Myeloproliferative Disorders

by

Dr.Zahraa Najah

Definition & classification of MPN

- Refer to **clonal** disorders of haemopoiesis that lead to an **increase** in the numbers of one or more mature blood cell progeny.
- Classical MPNs:

1. Polycythemia Vera (**PV**)
2. Essential Thrombocythemia (**ET**)
3. Primary myelofibrosis (**PMF**)

- The chronic myeloid leukemia (**CML)** would fit definition of MPN and share pathogenetic features with some of the MPNs, but have, historically (since the discovery of the Philadelphia chromosome), been studied separately from the MPNs

Polycythemia Vera (PV)

- It is an **absolute increase** in total body red cell volume (or mass), which usually manifests itself as a raised hemoglobin concentration (Hb) and/or hematocrit(PCV). although elevations in the platelet and/or neutrophil counts are relatively common.
- **Red cell mass more than 25%** above the predicted value constitute true or absolute polycythemia.
- When the PCV is raised but the red cell mass is not, the condition is known as apparent or **relative** polycythemia occur secondary to a reduction in plasma volume.

- polycythemia is **subdivided into:**

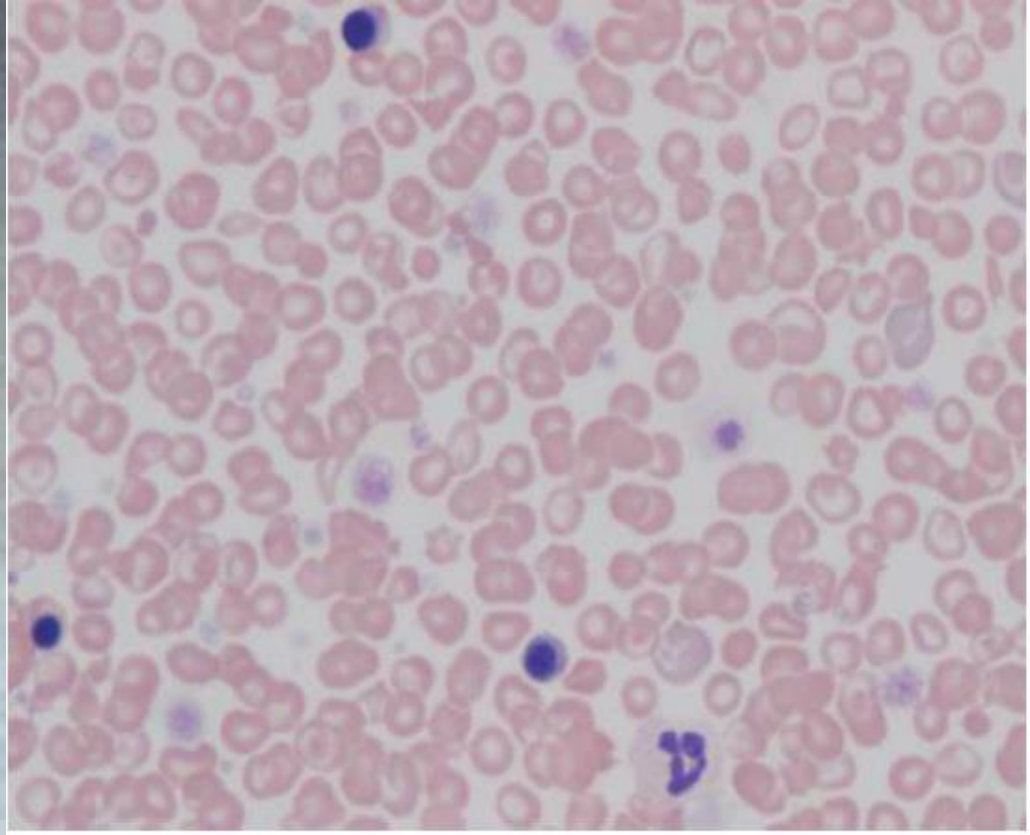
  primary polycythemia (Hemopoiesis is intrinsically abnormal as in PV)

  Secondary polycythemia, which results from an increased erythropoietin drive, either in the presence or in the absence of hypoxia.
- **Erythropoiesis** in PV is autonomous and does not related to erythropoietin (EPO).
- Plasma levels of (**EPO) are reduced** in PV patients

- **progenitor cells** can survive in vitro and give rise to erythroid colonies (BFU-E) in the absence of added erythropoietin and show an **increased sensitivity to EPO**
- In 2005, several groups identified **acquired mutation** in the cytoplasmic tyrosine kinase **JAK2 (at V617F** responsible for depressing its kinase activity) in myeloid cells from the great majority of patients with PV.
- The V617F mutation leads to **increased kinase activity**, results in persistent erythropoiesis.
- V617F mutation, about **95% of PV** patients are positive
- The **median age** at onset is 55–60 years and although incidence increases with age

Clinical feature

- **Thrombotic complications** : (arterial or venous)
- **Neurological features** : as consequences of occlusive vascular lesions
- **Pruritus** occurs in about one-quarter of PV patients and in some it may be severe
- **Skin** :Plethora, brown discoloration of the skin and erythromelalgia
- **Splenomegaly** : Palpable splenomegaly is seen in 30–50% of cases
- **Hypertension** commonly seen **and gout** seen in 5% of pt.
- **Transformation to (Leukemia or Myelofibrosis)**



Erythromelalgia

Figure 26.4 Blood film from a case of postpolycythaemic myelofibrosis after splenectomy. Note the presence of nucleated erythrocytes, giant platelets and features of splenectomy including target cells, spherocytes and acanthocytes.

Table 4. WHO criteria for PV

WHO PV criteria
Major criteria
1. Hemoglobin >16.5 g/dL in men
Hemoglobin >16.0 g/dL in women
or,
Hematocrit >49% in men
Hematocrit >48% in women
or,
increased red cell mass (RCM)*
2. BM biopsy showing hypercellularity for age with trilineage growth (panmyelosis) including prominent erythroid, granulocytic, and megakaryocytic proliferation with pleomorphic, mature megakaryocytes (differences in size)
3. Presence of *JAK2*V617F or *JAK2* exon 12 mutation
Minor criterion
Subnormal serum erythropoietin level
Diagnosis of PV requires meeting either all 3 major criteria, or the first 2 major criteria and the minor criterion†

Treatment

1. **Phlebotomy**

✓ Generally, the best initial treatment
- No increase in progression to AML
- Rapid effect
- No BM suppression

✓ Remove 500 cc blood /wk to target Hct <45%.

disadvantage:
- Increased risk of thrombosis
- May be insufficient to control disease

2. Myelosuppressive agents

- **Hydroxyurea**
  - can be used in conjunction with phlebotomy
  - May increase the risk of leukemic transformation from 1-2% to 4-5%
- ^{32*}**P** (radioactive phosphorus)
  - increase the risk of leukemic transformation from 1-2% to 11%
  - May be appropriate for pts intolerant of medications or for elderly patients
  - Single injection may control hemoglobin and platelet count for a year or more.

3. Interferon alpha

- **Benefits**
  - No myelosuppression
  - No increase in progression to AML
  - No increase in thrombosis risk
  - OK in pregnancy
- **disadvantage**:
  - Must be given by injection
  - Side effects may be intolerable in many pts, include flu-like symptoms ,fatigue , fever, myalgias , malaise

Essential Thrombocythemia (ET)

- (ET) is a **persistent elevation in the platelet count**.
- **incidence** of ET is similar to that of PV
- The **median age** at onset is 50–55 years.
- For 80–90% of patients, **a molecular basis** for the clonality can be found,with~55%, 30% and 5% of ET patients positive for the **JAK2, CALR and MPL mutations**, respectively.

Clinical feature

- **Thrombotic complications** :15–20% of patients at presentation
- **Hemorrhagic complications**: less common than thrombosis but can be dramatic when it happens
- **Splenomegaly and hyposplenism:** 5% of ET patients at diagnosis
- **Transformation** to myelofibrosis ,polycythemia Vera or leukemia

WHO ET criteria
Major criteria
1. Platelet count ≥450 × 10^9/L
2. BM biopsy showing proliferation mainly of the megakaryocyte lineage with increased numbers of enlarged, mature megakaryocytes with hyperlobulated nuclei. No significant increase or left shift in neutrophil granulopoiesis or erythropoiesis and very rarely minor (grade 1) increase in reticulin fibers
3. Not meeting WHO criteria for *BCR-ABL1*$^+$ CML, PV, PMF, myelodysplastic syndromes, or other myeloid neoplasms
4. Presence of *JAK2*, *CALR*, or *MPL* mutation
Minor criterion
Presence of a clonal marker or absence of evidence for reactive thrombocytosis
Diagnosis of ET requires meeting all 4 major criteria or the first 3 major criteria and the minor criterion

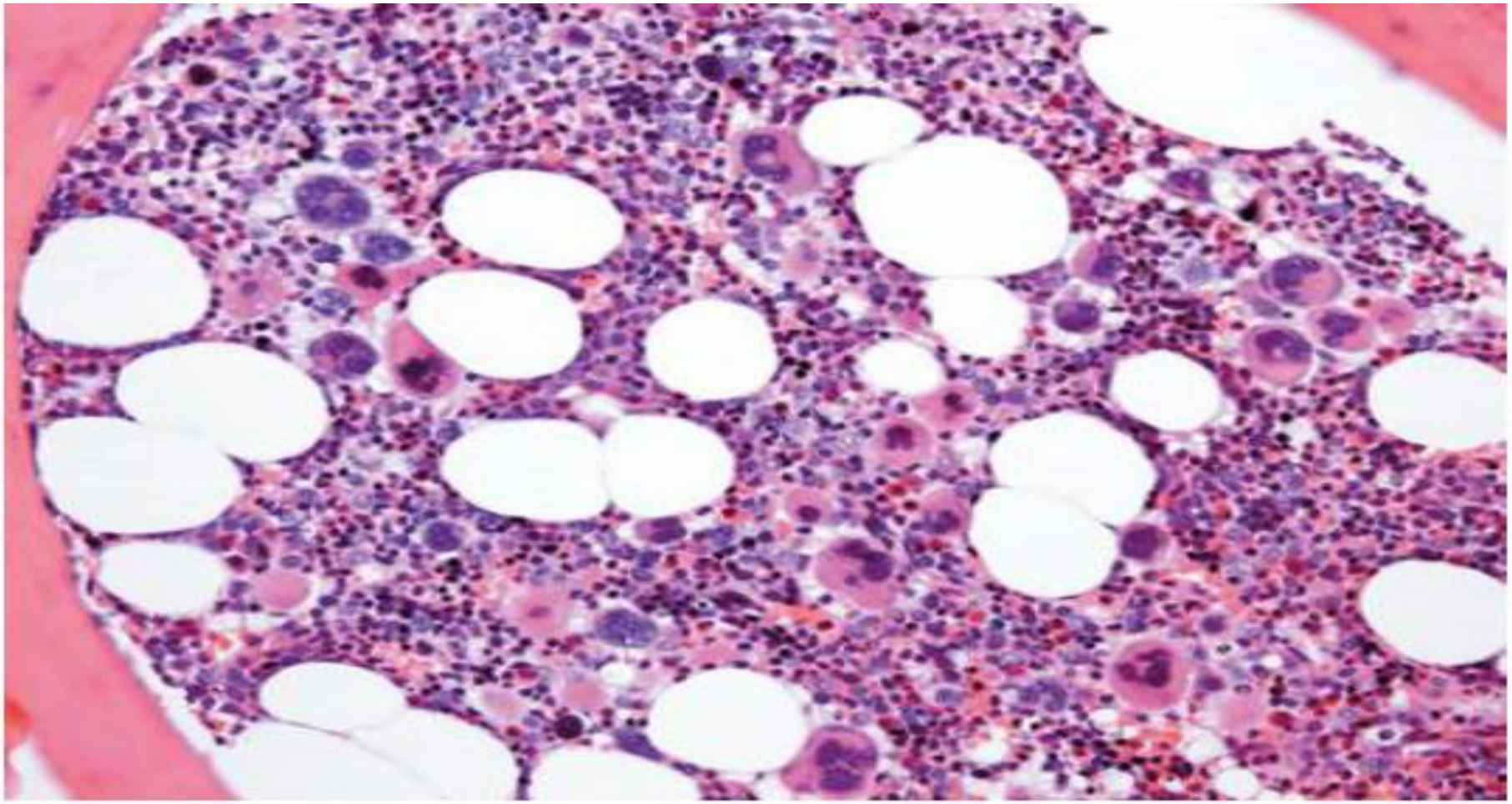


Figure 26.6 Bone marrow trephine section (haematoxylin and eosin, H&E) from a 60-year-old man with essential thrombocythaemia. Note the hypercellularity and marked increase in megakaryocyte numbers, consisting largely of clusters of mature, multilobated forms.

Treatment

- Targeted to reducing the platelet count.
- Treat those who have had or are at risk for thrombosis, those >65 y.o.,or pts with plts > 1-1.5 million
- Why treat?

– In pts at risk for thrombosis, Rx reduces risk of thrombosis and may reduce 2º myelofibrosis.

Treatment include:

1. **Anagrelide**:Interferes with megakaryocyte development without causing depression of other cell lines
2. **Hydroxyurea**
3. **Interferon alpha**

Primary myelofibrosis (MF)

- **Clonal disorder of the pluripotent haemopoietic stem** cell, in which the proliferation of multiple cell lineages is accompanied by **progressive bone marrow fibrosis.**
- Marrow fibrosis is thought to be **secondary to** the release of proinflammatory cytokines from abnormal clonal cells (primarily megakaryocytes), which act to stimulate fibroblast proliferation and fibrosis.
- Most patients diagnosed in the **sixth decade** and roughly **equal involvement of the two sexes.**

Clinical features

- **Splenomegaly** :in almost **all** patients at presentation, about 10% of cases develop massive splenomegaly,
- **Extramedullary Hemopoiesis :**The spleen is the commonest site of extramedullary Hemopoiesis in PMF. The liver is also usually involved and this can lead to significant hepatomegaly.
- **Systemic symptoms:**A hypermetabolic state presenting with fevers, anorexia, weight loss and night sweats these symptoms associated with a poor prognosis.
- **Anemia:**
- **Platelet abnormalities**
- **White cells and leukemic transformation**

Lab findings

1. Early on, pts may have ↑ **Plts and normal Hb and WBC.**
2. **Anemia, and ↓Plts and ↓WBC** seen as disease progresses
3. Peripheral smear shows l**eukoerythroblastic picture,** with teardrops, NRBC and early granulocytes
4. **"Dry tap"** or inability to aspirate liquid marrow frequently seen
5. Increased collagen and reticulin fibrosis on BM biopsy
6. 40-75% may have JAK2 mutation

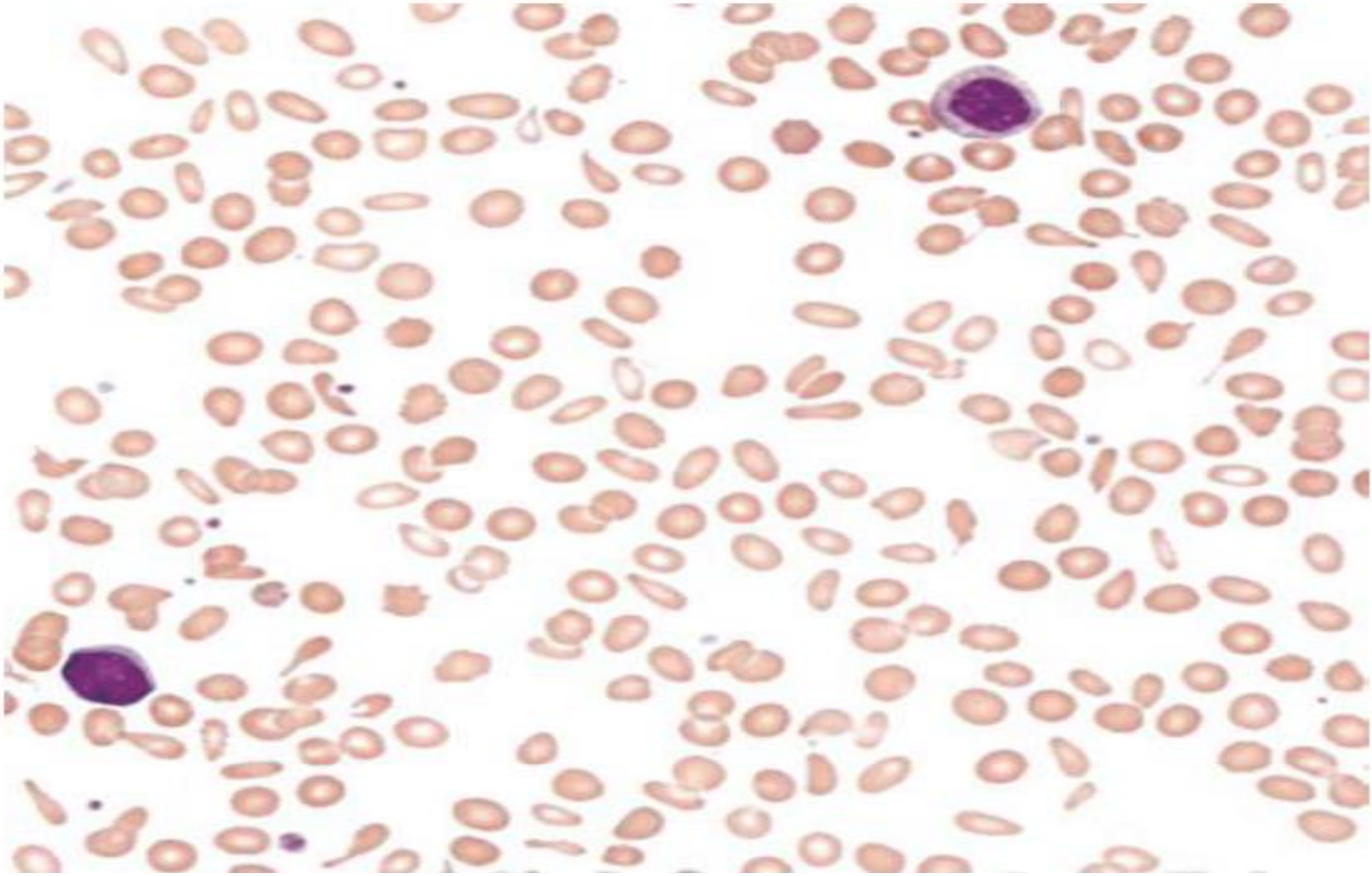
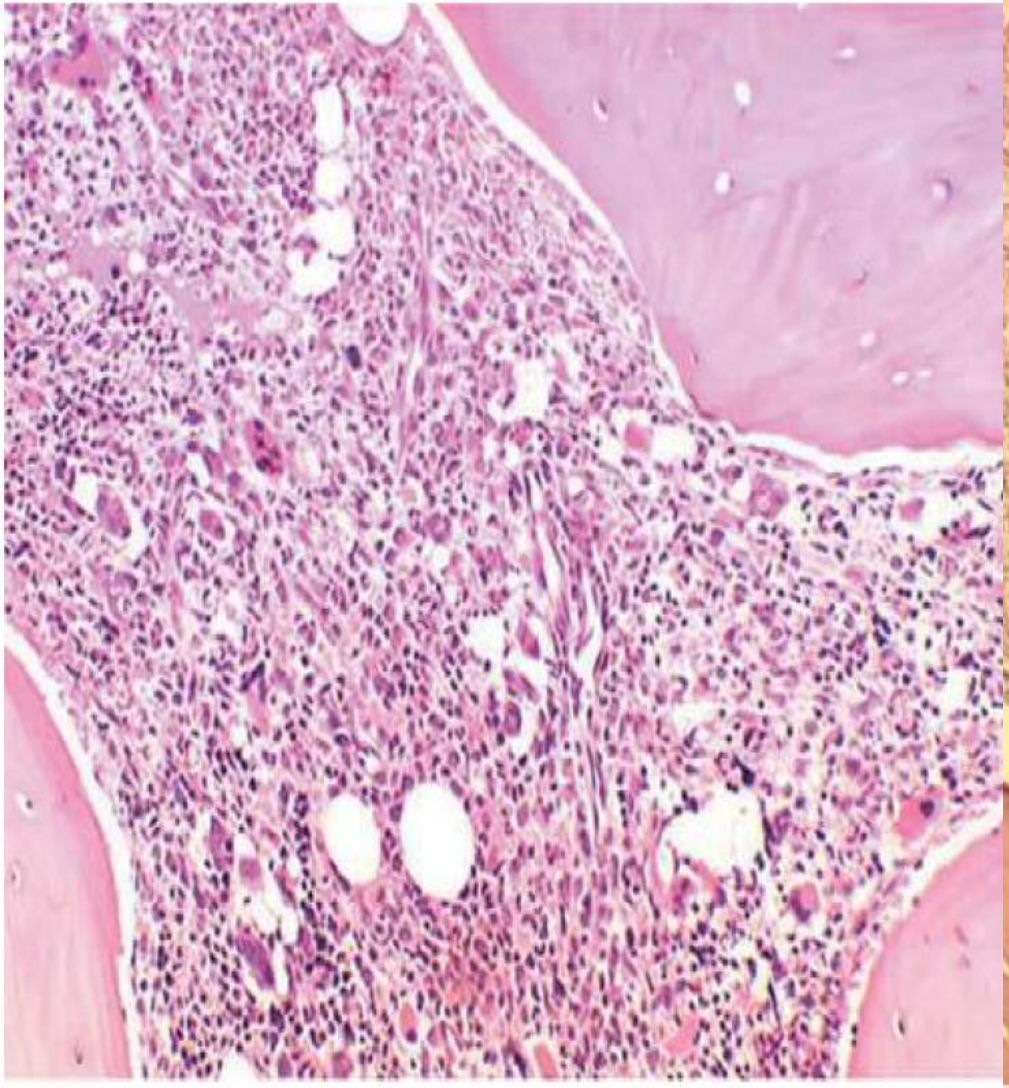
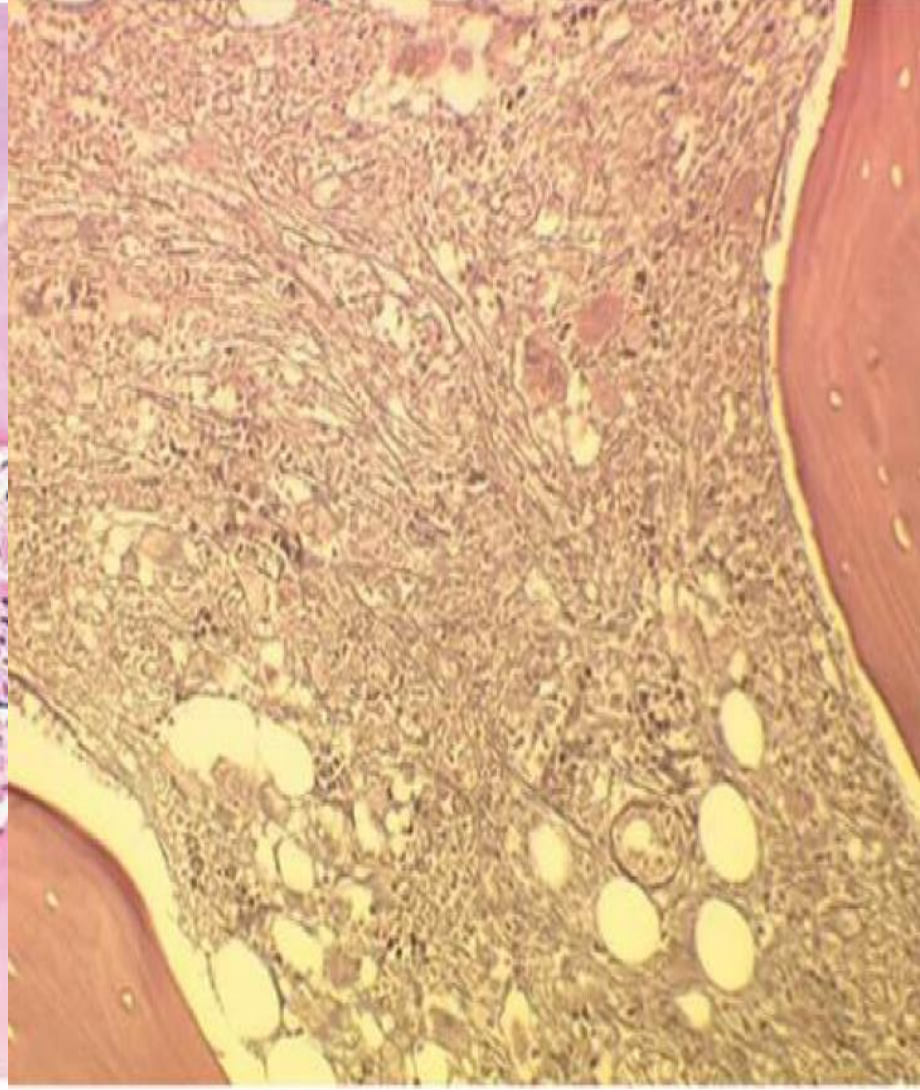


Figure 26.8 Peripheral blood film in PMF, showing a blast, an abnormal myelocyte, teardrop red cells and marked anisopoikilocytosis.



(a)



(b)

Figure 26.9 Bone marrow trephine sections from a patient with early-stage PMF. The H&E stain (a) shows hypercellularity, disorganized architecture, increase in megakaryocyte numbers and prominent sinusoids. The silver stain (b) also shows a marked increase in reticulin fibres.

WHO overt PMF criteria

Major criteria

1. Presence of megakaryocytic proliferation and atypia, accompanied by either reticulin and/or collagen fibrosis grades 2 or 3*
2. Not meeting WHO criteria for ET, PV, *BCR-ABL1*$^{+}$ CML, myelodysplastic syndromes, or other myeloid neoplasms
3. Presence of *JAK2*, *CALR*, or *MPL* mutation or in the absence of these mutations, presence of another clonal marker,† or absence of reactive myelofibrosis‡

Minor criteria

Presence of at least 1 of the following, confirmed in 2 consecutive determinations:

a. Anemia not attributed to a comorbid condition

b. Leukocytosis $\geq 11 \times 10^{9}$/L

c. Palpable splenomegaly

d. LDH increased to above upper normal limit of institutional reference range

e. Leukoerythroblastosis

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

Causes of leucoerythroblastic blood picture

1. Idiopathic myelofibrosis
2. Bone marrow infiltration
3. Severe sepsis
4. Severe hemolysis
5. Sick neonate

Treatment

- ✓ There is no definitive therapy
- ✓ If patient is young, BM transplant can be done, but older patients have too high mortality
- ✓ Rx is supportive, with transfusions
- ✓ Splenectomy can be done for sx of abdominal pain, but have frequent complications of thrombosis, hemorrhage, and infection.


Thank You