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CASE REPORT

Two cases of mantle cell lymphoma mimicking marginal zone lymphoma

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Abstract Mantle cell lymphoma (MCL) is a B cell lymphoma with four morphologic variants recognized by the current World Health Organization classification. MCL mimicking marginal zone lymphoma (MZL) (MCL mimicking MZL) is the rarest variant and could be a potential diagnostic pitfall due to its deceiving "monocytoid" appearance. We report two cases of extranodal MCL mimicking MZL occurring at different sites—the oropharynx and the rectosigmoid colon. Both cases showed unexpected diffuse submucosal lymphoid infiltration of small- to medium-sized lymphocytes with focal monocytoid appearance. Immunohistochemistry showed the presence of an abnormal CD5(−)/CD10(−) B cell population expressing cyclin D1. The diagnosis of MCL was further substantiated by cytogenetic evidence of t(11;14)(q13;q32). Ki-67 proliferation indexes of both cases were low. In summary, MCL mimicking MZL may have unusual morphologic and immunophenotypic characteristics that could be a diagnostic pitfall.

Keywords Mantle cell lymphoma · Mantle cell lymphoma mimicking marginal zone lymphoma · t(11;14)(q13;q32)/CCND1-IGH · CD5 negativity

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Introduction

Mantle cell lymphoma (MCL) is a B cell lymphoma with characteristic overexpression of cyclin D1 resulting from t(11;14)(q13;q32) involving the CCND1 gene and immunoglobulin heavy chain (IGH). It comprises 3–10 % of non-Hodgkin lymphomas and frequently involves lymph nodes, spleen, bone marrow, peripheral blood, gastrointestinal tract, and Waldeyer's ring [1].

The neoplastic cells in MCL are usually positive for pan-B cell markers, such as CD19, CD20, CD79a, Pax5 and show a strong expression of surface IgM/IgD. They often express CD5, FMC-7, CD43, BCL-2, but lack CD23 and germinal center markers of CD10 and BCL-6. The vast majority of cases overexpress cyclin D1 and have the hallmark t(11;14)(q13;q32). However, rare MCL cases lacking cyclin D1 expression and/or the absence of t(11;14)(q13;q32) have been reported [2]. Cytologically, MCL is composed of monomorphic small- to medium-sized lymphoid cells with irregular nuclear contour with architectural patterns including mantle zone, nodular, and diffuse. Recently, the WHO recognized four morphologic variants of MCLs: blastoid, pleomorphic, small cell, and marginal zone-like [1].

In the current WHO classification, the description of marginal zone-like MCL or MCL mimicking marginal zone lymphoma (MZL) (MCL mimicking MZL) is limited, and few diagnostic criteria are provided. Based on our understanding, it remains controversial whether MCL mimicking MZL truly represents a distinct entity.

On the other hand, the so-called MCL mimicking MZL carries clinical significance because the "monocytoid" or "marginal-zone-like" features could cause it to be misdiagnosed as mucosa-associated lymphoid tissue lymphoma or nodal marginal zone lymphomas. Since MCL has a more aggressive clinical course, it is critical to distinguish it from

the low-grade small B cell neoplasms with monocytoid features.

Reported MCL cases fulfilling the WHO's description of "marginal-zone like" features are extremely rare—only six cases have been published in English literature [3–6]. To further characterize this variant and highlight some observed unique features, we report two cases of MCL mimicking MZL. Patient 1 was a 70-year-old male with a tongue-based mass and lymphadenopathy of the neck region. Patient 2 was a 63-year-old male with incidental findings of colonic polypoid lesions during a screening colonoscopy.

Clinical history

Patient 1 was a 70-year-old male with a past medical history of invasive squamous cell carcinoma on the lower lip who underwent radiation therapy in May 2009. In October 2010, he presented with 5 weeks of right neck discomfort. A CT scan of the neck showed a 2.2-cm mass at the tongue base with thickening of the oropharyngeal wall and multiple enlarged cervical lymph nodes. Based on the patient's past medical history, initially a metastatic squamous cell carcinoma was suspected.

Patient 2 was a 63-year-old male who underwent a screening colonoscopy, and a small colonic polyp was biopsied. After the initial diagnosis, a follow-up colonoscopy identified multiple intestinal polyps, raising the clinical suspicion for lymphomatoid polyposis (mantle cell lymphoma).

Results

Tissue

Multiple frozen sections from various oropharyngeal locations showed no evidence of metastatic squamous cell carcinoma. All of the biopsy specimens, unexpectedly, showed a diffuse to vaguely nodular submucosal lymphoid proliferation with lymphoepithelial lesions (Fig. 1a). The infiltrate was composed of a monotonous population of small- to medium-sized lymphocytes with irregular nuclear contours including nuclear notches and condensed chromatin. Many of the lymphocytes showed monocytoid morphology with moderate amounts of cytoplasm (Fig. 1b, c), and mitotic figures were not readily identified. Background plasma cells and epithelioid histiocytes were not prominent.

H&E sections of the colon polyp from patient 2 revealed a dense and diffuse mucosal/submucosal lymphoid infiltrate with rare lymphoepithelial lesions noted. This infiltrate consisted of prominent populations of small lymphocytes with irregular nuclear contours including some with elongated nuclei (centrocyte-like), condensed chromatin, and inconspicuous nucleoli. In some areas, the lymphocytes had moderate amounts of cytoplasm, imparting a "monocytoid" appearance (Fig. 2a, b). Admixed scattered large cells with irregular contours, vesicular chromatin, and nucleoli were noted (Fig. 2c), and background plasma cells and histiocytes were not prominent. The following biopsies of colonic polyps showed similar histologic findings (data not shown).

Bone marrow

A bone marrow biopsy for case 1 showed a moderately hypercellular marrow with trilineage hematopoiesis and involvement by lymphoma. There were multiple small lymphoid aggregates involving approximately 10 % of the bone marrow volume. A bone marrow biopsy from case 2 showed no marrow involvement by lymphoma.

Immunohistochemistry

For the oropharyngeal biopsy from case 1, the neoplastic cells were CD20-positive with kappa immunoglobulin light chain restriction and lacked CD5 expression (Fig. 1d). In addition, the neoplastic cells were positive for BCL-2, CD43, and IgM but negative for CD10, BCL-6, CD23, and IgD (data not shown). Further immunohistochemistry (IHC) showed the neoplastic cells were positive for cyclin D1 (rabbit monoclonal anti-human antibodies, Thermo Scientific, Waltham, MA; Fig. 1e). The Ki-67 proliferation rate was approximately 10 %. SOX11 (rabbit polyclonal anti-human antibodies, Sigma Aldrich, St. Louis, MO) was largely negative except for a rare weakly positive nuclear staining; however, internal positive control staining was not observed (data not shown). IHC on the case 1 bone marrow showed few cyclin D1-positive cells within the lymphoid aggregates, confirming marrow involvement by mantle cell lymphoma

For the colonic biopsy from case 2, the majority of the lymphocytes were CD20-positive B cells with kappa immunoglobulin light chain restriction and negative for CD5 (Fig. 2d). In addition, the lymphoma cells expressed BCL-2, CD43, IgM, but were negative for BLC-6, CD23, CD10, and IgD (data not shown). Importantly, the neoplastic cells were positive for cyclin D1 (Fig. 2e). The Ki-67 proliferation index was less than 10 %.

Flow cytometry

Flow cytometry from the oropharyngeal biopsies (case 1) showed approximately 35 % of the total cells were

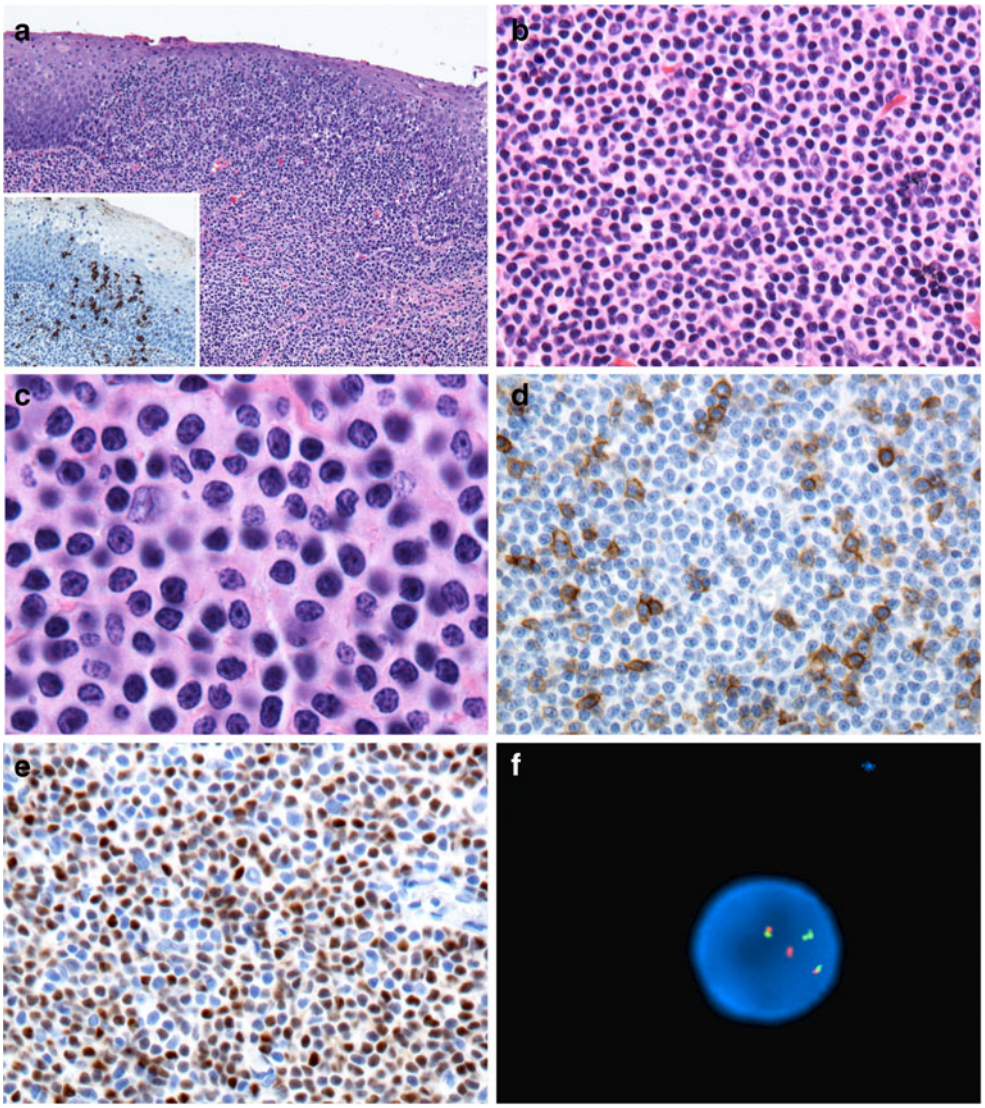

Fig. 1 Morphologic and immunohistochemical features of the oropharyngeal biopsy (case 1). **a** Dense lymphocytic infiltrates are composed of small-sized lymphocytes and lymphoepithelial lesions. (H&E, ×100) The *inset* shows CD20 (+) B cells within the mucosa (IHC, ×100). **b** The lymphoma cells with moderate amount of cytoplasm and monocytoid morphology (H&E, ×400). **c** The lymphoma cells with irregular nuclear contours including notches (H&E, ×1,000). **d** CD5-negative lymphoma cells with scattered T cells positive for CD5, ×400. **e** Cyclin D1 strong nuclear positive, ×400. **f** FISH with dual-color, dual-fusion probes: the fused *green–red* signals indicate t(11;14))(q13; q32) and CCND1/IGH gene fusion

CD5(−)/CD10(−) kappa-restricted B cells. Flow cytometry of the marrow aspirates showed minimal involvement (approximately 1 % of total cells) by MCL. Flow cytometry from the colonic polyp (case 2) was not performed, and the bone marrow was negative for a monotypic B cell population.

Molecular/cytogenetic

Fluorescence in situ hybridization (FISH) was performed on formalin-fixed, paraffin-embedded tissues with a dual-color, dual-fusion CCND1/IGH probe (Vysis, Inc, Des Plaines, IL). It detected t(11;14)(q13;q32) in 89 and 85 % of cells examined in case 1 (Fig. 1f) and case 2, respectively. Overall, the morphologic, immunohistochemical, flow cytometric, and cytogenetic findings in both cases were consistent with MCL mimicking MZL as described in the WHO classification.

Discussion

MCL is a moderately aggressive mature B cell lymphoma with a median survival of 3–5 years. Usually patients with MCL require more aggressive chemotherapy than patients with other low-grade small B cell lymphomas. Therefore, it is critical to distinguish MCL from other indolent MCL mimics. In the WHO 2008, a new MCL morphologic variant was recognized with “marginal zone-like” features. This entity’s description is fairly limited, and the diagnostic criteria are not clearly defined. MCL can also mimic other low-grade lymphomas, such as marginal zone B cell lymphoma, which has significant clinical implications and may pose a potential diagnostic pitfall.

Both of our cases were unusual in that they presented with a deceiving monocytoid morphology, lymphoepithelial lesions, and unusual immunohistochemical features. In both cases, the neoplastic cells showed variable degrees of

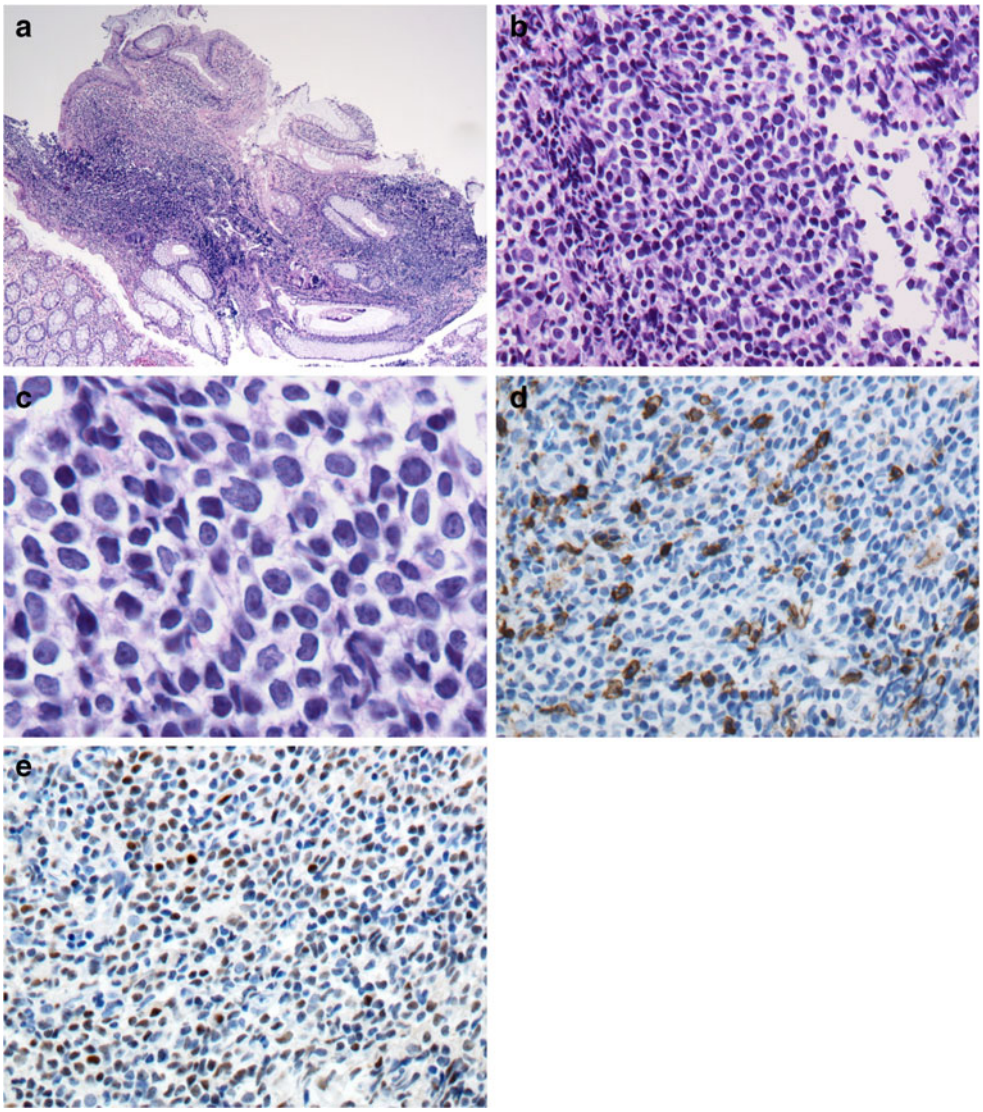

Fig. 2 Morphologic and immunohistochemical features of the colonic polyp biopsy of case 2. **a** Colon biopsy shows dense lymphocytic infiltrates (H&E, ×40). **b** Focus of "monocytoid" lymphoid cells with moderate amount of clear cytoplasm (H&E, ×400). **c** Infiltrates are comprised of predominately small/medium-sized lymphocytes with some scattered large cells. (H&E, ×1,000). **d** CD5-negative lymphoma cells with scattered CD5-positive reactive T cells, ×400. **e** Cyclin D1 positivity of lymphoma cells, ×400

monocytoid differentiation and lacked CD5 expression, therefore deviating from conventional MCLs. The Ki-67 proliferation rates were both low (approximately 10 %). Combined with the unusual morphologic and immunophenotypic features, both cases deceivingly mimicked an extranodal marginal zone B cell lymphoma. If the cyclin D1 immunostain was not evaluated, it could have resulted in an incorrect diagnosis as the neoplastic cells of both cases were CD5(−), CD10(−), and CD23(−). FISH studies demonstrated the presence of t(11;14)(q13;q32), confirming the diagnosis of MCL.

Including our cases, there are a total of eight published cases of MCL mimicking MZL (Table 1). All eight patients

Table 1 Summary of eight cases of mantle cell lymphoma with "marginal zone-like" morphology

Patient ID	Age/ sex	B symptoms	Nodal presentation	CD5	Proliferation rate	Ref
Patient 1	53/M	N/A	Yes	P (weak)	80 %	[3]
Patient 2	83/M	N/A	No	P (weak)	N/A	[4]
Patient 3	72/M	N/A	Yes	N	50 %	[5], #1
Patient 4	59/M	N/A	Yes	N	25 %	[5], #2
Patient 5	75/M	N/A	No	P	N/A	[5], #3
Patient 6	83/M	No	Yes	N	N/A	[6]
Patient 7	70/M	No	Yes	N	10 %	Current study
Patient 8	63/M	No	No	N	10 %	Current study

N negative, *P* positive, *N/A* not available

were male with a median age of 71 years, and 63 % (five out of eight) of the patients had nodal presentations. Ki-67 proliferation rates ranged from 10 to 80 %. Interestingly, 63 % (five out of eight) of the cases were CD5 negative (1 and 2 of [5, 6], and current two cases). Two other cases ([3, 4]) showed weak CD5 expression. Therefore, the observed CD5 downregulation in MCL mimicking MZL seems much more frequent than the reported 10 % CD5 negativity in classic MCL cases [7]. The significance of the CD5 negativity is unclear.

The diagnostic challenge of MCL mimicking MZL is reflected in prior case reports. These cases all showed monocytoid morphology, and many demonstrated an interfollicular growth pattern when involving nodal sites [3–6]. The major diagnostic pitfalls included MZL due to the presence of monocytoid cells [3] and follicular lymphoma when monocytoid cleaved cells were prominent [6]. In the two misdiagnosed cases, cyclin D1 was not initially evaluated, and a correct diagnosis was rendered at re-evaluation when the clinical presentation/prognosis was unusual [3, 6]. In addition, from all the three cases reported by Mansoor et al. [5], the favored differential diagnoses were MZL due to the monocytoid morphology, as well as the lack of CD5 expression seen in two of the three cases. The literature suggests that MCL mimicking MZL involving lymph tissues often shows an interfollicular pattern [3–6]. Aside from our two cases, only Mansoor et al. [5] reported a case of MCL mimicking MZL involving an extranodal site (salivary gland) which did not show an interfollicular pattern similar to our cases reported here. These publications and our cases highlight the importance of comprehensive immunophenotyping including cyclin D1 in lymphomas with "marginal zone" morphology. This is particularly critical in situations where there is a discrepancy between the pathologic diagnosis and the clinical presentation or behavior.

SOX11, a transcription factor in neurogenesis, has been reported to stain 91–95 % of conventional MCLs [8–10]. There is limited experience with SOX11 in variant MCLs, and no reported studies of its utility in MCL mimicking MZLs have been published. Our limited experience highlights an unusual focal staining pattern of SOX11 with both weak nuclear and cytoplasmic positivity (less than 5 % of total cells). Hence, the diagnostic utility of SOX11 in variant MCLs remains unclear.

It is well established that the prognosis is different among MCL variants, with blastoid and pleomorphic variants having the most aggressive clinical course [1, 11]. Due to the rarity of MCL mimicking MZL and the incomplete clinical and/or pathologic features in previous case reports, the prognosis of MCL mimicking MZL has not been reported. While general conclusions about MCL mimicking MZL cannot be made from these two presented cases, it is important to contribute to the future understanding of this entity by reporting the detailed clinicopathologic features that have been deemed prognostically meaningful in classic MCLs, such as B symptoms, nodal presentation, Eastern Cooperative Oncology Group (ECOG) scores, genomic imbalance, Mantle Cell International Prognostic Index (MIPI), and IGHV gene hypermutations [12]. The clinicopathologic features of our cases are listed in the Supplemental Table. For both patients, there were no B symptoms, splenomegaly, or anemia. The absolute lymphocyte counts and LDH levels were normal. The ECOG performance status was low, either 0 or 1. No bulky disease was detected in either case. Both cases had low Ki-67 proliferation indexes. The MIPI scores were similar and suggested an intermediate risk with a median survival of 58 months [13]. Clinical follow-up showed fair/good responses in both cases thus far. Patient 1 had a complete response to four cycles of rituximab/bendamustine chemotherapy and remained in complete remission 15 months after the initial diagnosis. Patient 2 had a nearly complete response to six cycles of R-CHOP (rituximab–cyclophosphamide, doxorubicin, vincristine, and prednisone) chemotherapy. Recently, he was started on maintenance rituximab therapy.

In conclusion, we report two cases of MCL mimicking MZL with detailed clinicopathologic features and preliminary insight of SOX11 status in this rare MCL variant. Literature reviews revealed that this rare entity has a male preponderance, monocytoid morphology, variable Ki-67 proliferation rate, and usually a lack of CD5 expression. MCL mimicking MZL poses a potential diagnostic pitfall, and application of an expanded immunohistochemical panel/ancillary studies are recommended to differentiate it from other indolent mature B cell lymphomas.

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Disclaimers The authors declare that they have no conflict of interest.

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