

Case report

IgA-producing lymphoplasmacytic lymphoma carrying the chromosomal abnormality t(8;14)

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IgA-producing lymphoplasmacytic lymphoma (LPL) is rare and *IgH/c-myc* translocation is rare in LPL. This is the first report of a case of IgA-producing LPL carrying t(8;14). An 86-year-old woman presented inguinal and intra-abdominal lymph node swelling, and lytic bone lesions in the lumbar vertebrae. A diagnosis of IgA-producing LPL was immunohistochemically made by inguinal lymph node biopsy. The serum IgA level was 1,180 mg/dL, which was revealed to be composed of IgA- λ monoclonal protein. Bone marrow chromosomal analysis demonstrated a complex abnormal karyotype, including t(8;14)(q24;q32), which was confirmed by FISH analysis. Abnormal lymphocytes positive for CD19, CD20, cyIgA, and cy λ were detected on flow cytometry analysis of marrow cells. Best supportive care was selected because of dementia and refractory urinary tract infection. Circulating lymphoplasmacytic cells with the same phenotype and karyotype were observed, and increased in number. The aggressive clinical course, including lytic bone lesions, may have been due to *IgH/c-myc* translocation or the nature of IgA-producing LPL.

Keywords: lymphoplasmacytic lymphoma, IgA, t(8;14)(q24;q32), non-IgM paraprotein, MyD88 L265P

INTRODUCTION

Lymphoplasmacytic lymphoma (LPL) is a mature B-cell lymphoma with intermediate differentiation between mature B-cells and plasma cells in B-cell ontogenesis. Due to this B-cell maturation, LPL produces monoclonal immunoglobulin, most of which is IgM paraprotein, and exhibits an indolent clinical course.¹ LPL typically expresses CD19, CD20, CD22, FMC7, BCL2, CD38, CD79a, and surface membrane (sm) and cytoplasmic (cy) immunoglobulin.² LPL shares a causative genetic background of MyD88 L265P mutation, which is observed in more than 90% of LPL cases.³ Regarding the immunoglobulin isotype produced by LPL, non-IgM subtypes comprise approximately 5% of paraprotein, the majority of which is the IgG type, and IgA-producing LPL is rare.⁴

The chromosomal abnormality t(8;14)(q24;q32) is usually observed in Burkitt lymphoma, by which reciprocal translocation of an immunoglobulin heavy chain (*IgH*) gene and an oncogene, *c-myc*, is generated, and plays an important

role in tumorigenesis.⁵ This chromosomal abnormality of t(8;14) has been reported in only 3 cases of LPL producing IgM, but not IgG or IgA.⁶⁻⁸ We report the first case of IgA-producing LPL carrying t(8;14).

CASE REPORT

An 86-year-old female with malignant lymphoma was referred to our hospital and admitted in October 2016. As her medical history, she had diabetes mellitus and developed repeated urinary tract infections, such as cystitis or pyelonephritis, since March 2015. She also developed dementia. In June 2016, she was hospitalized because of post-renal kidney failure, and CT revealed intra-abdominal and inguinal lymph node swelling and lytic bone lesions at the thoracic and lumbar vertebrae. She was immunohistopathologically diagnosed with IgA-producing LPL by right inguinal lymph node biopsy and transferred to our hospital.

On admission, she exhibited severe low back pain. Physically, she had slight fever of 37.4°C. Neither

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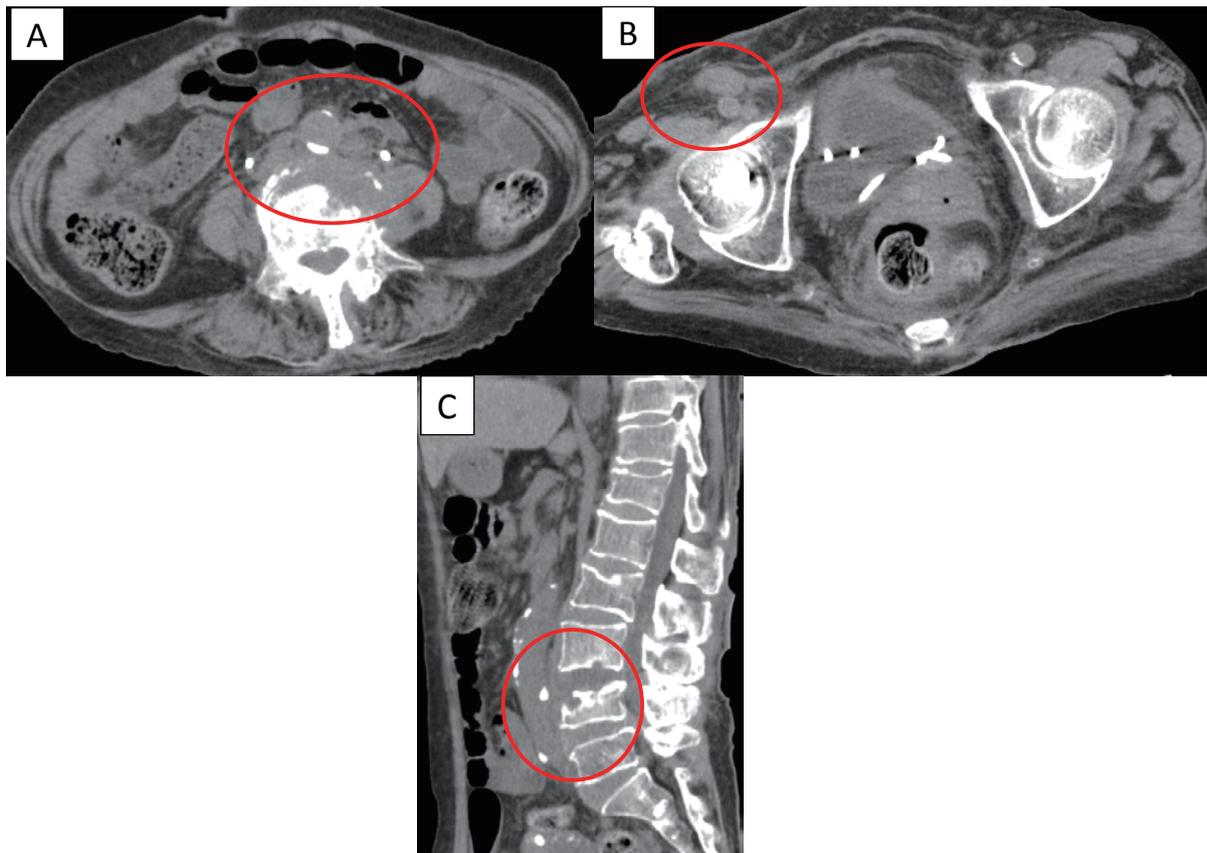


Fig. 1. Abdominal CT on admission to the previous hospital. Paraaortic (A) and left inguinal (B) lymph node swelling, and bone destruction at the level of L4 to L5 (C) were observed.

superficial lymph node swelling nor hepatosplenomegaly was noted. Cognitive dysfunction, such as recent memory disturbance and disorientation, was confirmed. Laboratory examination revealed a white blood cell (WBC) count of $4.2 \times 10^9/L$ with 0.4% abnormal lymphocytes, a hemoglobin concentration of 10.6 g/dL, and a platelet count of $245 \times 10^9/L$. Serum concentrations of IgA, C-reactive protein (CRP), and soluble interleukin-2 receptor (sIL-2R) increased to 1,180 mg/dL (normally 110 to 410 mg/dL), 1.0 mg/dL (normally below 0.3 mg/dL), and 839 U/mL (normally 145 to 519 U/mL), respectively. Serum electrophoresis demonstrated an M peak, which was revealed to be IgA- λ by immunofixation. The serum concentration of lactate dehydrogenase (LDH) was 192 IU/dL (normally 120 to 230 IU/dL); however, the LDH concentration exceeded 700 IU/mL in December 2016 when circulating LPL cells increased in number. Many WBC and bacteria were noted in the urinary sediment, and multidrug-resistant *Citrobacter freundii* was detected at more than $10^9/mL$ in urine bacterial culture.

On abdominal CT at the previous hospital, para-aortic lymph node swelling, L4 vertebral body destruction, tumoral invasion around L4 and L5 vertebral bodies, and right inguinal lymph node swelling were observed (Figure 1). Histopathological examination of a biopsied inguinal lymph node revealed a mosaic pattern with medium-sized lymphocytes and plasma cells or lymphocytes exhibiting differentiation toward plasma cells (Figure 2). On immunohistochemical

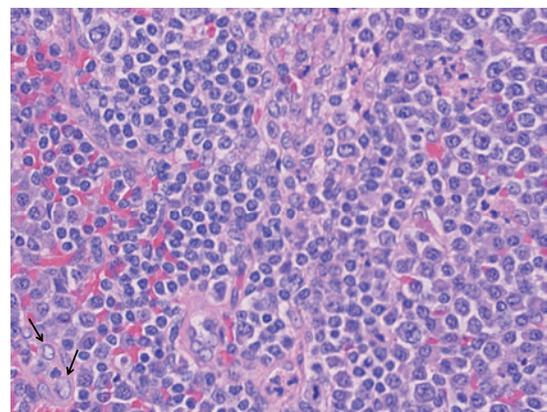


Fig. 2. Histological image of a biopsied left inguinal lymph node.

A mosaic pattern with medium-sized mature lymphocytes (the left half of the field), which were smaller than vascular endothelial cells (arrows), and plasma cells or lymphocytes, which exhibited plasmacytic differentiation (the right half of the field), were observed (H-E staining, $\times 200$).

examination, these abnormal lymphocytes were positive for CD20 (weakly), IgA, and λ -light chain (Figure 3A, C, D, respectively), but negative for CD138 (Figure 3B) and CD56 (data not shown). A diagnosis of IgA-producing LPL was made. However, *c-myc* staining, which was performed at

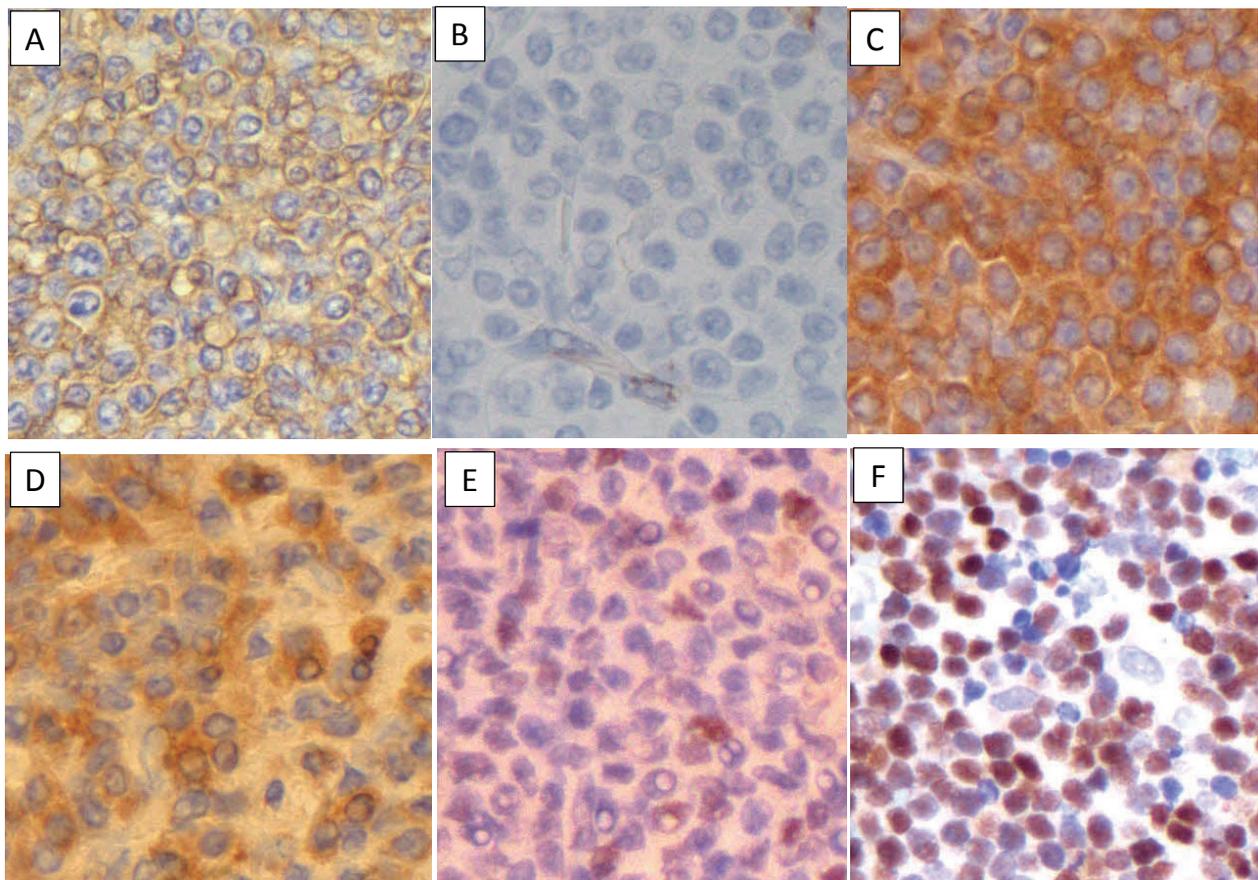


Fig. 3. Immunohistochemistry of the lymph node. These lymphocytes were weakly positive for CD20 (A) but negative for CD138 (B). They were positive for IgA (C) and λ (D) but negative for *c-myc* (E) when compared with control staining for *c-myc* (F) ($\times 200$).

our hospital, was negative (Figure 3E). The MIB-1 (Ki-67) index was 20.0%. The bone marrow aspirate included lymphoplasmacytic cells that comprised 2.3% of the nucleated cells (Figure 4). Abnormal lymphocytes were positive for CD20, CD38, HLA-DR, sm/cyIgA, and the sm/cy λ -light chain, but negative for CD10, CD20, CD138, and sm/cyIgG, IgM, IgD, and κ -light chains, accounting for 2.5% of the marrow cells on flow cytometry (FCM) analysis. Chromosomal analysis of the marrow cells demonstrated an abnormal complex karyotype of 49,XX,+add(1)(p11) $\times 2$,der(1;16)(q10;q10),+7,t(8;14)(q24;q32),der(10)t(1;10)(p13;p11.2),+12 in 2 of 20 cells analyzed. The fusion signal of the *IgH* gene and *c-myc* was detected by fluorescence in situ hybridization (FISH) in 2.0% of the mononuclear cells analyzed (data not shown).

Best supportive care and no chemotherapy were selected because of dementia and persistent refractory urinary tract infection, and irradiation of L4/L5 was performed to relieve the severe low back pain. Two months after admission (December 2016), lymphoplasmacytic cells were observed in the peripheral blood and gradually increased in number to approximately 15% of the WBC. On chromosomal analysis of peripheral blood at this time, the same abnormal karyotype was noted in 10 of the 20 cells analyzed (Figure 5). No other abnormal karyotype was found in 2 chromosomal

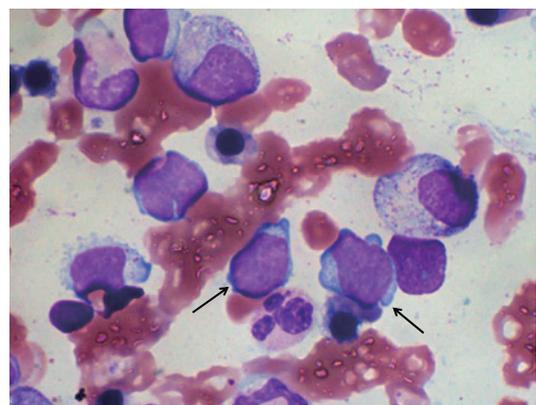


Fig. 4. Abnormal lymphoplasmacytic cells in the bone marrow (arrows) (Wright-Giemsa staining, $\times 1,000$).

analyses (October 2016: bone marrow; December 2016: peripheral blood). The t(8;14) FISH analyses of the peripheral blood were performed twice in December 2016, revealing *IgH/c-myc* fusion signals in 8.0 and 24.0% of the circulating mononuclear cells, respectively (Figure 6). FCM analysis of the peripheral blood demonstrated abnormal lymphocytes with the same phenotype as previously described in the bone marrow analysis, comprising 22.5% of the WBC;



Fig. 5. Chromosomal examination of peripheral blood demonstrated an abnormal karyotype of 49,XX,+add(1)(p11)×2,der(1;16)(q10;q10),+7, t(8;14)(q24;q32),der(10)t(1;10)(p13;p11.2),+12 in 10 of the 20 dividing cells analyzed .

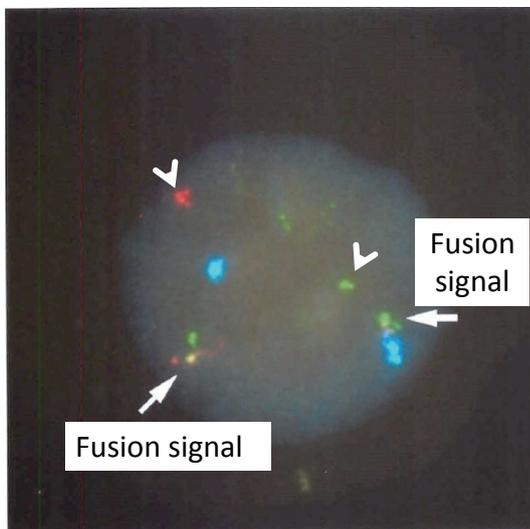


Fig. 6. Fluorescence in situ hybridization (FISH) analysis of circulating mononuclear cells for *IgH/c-myc* fusion signals performed in December 2016. The fusion signals (arrows) were observed in 24% of the mononuclear cells. Single signals for *IgH* (green) and *c-myc* (red) were noted (arrow heads). Two fusion signals are observed because the probe used in this analysis spans the break points of both *IgH* and *c-myc*.

however, these cells were partially positive for CD138 (Figure 7). No other abnormal B-cells were detected in 2 other FCM analyses (October 2016: bone marrow; December 2016: peripheral blood). The results of FISH and FCM analyses were consistent with the morphologically evaluated

percentages of circulating lymphoplasmacytic cells. Circulating mononuclear cells were examined by Sanger sequencing for MyD88 L265P gene mutation, with a negative result. The patient died 3 months after hospitalization because of renal insufficiency due to persistent urinary tract infection.

DISCUSSION

The clinical features of the present patient were slightly aggressive, exhibiting destructive bone lesions, possibly due to the presence of t(8;14)(q24;q32) or the nature of IgA-producing LPL, compared with those in cases of conventional IgM-producing LPL. Therefore, we performed immunostaining for *c-myc* using the biopsied lymph node, which was negative, suggesting a different role for *c-myc* in lymphoma growth in the present patient because this oncogene potently promotes neoplastic growth in Burkitt lymphoma⁵ or double-hit/double expressor diffuse large B-cell type malignant lymphoma (DLBCL).^{9,10} In DLBCL, *c-myc* immunostaining becomes positive when *c-myc* is solely rearranged and involved in tumorigenesis, but it becomes negative when the *c-myc* rearrangement is secondary to clonal evolution of pre-existing chromosomal abnormalities.¹¹ In this situation, the t(8;14)(q24;q32) observed in the present patient may have been an additional chromosomal abnormality. However, independent of t(8;14), non-IgM-producing LPL, especially the IgA-producing type, exhibits more aggressive clinical features, including extramedullary lesions or organ

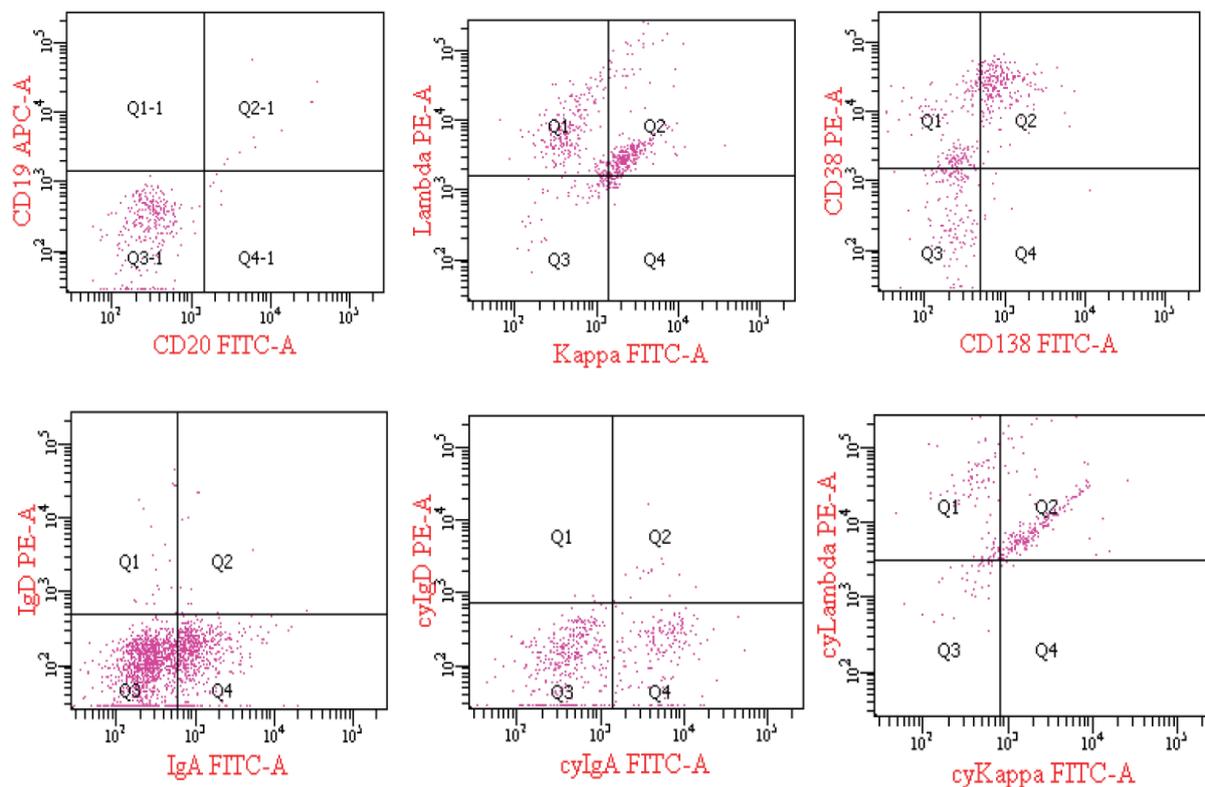


Fig. 7. Flow cytometry analysis of peripheral blood by weak CD45 gating. Abnormal lymphocytes were positive for CD19 (partial), CD20 (partial), CD38, CD138 (partial), sm λ , smIgA, cyIgA, and cy λ .

involvement, than IgM-producing LPL.⁴ In addition, as recurrent chromosomal abnormalities involved in LPL tumorigenesis, del6q, t(9;14)(p13;q32), trisomy 4, trisomy 12, and +18q22.1 have been reported.¹² However, none of these were observed in the abnormal karyotype in the present patient. Therefore, the genetic background in this case may be highly unique among LPL.

Due to the lytic bone lesions in the present patient, IgA-type multiple myeloma was considered. However, myeloma was able to be ruled out by the following findings: First, the surface antigen expression of the biopsied lymph node cells was typical of LPL in terms of CD19⁺, CD20⁺, CD38⁺, sm/cyIgA- λ ⁺, and CD138^{-1,2}; second, the abnormal cells in the bone marrow were morphologically lymphoplasmacytic cells composed of 2.3% nucleated cells (Figure 4) and the percentage of cells with typically plasmacytic morphology was 1.4%; third, the lymph node was histologically consistent with LPL (Figures 2, 3), and t(11;14), which is observed in a subset of multiple myeloma cases with lymphoplasmacytic morphology,^{13,14} was absent on chromosomal analysis; and fourth, the number of enlarged lymph nodes observed in the present patient is atypical for multiple myeloma.

In the present patient, MyD88 L265P mutation was not observed. Regarding this result, the incidence of this mutation in non-IgM-producing LPL has been reported to be as low as 43%.¹⁵ Although the reason for this low incidence is unclear, the genetic background of the development of non-IgM-producing LPL may be different from that of conventional IgM-producing LPL, as in IgM-producing LPL

associated with cold hemagglutininemia in which MyD88 L265P mutation is absent.¹⁶ Furthermore, isotype switching from IgM to IgG or IgA during the course of IgM-producing LPL/Waldenström's macroglobulinemia is only rarely observed.¹⁷ In this context, the genetic mechanism of the development of non-IgM-producing LPL may be different from that of IgM-producing LPL.

In conclusion, we report the first case of IgA-producing LPL carrying t(8;14)(q24;q32) in which MyD88 L265P mutation was negative and *c-myc* expression was limited. Further chromosomal and molecular investigations are required to elucidate the molecular mechanism underlying the development of LPL, including its subtypes.

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CONFLICT OF INTEREST

The authors declare no conflict of interest in this study.

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