Neoplastic Proliferations of White Cells

~ Myeloid Neoplasms III

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Essential Thrombocythemia (ET)

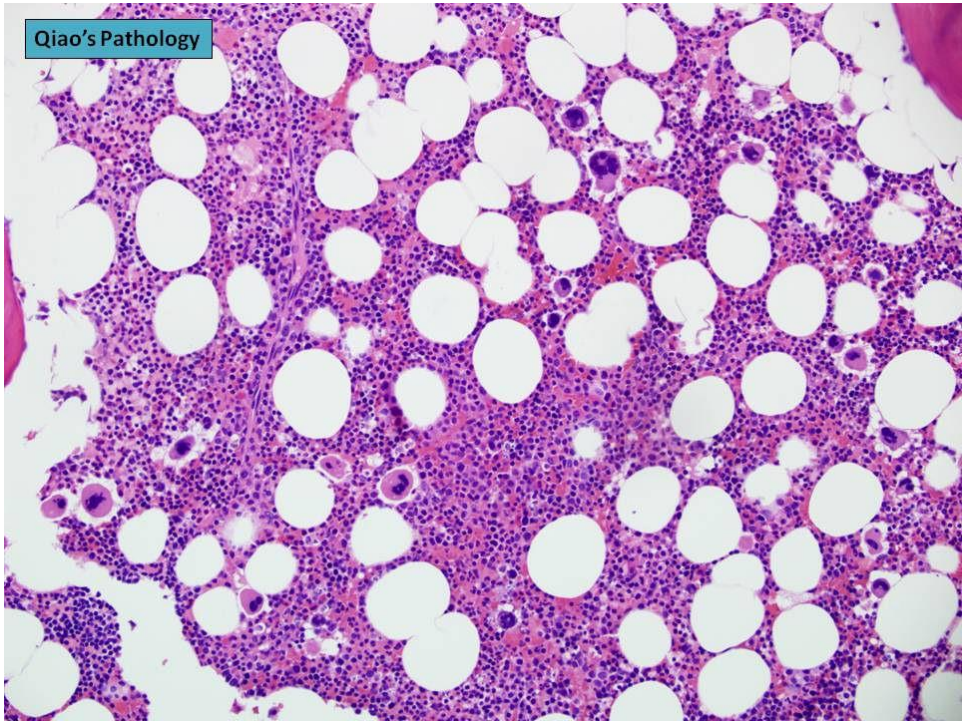
- Megakaryocyte proliferation with overproduction of platelets.
- Elevated platelet counts (>600x10^{x9}/L).
- Separated from PCV and primary myelofibrosis based on the absence of polycythemia and marrow fibrosis, respectively.

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 understood.

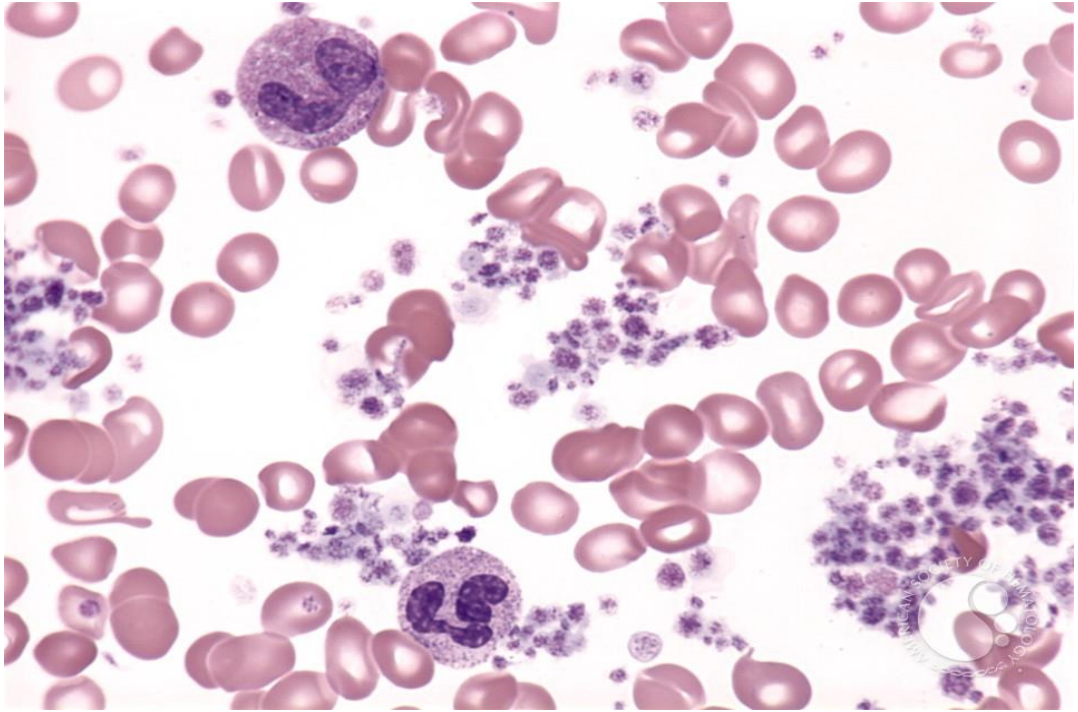
Essential Thrombocythemia – Morphology

- 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

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.

ET– Prognosis

- 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 →

1) Cytopenias.
2) Extensive extramedullary hematopoiesis.

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

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 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):

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

PM – Morphology

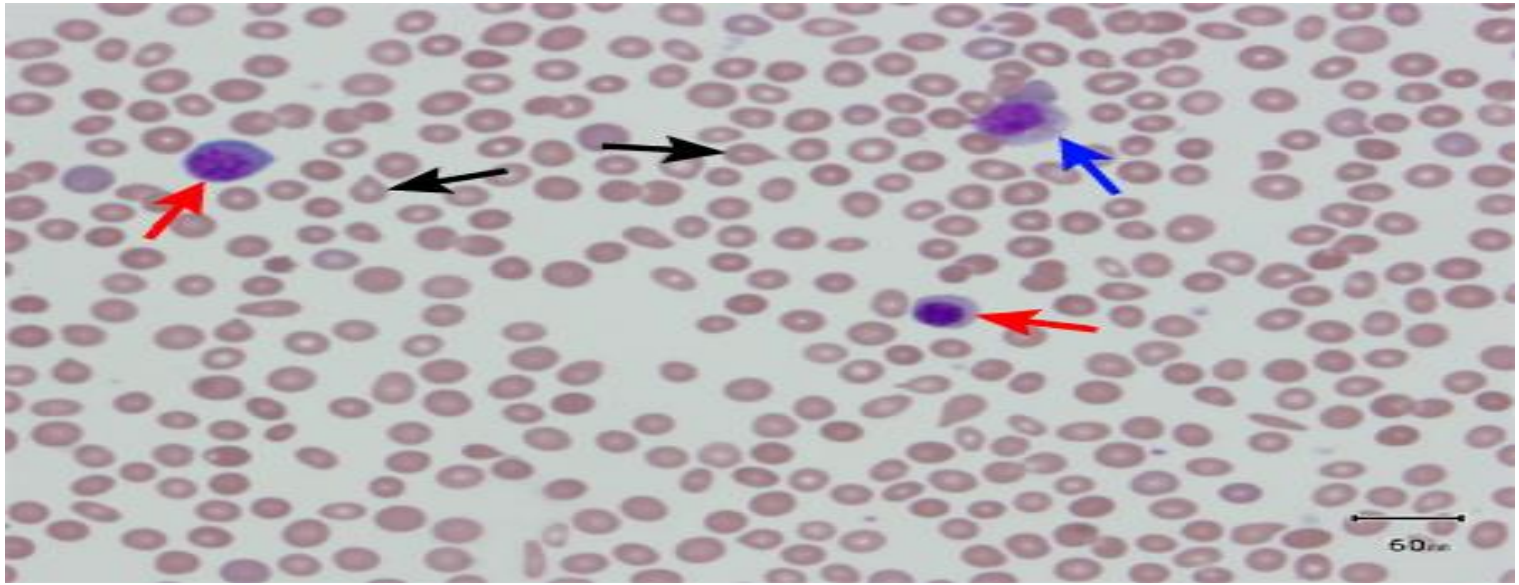
- PB smear is markedly abnormal →**Leukoerythroblastosis**

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 .

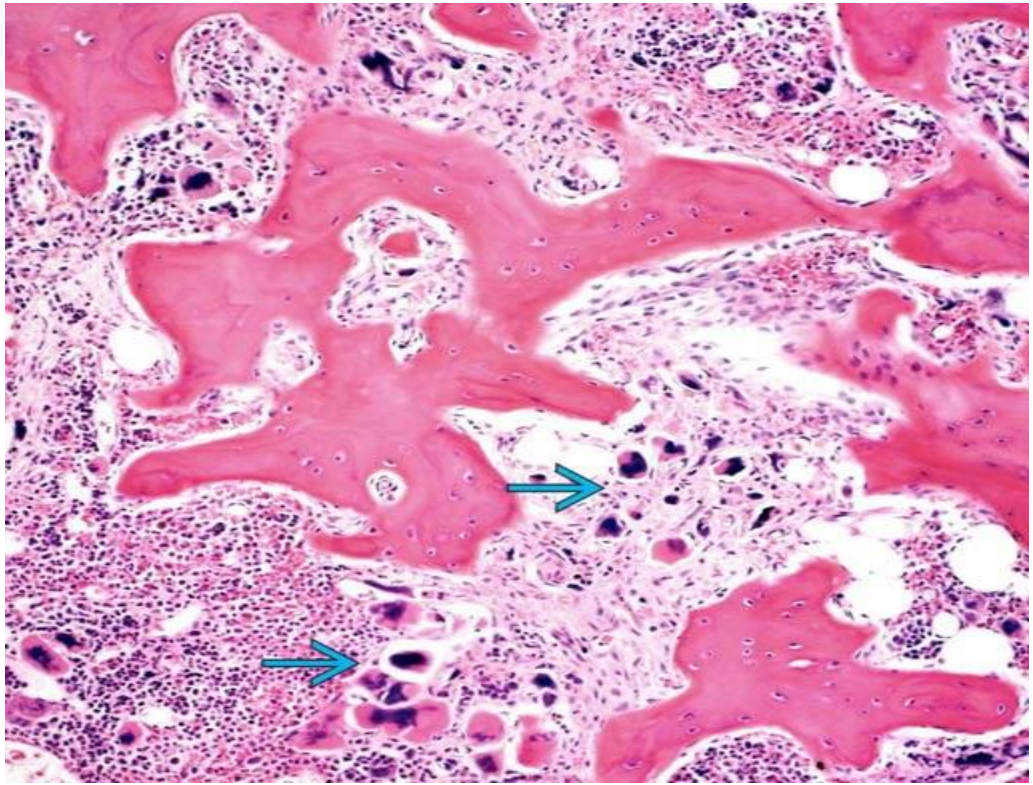
PM – Morphology

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



PM – Morphology

+BM in advanced cases is hypocellular & diffusely fibrotic.
+ In early cases it may be hypercellular & only focal fibrosis.
+Abnormally large and clustered megakaryocytes.

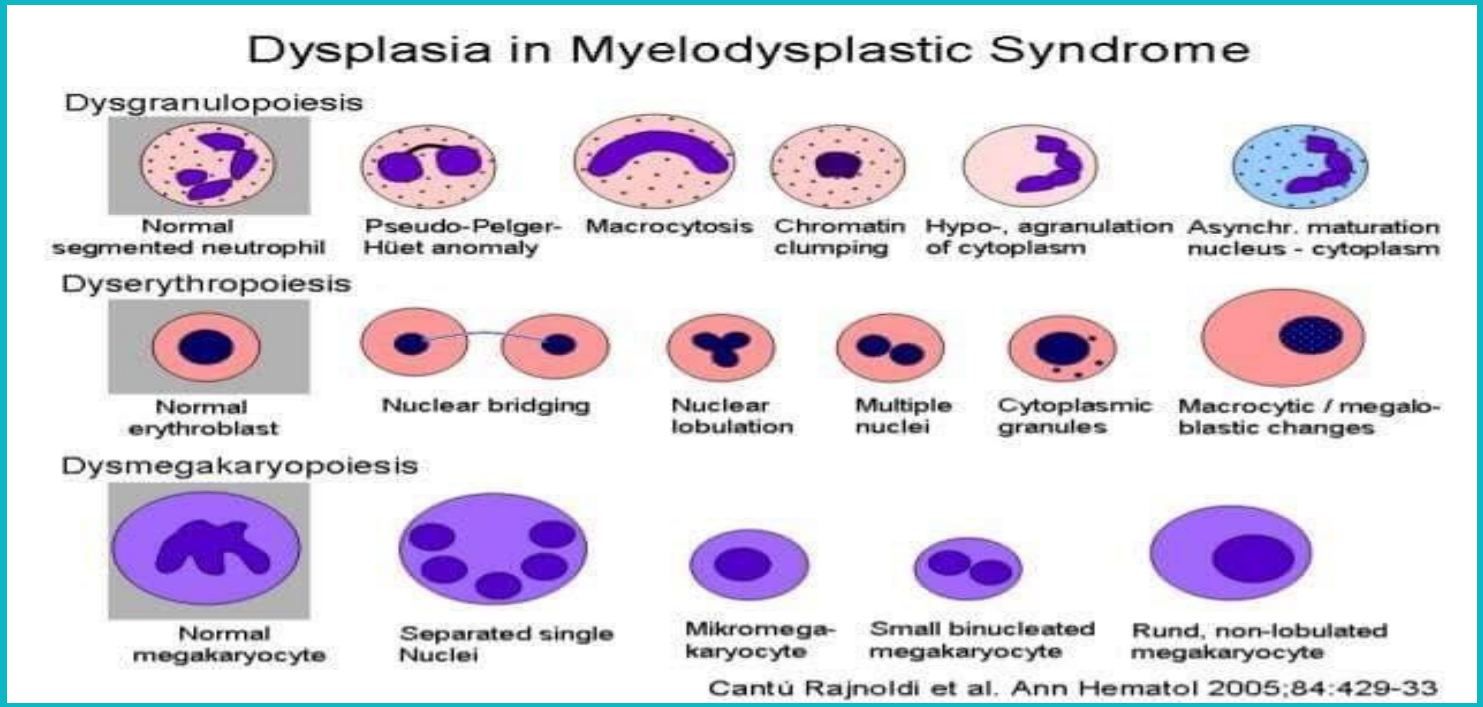


PM – Clinical Features

- 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.



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Myelodysplastic Syndromes (MDS)

Myelodysplastic Syndromes (MDS)

- 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.

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

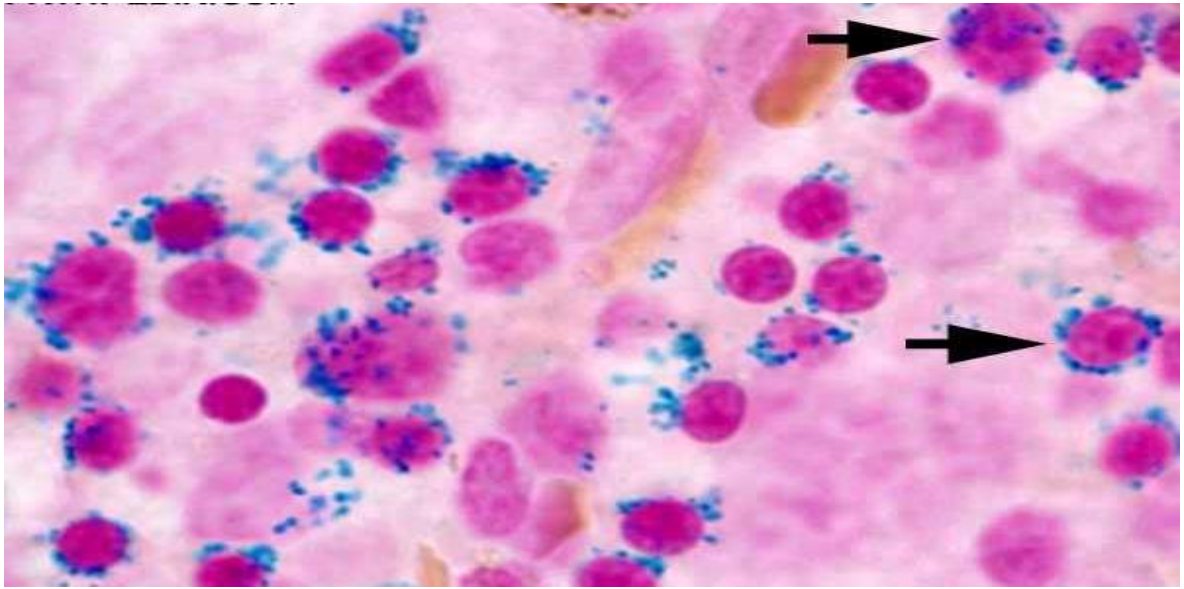
MDS – Morphology

- Hypercellular bone marrow.
- Dysplastic changes

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.

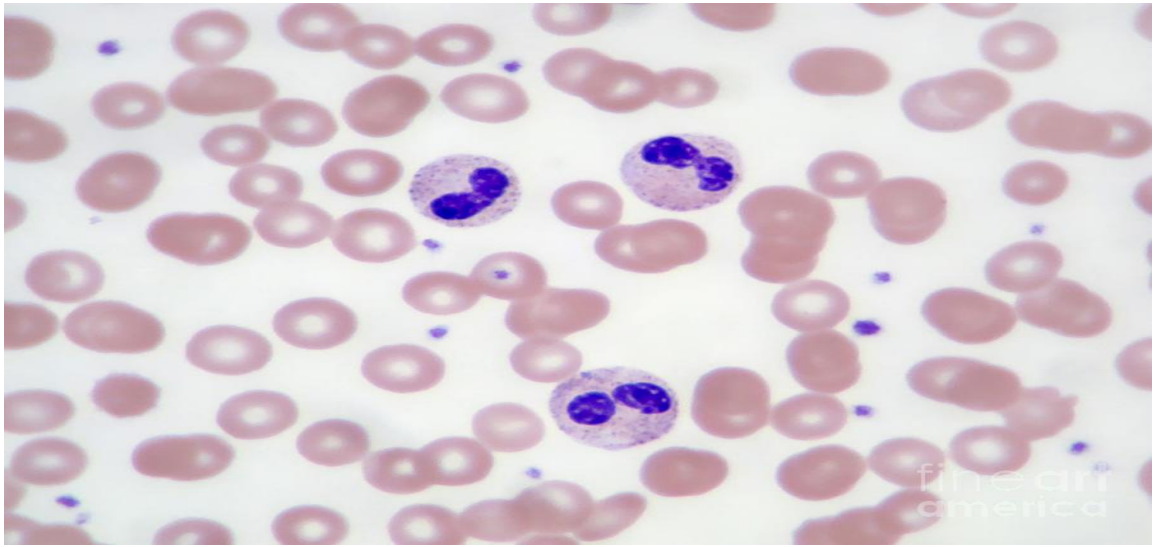
MDS – Morphology

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



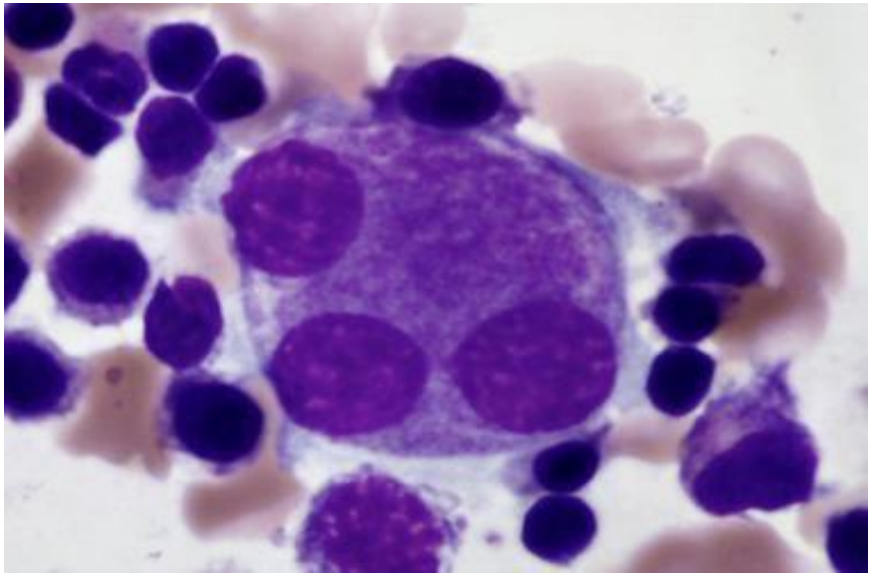
MDS – Morphology

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



MDS – Morphology

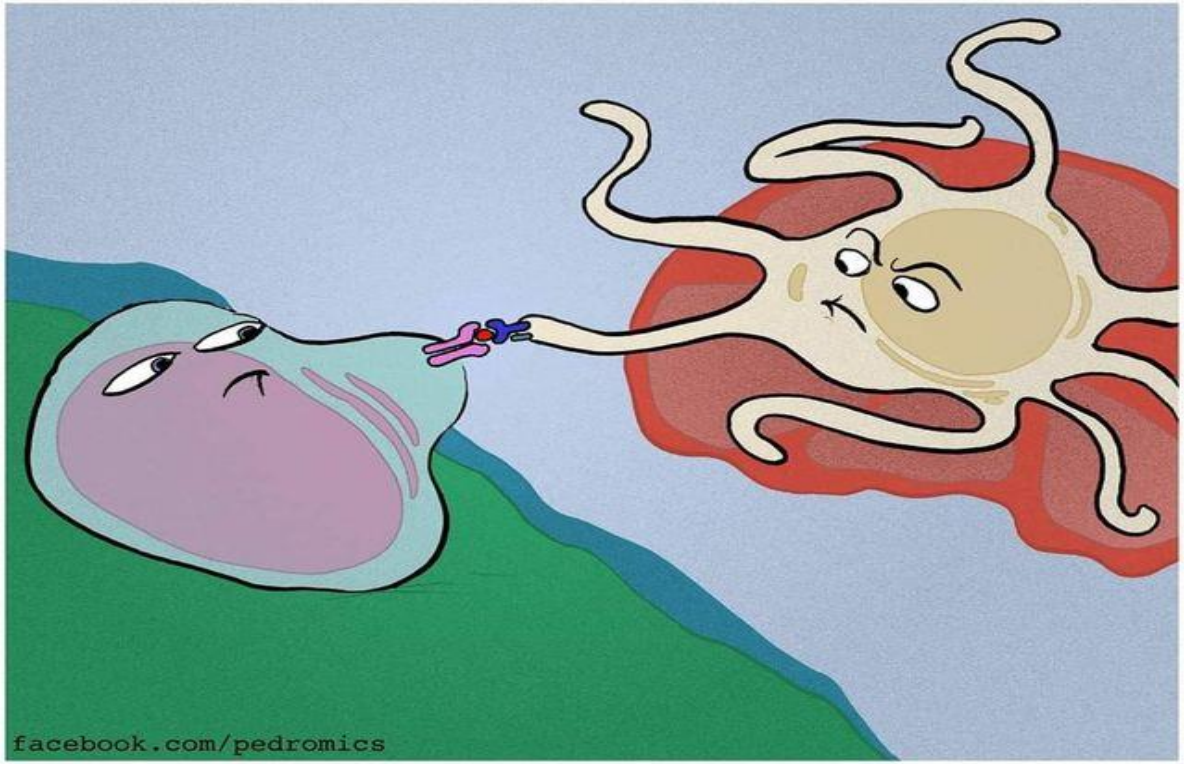
Megakaryocyte: single nuclear lobes or multiple separate nuclei (pawn ball megakaryocytes)



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.
- 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.

PRESENTATION OF THE ANTIGEN



THE CYSTEINE CHAPEL