Case Report

Idiopathic myelofibrosis with recurrent spontaneous abortions and coexistent antinuclear antibodies - A Rare Case report

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Abstract

Primary Myelofibrosis (PMF) is a clonal myeloproliferative neoplasm characterized by a proliferation of megakaryocytes and granulocytes in the bone marrow, associated with reactive deposition of fibrous connective tissue and with extramedullary hematopoises. It occurs most commonly in the decade six of life and it is very rare in the young ones. Among all myeloproliferative disorders the prevalence of Idiopathic myelofibrosis in women of child bearing age group is very less and the prognosis is variable but generally poor. The risk of spontaneous abortion is 2.5-fold higher than in the control population, while the incidence of maternal complications is lower 3% for major thromboembolic and 2% for major bleeding event. There is only few literature data about pregnancy, complications in pregnancy, recommended treatment and delivery in these patients. So far only eight pregnancies in four patients with idiopathic myelofibrosis have been reported. We report such a rare case of idiopathic myelofibrosis with recurrent miscarriages. Myelofibrosis (MF), including primary myelofibrosis, post-essential thrombocythemia MF, and post-polycythemia vera MF, has been reported to be associated with autoimmune phenomena. A 30-year-old with a history of recurrent spontaneous abortion in the mid trimester and an IUD was admitted to our hospital for further management. Diagnosis: ANA Profile by IF was suggestive of auto antibodies against sd70,pm SdFibillarin, RNP Polymerase. The diagnosis of PMF was made based on the WBC and platelet counts, bone marrow biopsy, and molecular biology testing. The autoimmune process is an incidental finding in this case which is reported in literature to be associated with primary Myelofibrosis. Recurrent spontaneous abortion in the mid trimester might be associated with PMF. Thus, a detailed investigation including blood routine examination to identify an abnormal platelet count is warranted

for pregnant patients with such a history in order to facilitate timely treatment. The autoimmune process is an incidental finding in this case which is reported in literature to be associated with primary myelofibrosis It is important to diagnose correctly as both conditions have distinct prognosis and course of disease.

Key words

Myeloproliferative disorders, Primary Myelofibrosis, Pregnancy, Recurrent spontaneous abortion.

Introduction

Primary Myelofibrosis (PMF) is a clonal myeloproliferative neoplasm characterized by a proliferation of megakaryocytes and granulocytes in the bone marrow, associated with reactive deposition of fibrous connective tissue and with extramedullary hematopoises [1, 2]. The cause of this disease is not known and no specific therapy exists. Among all myeloproliferative disorders the prevalence of Idiopathic myelofibrosis in women of child bearing age group is very less and the prognosis is variable but generally poor [3, 4]. So far only eight pregnancies in four patients with Idiopathic myelofibrosis have been reported in the literature. PMF is least prevalent of all myeloproliferative neoplasms in women of child bearing age – the prevalence is 0.023–0.06/100.000 in this age-group [4]. We report such a rare case of Idiopathic myelofibrosis with recurrent miscarriages. The autoimmune phenomenon including Antinuclear antibodies (ANA) positivity, Rheumatoid factor or positive coombs test can also be observed in Primary Myelofibrosis. The autoimmune process as an incidental finding is reported in literature to be associated with primary myelofibrosis [18]. It is important to diagnose correctly as both conditions, autoimmune myelofibrosis and primary myelofibrosis have distinct prognosis and course of disease [17, 19]. The neoplastic cause of primary myelofibrosis can sometimes have overlapping features with non-neoplastic causes like autoimmune myelofibrosis, secondary to SLE or primary autoimmune Myelofibrosis [17].

Case Report

A 30-year-old woman was referred to the Hematologist, for persistent leucocytosis and mild thrombocytosis for past 6 months. She has a medical history of three recurrent abortions. The patient was in good health and no history of vascular head ache, dizziness or blurred vision. She also had no symptoms of microcirculatory disturbances (e.g. acroparesthesia or acrocyanosis), fatigue, abdominal discomfort, pruritus, night sweats, bone pain, or weight loss. She had no major risk factors for cardiovascular disease and no history of vascular embolism. Her family history was unremarkable. The patient's obstetrical status is that she had a history of two medical abortions at 8 and12 weeks respectively and an IUD at 28 Weeks. Two years before that she had a normal pregnancy and delivery.

Physical examination did not show peripheral lymphadenopathy, or signs of skin and mucosal bleeding. Mild splenomegaly noted.

Laboratory findings, The Hemogram findings were elevated platelet count, leucocytosis with shift to left and basophilia (HB 12.4g MCV 84.9, RBC count - 4.4 million/ WBC – 16.5 *103 and plt 5.5 lakhs), RBC morphology showed anisopoikilocytosis with prominence of teardropcells, Nucleated RBC were 1-2/100 wbc Peripheral blood findings were of Leucoerythroblastic blood picture (**Figure - 1**). Her blood coagulation profile showed borderline elevated APTT. ANA Profile by IF was suggestive of auto antibodies against sd70,pm SdFibillarin, RNP Polymerase. Bio-chemistry and Erythrocyte sedimentation Rate were normal. Ultra-sonography of the abdomen and pelvis showed enlarged spleen (14.2 cm).

The Bone marrow aspirate was hemodilute. Bone marrow Trephine biopsy with subsequent hematoxylin and eosin staining showed a hematopoietic area of 70% (31–49%), fat area of 10% (20–36%), and trabecular bone area of 20% (21–31%).The granulocytic /erythroid (G/E) ratio was normal. Myelopoiesis show prominence of precursor forms. Moderate proliferation of megakaryocytes, increased in number, which were mostly enlarged, hyperlobulated, polymorphic, forming tight clusters of variable size (**Figure - 2.2**). No abnormal cells were found in the bone marrow hematopoietic area.bone marrow showed fibrosis (**Figure - 2.1**). Special stains, Reticulin and Masons Trichrome done for fibrosis show grade MF 3 reticulin condensation with diffuse collagenisation (**Figure - 3.1**) (**Figure - 3.2**).

Figure - 1: Peripheral blood smear showing tear drop cells.

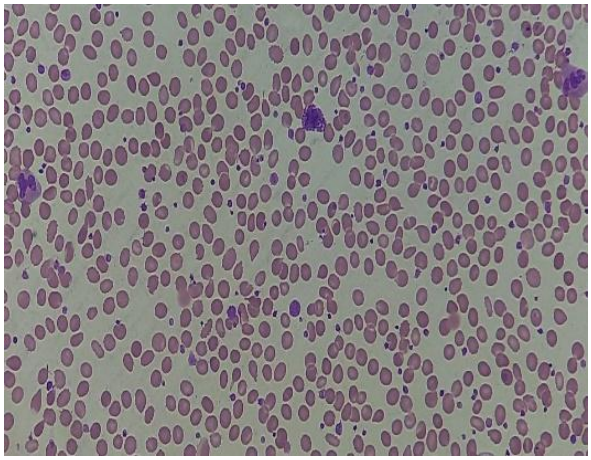
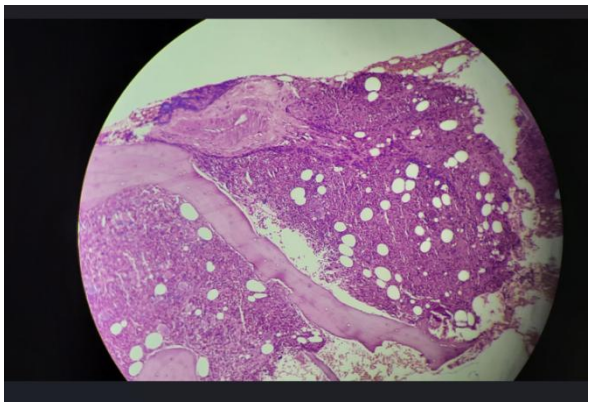


Figure - 2.1: Bone marrow biopsy showing marrow fibrosis.



Karyotype was normal, 46 XX. Janus kinase 2 (JAK2) (V617F) mutation was identified, negative for the MPLW515L/K and CALR mutations. BCR-ABL rearrangement was not seen.

Figure - 2.2: Megakaryocytes showing nuclear atypia and clustering.

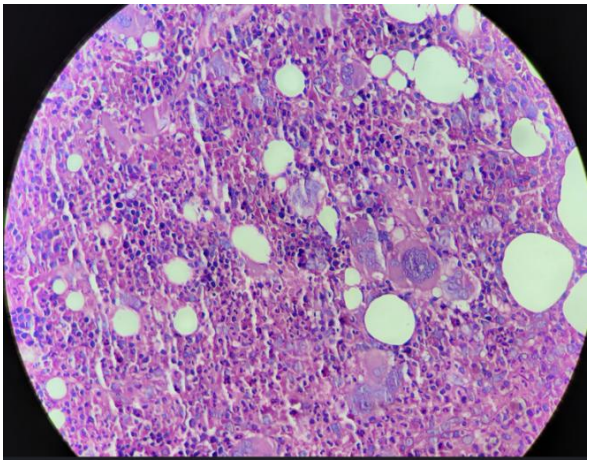


Figure - 3.1: Reticulin stain highlighting fibrosis.

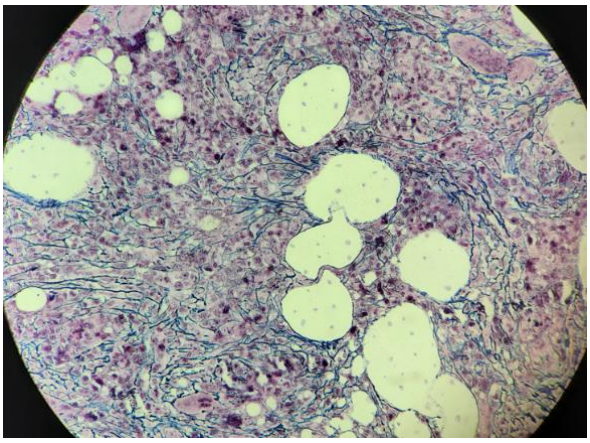
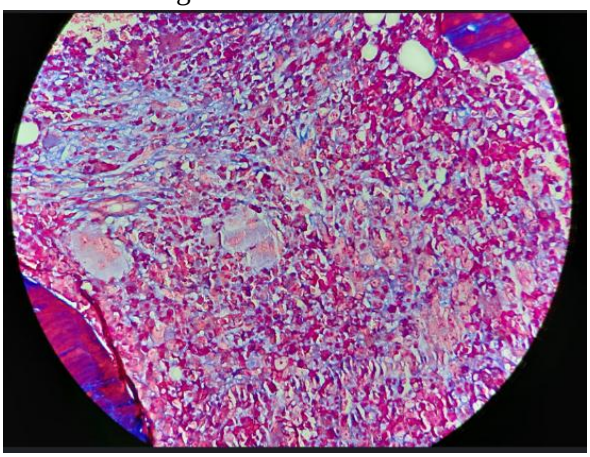


Figure - 3.2: Masson's trichome showing blue bundle of collagen.



Discussion

According to the World Health Organization (WHO) criteria for diagnosis [8] PMF diagnosis requires all three major criteria and at least one minor criterion. The major criteria include 1.Megakaryocyte proliferation and atypia accompanied by either reticulin and/or collagen fibrosis (grade 2 or 3)
2. Not meeting the WHO diagnostic criteria for BCR–ABL positiveChronic myelogenous leukemia (CML), Polycythemia vera (PV),Primary myelofibrosis (PMF), Myelodysplastic syndrome, or other myeloid neoplasms;
3. Presence of JAK2, CALR, or MPL mutation or in the absence, the presence of another clonal marker or absence of evidence for reactive bone marrow fibrosis.

Minor criterion presence of at least one of the following, confirmed in 2 consecutive determinations.
1. Anemia not attributed to a co morbid condition.
2. Leucocytosis greater than 11*10 9/L.
3. Palpable splenomegaly
4. LDH level above the upper limit of the instittutional reference range.
5. Leucoerythroblastosis.

Most of the patients are asymptomatic at presentation and the disease is usually detected by the presence of splenic enlargement or abnormal blood count. In Idiopathic myelofibrosis the blood smear shows the characteristic feature of extramedullary hematopoiesis i.e tear drop cells, nucleated red cells, myelocytes, promyelocytes. Myeloblasts may also be present. WBCs and platelets may be increased/decreased/normal. Marrow is usually inaspirable due to fibrosis. Biopsy will reveal a hypercellular marrow with trilineage hyperplasia and in particular increased number of megakaryocytes in clusters and with large dysplastic nucleus [17].

Autoimmune abnormalities such as immune complexes, Antinuclear antibodies, Rheumatoid factor or a positive Coomb's test can also be observed in Idiopathic myelofibrosis. The autoimmune process is an incidental finding in this case which is reported in literature to be associated with primary myelofibrosis [2]. It is important to diagnose correctly as both conditions have distinct prognosis and course of disease [3, 17]. The neoplastic cause of primary myelofibrosis can sometimes have overlapping features with non-neoplastic causes like autoimmune myelofibrosis, secondary to SLE or primary autoimmune myelofibrosis. The features of primary autoimmune myelofibrosis have been well elucidated by Pullarkat, et al. [19] include

1. grade 3 or 4 reticulin fibrosis of the bone marrow;
2. lack of clustered or atypical megakaryocytes;
3. lack of myeloid or erythroid dysplasia, eosinophilia, or basophilia;
4. lymphocyte infiltration of the bone marrow;
5. lack of osteosclerosis;
6. absent or mild splenomegaly;
7. presence of autoantibodies; and
8. absence of a disorder known to cause MF Our patient, did not meet above criteria. The features favoring primary myelofibrosis over autoimmune myelofibrosis (AIMF) were presence of significant splenomegaly and leukoerythroblastic blood picture, atypical megakaryocytes on bone marrow and jak 2 mutation. In this case the presence, leucocytosis, thrombocytosis, presence of tear drop cells, target cells, myelocytes in pheripheral smear, hypercellular marrow with megakaryocytosis and fibrosis favors the diagnosis of Idiopathic myelofibrosis and excludes Polycythemia vera and Chronic Myeloid Leukemia.

PMF is at least prevalent of all myeloproliferative neoplasms in women of child bearing age – the prevalence is 0.023–0.06/100.000 in this age-group [4]. Pregnancy in

patients with chronic myeloproliferative disease has many risks [8, 9], particularly increased risk for thrombosis. Harrison [10] shows that such risk is similar to risk in patients with thrombophilia and antiphospholipid syndrome. The most frequent complication in pregnant women with Philadelphia negative myeloproliferative neoplasms is abortion, while other maternal complications are relatively low with 3% for major thromboembolic and 2% for major bleeding events [3]. The presence of JAK2 mutation seemed to be an independent predictor of pregnancy complication [3, 14].

Persistently high platelet counts cause platelet aggregation, increased blood viscosity, and tissue hypoxia. Activation of platelets leads to the production of thromboxane, which in turn induces platelet aggregation and triggers release responses, leading to microvascular thrombosis Placental micro-infarctions due to the increased platelet number and placental damage from autoantibodies are among the underlying pathological basis of first trimester abortion [6].

As thrombosis is an important complication of Idiopathic myelofibrosis (Cervantes, et al. 2006) [8] the history of two abortions in this patient may be due to placental infarction which might have caused due to thrombosis.

Similar history of abortions was also noted in pregnant women with Idiopathic myelofibrosis in a study by Taylor, et al .[5], Gotic, et al. (2001) [6] who described one patient each with previous thrombosis and fetal loss with one successful pregnancy and child birth, while Tulpule, et al. [7] in 2008 described two patients with 4 pregnancies. In his study, Sameer tulpule successfully managed these patients with aspirin and low molecular weight heparin who presented with thrombocytosis to avoid recurrent pregnancy loss.

The neoplastic cause of primary myelofibrosis can sometimes have overlapping features with non-neoplastic causes like autoimmune myelofibrosis, secondary to SLE or primary autoimmune myelofibrosis. The prognosis of IMF is variable but generally poorer than other myeloproliferative disorders. Even though pancytopenia and leukemic transformation is common in primary myelofibrosis, thrombosis is also a dominant clinical complication [16]. The review of literature showed that ANA positivity is also reported in some sporadic cases of primary myelofibrosis (PMF), such cases were also shown to respond well to steroids [18].

New drugs such as JAK2 inhibitors, mTOR (target of rapamycin) inhibitors, histone deacetylase inhibitors and pomalidomide show encouraging results in treatment of patients with PMF [12, 13]. Interferon-alpha also showed some promising results in reducing the fibrosis in Philadelphia-negative chronic myeloproliferative neoplasms [14], and it can possibly be used in combination with new drugs.

In MPN diseases, interferon-α 2a (IFN-α 2a) has been revived and promising results have been observed [14, 15] in which IFNα 2a was shown to exert potent effects on Treg cells [16]. The JAK inhibitor, Ruxolitinib, which has been approved for the treatment of myelofibrosis was also found to have potent immune inhibitory effects on dendritic cells [18].

Conclusion

Routine blood examination in early pregnancy and molecular biology analysis should be performed in patients with recurrent spontaneous abortion in order to avoid missed diagnosis of Myeloproliferative neoplasms. Specifically, close monitoring of platelet count is useful for pregnancy management and improved outcomes in these patients. This case has highlights the need to have high level of suspicion of underlying myeloproliferative neoplasms in cases of persistent leucocytosis and thrombocytosis. These cases should be systematically investigated including bone marrow examination and molecular studies to confirm. It should be kept in mind that Antinuclear antibodies (ANA) positivity and

autoimmune features can superimpose or coexist with myeloproliferative neoplasms. Thus this case demonstrates the difficulty posed due to overlapping features of AIMF and PMF creates possibly indicating an associated etiology. It is pertinent to be able to distinguish between the two as they have differences in therapy, also whereas PMF has limited survival other causes including AIMF have a favorable clinical outcome.

Because no other treatment modalities except bone marrow transplantation have been found to be a possible curative treatment in MF, further exploration of immunotherapy may be likely to open a new era in the treatment of MPN diseases in the future. Further exploration of basic immune pathology in myelofibrosis may shade light on treating this incurable disease.

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