Myeloprolifeative Neoplasms

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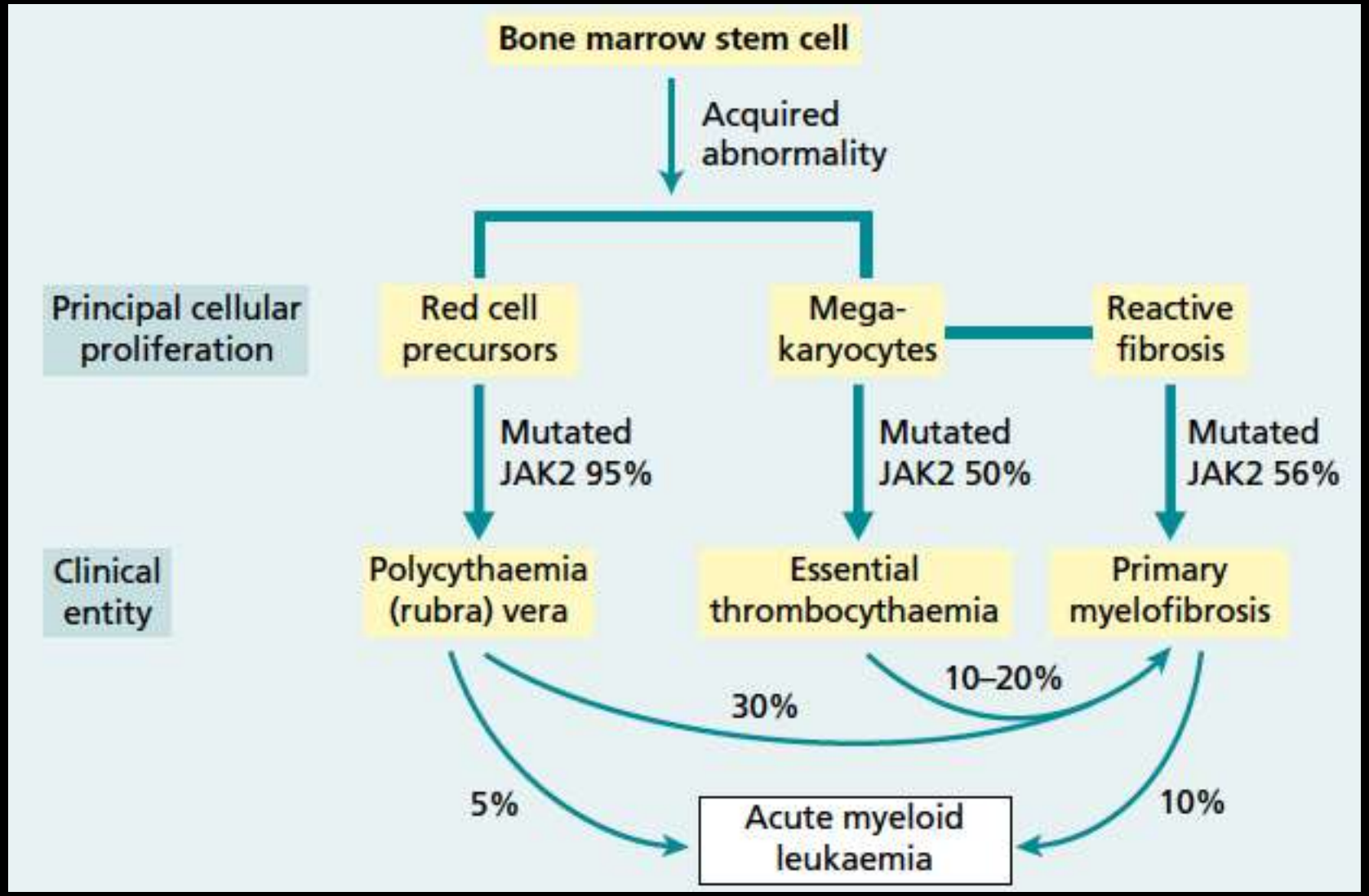
The term myeloproliferative neoplasms (MPN) describes a group of conditions arising from marrow stem cells and characterized by clonal proliferation of one or more hemopoietic components in the bone marrow and, in many cases, the liver and spleen..

The three major non - leukemic disorders included in this classification are:

- 1 Polycythaemia vera (PV);
- 2 Essential thrombocythaemia (ET); and
- 3 Primary myelofi brosis.

Non–leukemic myeloproliferative disorders

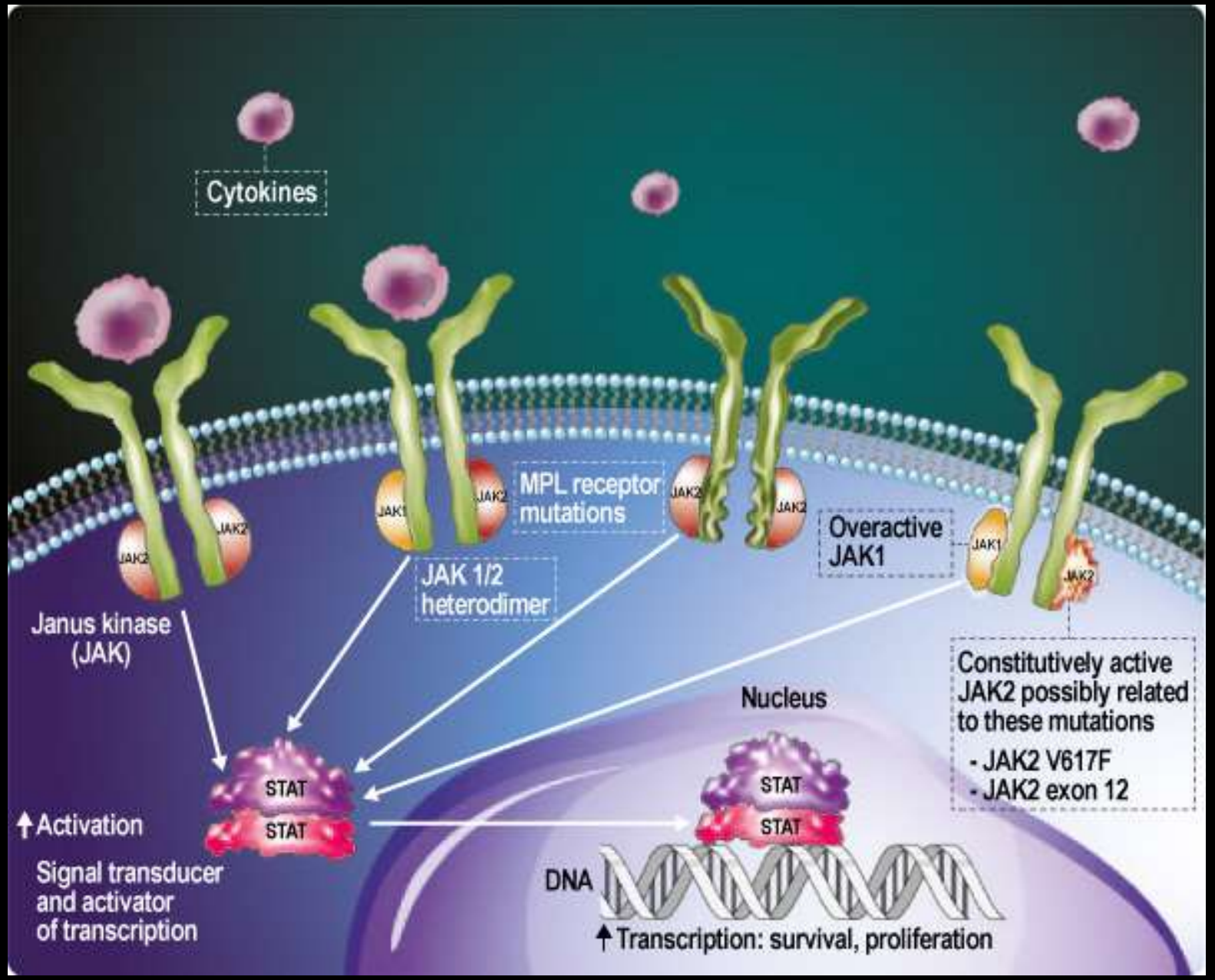
The non - leukemic myeloproliferative disorders are closely related to each other and transitional forms can occur with evolution from one entity into another during the course of the disease.

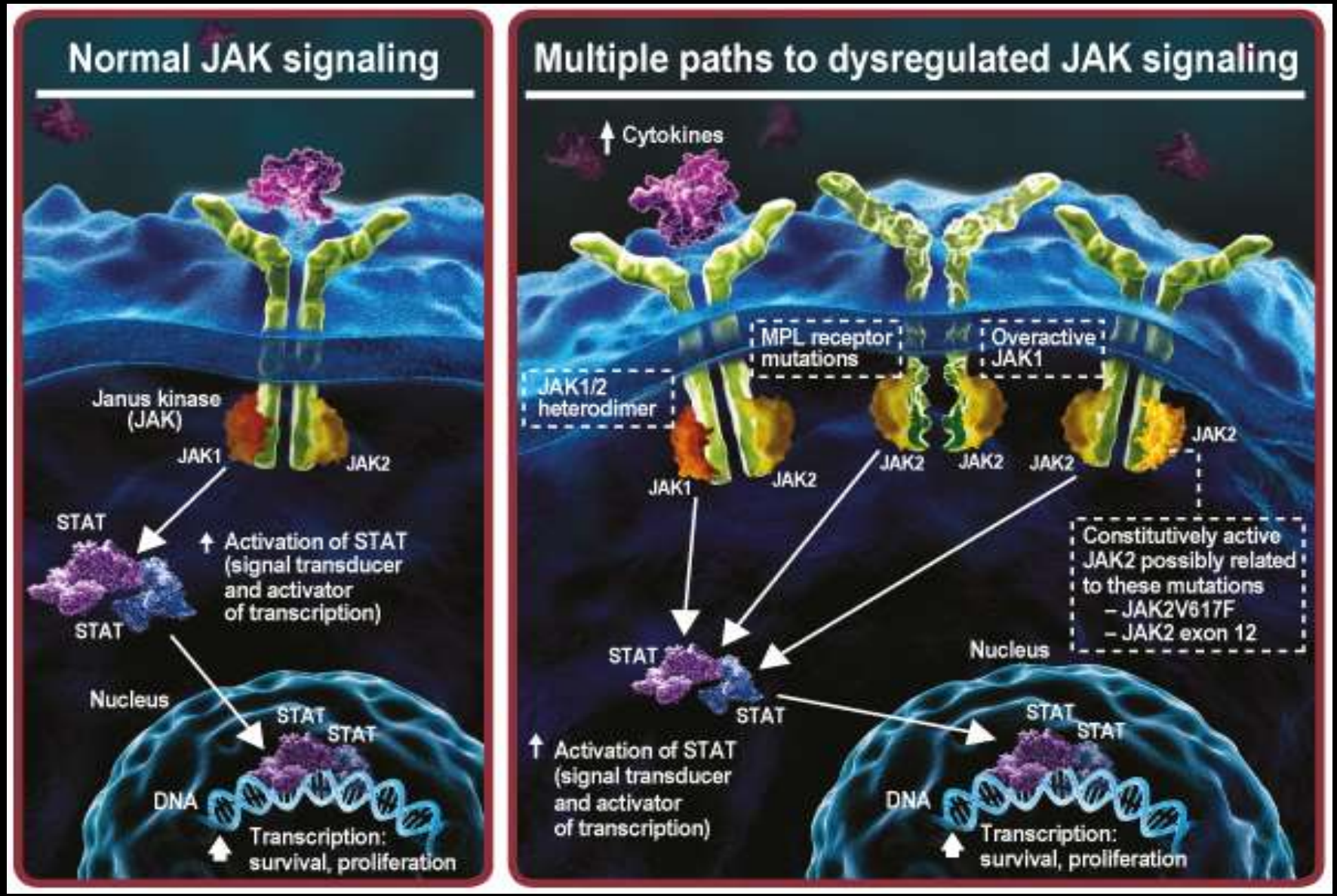

Bone marrow stem cell
Acquired abnormality
Principal cellular proliferation
Red cell precursors
Mega-karyocytes
Reactive fibrosis
Mutated JAK2 95%
Mutated JAK2 50%
Mutated JAK2 56%
Clinical entity
Polycythaemia (rubra) vera
Essential thrombocythaemia
Primary myelofibrosis
30%
10–20%
5%
10%
Acute myeloid leukaemia

JAK 2

JAKs, which are essentially proteins with tyrosine kinase (TK) activity, mediate signalling in pathways triggered by cytokines and hematopoietic growth factors. Dysregulation of the JAK pathway is strongly associated with the development of myeloproliferative neoplasms (MPNs)

JAK2 V617F mutation is found in 95% of polycythemia vera cases and about half of the essential thrombocythemia and myelofibrosis cases.


Cytokines
MPL receptor mutations
Overactive JAK1
JAK 1/2 heterodimer
Janus kinase (JAK)
Constitutively active JAK2 possibly related to these mutations
- JAK2 V617F
- JAK2 exon 12
Nucleus
STAT
STAT
Activation
Signal transducer and activator of transcription
DNA
Transcription: survival, proliferation


Normal JAK signaling
Janus kinase (JAK)
JAK1
JAK2
STAT
STAT
Activation of STAT (signal transducer and activator of transcription)
Nucleus
STAT
STAT
DNA
Transcription: survival, proliferation
Multiple paths to dysregulated JAK signaling
Cytokines
MPL receptor mutations
Overactive JAK1
JAK1/2 heterodimer
JAK1
JAK2
JAK2
JAK2
JAK2
JAK2
Constitutively active JAK2 possibly related to these mutations
– JAK2V617F
– JAK2 exon 12
STAT
STAT
Activation of STAT (signal transducer and activator of transcription)
Nucleus
STAT
STAT
DNA
Transcription: survival, proliferation

Polycythemia

Polycythemia refers to a pattern of blood cell changes that includes an increase in hemoglobin above 18.5 g /dl in adult males and 16.5 g /dl in females,

- Usually with an accompanying rise in red cell count and hematocrit (PCV).

Causes of Polycythemia:

1. ***Primary:*** polycythemia vera Absolute
2. ***Secondary:*** Absolute

A. Due to compensatory erythropoietin increase in:

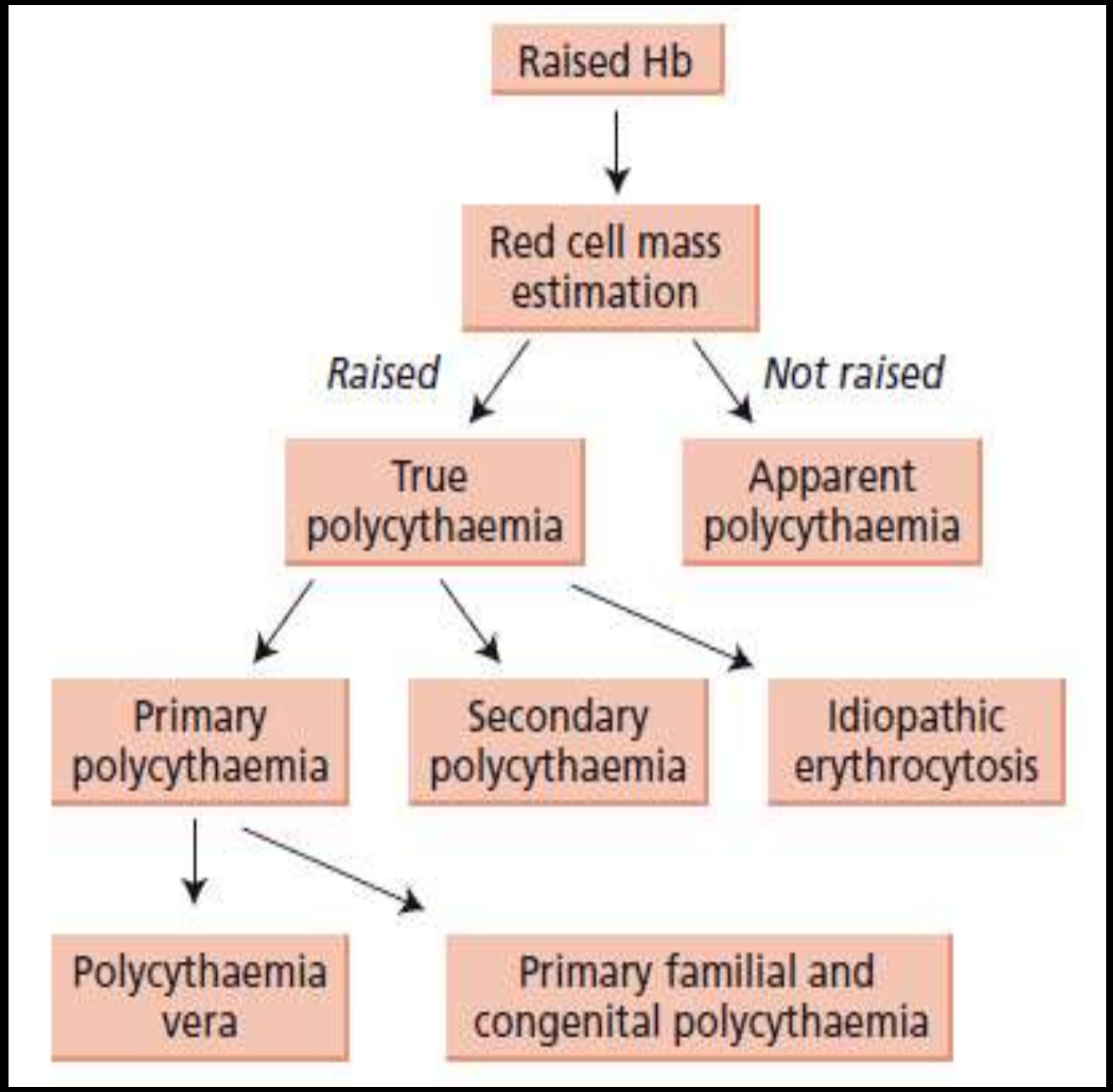
- High altitudes
- Cardiovascular disease especially congenital with cyanosis
- Pulmonary disease and alveolar hypoventilation

B. Due to inappropriate erythropoietin increase in:

- Renal diseases e.g. hydronephrosis, vascular impairment, cysts, carcinoma.
- Massive uterine fibroid
- Hepatocellular carcinoma
- Cerebellar hemangioblastoma.

3. ***Relative:***

- Stress or pseudo-polycythemia
- Cigarette smoking
- Dehydration: water deprivation, vomiting
- Plasma loss: burns, enteropathy


Raised Hb
Red cell mass estimation
Raised
Not raised
True polycythaemia
Apparent polycythaemia
Primary polycythaemia
Secondary polycythaemia
Idiopathic erythrocytosis
Polycythaemia vera
Primary familial and congenital polycythaemia

Polycythemia vera (PV)

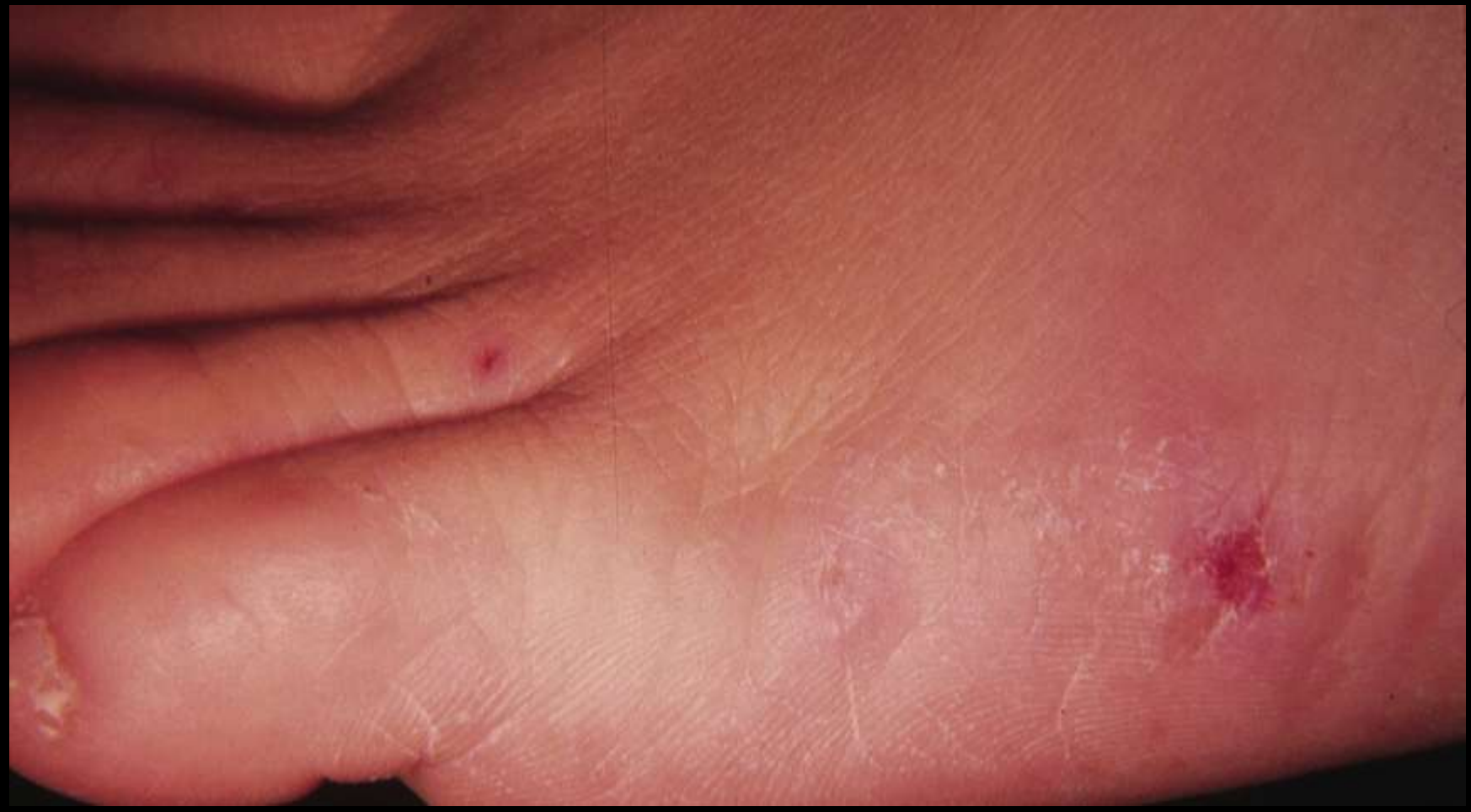
Polycythemia vera (previously Polycythemia rubra vera) is a clonal stem cell disorder in which red cell mass is increased by endogenous myeloproliferation. The red cells, granulocytes and platelets are all derived from the abnormal clone.

Clinical Features:

- Epidemiology
- Annual incidence increases with age and varies from 0.7 to 2.6 per 100,000 inhabitants in Europe and North America; less frequent in Japan
- Slight male predominance reported, with male-to female ratio ranging from 1-2 : 1
- Median age at diagnosis is 60 years; patients younger than 20 years old rare

- Clinical features are the result of hyperviscosity, hypervolemia or hypermetabolism.

1. Headache, pruritus (especially after a hot bath), dyspnea, blurred vision and night sweat.

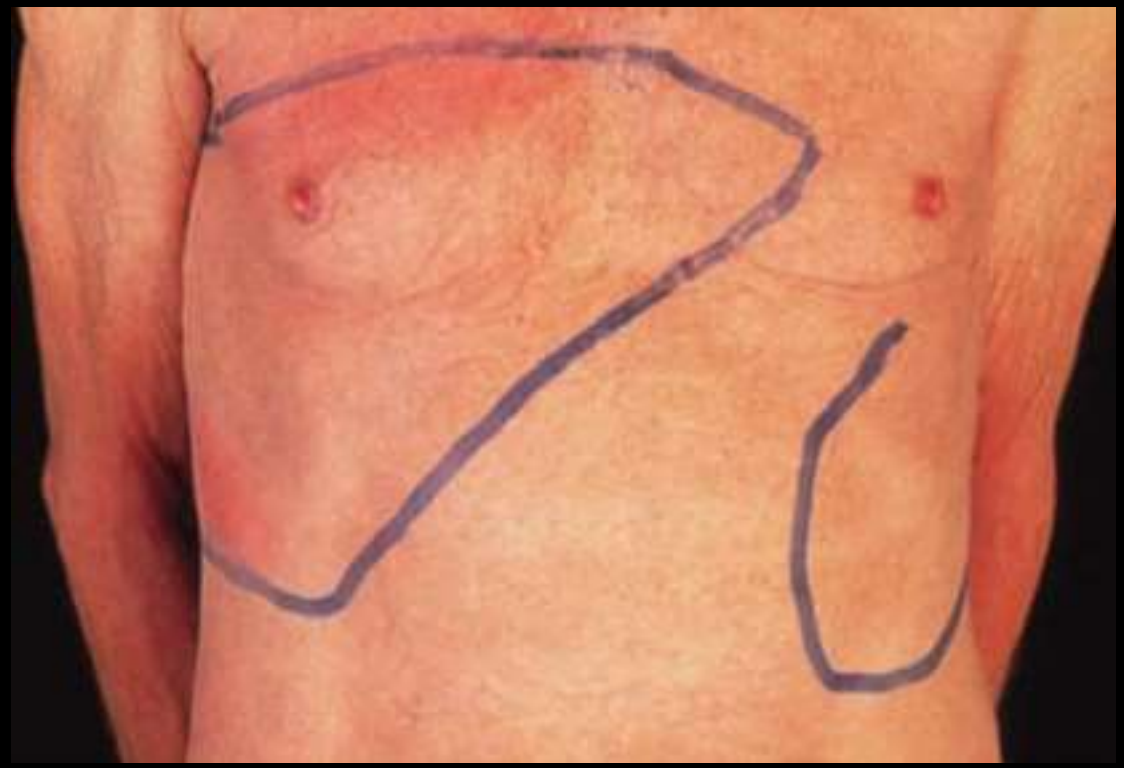


Aquagenic pruritus, which one may see with exposure to warm or hot water, may be a precursor symptom of polycythemia vera.

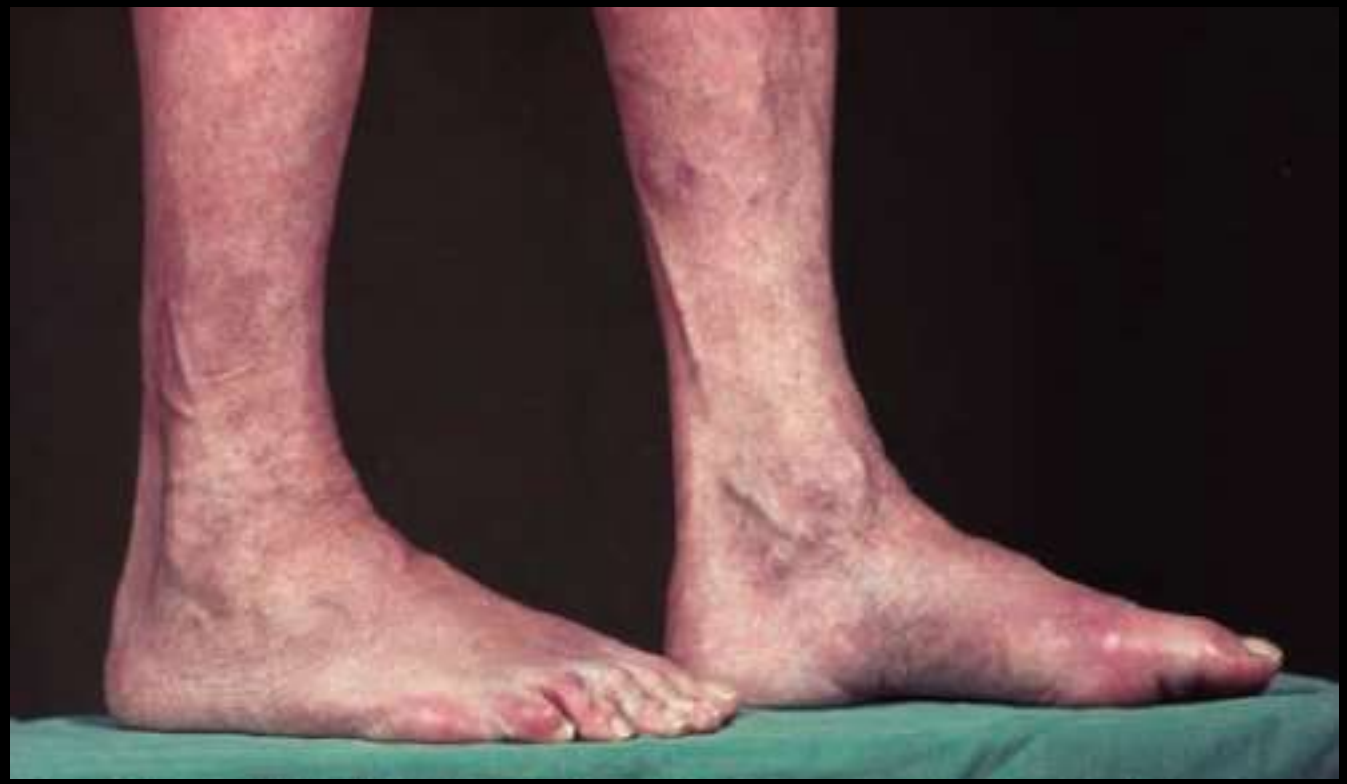
2. Plethoric appearance: ruddy cyanosis, conjuctival suffusion and retinal venous engorgement.
3. Splenomegaly in two thirds of patients.
4. Hypertension in one thirds of patients.
5. Gout (due to raised uric acid production).

Polycythemia vera: facial plethora

Polycythemia vera: facial plethora and conjunctival suffusion



Polycythemia vera:



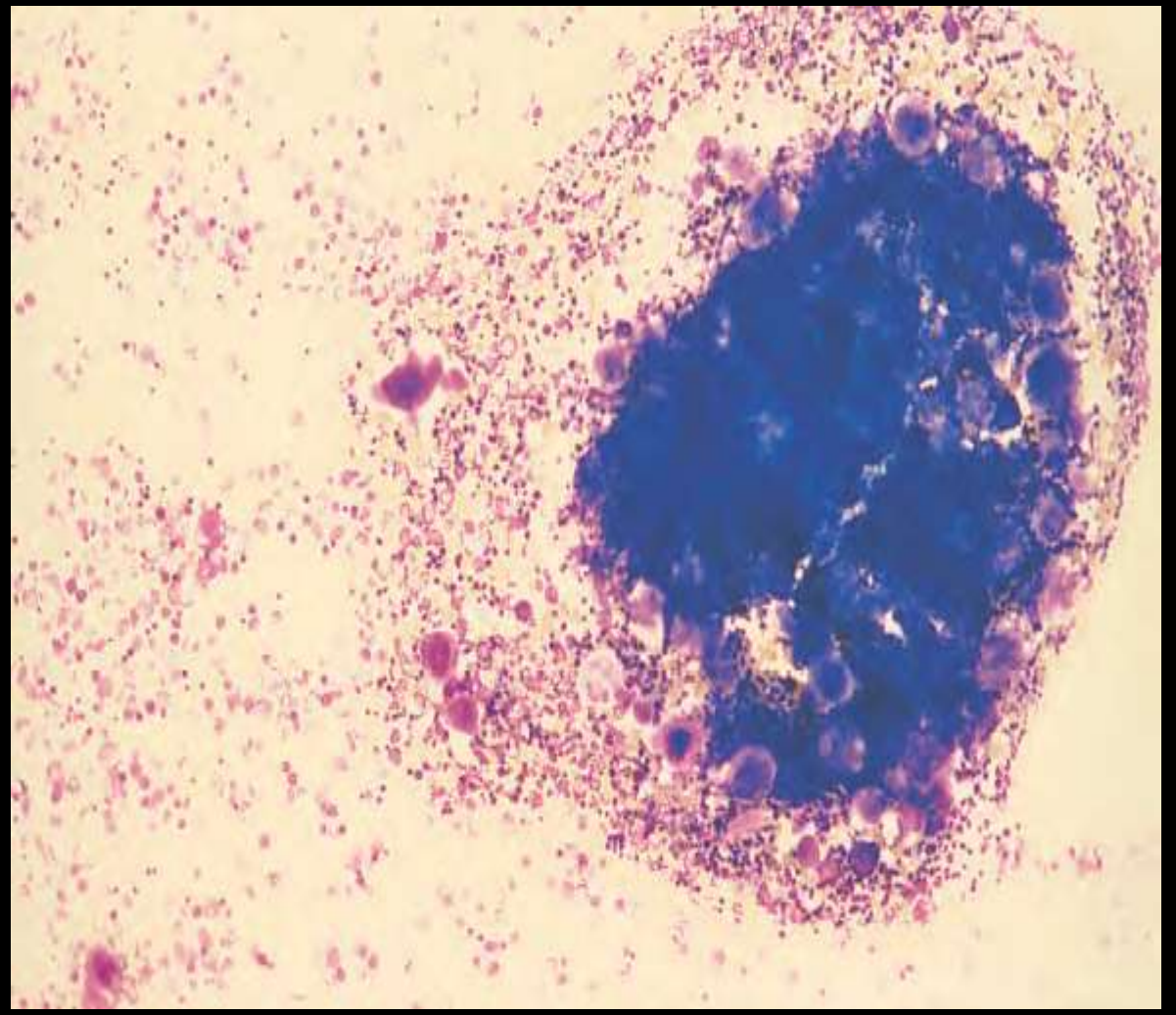
Polycythemia vera. There is inflammation of the right metatarsophalangeal and other joints caused by uric acid deposits

6. Hemorrhage (e.g.: gastrointestinal, uterine, cerebral) or thrombosis either arterial (e.g.: cardiac, cerebral, peripheral) or venous (e.g.: deep or superficial leg veins, cerebral, portal or hepatic veins).
7. Peptic ulceration occurs in 5-10% of patients.

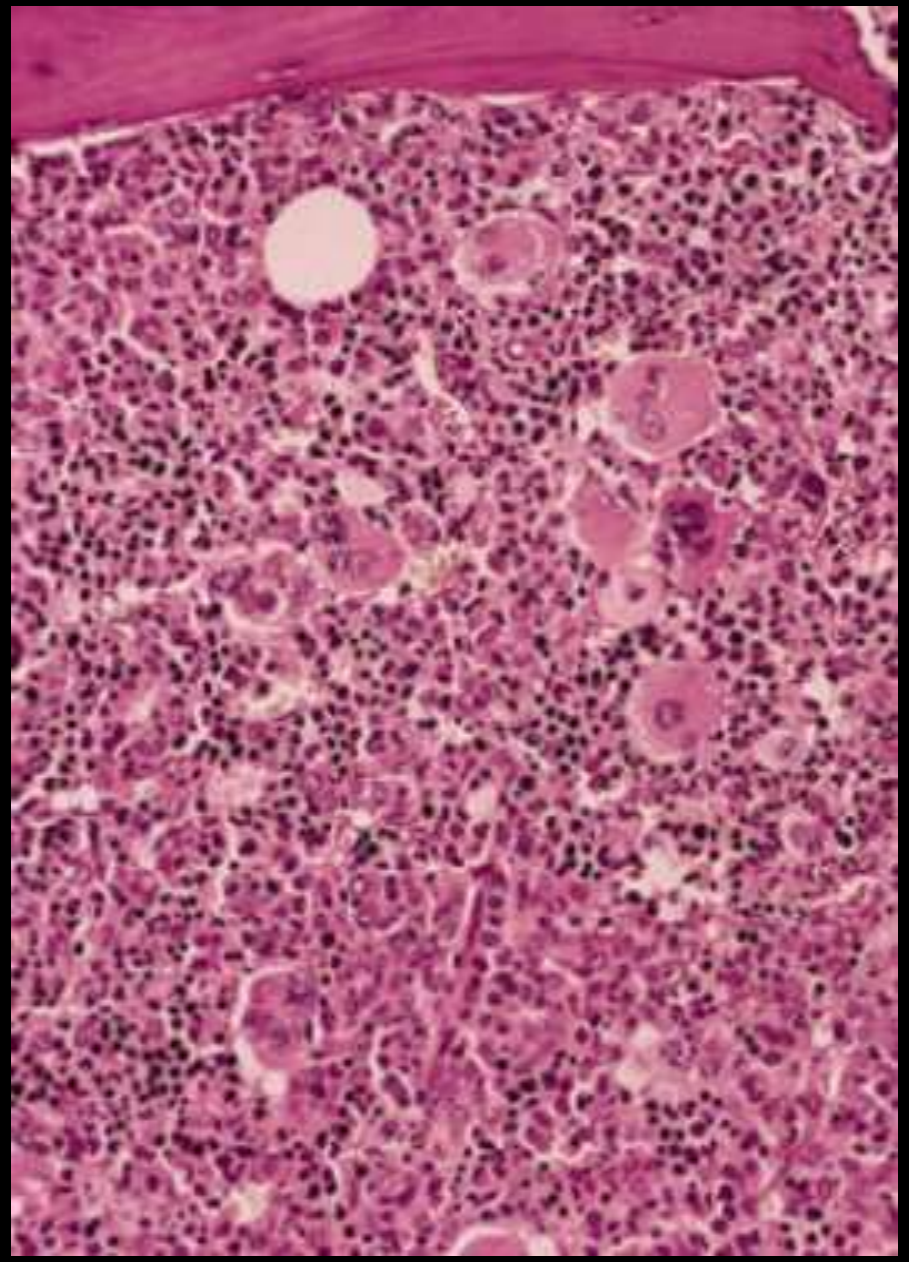
Laboratory Findings:

1. The Hb, PCV, and red cell count are increased.
2. Red cell mass is increased.
3. Neutrophil leukocytosis is seen in over half the patients.
4. Thrombocytosis is present in about half the patients.
5. JAK2 mutation is present in 95% of patients.

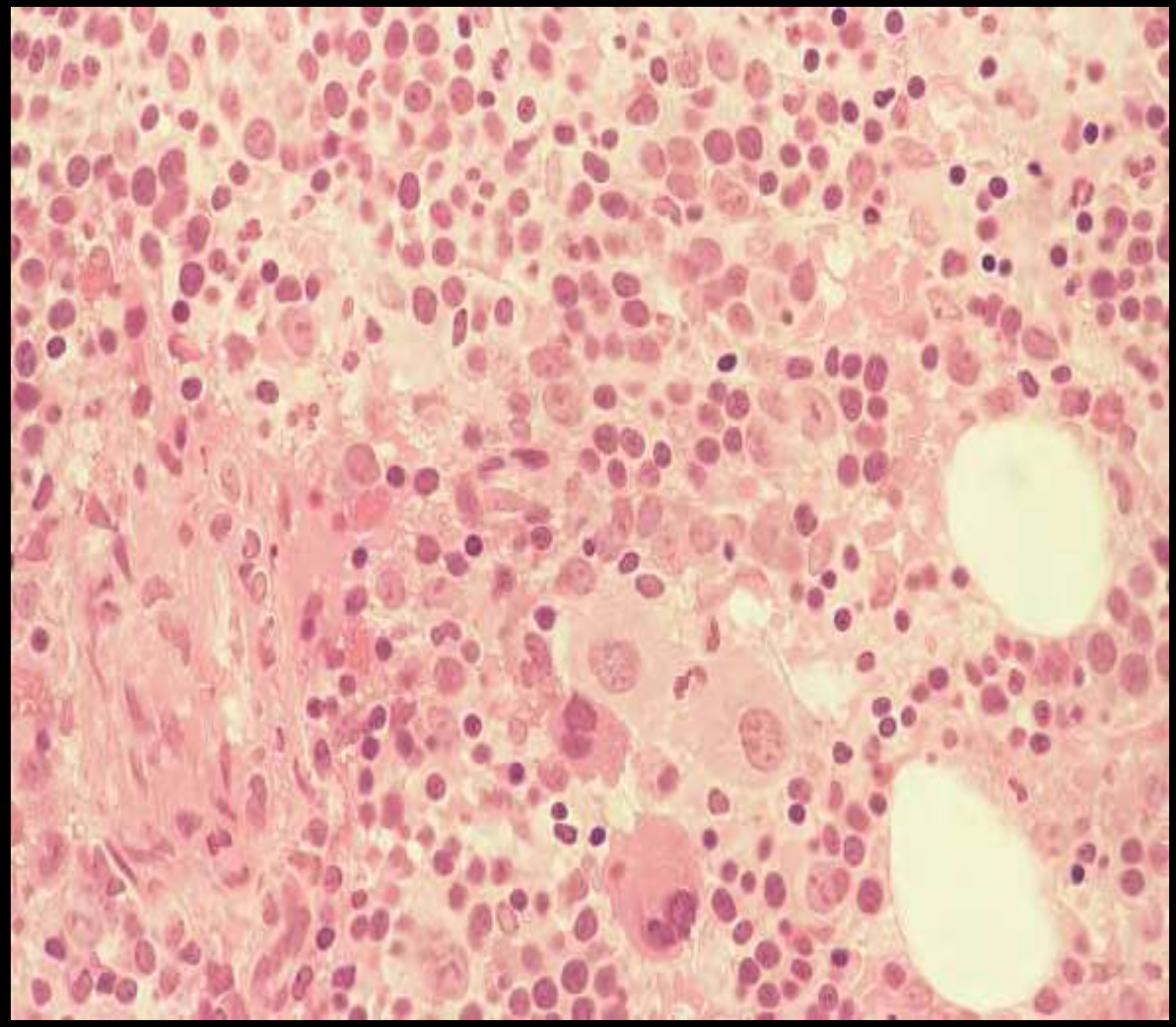
6. Neutrophil alkaline phosphotase score is usually increased.
7. Hypercellular bone marrow with hyperplasia of all lineages.
8. Increased blood viscosity.
9. Increased serum uric acid.
10. Philadelphia chromosome: negative



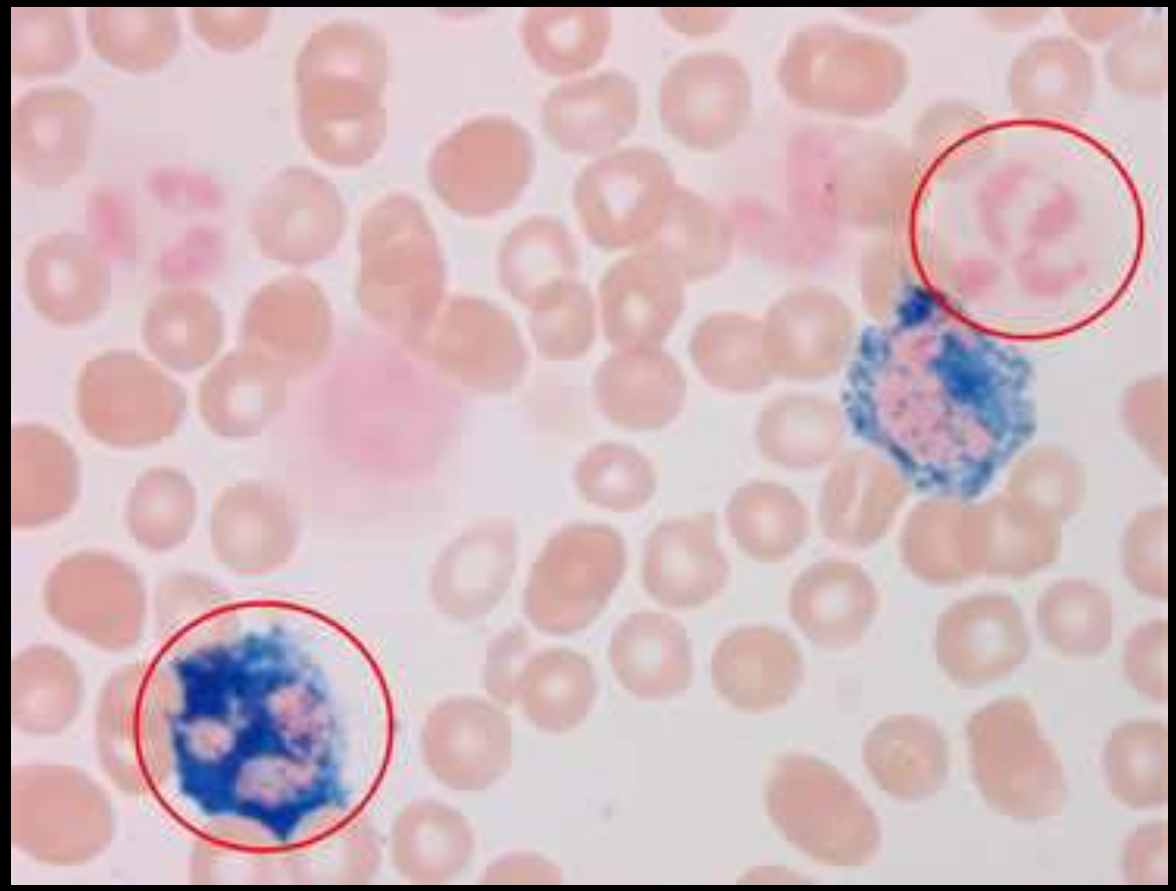
Marrow aspirate: polycythemia



Polycythemia vera: Bone marrow biopsy showing increased cellularity and prominent megakaryocytes.



Marrow biopsy:polycythemia



Neutrophil alkaline phosphatase

Course and prognosis of polycythemia vera:

Thrombosis and hemorrhage are common and vascular accidents are a frequent cause of death. Median survival is 10-16 years. Transition from polycythemia vera to acute leukemia occurs in about 5% of patients.

Primary Thrombocythemia (Essential Thrombocythemia)

Primary thrombocythemia is a clonal disorder involving a multipotent stem cell and characterized by megakaryocytic proliferation in the marrow and raised circulating platelet number.

(N.R. platelet count=150-400×10^9 /L).

Clinical Features:

Epidemiology

- Incidence estimated to be 0.6-2.5 per 100,000 persons

per year

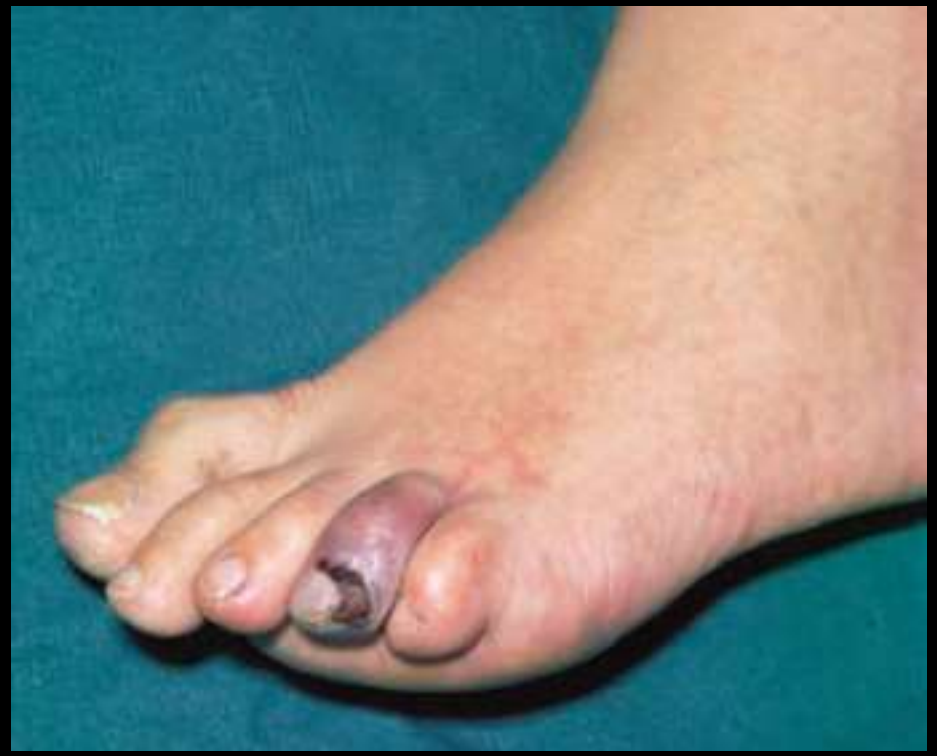
- Most cases occur in patients 50-60 years of age;

however, there is a second peak in incidence in younger adults (usually in their 30s) who are usually women

- Rare in children, in whom it must be distinguished from hereditary thrombocytosis
- About half of patients are asymptomatic at diagnosis.

In symptomatic patients, the presenting features are either due to vascular occlusion or hemorrhage, sometimes both. Vascular occlusion symptoms are usually due to small vessels obstruction leading to pre-gangrenous and gangrenous changes, transient visual loss…etc.

- There may be anemia due to iron deficiency from hemorrhage or due to the marrow disorder itself. Sometimes there is polycythemia.
- Splenic enlargement is seen in the early phase but splenic atrophy due to blocking of splenic microcirculation is seen in some patients.

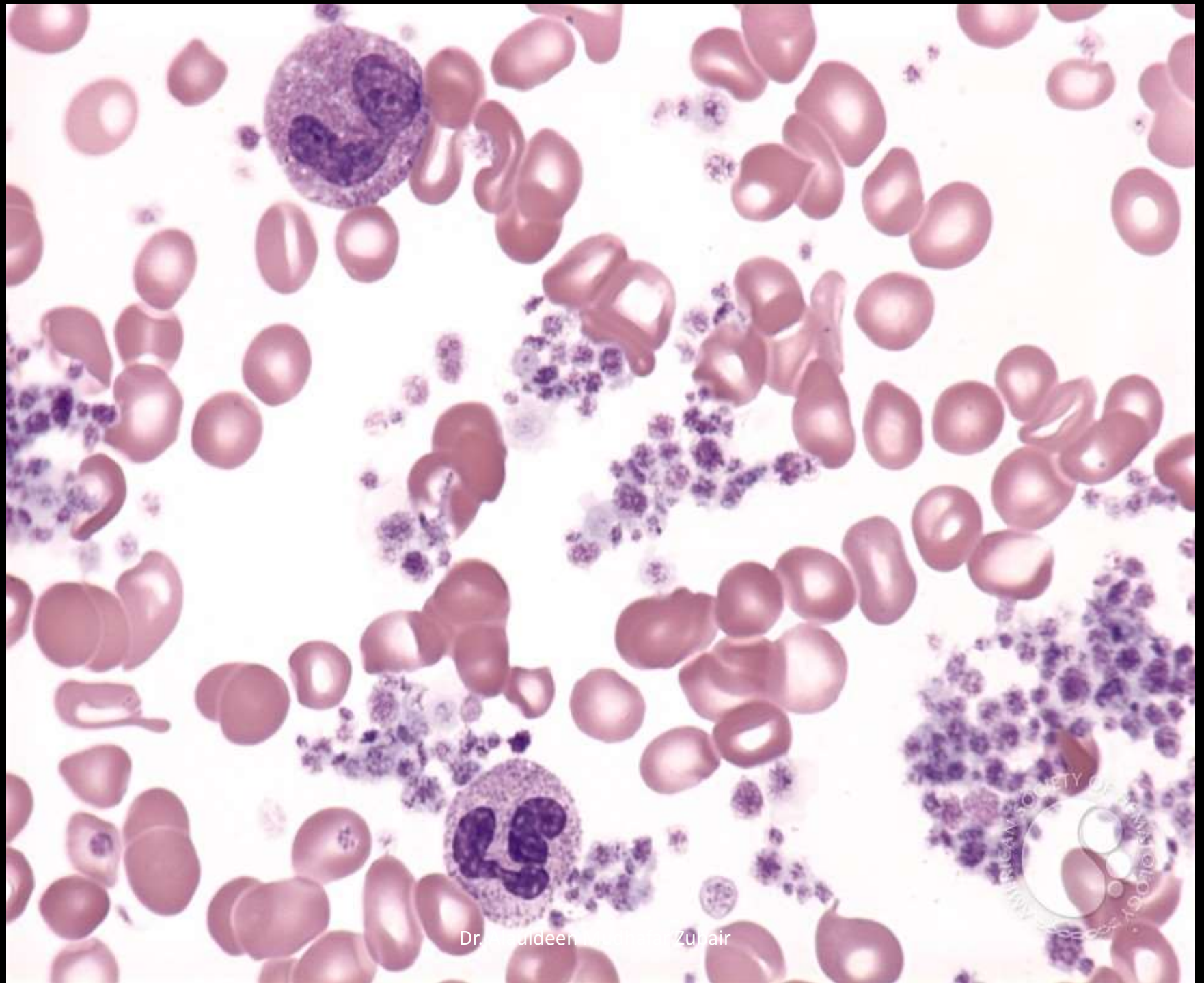


Gangrene in essential thrombocythemia

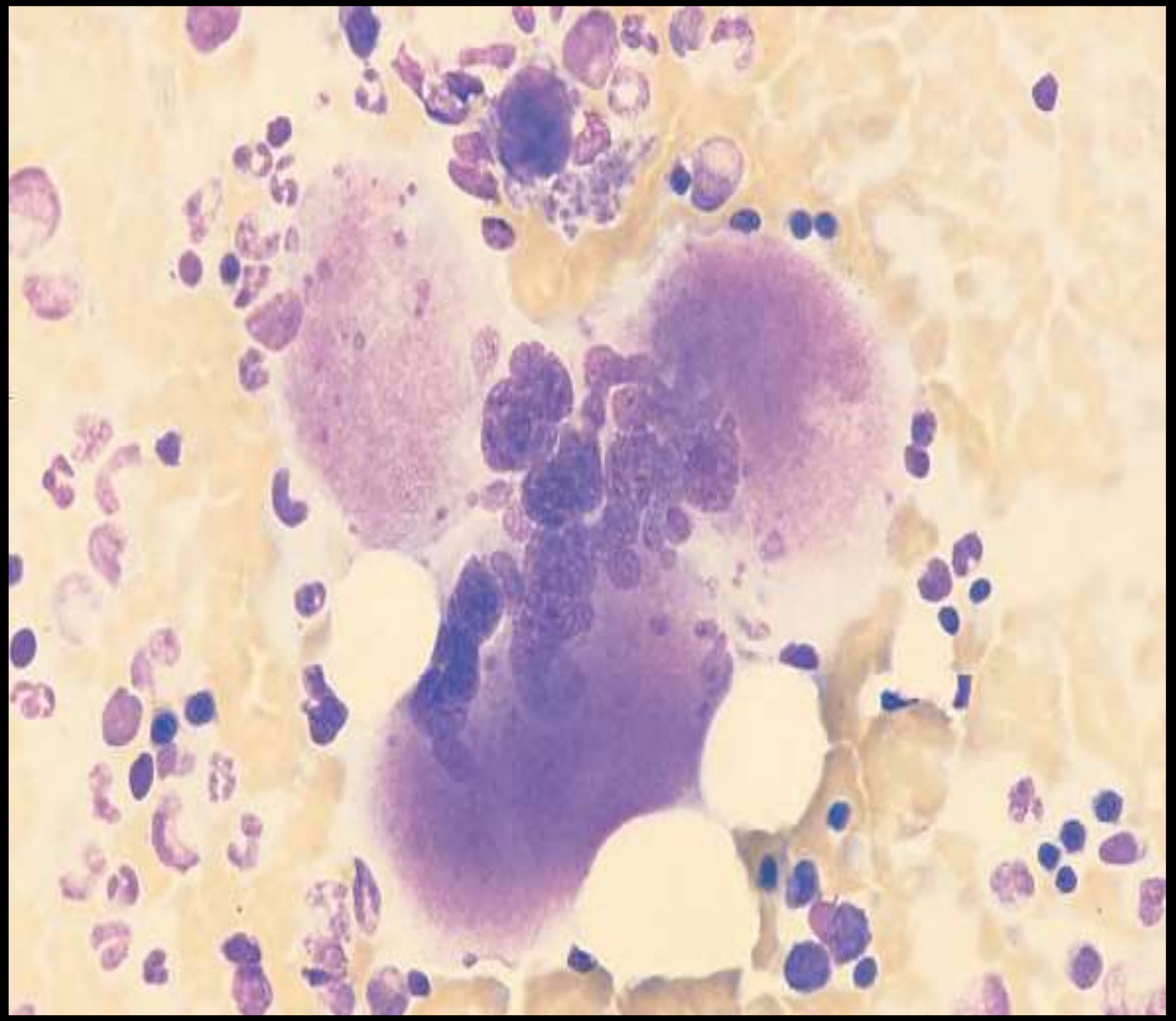
Laboratory Findings:

- The platelets count is raised, usually in the range of 600-2500 × 10^9 /L.
- The Hb and PCV are normal or moderately reduced.
- The WBC count is mildly raised in ⅓ of patients.

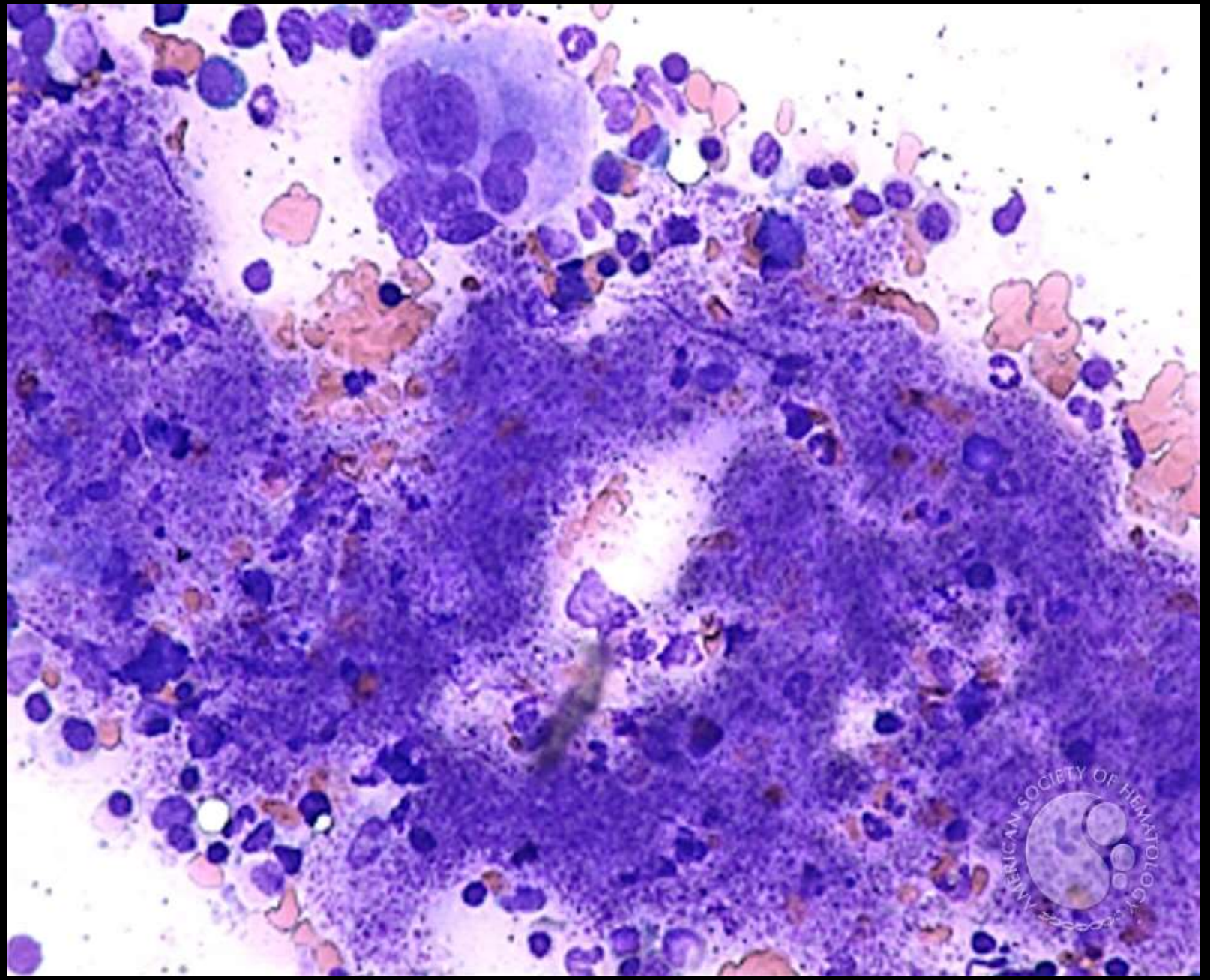
- Blood film: shows increased number of platelets with abnormal large platelets and anisocytosis. Megaryocyte fragment may be seen.
- Among patients with ET, the common molecular finding is a JAK2 V617F mutation. This mutation occurs in about half of all ET patients

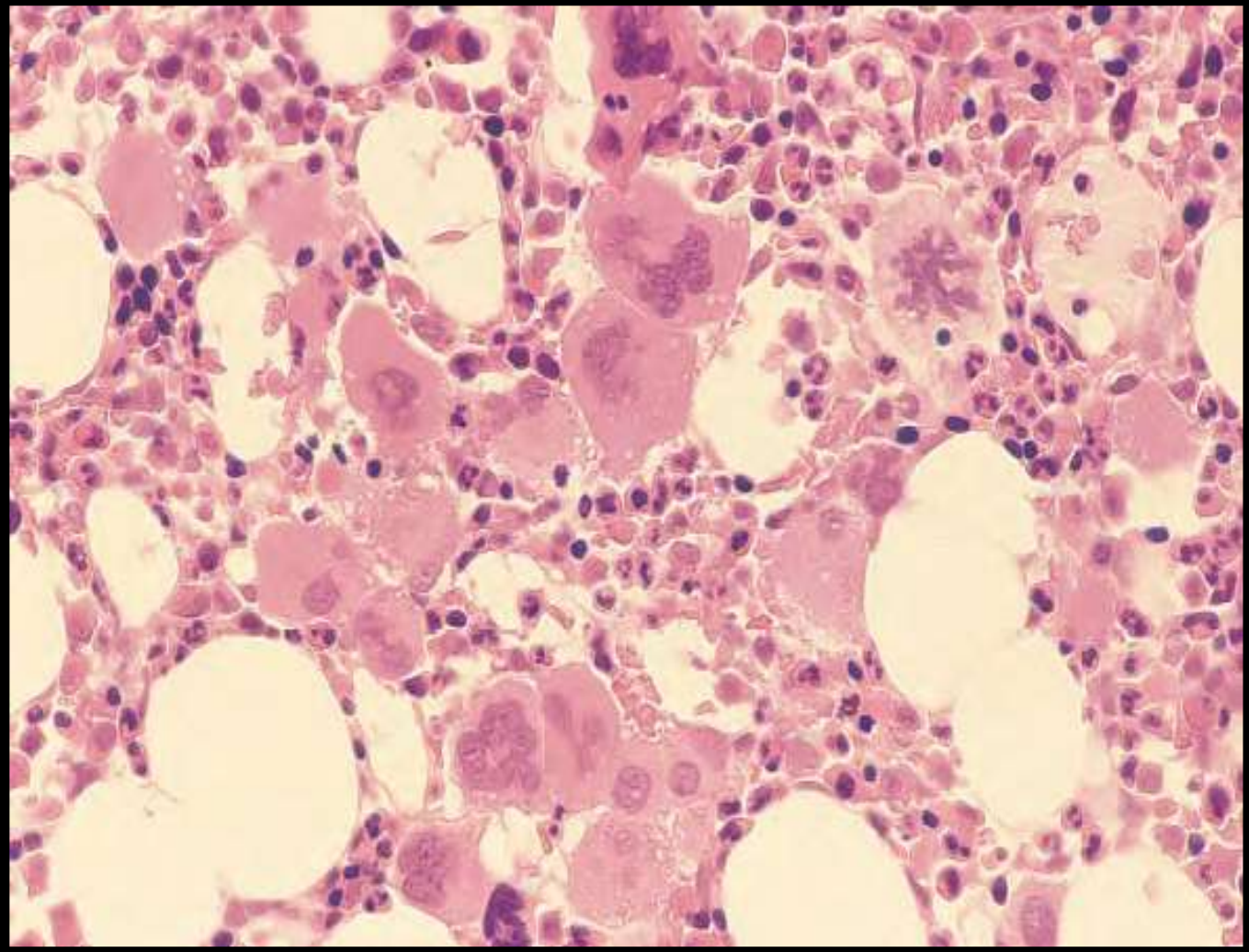


- Red cell morphology is usually normal unless there is iron deficiency anemia.
- Bone marrow shows hypercellularity with increased number of megakaryocytes and masses of aggregated platelets.
- Megakaryocytes tend to form clusters.
- Platelets function tests are abnormal.



Bone marrow aspirate in thrombocythemia





Bone marrow biopsy in thrombocythemia

Course and Prognosis of Primary Thrombocythemia:

Patients may transform after a number of years to polycythemia vera, myelofibrosis or acute leukemia providing death does not occur from hemorrhage or thrombosis. Often the disease is stable for 10-20 years or more.

Causes of reactive thrombocytosis:

- Hemorrhage
- Trauma
- Post-operative
- Malignancy
- Chronic Infection
- Connective Tissue Diseases
- Post Splenectomy
- Chronic Iron Deficiency

Chronic (Primary) Myelofibrosis

It is a chronic myeloproliferative disorder characterized by bone marrow fibrosis, extra-medullary hemopoiesis and splenomegaly.

Pathophysiology:

There is an increase in circulating stem cells associated with establishment of extra-medullary hemopoiesis especially in liver and spleen (myeloid metaplasia). The fibrosis in the bone marrow is reactive secondary to hyperplasia of abnormal megakaryocytes.

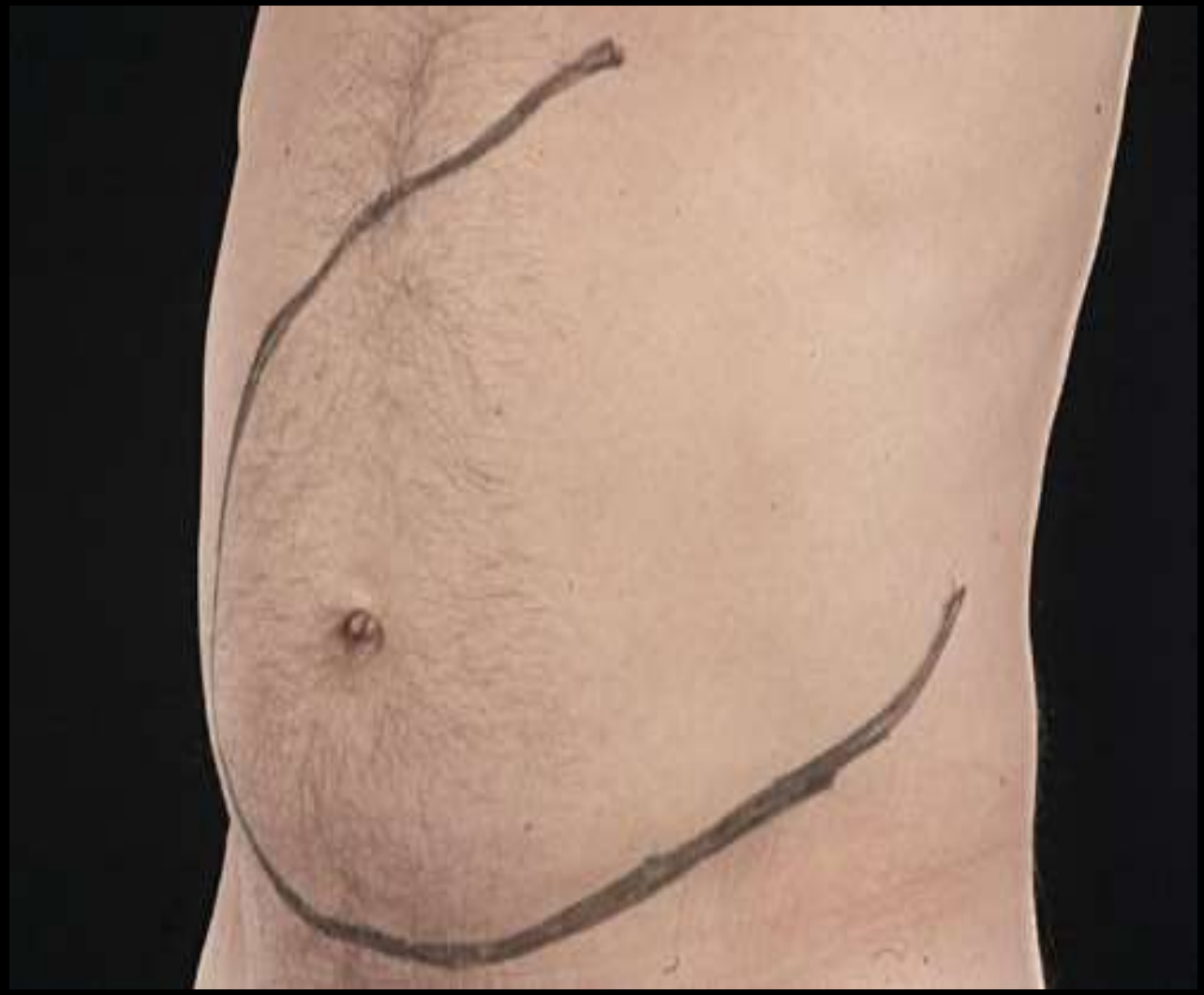
There is stimulation of fibroblast probably by platelet derived growth factor secreted by megakaryocyters and platelets, also inhibition of collagenase by platelet factor IV.

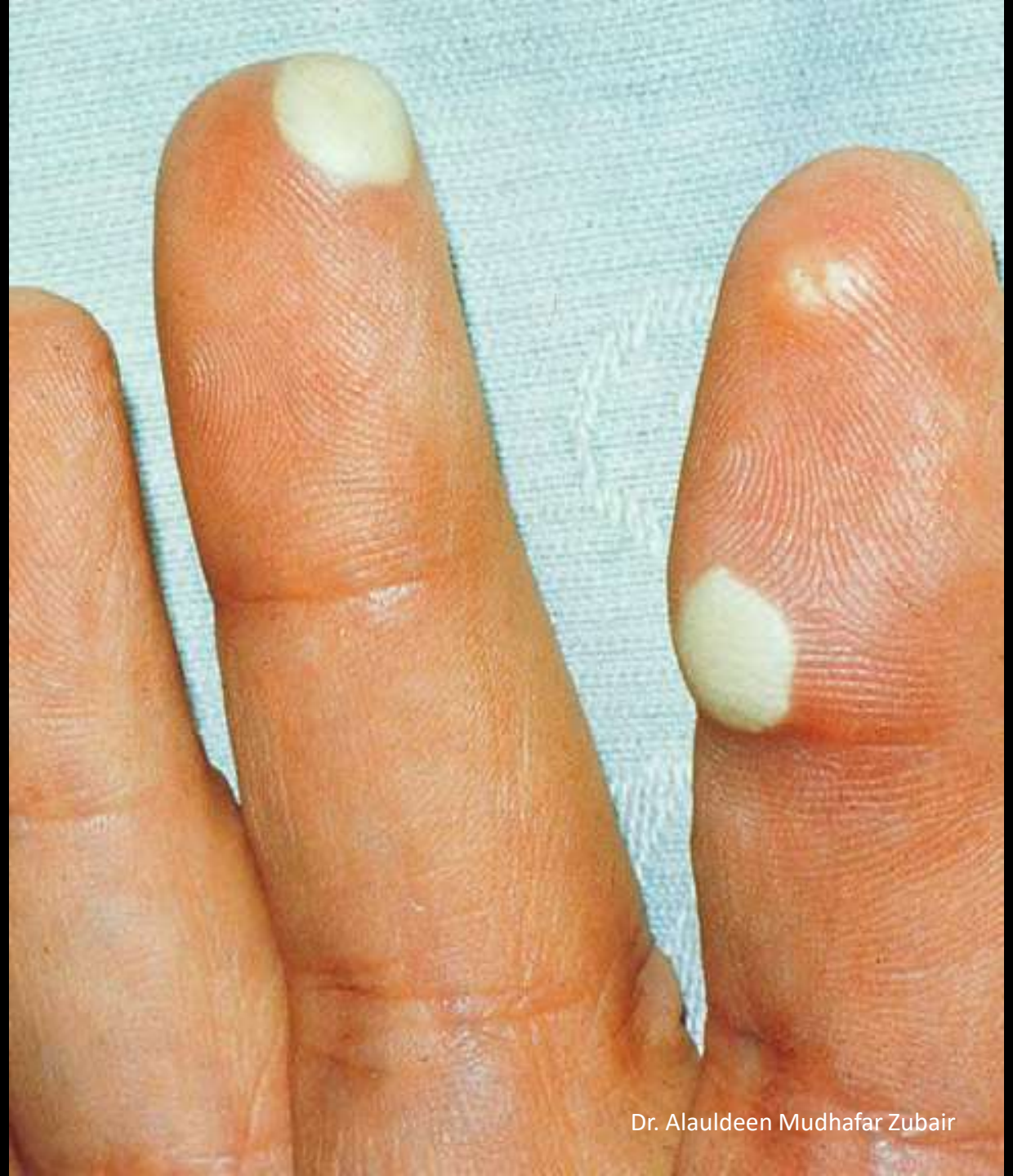
JAK2 V617F mutation is found in approximately half the cases of PMF

Clinical Features:

- An insidious onset in older people is usual with symptoms of anemia.
- Epidemiology
- 1.0 per 100,000 individuals per year
- Typically sixth to seventh decade of life; male-to female ratio 1 : 1

- Symptoms due to massive splenomegaly (e.g.: abdominal discomfort, pain or indigestion) are frequent. Splenomegaly is the main physical finding.



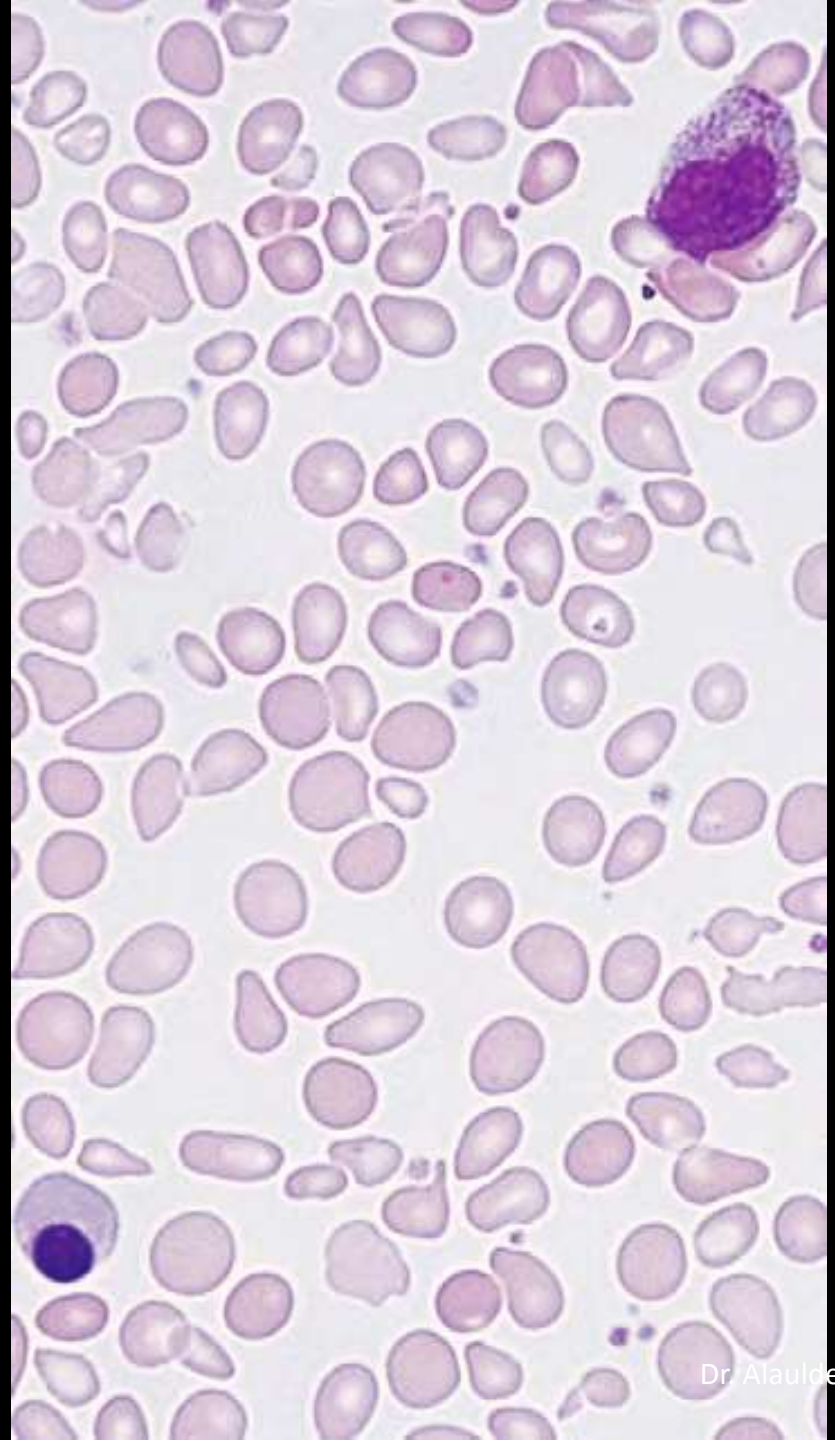


Myelofibrosis: gouty tophi

- Hypermetabolic symptoms: Loss of weight, anorexia, and night sweats are common.
- Bleeding problems, bone pain or Gout occurs in a minority of patients.
- ⅓ lack constitutional symptoms, diagnosed on the basis of splenomegaly, anemia, leukocytosis, and/or thrombocytosis

Laboratory findings:

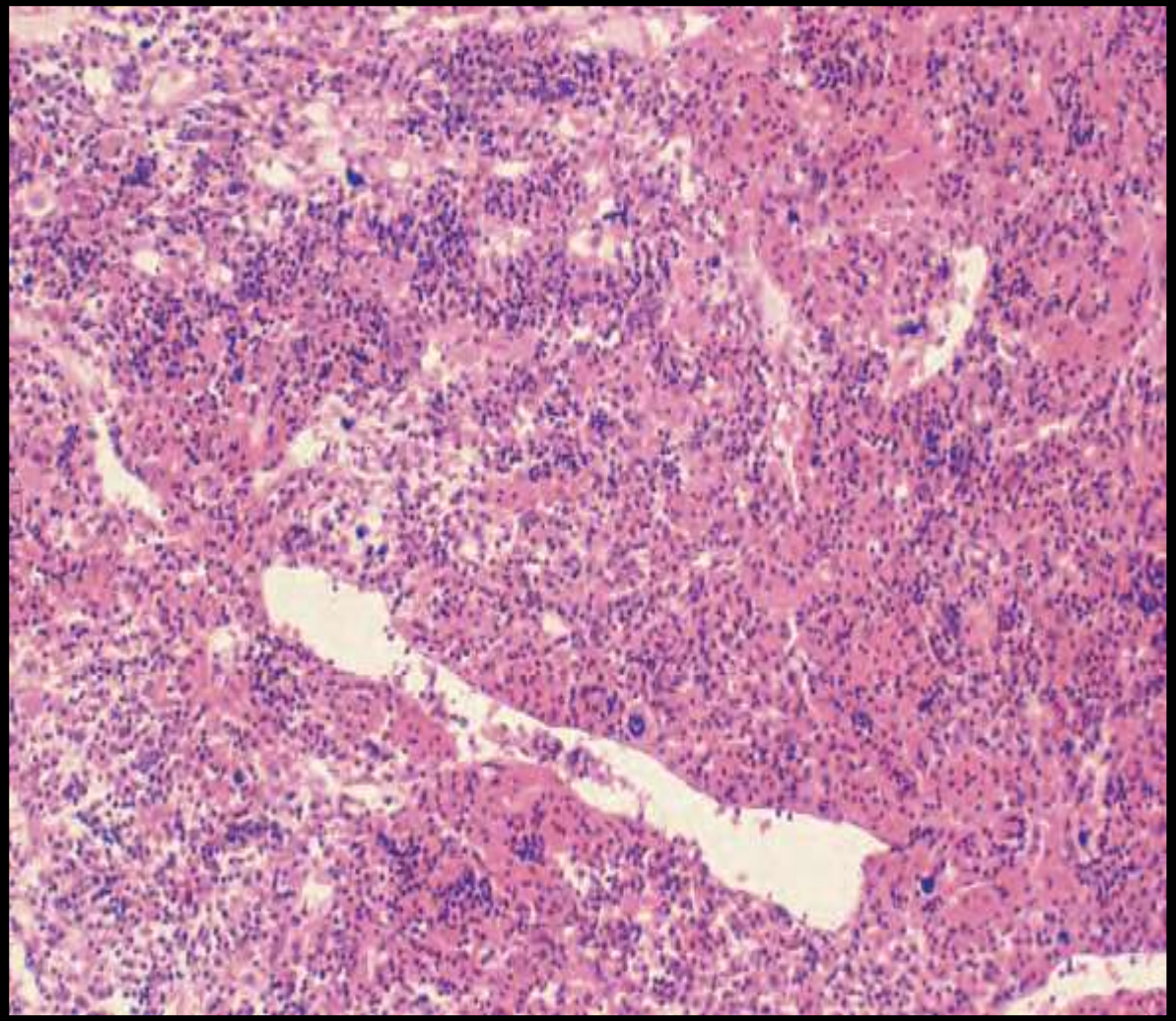
- Anemia is usual but a normal or increased hemoglobin level may be found in some patients.
- The white cell and platelet counts are frequently high in early presentation. Later in the disease leucopenia and thrombocytopenia are common.
- A leuko-erythroblastic blood film is found. The red cells showed characteristic tear drop poikilocytes.



Blood film: primary myelofibrosis

The bone marrow is usually unobtainable by aspiration. Trephine biopsy may show hypercellular marrow and increased megakaryocytes in early stages. There is an increased reticulin fibrosis seen by reticulin stain.

- JAK2 kinase is mutated in approximately 50% of cases.
- High serum urate and LDH levels reflect the increased but largely ineffective turnover of hemopoietic cells.
- Transformation to acute myeloid leukemia occurs in 10 – 20% of patients.

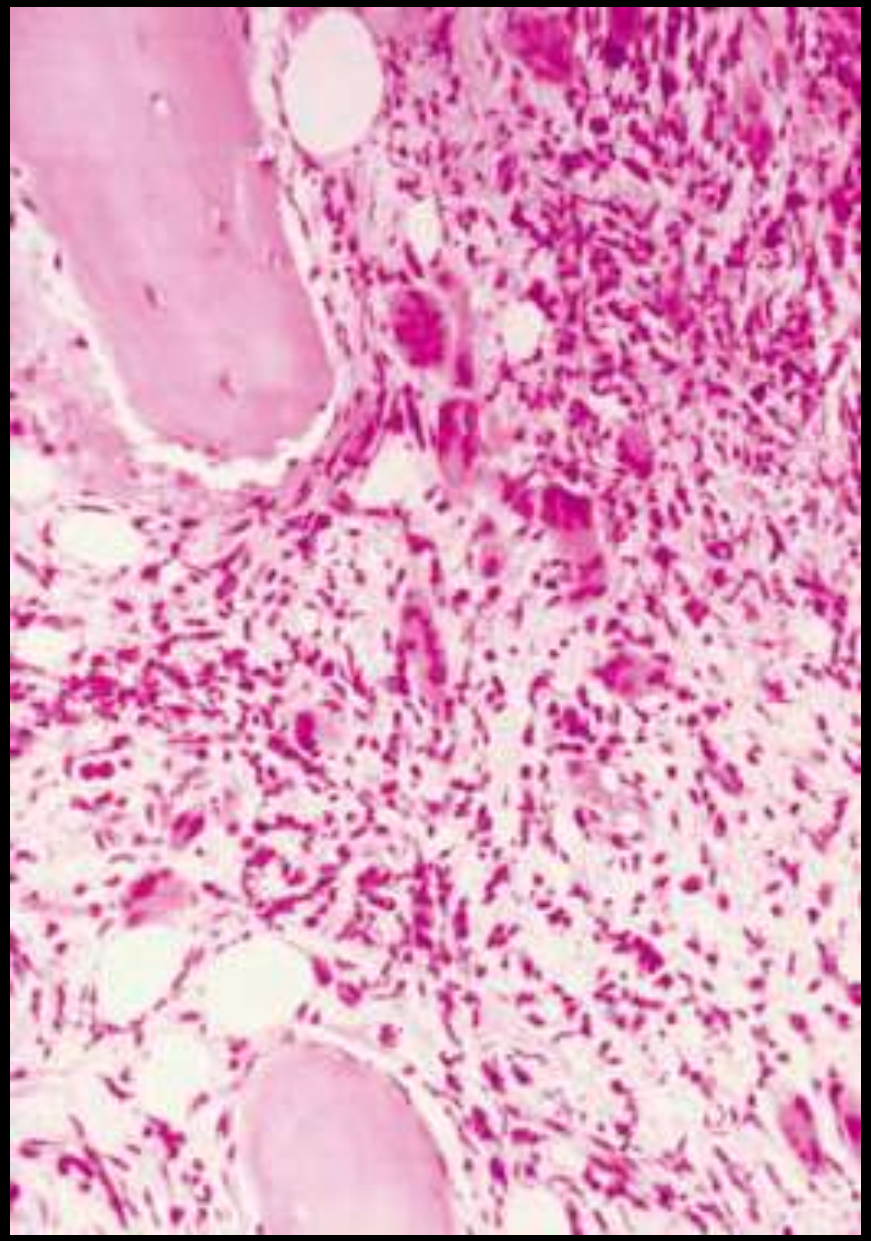


Myelofibrosis: cellular phase

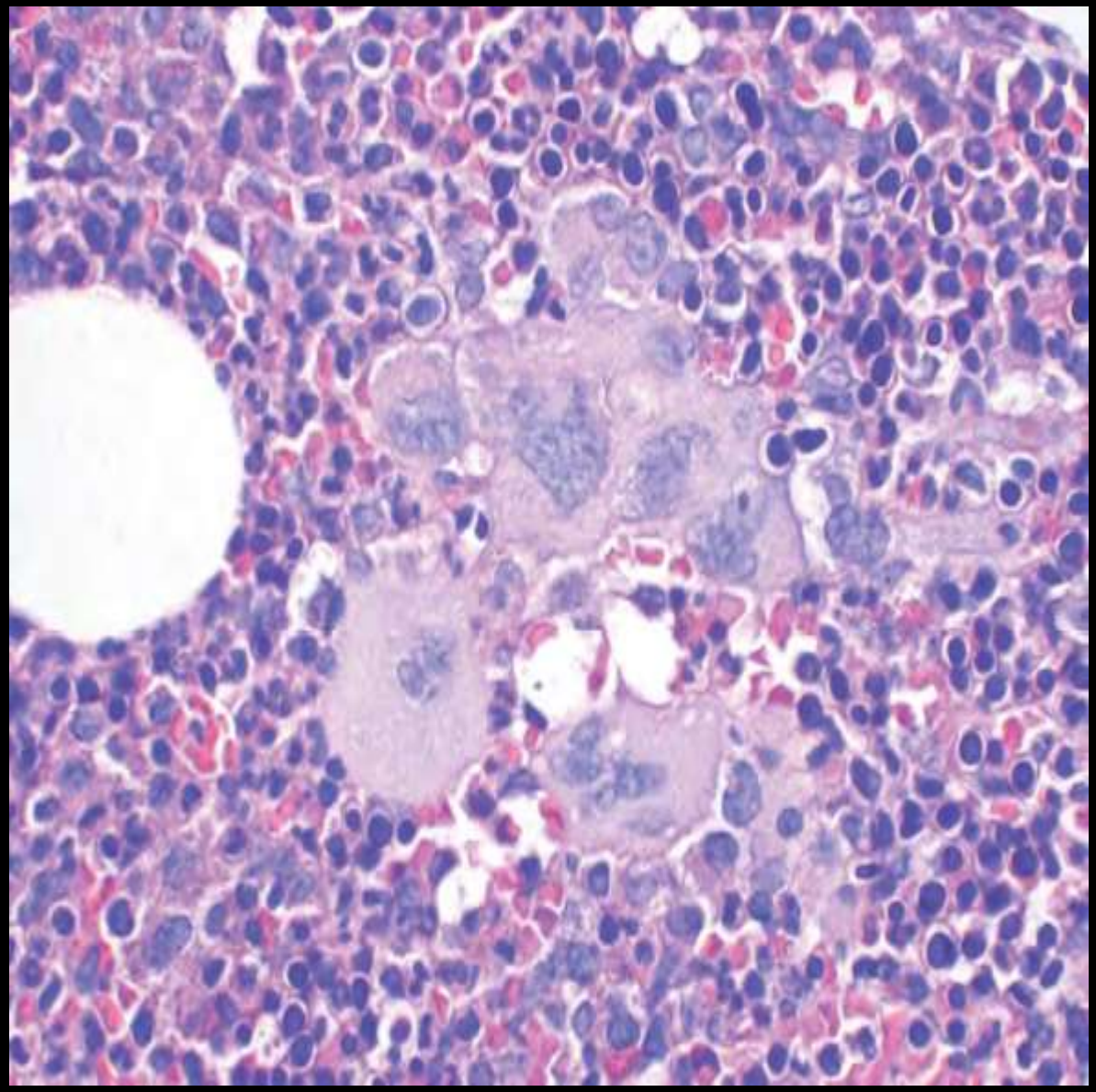
Later there is decreased number of hemopoietic cells and increased collagen fibrosis leading to marrow failure. In some cases there is increased bone formation with increased bone density on X-Ray. This is called **osteomyelosclerosis.**

CAUSES OF MARROW FIBROSIS

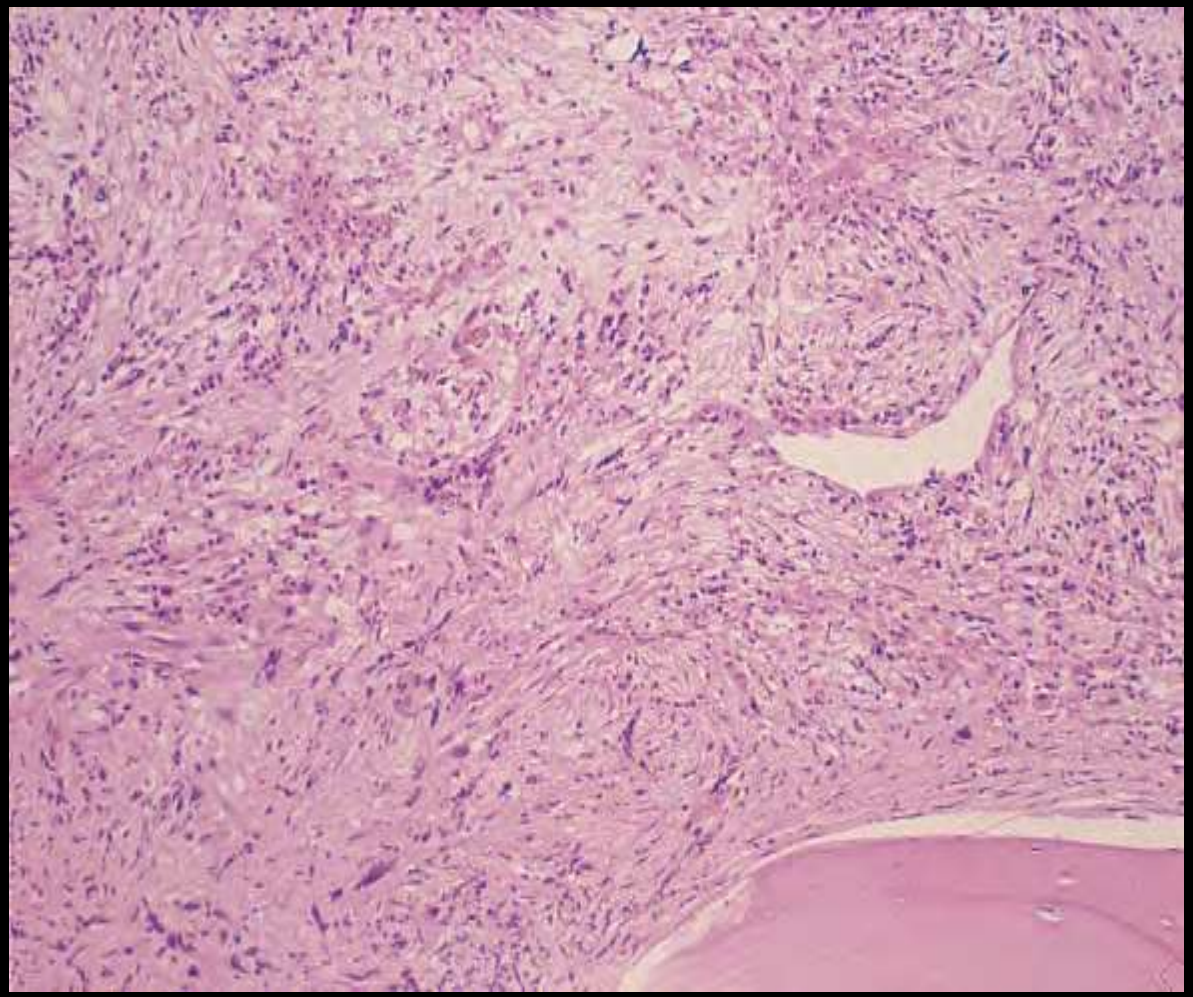
- Myelofibrosis
- Infections: tuberculosis; osteomyelitis (focal fibrosis)
- Malignant lymphoma, including Hodgkin lymphoma
- Occasionally, chronic myeloid leukemia and other leukemias, especially AML M7
- Metastatic carcinoma, especially breast and prostate
- Excess irradiation Benzene poisoning Excess fluorine Paget's disease (focal fibrosis; Osteopetrosis



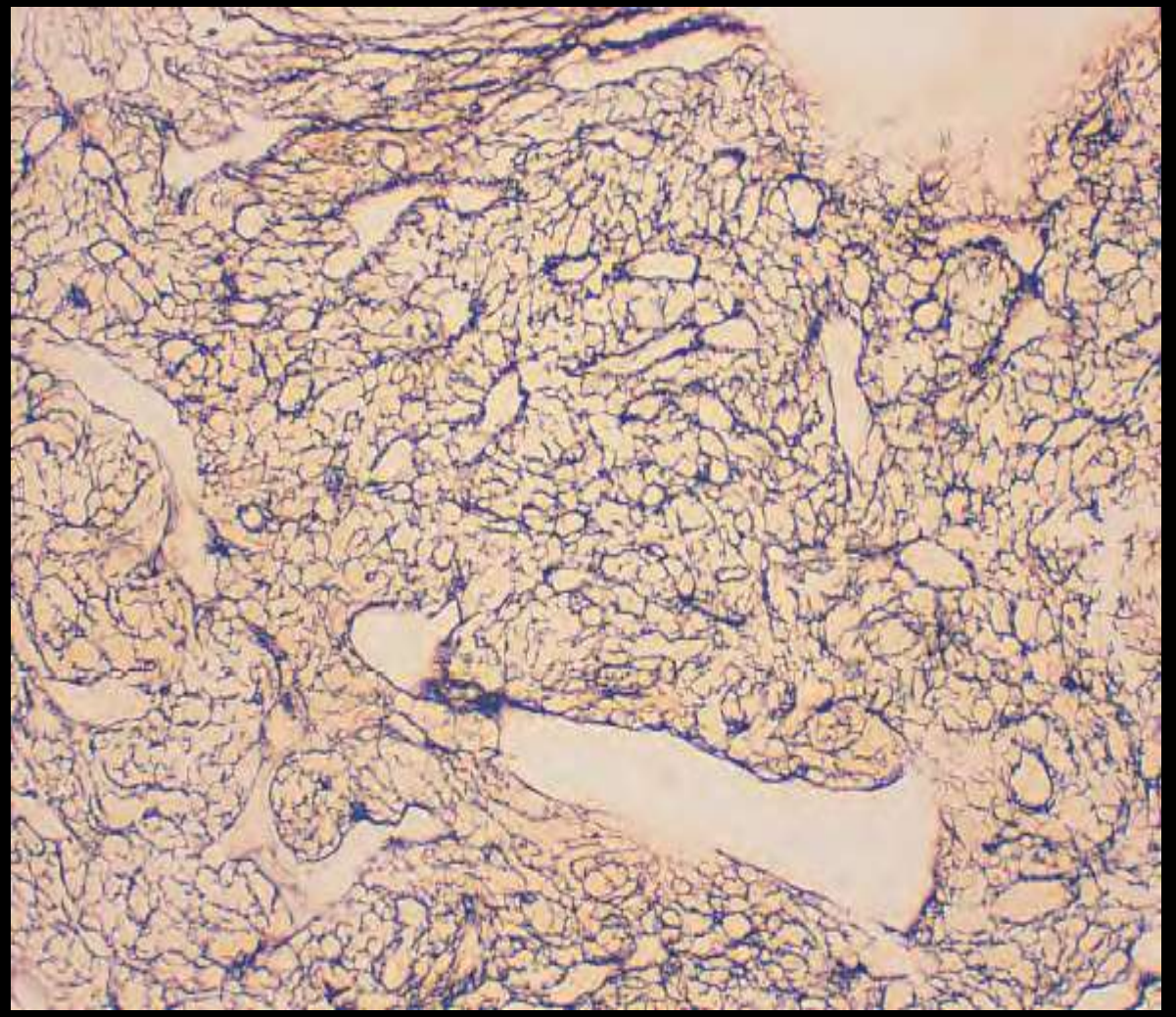
Primary myelofibrosis: normal marrow architecture is lost and hemopoietic cells are surrounded by increased fibrosis



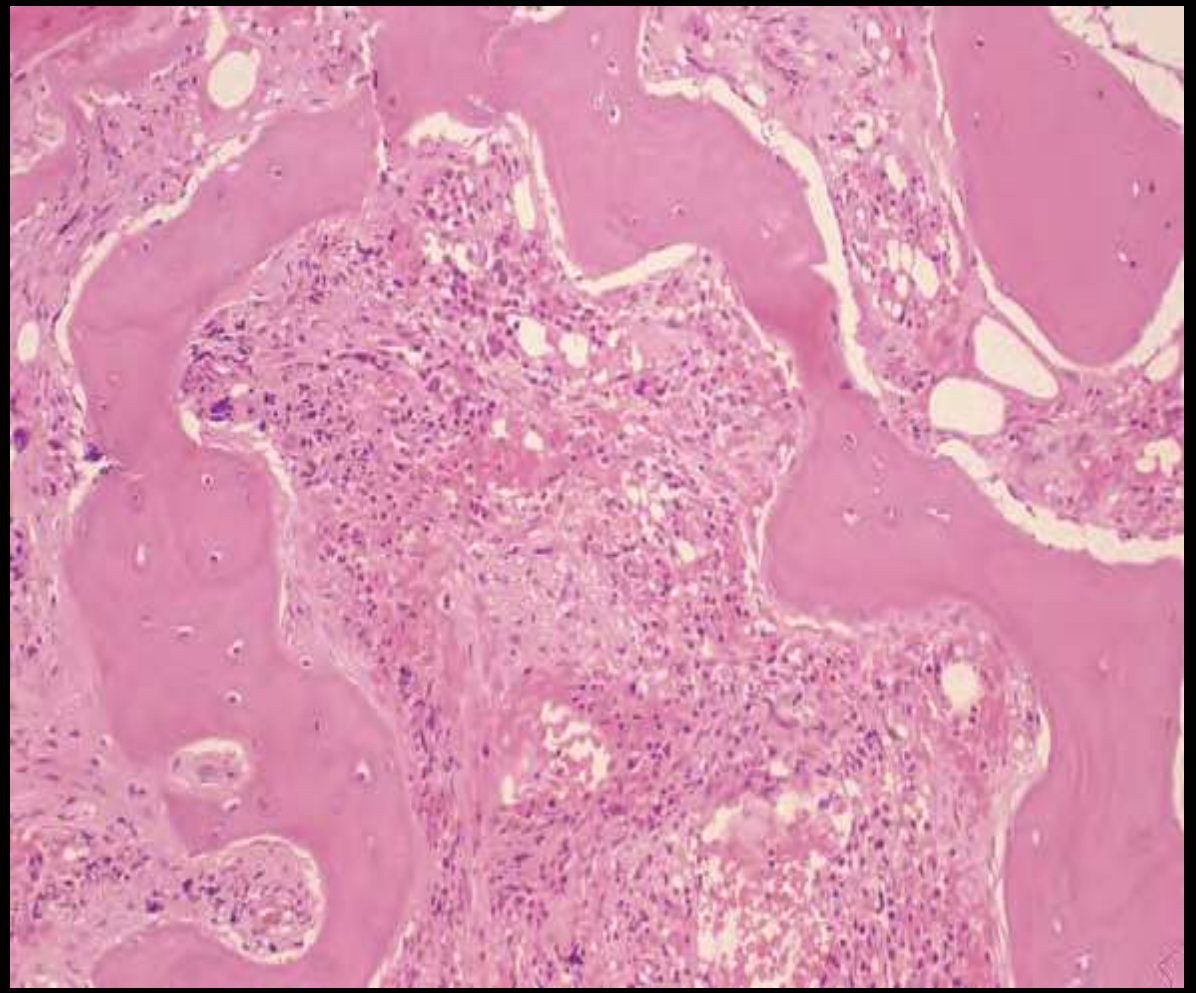
Megakaryocytes cluster



Myelofibrosis:fibrotic phase



Reticulin stain



Osteomyelosclerosis