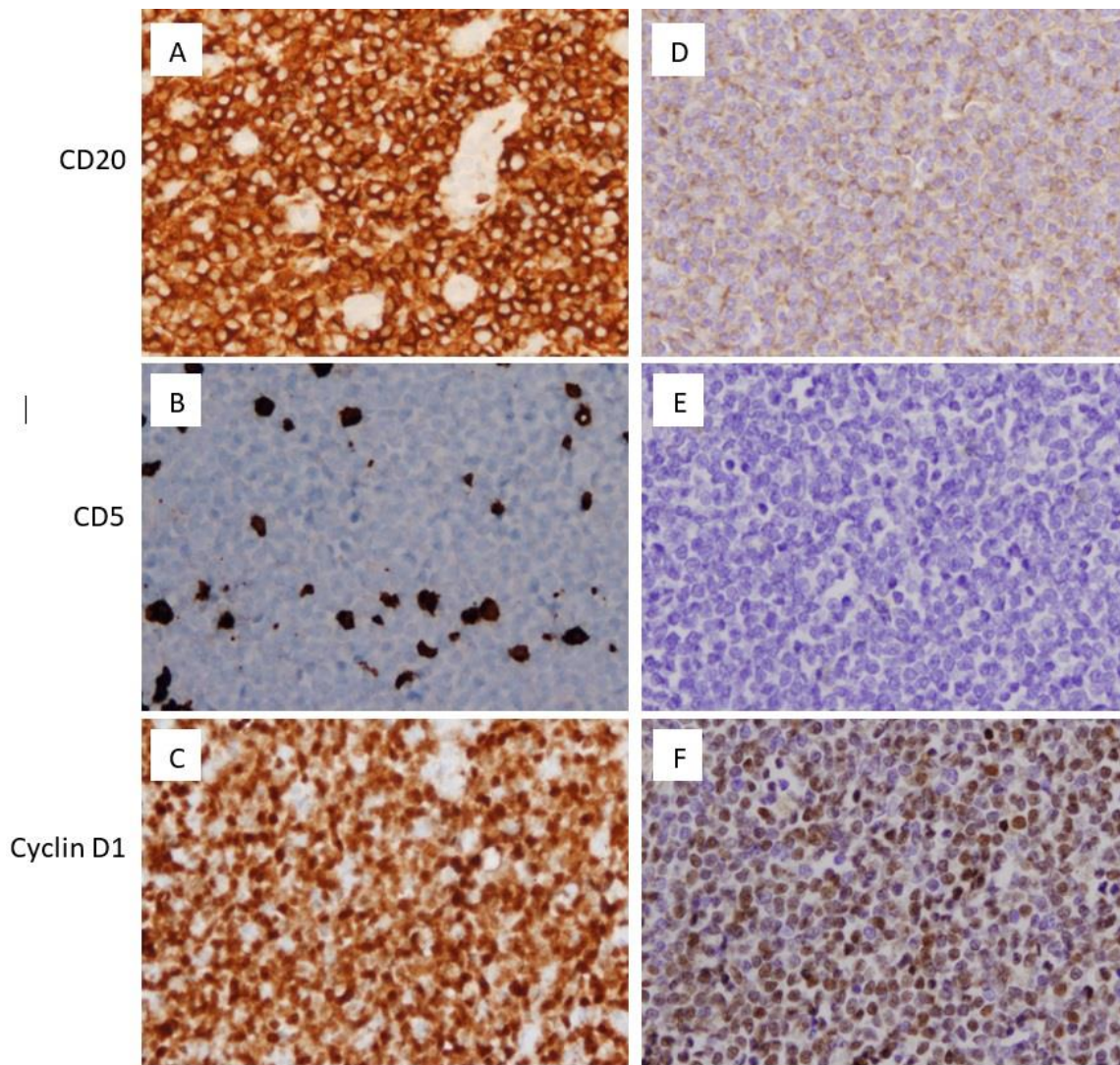
**Figure 2.** Immunohistochemical staining of the lymphoma cells from the lacrimal duct biopsy and the spleen with CD20 (**A** and **D**), CD5 (**B** and **E**), and cyclin D1 (**C** and **F**).

Throughout her clinical course, multiple biopsies had been taken from different body sites including retroperitoneal lymph nodes, spleen, left axillary lymph nodes of the breast, and right lacrimal duct. The morphology of the lymphoma from various locations are similar and showed the vague nodular architecture of the tumor composed of monotonous small to medium-sized abnormal lymphoid cells with round to oval nuclear contours, condensed chromatin, inconspicuous nucleoli, and moderate to abundant pale cytoplasm (**Figure 1, A-F**). The lymphoma cells also maintained the similar immunophenotypes at different time-points of the clinical course (as summarized in **Table1**). Particularly, they are CD5-, CD20+, cyclin D1+, BCL-2+, CD23-, CD43- with a Ki-67(MiB-1) proliferation index of 5-10% (**Figure 2, A-F, Figure 3, A, B, G, H, and J**). CD10 was initially positive in the lymphoma cells from bone marrow and retroperitoneal lymph nodes, became negative in the spleen and the axillary lymph nodes after chemotherapies, regained positivity in the tumor cells from the lacrimal duct

tissue eight years later (**Figure 3, C and D**). BCL-6 was negative in the lymphoma cells in the bone marrow initially, remained negative in the spleen and axillary lymph nodes after chemotherapies, and become positive in the lacrimal gland (**Figure 3, E and F**). No BCL-2 or BCL-6 gene rearrangements were observed in the lymphoma cells from both spleen and the lacrimal duct by FISH studies. Additionally, the neoplastic lymphocytes in the lacrimal duct were negative for SOX11 (**Figure 3, I**).

## DISCUSSION

MCL is believed to be derived from a subset of naive, CD5 positive pre-germinal center cells in the primary follicle or the mantle zone region of secondary follicles. They are usually negative for germinal center markers, like CD10 and BCL6, negative for CD23, the germinal center development marker, and lack somatic mutation of the immunoglobulin gene.[1,2,24] The classic MCL morphology shows a monotonous population of small to medium-sized centrocyte-like cells

growing in a diffuse, or mantle zone pattern, which may cause confusion with lower-grade lymphoproliferative diseases, such as SLL. In practice, MCL can be distinguished from those lower-grade lymphoproliferative diseases by

morphology, immunophenotypes, and CCND1 FISH result. For example, SLL/CLL is usually positive for CD5 and CD23, negative for cyclin D1 expression and CCND1 rearrangement by FISH.
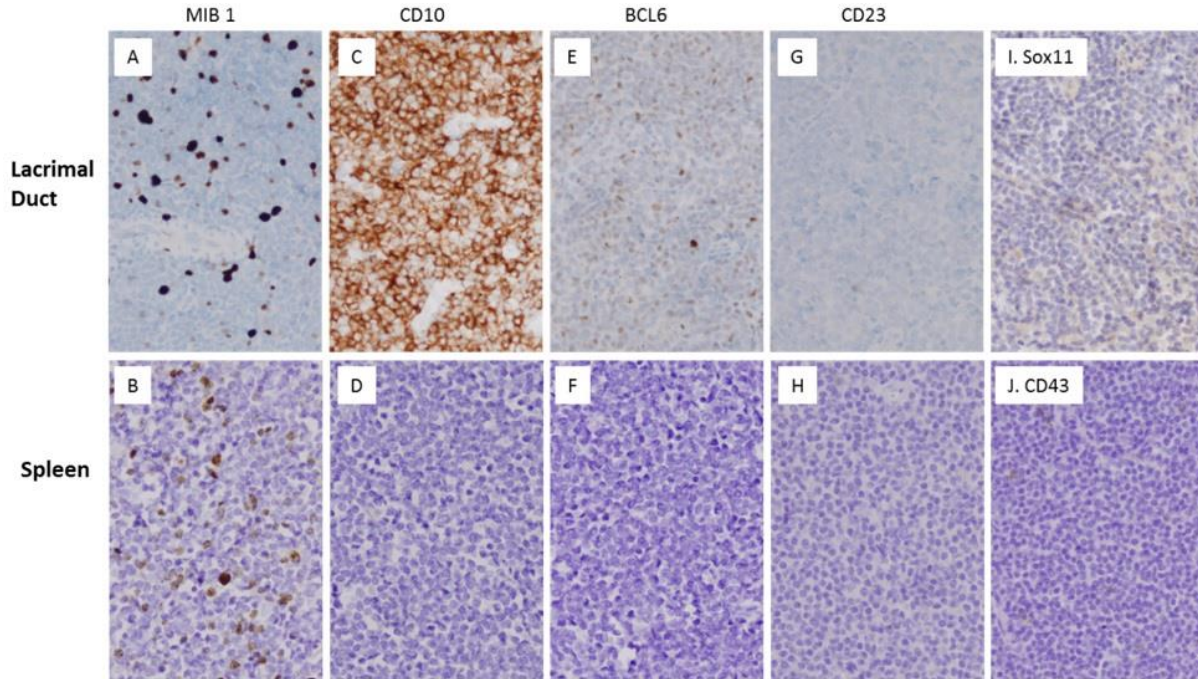


**Figure 3.** Immunohistochemical staining of the lymphoma cells from the lacrimal duct biopsy and the spleen with MIB-1 (Ki-67) (**A and B**), CD10 (**C and D**), BCL6 (**E and F**), CD23 (**G and H**), Sox 11 (**I in lacrimal duct**), and CD43 (**J in spleen**).

CD5-negative cases of MCL with variable expression of CD10 and BCL6 have been reported with an incidence of about 11-13%.[25-27] Such lymphomas are thought to have other genetic alterations that can bypass the CD5-IL10 pathway to promote tumor cell growth. Indeed, genetic alterations involving BCL6 or somatic mutations in the heavy chain variable region of the immunoglobulin molecule (IGHV) have been identified in up to 20% to 60% of cases, most of them are CD5 negative.[25,26] The gold standard for the diagnosis of suspected MCL is to identify the t(11; 14)(q13; q32) translocation, which leads to overexpression of cyclin D1. Deregulated expression of cyclin D1 is assumed to overcome the cell cycle suppressive effect of RB1 and p27kip1, resulting in the development of MCL.[28] While routine cytogenetic studies detect the translocation in only 65% of cases, FISH can be successful in almost 100% of the MCL cases but not routinely performed.[16,29,30] However, cautions need to be taken as cyclin D1 negative MCL with an expression profile and other features indistinguishable from conventional MCL have been reported. In those cases, a high expression of cyclin D2 or cyclin D3 or t(11; 14)(q13; q32) translocation has been detected.[17,18] These CD5 negative MCL must be distinguished from other CD5 negative low grade B cell lymphomas, such as nodal marginal zone B cell

lymphoma, splenic marginal zone lymphoma, follicular lymphoma, and hairy cell leukemia, all of which have a much more indolent clinical behavior. One of the most useful markers would be testing the expression of cyclin D1. Also, SOX11 has become a highly specific marker for both cyclin D1 positive and cyclin D1-negative MCL.

Although MCL is classically considered an aggressive lymphoma, some studies have reported a subset of patients with an indolent behavior of MCL.[20,31,32] These cases are frequently associated with the lack of expression of SOX11, hypermutated IGHV, low karyotype complexity, nonnodal leukemic disease, suggesting that these clinicopathological features may identify a different subtype of MCL (proposed as 'non-nodal'type).[33] However, certain SOX11-negative tumors progress rapidly after initial diagnosis. Alternatively, some of the SOX11-negative MCLs may have a long leukemic, non-nodal phase followed by the progression to an aggressive lymphoma associated with the acquisition of 17p/TP53 abnormality and complex karyotypes.[34]

In our case, the MCL involves bone marrow, spleen, multiple lymph nodes, without a leukemic phase of the disease. Although the immunophenotype (CD5-/CD10+/Cyclin

D1+/SOX11-) is unusual, the diagnosis was based on the histological features, overexpression of cyclin D1, and the presence of t (11; 14) translocation. Interestingly, CD10 expression was positive in the lymphoma cells at the initial diagnoses (both retroperitoneal lymph node and bone marrow) and subsequently disappeared after chemotherapy. When the lymphoma relapsed eight years later, the right lacrimal duct mantle cell lymphoma was positive for CD10 again. The changing of surface CD10 expression overtime is intriguing and may represent variable clonal repopulation dynamics after chemotherapy, which may promote the dominance of previously minor/dormant lineage(s) for a certain period of time.

This case report clearly reflected the heterogeneity of MCL. It represents an indolent subtype of MCL other than the proposed non-nodal type, due to the early nodal involvement, and absence of a leukemic phase of the disease. The clinicopathological and molecular characterization of the indolent type of MCL needs to be further elucidated. A multicenter large-scale case study might be required to unravel this issue.

**CONFLICT OF INTEREST**
The authors have no conflicts of interest to disclose.

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