

Primary Myelofibrosis in a Young Girl- A Case Report

HT HOSSAIN¹, A RAHMAN², MMI MAZUMDER³, MM RISHAD⁴, QT ISLAM⁵, M ZAHIRUDDIN⁶

Abstract:

Myelofibrosis (MF) is a rare disorder that is classified as one of the myeloproliferative disorders. It is a BCR-ABL1-negative myeloproliferative neoplasm characterized by abnormal proliferation of hemopoietic stem cells within the bone marrow, which leads to overproduction of fibrous tissue. Our patient a young girl of 17 year old presented with lump in left upper abdomen, shortness of breath & generalized swelling. The diagnosis was made based on severe anaemia, pancytopenia in peripheral blood film. Bone marrow

trephine biopsy from the tibia revealed myelofibrosis. Splenectomy was done in an attempt to reduce the total volume of malignant cells and improve the features of hypersplenism. Myelofibrosis with hypersplenism in a 17- year- old girl is reported rarely. However, when it does, it usually runs rapid and fatal course.

Keywords: Myelofibrosis, Pancytopenia, Hypersplenism, Splenectomy

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Introduction:

Myelofibrosis is a myeloproliferative disease that is characterized by histological megakaryocyte proliferation, cytokine dysregulation and bone marrow fibrosis. Myeloproliferative neoplasms are a group of chronic hematologic neoplasms of myeloid origin that occur predominantly in middle aged & older adults over the age of 64 years. Both genders are equally affected.

The incidence of myelofibrosis is approximately 0.1 to 1 per 100,000 individuals per year with the median age of presentation at 64 years old^{1, 2}. Myelofibrosis is a rare disorder during childhood & either idiopathic or secondary. Both are characterized by reticulin fibrosis in marrow & pancytopenia.

The underlying pathogenesis of myelofibrosis is still not fully understood. A mutation in the tyrosine-protein kinase janus-activated kinase 2 (JAK 2) is thought to result in up regulation of pro-inflammatory cytokines³.

Patients commonly exhibit symptoms such as weight loss, night sweats, anorexia, fatigue, the presence of a lump in the left hypochondrium, or hepatosplenomegaly. Additionally, a subset of patients may also present with manifestations of gout and renal colic. petechiae, ecchymosis and lymphadenopathy may present in few patients^[4] All patients have anaemia with Hb <10 gm/dl and it demonstrates anisopoikilocytosis with tear drop cells. There is also “Leukoerythroblastic 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. White blood cell 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 is also high^{4, 5}.

The survival rate following a diagnosis of myelofibrosis is variable and many scoring systems exist in an attempt to quantify the average years of survival following diagnosis [6-7]. These scoring systems provide a risk group score based on some of the following factors: patient’s age, hemoglobin level, white blood cell count, presence of constitutional symptoms, platelet level, genetic mutations and percentage of myeloblasts within the peripheral blood [8]. We have incorporated the new prognostic information to the clinical decision-making process. At present, there is no curative treatment other than allogenic hemopoietic stem cell transplantation which can be applied to a minority of patients. Therefore, treatment remains essentially palliative and aimed at controlling disease symptoms and complications and improving the patient quality of life. The therapeutic landscape of MF has changed with the introduction of the JAK inhibitors⁹⁻¹⁰.

1. Dr. Homayra Tahseen, Associate Professor, Department of Medicine, Popular Medical College, Dhaka, Bangladesh
2. Dr Arfa Rahman, Assistant Registrar, Department of Medicine, Popular Medical College, Dhaka, Bangladesh
3. Dr Md. Maksudul Islam Mazumder, Registrar, Department of Medicine, Popular Medical College, Dhaka, Bangladesh
4. Dr Mahbub Mayukh Rishad, Registrar, Department of Medicine, Popular Medical College, Dhaka, Bangladesh
5. Professor Quazi Tarikul Islam, Professor of Medicine, Popular Medical College, Dhaka, Bangladesh
6. Professor Md. Zahiruddin, Professor of Medicine, Popular Medical College, Dhaka, Bangladesh

Address of Correspondence: Dr. Homayra Tahseen Hossain, Associate Professor, Medicine, Popular Medical College Hospital, Dhaka, Bangladesh. 01712234824, homayra.tahseen@gmail.com

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We report a case of 17-year-old young girl presented with lump in left upper abdomen, shortness of breath & generalized swelling. In this article, we report the case of the patient & discussed about the difficulties to confirm our diagnosis along with treatment options currently available for myelofibrosis.

Case Report

A 17-year-old girl was admitted to the hospital with the complaints of lump in left upper abdomen & heaviness for 18 months, generalized swelling & shortness of breath for 1 month and occasional low grade fever. She stated that she was reasonably well 18 months back with average body built. Then she noticed a lump in left upper abdomen which gradually increasing in size over the next 2-3 months. As the size increased, she felt heaviness in her left upper abdomen but there was no pain. She became extremely lethargic. Her parents noticed that she was becoming pale. On query, she had several episodes of low grade fever over the last 18 months which was not associated with chills & rigor, night sweat, although there was no recorded temperature. Her parents have history of consanguinity in marriage & siblings are healthy. She remained at home with occasional visits to hospital & received approximately 15 units of blood over the last 18 months. There was no history of bleeding from any site of body. She noticed swelling of her legs followed by swelling of face. Eventually her whole body was swollen. Her fatigue increased over the last 2 months. For the last 9 days before admission, she developed shortness of breath which was mild to moderate in nature. It hampered her day to day activities. Breathlessness was associated with cough with frothy, white sputum. She had to stay upright to relieve her breathlessness.

On general examination, the patient appeared ill looking, dyspnoeic, decubitus propped up position. She had severe anaemia, jaundice, leuconychia & bilateral pitting leg edema, raised JVP. Her pulse was 110 beats/min, high volume, respiratory rate 24 breath/min, moderate hepatomegaly (extending 10 cm from right costal margin) & huge splenomegaly (extending 28 cm from left costal margin), ascites as evidenced by presence of shifting dullness & bilateral fine basal crepitation in both lung fields. All other systemic examinations were normal. Bedside urine test for protein was negative.

During her hospital stay, she developed fever & productive cough. Her highest recorded temperature was 105°F, subsided upon taking anti-pyretics. To find out the cause of fever, we did some investigations. After admission, patient received total 7 units of packed cell. We took regular consultation from both haematologist & surgeon for splenectomy and necessary vaccination before splenectomy. Surgery consultant advised to correct her medical condition including platelet count before any operative procedure (to prevent complications).

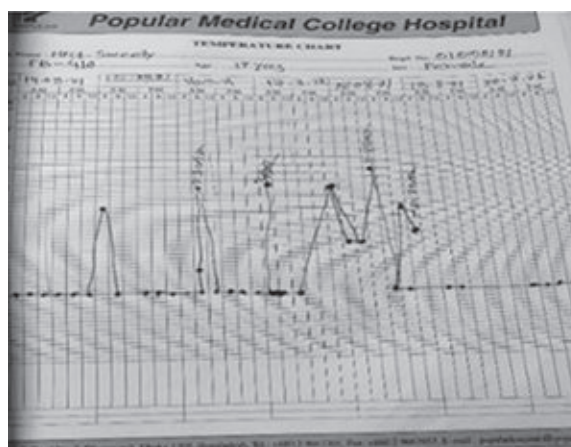


Fig.-1: Temperature Chart

Her baseline investigations showed in complete blood count progressive Leukopenia (total count of WBC 1.7k/ μ L), Haemoglobin 4 gm/dl (During hospital stay, transfused 5 units of whole blood, then hemoglobin raise to 9.40g/dl. Few days later, decreasing hemoglobin level to 5gm/dl), Platelet count 45k/ μ L (low), ESR was 80 mmHg in 1st hour, PBF revealed pancytopenia, CRP was normal (12 mg/L), Serum Electrolytes, serum Creatinine, Iron Profile (Serum Iron 22 μ g/dl, TIBC 298 μ g/dl, % saturation 7.38%, S. Ferritin 269 ng/ml) and Hb Electrophoresis-was normal. Others including ICT for malaria, ICT for kala-azar, HBsAg, Anti-HCV, HIV, ANA screening all test result were negative. Liver Function Test showed total Bilirubin 2.7 mg/dl (High), SGPT 17U/L (Normal), SGOT 23U/L (Normal), S. Albumin 2.7 gm/dl (Low), PT 12s (Normal), LDH 546 U/L (High).

Ultrasonography of Whole Abdomen revealed moderate hepatomegaly (liver is enlarged in size 18.8cm), huge splenomegaly with mildly dilated splenic vein (spleen is hugely enlarged in size about 30.1 cm), dilated portal

vein (15-16mm), mild Ascites. Upper GI Endoscopy revealed Erosive Gastritis (done to rule out oesophageal varices).

As fever did not subside, to find out the aetiology, some investigations were done-



Fig.-2: CXR PA View: *Inflammatory lung lesion in right upper zone. Right sided basal pleural thickening Or small effusion.*

Sputum Culture: Growth of *Acinetobacter* species; Colony count: moderate ; Sputum for AFB & Gene Xpert : MTB not detected; Tuberculin Test : Negative; Ascitic fluid study: Cytology : Lymphocyte: 85%, Neutrophil : 05%; Biochemical tests : Protein 5.33 gm/dL, Fluid for Albumin 3.44 gm/dl .

Bone Marrow Study revealed hypercellular, myeloid-erythroid ratio increased, erythropoiesis hyperactive & dimorphic, granulopoiesis hyperactive & maturing to segmented form, megakaryocytes seen and the impression was Myeloid hyperplasia. Bone Marrow Trepine Biopsy revealed patchy cellular areas and focal areas of increased deposition of fibrous tissue. Erythropoiesis is active and normoblastic. Granulopoiesis is also active & maturing into segmented form. Megakaryocytes are normal in number. Reticulin stained sections revealed dense increase in reticulin with focal coarse bundles of fibers consistent with collagen at patchy fibrous area. Diagnosis compatible with Myelofibrosis, Grade 2.

After all clinical information & necessary investigations, our confirmatory diagnosis Myelofibrosis (Grade 2

fibrosis) with anaemic heart failure with hospital acquired pneumonia.

We managed this patient symptomatically. Management of fluid overload (by diuretics), repeated blood transfusions, correction of respiratory tract infections by broad spectrum antibiotics, nutritional Support (folic acid supplementation). With proper vaccination open splenectomy was done. After splenectomy, the RBC, hemoglobin and platelet counts increased gradually, and repeated blood transfusion were stopped on 3rd post-operative day. During discharge, lifelong penicillin prophylaxis & nutritional support was given.

Discussion:

Myelofibrosis is characterized by production of cytokines such as fibroblast growth factor by the abnormal hemopoietic cell clone (particularly by megakaryocytes) leads to replacement of the hemopoietic tissue of the bone marrow by connective tissue via collagen fibrosis. It may be either idiopathic or secondary^[2]. The incidence of this disease is 0.5-1 in 100,000 population. Fewer than 100 cases have been described in the medical literature^[5]. By investigating a large data-base of consecutive patients (retrospective study) with PMF collected during a period of 21 years, 112 cases were identified as PMF^[11-12]. Cytogenetic studies were performed either at diagnosis or during the disease course. Median age at diagnosis was 62 year (range 28-92)^[2,4]. Among all 165 cases, abnormal karyotype was found in 94 (57%) patients; 62 (55%) in PMF. Median follow up was 44 months (range: 0-475) from diagnosis and 16 months (0.1-114) from the time of karyotype analysis. Forty-three patients had multiple cytogenetic studies during their clinical course. The 2008 revision of the world health organization (WHO) classification of myeloid neoplasms defines myeloproliferative neoplasms as clonal hemopoietic stem cell neoplasms with hypercellular forms in peripheral blood. This group includes primary myelofibrosis^[11]. Primary myelofibrosis in children rare entity. There are 13 cases of pediatric primary myelofibrosis reported in the literature with the largest series reporting only three such patients^[4,5]. The presence of abnormal karyotype is associated with a poorer prognosis^[4]. Although either JAK2V617F mutations are present in the majority of primary myelofibrosis in adults. The prevalence of these mutations in paediatric patients with primary

myelofibrosis has not been elucidated. This study revealed that pre-MF possesses several epidemiological and clinical features not previously come to light. Bone marrow aspirates are dry in the majority of patients [15]. However, a bone marrow biopsy is essential for confirming the diagnosis. Myelofibrosis in children have been shown to follow a more benign course than adult cases and are managed supportively such as blood transfusion and prophylactic antibiotics for infections [4,5] Apart from evolution to a malignancy, most of the childhood MF cases reported have an indolent course on supportive therapy. Long term survival is possible. Two cases were reported to undergo spontaneous remission, one of which was of 16 years [11]. Cytogenetic analysis was performed in our patient. Several studies in PMF have demonstrated shortened survival in the presence of either an 'abnormal' (10, 11, 15) or 'unfavourable' (8, 9, 12, 19) karyotype [7,8]. A few cases have been shown to resolve spontaneously without progression or transformation. Other treatment modalities include intravenous infusion of immunoglobulin, splenectomy & stem cell transplantation.

In our study, 17 year girl presented with generalized weakness followed by pallor & low grade fever. On

physical examination she had anaemia, jaundice, leuconychia, moderate hepatomegaly, huge splenomegaly and ascites. Blood examination revealed progressive pancytopenia & bone marrow aspiration trephine biopsy which revealed increase reticulin with focal coarse bundles of fibers consistent with collagen at fibrous area. Our patient had normal diploid karyotype and no mutation was detected by molecular testing. The diagnosis of primary myelofibrosis is based on the 2008 world health organization (WHO) criteria, which include histopathological, morphological, clinical and molecular-cytogenetic variables^{3,9}

To confirm a diagnosis of PMF, patients must meet all three major criteria plus two minor criteria. Median survival of the entire cohort of PMF cases was 21 years. Hypersplenism is a syndrome characterized by splenomegaly, reduction of one or more blood cells (pancytopenia), increased cellularity of bone marrow and improvement of blood picture after splenectomy. Any cause of splenomegaly may cause hypersplenism commonly found in haematological disease and portal hypertension. Many studies shown that splenectomy, although not free of complications, is relatively safe; morbidity can reach 8% and long term post-surgical mortality 4.5%. Ninety-eight, eighty-one and fifty-six

Diagnostic Criteria of Primary Myelofibrosis (WHO, 2008)

Pre-fibrotic Myelofibrosis [13, 15]	Overt Myelofibrosis [13,15]
<p>Major Criteria :</p> <ul style="list-style-type: none"> • Bone marrow examination: hyper and dysmegakaryocytopoiesis without a significant fibrosis, granulocytic proliferation & decreased erythrocytosis. • Molecular analysis: identification of a clonal marker (e.g. JAK2 V617F) • Absence of another myeloid disorder. 	<ul style="list-style-type: none"> • Bone marrow exam: megakaryocytic proliferation and atypia with reticulin fibrosis (WHO fibrotic grade 2-3) • Molecular analysis: identification of a clonal marker (e.g. JAK2 V617F) • Absence of another myeloid disorder.
<p>Minor Criteria :</p> <ul style="list-style-type: none"> • Presence of clinical or biological parameters • Anaemia (not attributed to a comorbid condition) • Leucocytosis (WBC count $\geq 11 \times 10^9 / L$) • Palpable splenomegaly • LDH level increased to above upper range of normal limit of institutional reference. 	<ul style="list-style-type: none"> • Presence of clinical or biological parameters • Anaemia (not attributed to a comorbid condition) • Leucocytosis (WBC count $\geq 11 \times 10^9 / L$) • Palpable splenomegaly • LDH level increased to above upper range of normal limit of institutional reference. • Leucoerythroblastosis

percent of patients with pre-MF, PMF-fibrotic type with early and with advanced BM fibrosis, respectively, were alive at 10 years from diagnosis^[6, 9] Further follow up is needed to assess the long-term outcomes with respect to efficacy and safety.

Conclusion:

We should not rule out myelofibrosis in a young patient who presents with huge splenomegaly. We also suggest that bone marrow trephine biopsy is an important diagnostic tool in haematology which helps to evaluate various cases of Pancytopenia^[11, 12] Splenectomy can be considered as a surgical treatment option with a curative purpose for patients with myelofibrosis (grade 2 fibrosis) & improvement of hypersplenism. Suitable treatment protects patients from potentially dangerous complications.

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