

Neoplastic Proliferations of White Cells

~ Myeloid Neoplasms III

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Essential Thrombocythemia (ET)

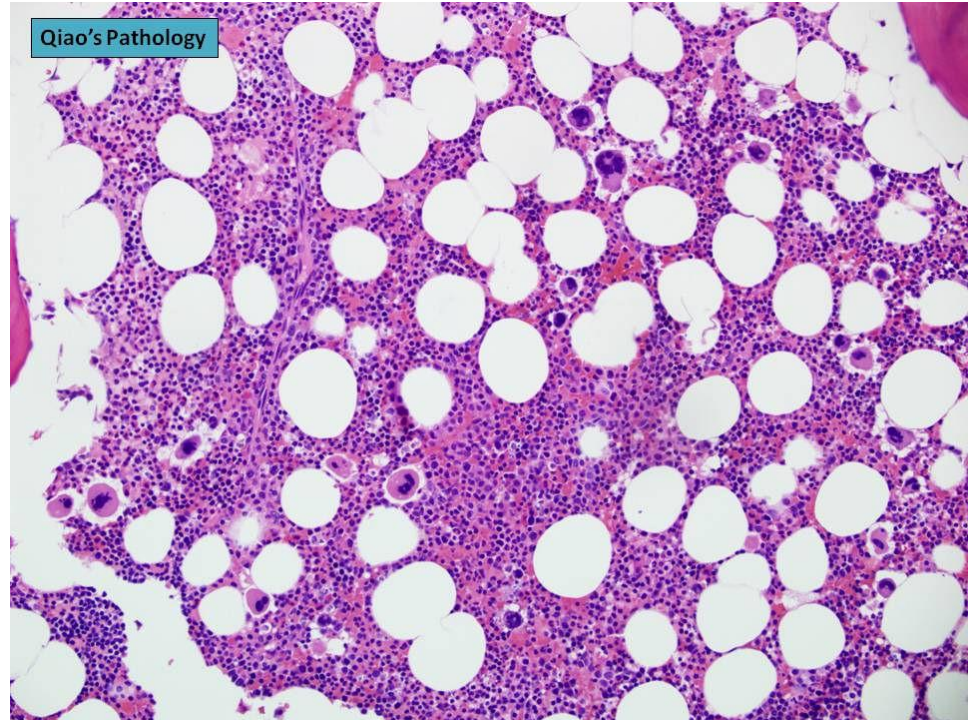
- ▶ Megakaryocyte proliferation with overproduction of platelets.
- ▶ Elevated platelet counts ($>600 \times 10^9/L$).
- ▶ Separated from PCV and primary myelofibrosis based on the absence of polycythemia and marrow fibrosis, respectively.

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.

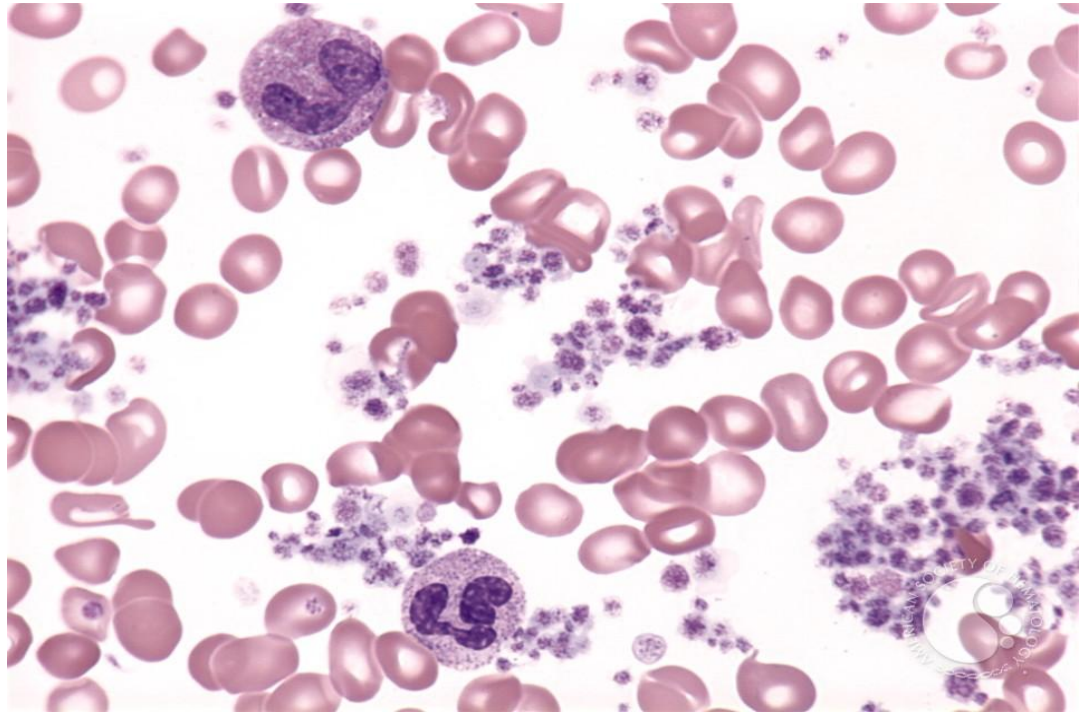
Essential Thrombocythemia – Morphology

- ▶ 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 fully understood.

PM - Pathogenesis

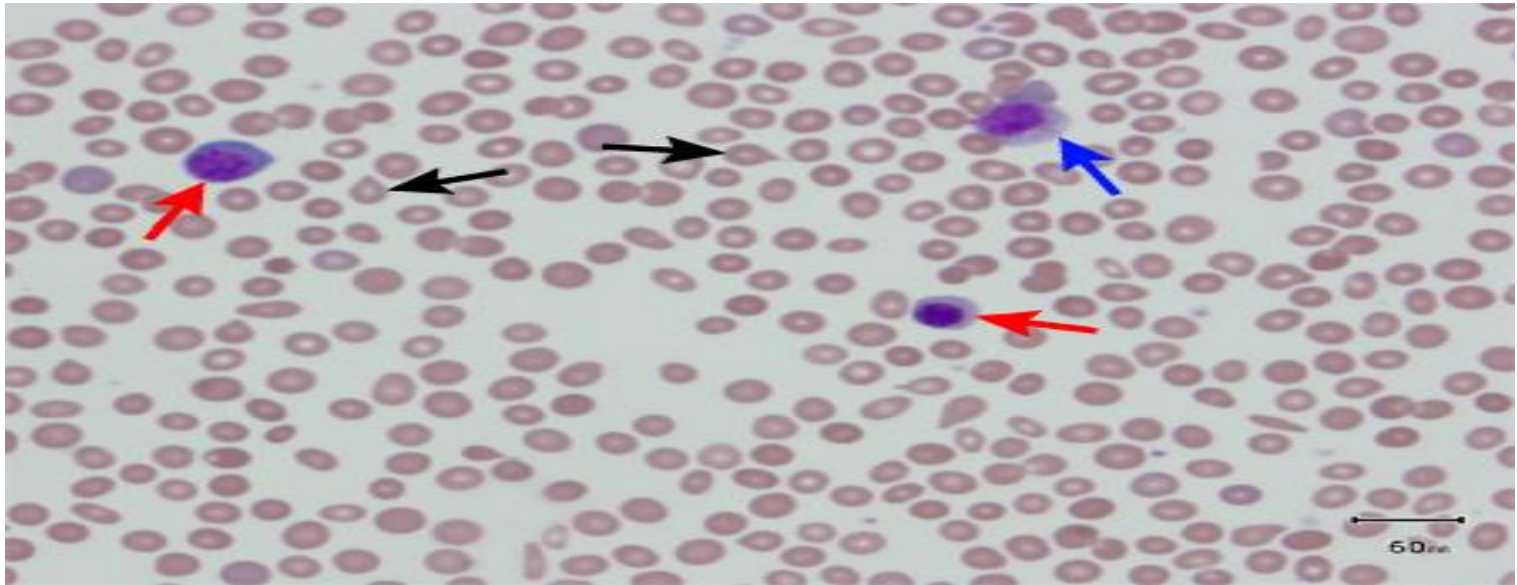
- ▶ Pathogenesis is similar between PM and spent phase MPN
- ▶ The characteristic marrow fibrosis is caused by the inappropriate release of **fibrogenic factors** from neoplastic **megakaryocytes**.
- ▶ Two factors synthesized by megakaryocytes have been implicated (**fibrogenic factors/fibroblast mitogens**):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

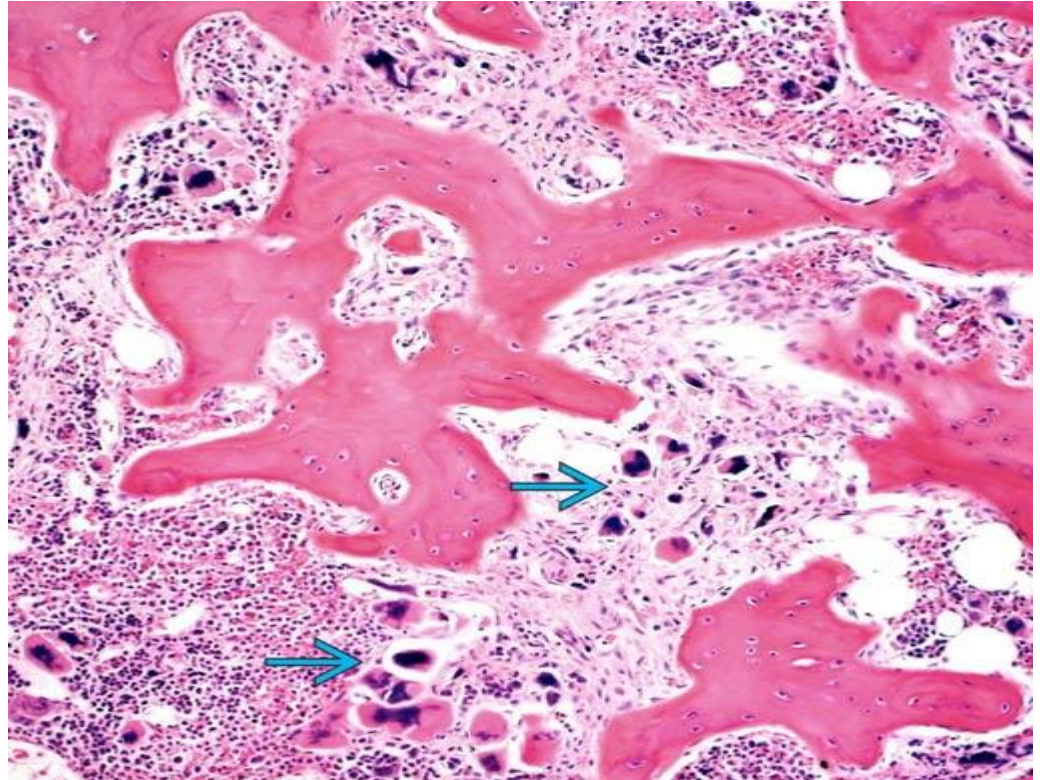
PM - Morphology

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.
- + thickened bone trabeculae.
- + In early cases it may be hypercellular & only focal fibrosis.
- +Abnormally large and clustered megakaryocytes, **arrows**



PM - Clinical Features

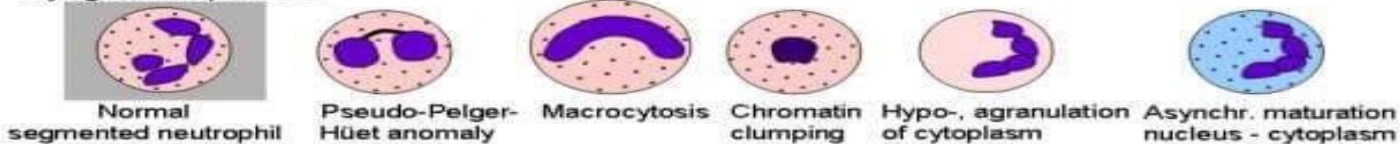
- ▶ Age more than 60
- ▶ Anemia and splenomegaly .
- ▶ Fatigue, weakness and night sweats
- ▶ Lab results; normochromic and normocytic anemia and Leukoerythroblatosis
- ▶ Bone marrow is essential for the diagnosis.

PM - Prognosis

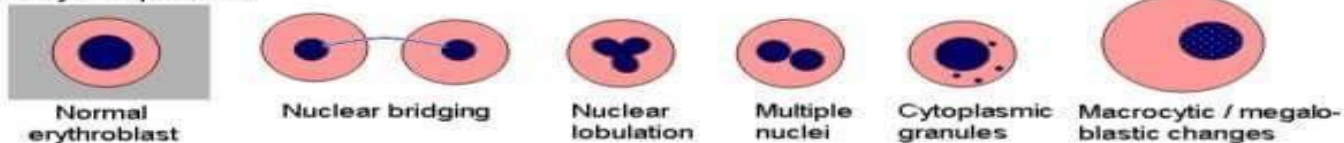
- ▶ Median survival is 4-5 years.
- ▶ 5-20% transform to AML.
- ▶ More difficult to treat than PCV and CML.
- ▶ Treat with JAK2 inhibitors and HSCT.

Dysplasia in Myelodysplastic Syndrome

Dysgranulopoiesis



Dyserythropoiesis



Dysmegakaryopoiesis



Cantù Rajnoldi et al. Ann Hematol 2005;84:429-33

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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

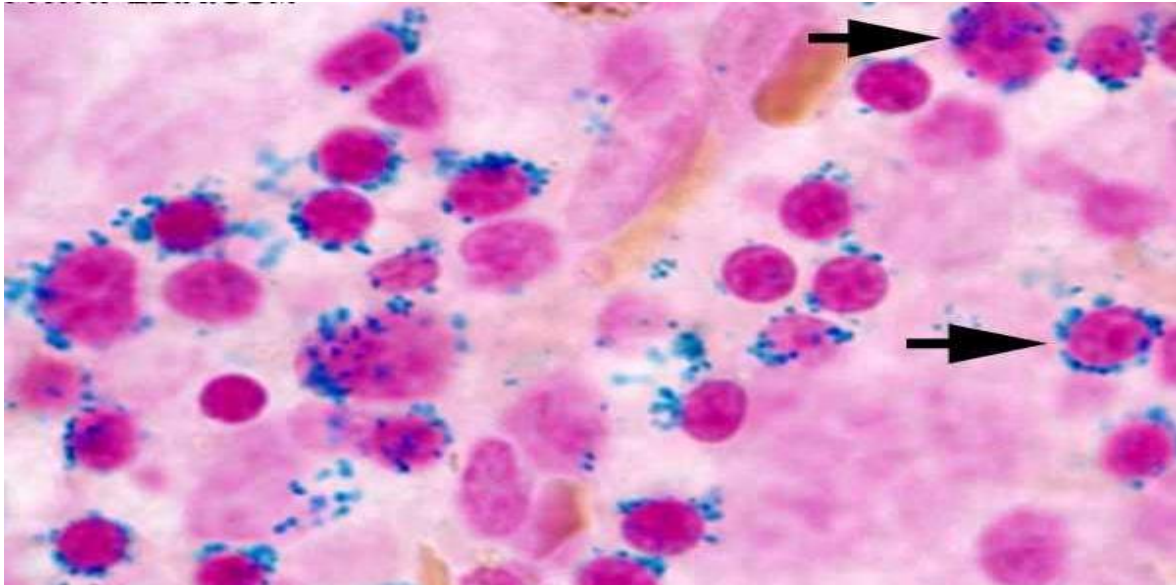
- ▶ Most cases are idiopathic, but some develop after exposure to carcinogens, previous cancer therapy, chemotherapy with alkylating agents or ionizing radiation therapy.
- ▶ ~10% of MDS have loss-of-function mutations in tumor-suppressor gene TP53 → often associated with chromosomal instability.
- ▶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

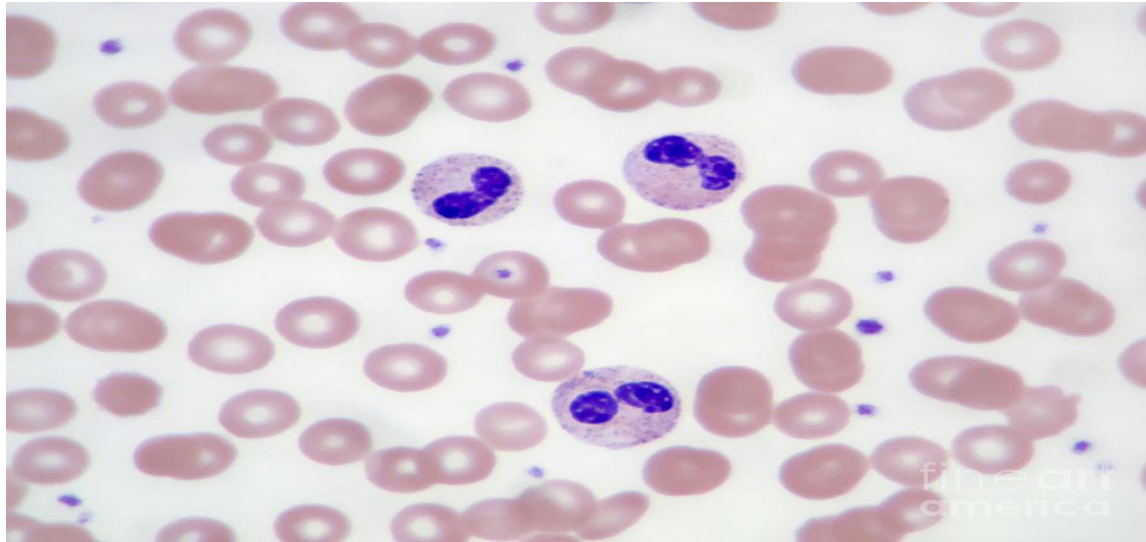
MDS - Morphology

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



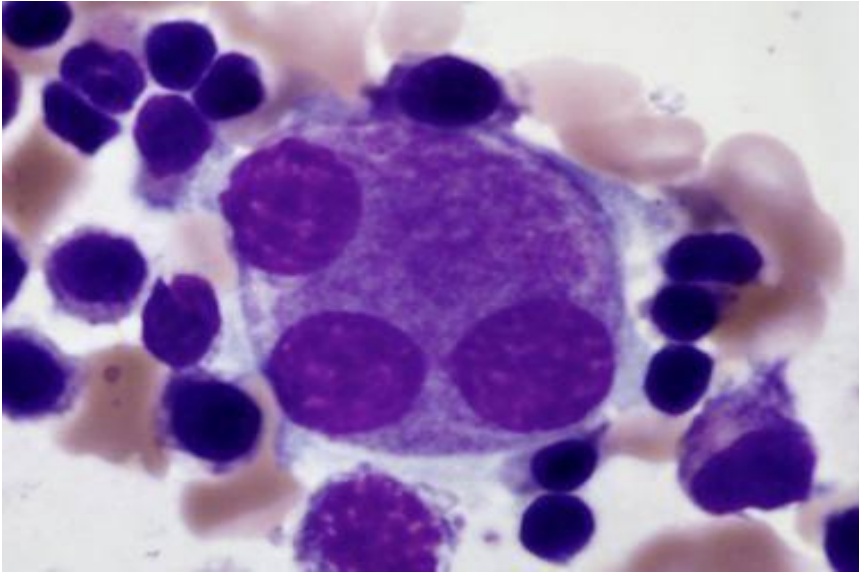
MDS - Morphology

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



MDS - Morphology

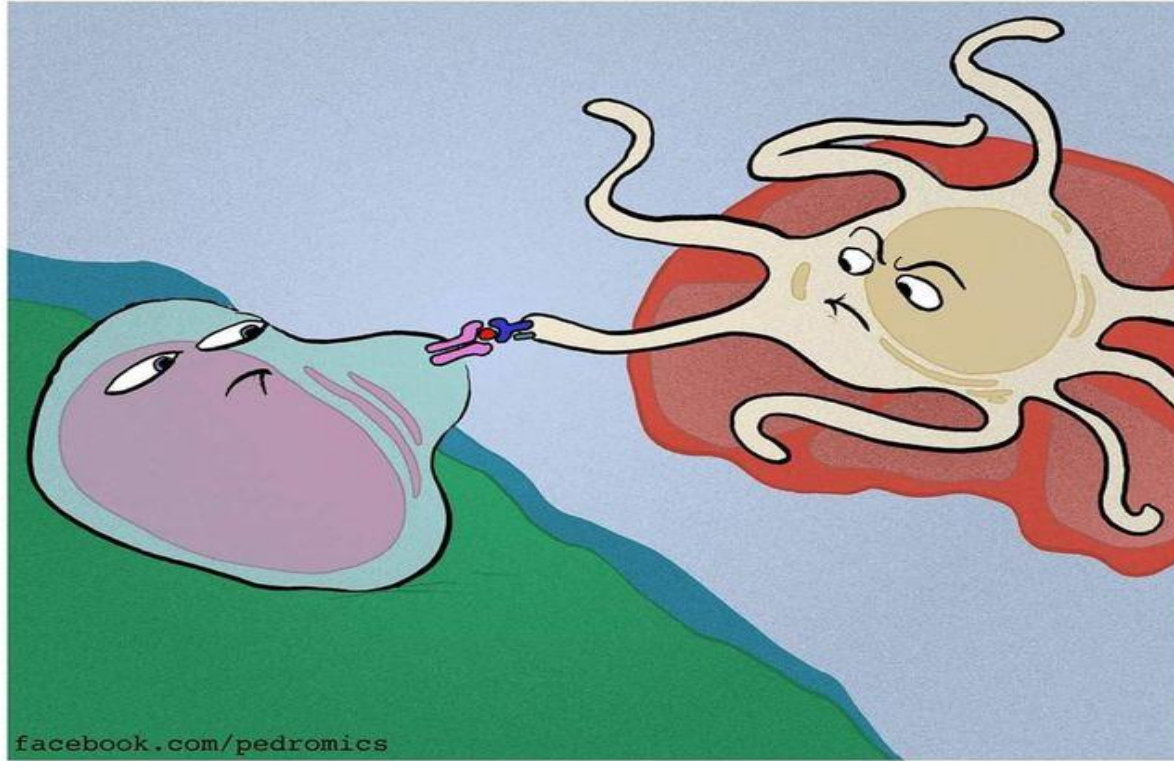
Megakaryocyte: single nuclear lobes or multiple separate nuclei (pawn ball megakaryocytes)



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