Primary Myelofibrosis- A Case Report

Himani Patel*, Preeti Jhaveri **, Krupali Patel***, Cherry Shah****

Abstract:

Primary myelofibrosis is a Philadelphia negative myeloproliferative neoplasm characterized by clonal myeloid expression, followed by progressive fibrous connective tissue deposition in bone marrow resulting in bone marrow failure. There is predominant proliferation of megakaryocytes and granulocytes in the bone marrow through dysregulation of the JAK-STAT pathway. Clonal evolution also occur with an increased risk of transformation to acute myeloid leukemia. It is often but not always accompanied by JAK2, CALR, or MPL mutations; additional disease features include bone marrow stromal reaction including reticulin fibrosis, abnormal cytokine expression, anemia, hepatosplenomegaly, extramedullary hematopoiesis (EMH), constitutional symptoms, cachexia, leukemic progression, and shortened survival. Mutations in epigenetic regulators and RNA splicing genes may also occur, and play critical roles in PMF disease progression. Based on revised World Health Organization diagnostic criteria for MPNs, both screening for driver mutations and bone marrow biopsy are required for a specific diagnosis.

Key Words: Extramedullary hematopoiesis, Myeloproliferative neoplasm, Primary myelofibrosis

Introduction:

Primary myelofibrosis is a disease of middle aged and elderly patients. Both sexes are equally affected. Patient present with weight loss, night sweats, anorexia, fatigue or lump in left hypochondrium (due to splenomegaly). Some patients also present with gout and renal colic manifestations. Petechiae, echymoses and lymphadenopathy may present in few patients. All patients have anemia with Hb < 10gm/dl and it demonstrates anisopoikilocytosis with tear drop cells. There is also “leucoerythroblastic reaction” with presence of nucleated red cells along with myelocytes and metamyelocytes in peripheral smear. Initially platelet count is high and it decreases at the terminal stage. WBC count is higher in the range of 15-30×10⁹/L with shift to left and sometimes leucopenia is present in terminal stage. NAP score is markedly increased and serum LDH level is also high. In 2016, prefibrotic primary myelofibrosis was formally classified as a distinct condition that progresses to overt PMF in many patients, the primary diagnostic difference being the grade of fibrosis.[1]

Case-Report:

A 39 year old male patient came to medicine OPD with the complaint of abdominal distention and black stool since 1 month. He was also having splenic infarct associated with melena. He was examined thoroughly and USG was carried out and there was massive splenomegaly. Portal hypertension and esophageal varices were also present in this patient. Peripheral smear findings were suggestive of normocytic normochromic anemia along with neutrophilic leukocytosis with shift to left. On evaluating the history patient was suffering from leukocytosis for 6 months. Reticulocyte count was <0.5% after staining with brilliant cresyl blue. Thereafter, bone marrow biopsy was advised by clinician to rule out the cause of leukocytosis. Bone marrow aspiration followed by trephine biopsy was done under strict aseptic condition. Bone marrow aspiration was dry tap which led to inconclusive result. Microscopic examination of trephine biopsy after proper fixation and H and E staining was done. Biopsy was adequate and hypercellular. Megakaryocytes increased in number and showed hyperchromatic nuclei with high N:C ratio. Hypolobated, hyperlobated and abnormal megakaryocytes were seen singly and in clusters. Abnormal localization of megakaryocytes was also seen. Myeloid series was moderately increased in number and showed normal maturation. Cells of erythroid series

* 3rd year Resident doctor
** Assistant Professor
*** Junior Lecturer
**** Professor & Head, Department of Pathology, Smt. N H L Municipal Medical College, Ahmedabad

Correspondence: Dr. Himani Patel
E-mail: hapatel1994@gmail.com
were mildly reduced in number and showed predominantly normoblastic maturation and few showing micronormoblastic maturation. On the H&E stain, evidence of fibrosis was seen for which special stain of Reticulin was done.

Reticulin stain was done for the specimen specially to evaluate stromal component. The slide showed absence of fat spaces. Fat cells, fibroblasts and network of blood vessels showed mild to moderate fibrosis around blood vessels. The findings were suggestive of moderate fibrosis, Grade II. The patient was diagnosed with Hyperplastic marrow with increased megakaryocytic proliferation with atypia and increased myeloid proliferation with mild to moderate fibrosis.

**Figure 1: Bone marrow biopsy showing fibrosis**

**Figure 2: Bone marrow biopsy showing abnormal megakaryocytic proliferation**

**Figure 3: Reticulin stain showing fibrosis**

**Discussion:**

In primary myelofibrosis production of cytokines such as fibroblast growth factor by the abnormal hematopoietic cell clone (particularly by megakaryocytes) leads to replacement of the hematopoietic tissue of the bone marrow by connective tissue via collagen fibrosis. The result is extramedullary hematoepoiesis, i.e. blood cell formation occurring in sites other than the bone marrow particularly the liver and spleen. This causes an enlargement of these organs. Enlargement of the spleen is also contributes to causing pancytopenia, particularly thrombocytopenia and anemia. Another complication of extramedullary hematopoiesis is poikilocytosis, or the presence of abnormally shaped red blood cells. The principal site of extramedullary hematoepoiesis in myelofibrosis is the spleen, which is usually markedly enlarged, sometimes weighing as much as 4000 g. As a result of massive enlargement of the spleen, multiple subcapsular infarcts often occur in the spleen, meaning that due to interrupted oxygen supply to the spleen partial or complete tissue death happens.

Stages of primary myelofibrosis according to megakaryocytic proliferation and reticulin or collagen fibrosis are: 1. Prefibrotic 2. Overt Fibrotic. Prefibrotic stage is characterized by mild normocytic anemia with poikilocytosis, tear drop cells, nucleated rbc's, thrombocytosis and mild leukocytosis with some immature forms. The marrow is hypercellular and contains abnormal megakaryocytes which clusters around sinuses and trabeculae. Bonemarrow shows atypical, enlarged and immature megakaryocytes with cloud like immature nuclei and small megakaryocytes. Intrasinusoidal hematoepoiesis is often present.

Diagnostic criteria for primary myelofibrosis, prefibrotic / early stage: must meet all 3 major criteria plus at least 2 minor criteria:

- Major
- Major criterion 1: megakaryocyte proliferation and atypia in the absence of reticulin fibrosis, accompanied by increased marrow cellularity, granulocytic proliferation and often decreased erythropoiesis
- Major criterion 2: not meeting WHO criteria for other myeloproliferative neoplasms or myelodysplastic syndromes
• Major criterion 3: demonstration of JAK2, CALR or MPL mutation OR other clonal marker OR no evidence of reactive marrow fibrosis
• Minor
• Minor criterion 1: leukoerythroblastosis
• Minor criterion 2: increased serum lactate dehydrogenase
• Minor criterion 3: anemia
• Minor criterion 4: palpable splenomegaly
• Comparing WHO 2017 to WHO 2008, only minor changes to the diagnostic criteria; the change involved the addition of CALR or MPL mutations in addition to the JAK2 mutation

Overt fibrotic stage includes moderate degree of normocytic normochromic anemia [with some hypochromic and basophilic stippling], moderate anisocytosis and marked poikilocytosis alongwith dacrocyes and few elliptocytes. Normoblasts increased in proportion to degree of anemia with slight reticulocytosis. Splenomegaly due to extramedullary hematopoiesis is typical.

Diagnostic criteria for primary myelofibrosis, overt fibrotic stage: all 3 major criteria and at least 1 minor criterion must be confirmed in 2 consecutive determinations.

• Major
• Major criterion 1: megalakaryocytic proliferation and atypia, accompanied by reticulin or collagen fibrosis grades 2 or 3
• Major criterion 2: not meeting WHO criteria for other myeloproliferative neoplasms or myelodysplastic syndromes
• Major criterion 3: demonstration of JAK2, CALR or MPL mutation OR other clonal marker OR no evidence of reactive marrow fibrosis
• Minor
• Minor criterion 1: anemia not attributed to a comorbid condition
• Minor criterion 2: leukocytosis
• Minor criterion 3: palpable splenomegaly
• Minor criterion 4: increased serum lactate dehydrogenase
• Minor criterion 5: leukoerythroblastosis

Grading of marrow fibrosis on reticulin stain:

A: Myelofibrosis grade 0 shows delicate reticulin fibrosis around blood vessels.
B: MF grade 1 shows a loose network of reticulin fibers especially in perivascular areas.
C: MF grade 2 shows diffuse increase in reticulin fibers with numerous intersections. Trichrome stain reveals a mild increase in collagen fibrosis
D: MF grade 3 shows diffuse and dense increased in thick reticulin fibers with encasing bone marrow cells. Trichrome stain reveals dense collagen fibrosis

Prognosis:

Primary myelofibrosis has the least favorable prognosis among the myeloproliferative neoplasms. Patients are at risk of death due to disease progression, leukemic transformation, thrombohemorrhagic complications and infections. In prefibrotic stage survival period is approximately 10-15 years and for overt fibrotic stage it is 3-5 years.

Treatment:

The prognosis for patients with PMF is dismal compared with other MPNs, and alloSCT is the only current potentially curative treatment. However, as the median age at onset of PMF is 66 years, very few patients are eligible for alloSCT. For those who are not, therapy is primarily symptomatic, such as treating anemia or splenomegaly.

References: