

Myeloproliferative Neoplasm 2

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MPN-Classification

Philadelphia (+)

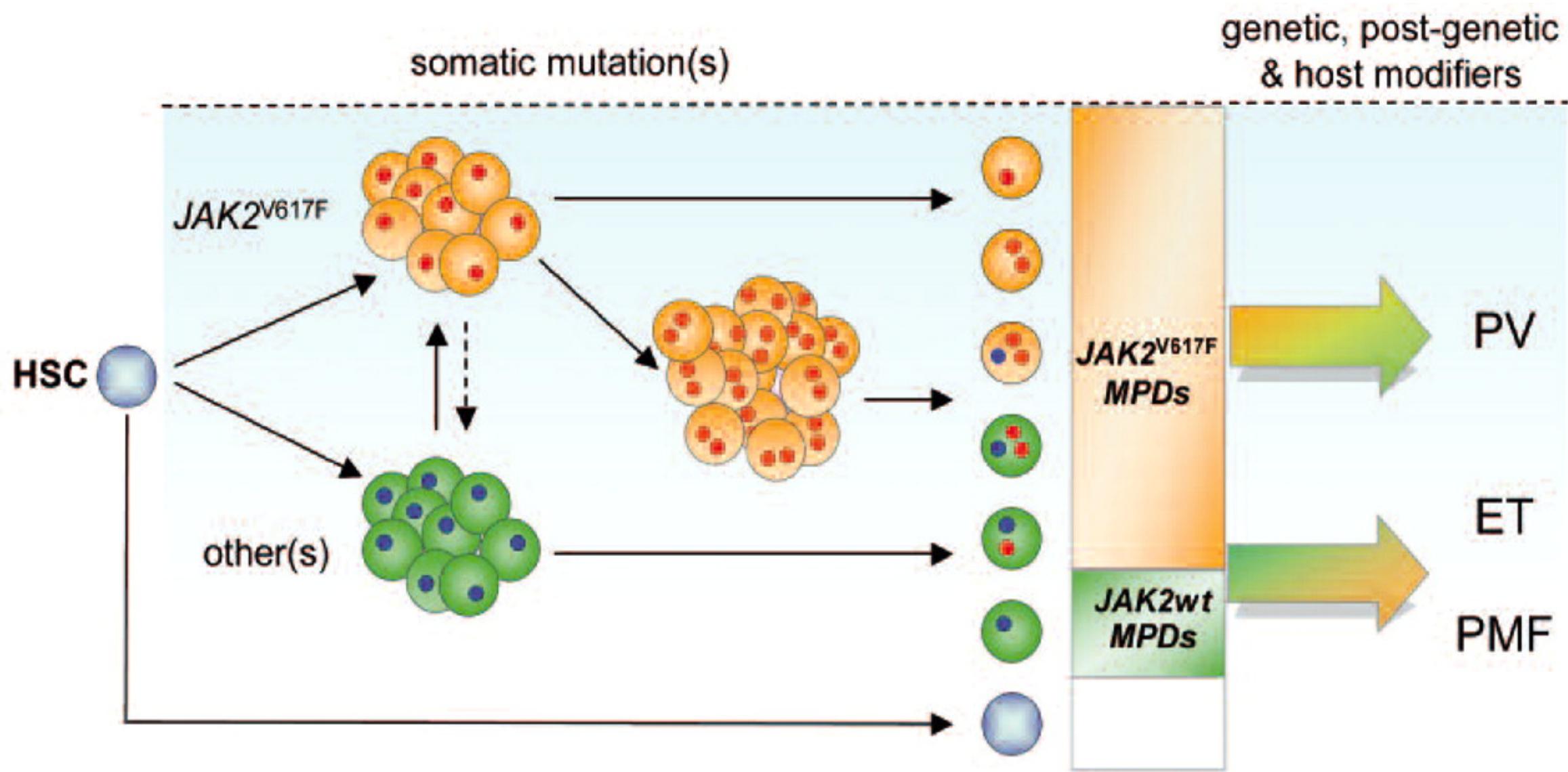
- Granulopoiesis-CML

Philadelphia(-)

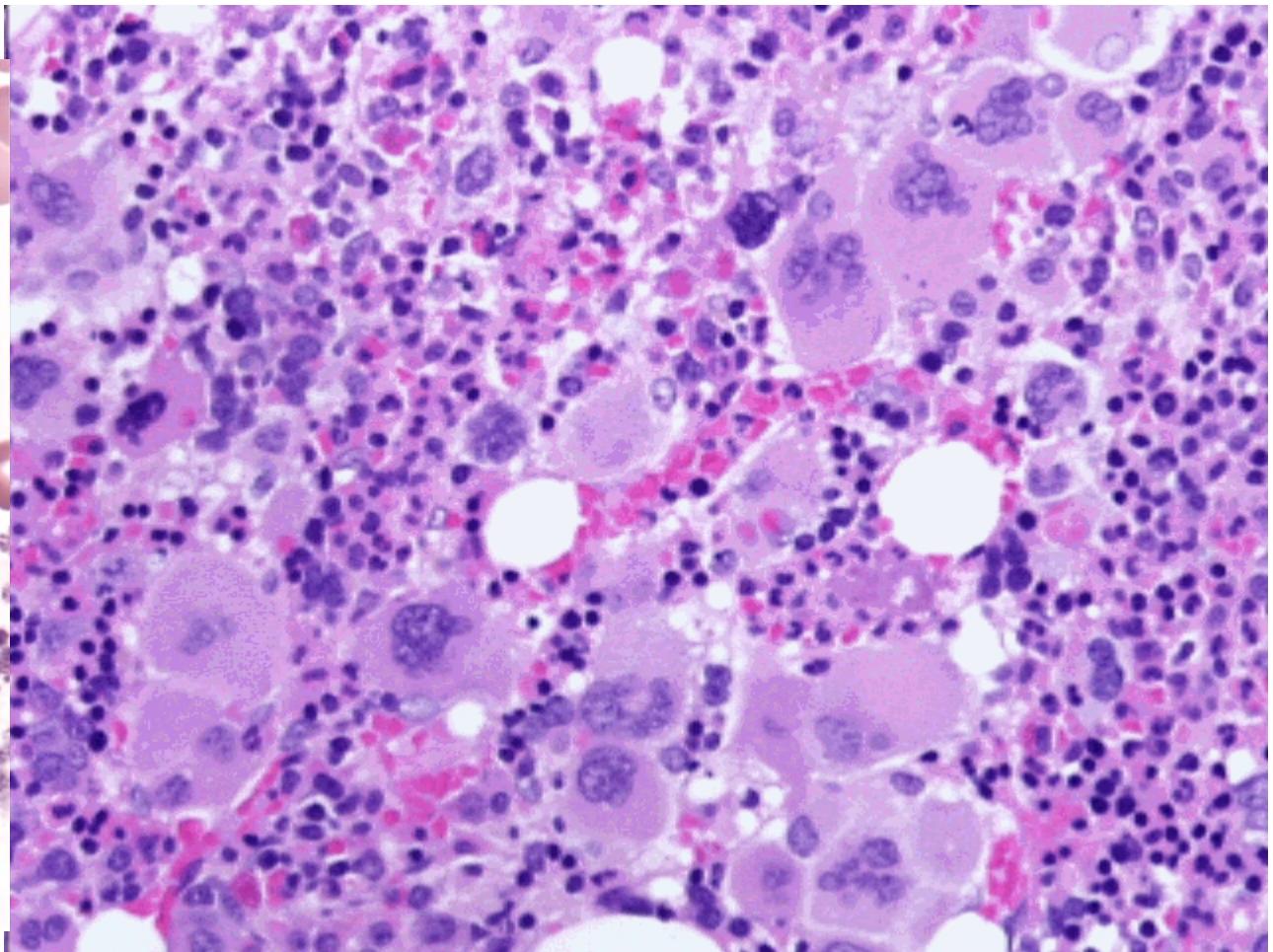
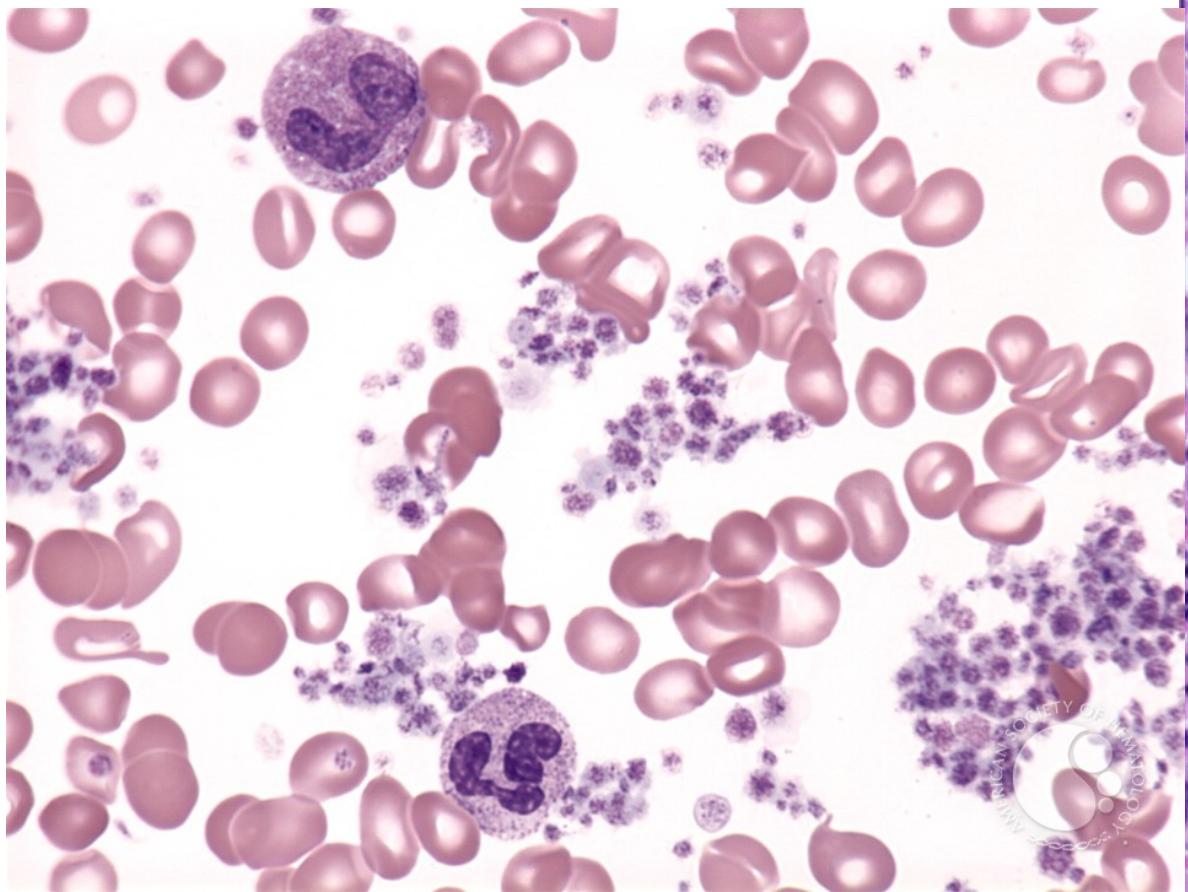
- Erythropoiesis- PV(Polycythaemia Vera)
- Thrombopoiesis- ET(**Essential Thrombocythaemia**)
- Primary Myelofibrosis - MF

MPD 2

- At the end of this lecture student should be able to:
- Define ET and MF
- Describe the clinical features ET and MF
- Describe the complications of ET and MF
- Describe the investigations done in suspected cases of ET and MF
- Describe the principles of management of ET and MF



Essential Thrombocythemia



ESSENTIAL THROMBOCYTHAEMIA

- MPN of Megakaryocytes
- Sustained thrombocytosis
- Mutations-
 - JAK 2 mutation –positive in 50%
 - MPL gene mutation

New- Calreticulin mutation

Diagnosis of exclusion

Thrombocytosis

Primary

ET

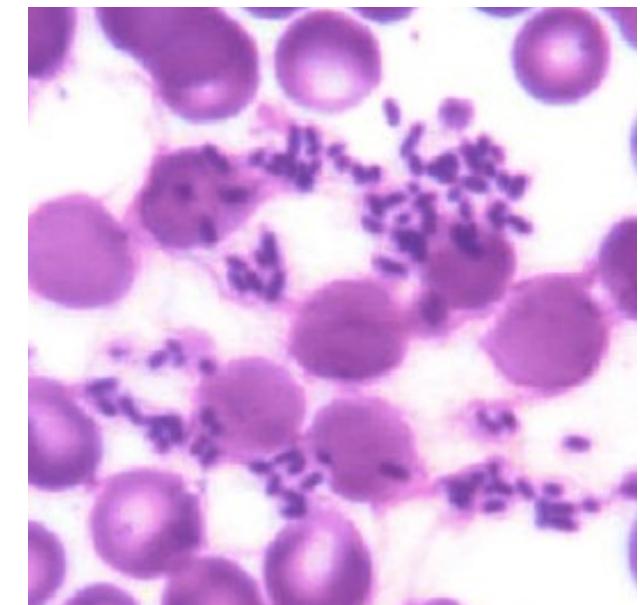
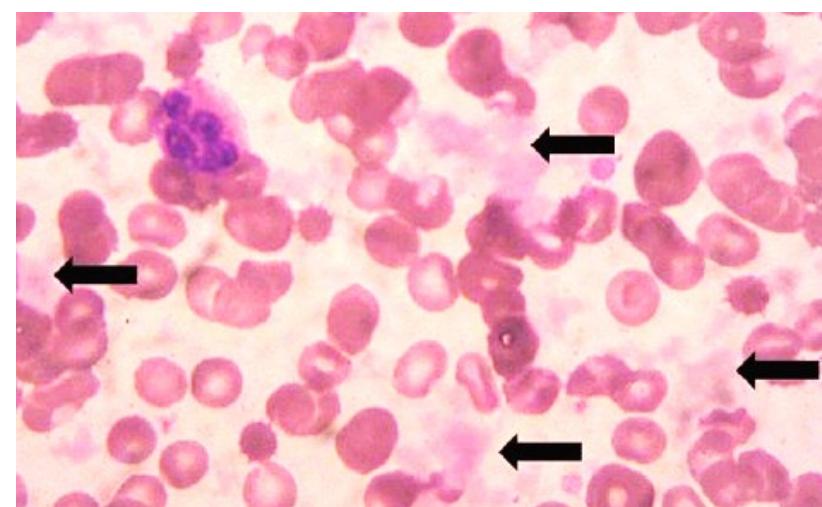
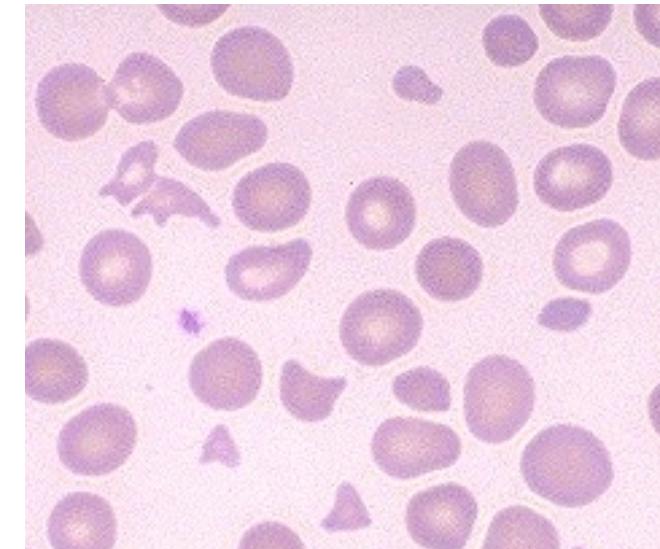
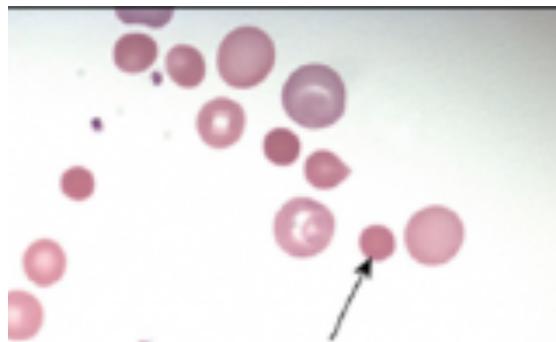
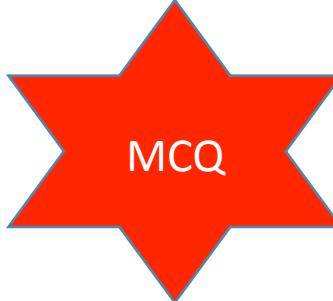
Secondary/reactive

Spurious



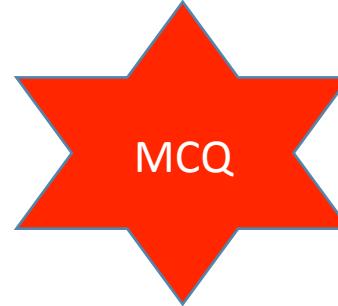
Spurious

- Microspherocytes
- Cryoglobulins
- Bacteria
- Fragmented neoplastic cells
- Schistocytes
- Papenheimer bodies



Reactive

- Bleeding
- Haemolysis
- Infection/inflammation
- Post op
- Hyposplenism
- Iron def
- Malignancy
- Drugs
- Cytokine administration
- Rebound following chemotherapy



Clinical features

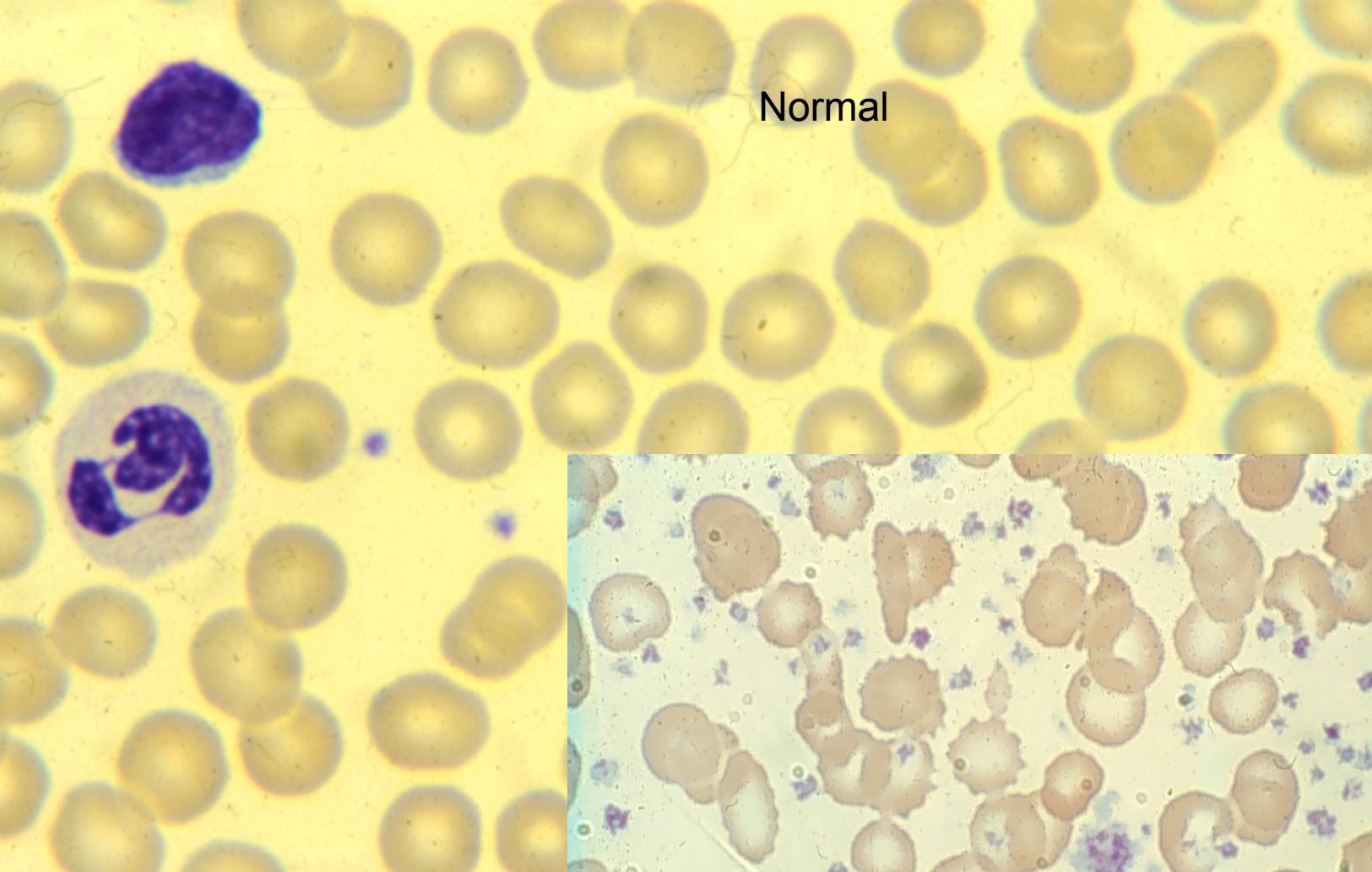
- Age - 50-60 yrs, 2nd peak at 30 yrs in females
- >1/2 – Asymptomatic
- Thrombosis

Erythromelalgia , arterial and venous

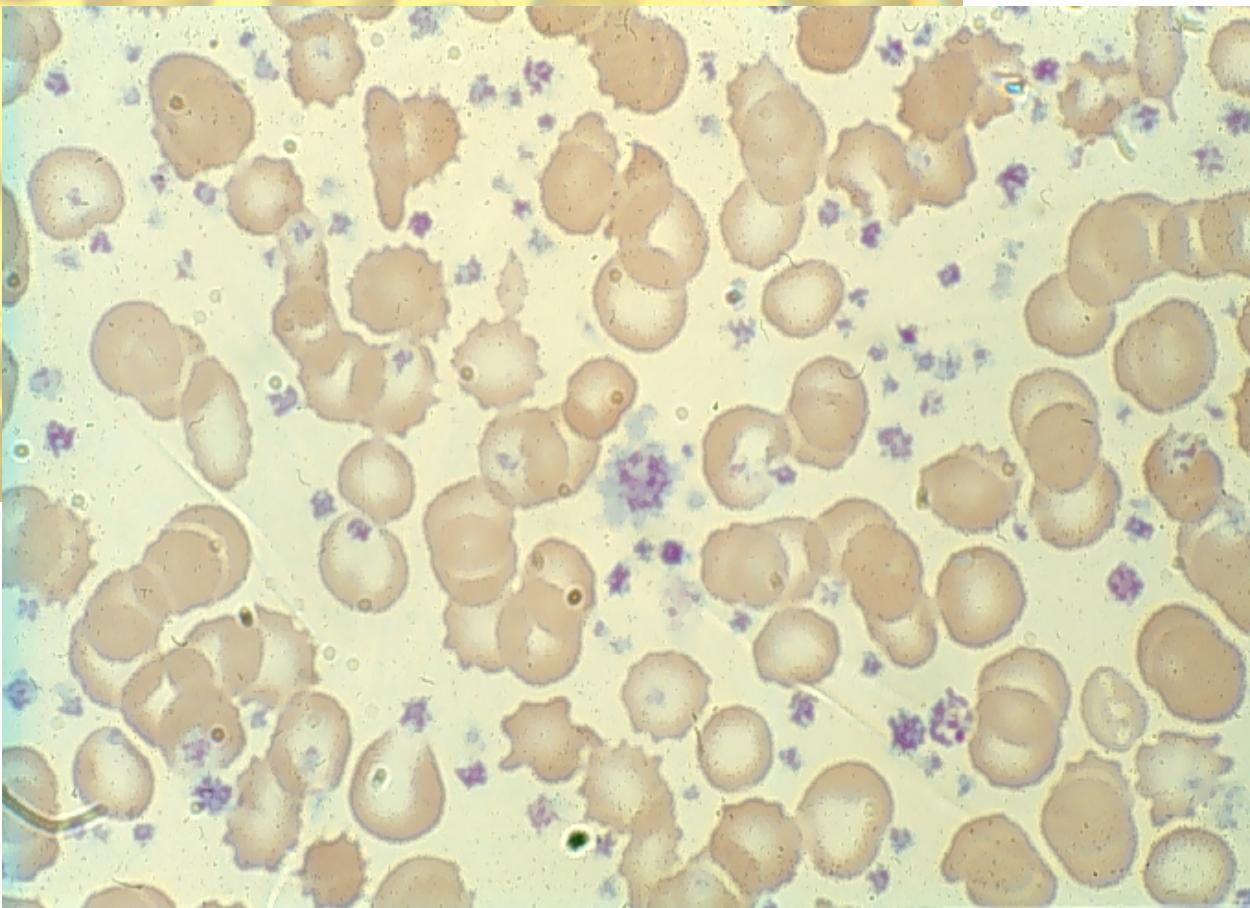
- Haemorrhage
- Splenomegaly-50%
- Hepatomegaly-15-20%
- Splenic atrophy

Laboratory features

- FBC-Thrombocytosis
- BP- Platelet anisocytosis, small- large bizarre forms
megakaryocyte fragments
sometimes HC/MC
- BM-Marked increase in megakaryocytes
large, giant forms; hyperlobulated ‘stag horn’ nuclei
Reticulin –not increased
- JAK 2 mutation positive in 50%
- Calreticulin mutation-1/3rd
- Platelet function tests-Abnormal

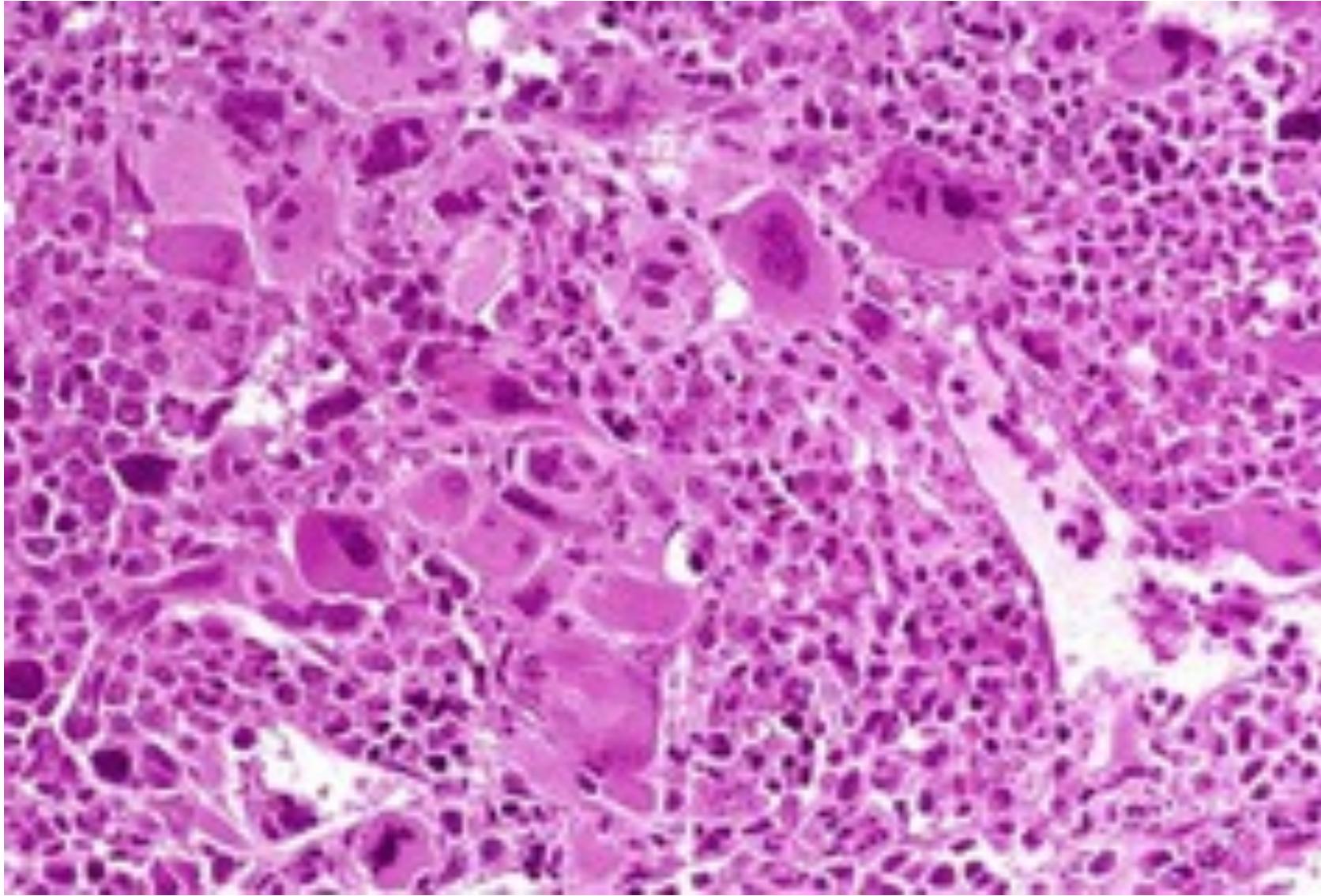


Normal



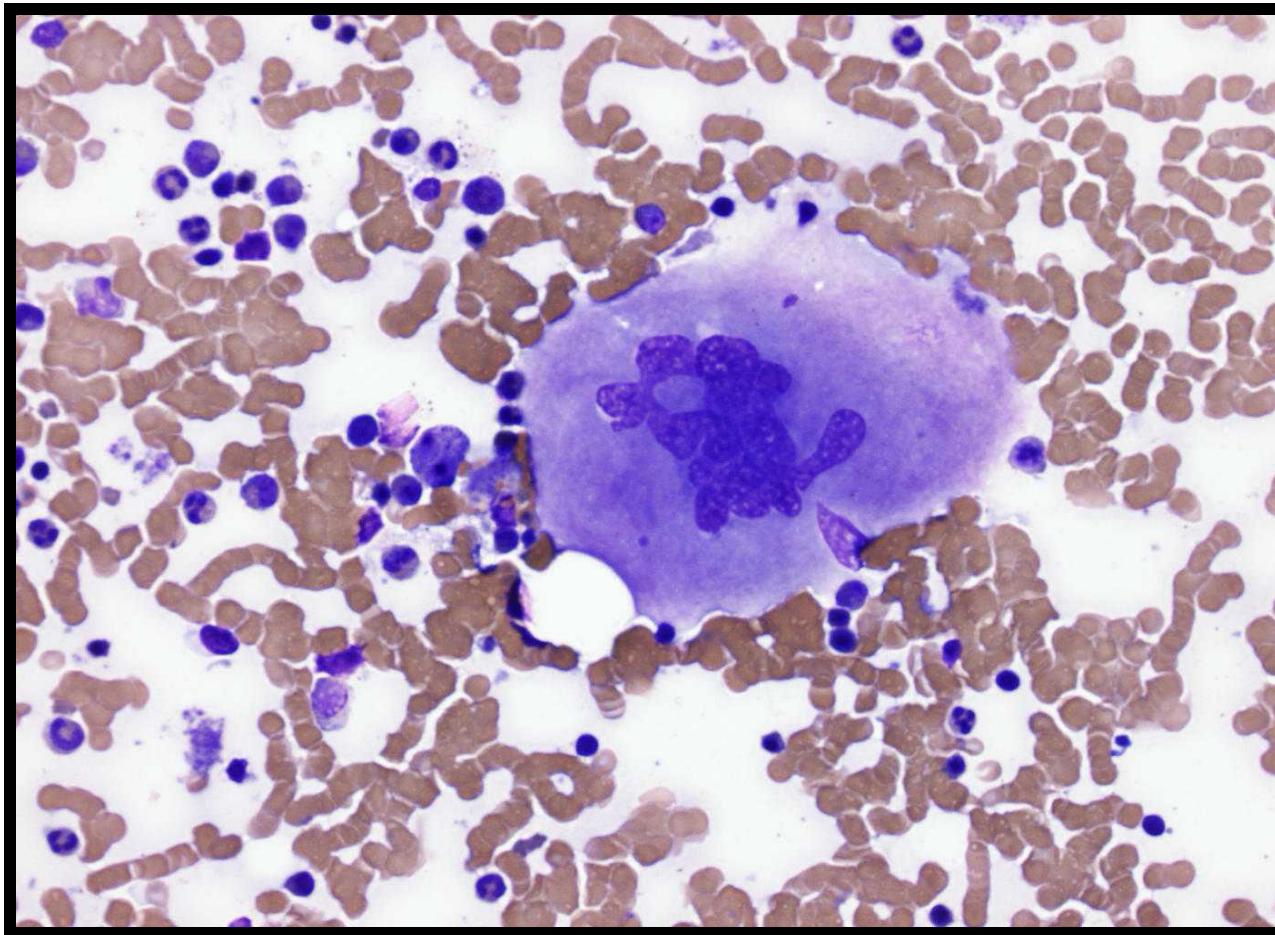
Essential Thrombocythemia

BM-ET

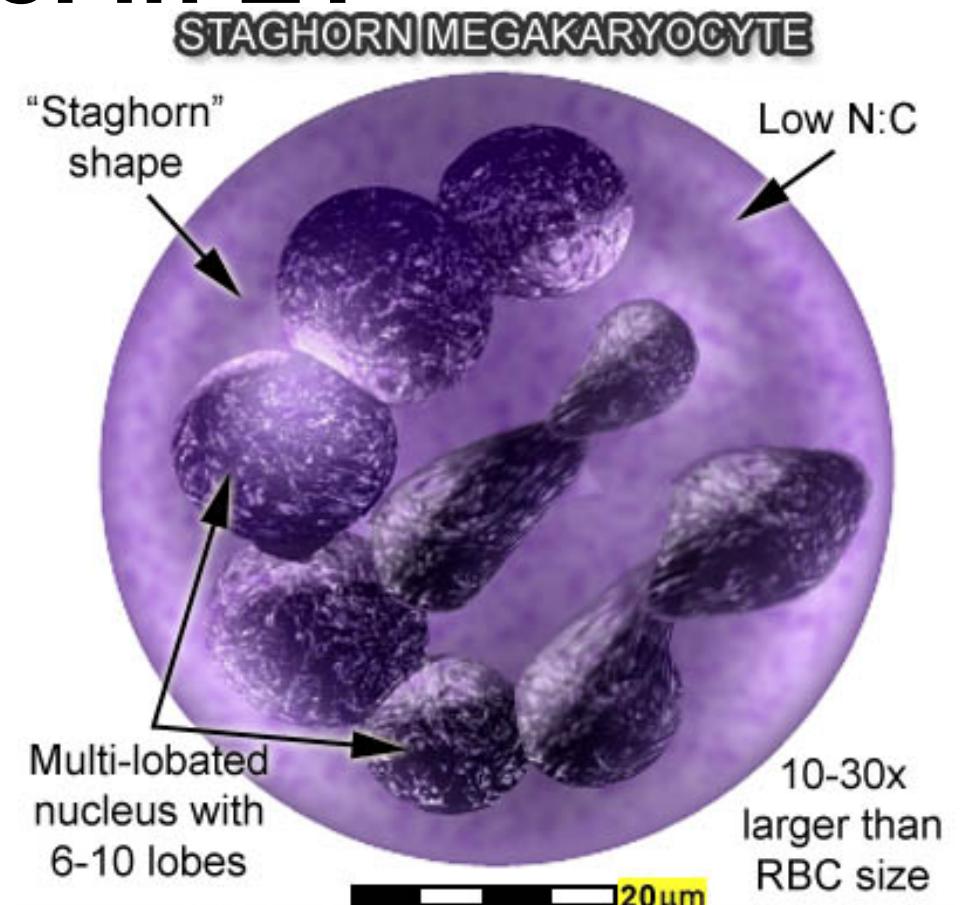
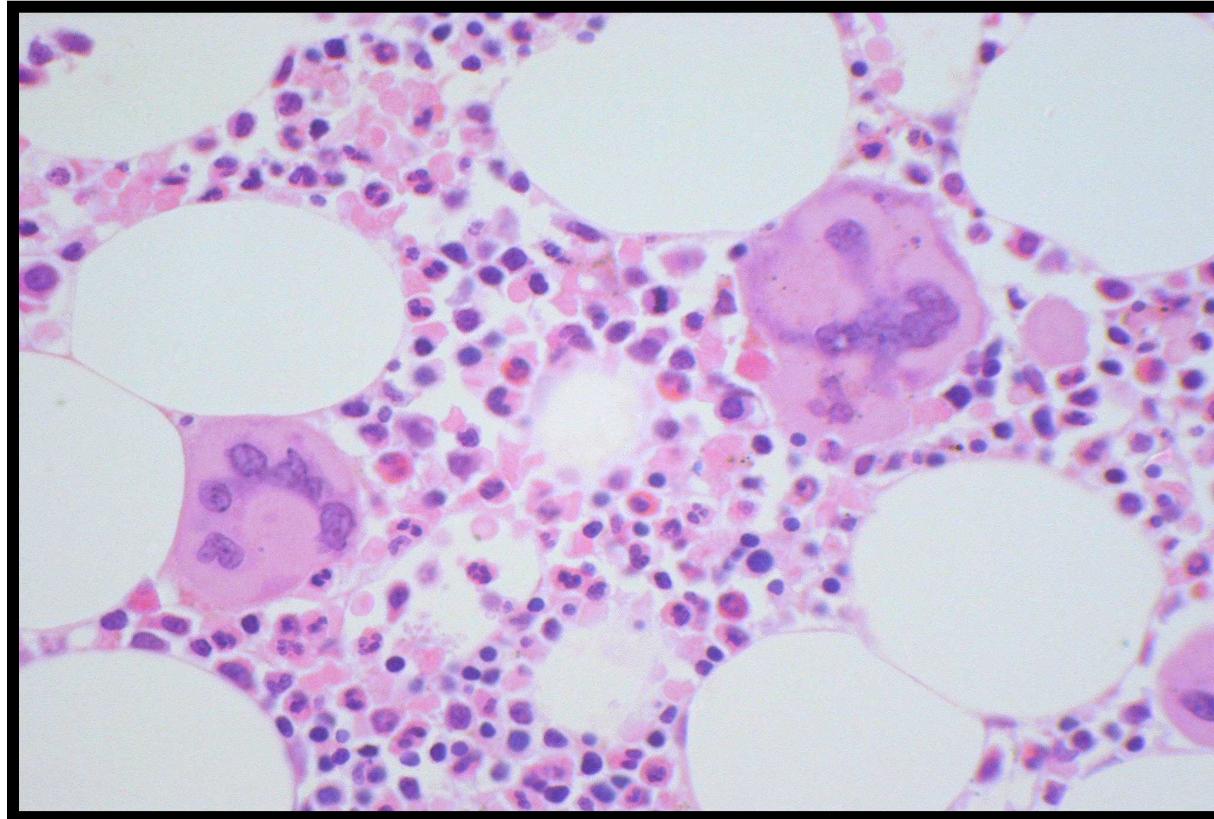


Increased megakaryocytes

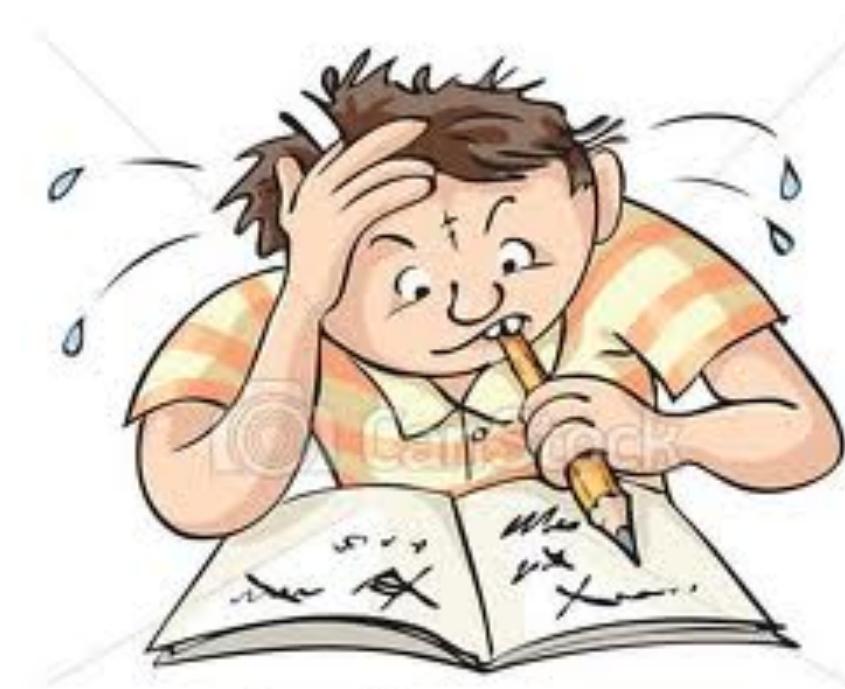
ET - Megakaryocyte Cytology in Aspirated Marrow



Large Megakaryocytes with 'Staghorn' nuclei in ET



Diagnosis -ET???



Diagnosis requires A1–A3 or A1 + A3–A5

A1-Sustained platelet count $>450 \times 10^9/l$

A2-Presence of an acquired pathogenetic mutation (e.g. in the *JAK2* or *MPL* genes)

A3-No other myeloid malignancy, especially PV*, PMF†, CML‡ or MDS§

A4-No reactive cause for thrombocytosis and normal iron stores

A5-BMA and trephine biopsy showing increased megakaryocyte numbers, large megakaryocytes, hyperlobated nuclei and abundant cytoplasm.

Reticulin is generally not increased (grades 0–2/4 or grade 0/3)

Prognosis and treatment

- Stable disease for 10-20 y
- Transform to MF
- Transformation to acute leukaemia <5%

Aim

- Reduce the risk of thrombosis and bleeding
- Identify risk factors for thrombosis and correct
Ex:HPT/DM/Hypercholesterolaemia/Obesity/Smoking
- Drug treatment-according to risk category

Risk stratification-ET

High risk	Not High risk	
>60 Y	Intermediate	Low
Hx of ET related thrombosis or bleeding	40-60 Y	<40 Y
Platelet>1500x10 ⁹ /l		

Treatment

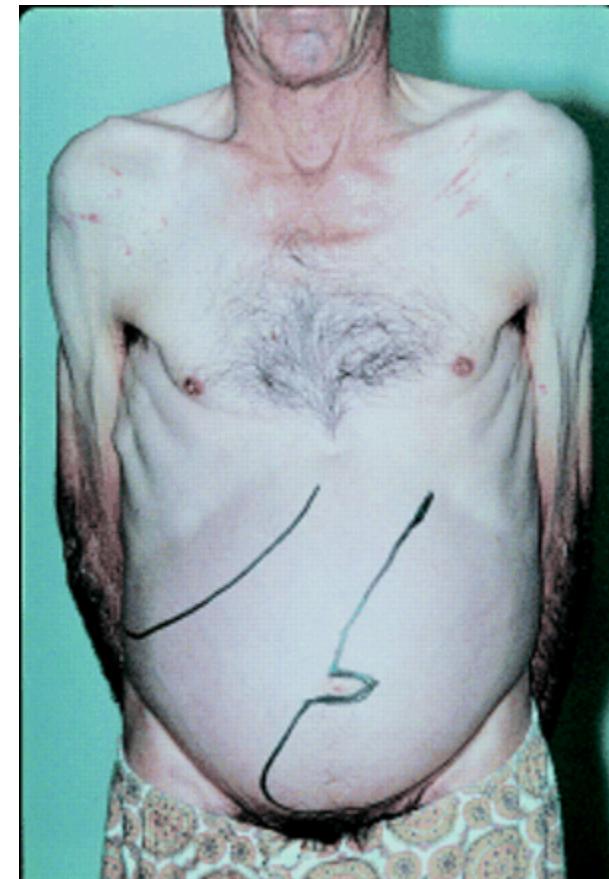
High risk	Intermediate	Low
Aspirin	Aspirin	Aspirin
Cytoreduction		
Hydroxyurea		
IF/Anagrelide		

Primary Myelofibrosis (MF)

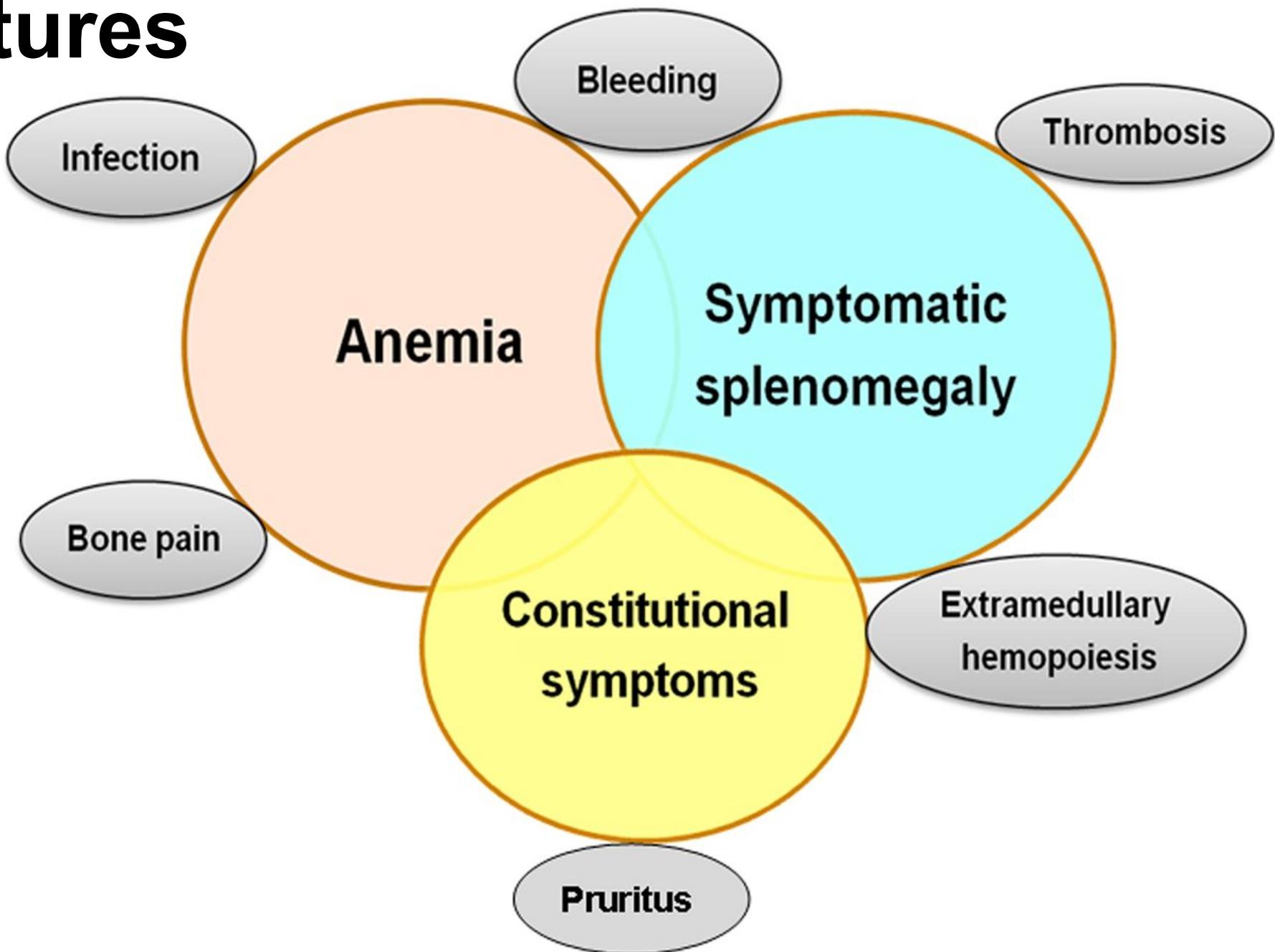
- Clonal Stem Cell disease
- Mutations-
 - JAK 2 mutation-50%
 - Calreticulin-30-40%
 - TET 2 mutation-15%
- 1/3-previous Hx of PV/ET
- 10-20% transform to leukaemia

- Increased Megakaryocytes
- Progressive reactive BM fibrosis
- Caused by fibroblast stimulation by PDGF
- Myeloid metaplasia - Haemopoiesis in liver & Spleen

Massive Splenomegaly



Clinical features



Laboratory findings

- **Anaemia**
- WBC/Platelets-could be initially high but later **leucopenia & thrombocytopenia**
- **Leucoerthroblastic** blood film with tear drop poikilocytosis
- BMA-dry tap
- Trephine Biopsy-Increased megakaryocytes , **Fibrosis**, osteosclerosis
- Reticulin stain-confirms increased fibrosis
- JAK 2 mutation- + in 50%
- Raised LDH/Uric acid

MF - typical blood count

WBC x 10 ⁹ /L	2.4	[4-11]
Hb g/L	88	[140-180]
MCV fl	85	[80-100]
Platelets x 10 ⁹ /L	60	[150-450]
Neuts x 10 ⁹ /L	1.0	[2-7.5]
Lymphs x 10 ⁹ /L	1.0	[1.5-4]
Monos x 10 ⁹ /L	0.2	[0.2-0.8]
Eos x 10 ⁹ /L	0.1	[0-0.7]
Basos x 10 ⁹ /L	0.1	[0-0.1]

Film Comment: *a few nucleated red cells and myelocytes (leukoerythroblastic). Tear-drop poikilocytes*

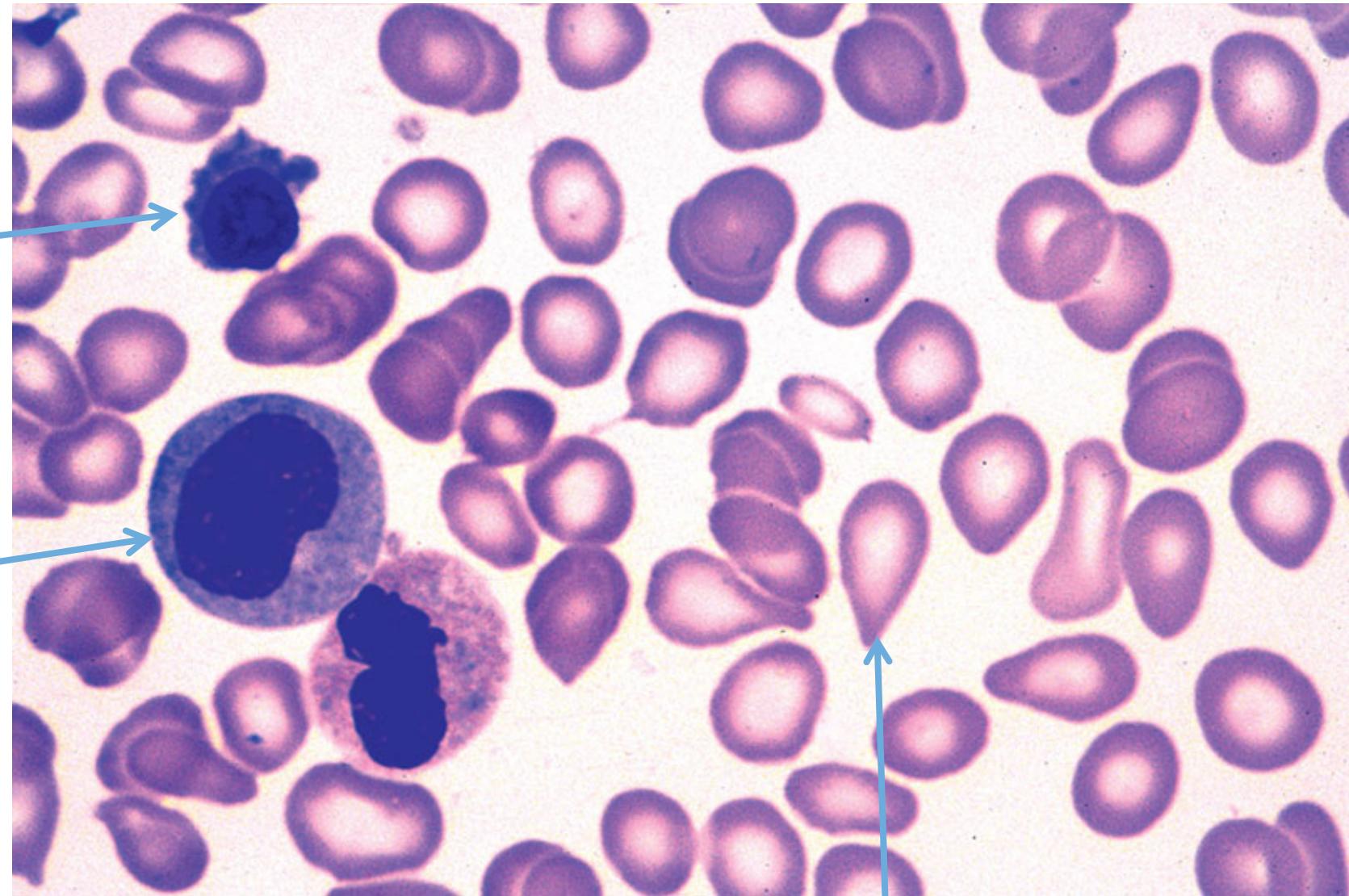
Nucleated red cells



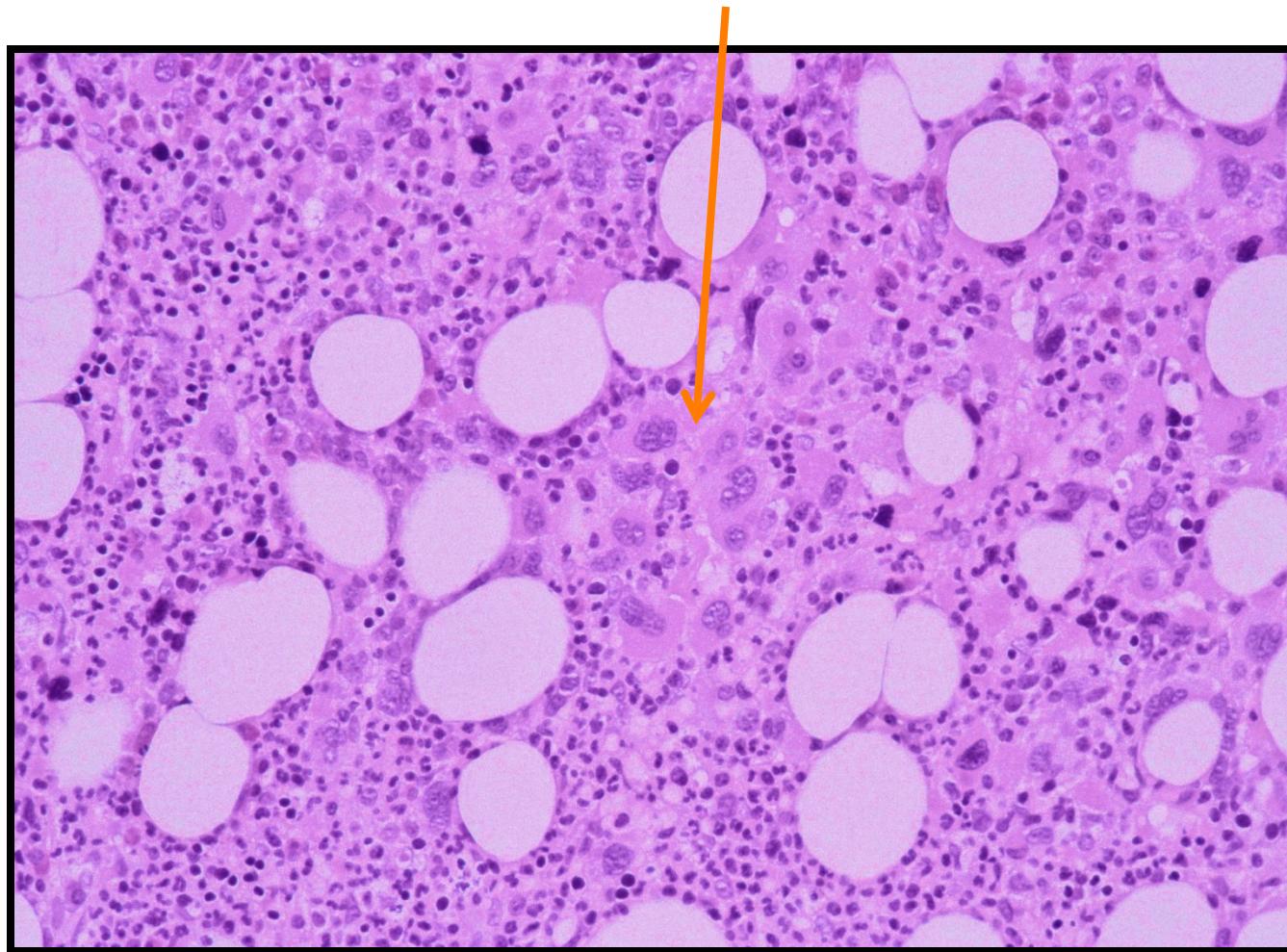
Myelocyte



Tear drop poikilocytes



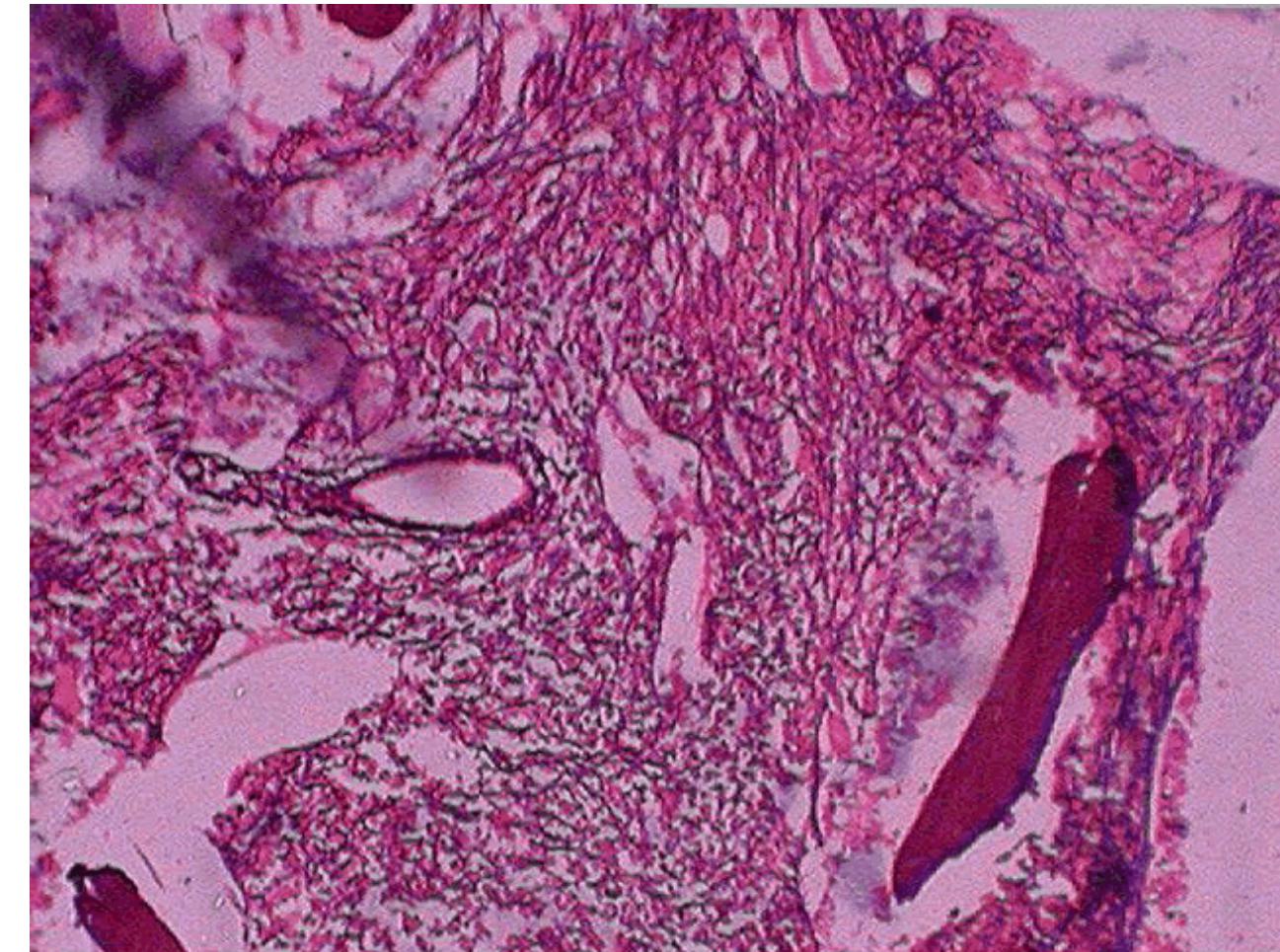
Clustering of Atypical Megakaryocytes in prefibrotic/early PMF



Normal marrow trephine



Myelofibrosis



fibrosis



new bone (arrows)

WHO diagnostic criteria for PMF- all 3 major criteria and >2 minor criteria

I. Major criteria

- a. Megakaryocyte proliferation- small-to-large megakaryocytes+ reticulin and/or collagen
- b. Not meeting WHO criteria for CML,PV,MDS or other myeloid neoplasm
- c. Demonstration of JAK2 V617F or other clonal marker or no evidence of reactive marrow fibrosis

II. Minor criteria

- a. Leukoerythroblastosis
- b. Increased serum lactate dehydrogenase
- c. Anaemia
- d. Palpable splenomegaly

Prognosis & Treatment

Prognostic factors

- Anaemia < 10g/dl
- Thrombocytopenia
- Leucocytosis
- TX dependence
- Bad cytogenetics
- Circulating blasts

Treatment

- Observation
- Supportive care-blood and blood product support
- Drugs-Hydroxyurea, Thalidomide, Prednisolone, Danazol, Androgend
- Allopurinol
- JAK 2 inhibitors
- Splenectomy, Radiation to spleen
- Allogeneic BMT-Young patients

Rare MPN

Systemic mastocytosis

- Neoplastic proliferation of mast cells
- BM, Heart, Spleen, LN, Skin
- KIT mutation
- Symptoms related to histamine, PG release

Flushing, pruritus, abdominal pain, bronchospasm

- Elevated S.tryptase
- Indolent / aggressive



Urticaria pigmentosa seen in systemic mastocytosis.

Summary

- ET is characterised by sustained increase in platelet count
- Diagnosis is by exclusion
- Treatment aims at reducing thrombosis and bleeding & depends on the risk category
- Aspirin or Aspirin+Cytoreduction

Summary

- MF –reactive BM fibrosis
- Leucoerythroblastic BF with tear drop poikilocytosis
- Myelod metaplasia –Massive splenomegaly
- Treatment options-supportive care, conventional and investigational drugs, surgical, BMT