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A case of mistaken identity: When lupus masquerades as primary myelofibrosis

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Abstract

Introduction: Autoimmune myelofibrosis is an uncommon hematologic disease characterized by anemia, bone marrow myelofibrosis, and an autoimmune feature. Myelofibrosis is often associated with other conditions, including infections, nutritional/endocrine dysfunction, toxin/drug exposure, and connective tissue diseases, including scleroderma and systemic lupus erythematosus. Absence of clonal markers (*JAK2*) and heterogeneity of the symptoms often complicate the diagnosis.

Case presentation: Here, we present two cases of systemic lupus erythematosus–induced autoimmune myelofibrosis. The first case is of a 36-year-old African American female with diagnosis of systemic lupus erythematosus at the age of 12 years. The second patient is a 44-year-old African American male with family history of systemic lupus erythematosus who developed anemia and constitutional symptoms later on. Both patients showed hypercellularity and fibrotic changes of the bone marrow. Moreover, mutational analysis showed that both patients were wild type for *JAK2* (V617F and exon 12) and *MPL* (exon 10).

Conclusions: These two cases illustrate that anemic patients with fibrotic changes in the bone marrow without other clinicopathologic features associated with primary myelofibrosis in the presence of clinical manifestations and history of an autoimmune disease should suggest an autoimmune myelofibrosis. These cases demonstrate that a good clinical history combined with molecular technologies and pathomorphologic criteria are helpful in distinguishing between primary myelofibrosis and a nonclonal myelofibrosis from an associated condition.

Keywords

Myeloproliferative neoplasm, myelofibrosis, lupus, *JAK2*

Introduction

The presence of varying degrees of bone marrow (BM) reticulin fibrosis in a patient with anemia, constitutional symptoms, and clinical manifestations related to extramedullary hematopoiesis is suspicious for an underlying myeloproliferative neoplasm (MPN), specifically primary myelofibrosis (PMF). PMF is a subtype of MPN that primarily affects older adults. The estimated disease incidence rate is about 0.5–1.0 in every 100,000 individuals per year. PMF can present at the prefibrotic or fibrotic stage, with diagnosis commonly taking place during the fibrotic stage.[1,2] Most medical centers use the World Health Organization (WHO) 2008 criteria to diagnose PMF.[3] The diagnostic criteria includes the presence of megakaryocytic atypia and proliferation with or without reticulin or collagenous fibrosis, not meeting WHO criteria for polycythemia vera, BCR–ABL1+ chronic myelogenous leukemia, myelodysplastic syndrome or other myeloid neoplasm, demonstration of a clonal marker such as *JAK2* V617F or its equivalent (*JAK2* exon 12 and *MPL* exon 10), and presence of leukoerythroblastosis, extramedullary hematopoiesis, anemia, splenomegaly, increased serum lactate dehydrogenase (LDH) level, and constitutional symptoms. However, the diagnosis may not always be straightforward, as some of the clinical and pathologic features of PMF are not specific. The limitation in making an unequivocal diagnosis is also due

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to the presence of "disease-defining" clonal markers such as *JAK2* V617F being present in only 50%–60% of cases.[4] Conditions associated with nonclonal MF include infections, such as tuberculosis and histoplasmosis; nutritional/endocrine perturbations like vitamin D deficiency and hyperparathyroidism; toxin/drug exposure with thorotrast and benzene; connective tissue diseases, including scleroderma and systemic lupus erythematosus (SLE); and some other rare conditions.[5–9] Distinguishing between PMF and a nonclonal MF from an associated condition has important clinical consequences. The only potential curative option for PMF is an allogeneic hematopoietic cell transplant (Allo-HCT) and more intensive treatments such as *JAK* inhibitors, hydroxyurea, and immunomodulatory agents are sometimes needed, whereas nonclonal MF requires that the underlying cause be addressed.

Although PMF is highly considered in patients with cytopenias and BM fibrosis, these features are not pathognomonic of the disease. Here, we highlight two patients who were subsequently diagnosed with SLE-induced autoimmune MF. The first case had a prior history of SLE and developed SLE-associated autoimmune MF after 23 years, while the second patient presented with severe anemia initially diagnosed with PMF and was later found to have SLE.

Case presentation

Our first patient, a 36-year-old African American female, was diagnosed with SLE at the age of 12 years. Persistent fatigue at the age of 35 led to a complete blood count (CBC) test, which showed leukocytes = 3270/μL, hemoglobin = 9.3 g/dL, hematocrit = 26.9%, mean corpuscular volume = 91.5 fL, platelet count = 252,000/μL, and absolute neutrophil count = 1,260/μL. Direct Coomb's test was negative. Reticulocyte count and haptoglobin levels were within normal limits. Hematologic parameters are shown in Figure 1(g). She had no other significant past medical, family, or exposure history. Her physical examination findings were unremarkable. She subsequently required red blood cell (RBC) transfusions. A BM biopsy showed a hypercellular BM (95%) with panhyperplasia associated with moderate reticulin fibrosis (grade 2+) (Figure 1(f)). Neither megakaryocytic atypia nor significant dysplastic changes in other hematopoietic lineages were noted. Also no mutation was detected for *JAK2* V617F, *JAK2* exon 12, and *MPL*. Her LDH levels were within normal limits, and she had no leukoerythroblastosis. Work up to evaluate for the presence of infectious and nutritional deficiencies were unremarkable, hence a diagnosis of autoimmune MF was made. She was treated with oral prednisone 60 mg/day, which resulted in RBC transfusion independence. Her isolated anemia relapsed when the prednisone was discontinued. Retreatment with pulse methylprednisolone was ineffective. Treatments with other immunosuppressive agents, including rituximab and mycophenolate mofetil, were unsuccessful. She then was

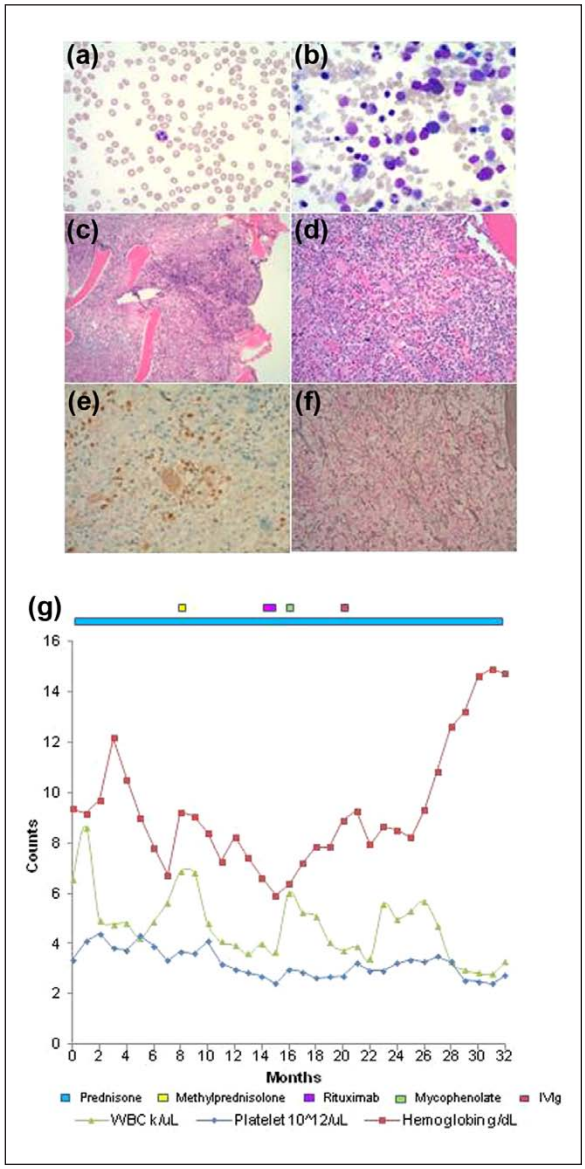

Figure 1. Morphology and CBC results of patient 1 with autoimmune myelofibrosis. PB and BM morphology. (a) PB smear revealed normocytic anemia with very rare teardrop cells, and mild leukopenia with no evidence of leukoerythroblastosis (Wright stain: ×50). (b) BM aspiration smear showed normal M:E ratio and no significant dysplasia in trilineage hematopoietic cells except occasional erythroid cells showing irregular nuclear contours, and unremarkable granulocytic and megakaryocytic lineages (Wright staining: ×50). (c and d) BM core biopsy displayed hypercellularity (95%) with panhyperplasia, megakaryocytic proliferation with focal clustering, and interstitial benign lymphoid aggregates (H&E stain: ×20). (e) Phospho-STAT5 immunostain on the core biopsy showed negative staining of megakaryocytic nuclei. (f) Reticulin stain on core biopsy showed moderate increase in reticulin fibers without increase in collagen fibers (myelofibrosis grade 2 on a scale of 0–3). (g) CBC values were reported for patient 1 for a range of 32 months. Types of treatment were indicated by different color bars that showed when treatment was given (light blue: prednisone; yellow: methylprednisolone; magenta: rituximab; green: mycophenolate; and red: IVIg).
CBC: complete blood count; PB: peripheral blood; BM: bone marrow; H&E: hematoxylin and eosin; M:E ratio: mass-to-charge ratio; IVIg: intravenous immunoglobulin.

treated with intravenous immunoglobulin (IVIg) infusion (1 gram/kg IV for 2 days), which resulted in a complete remission. She remained transfusion independent for 2 years after treatment with IVIg.

Our second patient is a 44-year-old African American gentleman, with a family history of SLE, who was diagnosed with PMF after presenting with severe anemia and constitutional symptoms such as fatigue and night sweats. His other accompanying symptoms include photosensitivity and nonspecific arthralgias. Physical examination was unremarkable. BM biopsy and aspirate revealed MF with slightly increased immature precursors. The BM was hypercellular (95%) with megakaryocytic proliferation but no sign of atypia. No dysplastic changes were noted. Reticulin staining showed moderate reticulin fibrosis (Figure 2(a)–(d)). Touch preps on the core biopsy revealed 3% blasts. LDH level was mildly elevated, but peripheral blood (PB) did not show leukoerythroblastosis. *JAK2* (V617F and exon 12) and *MPL* mutational screening was negative. The patient required RBC transfusions every 1–2 weeks for a full year and then, suddenly became transfusion independent with complete normalization of hemoglobin levels (Figure 2(e)). The following year, he relapsed and again became RBC transfusion dependent. His direct Coomb's test was negative, while his reticulocyte counts and haptoglobin levels were within normal limits. He developed multiple alloantibodies to RBC units and was started on dexamethasone, which resulted in resolution of the anemia. Although his hemoglobin levels were normal for several months, anemia again worsened after steroids were discontinued. The absence of typical PMF-related BM findings, family history of SLE, and the presence of connective tissue disease–related symptoms prompted an evaluation for SLE. Anti-nuclear antibody (positive in titer 1:640, nucleolar, speckled, and speckled pattern) and anti-dsDNA (>45 IU/mL) levels were both elevated, which along with additional clinical criteria confirmed the SLE diagnosis. Retreatment with steroids resulted in normalization of blood counts and RBC transfusion independence.

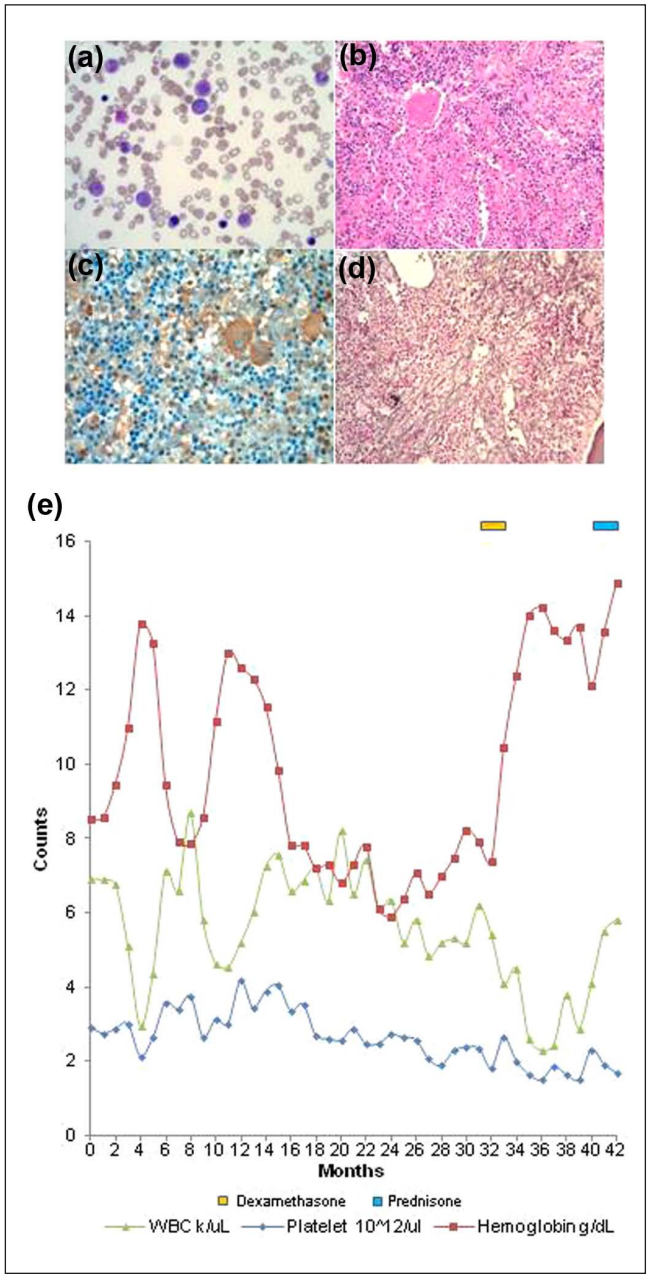

Figure 2. Morphology and CBC results of patient II with autoimmune myelofibrosis. BM morphology: (a) BM aspiration smear revealed slightly low M:E ratio, mild megaloblastoid changes in erythroid cells, and unremarkable granulocytic and megakaryocytic lineages (Wright stain: ×50). (b) BM core biopsy displayed hypercellularity (95%) with panhyperplasia, megakaryocytic proliferation with focal clustering (H&E stain: ×20). (c) Phospho-STAT5 immunostain on the core biopsy showed negative staining of megakaryocytic nuclei. (d) Reticulin stain showed diffuse and dense increase in reticulin fibers without increase in collagen fibers (myelofibrosis grade 2 on a scale of 0–3). (e) Routine CBC tests were performed and results are displayed for a period of 42 months. Types of treatments were indicated by different color bars that showed when treatment was given (orange: dexamethasone and light blue: prednisone).
CBC: complete blood count; BM: bone marrow; H&E: hematoxylin and eosin; M:E ratio: myeloid to erythroid ratio

Discussion

Autoimmune MF is an uncommon, distinct, hematologic disease entity clinically characterized by the presence of anemia, BM MF, and an autoimmune feature.[10] The most common cause of autoimmune MF is SLE, although other autoimmune diseases such as scleroderma and Sjögren's syndrome have also been implicated. Autoimmune MF can also manifest in the absence of another recognized autoimmune/connective tissue disease. The hematologic changes seen with SLE-induced autoimmune MF may either pre-date the diagnosis of SLE or may develop during the disease course of SLE. In a patient with SLE, autoimmune MF is a differential diagnosis aside from anemia of inflammation, nutritional deficiencies, hypersplenism, and PB cell destruction.[8] Identification of the

correct cause of anemia in patients with SLE is crucial because it has an important diagnostic, therapeutic, and prognostic relevance. Patients with SLE-associated MF usually respond well to initial steroid therapy. The discontinuation of steroid therapy can sometimes lead to relapse, which may not always respond to retreatment with corticosteroids. IVIg is shown to be clinically useful as a salvage regimen.[11] Other agents can be considered as therapeutic options, such as mycophenolate mofetil, rituximab, and cyclosporine. Similarly, anemic patients with fibrotic changes in the BM without accompanying clinicopathologic features associated with PMF in the presence of clinical manifestations and history suggesting an autoimmune disease should alert one to the possibility of an autoimmune MF. These two cases illustrate that not all patients with anemia and reticulin fibrosis of the BM have PMF. Mutational analysis for genes recently implicated in the PMF pathogenesis; *ASXL1, TET2, IDH1/2, DNMT3A, SH2B3 (LNK), TP53, EZH2*, and *CBL* showed wild-type configuration, further supporting the nonclonal nature of this condition.

Conclusion

Our case report together with others demonstrates that the collection of a good clinical history remains paramount in the era of modern molecular technologies.[12]Altogether, clinical history, with additional pathomorphologic criteria and clonal markers, is important in making a correct diagnosis of PMF. Currently, both patients are on maintenance steroids with completely normal blood counts.

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Consent

Written informed consent was obtained from the patients for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Declaration of conflicting interests

The authors declare that they have no competing interests.

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