

Angioimmunoblastic T-cell lymphoma: A relatively common type of T-cell lymphoma in Sjögren's syndrome

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ABSTRACT

An increased risk of developing lymphoma has been indicated in Sjögren's syndrome (SS), and the lymphomas in SS are usually B-cell type in origin. Interestingly, despite the rather low frequency of T-cell lymphoma in SS, angioimmunoblastic T-cell lymphoma (AILD) constitute the majority of T-cell lymphomas associated with SS. To the best of our knowledge, including our case, at least 11 out of 23 (48%) cases of T-cell lymphoma reported in association with SS, were AILD. The fact that the development of B-cell lymphoma in SS is much more frequent than that of T-cell lymphoma, might be explained by differences in the situation between B and T cells, although the exact mechanism still remains uncertain.

Introduction

Sjögren's syndrome (SS) is well known to constitute a risk factor of lymphomagenesis, and the majority of lymphomas developed in patients with SS have been demonstrated to be B-cell type of origin (1). Although relatively rare, several types of T-cell lymphoma associated with SS have been reported in the literature (2-21). Among them, angioimmunoblastic T-cell lymphoma is a relatively common type of T-cell lymphoma in Sjögren's syndrome.

Case report

A 60-year-old Japanese woman visited us with subfever, arthralgia, and muscle pain of the upper arms. She also complained of a three-month history of dry eyes and mouth. On physical examination, systemic dry skin and generalized superficial lymphadenopathy were recognized. Parotid glands and other salivary glands were neither swollen nor painful. Laboratory tests revealed hemolytic anemia (8.1 g/dl) with a positive direct Coombs' test, serum hypergammaglobulinemia (IgG 4615 mg/dl), which was ascertained to be polyclonal by immunoelectrophoresis, low levels of serum C3 (25mg/dl) and C4 (10 mg/dl), positive antinuclear antibodies at a titer of 1:320 with a speckled pattern, and positive anti-SSB antibodies. Anti-SSA antibodies, however, were negative. In addition, she had keratocon-

junctivitis sicca with positive results of both the Schirmer's test and Rose-Bengal staining test.

She was then diagnosed as having Sjögren's syndrome. Systemic lymphadenopathy was demonstrated by ultrasonography, computed tomography, and 67Ga-scintigraphy. Hepatosplenomegaly was not observed. Histopathology of the biopsy specimen from the enlarged lymph nodes in the left groin revealed, in addition to an effacement of normal lymph node architecture, extreme proliferation of arborizing high endothelial venules, and infiltration by medium to large-sized atypical lymphocytes admixed with plasma cells and eosinophils (Figs. 1a, b, c). Characteristic clustered or sheet-like proliferations of clear cells were also recognized (Fig. 1d). The atypical cells were stained positive for T-cell markers such as CD3 and CD45RO, and most of them were positive for CD4. Southern blot analysis of the lymph node specimen was performed, revealing a clonal band of rearrangement of the T-cell receptor (TCR) β-chain gene. Immunoglobulin (Ig) gene rearrangement was not detected. According to the clinical features and histopathological appearances, a diagnosis of angioimmunoblastic T-cell lymphoma was established. Systemic chemotherapy with cyclophosphamide, doxorubicin, vincristine, and prednisolone (CHOP) was immediately initiated. After finishing 6 courses of CHOP therapy, complete remission was accomplished, with her symptoms of SS diminished.

Discussion

Sjögren's syndrome (SS) is an autoimmune disease characterized by dry eyes and mouth, which result from the destruction of salivary and lacrimal glands caused by lymphocytic infiltration (1). An increased risk of developing lymphoma has been indicated in SS, and the lymphomas in SS are usually B-cell type in origin (22-24). Interestingly, despite the rather low frequency of T-cell lymphoma in SS, angioimmunoblastic T-cell lymphoma (AILD) constitutes the majority of T-cell lymphomas associated with SS (3, 13, 16-21). To the best of our knowledge, includ-

ing our case, at least 11 out of 23 (48%) cases of T-cell lymphoma reported in association with SS, were AILD (2-21). AILD, originally described as angioimmunoblastic lymphadenopathy with dysproteinemia, is a rare, acute, and systemic type of peripheral T-cell lymphoma characterized clinically by high fever, hemolytic anemia, hypergamma-globulinemia, generalized lymphadenopathy, skin rash, and hepatosplenomegaly, and histologically by an effacement of lymph node architecture, a proliferation of arborizing high endothelial venules, and an infiltration by atypical lymphoid cells admixed with plasma cells, eosinophils, and histiocytes (25). Moreover, characteristic clear cells could occasionally be seen as clusters or sheets. Atypical neoplastic cells have been demonstrated to possess a mature helper T-cell phenotype, and frequent detection of TCR gene rearrangement indicates a clonal feature as lymphoma, although there was no detectable clonality in some cases (26). Interestingly, there are reports demonstrating the frequent coexistence of TCR and Ig gene rearrangements in the cases of AILD, and it has been proposed that these apparently paradoxical dual gene rearrangements could be ascribed to the coexistence of an occult B-cell lymphoproliferative disorder (27, 28).

Although the exact mechanisms remain uncertain, it has been speculated that continual antigenic stimulation of B cells within salivary or lacrimal glands induce multiple clonal expansions in those tissues, which at first are reactive and benign changes, but might undergo karyotic alteration to become malignant B-cell lymphoma (2, 6, 8). Since the development of T-cell lymphoma in SS is rather rare in contrast to that of B-cell lymphoma, the relationship between SS and the lymphoproliferative status of T cells in SS has been less discussed than that of B cells. However, clonal expansions of not only B cells, but also T cells, which might be induced by continuous antigenic stimulation, have been demonstrated in the target tissues in SS (7). From those expansions might emerge neoplastic B or T-cell clones, which at first would be still

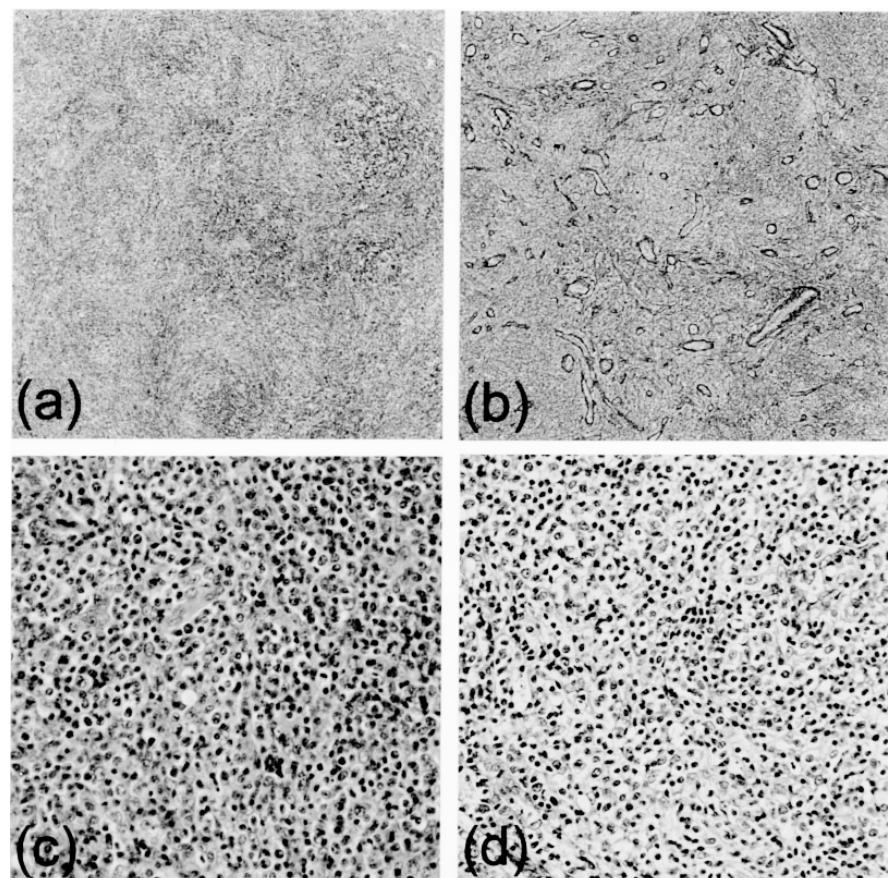


Fig. 1. Biopsy of the left inguinal lymph nodes (a, c, d: H & E stain; b: silver impregnation stain). (a) Effacement of normal lymph node architecture. (b) Extreme proliferation of arborizing high endothelial venules. (c) Infiltration by medium to large-sized atypical lymphocytes, admixed with plasma cells and eosinophils. (d) Clustered or sheet-like proliferation of clear cells. (original magnification: a, b x10; c, d x 100).

reactive and under control of the endogenous immune system, but undergo additional karyotic changes and finally obtain the nature of malignant lymphoma (8). The fact that the development of B-cell lymphoma in SS is much more frequent than that of T-cell lymphoma, might be explained by the differences of the situation between B and T cells, although the exact mechanism still remains uncertain. As one fundamental difference between B and T cells, B cells undergo somatic hypermutation to increase the variability of the B-cell receptor, which raises the possibility of malignant changes (15). The prolonged life span of B cells with an increased functional expression of the bcl-2 gene, which results from the actions by T cells, may also be another significant difference between them, supporting the concept that B cells can more easily acquire malignant changes than T cells and leading to the fact that

the great majority of lymphomas in SS are B-cell type.

How the differences of the environment between B and T cells contribute to higher occurrences of B-cell lymphoma in SS than T-cell lymphoma is still under speculation, but at least we can present the fact that AILD is a relatively common type of T-cell lymphoma in SS.

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