□ **CASE REPORT** □

Lymphoplasmacytic Lymphoma Presenting with Diarrhea and Joint Pain Which was Successfully Diagnosed by an MYD88 Mutation Analysis

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Abstract

A 55-year-old man presented to our department with diarrhea, weight loss, fatigability, and polyarthralgia. Blood tests revealed elevated soluble interleukin-2 receptor levels and IgG-type M protein positivity, without any findings that were suggestive of collagen disease. After computed tomography (CT) detected enlarged lymph nodes in the abdominal para-aortic region, lymphoma was suspected. CT-guided needle biopsy of the lymph node did not help to achieve a definitive diagnosis; however, a bone marrow test showed the pathological features of B-cell lymphoma. A genetic examination detected a MYD88 L265P mutation; the mutation analysis was valuable in diagnosing lymphoplasmacytic lymphoma in a IgM-type M protein-negative patient.

Key words: lymphoplasmacytic lymphoma, M protein, Waldenstrom macroglobulinemia, MYD88 mutation

Introduction

Lymphoplasmacytic lymphoma (LPL) is a class of indolent B-cell lymphoma, which typically involves the bone marrow and sometimes the lymph nodes, spleen, and other extranodal sites (1, 2). IgM serum paraprotein, which characterizes a subset of Waldenstrom macroglobulinemia (WM), is detected in most patients (3); however, other patients may have other paraproteins or no paraproteins at all. Paraproteins may cause hyperviscosity, autoantibody or cryoglobulin activity, resulting in various clinical manifestations, including neuropathy, diarrhea, and coagulopathy. LPL, including WM, does not have disease-specific clinical features. It is occasionally difficult to distinguish LPL from other disorders, such as marginal-zone lymphoma or multiple myeloma. In recent years, some studies have reported the diagnostic significance of MYD88 L265P mutations in LPL (4, 5).

We herein report a case of LPL in which a genetic analysis of a bone marrow sample positively contributed to the diagnosis.

Case Report

A 55-year-old man was referred to our institution from a regional hospital, with complaints of migrating finger joint pain, prolonged diarrhea (which had begun 2 years previously), and a body weight loss of 10 kg (from 70 to 60 kg; which had occurred over the previous year).
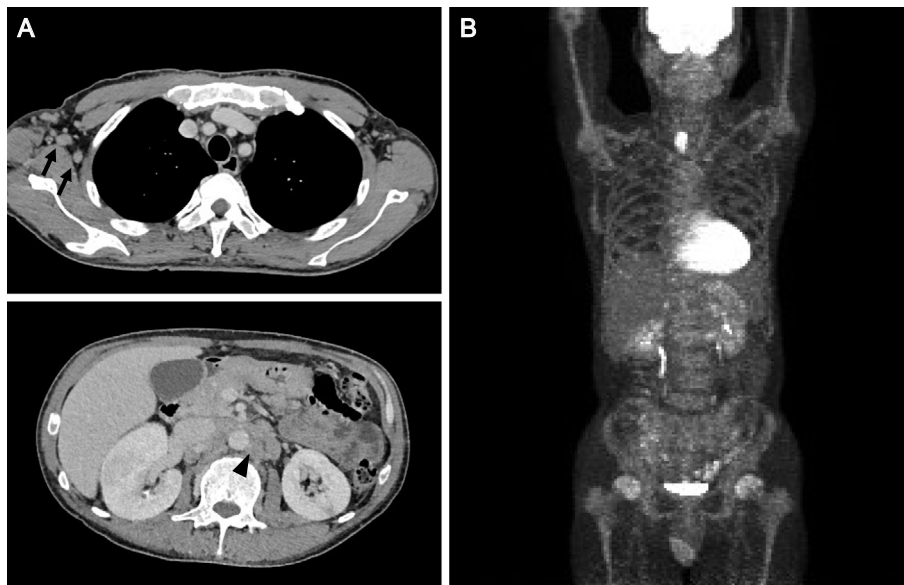
At the appointment, he presented with right first metacarpophalangeal joint swelling and aching pain. The patient's blood tests showed an elevated WBC count, 10,600/uL, without any significant differential abnormalities; normocytic anemia, Hb 10.4 g/dL; C-reactive protein (CRP), 4.09 mg/dL; abnormally high soluble interleukin-2 receptor levels,

Figure 1. Representative computed tomography and positron emission tomography (PET) images. (A) Swollen lymph nodes were observed in the right axilla (arrows) and abdominal para-aortic region (arrowhead). (B) A PET scan showed a 20 mm-nodule in the right lobe of the thyroid with the uptake of fluorodeoxyglucose (FDG) (maximum standardized uptake value, 11.13 units). The swollen lymph nodes, including those shown in (A), did not show the significant uptake of FDG.

5,973 U/mL (reference value 122–496); elevated IgG, 2,248 mg/dL; IgG-kappa M protein was detected. The blood tests were positive for the rheumatoid factor, but negative for serum matrix metalloproteinase-3 or antinuclear antibody. Computed tomography (CT) revealed multiple enlarged lymph nodes in the abdominal para-aortic region (maximum diameter, 20 mm). Although a CT-guided needle biopsy did not reveal severe dysplasia, the possibility of malignant lymphoma could not be excluded due to the small specimen size. To explore the possibility of lymphoma and assess a proper biopsy site, fluorodeoxyglucose (FDG)-positron emission tomography/CT was performed at one month after the initial CT scan. It showed a 20-mm nodule in the right lobe of the thyroid, which showed the most significant uptake of FDG (maximum standardized uptake value, 11.13 units) (Fig. 1), and swelling of the bilateral axillary (maximum, 12 mm), inguinal (maximum, 10 mm), and the abdominal para-aortic lymph nodes, without the significant uptake of FDG. A thyroid nodule biopsy was performed, and a benign adenomatous goiter was diagnosed.

Colonoscopy was performed because of the patient's chronic diarrhea and weight loss, which showed a normal appearance, although a mucosal biopsy of the colon revealed the infiltration of plasma cells (Fig. 2A). An *in situ* hybridization assay for immunoglobulin light chains showed a deviation in the kappa light chain (Fig. 2B), suggesting that these plasma cells were clonal and consistent with the M protein.

A bone marrow examination disclosed an abnormal increase in the numbers of lymphocytes, including lymphoplasmacytic cells. These lymphocytes and plasma cells accounted for 25.9% and 0.4% of a myelogram, respec-

tively. In flow cytometry, the cells in the lymphocyte gate (CD45^{high} and side scatter^{low}) were positive for CD19 and CD20 and negative for CD3, CD5, CD10, CD11c, CD23, and CD25. Immunohistochemistry of the bone marrow clot and a trephine biopsy revealed that the lymphocytes were positive for CD20 and the plasma cells were positive for CD138; both the lymphocytes and the plasma cells were negative for CD56 and Cyclin D1. In summary, lymphocytes with plasmacytic differentiation were increased in the bone marrow. The *in situ* hybridization assay again showed immunoglobulin light chain restriction, with an elevated kappa/lambda ratio (Fig. 3). These kappa-positive cells were presumed to be plasma cells and the lymphocytes were negative or weakly positive in *in situ* hybridization (the positive rate might depend on the amount of messenger RNA in each cell). A chromosomal abnormality of add(6)(q13) was detected in G-banding, and an immunoglobulin heavy-chain JH rearrangement analysis by Southern blotting was positive for a clonal band. Finally, a mutation analysis using an allele-specific primer-polymerase chain reaction (PCR) detected an MYD88 L265P mutation (a substitution of leucine to proline at amino acid position 265) in the bone marrow specimen.

Collectively, the patient was diagnosed with LPL, and anti-CD20 monoclonal antibody (rituximab) therapy was initiated. After the therapy was administered four times, the patient's diarrhea improved; however, he subsequently developed novel arthritis of the right wrist and the left knee without specific orthopedic findings. Hypocomplementemia of C4 complement was observed (6 mg/dL, reference value 14-39 mg/dL), but the C3 and CH50 levels remained within the normal limits. The patient's uric acid levels were normal. He
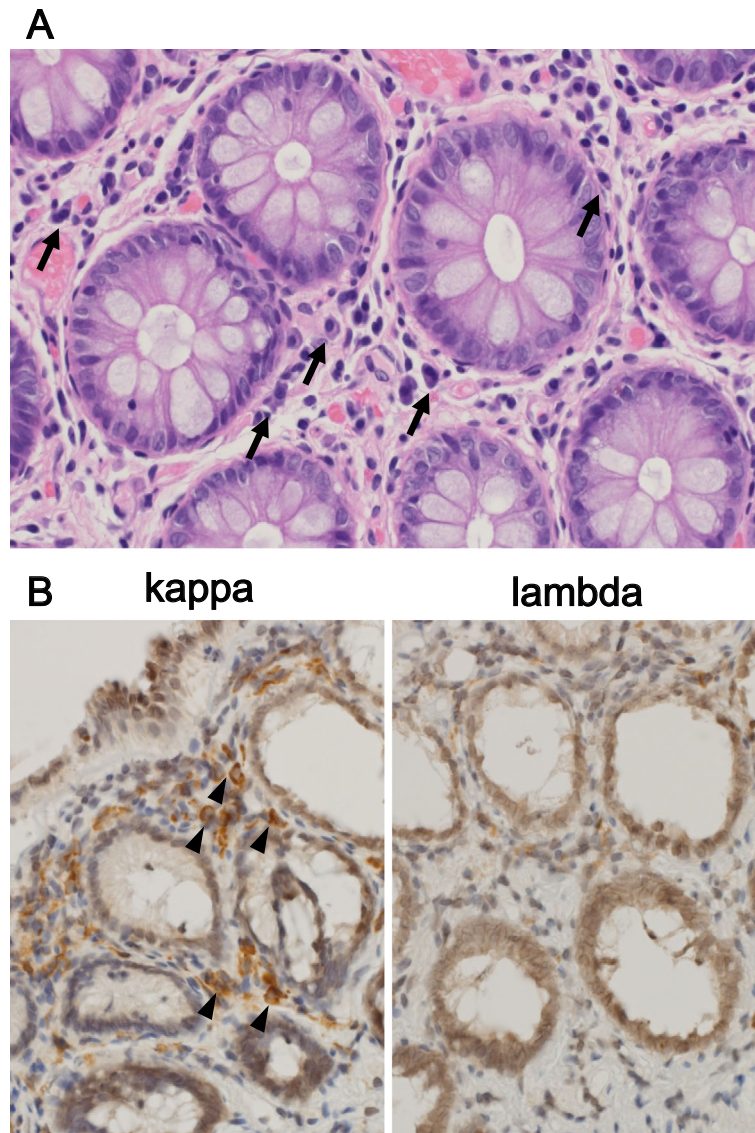
Figure 2.   **The histology of the sigmoid colon biopsy specimens. (A) The infiltration of inflammatory cells (mostly plasma cells) was observed (arrows). Malignant findings were not indicated (Hematoxylin and Eosin staining, magnification ×400). (B) Most of the plasma cells were positive for immunoglobulin light chain kappa (arrowheads) (*In situ* hybridization for immunoglobulin light chains; magnification: ×400).**

had a fever of >38°C, and his generalized lymphadenopathy, which was observed on CT, persisted. Combination therapy with bendamustine and rituximab (6) was started 2 months after the initiation of rituximab monotherapy, and the prompt regression of these symptoms was noted. Follow-up colonoscopy was performed five months after the initiation of rituximab. A random biopsy from the terminal ileum to the rectum showed the moderate infiltration of inflammatory cells, mainly small lymphocytes and plasma cells. Both kappa and lambda-positive plasma cells were seen; no light chain deviation was apparent at this time, suggesting that the therapy was effective.

Discussion

The common clinical manifestations of LPL include weakness, fatigue and B symptoms (fever, night sweats, or weight loss), and cytopenia (2). In this case, colonoscopy revealed the infiltration of tumor cells into the colonic mucosa, which may have been responsible for the patient's chronic diarrhea. Some LPL patients have been reported to have diarrhea due to immunoglobulin deposition in the gastrointestinal tract (7, 8); however, deposition was not observed in our case.

The patient manifested migrating arthritis even after the administration of rituximab. These joint symptoms might be due to the induction of cryoglobulinemia by LPL (2). Unfortunately, this could not be confirmed because we did not assess the cryoglobulin levels before the initiation of bendamustine chemotherapy. Raynaud phenomenon, purpura, neuropathy, and proteinuria were not observed in the present patient.
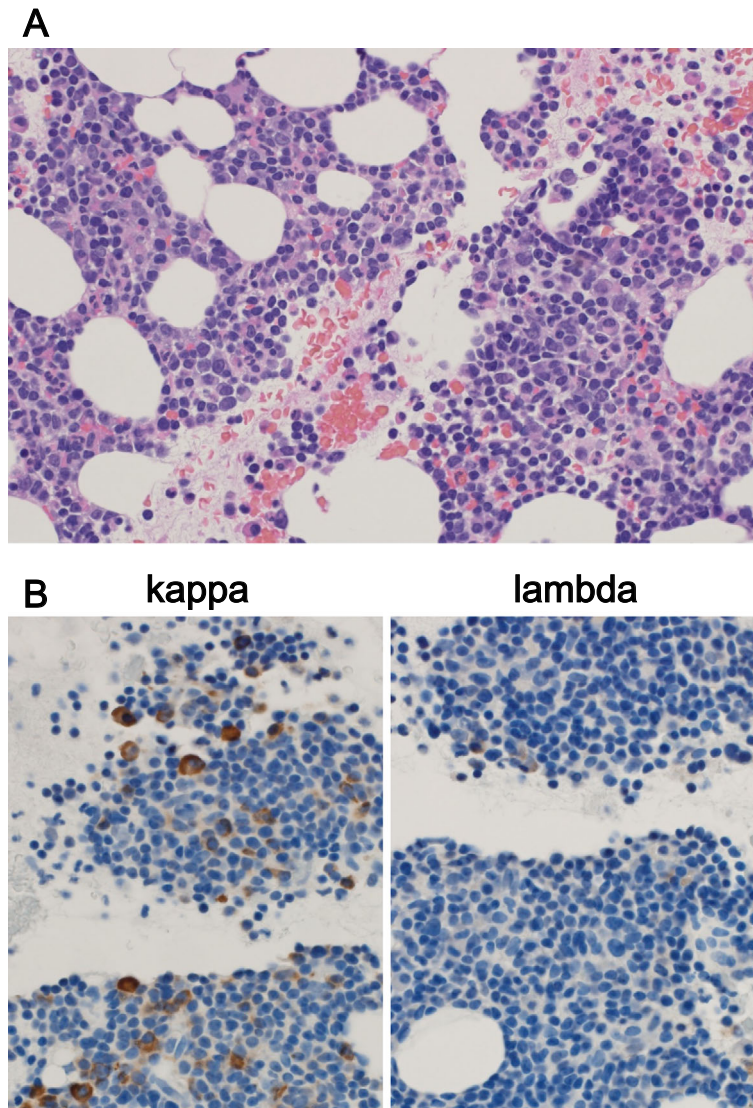
Figure 3. **The bone marrow histology (clot section). (A) A bone marrow section revealed the infiltration of lymphocyte- and plasmacyte-like atypical cells of various sizes (Hematoxylin and Eosin staining; magnification: ×400). (B) The tumor cells showed the restriction of the immunoglobulin light chain, with an elevated kappa/lambda ratio, consistent with the findings in sigmoid colon tissue (*In situ* hybridization for immunoglobulin light chains; magnification: ×400).**

The secretion of IgG or IgA (non-IgM LPL) is rare in LPL. Cao et al. evaluated 17 patients with non-IgM LPL and detected the expression of IgA and IgG in 8 patients (47%) and 9 patients (53%), respectively (9). Patients with non-IgM LPL showed clinical and pathological features that were similar to those observed with WM, but showed higher mortality within the first year after the diagnosis and worse overall survival. Furthermore, it was reported that patients with IgA-LPL were more likely to present B symptoms, high beta2-microglobulin levels and extramedullary involvement.

The pathological manifestations of LPL include the neoplastic proliferation of B cells and plasmacytes. However, it is often difficult to distinguish LPL from other types of indolent lymphoma on the basis of the clinical and pathological features. Meanwhile, the detection of MYD88 L265P

mutations has been reported to be valuable for diagnosing LPL (4). This mutation is also detected in patients with non-IgM LPL. Cao et al. reported that 6 (40%) of 15 patients with non-IgM LPL had the mutation (9). Similarly, King et al. reported that the mutation was present in 10 (43%) of 23 cases (10). Thus, the incidence of mutations in patients with non-IgM LPL seems lower than that in WM, which is reported to be 91–100% (4, 5). In addition, this mutation is not disease-specific. Some B-cell neoplasms, such as chronic lymphocytic leukemia/small lymphocytic lymphoma, splenic marginal zone lymphoma and diffuse large B-cell lymphoma are also positive for the mutation (11-13). Taken together, the detection of an MYD88 L265P mutation can be complementary for a diagnosis of LPL, especially in patients with non-IgM LPL. In our case, the clinical manifestations and histological findings indicated a diagnosis of LPL, differen-

tiating other indolent B-cell lymphomas with plasma cell differentiation. This diagnosis was finally supported by the detection of an MYD88 L265P mutation.

MYD88 is an adaptor protein, which mediates toll-like receptor and interleukin-1 receptor signaling (14). The stimulation of these receptors with their ligands leads to the activation of NF-kappaB signaling. It has been reported that MYD88 with L265P mutation is constitutively active in lymphoma cells and that it heightens cellular proliferation and the secretion of cytokines, thereby contributing to disease progression (15).

After the failure of rituximab monotherapy, we treated the patient with bendamustine and rituximab (BR). In general, the choice of regimen is made considering whether the patient is a candidate for high-dose chemotherapy followed by autologous hematopoietic cell transplantation (autoHCT). AutoHCT may be a treatment option for selected patients with relapsed refractory lymphoma, especially in patients with aggressive lymphoma. Patients who are candidates for autoHCT should avoid treatment with agents that might interfere with stem cell collection. LPL is, however, an indolent lymphoma and we believe that the role autoHCT has not been determined. Rummel et al. reported the superiority of BR to CHOP (cyclophosphamide, hydroxydaunorubicin, oncovin and prednisolone) and rituximab in WM (6). Thus, we select BR, despite the possibility that bendamustine may be toxic for hematopoietic stem cells. The role of bendamustine for non-IgM LPL should be further elucidated.

In summary, we reported a case of non-IgM LPL that was successfully diagnosed due to the detection of an MYD88 L265P mutation. Thus, the mutation analysis, in addition to conventional histology, is useful for reaching a precise diagnosis.

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