

## OSTEOMYELOSCLEROSIS: A RARE PRESENTATION OF MYELOPROLIFERATIVE NEOPLASM: A RARE CASE REPORT AND REVIEW OF LITERATURE

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### ABSTRACT

Primary myelofibrosis (PMF) is a chronic myeloproliferative neoplasm (MPN) characterised by neoplastic megakaryocytic proliferation and extensive marrow fibrosis. Rarely in later stages, the bone marrow is replaced by calcified connective tissue referred to as osteomyelosclerosis, but it is seldom seen at presentation. Leukemic transformation in PMF is frequently seen in later stages of primary myelofibrosis and is associated with a dismal prognosis. Here, we present a case of a 44-year-old female presenting with MPO negative acute leukemia as a primary presentation of PMF with histological finding of osteomyelosclerosis on trephine biopsy, which is a relatively rare presenting feature and a rare histological finding in PMF.

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### INTRODUCTION

Primary myelofibrosis (PMF) is a chronic myeloproliferative neoplasm (MPN), characterized by a short median survival and a higher risk of progression to acute myeloid leukemia (AML) compared to other MPNs, which is noted in a small subset of the cases and is usually a terminal event (Treaba, 2012). In our paper, we present a 44-year-old female presenting with MPO negative acute leukemia as a primary presentation of PMF with histological finding of osteomyelosclerosis on trephine biopsy which is a relatively rare presenting feature and a rare histological finding in PMF.

#### Case description

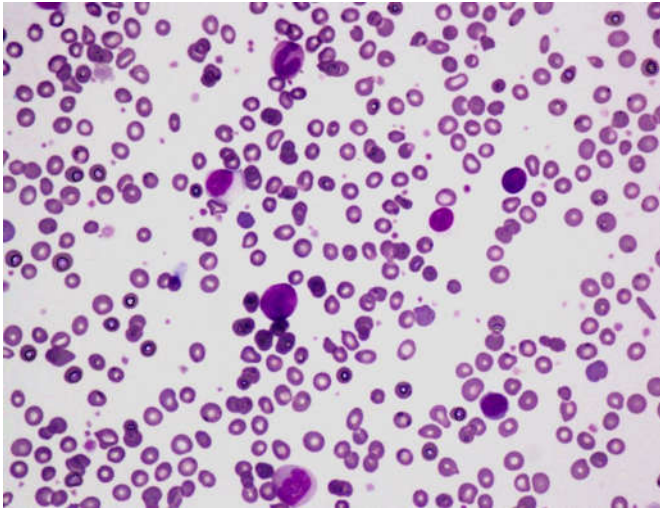
A 44-year-old female patient presented with history of abdominal pain and fatigue since a period of 1 year. General physical examination revealed pallor, with no significant lymphadenopathy.

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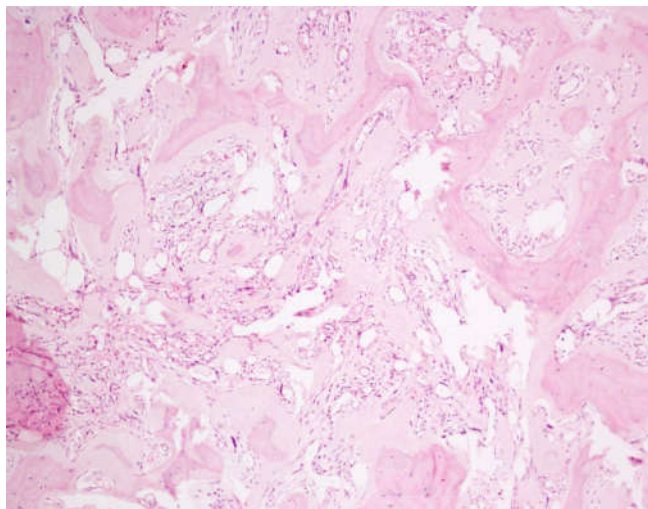
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On examination, the spleen was palpable below the umbilicus and liver was not palpable. Ultrasound revealed massive splenomegaly measuring 20 cm span and mild hepatomegaly measuring 16 cm maximum span. The complete blood count (CBC) showed leukocytosis (White blood cell (WBC) count  $16.2 \times 10^9/L$ ; normal range  $4.0-11.0 \times 10^9/L$ ) and thrombocytosis of  $553 \times 10^9/L$  (normal range  $150-400 \times 10^9/L$ ). The white blood cell differential included blasts 34%, neutrophils 27%, lymphocytes 27%, monocytes 04% and eosinophils 05%. Her red blood cell (RBC) count was  $3.8 \times 10^{12}/L$  (normal range  $4.2-5.5 \times 10^{12}/L$ ), hemoglobin 9.1g/dL (normal range 13.5–16.0 g/dL) and the RDW was 19% (normal range 11.5–14.5%). The peripheral blood smear showed 34% blasts showing a high nucleocytoplasmic ratio, fine nuclear chromatin and scant agranular cytoplasm (Figure 1). The RBC morphology showed moderate anisopoikilocytosis with tear drop cells, 3nRBCs/100WBCs and also thrombocytosis. Cytochemical stains on peripheral blood showed, blasts which were negative for MPO, SBB and PAS. Serum lactate dehydrogenase (LDH) was significantly raised (515 IU/L). The bone marrow aspirate was a dry tap and the imprint smears also did not yield any cellularity. The trephine biopsy showed variably cellular marrow spaces with

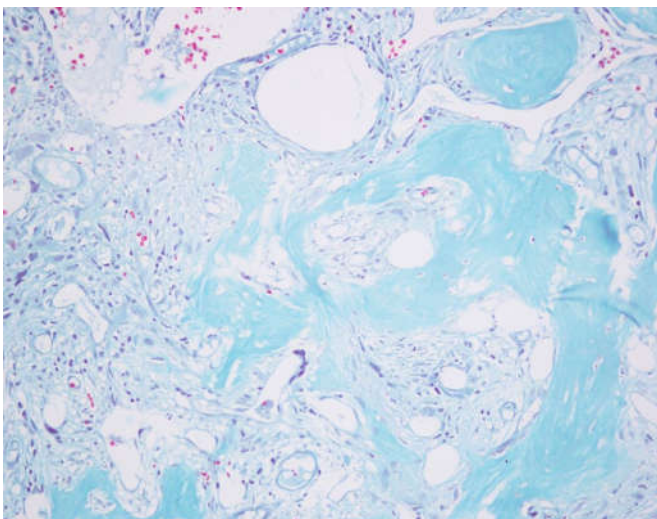
patches of active hematopoiesis alternating with areas of fibroblastic proliferation showing scattered immature cells and loose connective tissue.



**Figure 1. Peripheral blood smear showing blasts having high nucleocytoplasmic ratio, fine nuclear chromatin and scant agranular cytoplasm (Leishman, 600x)**



**Figure 2a. Trephine biopsy showing appositional new bone formation (H&E, 400x)**



**Figure 2b. Increased deposition of reticulin fibres. (Masson's trichrome, 400x)**

Myeloid and erythroid series were suppressed while the megakaryocytic series were adequately represented and occasionally the megakaryocytes were seen in clusters within the pockets of active hematopoiesis. The megakaryocytes showed dysplastic features in form of hyperchromatic, hypoblobated nuclei showing multinucleation at places. There was significant proliferation of vessels showing marked tortuosity and luminal distention. Broad and irregular trabeculae and appositional new bone formation showing osteoblastic rimming was also seen which was suggestive of osteomyelosclerosis (Figure 2a). A reticulin stain was remarkable for an increased (3+) deposition of reticulin fibers which were also positive for Masson's Trichrome (Figure 2b). The molecular analysis showed negativity for BCR-ABL.

## DISCUSSION

Primary myelofibrosis is Philadelphia chromosome negative stem cell-derived clonal myeloproliferative disorder. It is associated with bone marrow stromal reaction including progression from a hypercellular bone marrow with atypical megakaryocytes to a fibrotic bone marrow showing collagen fibrosis, osteosclerosis and angiogenesis. Clinical presentation includes progressive anemia, massive hepatosplenomegaly and leukoerythroblastic picture (Barosi, 2001; Ciurea, 2007; Tefferi, 2005). It is a relatively rare disease with incidence ranging from 0.5-1.5 per 100,000 person per year in United States. It is more common in middle aged and elderly with a median age of presentation being 67 years (Mesa, 2005). Leukemic transformation (LT) occurs in 8% to 23% of patients of PMF occurring generally in the first 10 years of diagnosis (Ciurea, 2007 and Okamura, 2001). Factors predicting the development of leukemic transformation are leucocytosis, percentage of blasts in PBF, progressive anemia and number of karyotypic abnormalities (Cervantes, 2009; Dupriez, 1996 and Huang, 2008). Majority of the transformations of PMF are into acute leukemias of myeloid origin with all FAB subtypes except M3, with a few transforming into lymphoblastic and mixed lineage leukemias. JAK2-V617F mutation positive PMFs have a higher risk on transformation into acute leukemias (Barosi, 2007 and Campbell, 2006). Here, we report a case of PMF in 44 year old female with an initial presentation of acute leukemia which is generally a terminal event. We diagnosed it as a case of leukemic transformation in PMF based on the clinical manifestations including hepatosplenomegaly, leukoerythroblastic picture and massive fibrosis and osteomyelosclerosis in the bone marrow trephine biopsy. The cytogenetic evaluation showed negativity for BCR-ABL which ruled out the possibility of blastic transformation in CML. The blasts showed negativity for cytochemical stains like MPO, SBB and PAS, which is still a rarer presentation of this disease since most common transformations seen were into AML.

Osteomyelosclerosis is a rare histological finding in a case of primary myelofibrosis characterised by replacement of bone marrow by calcified connective tissue matrix. Osteomyelosclerosis may be found post irradiation or under influence of chemicals like benzene. Bone marrow shows gradual progression from reticulosis to fibrosis eventually into sclerosis. Clinically, osteomyelosclerosis presents as marked splenomegaly and hepatomegaly. Signs of hypersplenism and leucocytosis are seen on laboratory investigations. Few studies in literature studied the histologic changes during leukemic transformation of primary myelofibrosis. However, increased

reticulin fibrosis and osteomyelosclerosis has not been reported so far to best of our knowledge (Mesa, 2005). The presentation of PMF complicated by the rare sequela of transformation into MPO negative acute leukemia raises important issues with regard to diagnosis and treatment. It also emphasizes the need of performing a bone marrow biopsy in any case presenting as acute leukemia on peripheral smear, to rule out the possibility of underlying PMF.

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