

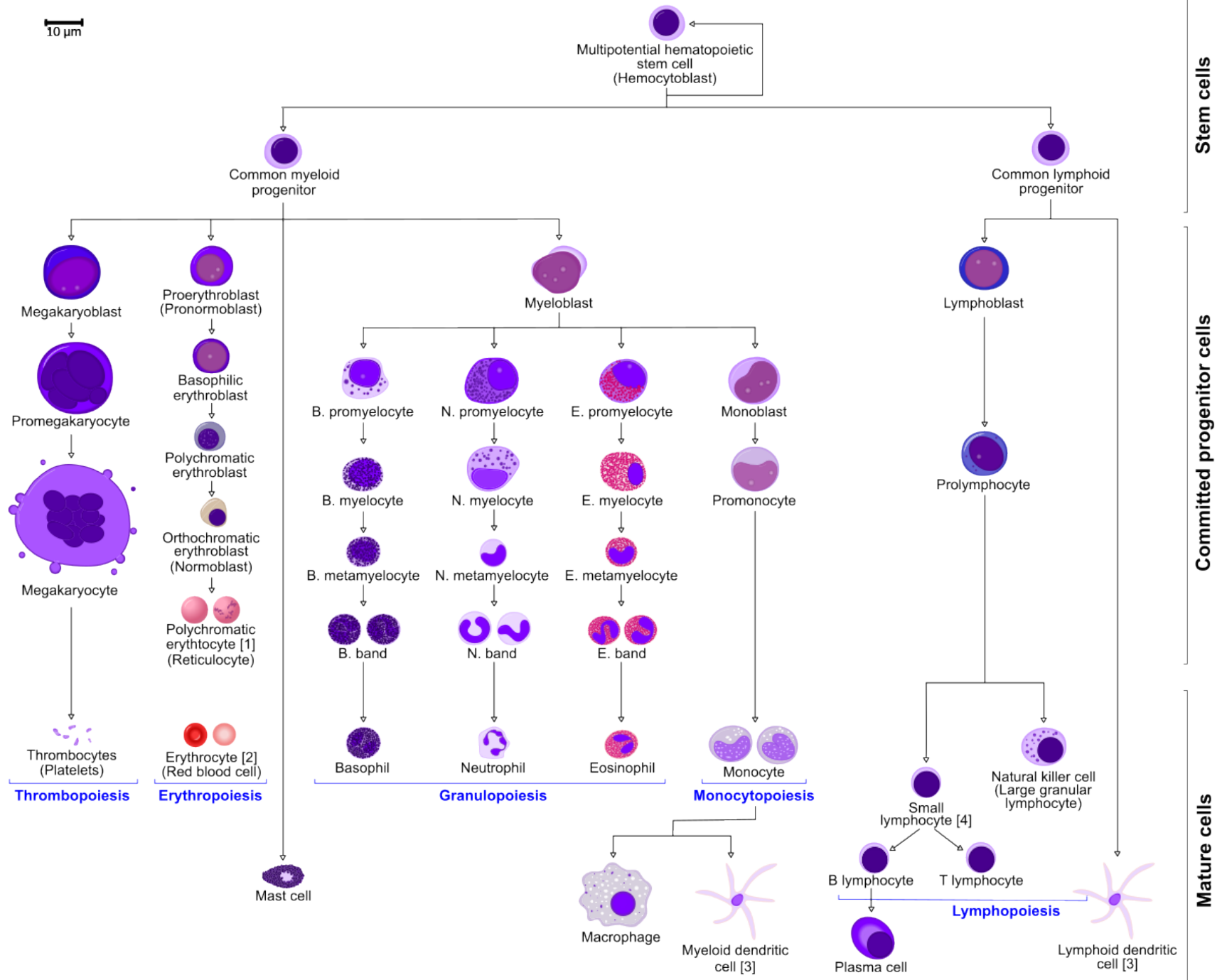
WBC disorders III

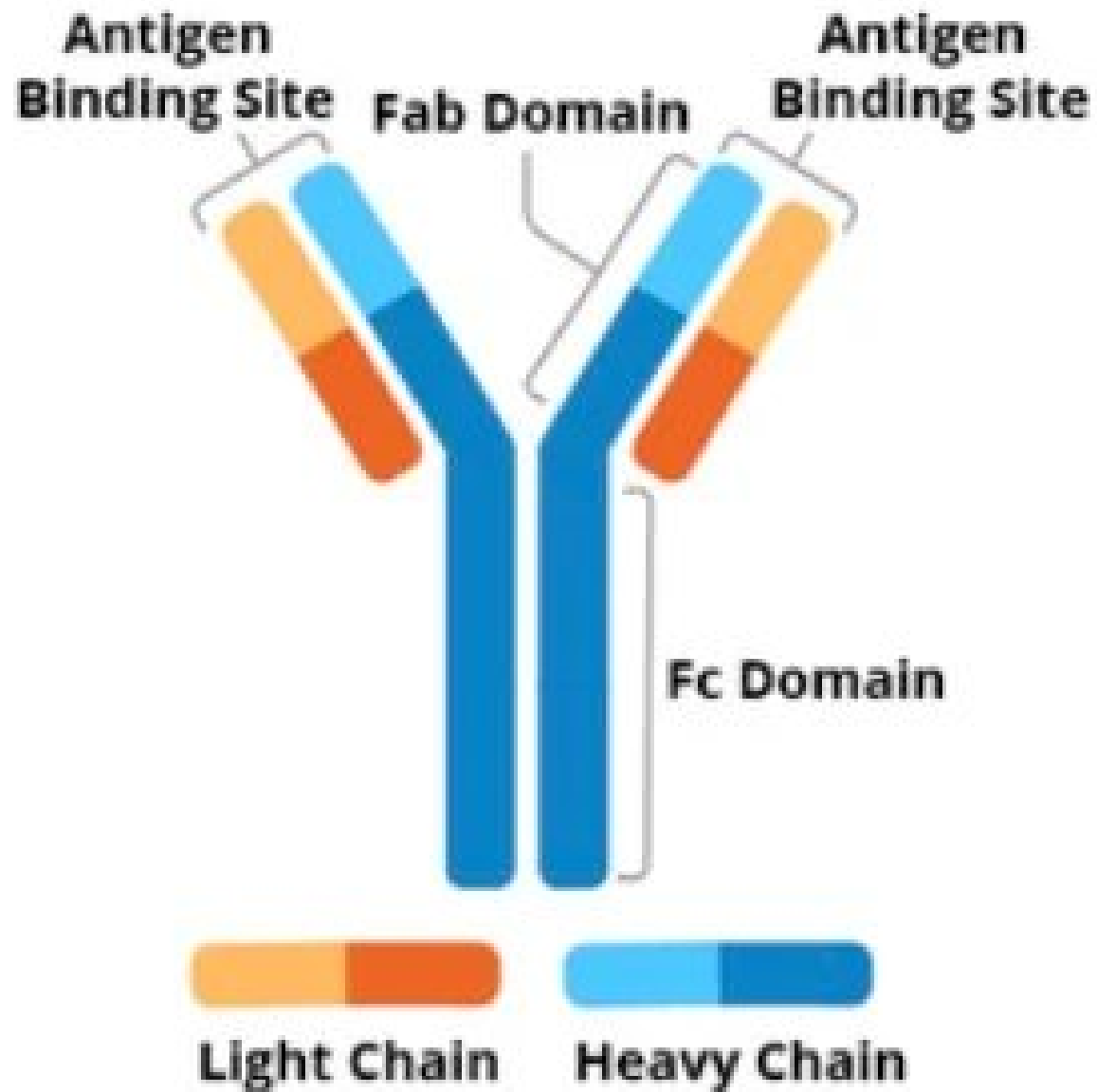
Momen Zeineddin

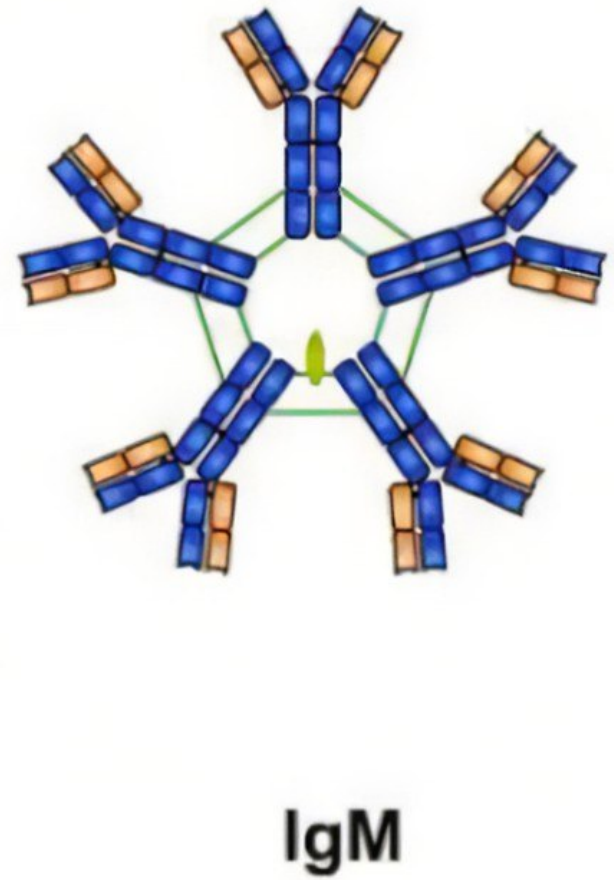
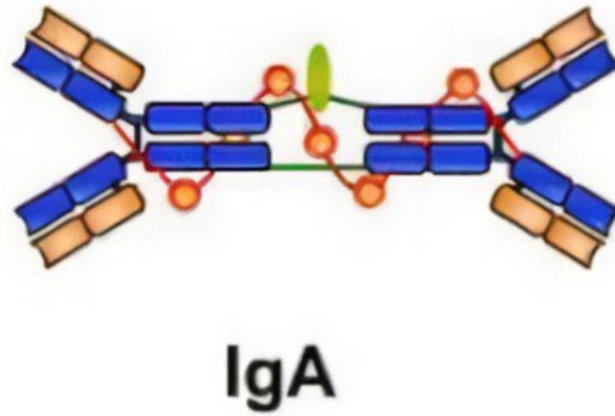
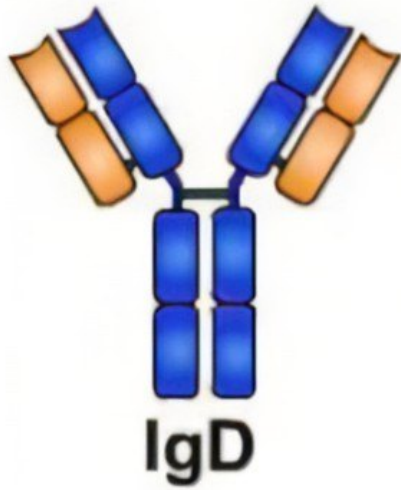
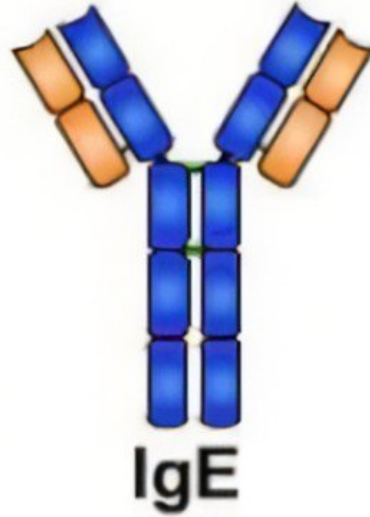
WBC disorders III

- ✓ Plasma cell disorder
- ✓ Myelodysplastic syndromes (MDS)
- ✓ Myeloproliferative disorders (MPV)
- ✓ LCH & HLH

10 μ m





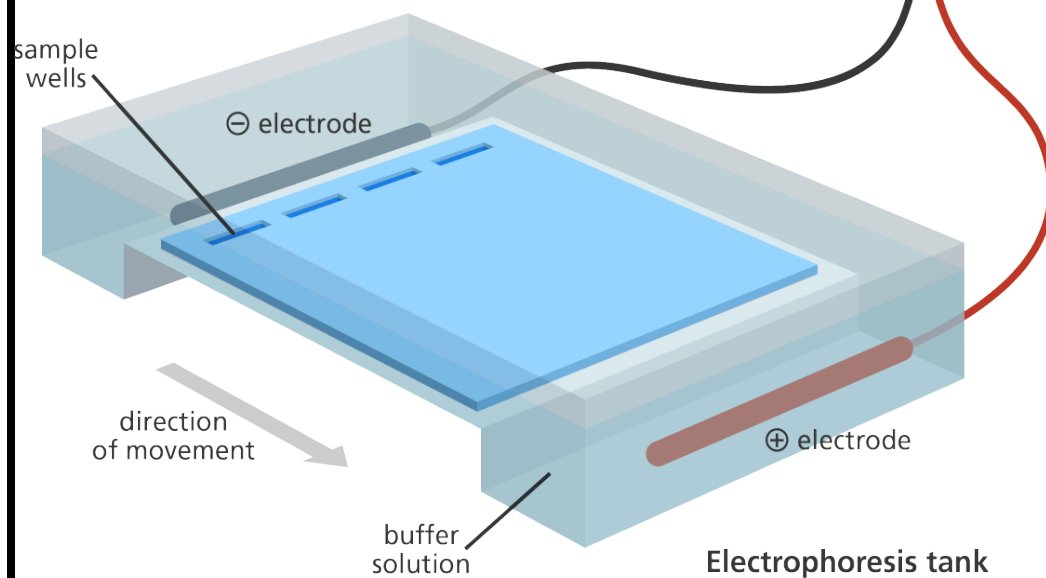


Albumin

Polyclonal antibodies pattern

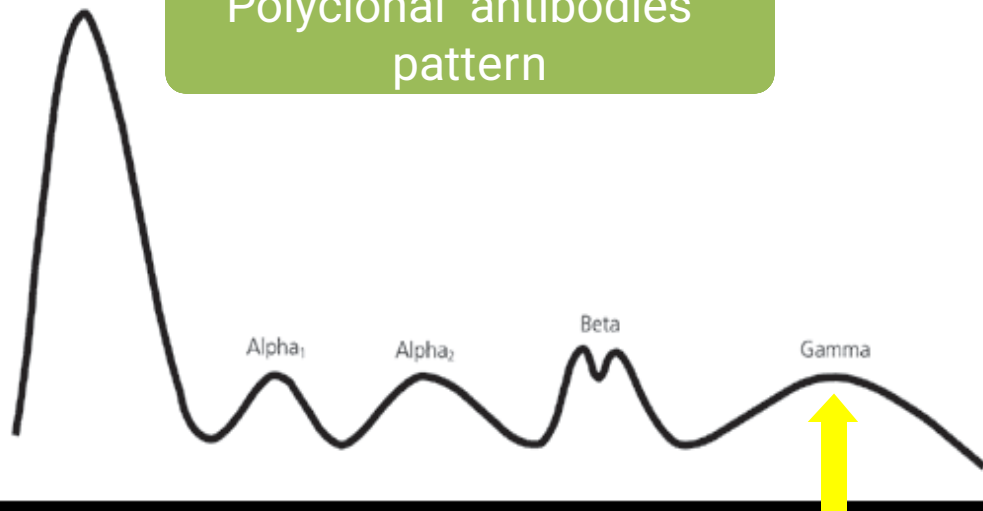


Power supply



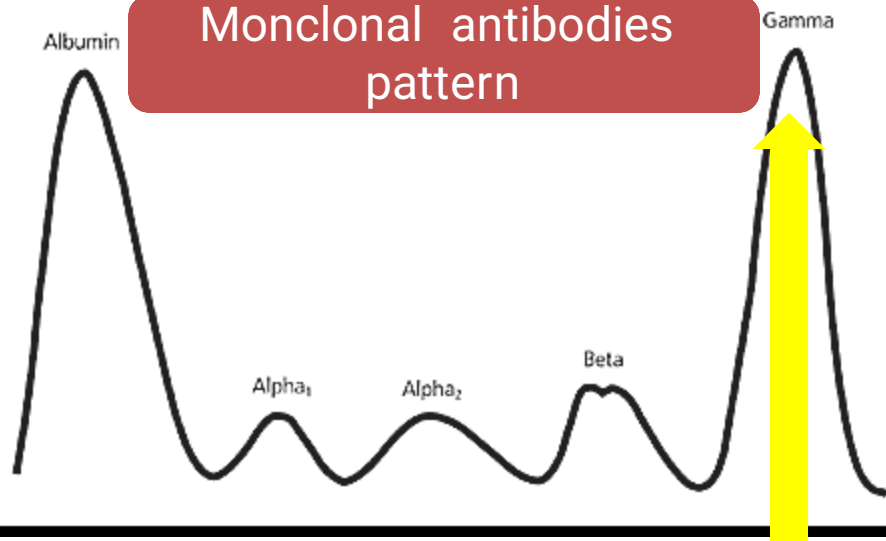
Albumin

Polyclonal antibodies pattern

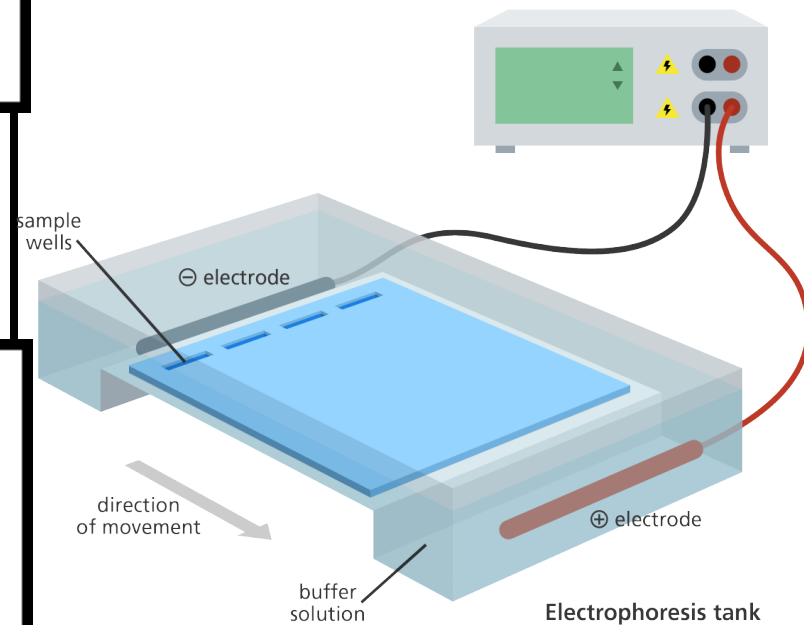


Albumin

Monoclonal antibodies pattern



Power supply



Amyloidosis

Deposition of amyloid

Amyloidosis is one of a group of disorders characterized by **abnormal protein folding**.

Plasma cell disorders

Plasma cells disorders are group of B-cell disorder characterized by monoclonal Ig or Ig fragment secretions.

The homogeneous Ig identified in high molecular weight structure found in the blood is called an **M component**

Monoclonal gammopathy = dysproteinemia=
paraproteinemia

Plasma cell disorders

15% of **deaths** from malignant WBC disorders

Most common in **middle-aged and elderly**
persons

Plasma cell disorders

Normally Ig not present in the urine (in the absence of glomerular damage).

Synthesize of **excess light chain (free) Kappa or lambda** which is small in size and secreted in urine (**Bence Jones protein**)

Occasionally only light chain or heavy chain are produced.

Plasma cell disorders

- 1) Multiple myeloma
- 2) Solitary plasmacytoma
- 3) Monoclonal gammopathy of undetermined significance(MGUS)
- 4) lymphoplasmacytic lymphoma

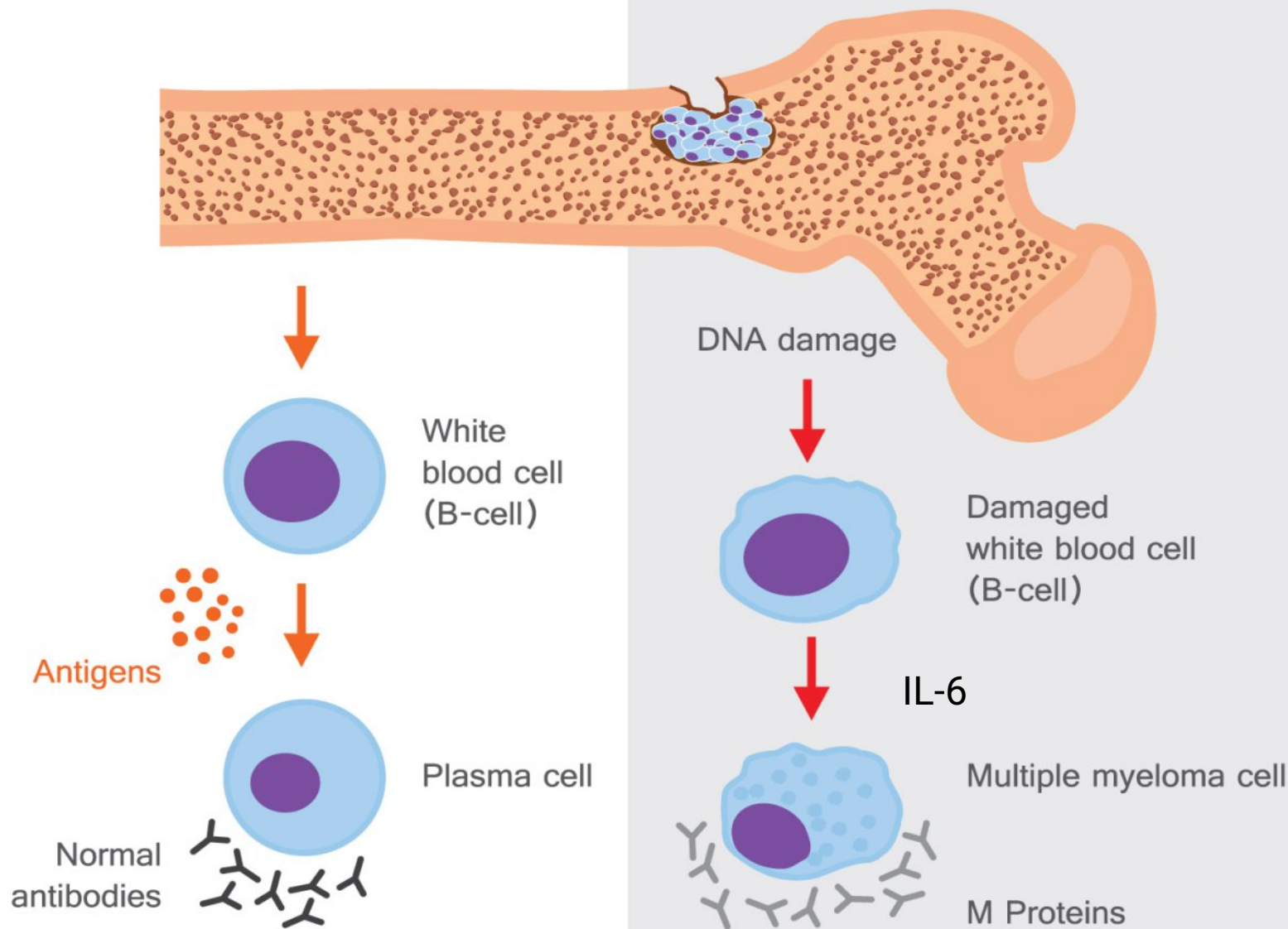
Multiple Myeloma

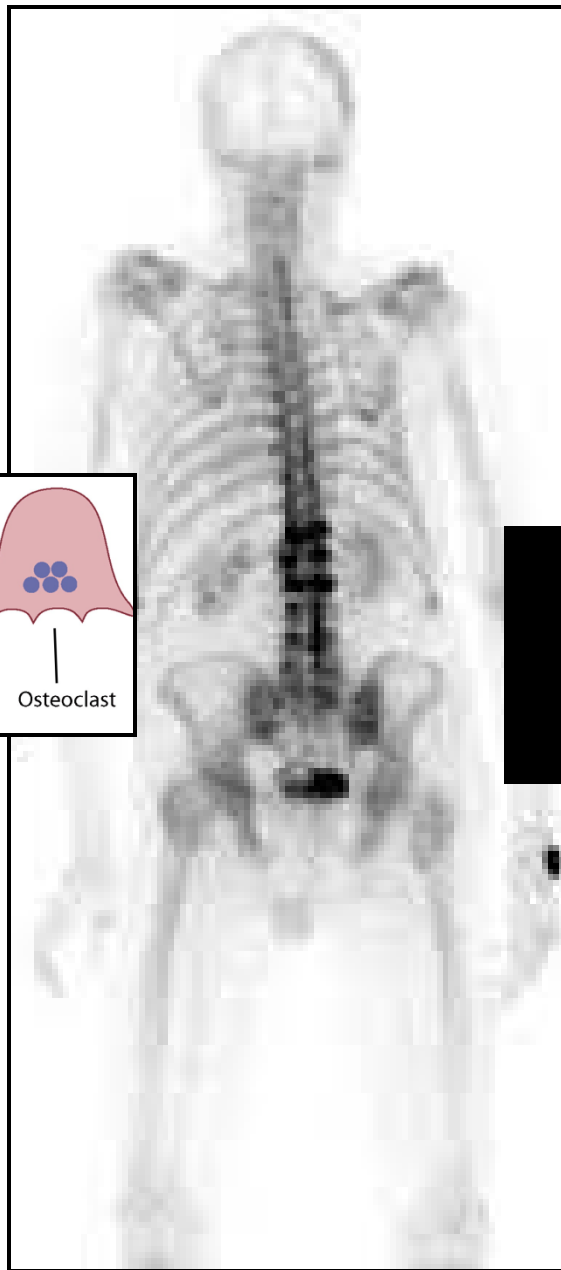
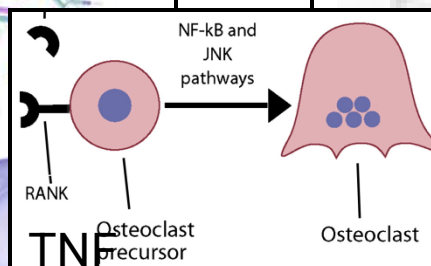
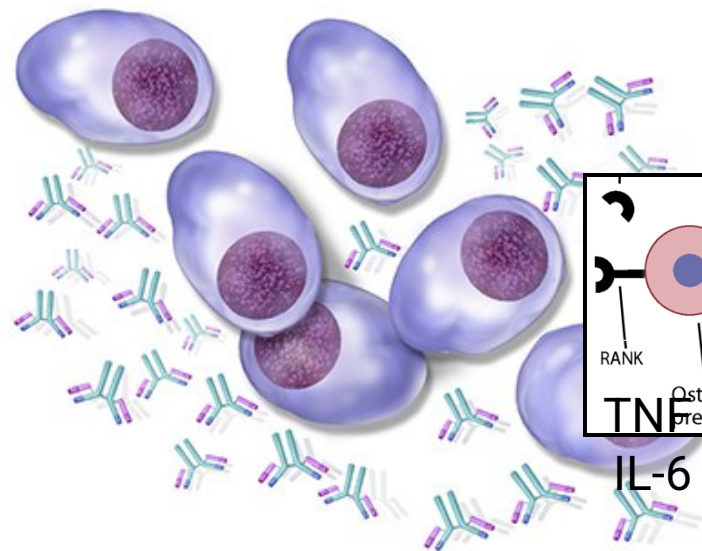
Clonal malignant proliferation of plasma cells in the bone marrow.

The most common malignant lesion of bone.

Healthy Bone Marrow

Multiple Myeloma





Bony pains
Pathological
fractures
Hypercalcemia
Lytic lesions

Multiple Myeloma

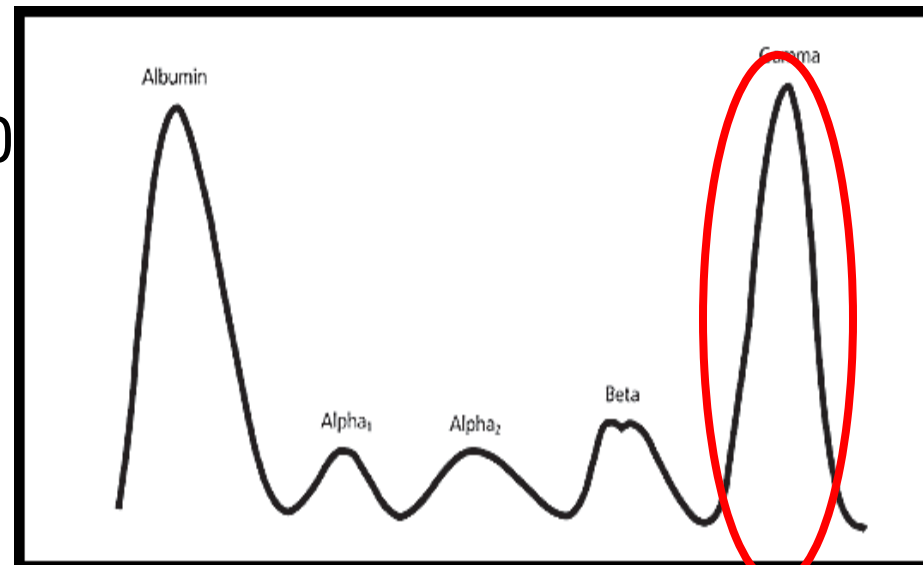
Associated with multifocal lytic lesions in the skeletal system

The M component is:

IgG in 60% of patients

IgA in 20-25 %

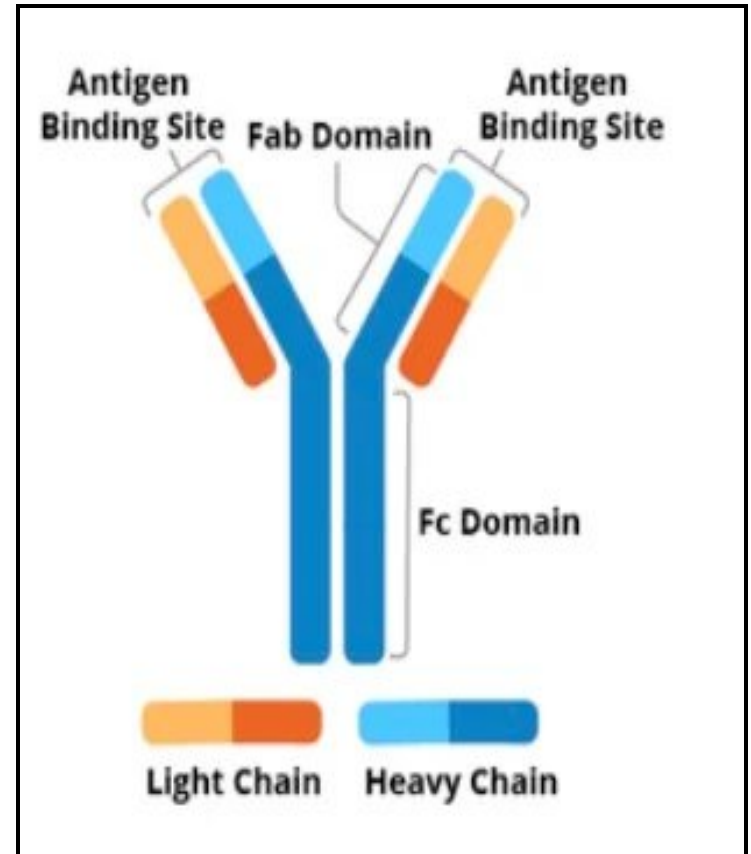
κ or λ light chains in 15-20
rarely, it is IgM, IgD, or IgE.



Multiple Myeloma

κ or λ light chains, when excreted in urine, termed Bence Jones proteins.

Bence Jones proteinuria without serum M component (light-chain disease)



Morphology

MM usually presents as destructive bone lesions throughout the skeletal system

Manifested as pains, pathological fractures, Lytic punched out X-ray lesions and hypercalcemia (confusion and lethargy).

Vertebral column, ribs, skull, pelvis, femur, clavicle and scapula.

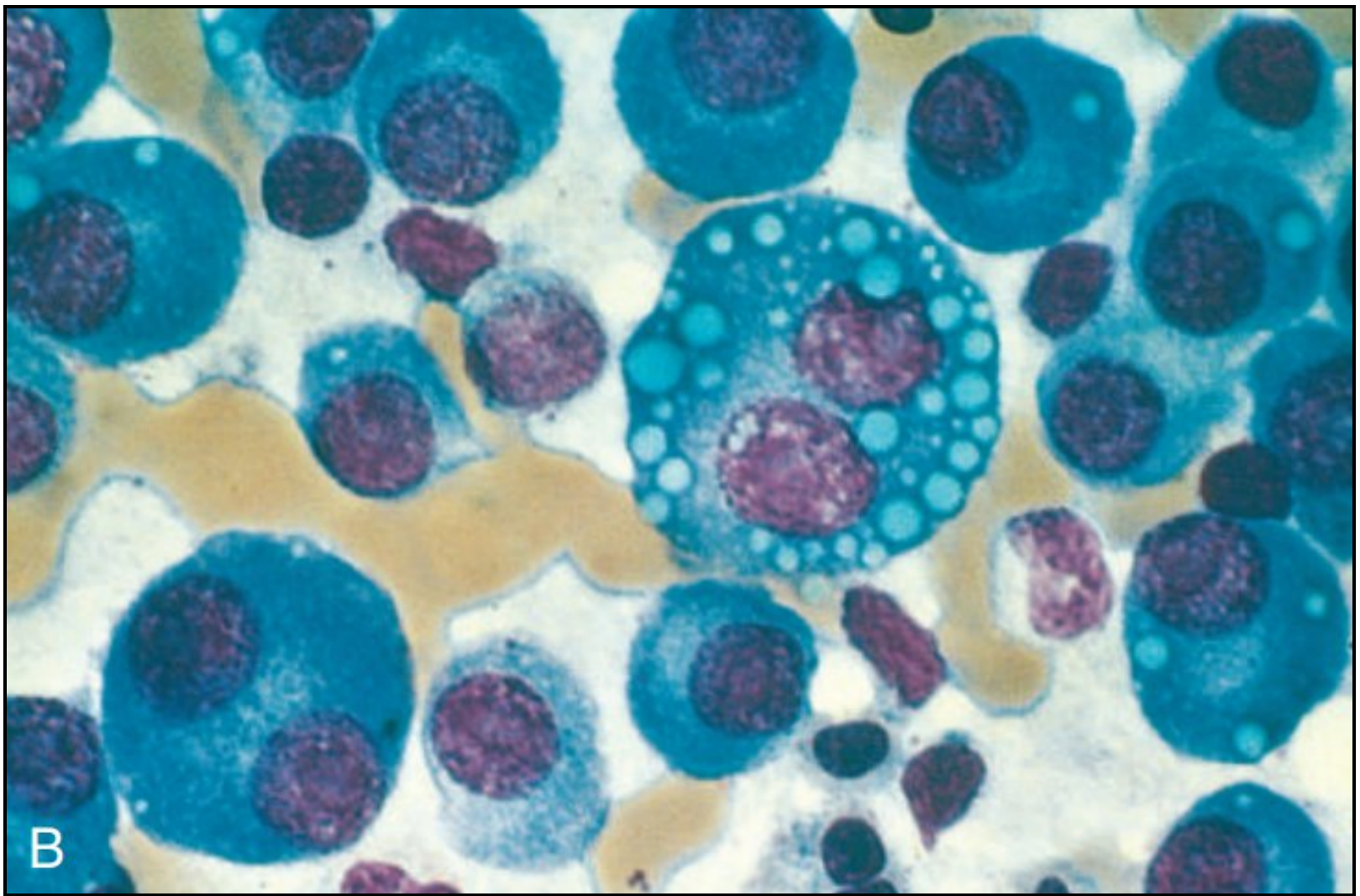
Morphology

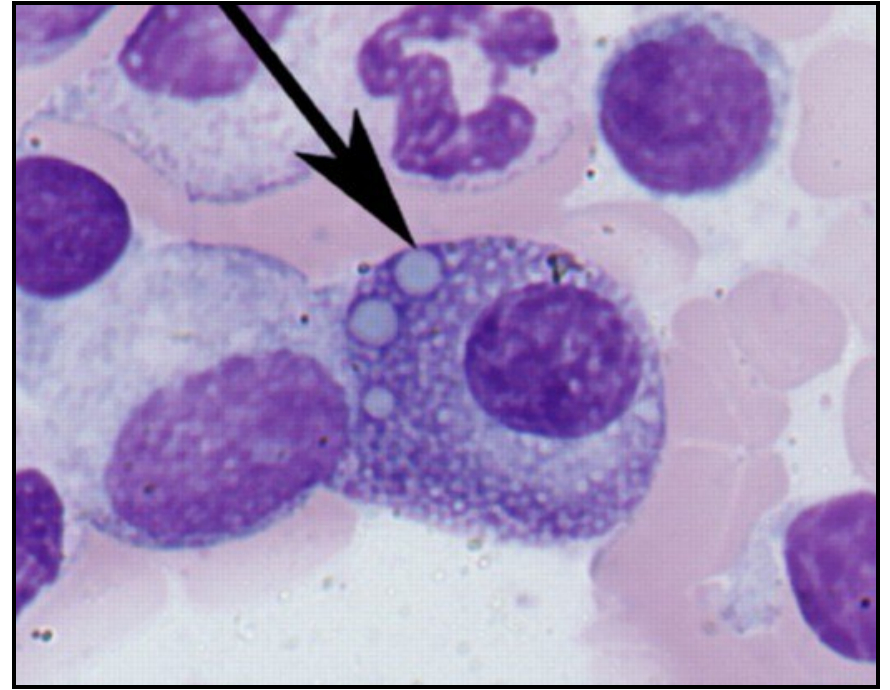
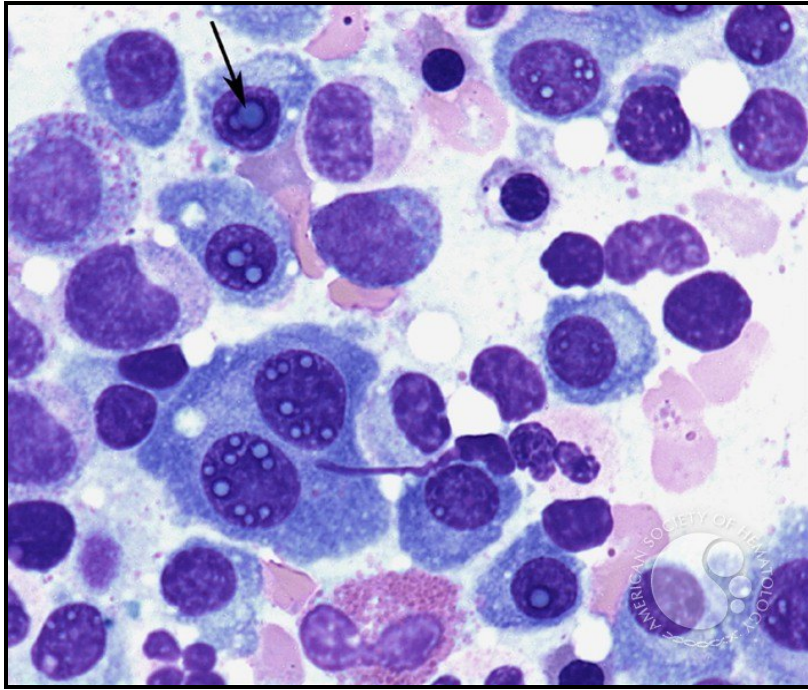
Increased number of plasma cells (10% - 90%) in BM.

The neoplastic plasma cells may resemble normal mature plasma cells but more often show abnormal features.

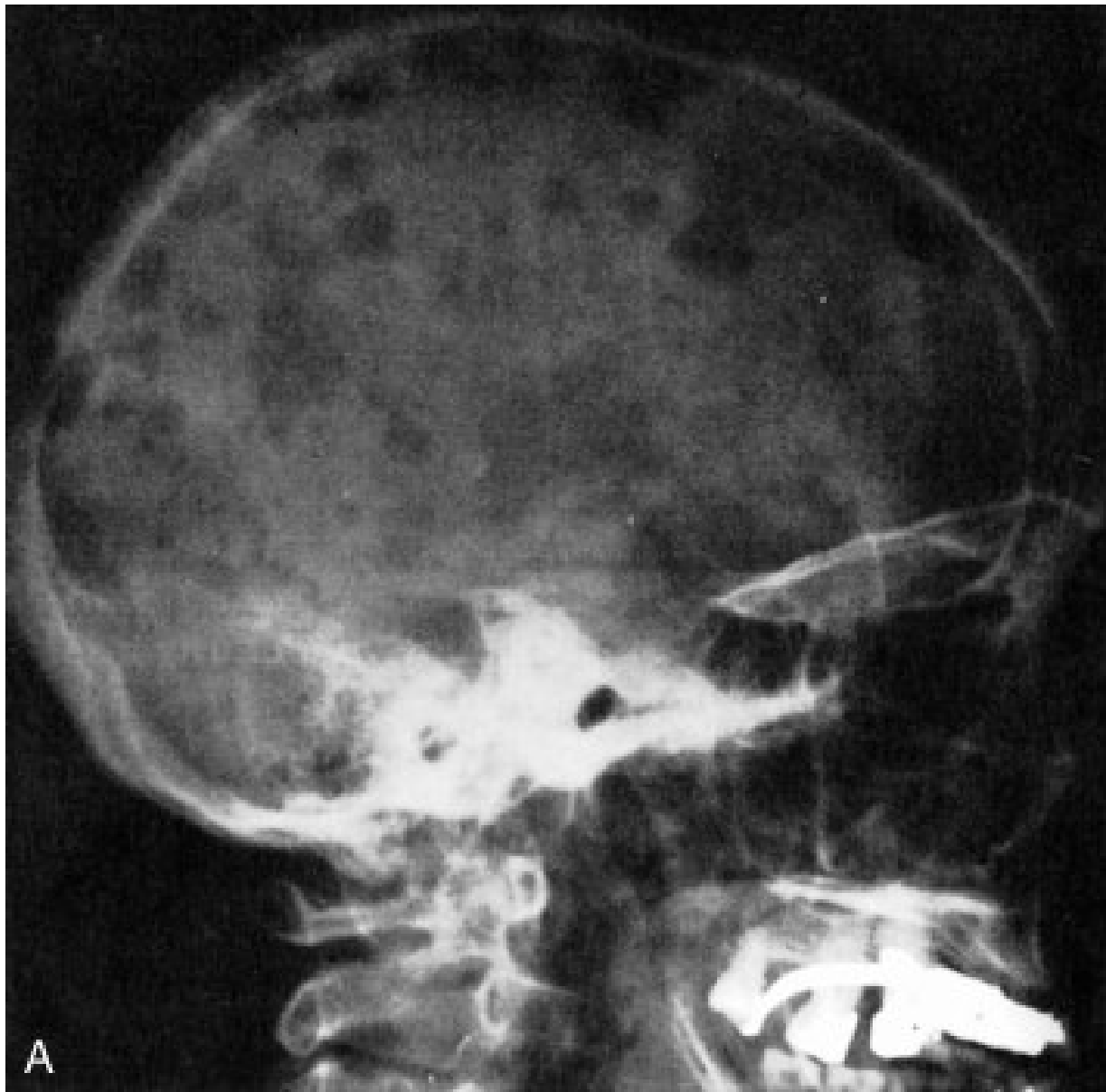
Plasma cell infiltrates the spleen, liver, kidneys, lungs, and LN.

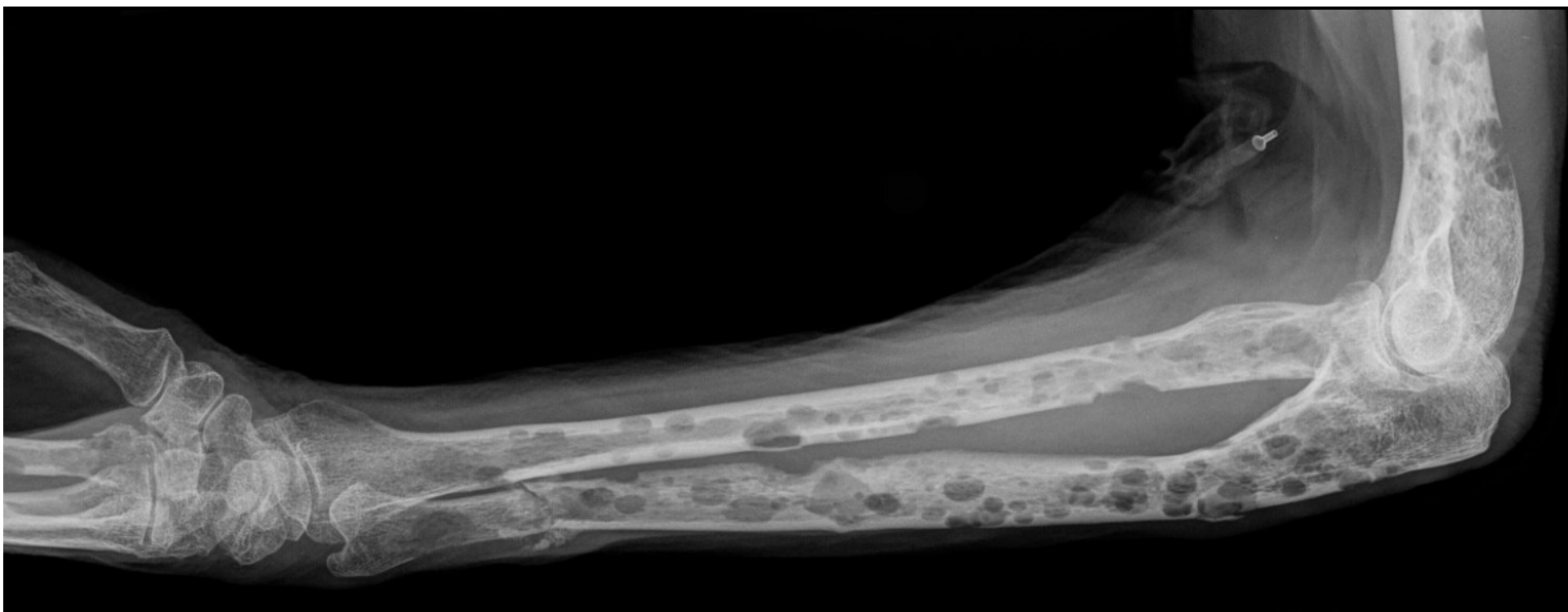
Rouleaux formation











Myeloma Kindney (nephrosis):

Deposition of **toxic light chains** to the renal tubules with surrounding **multinucleate giant cells** (macrophages).

Leading to myeloma kidney and Amyloidosis.

Metastatic calcification within the kidney
(hypercalcemia)

Pyelonephritis may occur.

Clinical Course:

The peak age is between 50 and 60 years

Progressive disease, with 5-year OS 50%

Clinical features :

Bone pain

Pathologic fractures

Hypercalcemia

Neurologic manifestations : confusion and lethargy

Anemia results from marrow replacement

Clinical Course:

Recurrent infections: severe suppression of normal Ig secretion

Hyperviscosity syndrome from excessive production and aggregation of myeloma proteins .

Renal insufficiency.

Diagnosis:

Radiologically : punched-out defects in the bone

Electrophoresis of the serum >> Monoclonal Ig

Electrophoresis the urine >> light chain >> **BJP**

Only 1% of cases, monoclonal IG can be found within the plasma cell masses but not in the serum or urine (**nonsecretory myelomas**)

Plasma cell disorders

- 1) Multiple myeloma
- 2) Solitary plasmacytoma
- 3) Monoclonal gammopathy of undetermined significance(MGUS)
- 4) lymphoplasmacytic lymphoma

2. Solitary Plasmacytoma

Solitary plasmacytoma is an infrequent variant that presents as a **single mass** in bone or soft tissue.

Solitary skeletal plasmacytoma.

Soft tissue: URT (sinuses, nasopharynx, larynx).

Modest elevations in the levels of M protein

Can progress to MM

Plasma cell disorders

- 1) Multiple myeloma
- 2) Solitary plasmacytoma
- 3) Monoclonal gammopathy of undetermined significance (MGUS)
- 4) lymphoplasmacytic lymphoma

3-Monoclonal Gammopathy of Undetermined Significance (MGUS)

Asymptomatic premalignant clonal plasma cell with serum protein without other MM manifestation.

Common in elderly (2% > 50 YO)

Most common plasma cell dyscrasis

20% of patients with MGUS develop plasma cell disorders (MM, lymphoplasmacytic lymphoma, or amyloidosis).

1 % of patients with MGUS develop MM yearly.

3-Monoclonal Gammopathy of Undetermined Significance (MGUS)

M spike on electrophoresis

MM features are absent (no lytic lesions, hypercalcemia, AL amyloid, or Bence Jones proteinuria).

Patients with MGUS have < 3 g/dL of monoclonal protein in the serum and **no Bence Jones proteinuria**

Plasma cell disorders

- 1) Multiple myeloma
- 2) Solitary plasmacytoma
- 3) Monoclonal gammopathy of undetermined significance(MGUS)
- 4) lymphoplasmacytic lymphoma

4. Lymphoplasmacytic Lymphoma

B-cell lymphoma with monoclonal IgM production.

Mixed proliferation of B cells: range from lymphocytes to plasma cells

The M component is mainly IgM

Affects older persons

The median survival is 4 to 5 years.

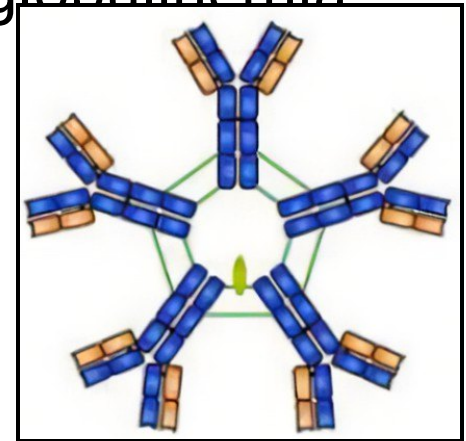
4. Lymphoplasmacytic Lymphoma

B-cell lymphomas

Lymphadenopathy, Spleen, & BM infiltrations

Lytic lesions are not seen

large amounts of IgM give rise to a hyperviscosity syndrome called Waldenström Macroglobulinemia



Waldenström macroglobulinemia

Hyperviscosity :-

Visual impairment (retinal hemorrhage)

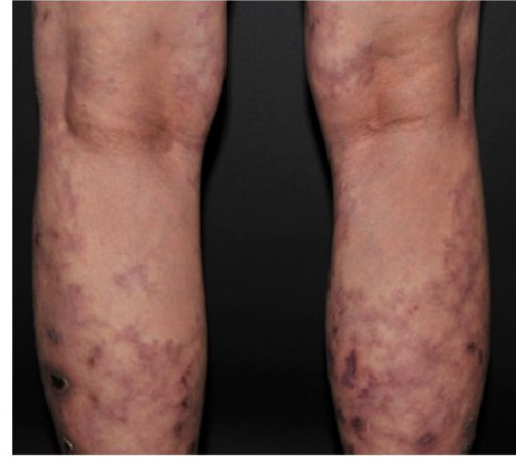
Neurologic deficits: headaches, dizziness, deafness, & stroke.

Bleeding: macroglobulins and clotting factors complexes (affects platelet aggregation).

Cryoglobulinemia : precipitation of macroglobulins at low temperatures (Raynaud phenomenon).

Plasmapheresis can be used in emergency situations.





Plasma cell disorders

- 1) Multiple myeloma
- 2) Solitary plasmacytoma
- 3) Monoclonal gammopathy of undetermined significance(MGUS)
- 4) lymphoplasmacytic lymphoma

WBC disorders III

- ✓ Plasma cell disorder
- ✓ Myelodysplastic syndromes (MDS)
- ✓ Myelopoietic disorders (MPD)
- ✓ LCH & HLH

Peripheral blood	BM	
Cytopenias	Hypocellular BM Fatty infiltrations	Aplastic anemia
Cytopenias		
Increased clonal cells Abnormal cells		

Myelodysplastic Syndromes

Myelo/dysplasia

A group of clonal stem cell disorders, Characterized by:

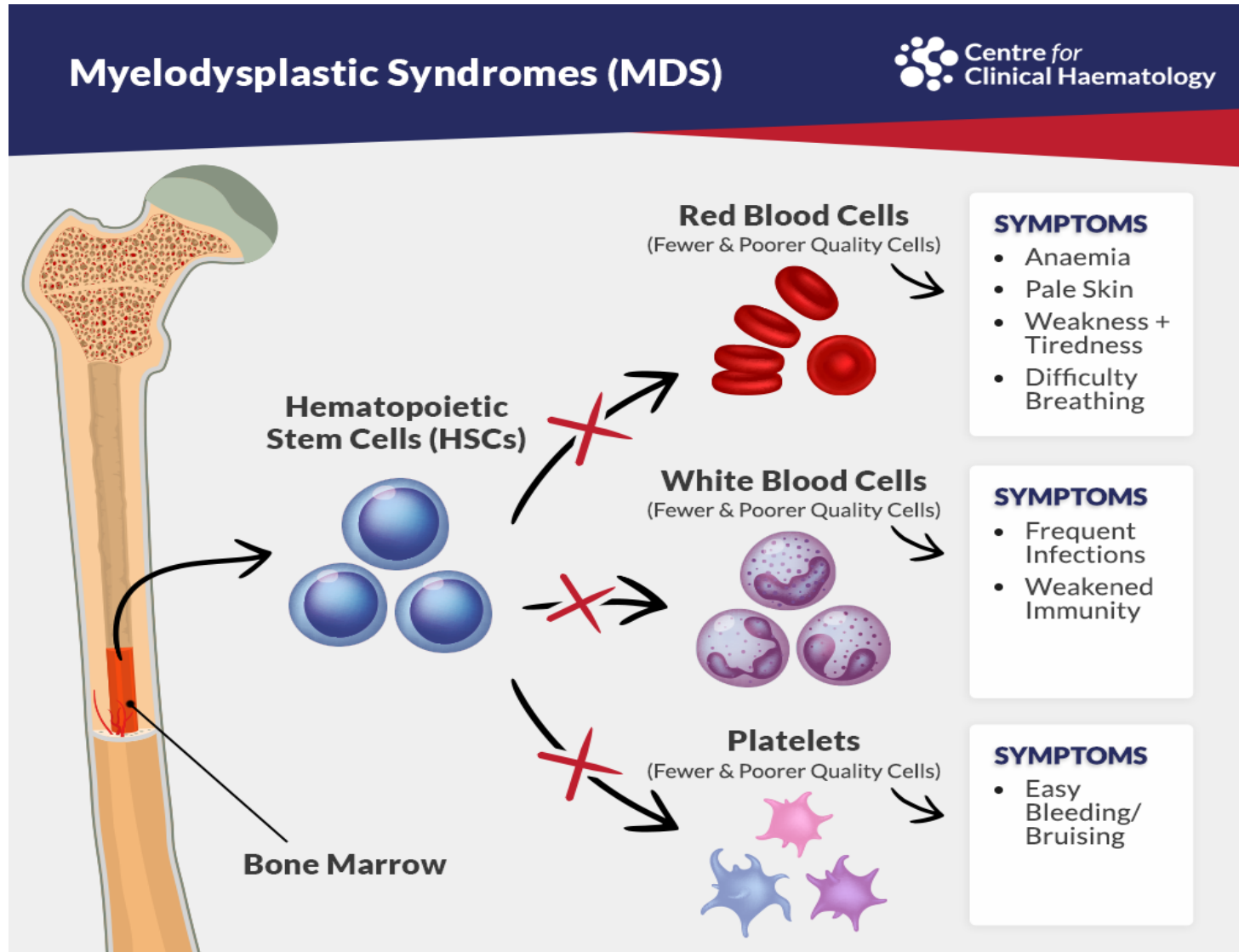
Maturation defects resulting in ineffective hematopoiesis

An increased risk of transformation to AML

BM is replaced by the multipotent stem cell that retains the capacity to differentiate but in an ineffective, disordered manner

Myelodysplastic Syndromes

BM is **hypercellular** or normocellular, while the peripheral blood shows **pancytopenia**



Myelodysplastic Syndromes

Causes:

Idiopathic

Post treatment: chemotherapy, radiation therapy

Associated with monosomy 5 & 7, deletions of 5q & 7q, & trisomy 8

Myelodysplastic Syndromes

Most patients are older males between 50 and 70 years

¼ MDS cases develop AML

Poor response to chemotherapy

Median survival time varies from 9 to 29 months

Most patients die from infection or bleeding, or AML

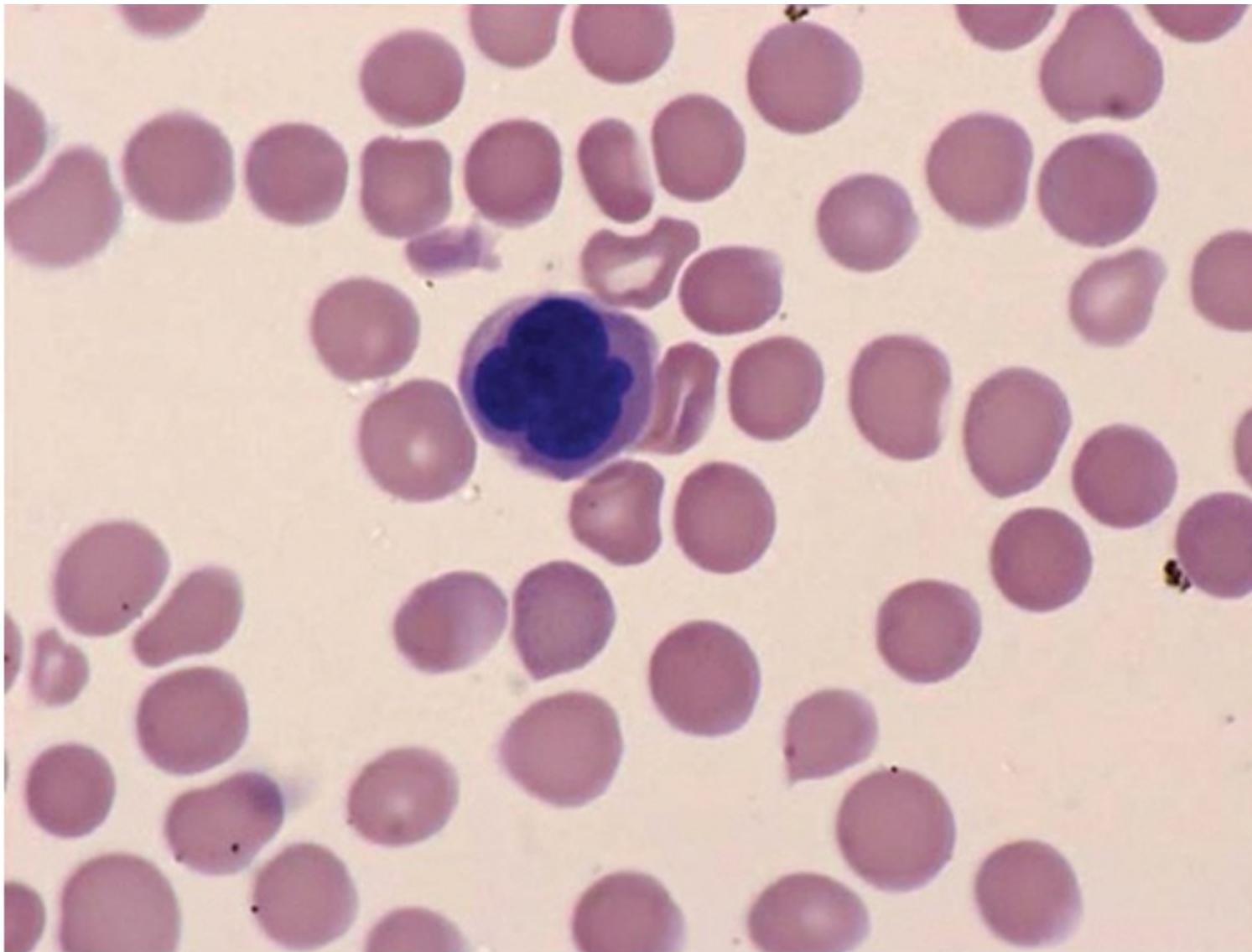
MDS

Morphologically:

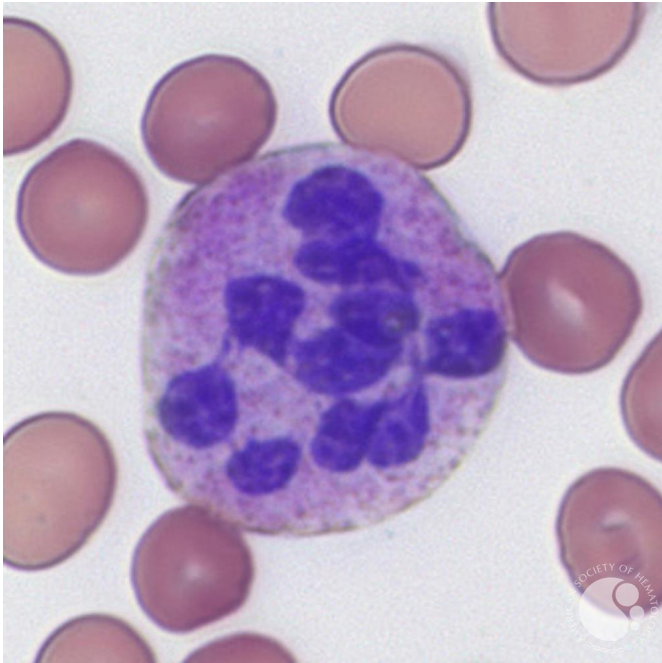
Megaloblastoid erythroid precursor,
ringed sideroblasts

Increased Bizarre-looking blasts, (< 20%)

Micromegakaryocytes,



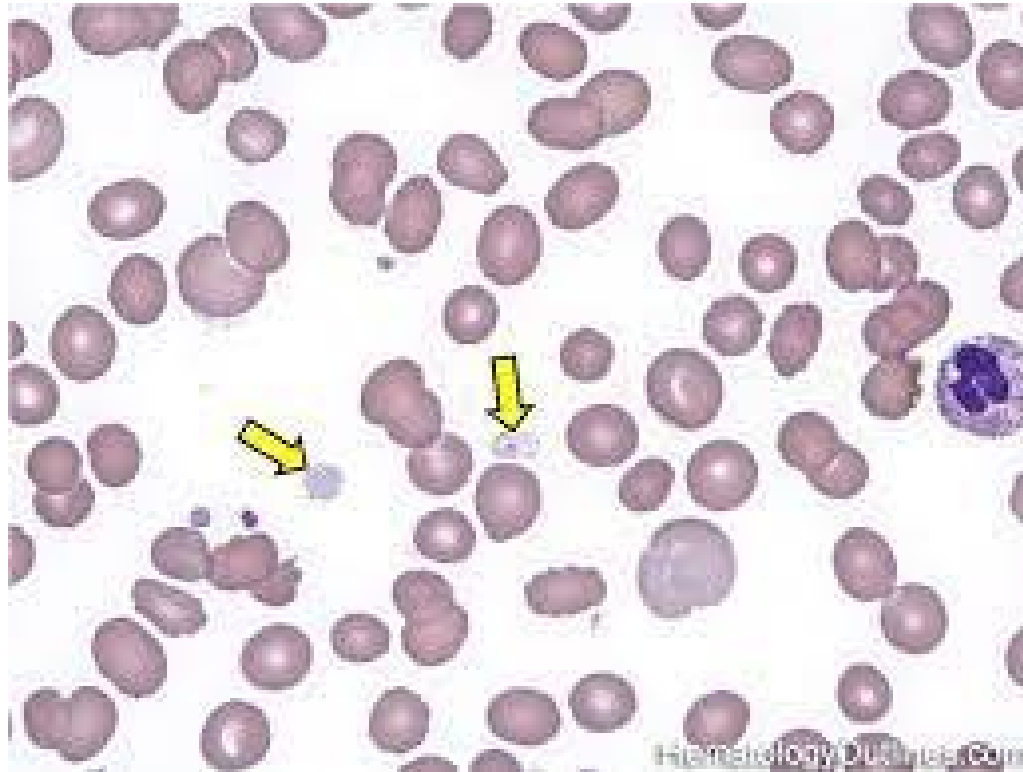
RBC peripheral blood. Dysplastic nucleated red blood cell, peripheral blood. The nucleus shows an abnormal shape and size.



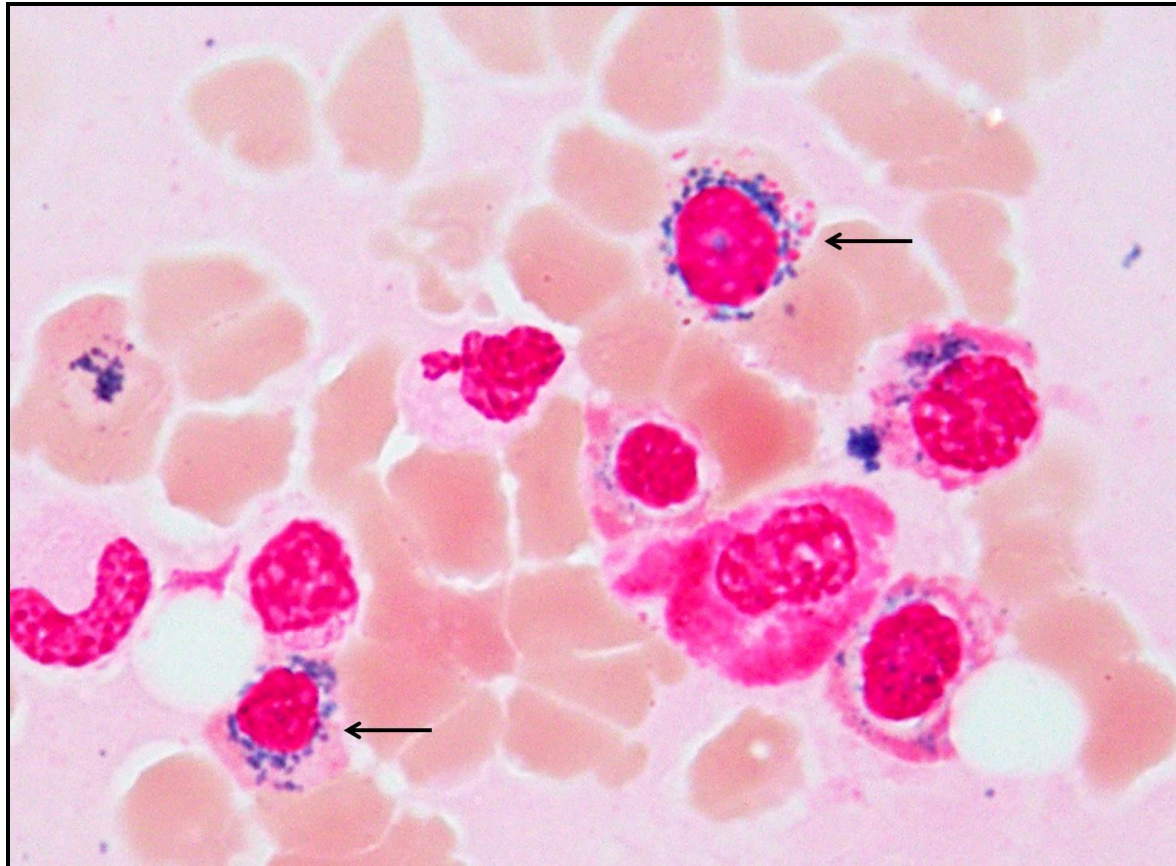
Pseudo Pelger Huet cell

- WBC BM :

giant hypogranular platelets

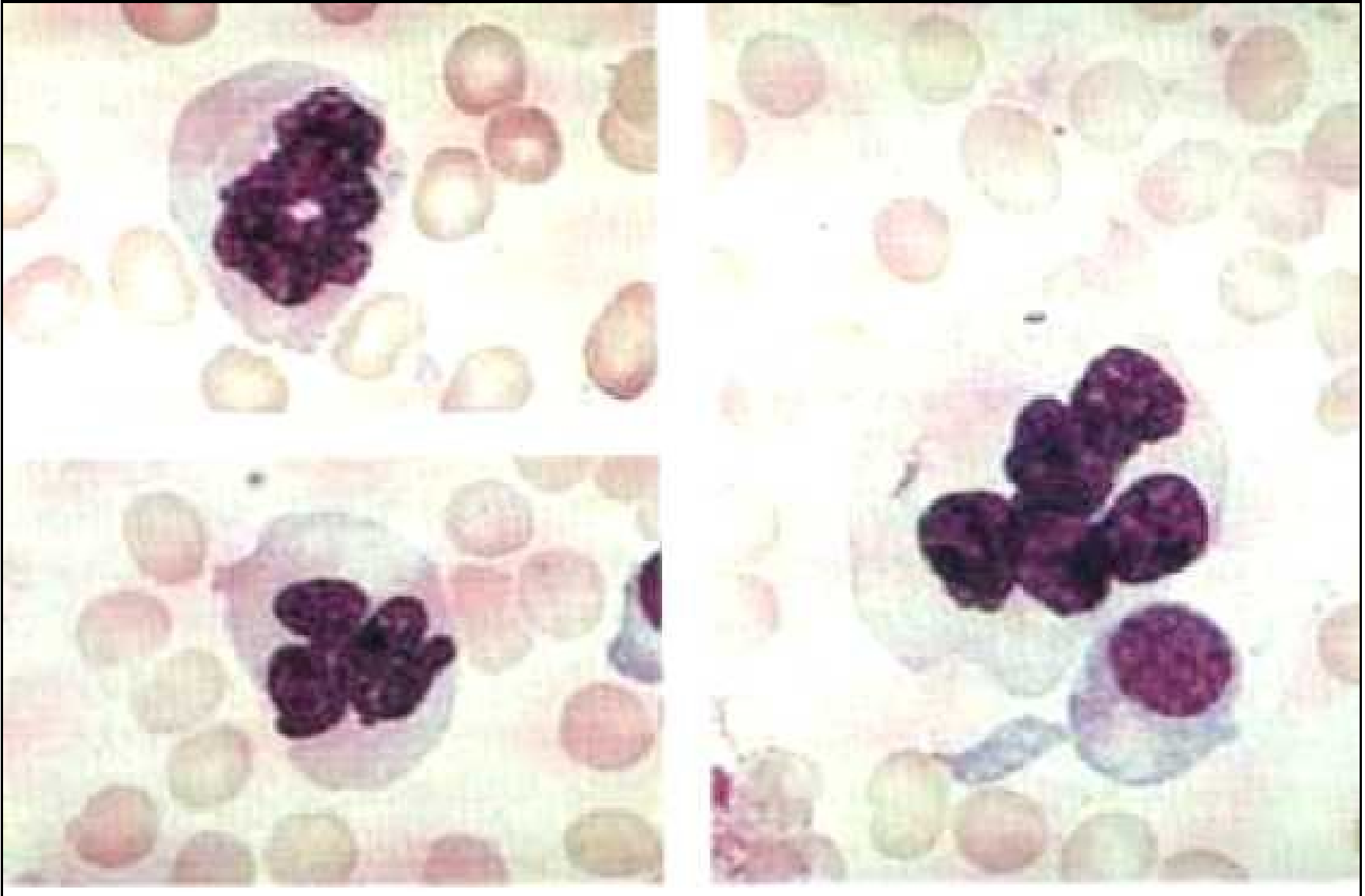


Ring Sideroblast

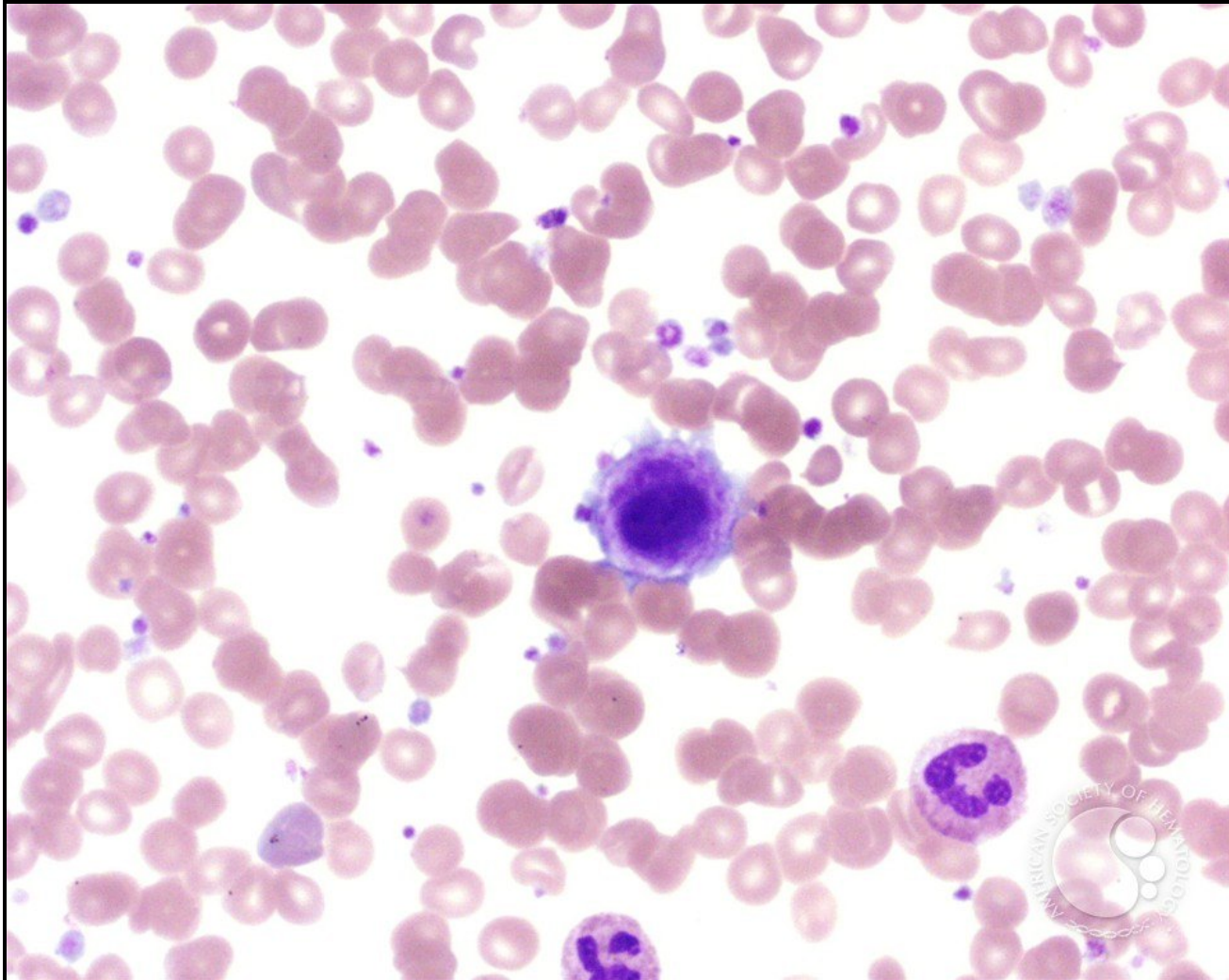


Ring sideroblast

MDS - Dysplastic Erythroblasts



Micromegakaryocytes



WBC disorders III

- ✓ Plasma cell disorder
- ✓ Myelodysplastic syndromes (MDS)
- ✓ Myeloproliferative disorders (MPV)
- ✓ LCH & HLH

Peripheral blood	BM	
Cytopenias	Hypoplastic BM Fatty infiltrations	Aplastic anemia
Cytopenias	Normocellular to Hypercellular BM with Dysplastic changes	MDS
Increased cells Abnormal cells	Hypercellular	MPV

Myeloproliferative disorders (MPV)

Neoplastic slow proliferation of mature cells of **myeloid** lineage.

Disease of late adulthood.

Increased functionally abnormal cells.

Myeloproliferative disorders (MPV)

Results in high peripheral counts with hypercellular BM.

All myeloid lineages increased, Naming based on predominant cell.

HSM, Mild LN.

MPV

Associated with acquired mutations leads to activation of tyrosine kinases, mimicking signals from normal growth factors.

BCR-ABL (associated with CML)

Mutated **JAK2** (PV , ET & 1ry myelofibrosis).

MPV complications

Hyperuricaemia & gout: High turning over of cells & purine degradation.

Progress to marrow fibrosis

Transformation to acute leukaemia.

Myeloproliferative disorders (MPV)

t (9,22)

JAK2

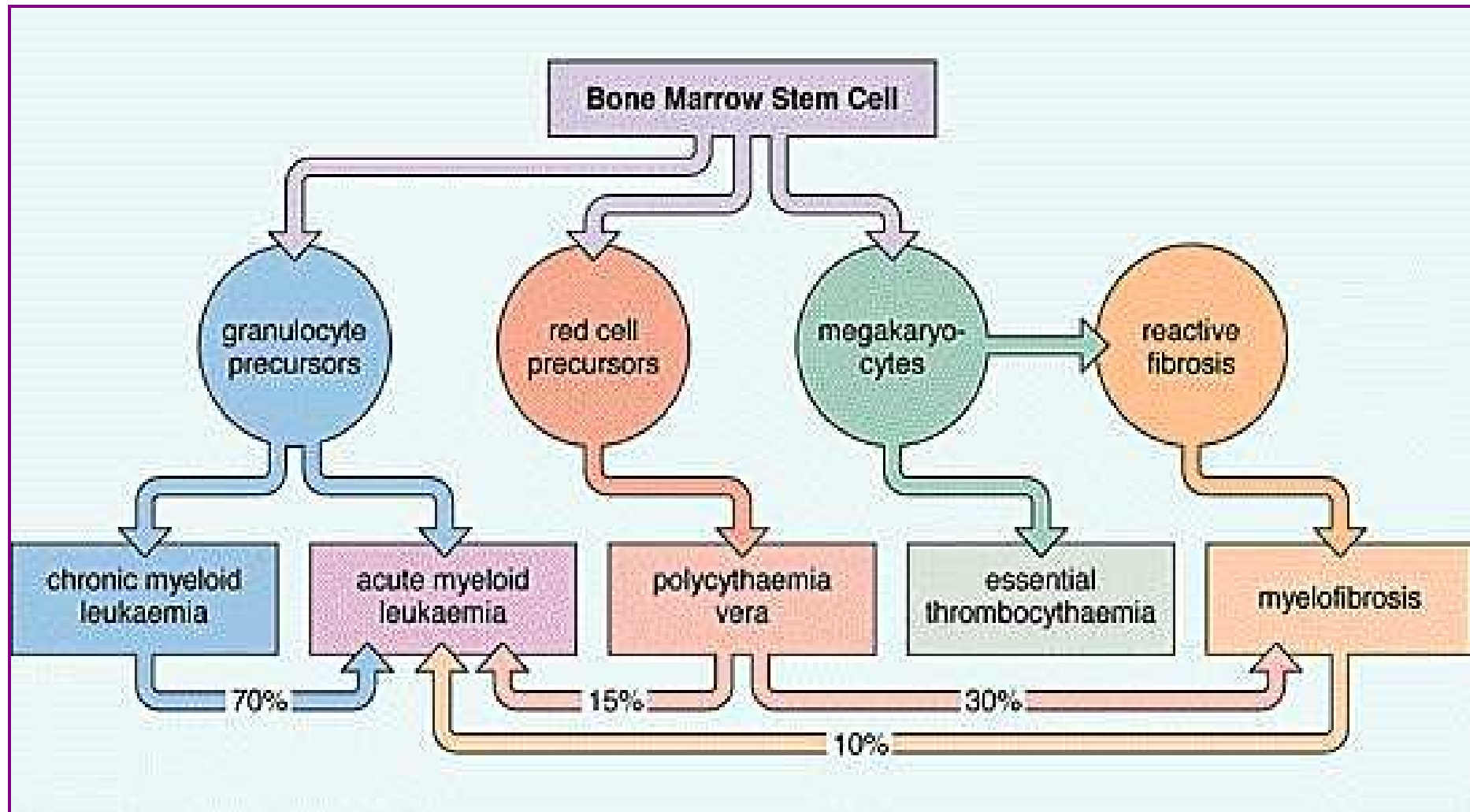
kinase

JAK2

kinase

1. Polycythemia rubra vera (**PV**)
2. Chronic Myeloid Leukemia (**CML**)
3. Essential Thrombocythemia (**ET**)
4. Myelofibrosis (**MF**)

MPV



Polycythemia vera

Polycythemia is an increased concentration of RBCs, usually with an increase in Hb level.

PV is a neoplastic proliferation of mature **myeloid** cells, **more prominent in RBCs**.

Proliferation of erythroid, granulocytic, and megakaryocytic elements.

Polycythemia vera

PV is associated with low erythropoietin level

Associated with JAK2 kinase mutation

Disease of late adulthood.

PV- Presentation

Patients with this disorder classically are plethoric.

Hyperviscosity :

- Blurry vision and headache

- Thrombosis (hepatic vein, portal vein, and dural sinus)

Itching, especially after bathing (due to histamine release from increased mast cells)

HSM



PV-Complications

Gout

Myelofibrosis (spent phase)

AML

Thrombotic complications, MI, stroke, budd chiarri synd

Hemorrhages, peptic ulcer

Polycythemia Vera: Diagnosis

CBC:

RBC counts increased (6 to 10 million/ μ L)

HCT often 60% or greater

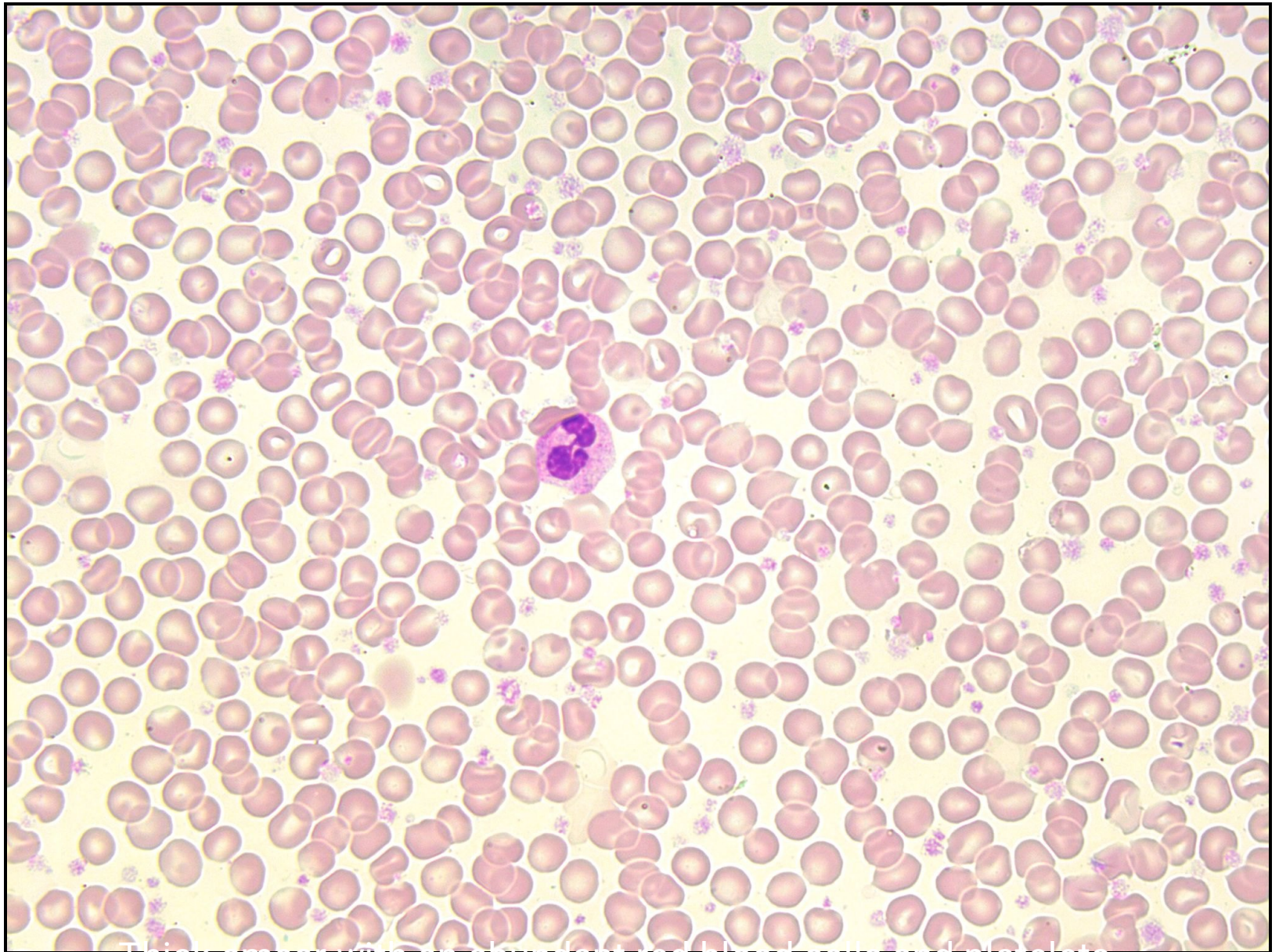
Sometimes increase in WBC, Plts, & basophils

Blood smear:

Thick smear with an abundant red blood cells and platelets

The platelets are morphologically abnormal

Giant forms and megakaryocytic fragments



Polycythemia Vera: Morphology

Hypercellular BM , with hyperplasia of erythroid, myeloid, and megakaryocytic forms

Bone marrow fibrosis is present in 10% of patients



Polycythemia vera, spent phase.

Late stage of PV (burn out) characterized by severe BM failure and scar tissue replaces the BM (Myelofibrosis)
severe anemia, Massive splenomegaly & BM myelofibrosis

Polycythemia (erythrocytosis)

Absolute polycythemia: increased RBC mass

Primary Polycythemia: low/normal erythropoietin

Polycythemia vera

Erythropoietin receptor mutation

Secondary polycythemia: high erythropoietin

Physiological polycythemia: Lung dz, cyanotic CHD, high altitude

Pathological polycythemia:

- Erythropoietin secreting tumors: -RCC, Hepatoma
- Exogenous erythropoietin: Athletes

Relative polycythemia: dehydration

Myeloproliferative disorders (MPV)

1. Polycythemia rubra vera (PV)
2. Chronic Myeloid Leukemia (CML)
3. Essential Thrombocythemia (ET)
4. Myelofibrosis (MF)

Essential thrombocythemia

Neoplastic proliferation of mature myeloid cells, especially platelets.

RBCs and granulocytes are also increased.

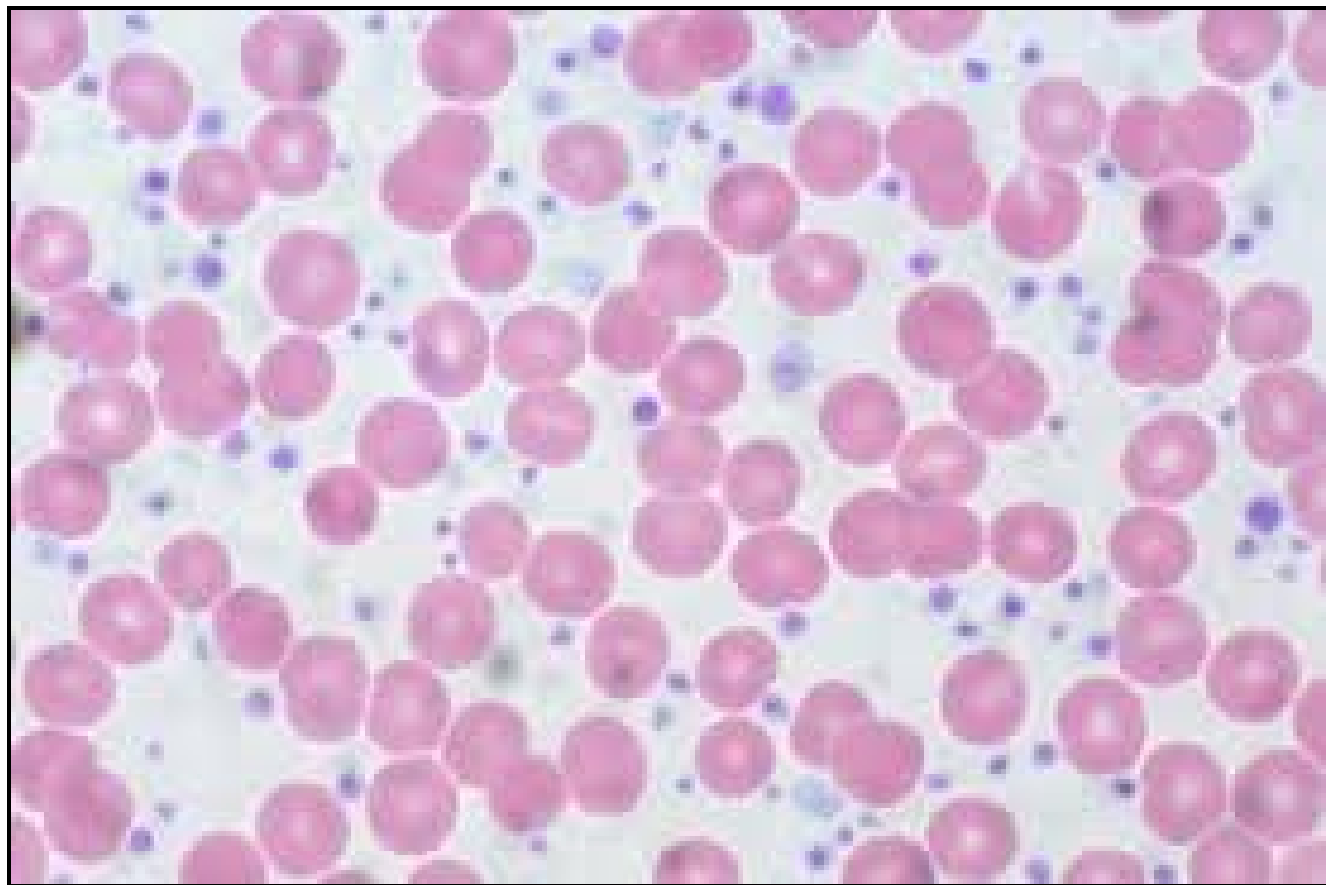
Associated with JAK2 kinase mutation

Essential thrombocythemia

Symptoms are related to an increased risk of bleeding and/or thrombosis.

Rarely progresses to marrow fibrosis or acute leukemia.

No significant risk for hyperuricemia.



Myeloproliferative disorders (MPV)

1. Polycythemia rubra vera (PV)
2. Chronic Myeloid Leukemia (CML)
3. Essential Thrombocythemia (ET)
4. Myelofibrosis (MF)

Myelofibrosis

Neoplastic proliferation of mature myeloid cells, mainly megakaryocytes.

Characterized by the development of **BM fibrosis**, reducing hematopoiesis and leads to cytopenias and extensive extramedullary hematopoiesis.

Associated with **JAK2 kinase** mutation

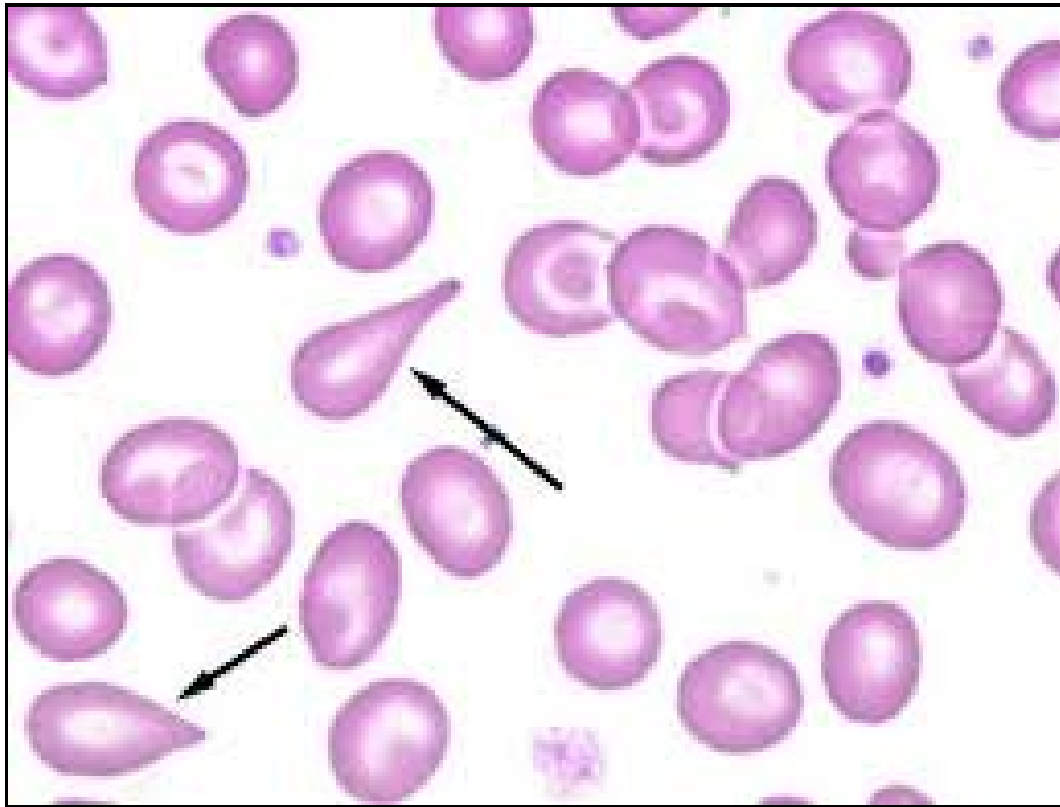
Myelofibrosis

Megakaryocytes produce excess PDGF causing marrow fibrosis.

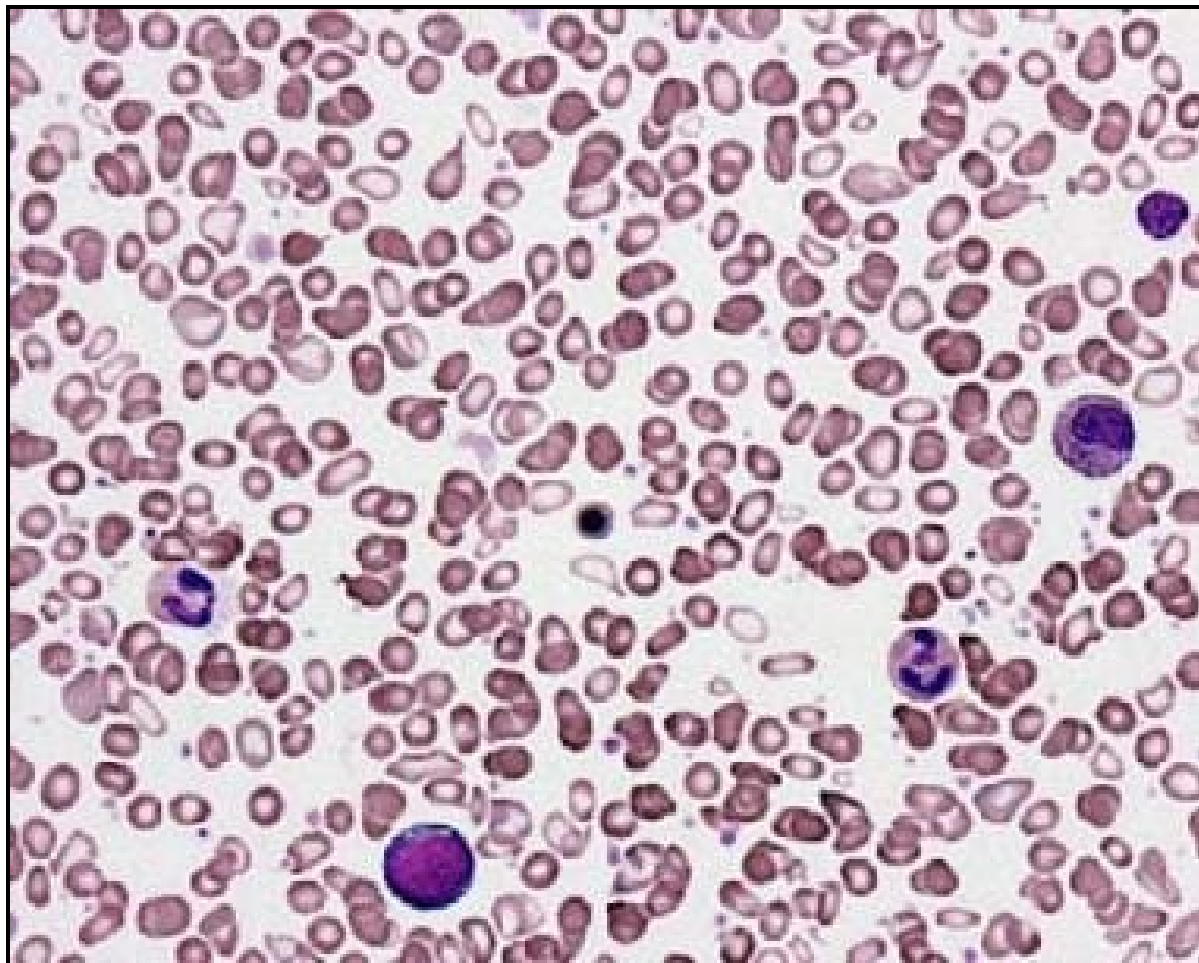
Clinically:

- Splenomegaly

- Increased risk of infection, thrombosis & bleeding



Tear drop cells (Dacryocytes)



Myeloproliferative disorders (MPV)

1. Polycythemia rubra vera (PV)
2. Chronic Myeloid Leukemia (CML)
3. Essential Thrombocythemia (ET)
4. Myelofibrosis (MF)

CML

Chronic myeloid leukemia

Neoplastic proliferation of mature myeloid cells, especially granulocytes.

Philadelphia chromosome $t(9,22)$

Clinically

Nonspecific (easy fatigability, weakness, and weight loss)

Abdominal distention (massive splenomegaly and hepatomegaly)

Infection and bleeding are not common

CML

Enlarging spleen suggests progression to accelerated phase of disease; transformation to acute leukemia usually follows shortly thereafter.

Blast crises: transformation to acute leukemia

AML (most of cases) or

ALL.

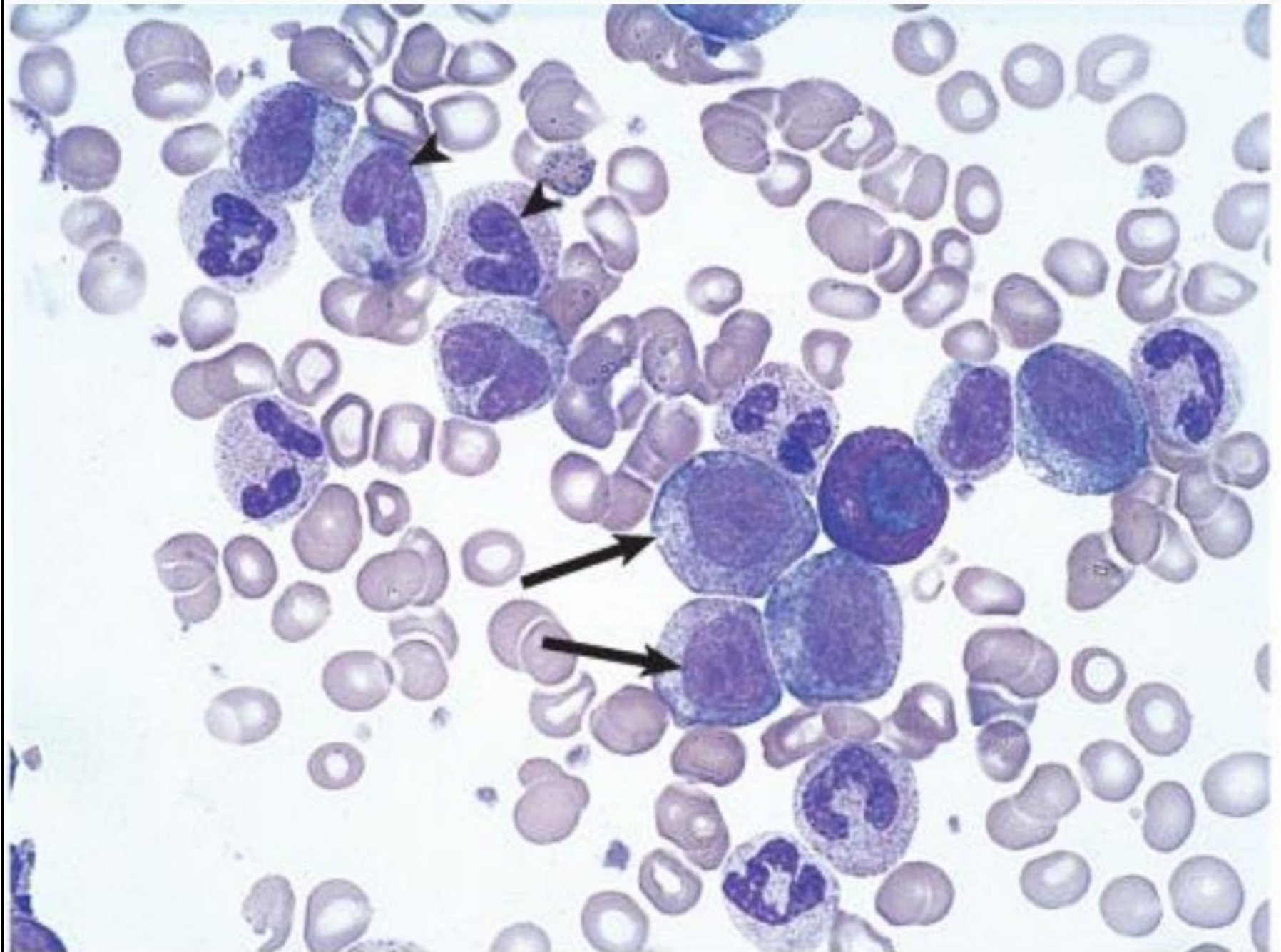
CML-labs

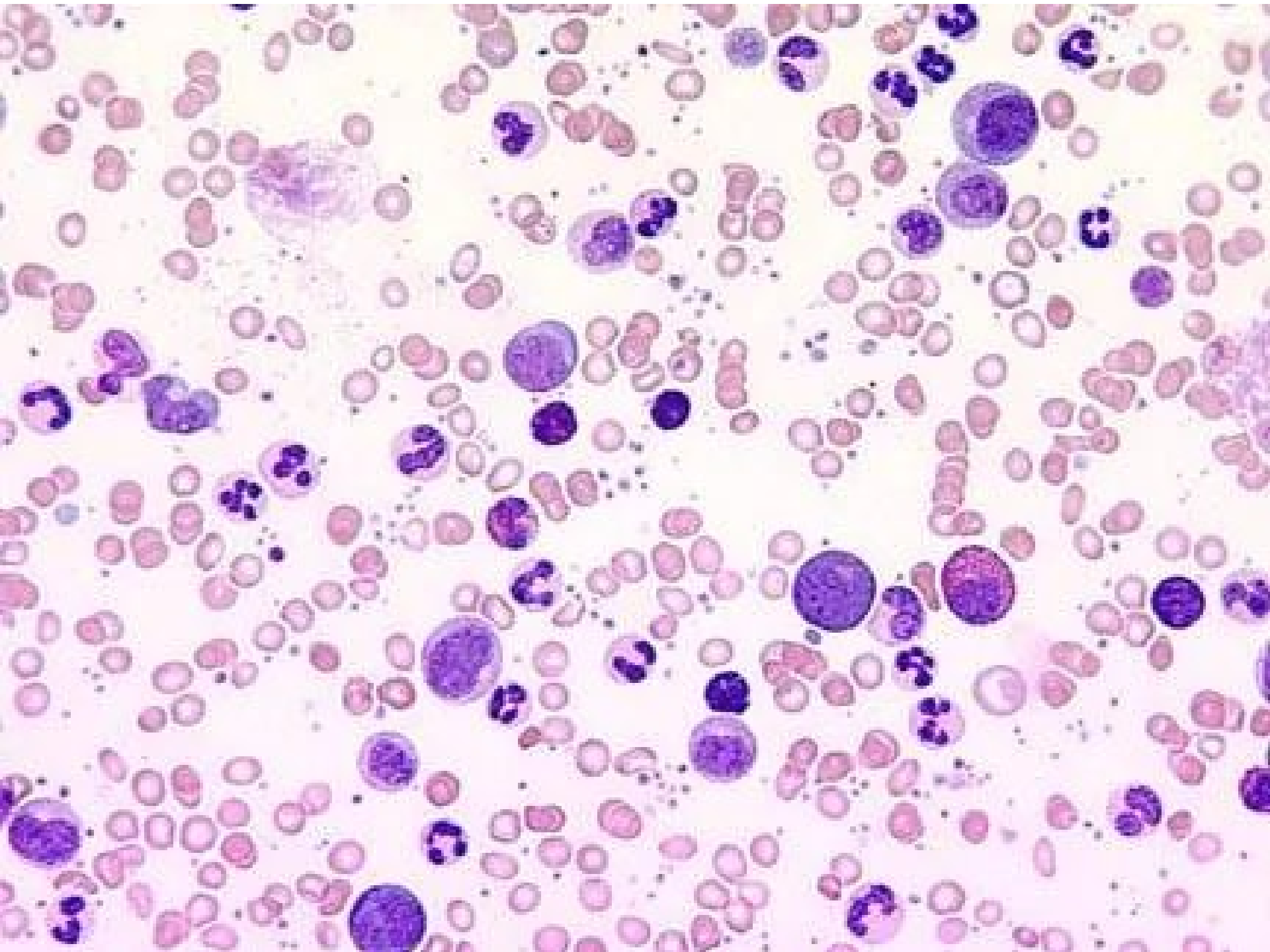
CBC: Leukocytosis, anemia, thrombocytosis.

Blood film.

Hypercellular bone marrow, with hyperplasia of granulocytic and megakaryocytic lineages

Myelocytes (arrows) and metamyelocytes (arrowheads)





CML treatment

TKI: imatinib

Bone marrow transplantation

Chemotherapy

WBC disorders III

- ✓ Plasma cell disorder
- ✓ Myelodysplastic syndromes (MDS)
- ✓ Myelopoietic disorders (MPD)
- ✓ LCH & HLH

Macrophage

A type of WBC that engulfs and digests microorganisms, cancer cells, debris & foreign substances (Phagocytosis).

LN >> Histiocyte

Liver >> Kupffer cells

Bone >> Osteoclast

Skin >> Langerhans cell

BM >> monocyte

Hemophagocytic Lymphohistiocytosis (HLH)

A life-threatening syndrome of excessive immune response and macrophages activation.

leading to phagocytosis of blood cells and their precursors, cytopenias, and symptoms related to systemic inflammation and organ dysfunction.

Hemophagocytic Lymphohistiocytosis (HLH)

Primary HLH(Genetic):

Inherited defects in several genes that regulate the function of immune cells
(immunodeficiency, familial)

Secondary HLH:

Reactivation in response to infection,
inflammation or malignancy

EBV, COVID19, MAS,Lymphoma

Hemophagocytic Lymphohistiocytosis (HLH)

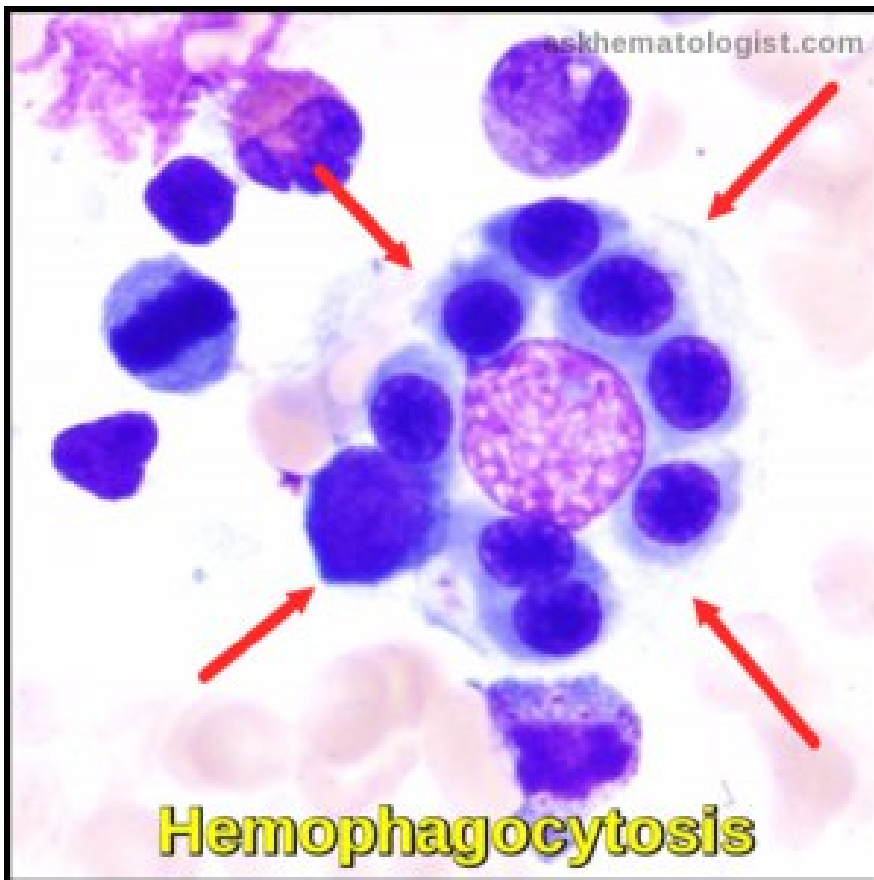
Fever

Splenomegaly

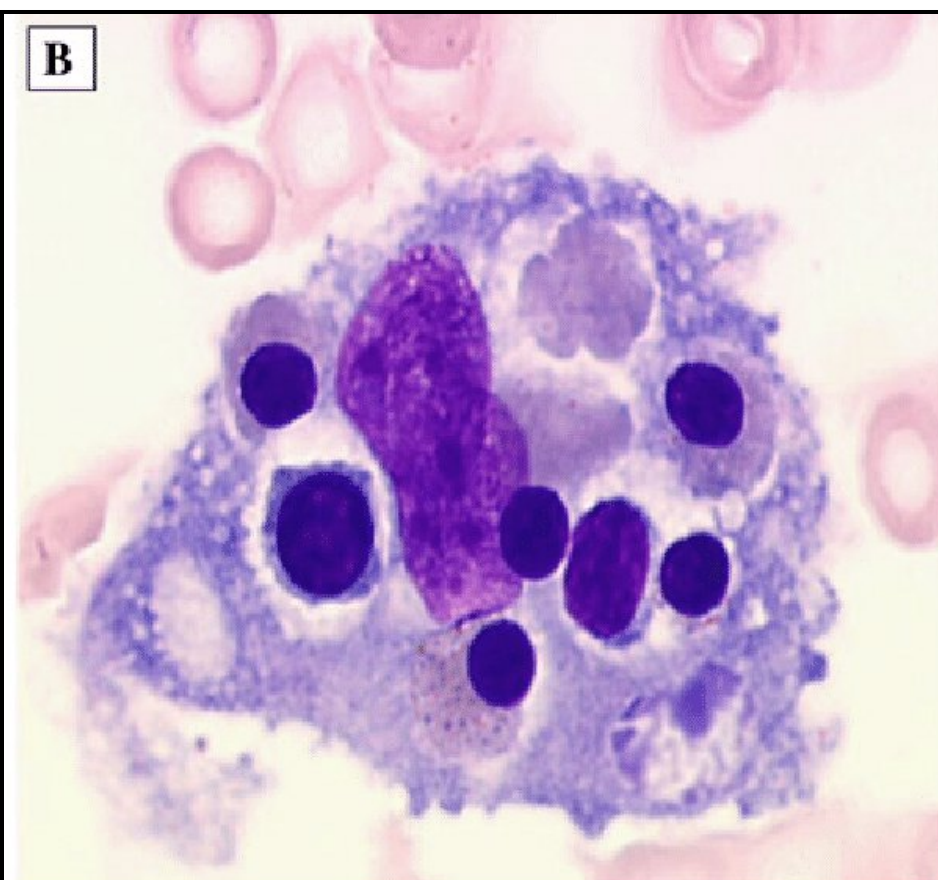
Cytopenias

Liver dysfunction.

High inflammatory markers eg. ferritin



B

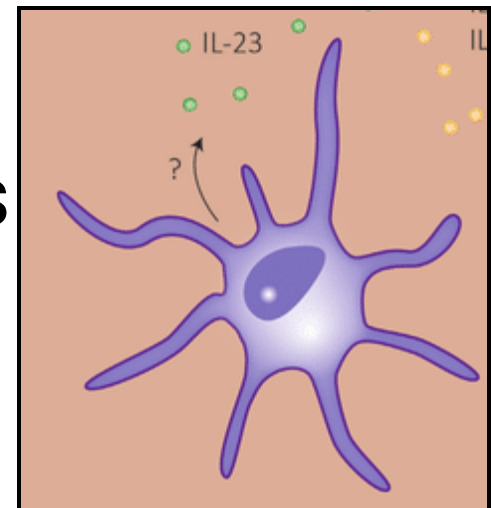


Langerhans cell histiocytosis

Langerhans cells are specialized dendritic cells found predominantly in the skin.

Derived from bone marrow monocytes

Present antigen to naïve T cells



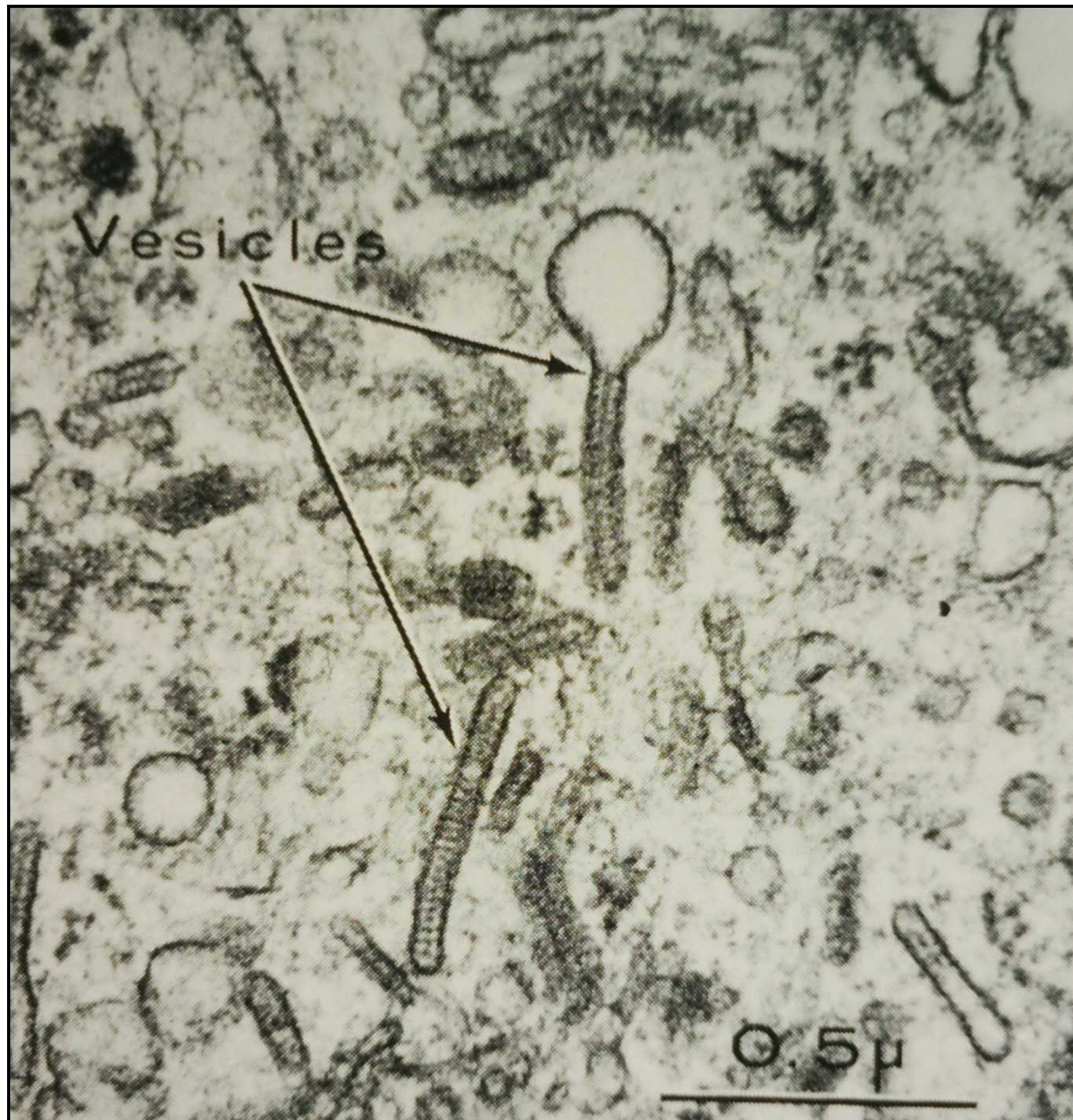
Langerhans cell histiocytosis

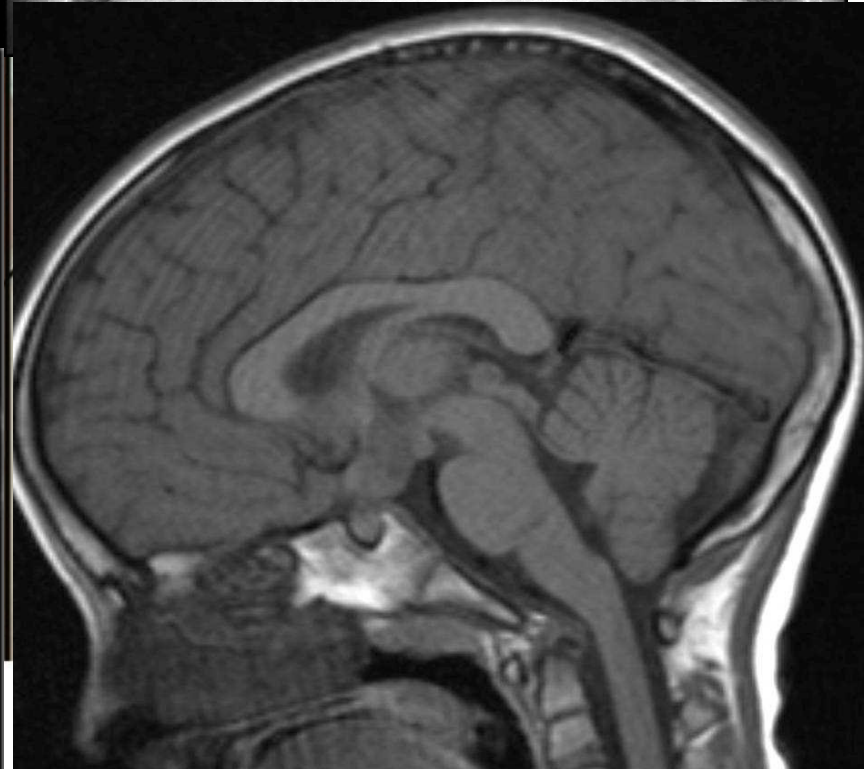
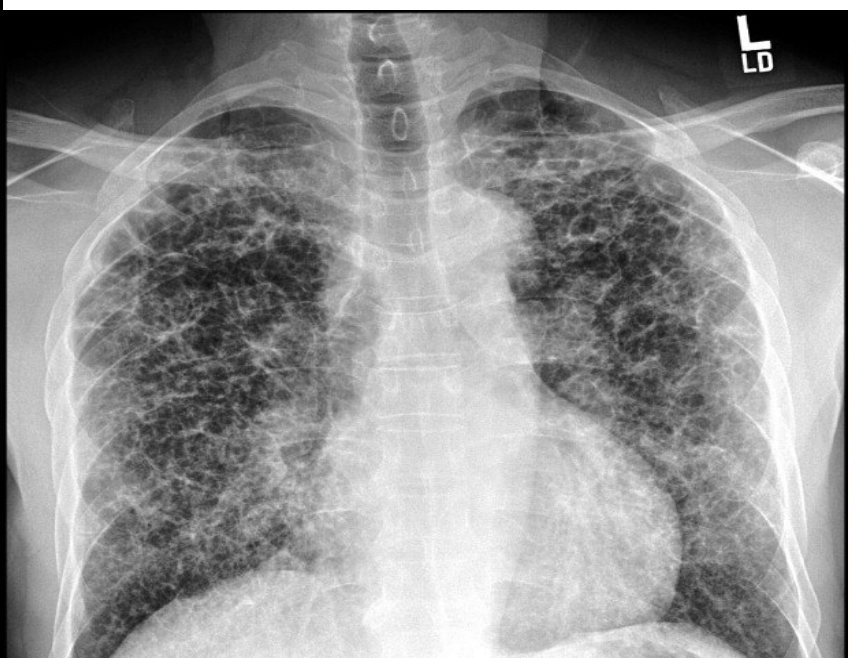
LCH is a neoplastic proliferation of Langerhans cells.

characteristic Birbeck granules (tennis racket) on electron microscopy.

Multisystem involvement : bone (Lytic lesions), BM, liver, spleen, skin & pituitary gland.

IPT: CD1a +ve , S-100 +ve







THANK
YOU

