Distinguishing Autoimmune Myelofibrosis from Primary Myelofibrosis

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Abstract: Bone marrow fibrosis (BMF) is a histologic finding in a wide range of diseases, including malignancies, endocrine disorders, autoimmune diseases, and infections. Autoimmune myelofibrosis (AIMF) is an uncommon etiology of BMF; it can be secondary to a defined autoimmune disease, or it can be primary in the absence of a clinically diagnosed autoimmune disease but the presence of serologic evidence of autoantibodies. Distinguishing between primary myelofibrosis (PMF) and non-neoplastic AIMF is of the utmost importance because the prognosis and therapeutic options are different. This distinction, however, can be complicated by overlapping findings in the 2 disease entities. Here, using the case of a patient with BMF in the setting of idiopathic thrombocytopenic purpura and autoimmune hemolytic anemia, we present a systematic approach to distinguishing between PMF and AIMF.

Introduction

Bone marrow fibrosis (BMF) can arise from a wide span of conditions, ranging from malignancies to non-neoplastic entities such as infections, endocrine disorders, and autoimmune disease (Table 1).[1] BMF is commonly seen in the setting of hematologic malignancies, including myeloproliferative neoplasms (MPNs), myelodysplastic syndrome (MDS), mast cell diseases, and rarely in lymphoproliferative disorders. The most common cause of BMF is primary myelofibrosis (PMF).[2,3] It is important to note, however, that BMF has also been reported to be associated with the clinical use of thrombopoietin-receptor agonists.[4]

Autoimmune myelofibrosis (AIMF) is an uncommon etiology of BMF and is most often accompanied by other autoimmune diseases, such as systemic lupus erythematosus and rheumatoid arthritis. When BMF is associated with a defined autoimmune disease, it is termed *secondary AIMF*.[5] However, in the absence of a primary autoimmune disease driving BMF, but the presence of serologic evidence of autoimmunity, it is termed *primary AIMF*. Primary AIMF is often associated with benign hematologic conditions, such as autoimmune hemolytic anemia, idiopathic thrombocytopenic purpura (ITP), and Evans syndrome.[6] Studies have shown that up to 40% of patients with ITP have BMF, with the majority demonstrating minimal reticulin fibrosis.[7,8]

It is imperative to differentiate AIMF from PMF because the clinical course, prognostic implication, and treatment options are vastly different. The ability to distinguish between the 2 disease entities is often complicated by overlapping pathologic features and the fact that autoimmune abnormalities, such as the presence of autoimmune serologies, can be identified in both entities.[9] Cytokine-dependent mechanisms drive BMF in both AIMF and PMF; however, the predominant source of cytokines—including transforming growth factor beta (TGF-β), interferon gamma (IFN-γ), interleukin 8 (IL-8), IL-2, IL-17, and lipocalin-2 (LCN2)—likely differs, with cytokines derived from lymphoid aggregates driving AIMF and those derived from megakaryocytes and platelets mediating fibrosis in PMF.[1,10-12] Ultimately, clonality is a defining feature of PMF, and a driver mutation (*JAK2*, *MPL*, or *CALR*) is found in 90% of cases.[13,14]

The morphologic criteria that favor AIMF rather than PMF, as proposed by Vergara-Lluri and colleagues, are the following:

1. Rarity or absence of a leukoerythroblastic reaction in the peripheral blood, including absence of teardrop cells, nucleated red blood cells (RBCs), and blasts;
2. Absence of peripheral eosinophilia or basophilia;
3. Mild degree of BMF (usually MF1);
4. Absence of osteosclerosis and bone changes;
5. Presence of hypercellular marrow characterized by erythroid and megakaryocytic hyperplasia (vs granulocytic hyperplasia in PMF);
5. Presence of lymphoid aggregates; and
6. Absence of dysplastic features in any of the lineages, especially the megakaryocytes.[15]

These criteria distinguish AIMF from PMF; however, the distinction can remain nebulous when not all of the criteria are met. In these scenarios, it is crucial to consider the whole clinical picture in context, including the clinical presentation, time line of the disease course, results of assessment for autoantibodies, bone marrow pathologic findings, and results of chromosomal/genetic studies. Here, we present a case of presumed AIMF with associated autoimmune-mediated hemolytic anemia and ITP to exemplify the process of distinguishing between PMF and AIMF.

Table 1. Disorders Associated With Myelofibrosis

Infectious diseases
- Tuberculosis
Endocrine disorders
- Hyperparathyroidism (primary or secondary)
- Vitamin D deficiency (nutritional or rickets)
- Osteomalacia
Autoimmune disorders
- Systemic lupus erythematosus
- Sjögren syndrome
- Systemic sclerosis
- Primary autoimmune myelofibrosis
- Connective tissue disease
Hematologic malignancies
- Myeloproliferative neoplasms (primary myelofibrosis, polycythemia vera, essential thrombocythemia)
- Myelodysplastic syndrome
- Chronic myelogenous leukemia
- Hodgkin lymphoma
- Non-Hodgkin lymphoma
- Acute myeloid leukemia (particularly acute megakaryoblastic leukemia)
- Acute lymphoblastic leukemia
- Adult T-cell leukemia/lymphoma
- Multiple myeloma
- Systemic mastocytosis
Other hematologic conditions
- Paroxysmal nocturnal hemoglobinuria
- Gray platelet syndrome
Drug-associated conditions
- Thrombopoietin receptor agonist toxicity
Other
- Primary hypertrophic osteoarthropathy
- Paget disease
- Metastatic solid malignancies

Case

Clinical Presentation

A 57-year-old man presented to our clinic for consultation regarding chronic thrombocytopenia. He had been found to have a platelet count of 10,000/μL 15 years prior but did not pursue an evaluation. He was lost to follow-up, without any bleeding complications. After 10 years, hypothyroidism was diagnosed and levothyroxine initiated. He was still thrombocytopenic at this time and was given a diagnosis of ITP; no treatment was initiated. Several months ago, he presented to his local hematologist with complaints of dyspnea, dizziness, lightheadedness, ankle swelling, and easy bruising. No constitutional symptoms were reported. He was found to have a hemoglobin level of 6.8 g/dL and a platelet count of 1000/μL, with a normal white blood cell count and differential. He received a transfusion of packed red blood cells and platelets, which led to the resolution of his presenting symptoms.

Laboratory Assessment

The patient was assessed for evidence of hematologic

Table 2. Results of Our Patient's Laboratory Assessment

White blood cell count, $10^3/\mu L$	11.5
Hemoglobin, g/dL	6.8
Platelet count, $10^3/\mu L$	1000
Iron, µg/dL	23
TIBC, µg/dL	359
Transferrin saturation, %	6
Ferritin, ng/mL	49
Folate, ng/mL	17.05
Vitamin B_{12}, pg/mL	570
Erythropoietin, mIU/mL	56.6
Coombs test	Positive: 2+ positive DAT polyspecific 2+ positive DAT IgG 2+ positive DAT C3
Platelet antibodies	Positive
ESR, mm/h	86
CRP, mg/L	2.3
ANA	Positive (>1:80)
Rheumatoid factor, IU/mL	Negative (<15)
Rheumatologic antibody panel (anti–smooth muscle Ab, anti–mitochondrial Ab, anti–PR3/MPO Abs, anti-SSA and anti-SSB Abs, anti–cyclic citrullinated peptide Ab)	Negative
Immunoglobulins - IgG, mg/dL - IgA, mg/dL - IgM, mg/dL	 1096 218 44
SPEP	No M spike
TCB and *TRG* gene rearrangement studies	Negative

Ab(s), antibody(ies); ANA, antinuclear antibody; CRP, C-reactive protein; DAT, direct antiglobulin test; ESR, erythrocyte sedimentation rate; Ig, immunoglobulin; SPEP, serum protein electrophoresis; anti-SSA/B, anti–Sjögren syndrome–related antigen A/B; *TCB*, T-cell receptor beta gene; *TCG*, T-cell receptor gamma gene; TIBC, total iron-binding capacity.

disease and rheumatologic disease; the pertinent laboratory results are shown in Table 2.

Pathology

Manual review of the peripheral smear revealed no evidence of leukoerythroblastosis (nucleated red blood cells, immature granulocytic cells) and no evidence of agglutination, rouleaux, or polychromasia. A bone marrow aspiration procedure produced a dry tap result. The biopsy specimen showed hypercellular marrow (90%) with trilineage hematopoiesis and full maturation; also noted was a disproportionate increase in atypical megakaryocytes seen singly and in clusters, with pleomorphism characterized by hypolobated and focally hyperlobated nuclei. Several small lymphocytic aggregates contained CD3+ T lymphocytes and CD20+ B lymphocytes. There was no evidence of dysplasia or excess plasma cells. Reticulin staining showed moderate to marked reticulin fibrosis (MF2-3/3), and trichrome staining was negative for collagen fibrosis.

Evaluation for Primary Myelofibrosis

The workup for a myeloproliferative neoplasm was largely unremarkable. Spleen size was normal by axial computed tomography. Peripheral blood cytogenetics showed a normal karyotype. Next-generation sequencing of 44 myeloid-relevant genes in his peripheral blood cells revealed a *GATA2* mutation of unknown significance with a variant allele frequency of 49%, suggesting germline origin. *JAK2*, *MPL*, and *CALR* were wild-type.

Clinical Course

The patient was put on a trial of prednisone at 20 mg daily for presumed AIMF. After 1 month of treatment, the anemic and thrombocytopenic cell counts had returned to nearly normal values. The prednisone was tapered, and the patient will be followed to ensure the durability of his hematologic response.

Discussion

AIMF is a distinct entity characterized by diffuse BMF, with recognizable morphologic and clinical features distinct from those of PMF. More importantly, AIMF is a benign condition with a good prognosis. BMF is often discovered during an evaluation of unexplained cytopenias. It is of particular importance to determine the etiology of BMF because the diagnosis dictates the prognosis and influences the therapeutic plan. PMF is a *BCR-ABL1*–negative MPN associated with a progressive clinical course and a poor prognosis in most patients. The median survival of patients with PMF and high-risk disease according to the International Prognostic Scoring System (IPSS) is less than 2 years, and hematopoietic stem cell transplant (HSCT) is the only curative option.[16,17] AIMF, on the other hand, has a favorable prognosis, with cytopenias that typically respond to a short course of corticosteroids.[18] The case we have presented here highlights the process of distinguishing between PMF and AIMF, with key distinguishing features listed in Table 3.

Table 3. Distinguishing Features of Primary Myelofibrosis and Autoimmune Myelofibrosis

Features	PMF	AIMF
Bone marrow features		
Megakaryocytes	Proliferation and atypia	Lack of clustering/atypia
Myeloid/erythroid dysplasia	+/–	–
Basophilia or eosinophilia	+/–	–
Lymphocytic infiltration	+/–	+
Osteosclerosis	+/–	–
Laboratory features		
Anemia	+/–	+/–
Leukocytosis	Usually +	+/–
Elevated LDH	Usually +	+/–
Autoantibodies	+/–	+
Clinical features		
Constitutional symptoms	Common	Uncommon
Splenomegaly	Common	Absent/mild
Other signs		
Leukoerythroblastosis	+	+/–
JAK2, *CALR*, or *MPL* mutation	+ (90% of cases)	–

+, present; –, absent; AIMF, autoimmune myelofibrosis; LDH, lactate dehydrogenase; PMF, primary myelofibrosis.

Cytokines such as TGF-β, platelet-derived growth factor (PDGF), vascular endothelial growth factor (VEGF), IFN-γ, IL-8, IL-2, IL-17, and LCN2, as well as potential activation of the complement system, are believed to act in concert to promote fibrotic deposition, but they have been studied primarily in a PMF model.[19] Ultimately, the proinflammatory/profibrogenic milieu stimulates nonclonal fibroblasts to produce excessive amounts of extracellular matrix composed of proteoglycans, including laminins, collagens, and heparin sulfate, resulting in the development of fibrosis. In PMF, the malignant clone is thought to drive this process through pathologic JAK-STAT signaling that promotes the release of inflammatory and fibrogenic cytokines from megakaryocytes. The mechanism by which cytokine release is stimulated in AIMF is not well understood but is believed to be due to aberrant CD8+ lymphocyte activation.[1,12,20-22]

A leukoerythroblastic reaction in the peripheral blood, characterized by teardrop forms, nucleated RBCs, and circulating blasts, is a classic feature of PMF. In a case series of AIMF, only 1 of 26 patients showed a leukoerythroblastic reaction.[15] Most cases of AIMF show hypercellular marrow with erythroid hyperplasia and/or megakaryocytic hyperplasia. Granulocytic hyperplasia is less common but frequently seen in PMF. Although intrasinusoidal hematopoiesis is found in almost all cases of AIMF, it is less profound than that seen in PMF. Most cases of AIMF show mild reticulin fibrosis (MF1), with a small number of cases (~10%) harboring moderate to marked fibrosis (MF2/3). Lymphocytic infiltration with a mixture of CD3+ and CD20+ lymphocytes is seen in virtually all cases of AIMF, mostly in the form of non-paratrabecular T-cell lymphoid aggregates. The absence of atypical megakaryocytes is probably the most important criterion that helps to distinguish between AIMF and PMF; bizarrely shaped atypical megakaryocytes with hyperchromasia and tight cluster formation are pathognomonic features of PMF. Primary and secondary AIMF have the same morphologic features.[5,6,10,15,23]

Distinguishing between a diagnosis of PMF and one of AIMF is made challenging primarily by 2 factors: (1) subtle differences in bone marrow morphology and (2) the possible presence of autoantibodies in PMF. According to the World Health Organization classification, a diagnosis of PMF requires the presence of megakaryocytic proliferation and atypia, accompanied by either reticulin and/or moderate to marked collagen fibrosis.[24] Of course, bone marrow pathology alone does not clearly indicate the diagnosis in many cases. In our patient, for instance, significant reticulin fibrosis could suggest either diagnosis, whereas lymphocytic infiltration would support a diagnosis of AIMF and megakaryocytic atypia would support a diagnosis of PMF. Overlap of the pathologic features

of PMF and AIMF has been reported within retrospective analyses of patients with a diagnosis of AIMF. These pathologic features lack consistency among patients, and often it is not possible to fulfill the complete set of diagnostic criteria.[6,10,15,18]

The second confounding diagnostic factor is the high prevalence of autoimmune phenomena associated with PMF. Although the presence of an associated autoimmune disease or serologic evidence of autoantibodies is expected in AIMF, typically documented by a positive antinuclear antibody, rheumatoid factor, or direct antiglobulin test result, none of these serologies is specific to AIMF.[18] In a Swedish study comparing 11,039 patients who had MPN with 43,550 matched controls, the patients with an existing defined autoimmune disease had a 20% increased risk for the development of an MPN. The autoimmune diseases associated with this increased risk were ITP, Crohn disease, polymyalgia rheumatica, giant cell arteritis, Reiter syndrome, and aplastic anemia. The relationship between autoimmune diseases and MPNs, however, remains unclear, and a variety of factors is likely involved. One hypothesis is that the inflammation associated with autoimmune disease drives neoplastic transformation. Alternatively, the overlap between autoimmune disease and MPNs may be attributed to an overlap between genetic and environmental susceptibilities. Also, it is possible that treatments for autoimmune disease, including anti-inflammatory and immunosuppressive agents, alter the cellular milieu of the bone marrow, which in turn primes the development of MPNs.[25]

Additionally, autoantibodies are often detected in patients with PMF. In a study of 100 patients with PMF, post–polycythemia vera MF (PPV-MF), or post–essential thrombocythemia MF (PET-MF), 45% had a positive result on a direct antiglobulin test and 15% had detectable antiplatelet antibodies. A positive direct antiglobulin test result did not correlate with hemoglobin level or transfusion dependence. Similarly, the presence of antiplatelet antibodies did not correlate with a low platelet count. Positive results of autoimmune serology were not found to be associated with BMF grade or risk category.[11]

Owing to the inability in some cases to differentiate clearly between PMF and AIMF on the basis of pathologic features and antibody testing alone, it is particularly important to assess the complete clinical picture. The presentations are quite different in the 2 entities. Both frequently present with cytopenias; however, patients who have PMF generally present with a much greater symptom burden, including constitutional symptoms, and frequently with debilitating fatigue and diffuse bone pain.[26] Patients who have AIMF often have minimal symptomatology, which may be a direct consequence of anemia when present. Splenomegaly can also be a distinguishing factor. One study showed that more than 60% of patients with PMF had a palpable spleen more than 6 cm below the left costal margin.[27] Another report estimated that 10% of patients with PMF have symptomatic splenomegaly at diagnosis and that 50% acquire it over a 4-year period.[28] Conversely, splenomegaly is rarely a clinical feature of AIMF and, when present, is usually minimal and asymptomatic.[10]

Although the bone marrow pathologic findings are not always entirely diagnostic for PMF, peripheral blood manifestations usually support the myelophthisic process of PMF. Peripheral blood leukoerythroblastosis, as well as teardrop red blood cells (dacrocytes), poikilocytosis, eosinophilia, and basophilia, are classic findings in PMF and typically are not present in AIMF.[23]

Clonality is a major distinguishing factor between PMF and AIMF. In 1967, it was found that PMF as well as the other MPNs arise from a single hematopoietic progenitor stem cell that is able to give rise to a clonal population of diseased cells with a proliferative advantage over normal cells. This aberrant clonal hematopoiesis compromises normal polyclonal hematopoiesis and ultimately leads to a state of bone marrow failure.[29] In the last decade, it has been revealed that mutations in 3 driver genes (*JAK2*, *CALR*, and *MPL)* are found in 90% of cases of PMF.[30] Additional mutations in epigenetic regulating genes, such as *ASXL1*, *TET2*, and *DNMT3A*, are associated with PMF and have been implicated in clonal evolution and progression of disease.[31] A driver mutation is not detected in fewer than 10% of cases of PMF and subclonal mutations are not seen in approximately 20%, which can pose a challenge in differentiating between PMF and AIMF.[13,14,32]

Ultimately, the response to treatment can often aid the clinician in deciphering the underlying cause of BMF. The cytopenias associated with AIMF frequently respond to a brief course of corticosteroids. In a review of 32 patients with AIMF, the cytopenias of 29 responded to treatment, and a third experienced a response within only 2 weeks after receiving corticosteroid therapy. For those patients who had no response or a minimal response, another immunosuppressive therapy, such as intravenous immunoglobulin, azathioprine, or cyclophosphamide, was effective.[5] Typically, neither the cytopenias nor the systemic symptoms of PMF are corrected with corticosteroid therapy. The only treatment for PMF currently approved by the US Food and Drug Administration is the JAK inhibitor ruxolitinib (Jakafi, Incyte), which offers a significant benefit in relieving symptoms and reducing spleen size. However, this benefit is offset by the potential worsening of cytopenias.

Table 4. Antifibrotic Therapies Under Investigation in Primary Myelofibrosis

Agent	Phase	Study Name (Identifier or First Author)	Status
Pirfenidone	2	A phase 2 study of pirfenidone, a novel anti-fibrosing agent, in myelofibrosis with myeloid metaplasia (Mesa et al[39])	Completed; no clinical activity.
PRM-151	2	A Phase 2 Study Of PRM-151 In Subjects With Myelofibrosis (NCT01981850)	In process; 72-week analysis shows bone marrow responses and clinical activity.
Simtuzumab (LOXL2 inhibitor)	2	Efficacy and Safety of Simtuzumab in Adults With Primary, Post Polycythemia Vera or Post Essential Thrombocythemia Myelofibrosis (NCT01369498)	Completed; no clinical activity.
Fresolimumab (TGF-β inhibitor)	1	Anti-TGF-Beta Therapy in Patients With Myelofibrosis (NCT01291784)	Completed.

LOXL2, lysyl oxidase–like 2; TGF-β, transforming growth factor beta.

In AIMF, therapy with corticosteroids and other immunosuppressants often results in BMF regression. In the original description of AIMF, the cytopenias of 6 of 7 treated patients normalized completely within 1 to 3 months after the initiation of prednisone at a starting dose of 1 mg/kg. All patients with a clinical response showed a decrease in BMF; however, not all experienced a complete resolution of their BMF, indicating that the bone marrow microenvironmental effects of fibrosis alone were not responsible for the observed cytopenias.[10] Corticosteroid therapy in PMF does not reliably result in regression of BMF, and except for HSCT, most therapies—including ruxolitinib—do not effectively address this pathologic finding.[33] In the COMFORT-II study (Controlled Myelofibrosis Study With Oral Janus-associated Kinase Inhibitor Treatment-II), which assessed ruxolitinib vs best available therapy in patients with MF, no effect of ruxolitinib on bone marrow histopathology was noted at initial evaluation.[34] Subsequent studies showed a modest reduction in BMF in a small subset of patients after 2 years of treatment with ruxolitinib.[35,36] HSCT in patients with MPN-associated MF can result in complete resolution of BMF within 6 months of transplant. Of 57 patients with PMF, PPV-MF, or PET-MF, MF0/1 was attained at day 30 after engraftment in 21% and at day 100 after engraftment in 54%. Resolution of BMF correlated with improved rates of overall survival at 5 years of 96% in patients with MF0/1 and 57% in patients with MF2/3 at day 100 after engraftment.[37]

Of particular interest is the development of antifibrotic therapies for MPN-associated BMF (Table 4). Several agents evaluated in clinical trials include the following: pirfenidone (Esbriet, Genentech), PRM-151, TGF-β inhibitors, and lysyl oxidase–like 2 (LOXL2) inhibitors. Pirfenidone, an antifibrotic agent used for the treatment of idiopathic pulmonary fibrosis, has been shown to inhibit the proliferation of fibroblasts, preventing the deposition of extracellular matrix proteins and modulating cytokine activity.[38] Pirfenidone specifically modulates the activity of cytokines underlying PMF, including TGF-β, PDGF, and tumor necrosis factor alfa and therefore appeared to be a potential candidate for the treatment of PMF. However, a phase 2 trial of pirfenidone in PMF showed no significant biological or clinical activity.[39]

PRM-151, a recombinant form of human pentraxin 2—a regulator of tissue repair through the promotion of macrophage differentiation—has been shown to prevent and reverse BMF in preclinical models.[40] It is currently being evaluated in a multicenter, multiple-arm phase 2 trial of patients with PMF. Long-term analysis of PRM-151 at 72 weeks has shown it to have efficacy in reducing BMF by at least 1 grade, relieving anemia and thrombocytopenia in a subset of treated patients, and reducing spleen size and decreasing the symptom burden in a proportion of patients (NCT01981850).[41] The results suggest that this novel antifibrotic agent can reduce the disruptive effect of BMF, resulting in meaningful clinical outcomes.

The cytokine TGF-β has 3 isoforms, with TGF-β1 appearing to be the most active mediator in the pathogenesis of BMF. TGF-β1 is secreted primarily by megakaryocytes and platelets as well as by other bone marrow cells, and through engagement of the cognate receptor, it activates the SMAD signaling pathway regulating the transcription of TGF-β–dependent genes. Through this pathway, TGF-β1 promotes BMF by inducing extracellular matrix deposition. It accomplishes this by increasing the production of collagen and proteoglycans and decreasing matrix degradation through the inhibition of matrix metalloproteinases.[42] In PMF, TGF-β signaling has been shown to favor malignant clonal hematopoiesis over normal polyclonal hematopoiesis, and inhibitors of this pathway can relieve the repressive effects of TGF-β on

normal hematopoiesis.[43] An abbreviated phase 1 study of fresolimumab, an anti–TGF-β monoclonal antibody, in PMF showed the feasibility of the anti–TGF-β approach. In the 3 patients receiving fresolimumab, no dose-limiting toxicities were observed. For a single patient, the improvement in anemia was sufficient to achieve transfusion independence. However, treatment with fresolimumab was not associated with a decrease in bone marrow cellularity or fibrosis in this small study.[44]

LOXL2 inhibitors, such as the monoclonal antibody simtuzumab, have also been evaluated in prospective trials. The lysyl oxidases cross-link the extracellular matrix proteins elastin and collagen and are therefore essential for connective tissue production and turnover. The lysyl oxidases were shown to be overexpressed in PMF and therefore appeared to be a viable therapeutic target.[45] However, in a phase 2 trial of simtuzumab alone or in combination with ruxolitinib in patients with PMF, PPV-MF, or PET-MF, clinical benefit or consistent reduction in BMF at 24 weeks of treatment was not observed.[46]

AIMF and PMF are distinct entities, but the overlap in their bone marrow and clinical features can pose a diagnostic challenge to the clinician. It is essential to consider the clinical presentation in addition to the laboratory, pathology, and molecular findings to distinguish between these 2 disparate diagnoses. Close collaboration between clinician and hematopathologist is imperative. Owing to the more favorable clinical course of AIMF and its responsiveness to corticosteroids, identifying this less common cause of BMF has significant implications for treatment and outcome.

Disclosures

The authors have no disclosures to report.

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