Neoplastic Proliferations of White Cells

~ Myeloid Neoplasms III

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Essential Thrombocythemia (ET)

- Megakaryocyte proliferation with overproduction of platelets.
- Elevated platelet counts (>600x10^{x9}/L).
- Separated from PCV and primary myelofibrosis based on the absence of polycythemia and marrow fibrosis, respectively.

Essential Thrombocythemia – Pathogenesis

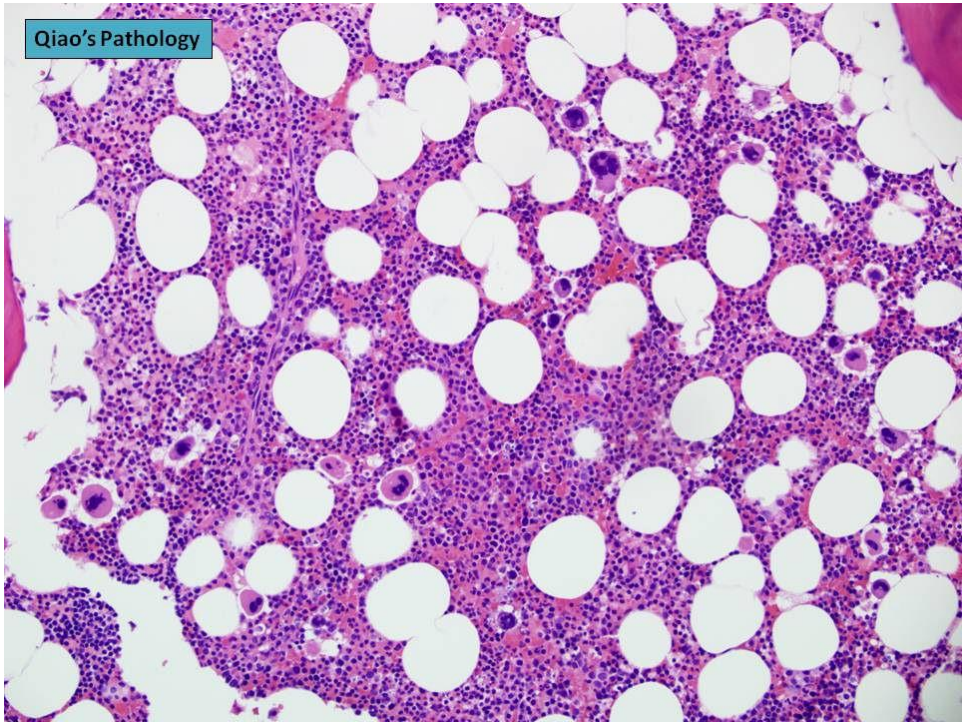
- ET is associated with activating point mutations in JAK2 (50%), a receptor tyrosine kinase that is normally activated by thrombopoietin.
- Constitutive JAK2 renders the progenitor thrombopoietin-independent and leads to hyperproliferation.
- The JAK2 mutation is the same as that found in almost all cases of PCV.
- Why some patients with JAK2 mutations present with PCV & others with ET → not fully understood.

They have many types but 2 is the most common

They share JK with PCV

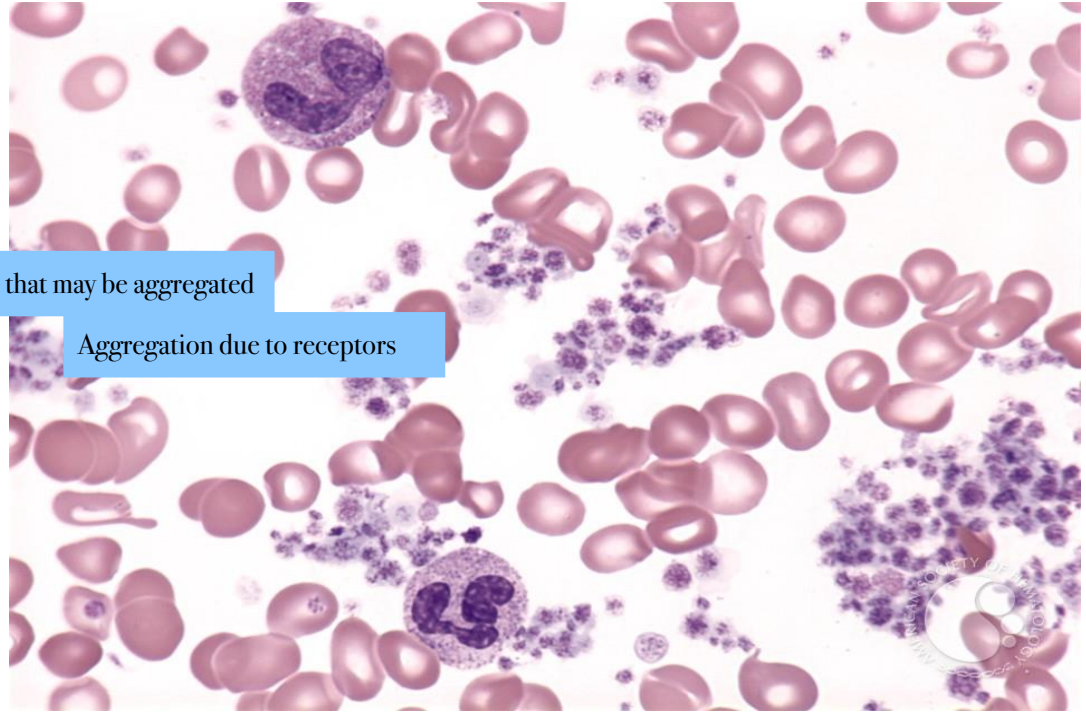
Essential Thrombocythemia – Morphology

- Bone marrow cellularity is usually only mildly increased, but megakaryocytes are often markedly increased in number with abnormal large forms.



Essential Thrombocythemia – Morphology

Peripheral smears usually reveal abnormally large platelets often accompanied by mild leukocytosis.



ET– Clinical features

- ET is an indolent disorder with long asymptomatic periods → only occasional thrombotic or hemorrhagic crises.
- ET manifests clinically with elevated platelet counts.
- Causes of reactive thrombocytosis, (such as inflammatory disorders & iron deficiency) must be excluded before the diagnosis can be established

Due to high erythropiotin

ET– Clinical features

- Platelets are not only increased in numbers but also frequently demonstrate qualitative abnormalities in functional tests.
- The types of thrombotic events resemble those observed in PCV.
- A characteristic symptom → **erythromelalgia**, a throbbing and burning of hands and feet caused by occlusion of small arterioles by platelet aggregates → may also be seen in PCV.

Pain in the small joints of the hand and foot

Conjusted

Pain is due to ischemia

Why hands and feet because they have small vessels

ET– Prognosis

Will be given aspirin to prevent aggregation

- Median survival times → 12~15years
- Transformation to myelofibrosis (spent phase)is uncommon.
- Transformation to acute leukemia is rare.

Primary Myelofibrosis (PM)

- The hallmark of primary myelofibrosis is the development of **obliterative** marrow fibrosis → reduces bone marrow hematopoiesis →

From the fibroblast

Will cause lesions:

1) Cytopenias.

Bone marrow is obliterated

2) Extensive extramedullary hematopoiesis.

- Histologically, the appearance is identical to the spent phase that occurs occasionally late in the course of other MPN.

Rarely in PCV in the phase of spent

PM – Pathogenesis

- JAK2 mutations are present in 50% to 60% of cases
- Most of the remaining cases have other mutations →which also give rise to increased JAK signaling.
- Why JAK2 mutations are associated PCV in some patients & PM in others is not fully understood.

PM – Pathogenesis

- Pathogenesis is similar between PM and spent phase MPN
- The characteristic marrow fibrosis is caused by the inappropriate release of **fibrogenic factors** from neoplastic **megakaryocytes.**
- Two factors synthesized by megakaryocytes have been implicated (**fibrogenic** factors/fibroblast mitogens):

Cytokines that activate the cell

1) Platelet-derived growth factor (PDGF).
2) TGF-β. (collagen deposition and angiogenesis)

PM – Morphology

- PB smear is markedly abnormal → **Leukoerythroblastosis**

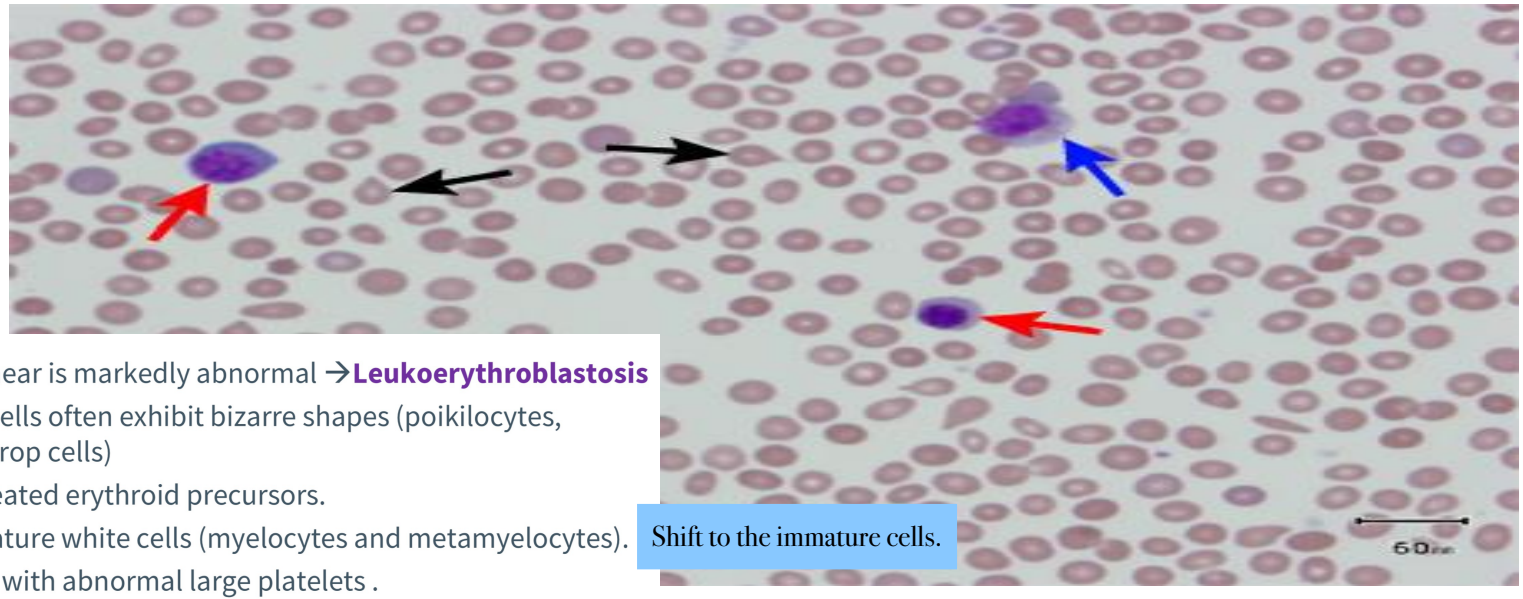
1) Red cells often exhibit bizarre shapes (poikilocytes, teardrop cells)
2) Nucleated erythroid precursors.
3) Immature white cells (myelocytes and metamyelocytes).

- Along with abnormal large platelets .

PM – Morphology

Peripheral blood

PB smear showing 2 nucleated RBCs (red), 2 tear drop RBCs (black) and a myelocyte (blue)



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Shift to the immature cells.

Osteoblastic activity that cause fibrosis and deposit that may go to lungs, brain and bone

PM – Morphology

Bone marrow

Collagen accumulation >> TGF beta

Hypercellualr of collagen fibroblast and causes aggregates

+BM in advanced cases is hypocellular & diffusely fibrotic.

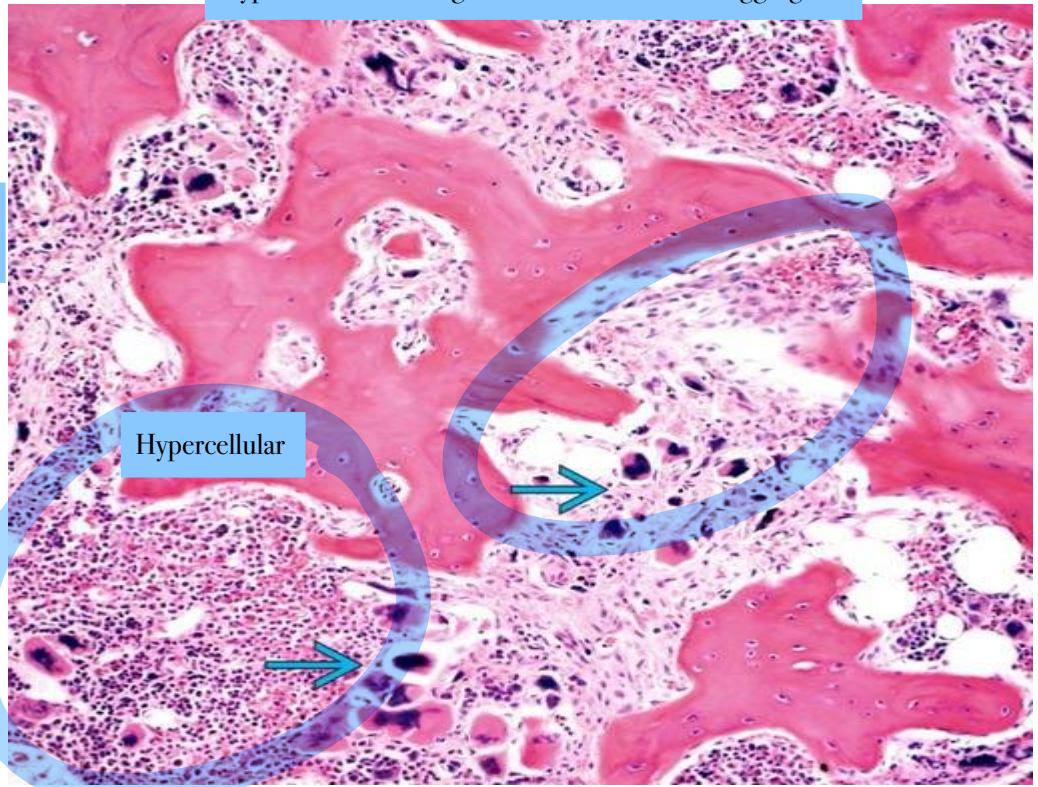
+ thickened bone trabeculae.

Hyper-chromatin
Large trabecular

& branched

+ In early cases it may be hypercellular & only focal fibrosis.

+Abnormally large and clustered megakaryocytes, arrows

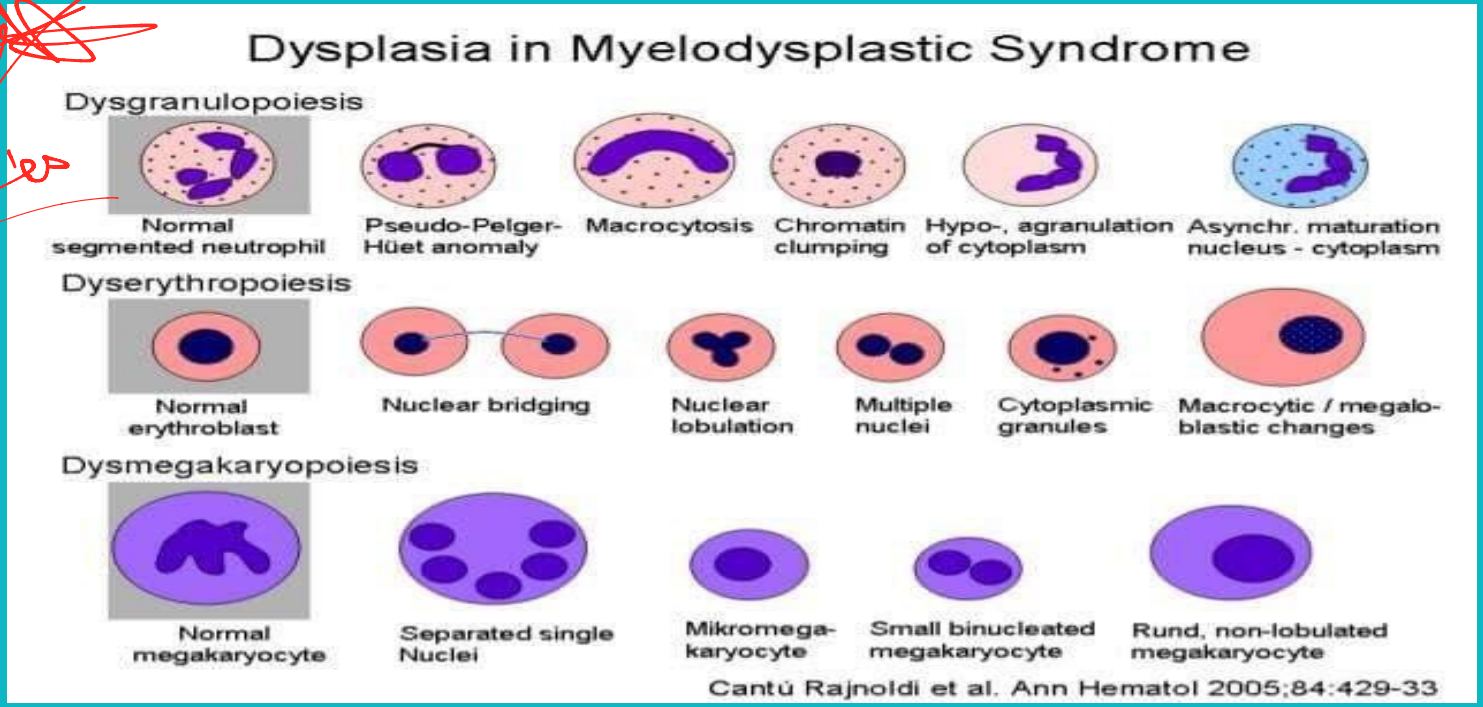


PM – Clinical Features

- Age more than 60
- Anemia and splenomegaly .
- Fatigue, weakness and night sweats
- Lab results; normochromic and normocytic anemia and Leukoerythroblatosis
- Bone marrow is essential for the diagnosis.

PM – Prognosis

- Median survival is 4-5 years.
- 5-20% transform to AML.
- More difficult to treat than PCV and CML.
- Treat with JAK2 inhibitors and HSCT.



Group of diseases

Myelodysplastic Syndromes (MDS)

Myelodysplastic Syndromes (MDS)

Proliferation
No arresting

- A group of clonal stem cell disorders characterized by **maturation defects** that are associated with **ineffective hematopoiesis** with **cytopenias** and a high risk of transformation to AML.

Defective

Myelodysplastic Syndromes (MDS)

- BM is replaced by the clonal transformed multipotent stem cell that retains the capacity to differentiate into red cells, granulocytes, and platelets, but in an ineffective & disordered fashion. (cells stay in the BM)
- So; BM is hypercellular or normocellular, but the PB shows one or more cytopenias.
- The abnormal cells in BM are genetically unstable & prone to the acquisition of additional mutations → transformation to AML.

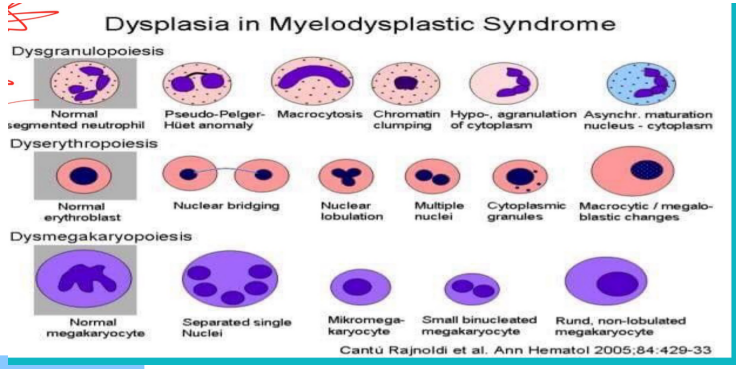
MDS – Pathogenesis

- Most cases are idiopathic, but some develop after exposure to carcinogens, previous cancer therapy, chemotherapy with alkylating agents or ionizing radiation therapy.
- ~10% of MDS have loss-of-function mutations in tumor-suppressor gene TP53→ often associated with chromosomal instability.
- Which is correlated with complex karyotype and poor clinical outcomes

May be addition / deletion/ translocation/ long arm ..

Will be seen in the genomic pathogenic patients

MDS – Morphology



- Hypercellular bone marrow.
- Dysplastic changes

Each one have a special feature

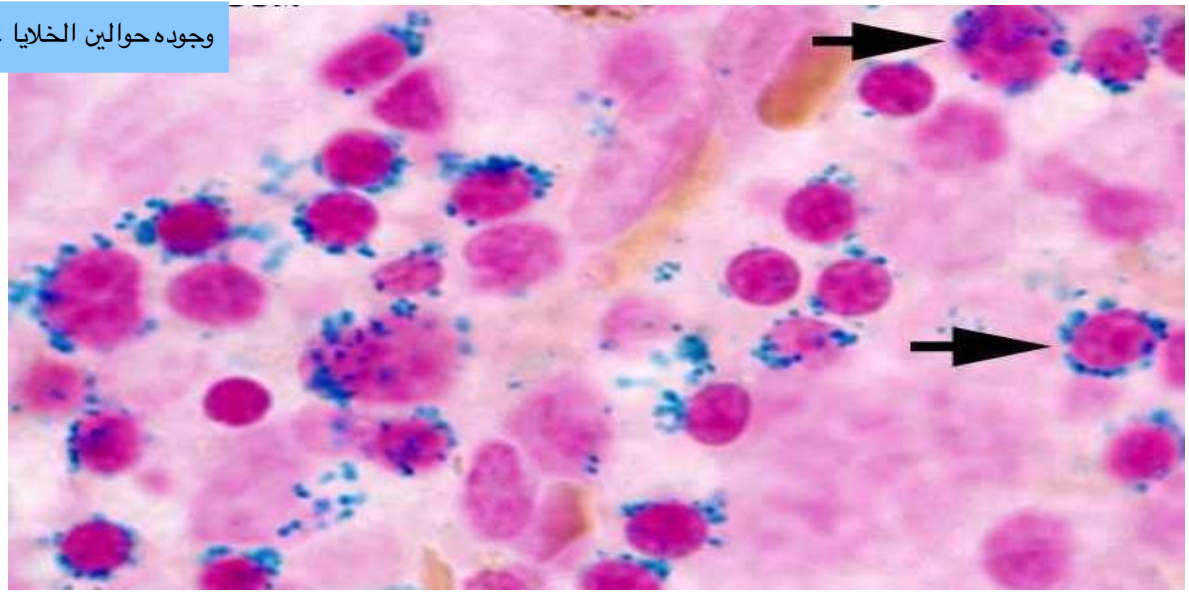
1) Erythroid: Abnormal nuclear contour and iron deposits (ring sideroblasts)
2) Myeloid: abnormal segmentation and granulation
3) Megakaryocyte: single nuclear lobes or multiple separate nuclei.

MDS – Morphology

Erythroid: Abnormal nuclear abnormalities & iron deposits (ring sideroblasts)

Pression blue

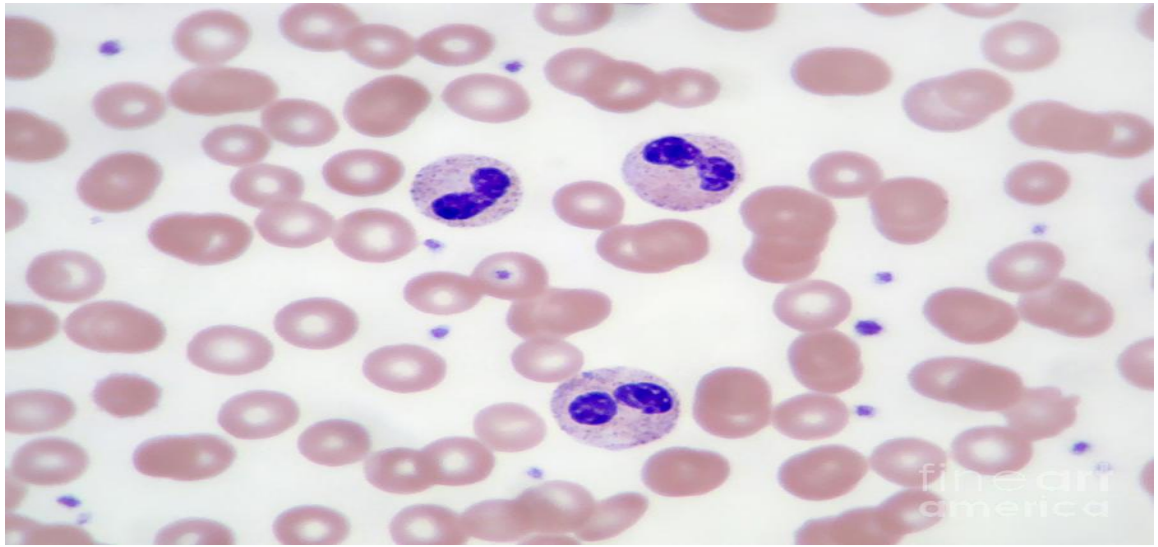
وجوده حوالين الخلايا غير طبيعي dysplastic



There are some drugs that may cause this condition like epileptic drugs

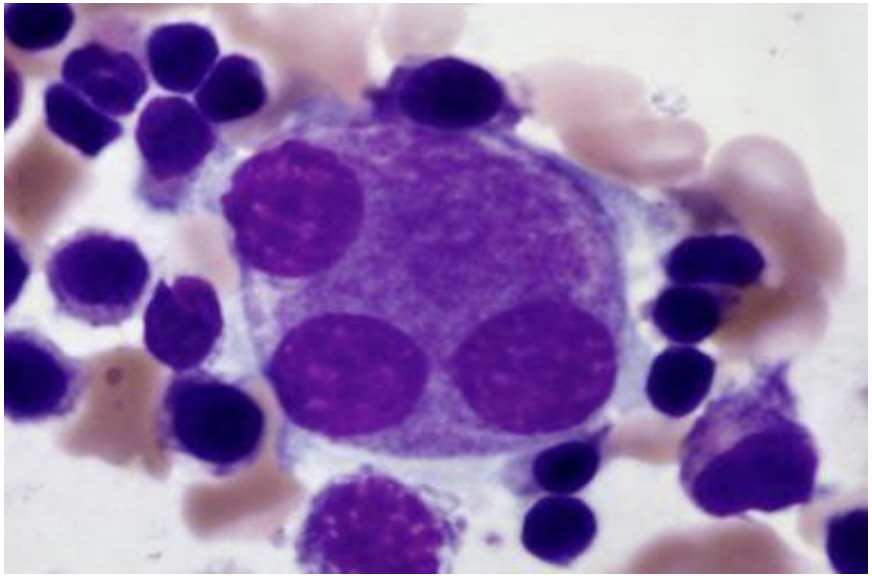
MDS – Morphology

Myeloid: abnormal segmentation; **Pseudo-Pelger-Hüet cells,** neutrophils with only two nuclear lobes



MDS – Morphology

Megakaryocyte: single nuclear lobes or multiple separate nuclei (pawn ball megakaryocytes)



MDS – Clinical features

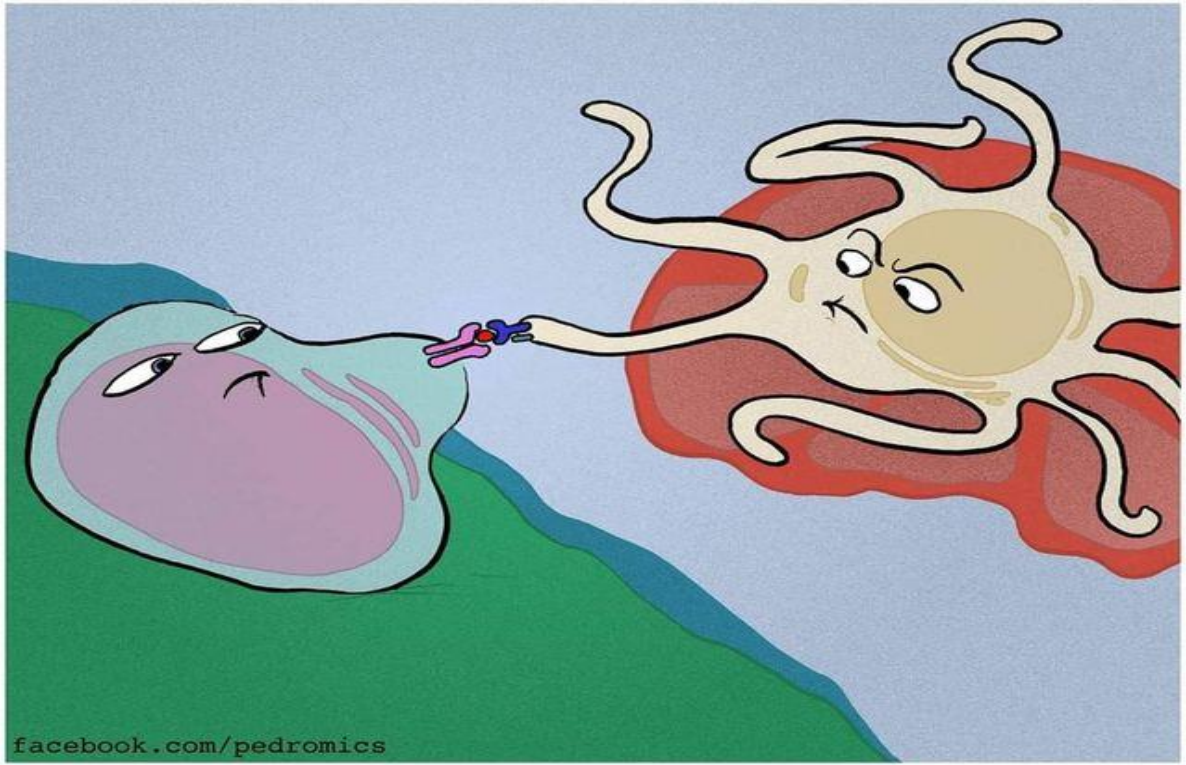
- Predominantly a disease of older adults, 70s
- Up to half of cases → discovered incidentally.
- If symptomatic, it presents with weakness, infections, and hemorrhages → all due to pancytopenia.

Mostly anaemia

- Poor response to conventional chemotherapy.
- Transformation to AML → in 10-40% (rapid in t-MDS)
- Prognosis is variable.
- Median survival time ranges from 9 to 29 months.

Therapy

PRESENTATION OF THE ANTIGEN



THE CYSTEINE CHAPEL