Case Report

Sjögren's Syndrome Associated T Cell Large Granular Lymphocyte Leukemia: A Possible Common Etiopathogenesis

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ABSTRACT. Two patients with primary Sjögren's syndrome and T cell large granular lymphocyte (LGL) leukemia are described. One patient had evidence of T cell LGL salivary gland infiltration, suggesting a possible common etiopathogenesis for these 2 conditions. (J Rheumatol 2001; 28:2551–2)

Key Indexing Terms:
SJÖGREN'S SYNDROME LARGE GRANULAR LYMPHOCYTOSIS LEUKEMIA

Sjögren's syndrome (SS) is an autoimmune exocrinopathy in which CD4+ α/ß-Th1 lymphocytes play an important pathogenic role[1,2]. The hematologic features of SS include anemia, thrombocytopenia, and leukopenia[3].

Large granular lymphocytosis (LGL) with neutropenia is considered a rare chronic leukemia of either natural killer cell (CD3-) or T cell (CD3+) origin, characterized by various autoimmune phenomena[4,6] and a remarkable association with arthropathy, especially with Felty's syndrome[7,8].

We describe 2 patients who had been diagnosed with primary SS and LGL leukemia.

Case 1. A 65-year-old Caucasian woman with evidence of arthritis of the proximal interphalangeal (PIP) joints, keratoconjunctivitis sicca, fatigue, and weight loss was referred to our clinic. Her initial blood test results were as follows: erythrocyte sedimentation rate 53 mm/h; hemoglobin 13.7 g/dl; white blood cell count (WBC) 5700/mm^3, with 39% (2300/mm^3) neutrophils, 51% (2900/mm^3) lymphocytes, 2% eosinophils; platelet count 175,000/mm^3. Rheumatoid factor measured 400 IU/ml (negative < 20), and antinuclear antibody was positive (1:320), as was anti-Ro (73 units, negative < 20).

Tests for antibodies to Sm, La, RNP, and double stranded DNA were negative.

She was diagnosed with primary SS and was treated with nonsteroidal antiinflammatory drugs and sulfasalazine, and subsequently, weekly oral methotrexate. Throughout the followup period, blood counts showed neutropenia with relative lymphocytosis. The neutrophil count declined from 2300 (29%) to 1420/mm^3 (20%), with a concomitant increase in absolute lymphocytosis to 4536/mm^3 (72%). The peripheral blood smear was remarkable for the presence of large lymphocytes with abundant cytoplasm containing azurophilic granules. Positive paranuclear staining of the Golgi zone with acid phosphatase established the lymphoid cells as T cells. Bone marrow aspiration and biopsy showed interstitial and paratrabecular infiltration by lymphoid cells. Immunophenotyping of the bone marrow aspirate revealed the following: CD2 54%, CD3 53%, CD4 12%, CD8 47%, CD16 42%, CD56 11%, CD57 45%.

Biopsy of the minor salivary glands showed patchy lymphoid infiltrates invading the ducts as well as the acini, with destruction of some of the glands. Immunohistochemical staining for CD20, CD3, CD45Ro, CD5, CD79A, CD57, and CD68 showed that most of the small lymphoid cells were T cells positive for CD3, CD5, and CD45Ro. Roughly 10% of them also stained positive for CD57 (Leu-7), which is a natural killer cell marker.

Abdominal ultrasound revealed a normal size liver and spleen, and serological tests for Epstein-Barr virus (EBV), cytomegalovirus, hepatitis B and C, human immunodeficiency virus (HIV), and human T cell leukemia/lymphoma virus (HTLV-1) were negative.

On the basis of these findings, the diagnosis was LGL leukemia with SS. Treatment consisted of cyclosporine A, which led to complete remission of the arthritis and improvement of the sicca symptoms, together with a gradual increase in the neutrophil count (up to an absolute count of 2810/mm^3, 47.3%).

Case 2. A 70-year-old woman with a history of Hashimoto's thyroiditis and postmenopausal osteoporosis was referred to our clinic for evaluation of neutropenia, dryness of the eyes

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and mouth, fatigue, and arthritis of the PIP joints of the hands and the wrist joints of both hands. Abdominal ultrasonography revealed moderately enlarged spleen with no evidence of lymphadenopathy.

Laboratory investigations revealed normal sedimentation rate, hemoglobin 13.6 g/dl, WBC 6970/mm^3, with 5% (348) neutrophils, 91% lymphocytes; platelet count was 138,000/mm^3. Rheumatoid factor was 1:320, antinuclear antibody 1:320, antimicrosomal and thyroglobulin antibodies 1:640 each; IgG and IgM anticardiolipin antibodies were slightly elevated. Tests for serum antibodies to dsDNA, Sm, Ro, La, and RNP were all negative, as were tests for hepatitis B surface antigen, hepatitis C RNA, HIV, and HTLV-1. Peripheral blood smear showed an increased number of large granular lymphocytes. Evaluation of the B and T lymphocyte subpopulations revealed an increase in the B cell subpopulation along with an abnormal helper/suppressor ratio of T cells due to elevation in the CD8+ cell count. Peripheral blood phenotype analysis of the T cells was as follows: CD3 92%, CD8 84%, CD16 69%, CD56 33%, CD57 41%, CD19 7%, and HLA-DR 70%. Bone marrow aspiration revealed normoblastic maturation with dyserythropoietic features, decrease in granulocyte population, and increase in the small lymphoid cell population. Biopsy of the minor salivary glands showed acinar fibrosis surrounded by a few lymphocytic infiltrates. The immunohistochemical study disclosed only few lymphoid cells, which stained positive for leukocyte common antigen, CD3, CD4, and negative for CD57.

DISCUSSION

We describe an association of primary SS with T cell LGL in 2 patients and suggest that these disorders may share a common etiology. Classically, histopathological studies of the lacrimal and salivary glands of patients with SS display CD4+ T and B cell infiltration[1,9]. Of particular note is the observation of Fox, *et al*[9] that the lymphocytes infiltrating the salivary glands in SS lack CD57 (Leu-7) and CD16 (Leu-11) antigens, which are present on peripheral blood lymphocytes of the patients. By contrast, one of our cases (Case 1) was unique with respect to the appearance of CD8+, CD57+ (Leu-7), and CD16+ (Leu-11) T cells, a finding compatible with the LGL found in the salivary gland biopsy. In addition, we found a striking phenotypic similarity between the LGL cells in the peripheral blood, bone marrow, and salivary gland.

This association of primary SS with CD3+ T cell LGL raises the possibility of a common etiology for both disorders. Although the etiology of SS is unclear, several studies have associated SS with viral etiology, such as EBV[10], hepatitis C[11], or retroviruses[12]. Of particular similarity is the HIV associated diffuse infiltrative lymphocytosis syndrome (DILS), in which the lymphocytic infiltration of the salivary and lacrimal glands are of the CD3+, CD8+, and CD57+ phenotype[13,14], suggesting that SS associated LGL could be an autoimmune reaction to an undefined retrovirus.

To our knowledge, this is the first report of an association of classical SS with T cell LGL. Moreover, our finding of LGL infiltration of the salivary glands of one of our patients raises the possibility that SS in this case has been preceded or caused by glandular infiltration of LGL cells, and that both disorders may constitute an autoimmune reaction to an undefined retrovirus.

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