Primary myelofibrosis but not autoimmune myelofibrosis accompanied by Sjögren’s syndrome and primary biliary cirrhosis in a patient with trisomy 8 mosaic: a case report and literature review

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ABSTRACT

Bone marrow fibrosis has been found to be associated with autoimmune disorders, and autoimmune myelofibrosis (AIMF) has been defined. Primary myelofibrosis (PMF), a clonal myeloproliferative disorder, should be distinguished from AIMF which has a good response to steroids, as the former has a high mortality and very bad response to conventional treatment. This case report describes a rare case of PMF accompanied by Sjögren’s syndrome (SJS) and primary biliary cirrhosis (PBC), in a patient with trisomy 8 mosaic. Careful clinical assessment, gene mutation screening, and bone marrow evaluation can lead to an accurate diagnosis.

Introduction

Bone marrow fibrosis is a lesion characterised by an increase of reticulin fibers or reticulin and collagen fibres, and/or proliferating fibroblasts. Two different primary bone marrow fibrosis disorders, primary myelofibrosis (PMF) and primary autoimmune myelofibrosis (primary AIMF), have been defined (1, 2). It can also be a secondary change associated with disorders such as inflammation, bone marrow necrosis, bone marrow injury, and disorders of myeloproliferation (e.g. acute myeloid leukaemia) and lymphoproliferation (e.g. lymphoma). Therefore, the manifestations of patients with bone marrow fibrosis are sometimes very complex. Here, we describe a rare case of bone marrow fibrosis diagnosed as primary myelofibrosis (PMF) accompanied with Sjögren’s syndrome (SJS) and primary biliary cirrhosis (PBC), which is different from AIMF, in a patient with trisomy 8 mosaic.

A 66-year-old woman presented in March 2015 with complaints of asthenia, weight loss and occasional fever over the previous 5 years. In May 2010, the patient was diagnosed as PMF on the basis of palpable spleen, anaemia, positive JAK2 V617F mutation, negative BCR-ABL rearrangement, karyotype analysis showing 47, XX, +8 in 11/20 cells (Fig. 1A), tear-drop erythrocytes in the blood and bone marrow (BM) biopsy disclosing clusters of megakaryocytes with several bizarre megakaryocytes, diffuse fibrosis of grade 3(3+). A combined therapy with thalidomide (100mg/d) and interferon had been administered during the previous 5 years. In March 2013, she went to another hospital complaining of discomfort in the right upper quadrant, and the diagnosis of primary biliary cirrhosis (PBC) was made because of a 3-years history of xerostomia and occasional pruritus, elevation of liver enzyme (γ-glutamyltransferase 310 U/L, alkaline phosphatase 264 U/L), positive antinuclear antibody (ANA) 1/320 with a cytoplasmic pattern and anti-mitochondrial-M2 antibody (AMA-M2), elevated serum liver enzyme (301 U/L, alkaline phosphatase 264 U/L), positive antinuclear antibody (ANA) 1/320 with a cytoplasmic pattern and anti-mitochondrial-M2 antibody (AMA-M2), elevated serum IgM and signs of portal hypertension (hepatosplenomegaly, wide portal vein). There was no bile duct stone and obstruction, no virus infection and neoplasm in the liver, except some enlarged lymph nodes between the head of pancreas and portal vein. She was treated with ursodesoxycholic acid (UDCA) 750 mg/day and improved. The patient has no history of exposure to both toxics and drugs. Moreover, her older sister died of autoimmune hepatitis and her younger brother suffers from rheumatoid arthritis.

Key words: primary myelofibrosis, autoimmune myelofibrosis, Sjögren’s syndrome, primary biliary cirrhosis, trisomy

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On admission, the patient was pale and physical examination revealed high body temperature (38–40°C), keratoconjunctivitis sicca, xerostomia, abnormal lung breathing sounds and splenomegaly. Otherwise, no parotid gland enlargement and superficial lymphadenopathy was observed. Full blood count showed: pancytopenia (WBC 1.26×10^{9} /L, haemoglobin 123g/L, platelet 90×10^{9}/L). Renal tests, serum folic acid, vitamin B_{12} and ferritin levels were within the normal limits. ESR was 2 mm/h and CPR 13.1 mg/L. Blood immunoelectrophoresis was generally within the normal range. Serum lactate dehydrogenase (LDH) (451 U/L) and γ-glutamyltransferase (65.3 U/L) were still higher than normal, but not alkaline phosphatase (90 U/L). Viral serologies [Human immunodeficiency virus (HIV), hepatitis virus, Epstein-Barr virus, cytomegalovirus] were all negative. Autoantibody screening was positive for ANA 1/320 CS, anti-SSA antibody and anti-mitochondrial-M2 antibody (>800 RU/mL); but antiphospholipid and anti-cardiolipin antibodies, anti-dsDNA antibody were negative. The Schirmer’s test [4mm/5minutes (left) and 6mm/5minutes (right)] and salivary flow rate test (0 ml/min unstimulated, 0.2 ml/min after stimulation) were abnormal. Salivary gland biopsy was cancelled for the low platelets count and bleeding tendency. Peripheral blood smear revealed numerous tear-drop erythrocytes (Fig. 1B). Bone marrow (BM) aspiration yielded a dry tap and BM biopsy showed hypercellularity, myeloid and erythroid cells in various stages of maturation, clusters of megakaryocytes with several bizarre megakaryocytes (Fig. 1C), rare lymphocytes, diffuse reticulin fibrosis of grade 3 (3+) (Fig. 1D). The diagnosis of primary myelofibrosis (PMF) is considered to be a clonal myeloproliferative disorder, characterised by an increased deposition of collagen, fibronectin and laminin within the bone marrow (3). In 2008, the WHO diagnostic criteria for PMF was proposed as the following: the major criteria includes present of JAK2 V617F or other clonal marker, BM biopsy shows proliferation of megakaryocytes, clusters of hyperlobobated megakaryocytes. (H&E, x100). D. Bone marrow biopsy highlights diffuse and dense increase in reticulin with extensive interactions (reticulin, x100).

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Although BM fibrosis and autoimmune phenomena came together in this case, our patient did not have some of the characteristic manifestations of AIMF, including lack of clusters or atypical megakaryocytes in BM biopsy. Conversely, the presence of splenomegaly, teardrop poikilocytosis on peripheral blood smear, megakaryocyte atypia and clustering on BM biopsy, and positive JAK2 V617F mutation further argued for the possibility of PMF.

It is generally accepted that approximately one third of patients with PBC will manifest another autoimmune condition, most frequently SJS, and growing evidence supports that chronic inflammation caused by B cells, cytokotic T cells and helper T cells are involved in both diseases (9). With introduction of UDCA, the typical course of PBC has changed substantially (10). Though there is no approved, specific treatment for SJS to date, some novel biologics capable to interfere with T cells migration and/or homeostasis, target costimulatory molecules involved in the cross talk between T and B cells/dendritic cells, or stromal cells in tertiary lymphoid structures are currently under investigation (11).

Another feature of this patient is trisomy 8 mosaic. Trisomy 8 is one of the most common chromosomal abnormalities in myeloid malignancies occurring in approximately 10–20% of cytogenetically abnormal acute myeloid leukemias (AML), myelodysplastic syndromes (MDSs), and myeloproliferative neoplasms (MPNs, formerly called myeloproliferative disorders) (12–14). Approximately one-third of patients with PMF present with cytogenetic abnormalities; the most frequent are del(20q), del(13q), trisomy 8 and 9, and abnormalities of chromosome 1 including duplication 1q (15). Taking these into consideration, our cytogenetic finding in this patient suggests essential origin of her disease and shed light on the possible genetic effect on its pathomechanism. Finally, the patient was diagnosed as PMF accompanied by SS and PBC with trisomy 8 mosaic.

The pathophysiology of PMF is controversial. There are two pathogenic processes have been implicated in the initiation and progression of PMF: reactive cytokine driven inflammatory fibrosis and stem cell derived clonal myeloproliferation (16). It has been suggested that BM fibrosis may play a central role in PMF, and therapies reverse the progress of myelofibrosis may improve patients’ syndromes. Although allogeneic stem cell transplant remains the only curative therapy for it (17), JAK1 and 2 selective inhibitor ruxolitinib, which can meaningfully reduce inflammatory markers and retard the advancement of BM fibrosis, can provide significant benefits for myelofibrosis patients (18, 19). Accordingly, the reduction of pro-inflammatory cytokines may also be beneficial in the context of concurrent autoimmune disorders and preliminary data show ruxolitinib (also known as INCB018424) improve clinical symptoms of some inflammation mediated diseases such as psoriasis (20) and rheumatoid arthritis (21). Although there is a lack of clinical trials, it could also be an option for AIMF in the future.

In conclusion, PMF accompanied with autoimmune diseases is a rare phenomenon that requires careful clinical assessment, gene mutation screening, and BM evaluation for accurate diagnosis. It is really essential to distinguish it from AIMF, as PMF has a bad prognosis and weak response to steroids. Additional studies are needed to further elucidate the pathophysiology and confirm the pathological implication of gene mutation or chromosome abnormality in autoimmune disorders.

References