Primary autoimmune myelofibrosis: a report of three cases and review of the literature

Primer otoimmün miyelofibrozis-üç olgunun sunumu ve literatürün gözden geçirilmesi

Rakhee Kar, Shyamali Dutta, Seema Tyagi

Department of Hematology, All India Institute of Medical Sciences, New Delhi, India

Abstract

Myelofibrosis in association with autoimmune disorders has been consistently recognized in sporadic case reports over a number of years. Autoimmune myelofibrosis has been described most commonly in association with systemic lupus erythematosus (SLE). In addition, myelofibrosis presenting as cytopenias and showing clinical response to immunosuppressant drugs, notably steroids, has been reported with a wide range of immune-mediated disorders, including Sjögren's syndrome, polyarteritis nodosa, rheumatoid arthritis, ulcerative colitis, and primary biliary cirrhosis. Attempts have been made to define a syndrome of primary autoimmune myelofibrosis (PAIMF), as a distinct steroid-responsive clinicopathologic entity with excellent prognosis. Herein, we describe three cases of autoimmune myelofibrosis with a review of the literature. *(Turk J Hematol 2009; 26: 146-50)*

Key words: Myelofibrosis, autoimmune, leukoerythroblastosis, splenomegaly, autoantibodies

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Özet

Otoimmün bozukluklar ile ilişkili miyelofibrozis birkaç yıldan bu yana, sürekli olarak sporadik olgu sunumlarında göze çarpmaktadır. Otoimmün miyelofibrozis en yaygın olarak sistemik lupus eritematozus (SLE) ile ilişkili olarak tanımlanmaktadır. Ayrıca, sitopeni ile kendini gösteren ve immün sistemi baskılayan ilaçlara, özellikle steroidlere, klinik yanıt oluşturan miyelofibrozis çok sayıda immun-aracılı bozuklukla beraber bildirilmektedir. Bunlar Sjögren sendromu, poliarteritis nodosa, romatoid artrit, ülseratif kolit ve primer biliyer sirozu içermektedir. Çok iyi bir prognoza sahip, steroide yanıt veren farklı bir klinikopatolojik antite olarak primer otoimmün miyelofibrozis (POIMF) sendromunu tanımlama girişimlerinde bulunulmuştur. Biz, burada literatürü gözden geçirerek, üç otoimmün miyelofibrozis olgusunu tanımlamaktayız.
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Anahtar kelimeler: Miyelofibrozis, otoimmün, lökoeritroblastozis, splenomegali, otoantikorlar

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Address for Correspondence: Dr. Seema Tyagi, Room No 160, Department of Hematology, IRCH Building, All India Institute of Medical Sciences 110029 New Delhi, India
Phone: 9868397234 E-mail: drseematyagi@hotmail.com

Introduction

Bone marrow fibrosis can arise as a result of a wide range of neoplastic and non-neoplastic disorders [1]. Whereas infection, metastasis and primary hematological malignancy are more frequently causative, systemic lupus erythematosus (SLE) is perhaps the disease that has been implicated earliest and most frequently in cases of myelofibrosis associated with autoimmune disorders. Reports in the literature [2,3] characterize primary autoimmune myelofibrosis (PAIMF) on the basis of a lack of an association with a well-defined autoimmune disorder. There may be positive serology for autoantibodies with variable cytopenias. Absence of splenomegaly, minimal teardrop poikilocytosis and leukoerythroblastosis in the peripheral blood are characteristic. The condition responds clinically to steroids, with improvement in cytopenias. Apart from SLE, myelofibrosis has been reported in several cases with established systemic immune disorders like juvenile rheumatoid arthritis [4], ulcerative colitis [5], primary biliary cirrhosis [6], and idiopathic thrombocytopenic purpura [7]. However, immunological abnormalities have also been reported in idiopathic myelofibrosis in the form of circulating immune complexes, positive serological tests like antinuclear antibodies (ANA), low complement levels, bone marrow lymphoid nodules, and therapeutic response to steroids [8-14].

Materials and Methods

Herein we present the clinico-hematological profile of three cases fitting the diagnosis of PAIMF amongst a total of 118 cases of myelofibrosis diagnosed within the last three years. The clinico-hematological characteristics of the cases are summarized in Table 1. An analysis of 10 case reports of AIMF reported in the literature is presented in Table 2.

Case 1

This 38-year-old male presented with weakness of two years' duration. On examination, he had pallor and hepatosplenomegaly. There was no lymphadenopathy, fever or bleeding manifestations. Peripheral blood examination revealed hemoglobin (Hb) 52 g/L, total leukocyte count (TLC) 3.2 x10^9/L and platelet count 126 x10^9/L. Peripheral blood smear showed normocytic, normochromic red blood cells (RBCs) and no teardrop poikilocytes or nucleated RBCs. There were no abnormal white blood cells (WBCs). Platelets were mildly reduced. The bone marrow trephine biopsy was hypercellular with 100% cellularity and no increase or clustering of megakaryocytes. However, dysplastic megakaryocytes with hypolobated nuclei and bare megakaryocyte nuclei were present (Figure 1). Intrasinusoidal hematopoiesis was absent. There was a moderate diffuse infiltrate of mature lymphocytes. Reticulin was Grade 2. The patient was treated with Inj methylprednisolone followed by oral prednisolone. At five months, his blood counts were normal. Spleen size regressed to 2 cm below the left costal margin.

Case 2

This 29-year-old male presented with generalized weakness of three months' duration. At presentation, he was pale but had no organomegaly, lymphadenopathy or bleeding. Peripheral blood examination revealed Hb 73 g/L, TLC 7.3 x10^9/L and platelets 162x10^9/L. His anemia progressed to Hb 68 g/L after two weeks, at which time the spleen became palpable up to 4 cm below the left costal margin. Peripheral blood smear showed predominantly normocytic, normochromic RBCs with small numbers of teardrop poikilocytes and nucleated RBCs. There were no abnormal WBCs. Platelets were adequate. Bone marrow trephine biopsy was normocellular with 40% marrow cellularity, consisting of a patchy distribution of myeloid and erythroid cells and normal numbers of non-clustered megakaryocytes, some of which had hypolobated nuclei. Scattered interstitial lymphocytes and focal non-paratrabecular aggregates of mature lymphocytes were present (Figure 2). There was no intrasinusoidal hematopoiesis. Reticulin was Grade 2. The patient was treated with Inj methylprednisolone and oral steroids. At one year of follow-up, his spleen remained palpable 2 cm below the left costal margin although blood counts were normal.

Case 3

This 33-year-old male presented with generalized weakness and low-grade fever of three years' duration. On examination, he had pallor, splenomegaly 3 cm below the left costal margin, and no lymphadenopathy or bleeding manifestations. Computerized tomography (CT) scan of the abdomen revealed

Table 1. Clinico-hematological characteristics of the three cases of primary autoimmune myelofibrosis in this report

Case No	Age/ Sex	Associated Disease	Spleen (below LCM)	Hb g/L	TLC x10^9/L	Platelet Count x10^9/L	Serology	Response to Steroids	Bone Marrow Histology
1	38/M	None	4 cm	52	3.2	126	ANA+, Anti ds DNA+	PR	Reticulin Grade 2
2	29/M	None	4 cm	68	7.3	162	ANA-, Anti ds DNA-, RF-	PR	Reticulin Grade 2
3	33/M	None	3 cm	59	2.9	95	DCT+ ANA-, Anti ds DNA-	PR	Reticulin Grade 3

LCM: Lower left costal margin; ANA: Antinuclear antibody; RF: Rheumatoid factor; PR: Partial remission (normal blood counts, still palpable spleen); DCT: Direct Coombs' test; -: Negative; +: Positive

Table 2. Clinico-hematological characteristics of 10 cases of primary autoimmune myelofibrosis reported in the literature referans

Case no	Age /Sex	Associated Disease	Spleen	Hb g/L	TLC x10^9/L	Platelet Countx10^9/L	Serology	Response to Steroids
1	73/M	Psoriasis, Kaposi's sarcoma	No	Anemia	NM	R	DCT+	CR
2	48/F	Diabetes mellitus, AIHA	No	Anemia	R	NM	DCT+	CR
3	40/F	Synovitis	No	Anemia	R	R	ANA+	CR
4	42/M	None	No	Anemia	R	R	ANA+	CR
5	22/M	None	No	Anemia	NM	NM	DCT+, ANA+	PR
6	47/F	Diabetes mellitus, Thyroiditis, AIHA	No	Anemia	NM	R	NM	CR
7	68/F	Autoimmune hepatitis	No	Anemia	R	R	ANA+, DCT+	CR
8	72/F	Sjögren's syndrome	No	115	1.3	206	RF+	CR
9	43/F	None	No	79	7.8	16	AntiNuMA+	CR
10	59/F	Sjögren's syndrome	No	122	2.38	246	RF+, ANA+, anti-SSA+	NR

NM: Not mentioned; RF: Rheumatoid factor; ANA: Antinuclear antibody; DCT: Direct Coombs' test; CR: Complete response; PR: Partial response; NR: No response; R: reduced; -: Negative; +: Positive

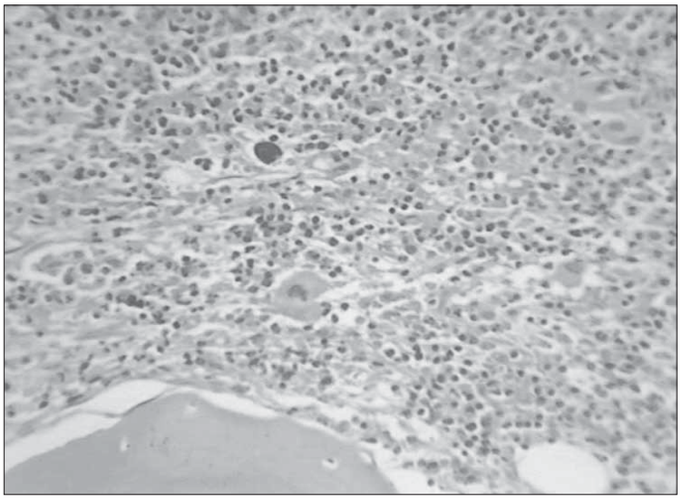

Figure 1. Bone marrow biopsy of Case 1 showing presence of dysplastic megakaryocytes with hypolobation and naked megakaryocytic nuclei. There is diffuse increase in mature lymphocytes (hematoxylin and eosin, x400)

a paravertebral mass. Fine needle aspiration cytology (FNAC) of the mass revealed extramedullary hematopoiesis. Peripheral blood examination revealed Hb 59 g/L, TLC 2.9 x10^9/L and platelets 95 x10^9/L. Peripheral blood smear showed predominantly normocytic, normochromic, red cells, no nucleated RBCs and small numbers of teardrop poikilocytes. There were no abnormal WBCs and platelets were moderately reduced. Bone marrow biopsy was hypocellular (marrow cellularity of 10%). Clustered megakaryocytes with hypolobated forms and naked megakaryocyte nuclei were present. Myeloid and erythroid cells were reduced. Focal non-paratrabecular aggregates of mature lymphocytes were present. There was no intrasinusoidal hematopoiesis. Reticulin was Grade 3 (Figure 3). The patient was treated with oral steroids. At one year of follow-up, his blood counts were normal and the paravertebral mass had regressed, but the spleen remained palpable 2 cm below the costal margin.

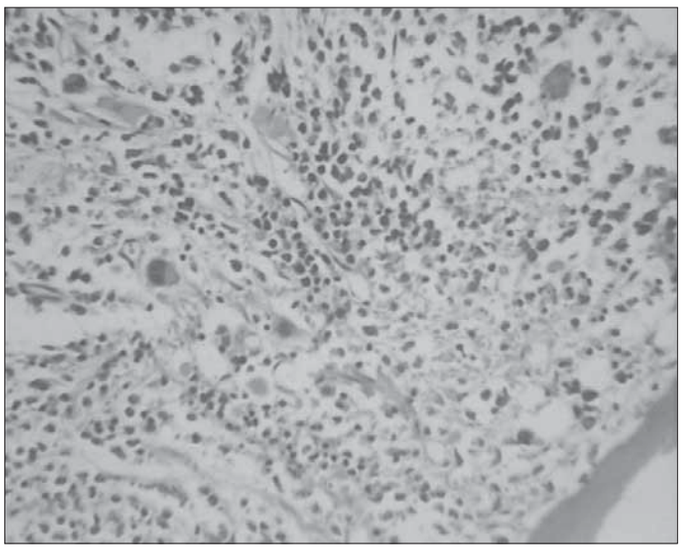

Figure 2. Bone marrow biopsy of Case 2 with non-clustered megakaryocytes, few with hypolobated nuclei and a scattered interstitial lymphocyte infiltrate with focal non-paratrabecular aggregates (hematoxylin and eosin, x400)

Discussion

In a survey of the literature dating back to 1969, Rizzi et al. [2] discovered 24 case reports of AIMF. They found 17 cases associated with SLE, and the rest with diverse diseases like Sjögren's syndrome, Hashimoto's thyroiditis, autoimmune hemolytic anemia, psoriasis, and synovitis and cases with isolated positive ANA test.

Pullarkat et al. [15] defined a syndrome of PAIMF, highlighting the features of a lack of association with a well-defined autoimmune syndrome, no splenomegaly, presence of autoantibodies and the absence of a disorder known to cause myelofibrosis. They emphasized lack of teardrop poikilocytes and leukoerythroblastosis in the peripheral blood with absence of clustered and atypical megakaryocytes and the presence of lymphoid infiltrates in the bone marrow in addition to fibrosis.

Bass et al. [16] similarly described rare or absent teardrop poikilocytes and nucleated RBCs in the peripheral blood smear. Their cases showed megakaryocytic dysplasia without clustering, lymphoid infiltrates and intrasinusoidal hematopoiesis. One case had autoimmune hemolytic anemia and splenomegaly at presentation.

Paquette et al. [3] defined AIMF as an uncommon disorder with anemia and thrombocytopenia with either limited clinical manifestations of an autoimmune disease or exacerbation of previously established SLE. They opined that absence of splenomegaly in myelofibrosis may suggest an autoimmune disorder and that tests for LE cell and ANA are invariably positive in such cases.

As is evident from our cases (Table 3), the hematological features of AIMF described in the literature also show some overlapping and some distinct features from chronic idiopathic myelofibrosis (CIMF). In the detailed analysis of 24 cases of AIMF, hypocellular marrows were found in half the cases, hypercellular marrow in 10 cases and normocellular marrow in two cases [2]. Reticulin fibrosis ranged from 2+ to 4+, and none of the cases had clustered megakaryocytes in the marrow. Two cases had lymphoid infiltration in the marrow. All cases showed absence of significant leukoerythroblastosis and teardrop poikilocytosis in the peripheral blood smears and lack of organomegaly.

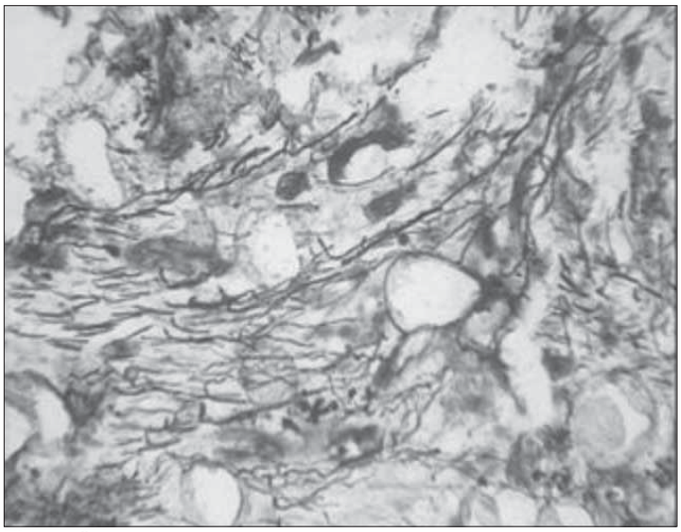

Figure 3. Bone marrow biopsy of Case 3 showing marked diffuse reticulin fibrosis (reticulin staining, x400)

Table 3. Comparison of salient features of CIMF and PAIMF

Features	CIMF	Primary AIMF (literature)	Primary (our cases)
Pancytopenia	+/-	+	+
Teardrop cells	++	+/-	+/-
Leukoerythroblastosis	++	+/-	_
Splenomegaly	present	absent	present
Bone marrow fibrosis	present	present	present
Clustered megakaryocytes	++	+/-	1 of 3
Dysplastic megakaryocytes	+/-	+/-	2 of 3
Lymphoid infiltrate	+/-	++	all cases
Intrasinusoidal hematopoiesis	+/-	+/-	none
Clonal cytogenetic abnormality	+/-	no study	not done
Association with autoimmune disease	-	+/-	-
Autoantibodies	+/-	+.	2 of 3
Response to steroids	no study	present	all cases

Bass et al. [16] in their cases found rare to moderate numbers of teardrop cells, rare nucleated RBCs with moderately reduced to normal platelet counts, mild to moderate anemia, and normal to mild reduction in the leukocyte counts. The bone marrow examination showed grade 3+ to 4+ reticulin fibrosis, cellularity ranging from 30% to 100% and non-clustered megakaryocytes. Erythroid hyperplasia and megakaryocyte abnormalities in the form of small size with hypolobated and hyperchromatic nuclei were present. The notable feature of intrasinusoidal myeloid, erythroid precursors and megakaryocytes was present in all three cases. Interstitial lymphoid infiltrates with non-paratrabecular polyclonal aggregates were present in the three cases.

An analysis of the 10 cases reported in the literature [2,15] (Table 2) reveals the association of a well-defined autoimmune disorder in 7/10 cases. This association was absent in our cases, although positive tests for auto-antibodies were present in two cases (Cases 1 and 3). Although Case 1 had ANA and anti-ds DNA positivity (immunologic disorder) along with hematologic disorder, other clinical manifestations to fulfil the criteria for SLE [17] were lacking. Similarly, Case 3 had direct Coombs' test positivity. However, no spherocytes or nucleated RBCs were seen in the peripheral smear; rather, a few teardrop cells were present. Bone marrow showed significant fibrosis and focal aggregates of mature lymphocytes. Thus, both cases fit the diagnosis of PAIMF, which was reinforced by their steroid responsiveness.

Splenomegaly was present in all our cases in contrast to what is reported in most of the cases in the literature. Peripheral blood examination revealed lack of prominent teardrop poikilocytosis and nucleated RBCs. All the cases had cytopenias. In addition to bone marrow fibrosis, megakaryocytic dysplasia was present in all cases, with clustered megakaryocytes in Case 3 (with extramedullary hematopoiesis). Bone marrow lymphoid infiltrates were present in all cases, mostly diffuse but also focal and non-paratrabecular. None of our cases had intrasinusoidal hematopoiesis in the bone marrow.

Treatment with steroids resulted in complete response in 8/10 cases [2,15] (Table 2). Complete response was defined as normalization of blood counts. Repeat bone marrow biopsies in 3/10 cases revealed only partial resolution of the fibrosis in one case after four months of therapy. Similarly, our cases showed normal blood counts following steroid therapy, at intervals ranging from five months to one year. There was only partial regression of splenomegaly. Bone marrow biopsies, however, were not repeated. Although some features overlapping with CIMF were present in our cases, the steroid responsiveness manifested in normalization of blood counts and

partial regression of splenomegaly is the unifying feature in all three cases that strongly favors the diagnosis of AIMF. As there was lack of a well-defined autoimmune disorder in these cases, they fit the diagnosis of PAIMF.

Bone marrow histology in at least one case (Case 3) showed some features resembling idiopathic myelofibrosis, in the form of clustered megakaryocytes and fibrosis. This case also had extramedullary hematopoiesis. Lymphoid infiltrates and autoimmune phenomenon have been reported in idiopathic myelofibrosis [8-13]. An analysis of clinical characteristics of these cases reveals that lymphoid nodules in the bone marrow in idiopathic myelofibrosis correlates with less-advanced disease, with smaller spleen size and lower WBC and platelet counts. Bone marrow biopsies with lymphoid nodules in cases of idiopathic myelofibrosis are more cellular and show less fibrosis [13]. However, presence of peripheral blood features of prominent teardrop poikilocytosis and nucleated RBCs, clonal cytogenetic abnormalities and lack of steroid responsiveness may serve to distinguish idiopathic myelofibrosis with autoimmune features from AIMF. In Table 3, we present a comparison between the salient features of CIMF and PAIMF reported in the literature and those revealed in our cases.

In conclusion, PAIMF is an uncommon entity, which needs to be diagnosed correctly since a specific treatment option is available. The definition of primary AIMF must necessarily include lack of association of a well-defined autoimmune disorder. Splenomegaly may or may not be present. Presence of splenomegaly should not negate the diagnosis as is evident from our cases. Lack of or minimal teardrop poikilocytes and nucleated RBCs in the peripheral blood together with fibrosis and lymphoid infiltrates in the bone marrow, positive tests for auto-antibodies and steroid responsiveness should be present. Diagnostic criteria may also include lack of clonal cytogenetic abnormalities. There should be documented regression of bone marrow fibrosis on steroid or other immunosuppressive therapy in the long term.

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