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## Brief communication

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### Myelofibrosis; a disease with different faces and a challenge to the clinician

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#### Introduction

Myelofibrosis (MF) is a BCR-ABK negative myeloproliferative neoplasm characterized by a clonal myeloproliferation in the bone marrow leading to release of abnormal cytokines.<sup>1</sup> This cytokine influx leads to marked megakaryocytic proliferation causing fibrosis of the bone marrow and ending up with bone marrow failure and pancytopenia. These patients also have a potential to transform into acute leukemia. This being a disease of the elderly, makes it difficult to offer them its only curative therapy which is a stem cell transplantation.<sup>2</sup> Current understanding of the disease has brought in new concepts in the prognosis and therapeutic implications of the disease. Detection of JAK2 V617F mutation in 60% of primary myelofibrosis (PMF) or essential thrombocythaemia myelofibrosis (ETMF)

was a major breakthrough in understanding the pathogenesis in 2005.<sup>3</sup> This paved way to introducing new therapeutic options such as JAK2 inhibitors. Ruxolitinib was the first drug used in 2011 and is currently being use. There are other options going through phase 3 trials this year. Recently a new mutation CALR, the gene encoding the endoplasmic reticulum Ca<sup>2+</sup> binding chaperone calreticulin was discovered. With this discovery, the proportion of essential thrombocythaemia (ET) and Primary myelofibrosis (PMF) patients with a known molecular marker is currently increased upto 80-85%.<sup>4</sup>

#### Clinical features and diagnosis

Myelofibrosis shows marked heterogeneity clinically, ranging from anemia, splenomegaly and constitutional symptoms as the predominant symptoms. (Fig.1)

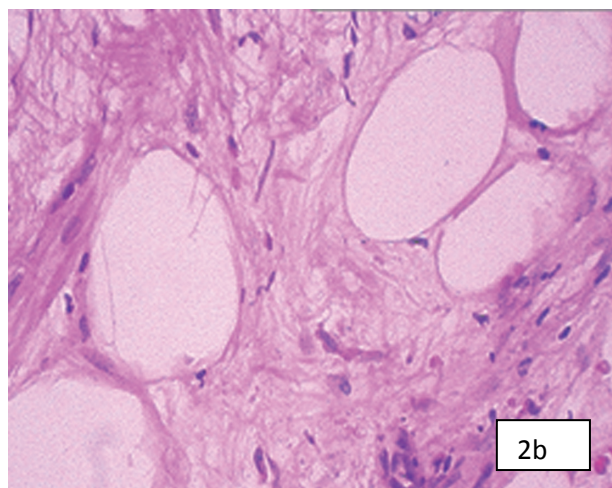
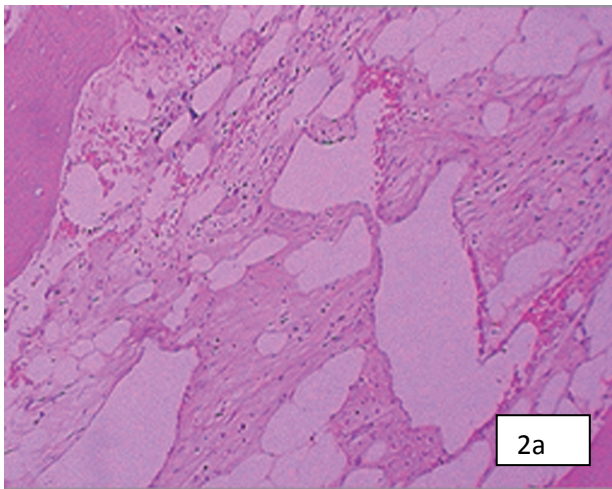
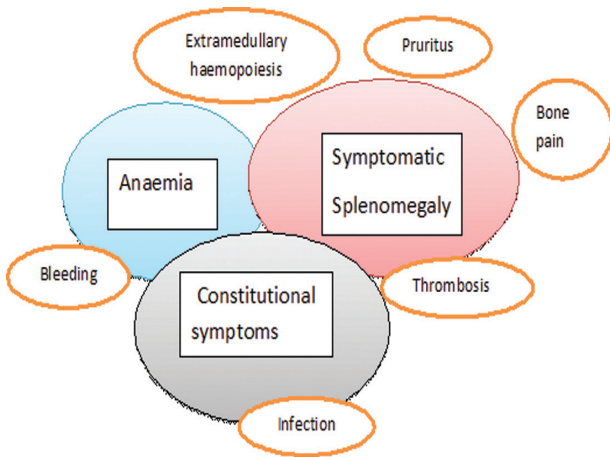
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**Fig. 1. Clinical features of MF**



**Fig.2.** Bone marrow trephine biopsy in MF. Intertrabecular spaces with absent haemopoietic elements which is replaced by bone and fibrosis. **2a.** (H and E x10) **2b.** (H and E x40)

PMF has a greater potential to transform into acute leukemia compared to its related counterparts namely ET and polycythaemia vera (PV). The morphological features in the bone marrow with marked reticulin fibrosis and megakaryocytic proliferation and atypia together with detecting a positive molecular marker of JAK2 mutation/ CALR mutation are the major criteria in diagnosing PMF (Fig.2).

However, other minor criteria such as excluding secondary causes of myelofibrosis and other myeloproliferative neoplasms become important in the diagnosis particularly if the mutation analysis is not possible due to financial constrains or lack of availability of molecular markers. The current WHO classification (introduced in 2007) is likely to change with the introduction of new molecular markers.

### Management

It is important to prognosticate the patient for the clinical decision making process. The modern therapeutic options vary greatly depending on the DIPSS Plus (Dynamic International Prognostic Scoring System -Plus) (Table 1).

<b>Table 1-Modified DIPSS-Plus Score</b>	
Age > 65yrs.	+
Constitutional symptoms	+
Hb <10g/dl	+
Leukocytes >25x10 <sup>9</sup> /l	+
Blood blasts > 1%	+
Platelets <100	+
RBC transfusion needed	+
Unfavorable karyotype	+

<b>Score-</b>	
Intermediate 1	- 1 point
Intermediate 2	- 2 points
High	- 3 or more points

The clinical heterogeneity of MF, has made the management very challenging as there is no one drug which can be used to manage all the problems and treatment for one symptom might even make the other symptom worse.<sup>1</sup>

Anaemia is one of the major clinical manifestations in MF which is multifactorial. Decreased bone marrow production, ineffective erythropoiesis, hypersplenism and bleeding are some of the causes. Unfortunately, there is no curative medical therapy for these patients who eventually end up becoming transfusion dependent.<sup>5</sup> Historically a variety of options have been practiced, which are erythropoietin

stimulation factors, androgens like danazole, immunomodulatory drugs such as thalidomide and lenalidomide.

Splenomegaly is a characteristic feature in patients with MF which is due to extramedullary haemopoiesis.<sup>1</sup> Often, splenomegaly can be associated with hepatomegaly. The discovery of ruxolitinib an oral JAK 2 inhibitor, is the first agent approved for the treatment of MF where splenomegaly and constitutional symptoms showed a dramatic response. This drug can be given regardless of the JAK 2 positive or negative status. Normalisation of several pro-inflammatory cytokines following this treatment correlates with symptomatic improvement. This drug causes an advantage in survival, reduction of splenic size and constitutional symptoms and in some cases reversal of bone marrow fibrosis.<sup>6</sup> However, it does not help in the treatment of anaemia and moreover a resultant low platelet count may be a dose limiting factor. Newer JAK 2 inhibitors are currently undergoing phase 3 trials which may be proven to be effective for anaemia and may also be used in other myeloproliferative disorders (MPD) which have a limited choice of therapy.

Since ruxolitinib is not freely available for treatment of MF in many countries, hydroxyurea remains the treatment of choice for splenic reduction, reduction of white cell counts and relief of constitutional symptoms.

Splenectomy can be tried for patients with large and tender spleens which is refractory to other therapy. However, the associated risks make individualised decision making necessary.<sup>1</sup>

### Conclusion

Myelofibrosis is a chronic myeloproliferative neoplasm which is characterized by anaemia, splenomegaly and constitutional symptoms which commonly occur in the elderly population. The behaviour of MF is more aggressive compared to the other MPD, PV and ET. The recent advances and the discovery of new molecular markers have improved the diagnosis.

JAK 2 inhibitors have made a paradigm shift of the management of MF which is now being given in high risk as well as low risk prognostic categories. However, there is no promising therapy for anaemia and most of the patients end up being transfusion dependent. Stem cell transplantation is the only curative therapy for MF and is often reserved for high risk patients. Allogenic stem cell transplantation is associated with a high rate of mortality and morbidity making it a less likely option for the elderly patient. Despite recent advances, we are yet to find a satisfactory option of therapy which will be effective for all symptoms of this heterogeneous disorder.

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