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Bicytopenia Secondary to Autoimmune Myelofibrosis as the First Presentation of an Undiagnosed Systemic Lupus Erythematosus: A Rare Case Report

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ABSTRACT

Autoimmune myelofibrosis (AIMF) is considered as an infrequent cause of bone marrow fibrosis (BMF) and a rare complication of systemic lupus erythematosus (SLE). Due to its rarity, it is mistakenly diagnosed as primary myelofibrosis (MF).

We describe the clinicopathologic features of a secondary form of AIMF in a 33-year- old female patient with an undiagnosed SLE which presented with acute bicytopenia. Absence of splenomegaly, leukopenia, anemia, BMF (grade MF-1), and presence of autoantibodies were some of noticeable features. Treatment with corticosteroid led to complete regeneration of the bone marrow and subsequently to an improved hematological status. Six- month follow-up showed that the patient was in good clinical condition.

Identification of AIMF is a diagnostic challenge and pitfall and it is actually a diagnosis of exclusion. It could be the first and only presenting feature of SLE and results in hematologic disturbances. So, we should consider SLE-associated AIMF in the differential diagnosis of pancytopenia.

Keywords: Autoimmune diseases, Primary Myelofibrosis, Fibrosis, Lupus Erythematosus, Systemic

Introduction

Bone marrow fibrosis (BMF) is seen in malignant neoplasm, endocrine diseases, autoimmune conditions, and infectious diseases. Autoimmune myelofibrosis (AIMF) is an uncommon etiology of BMF (1, 2). Because of paucity of AIMF, it is frequently mistaken as primary MF (PMF) which is a myeloproliferative neoplasm (MPN) (3). Myelofibrosis is a less common and far less recognized complication of systemic lupus erythematosus (SLE) (4-6). Pancytopenia in SLE is rarely related to AIMF (7-9).

Case Report

A 33- year-old female patient referred to local oncology center with a chief complaint of acute bicytopenia on routine checkup laboratory blood tests. The patient had referred to various physicians to treat the disease but did not respond to various lines of therapies. Clinical examination revealed pleural effusion which was later confirmed by chest X-rays. There was no evidence of hepatosplenomegaly. A new laboratory evaluation again revealed bicytopenia in complete blood count (CBC) with increased erythrocyte sedimentation rate (ESR) of 40 mm/hr, marked anemia, mild leukopenia and normal platelet count. The white blood cell count was 3000 per microliter of blood (3×10^9/L) (neutrophils: 48%, monocytes: 8% and lymphocytes: 42%); hemoglobin was 8.6 grams per decilitre and the platelet count was 180000 per microliter of blood (180×10^9/L). Mean corpuscular hemoglobin (MCH) was 27.1 picograms/ cell and red blood cell distribution width (RDW) was 14.2%. Increased lactate dehydrogenase (LDH) and high level of C-reactive protein (CRP) were also noticeable. Peripheral blood smear (PBS) showed mild anisocytosis with moderate poikilocytosis. Varied sizes of platelets and platelet aggregation were also seen.

Bone marrow aspiration (BMA) failed to obtain bone marrow (BM). BM trephine biopsy (BMTB) was carried out. Microscopic examination showed mature bony trabeculae with intervening bone marrow. Bone marrow was hypercellular with about 80% active marrow and 20% fat cells. Megakaryocytes were significantly increased with mature and immature mononuclear and bilobed nuclei. Also, significant decrease in erythroid lineage was evident. Small lymphocytes scattered as single cells or small groups comprising nearly 1% of bone marrow cells were present. A few undetermined atypical cells with scant cytoplasm and large vesicular nuclei with occasional prominent nucleoli comprising about 2% of bone marrow cells were noted. In one focus hyperchromatic spindle cells in a sarcomatoid pattern were found (Figures 1 and 2).

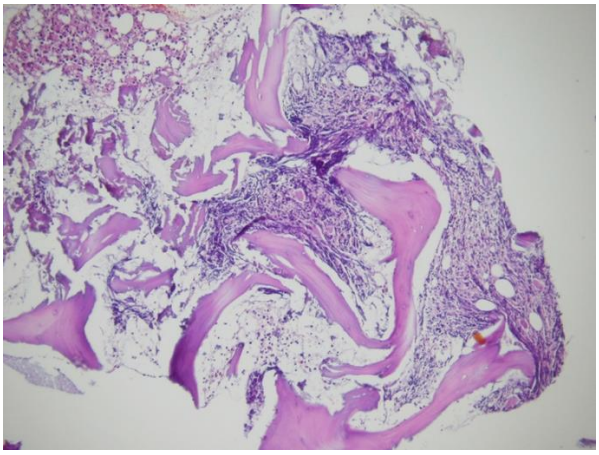

Figure 1. Bone marrow fibrosis in intertrabecular spaces (100X magnification)

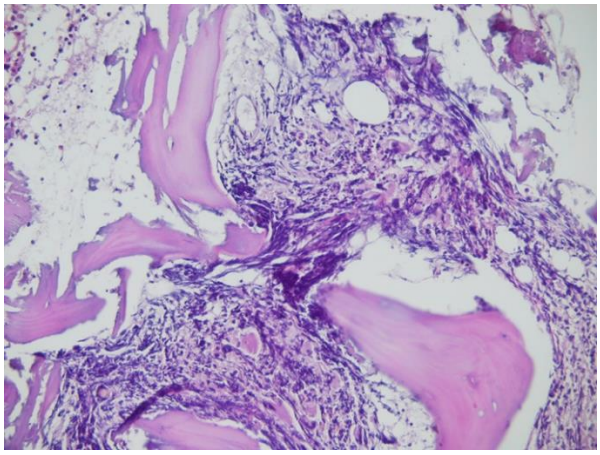

Figure 2. Bone marrow fibrosis in intertrabecular spaces (200X magnification)

Reticulin stain showed mild increase in reticular fibers of bone marrow with many intersections; trichrome stain showed no significant collagen deposition (MF grade 1). Based on BMTB, BMA and PBS, hypercellular bone marrow with mild dysplastic change and mild reticulosis and lymphocytosis was reported. These morphologic features could be in favor of myelodysplastic syndrome/myeloproliferative disorder (MDS/ MPD) and secondary involvement of BM by a lymphoproliferative disorder (LPD). Based on reticulin fibrosis of BM, differential diagnoses include wide variety of causes of BMF from malignancies (hematologic malignancies including MPDs, MDS, LPD and metastatic tumor) to non-tumor conditions entities such as infectious diseases, endocrine diseases, and autoimmune conditions.

Immunohistochemical (IHC) tests were carried out on paraffin embedded tissue fragment of bone marrow to determine the origin of bone marrow resident cells. CD15 was positive in some myeloid cells. CD3 was positive in about 15% of bone marrow cells. CD20 was positive in about 5% of bone marrow cells. CD30 was negative in all bone marrow cells. Although IHC features could be in favor of secondary BM involvement by an LPD as well as a primary BM proliferative disorder, it was not adequate for such a problematic case, so the results were not diagnostic. Cytogenetic studies were carried out for detection of clonal abnormalities. Lack of special properties of PMF and non-existence of clonality for JAK2, CALR, and MPL mutations, approved a non-neoplastic process.

The patient had no known autoimmune disease, including SLE, Sjogren syndrome, and systemic sclerosis. Additional specialized immunological tests were requested. Lupus anticoagulant (LA) testing was negative. Fluorescent Antinuclear Antibody (F ANA) was positive (ANA titer >1:80) (homogeneous pattern). Anti double strand DNA (Anti dsDNA) was high (1407 International units per milliliter; reference range: positive ≥100). The anti-cardiolipin antibody (IgM) was also high. C3 and C4 were low. Anti β2 glycoprotein I antibody (IgM) was high (12.13 RU/ml; reference range: positive ≥10). The ANA profile (IgG) was positive (+++) for anti-dsDNA, anti-nucleosomes and anti-histone.

According to the 2019 EULAR/ACR diagnostic criterion of SLE, positive ANA test together with ≥10 points from other clinical (hematologic and serosal) and immunological (antibodies against phospholipid, complement components, antibodies which are specific for SLE) dimensions confirmed a final diagnosis of SLE and SLE-associated AIMF.

Methylprednisolone 1 gr intravenously per day was started, it went on for three days, leading to gradual amelioration of clinical status and hematological indices. Prednisone dose was gradually decreased from 25 milligram per day to 10 milligram per day in a period of about three months.

After six months of treatment and follow-up, the patient's clinical status developed, CBC was normal, and check-up BMB demonstrated full improvement of BMF (MF-0). Maintenance therapy is still continued with prednisone 5 mg/daily.

Discussion

BMF is seen in different situations like MPN, leukemia, lymphoma, plasma cell myeloma, Gaucher disease, metastasis, hyperparathyroidism, chronic renal failure, and AI conditions disorders. **(1, 2)**

AIMF is considered as non-tumor etiology of MF. It is accompanied by AI diseases with a good prognosis. When an AI disease such as SLE exists, it is considered secondary AIMF. Primary AIMFs (PAIMFs) are AIMF with autoantibodies but without known AI diseases. Pathogenesis of AIMF is not well known. Reaction of fibroblasts to growth factors (GF) is the probable hypothesis. Some studies suggest that cytokine-dependent mechanisms drive BMF in AIMF.In people with SLE, antigen-antibody combination causes liberation of PDGF from megakaryocyte **(7)**. Table 1 provides case reports of AIMF in SLE.

Table 1. Case reports of autoimmune myelofibrosis in patients affected by systemic lupus erythematosus

Author, year	Sex, age	Autoantibodies, complement	Cytopenia LDH	BMTB	therapy	response	other features	Hepatosplenomegaly.
Belfeki [2], 2019	F, 44	ANA, anti-dsDNA, anti-SSA, anti-Sm, Coombs , anti-CL, β2GPI, LA ↓C3, ↓C4	Pancytopenia, LDH nr	No dysplasia, Hypocellular, MF-2	Oral Pred, HCQ	PBC improvement, BMB nr	fatigue, oral ulcerations, sicca syndrome and joint pains, erythematosus malar rash, proteinuria, haematuria, patchy alopecia	No
Driouach [6], 2019	M, 42	ANA, anti-dsDNA , anti-RNP, anti-Sm, anti-SSA, anti-SSB, β2GPI, anti-CL ↓C3, ↓C4	Pancytopenia LDH na	Hypercellular, ↓myeloid, ↑ erythroid, ↑megakaryocyte, MF-2	Oral Pred	PBC improvement, BMB nr	Thrombophlebitis, Pneumonia, Fever	Yes, splenomegaly
Gauiran [5], 2019	F, 30	ANA, C3 nr,	Anemia, pancytopenia after 10 days ↑LDH	Normocellular, ↑megakaryocyte, MF-2	IV hydrocortisone, HCQ, oral Prednisone and HCQ as maintenace	PBC improvement, BMB nr	Fever, malaise, generalized weakness, anorexia, unintentional weight loss, alopecia, throat discomfort, exertional dyspnea, easy fatigability, and additive arthritis of bilateral knees, elbows, and small joints of both hands	Yes, hepatomegaly
Kaul [8], 2019	F, 36	ANA, anti-Ro,	Pancytopaenia LDH na	Hypercellular, ↑in all haematopoietic	Oral Pred, HCQ	initial PBC improvement but later	recurrent epistaxis, arthralgias,	Yes, splenomegaly

Author, year	Sex, age	Autoantibodies, complement	Cytopenia LDH	BMTB	therapy	response	other features	Hepatosplenomegaly.
		anti-La, anti-RNP , anti-dsDNA ↓C4		cell lines, MF-3		returen of pancytopenia and other sign and symptom worsening sign and symptom PBC improvement BMB na	cough, fevers and weight, malar skin rash and mild diffuse alopecia	
					Methotrexate , Ciclosporin , MMF ,Azathioprine (All stopped) Rituximab			
Mbonu [4], 2019	F, 20	ANA, anti-dsDNA , rheumatoid factor, anti-Sm, anti-SSA, ↓C3, ↓C4	Anemia, leukopenia ,	↑megakaryocyte, MF-2	IV Solu-Medrol and then a steroid taper and Plaquenil	na	worsening fatigue, dyspnea on exertion, and palpitations, bone pain and fevers later	No
Wu [9], 2019	M, 39	ANA, ant-RNP, anti-Sm, anti-Centromere B, LA, Coombs	Pancytopenia LDH na	Hypercellular , normal myeloid/erythroid, ↑megakaryocyte, MF-2	HCQ, Oral Pred,	PBC improvement BMB na	Raynaud's phenomenon, abdominal pain, weakness, fatigue, dizziness, and left flank pain	Yes, splenomegaly
Wibowo [1], 2020	F, 66	ANA, Anti-dsDNA, β2GPI, anti-CL, Direct Coombs ↓C3, ↓C4	Pancytopenia LDH nr	Hypocellular, MF-2, T cells and B cells infiltration, clustering of atypical megakaryocytes, but no increase in megakaryocytes	Oral Pred	PBC improvement BMB nr	Fatigue and dizziness. light-headedness	Yes, mild splenomegaly

Anti-dsDNA: Anti-double stranded DNA; anti-CL: Anti-cardiolipin; β2GPI: Anti-β2 glycoprotein I; LA: Lupus anticoagulant; C: complement; BMTB: Bone marrow trephine biopsy; MF: Marrow fibrosis, Hydroxychloroquine: HCQ; Pred: prednisone; IVIG: intavenous immunoglobulins; MMF:mycophenolate mofetil; MTHYP: methylprednisolone; PBC: peripheral blood cell count; BMB: bone marrow biopsy; nr: Normal; na: not available; F: Female; M: Male; intravenous: IV

According to world health organization (WHO) categorization, MF scoring is based on reticulin stain divided into MF0 to MF3 **(10)**. Features of our case were compatible with MF grade1.

AIMF usually occurs in women, before forty years of age **(10)**. Our case was also a female under 40 years old. Lab findings of AIMF consist of anemia, thrombocytopenia, left-shifted granulocytes, scarce erythroblasts, presence of autoantibodies, decreased complement levels, and presence of antibodies that act against red blood cells **(10)**. From the above-mentioned features, our case had anemia, presence of autoantibodies, and hypocomplementemia. In AIMF patients, physical examination may demonstrate enlargement of spleen or swelling and enlargement of the liver and spleen and joint pain or, infrequently, ulcer in the mouth, hemorrhage from gingiva, petechiae, pleurisy, inflammation of the pericardium, adenopathy, and butterfly eruption on the cheeks **(10)**. Among these signs, our case only had pleuritis.

Differentiation of AIMF from PMF is mandatory; clinic, outcome and treatment are not the same. Monoclonality is the characteristic property of PMF. **(3)**

According to EULAR/ACR categorization, persons with ≥10 scores are categorized as SLE (8). Our case had Leukopenia (WBC <4,000/mm³) (score 3) and evidence of autoimmune hemolysis (elevated Lactate dehydrogenase [LDH]) (score 4); the patient gained 4 scores at hematologic domain. The patient had pleural effusion as imaging evidence (chest x-ray) indicated, and in serosal domain she gained 5 scores. An anti-cardiolipin antibody titer (IgM) was high in our case. Anti-β2 glycoprotein I (GPI) antibody (IgM) was also positive, and she gained 2 scores at antiphospholipid antibodies domain. In our case, C3 and C4 levels were low, and she gained 4 scores at complements domain. The anti dsDNA was positive in our case, and she gained 6 scores at SLE-specific antibodies domain. Patient score at all domains was 21. Since our case had the obligatory entry criterion (ANA positive test for at least once) and patient accumulated ≥10 points or scores, she was classified as having SLE and met SLE classification criteria.

AIMF in SLE is reversible with treatment of the underlying condition. Corticosteroids have been shown to be useful in treating both SLE and the associated autoimmune myelofibrosis **(5)**.

Conclusion

Identification of AIMF is a diagnostic challenge and pitfall and it isactually a diagnosis of exclusion. It could be the first and only presenting feature of SLE and results in hematologic disturbances. So, we should consider SLE-associated AIMF in the differential diagnosis of pancytopenia.

Acknowledgments

None.

Conflict of Interest

There was no COI to report by the authors.

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