Case Study

CD5-Negative Mantle Cell Lymphoma Resembling Extranodal Marginal Zone Lymphoma of Mucosa-Associated Lymphoid Tissue: A Case Report

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A 71-year-old male underwent an upper gastrointestinal endoscopy; as a result of a biopsy, extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma) was suspected. Abdominal computed tomography scan disclosed an approximately 4-cm-large mass in the ileocecal region. After ileocecal resection, the patient was diagnosed with MALT lymphoma (CD79a+, CD20+, CD3-, CD5-, CD10-, and cyclin D1-). He achieved complete remission after receiving chemotherapy. However, four years after the primary onset, he was diagnosed with recurrence. Although he achieved remission again by salvage therapy, six years after the primary onset, he was referred to our hospital with second recurrence. Colonoscopy revealed the appearance of multiple lymphomatous polyposis and biopsy specimens showed monotonous proliferation of centrocyte-like cells (CD79a+, CD20+, CD3-, CD5-, CD10-, and cyclin D1+), which were consistent with mantle cell lymphoma (MCL) except for CD5. The result of reactivity to cyclin D1 was different from that at initial diagnosis, so we reexamined the initial surgical specimens, the histological and histochemical features of which were proven to be the same as those of colonic biopsy specimens. Finally, the patient was diagnosed with CD5-negative MCL (marginal zone-like variant). As MALT lymphoma and MCL sometimes show similar histological features, they are difficult to distinguish from each other. It is necessary to take the possibility of this rare phenotype of MCL into consideration and to reexamine the initial diagnosis, especially if the clinical course is unusual for MALT lymphoma. This case is very interesting in view of its indolent clinical feature and phenotype. [J Clin Exp Hematopathol 52(3): 185-191, 2012]

Keywords: mantle cell lymphoma, marginal zone-like, CD5, extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue

INTRODUCTION

Mantle cell lymphoma (MCL) is a lymphoma, with B cells comprising the mantle zone in lymphoid follicles being its normal counterpart. Chromosomal translocation t(11;14) (q13;q32) is frequently observed in MCL, which is characterized by overexpression of cyclin D1.1 In the United States and Europe, it accounts for approximately 3-10% of non-Hodgkin’s lymphomas, and the frequency in Japan is reported to be 2-3%, occurring most frequently in middle-aged and older males.2 While MCL occurs most commonly in lymph nodes, it frequently infiltrates into the spleen, bone marrow and peripheral blood, occasionally resulting in findings of multiple lymphomatous polyposis (MLP) in cases of gastrointestinal infiltration. At the time of initial diagnosis, many MCLs are diagnosed in the advanced stage, such as stage III or IV. A typical MCL shows relatively uniform small to medium-sized cell proliferation with irregular nuclear contours, inconspicuous nucleoli and aggregated nuclear chromatin. Centroblasts, immunoblasts and proliferation centers are not recognized. According to the World Health Organization (WHO) Classification version 4, the blastoid and pleomorphic variants are classified as the aggressive variants of MCL, while the small-cell and marginal zone-like variants are classified as other variants.3 As for immunophenotypes, normal B-cell-related molecules, CD5, CD43 and BCL2, are positive, while CD10, BCL6 and CD23 are negative in most cases. In addition, a few CD5-negative cases have been reported.3 The prognosis is poor, with an overall survival rate of about 3 years, and it is not generally curable by chemotherapy. Histologically evaluable prognostic factors include mitotic figure increase (> 20 mitotic figures per 10 high-power fields)4 and Ki-67-positive cell proliferation.5,6
reports stating that aggressive variants have poor prognosis, while the small-cell variant and cases with a localized tumor within the mantle zone ("in situ" MCL) have a benign prognosis.1

We report a CD5-negative MCL case that had an indolent clinical course and was considered to be a marginal zone-like variant.

**CASE REPORT**

A 71-year-old male underwent an upper gastrointestinal endoscopy for the purpose of medical examination at a local hospital. A diffuse lesion was recognized at the lesser gastric curvature; as a result of biopsy, MALT lymphoma was suspected. On abdominal computed tomography (CT) scan, an approximately 4-cm-large mass and enlarged lymph nodes were recognized from the ileocecal region to the retroperitoneum. After the ileocecal resection, the patient was diagnosed as having MALT lymphoma (CD79a+, CD20+, CD3-, CD5-, CD10-, and cyclin D1-). He achieved complete remission after receiving six courses of combined chemotherapy with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP). Four years after the primary onset, gastric lesion and intraperitoneal enlarged lymph nodes were recognized in the abdominal cavity, and he was diagnosed with recurrence. After six courses of CHOP-like therapy, he again achieved remission. Six years after the primary onset, however, as enlarged lymph nodes were recognized again in the abdominal cavity with an increase in the soluble interleukin-2 receptor (sIL-2R) level, he was referred to our hospital.

A blood test at the time of hospitalization showed increases in lactate dehydrogenase, C-reactive protein, β2-microglobulin, and sIL-2R levels (Table 1). Significantly enlarged intraperitoneal lymph nodes were observed in an abdominal CT scan (Fig. 1). In bone marrow examination, there were no findings suggesting bone marrow infiltration, while no clear neoplastic lesions were recognized by upper gastrointestinal endoscopy, either. However, erosions, redening, and MLP were recognized in the ascending colon by colonoscopy (Fig. 2). A biopsy tissue image of the lesion is shown in Fig. 3. Mitotic figure and plasma cell differentiation were not found, but the findings were consistent with those of MALT lymphoma, with the dense proliferation of centrocyte-like cells and lymphoepithelial lesions (LELs). In immunohistochemical staining (Fig. 4), however, neoplastic cells were positive for CD79, CD20, and cyclin D1 and negative for CD3, CD5, and CD10, which suggested MCL, apart from the phenotype of CD5. The immunoglobulin heavy chain (IGH)/CCND1 fusion gene was detected by fluorescent in situ hybridization (FISH) analysis. Therefore, the surgical specimen taken at the time of initial diagnosis from six years previously was reevaluated. As a result, the morphology of the neoplastic cells, as well as the immunohistochemical findings, was found to be the same as in the colon biopsy (Fig. 5). By FISH analysis using the surgical specimen from the initial diagnosis, the API2/MALT1 fusion gene was shown to be negative, which is said to be frequently observed in intestinal MALT lymphomas. Finally, the patient was diagnosed as having CD5-negative MCL (marginal zone-like variant). After completing four courses of combined chemotherapy with cyclophosphamide, high-dose cytarabine, dexamethasone, etoposide, and rituximab (CHASER), he achieved third remission.

**DISCUSSION**

MALT lymphoma, a disease concept advocated by Isaacson and Write in 1983, is a low-grade B-cell lymphoma

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<tr>
<th>Peripheral blood</th>
<th>Chemistry</th>
<th>Fe</th>
<th>UIBC</th>
<th>Ferritin</th>
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<tr>
<td>White blood cell 5,020μL</td>
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<td>43 μg/dL</td>
<td>241 μg/dL</td>
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<td>Lymphocyte 35.0%</td>
<td>AST 18 IU/L</td>
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<td>Monocyte 5.0%</td>
<td>ALT 11 IU/L</td>
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<td>Eosinophil 4.0%</td>
<td>ALP 292 IU/L</td>
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<td>Basophil 0%</td>
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<td>Hemoglobin 13.4 g/dL</td>
<td>BUN 18.3 mg/dL</td>
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<td>Creatinin 0.81 mg/dL</td>
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<td>Reticulocyte 2.0 x 10⁴/μL</td>
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<td>Platelet 20.1 x 10⁶/μL</td>
<td>K 4.2 mEq/L</td>
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<td>Uric acid 4.8 mg/dL</td>
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AST, Aspartate aminotransferase; ALT, Alanine aminotransferase; ALP, Alkaline phosphatase; γ-GTP, γ-glutamyl transpeptidase; LDH, Lactate dehydrogenase; BUN, Blood urea nitrogen; UIBC, unsaturated iron binding capacity; sIL-2R, soluble interleukin-2 receptor; PT-INR, Prothrombin time-international normalized ratio; APTT, Activated partial thromboplastin time; ATIII, Antithrombin III; FDP, Fibrin/fibrinogen degradation products

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**Table 1.** Laboratory examination at the first admission
occurring in mucosa-associated lymphoid tissues.\textsuperscript{1} In Japan, it accounts for 8.45% of all malignant lymphomas.\textsuperscript{7} With the background of chronic inflammation, it occurs in various organs and most commonly in the stomach within the digestive tract, and \textit{Helicobacter pylori} infection is recognized in about 90% of gastric MALT lymphoma cases.\textsuperscript{8} As involvement of various chromosomal translocations such as \textit{API2/MALT1} fusion gene by t(11;18)(q21;q21) and trisomy were reported as other pathogenic mechanisms, it is drawing attention in terms of not only pathology, but also its response to therapy. Histopathologically, proliferations of small to medium-sized centrocyte-like cells and monocytoid B-cells are recognized in the area centering around the reactive lymphoid follicle and interfollicular region. In addition, lymphoma cells infiltrate into the epithelium, destroying it and forming LELs. Regardless of the organ involved, MALT lymphoma tends to stay in the organ of origin over a long period of time. Many cases are diagnosed in stage I or II, and the prognosis of patients with limited-stage MALT lymphoma is good.

\textbf{Fig. 1.} Abdominal computed tomography scan disclosed significantly enlarged intraperitoneal lymph nodes in the abdominal cavity.

\textbf{Fig. 2.} Colonoscopy revealed erosions, reddening, and multiple lymphomatous polyposis in the ascending colon.
As such, as morphological similarities are observed in MALT lymphoma and MCL, distinguishing them is difficult at times. The patient in this study was initially suspected of having MALT lymphoma, owing to the CD5 phenotype and differences between facilities in cyclin D1 antigen activation methods and detection systems.

As the small-cell and marginal zone-like variants have been included as morphological variants of MCL in the WHO Classification version 4, the existence of MCL variants similar to nodal marginal zone lymphoma, MALT lymphoma, and chronic lymphocytic lymphoma/small lymphocytic lymphoma has drawn attention. Including this case, eight cases of marginal zone-like MCL have been reported so far (Table 2).\(^9\)\(^-\)\(^{13}\) Golardi et al.\(^9\) reported an advanced-age male patient who

![Fig. 3. Histological features of the colon biopsy specimens. The biopsy specimen showed monotonous proliferation of centrocyte-like cells and lymphoepithelial lesions. Mitotic figure and plasma cell differentiation were not found. H&E stain, × 400.](image)

![Fig. 4. Immunohistochemical features of the colon biopsy specimens. (4a) Neoplastic cells were positive for CD20. (4b) Neoplastic cells were negative for CD5. (4c) Neoplastic cells were positive for cyclin D1. (4a)-(4c) counterstained with hematoxylin, × 400.](image)
CD5-negative MCL (marginal zone-like)

Fig. 5. Histological and immunohistochemical features of the surgical specimen at the time of initial diagnosis. (5a & 5b) There was monotonous proliferation of centrocyte-like cells. Mitotic figure and plasma cell differentiation were not found. (5c & 5d) Neoplastic cells were positive for CD20. (5e & 5f) Neoplastic cells were negative for CD5. (5g & 5h) Neoplastic cells were positive for cyclin D1 and mantle zone growth pattern was seen. (5a) & (5b) H&E stain, (5c)-(5h) counterstained with hematoxylin, (5a), (5c), (5e) & (5g) × 200, (5b), (5d), (5f) & (5h) × 400.
had proliferation of monocytoid cells surrounding the reactive follicle in the interfollicular region. He was cyclin D1-positive and CD5-negative. While Jacobson et al. reported a case with very similar morphology and proliferation patterns, it was positive for both cyclin D1 and CD5. Mansoor et al.\(^3,14,15\) Liu et al.\(^1\) reported that three out of seven CD5-negative MCL patients became long-time survivors, multiple organ infiltration is recognized in many CD5-negative MCL patients at the time of diagnosis, and a clinical outcome similar to that of CD5-positive MCL can be assumed, suggesting the need for a cohort study on a large population.

Since CD5-negative MCL cases are occasionally reported, reevaluation will be necessary when CD5-negative B-cell lymphoma including MALT lymphoma is suspected and it has an atypical clinical course or is treatment-resistant, keeping in mind the possibility of MCL. CD5-negative cases in MCL have not been sufficiently evaluated. As it is said that MCL cases with an indolent course exist, stratification through case accumulation is desired.

### REFERENCES

9. Golardi N, Velasco MR, Elghetany MT: Marginal zone variant of


