Autoimmune Myelofibrosis: A Diagnosis by Exclusion

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29.1 Background

Myelofibrosis or bone marrow (BM) fibrosis is a common phenomenon occurring with various benign and malignant disorders. Neoplastic causes of BM fibrosis include various myeloproliferative neoplasms (MPNs), acute megakaryocytic leukemia, lymphoid malignancies, and metastasis of various solid malignancies. Non-neoplastic causes of BM fibrosis include chronic infections (e.g., tuberculosis, kala azar), metabolic causes, storage disorders, drug reactions, and autoimmune disorders [1]. Despite varied etiology and pathogenesis, it is the aberrant production of the fibrogenic cytokines, which is the main cause mediating the fibrosis of BM through stimulation of BM fibroblasts [1].

Autoimmune myelofibrosis (AIMF) is a benign disorder that was first described in 1994 by Paquette et al. as a distinct clinicopathological entity associated with diffuse bone marrow fibrosis and autoimmune phenomenon [2]. However, it has been recently found to be present even in the absence of a well-defined autoimmune disorder (Primary AIMF) [3]. The disease is characterized by isolated or combined cytopenia, autoimmune phenomenon, and bone marrow fibrosis. However, due to the rarity of the disease, patients are frequently misdiagnosed as primary myelofibrosis (PMF) which is otherwise a common neoplastic cause of BM fibrosis. Given the significant therapeutic and prognostic differences between the two disorders, it is essential to correctly identify patients with autoimmune myelofibrosis, which has a favorable course as compared to primary myelofibrosis [3].

29.2 Classification and Diagnostic Criteria

Autoimmune myelofibrosis can be classified as follows:

- Primary autoimmune myelofibrosis (primary AIMF)
- Secondary autoimmune myelofibrosis (secondary AIMF)

Primary autoimmune myelofibrosis refers to AIMF cases in which patients have the presence of autoantibodies but do not have a well-characterized autoimmune disorder. It has been recently recognized as a distinct entity as described by Pullarkat et al. (2003).

Secondary autoimmune myelofibrosis refers to AIMF secondary to an autoimmune disorder. It is well recognized in context of various autoimmune disorders, e.g., systemic lupus erythromatosus

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Table 29.1 Autoimmune disorders found to be associated with secondary AIMF

Systemic lupus erythromatosus
Rheumatoid arthritis
Autoimmune hemolytic anemia
Evans syndrome
Autoimmune hepatitis
Antiphospholipid syndrome
Autoimmune demyelinating polymyositis
Diabetes mellitus type 1
Hashimotos thyroiditis
Primary sclerosing cholangitis
Psoriasis
Vitiligo

Table 29.2 Diagnostic criteria for primary AIMF

(a) Grade 3 or 4 reticulin fibrosis of bone marrow (WHO grading)
(b) Lack of clustered or atypical megakaryocytes
(c) Lack of myeloid or erythroid dysplasia, eosinophilia, or basophilia
(d) Lymphocytic infiltration of bone marrow
(e) Lack of osteosclerosis
(f) Absent or mild splenomegaly
(g) Presence of autoantibodies
(h) Absence of a disorder known to cause MF

(SLE), rheumatoid arthritis, and autoimmune hemolytic anemia. [4]. Table 29.1 provides list of autoimmune disorders found to be associated with AIMF.

Primary and secondary autoimmune myelofibrosis are pathologically indistinguishable from each other and can be differentiated only clinically by the presence of a well-defined autoimmune disorder in cases of secondary AIMF. To diagnose primary AIMF and to differentiate it from other causes of myelofibrosis, Pullarkat et al. described following criteria as shown below. Only cases satisfying *all* the eight criteria mentioned in Table 29.2 *and not meeting* the WHO criteria of any myeloproliferative disorders can be diagnosed as primary AIMF [3].

29.3 Epidemiology

In addition to being a rare entity, AIMF is also an underecognized disorder due to general unawareness, incomplete work up of cases, and lack of definite diagnostic criteria. Presently, there is no available data regarding prevalence of the disease and the current knowledge about the entity mainly stems from the case reports and series. Larger series like Vergara-Lluri et al. and Pullarkat et.al. describe a prominence of female patients in their series with mean age of 40–45 years [4, 5]. In series described by Pullarkat et al. (2003), 69% patients had established diagnosis of an autoimmune disorder (secondary AIMF) while 31% patients had only elevated levels of autoantibodies in the absence of any well-established autoimmune disorder [3].

29.4 Pathogenesis

Although the pathophysiology of autoimmune myelofibrosis remains poorly understood, aberrant cytokine production by monocytes and T cells has been found to play pivotal role. Harrison and colleagues reported significantly higher levels of fibrogenic cytokines (e.g., TGF-β, FGF-β, peptide substance P) in an AIMF patient as compared to healthy controls and showed dramatic reduction in their serum levels with treatment, indicating the role of immune dysregulation, including T cell dysfunction, in the development of AIMF [6].

29.5 Clinical Features

The clinical spectrum of patients with AIMF is broad, with patients presenting either with classical features of autoimmune disorders first or with just cytopenias initially. Common signs and symptoms of underlying autoimmune disorder include arthralgias, oral ulcers, pain abdomen, gingival bleedings, pleuritis, pericarditis, lymphadenopathy, and malar rash. Patients usually do not have hepatosplenomegaly, spleen if present, may be mildly enlarged but massive splenomegaly (as described in PMF) is rare in AIMF [7]. Patients with primary AIMF may be missed altogether if BM examination and autoimmune work up is not taken up in these cases due to lack of any other definitive features. The various antibodies found

Table 29.3 Approach to a suspected case of autoimmune myelofibrosis

(a) *History*
Duration of illness
Any underlying disorder
Low grade fever of long duration
Unexplained fatigue
Joint pains
Skin rash or any history of photosensitivity
Pain abdomen/altered bowel movements
Xerostomia/dry conjunctiva
Numbness and tingling of extremities
Neuropsychiatric symptoms
(b) *Clinical examination*
Oral ulcers
Malar rash
Pleuritis/pericarditis
Lymphadenopathy
Hepatosplenomegaly
Deformities in hand/spine
Neuromuscular system
(c) *Investigations*
Complete blood count
Peripheral smear examination
Liver function tests
Renal function tests
Autoimmune work up
Antinuclear antibody
Direct coombs test
Anti-double-stranded DNA (dsDNA)
Rheumatoid factor
Anti-cyclic citrullinated peptide Ab (Anti-CCP)
Lupus anticoagulant
Anticardiolipin antibody
pANCA and cANCA
Anti-smooth muscle antibody (ASMA)
Anti-SSA
Anti-SSB
Bone marrow examination with reticulin staining
BM cytogenetics
Mutation study; JAK2 V617F, CAL-R, and MPL mutations

in association of AIMF are: ANA, dsDNA, RF, anti-CCP, DAT, lupus anticoagulant, anticardiolipin AB, pANCA, anti-MPO, anti-SMA, anti-SSA, and anti-SSB [8]. Table 29.3 provides the list of suggested work up in a suspected case of autoimmune myelofibrosis.

Nearly all patients of autoimmune myelofibrosis have cytopenias during the course of evolution and almost 50% cases present with it. Hence, autoimmune myelofibrosis should be kept as a differential in patients presenting with idiopathic long standing cytopenias [7]. Vergara-Lluri et al. described pancytopenia (28%) as the most common manifestation followed by anemia and thrombocytopenia (24%), isolated anemia (21%), and lastly combined anemia and leucopenia (14%) [5]. The cytopenia is generally mild to moderate and clinical symptoms due to cytopenias per se is rare [9, 10]. However, if compounded with other causative variables may lead to symptoms.

29.5.1 Peripheral Smear Morphology

Peripheral smear in AIMF patients may show bi- or pancytopenia. Cases with underlying AIHA or ITP may show classical blood picture. No evidence of eosinophilia/basophilia/dysplasia is noted. Few cases may show mild tear drop poikilocytosis and occasional nucleated red cells but frank leukoerythroblastic picture with immature myeloid forms is rare [3, 7].

29.5.2 Bone Marrow Morphology

BM aspirates are cellular with preserved myeloid to erythroid ratio and normal morphology. No evidence of dysplasia is noted. Cases with associated AIHA/Evans syndrome may show erythroid hyperplasia. BM biopsy usually shows hypercellularity; however, occasional cases of normocellular/hypocellular BM are also described (Fig. 29.1) [3]. Reticulin stain shows mild to moderate increase in fibrosis (MF grade 1–3) (Figs. 29.2 and 29.3). Even grade 3 fibrosis has also been described in cases of AIMF; however, osteosclerosis is not common [3, 5]. Megakaryocytes may be increased or normal in number. However, their distribution and morphology remains normal. Clustering is not a feature of AIMF and increases suspicion for underlying MPNs.

Increased lymphoid aggregates/interstitial lymphocytes (Figs. 29.4 and 29.5) are a common finding which are non-paratrabecular generally

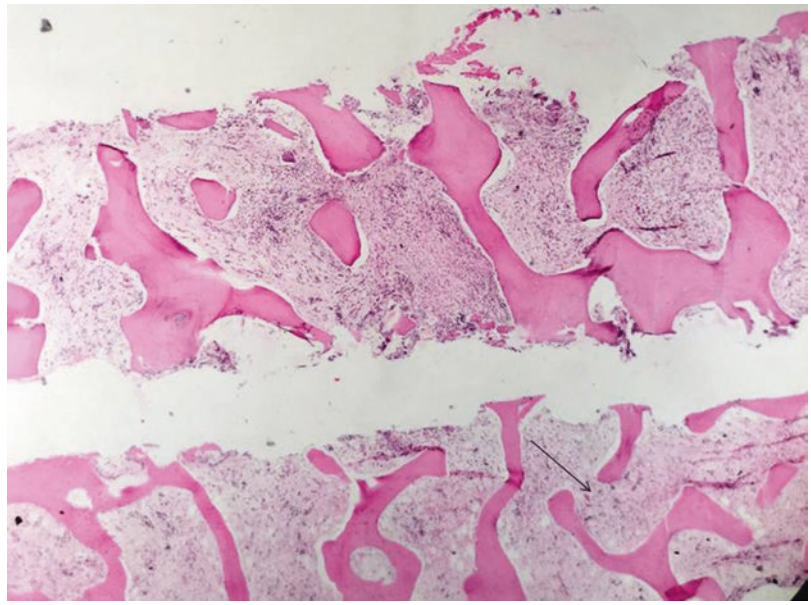

Fig. 29.1 Bone marrow biopsy showing presence of diffuse fibrosis, and presence of hypocellular areas (arrow) (10×, Hematoxylin and Eosin)

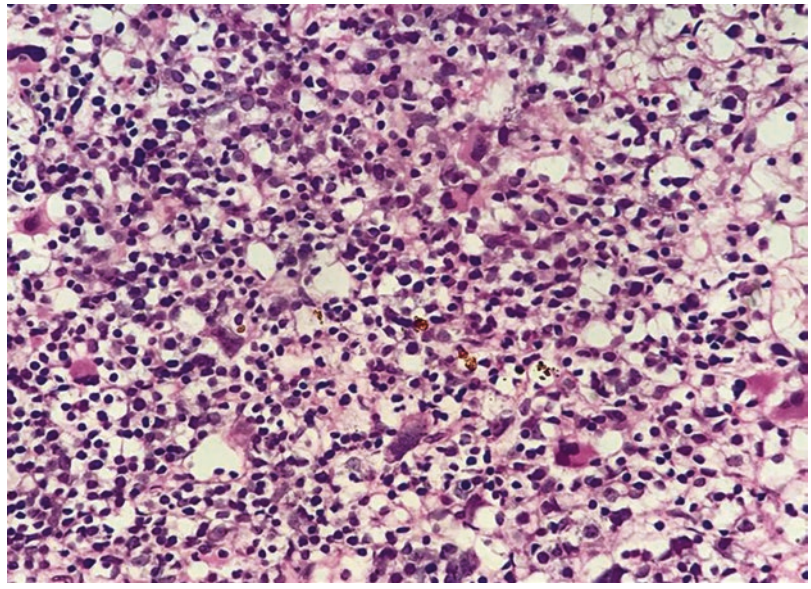

Fig. 29.2 Bone marrow biopsy showing hypercellular area in a case of AIMF. Presence of lymphocytes and background fibrosis is also seen (40×, Hematoxylin and Eosin)

and on immunohistochemistry show benign pattern (mixture of B and T lymphocytes) [3, 5]. Prominent plasma cells infiltration which is a feature of all autoimmune disorders are common in AIMF too and should not show any Kappa/lambda restriction. Intrasinusoidal hematopoiesis may be noted [7].

29.6 Differential Diagnosis

Clinically, patients of autoimmune myelofibrosis present with cytopenias hence need to be differentiated from aplastic anemia/BM failure syndrome. Presence of increased reticulin fibers in bone marrow biopsy should exclude aplastic anemia.

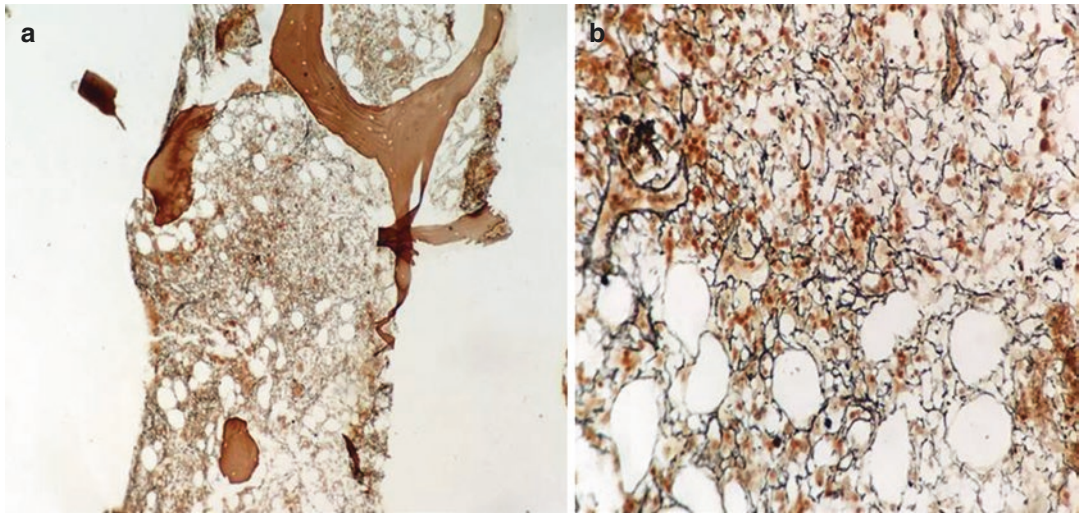

Fig. 29.3 Bone marrow biopsy showing Grade 1 fibrosis (10× (**a**), 40× (**b**), Reticulin stain)

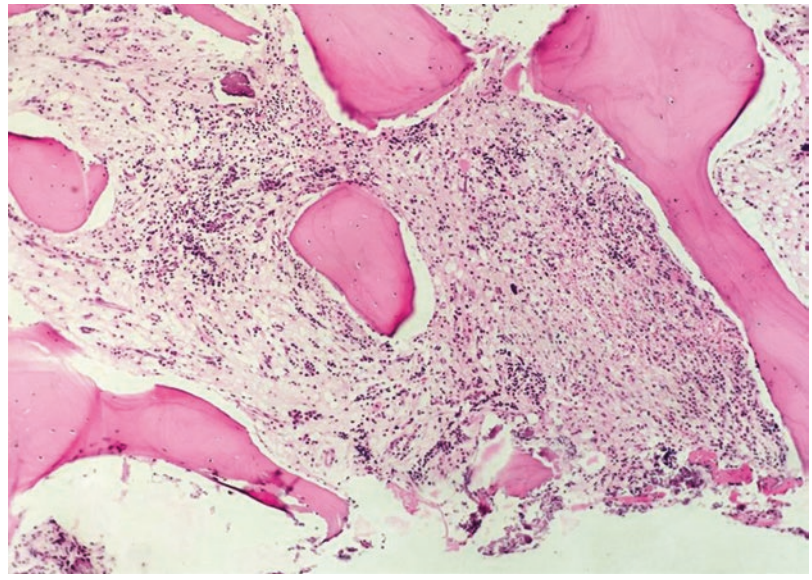

Fig. 29.4 Presence of marrow fibrosis along with lymphoid aggregates (20×, Hematoxylin and Eosin)

On morphology, the close differentials of autoimmune myelofibrosis include myelodysplastic syndrome with fibrosis, acute panmyelosis with myelofibrosis, lymphoproliferative disorders, and primary myelofibrosis. Patients with myelodysplastic syndrome with fibrosis and acute myelofibrosis may have similar clinical presentation as AIMF (pancytopenia with lack of organomegaly and significant leukoerythroblastosis). Presence of dysplasia and increase in blast count and cytogenetic study may help to exclude these two conditions, respectively.

Lymphoproliferative disorders may be suspected due to increased lymphoid cell infiltrate. Any lymphadenopathy or hepatosplenomegaly along with atypical lymphocytes on peripheral smear or bone marrow would point towards a diagnosis of lymphoid malignancy. In suspected cases, the lymphoid aggregates should be subjected to immunohistochemistry to exclude any clonal disease [5].

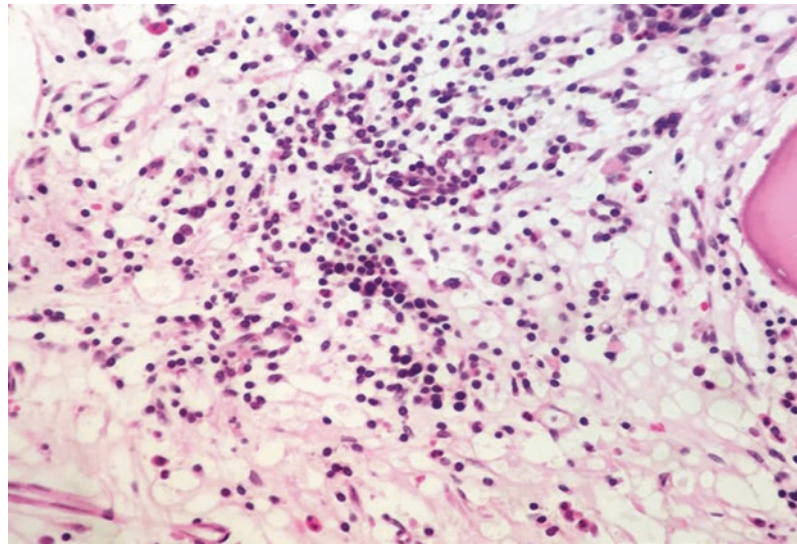

Fig. 29.5 Collection of lymphocytes and plasma cells in a background of fibrosis and stromal edema (40×, Hematoxylin and Eosin)

Table 29.4 Distinguishing features of AIMF and PMF

	Features	AIMF	PMF
Clinical	Underlying autoimmune disorder	May be present/absent	Absent
	Spleen	Absent/mild	Moderate/massive
Peripheral smear	Cytopenia	Bi/pancytopenia	May have increase TLC/platelet count
	Leukoerthyroblastic picture	Rare	Common
	Eosinophilia/basophilia	Absent	May be present
Bone marrow	Cellularity	Mostly hypercellular	Variable (hypocellular)
	Megakaryocytes	Increased with normal morphology	Increased and dysplastic morphology
	Megakaryocytic clustering	Absent	Present
	Intrasinusoidal hematopoiesis	Rare	Prominent
	Lymphoid infiltrates	Frequent	Rare
	Plasma cells	Prominent	Absent
	Reticulin fibrosis	MF gd 1–2 (rare3)	MF gd 2–3 with osteosclerosis
Investigations	Autoimmune Abs	Positive	Negative
	Clonality marker	Negative	Positive (e.g., JAK V 617F, CAL-R or MPL)
Management	Treatment	Steroids	Supportive/HS CT/JAK2 inhibitors
	Prognosis	Favorable	Unfavorable

It is a difficult task to distinguish primary AIMF from primary myelofibrosis and close observation of morphological details are required in the absence of mutation positivity (Jak2/CAL R/MPL) and other evidence of clonality. Usually, patients with PMF have appreciable to significantly palpable spleen, leukoerythroblastic picture, megakaryocytic clustering, and atypia on bone marrow. Table 29.4 provides the list of distinguishing features between AIMF and PMF.

29.7 Management

Steroids are the mainstay in the treatment of autoimmune myelofibrosis with patients showing rapid improvements in cytopenias [1, 11]. Those

who fail to respond to corticosteroids can benefit from other immunosuppressive therapies [11]. Definition of complete response includes normalization of hemoglobin level and platelet count in the absence of transfusion requirements [7]. Count recovery generally precedes resolution of BM fibrosis with 50% patients showing residual fibrosis even with complete response [3]. Overall, AIMF patients have a significant better overall survival as compared to primary myelofibrosis.

29.8 Conclusion

Autoimmune myelofibrosis is an underrecognized cause of myelofibrosis in patients presenting with cytopenias that responds to steroids and has a good clinical outcome in majority of patients. The spectrum of clinical presentation of primary and secondary AIMF may be broad but the BM findings are usually similar. It is imperative to differentiate AIMF from PMF due to drastic prognostic and therapeutic differences between these entities.

Points to Remember

1. Autoimmune myelofibrosis (AIMF) is a distinct clinicopathological entity.
2. Two types: primary AIMF and secondary AIMF.
3. Usual presentation includes—cytopenias with or without preexisting autoimmune disorder.
4. Splenomegaly is rare.
5. Immunosuppressive therapy leads to complete or partial response of cytopenias (independent of resolution of fibrosis).
6. Good morphological assessment of BM biopsy features clinches the diagnosis.

Conflicts of Interest Nil.

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