CASE REPORT

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Systemic amyloidosis associated with non-IgM type paraprotein with lymphoplasmacytic lymphoma

Taiki HORI[1,2], Saya YASUI[1], Minae HOSOKI[1], Hiroki YAMAGAMI[1,2], Toshiki OTODA[3], Tomoyuki YUASA[3], Ken-ichi AIHARA[3], Makoto TAKISHITA[1], Akihiko YOKOHAMA[4], Mitsuharu UEDA[5], Masahiro ABE[2] and Shingen NAKAMURA[3]

We present the case of an 81-year-old woman with right shoulder discomfort and right supraclavicular lymph node swelling who referred to our hospital. Blood tests results showed normal immunoglobulin levels, but free light chain assay showed abnormal κ/λ ratio. Serum immunoelectrophoresis detected immunoglobulin G-λ type M proteins. ^{18}F-fluorodeoxyglucose computed tomography revealed swelling of the right supraclavicular and mediastinal lymph nodes. Biopsy of the right supraclavicular lymph node showed a mixture of small lymphocytes with plasma cell-like round cells that were positive for cell surface CD20, CD138, CD56, IgG and λ, and negative for transthyretin and amyloid A. They had a Congo red stain-positive, glass-like surrounding structure and apple-green birefringence was observed under polarized light. Duodenal, gastric, and skin biopsies also showed amyloid deposits. We diagnosed the patient with lymphoplasmacytic lymphoma complicated by systemic light-chain amyloidosis. Rituximab monotherapy led to complete metabolic response. Systemic amyloidosis is a rare complication of B-cell lymphoma; however, the possibility of amyloidosis should be considered, even in patients with lymphadenopathy.

Key words: lymphoplasmacytic lymphoma, amyloidosis, rituximab

Introduction

Lymphoplasmacytic lymphoma (LPL) is a lymphoproliferative neoplasm that originates from small B-cell lymphocytes and from lymphocytes that tend to differentiate into plasma cells [1, 2]. LPL with immunoglobulin (Ig) M-type paraproteinemia is called Waldenström macroglobulinemia (WM) [3]. Amyloidosis is a known rare complication of WM or plasma cell dyscrasia, not known to occur in patients with malignant lymphomas with lymphadenopathy. We report a case of a patient with cervical lymphadenopathy, who was diagnosed with LPL with non-IgM type paraproteinemia complicated by systemic amyloidosis.

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[1]Department of Internal Medicine, Anan Medical Center, Tokushima, Japan
[2]Department of Hematology, Endocrinology and Metabolism, Tokushima University Graduate School of Biomedical Sciences, Tokushima, Japan
[3]Department of Community Medicine and Medical Science, Tokushima University Graduate School of Biomedical Sciences, Tokushima, Japan
[4]Division of Blood Transfusion Service, Gunma University Hospital, Maebashi, Japan
[5]Department of Neurology, Kumamoto University Graduate School of Medical Sciences, Kumamoto, Japan

Corresponding author: Shingen Nakamura
Department of Community Medicine and Medical Science, Tokushima University Graduate School of Biomedical Sciences, 3-18-15 Kuramoto-cho, Tokushima-shi, Tokushima, 770-8503, Japan
E-mail: shingen@tokushima-u.ac.jp

Case Report

An 81-year-old woman with a history of hypertension developed a sense of discomfort in her right shoulder in October 2020. She visited a local doctor, who noted a swollen lymph node in the right supraclavicular fossa. She was referred to our hospital in November 2020. On physical examination, she had a rubbery, hard lymph node in the right supraclavicular fossa and no other superficial lymphadenopathy. Her blood pressure was 132/71 mmHg, and other vital signs showed no abnormalities. The patient exhibited no gastrointestinal symptoms, macroglossia, hepatomegaly, and splenomegaly. Blood tests revealed white blood cell count 9,400/μL, hemoglobin level 12.7 g/dL, and platelet count 242 × 10^3/μL. Blood patho-

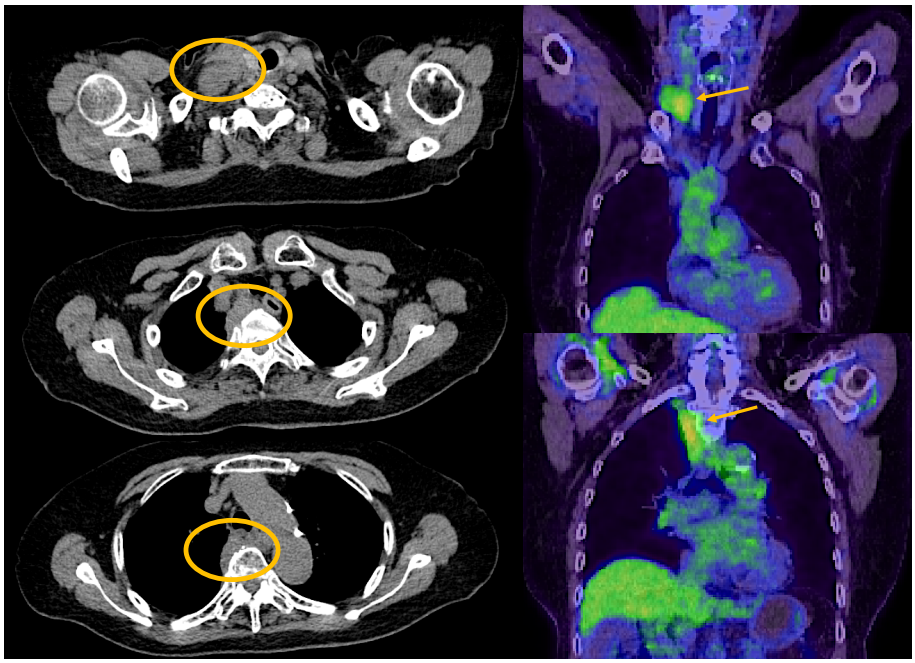

Figure 1. FDG-PET/CT imaging. Lymphadenopathy in the right supraclavicular fossa and a paraspinal lesion of the thoracic spine were observed (circled). Abnormal accumulation of FDG was observed at SUVmax 4.0, in accordance with swollen lymph nodes and the mediastinum (arrow). Abbreviation: FDG-PET/CT (fluorodeoxyglucose-positron emission tomography/computed tomography)

logical and immunological analyses showed total protein, albumin, alkaline phosphatase, lactate dehydrogenase, creatinine, IgG, A and M levels of 7.0 g/dL, 3.9 g/dL, 215 U/L, 177 U/L, 0.61 mg/dL, 1,609 mg/dL, 224 mg/dL, and 23 mg/dL, respectively. We also observed soluble interleukin-2 receptor (sIL-2R), and free light chain κ and λ levels of 572 U/mL, 25 mg/L and 133 mg/L, respectively. BNP 42.2 pg/mL, urine qualitative test result was negative for urinary protein. Serum immunoelectrophoresis detected a slight M peak, and IgG-λ-type paraprotein. No Bence Jones protein was detected in urine. Positron emission tomography/computed tomography (PET/CT) confirmed swollen lymph nodes in the right supraclavicular fossa and lesions along the vertebral body with slight ^{18}F-fluorodeoxyglucose (FDG) accumulation, with a maximum standardized uptake value (SUVmax) of 4.0 (Fig. 1). Bone degrading lesions were not observed. Hematoxylin and eosin (H&E) staining of a biopsied supraclavicular lymph node showed a mixture of small lymphocytes with plasma cell-like round cells (Fig. 2A) and a glass-like structure markedly spread surrounding the cells (Fig. 2B). Immunohistochemical staining of the round cells was positive for cell surface CD20 (Fig. 2C), CD138 (Fig. 2D), CD56, IgG (Fig. 2E), and λ (Fig. 2F), and negative for κ (Fig. 2G), transthyretin and amyloid A . This structure was positive for Congo red staining and apple-green birefringence was observed under polarized light (Fig. 2H). Follicular structure was not observed, and the Ki-67 index was 30%. In the bone marrow (BM), 0.7% cells were found to be CD38-positive and neither clonal plasma cells nor CD20-positive lymphocytes were detected by flow cytometry. Amyloid was not found to be deposited in the BM. We diagnosed the patient with LPL rather than plasmacytoma although flow cytometry and chromosomal analysis were not performed with enlarged lymph nodes. Using the allele-specific oligonucleotide polymerase chain reaction method, the formalin-fixed paraffin-embedded lymph node samples were found to be negative for the *MYD88* L265P mutation. Further, amyloid deposits were found in specimens biopsied from the lesser curvatures of the body and the angular incisure of the posterior gastric wall, and the posterior wall of the duodenal bulb (Fig. 3A, B). Amyloid was also detected in biopsy specimens taken from the skin of the face, forearms, and lower legs (Fig. 3C, D). Ultrasound cardiography showed 69% of the ejection fraction with an interventricular septum thickness of 9 mm, and electrocardiography did not suggest amyloid cardiomyopathy although no myocardial biopsy or cardiac MRI was performed. The patient's total liver span 10 < 15 cm, and she had not autonomic symptoms, including orthostatic hypotension, dysuria, gastrointestinal symptoms, and lower extremity sensorimotor peripheral neuropathy. Based on the above findings, we finally diagnosed the patient with LPL Stage II (according to the Lugano classification) with asymptomatic systemic amyloid light-chain (AL) amyloidosis. Since a standard treatment for LPL with systemic AL amyloidosis has not been yet established, rituximab (375 mg/m^2) was administered once

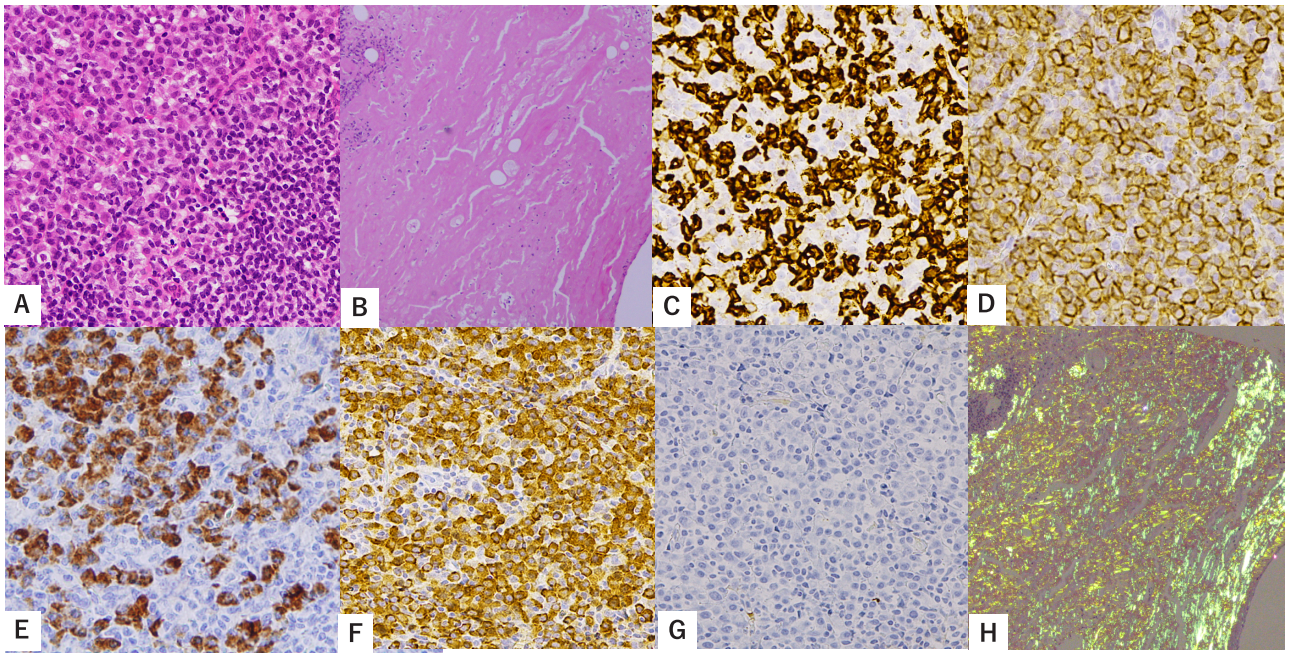

Figure 2. Histopathology of supraclavicular lymph node. Biopsy of the supraclavicular lymph nodes revealed proliferation of small abnormal lymphocytes in hematoxylin and eosin (H&E) staining (×200) A. A glass-like structure was observed in some parts of the lymph nodes in H&E staining (×40) B. Immunohistochemistry showed positivity for CD20 (×200) C, CD138 (×200) D, IgG (×200) E, and λ (×200) F, and negativity for κ (×200) G, amyloid A, and transthyretin, and apple-green birefringence was observed under polarized light (×40) H.

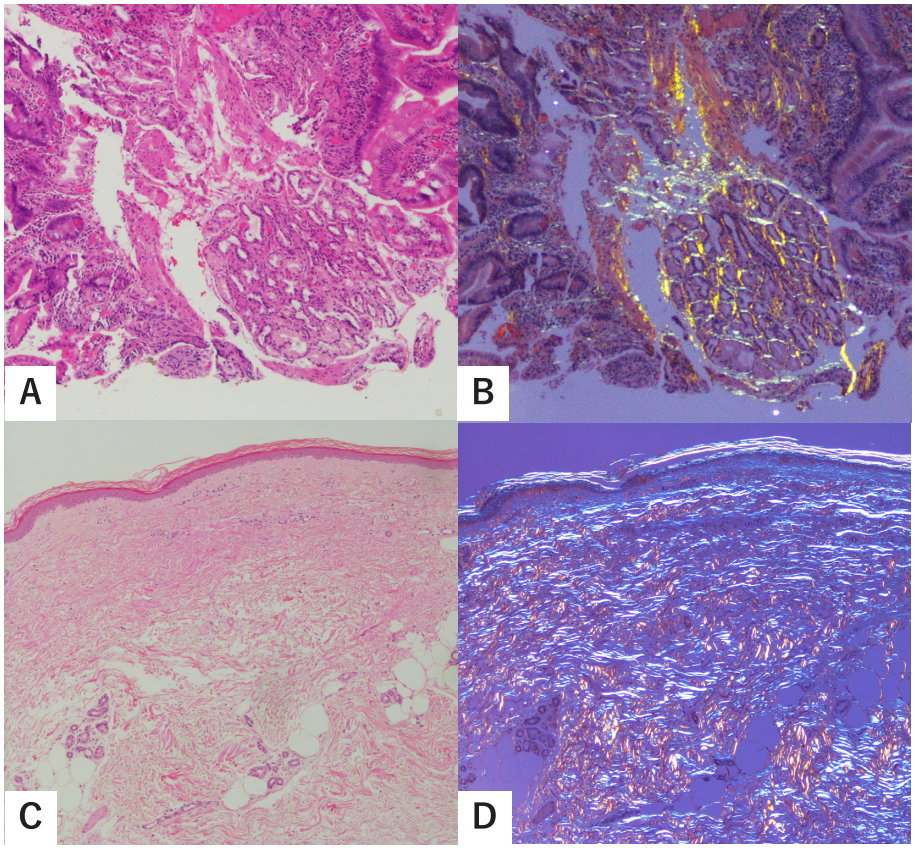

Figure 3. Histopathological findings of the gastrointestinal tract and skin. Biopsy of the duodenum showed pinkish interstitial deposits in H&E staining (×40) A, and apple-green birefringence was observed under polarized light (×40) B. Amyloid deposits were also observed in the dermis of the skin with apple-green birefringence under polarized light (×40 magnification) C, D.

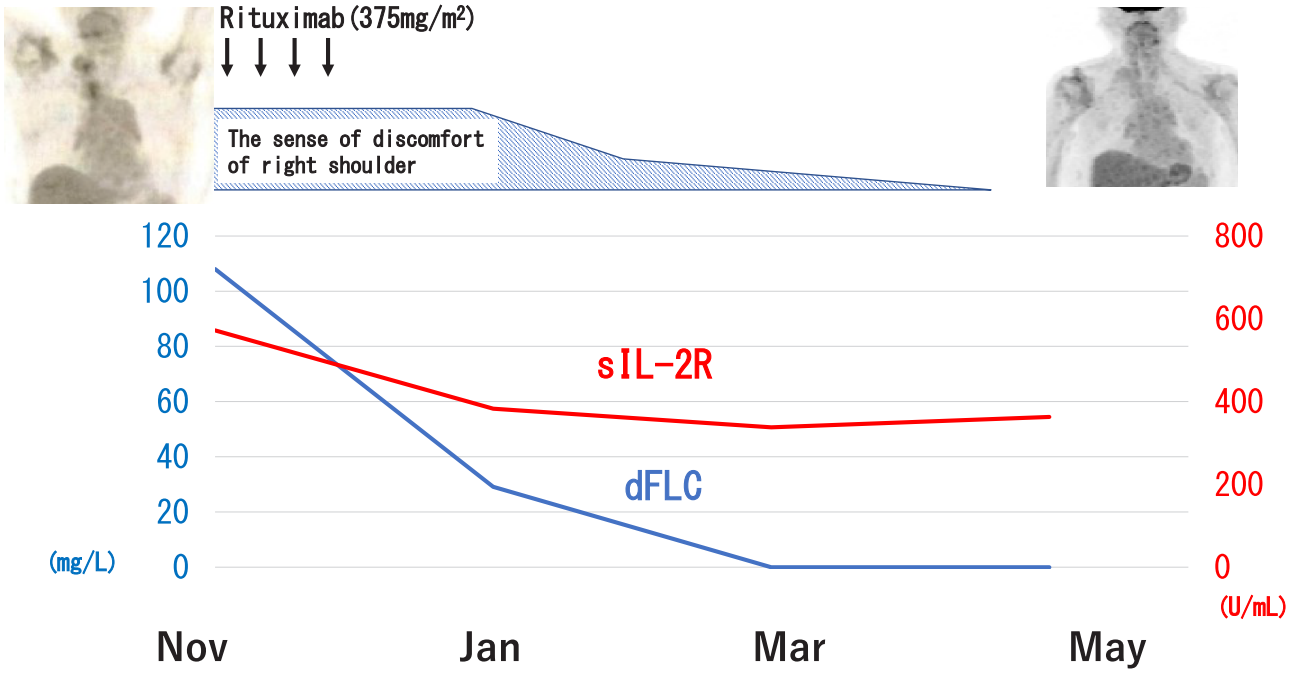

Figure 4. Clinical course. Rituximab (375 mg/m^2) was administered once a week in four doses for LPL complicated with systemic amyloidosis. sIL-2R and difference free light chain (dFLC) normalized, and swollen lymph nodes at the right supraclavicular fossa gradually shrunk. PET/CT showed complete metabolic response after five months.

weekly for four weeks. After four weeks, the sIL-2R levels and difference free light chain (dFLC) were normalized. The swollen lymph node in the right supraclavicular fossa gradually shrank, and the sense of discomfort in her right shoulder disappeared. A complete metabolic response (CMR) was confirmed by post-treatment PET/CT. Five months after treatment, the CMR was maintained, and there were no signs of amyloidosis (Fig. 4).

Discussion

Here, we report the case of a patient with LPL complicated by systemic AL amyloidosis associated with non-IgM paraproteinemia. The initial symptom was lymphadenopathy, without the characteristic symptoms of amyloidosis. The clinical course seemed to be indolent, and rituximab monotherapy was effective for both lymphadenopathy and paraprotein reduction.

Most cases of AL amyloidosis develop from plasma cell dyscrasias, but approximately 2–4% of the total amyloidosis cases are attributed to low grade B-cell lymphomas. They are classified into three main categories, IgM-associated, Sjogren's syndrome-associated, and other lymphoma-associated [4, 5]. In a previous study conducted on WM with IgM type paraproteinemia, out of 997 patients with WM, 75 (7.5%) had concurrent or subsequent light chain or heavy chain amyloidosis [6]. The accurate frequency of amyloidosis occurrence in B-cell lymphoma is unknown, since information on AL amyloidosis in B-cell lymphoma is limited.

The initial chief complaint in this case was lymphadenopathy without tenderness or any other symptoms that suggested systemic amyloidosis. We considered the primary concerns of malignant lymphoma, infectious disease, autoimmune disease, sarcoidosis, and metastatic cancers. Lymphoma with plasma cell differentiation were more likely to express surface immunoglobulin than those in myeloma [7]. The proliferating cells appeared to be lymphoplasmacytes and did not meet diagnostic criteria for myeloma or other B-cell malignancies. Bone degrading lesions were not observed around the tumor along with the vertebrae and morphology of the tumor growing vertically along the vertebral body was preferably diagnosed as LPL rather than myeloma/plasmacytoma. Systemic deposits of amyloid fibrils were thought to be produced by lymphoma cells in swollen lymph nodes, and not in the bone marrow.

Although we diagnosed our patient with LPL, her paraprotein isotype was IgG type, which is atypical for LPL. A previous epidemiological study comparing 45 patients with non-IgM LPL amongst 142 patients with typical WM revealed that non-IgM LPL had significantly higher prevalence in females than in males (60 vs. 39%, $p = 0.016$) [8]. Compared with IgM LPL, patients with non-IgM LPL more frequently presented with lymphadenopathies (53 vs. 15%, $p < 0.001$), splenomegaly (22 vs. 8%, $p = 0.015$), or extranodal involvement (20 vs. 8%, $p = 0.05$). The *MYD88* L265P mutation is common in patients with WM, with 93–97% prevalence [9], but this mutation is less

Table 1. Case series of lymphoma with systemic AL amyloidosis by non-IgM paraprotein

Age	Sex	Lymphoma	Paraprotein	Involved organ	Mayo Staging	MYD88 L265P mutation	Treatment	Outcome	Reference
68	M	LPL	IgA-λ, IgG-λ, IgM-κ	Temporal artery, Muscle, Rectum, Heart	N/A	N/A	PSL, chlorambucil, colchicine	Dead at 3 months	11)
53	M	LPL	IgG-λ	Kidney, Peripheral nerve	N/A	N/A	R, CY, auto-SCT	Stable for 2 years	12)
46	F	LPL	IgG-κ	LN, liver	N/A	N/A	Dex, R	Alive at 10 months	12)
60	M	LPL	Light chain (κ)	Lung LN	N/A	(+)	N/A	N/A	13)
55	M	LPL	IgG-κ	Heart	III	(+)	Bortezomib, Dex →ibrutinib	N/A	14)
68	M	MALT	Light chain (κ)	Heart, skin	III	N/A	R, lenalidomide	Dead at 16 months	15)
81	F	LPL	IgG-λ	LN, stomach, duodenum, skin	N/A	(–)	R	Alive at 5 months	present case

Abbreviation: LPL, lymphoplasmacytic lymphoma; LN, lymphnode; N/A, not available; PSL, prednisolone; R, rituximab; CY, cyclophosphamide; Dex, dexamethasone

common in patients with non-IgM LPL (42.1%). Five-year overall survival (OS) is 84% in patients with non-IgM LPL, which is similar to that of patients with WM [8]. King et al. reported 23 cases of LPL with non-IgM paraprotein in which amyloidosis was present in 17% cases, and *MYD88* mutations were found in 75% patients [10]. Our patient with non-IgM paraproteinemia was a female with lymphadenopathy, but without splenomegaly, extranodal involvement, or *MYD88* L265P mutation. Therefore, our case of complicated systemic AL amyloidosis with non-IgM paraproteinemia is considered relatively rare.

Treon et al. advocated a genomic-based treatment algorithm for treatment-naive symptomatic patients with WM. Ibrutinib monotherapy can be considered for patients without bulky disease, who have symptomatic amyloidosis with wild type *CXCR4* and mutated *MYD88* [9]. Bendamustine and rituximab or a proteasome inhibitor (PI)-based combination therapy is recommended for patients, with or without this mutation, who need a rapid response. If a rapid response is not needed, rituximab and Bruton's tyrosine kinase inhibitors are indicated. PI-based regimens should be considered in patients with symptomatic amyloidosis. However, the treatment for systemic AL amyloidosis complicated by malignant lymphoma has not yet been established. Although the mutation status of *CXCR4* was not evaluated, CD20 expression was very high in the enlarged lymph node. Considering the indolent clinical course and non-IgM paraproteinemia, meaning the patient was safe from IgM flares, we administered rituximab alone, which achieved a CMR.

Amyloidosis complicated by malignant lymphoma has not yet been fully understood. In most of cases other than WM or Sjogren syndrome related amyloidosis, amyloid deposition was reported to be localized. So far, six cases of lymphoma with systemic AL amyloidosis by non-IgM paraprotein were reported [11–15] (Table 1). Five cases were male, and five were LPL derived amyloidosis. Three cases had paraprotein with IgG type, three had κ chain, and three had heart involvement. The MYD88L265P mutation was investigated in two patients who were positive. Two patients (with heart involvement) were died at 3, 16 months, respectively. In our case, the patient was negative for MYD88 L265P mutation, and unlike typical WM, her paraprotein was non-IgM type with no heart involvement. In a study involving 75 cases of newly diagnosed IgM amyloidosis and 1,099 cases of non-IgM light chain amyloidosis, heart (56 vs. 73 %, $p = 0.002$), >1 organ involvement (31 vs. 44%, $p = 0.02$), and t(11;14) (27 vs. 50%, $p = 0.008$) were less common in IgM amyloidosis and OS was shorter in IgM amyloidosis than in non-IgM amyloidosis, when stratified by Mayo 2012 stage; stage 1/2 (59 vs. 125.9 months, $p = 0.003$) , stage 3/4 (6.5 vs. 12.9 months, $p = 0.075$) [16]. Although systemic light-chain amyloidosis is not usually detected until it has progressed to organ involvement, superficial lymphadenopathy developed prior to organ failure in this case, indicating that earlier diagnosis might also lead to her favorable prognosis.

In conclusion, we described the case of a patient with LPL complicated by systemic AL amyloidosis from a non-IgM paraprotein, who initially presented with lymphadenopathy only. Systemic AL amyloidosis is a rare complication of B-cell lymphoma, but we should consider the possibility of this disease in the patients with lymphadenopathy, which is typical for malignant lymphoma, but rare for amyloidosis.

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Conflicts of Interest

All authors declare that there is no conflict of interest in this work.

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