HEMATOPOIETIC & LYMPHATIC SYSTEM

SUBJECT : Pathology

LEC NO. : 8

DONE BY : Hamza alsyouri

وَقُل رَّبِّ زِدْنِي عِلْمًا

3. Essential Thrombocythemia (ET)

mainly لانه Thrombocthemia اسمه

- **A clonal stem cell disorder characterized by elevated platelet counts** and fulfills all 4 WHO criteria:

1. Sustained Platelet count > 450,000 /µl
2. Hyperplasia of large mature marrow megakaryocytes with no significant granulopoiesis or erythropoiesis.

لانه حكينا بس ال megakaryocytes هي ال effected

3. Not meeting WHO criteria for PV, PMF, BCR-ABL1+CML or MDS, or other Myeloid Neoplasms
4. JAK2, MPL or another clonal marker, if not: absence of known causes of reactive thrombocytosis.

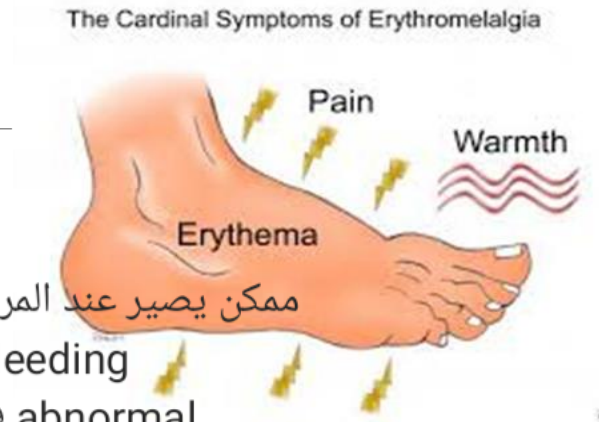
شرح نقطة ٣ : يعني اذا شفت مريض عنده
Hyperplasia in the megakaryocytes
granulopoiesis significant وعنده كمان
(CML) بصير مثلا (ET) ببطل هاد
Effected عشان هيك لازم اعرف مكان ال

primary not secondery لانه لازم تكون

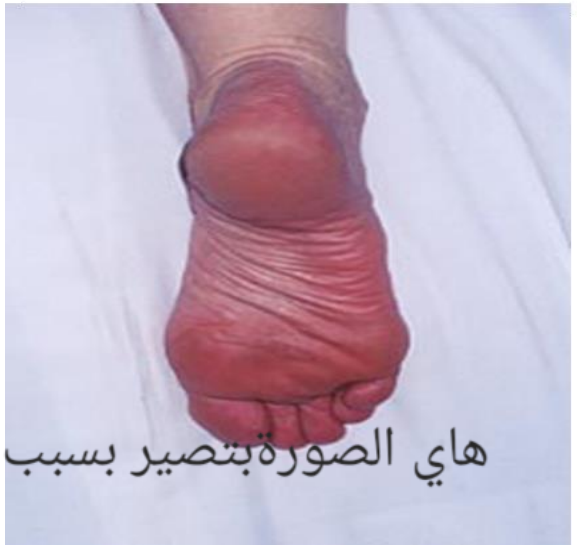
❑ Clinical Findings

بس لما يصير عندي اعراض بكون بسبب ال thrombosis بسبب وجود كميات كبيرة من ال plateletes

- Usually, > 60 yrs.
- No symptoms early in the clinical course.
- Hemorrhage or thrombotic episodes.
  - Recurrent gastrointestinal bleeding and epistaxis are common.
  - Venous or arterial thrombosis.
  - Throbbing and burning in palms, soles, and toes (erythromelalgia).
  - Iron deficiency due to recurrent bleeding episodes.
  - Splenomegaly.
  - Acute leukemia 10% of patients



ممكن يصير عند المريض attack فجأة بصير عنده Hemorrhage او bleeding بسبب استهلاك ال platelets وال normal فبتصير حلقة من hemrrhage وال thrombotic abnormal



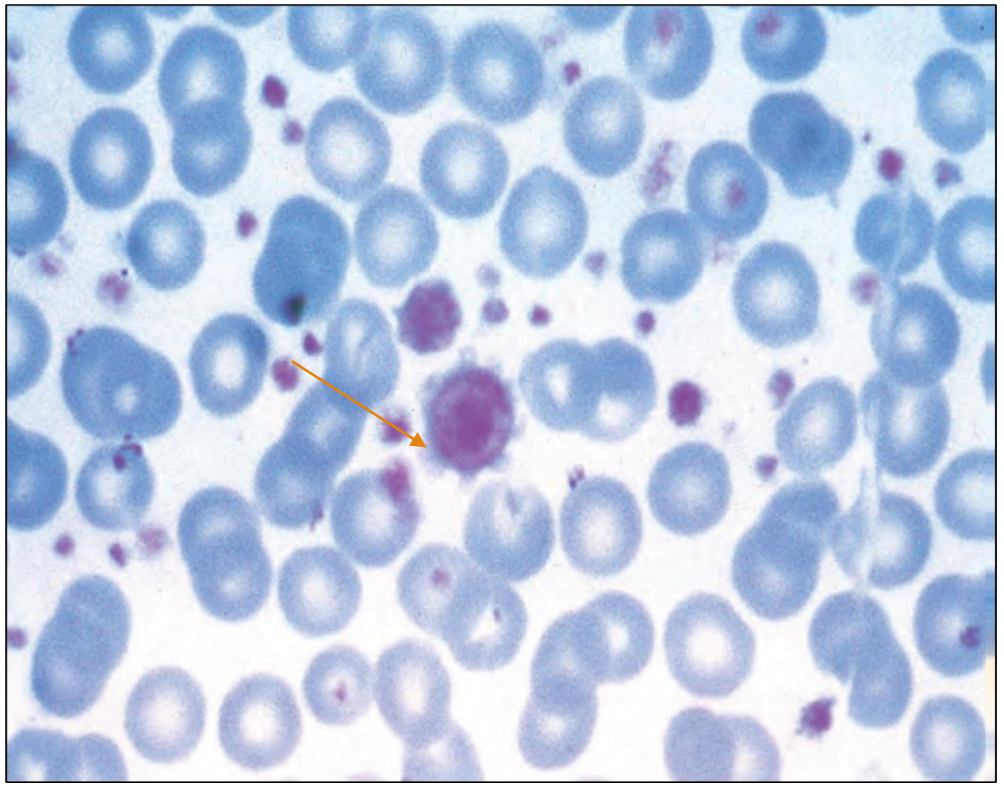
هاي الصورةبتصير بسبب تسكير ال small arteriols بسبب الthrombosis

❑ Pathology:

Peripheral blood smear shows marked thrombocytosis, including giant platelets approximating the size of surrounding red cells.

❑ **Bone marrow:**

- Cellularity is usually only mildly increased, but megakaryocytes are often markedly increased in number and include abnormally large forms (hyper lobulated nuclei (staghorn nuclear appearance).

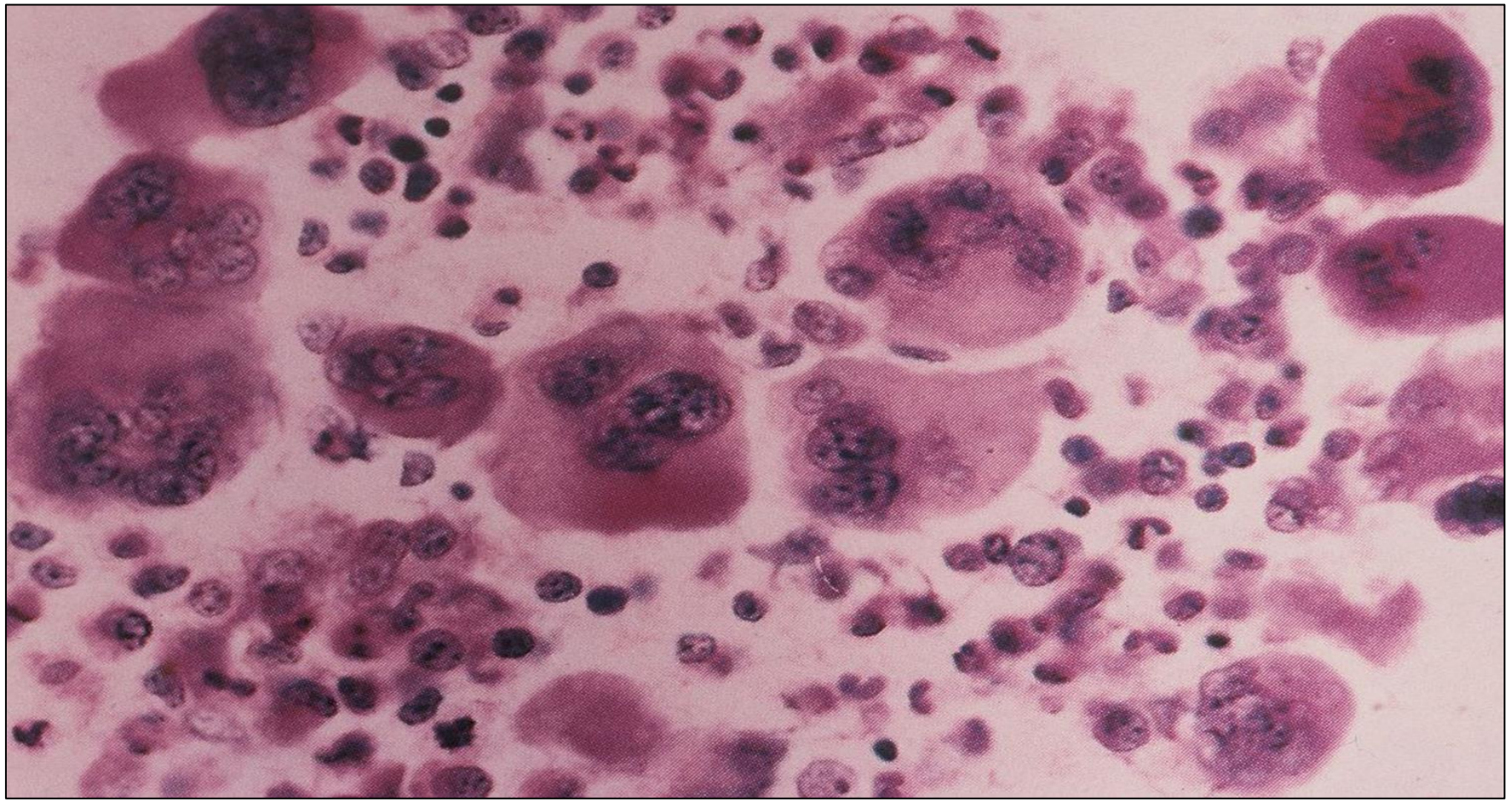


❑ **Peripheral smears**

- Usually reveal abnormally large platelets

❑ Modest degrees of extramedullary hematopoiesis may occur, producing mild organomegaly.

Essential Thrombocythemia (ET)



4. Primary Myelofibrosis

A chronic myeloproliferative disorder characterized by:

- Bone marrow fibrosis
- Leukoerythroblastosis
- Splenomegaly and extramedullary hematopoiesis

سبب ال fibrosis اللي في الBone marrow

- Fibroblast proliferation stimulated by platelet-derived growth factor(PDGF)and transforming growth factor β (TGF β) released from neoplastic megakaryocytes.

بنستنتج انه ال megakaryocytes السبب في
primary myelofibrosisال

حكينا overt fibrotic لانها هي مش stage وحدة في عندي 3stages مرحلة بتسبق الfibrotic بتكون prefibrotic وفي مرحلة بعد ال fibrotic اللي هي postfibrotic بس احنا بهمنا مرحلة ال fibrotic فقط

❑ WHO Criteria: overt fibrotic stage, all 3 major and at least 1 minor for Dx

Major:

1. Megakaryocytes proliferation+ fibrosis
2. Not meeting PV, CML, MDS, or MN by WHO criteria
3. JAK2 or other clonal but if not: no evidence of reactive fibrosis

Minor:

1. Leukoerythroblastosis
2. Increase in LDH
3. Anemia
4. splenomegaly
5. Leukocytosis

The median survival is in the range of 4 to 5 years.

❑ Clinical Findings

- Usually, > 60 yrs.

- Progressive anemia and splenomegaly.

- Fatigue, weight loss, and night sweats are common.

- Hyperuricemia and secondary gout resulting from a high rate of cell turnover are also frequent.

- Morphology

بما انه ال primary myelofibrosis ما ببلش بال fibrosis
ولانه في مرحلة بتسبقها فالتغيرات بتكون تدريجية فبكون مثلا
في مرحلة الprefibrosis مرتفع وبعدين بقل لما يوصل مرحل
الfibrosis زي مثلا الWBC

- Peripheral blood:

- Anemia with progressive worsening. Teardrop cells
- WBC count: Elevated (early), normal or reduced
- PLt: Normal or elevated (Early), decreased (Late)
- **Leukoerythroblastosis** (Red cells exhibit bizarre shapes **(poikilocytes, teardrop cells)**, and nucleated erythroid precursors along with immature white cells (myelocytes and metamyelocytes)).

بالاضافة الى

الleukoerythroblastosis اول ما اشوفها بكون
التشخيص primary myelofibrosis

- Abnormally large platelets

- Bone marrow:

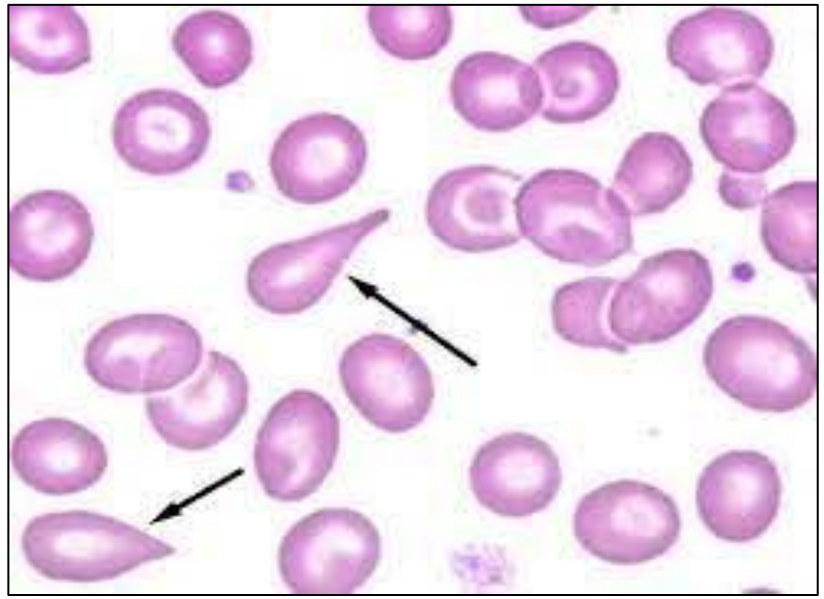
- Hypercellular (Early), Hypocellular, and diffusely fibrotic (Advanced)
- Bone marrow aspiration usually results in a "dry" tap.
- Throughout the course, marrow megakaryocytes are present in clusters and have characteristic **hyperchromatic nuclei with “cloudlike” outlines**.

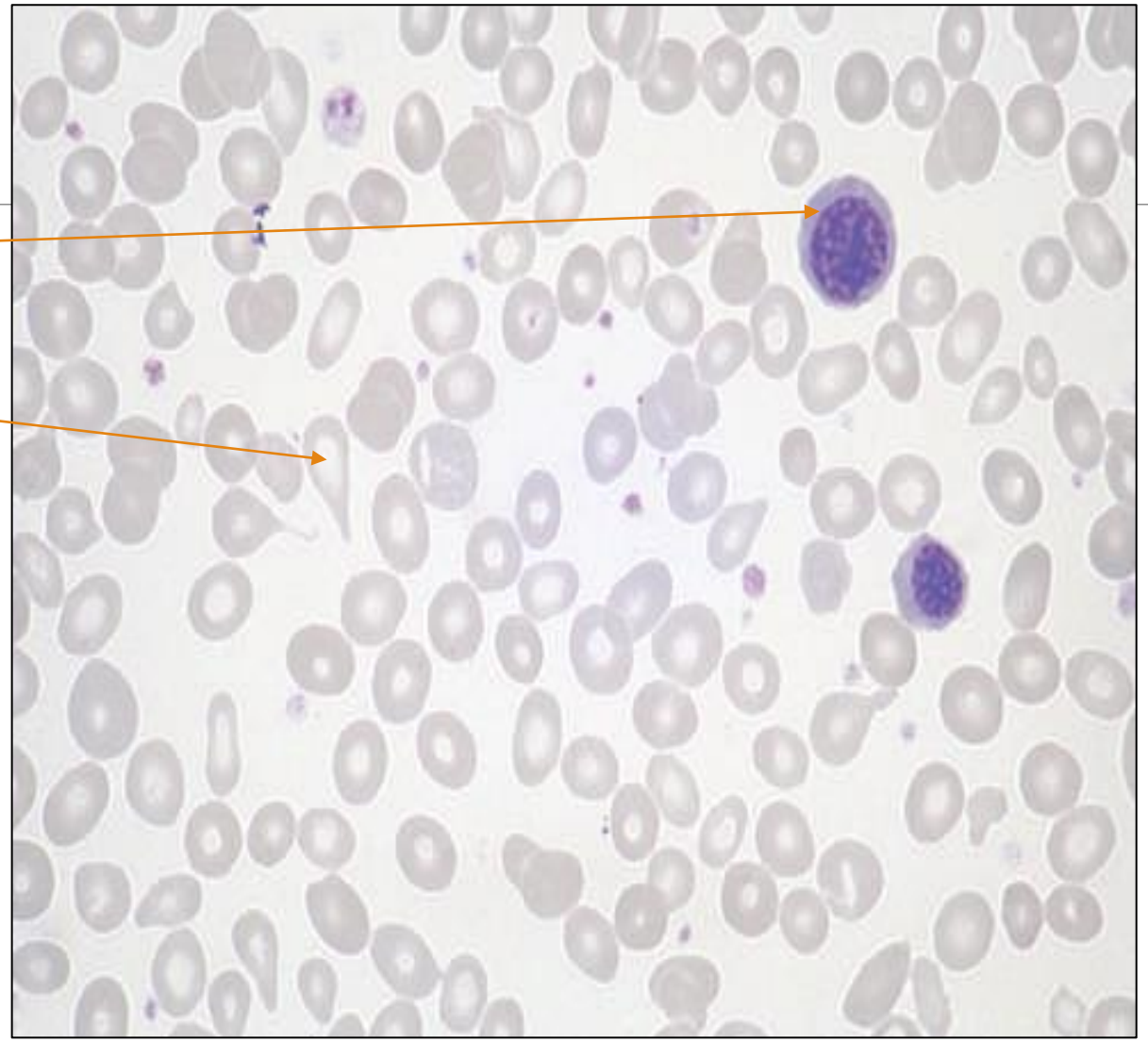
اذا في مرحلة الfibrosis بصير fibrotic Hypocellular
marrow and clusters from large megakaryoctes

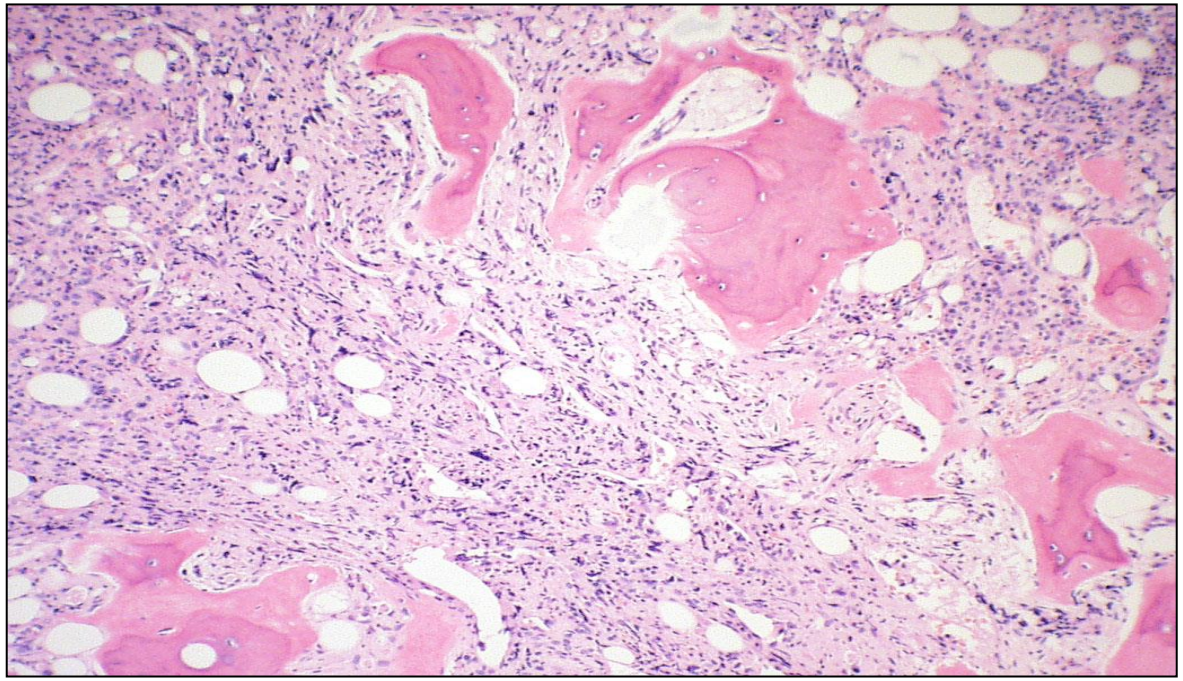
بكون برضو peripheral bloodوفي ال
مع وجود fibrosisفي مرحلة ال Hypocellular
Leukoerythroblastosisال

Primary myelofibrosis—peripheral blood smear.

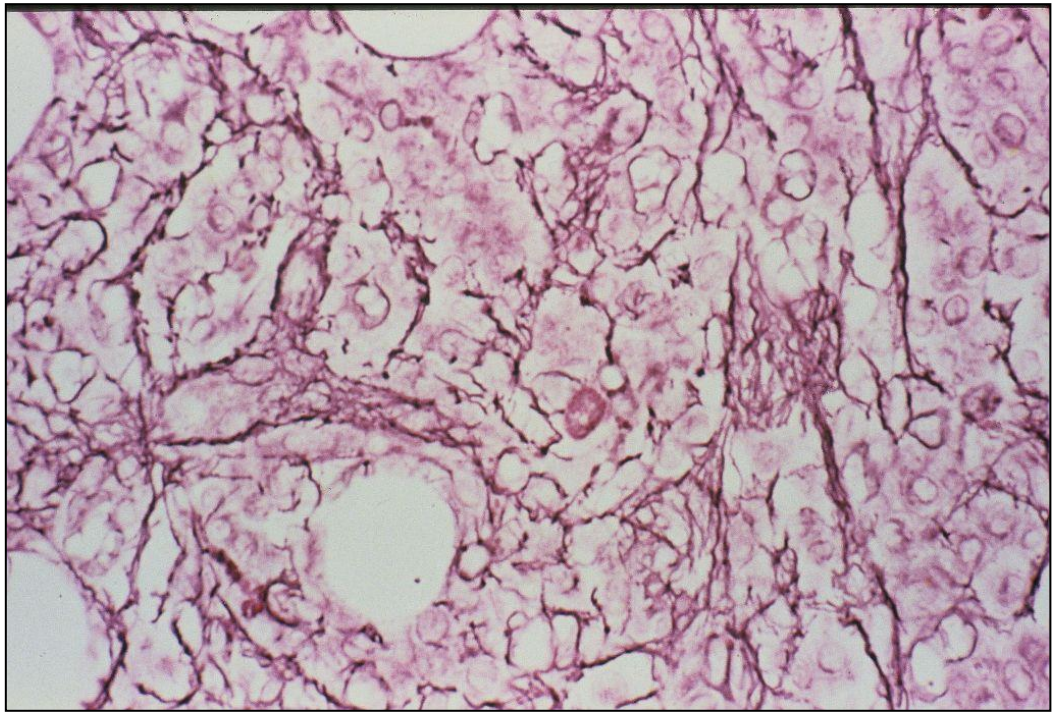
-Two nucleated erythroid precursors and several teardrop-shaped red cells are evident.





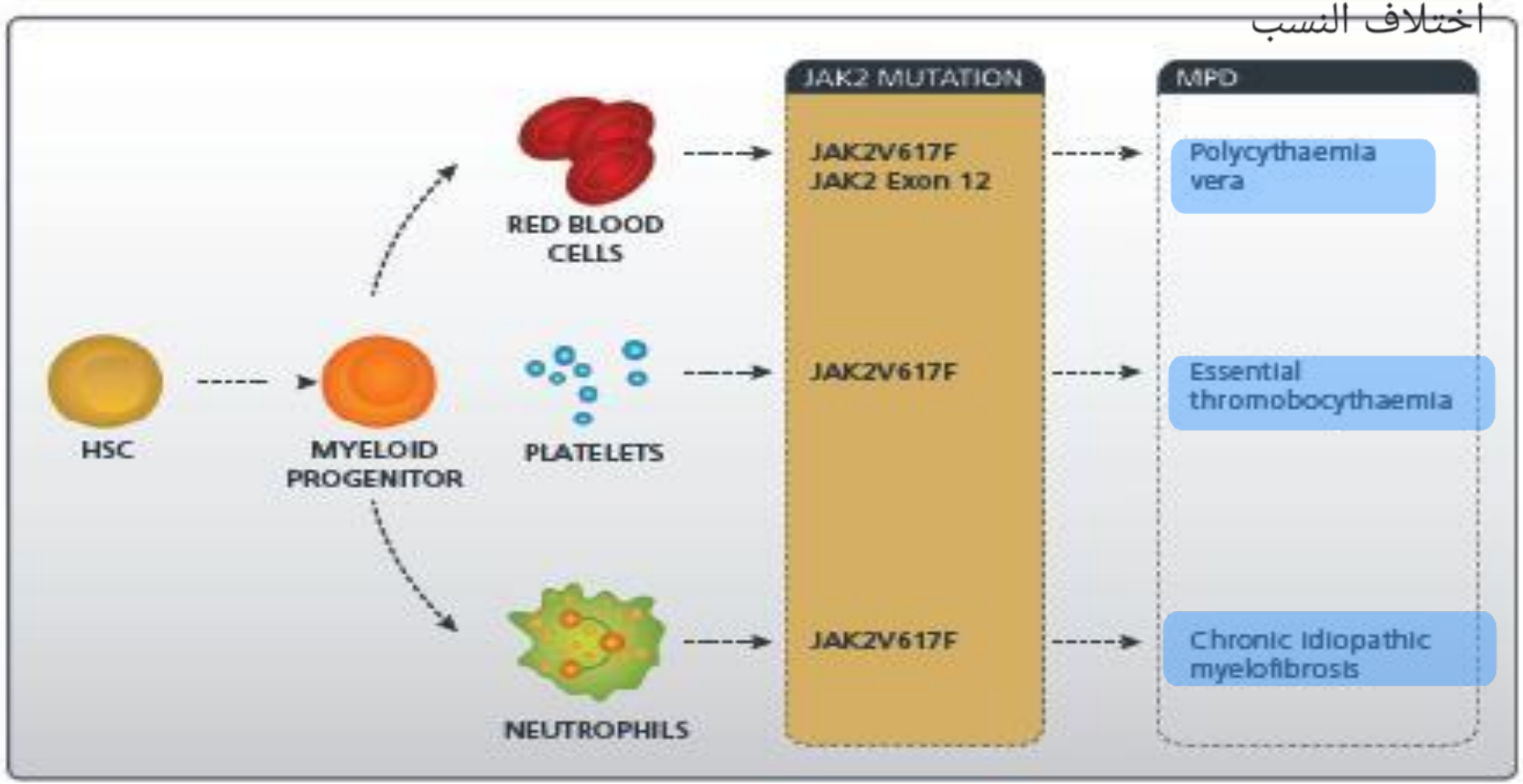


Reticulin Fibrosis



JAK2 Mutations in MPN

هاد السلايد للتذكير بأن ال JAK2 Mutations هو ال most common mutation للجدول اللي اعلاه MPD مع اختلاف النسب



كلام الدكتورة : مهم نرجع نركز على ال lineage اللي بتكون effeted وبالتالي كيف بينعكس على ال bone marrow هل هو Hypercellylar ولا Hypo والperipheral blood نفس الاشي واذا في تغيرات معينة بتكون بتعطينا اشارة ايش هذا المرض وبالاضافة الى ال genetic changes

هو seperate entity عن ال chronic myeloid disorder لانه
خصائصه من classification وغيره مختلفة

Myelodysplastic Syndromes (MDS)

Clonal disorders of hematopoietic stem cells characterized by maturation defects and:

- Ineffective hematopoiesis (bone marrow failure).
  - **hyper**cellular bone marrow.
  - Peripheral pancytopenia.
- Morphologic abnormalities (dysplasia) of peripheral blood and bone marrow cell
- A tendency to develop acute myeloid leukemia.

لا يعني انها راح تعمل block لل deferentiation ولكن
اللي بصير انه طريقة ال maturation تاعها بيعطيها اشكال
غريبة غير عن ال normal

يعني
اشكال
غريبة

بسبب اشكالها الغريبة بالعادة بصيرلها destruction او بتتكسر وما
بتطلع على ال peripheral blood فبصير عندي cytopenia بال
peripheral blood سواء كان بكل انواع ال lineage او بنوع واحد
لان ال MDS مش مجرد single entity هو فعليا مجموعة من ال
disorders

- Idiopathic or secondary to radiation and alkylating chemotherapy

بنسميه bone marrow failure او ineffective hematopoiesis لانه ال bone marrow معبا بالخلايا لكن ال peripheral
blood قاعد بينقص في الخلايا زي كانه في فشل في ال bone marrow

❖ Pathogenesis

- Mutations in transcription factors

- Frequent mutations in factors that regulate DNA methylation.

- May have mutations in TP53.

- Recurrent chromosomal abnormalities, including deletions of 5q, 7q, and 20q, and trisomy 8.

الجدول مش حفظ

Clinical Features and prognosis:

- Presents between the ages of 50 and 70 yrs

- Infections, symptoms related to anemia or hemorrhage.

- **Response to conventional chemotherapy is poor**

- Prognosis variable: the median survival time ranges from 9 to 29 months

ال prognosis تبعه سيء

WHO (2016) Classification for MDS
MDS with single lineage dysplasia (MDS-SLD)
MDS with multilineage dysplasia (MDS-MLD)
MDS with ringed sideroblasts and single lineage dysplasia (MDS-RSSLD)
MDS with ringed sideroblasts and multilineage dysplasia (MDS-RSMLD)
MDS with excess blasts-1 (MDS-EB1)
MDS with excess blasts-2 (MDS-EB2)
MDS, unclassified
MDS indicates myelodysplastic syndromes; WHO, World Health Organization. Adapted from Arber DA, et al.[39]

❖ Morphology

The marrow is populated by abnormal-appearing hematopoietic precursors. Some of the more common abnormalities include:

- Megaloblastoid erythroid precursors resembling those seen in the megaloblastic anemias.
- Erythroid forms with iron deposits within their mitochondria (**ring sideroblasts**)
- Granulocyte precursors with abnormal granules or nuclear maturation (Hyposegmented and occasionally hypersegmented neutrophils
- Small megakaryocytes (Micromegakaryocytes) with single small nuclei or multiple separate nuclei.

هي بالاصل nucleus وحدة و صارلها seperation
فأحيانا ممكن نشوف single small nuclei فبكون ما
صارلها seperation واحيانا بتكون multiple مش معناته
انه ال nuclei صارلها تجزئة لا هم فعليا اكثر من nucleus

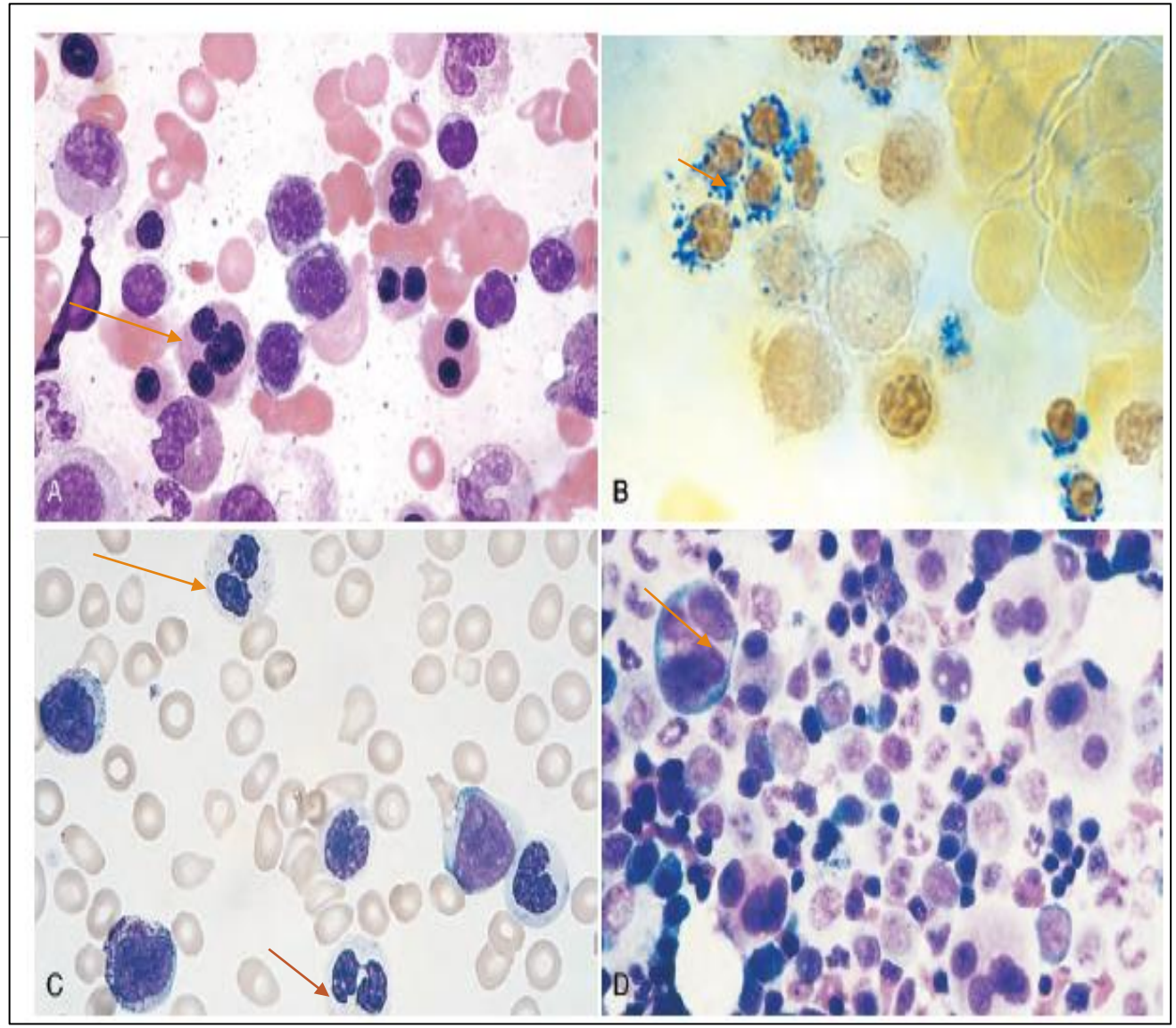
Myelodysplasia. Characteristic forms of dysplasia are shown (**A, B, D,** Marrow aspirates; **C,** peripheral blood smear.)

A, Nucleated red cell progenitors with multilobated or multiple nuclei.

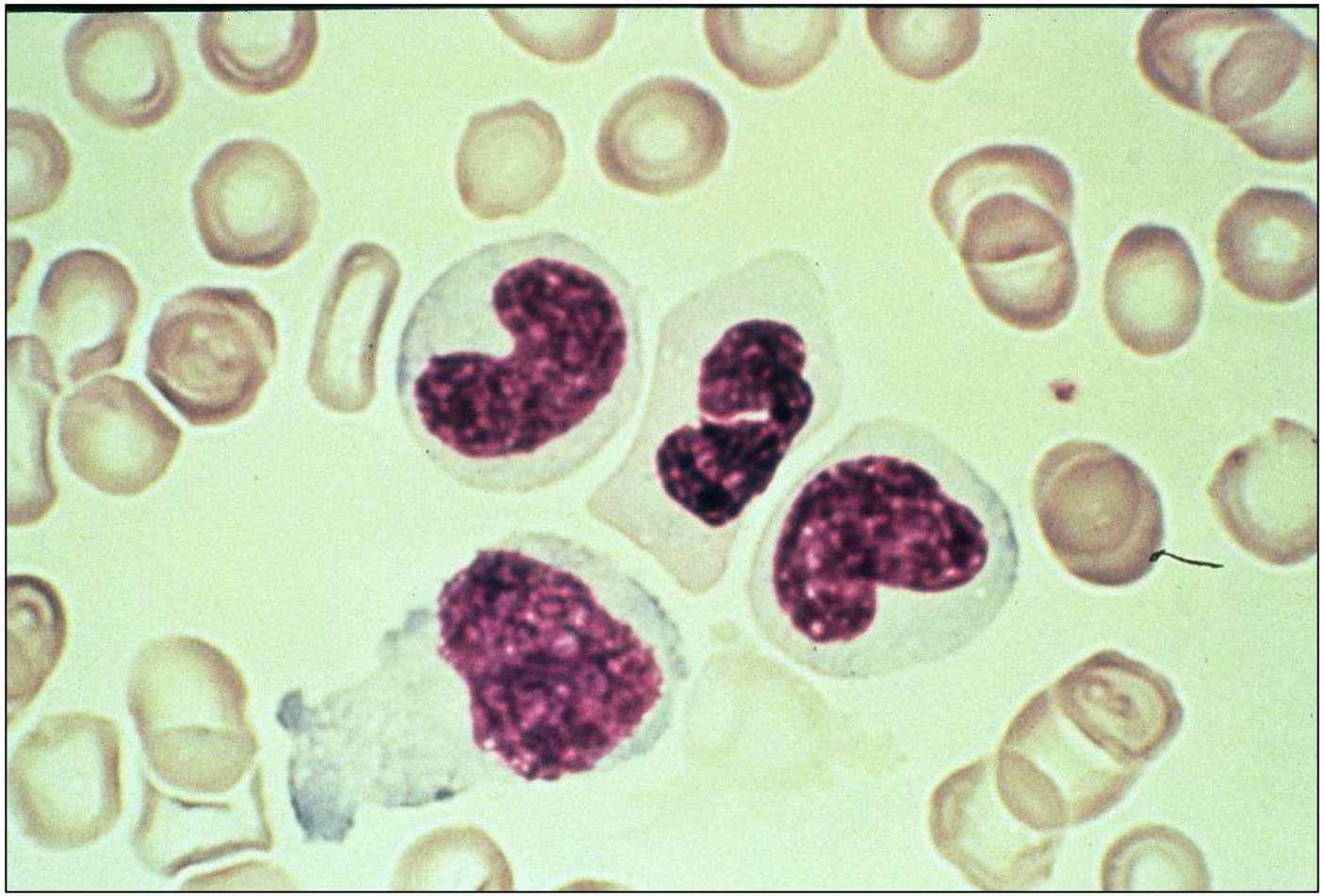
B, Ringed sideroblasts, erythroid progenitors with iron-laden mitochondria seen as blue perinuclear granules (Prussian blue stain).

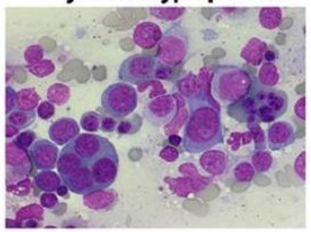
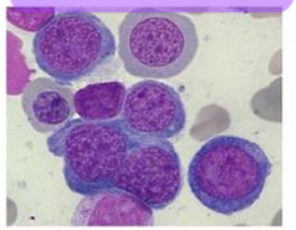
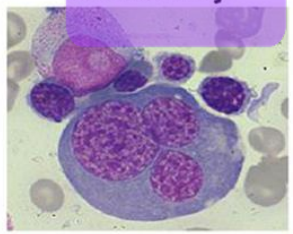
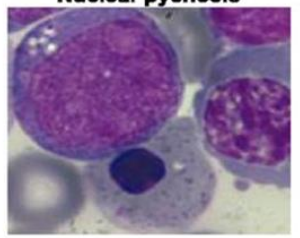
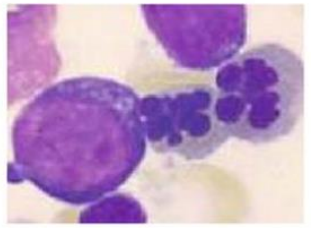
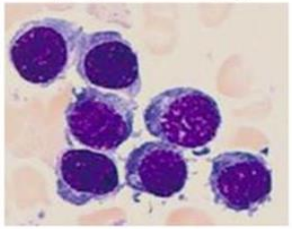
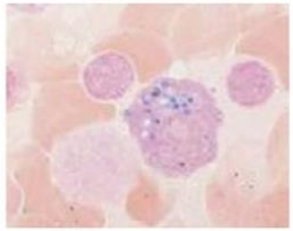
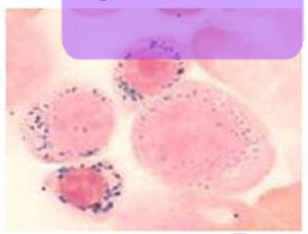
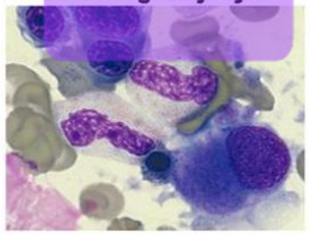
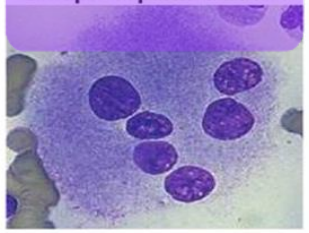
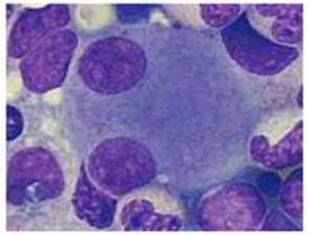
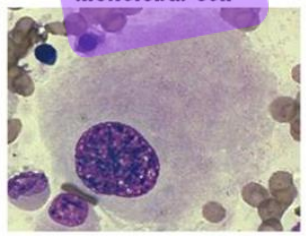
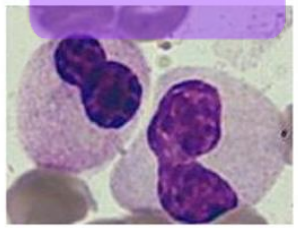
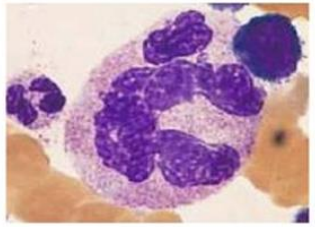
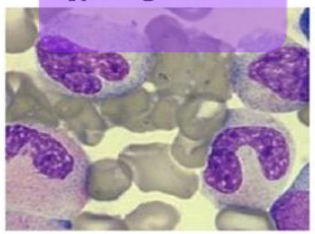
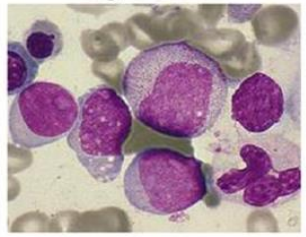
C, Neutrophils with only two nuclear lobes instead of the normal three to four

D, Megakaryocytes with multiple nuclei instead of the normal single multilobated nucleus.



Hpogranular Myeloid Cells



Erythroid lineage	Erythroid hyperplasia 	Megaloblastoid changes 	Multinuclearity 	Nuclear pycnosis 
	Nuclear lobulation 	Cytoplasmic fraying 	Ferritin sideroblast 	Ring sideroblasts 
Megakaryocyte lineage	Micromegakaryocyte 	Multiple separated nuclei 	Small binucleated cell 	Monolobar cell 
Granulocytic lineage	Pseudo-Pelger anomaly 	Abnormal nuclear shape 	Hypo-degranulation 	Myeloblasts 

1. A 60-year-old male patient presented with weakness and unexplained bleeding. On examination, he was pale with cutaneous hemorrhage, and a palpable spleen. His CBC showed low hemoglobin and platelet levels. A bone marrow biopsy revealed a hypercellular marrow with about 36% of cells having delicate nuclear chromatin, multiple nucleoli, and fine cytoplasmic granules with some red rods (needle-like structures). These cells were positive for CD14 and CD13. Which of the following best describes the patient's underlying disease:

A. The cells with monocytic differentiation are characteristically negative for NSE while positive for MPO
B. The presence of del 5 or 7 represents a good prognostic factor
C. The described marrow cells are fully differentiated, mature, and usually positive for TDT
D. The promyelocytic subgroup usually associated with t (15,17)
E. This disease occurs absolutely in children

---

2. A 65-year-old patient presented with fatigue and was found to have pancytopenia with nucleated erythroid precursors and teardrop cells and myelocytes and metamyelocytes in the peripheral blood. Further bone marrow aspiration resulted in a dry tap, whereas the biopsy showed a hypocellular fibrotic marrow with clusters of megakaryocytes with "cloudlike" outlines. Which of the following regarding the patient's disease is true:

A. JAk2 mutation is never seen in this disease
B. Fibroblast proliferation is stimulated by factors released by granulocytes
C. It is associated with changes called Leukoerythroblastosis
D. It is never associated with splenomegaly
E. The diagnosis is acute leukemia

حل السؤالين في الريكورد الدقيقة 32.20

Thank you