Case study

THE ETIOLOGY AND DIAGNOSIS OF PRIMARY MYELOFIBROSIS: CASE STUDY

Abstract

Primary myelofibrosis is a myeloproliferative neoplasm. It is the rarest among the group of myeloproliferative neoplasms and the incidence is 0.1-1 per 1,00,000 per year. This is characterised by the replacement of normal marrow by fibrous tissue. Patients may present with hepatosplenomegaly due to extramedullary erythropoiesis. A high index of suspicion is needed to diagnose the same. This study describes a case that was diagnosed to have myelofibrosis when he presented with splenomegaly as a main symptom.

Keywords: Primary Myelofibrosis, splenomegaly, extramedullary erythropoiesis, myeloproliferative disorder

Introduction

Myelofibrosis is a chronic myeloproliferative disorder characterized by a clonal proliferation of defective multipotential stem cells in the bone marrow. Overproduction and premature death of atypical megakaryocytes in the bone marrow produce excess amounts of platelet-derived growth factor which is a potent stimulus for fibroblast proliferation and collagen production. Myelofibrosis can either be primary or secondary. Secondary myelofibrosis occurs more commonly than primary myelofibrosis and develops as a

result of other diseases that affect bone marrow fibroblastic activity. The common notion that myelofibrosis presents with pancytopenia us true at later stages only. Initial stages of myelofibrosis may have leucocytosis and thrombocytosis. It is important to differentiate between the various myeloproliferative neoplasms at the earliest. If one presents at a stage of overt myelofibrosis, the differentiation between primary and secondary myelofibrosis is difficult especially when no prior history or hematological investigations are available. The histopathology of overt fibrosis is similar in both primary and secondary myelofibrosis. The treatment modalities for myeloproliferative neoplasms varies and hence it is important to diagnose the etiology.

TABLE 1: Diagnostic criteria for Primary myelofibrosis (2016 WHO classification[2])

MAJOR CRITERIA	
1) Megakaryocte atypia PLUS	▪ Small to large megakaryocytes ▪ Aberrant nuclear cytoplasmic ratio ▪ Irregulary folded hyperchromatic nuclei
Reticulin fibrosis	▪ Absent or less than grade 1

	in pre-PMF May be associated with increased bone marrow cellularity adjusted for age, granulocyte proliferation and decreased erythropoiesis ▪ Grade 2 and 3 reticulin fibrosis and collagen deposition.
2) Exclude other MPN	▪ WHO criteria for other MPN like CML, PV, ET, Myelodysplastic syndrome or other myeloid neoplasm not met
3) Presence of driver mutations **	▪ JAK STAT2 ▪ MPL2 ▪ CALR
MINOR CRITERIA	One or more of these to be confirmed in two consecutive determinations
1)Anemia	Not attributed to other comorbid conditions
2) Leucocytosis	$\geq 11 \times 10^9/L$
3)Palpable Splenomegaly	
4)LDH levels > upper limit of normal	
5)Leucoerythroblastosis	This is a minor criteria in addition to the other four in

	cases of overt PMF.

PMF- Primary myelofibrosis; LDH – lactate dehydrogenase; MPN- myeloproliferative neoplasms; CML- Chronic myeloid leukemia ; PV- Polycythemia vera; ET- essential thrombocytosis; JAK STAT2- Janus kinase signal transducer and activator of transcription ; MPL2-myeloproliferative leukemia virus ; CALR- calreticulin

Aims

To give an insight on

a) Importance of evaluation of constitutional symptoms
b) Work up of myeloproliferative neoplasms

Presentation of Case

This case study is done based on observation and evaluation of a 52 years old male presented with history of fever, loss of weight and appetite, dragging sensation and fullness in left side of abdomen and early satiety for 6 months duration. On examination, he had pallor and sternal tenderness. Spleen was palpable 10 cms below the left costal margin and was crossing the midline towards the right inguinal fossa. Liver was just palpable below the right costal margin.

Investigations showed; haemoglobin of 12.5 g/dL; total white blood cell counts of 27,700 cells/mm3; Differential counts – were Neutrophils (73%), Lymphocytes (10%),

Mononocytes(5%), Eosinophils (1%), Basophils (2%), Myelocytes (7%) and metamyelocytes (2%); platelet count was 6.35 lakh cells/mm3. Peripheral blood smear showed thrombocytosis and leucocytosis with shift to left; White blood cell series showed basophilia and eosinophilia with occasional blasts, red blood cells were normochromic, normocytic with occasional polychromatophils and few nucleated red blood cells. Erythrocyte sedimentation rate was 10mm at the end of first hour. Renal and liver function tests were normal. Serum Lactate Dehydrogenase level was raised (554U/mL). RK 39, malarial antigen and antibody, widal test, blood, urine culture, procalcitonin and viral serology for HIV, hepatitis B and C were negative. Ultrasonography of abdomen revealed massive splenomegaly and mild hepatomegaly.

Bone marrow aspiration was dry. BCR-ABL gene was negative. Bone marrow biopsy showed bony trabeculae enclosing bone marrow spaces completely replaced by grade 3 reticulin fibrosis and diffuse collagen fibrosis with occasional granulocytes and megakaryocytes. Immunohistochemistry for CD34 was negative. JAK STAT mutation was positive.

Discussion

Myelofibrosis is a disease characterised by the replacement of bone marrow by fibrous tissue. It can be primary or secondary. Primary myelofibrosis is the rarest among the myeloproliferative neoplasms with an incidence of 0.1 to 1 per 100000 per year [1]. The spent phase of the other

myeloproliferative neoplasmss by histology too resembles primary myelofibrosis.

Insidious onset of easy fatiguability, weight loss, anorexia and splenomegaly in a middle aged man would prompt one to consider haematological malignancies including myeloproliferative neoplasms as the first among the various differential diagnosis.

The 2016 WHO classification for myeloproliferative neoplasms includes seven subcategories: three major subcategories of JAK2/CALR/MPL (Janus kinus 2/ Calreticulin/ myeloproliferative leukemia virus) mutation related myeloproliferative neoplasms (Polycythemiavera, Essential thrombocytosis and Primary myelofibrosis and four clinicopathologic entities (Chronic myeloid leukemia, Chronic neutrophilic leukemia, Chronic eosinophilic leukemia not otherwise specified and unclassifiable yet) [2].

Investigations revealed peripheral leucocytosis (neutrophilic shift to left , basophilia and eosinophilia) and thrombocytosis. This toned up the possibility of myeloproliferative neoplasm like chronic myeloid leukemia. But, BCR-ABL mutation (the diagnostic hallmark for chronic myeloid leukaemia which differentiates it from other myeloproliferative neoplasms) was not present in this case study.

Dry bone marrow tap was the next leading clue.The bone marrow biopsy showed bone marrow spaces completely replaced by diffuse reticulin and collagen fibrosis(myelofibrosis). As mutation screening has a complementary role in diagnosis of myeloproliferative

neoplasms, the same was send. JAK2 mutation came out to be positive in our patient. The JAK2 V617 is the most common mutation in BCR-ABL negative myeloproliferative neoplasms and accounts for 95% cases of polycythaemia vera and 50 % cases of essential thrombocytosis and Primary myelofibrosis [3]. JAK 2 is a cytoplasmic kinase and is crucial for intracellular signalling by receptors for erythropoietin, thrombopoietin, interleukin 4 and granulocyte colony stimulating factor. JAK 2 mutation in myeloproliferative neoplasms is acquired [4] and causes reduction in apoptosis, promotes cellular proliferation and differentiation [5].

As per the 2016 WHO classification and diagnostic criteria, a combination of clinical, morphological and molecular genetic features is required for the diagnosis of myeloproliferative neoplasms [2]. Three of the major and at least one minor criteria is required for the diagnosis of Primary myelofibrosis(Table 1).

Our patient had megakaryocyte atypia with grade 3 myelofibrosis on bone marrow biopsy and presence of JAK2 mutation among the major criteria and all the minor criteria were met. Myelofibrosis can be primary or secondary. A diagnosis of PMF can be made only when other MPNs and other myeloid neoplasms are excluded. Thus, the etiology of myelofibrosis was the next point to ponder. Secondary myelofibrosis may also occur post polycythemia or essential thrombocytosis. By histology, the appearance of PMF is

identical to the spent phase of other myeloproliferative neoplasms.

In this case study, no prior hemogram reports were available. The patient had hemoglobin of 12.5 g/dL. The major diagnostic criteria for Polycythemia vera needs hemoglobin> 16.5 g/dL for men.

He also had thrombocytosis (6.5 lakh cells/mm ^{3}) in addition to leucocytosis.The diagnosis of essential thrombocytosis needs peripheral thrombocytosis (platelet > 4.5 lakh/mm ^{3}), presence of driver gene mutations, exclusion of causes of reactive thrombocytosis and other myeloproliferative neoplasms and bone marrow biopsy findings. The first three of the major criteria were present in this case. However, typical bone marrow biopsy findings showing megakaryocyte proliferation(enlarged mature megakaryocytes with hyperlobulated nuclei) were not present in this case. Moreover, significant left shift of neutrophil granulopoiesis is not seen in essential thrombocytosis.

Essential thrombocytosis, Polycythemia vera and Primary myelofibrosis transform to each other during the course of illness and hence cannot be strictly differentiated by bone marrow studies [6]. It is also not clear if primary myelofibrosis (especially when associated with JAK2 or MPL mutations) is truly distinct from Polycythemia vera or essential thrombocytosis, or merely reflects a rapidly progressive course of these myeloproliferative neoplasms to their spent phase [7]. Thus, the differentiation between primary and

secondary myelofibrosis is difficult especially when patients have no history or prior hemogram suggestive of polycythemia or essential thrombocytosis. Either de-novo or secondary to Myeloproliferative Neoplasms, the disease myelofibrosis is the same. Since,no evidence of primary essential thrombocytosis and Polycythemia vera could be gathered in our patient , so we considered a possibility of Primary myelofibrosis.

This case was referred to hematology centre for further management. He neither had cytopenias despite grade 3 myelofibrosis, nor any complications related to massive splenomegaly. Hence, he is kept under follow up and is being given supportive treatment.

Primary myelofibrosis is characterised by the abnormal clonal proliferation of mature myeloid lineages variable degrees of megakaryocytic atypia (large and dysplastic). Thus, early in the course of the disease, marrow is hypercellular with increased white blood cells and platelets with minimal fibrosis. With the progression of disease, the abnormal stem cells cause increased collagen and reticulin production which leads to marrow fibrosis and suppression of hematopoiesis. This leads to progressive cytopenias and extensive extramedullary erythropoiesis. Clusters of abnormal giant megakaryocytes can be seen in the dilated sinusoids (as seen in our case). Very late in the disease, the fibrotic bone marrow would be converted to bone- osteosclerosis.

Age of presentation is in the adulthood-usually older than 60 years of age. The disease course is variable. Most of the patients present later in the disease course either due to progressive anemia or due to symptoms related to massive splenomegaly as in our patient. Patients may present with complications like recurrent infections, thrombotic episodes, bleeding manifestations secondary to platelet dysfunction and transformation to acute myeloid leukemia [8] . Pallor and hepatosplenomegaly may be present. Peripheral blood findings are non specific. Bone marrow studies are crucial in diagnosis. A dry bone marrow aspiration is a clue and a definitive diagnosis can be made by bone marrow biopsy [8].

Primary myelofibrosis is more difficult to treat when compared to essential thrombocytosis or Polycythemia vera. The median survival is in the range of 3 to 5 years [8]. Treatment goals are individualised and in most cases cure is not the goal. Conventional treatment includes a)wait and watch approach for asymptomatic patients, b)erythropoiesis stimulating agents and androgens for anemia, c) cytoreductive agents for splenomegaly and constitutional symptoms d) splenectomy or radiotherapy in patients patients with overt portal hypertension, progressive anemia requiring multiple transfusions or symptomatic and refractory to treatment [9].

The novel strategies for treatment of myelofibrosis is JAK targeted molecular therapy. JAK1/2 inhibitor Ruxolitinib (15-20 mg twice daily) is the first chemotherapeutic agent approved by Food and Drug Administration for the same [10].

Fedratinib, Pacritinib and momelotinib are the other available JAK inhibitors.

Allogenic stem cell transplant is the only potentially curative treatment. But is associated with high morbidity and mortality and hence is considered in high and intermediate 2 risk cases of primary myelofibrosis[9].

Conclusion

Constitutional symptoms in middle aged may herald the onset of malignancy or chronic infections. A thorough examination and investigation is warranted in case of any such complaints. Myelofibrosis may be primary or more commonly secondary to other MPNs. Etiology of myelofibrosis must be sought in every case even though treatment of end stages of overt marrow fibrosis remains the same.

Consent

As per international standard or university standard, patients' written consent has been collected and preserved by the author(s).

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