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Primary autoimmune myelofibrosis in a 36-year old patient presenting with isolated extreme anemia

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Abstract

Primary autoimmune myelofibrosis is a very rare condition characterized by peripheral blood cytopenias, bone marrow fibrosis with lymphoid aggregates, and by the finding of autoantibodies in peripheral blood, suggesting a systemic autoimmune process. Patients can be frequently misdiagnosed as having the more common disorder primary myelofibrosis, a myeloproliferative neoplasm. We report the case of a patient with primary autoimmune myelofibrosis with emphasis on the clinical and pathological features that lead to the diagnosis.

Keywords

autoimmune myelofibrosis; anemia; diagnosis; pathology

1. Introduction

Fibrosis of the bone marrow is a pathological condition associated with a variety of bone marrow neoplasms, including, for example, myeloproliferative neoplasms (MPN), acute megakaryoblastic leukemia, and hairy cell leukemia. Bone marrow fibrosis can also be seen with infections of the bone marrow, such as tuberculosis, or associated with metastatic disease in the bone marrow, of the solid organ cancer [1]. In cases where a cause for bone

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marrow fibrosis cannot be readily identified, primary myelofibrosis (PMF) is frequently diagnosed. Histological features of bone marrow in PMF include significant deposits of extracellular matrix proteins, increased angiogenesis, osteosclerosis and increased hematopoiesis [2]. Patients with PMF usually present with anemia, peripheral blood smear showing teardrop red cells and leukoerythroblastosis, high lactate dehydrogenase (LDH), and splenomegaly [2]. Approximately half of the PMF patients carry *JAK2V617F* mutation, and up to 40% have cytogenetic abnormalities [2].

Autoimmune myelofibrosis (AIMF) is a very rare condition characterized by peripheral blood cytopenias, bone marrow fibrosis with lymphoid aggregates, and frequently by the finding of autoantibodies in peripheral blood, suggesting the presence of a systemic autoimmune process [3]. AIMF is frequently misdiagnosed as PMF, but it has distinguishing clinical and pathological features. Here we report a case of primary AIMF in 36-year old female patient who presented with isolated severe anemia.

2. Case Report

A 36-year old female presented in April 2007 to her local hospital with complaints of increasing fatigue, dyspnea, and occasional headaches over previous 2 years. Patient was a previously healthy white female, with no history of systemic disorders and no regular use of medications (only occasional acetaminophen and pseudoephedrine). She had no family history of hematological disorders. Physical exam was normal and did not reveal hepatomegaly or splenomegaly. Laboratory evaluation revealed severe anemia (hemoglobin [Hb] of 3.7g/dL) with a normal white blood cell (WBC) count and differential and normal platelet count. No circulating nucleated red blood cells were detected; peripheral blood smear was unremarkable. LDH was normal (383 IU/L). Kidney and liver function tests were not elevated. The patient was transfused 5 units of packed red blood cells. A bone marrow biopsy performed afterwards at an outside institution in April 2007 (reviewed later at our institution), revealed a hypercellular (100%) bone marrow with increased megakaryocytes, some of which were hypolobated; no megakaryocyte clustering was noted. Reticulin stain demonstrated diffuse increase in reticulin fibers; trichrome stain to assess collagen fibrosis was not performed. Bone trabeculae were unremarkable. Bone marrow smears were inadequate.

Due to the presence of bone marrow fibrosis with anemia, a working diagnosis of PMF was given. Despite erythropoietin (EPO) therapy for 6 months, the patient remained transfusion dependent, requiring RBC transfusions every 2–3 weeks. She first came to our institution in January 2008. Physical exam was normal, without splenomegaly or hepatomegaly. A complete blood cell count revealed Hb 7.2g/dL, WBC $3.1 \times 10^9/L$ with normal differential, and platelets $367 \times 10^9/L$. Peripheral blood smear was unremarkable, without normoblasts or immature WBC. Lymphocyte number or percentage was not increased. LDH was normal. EPO level was high (5,331 mIU/mL) as well as ferritin (1,509 ng/mL). Repeat bone marrow biopsy showed 100% cellularity (Fig. 1A). Megakaryocytes were increased in number (up to 10 per 1 high power field, $\times 400$) and did not form clusters; several small hypolobated forms were found. The erythroid series was markedly hypoplastic. Several lymphoid aggregates in non-paratrabeular location were detected. Reticulin stain highlighted diffuse and dense

increase in reticulin with extensive intersections in all areas, and trichrome stain demonstrated coarse bundles of collagen (Fig. 1B and 1C) corresponding to bone marrow fibrosis grade MF-3 [4]. Immunohistochemical stains demonstrated a mixture of B- and T-lymphocytes within the lymphoid aggregates, with a predominance of CD8⁺ T-lymphocytes (Figs. 2A and 2B). Anti-CD61 antibody highlighted numerous clustering megakaryocytes (Fig. 2C). Anti-CD34 antibody highlighted small vessels and dilated sinuses with intrasinusoidal hematopoiesis and rare single immature hematopoietic cells (Fig. 2D). Immunohistochemistry stains of bone marrow were negative for parvovirus, Epstein-Barr virus and cytomegalovirus, and a PCR for parvovirus in the bone marrow was negative. There was neither dysplasia nor increased number of blasts. Karyotype was normal. No *BCR-ABL1* fusion transcript and neither *JAK2V617F* nor *MPLW515K/L* mutation were detected. No clonal TCR γ gene rearrangements were detected.

Clinically, the patient did not have any signs or symptoms suggestive of autoimmune or rheumatic disease. Rheumatoid factor level was negative; anti-nuclear antibody was undetectable and anti-Smith antibodies were negative. She had a positive direct antiglobulin test (DAT) for IgG with unknown specificity, and elution studies confirmed the presence of an antibody directed to the patient's own red blood cells. The patient did not have features of autoimmune hemolytic anemia, with normal LDH and haptoglobin. A diagnosis of AIMF was established and the patient was treated with 30mg/day of prednisone for 1 month without a response. The patient was then treated with an immunosuppressive regimen of rabbit anti-thymocyte globulin (ATG) (3.5mg/Kg/day IV for 5 days), cyclosporine (starting after ATG; 300mg/day, titrated to a blood level over 200ng/ml) and prednisone (60mg/day, tapered slowly over 2 months). After 6 months of therapy, no improvement was seen and therapy was stopped. Rituximab was then prescribed at a dose of 375mg/m² IV weekly for 4 weeks, which also did not result in any improvement in anemia. Patient continues with frequent blood transfusions and is being treated with an iron chelator for iron overload. Bone marrow transplant option is being explored considering patient's young age and the lack of a response to standard therapy.

3. Discussion

AIMF is a very rare condition that has been describe in association with autoimmune disorders such as systemic lupus erythematosus, scleroderma, and Sjogren's Syndrome [5–7]. Several cases have been reported as having a clinical presentation consistent with AIMF but without an identifiable systemic autoimmune disorder ("primary AIMF") [3]. AIMF has been recently defined by a set of diagnostic criteria: (1) Grade 3 or 4 reticulin fibrosis of the bone marrow; (2) Lack of clustered or atypical megakaryocytes; (3) Lack of myeloid or erythroid dysplasia, eosinophilia and basophilia; (4) Lymphocyte infiltration of the bone marrow; (5) Lack of osteosclerosis; (6) Absent or mild splenomegaly; (7) Presence of autoantibodies; (8) Absence of a disorder known to cause myelofibrosis [3]. Patients should satisfy all criteria to be considered as having AIMF [3]. Patients who present with myelofibrosis of unknown etiology are often considered to have PMF. However, the World Health Organization (WHO) classification of hematologic malignancies defines specific criteria for the diagnosis of PMF [2]. Patients who present with myelofibrosis of unknown cause should not be assumed as having PMF just because no etiology is found for the bone

marrow fibrosis. Our patient had several clinical and laboratory features which were more suggestive of AIMF, including young age, normal spleen size, normal LDH and absence of circulating normoblasts. Megakaryocytes were small and hypolobated, which is a common feature of AIMF [8]. The bizarre shaped megakaryocytes seen in PMF were not found in this patient. In the laboratory evaluation she had a positive DAT, a common finding in patients with AIMF, even in the absence of autoimmune hemolytic anemia [3]. Hallmark of AIMF is the presence of an increased number of lymphocytes in the bone marrow, often forming non-paratrabecular aggregates, which have been shown to be a mixture of polyclonal T- and B- lymphocytes [8]. In our patient we found a predominance of CD8⁺ T-lymphocytes in these lymphoid aggregates.

The pathogenesis of AIMF is not well known. It probably involves the production of fibrogenic cytokines (such as transforming growth factor- β and the peptide substance P) by inflammatory cells [9]. The primary treatment of AIMF is corticosteroids [3, 7], with most patients having a rapid response in cytopenias but usually mild or no improvement in myelofibrosis [3]. In some cases the use of other immunosuppressive drugs may be necessary [10]. Further studies are necessary to elucidate the pathophysiology and therapy of AIMF.

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Fig. 1.

a. Hypercellular bone marrow with increased megakaryocytes and a prominent non-paratrabecular lymphoid aggregate (H&E, $\times 100$ erythroid cells). **b.** Reticulin stain highlights diffuse and dense increase in reticulin with extensive intersections (Reticulin, X100). **c.** Trichrome stain demonstrates coarse bundles of collagen (Trichrome, X100).

Fig. 2.

a. Anti-CD3 antibody highlights numerous T-cells within lymphoid aggregates (CD3, IHC, X100). **b.** Anti-CD20 antibody demonstrates substantially smaller amount of B-cells within lymphoid aggregates (CD20, IHC, X100). **c.** Anti-CD61 antibody highlights numerous megakaryocytes including small monolobated forms (CD61, IHC, X100). **d.** Anti-CD34 antibody highlights small vessels and dilated sinuses with intrasinusoidal hematopoiesis and rare single immature hematopoietic cells (CD34, IHC X100).