PRIMARY MYELOFIBROSIS

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MYELOFIBROSIS (MF)

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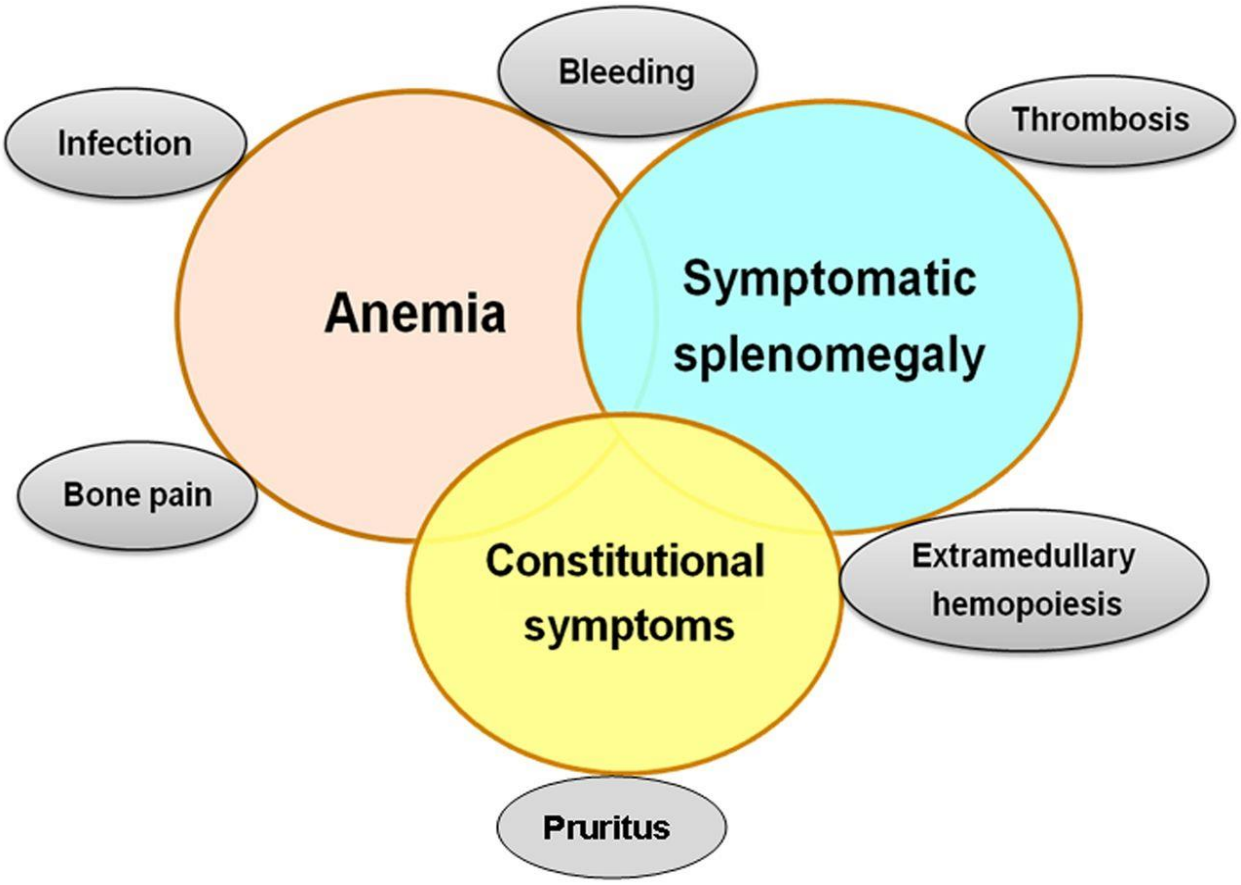
Myelofibrosis (MF) consists of 2 entities:

Primary MF : appearing de novo (***PMF***)

or following a previous ET or PV (post-ET or post-PV MF), the disease is essentially the same.

Post–polycythemia vera (PPV) and post–essential thrombocythemia (PET) MF, also known as ***secondary MF (SMF).***

- Myelofibrosis (MF), formerly known as idiopathic MF, MF with myeloid metaplasia, or agnogeneic myeloid metaplasia, is one of the chronic myeloproliferative neoplasms (MPNs)
- MPN as a group also including essential thrombocythemia (ET) and polycythemia vera (PV).
- MF is a clonal proliferation of a pluripotent hematopoietic stem cell, in which the abnormal cell population releases several cytokines and growth factors in the bone marrow that lead to marrow fibrosis and stroma changes and colonizes extramedullary organs such as the spleen and liver.
- MF is a myeloproliferative neoplasm (MPN)
    - clinical phenotype dominated by splenomegaly, constitutional symptoms
    - variety of blood cell alterations
    - tendency to develop vascular complications and blast phase (BP).
- **Clinical manifestations of MF.**

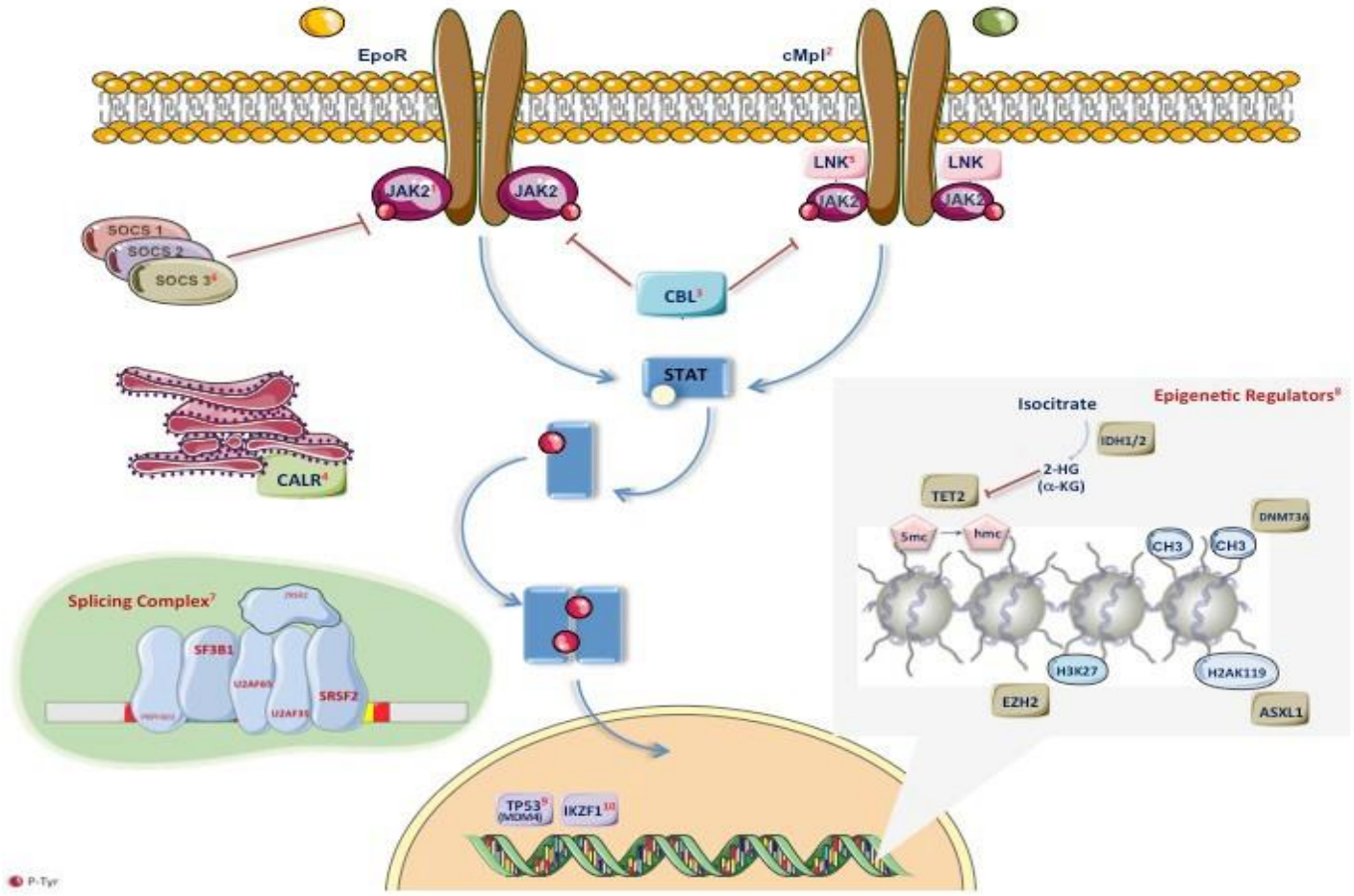


MF- Molecular Pathology

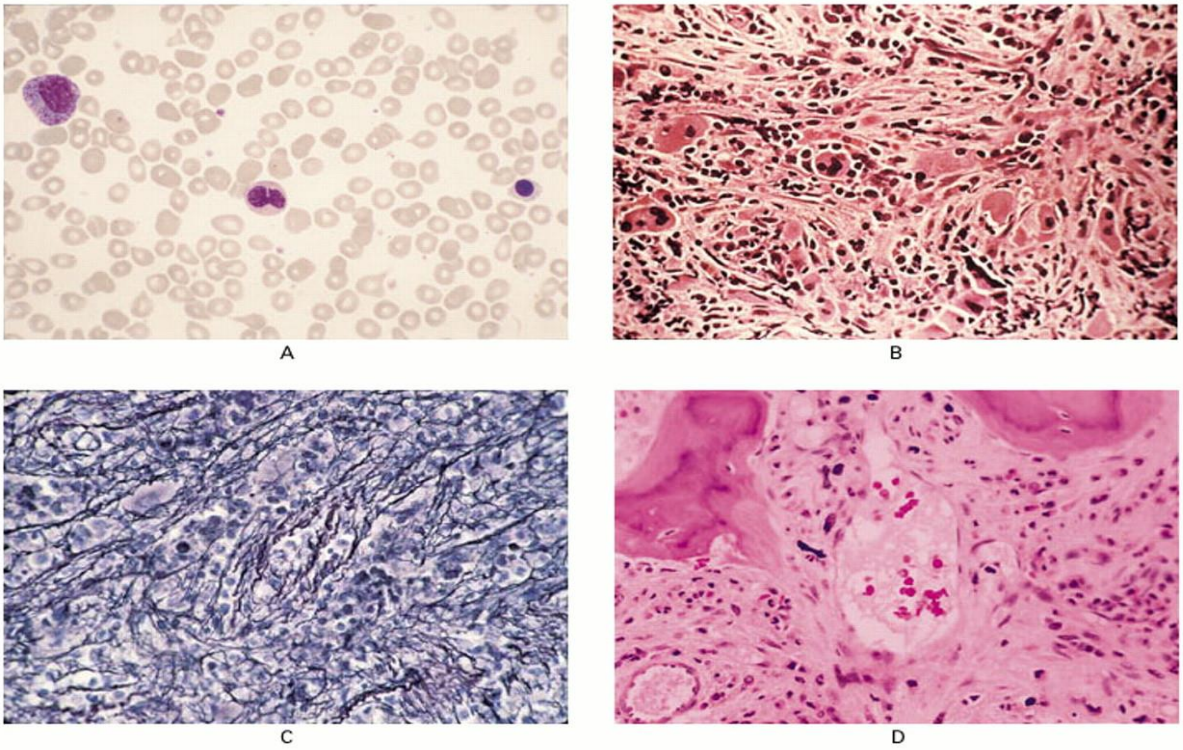
- Discovery of the V617F mutation of the Janus kinase (***JAK)2*** gene in 60% of patients with PMF or post-ET MF and 95% of those with post-PV MF represented an important step in the understanding of the pathogenesis of MF.
- Mutations in the thrombopoietin receptor gene (***MPL***) were subsequently found in 3% to 8% of patients with PMF and post-ET MF
- Mutations in the calreticulin gene (***CALR***) have been observed in half of patients with PMF and post-ET MF lacking *JAK2* and *MPL* mutations.

However, the genetic trigger of MF is unknown.

PMF: much more complex than anticipated



Pathological Features of Peripheral Blood and Bone Marrow in Patients with Myelofibrosis with Myeloid Metaplasia



Diagnostic Criteria- MF

Major criteria

- Presence of megakaryocytic proliferation and atypia, accompanied by either reticulin and/or collagen fibrosis grades 2 or 3
- Not meeting WHO criteria for BCR-ABL1-positive chronic myeloid leukemia, Polycythemia Vera, Essential Thrombocythemia, Myelodysplastic syndromes, or other Myeloid neoplasms
- Presence of JAK2, CALR or MPL mutation or in the absence of these mutations, presence of another clonal marker (eg, ASXL1, EZH2, TET2, IDH1/IDH2, SRSF2, SF3B1)

Minor criteria

- Presence of at least 1 of the following, confirmed in 2 consecutive determinations:
    - Anemia not attributed to a comorbid condition
    - Leukocytosis (WBC count ≥11 × 109/L)
    - Palpable splenomegaly

- Lactate dehydrogenase (LDH) level increased to above upper normal limit of institutional reference range

- Diagnosis of overt primary myelofibrosis requires meeting all 3 major criteria, and at least 1 minor criterion

TABLE 69-7 Median Survival of Each Risk Group in Four Prognostic Scoring Systems for Primary Myelofibrosis

Risk Group	Lille	IPSS	DIPSS	DIPSS Plus
Low	93 months	135 months	Not reached	185 months
Intermediate-1	26 months	95 months	170 months	78 months
Intermediate-2		48 months	48 months	35 months
High	13 months	27 months	18 months	16 months

DIPSS, Dynamic international prognostic scoring system; *IPSS*, international prognostic scoring system.

Therapeutic options available to patients with Myelofibrosis

- Non-transplant options

- Conventional
- Treatment for anemia
- Transfusion support
- Erythropoietin
- Corticosteriods
- Androgen + prednisone
- IMiDs

- Treatment for splenomegaly

- Hydroxyurea
- Splenectomy
- Low-dose irradiation
- First approved medication
- Ruxolitinib

- **Transplant options**

- Myeloablative
- Reduced-intensity

Anemia:

- EPO: Transfusion independence with normal Hb, transfusion decrease>50%: achieved in 23% to 60% of patients.
    - Usually restricted to patients with inadequate Epo levels (125 mU/mL).
- Androgens: Improve anemia in 30% to 60% of patients. Factors associated with a favorable response are female gender, previous splenectomy or lack of huge splenomegaly and normal karyotype.
- Lenalidomide: 22% anemia responses and 10% to 42% responses in splenomegaly. Dose is 5 to 10 mg daily (depending on platelet count) for 3 weeks, every 4 weeks.

Splenomegaly

Hydroxyurea:

- was the choice of therapy for many years.
- Accentuation of anemia, requiring anemia-alleviating drugs, is often seen.
- Oral or leg ulcers are the most characteristic nonhematologic toxicity of hydroxyurea.
- The overall response is 40%
- median duration is 13.2 months

Splenectomy

- May be indicated for large and painful splenomegaly, refractory to drug therapy.
- Decision must be individualized due to the associated risks. Perioperative morbidity 31% and mortality was 9%.
- Durable responses
- in transfusion-dependent anemia are 23%.

Splenic radiation

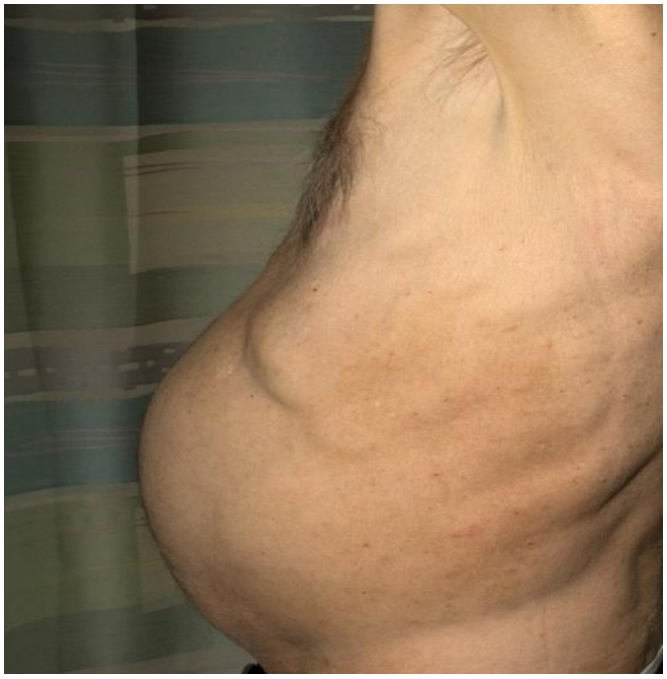
- on a fractioned basis, at a daily dose of 0.4 to 1 Gy, with weekly evaluation of spleen size and hematologic values
- Can be applied to patients that are refractory to JAK2 inhibitors and poor candidates to surgery.
- benefit is transient, whereas, due to the effect on circulating progenitors
- it involves the risk of severe and prolonged cytopenias,

Jak-2 inhibitors in PMF

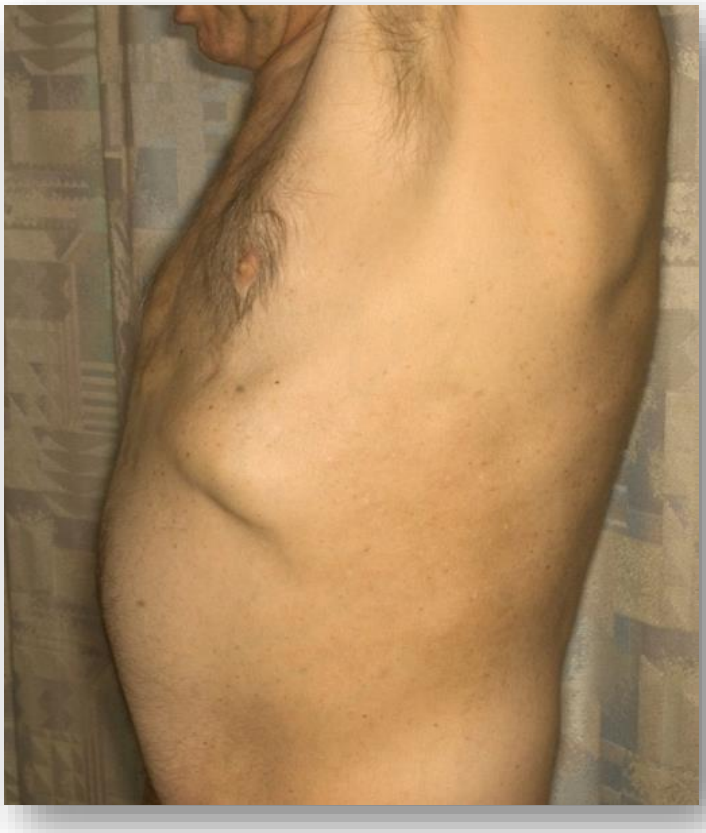
Ruxolitinib:

- Striking responses in terms of symptom improvement and *spleen volume reduction.*
- Phase III studies of COMFORT trials: led ultimately to the *approval of Ruxolitinib* for the treatment of Myelofibrosis by the Food and Drug Administration in 2011.
- Probability of maintaining a spleen response was 0.53 at 144 weeks and that the median spleen volume reduction at 144 weeks was 34% for the 50% of patients.
- Hazard ratio for survival advantage of Ruxolitinib therapy *versus* control management was 0.48 (95% confidence interval 0.28–0.85, P=0.009).
- Benefits regardless of whether patients do or do not have the *JAK2* mutation.
- Shown in a sub-analysis of COMFORT-2, will benefit Myelofibrosis patients with High Molecular Risk profile (i.e. at least one of – EZH2, ASXL-1, IDH1/2, SRSF2).

Spleen size reduction in patient
treated with Ruxolitinib



Myelofibrosis patient pre-therapy



Patient after 2 months of therapy

Transplantation for Myelofibrosis

While the efficacy of HSCT is well established in CML, acute leukemia and MDS, the literature on the outcomes of HSCT in Ph- MPNs and CMML is relatively small.

Without randomized prospective trials comparing HSCT to non-HSCT options, physicians must rely on prognostic scoring systems and clinical experience when making decisions about who and when to transplant patients with Ph- MPNs.

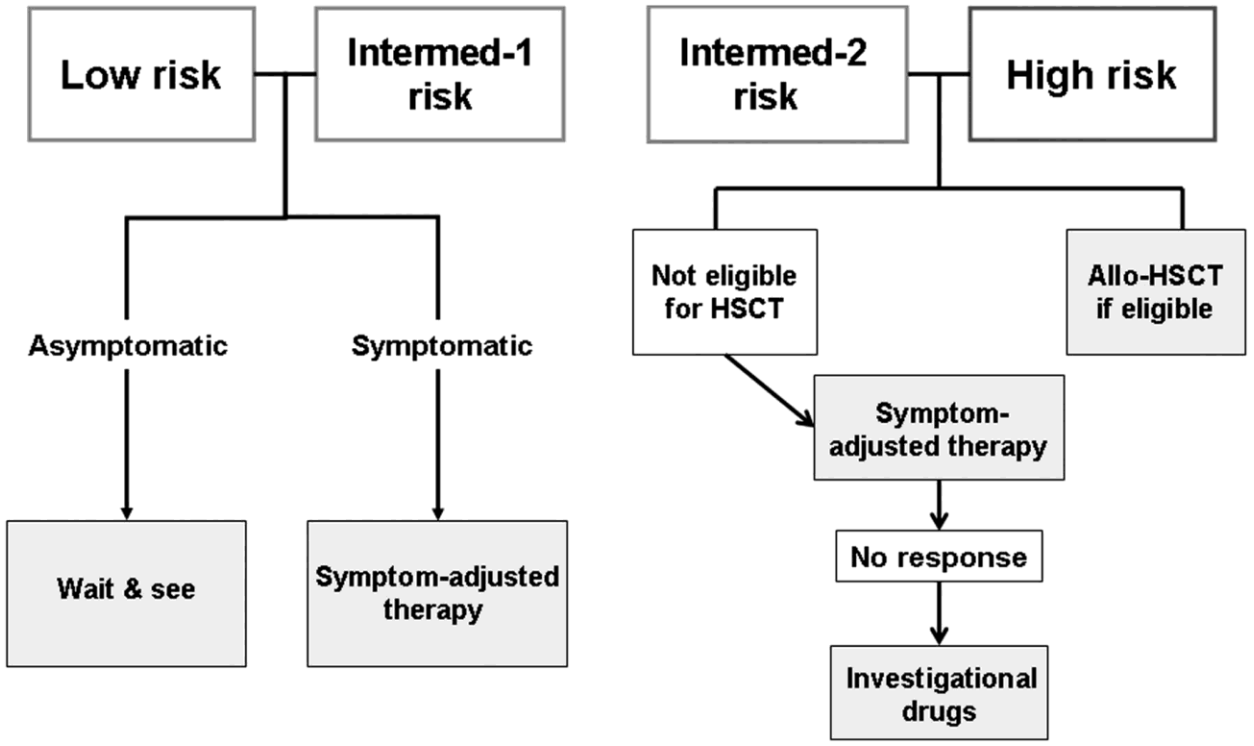
Furthermore, patients with PMF may become more vulnerable to hepatic toxicity and graft failure, due to their increased likelihood of portal hypertension, massive splenomegaly, and extensive bone marrow fibrosis.

Transplantation for Myelofibrosis

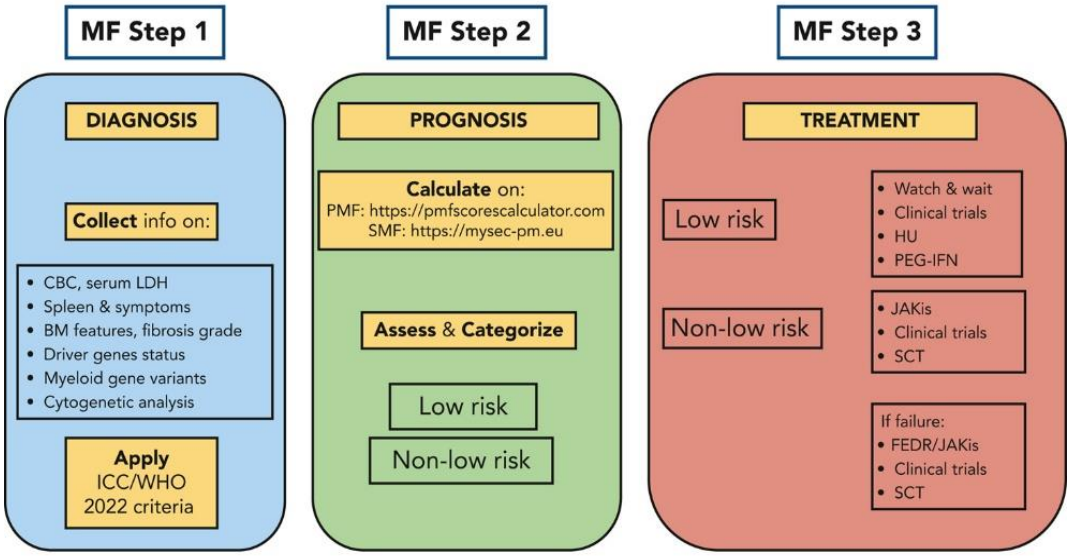
- Potentially curative option
- Can have high risk of significant complications
- Optimal timing of transplant can be complex decision
- Option for transplant in every MF patients in the transplant age group should be considered.
    - **Early vs. delayed vs. never**

Who are the candidates for transplantation for Myelofibrosis?

- When is transplant an appropriate option?
    - DIPSS - Intermediate-2/ high-risk
    - *? DIPSS - Intermediate – 1*
- High risk cytogenetics
- Severely cytopenic patients
- Transfusion dependent (non-responders to conservative options)
- Severe thrombocytopenia
- High-risk mutations (*ASLX1*+ patients, ≥3 somatic mutations)
- **How I treat MF : Summary**



The 3 steps of MF management



Legend: BM= bone marrow; CBC= complete blood count; FEDR= fedratinib, HU= hydroxyurea; ICC= International Consensus Classification; JAKis= JAK inhibitors; LDH= lactate dehydrogenase; MF= myelofibrosis; PEG-IFN= PEGylated-Interferon; PMF= primary myelofibrosis; SCT= stem cells transplantation; SMF= secondary myelofibrosis; WHO= World Health Organization.

MYELOFIBROSIS

Dr. Rahi Shetye
Junior Resident
Department of Radiodiagnosis
Goa Medical College

A 63 year old female presented to the casualty with breathlessness and giddiness.

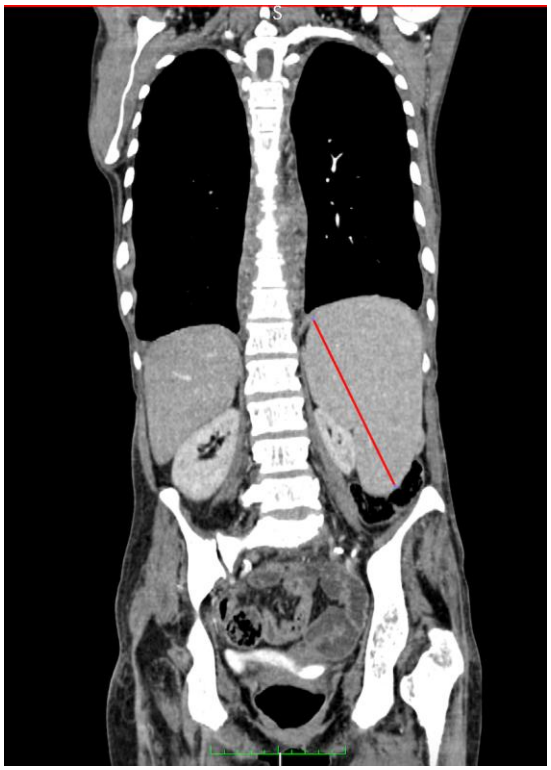
Clinical examination revealed hepatosplenomegaly and severe anemia.

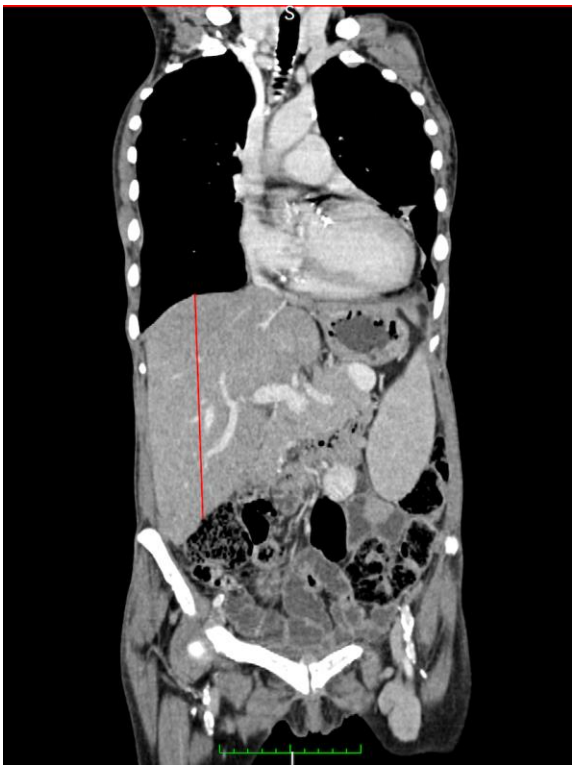
Contrast enhanced CT scan of the abdomen revealed:

Ill-defined bilateral fairly symmetrical nodular enhancing paraspinal soft tissue along the dorsal vertebrae

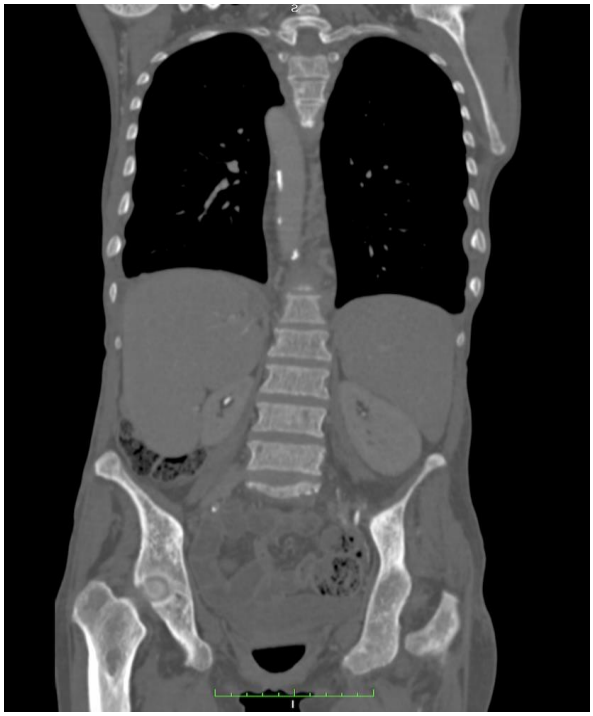
Diffuse sclerosis of the dorsal vertebral column and pelvic bones.

Hepatosplenomegaly

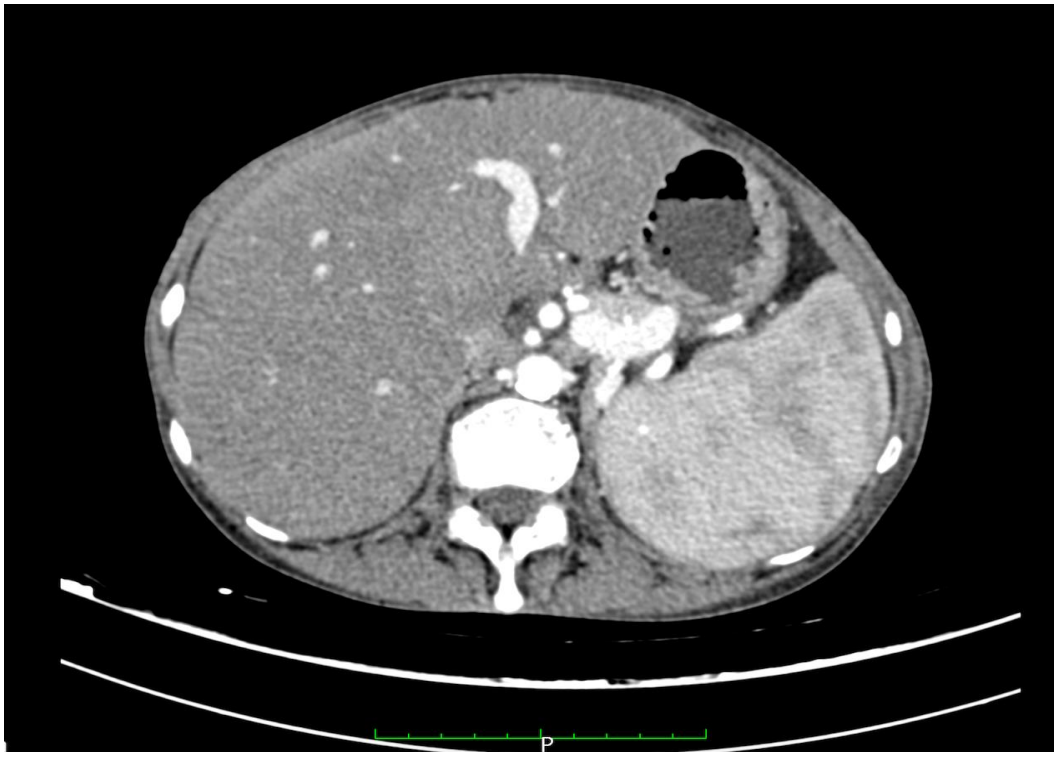




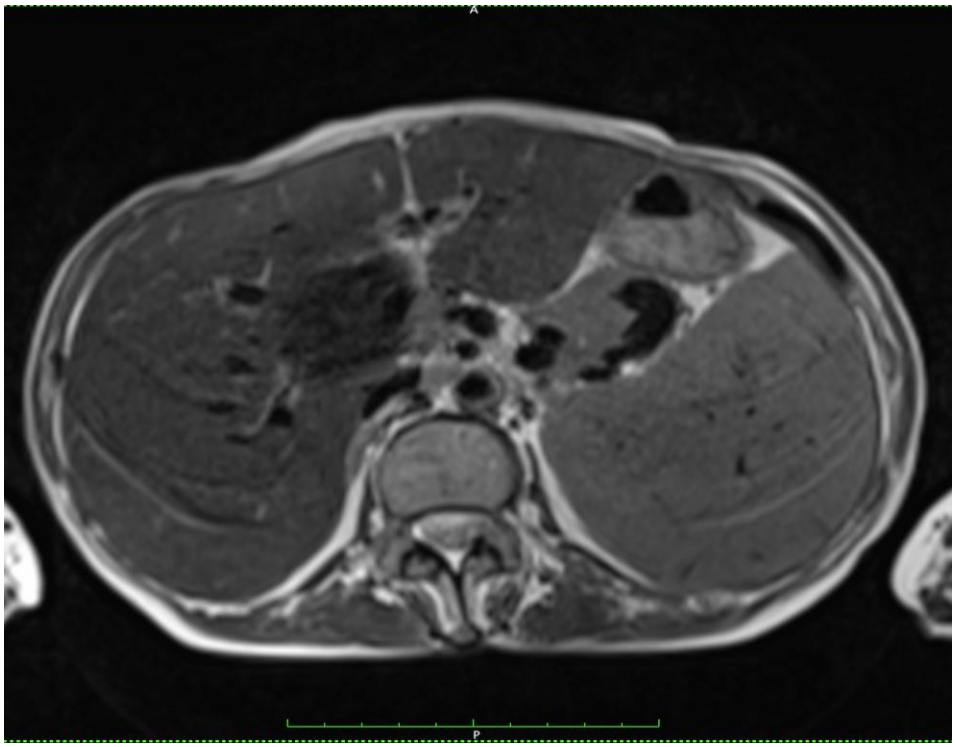
- Ill-defined bilateral fairly symmetrical nodular enhancing paraspinal soft tissue along the dorsal vertebrae
- Hepatosplenomegaly



Diffuse sclerosis of the dorsal vertebral column and pelvic bones.

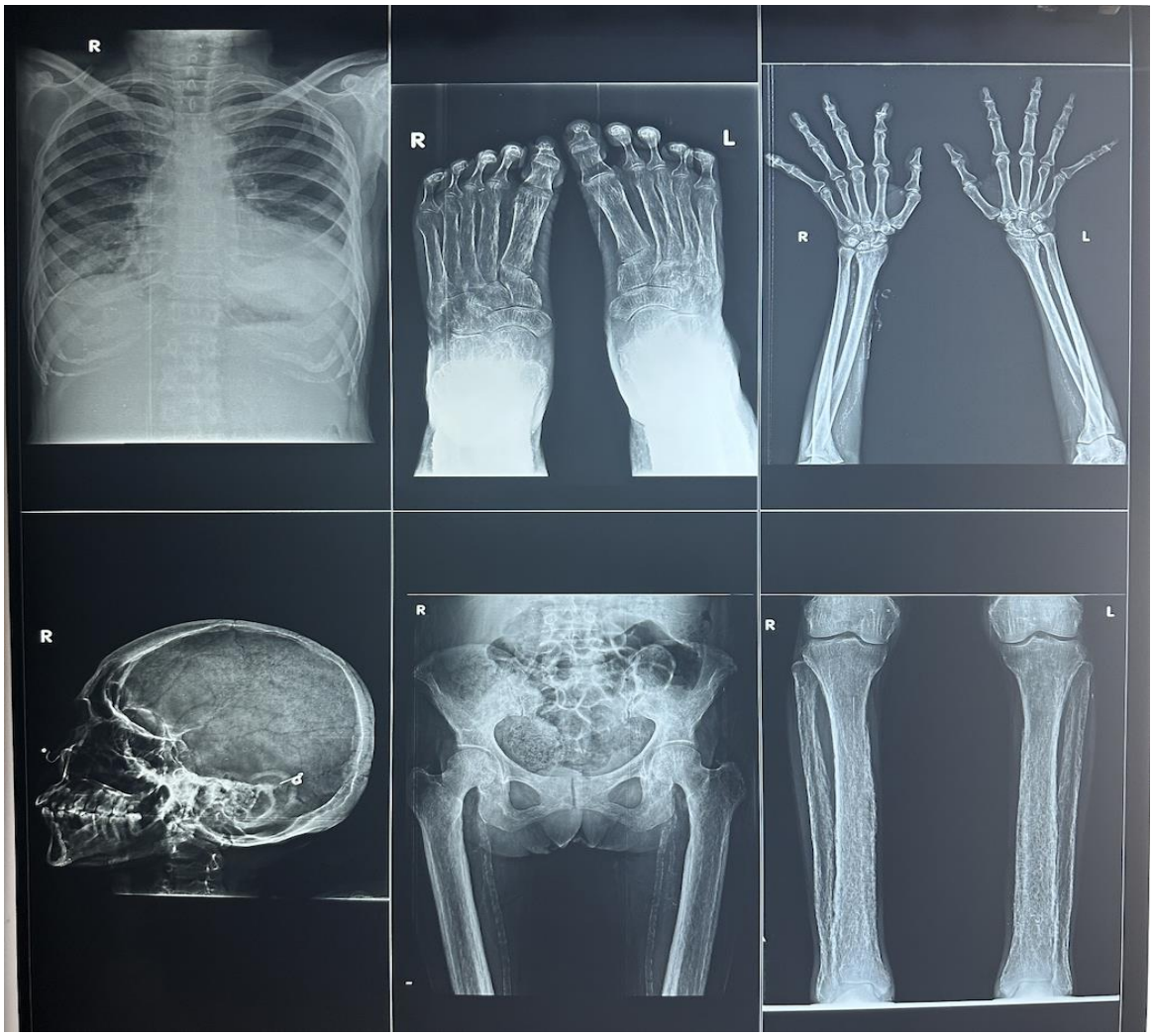


This mass was found to appear as a well defined, lobulated mass at the porta hepatis measuring approximately 5.8 x 3 cm in size. It appears isodense to the liver on arterial and venous phases and mildly hyperdense on delayed images.



Well defined, lobulated mass at the porta hepatis measuring approximately 5.8 x 3 cm in size which appears hypointense on MR images.

Chest xray reveals Mild cardiomegaly
Minimal paraspinal soft tissue noted along the dorsal vertebrae.



Pelvis: There is mild sclerosis of the pelvic bone with linear solid periosteal reaction along bilateral femur.

Knee and foot: There is widening of the medullary cavity with thinning of the overlying cortex. There is coarsening of the trabeculae.

Linear solid periosteal reaction noted along bilateral tibia, fibula and femur.

After the radiological work up we had two differential diagnosis in mind:

Lymphoma

Myelofibrosis

HOA is a clinical syndrome characterized by

digital clubbing and periosteal proliferation

HOA includes skin manifestations such as thickened skin on face and scalp, and coarse facial features along with clubbing, periostosis, acroosteolysis, and painful joint motion.

HOA may be associated with various disorders including intrathoracic malignancies, cyanotic heart diseases, gastrointestinal tumors and inflammatory bowel diseases. One of the rare causes of secondary HOA is myelofibrosis.

Platelet derived growth factor

transforming growth factor beta (TGF-β)

epidermal growth factor (EGF)

Increased levels of TGF and EGF cause excess production of collagen type III. This increase in collagen type III causes clubbing and periostitis.

Plasma levels of pro-inflammatory cytokines such as tumor necrosis factor-alfa (TNF-alfa), interleukin-6 (IL-6), and vascular endothelial growth factor (VEGF) were also reported to be increased.

CLINICAL PATHOLOGICAL CASE PRESENTATION
MYELOFIBROSIS

Dr Vikas G
Junior Resident
Department of General Medicine

- Myelofibrosis Is one of the rare Hematological Malignancy
- It affects the bone marrow characterised by Marrow fibrosis (1)
- It Leads to decreased production of Blood cells resulting in Anemia Bicytopenia/Pancytopenia with ExtraMedullary Hematopoeisis(1)
- Myelofibrosis is typically associated with progressive splenomegaly and, in many cases, with hepatomegaly(2)
- In Myelofibrosis, in some patients there is Osteosclerosis(3)

History

- Patient is a 63 year elderly female , House-wife.
- She is a Known Case of Old Abdominal Koch's - Completed Treatment

And Not a known case of any other chronic illness

Came to GMC with the complaints

- Generalised weakness
- Weight loss with Loss of appetite
- Multiple episodes of giddiness which were not associated with Blackouts and not suggestive of seizures, from around 4 months.
- Bone pains from many years

Diet - Mixed Appetite - Decreased

- No History of Bleeding from any sites
- No History of Jaundice in the past
- No History of Recent Trauma or surgeries with Blood Loss
- No History of worm infestation
- No History of past blood transfusions
- No History suggestive of Bleeding Disorders
- No History suggestive of Frequent Infections

On Examination

Patient is poorly built and nourished , looks emaciated.

Concious, Co-operative for examination.

General Physical Examination

Severe Pallor Present

Bilateral Pitting Type of Pedal Edema Present Till Ankles, Which is Symmetrical , Non Tender.

Bilateral Inguinal Lymphadenopathy Present

Bilateral 2*1 cm Lymph Nodes - Non Matted , Non tender

No other Lymph Nodes palpable

No Icterus / No Cyanosis / No Clubbing

Pulse - 96 beats per Minute , Regular Rhythm, High Volume , Bounding Type , No Radio-Radial delay and No Radio-Femoral Delay

BP - 108/66 mmHg in Bilateral Brachial Arteries

Bilateral Carotids Well Felt

JVP Not Raised

All Peripheral Pulses Felt

RS - Bilateral Normal Vesicular Breath Sounds Heard , No Added Sounds

CVS - S1 , S2 Heard , No **S3 ,** No Murmurs

CNS - Concious, Oriented to Time, Place and Person

No Cranial Nerve Deficits / No Focal Neurological Deficits.

Per Abdomen - Soft , Non Tender , Bowel Sounds Well Heard

LIVER- 3 cm palpable from the costal margin

NonTender with Smooth Border

SPLEEN - 2 cm palpable from the costal margin. Non Tender with Smooth Border

Differential Diagnosis

HepatoSplenomegaly and Weight Loss with Bi-Cytopenia 2^0 to

- Hematological Malignancy
- Multiple Myeloma
- Myelodysplastic Syndrome
- Myelofibrosis

Blood Investigations

CBC

- Hb- 6.5
- TC-6970 with Neutrophilic Predominance(73%)
- Absolute Neutrophil count - 5130
- Platelets -70000

COMPLETE HEMOGRAM-

- Hb-7.4 , TC-7580 , Platelets- 1.6 Lakhs.
- RBCs- Moderate hypochromia , Moderate anisocytosis , Mild poikilocytosis Polychromasia present , Macrocytes & microcytes present.
- WBCs- Neutrophilic Predominance - 81% , 7 Normoblasts/100WBCs , and Stabs-1
- Platelets - Adequate In number

Blood Investigations (CH and CBC , From left to Right)

SR. No.	TEST	RESULT	UNIT	ANALYTICAL METHOD	BIOLOGICAL REFERENCE INTERVAL
1	Haemoglobin	7.4	gm%	Cell Counter	
2	Total WBC Count	7500	/cu.mm.		
3	Differential Count	Stabs 01 N: 81 L: 16 E: 01 Mo: 01 Ba: –	%	7 Normoblasts/100 WBC's	
4	RBC Count	2.74	million/cu. mm.		
5	PCV	21.7	%		
6	Platelet Count	1.6 lacs	/cu. mm.		
7	MCV	79.0	fl		
8	MCH	27.2	pg		
9	MCHC	34.4	gm/dl		
10	ESR	–	mm/hr (Wintrobe's)		

Peripheral Smear: Moderate hypochromia, moderate anisocytosis
Mild poikilocytosis.
Polychromasia present. Macrocytes & microcytes present.
Platelets adequate in number

Page 1 of 2

	OBSERVED VALUE	UNIT
Hemoglobin	6.51	g/dL
Total W.B.C. Count	6.97	10e3/uL
Neutrophil	73.60	%
Lymphocyte	17.70	%
Monocyte	5.43	%
Eosniophil	1.77	%
Basophil	1.45	%
Platelet Count	70,000	10e3/uL
PCV	57.90	%
Red Blood Cells	18.10	10e6/uL
RDW	2.26	%
MCH	14.50	pg
MCHC	28.80	g/dL
MCV	35.90	fL
Absolute Monocyte	80.30	10e3/uL
Absolute Neutrophil	0.378	10e3/uL
Absolute Lymphocyte	5.130	10e3/uL
Absolute Eosniophil	1.234	10e3/uL
Absolute Basophil	0.123	10e3/uL
	0.101	10e3/uL

-- END OF REPORT --

MENTS / IMPRESSIONS:-

BY : dolcy

Liver Function Tests and Renal Function Tests

- Within Normal Limits
- And no evidence of Intravascular hemolysis
- Serum Calcium - 8.2
- Serum Albumin - 3.4
- Corrected Calcium - 8.68

IRON STUDIES

- Serum.Fe- 43
- UIBC -68
- Ferritin-561

Suggestive of **Anemia of Chronic Disease**

- **LDH** - 652

Serum Protein Electrophoresis

- Faint Band in Gamma Globulin Region

Malignancy Markers

- Negative

Serum Protein Electrophoresis

- Sputum CBNAAT - Negative
- HIV ELISA - Non Reactive
- HbsAg - Negative
- Anti HCV - Negative
- Anti HEV - Negative
- 2D Echo - Normal

Radiological Investigations

USG Abdomen

- Hypoechoeic lesion in segment VIII of the Liver in close proximity to Right branch of Portal Vein

CECT Abdomen and Thorax

- HepatoSplenomegaly
- Paraspinal soft tissue

- Lobulated mass at Porta Hepatis
- Multiple enlarged Non-necrotic Lymph Nodes in B/L Inguinal region
- Diffuse sclerosis of Vertebrae, pelvis , bony rib cage ,and sternum.

Suggestive of **Myelosclerosis with Extra Medullary Hematopoeisis**

Skeletal Survey

- X-Ray of B/L Foot - Osteopenic with Marrow Expansion and Cortical Thickening
- X-Ray Pelvis - Mild Sclerosis of Pelvic Bone with Linear Solid Periosteal Reaction along Femur
- X-Ray Knees and Leg - Widening of Medullary Cavity with Thickening of Overlying Cortex and Coarsening of Trabaculae And Linear Solid Periosteal Reaction along Tibia and Fibula.

Suggestive of **Hypertrophic Pulmonary Osteoarthropathy or Extra Medullary Hematopoeisis.**

Inguinal Lymph Node Study

Inguinal Lymph Node FNAC

Shows Amorphous material with few Lymphoid cells and Neutrophils.

Inguinal Lymph Node Biopsy

shows fibrosis , myeloid metaplasia , Hematopoeitic cells - Myeloid cells , Megakaryocytes and Erythroid Cells.

Suggestive of **Extra Medullary Hematopoeisis**

Bone Marrow Study

Bone Marrow Aspirate and Imprint Smear

Bone Marrow Aspirate didn't contain any narrow fragments ,only few peripheral blood admixed with scanty sinusoidal blood.

No Definitive Diagnosis could be made.

Bone Marrow Trephine Biopsy

Shows Decreased cellularity of Marrow cells, Marked Fibrosis and collection of Lymphoid cells.

Suggestive of **MYELOFIBROSIS**

Conclusion

- Malignancy ruled out as the malignancy Markers were Negative
- Multiple Myeloma ruled out as it could not fulfill **SLiM CRAB** criteria
- Myelodysplastic Syndrome ruled out as Bone Marrow studies didnot show any evidence of Dysplasia.

And

- With HepatoSplenomegaly , Osteosclerosis , Coarse Trabaculae , Mass In Porta Hepatis and ParaSpinal soft tissue , And Lymph Node studies
- All suggestive of **ExtraMedullary Hematopoeisis**
- And Bone Marrow Studies suggesting Marrow Fibrosis.
- HepatoSplenomegaly + ExtraMedullary Hematopoeisis with Marrow Fibrosis giving us a Diagnosis of **MYELOFIBROSIS.**

PATHOLOGICAL ASPECTS

PRIMARY MYELOFIBROSIS

Dr.Sanjana Lotlikar
Assistant Lecturer on Bond
Department of Pathology

Clinical History

63 year old/ Female, Housewife

Presented with:

Bilateral pedal edema x 6-9 months

Giddiness x 1-1/2 yrs

Grade 2 breathlessness x 2 years

H/o old abdominal Kochs → completed treatment

Significant weight loss +

Investigations

USG: Hepatosplenomegaly

CECT abdomen: Hepatomegaly + massive splenomegaly

Multiple lytic lesions in iliac bone, ribs, paraspinal enhancement of soft tissue

Bilateral inguinal lymph nodes

2D Echo Normal

Sputum CBNAAT -Negative

Viral markers - Negative

HIV Elisa -Negative

Serum protein electrophoresis- faint band in gamma globin region.

Indirect Coombs test- 1+ positive

Direct Coombs Test- Negative

TIBC- 68

B.12 - 128

Malignancy markers - Negative

LFTS |RFTS - Normal

Biochemical tests

Se. LDH- 663

Se. Iron - 43

Se. Ferritin- 561

Peripheral Smear

Moderate Hypochromia

Moderate Anisocytosis- Microcytes+ ,Macrocytes+

Mild Poikilocytosis

Mild Polychromasia

Platelets Adequate (Manual count)

Provisional Clinical Diagnosis

Bicytopenia 2° to ? Malignancy

?Extramedullary haematopoiesis

? Multiple myeloma

? Myelofibrosis

? Myelodysplastic syndrome

Bone Marrow Aspirate+ Imprintsmear(Sternal)

No marrow fragments

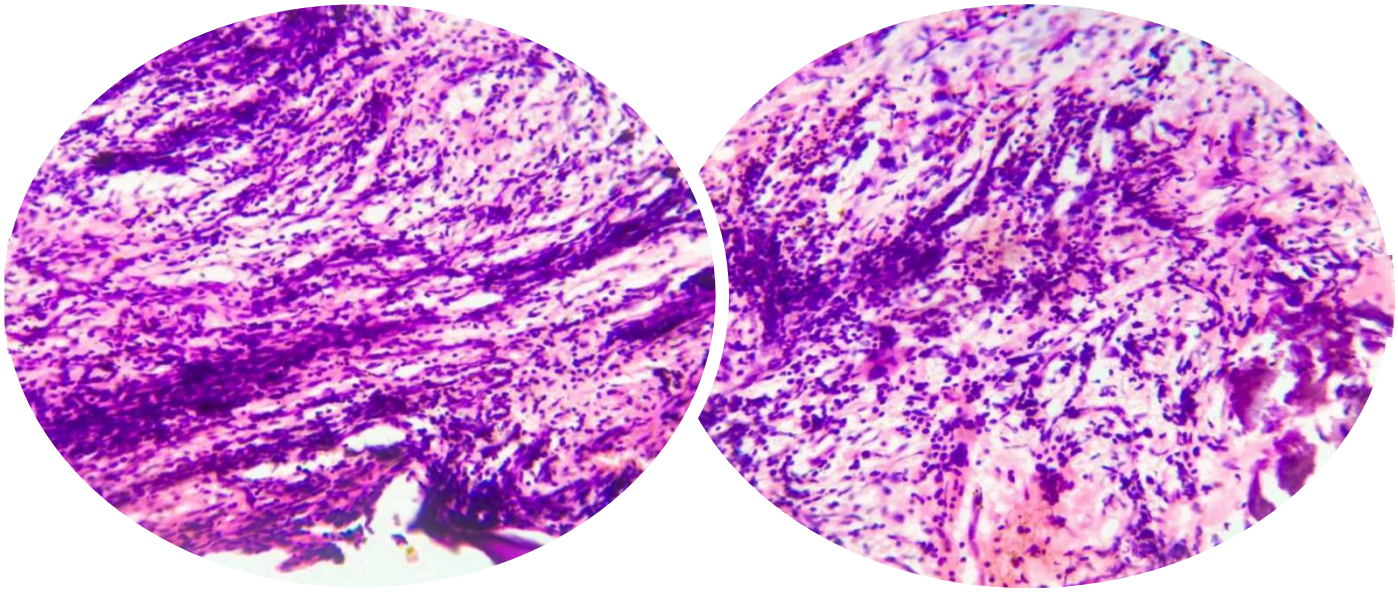
Scanty Sinusoidal blood admixed with peripheral blood

Bone Marrow Trephine biopsy

Decreased cellularity of marrow cells, marked **fibrosis** and collection of lymphoidcell

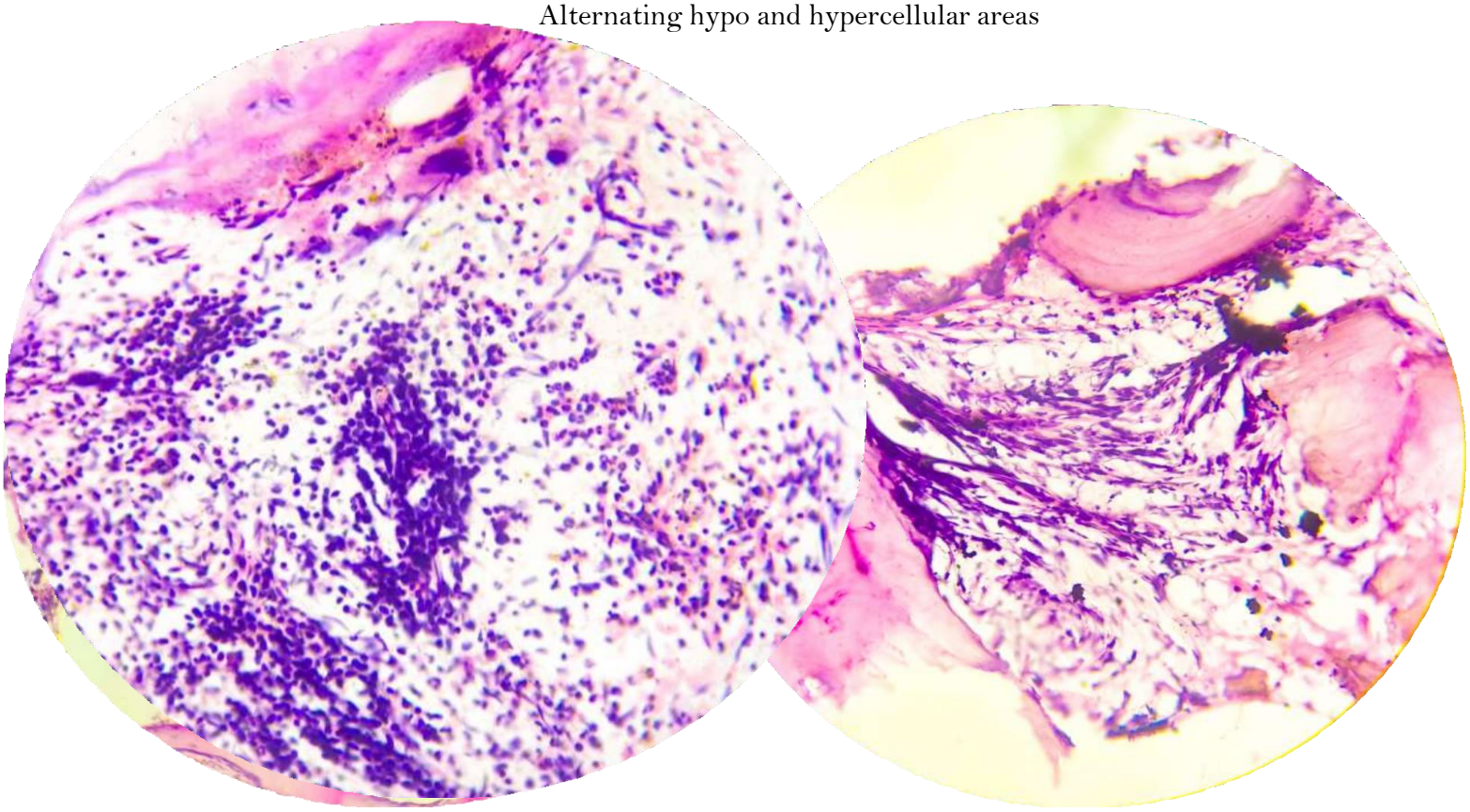
Conclusion - Myelofibrosis

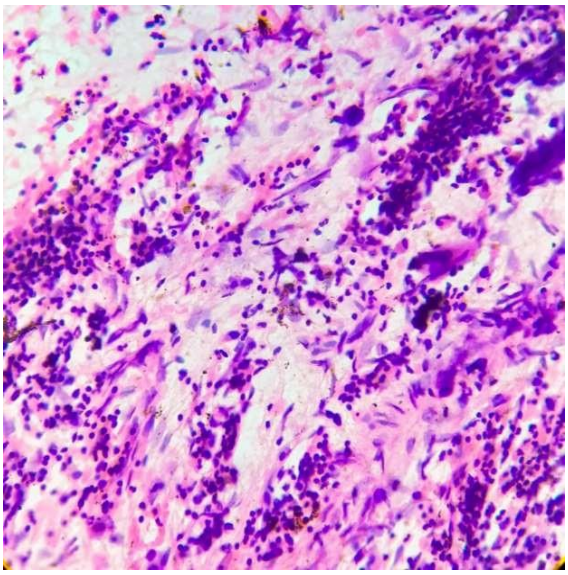
- Advised IHC for lymphoid cells.

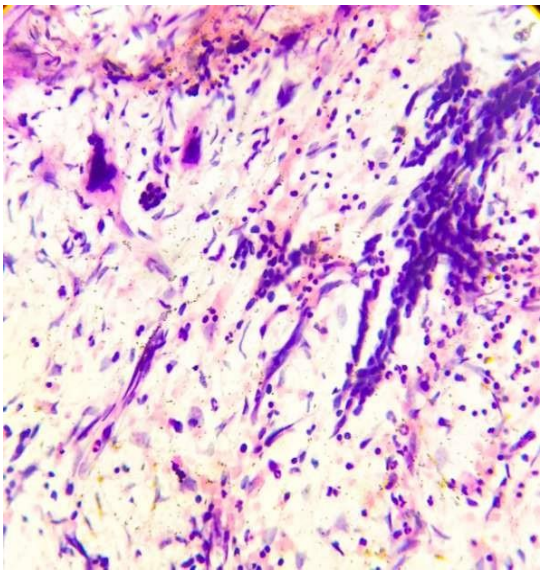


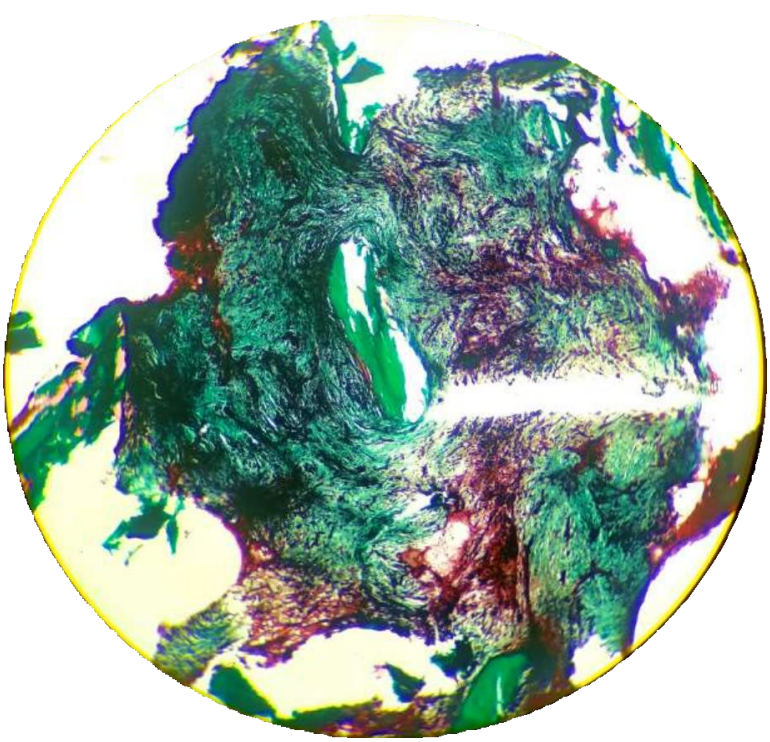
fibrosis of the marrow with streaming effect of the hematopoietic cells

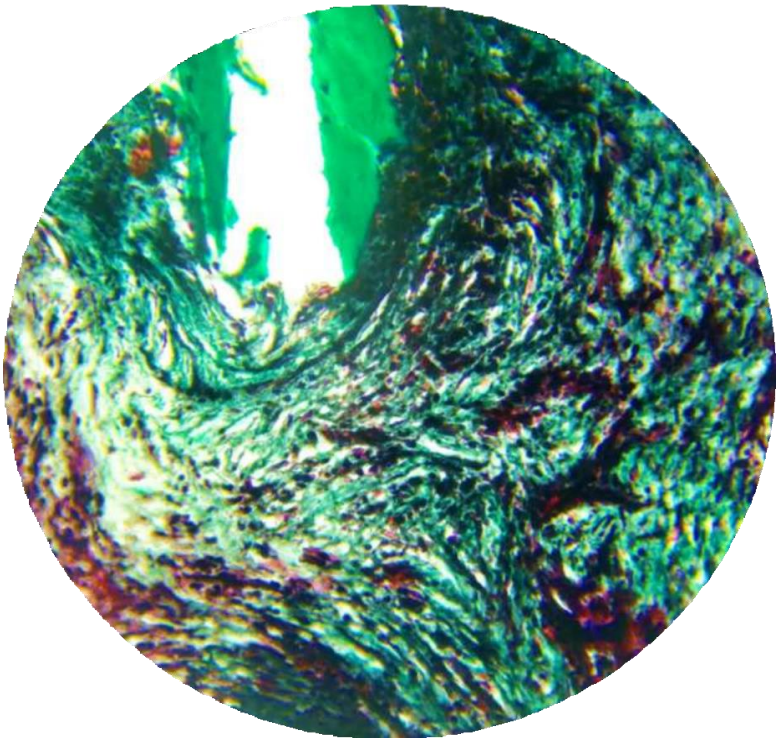
Alternating hypo and hypercellular areas











Left inguinal lymph node biopsy

Sections show fibrosis and myeloid metaplasia with trilineage hematopoietic cells,myeloid cells, erythroid cells, and dysplastic megakaryocytes.
Conclusion: Primary Myelofibrosis

Advised - Immunohistochemistry

Definition

Primary myelofibrosis (PMF) is a **clonal myeloproliferative neoplasm** (MPN)characterized by a proliferation of predominantly **abnormal megakaryocytes** and **granulocytes** in the bone marrow, which in fully developed disease is associated with **reactive deposition** of fibrous connective tissue and with **extramedullary haematopoiesis**.

There is a stepwise evolution from an initial **prefibrotic/early stage**, characterized by hypercellular bone marrow with absent or minimal reticulin fibrosis, to an **overt fibrotic stage** with marked reticulin or collagen fibrosis in the bone marrow, and often **osteosclerosis**.

The **fibrotic stage** of PMF is clinically characterized by **leukoerythroblastosis** in the blood (with teardrop—shaped red blood cells), **hepatomegaly**, and **splenomegaly**.

Synonyms

- Chronic idiopathic myelofibrosis
- Myelofibrosis/sclerosis with myeloid metaplasia
- **Agnogenic myeloid metaplasia**
- Megakaryocytic myelosclerosis
- Idiopathic myelofibrosis
- Myelofibrosis with myeloid metaplasia
- Myelofibrosis as a result of myeloproliferative disease

- **Epidemiology**
- The estimated annual incidence of **overt PMF** is **0.5—1.5 cases** per **100 000population**
- **Prefibrotic/early** stage accounts for **30—50%** of all PMF cases.
- The prevalence of PMF is probably increasing due to earlier diagnosis of pre—PMF and prolonged survival.
- It affects **men and women** nearly **equally**
- It occurs most commonly in the **sixth to seventh decades** of life, and only about

10% of overt PMF cases are diagnosed in patients aged **< 40 years**

- Children are rarely affected, few reported cases of Pediatric Myelofibrosis

Etiology

- Exposure to **benzene** or **ionizing radiation** has been documented in some cases
- Rare **familial** cases of bone marrow fibrosis in **young children** have been reported; how many of these constitute MPNs is unknown, but at least some cases appear to constitute an **autosomal recessive** inherited condition.
- In other families, with a somewhat **older patient** age at onset, the features have been **consistent with an MPN**, suggesting a familial predisposition to PMF.

Molecular / cytogenetics

- Driver mutations
- ***JAK2* V617F** mutation **(50 - 60%)**
- ***CALR*** mutations **(25 - 30%)**
- ***MPL*** mutations **(5 - 10%)**
- **Triple negative** for mutations in *JAK2*, *CALR* and *MPL* **(8 - 12%)**
- Other gene mutations include ***ASXL1, EZH2, TET2, IDH1 / IDH2, SRSF2*** or ***SF3B1***
- Shows karyotypic abnormalities in up to 50% of cases
- Frequent abnormalities include **del(20q), del(13q), +8, +9** and abnormalities of **1q,** also **-7 / 7q-**, **i(17q), inv(3), -5 / del(5q), 12p-** or **11q23.3**
- Driver mutational profile is associated with overall survival
- ***CALR*** mutated cases have **better** survival compared to others
- **Triple negative** cases have the **worst** survival compared to others
- No *BCR-ABL* fusion gene, but may acquire a *BCR-ABL1* rearrangement

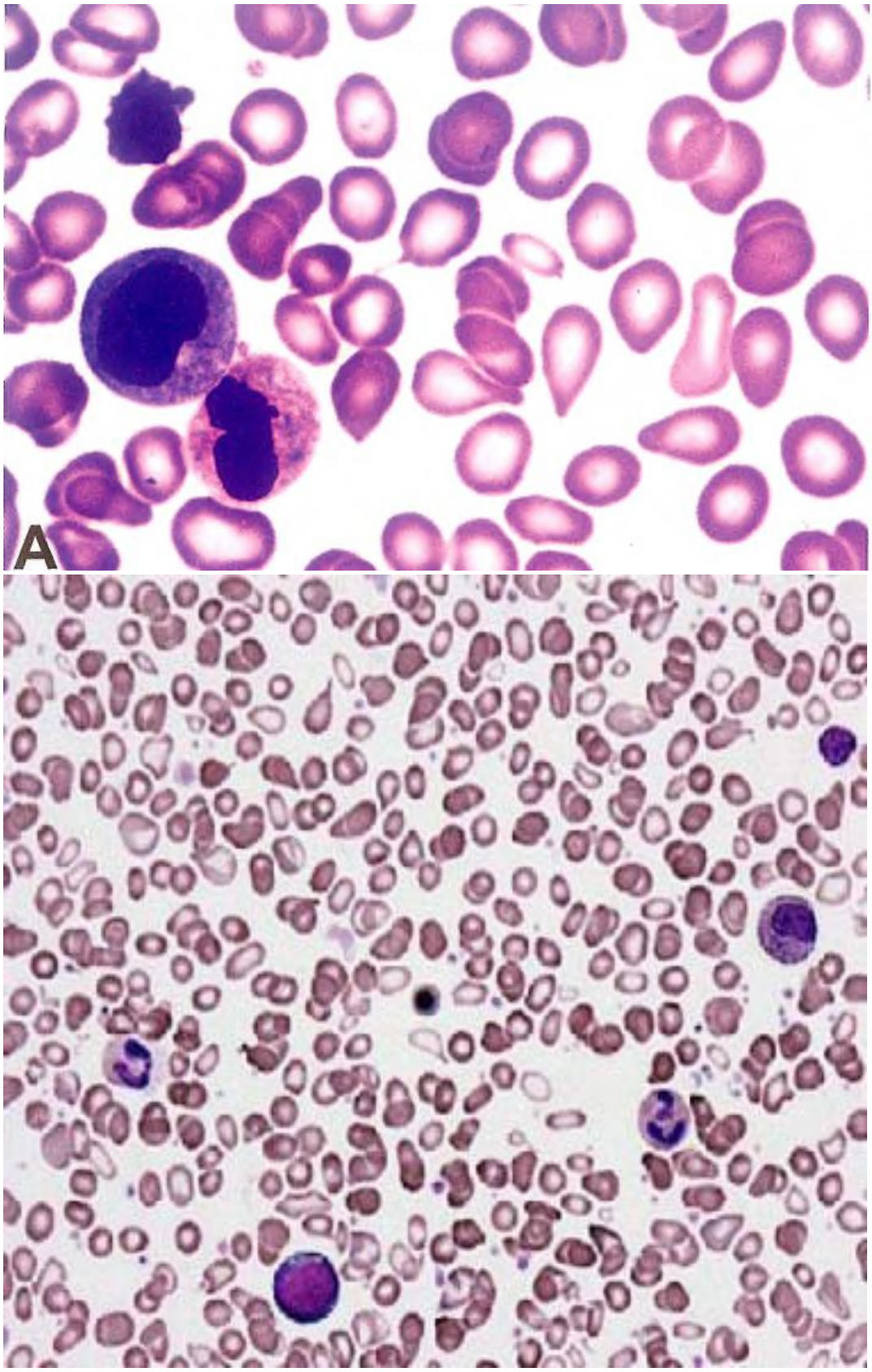
The stages of PMF are

- Prefibrotic PMF

- Overt PMF (fibrotic phase)
- Osteomyelosclerosis
- Accelerated phase PMF
- Blastic phase PMF

Hematological Investigations
Peripheral blood smear

- **Anemia** with hemoglobin less than **10 g/dl**.
- **Anisopoikilocytosis** with characteristic " **tear drop**" cells/ dacrocytes.
- RBCs are normocytic normochromic (concomitant Vit. B12 or folic acid deficiency - macrocytic anemia)
- Few **nucleated RBCs** along with metamyelocytes and myelocytes - "**Leucoerythroblastic blood picture**".
- Initially, high Platelet count ; in terminal phase it decreases.
- Total leucocyte count is higher in the range of 15-30 x 10'9/L with shift to left, and in many cases and in the terminal stages leucopenia is present.
- In terminal stage **pancytopenia** develops.
- **NAP** score is markedly increased to **200-300** (Normal 40-100)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Complete blood count / peripheral blood smear

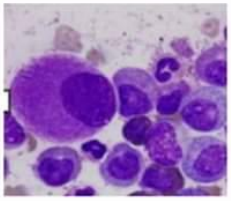
- Prefibrotic:
- Initially normal or increased blood counts
    - Mild neutrophilia with a left shift
    - Thrombocytosis (mild / moderate)
- No / borderline anemia
- No myeloblasts
- No leukoerythroblastosis
- Overt:
- Thrombocytopenia with bizarre abnormal large platelets with altered granulation; in addition, fragmented megakaryocytes can be seen on the peripheral smear
- Leukoerythroblastosis and anemia
- Myeloblasts (usually > 5%)

Bone marrow aspirate / biopsy

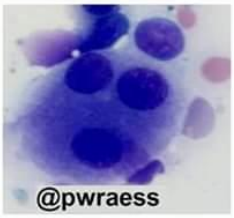
- Prefibrotic:
- **Hypercellular** bone marrow with granulocytic and megakaryocytic proliferations
    - Megakaryocytes morphologically more variable in size, **atypical and bizarre;** have aberrant nuclear/cytoplasmic ratios and hyperchromatic, **bulbous hypolobated** or irregularly folded, **cloud like** nuclei; Often bare megakaryocytic nuclei
    - Increased **reticulin** is present around clusters of megakaryocytes
    - Erythropoiesis is reduced
- **Absent** or only **slight** reticulin fibrosis
- Overt:
- **Hypocellular** bone marrow with usually **alternating cellular and hypocellular** regions

- Atypical megakaryocytes can form clusters or sheets, located **paratrabecular** and around **dilated** sinusoids (change in topography)
- Hypocellular and diffusely fibrotic bone marrow with **atypical streaming** megakaryocytes and hematopoietic cells
- Marrow **osteosclerosis** with irregular, broad bony trabeculae, osteoid seams and reams
- Markedly **dilated sinuses**; associated with dry bone marrow taps
- Marked **reticulin or collagen fibrosis**
- **New bone formation** and osteosclerosis
- **Vascular proliferation** is mildly increased in the bone marrow. In the overt stage, there is a significant proliferation of vessels showing **marked tortuosity** and luminal distension, often also associated with conspicuous **intrasinusoidal haematopoiesis**
- **Lymphoid nodules** are found in as many as **20%** of cases
- In the initial stages, the number of randomly distributed **CD34+ progenitors** is slightly increased in the bone marrow, but not in the peripheral blood. The frequency of **bone marrow CD34+** cells is **inversely** related to the number of **circulating CD34+** cells; only in the later stages do they appear in large numbers in the peripheral blood.

MEGAKARYOCYTIC MORPHOLOGY IN MYELOID NEOPLASMS



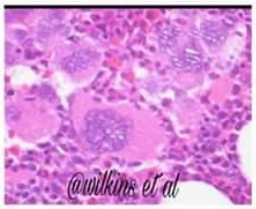
Micromegakaryocytes, or dwarf megakaryocytes, are abnormally small megakaryocytes with increased nuclear to cytoplasmic ratios and hypolobated nuclei seen in chronic myelogenous leukemia, myelodysplasia.



Pawnball

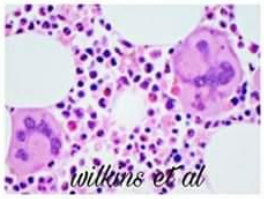
Megakaryocytes with multiple, widely separated nuclei . seen in MDS

The pawnbrokers' symbol of three separate spheres suspended from a bar is used to describe these megakaryocytes



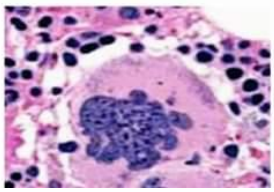
Cloudlike megakaryocyte

Bulbous or balloon like lobulations in megakaryocytic nuclei seen in Primary myelofibrosis



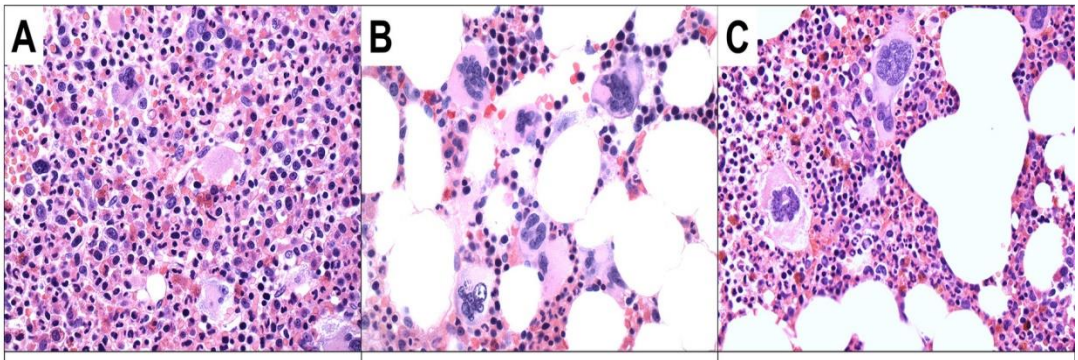
Staghorn megakaryocyte

Large size with staghorn like multinucleated nuclei and exhibiting large amount of cytoplasm and characteristically seen in Essential Thrombocythemia



Pleomorphic/atypical/bizarre megakaryocyte

Atypical small clusters of bizarre, bulky nuclei with prominent nuclear-cytoplasmic dyssynchrony seen in Polycythemia vera (large clusters>7MK are seen in PMF)



	Polycythemia vera (PV)	Essential thrombocythemia (ET)	Prefibrotic primary myelofibrosis (pre-PMF)
Age-matched cellularity	increased	normal	increased
Myeloid hyperplasia	present	absent	present
Erythroid hyperplasia	present	absent	absent
Megakaryocyte morphology	pleomorphic	staghorn	bulbous
Megakaryocyte size	small to large	large	large
Megakaryocyte clusters	absent	loose	tight
Reticulin fibrosis	MF-0 >> MF-1	MF-0	MF-0 or MF-1

Extramedullary Haematopoiesis

- Most common sites are the **spleen** and **liver.** In no other MPN is the extramedullary hemopoiesis so pronounced.
- It is due to the ability of the spleen to **sequester** the circulating **CD34+ cells**, which proliferate in the **red pulp**. There may be **fibrosis** of the red pulp cord.
- Other possible sites of extramedullary haematopoiesis are the **Liver, Lymph Nodes, Kidneys, Adrenal Glands, Dura Mater, Gastrointestinal Tract, Lungs and Pleura, Breasts, Skin,** and **Soft Tissue**.
- Extramedullary hematopoietic tumors are silent clinically. These are **greyish brown**, fleshy encapsulated tumor masses made up of hematopoietic tissue.

Immunohistochemistry and flow Cytometry

- **Positive Stains**
  - **VEGF**
  - CD105

        - **CD61, CD41** highlights **megakaryocytic** clusters
        - CD45 and MPO scattered positivity
        - **Negative stains**
        - TdT, CD3, CD20, CKAE1/AE3, synaptophysin, TTF-1, and PSA
- **Flow Cytometry** for **CD34+** stem cells

Prognostic factors

- Has the **least favorable** prognosis among the myeloproliferative neoplasms
- **Survival**
    - Prefibrotic: 10 - 15 years
    - Overt: 3 - 5 years
- **Absolute monocyte count ≥ 1×10^9/L** confers an unfavorable outcome
- **Unfavorable** karyotype
    - Complex karyotype, sole abnormality
    - 2 abnormalities that include +8, -7 / 7q-, i(17q), inv(3), -5 / del(5q), 12p- or 11q23.3 rearrangement
- *CALR* mutation confers a better prognosis compared to other mutations

Dynamic International Prognostic Scoring System (DIPSS plus)

- Includes 8 predictors of inferior survival:
- Patient age > 65 years
- Red blood cell transfusion dependency
- Unfavorable karyotype*
- Hemoglobin < 10 g/dL
- White blood cells > 25×10^9/L
- Constitutional symptoms (fever, night sweats, weight loss)
- Circulating blasts ≥ 1%

- Platelet count < 100×10^9/L
- Risk status is defined by the number of adverse prognostic factors present: 0 (low risk), 1 (intermediate - 1 risk), 2 or 3 (intermediate - 2 risk) or > 4 (high risk)

Complications

Major causes of morbidity and mortality are

- **Bone marrow failure** (**infection**, **haemorrhage**)
- **Thromboembolic** events
- **Portal hypertension**
- **Cardiac failure**
- **Leukemic transformation** and Blast-phase disease (Secondary **AML/ ALL**). The reported frequency of the blast phase is ***5—30%***

Differential diagnosis

- Other causes of **leukoerythroblastosis or dry taps**:
    - Granulomatous marrow disease,
    - metastases to marrow (desmoplasia but no increased reticulin) or
    - lymphoma
- **Myeloproliferative neoplasms**:
    - Chronic myelogenous leukemia
    - Polycythemia vera
    - Essential thrombocythemia
- **Myelodysplastic / myeloproliferative neoplasms**
- **Mastocytosis**
- **Reactive thrombocythemia**
- **Primary Autoimmune Myelofibrosis**
- Acute myelofibrosis /AML-M7

- Causes of Secondary Myelofibrosis

Myelofibrosis secondary to essential thrombocytopenia or polycythemia vera
Chronic myeloid leukemia
Acute myeloid leukemia
Acute lymphoid leukemia
Hairy cell leukemia
Myelodysplastic syndrome
Acute panmyelosis with myelofibrosis
Hodgkin lymphoma
Non-Hodgkin lymphoma
Plasma cell myeloma
Metastatic tumors
Connective tissue diseases
Vitamin D deficiency
Osteoporosis
Primary and secondary hyperparathyroidism
Tuberculosis
Primary autoimmune myelofibrosis
Systemic sclerosis
HIV infection
Pulmonary arterial hypertension
Visceral leishmaniasis