Original Article

Atypical Lymphoplasmacytic and Immunoblastic Proliferation of Autoimmune Disease : Clinicopathologic and Immunohistochemical Study of 9 Cases

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Atypical lymphoplasmacytic immunoblastic proliferation (ALPIB) is a rare lymphoproliferative disorder (LPD) associated with autoimmune disease (AID). To further clarify the clinicopathologic, immunohistological, and genotypic findings of ALPIB in lymph nodes associated with well-documented AIDs, 9 cases are presented. These 9 patients consisted of 4 patients with systemic lupus erythematosus, 3 patients with rheumatoid arthritis, and one case each with Sjögren's syndrome and dermatomyositis. All 9 patients were females aged from 25 to 71 years with a median age of 49 years. Four cases presented with lymphadenopathy as the initial manifestation. In 4 patients, immunosuppressive drugs were administered before the onset of lymph node lesion. However, none of the 9 patients received methotrexate therapy. The present 9 cases were characterized by : (i) prominent lymphoplasmacytic and B-immunoblastic infiltration ; (ii) absence of pronounced arborizing vascular proliferation ; (iii) absence of CD10^{+} "clear cells" ; (iv) presence of hyperplastic germinal center in 7 cases ; (v) immunohistochemistry, flow cytometry, and polymerase chain reaction demonstrated a reactive nature of the T- and B-lymphocytes ; and (vi) on *in situ* hybridization, there were no Epstein-Barr virus -infected lymphoid cells in any of the 9 cases. Overall 5-year survival of our patients was 83%. The combination of clinical, immunophenotypic, and genotypic findings indicated that the present 9 cases can be regarded as having an essentially benign reactive process. Finally, we emphasized that ALPIB should be added to the differential diagnostic problems of atypical LPDs, particularly lymph node lesions of IgG4-related diseases. 〔*J Clin Exp Hematopathol 50(2) : 113-119, 2010*〕

Keywords: autoimmune disease, lymphadenopathy/atypical lymphoplasmacytic and immunoblastic proliferation, IgG4-related disease

INTRODUCTION

Reactive lymph node lesions in patients with autoimmune disease (AID) and its related disorders exhibit marked histological diversity and are occasionally associated with atypical lymphoproliferative disorders (LPDs).[1,2] In 1984, Koo *et al*. reported an unusual lymph node lesion associated with various AIDs including systemic lupus erythematosus, rheumatoid arthritis (RA), Sjögren's syndrome, and autoimmune hemolytic anemia.[3] Histopathologically, the lesion was characterized by prominent lymphoplasmacytic infiltration with various numbers of immunoblasts, namely, atypical lymphoplasmacytic and immunoblastic proliferation (ALPIB).[3] Although ALPIB is a rare lymphoproliferative disorder associated with AIDs, it occasionally presents serious problems in the differential diagnosis from atypical or malignant LPDs containing numerous plasma cells and immunoblasts, and

exhibiting autoimmune disease-like clinical manifestations, particularly angioimmunoblastic T-cell lymphoma (AITL). However, except for an earlier report by Koo *et al.*,[3] only sporadic case reports have been published.[4-7] Previously, we reported clinicopathologic findings of 5 such cases.[5-7] Recently, several authors have emphasized the differential diagnostic problems for ALPIB from lymph node lesions of IgG4-related diseases.[8-10] Because limited clinicopathological information is available for ALPIB, the present study documented essential data in 9 patients with ALPIB due to AIDs and discussed the differential diagnostic problems between ALPIB and atypical LPDs including lymph node lesions of IgG4-related disorders.

MATERIAL AND METHODS

Nine cases were collected from a series treated by one of the authors (M.K.) between 1999 and 2009. Medical records of these 9 cases were extensively reviewed. Five cases (nos. 2, 4, 5, 8, and 9) were reported previously.[5-7]

Tissue specimens were fixed in formalin solution, routinely processed, and embedded in paraffin. For light microscopic examination, the sections were stained with hematoxylin-eosin.

Immunohistochemical studies were performed using Ventana automated stainer (BenchMark[TM], Tucson, Arizona, USA) or Histofine Histostainer (Nichirei Bioscience Inc., Tokyo, Japan) according to the manufacturer's instructions.

A panel of antibodies against human immunoglobulin light chains ($\varkappa$ and λ) (Novocastra, Newcastle, UK, or Nichirei Co., Tokyo, Japan), IgG (Novocastra), IgA (Novocastra), IgM (Novocastra), IgG4 (MCC011 ; Binding Site, Birmingham, UK), CD3 (PS-1 ; Immunotech, Marseille, France), CD5 (4C7 ; Novocastra), CD15 (C3D-1 ; Dako A/ S, Glostrup, Denmark), CD20 (L26 ; Dako A/S), cocktail of CD21 (2G9 ; Novocastra), CD35 (RB L25 ; Novocastra), CD30 (Ber-H2 ; Dako A/ S), CD43 (DFT-1 ; Dako), antifollicular dendritic cell antibody CNA 42 ; Dako), and humanherpes virus-8 (137B1 ; Novocastra) were used. Sections with known reactivity for the antibodies assayed served as positive controls and sections treated with normal rabbit and mouse serum served as negative controls.

In situ hybridization (ISH) with Epstein-Barr virus (EBV)-encoded small RNA (EBER) oligonucleotides was performed to test for the presence of EBV small RNA in formalin-fixed paraffin-embedded sections using a Ventana automated (BenchMark[TM]) stainer or a hybridization kit (Dako).

Genomic DNA was extracted from formalin-fixed tissues after dewaxing of paraffin sections, then immunoglobulin heavy chain (8 cases : nos. 1-8) and T-cell receptor (TCR) γ-chain gene (4 cases : nos. 2, 4, 5, and 8) rearrangements were analyzed by polymerase chain reaction (PCR) as described

previously.[11,12]

Actuarial overall survival curve distributions were calculated by the Kaplan Meier method.[13]

RESULTS

The main clinicopathologic findings are shown in Tables 1 and 2.

Clinical findings

All 9 patients were females and ranged in age from 25 to 71 years, with a mean age of 49 and a median age of 49. At the time of the initial lymph node biopsy, 4 cases (nos. 1-3 and 7) fulfilled the diagnostic criteria for systemic lupus erythematosus,[14] while 3 cases (4, 8, and 9) were diagnosed as RA,[15] and 1 each was diagnosed as dermatomyositis (no. 5)[16] and Sjögren's syndrome (no. 6).[17]

AIDs were active in 7 patients (nos. 1, 4-9) and inactive in only 2 patients (nos. 2 and 3). Seven patients (nos. 1, 2, 4-7, and 9) had constitutional symptoms such as fever at lymph node biopsy. Four cases (nos. 1 and 5-7) presented with lymphadenopathy at the onset of disease. Multicentric lymph node enlargement was present in 6 cases (nos. 4-9). Analysis of patient lifestyles did not suggest any risk factors for human immunodeficiency virus type-1 infection, although serological data on anti-human immunodeficiency virus type-1 antibody were available in only 4 cases (nos. 1, 3, 6, and 7). Polyclonal hyper-γ-globulinemia was observed in 5 cases (nos. 3, 5-7, and 9). Various autoantibodies including positive rheumatoid factor and antinuclear antibody were detected in all but one case (no. 5). The level of total functional hemolytic complement (CH50) was decreased in 2 (nos. 1 and 7) of the 7 cases (nos. 1-4, 7-9) examined. Serum IgG4-level was examined in 3 cases (nos. 3, 6, and 7). Serum IgG4 level was within the normal range (< 135 mg/dL) in 2 cases (nos. 3 and 6), whereas elevated serum IgG4 level (221 mg/dL) was recorded in the remaining 1 case (no. 7). However, elevated interleukin-6 (IL-6) level was also recorded in Case 7 (19 pg/mL, normal range < 4.62).

All 5 cases (nos. 2-4, 6, and 7) with analyzable metaphases had a normal karyotype. Information from flow cytometry of the biopsied specimens showed a polyclonal B-cell population in 6 cases (nos. 2-4, 6, 7, and 9) examined. There was no absence of pan-T-cell markers in any of the 6 cases examined.

At lymph node biopsy, 3 patients (nos. 2-4) were receiving steroid therapy, and 1 patient each was receiving nonsteroidal anti-inflammatory drug (no. 1), gold therapy (no. 8), and mizoribine (no. 9). However, none of the 9 patients received methotrexate (MTX) therapy. The remaining 3 cases (no. 5-7) had not received any medications, but soon after the lymph node biopsy, all 3 of these patients were treated with predni-

Table 1. Summary of clinical findings

No	Age/gender	Disease	Disease activity	Site of lymph node swelling	Interval (months)	Symptom and sign	Abnormal laboratory findings	Immunosuppressive therapy	Outcome
1	25/F	SLE	Active	Bilateral neck	Onset	Fever, skin rash, convulsion, arthralgia	Leukopenia, ANA (+), hypocomplementemia	—	CHOP, 6 m, recurrence, 34 m, died with sepsis
2	30/F	SLE	Inactive	Right neck	216	Fever	Anemia, leukocytosis, ADNA (+)	β-methasone	β-methasone, 69 m, alive
3	39/F	SLE	Inactive	Bilateral neck	240	—	Anemia, ANA (+), SS-A/b antibody (+), polyclonal hyper-γ-globulinemia	Prednisolone	Prednisolone 1 m, alive
4	48/F	RA	Active	Systemic	120	Fever	RF (+)	Prednisolone	Prednisolone 48 m, Alive
5	49/F	DM	Active	Left axilla & groin	Onset	Fever, general fatigue	↑ creatine kinase, ↑ aldolase, polyclonal hyper-γ-globulinemia	—	Prednisolone 120 m, alive
6	50/F	SJS	Active	Systemic	Onset	Fever, dry eye & mouth	ANA (+), polyclonal hyper-γ-globulinemia	—	Prednisolone, 20 m, alive
7	61/F	SLE	Active	Systemic	Onset	Body weight loss	ANA (+), polyclonal hyper-γ-globulinemia, hypocomplementemia	—	25 m, alive
8	68/F	RA	Active	Right neck & mediastinum	72	—	RF (+), ANA (+)	—	Gold therapy 57 m, alive
9	71/F	RA	Active	Left neck & bilateral axilla	276	Fever, arthralgia, pulmpnary infiltration	RF, ANA (+), polyclonal hyper-γ-globulinemia,	Mizoribine	Mizoribine+, prednisolone, lost

Abbreviations: Interval, interval between onset of disease and lymphadenopathy; SLE, systemic lupus erythematosus; DM, dermatomyositis; RA, rheumatoid arthritis; SJS, Sjögren's syndrome; ANA, anti-nuclear antibody; ADNA, anti-DNA antibody; RF, rheumatoid factor; CHOP, cyclophosphamide, doxorubicin, vincristine, & prednisone; m, months

Table 2. Summary of pathological findings

	Size (cm)	Follicles		Interfollicular area							Sinus
		Folliclular hyperplasia	Follicular dendritic cell network	Small vessels	Plasma cells	Immunoblasts	Monocytoid B-cells	Neutrophils	Eosinophils	Histiocytes	
1	1.0	—	—	+	+	+++	—	+	+	++	obliterated
2	1.5	—	abnormal proliferation	++	++	++	—	—	+	+	obliterated
3	1.8	++	normal	+	++	++	+	—	+	+	apparent
4	2.5	++	normal	++	++	+++	+	—	—	+	apparent
5	1.2	+	broken up	+	+++	+	—	—	—	+	apparent
6	3.0	++	broken up	++	+++	+	—	—	—	+	apparent
7	1.5	++	normal	+	+++	+	—	—	—	+	apparent
8	1.2	++	broken up	++	+	+	—	—	+	++	obliterated
9	1.0	++	broken up	++	++	++	—	++	—	++	apparent

—, negative, only a few or absent; +, scattered or mild; ++, moderate; +++, numerous or prominent

solone. One patient (no. 8) was treated with mizoribine and prednisolone. Four patients (nos. 2-4 and 9) continued to receive the same therapeutic agents as before the lymph node biopsy. The remaining one case (no. 1) received CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisolone) therapy, because clinically malignant lymphoma was highly suspected.

Follow-up data were obtained from 8 cases (nos. 1-8). None of the 8 surviving cases developed malignant lymphoma during the follow-up period from 1 to 120 months (mean, 47 mon; median, 41 mon). One patient (no. 1) developed recurrent lymph node swelling after 6 months and died with sepsis after 34 months, while the remaining 7 cases were alive at the last follow-up. The overall survival rate of the 8 cases was 83% at 5 years (Fig. 1).

Pathological, immunohistochemical, and EBV findings

All enlarged lymph nodes had a diameter of less than 3.0 cm. On low-power field, the biopsy specimens were characterized by obvious paracortical expansion with diffuse effaced lymph node architecture (Fig. 2a). Lymphoid follicles were seen in 7 cases (nos. 3-9), and their germinal centers were usually hyperplastic, although a few were rather atrophic.
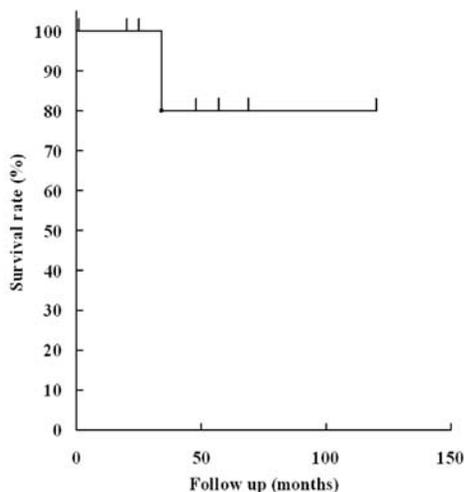
Fig. 1. Overall survival of the 8 patients with atypical lymphoplasmacytic immunoblastic proliferation.

Each case contained mild to moderate small vessels in the interfollicular area. Lymphoid sinuses appeared to be obliterated in 3 cases (nos. 1, 2, and 8). Perivascular fibrous masses were observed in 1 case (no. 9).

On high-power field, the paracortical area was diffusely infiltrated by a polymorphous population consisting of numerous mature plasma cells, plasmacytoid cells, large basophilic transformed lymphocytes (immunoblasts), and small- to medium-sized lymphocytes (Fig. 2b). A proportion of immunoblasts with large vesicular nuclei and prominent nucleoli resembling Hodgkin cells were observed in 4 cases (nos. 2, 4, 8, and 9), but typical Reed-Sternberg cells were not detected (Fig. 2b). Small- to medium-sized lymphocytes exhibited minimal cytological atypia. There were no medium to large lymphoid cells with clear cytoplasm (clear cells). Moderate numbers of histiocytes with or without epithelioid cell features were seen in 3 cases (nos. 1, 8, and 9).

Scattered eosinophils were observed in 4 cases (nos. 1-3 and 8) (Fig. 2b). In the paracortical area, small vessels usually had plump nuclei, however, high endothelial venules showing arborization were not prominent. In 2 cases (nos. 3 and 4), foci of monocytoid B-cells were seen.

Staining with CD20, CD3, and CD5 showed a mixture of small- and medium-sized lymphocytes. The majority of immunoblasts in 5 cases (nos. 1, 4, 5, 8, and 9) showed the B-cell phenotype (Fig. 2c, d). The other 4 cases (nos. 2, 3, 6, and 7) showed polytypic immunoblasts. A proportion of the B-immunoblasts were CD30-positive but CD15-negative. There were no CD43-positive lymphocytes detected. In the interfollicular area, 60% of these paracortical T cells expressed CD4, and the remaining 40% were CD8-positive in the 3 cases examined (nos. 1, 2, and 8). Immunohistochemical studies of light chain determinants for interfollicular plasma cells, plasmacytoid cells, and B-immunoblasts demonstrated a polyclonal pattern (Fig. 2e, f).

A monoclonal antibody cocktail of 2G9 and RB L25, as well as CNA 42 highlighted the meshwork of follicular dendritic cells (FDCs). The FDC meshwork maintained a regular arrangement in 3 cases (nos. 3, 4, and 7), whereas a few of the meshworks were broken up into clusters in 4 cases (nos. 5, 6, 8, and 9) (Fig. 2g). In 1 case (no. 2), a monoclonal antibody cocktail of 2G9 and RB L25 demonstrated scattered large irregularly shaped accumulations of FDCs surrounding the small vessels (Fig. 2h). The remaining 1 lesion (no. 1) did not contain FDC meshwork.

There were no human-herpes virus-8- or EBER-positive cells in any of the 9 cases.

Immunogenotypic results

PCR assays for *TCR-γ* and/or *IgH* genes were performed in 8 cases (nos. 1-8). None of 4 cases (nos. 2, 4, 5, and 8) demonstrated clonal bands on TCR-γ PCR. PCR assay for *IgH* gene demonstrated only germline bands with IgH chain probes in 8 cases (nos. 1-8).

DISCUSSION

The clinical manifestations of our 9 cases including multicentric lymphadenopathy with systemic symptoms and abnormal immunological findings raised the possibility of malignant lymphoma, prompting a lymph node biopsy. Histologically, the present 9 cases were characterized by : (i) prominent lymphoplasmacytic and B-immunoblastic infiltration ; (ii) an absence of pronounced arborizing vascular proliferation ; (iii) absence of CD10^{+} "clear cells" ; (iv) presence of hyperplastic germinal center in 7 cases ; (v) a polyclonal nature of both T- and B-lymphocytes on immunophenotypic and genotypic analysis ; (vi) flowcytometry demonstrated that there was no absence of pan T-cell marker, which is a characteristic flowcytometric finding of AITL ;[18] and (vii) EBV-infected lymphoid cells were absent in all 9 cases. The overall histologic, immunohistochemical, genotypic, and EBV findings of this case were similar to those of previous reports,[3-7] and the present 9 cases may be classified as ALPIB associated with AIDs.

The present 9 cases indicate that ALPIB should be differentiated from various atypical and malignant LPDs containing numerous B-immunoblasts, plasma cells, and cells with plasma cell differentiation and exhibiting AID-like clinical manifestations.

The differential diagnostic problems between ALPIB and non-Hodgkin's, and in particular AILT, have been well described in the literature.[5-7,9,10,19,20] AITL rarely occurs in systemic rheumatic diseases such as RA.[21] However, histological, immunohistochemical, flowcytometric, and genotypic
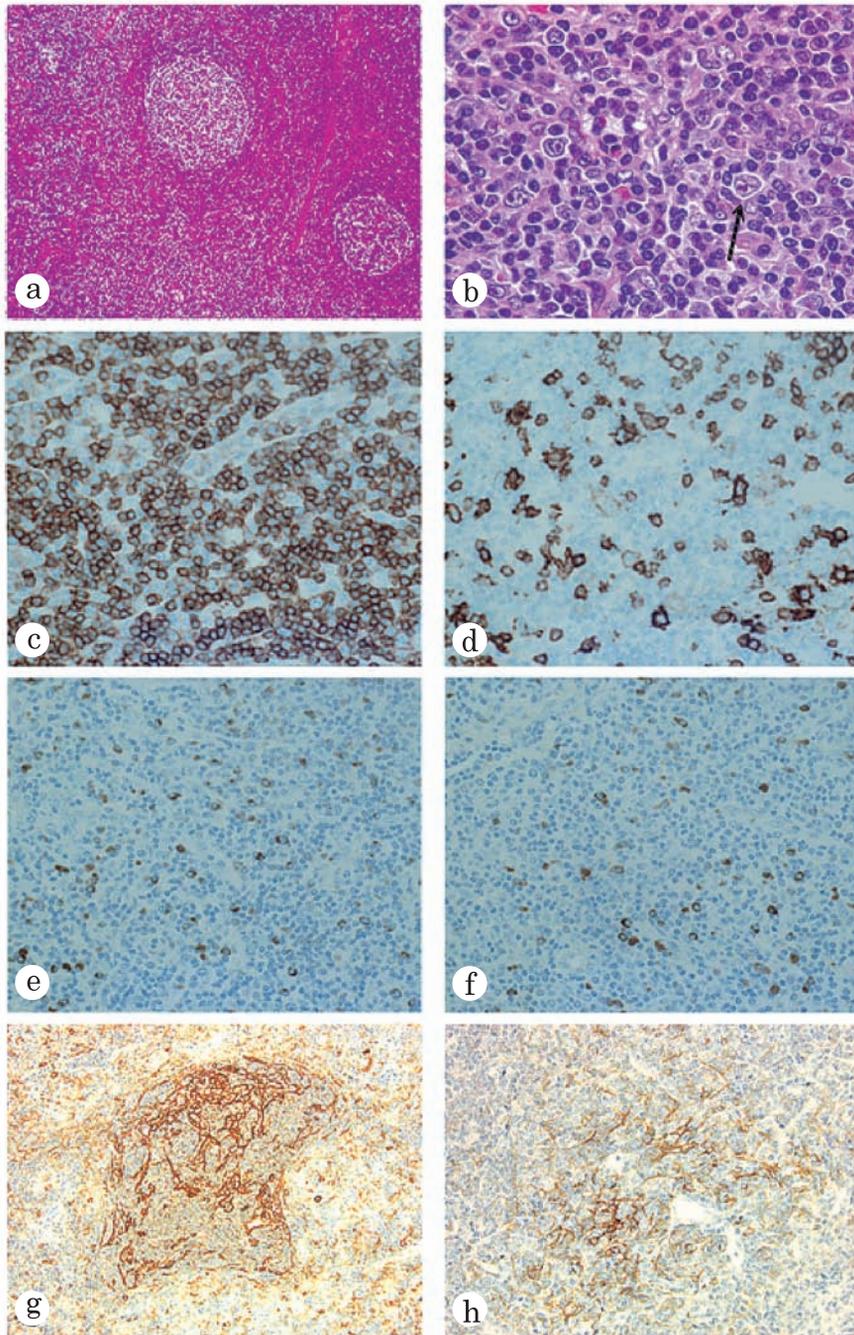
Fig. 2. Histological and immunohistochemical findings of atypical lymphoplasmacytic immunoblastic proliferation. (*2a*) Low-power field of biopsy specimen. The lesion was characterized by diffuse paracortical hyperplasia with small vessel proliferation and a hyperplastic germinal center. Case 7, H&E stain, ×25. (*2b*) On high-power field, the paracortical area contained mature plasma cells, plasmacytoid cells, immunoblasts, small- and medium-sized lymphocytes, and an eosinophil. Note a Hodgkin-like cell (*arrow*). Case 2, H&E stain, ×150. (*2c*) & (*2d*) Immunohistochemical study demonstrated that the majority of small- and medium-sized lymphocytes were positive for CD5 (*2c*), whereas immunoblasts were usually positive for CD20 (*2d*). Case 4, counterstained with hematoxylin, ×100. (*2e*) & (*2f*) Immunostaining for light chain determinant of the immunoglobulins demonstrated the polytypic nature of the plasma cells and their precursors ϰ (*2e*) and λ (*2f*). Case 2, counterstained with hematoxylin, ×100. (*2g*) Staining with CNA 42 highlighted the broken follicular dendritic cell meshwork. Case 8, counterstained with hematoxylin, ×25. (*2h*) Staining with a monoclonal antibody cocktail of 2G9 and RBL25 highlighted the large irregularly shaped accumulations of follicular dendritic cells surrounding the small vessels. Case 2, counterstained with hematoxylin, ×50.

study demonstrated the non-neoplastic nature of the present 9 cases.

Little attention has been paid to the differential diagnostic problem between ALPIB and atypical LPDs.[5-7] Among the few reported studies in the Far East including Japan, lymph node lesions in IgG4-related disease appear to be the most important differential diagnostic problem.[8-10] Histologically, a proportion of the lymph node lesions in IgG4-related disease are characterized by prominent lymphoplasmacytic infiltration with various numbers of immunoblasts.[9,10] However, there was no evidence of definite autoimmune disease in IgG4-related disease.[8] Interestingly, elevated serum IgG4 level was detected in 1 (no. 7) of 3 cases examined. However, elevated serum IL-6 level was also recorded in Case 7. Autoimmune disease is a form of IL-6 disorder.[22] It is well known that human IgG4 production is regulated by IL-6.[23]

In middle-aged and elderly patients, EBV-associated reactive lymph node lesions rarely exhibit autoimmune disease-like clinical manifestations.[24] Histologically, lymph node lesions in these patients were similar to those of ALPIB in some aspects. The biopsy specimens contained numerous lymphoid follicles with hyperplastic germinal centers and pronounced arborizing vasculature in the expanded paracortex. The paracortical area contained polymorphic infiltrates with numerous small- and medium-sized lymphocytes and plasma cells, and variable numbers of immunoblasts, epithelioid histiocytes, and occasional eosinophils. However, their autoimmune disease-like clinical manifestations were usually transient. Moreover, there were no EBER^{+} cells in any of the present 9 cases.

Since the early 1990s, atypical or malignant LPDs in patients immunosuppressed with MTX for treatment of RA have been reported.[25-28] A proportion of MTX-induced LPD exhibited atypical lymphoplasmacytic infiltrations showing histological findings similar to those in our cases including the presence of (i) an expanded paracortical area consisting of a mixed cell population, including small- and medium-sized lymphocytes, plasmacytoid lymphocytes, and immunoblasts, and (ii) immunoblasts including Hodgkin-like cells usually showing a B-cell phenotype, and a proportion of these cells were CD30-positive but CD15-negative.[27,28] However, there was no history of MTX therapy in the present 9 cases.

As previously suggested by Blanco *et al*.,[4] the absence of EBV as determined by ISH studies in all our 9 cases indicates that EBV was not related to the lymphoproliferative process in the majority of ALPIB cases. Moreover, the present study suggests that the underlying cause of lymphadenopathy in these ALPIB patients may involve the chronic immune problems caused by AID.

Overall 5-year survival of our series was 83%. The combination of clinical, immunophenotypic, and genotypic findings indicated that the present cases should be regarded as having an essentially benign reactive process. However, 4 of our 9 cases demonstrated lymphadenopathy at the onset of autoimmune disease. We emphasize that ALPIB should be differentiated from various LPDS showing autoimmune disease-like clinical findings.

ACKNOWLEDGEMENTS

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