Autoimmune Hemolytic Anemia in an Elderly Patient with Primary Sjögren’s Syndrome

Masayuki KIKAWADA, Daisuke WATANABE, Akihiro KIMURA, Haruo HANYU, Hiromi SERIZAWA* and Toshihiko IWAMOTO

Abstract

Primary Sjögren’s syndrome is an autoimmune disease characterized by lymphocytic infiltration of the salivary glands and lacrimal glands. The histological features of chronic inflammation in primary Sjögren’s syndrome may be associated with B cell hyper-reactivity. This syndrome also has various manifestations associated with other exocrine glands and nonglandular tissues. The hematological abnormalities usually seen in Sjögren’s syndrome are lymphopenia, leucopenia, and thrombocytopenia. Although the direct Coomb’s test is often positive, the occurrence of autoimmune hemolytic anemia (AIHA) is rare. Here, we report an elderly patient with primary Sjögren’s syndrome who developed AIHA during the clinical course.

Case Report

An 81-year-old woman developed exertional dyspnea and palpitations in October 2004. She was referred to our hospital, and was admitted on November 15, 2004 with progressive anemia and jaundice. About 20 years previously, sicca syndrome had been diagnosed because of persistent xerostomia and xerophthalmia. She had undergone subtotal thyroidectomy for a simple goiter in 1999, as well as left knee replacement for osteoarthritis. She had never smoked cigarettes and was not on any medications.

On admission, her temperature was 35.6°C, her pulse rate was 85/min (regular), and her blood pressure was 130/60 mmHg. She had pallor of the palpebral conjunctiva and mild icterus of the bulbar conjunctiva. There was slightly painful swelling of the left parotid gland and the oral mucosa was dry. Breath sounds and heart sounds were normal, except for a grade 2 systolic murmur. There was slight splenomegaly which could be felt 1 cm below the left costal margin. Neurological examination was normal. She had no symptoms, such as morning stiffness, esophageal dysphagia, or edema. In addition, there were no clinical findings, such as Raynaud’s phenomenon, photosensitivity, butterfly rash, or other evidence of lupus erythematosus, sclerodactyly, telangiectasia, arthritis, and subcutaneous calcinosis. Laboratory data were as follows: white blood cell count, 8.6×10^9/l; red blood cell count, 1.9×10^12/l; hemoglobin, 7.1 g/dl; mean corpuscular volume, 111.5 fl; platelet count, 2.010×10^9/l; reticulocyte count, 12.0%; lactic dehydrogenase (LDH), 644 U/l; aspartate aminotransferase (AST), 28 U/l; alanine aminotransferase (ALT), 12 U/l; total bilirubin, 3.05 mg/dl; IgG, 1,512 mg/dl; IgA, 208 mg/dl; IgM, 345 mg/dl; KL-6, 705 U/ml. The direct Coomb’s test gave a positive result (warm, polyspecific IgG). The indirect Coomb’s test was also positive, and the serum haptoglobin level was 0.12 g/l.
Serum folate was 8.0 µg/l, and B₁₂ was 630 ng/l (within the normal range). Antinuclear antibodies (ANA) were detected (titer >1 : 1,280) and showed a discrete speckled pattern. Anti-centromere antibody (ACA) was positive by enzyme-linked immunosorbent assay (160.8 index). LE cells were low, as was the serum complement level (C₃, C₄, and CH50). Other autoantibodies related to collagen diseases were also negative, including rheumatoid factor, anti-DNA antibody, anti-Ro/SS-A antibody, anti-La/SS-B antibody, anti-histidyl-tRNA synthetase (Jo-1) antibody, antibody to cardiolipin, nucleoprotein (RNP) antibody, anti-Sm antibody, and anti-antihistidyl-tRNA synthetase (Jo-1) antibody, anti-ribonucleoprotein (RNP) antibody, anti-Sm antibody, and anti-topoisomerase-I (Scl-70) antibody. Antibody to cardiolipin, lupus anticoagulant, and beta 2-glycoprotein inhibitor (β2-GPI) were negative. Serum free triiodothyronine (FT3), free thyroxine (FT4), and thyroid stimulating hormone (TSH) were within the normal range, while anti-thyroid peroxidase (anti-TPO) antibody and antithyroglobulin (anti-TG) antibody were negative. In addition, anti-mitochondrial antibody (AMA), myeloperoxidase antineutrophil cytoplasmic antibody (MPO-ANCA), and proteinase-3 antineutrophil cytoplasmic antibody (PR3-ANCA) were all negative. Urinalysis did not show any proteinuria, hematuria, or casts. The plain chest X-ray film and computed tomography (CT) revealed mild interstitial changes in the bilateral lower lung fields. Abdominal CT findings were normal apart from slight splenomegaly. Arterial blood gas analysis (room air) gave a PaO₂ of 87.2 Torr, PaCO₂ of 34.5 Torr, and pH of 7.45. Lung function tests yielded the following results: forced expiratory volume in one second (FEV₁,₀) was 1.81 l, percent predicted FEV₁,₀ was 103.3%, vital capacity (VC) was 2.46 l, and percent predicted VC was 120.0%. The bone marrow was hyperplastic with an increase of erythrocytes, but showed no morphological abnormalities. Minor labial salivary gland biopsy showed two clusters of >50 mononuclear cells/4 mm², which was compatible with Sjögren’s syndrome (Fig. 1). Schirmer’s test was positive (0 mm per 5 minutes on the left and 2 mm per 5 minutes on the right) and fluorescein staining was positive (grade 6/18 on the left and grade 7/18 on the right) (3).

We diagnosed AIHA complicated by primary Sjögren’s syndrome in the present patient based on these findings. Primary Sjögren’s syndrome was diagnosed on the basis of the revised Japanese criteria for Sjögren’s syndrome approved by the Japanese Ministry of Health and Welfare (4). The histopathological findings obtained by biopsy of a minor salivary gland and the results of ocular examination (positive Schirmer’s test and fluorescein test) confirmed the diagnosis of Sjögren’s syndrome in our patient. Steroid therapy was administered with a modified dosage of prednisolone due to the patient’s advanced age. Accordingly, oral prednisolone was started at 30 mg/day, and her hemoglobin returned to the normal range after four weeks.

**Discussion**

Some previous reports have described hematological abnormalities in patients with primary Sjögren’s syndrome. Ramakrishna et al (5) reported that 11 out of 27 patients with primary Sjögren’s syndrome had some hematological abnormalities. Leucopenia is one of the most frequent hematological changes in patients with this syndrome (13.8–15%, median: 14.4%) (2, 5), while anemia occurs in 11.2–19% (median: 15%) of patients and thrombocytopenia affects about 5–18.5% (median: 12%) (2, 5). Direct Coomb’s test positivity is also among the most common hematological abnormalities recognized in primary Sjögren’s syndrome (5–8), but AIHA is rarely associated with this syndrome (5). It has been suggested that these hematological abnormalities are caused by an immune mechanism. This hypothesis is supported by the findings that some patients with primary Sjögren’s syndrome have anti-RBC antibodies or antineutrophil antibodies (5, 9). There have been some previous reports of anemia associated with primary Sjögren’s syndrome, including patients with aplastic anemia (10, 11), pernicious anemia (12), and low titer cold agglutinin disease (13).

However, AIHA associated with primary Sjögren’s syndrome has only been described in a few cases (14–18) (Table 1). Most of the patients also had other autoimmune diseases, such as chronic thyroiditis, primary biliary cirrhosis (PBC), and autoimmune cholangiopathy (AIC), and primary Sjögren’s syndrome without other autoimmune diseases has only been associated with AIHA in one previous case (15). Therefore, the present patient is a rare case of primary Sjögren’s syndrome with AIHA.

Anti-centromere antibody (ACA) and Scl-70 are important autoantibodies that are associated with systemic sclerosis (SSc). In particular, ACA can be detected in about 70–90% of patients with limited cutaneous SSc or CREST syndrome (19, 20). However, this antibody is not a specific

**Figure 1.** Light microscopy of a biopsy specimen obtained from a minor salivary gland biopsy (HE stain, ×40). Lymphocytes show interlobular and intralobular infiltration into the salivary gland.
Abnormalities that occur in primary Sjögren’s syndrome are significant. In the present patient, hemolytic anemia was found as a hematological change in primary Sjögren’s syndrome. Although only levels of immunoinflammatory markers, but anemia was not significantly correlated with such markers. Although only hemolytic anemia was found as a hematological change in the present patient with primary Sjögren’s syndrome, other manifestations of autoimmunity inflammation may appear in the future.

In conclusion, we reported a patient with primary Sjögren’s syndrome and AIHA. Most of the hematological abnormalities that occur in primary Sjögren’s syndrome are not of clinical significance, but progressive anemia may indicate the existence of AIHA as in the present case.

References
