Pathology of Autoimmune Myelofibrosis

A Report of Three Cases and a Review of the Literature

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Key Words: Autoimmune myelofibrosis; Collagen vascular disease; Chronic idiopathic myelofibrosis

Abstract

We identified 3 patients with autoimmune myelofibrosis (AM) lacking American Rheumatism Association criteria for systemic lupus erythematosus (SLE). They had 1 or 2 cytopenias and lacked serologic evidence for SLE. Autoimmune features included psoriatic arthritis and positive direct Coombs test (DCT) result, DCT-positive autoimmune hemolytic anemia, and synovitis with polyclonal hypergammaglobulinemia. Bone marrow biopsy specimens from each patient were evaluated by routine morphologic and immunohistochemical examination. They demonstrated marked hypercellularity (2 cases) or hypocellularity (1 case), moderate erythroid hyperplasia (all cases) with left-shifted maturation (2 cases), intrasinusoidal hematopoiesis (all cases), slightly to moderately increased megakaryocytes (2 cases), and grade 3 to 4 reticulin fibrosis (all cases). All lacked basophilia, eosinophilia, bizarre megakaryocytes, clusters of megakaryocytes, and osteosclerosis. Mild to moderate bone marrow lymphocytosis was noted in all cases. In 2 cases, increased small T cells and B cells formed nonparatrabecular, loose aggregates.

AM is a clinicopathologic entity that may lack features of SLE. Loose aggregates of bone marrow T and B lymphocytes and the absence of morphologic and clinical features of myeloproliferative disease or low-grade lymphoproliferative disease are clues that distinguish AM from better known causes of bone marrow fibrosis.

Bone marrow fibrosis is associated with numerous causes including myeloproliferative disease, other hematologic and nonhematologic malignant neoplasms, autoimmune disorders, and endocrine disorders.1 Cases reported as autoimmune myelofibrosis (AM) have been associated with collagen vascular disease, in particular, systemic lupus erythematosus (SLE).2-14 This rare bone marrow failure syndrome may predate the diagnosis of SLE or SLE-like disease or develop during the course of documented disease. Rare cases of AM have been described in patients with Sjögren syndrome and progressive systemic sclerosis.15,16 In addition, 1 case of AM has been described with a positive direct Coombs test result, splenomegaly, and bone marrow lymphoid infiltrate mimicking hairy cell leukemia.17 AM typically occurs in females, with most cases developing before the age of 40 years.2-17 Laboratory features of AM include anemia, thrombocytopenia, left-shifted granulocytes, rare circulating nucleated RBCs, serologic evidence of autoimmune disease, hypocomplementemia, and a positive direct Coombs test result.2 Physical examination may demonstrate splenomegaly or hepatosplenomegaly and arthralgias or, less commonly, oral ulcers, gingival bleeding, petechiae, pleuritis, pericarditis, lymphadenopathy, and malar rash.2

We describe 3 new cases of AM in order to further define the morphologic and immunohistochemical features characteristic of this entity and to review the clinical and pathologic features of cases reported in the literature.

Case Reports

Case 1

A 73-year-old white man with a 7-year history of psoriatic arthritis received a 5-week course of low-dose...
methotrexate. Seven months later, he had fatigue, anemia, and thrombocytopenia. Skin lesions developed on the upper and lower extremities 1 month later. Physical examination demonstrated a fading erythematous rash on the knees and upper arms, hyperpigmented papular and raised lesions on upper and lower extremities (particularly feet and ankles), and no peripheral lymphadenopathy or splenomegaly. Skin biopsies of the raised lesions documented Kaposi sarcoma. Vitamin B<sub>12</sub> and folate levels, iron studies, prostate-specific antigen, and liver function tests were normal. Pertinent laboratory results are shown in Table 1. Computed tomography scans of the chest, abdomen, and pelvis were negative. Two bone marrow trephine biopsies performed 7 weeks apart showed myelofibrosis (Table 2). Bone marrow aspiration attempts were unsuccessful on both occasions. The peripheral blood cytopenias improved after a course of corticosteroid therapy.

Recent follow-up showed correction of the thrombocytopenia but persistent mild anemia requiring erythropoietin therapy. Kaposi sarcoma lesions responded to therapy with thalidomide.

**Case 2**

A 48-year-old woman from El Salvador with a history of diabetes mellitus and Helicobacter pylori–induced peptic ulcer disease was admitted with warm antibody (IgG) autoimmune hemolytic anemia and fever. Pertinent laboratory results are listed in Table 1. Two bone marrow trephine biopsies performed approximately 2 weeks apart showed myelofibrosis (Table 2). Both biopsies were associated with unsuccessful attempts at bone marrow aspiration. Cytogenetic evaluation of the bone marrow revealed a normal female karyotype (46,XX). Peripheral blood cytopenias improved during a 4-month course of prednisone.

One year after diagnosis, a follow-up bone marrow trephine biopsy was performed with successful marrow aspiration. At the time of this biopsy, there was normalization of the peripheral blood counts.

**Case 3**

A 40-year-old African American woman was examined because of left wrist synovitis, persistent night sweats, and a 30-pound weight loss. The synovitis resolved with nonsteroidal anti-inflammatory drug therapy. The pertinent laboratory results are listed in Table 1. She was transfusion dependent. Additional laboratory workup revealed a total protein of 7.6 g/dL (76 g/L; reference range, 6.2-7.9 g/dL [62-79 g/L]). An anti-nuclear antibody assay initially was positive with a titer of 1:160 and a speckled pattern, but was negative on repeated analysis. Serum iron studies and increased bone marrow storage iron were most consistent with anemia of chronic disease. Vitamin B<sub>12</sub> and folate levels were normal. Results of upper gastrointestinal endoscopy, colonoscopy, and barium studies of the small intestine for suspected chronic gastrointestinal bleeding were normal. A bone marrow trephine biopsy showed myelofibrosis (Table 2). The biopsy was associated with unsuccessful attempts at bone marrow aspiration. Recent follow-up indicates the CBC count normalized with prednisone therapy.

### Table 1

#### Clinical Features and Laboratory Data for 3 Cases

<table>
<thead>
<tr>
<th>Case 1</th>
<th>Case 2</th>
<th>Case 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)/sex</td>
<td>73/M</td>
<td>48/F</td>
</tr>
<tr>
<td>Associated conditions</td>
<td>Psoriasis; Kaposi sarcoma</td>
<td>Diabetes; peptic ulcer</td>
</tr>
<tr>
<td>Hepatosplenomegaly</td>
<td>–</td>
<td>+</td>
</tr>
<tr>
<td>WBCs/µL (× 10³/L)</td>
<td>4,600 (4.6)</td>
<td>3,200 (3.2)</td>
</tr>
<tr>
<td>Hemoglobin, g/dL (g/L)</td>
<td>9.1 (91)</td>
<td>9.2 (92)</td>
</tr>
<tr>
<td>Mean corpuscular volume, µm³ (fL)</td>
<td>99 (99)</td>
<td>87 (87)</td>
</tr>
<tr>
<td>Platelets, × 10³/µL (× 10⁹/L)</td>
<td>77 (77)</td>
<td>192 (192)</td>
</tr>
<tr>
<td>Reticulocyte count, %</td>
<td>0.9 (0.009)</td>
<td>3.0 (0.03)</td>
</tr>
<tr>
<td>Antinuclear antibody</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Antimitochondrial antibody</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>Anti–smooth muscle antibody</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>Rheumatoid factor, IU/mL</td>
<td>&lt;20</td>
<td>ND</td>
</tr>
<tr>
<td>Erythrocyte sedimentation rate (mm/h)</td>
<td>18</td>
<td>148 (148)</td>
</tr>
<tr>
<td>Erythropoietin, mIU/mL (IU/L)</td>
<td>31 (31)</td>
<td>148 (148)</td>
</tr>
<tr>
<td>Direct Coombs test</td>
<td>+</td>
<td>ND</td>
</tr>
<tr>
<td>Autoimmune hemolytic anemia</td>
<td>–</td>
<td>+</td>
</tr>
<tr>
<td>Antibody specificity</td>
<td>ND</td>
<td>Anti-Fy&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Warm autoantibody (IgG)</td>
<td>ND</td>
<td>–</td>
</tr>
<tr>
<td>HIV</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>SLE criteria*</td>
<td>1/11</td>
<td>1/11</td>
</tr>
</tbody>
</table>

ND, not done; +, positive or present; –, negative or absent.

* Four or more American Rheumatism Association criteria are required for the diagnosis of systemic lupus erythematosus (SLE).<sup>28</sup>
Results

Our patients ranged from 40 to 73 years in age and included 2 women and 1 man. All had signs and symptoms of autoimmune disease (psoriatic arthritis, autoimmune hemolytic anemia, and synovitis). None of our patients had conclusive serologic evidence of SLE, although one initially had a positive antinuclear antibody result. The American Rheumatism Association (ARA) has published criteria for the diagnosis of SLE.18 These include cutaneous, renal, oral, rheumatologic, neurologic, hematologic, and serologic manifestations. Four or more features are required for this diagnosis. None of our patients demonstrated more than 1 criterion. They included thrombocytopenia (case 1), autoimmune hemolytic anemia (case 2), and synovitis (case 3).

The morphologic features of the blood and bone marrow specimens are summarized in Table 2. At presentation, all patients had mild to moderate anemia, which was normochromic and normocytic (cases 1 and 2) or normochromic and microcytic (case 3). In all cases, rare to moderate teardrop cells and rare normoblasts were detected on the blood smear of case 2. The WBC count was mildly decreased in case 2 but normal in the other 2 cases. The WBCs were mildly left-shifted with rare myelocytes and occasional hypersegmented neutrophils (cases 2 and 3). Platelets were moderately decreased only in case 1. Rare circulating megakaryocytes were noted on the peripheral blood smear of case 2.

Aspiration of the initial bone marrow was unsuccessful in all cases. The trephine biopsy cellularity was moderately hypocellular in case 1 and markedly hypercellular in the other 2 cases. Erythroid hyperplasia was present in all cases. In 2 cases, there was left-shifted erythroid maturation and increased pronormoblast islands. Intrasinusoidal hematopoiesis including megakaryocytes was identified in all cases. The number of megakaryocytes was moderately decreased in case 1 and slightly to moderately increased in the other 2 cases. Megakaryocytes were often small with hypolobated darkly staining nuclei (cases 2 and 3), but no megakaryocytes were found in clusters, nor were there bizarre shaped megakaryocytes. Marked, diffuse reticulin fibrosis was a consistent feature in all cases. In cases 1 and 3, large zones of collagen fibrosis also were seen.

The initial trephine biopsy specimens demonstrated a moderate lymphocytosis with increased numbers of small lymphocytes. These cells had a delicate interstitial distribution in all cases and produced ill-defined, nonparatrabecular aggregates in cases 1 and 2. Both components were composed of equal numbers of CD3+ T cells and CD20+ B cells. These lymphoid infiltrates failed to stain for kappa or lambda immunoglobulin light chains. Two patients had a mild to moderate increase in small, mature plasma cells.
cells that expressed polytypic kappa and lambda immunoglobulin light chain staining.

Follow-up bone marrow studies were performed only on case 2. The trephine and aspiration bone marrow biopsy specimens obtained following corticosteroid therapy showed marked hypercellularity with mild erythroid hyperplasia and moderately increased numbers of interstitial small lymphocytes and rare small, nonparatrabecular, poorly cohesive aggregates. Intrasinusoidal myeloid and erythroid hematopoiesis but no intrasinusoidal megakaryocytes were noted. A reticulin stain showed a marked delicate diffuse reticulin fibrosis, which was slightly less than that seen on the initial biopsy specimen. Immunohistochemical evaluation of the trephine biopsy specimen again demonstrated equal numbers of CD3+ T cells and CD20+ B cells within the interstitial infiltrate and lymphoid aggregates. Flow cytometric analysis of the bone marrow aspirate showed a normal distribution of T cells and B cells.
Discussion

AM has been identified in association with SLE, SLE-like disease, rarely in Sjögren syndrome, and progressive systemic sclerosis.\(^2\)\(^-\)\(^16\) The ARA requires a minimum of 4 criteria for the diagnosis of SLE.\(^18\) A previous study of AM found 4 or more criteria in 5 of 8 cases.\(^2\) Only 1 ARA feature was identified in each of our 3 cases: thrombocytopenia (case 1), autoimmune hemolytic anemia (case 2), and synovitis (case 3). Thus, none of our cases met standard criteria for the diagnosis of SLE. Rather, the abnormalities identified in these cases seem to be features of a heterogeneous group of autoimmune disorders associated with AM.

Our 3 cases of AM had 1 or more cytopenias with rare to moderate teardrop cells, rare normoblasts, slightly left-shifted granulocytic maturation, and normal platelet morphologic features, with occasional giant platelets noted only in case 3. The lack of marked teardrop poikilocytosis and rarity of circulating immature myeloid precursor cells are useful features to differentiate AM from chronic idiopathic myelofibrosis.

The bone marrow morphologic features of AM have been described inconsistently; hence, the main purpose for our study. We identified 25 cases of AM in the literature from 1966 to 2000 using the National Library of Medicine PubMed search service.\(^2\)\(^-\)\(^17\) Morphologic assessment often was incomplete; however, the most commonly reported bone marrow biopsy features included the following: hypocellularity (10 of 21 evaluable cases); hypercellularity (8 of 21 evaluable cases, including 1 case of “focal” hypercellularity); normocellularity (3 of 21 evaluable cases); megakaryocytic hyperplasia (13 of 18 evaluable cases); and megakaryocyte clusters (4 of 4 evaluable cases). As expected, fibrosis was identified in all cases.\(^2\)\(^-\)\(^17\) Bone marrow reticulin fibrosis or “fibrosis” was compared before and after corticosteroid therapy in a total of 15 cases. In 7 of these cases, there was no change in the degree of bone marrow reticulin fibrosis. However, peripheral blood parameters improved in 5 of these 7 cases after corticosteroid therapy. In the remaining 8 cases, bone marrow fibrosis following corticosteroid therapy was reportedly decreased in amount (4 cases), almost completely reversed (2 cases), and completely reversed (2 cases) with improvement or normalization of the peripheral blood parameters.

The bone marrow trephine biopsy specimens in our cases differed from those described in the literature in that our cases were more often hypercellular and exhibited left-shifted erythroid hyperplasia and slightly to moderately increased numbers of megakaryocytes. Intrasinusoidal hematopoiesis including megakaryocytes, absence of megakaryocyte clusters, and marked reticulin fibrosis (case 2) with large zones of collagen fibrosis (cases 1 and 3) also were seen. A follow-up bone marrow biopsy specimen after corticosteroid therapy was available for only 1 case (case 2). Although counts normalized, there was no change in the morphologic features other than a slight decrease in reticulin fibrosis. Our remaining cases showed improvement in the CBC count after corticosteroid and erythropoietin therapy (case 1) and corticosteroid therapy alone (case 3).

Bone marrow lymphoid infiltrates have been described in only 2 previously reported cases.\(^2\)\(^,\)^\(^17\) In both of these studies, the lymphoid infiltrate initially was thought to represent hairy cell leukemia. In 1 of these cases, the infiltrate was described as “a lymphoid aggregate composed of mature lymphocytes.”\(^2\) In the other case, the bone marrow lymphoid infiltrate was described as a “heavy spongy infiltration by large lymphocytic cells.”\(^17\) The lymphoid infiltrates in these cases were not further defined immunophenotypically.

The bone marrow trephine biopsy specimens in our cases demonstrated slight to moderate lymphocytosis consisting of equal numbers of interstitial small T cells and B cells (all cases) and small, nonparatrabecular, loose lymphoid aggregates of similar composition (cases 1 and 2). In addition, 2 of our cases (cases 2 and 3) showed a mild to moderate increase in plasma cells with a polytypic immunoglobulin light chain staining pattern. This reactive lymphoid infiltration is consistent with an underlying autoimmune process.

The differential diagnosis of AM includes myeloproliferative disorders (including the accelerated phase of chronic myelogenous leukemia, spent phase of polycythemia vera, and chronic idiopathic myelofibrosis), low-grade non-Hodgkin lymphoma, and hairy cell leukemia. Our cases lacked the characteristic features of myeloproliferative disorders in that there was no basophilia, eosinophilia, megakaryocyte clustering, or bizarre shaped megakaryocytes. Furthermore, morphologic and immunohistochemical features suggestive of malignant lymphoma or hairy cell leukemia were not identified. Although the cause of the bone marrow fibrosis is obscure, AM is a clinicopathologic manifestation of a diverse group of immune mediated disorders requiring a thorough clinical history and careful bone marrow morphologic assessment for accurate diagnosis.

References


