Letter to the Editor

A case of adult T-cell leukemia presenting primary Sjögren's syndrome like symptoms

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Running title: **ATL representing SS like symptoms**

Sjögren's syndrome (SS) is an autoimmune disorder characterized by xerostomia, xerophthalmia, the presence of autoantibodies and extraglandular manifestations **(1)**. Exclusion criteria for SS involve various conditions, including hepatitis C infection or graft versus host disease (GVHD) **(2, 3)**, because patients with these conditions show sicca symptoms resembling those of SS. Although human T-cell leukemia virus type 1 (HTLV-1) is not included in the exclusion criteria, HTLV-1 is thought of as a causative agent for SS. Although patients with HTLV-1-associated myelopathy (HAM) often have SS **(4, 5)**, there is no report of adult T-cell leukemia (ATL) cells infiltrating salivary glands, causing patients to show sicca symptoms. Here, we report a case of ATL presenting with sicca symptoms.

A 53-year-old male who had xerostomia and xerophthalmia visited our hospital with complaints of swelling of bilateral parotid glands on November 7, 2008. Physical examination showed mild submandibular lymphadenopathy without anemia. Blood tests showed a total leukocyte count of 6,300/mm^3, with a normal

hemoglobin level of 14.4 g/dl and a platelet count of 14.7 x 10^4/mm^3; however, 24% of leukocytes were abnormal lymphocytes. A peripheral blood smear revealed numerous lymphocytes, some of which showed irregular, lobulated nuclei, presenting a flower shape. Other laboratory data showed slightly elevated lactate dehydrogenase (507 IU/l; normal: 119-229), normal C-reactive protein (0.02 mg/dl; normal: less than 0.17), normal IgG (1220 mg/dl; normal: 870-1700), normal calcium (9.3 mg/dl; normal: 9.0-10.6), elevated soluble interleukin 2 receptor (sIL2R) (6,080 U/ml, normal: 124-466) and elevated parathyroid hormone-related protein (4.9 pmol/l, normal: less than 1.1). Anti-hepatitis C virus antibody, rheumatoid factor, anti-nuclear antibody (ANA), anti-SS-A antibody and anti-SS-B antibody were negative. Antibody for HTLV-1 was positive, and monoclonal integration of HTLV-1 proviral DNA in peripheral blood mononuclear cells was verified by Southern blot analysis. Schirmer's test was 6 mm/5 minutes (less than 5 mm = positive), and Saxon's test was positive (0.72 g/2 minutes; less than 2g = positive). Chest X-rays and abdominal CT scans were all normal. The patient was diagnosed with adult T-cell leukemia (ATL) and classified as having the chronic type of ATL. To confirm SS as an auxiliary diagnosis, magnetic resonance imaging (MRI) of the parotid gland and

a labial salivary gland (LSG) biopsy were carried out. The MRI showed diffuse enlargement of the parotid gland, and ultrasound images **(Fig.1)** showed aggregation of hypoechoic nodules in enlarged parotid glands with irregular septal structure. The LSG biopsy showed massive infiltrating mononuclear cells (MNCs) with cellular atypia. Immunohistochemistry showed CD4-positive T-lymphocytes-dominant infiltration **(Fig. 2A-D)**. Furthermore, HTLV-I-related proteins were shown in LSG of this patient, although not all of these proteins were observed in LSG from a patient with HTLV-I-seronegative SS **(Fig. 2E-H)**. This was considered evidence of ATL cell infiltration of the labial salivary gland. Although the classification criteria of SS **(2)** according to the American-European Consensus Group were not fulfilled, decreased salivary secretion and massive numbers of MNCs in the LSG resembled SS. Definitely, we should consider other conditions including GVHD, chronic viral infection and usage of anticholinergic agents as was suggested in the exclusion criteria they published.

In 2009, chronic type ATL was converted to acute crisis status with elevation of serum calcium (12.3 mg/dl) and sIL2R (11,111 U/ml). After remission induction chemotherapy followed by unrelated cord blood

transplantation with a reduced-intensity conditioning regimen, the patient was treated in the outpatient clinic in the Department of Hematology.

Although HTLV-I infection causes both HAM and ATL, a relationship with SS is usually observed in HAM. In the case of HAM, viral regulatory protein Tax encoded by pX, which is a unique region located between env and the 3'LTR in the HTLV-I provirus, has the potential to immortalize CD4+ T-cells and produce pro-inflammatory cytokines **(6)**. Furthermore, HTLV-I-specific cytotoxic T-cells whose purpose is to inhibit HTLV-I-infected CD4+ T-cells that are accumulated in the thoracic spinal cord accelerate cytokine production. In contrast, an oncogenic viral HTLV-I bZIP factor (HBZ) that has leukemogenesis was shown to be expressed in ATL cells **(7)**. Different from the tax gene, HBZ is shown in all ATL cases, suggesting that these differences might explain why SS is dominantly found in patients with HAM.

Regarding non-Hodgkin lymphoma (NHL), mucosa-associated lymphoid tissue is the most popular subtype found in SS **(8)**. With regard to leukemogenesis in SS, diffuse large B-cell lymphomas (DLBCLs) and marginal zone lymphomas are also detected. It is likely that polyclonal B cell expansion in the early disease phase of SS changes to oligoclonal or monoclonal proliferation,

leading to B-cell-type lymphomas. The association of germinal center formation along with the overexpression of chemokines such as CXCL13 is known as NHL in SS **(9)**. Based on these observations, ATL is not considered to be lymphoma that is allied to SS. Meanwhile, the lack of serological abnormality in our patient could be one of the differences between ATL resembling SS and SS complicated with HAM. HTLV-I-associated SS showed equal frequency with regard to the appearance of ANA and anti-SS-A/SS-B antibodies in our previous study **(5)**, suggesting that HAM and ATL might show distinct features with respect to frequency of comorbid SS.

In summary, this is the first case report of ATL mimicking SS, showing sicca symptoms. When the relationship between HTLV-I and SS is considered, the existence of ATL tends to be neglected. The LSG biopsy with immunohistochemistry was instrumental in determining whether the infiltration of MNCs in LSG is derived from ATL or not. Collecting cases of ATL presenting with sicca symptoms is required to prove the relationship between ATL and sicca symptoms.

Disclosure statement: The authors have declared no conflicts of interest.

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Figure legend

Figure 1

Ultrasonic examination showed bilateral swelling of parotid glands with aggregated 5-10 mm sized hypoechoic nodules. Parotid glands showed irregular septal structure, suggesting suspected malignant lymphoma.

Figure 2   Immunostaining of cell surface markers and HTLV-I-related molecules in the LSG

Immunohistochemistry for formalin-fixed, paraffin-embedded sections from the LSG of this patient. The primary antibodies used for immunohistochemistry were **A:**CD3, **B:**CD4, **C:**CD8, **D:**CD20. LSG of this patient was stained with **E:** p19, p28, GAG and **F:** mouse IgG1 as a negative control. Lower left **(G)** showed staining of HTLV-I-related proteins for another patient with HTLV-I-seronegative primary Sjögren's syndrome. Lower right **(H)** showed staining of HTLV-I-related proteins (p19, p28, GAG) for lymph node from another patient with adult T cell leukemia as a positive control Hematoxylin was used as a counterstain. (Original magnification; x200)
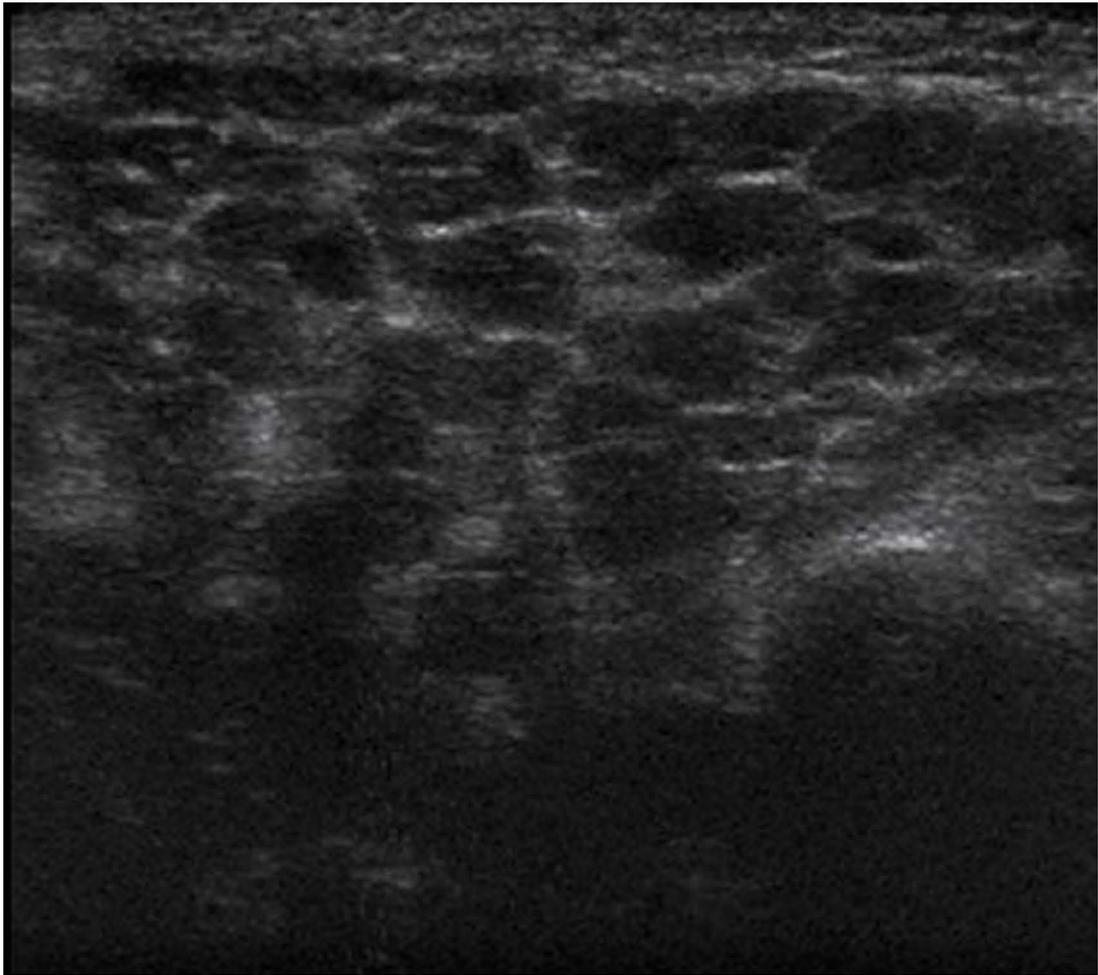
Figure 1

Figure 2