Myeloproliferative Neoplasms: What's New in Diagnosis

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Myeloproliferative Neoplasms

- Abnormalities usually in the blood: count
- Too many cells are being made in the bone marrow
- Different appearances in each type of MPN
- Megakaryocytes are the most abnormal cell
- Scar tissue forms in the bone marrow stopping blood cell production (fibrosis)
- Bone overgrowth can occur
- Importance to assess bone marrow aspirate and (trephine) biopsy to diagnose and monitor

A Language Lesson – Part 1

From Greek (*haimo-*) & Latin (*haemo*) for blood
Prefix and Suffix

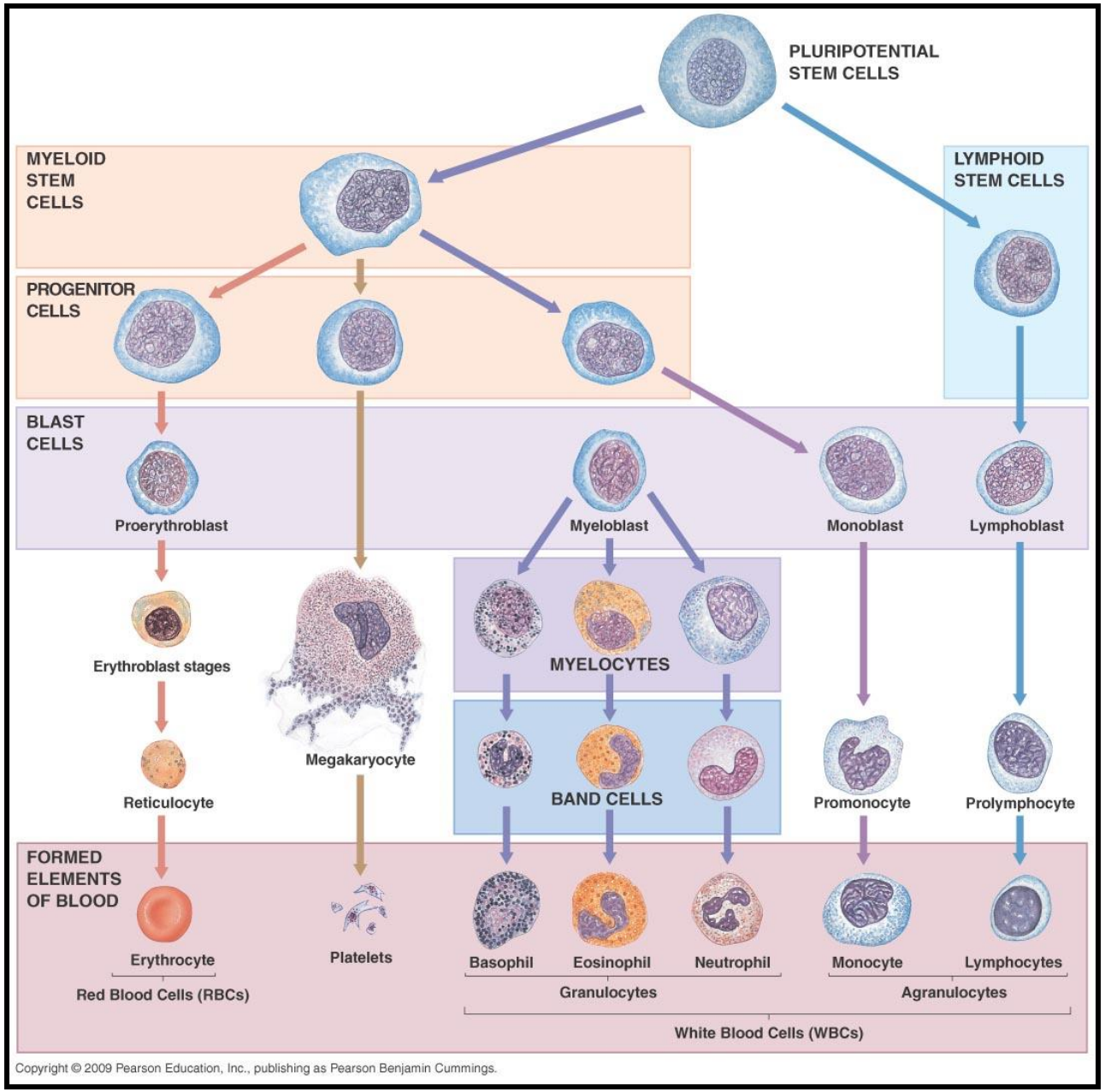
Prefix	Meaning	Example	Explanation
An-	Without	Anaemia	Without blood
-osis	Increased	Leucocytosis	Increased WBC count
-penia	Reduced	Leucopenia	Reduced WBCcount
-aemia	Blood	Thrombocythaemia	Increased platelets in blood
Cyto-	Cell	Cytopenia	Reduction in cells
-cytosis	Cell increased	Erythrocytosis	Increased RBC in the blood
Erythro-	Red	Erythrocyte	Red blood cell
Leuco-	White	Leucocyte	White blood cell
Thrombo-	Plug	Thrombocyte	Platelet
Pan-	Everything	Pancytopenia	All cells reduced

A Language Lesson – Part 2

From Greek (*haimo-*) & Latin (*haemo*) for blood
Prefix and Suffix

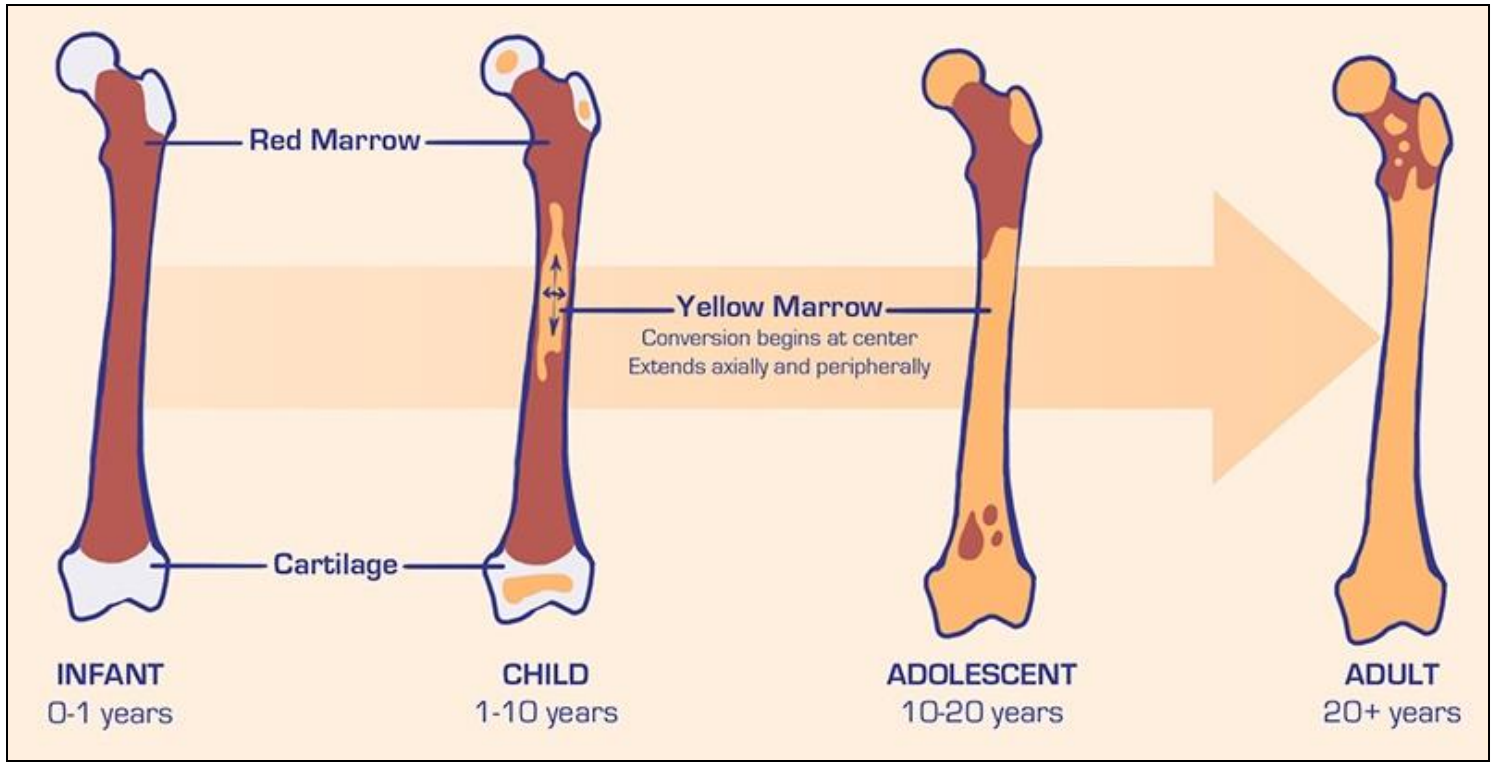
Prefix	Meaning	Example	Explanation
Blastos-	Germ; bud	Blast cell	Immature cell (myeloblast)
Macro-	Big	Macrocytic	Large red blood cell
Mega-	Big	Megakaryocyte	BM cell making platelets
Micro-	Small	Microcytic	Small red blood cells
Myelos-	Bone marrow	Myelofibrosis	Scarring of marrow
Pleio-	More than 1 form	Pleiomorphic	Variable appearance
-poiesis	To make	Erythropoiesis	Red cell production in BM
Poikilos-	Varied	Poikilocytes	Variation in shape of RBC
Poly-	Many	Polychromasia	Many colours
Vera	Red	PRV	Polycythaemia vera

Blood Cell Production: *haemopoiesis*



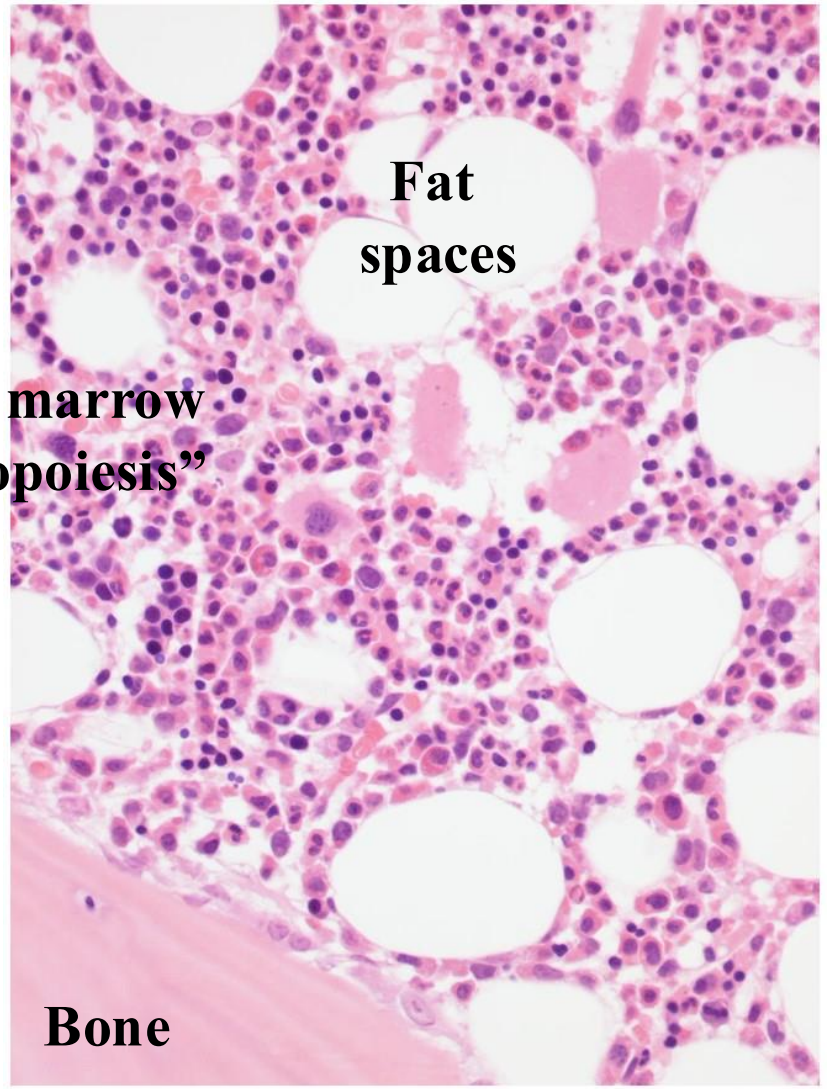
Sites of Bone Marrow Activity

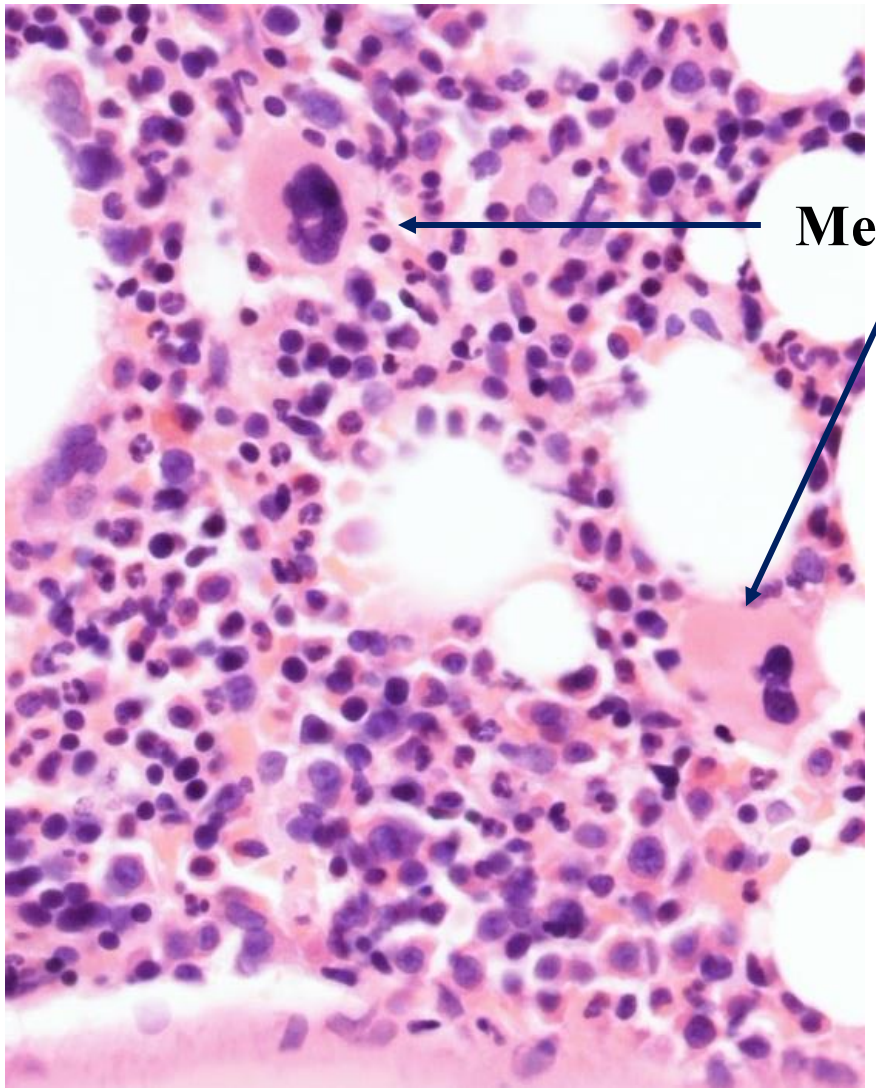
- **Red marrow**: sites of active haemopoiesis; changes to inactive (fat / yellow) with age
- **Yellow marrow**: contains mainly fat; long bones; can revert to active with increased demand



https://www.orthobullets.com/basic-science/9004/bone-marrow

Normal Bone Marrow





Outline: what's new in diagnosis?

- Understanding blood tests
- Bone marrow morphology in MPN
- Why bone marrows are needed
- When bone marrows are needed

Blood count analyser

	03/04 11:01		03/04 11:00		03/04 10:58		3/04 10:
WBC	6.4		6.3		6.3		6.0
RBC	4.14		4.12		4.12		4.05
HGB	12.1		12.2		12.2		11.9
HCT	35.7		35.4		35.4		35.3
NE#	3.85		3.84		3.80		3.60
LY#	1.91		1.90		1.96		1.80
MO#							0.5
EO#	0.07		0.07		0.07		0.10
BA#	0.03	V__	0.04	V__	0.04	V__	0.00
NRBC#	0.51		0.50		0.49		

A blood count (FBC)

Bone marrow aspirate

Bone marrow trephine

"What's New in MPN Diagnosis"?
Two competing classifications

- **WHO Classification**:
  - Polycythaemia vera
  - Essential thrombocythaemia
  - Primary myelofibrosis
  - Chronic myeloid leukaemia
  - Chronic neutrophilic leukaemia
  - Chronic eosinophilic leukaemia
  - Juvenile myelomonocytic leukaemia
  - Myeloproliferative neoplasms NOS

- **International Consensus Classification:**
  - Polycythaemia vera
  - Essential thrombocythaemia
  - Primary myelofibrosis
  - Chronic myeloid leukaemia
  - Chronic neutrophilic leukaemia
  - Chronic eosinophilic leukaemia
  - Myeloproliferative neoplasms, unclassifiable

What's new? "Myeloid Madness"

- Classification of haematological neoplasms: recent revision
- Two separate schemes:
  - WHO classification, 5th edition
  - International Consensus Classification
- Presents challenges for haematopathologists and patients
- "Myeloid Madness" Benton et al. 2023 Dec 14;77(1):68-72
- What does this mean for Myeloproliferative Neoplasms?

Comparison of Classifications: blood and BM

	Polycythaemia vera		Essential Thrombocythaemia		Myelofibrosis	
	WHO	**ICC**	**WHO**	**ICC**	**WHO**	**ICC**
Hb	F >160 (>48%) M >165 (>49%)	F >160 (>48%) M >165 (>49%)			Anaemia	Anaemia
WCC	Mild increase	Mild increase			> 11 x 10^9/L	Variable
Platelet	Normal/ increase	Normal/ increase	> 450 x 10^9/L	> 450 x 10^9/L	Low	
BM	Panmyelosis	Panmyelosis	Normocellular	Normocellular	Varies	Varies
M:E ratio	Normal	Variable	Normal	Normal	Increased	Variable
Megakaryocyte	Atypia	Variation	Some large	Some large	Atypia	Atypia
Reticulin	0 or 1	0 or 1 (20%)	0 or 1	Not increased	2 or 3	2 or 3

… not much different?

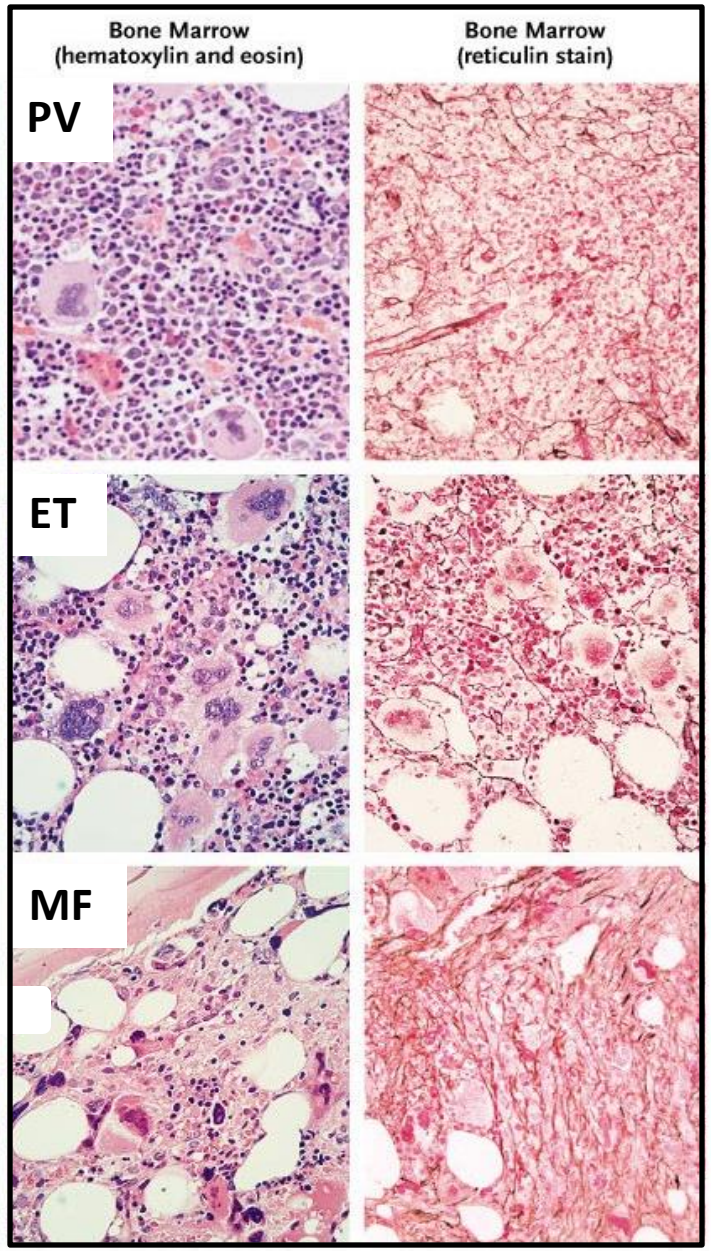
Blood Count

- Person 1
  - High Hb
  - Mild leucocytosis
  - Mild thrombocythaemia
- Person 2
  - Isolated thrombocytosis
  - Normal Hb
  - Normal WCC
- Person 3
  - Pancytopenia
  - Hb, WCC, Platelets: all reduced (pancytopenia)

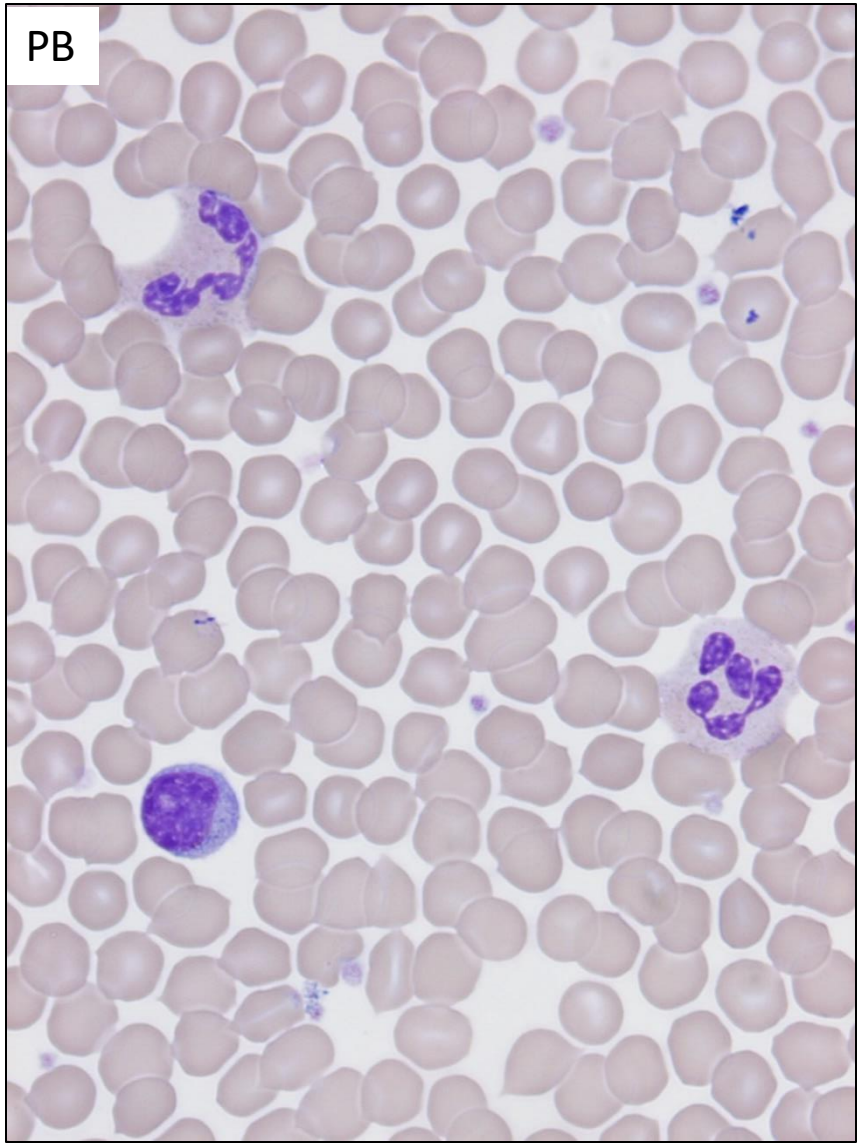
	Person 1	Reference
Hb	180	135 – 170 g/L
MCV	82	80 – 100 fL
WCC	12.4	4 – 11 x 10^9/L
Platelets	460	150 – 400 x 10^9/L
	Person 2	**Reference**
Hb	140	135 – 170 g/L
MCV	85	80 – 100 fL
WCC	5.4	4 – 11 x 10^9/L
Platelets	660	150 – 400 x 10^9/L
	Person 3	**Reference**
Hb	111	135 – 170 g/L
MCV	82	80 – 100 fL
WCC	2.4	4 – 11 x 10^9/L
Platelets	120	150 – 400 x 10^9/L

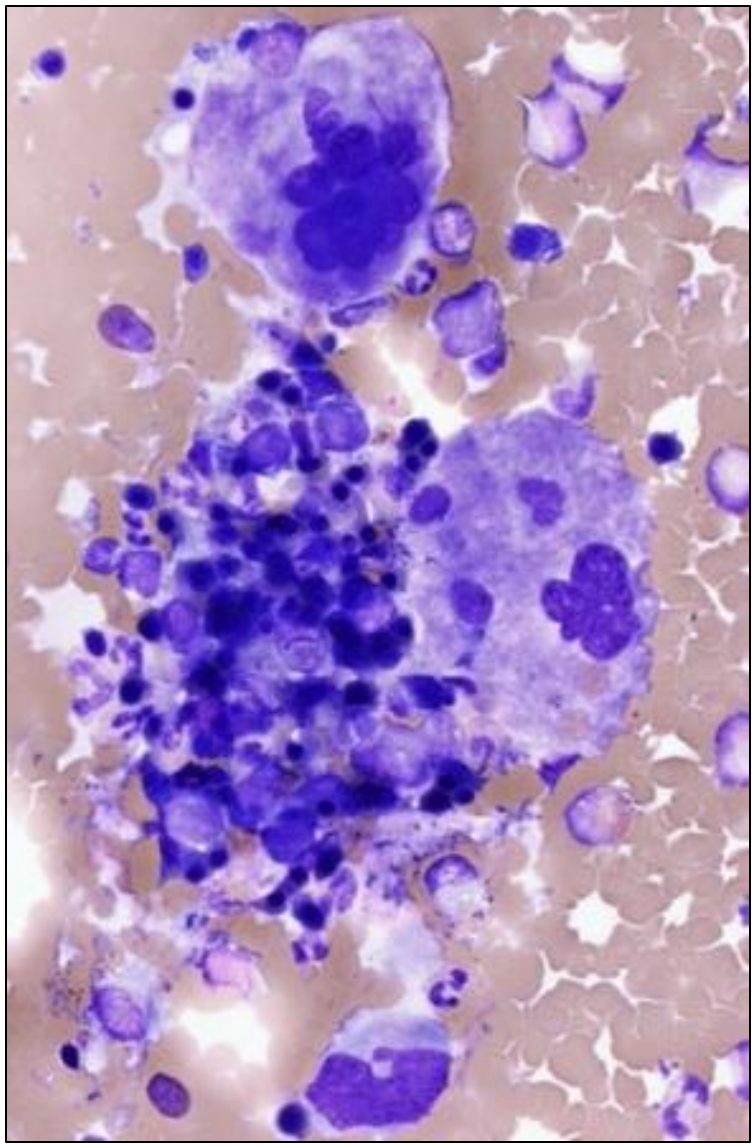
What are the MPN Entities

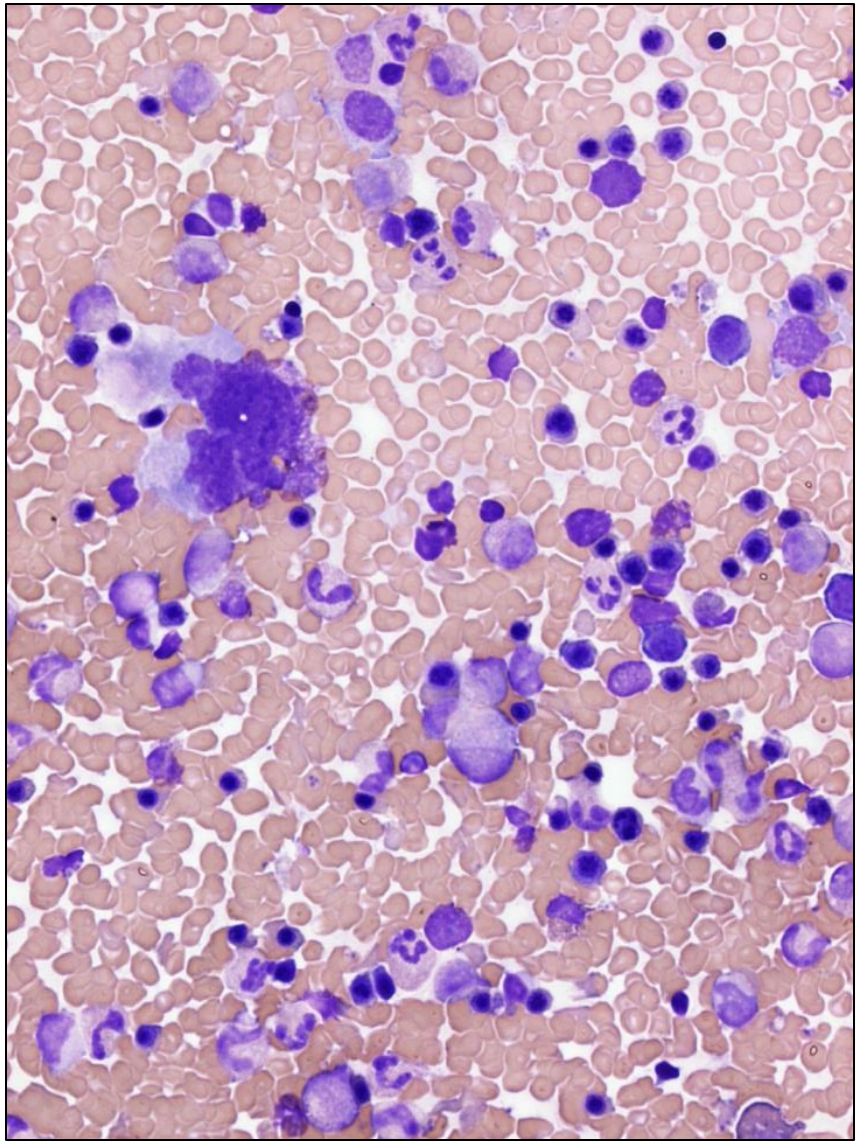
- **Polycythaemia vera (PV)**
  - High blood counts ("*pan*")
  - *JAK2* mutations
- **Essential Thrombocythaemia (ET)**
  - High platelet count
  - Increased megakaryocytes in marrow
  - *JAK2*, *CALR*, *MPL* mutations
- **Primary Myelofibrosis (PMF)**
  - Generally anaemia; variable WCC and platelet counts
  - Primary or secondary to ET/PV
  - *JAK2*, *CALR*, *MPL* mutations
  - Marrow scarring (reticulin stain)



Polycythaemia Vera: PB & BM Aspirate

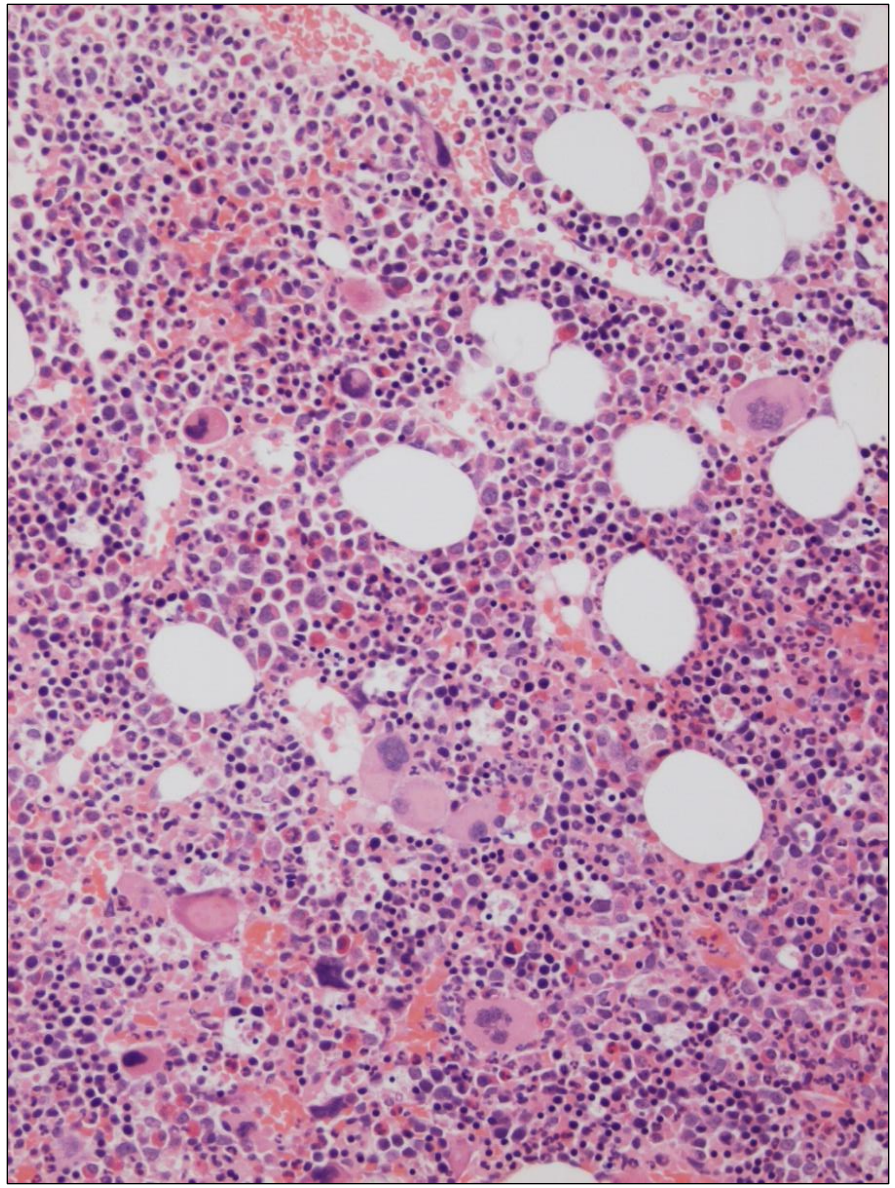


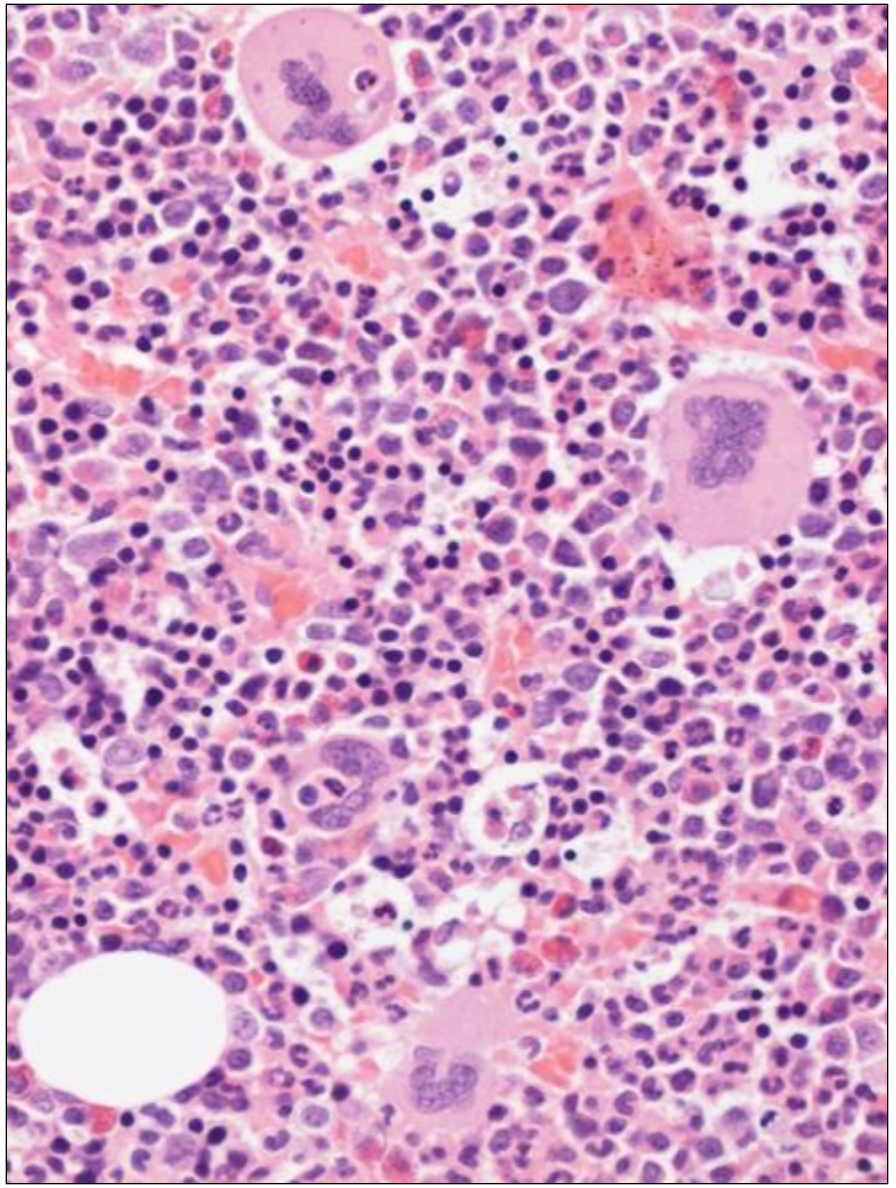




Polycythemia Vera (Bone marrow)

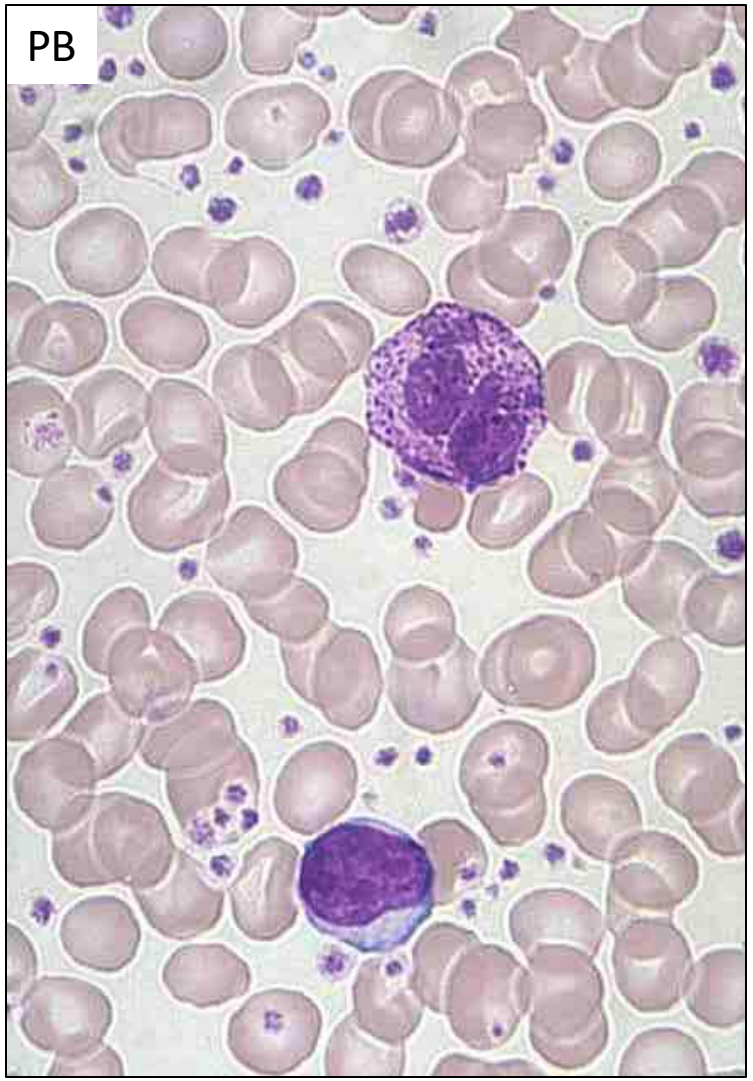
Pan-myelosis and pleiomorphic megakaryocytes

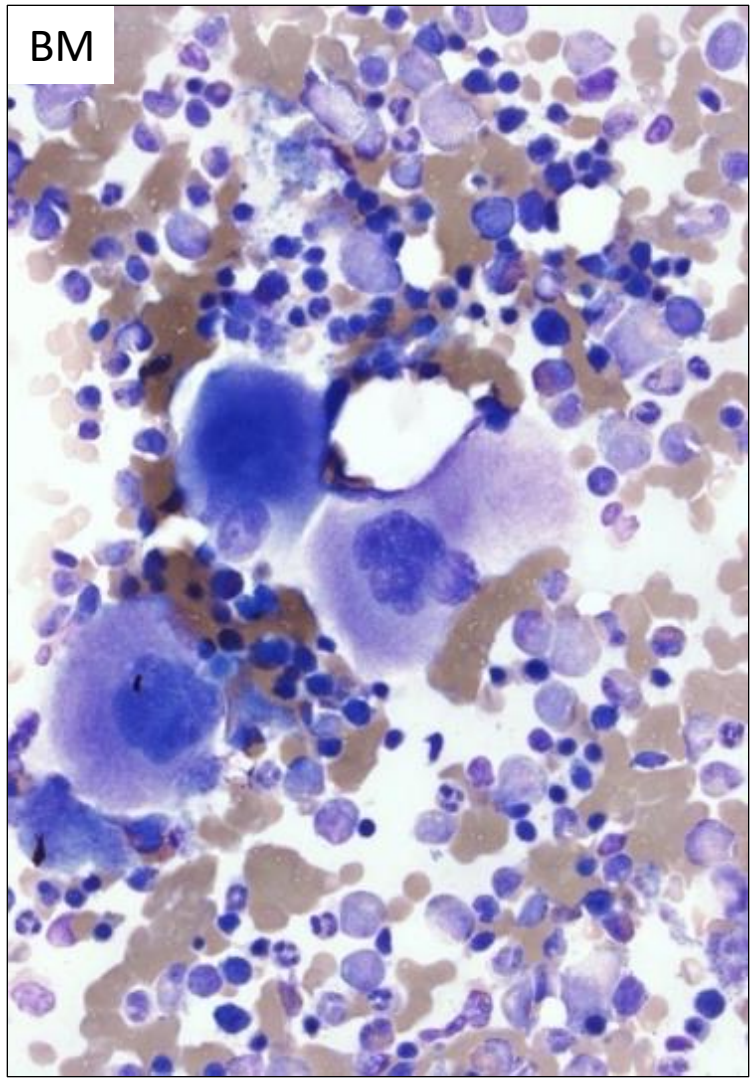


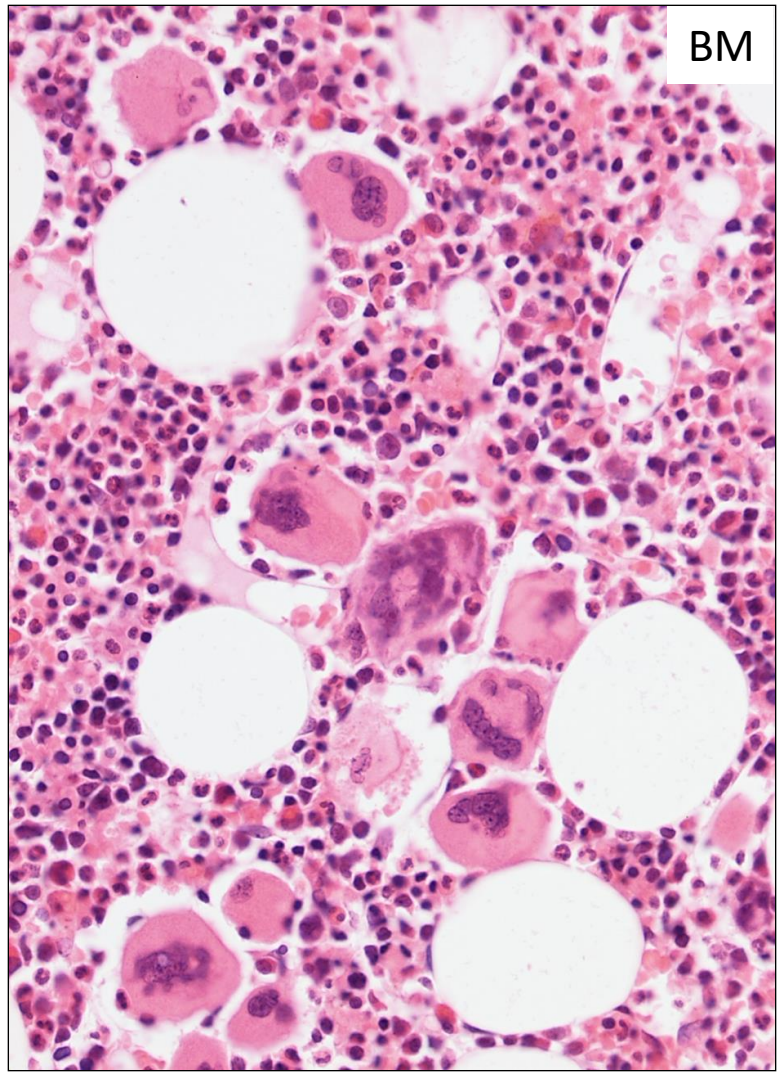


Essential Thrombocythemia (Blood & BM)

Thrombocytosis and “isolated” megakaryocytic hyperplasia

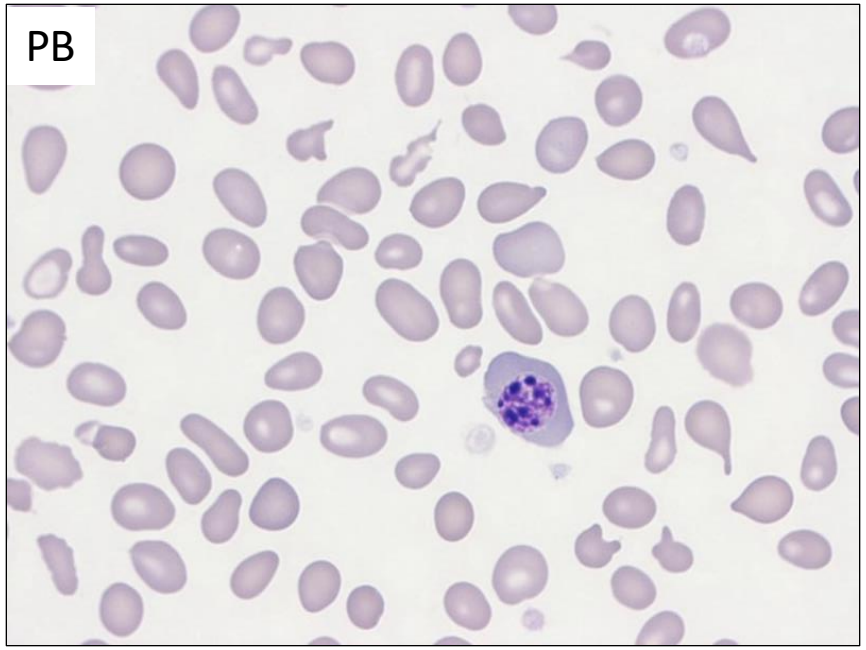




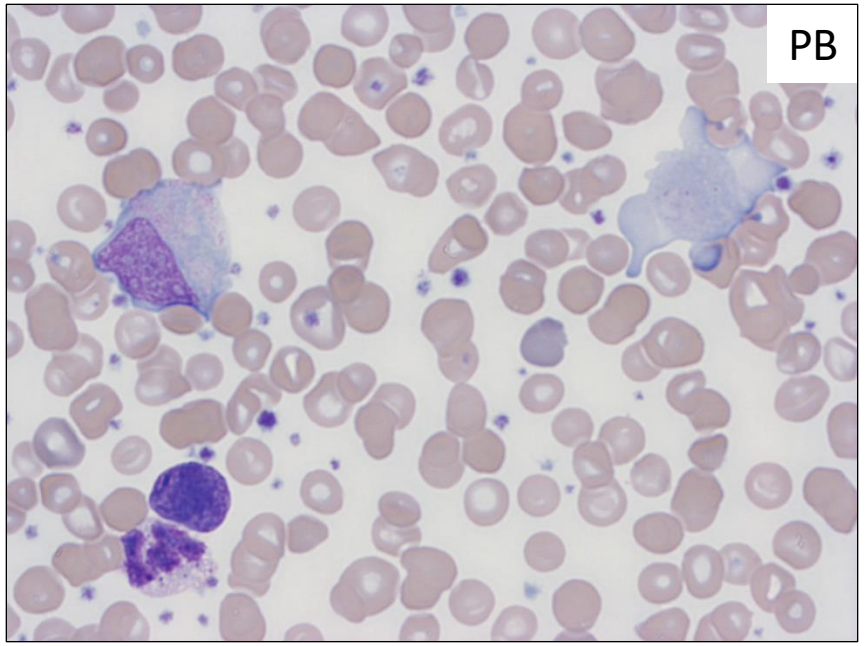


Myelofibrosis (Blood)

- Variable cytopenias (low Hb, low white cell, low platelets)
- Abnormal blood appearances: teardrop shaped red blood cells (*dacrocytes*: Latin *dacry* "tear")
- Immature cells in blood: nucleated RBC; blast cells
- Abnormal platelets: large size and lack granules



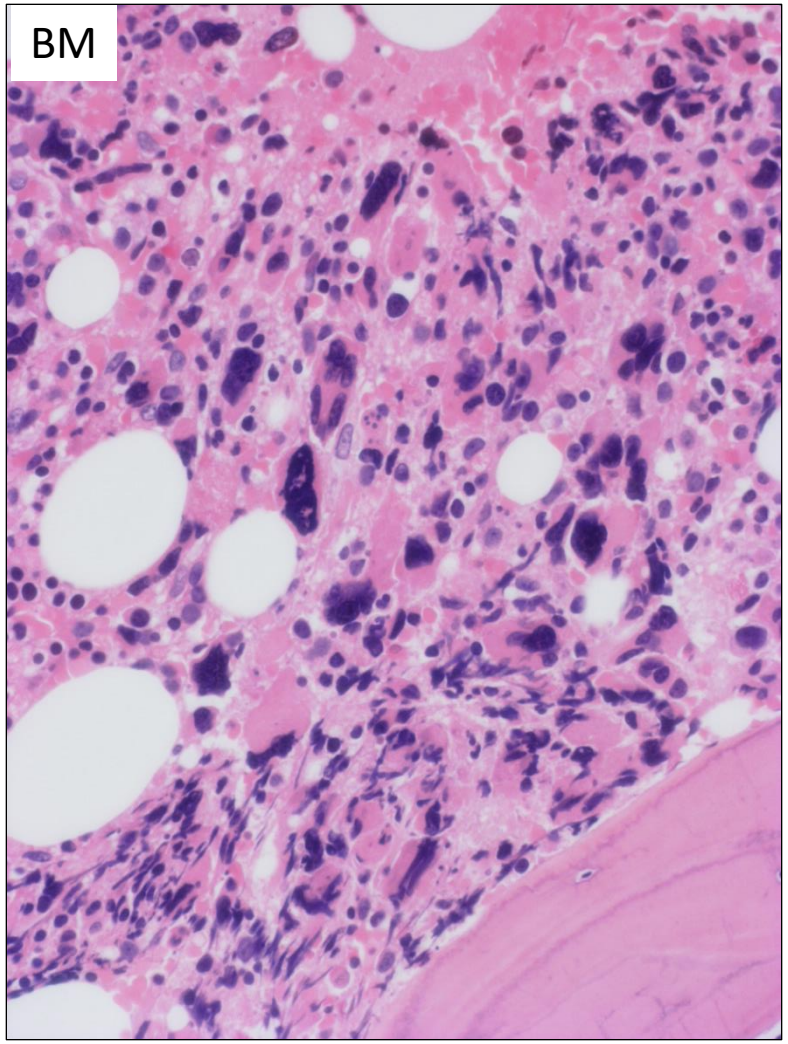
Teardrop shaped red cells; nucleated RBC

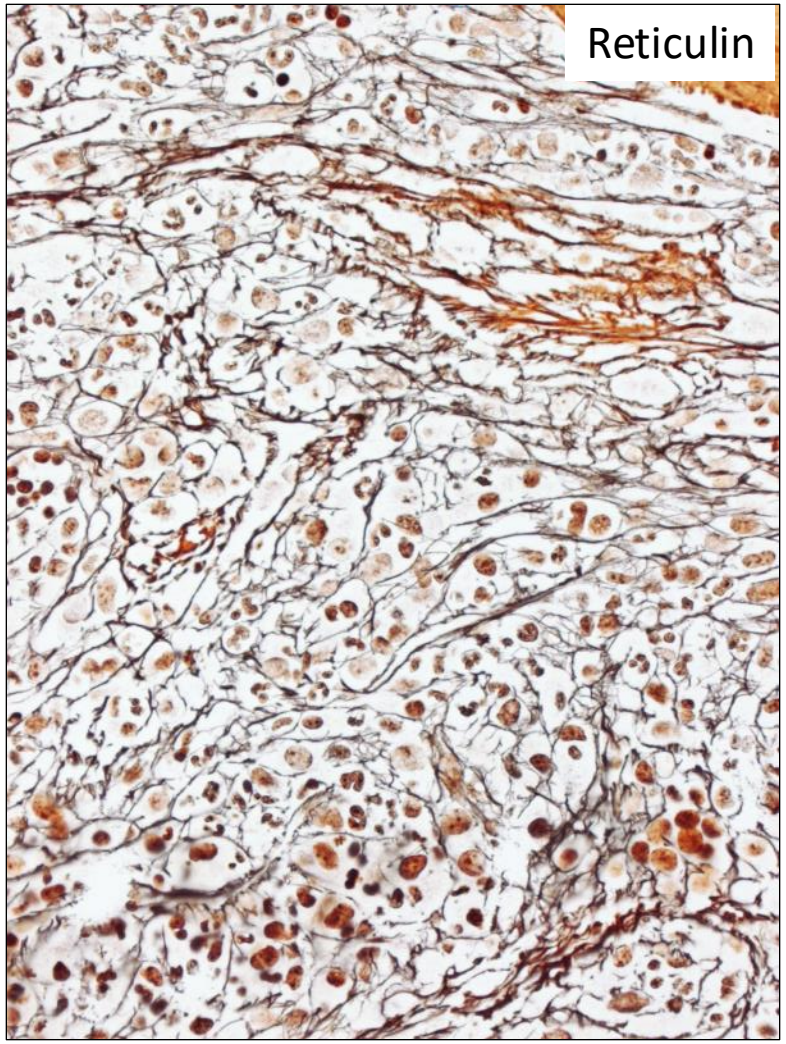


Abnormal platelet and white blood cells

Myelofibrosis (Bone marrow)

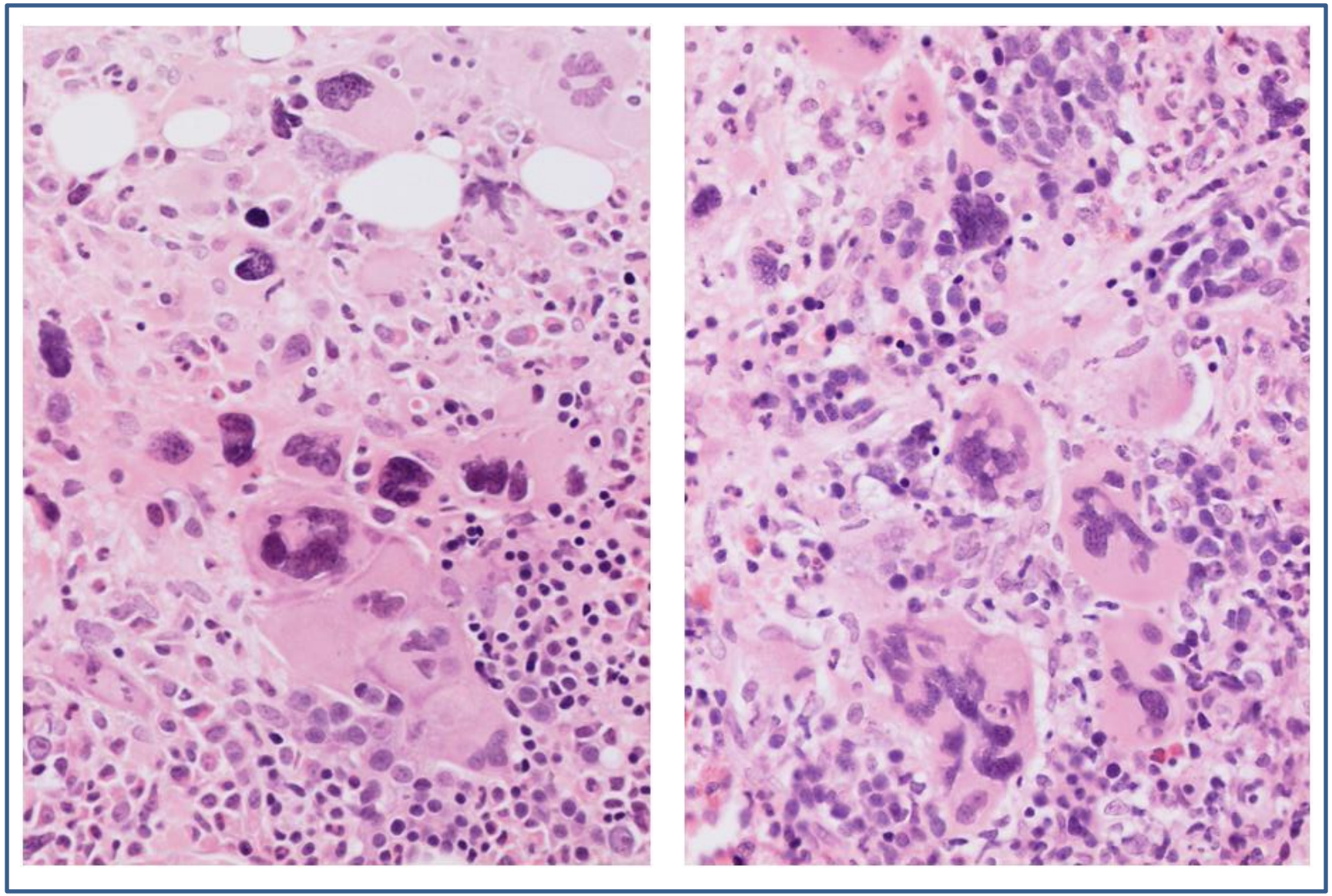
Hypercellular, disorganised and abnormal megakaryocytes in tight clusters and/or sheets and near bone. Increased reticulin fibres.





Myelofibrosis

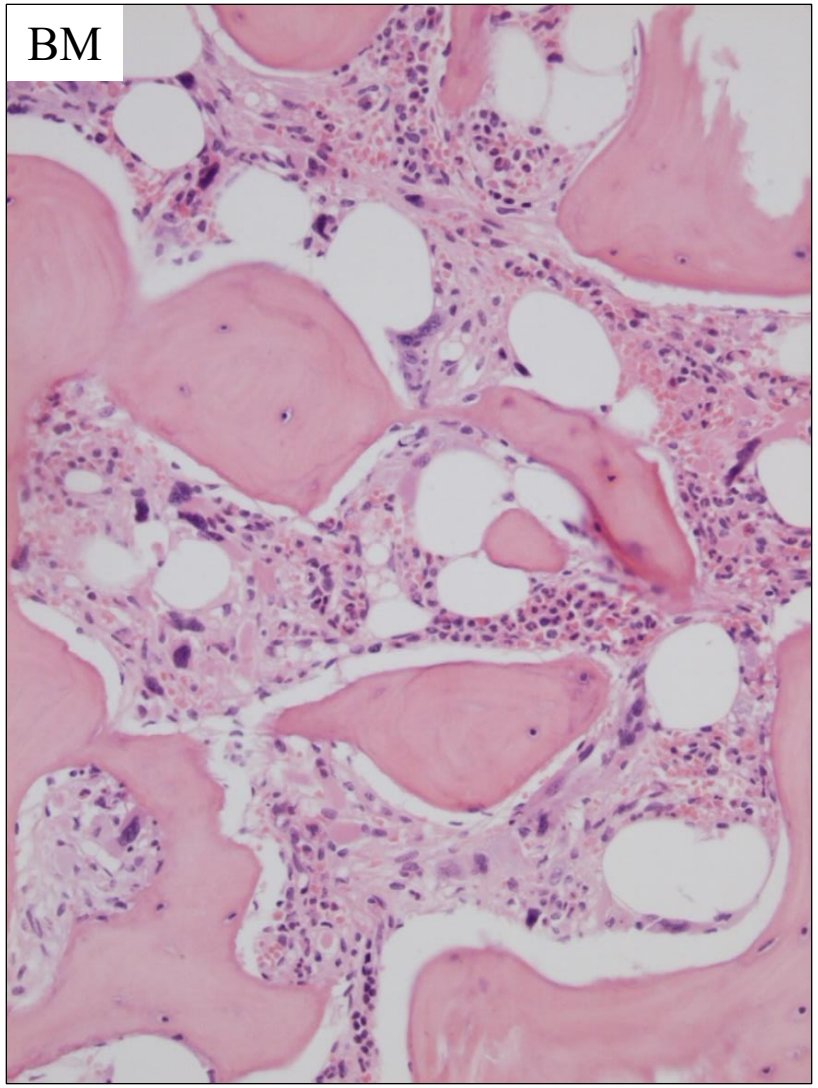
Bone marrow is disorganised; sheets of abnormal megakaryocytes

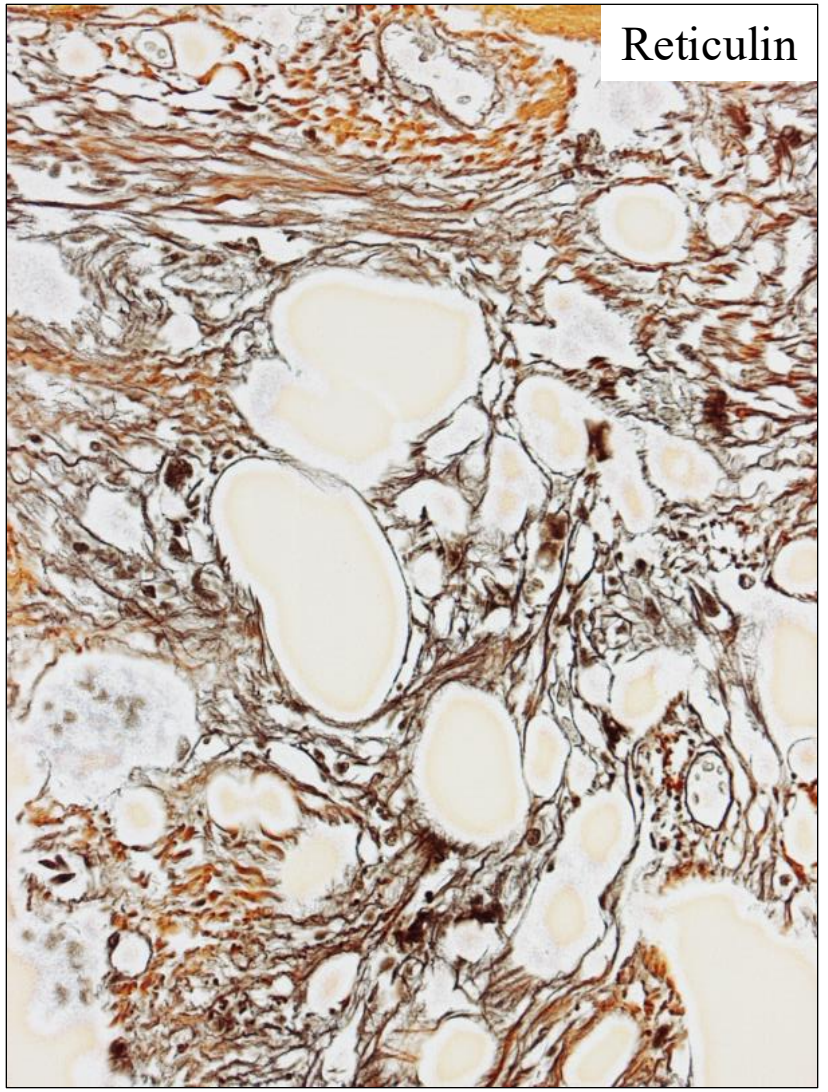


Osteomyelosclerosis

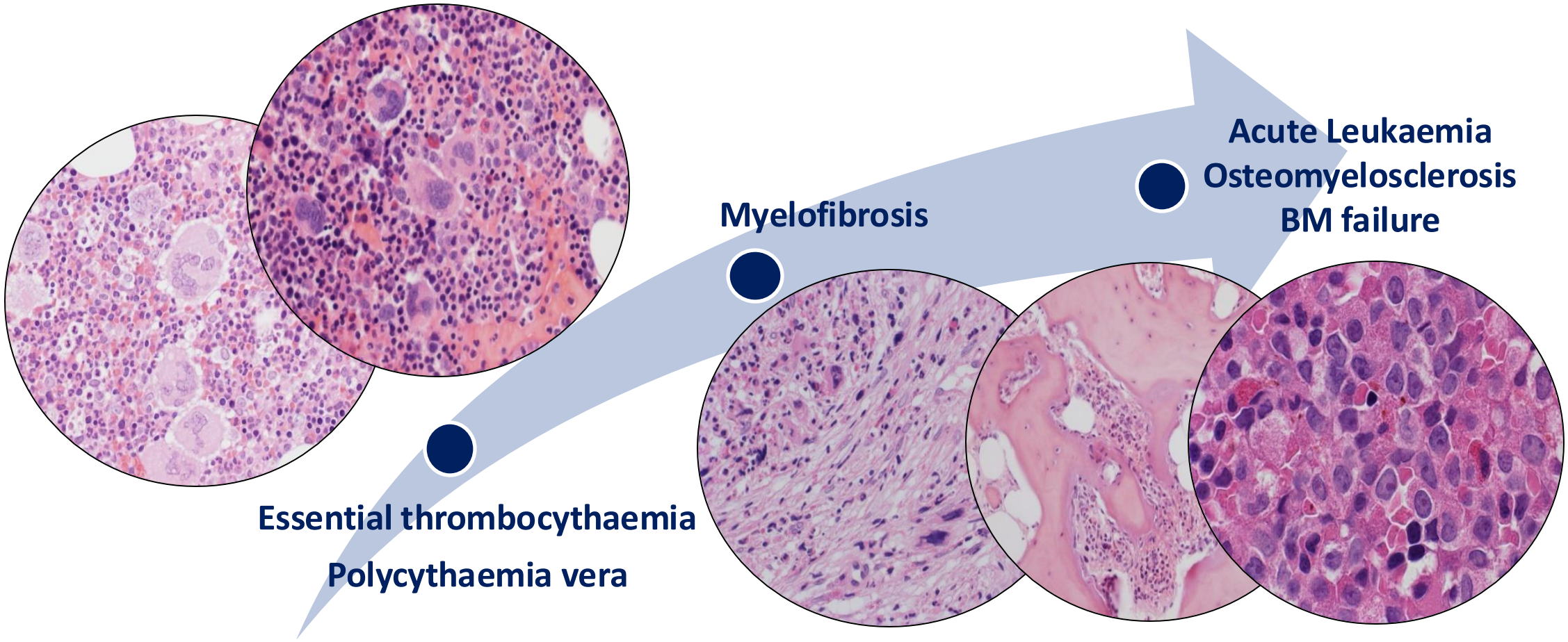
"*Osteo*": new bone formation; reduced inter-trabecular spaces

Reduced and markedly abnormal haemopoiesis. Increased reticulin fibres (scar tissue)





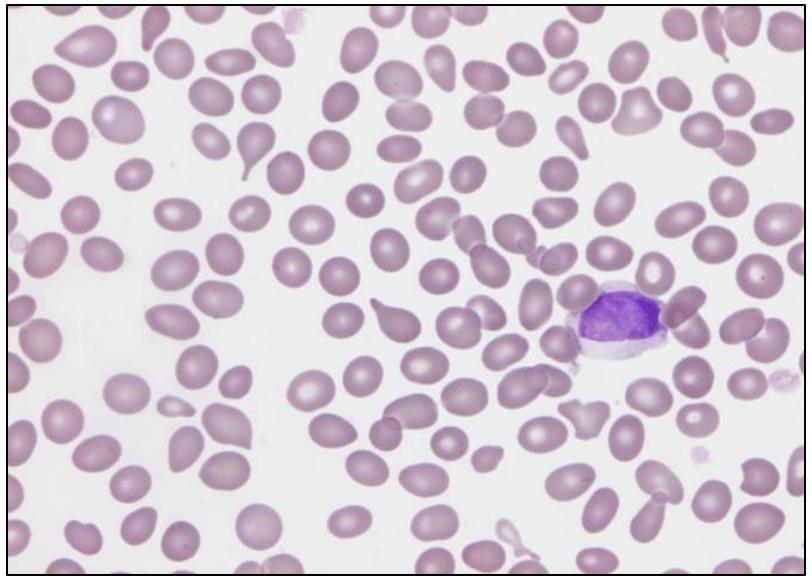
MPN is not a static disease: a “continuum”

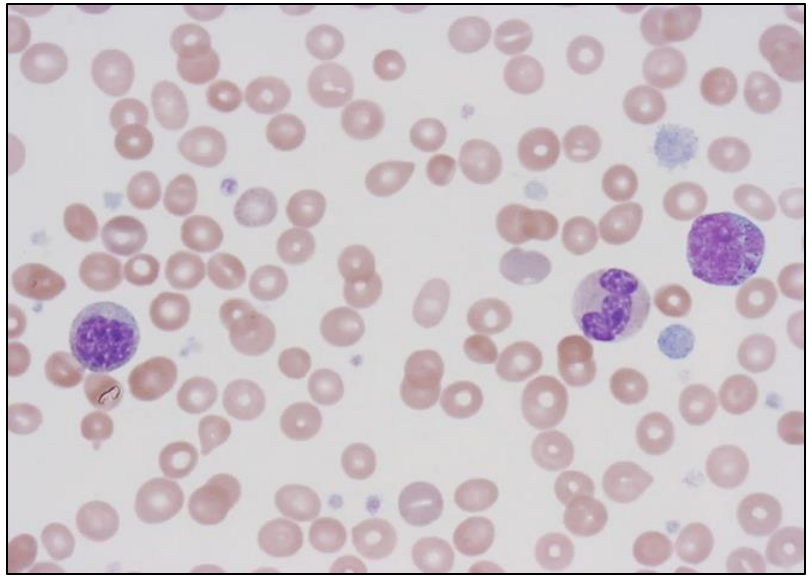


Time course and natural history of myeloproliferative neoplasms

Haematology of MPN Progression

- Knowing baseline counts and morphology at presentation
- Progression = change from previous
- The role of the diagnostician:
  1. Blood count
  2. Blood film
  3. Blast cells
  4. Bone marrow morphology
  5. Genetics
  6. Tests in development





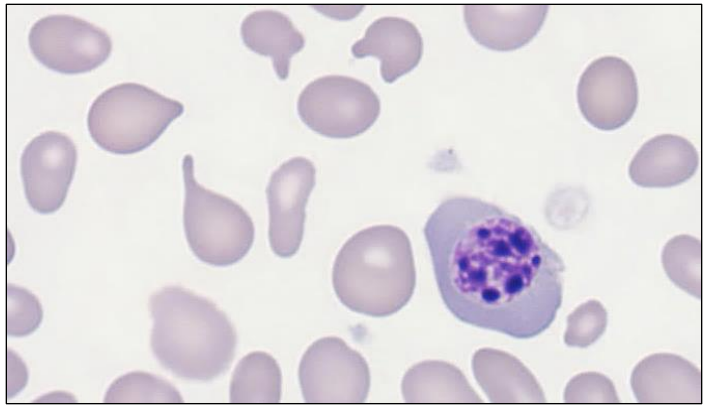
The Blood Count

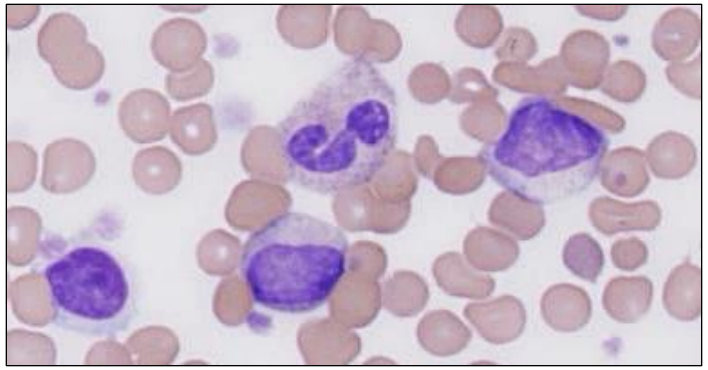
- Unexplained changes on FBC: due to therapy or disease?
- **Red cells**: *anaemia*
  - Change in MCV: microcytic
  - Nucleated RBC (immature forms)
- **Leucocytes**: *leucocytosis*
  - Neutrophilia; left shift
  - Basophilia
  - Blast cells ("flagged" on FBC)
- **Platelets**: *thrombocytopenia*
  - Increased or decreased
  - Analyser unable to obtain a platelet count

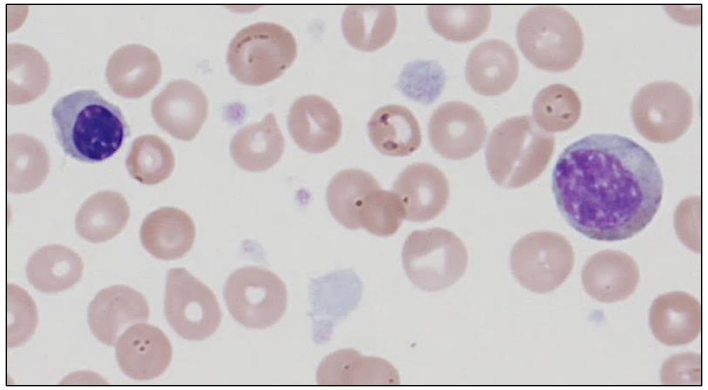
	Person 4	Reference
Hb	101	115 – 150 g/L
MCV	78	80 – 100 fL
WCC	22.4	4 – 11 x 10^9/L
Platelets	109	150 – 400 x 10^9/L

The Blood Film

- **Red cells:**
  - Poikilocytes (especially teardrops)
  - Nucleated red blood cells
- **Leucocytes:**
  - Immature cells; left shift
  - Dysplasia; abnormal morphology
  - Blast (leukaemic) cells
  - Leucoerythroblastic film
- **Platelets:**
  - Size: large (megakaryocyte fragments)
  - Granules: reduced; grey
  - Circulating megakaryocytes

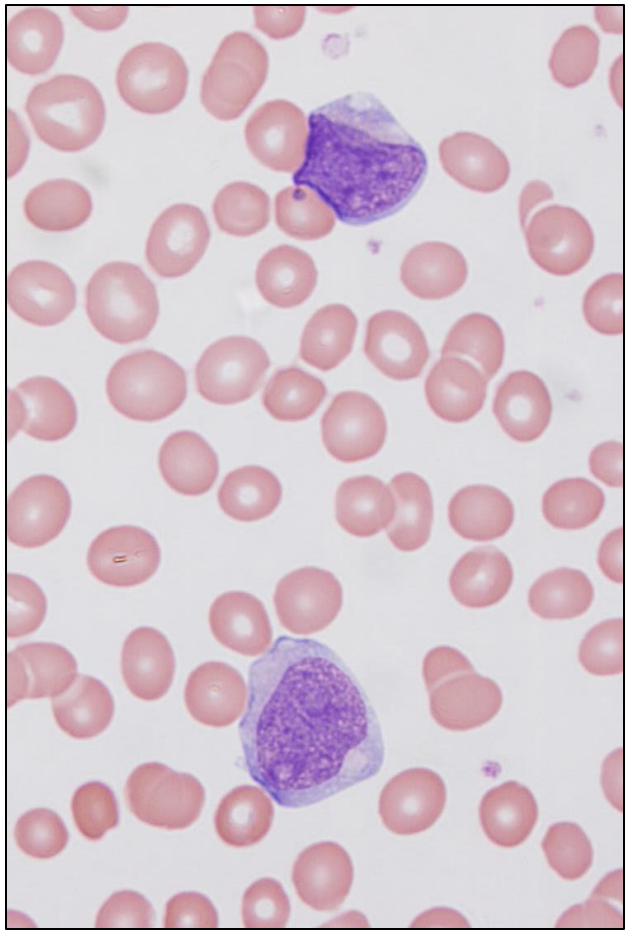


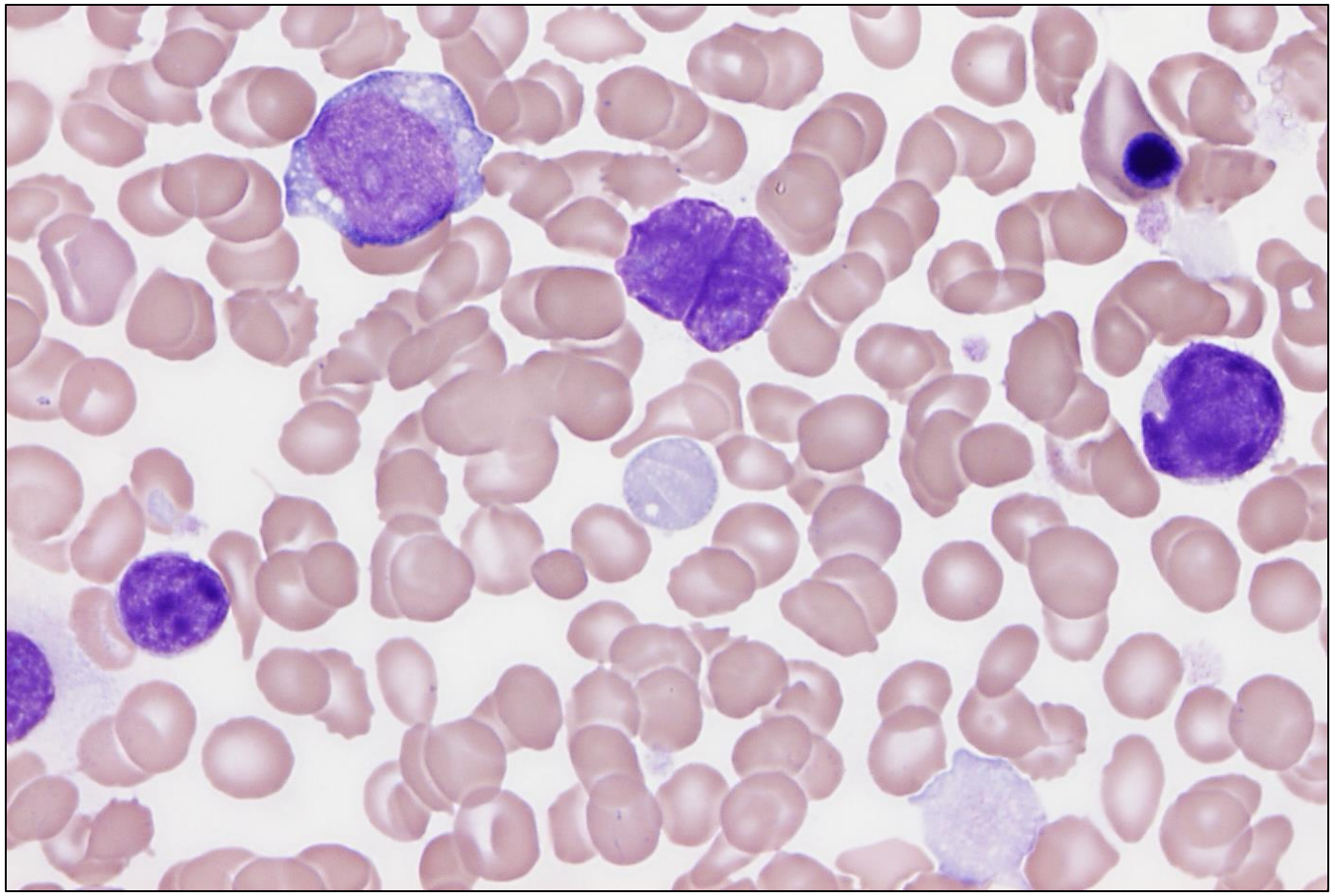




The Blood Film

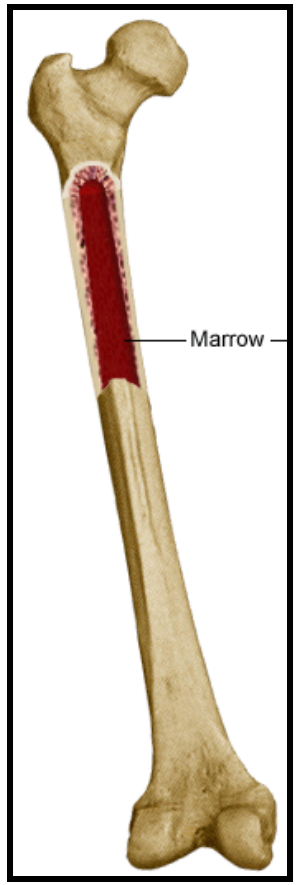
Blast cells; NRBC; megakaryocyte nucleus; giant hypogranular platelets

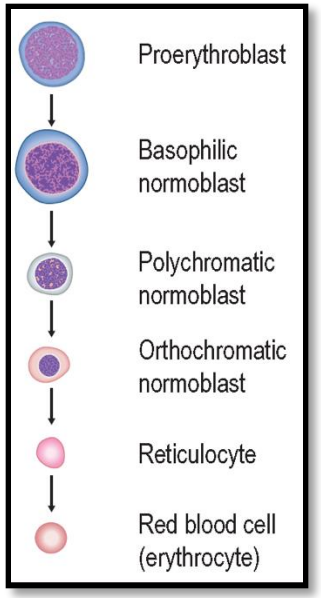


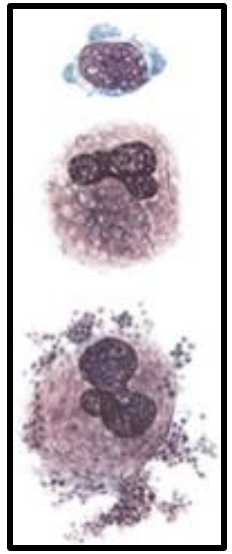


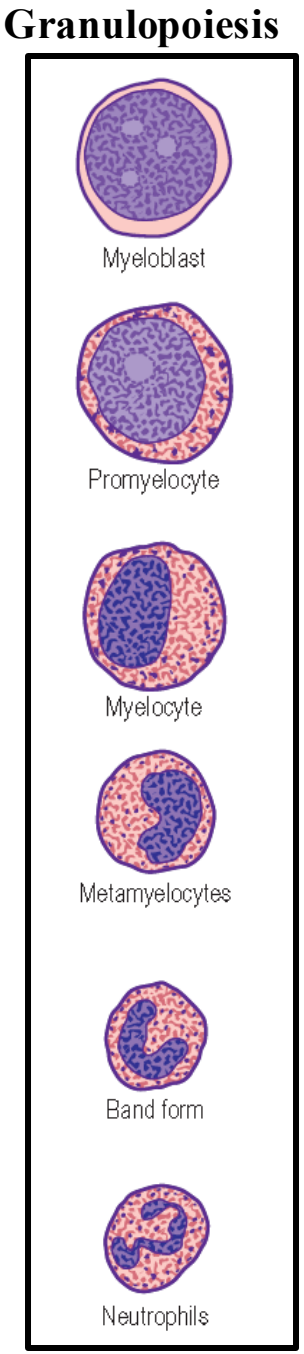
Bone Marrows: why are they needed?

- To assess haemopoiesis
- To determine cause of altered blood counts
- To make the initial diagnosis
- To give baseline status
- To assess changes over time
- Progression to myelofibrosis?
- Progression to secondary leukaemia?
- Therapy-related changes?



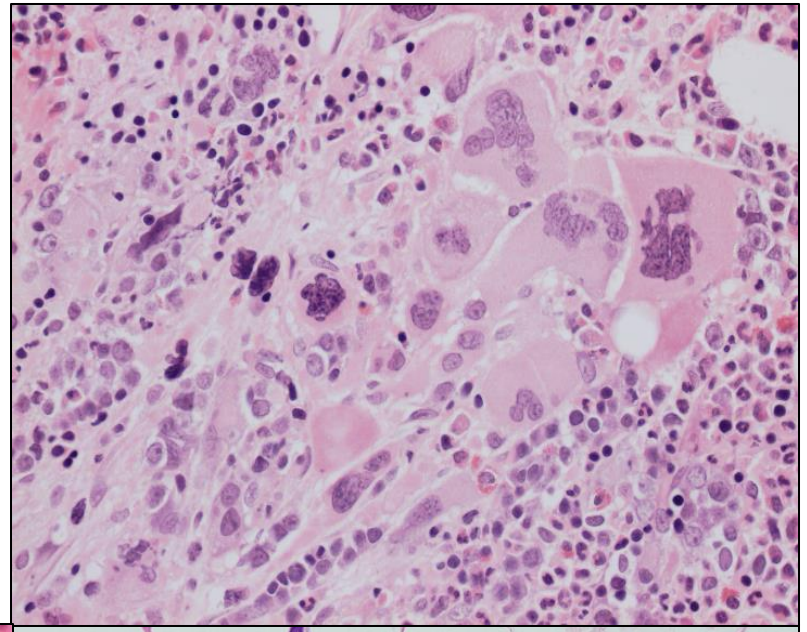


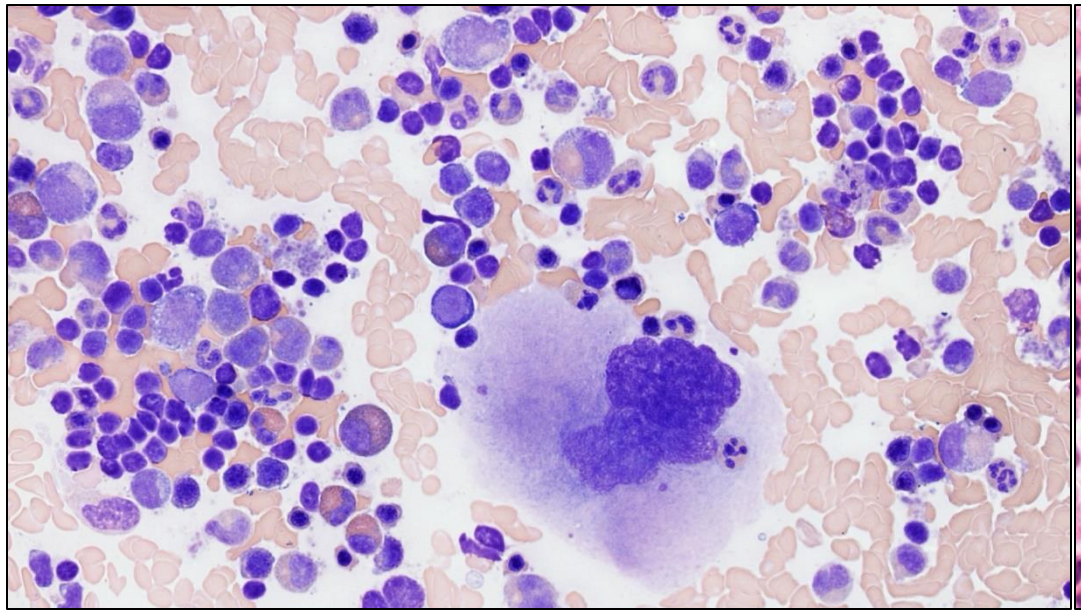


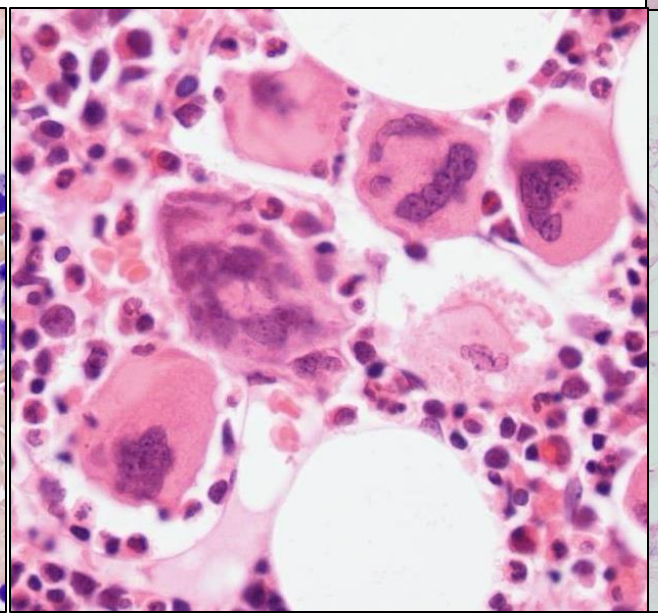


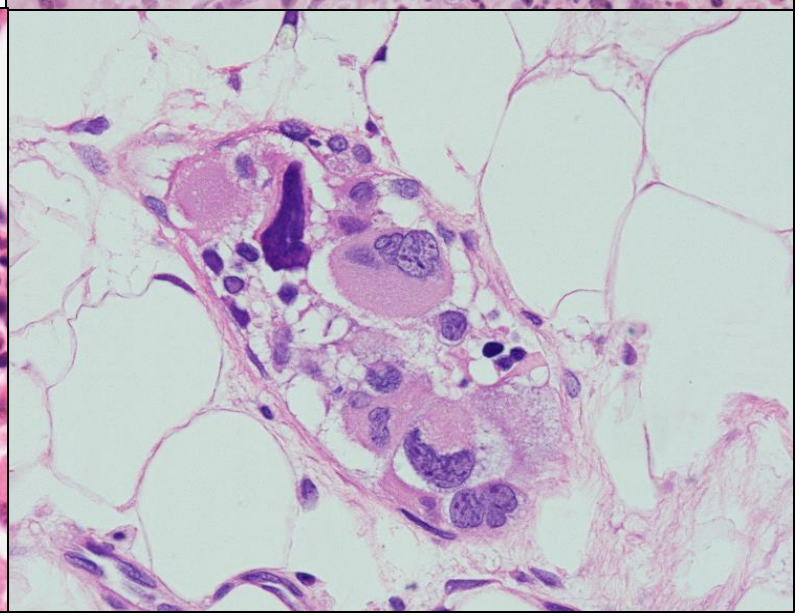
Bone Marrow: what do we look for?

- Cellularity and individual cell types
- Number and appearance
- Pattern within the bone marrow cavity
- The amount of scar tissue (reticulin)
- The bone structure, blood vessels, fat
- Changes over time



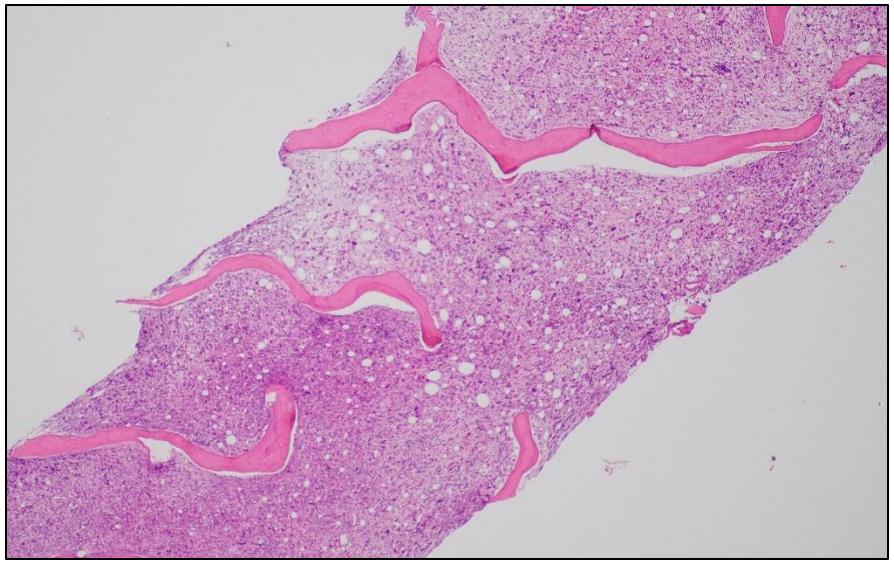


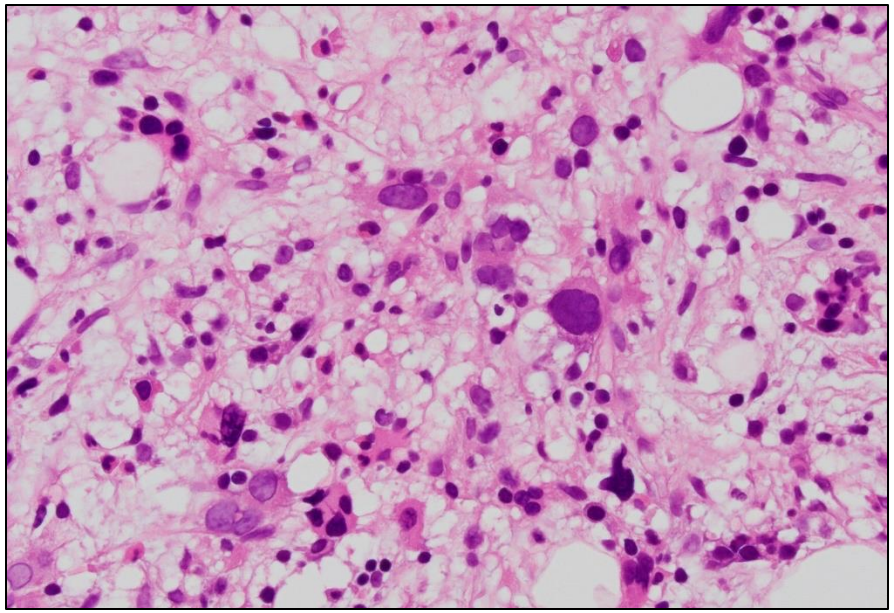




Bone Marrow: what do we look for and why?

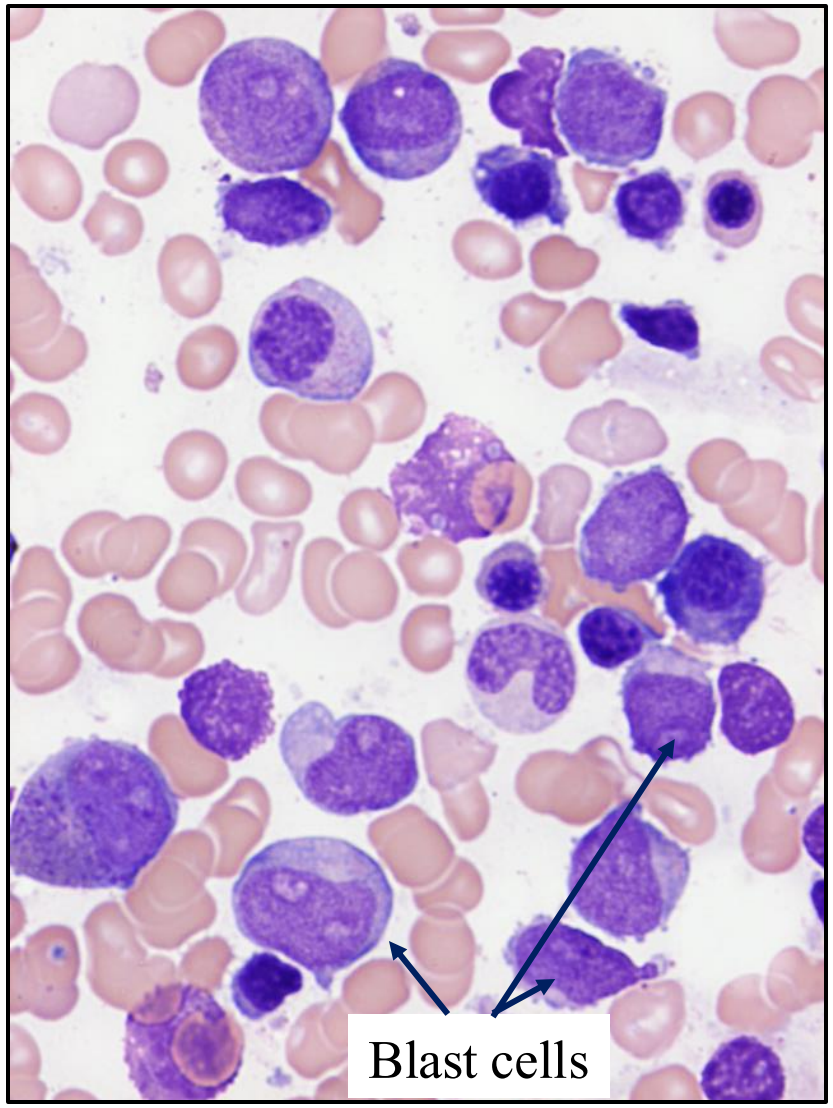
- To explain changes in the blood count / film
- Cellular composition of the bone marrow
- Granulopoiesis: increased or reduced
- Erythropoiesis: increased or reduced
- Megakaryocytes: increased or reduced
- Appearance: do the cells look normal?
- Blast cells: present; how many
- Biopsy: pattern; reticulin; bone
- Monitor treatment and the disease



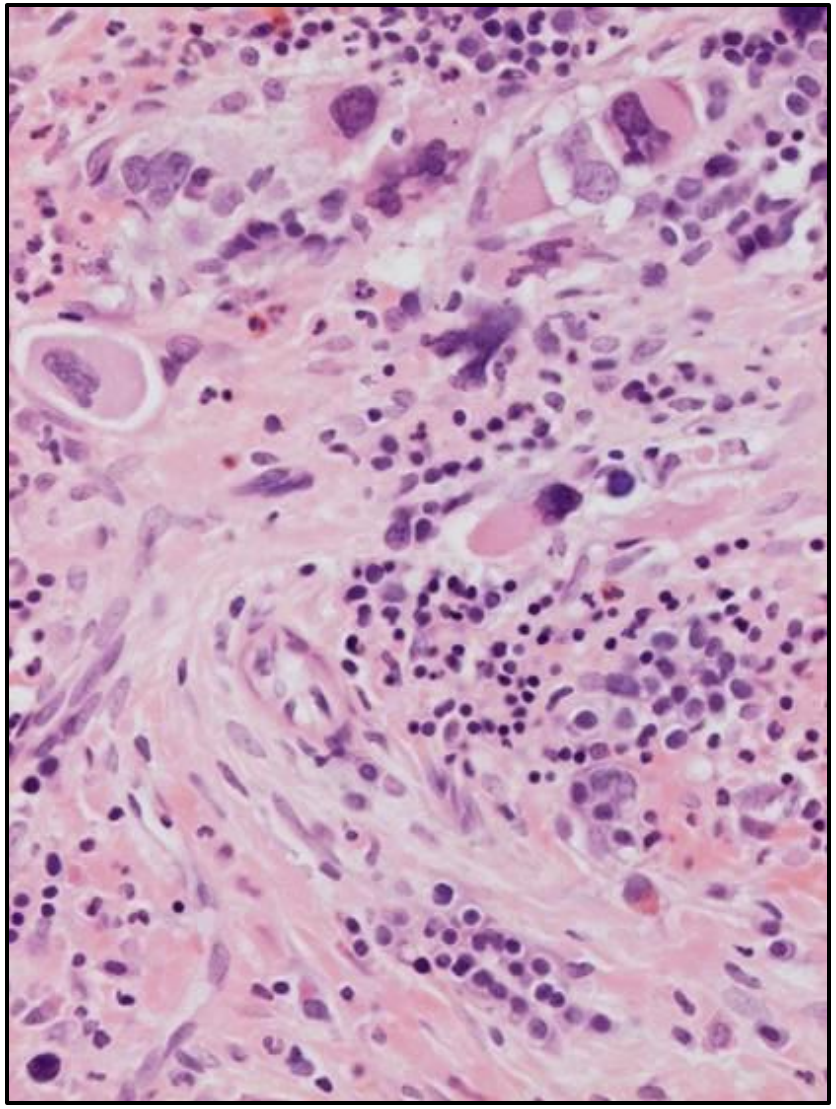


Polycythaemia Vera: disease progression

Acute Leukaemia

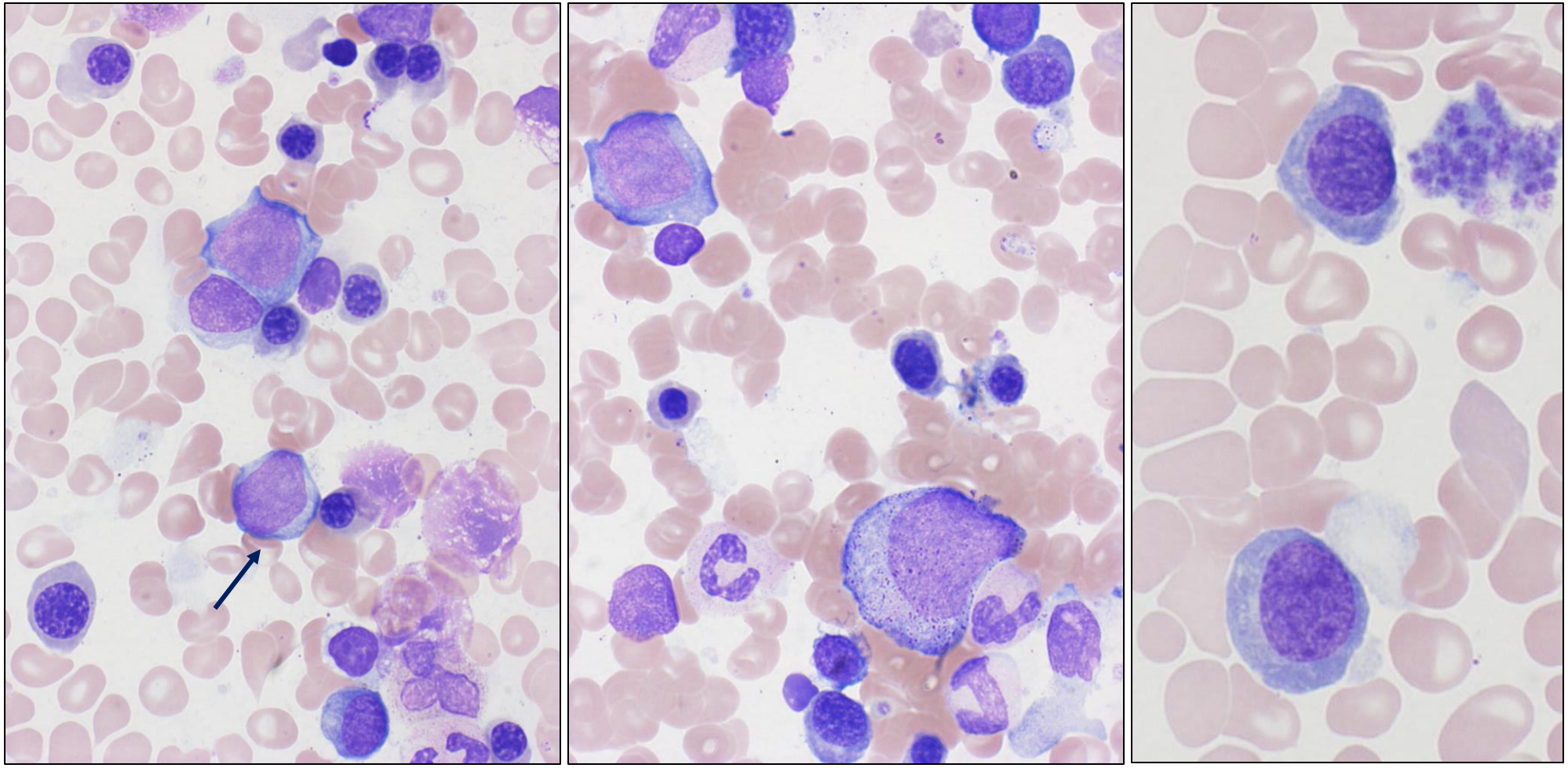


Marrow scarring (myelofibrosis)



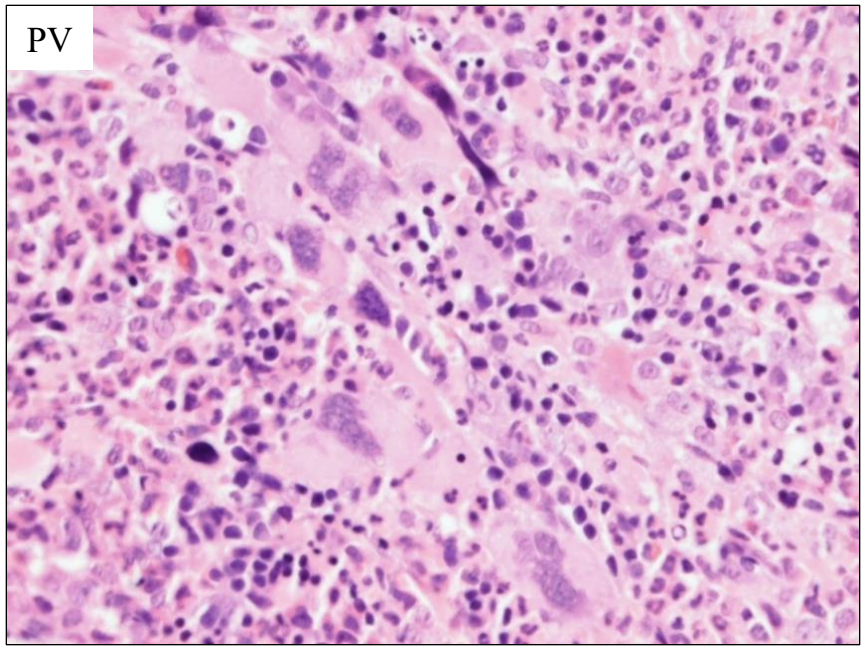
BM Changes Secondary to Treatment

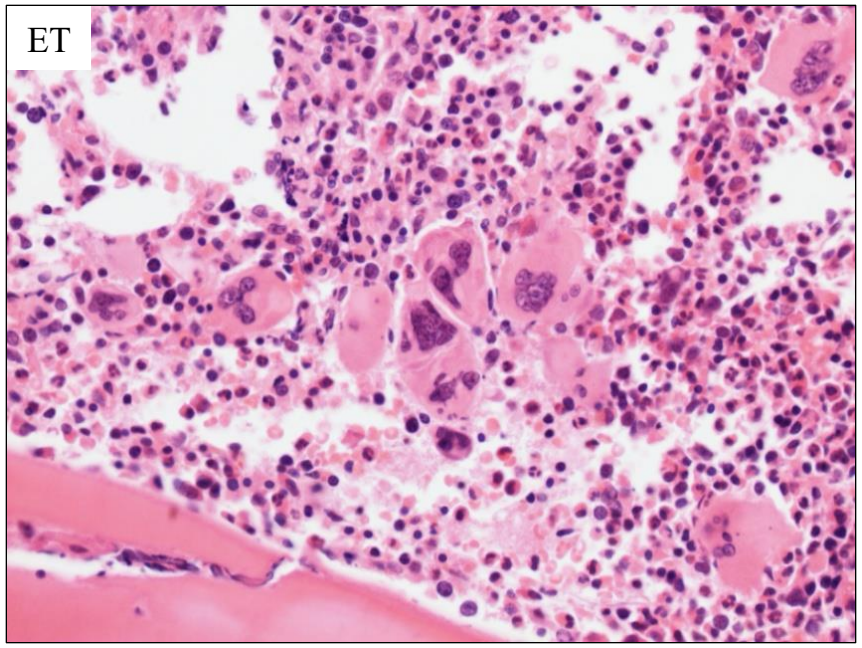
Polycythaemia vera on hydroxyurea
Megaloblastic erythropoiesis and blast cells

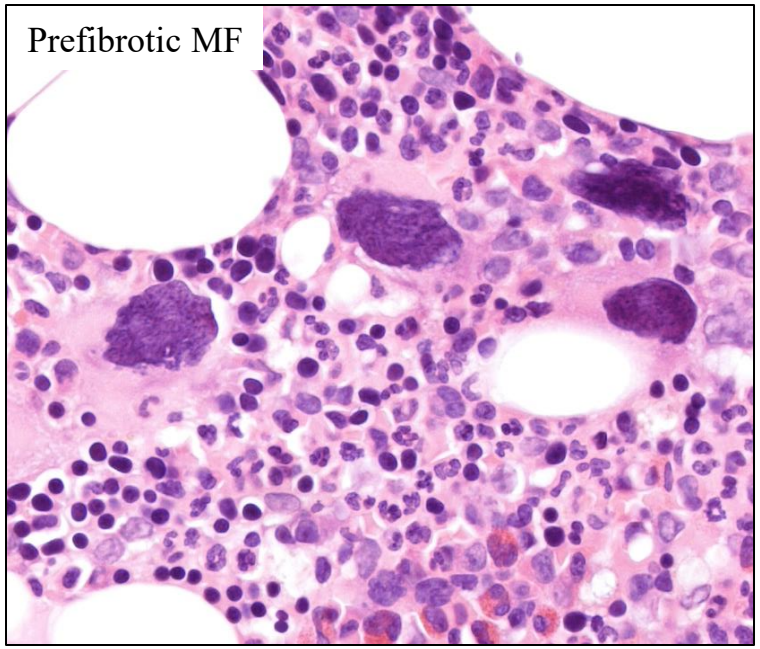


It's Challenging for Haematologists!

- Treatment effect vs disease progression (cellularity, reticulin)
- Overlapping morphology between ET / PV and MF (fibrotic progression)
- When does leukaemic progression start?
- Monitor changes over time (natural history)
- Compare current with previous: role of bone marrow examinations!

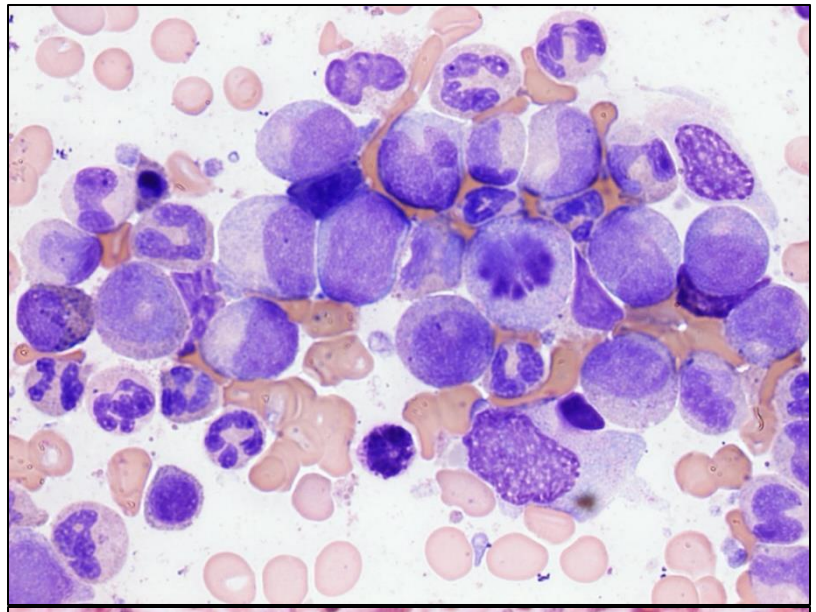


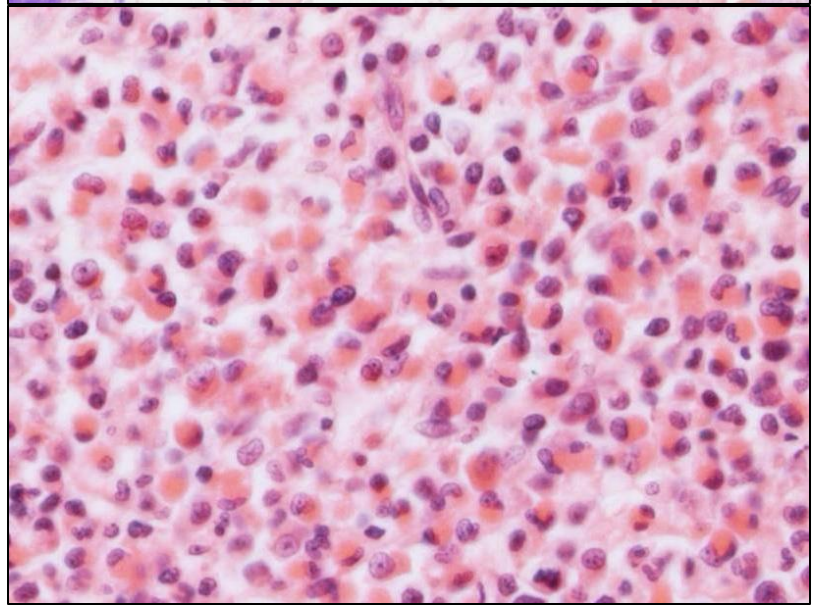




"What's New in MPN Diagnosis"?

- Two classifications of MPN:
  - Polycythaemia vera
  - Essential thrombocythaemia
  - Primary myelofibrosis
- Ng et al. IJLH 2023
- *What's not new*: morphology is critical!
- Which MPN have I not discussed?
  - Chronic myeloid leukaemia
  - Chronic neutrophilic leukaemia
  - Chronic eosinophilic leukaemia





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REVIEW

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Morphology of myeloproliferative neoplasms

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Abstract

Myeloproliferative neoplasms (MPN) are a group of clonal haematological malignancies first described by Dameshek in 1957. The Philadelphia-negative MPN that will be described are polycythaemia vera (PV), essential thrombocythaemia (ET), pre-fibrotic myelofibrosis and primary myelofibrosis (PMF). The blood and bone marrow morphology are essential in diagnosis, for WHO classification, establishing a baseline, monitoring response to treatment and identifying changes that may indicate disease progression. The blood film changes may be in any of the cellular elements. The key bone marrow features are architecture and cellularity, relative complement of individual cell types, reticulin content and bony structure. Megakaryocytes are the most abnormal cell and key to classification, as their number, location, size and cytology are all disease-defining. Reticulin content and grade are integral to assignment of the diagnosis of myelofibrosis. Even with careful assessment of all these features, not all cases fit neatly into the diagnostic entities; there is frequent overlap reflecting the biological disease continuum rather than distinct entities. Notwithstanding this, an accurate morphologic diagnosis in MPN is crucial due to the significant differences in prognosis between different subtypes and the availability of different therapies in the era of novel agents. The distinction between "reactive" and MPN is also not always straightforward and caution needs to be exercised given the prevalence of "triple negative" MPN. Here we describe the morphology of MPN including comments on changes with disease evolution and with treatment.