

## The muddled pancytopenia

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### ABSTRACT

Pancytopenia always remains a challenge for its detailed diagnostics evaluation, ranging from megaloblastic anemia to marrow aplasia and leukemia. Here, we report the case scenario of a 70-year-old male who presented with pancytopenia and his elaborated diagnostics approach, concluding the diagnosis of myelofibrosis with positive W515L. This case illustrates the uniqueness of establishing the diagnosis of myelofibrosis.

**Key words:** Hematopoiesis, Myelofibrosis, Pancytopenia, Splenomegaly

**M**yelofibrosis is a clonal disorder of multipotent hematopoietic progenitor cells characterized by marrow fibrosis, splenomegaly, and extramedullary hematopoiesis [1]. Pancytopenia, characterized by a decrease of all three hematological cell lines, is not a disease in itself but a manifestation of various etiologies [1-3].

Here, we present the case of a 70-year-old male in whom the presence of atypical megakaryocyte proliferation/fibrosis along with increased lactate dehydrogenase (LDH), splenomegaly, and a positive MPL W515L all favored the diagnosis of myelofibrosis. In this case, pancytopenia was attributed to myelofibrosis, which can occur either as a primary hematological disease or as a secondary process-myelophthisis.


### CASE REPORT

A 70-year-old male presented with complaints of easy fatigability, loss of appetite, and nausea for 1 month of duration. He had no complaints of loss of weight, cough, or evening rise of temperature. There was no pain abdomen, vomiting, or any other constitutional symptoms. However, he had a significant past history of pancytopenia for which the diagnosis was not established. He had no history of gum bleeding, melena, rashes, or any signs of recurrent infections. No recent history of transfusion, but there was a history of recurrent visits for the same. There was no history of native medications as well. He was an alcoholic and a smoker. He had a history of hypertension and was on medications regularly.

On general examination, he was conscious, oriented, and was pale. There was no petechia, purpura, or lymphadenopathy. He had no glossitis or cheilitis ruling out the vitamin B12 deficiency clinically. His vitals were a blood pressure of 130/80 mmHg with a pulse rate of 108 bpm, and a saturation of 98% at room air. On per abdomen examination, the spleen was palpable 8 cm below the left costal margin which was non-tender. Liver span was normal with no shifting dullness, ruling out the liver parenchymal disease/portal hypertension clinically. The other systemic examination was normal.

His hematological workup revealed pancytopenia with a Hemoglobin of 5.0 gm/dl, White Blood Cells (WBC) of 1,890, and platelets of 115 10<sup>3</sup>/ul. A peripheral smear was sent and showed a picture of microcytic hypochromic, moderate anisopoikilocytosis, teardrop cells, and NRBC's 2/100. The total count of WBC was decreased but the differential count was within normal limits. The platelets were reduced with normal morphology. No abnormal cells/hemiparasites were found. However, an iron study was also done and it showed serum iron-17.4 ug/dl, serum ferritin-319 ng/ml, and total iron-binding capacity of 356 microgram/dl. His Erythrocyte Sedimentation Rate was also elevated to 50. His reticulocyte count was 5% with normal LDH of 540 u/l.

On per abdomen examination, he had splenomegaly which was later confirmed by an Ultrasonogram of the abdomen which showed 16 cm of splenomegaly with no other significant abnormality. Various differential diagnosis of pancytopenia was considered. Reticulocyte production index was calculated favoring hypoproliferative disorder. Vitamin B12 deficiency was ruled out with a Vit B12 level of 524 pg/ml. Constitutional aplastic anemia was ruled out. Alcoholic liver disease was also

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ruled out as the liver span was normal with no evidence of portal hypertension.

Bone marrow aspirate/biopsy shows a hypocellular marrow with erythroid hyperplasia (cellularity-20%), marrow spaces show trilineage hematopoiesis, erythroid precursors show mild megaloblastic changes, myeloid precursors appears reduced, and the iron store was grade 2.

The iron correction was done along with blood transfusion. The patient improved clinically but still the cause of pancytopenia was not established. He was advised for a Myelodysplastic syndromes (MDS) panel workup but he hesitated and was on strict follow-up with regular monitoring. In his follow-up, he was found to deteriorate again. A repeat complete blood count revealed pancytopenia with a repeat peripheral smear showing a microcytic hypochromic to macrocytic, polychromasia (2+) picture. The NRBC'S were 4/100. WBCs were shifted to the left along with myelocyte-06% and metamyelocyte-04%. Other blood investigations were a reticulocyte count of 7% with an elevated LDH of 1016 u/l. Hence, a Coombs test was done and was negative. After which a repeat bone marrow biopsy showed a solidly cellular marrow with atypical megakaryocyte proliferation and fibrosis. The patient was advised for a molecular analysis which revealed negative BCR-ABL1, JAK2 V617F, JAK2 EXON12, CALR genes but positive MPL (EXON10) W515L. The patient was positive for W515L mutation in MPL GENE and negative for CALR/JAK2. A hemato-oncologist opinion was obtained. The peripheral smear, bone marrow biopsy, and molecular analysis along with the diagnostic criteria all favored the diagnosis of myelofibrosis. His Dynamic International Prognostic Scoring System plus score was around 4. He was started on steroids and hydroxyurea and is now on regular follow-up.

## DISCUSSION

The World Health Organization (WHO) has classified chronic myeloproliferative neoplasms (MPNs) into eight disorders [4] some of which are rare or poorly characterized but all of them share an origin of multipotent hematopoietic progenitor cell. They are classified as Chronic myelogenous leukemia (CML), Chronic neutrophilic leukemia (CNL), Chronic eosinophilic leukemia, Polycythemia vera (PV), Primary myelofibrosis (PMF), Essential thrombocytosis (ET), Mastocytosis, and Myeloproliferative neoplasms (unclassifiable). Each of the diseases has a different genetic basis; such as CML is the consequence of the balanced translocation between chromosomes 9 and 22 (t[9;22][q34;11]); while CNL has been associated with a t(15;19) translocation, whereas, PV, PMF, and ET are characterized by a mutation, V617F, that causes constitutive activation of JAK2.

Myelofibrosis is the least common chronic MPN and afflicts men in their sixth decade or later. Myelofibrosis is also known as agnogenic myeloid metaplasia or myelofibrosis with myeloid metaplasia [1,5]. It is a clonal disorder of a multipotent hematopoietic progenitor cell of unknown etiology characterized by marrow fibrosis, extramedullary hematopoiesis, and splenomegaly. The mutations present here are seen in

the CALR, JAK2 V617F, and MPL genes. However, JAK2 V617F is present in approximately 50% of PMF patients, while mutations in the thrombopoietin receptor MPL occur in about 5% [4,5]. Rest of them have mutations in Calreticulin (CALR) gene [4,5]. Here, the mutations were present in the MPL gene which encodes thrombopoietin receptor protein. This receptor gets activated when thrombopoietin attaches to it. The activated thrombopoietin receptor now stimulates JAK/STAT pathway. Hence, when there is a mutation in exon 10 at codon 515, there is a loss of autoinhibition of the thrombopoietin receptor resulting in constitutive activation.

Myelofibrosis is remarkable for pancytopenia despite very large numbers of circulating hematopoietic progenitor cells. It has three distinct features. The proliferation of fibroblasts in the marrow space (myelofibrosis); the extension of hematopoiesis into the long bones and into extramedullary sites, usually the spleen, liver, and lymph nodes (myeloid metaplasia); and ineffective erythropoiesis. The dysregulated production of growth factors has been implicated in etiopathogenesis along with abnormal regulation of other hematopoietins leading to localization of blood-producing cells in non-hematopoietic tissues. Fibrosis in this disorder is associated with the overproduction of transforming growth factor  $\beta$  and tissue inhibitors of metalloproteinases.

The clinical features are night sweats, fatigue, and weight loss. They are usually asymptomatic at their initial presentation. Initially, the presence of mild anemia is the rule, whereas, the leukocyte and platelet counts are either normal or increased, but either can be depressed. The disease is usually detected by the discovery of splenic enlargement which occurs due to extramedullary hematopoiesis. Both serum LDH and alkaline phosphatase levels can be elevated.

The diagnosis of myelofibrosis is based on the peripheral smear, diagnostic criteria, bone marrow biopsy, and molecular analysis. The major criteria [6,7] to meet are megakaryocyte proliferation and atypia accompanied by either reticulin or collagen fibrosis or in its absence increased marrow cellularity and granulocyte proliferation; not meeting WHO criteria for CML, PV, MDS, or other myeloid neoplasms; and demonstration of JAK2V617F or other clonal markers. The minor criteria are leukoerythroblastosis, increased serum LDH, anemia, and palpable splenomegaly

In myelofibrosis, the blood smear will show the characteristic features of extramedullary hematopoiesis: teardrop-shaped red cells, nucleated red cells, myelocytes, and promyelocytes; myeloblasts may also be present. The diagnosis is suggested by the characteristic leukoerythroblastic smear WBC numbers are often elevated, sometimes mimicking a leukemoid reaction, with circulating myelocytes, promyelocytes, and myeloblasts. Platelets may be abundant and are often of giant size [8].

Marrow is usually inaspirable due to the increased marrow reticulin "dry tap," marrow biopsy will reveal a hypercellular marrow with trilineage hyperplasia [9,10]. Bone X-rays may reveal osteosclerosis. Exuberant extramedullary hematopoiesis can cause ascites; portal, pulmonary, or intracranial hypertension, pericardial tamponade, and spinal cord compression. Splenic

enlargement can be sufficiently rapid to cause splenic infarction with fever. Molecular analysis for JAK2 v617f, CALR, and MPL mutation. Those who express the MPL mutation tend to be more anemic and have a lower leukocyte count.

## CONCLUSION

The diagnosis of pancytopenia is always a medical mystery. Only a keen hematological workup along with the bone marrow examination can aid in fetching the diagnosis. Besides being the least common disease among the MPN's, myelofibrosis should also be considered in the differential diagnosis in a patient who presents with increased LDH and massive splenomegaly. However, bone marrow biopsy confirms it, the hematological workup helps in ruling out reactive myelofibrosis. The CALR/MPN mutation has an extensive impact on the diagnosis apart from JAK mutations. Both bone marrow examination and hematological workup complement each other in the diagnosis of pancytopenia.

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