

Case Report

An uncommon case of *de novo* CD10⁺ CD5⁻ mantle cell lymphoma mimics follicle center B cell lymphoma

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Abstract: Mantle cell lymphoma (MCL) is a mature B-cell lymphoma characterized by expression of CD5, overexpression of Cyclin D1 as a result of chromosomal translocation t(11;14)(q13;q32), and poor prognosis. Cases of MCL lacking CD5 expression as well as cases with coexpression of CD5 and CD10 have also been reported. Here we describe an uncommon case of *de novo* MCL with expression of CD10, but not CD5, mimicking lymphoma of germinal center-derived B cells. The lymphoma cells in this case demonstrated a diffuse pattern of proliferation, and were strongly positive for Cyclin D1 by immunohistochemical stain. Fluorescence in situ hybridization studies demonstrated the presence of t(11;14)(q13;q32) involving *BCL1*, but not chromosomal translocations involving *C-MYC* or *BCL2*, confirming the diagnosis of MCL. This case further highlights the importance of comprehensive immunophenotypic and genetic characterization in the diagnosis and classification of B-cell lymphomas.

Keywords: Mantle cell lymphoma, follicular lymphoma, germinal center B cell, CD10, CD5, *BCL1*, Cyclin D1, fluorescence in situ hybridization

Introduction

Mantle cell lymphoma (MCL) is a unique type of mature B cell lymphoma with characteristic morphology, immunophenotypic profile and molecular genetic abnormality [1, 2]. The lymphoma cells are small to medium in size with angulated nuclei, resembling centrocytes. However, they typically express CD5, not the germinal center-associated marker CD10 [3, 4]. They also harbor the characteristic translocation t(11;14) involving *BCL1*, which results in overexpression of Cyclin D1 [5, 6]. Although the lymphoma cells appear low grade morphologically, they behave more aggressively than other small B cell lymphomas, and are non-curable [7, 8].

Malignant lymphomas derived from germinal center B cells include follicular lymphoma, germinal center B-cell-like diffuse large B-cell lymphoma (DLBL) and Burkitt lymphoma. They are typically CD10⁺ CD5⁻ with various clinical treatment outcomes. Grade 1-2 follicular lymphoma has an indolent disease course, but non-curable [9]. Burkitt lymphoma, on the hand, is an ag-

gressive lymphoma, but is potentially curable with high dose chemotherapy [10]. Grade 3 follicular lymphoma and germinal center B-cell-like DLBL have an intermediate prognosis, and are also potentially curable with aggressive treatment regimens [11, 12].

Because of the differences in treatment strategy and clinical outcome, it is important to distinguish MCL from germinal center B-cell-derived lymphomas. In most cases, this distinction is straightforward based on morphological assessment and immunophenotypic profiling. The demonstration of translocation t(11;14) involving *BCL1* confirms the diagnosis of MCL. However, molecular studies are not routinely performed. MCL with aberrant immunophenotype, such as lacking of CD5 expression or coexpression of CD5 and CD10, has also been reported, complicating the routinely used immunophenotypic differentiation between MCL and other B-cell lymphoproliferative disorders [13-24]. In this report, we describe an uncommon case of *de novo* CD10⁺CD5⁻ MCL, further illustrating the importance of an integrated ap-

proach in the accurate diagnosis and classification of B cell lymphoproliferative disorders.

Materials and methods

Case report

The patient was 49 year old, previously healthy male who presented to a dentist with pain of teeth #18 and #19. A large mass in the right submandibular area was noted. An incisional biopsy of the mass was performed at the dental office and the sample was sent to Emory Medical Laboratories in 10% buffered formalin for pathological evaluation.

On physical examination, he was found to have right cervical and axillary lymphadenopathy. Computerized tomography scan revealed extensive visceral lymphadenopathy and splenic enlargement. A staging marrow was positive for lymphoma involvement (5% of marrow cellularity) by morphology and immunohistochemistry performed at outside institution and reviewed at Emory. Unfortunately, no flow cytometric immunophenotyping was performed on the staging bone marrow aspirate. He received 6 cycles of R-Hyper-CVAD (rituximab-fractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone) for his newly diagnosed stage IV non-Hodgkin lymphoma. He was alive and disease-free 6 months following the last treatment.

Histological examination

The submandibular mass biopsy was fixed in 10% buffered formalin and paraffin-embedded. Sections were stained with hematoxylin and eosin per standard protocol for morphological examination.

Immunohistochemistry

The following antibodies were used for immunohistochemical stains using the Dako Autostainer with appropriate positive and negative controls: CD3 (F7.2.38; 1:80 dilution), CD20 (L26; 1:80 dilution), CD5 (F6; 1:40 dilution), CD10 (56C6; 1:20 dilution; Novocastra, NewCastle upon Tyne), BCL1 (Cyclin D1; 1:70 dilution; NeoMarkers, Fremont, CA), BCL6 (1:20 dilution), MUM1 (1:40 dilution) and Ki-67 (MIB1; 1:160 dilution). All antibodies were purchased from Dako, Carpinteria, CA except for those specifically indicated.

Fluorescence in situ hybridization (FISH)

The dual color, dual fusion LSI probes for t(11;14)(BCL1/IGH) and t(14;18)(IGH/BCL2) as well as the dual color, breakapart probe to detect translocations involving C-MYC (Abbott Molecular, Inc) were used to perform FISH on the formalin-fixed paraffin-embedded tissue sections. Briefly, 5 µm tissue sections were cut, dewaxed and digested with proteinase using the VP2000 semiautomated processor. The slides were then incubated with the denatured probes, washed and visualized under fluorescent microscopy using the Cytovision imaging software (Applied Imaging Inc, San Jose, CA). A score of 10% or more of the interphase nuclei with appropriate signal patterns is considered positive.

Results

Histomorphology

Morphologically, the lymphoma cells demonstrated a diffuse pattern of proliferation (**Figure 1A**). They were relatively uniform in size, small to medium, with irregular nuclear membrane, resembling centrocytes. Mitotic figures are infrequent. The tumor cells appeared to have a slightly immature chromatin with some of them having several small nucleoli (**Figure 1B**), but are not blastoid. Bone marrow biopsy displayed patchy involvement by the lymphoma with similar morphology (data not shown).

Immunophenotypic profiling

Flow cytometric immunophenotyping was not performed because the biopsy sample was submitted in formalin. On immunohistochemical stains, the lymphoma cells were strongly positive for CD20, CD10 and Cyclin D1, but were negative for CD3 (**Figures 2A, 2B, 2D, 2E**). Repeated immunostains for CD5 were negative with appropriate positive and negative controls (**Figure 2C**). They were also negative for BCL6 and MUM1 (data not shown). Though mitotic figures are infrequent, the lymphoma cells demonstrated a relatively high proliferation index, about 50% as assessed by immunohistochemical stain for MIB1 (**Figure 2F**).

Fluorescence in situ hybridization (FISH)

FISH studies demonstrated the presence of chromosomal translocation t(11;14)(q13;q32)

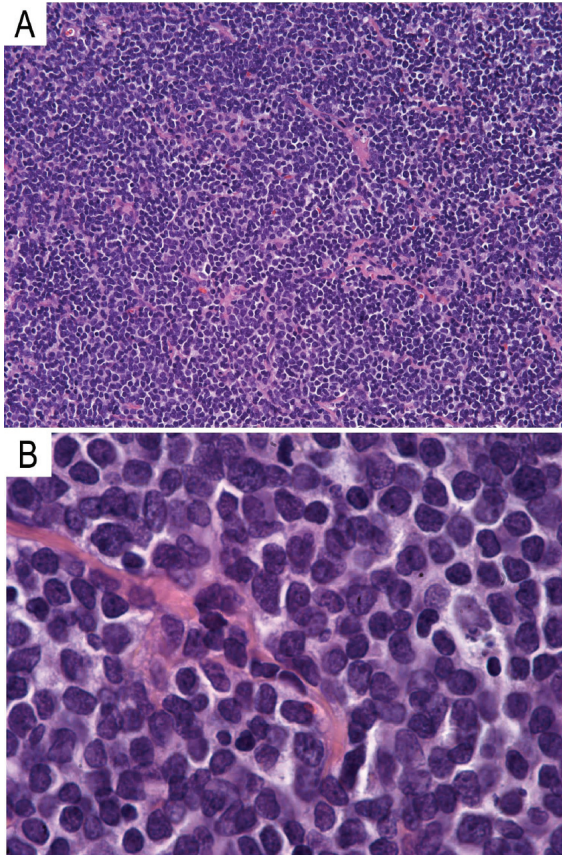


Figure 1. Histomorphology of the *de novo* CD10⁺CD5⁻ mantle cell lymphoma. The lymphoma cells demonstrate a diffuse pattern of proliferation (A; hematoxylin and eosin stain, 40 x magnification). They are small to medium in size with slightly irregular nuclear contours (B; hematoxylin and eosin stain; 400 x magnification).

involving *BCL1* gene as indicated by the two fusion signals of the interphase nuclei (**Figure 3A**), confirming the diagnosis of MCL. FISH studies failed to demonstrate t(14;18) involving *BCL2* gene or translocations involving *C-MYC* oncogene (**Figures 3B** and **3C**), making the diagnosis of transformation of MCL to Burkitt lymphoma or transformation of follicular lymphoma to MCL unlikely.

Discussion

MCL is a very well characterized entity of peripheral B-cell lymphoma with aggressive clinical behavior. Morphologically, the lymphoma cells are small to medium in size with scant cytoplasm and slightly irregular nuclear contours, similar to the centrocytes seen in low-grade folli-

cle center cell lymphoma. Rare or no admixed large cells are present. The majority of MCL display a diffuse proliferation pattern, though nodular as well as mantle zone pattern have also be observed. Immunophenotypically, the lymphoma cells are characteristically positive for CD5, CD20, FMC7 and Cyclin D1 without expression of germinal center cell markers, such as CD10. The demonstration of t(11;14) involving *BCL1* gene is diagnostic of MCL with the appropriate morphology and immunophenotype. Most MCLs lack significant somatic hypermutation of the immunoglobulin genes, consistent with the notion that MCL is derived from naïve pregerminal center or mantle zone B lymphocytes [25-27].

Despite the usual uniformity, cases of MCL with morphologic, immunophenotypic, genetic and clinical heterogeneity have been documented. Pleomorphic or blastoid variants of MCL usually have additional genetic changes and are more aggressive than the classical form [28]. Morphologically, the neoplastic cells may be confused with diffuse large cell lymphoma or other blastic hematolymphoid neoplasms. MCL with plasmacytic differentiation or marginal zone pattern has also been recognized [29-31]. The lymphoma cells in these cases have relatively more abundant cytoplasm compared to the classical form, mimicking small lymphocytic lymphoma/chronic lymphocytic leukemia, lymphoplasmacytic lymphoma or marginal zone lymphoma. In addition, MCL with an indolent course as well as MCL with somatic mutations of the immunoglobulin heavy chain genes have also been described, suggesting that the neoplastic cells have been exposed to the germinal center microenvironment and the neoplastic cells may be derived from germinal center or even post-germinal center B lymphocytes.

The mainstay to diagnose MCL is immunophenotypic profiling by flow cytometry and/or immunohistochemical stain. The lymphoma cells are typically positive for CD5, pan-B cell markers including CD20 and FMC7 with surface immunoglobulin light chain restriction. With appropriate morphology and phenotype, positive immunohistochemical staining for Cyclin D1 essentially confirms the diagnosis of MCL. Cytogenetic or FISH studies, if performed, demonstrate the presence of chromosomal translocation t(11;14) involving *BCL1* and *IGH* in the majority of MCL cases.

de novo CD10⁺ CD5⁻ mantle cell lymphoma

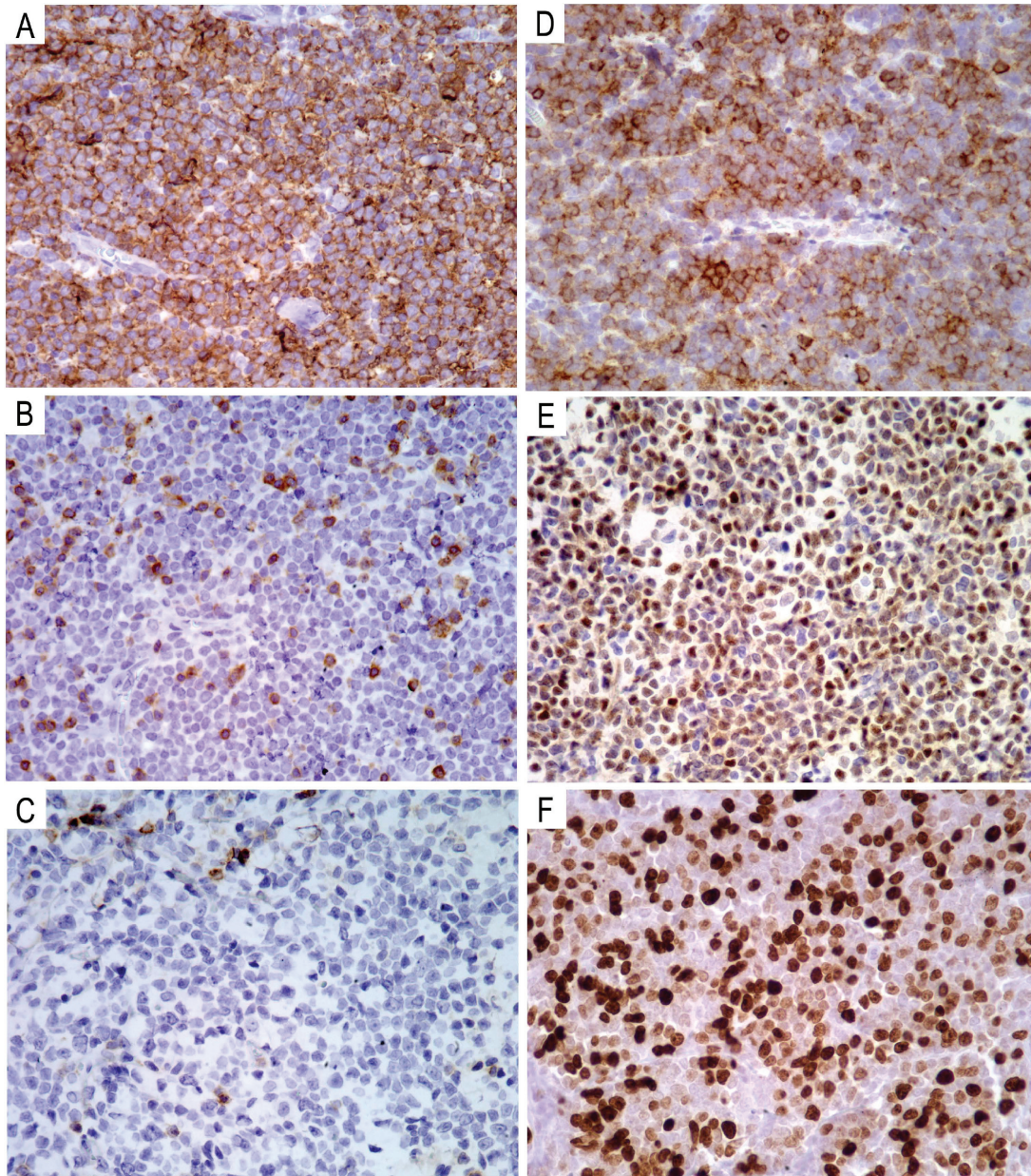


Figure 2. Immunohistochemical profile of the *de novo* CD10⁺CD5⁻ mantle cell lymphoma. The lymphoma cells are strongly positive for CD20 (A), CD10 (D) and Cyclin D1 (E) with a high proliferation index (F: MIB1 stain). They are negative for CD3 (B) and CD5 (C).

The characteristic immunophenotypic profile is not always seen in MCL. Chronic lymphocytic leukemia/small lymphocytic lymphoma may have an immunophenotypic profile identical to MCL [13, 16, 32]. Lack of CD5 expression has been observed in about 10% of MCLs [19, 33]. Markers associated with germinal and post-germinal center B cell differentiation, such as CD10, BCL6 and MUM1 have all been reported in MCL [14-18, 20-23, 34, 35]. These variations

from the typical immunophenotypic profile could be misleading and cause diagnostic difficulties, particularly when the morphological features are not classical or the biopsy specimen is small.

CD10 is a zinc metalloproteinase expressed in many normal tissue cell types, including early lymphoid progenitors and normal germinal center B cells. CD10 expression has been used as a

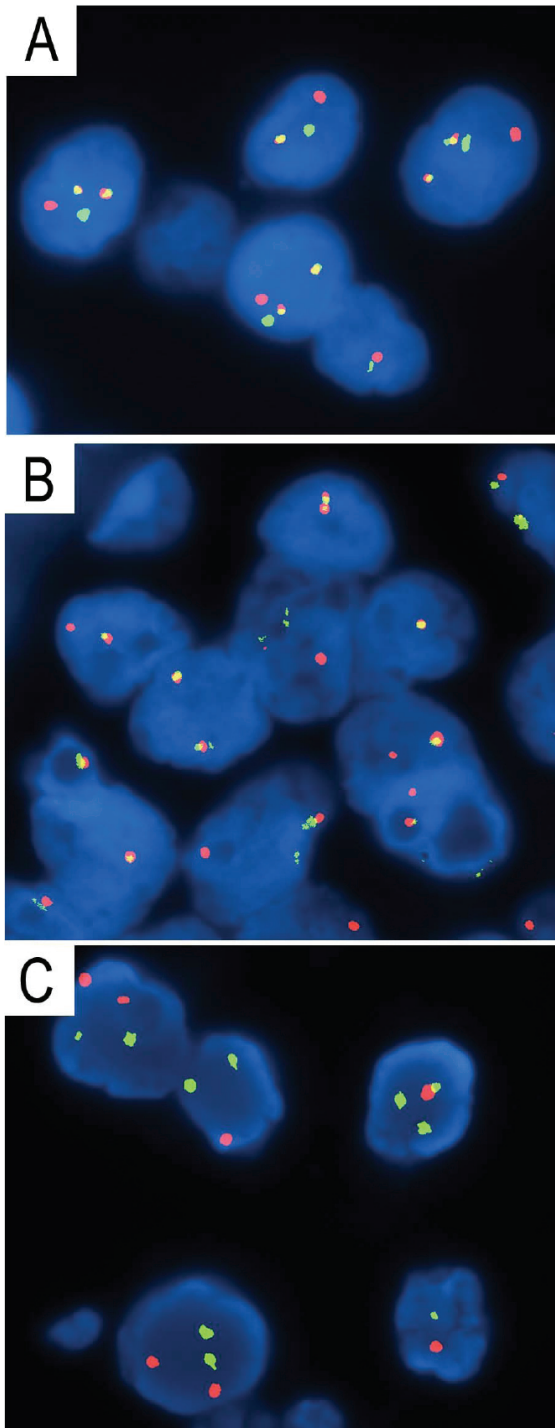


Figure 3. Fluorescence in situ hybridization study of the *de novo* CD10⁺CD5⁻ mantle cell lymphoma. The lymphoma cells demonstrate the presence of t (11;14) translocation involving *BCL1* (A), but not translocations involving *C-MYC* (B) or t(14;18) translocation involving *BCL2* (C).

diagnostic marker of germinal center-derived B cell lymphomas, including follicular lymphoma, germinal center B-cell-like DLBL and Burkitt lymphoma. Aberrant expression of CD10 has also been observed in a variety of non-germinal center B-cell lymphomas, such as hairy cell leukemia, chronic lymphocytic leukemia/small lymphocytic lymphoma, lymphoplasmacytic lymphoma, marginal zone lymphoma, and MCL.

The first case of MCL with aberrant expression of CD10 was reported by Xu *et al* in their multiparameter flow cytometric study of small B-cell lymphomas [20]. Except for expression of CD10, this case has a morphology and immunophenotypic profile characteristic of MCL. To date, a total of 38 MCLs with aberrant expression of CD10 have been reported in the literature. The majority of these cases express CD5 and other markers typically seen in MCL [15-18, 20, 22, 23, 35]. Most of them are also of classical morphology. Among the 13 MCLs with a CD10⁺CD5⁻ phenotype, 6 of them represent pleomorphic blastoid MCL transformed from a preexistent classical MCL [14, 21, 23, 34]. The remaining 6 cases plus the one reported here are *de novo* CD10⁺CD5⁻MCL (Table 1) [16, 23, 24]. Interestingly, all *de novo* cases have a classical morphology.

Kostopoulos *et al* reported the first case of *de novo* CD10⁺CD5⁻ MCL [24]. The lymphoma cells demonstrated a classical cytomorphology arranged in a nodular proliferation pattern with residual follicular dendritic network, closely mimicking low-grade follicular lymphoma. In addition, the neoplastic cells were also focally positive for Bcl6. FISH studies demonstrated the presence of t(11;14) involving *BCL1*, but not t(14;18) translocations involving *BCL2* characteristic of follicular lymphoma. More than 50% of the cells were positive for MIB1. The patient was in remission for 1 year before relapse. In the largest series of MCL with aberrant expression of CD10, Zanetto *et al* described 2 cases of *de novo* CD10⁺CD5⁻ MCL [23]. Both were weakly positive for BCL6. Molecular studies demonstrated gain of *BCL6* gene copy number in addition to the t(11;14). One patient was in remission 1 year after treatment and the other patient died of intracranial hemorrhage before initiation of treatment. Gao *et al* described 3 cases of *de novo* CD10⁺CD5⁻ MCL in their study with multiparameter flow cytometric immunophenotyping [16]. The lymphoma cells in all 3

cases demonstrated low proliferation rate. No follow-up information was available. Our case has features similar to those reported by Zanetto *et al* [23]. But repeated staining for BCL6 was negative and we did not study the chromosomal change or copy number gain of BCL6 gene. The likelihood that our case may represent transformation from a preexistent typical MCL with acquisition of CD10 and loss of CD5 expression is very low since all transformed CD10⁺CD5⁻ MCLs have a pleomorphic blastoid morphology. Though repeated immunohistochemical stains for CD5 was negative, we cannot completely rule out very low level CD5 expression detectable only by more sensitive multiparameter flow cytometric immunophenotyping.

The mechanism of aberrant CD10 expression in MCL is unclear, but it does not appear to be related to the germinal center cell ontogeny of the lymphoma cells since most CD10-positive MCL analyzed do not show somatic hypermutation of the immunoglobulin heavy chain genes. The clinical significance is also unknown and remains to be determined because the number of reported cases is small and aberrant expression of CD10 has been seen in MCL with both classical and pleomorphic blastoid morphology.

In conclusion, *de novo* CD10⁺CD5⁻ MCL is extremely rare. Pathologists, however, should be aware of its existence to avoid misdiagnosis and inappropriate treatment. In cases with atypical phenotype, but morphologically suspicious for MCL, a simple immunostain for Cyclin D1 will be helpful in the final diagnosis. FISH or molecular genetic studies might be needed to confirm or exclude the diagnosis of *de novo* CD10⁺CD5⁻ MCL.

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