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Original Article

B-Cell Lymphoma Associated with Sjögren's Syndrome among Japanese Patients : A Clinicopathologic and Immunohistochemical Study of 15 Cases

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To clarify the clinicopathological findings of B-cell lymphoma associated with Sjögren's syndrome (SJS) among Japanese Patients, 15 individuals with this disease were studied. The patients, 14 females and one male, ranged in age from 41 to 73 years with a median age of 56 years. These lymphomas arose not only in the salivary gland (n = 4) but also in other mucosal extranodal sites (n = 5). Histologically, six cases were marginal zone B-cell lymphoma (MZBL) of the mucosa-associated lymphoid tissue (MALT) type, three cases were diffuse large B-cell lymphoma (DLBCL) + MALT type lymphoma, two cases were nodal MZBL and one case each was small lymphocytic lymphoma, Burkitt's lymphoma, $CD10^+$ DLBCL and DLBCL + nodal MZBL. Using *in situ* hybridization, numerous Epstein-Barr $virus^+$ tumor cells were detected only in the case of Burkitt lymphoma. There were no human-herpes $type\ 8^+$ tumor cells in any of the 15 cases. There was no API2-MALT1 fusion transcript in any of the eight cases examined. B-cell lymphoma associated with SJS also frequently affected extranodal organs in patients from Japan as well as from patients in Western countries. The majority of B-cell lymphomas in patients with SJS also appear to be low-grade MZBLs or high-grade lymphomas probably derived from MZBL both in Western countries and in Japan. 〔*J Clin Exp Hematopathol 49(2) : 89-95, 2009*〕

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INTRODUCTION

Sjögren's syndrome (SJS) is an autoimmune disease of the exocrine gland, involving in particular the salivary glands and lacrimal glands. It may occur alone (primary SJS), or in association with a variety of connective tissue diseases and autoimmune diseases (secondary SJS).[1] An association with B-cell non-Hodgkin's lymphoma (NHL) appears to be one of the major complications in the course of SJS patients.[2-4] The risk of developing NHL, which is equivalent in both primary and secondary SJS, was estimated to be 6.5 − 44 fold greater than that observed in comparable normal populations.[2-4] NHL in SJS patients preferentially involved the salivary gland and other mucosa-associated lymphoid tissues (MALT) as well as the lymph node and bone marrow.[2-8]

In Western countries, the clinicopathological and immunohistochemical features of B-cell NHL associated with SJS have been well discussed in the literature.[5-7] The majority of B-NHL in patients with SJS have low-grade MALT lymphomas or high-grade lymphomas probably derived from margin-

al zone B-cell lymphoma (MZBL) in Western countries. However, little is known about the clinicopathological findings of B-cell NHL associated with SJS among Japanese patients.[8] We conducted clinicopathologic and immunohistochemical analyses in 15 cases of B-cell NHL associated with SJS in the Northern Kanto district, which is located in the central area of Japan, outside the area endemic for human T-cell leukemia virus (HTLV-1).

MATERIALS AND METHODS

Fifteen cases were collected from a series treated by one of the authors (M.K.) between 1987 and 2007. Medical records of these 15 cases were extensively reviewed. Nine cases (Nos. 2, 4, 5, 7-11 and 15) have been reported previously.[9-12]

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

A basic immunohistochemical panel including B [L26 (CD20 ; Dako A/S, Glostrup, Denmark)] and T cell markers [PS-1 (CD3 ; MBL, Nagoya, Japan), UCHL-1 (CD45RO ; Dako)] had been performed in all cases. When additional slides and/or paraffin blocks were available, immunohistochemical analysis was expanded to include antibodies against human immunoglobulin light chain (κ and λ) (Novocastra, Newcastle, UK), 4C7 (CD5 ; Novocastra), 56C6 (CD10 ; Novocastra), 1B12 (CD23 ; Novocastra), DFT-1 (CD43 ; Dako), 124 (bcl-2 ; Dako), 151 (bcl-10 ; Dako), SP4 (Cyclin D1 ; Nichirei Co., Tokyo, Japan), MIB-1 (K-67 ; Dako), JC12 [forkhead box protein-1 (FOXP1) ; Abcam plc, Cambridge, UK] and E137B1 [human herpes virus type-8 (HHV-8) ; Novocastra]. Immunohistochemical studies were performed using the antigen retrieval method on avidin-biotin-peroxidase method or Ventana automated (BenchMark^{TM}) stainer according to the manufacturer's instructions.

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 also using a Ventana automated (BenchMark^{TM}) stainer.

In eight cases (Nos. 1, 2, 5-8, 11 and 16), the API2-MALT1 fusion transcript was examined using formalin-fixed and paraffin-embedded tissue according to the method we recently described.[13]

RESULTS

Clinical presentation

The main clinical findings are shown in Table 1. All 15 patients were diagnosed having SJS based on the revised Japanese criteria for SJS (1999).[14] The patients, 14 females and one male, ranged in age from 41 to 73 years with a median age of 56 years. SJS was primary in 13 cases and secondary to rheumatoid arthritis in two cases (Nos. 6 and 11). One case each was associated with Hashimoto's thyroiditis (No. 4) and primary biliary cirrhosis (No. 10). In 13 patients, the diagnosis of SJS was established two months to 20 years before the diagnosis of B-cell NHL. In two patients (Nos. 4 and 8) SJS and NHL were diagnosed simultaneously. However, these two patients had a history of sicca symptoms for several years before NHL.

Five patients received an immunosuppressive therapy before the onset of NHL : prednisone = 2 (Nos. 1 and 6), low-dose methotrexate = 2 (Nos. 7 and 11) and prednisone + endoxane = 1 (No. 12).

Mucosal localization was demonstrated in the nine cases (60%), including the parotid gland = 4 (Nos. 2, 5, 8 and 9), thymus = 2 (Nos. 3 and 6), lung = 1 (No. 10), rectum = 1 (No. 11), and vocal cord = 1 (No. 13). The lymphoma was exclusively nodal in only three cases (Nos. 4, 7 and 15). One case each showed involvement of peripheral blood (No. 1), retroperitoneum (No. 12) and systemic organ (No. 14).

Autoantibodies associated with SJS were detectable in the majority of patients : anti-SS-A and/or anti-SS-B antibodies (13 of 15 cases). There was no M-protein in any of the 15 cases. Antibodies to human immunodeficiency virus (HIV) and hepatitis C virus (HCV) were not detected in patients' sera.

Therapy and follow up

Five patients (Nos. 8, and 12-15) were treated with radiotherapy and/or combination chemotherapy regimens, usually consisting of CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisolone) or Rituximab + CHOP, five patients (Nos. 1-3, 5 and 9) were treated with radiotherapy alone, and one (No. 4) was treated with prednisolone. Four patients (Nos. 6, 7, 10 and 11) underwent total excision of the tumor without radiation and/or chemotherapy.

Follow-up information was available in all 15 cases and durations ranged from four to 123 mon (mean, 67 mon ; median 72 mon). Relapse was recorded in three cases (Nos. 8, 9 and 12). Local relapse, including recurrent disease in regional lymph nodes occurred in two cases (Nos. 9 and 12). Distant relapse was reported in one case (No. 8 ; lung). One case (No. 12) died of disease 24 mon after the onset of NHL. One case (No. 14) died without disease 24 mon after the onset of NHL. One case (No. 4) received prednisolone was alive with disease (partial remission) 108 mon after the onset of disease.

Table 1. Summary of clinical findings of 15 cases

Case No.	Age/ gender	Duration SS (mon)	Site of disease	Systemic symptoms	Imm. Sup	Anti-SS-A/ SS-B	Autoimmune disease	M-protein	HCV	HIV	Therapy	Follow up (mon)	Histology
1	41/ F	12	Bil. parotid gland, peripheral blood	−	P	+/−	−	−	−	−	RT	41A (+)	CLL/ SLL
2	48/F	60	Rt. parotid gland	−	−	+/−	−	−	−	NE	RT	132A (−)	MALT
3	49/F	12	Thymus, lung, mediastinal LN	−	−	+/+	−	−	−	−	RT	4A (−)	MALT
4	50/M	0	Systemic LN	+	−	+/+	HT	−	−	NE	P	108A (+)	NMZB
5	53/F	24	Lt. parotid gland + LN	−	−	−/−	−	−	−	−	RT	123A (−)	MALT + DLBCL
6	54/F	2	Thymus	−	P	+/+	RA	−	−	−	Resection	4A (−)	MALT
7	56/F	108	Rt. neck LN	−	MTX	+/−	−	−	−	NE	Resection	64A (−)	NMZB
8	56/F	0	Rt. parotid gland	−	−	+/−	−	−	−	NE	CHOP	82, recurrence lung, A (+)	MALT + DLBCL
9	64/F	240	Rt. parotid gland + neck LN	−	−	+/+	−	−	NE	NE	RT	4, neck LN recurrence, 94, stomach, recurrence 97A (+)	MALT
10	66/F	192	Lt. lung	−	−	+/+	PBC	−	−	−	Resection	84A (−)	MALT + DLBCL
11	67/F	2	Rectum	−	MTX	+/−	RA	−	NE	NE	Resection	34A (−)	MALT
12	68/F	168	Retroperitoneum	−	P + E	+/−	−	−	−	NE	Resection + THP-COP	6, abdominal LN, recurrence, 24D (+)	DLBCL
13	70/F	5	Bil. vocal cord	−	−	+/+	−	−	−	−	RT + THP-COP	95A (−)	MALT
14	71/F	72	Systemic LN, salivary gland, stomach	+	−	−/−	−	−	−	−	CHOP	24D (−)	Burkitt
15	73/F	24	Rt. inguinal LN	−	−	+/−	−	−	−	NE	R+THP-COP	23A (−)	MALT + DLBCL

Abbreviations : Duration SS, period between onset of Sjögren's syndrome and onset of lymphoma ; Imm. Sup, Immunosuppressive therapy for Sjögren's syndrome ; NE, not examined ; HCV, Hepatitis C virus antibody ; HIV, human immunodeficiency virus type-1 antibody ; Bil., bilateral ; Lt., left ; Rt., right ; LN, lymph node ; P, prednisone ; MTX, methotrexate ; E, endoxan ; HT, Hashimoto's thyroiditis ; RA, rheumatoid arthritis ; PBC, primary biliary cirrhosis ; RT, radiation therapy ; CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone ; THP-COP, pirarubuicin, cyclophosphamide, vincristine, prednisone ; R, Rituximab. A, alive ; D, died ; (+), with disease ; (−), without disease ; CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma ; MALT, extranodal marginal zone B-cell lymphoma of mucosa- associated lymphoid tissue type ; NMZB, nodal marginal zone B-cell lymphoma ; DLBCL, diffuse large B-cell lymphoma.

Histological, immunohistochemical, EBV and genotypic findings

Histological findings are shown in Table 2. Patients could be subdivided into seven types based on the clinical, morphological and immunohistological features, as follows :[15] (i) MZBL of MALT type (n = 6), (ii) diffuse large B-cell lymphoma (DLBCL) + MALT type lymphoma (n = 3), (iii) nodal MZBL (n = 2), (iv) small lymphocytic lymphoma (SLL) (n = 1), (v) CD10 + DLBCL (n = 1), (vi) Burkitt lymphoma (n = 1) and (vii) DLBCL + nodal MZBL (n = 1). The histological and immunohistochemical findings of each variant have been well described previously.

The histological pattern on infiltration of MALT type lymphoma or nodal MZBL was peri- or interfollicular with occasional follicular colonization (Fig. 1a). Centrocyte-like (CCL) cells were intermediate in size and usually had round or indented nuclei and moderate to abundant cytoplasm. The CCL cell lymphoepithelial lesion were observed in each case of MALT lymphoma (Fig. 1b). Occasionally large cells resembling centroblasts or immunoblasts were also identified. Plasmacytoid differentiation of tumor cells was frequent. One case (No. 4) showed prominent plasma cell differentiation.

As described by Berger *et al.*,[16] DLBCL + MALT type lymphoma or DLBCL + nodal MZBL contained more than 50% of transformed cells or a sheet of transformed cells in addition to characteristic histological findings of MALT type lymphoma or nodal MZBL (Figs. 1c and 1d).[15]

Immunohistochemical studies demonstrated that MALT type lymphoma, nodal MZBL, MALT type lymphoma + DLBCL and NMZBL + DLBCL were $CD5^-$, $CD10^-$, $CD20^+$,

Table 2. Summary of pathological findings of 15 cases

Case No	Histology	cIg	CD5	CD10	CD20	CD23	CD43	Bcl-2	Cyclin D1	Bcl-10	p53	FOXP1	HHV-8	EBER	API2-MALT1 transcript
1	CLL/SLL	λ	+	−	+	+	NE	NE	−	NE	+/−	−	−	+/−	−
2	MALT	NE	−	−	+	−	−	+	−	−	−	−	−	−	−
3	MALT	−	−	−	+	−	+	+	−	−	+/−	−	−	+/−	NE
4	NMZB	κ	−	−	+	−	−	−	−	−	−	NE	−	−	NE
5	MALT	NE	−	−	+	−	+	−	−	−	+/−	−	−	−	−
	DLBCL	NE	−	−	+	−	+	−	−	−	+/−	−	−	−	−
6	MALT	−	−	−	+	−	−	+	−	−	+/−	−	−	−	−
7	NMZB	−	−	−	+	−	+	−	−	−	+/−	−	−	−	−
8	MALT	−	−	−	+	−	NE	+	−	−	−	−	−	−	−
	DLBCL	−	−	−	+	−	NE	+	−	−	−	−	−	−	−
9	MALT	κ	−	−	+	−	NE	+	−	NE	−	NE	−	−	NE
10	MALT	κ	−	−	+	−	−	+	−	−	−	NE	−	−	NE
	DLBCL	κ	−	−	+	−	−	+	−	−	−	NE	−	−	NE
11	MALT	−	−	−	+	−	+	+	−	−	−	NE	−	−	−
12	DLBCL	−	−	+	+	NE	NE	+	NE	NE	+	−	−	−	NE
13	MALT	−	−	−	+	−	−	+	−	−	NE	NE	−	−	NE
14	Burkitt	−	−	+	+	NE	NE	−	NE	NE	+	−	−	+	NE
15	NMZB	−	−	−	+	−	+	+	−	−	−	+	−	−	−
	DLBCL	−	−	−	+	−	+	+	−	−	−	+	−	−	−

Abbreviations : cIg, cytoplasmic immunoglobulin ; FOXP1, forkhead box protein-1 ; HHV-8, human herpes virus type-8 ; EBER, Epstein-Barr virus-encoded small RNA ; CLL/ SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma ; MALT, extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue type ; NMZB, nodal marginal zone B-cell lymphoma ; DLBCL, diffuse large B-cell lymphoma ; NE, not examined.
−, negative ; +/−, a few scattered positive tumor cells ; +, majority of the tumor cells positive.

CD23$^-$, CD43$^{+/-}$, Bcl-2$^{+/-}$, Bcl-10$^-$, cyclin D1$^-$ and intracytoplasmic immunoglobulin$^{+/-}$.[15,17,18] One case of SLL (No. 1) was CD5$^+$, CD10$^-$, CD23$^+$, cyclinD1$^-$ and intracytoplasmic λ light chain$^+$.[15] One case of Burkitt lymphoma (No. 14) was CD5$^-$, CD10$^+$, CD20$^+$ and bcl-2$^-$.[15] More than 95% of the tumor cells of the Burkitt lymphoma were MIB-1$^+$.[15]

Numerous FOXP1$^+$ medium- to large-tumor cells (low-grade MZBL and DLBCL) were present in one case of DLBCL + nodal MZBL in 9 cases examined (No. 15) (Fig. 1e).

There were no HHV-8$^+$ tumor cells in any of the 15 cases.

Numerous EBER$^+$ tumor cells were detected in one case of Burkitt lymphoma and a few EBER$^+$ tumor cells were detected in two other cases (SLL = 1, MALT type lymphoma = 1).

There was no API2-MALT1 fusion transcript detected in any of the 8 cases examined.

DISCUSSION

In Japan, Masaki *et al*. reported that NHL associated with SJS affected extranodal organs slightly more often than lymph node.[8] However, in Western countries, the majority of the NHL arose in extranodal MALT tissue and only a few patients showed lymph node involvement.[5,6] Among extranodal organs, the salivary gland is most frequently affected.[3,4,6] The present study also showed that 80% (12/15) of B-NHL affected extranodal sites. However, as Royer *et al*. reported,[6] extranodal B-NHL arose not only in the salivary gland (n = 4) but also in other mucosal extranodal sites (thymus = 2, lung = 1, rectum = 1, vocal cord = 1).

Histologically, it has been said that in Western countries, the majority of NHL associated with SJS was MALT type lymphoma and DLBCL + MALT type lymphoma, whereas nodal MZBL comprised only a minority of B-NHL.[5-7] In this study, 9 of 15 (60%) cases were MALT type lymphoma and DLBCL + MALT type lymphoma, whereas only three cases were nodal MZBL or DLBCL + nodal MZBL. This result confirmed the previous observation made in Western countries. Smedby *et al*. described that the risk of DLBCL was also increased 9-fold in SJS.[4] Royer indicated that DLBCL associated with SJS was probably a histological transformation of underlying low-grade MZBL.[6] We found 5 cases of DLBCL among 15 B-NHLs in our series. Four cases were DLBCL + MZBL, whereas only one case of DLBCL showed a germinal center cell origin. It has been suggested that there was an increased frequency of DLBCL in patients with systemic rheumatic disease including rheumatoid arthritis and systemic lupus erythematosus.[10,19,20] Interestingly, all of 10 cases DLBCL associated with systemic rheumatic disease such as rheumatoid arthritis, and dermatomyositis showed a non-germinal center cell phenotype.[10]

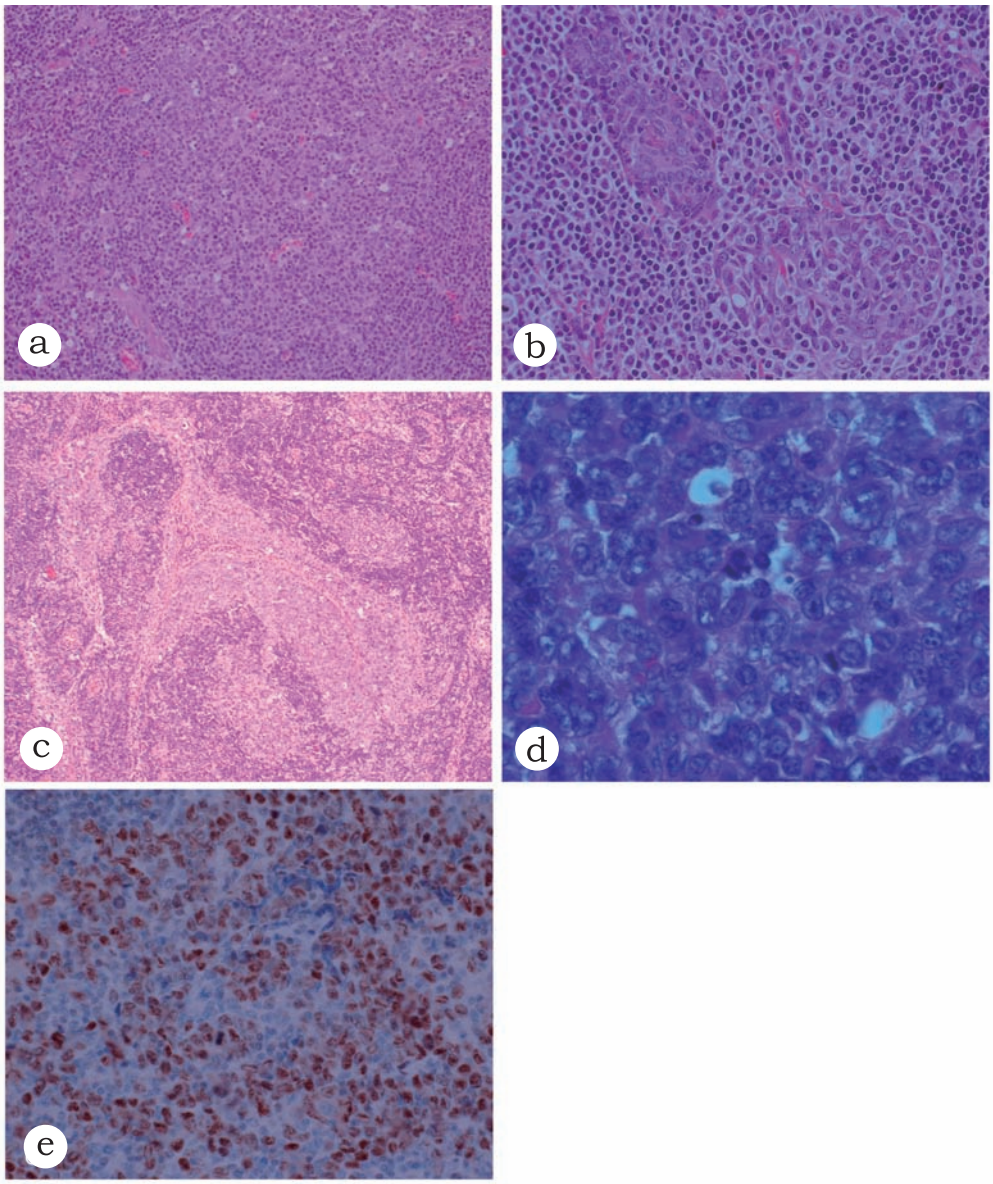

Fig. 1. Histological and immunohistopathological findings of B-cell lymphoma. **(*1a*)** Mucosa-associated lymphoid tissue (MALT) lymphoma. On medium power field, a colonized lymphoid follicle with indistinct mantle zone was surrounded by neoplastic cells. Hematoxylin and eosin (HE) stain, × 50 (Case 6). **(*1b*)** MALT lymphoma. On high power field, medium-sized lymphocytes with round or indented nuclei and moderate to abundant cytoplasm (centrocyte-like cells) invaded the salivary gland duct. HE stain, × 100 (Case 9). **(*1c*)** Diffuse large B-cell lymphoma (DLBCL) + nodal marginal zone B-cell lymphoma (MZBL). On low-power field, the lymphoid infiltrate showed a mainly sinusoidal pattern with interfollicular extension. HE stain, × 25 (Case 15). **(*1d*)** DLBCL + nodal MZBL. On high power field, the lesion was composed of scattered monocytoid B-cells showing monocytoid appearance with reniform nuclei and abundant clear cytoplasm and numerous large lymphoma cells. HE stain, × 250 (Case 15). **(*1e*)** DLBCL + nodal MZBL. The medium- to large-tumor cells showing strong nuclear expression for FPOX1. × 100 (Case 15).

In patients with SJS, it has been reported that the number of CD5/23$^+$ B-cells were increased in peripheral blood.[21] However, CD5/23$^+$ tumor cells were detected in only one of SLL in our 15 cases. As Smedby described, an association SLL and SJS appears to be a very rare event.[5]

The present series included a case of Burkitt lymphoma. However, the association of Burkitt lymphoma and SJS is probably an incidental finding since the oncogenic events underlying the development of Burkitt lymphoma are very different from MALT type lymphomas.[15] However, c-myc translocation could not be examined in this case.

Previous studies in Western countries indicated that B-NHL complicating SJS are not associated with viruses, including HCV, EBV, HHV-8 or HTLV-1.[6,7] In this series, none of the patients demonstrated HCV infection upon serological test. On ISH, numerous EBER$^+$ tumor cells were found in only one case of Burkitt lymphoma. Immunohistochemical studies demonstrated that there were no HHV-8$^+$ tumor cells in any of our 15 cases. A serological finding of HTLV-1 was obtained in only 2 cases. However, there was no serologic data identifying evidence of HTLV-1 infection in serum specimens from these 2 cases (data not shown). The present 15 cases did not appear to be associated with HTLV-1, because the area studies were the Northern Kanto district, which is outside of the area that is endemic for human HTLV-1. The present findings confirmed previous observations.[6,7]

Recent studies demonstrated that t(11;18)/*API2-MALT1*, t(1;14)/*IGH-BCL10*, t(14;18)/*IGH-MALT1* and t(3;14)/ *IGH-FOXP1* occur at considerably variable incidences of MZBL at different sites.[13,22-29] Using reverse transcriptase-polymerase reaction, Wöhrer *et al*. found API2-MALT1 fusion transcript in six (17%) of 36 cases of MALT type lymphoma associated with SJS.[28] However, there was no API2-MALT1 fusion transcript in any of the eight cases examined in our series. Immunohistochemical studies demonstrated that there is moderate nuclear BCL-10 expression in cases having t(11;18), whereas there is strong nuclear BCL-10 expression in cases having t(1;14).[22,24] Moreover, t(14;18)(q32;q21)/*IGH-MALT1* is characterized by strong cytoplasmic MALT1 and BCL-10 expression.[23] However, there was neither nuclear nor cytoplasmic expression of BCL-10 in any of the 12 patients examined.

Immunohistochemical studies demonstrated numerous FOXP-1$^+$ tumor cells in only one of the present 15 cases. Sagaert *et al*. suggested that FOXP1 expression in MALT type lymphomas detected by immunohistochemistry is associated with a higher risk of transformation and poor outcome.[28] FOXP1 expression in both low-grade MZBL and DLBCL suggested that low grade MZBL transformed into DLBCL in this case.

However, no conclusions can be drawn by the immunohistoichemical study with regards to the occurrence of t(11;18)/*API2-MALT1*, t(1;14)/*IGH-BCL10*, t(14;18)/*IGH-MALT1* and t(3;14)/ *IGH-FOXP1* in MZBL associated with SJS. To clarify this issue, cytogenetic and molecular studies are needed.

Two of our patients had been treated with low-dose methotrexate before MZBL was detected. However, it is unlikely that the methotrexate administration played any role in the development of the lymphoma in these two cases because the disease did not display any of the characteristic of methotrexate-associated lymphomas.[30]

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