Autoimmune Myelofibrosis Accompanied by Sjögren’s Syndrome in a 47, XXX/46, XX Mosaic Woman

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Abstract

This report describes a patient with autoimmune myelofibrosis accompanied by Sjögren’s syndrome (SS). A 36-year-old woman was admitted due to petechiae, purpura, gingival bleeding, dyspnea on exertion, and a lack of concentration. She had pancytopenia and was diagnosed with SS. A bone marrow study showed hypercellular marrow with reticulin fibrosis. Lymphocytic infiltrates and aggregates composed of a mixture of T and B cells in the marrow were also observed. A chromosomal analysis of the marrow cells showed 47, XXX and an analysis of peripheral lymphocytes revealed 47, XXX/46, XX mosaic results. The patient’s cytopenia resolved following treatment with oral prednisolone.

Key words: autoimmune myelofibrosis, Sjögren’s syndrome, triple X syndrome, Hashimoto’s thyroiditis


Introduction

Primary myelofibrosis (PMF) is a clonal hematopoietic stem cell disorder classified into myeloproliferative neoplasms (1). Apart from PMF, myelofibrosis has been reported to develop secondary to a variety of conditions, such as other hematopoietic malignancies, metastatic cancers, and adverse reactions to drugs. Myelofibrosis has also been rarely described in patients with autoimmune disorders. Autoimmune myelofibrosis (AIMF) is the term introduced by Paquette et al. to refer to the primary immunopathogenesis of this syndrome (2). AIMF is mostly observed in association with systemic lupus erythematosus (SLE) and rarely with Sjögren’s syndrome (SS) (3-6). Pullarkat et al. also described the clinicopathologic features of a primary form of AIMF in patients without SLE or another well-defined autoimmune syndrome, and proposed the term primary autoimmune myelofibrosis (7). I herein describe the case of a patient with marrow fibrosis, pancytopenia and SS in whom the cytopenia was successfully treated with steroid therapy.

Case Report

A 36-year-old woman was admitted in August 2012 due to petechiae, purpura, gingival bleeding, dyspnea on exertion, and lack of concentration. She underwent surgery for vesicoureteral reflux at 3 years of age. She had two healthy children and experienced no troubles with her pregnancies or deliveries. Upon a physical examination, the patient’s superficial lymph nodes, liver and spleen were not palpated. The thyroid gland was palpable, but not enlarged, and its surface was smooth. She exhibited no swelling of the joints or skin lesions except for petechiae and purpura, and no neurological deficits were observed.

The patient had pancytopenia; the white cell count was 2,900/μL, with 50.5% neutrophils, 29.5% lymphocytes, 18.0% monocytes and 2.0% eosinophils. The hemoglobin concentration was 10.0 g/dL, the platelet count was 13,000/μL and the reticulocyte count was 29,200/μL. The results of coagulation tests were normal. Blood biochemistry tests were normal, except for an elevated total protein level (9.3 g/dL; reference range, 6.5-8.2). Polyclonal hypergammaglobulinemia was observed, and the serum IgG level was very high at 4,841 mg/dL. Anti-platelet antibodies were positive, and the platelet-associated IgG was elevated at 102.5 ng/10^7 platelets (reference range, 9.0-25.0). These data suggested that the patient’s thrombocytopenia was autoimmune-mediated.

Both direct and indirect Coombs’ tests were positive;
however, there were no signs or symptoms of hemolysis (i.e., no elevation of lactate dehydrogenase (LDH), indirect bilirubin or reticulocytes, and a detectable level of haptoglobin at 132 EU; reference range, 19-170). Anti-nuclear antibodies (1,280×, speckled pattern), anti-SS-A antibodies, and anti-ribonucleoprotein (RNP) antibodies were positive, although anti-Sm antibodies were negative. Decreased salivary secretion was observed (gum test: 6 mL/10 minutes), and a Shirmer test and Rose-Bengal test were positive. Although biopsy of salivary glands was not performed, the patient was diagnosed with Sjögren’s syndrome. She did not meet the criteria for a diagnosis of SLE. A diagnosis of subclinical Hashimoto’s thyroiditis was also suspected since the thyroid-stimulating hormone was elevated at 8.14 μIU/mL (reference range, 0.4-4.0) and the titer of antithyroperoxydase antibodies were high (145.7 IU/mL). A thoracoabdominal contrast-enhanced CT scan showed mild splenomegaly (Fig. 1); however no internal lymphadenopathy was observed. Therefore, the polyclonal hypergammaglobulinemia and positive results for various autoantibodies could not be ascribed to any lymphoproliferative disorders, such as multicentric Castleman’s disease or angioimmunoblastic T cell lymphoma.

Bone marrow aspiration did not show myelodysplastic changes, and a chromosomal analysis of the marrow cells revealed finding of 47, XXX [20] (Fig. 2). A chromosomal analysis of peripheral blood lymphocytes demonstrated findings of 47, XXX [21]/46, XX [9]. Therefore, the chromosomal anomaly was congenital, and the patient was considered to be a 47, XXX/46, XX mosaic woman. Bone marrow biopsy showed hypercellular marrow with reticulin fibrosis, confirmed on Gitter staining (Fig. 3). No collagen fibrosis was detected on Masson trichrome staining (data not shown). The patient’s cytopenia was considered to be related to AIMF, since she was diagnosed as having SS. An increased number of small lymphocytes arranged in ill-defined aggregates was also observed in the marrow. Immunostaining for CD3 and CD20 showed that the lymphocytic infiltrates and aggregates were composed of a mixture of T and B cells and that the aggregated T cells primarily consisted of CD4-positive cells (Fig. 4).

Platelets were transfused on a few occasions with a modest or slight increase in the platelet count (Fig. 5). This finding is in accordance with the fact that anti-platelet antibodies were positive. The patient was treated with oral prednisolone at a starting dose of 30 mg/day. Her white blood cell and platelet counts promptly increased, and the dose of prednisolone was gradually tapered to 10 mg/day. The hypergammaglobulinemia also resolved (total protein: 7.1 g/dL, and IgG: 1,515 mg/dL, in October 2012), and she experienced no further decreases in thel concentration. Unfortunately, she was lost to follow-up after the middle of November 2012, and no bone marrow examinations were performed following the resolution of symptoms.

**Discussion**

AIMF appears to be unusual and is usually only detected when a bone marrow biopsy is performed in the setting of an autoimmune disease with peripheral cytopenia (2). Its clinicopathological features have been progressively defined. In addition to a significant increase in reticulin and/or collagen fibrosis with impaired hematopoiesis, the disease presents with a variable degree of bone marrow cellularity without clustered megakaryocytes or marrow dysplasia (4). Mild to moderate bone marrow lymphocytosis consisting of equal numbers of interstitial T cells and B cells and loose lymphoid aggregates has also been described (8). In the present case, reticulin fibrosis was present in the marrow, and there were lymphocytic infiltrates and aggregates composed
Figure 2. A chromosome analysis of bone marrow cells. 47, XXX.

Figure 3. A bone marrow biopsy. (A) Hyper cellular marrow with infiltration of small lymphocytes was observed (May-Giemsas). (B) Prominent reticulin fibrosis was noted on Gitter staining.

Figure 4. Immunostaining of bone marrow cells. The marrow cells were stained with anti-CD3 (A), anti-CD4 (B) and anti-CD20 (C) antibodies.
of a mixture of T and B cells. These findings are consistent with previously reported features of AIMF. Although we did not analyze the prevalence of JAK2V617F, a diagnosis of PMF was unlikely in this case due to lack of collagen fibrosis or significant splenomegaly.

There are few data regarding the pathophysiology of myelofibrosis in patients with autoimmune disorders. Harrison et al. reported a case of AIMF with pancytopenia in which peripheral blood monocytes and CD4-positive lymphocytes produced significantly elevated levels of transforming growth factor β (TGF-β), compared to that observed in similar cells obtained from healthy volunteer controls (9). Furthermore, substance P was also detected at an elevated level in the patient’s serum and was found to be negatively correlated with blood counts. The authors suggested both TGF-β and substance P play a role in the pathophysiology of AIMF. The serum levels of TGF-β and substance P were not examined in the present case. However, the aggregated T cells were primarily consisted of CD4-positive cells. CD4-positive cells may play a role in the development of AIMF, thus producing some cytokines.

Hematological disorders are common in patients with SS, possibly due to dysfunction of both cell and humoral immunity. SS has been reported to be associated with autoimmune cytopenia, aplastic anemia and lymphoid malignancies (10, 11). However, AIMF is extremely rare in patients with SS, and, to the best of our knowledge, only five cases have been reported to date (3-6). The majority of patients successfully responded to corticosteroids.

A chromosome analysis of the peripheral blood lymphocytes showed a 47, XXX/46, XX mosaic pattern in the present case. 47, XXX is a sex chromosome abnormality characterized by the presence of an extra X chromosome. Triple X syndrome (47, XXX) is not extremely rare, with an incidence of 1/1,000 women; however, the majority of cases remain undiagnosed (12). The physical phenotype presents with earlier growth and longer legs. The behavioral phenotype often manifest as auditory processing disorders, disorders in language development and problems in forming stable interpersonal relationships. Psychiatric disorders appear to be more common in patients with triple X syndrome. The present patient had none of the features described above. She exhibited the 47, XXX/46, XX mosaic pattern; therefore, the effects of triple X may be milder, lessened by the presence of cells with a normal number of X chromosomes in some tissues of the body. Goswami et al. reported two cases of triple X syndrome with premature ovarian failure and autoimmune thyroid disorders (13). It is interesting to note that the present patient was also considered to have subclinical Hashimoto’s disease. It is also interesting to note that the marrow cells included only 47, XXX cells, while the peripheral lymphocytes exhibited the 47, XXX/46, XX mosaic pattern. Bone marrow cells with the 47, XXX pattern may have some survival advantages over those with the 46, XX pattern. The relationship between triple X syndrome and AIMF remains to be elucidated.

I herein described, a patient with AIMF accompanied by SS. The patient was also considered to have idiopathic thrombocytopenic purpura (ITP) and subclinical Hashimoto’s disease. This is the fifth reported case of AIMF associated with SS. Furthermore, this is the first reported case of AIMF to occur in a woman with triple X syndrome.

The author states that he has no Conflict of Interest (COI).

References

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