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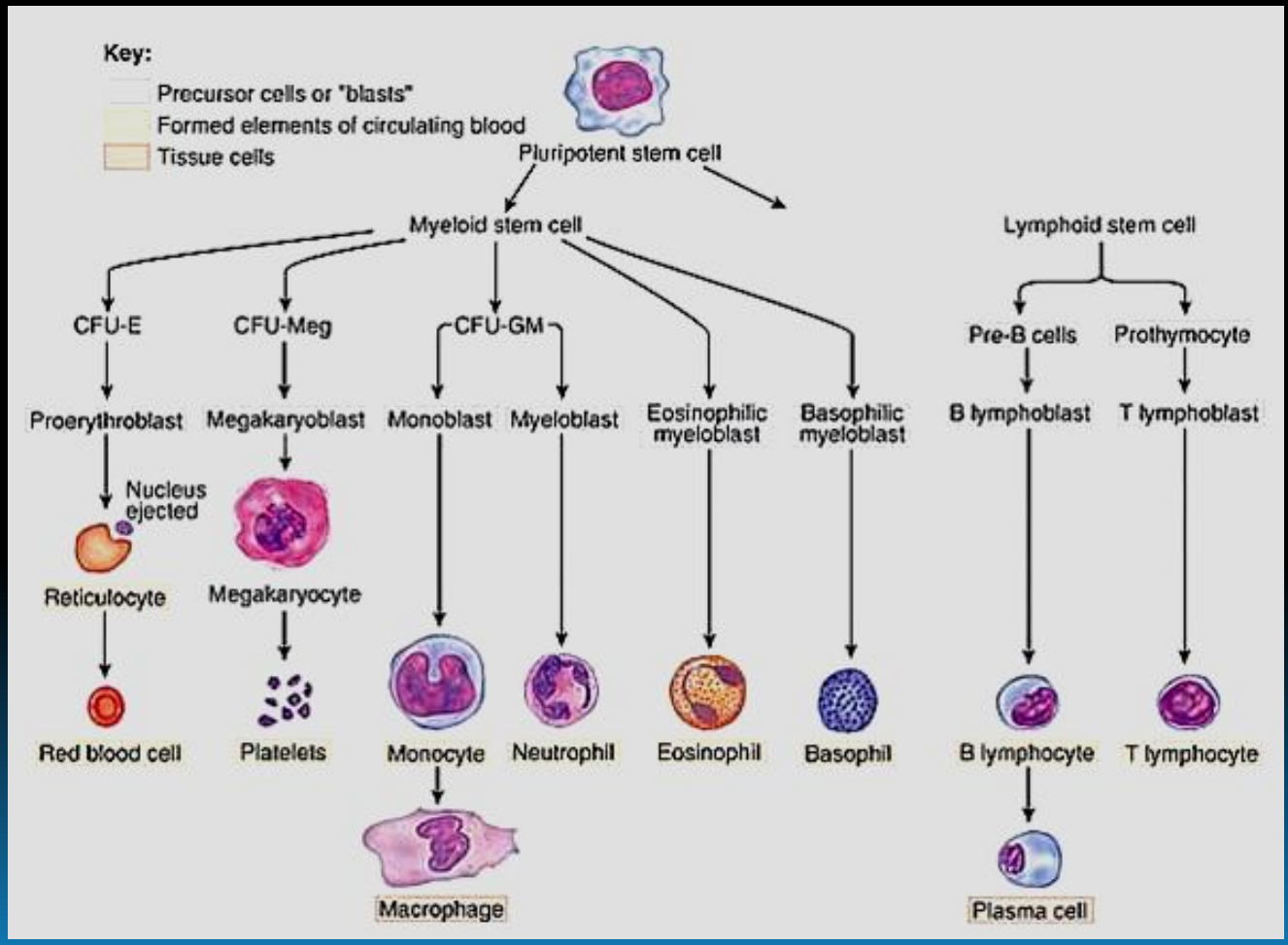
MYELOPROLIFERATIVE DISORDERS

Introduction

- Hematopoietic stem cell disorder
  - Clonal
  - Characterized by proliferation
    - Granulocytic
    - Erythroid
    - Megakaryocytic
- Interrelationship between
  - Polycythaemia
  - Essential thrombocythaemia
  - myelofibrosis

Introduction / haemopoiesis



Introduction

- Normal maturation (effective)
  - Increased number of
    - Red cells
    - Granulocytes
    - Platelets

  (Note: myeloproliferation in myelodysplastic syndrome is ineffective)
  - Frequent overlap of the clinical, laboratory & morphologic findings
    - Leucocytosis, thrombocytosis, increased megakaeryocytes, fibrosis & organomegaly blurs the boundaries
- Hepatosplenomegaly
  - Sequestration of excess blood
  - Extramedullary haematopoiesis
  - Leukaemic infiltration

Rationale for classification

- Classification is based on the lineage of the predominant proliferation
- Level of marrow fibrosis
- Clinical and laboratory data (FBP, BM, cytogenetic & molecular genetic)

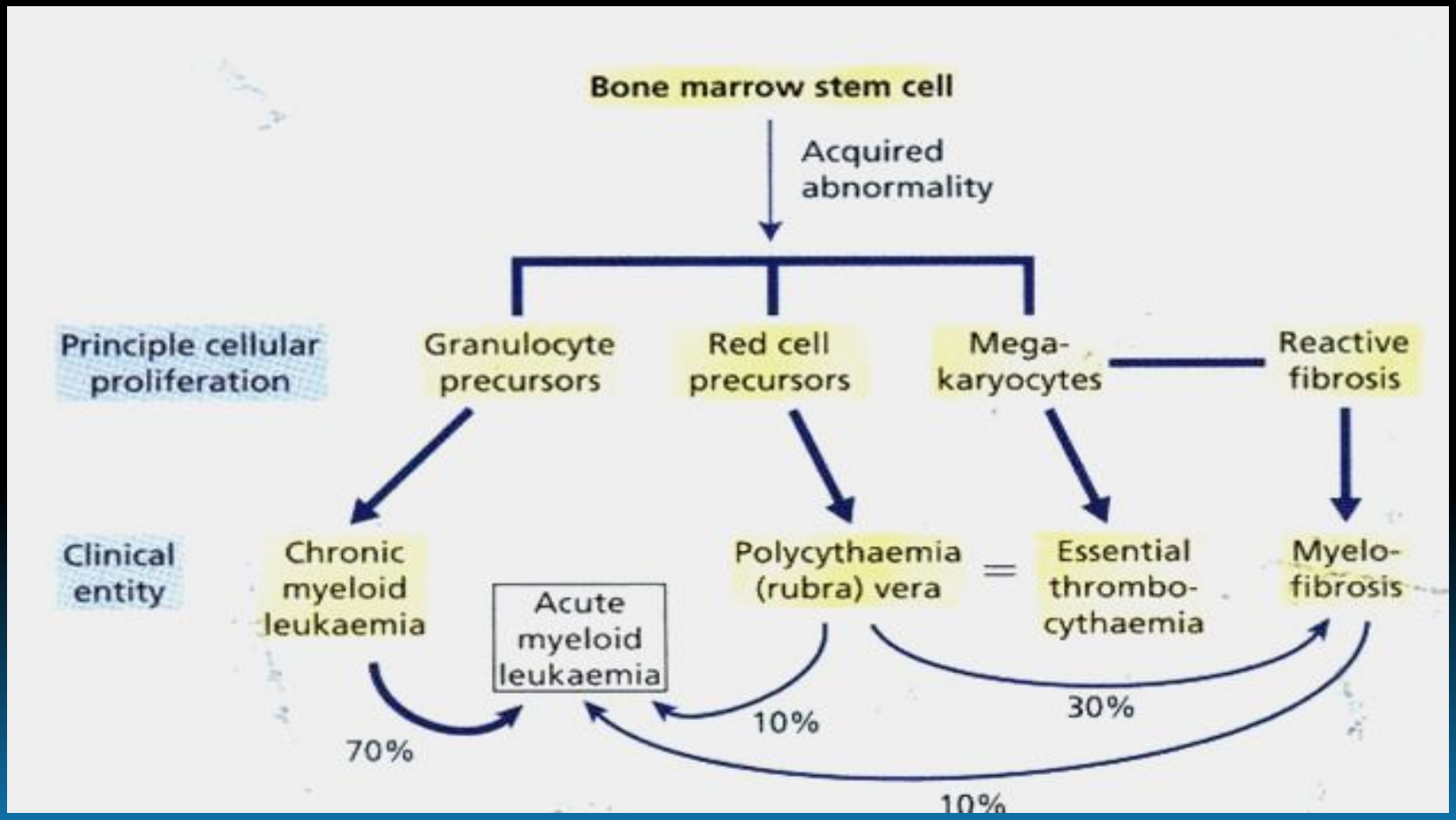
Differential diagnosis

Features distinguishing MPD from MDS, MDS/MPD & AML

Disease	BM cellularity	% marrow blasts	Maturation	Morphology	Haemato-poiesis	Blood counts	Large organs
MPD	Increased	Normal or < 10%	Present	Normal	Effective	One or more myeloid increased	Common
MDS	Usually increased	Normal or < 20%	Present	Abnormal	In-effective	Low one or more cytopenia	Un-common
MDS/ MPD	Usually increased	Normal or <20%	Present	Abnormal	Effective or in-effective	Variable	Common
AML	Usually increased	Increased >20%	Minimal	Dysplasia can be present	In-effective	Variable	Un-common

Clonal evolution

Clonal evolution & stepwise progression to fibrosis, marrow failure or acute blast phase



Incidence and epidemiology

- Disease of adult
- Peak incidence in 7th decade
- 6-9/100,000

Pathogenesis

- Dysregulated proliferation
- No specific genetic abnormality
  - CML (Ph chromosome t(9;22) BCR/ABL)
    - Growth-factor independent proliferation
  - PV, hypersensitiviy to IGF-1

- Bone marrow fibrosis in all MPD
  - Fibrosis is secondary phenomena
    - Fibroblasts are not from malignant clone
    - TGF-β & Platelet like growth factor

Molecular basis of Philadelphia-negative myeloproliferative neoplasms

- Polycythemia Vera:~95% *JAK2(V617F)*
- Essential thrombocythemia: 50-60% *JAK2(V617F)*
- Primary myelofibrosis 50-60% *JAK2(V617F)*

Prognosis

- Depends on the proper diagnosis and early treatment
  - Role of
    - IFN
    - BMT
    - Tyrosine kinase inhibitors

Polycythaemia vera
(Polycythaemia rubra vera)

- Definition of polycythemia
  - Raised packed cell volume (PCV / HCT)
  - Male > 0.51 (50%)
  - Female > 0.48 (48%)
- Classification
  - Absolute
    - Primary proliferative polycythaemia (polycythaemia vera)
    - Secondary polycythaemia
    - Idiopathic erythrocytosis
  - Apparent
    - Plasma volume or red cell mass changes

Polycythaemia vera
(Polycythaemia rubra vera)

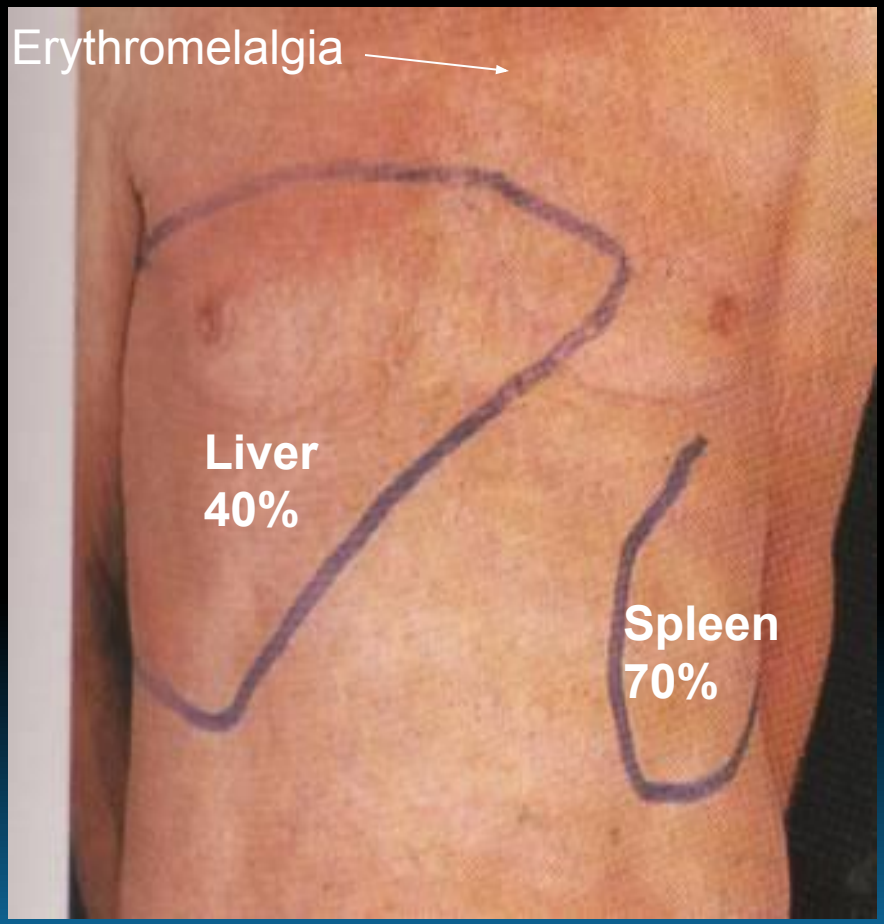
- Polycythaemia vera is a clonal stem cell disorder characterised by increased red cell production
  - Abnormal clones behave autonomous
  - Same abnormal stem cell give rise to granulocytes and platelets
- Disease phase
  - Proliferative phase
  - "Spent" post-polycythaemic phase
  - Rarely transformed into acute leukemia

Polycythaemia vera
(Polycythaemia rubra vera)

- Clinical features
  - Age
    - 55-60 years
    - May occur in young adults and rare in childhood
  - Majority patients present due to vascular complications
    - Thrombosis (including portal and splenic vein)
    - DVT
    - Hypertension
    - Headache, poor vision and dizziness
    - Skin complications (pruritus, erythromelalgia)
    - Haemorrhage (GIT) due to platelet defect

Polycythaemia vera
(Polycythaemia rubra vera)

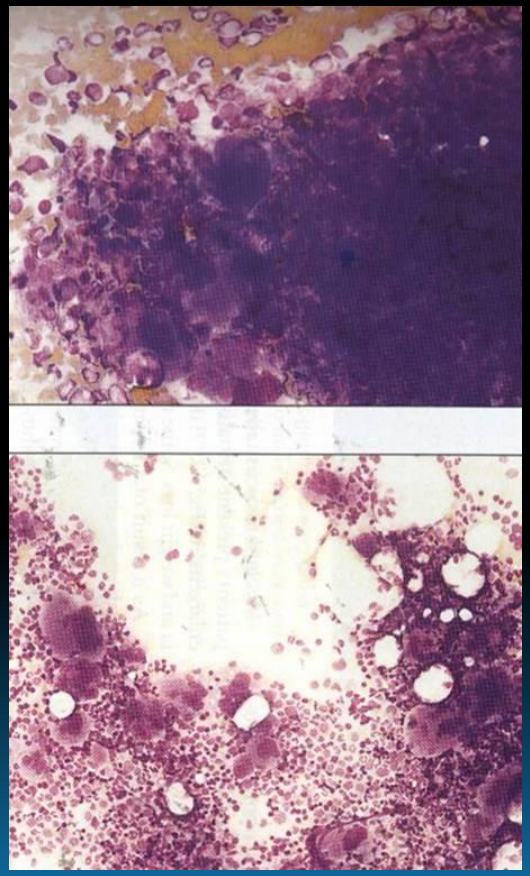
- Hepato-splenomegaly
- Erythromelalgia
  - Increased skin temp
  - Burning sensation
  - Redness



Polycythaemia vera
(Polycythaemia rubra vera)

- Laboratory features and morphology
  - Hb, PCV (HCT), and Red cell mass increased
  - Increased neutrophils and platelets
  - Jak-2 positive >90%, exon 12
  - Plasma urate high
  - Circulation erythroid precursors
  - Hypercellular bone marrow
  - Low serum erythropoietin

Bone marrow in PV



Polycythaemia vera
(Polycythaemia rubra vera)

- Treatment
  - To decrease PVC (HCT)
    - Venesection
    - Chemotherapy
  - Treatment of complications

Secondary polycythaemia

- Polycythaemia due to known causes
- Compensatory increased in EPO
  - High altitude
  - Pulmonary diseases
  - Heart disease - cyanotic heart disease
  - Abnormal hemoglobin- High affinity Hb
  - Heavy cigarette smoker
- Inappropriate EPO production
  - Renal disease-carcinoma, hydronephrosis, cysts
  - Tumors-fibromyoma and liver carcinoma

Secondary polycythaemia

- Arterial blood gas
- Hb electrophoresis
- Oxygen dissociation curve
- EPO level
- Ultrasound abdomen
- Chest X ray
- Total red cell volume(51Cr)
- Total plasma volume(125 I-albumin)

Relative polycythaemia

- Apparent polycythaemia or pseudopolycythaemia due to plasma volume contraction

- Causes
  - Stress
  - Cigarette smoker or alcohol intake
  - Dehydration
  - Plasma loss- burn injury

Myelofibrosis

Chronic idiopathic myelofibrosis

- Progressive fibrosis of the marrow & increase connective tissue element

- Agnogenic myeloid metaplasia
  - Extramedullary erythropoiesis
    - Spleen
    - Liver

- Abnormal megakaryocytes
  - Platelet derived growth factor (PDGF)
  - Platelet factor 4 (PF-4)

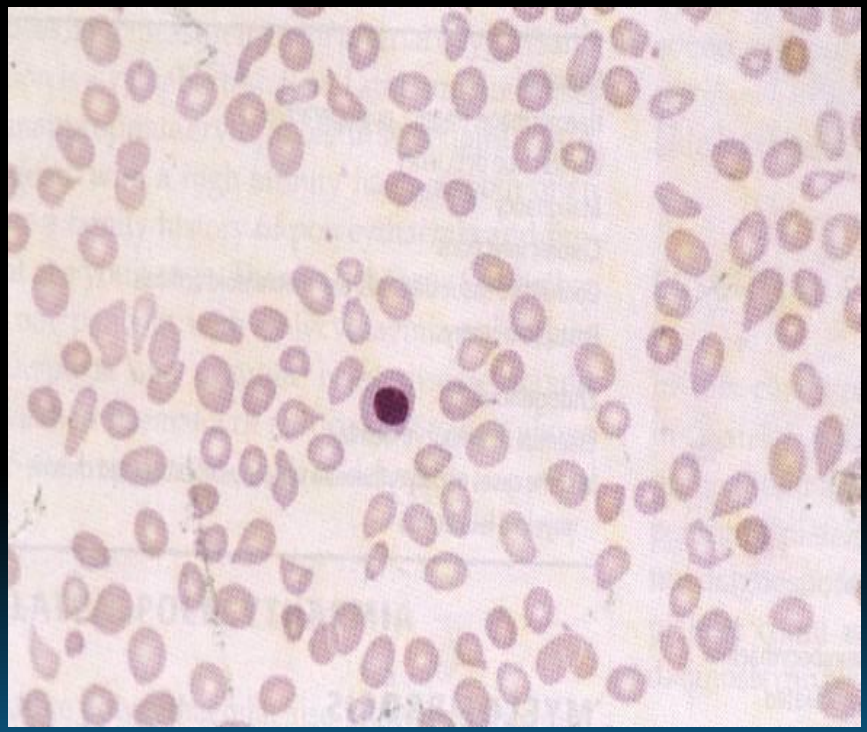
Myelofibrosis
Chronic idiopathic myelofibrosis

- Insidious onset in older people
- Splenomegaly- massive
- Hypermetabolic symptoms
  - Loss of weight, fever and night sweats Myelofibrosis
    Chronic idiopathic myelofibrosisc
- Bleeding problems
- Bone pain
- Gout
- Can transform to acute leukaemia in 10-20% of cases

Myelofibrosis

Chronic idiopathic myelofibrosis

- Anaemia (bad prognosis)
- High WBC at presentation
- Later leucopenia and thrombocytopenia
- Leucoerythroblastic blood film
- Tear drops red cells
- Bone marrow aspiration- Failed due to fibrosis
- Trephine biopsy- fibrotic hypercellular marrow
- Increase in LAP score



Essential thrombocythaemia

Primary thrombocytosis / idiopathic thrombocytosis

- Clonal myeloproliferative disease of megakaryocytic lineage
  - Sustained thrombocytosis
  - Increase megakaeryocytes
  - Thrombotic or/and haemorrhage episodes
- Positive criteria
  - Platelet count >600 x 10^9/L
  - Bone marrow biopsy; large and increased megakaryocytes.
  - CALR, MPL

Essential thrombocythaemia

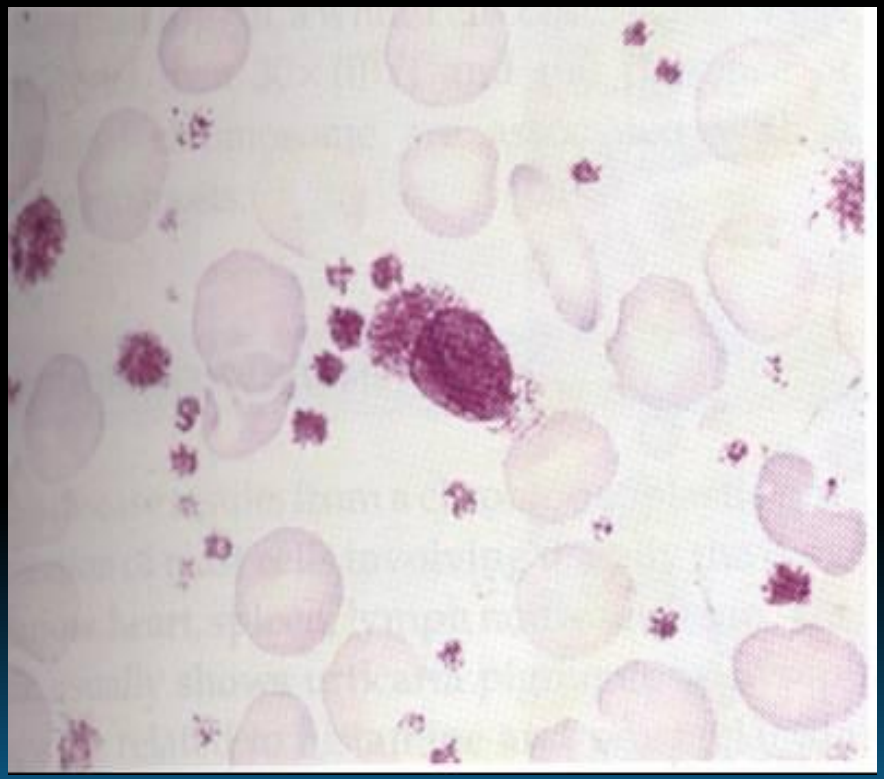
Primary thrombocytosis / idiopathic thrombocytosis

- Criteria of exclusion
  - No evidence of Polycythaemia vera
  - No evidence of CML
  - No evidence of myelofibrosis (CIMF)
  - No evidence of myelodysplastic syndrome
  - No evidence of reactive thrombocytosis
    - Bleeding
    - Trauma
    - Post operation
    - Chronic iron def
    - Malignancy
    - Chronic infection
    - Connective tissue disorders
    - Post splenectomy

Essential thrombocythaemia

Primary thrombocytosis / idiopathic thrombocytosis

- Clinical features
  - Haemorrhage
  - Microvascular occlusion
    - TIA, gangrene
  - Splenic or hepatic vein thrombosis
  - Hepatosplenomegaly



Essential thrombocythaemia

Primary thrombocytosis / idiopathic thrombocytosis

- Treatment
  - Anticoagulant
  - Chemotherapy
  - Role of aspirin
- Disease course and prognosis
  - 25 % develops myelofibrosis
  - Acute leukemia transformation
  - Death due to cardiovascular complication

Thanks