MYELOPROLIFERATIVE NEOPLASM

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Learning objectives

- By the end of this lecture students will be able to:
- Classify Myeloproliferative disorders (MPN)
- Discuss the pathophysiology of MPN
- Describe the clinical course and morphological feature of MPN
- Diagnose a case of MPN

Myeloproliferative Disorders

- Clonal hematopoietic disorders
- Characterized by Leukocytosis, Thrombocytosis and Erythrocytosis due to excess proliferation
- Splenomegaly and hepatomegaly are common
- Caused by the sequestration of excess blood cells and extramedullary hematopoiesis
- Variable transformation to acute leukemia

Pathogenesis of MPN

- Nonrandom chromosomal abnormalities such as translocations
- The genes that are mutated often play crucial roles in the development, growth, or survival of the normal cell
- Common pathology is the presence of mutated, activated tyrosine kinases
- Activated tyrosine kinases is required to promote growth and survival
- The mutated tyrosine kinases lead to the growth factor–independent proliferation and survival of marrow progenitors

Classification of MPN

TABLE 13-11 -- Tyrosine Kinase Mutations in Myeloproliferative Disorders

Disorder	Mutation	Frequency [¶]	Consequences [*]
Chronic myeloid leukemia	*BCR-ABL* fusion gene	100%	Constitutive ABL kinase activation [†]
Polycythemia vera	*JAK2* point mutations	>95%	Constitutive JAK2 kinase activation
Essential thrombocythemia	*JAK2* point muations	50% to 60%	Constitutive JAK2 kinase activation
	MPL point mutations	5% to 10%	Constitutive MPL kinase activation
Primary myelofibrosis	*JAK2* point mutations	50% to 60%	Constitutive JAK2 kinase activation
	MPL point mutations	5% to 10%	Constitutive MPL kinase activation
Systemic mastocytosis	*c-KIT* point mutations	>90%	Constitutive c-KIT kinase activation
Chronic eosinophilic leukemia [‡]	*FIP1L1-PDGFRα* fusion gene	Common	Constitutive PDGFRα kinase activation
	PDE4DIP-PDGFRβ fusion gene	Rare	Constitutive PDGFRβ kinase activation [†]

POLYCYTHEMIA VERA

Introduction

- Polycythemia vera is a chronic myeloproliferative disorder characterized by increased Hemoglobin level, red blood cell mass (RCM), or erythrocytosis

- Resultant hyperviscosity of the blood predisposes such patients to thrombosis

Classification

- Absolute polycythemia

  there is increased red cell mass

  Further divided into primary and secondary

- Relative polycythemia

  Red cell mass is normal but the plasma volume is reduced as in diarrhea

Secondary polycythemia

- Increased red cell mass due to some other conditions
- Resolves when the underlying cause is treated
- increased erythropoietin drive
- Causes of secondary polycythemia:

- High altitudes
- Pulmonary disease
- Cardiovascular disease especially congenital
- Tumors such as uterine , hepatocellular carcinoma
- Erythropoietin secreting tumors

Relative Polycythemia

- Results from plasma volume contraction
- More common
- Causes:

- Stress
- Cigarette smoking
- Dehydration: water deprivation, vomiting
- Plasma loss: burns

Primary Polycythemia

- Clonal myeloproliferative disorder
- Increased marrow production of red cells
- Associated leukocytosis and thrombocytosis may be seen
- Activating point mutations of tyrosine kinase JAK2 almost 100%
- JAK2 participates in the JAK/STAT pathway, which lies downstream of multiple hematopoietic growth factor receptors, including the erythropoietin receptor.

Molecular Pathogenesis

- The progenitor cells have markedly decreased requirements for erythropoietin and other hematopoietic growth factors due to repetitive JAK2 signaling
- Serum erythropoietin levels is very low
- Secondary forms of absolute polycythemia have high erythropoietin levels

- JAK2 mutation results from valine-to-phenylalanine substitution at position 617
- Mutated JAK2 render hematopoietic cell lines proliferation growth factor–independent
- Homozygous genotype is associated with higher white cell counts, more significant splenomegaly, symptomatic pruritus

WHO 2016 Diagnostic Criteria for PV

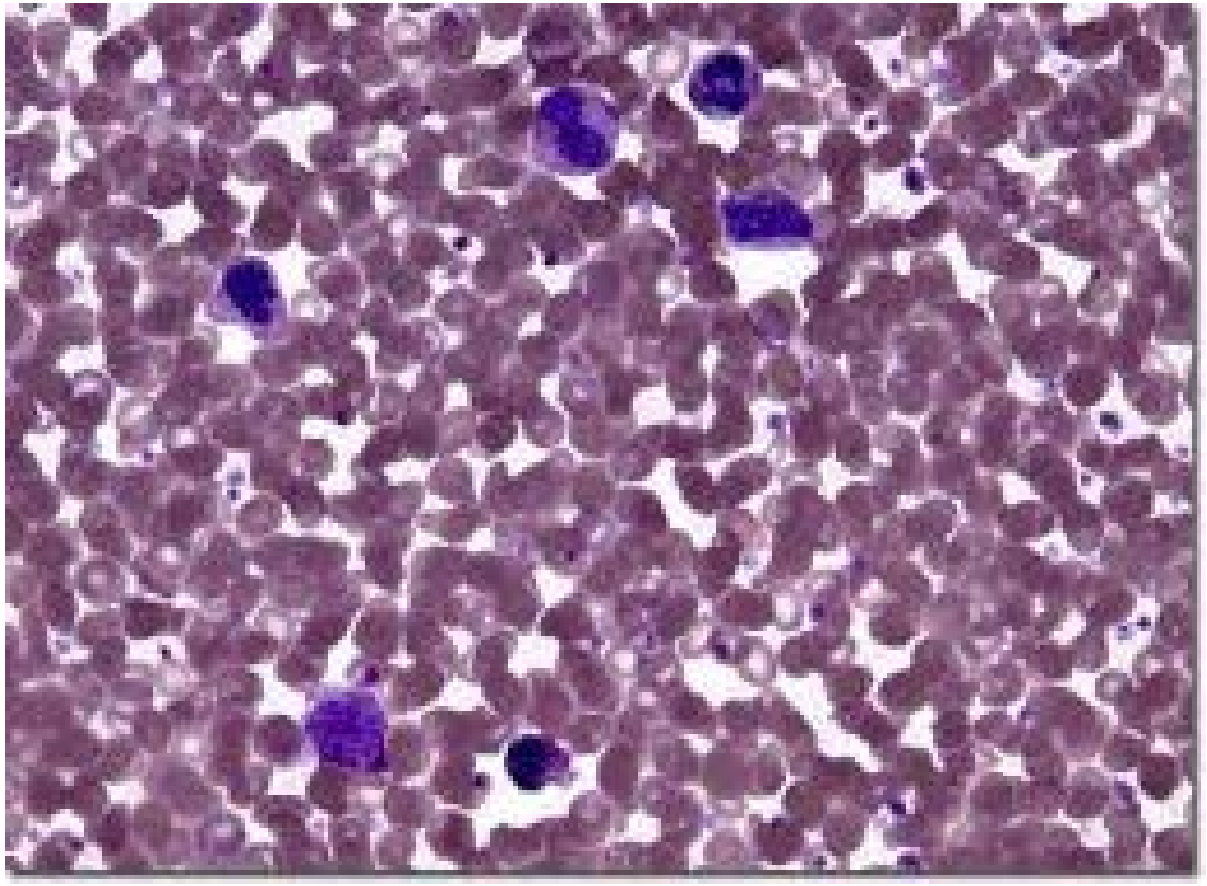
Stratification of Criteria	Clinical and Laboratory Features
Major criteria	1. HGB >16.5 g/dL (men), >16.0 g/dL (women) ***OR*** HCT >49% (men), >48% (women) ***OR*** increased red cell mass 2. BM biopsy showing hypercellularity for age with trilineage growth, including prominent erythroid, granulocytic, and megakaryocytic proliferation with pleomorphic, mature megakaryocytes 3. Presence of *JAK2 V617F* or *JAK2* exon 12 mutation
Minor criterion	• Subnormal serum EPO level

- Patients must meet either all 3 major criteria ***or*** the first 2 major criteria and the minor criterion

Arber DA, et al. *Blood*. 2016;127:2391-2405.

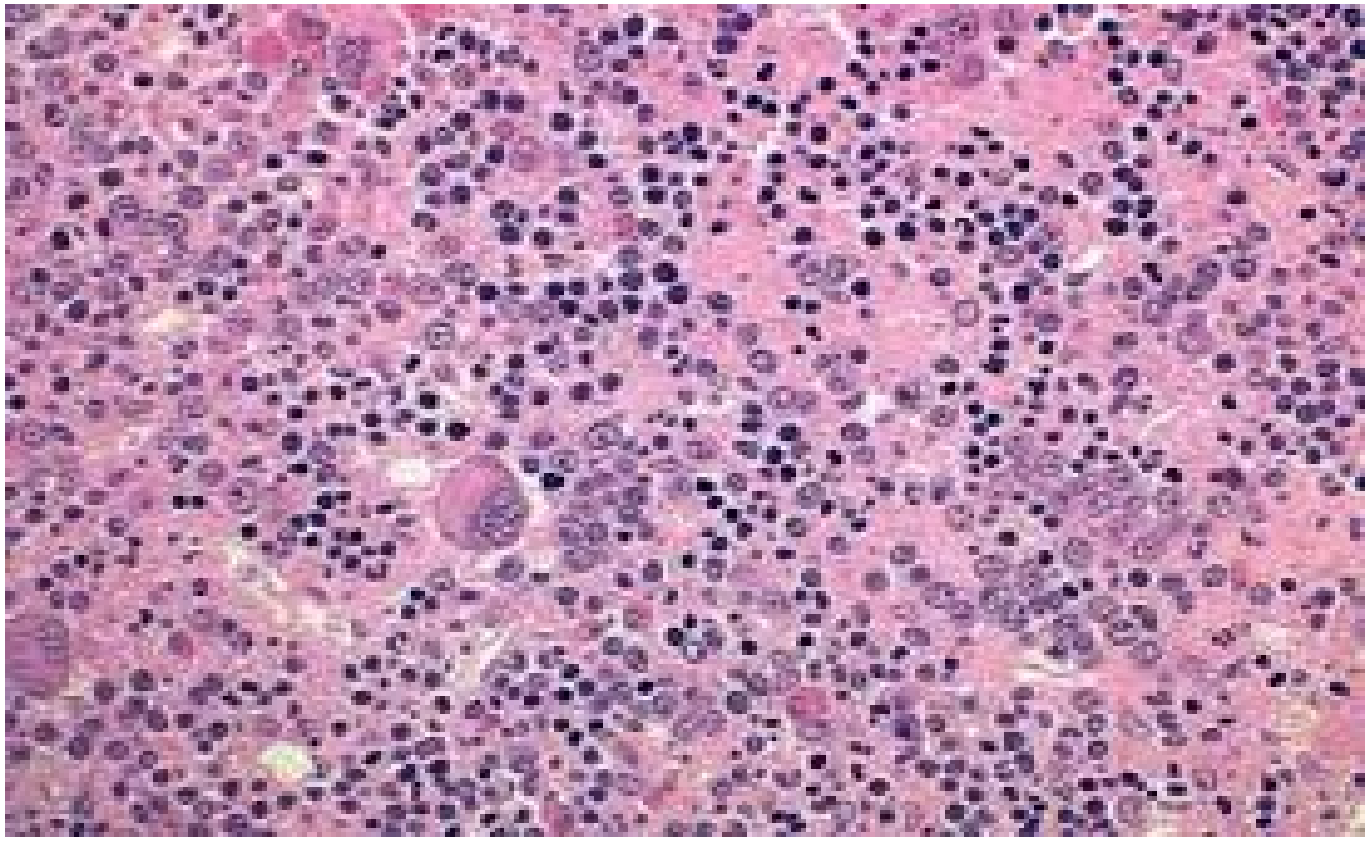
Blood picture

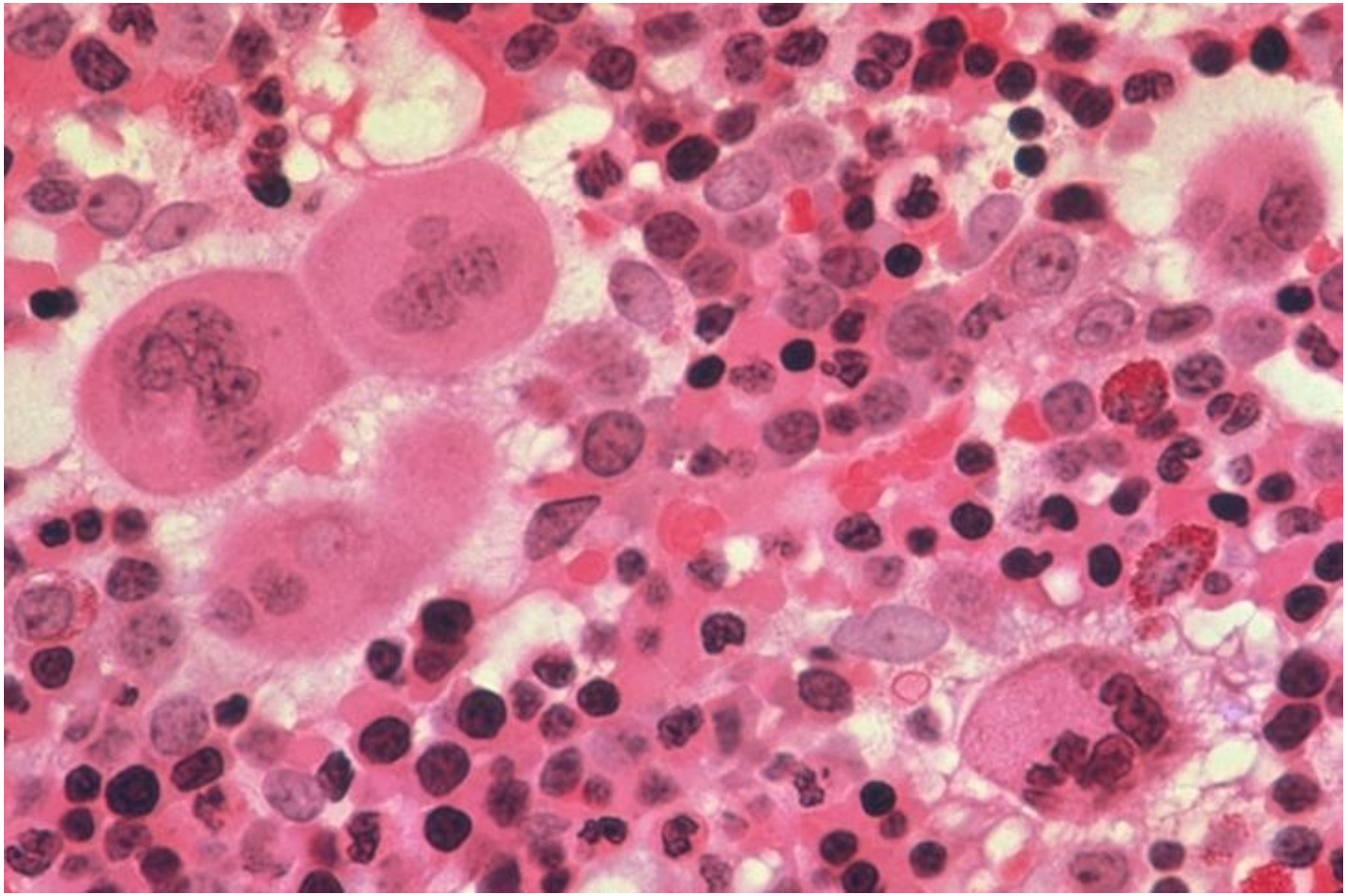
- Erythrocytosis
- Elevated HCT more than 52 %
- Increased Hemoglobin 18 to 28 g/dl
- Incresed blood volume
- High TLC
- Increase Neutrophil count
- Basophilia
- Thrombocytosis > 500,000/cmm
- Large platelets may be seen



Bone marrow

- The marrow is hypercellular
- Increase in red cell progenitors along with granulocytic precursors and megakaryocytes
- At diagnosis, a moderate to marked increase in reticulin fibers is seen in about 10% of marrows
- Mild organomegaly is common
- Extramedullary hematopoiesis is minimal
- Late in the course, extensive marrow fibrosis
- Transformation to AML occurs in about 1% of patients





Clinical Features

- Appears insidiously
- Patients are plethoric and cyanotic due to stagnation and deoxygenation of blood
- Headache, Dizziness,Gastrointestinal symptoms
- Intense pruritus and peptic ulceration due to release of histamine from basophils
- High cell turnover gives rise to hyperuricemia
- High risk of Hypertension, deep venous thrombosis, myocardial infarction, or stroke

Treatment & prognosis

- Without treatment, death from bleeding or thrombosis occurs within 6 to 18 months
- Repeated phlebotomies to keep red blood cells at near normal levels i-e HCT of 45 %
- JAK2 inhibitors represent a promising targeted therapy
- Anagralide which inhibit megakaryocytes proliferation
- Interferon Alpha

ESSENTIAL THROMBOCYTHEMIA

- Characterized by sustained thromocytosis of more than 450, 000/cmm
- Increased number of large ,mature pleomorphic megakaryocytes in the bone marrow
- Presence of activationg point mutation in JAK 2 (50%) or MPL(5-10%)
- Absence of BCR-ABL 1 fusion gene
- Absence of reactive causes of thrombocytosis such inflammatory causes and hemorrhages

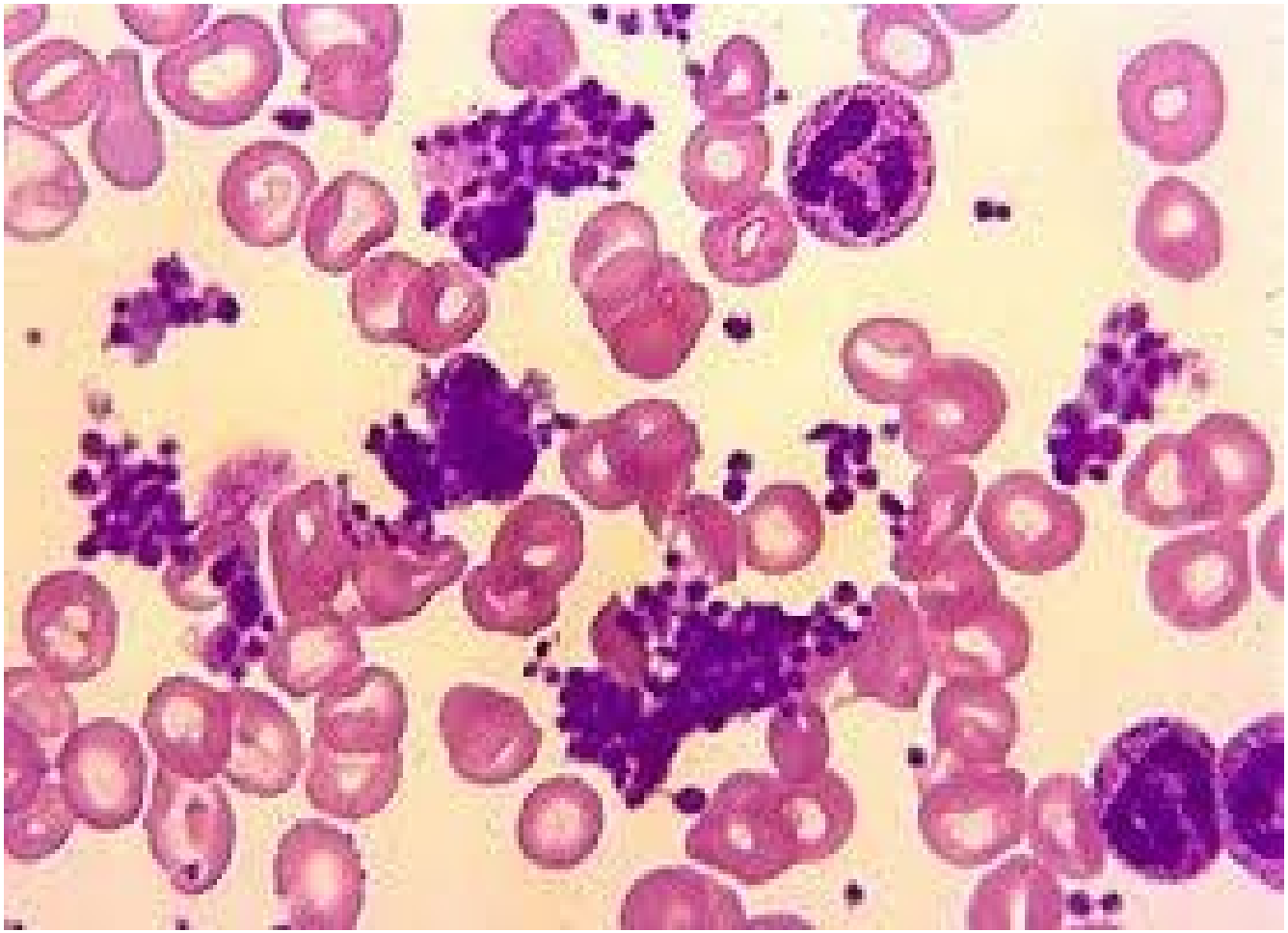
Epidemiology

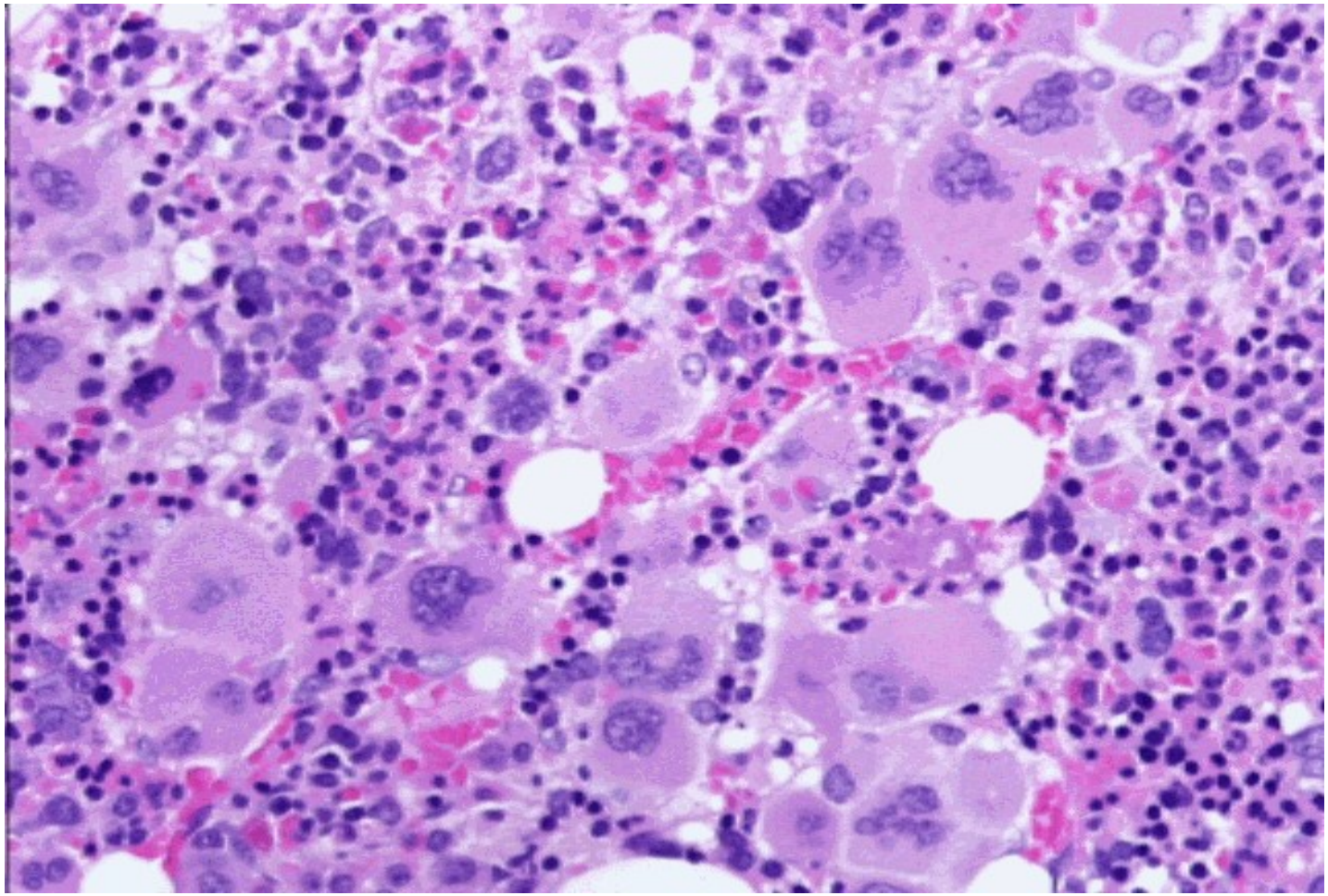
- Clonal myeloproliferative disorder
- Common at 50 to 60 yrs
- Both sexes equally affected
- Most people are asymptomatic at onset
- Continous JAK2 or MPL signaling renders the progenitors thrombopoietin-independent

Diagnosis of ET

- Platelet count of 450,000 or more sustained for at least 02 months
- Platelets show anisocytosis from tiny to giant platelets
- White blood count and hemoglobin are normal
- Bone marrow is hypercellular
- Marked proliferation of megakaryocytes in bone marrow
- Megakaryocytes are bizarre shaped ,hyperlobulated or hypolobulated
- Some degree of fibrosis seen

- No evidence of Polycythemia, Myelofibrosis and chronic myeloid leukemia
- All reactive causes of thrombocytosis should be excluded
- No evidence of iron deficiency anemia
- No evidence of myelodysplastic syndrome





Clinical features

- 50% patients asymptomatic
- Common manifestations are hemorrhages or thrombosis because of clonal platelets
- Hepatic and splenic vein thrombosis
- headache, nausea, vomiting, abdominal pain
- Visual disturbances, dizziness, numbness in the extremities
- Splenomegaly and hepatomegaly

Treatment

- Platelets lowering agents
- Hydroxycarbamide, interferon-α and anagrelide
- Low-dose aspirin is used to reduce the risk of blood clot formation
- Hydroxyurea treated patients had a lower incidence of arterial thrombosis and lower incidence of transformation to myelofibrosis
- Plateletpheresis can be used to remove platelets from the blood to reduce the risk of thrombosis.

Primary myelofibrosis

- Clonal myeloproliferative disorder
- Proliferation of granulocytes and megakaryocytes
- In fully devolved disease is associated with reactive deposition of fibrous connective tissue and extrmedullary hematopoeisis
- Marked splenomegaly
- Leukoerytroblastic blood picture
- Marked tear drops RBCs
- Hepatomegaly in some cases

Pathogensis

- Activating JAK2 mutations are present in 50% to 60%
- Activating MPL mutations in an additional 1% to 5%
- The chief pathologic feature is the extensive deposition of collagen in the marrow by non-neoplastic fibroblasts
- The fibrosis displaces hematopoietic elements, including stem cells leading to marrow failure
- Caused by the inappropriate release of fibrogenic factors from neoplastic megakaryocytes
- Two factors synthesized by megakaryocytes have been implicated: platelet-derived growth factor and TGF-β

- TGF-β promotes collagen deposition and causes angiogenesis, both of which are observed in myelofibrosis

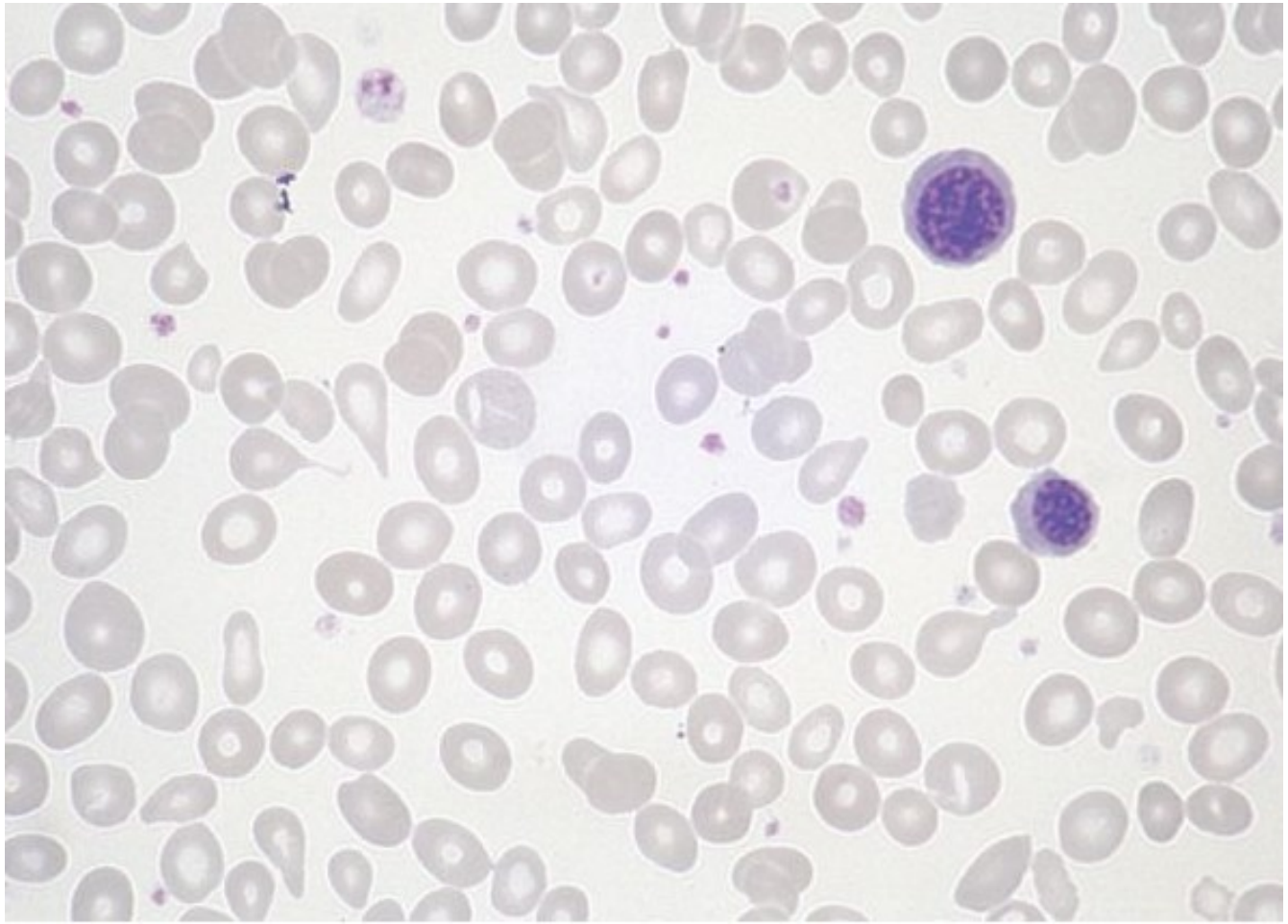
- As marrow fibrosis progresses, circulating hematopoietic stem cells deposite in secondary hematopoietic organs, such as the spleen, the liver, and the lymph nodes, leading to the appearance of extramedullary hematopoiesis

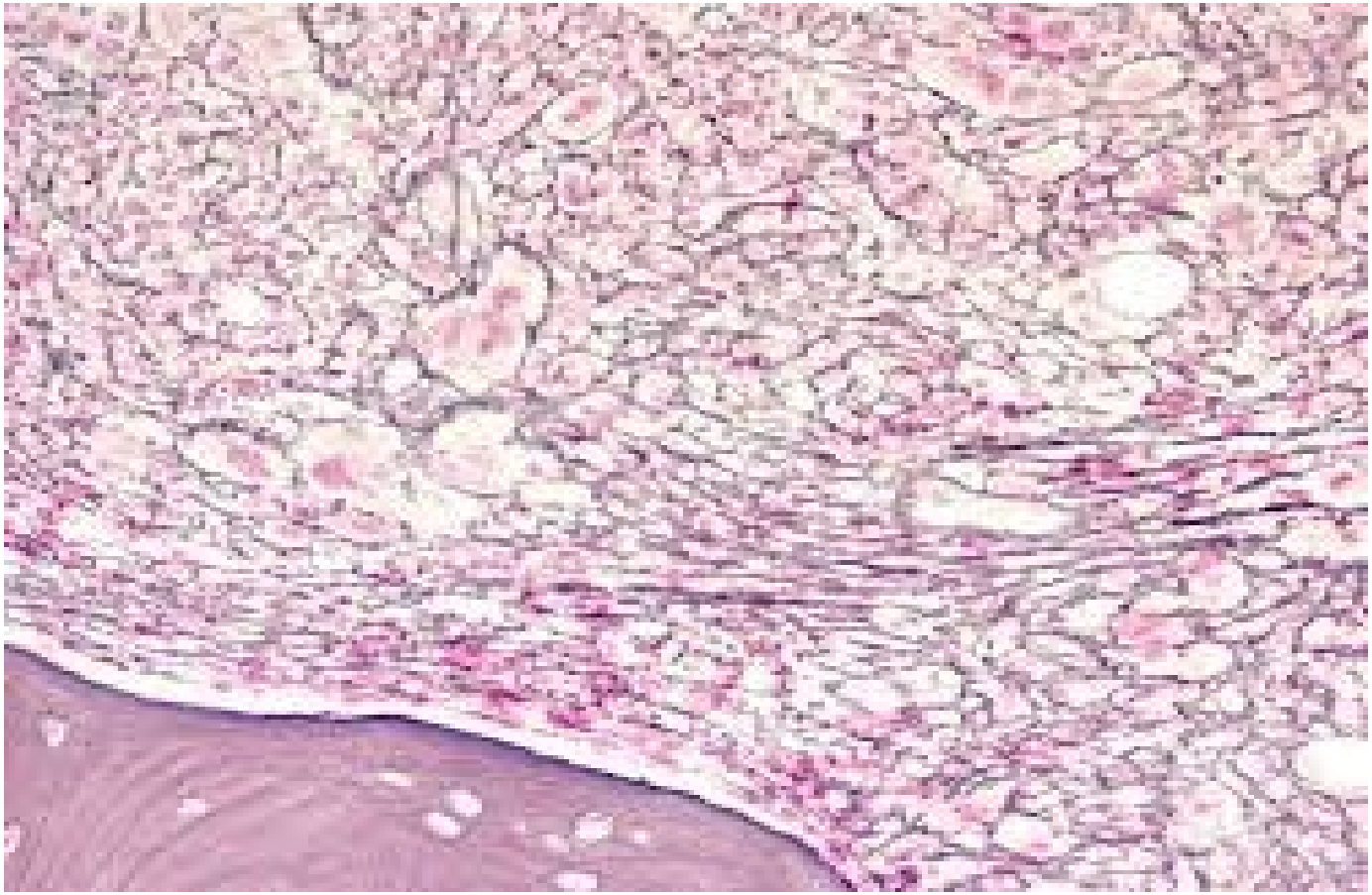
Morphology

- Early in the course, the marrow is often hypercellular
- Morphologically, the erythroid and granulocytic precursors appear normal
- Megakaryocytes are large, dysplastic, and abnormally clustered
- Fibrosis is minimal and the blood may show leukocytosis and thrombocytosis

- With progression, the marrow becomes hypocellular and diffusely fibrotic
- Clusters of atypical megakaryocytes are seen
- Very late in the course, the fibrotic marrow space may be converted into bone, a change called “osteosclerosis.”
- There is extensive extramedullary hematopoiesis
- Massive splenomegaly
- Hematopoiesis can also appear within lymph nodes

- Marrow fibrosis leads to the premature release of nucleated erythroid and early granulocyte progenitors
- Teardrop-shaped red cells, probably damaged during the birthing process in the fibrotic marrow
- Leukoerythroblastosis and teardrop red cells are seen in many infiltrative disorders of the marrow, including granulomatous diseases and metastatic tumors





Clinical features

- Primary myelofibrosis occur at 60 years of age
- Comes to attention because of progressive anemia and splenomegaly
- Nonspecific symptoms such as fatigue, weight loss, and night sweats result from an increase in metabolism associated with the expanding mass of hematopoietic cells
- Cytopenias especially thrombocytopenia as disease progress

Treatment

- Primary myelofibrosis is a much more difficult disease to treat
- Median survival is in the range of 3 to 5 years
- Common causes of mortality are intercurrent infections, thrombotic episodes, bleeding related to platelet abnormalities,
- More severe is transformation to AML, which occurs in 5% to 20% of cases
- Bone marrow transplantation only hope for younger patients
- Kinase inhibitors are in trails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