HEMATOPOIETIC & LYMPHATIC SYSTEM

SUBJECT : Pathology

LEC NO. : 7

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وَقُل رَّبِّ زِدْنِي عِلْمًا

2 types of classification

1. WHO

2. FAB

❖ Classification

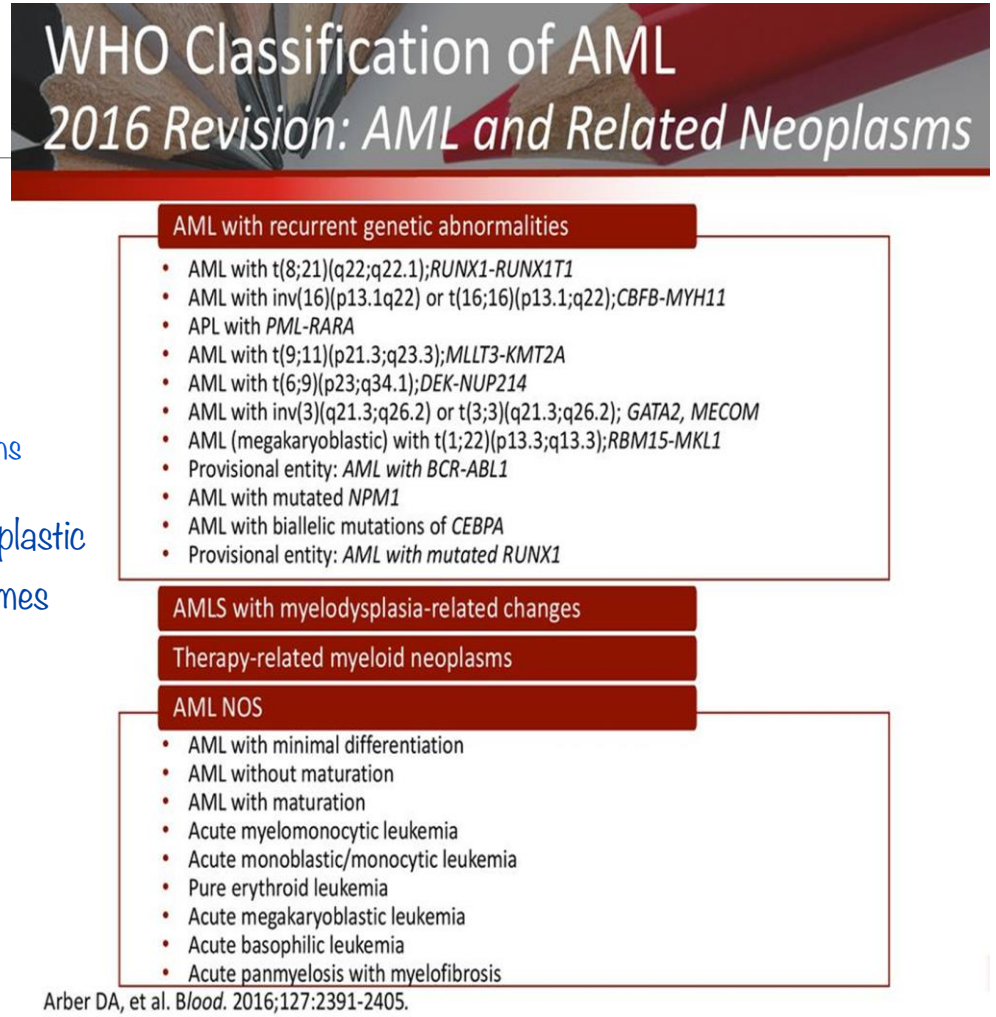
- AMLs are diverse in terms of genetics, cellular lineage, and degree of maturation.
- **The WHO classification relies on these features to divide AML into four categories:**

(1) AMLs associated with specific genetic aberrations Ex : translocations

(2) AMLs with dysplasia, many of which arise from MDSs (abnormal morphological changes in cells) (myelodysplastic syndromes)

(3) AMLs occurring after chemotherapy

(4) AMLs lacking any of the foregoing features (subclassified based on the predominant line of differentiation that the tumor exhibits) NOS



Arber DA, et al. Blood. 2016;127:2391-2405.

FAB (French American British) classification of AML

الدكتورة ما بدها الأرقام بس مطالبين من التصنيف فقط M0 to M7

AML-M0 (minimally differentiated) → **>20% blasts**
<3% blasts are MPO +

Myeloid antigens +

No Auer rods

AML-M1 (without maturation) → **>20% blasts**

With differentiation

Most of the cells are myloblast

>3% blasts are MPO+

<10% promyelocytes or mature cells

AML-M2 (with maturation) → **>20% blasts**

نسبة اكبر من الخلايا صارت تشبه promyelocyte

>3% blasts are MPO+

>10% promyelocytes or mature cells

<20% monoblasts and promonocytes

AML-M3 (acute promyelocytic leukemia)

نسبة ال promyelocye أكبر من M2

① تتميز بوجود عدد من ال Auer rods

>20% **blasts and promyelocytes**

Intense MPO reactivity

② **Associated with t(15,17)**

③ **High incidence of DIC** (Disseminated Intravascular Coagulation)

AML-M4 (acute myelomonocytic leukemia)

Mixture of cells (myeloblasts, monoblasts, promonocytes)

>20% **myeloblasts, monoblasts, promonocytes**

Monocytic cells range from 20%-80%

Cells stain positive with lysosomal non-specific esterase.

AML-M5 (acute monoblastic and monocytic leukemia)

معظم الخلايا تشبه ال monoblasts + monocytes

>20% monoblasts, promoncytes and myeloblasts

>80% monoblastic cells (5A) or monocytic (5B)
No Auer rods

MPO -

AML-M6a (Erythroleukemia)

Mix with erythroid precursors

بس نسبتهم اقل

>50% are erythroid precursors

>20% myeloblasts among non-erythroid cells

AML-M6b (pure erythroid)

erythroid precursor زادت نسبة ال

>80% of marrow cells are immature erythroid cells

No significant myeloblastic component

AML-M7 (megakaryocytic)

>20% blasts

>50% megakaryocytic cells

AML Course & Prognosis

ال prognosis افضل للـ ALL

- Rapidly fatal if untreated.

- With chemotherapy, 70% remission rate and 15-20% 5-year survival.

-Prognostic Factors

Patient age

WBC count at presentation

De novo vs. Secondary leukemia

Cytogenetic abnormalities

Important

❖ **Good prognosis**

t(15;17)
t(8,21)
inv(16)

Some genetic abnormalities

❖ **Poor prognosis**

Age >60 y
Prior MDS (dysplasia)
Therapy-related AML
Leukocytosis >100,000/µL
Early relapse بعد علاج ال tumour رجع كمان مرة
del 5 or 7
t(9;22)

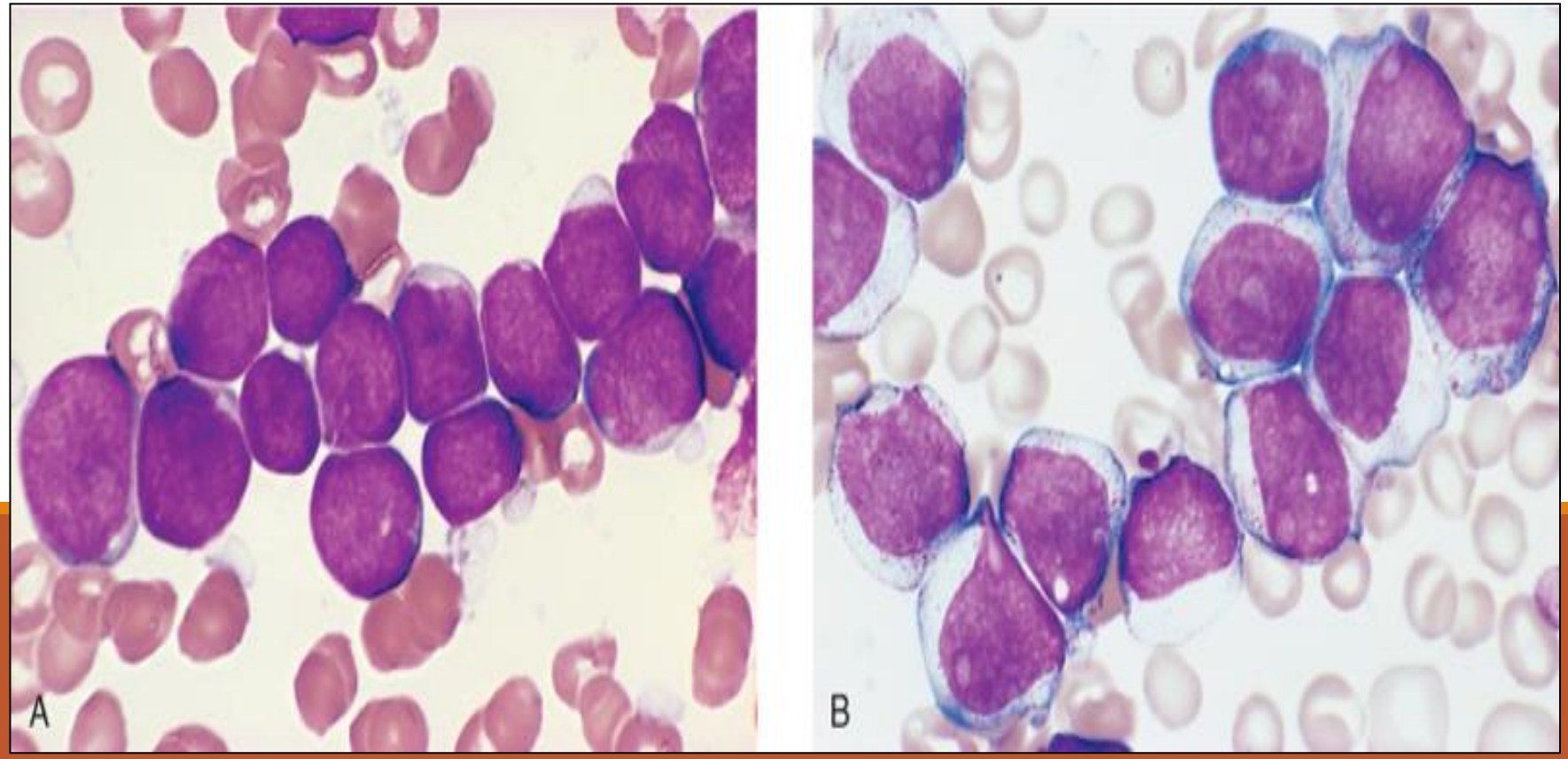
The major differences between AML and ALL

Feature	AML	ALL
Age	Common in adults Rare in children	Common in children Rare in adults
Blood	Myeloblasts	Lymphoblasts
Morphology	Medium to large blasts More cytoplasm Cytoplasmic granules Auer rods Fine chromatin Distinct nucleoli Large	Small to medium blasts Little cytoplasm No granules (90%) No Auer rods Fine chromatin Indistinct nucleoli Small
Myeloperoxidase	Positive	Negative
TdT	Negative	Positive
CD Markers	CD13,CD14 CD15,CD33,CD64	CD10,CD19,CD20 CD21,CD23,CD79a

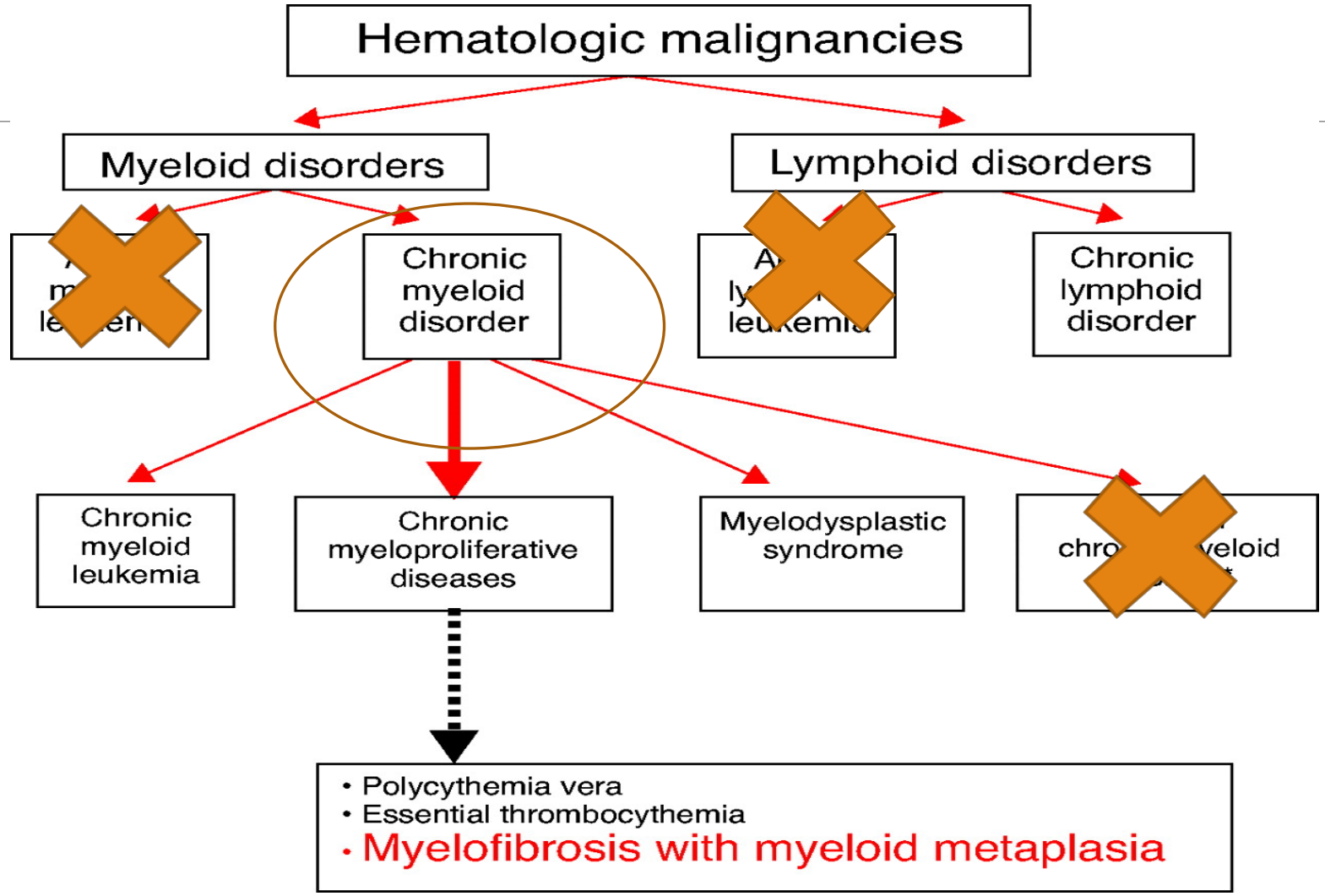
Morphologic comparison of lymphoblasts and myeloblasts.

A. ALL: Lymphoblasts have fewer nucleoli than do myeloblasts, and the nuclear chromatin is more condensed. Cytoplasmic granules are absent.

B. AML: Myeloblasts have delicate nuclear chromatin, prominent nucleoli, and fine azurophilic granules in the cytoplasm



Neoplastic Proliferations Of White Cells



Myeloproliferative Neoplasms (MPN)

ممكن تأثر على اي نوع من الخلايا

- A family of acquired malignant clonal disorders of pluripotent stem cells with resulting abnormalities in one or more cell lines.
- At least initially, the clonal stem cells **retain their capacity for terminal differentiation**.
- The hallmark of MPN is the presence of mutated, constituently **active tyrosine kinases** or other acquired aberrations that lead to **growth factor independence.**

ال acute leukaemia بختلف بانه عنده مشكلة في ال differentiation فبتكون من immature cells

اما ال MPN بكون مكون من mature looking بس هي abnormal functionally

- Four major diagnostic entities are recognized

1. Chronic myeloid leukemia (CML)
2. Polycythemia vera
3. Essential thrombocythemia
4. Primary myelofibrosis

General characteristics

- Hypercellular marrow with **maturation**
- **Effective** hematopoiesis لانه الخلايا الموجودة في ال bone marrow رح تطلع على ال peripheral blood
- Elevated peripheral blood levels of one or more cell lines:
  - granulocytic (CML)
  - erythroid (polycythemia vera)
  - platelets (essential thrombocythemia)

  اي نوع من الخلايا ممكن يتأثر و حسب نوع Myeloproliferative Neoplasms رح تكون الزيادة
- Hepatosplenomegaly
- These disorders have many overlapping features.

1. Chronic Myeloid Leukemia (CML)

- A disorder characterized by massive overproduction of normal-appearing but somewhat defective granulocytes.

- Adults between 25 and 60 years (peak in 4^{th}-5^{th} decades).

❑ Differential diagnosis

في هاي الحالات بنروح لل genetic testing مثل :

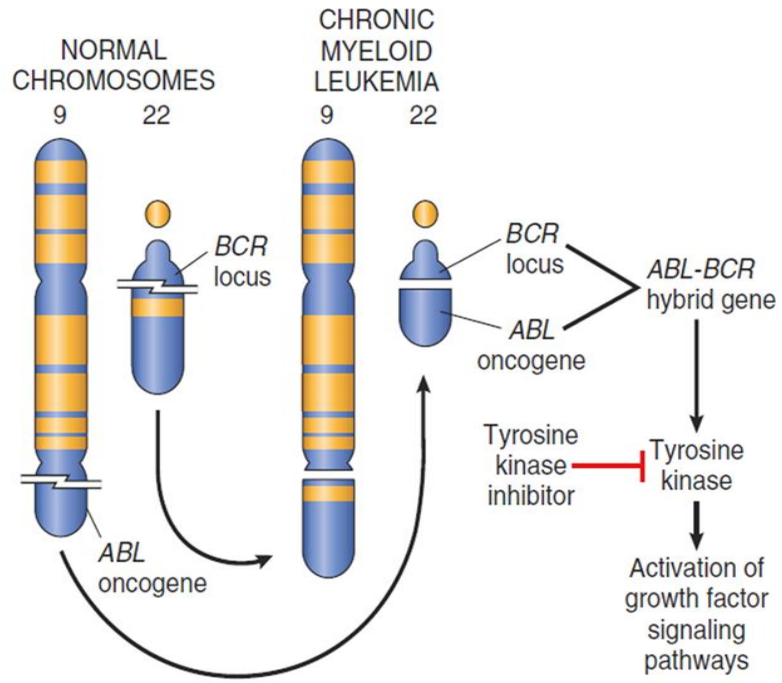
1. - Leukemoid reaction (a dramatic elevation of the granulocyte count in response to infection, and chronic inflammation),,,,,, Distinction can be achieved by testing for the presence of the BCR-ABL fusion gene.

2. - Other MPN

Pathogenesis:

- In ~ 95% of cases, there is a **t(9;22) (Philadelphia chromosome)** that *results in* **a chimeric *BCR-ABL* gene which** encodes a fusion protein with **tyrosine kinase activity.** proliferation ال على بزيد من قدرت الخلايا hybrid gene ال

-The mutation is a stem cell mutation (found in granulocytes, erythroid, megakaryocytes, B and T precursors); however, **the effect is limited to granulocyte and megakaryocyte.**



The BCR-ABL1 fusion gene is present in hematopoietic stem cells, as well as their progeny, including granulocytes, erythroid cells, megakaryocytes, and B and T cell precursors. However, the oncogenic effect of the BCR-ABL1 fusion protein is primarily limited to the granulocyte and megakaryocyte lineages

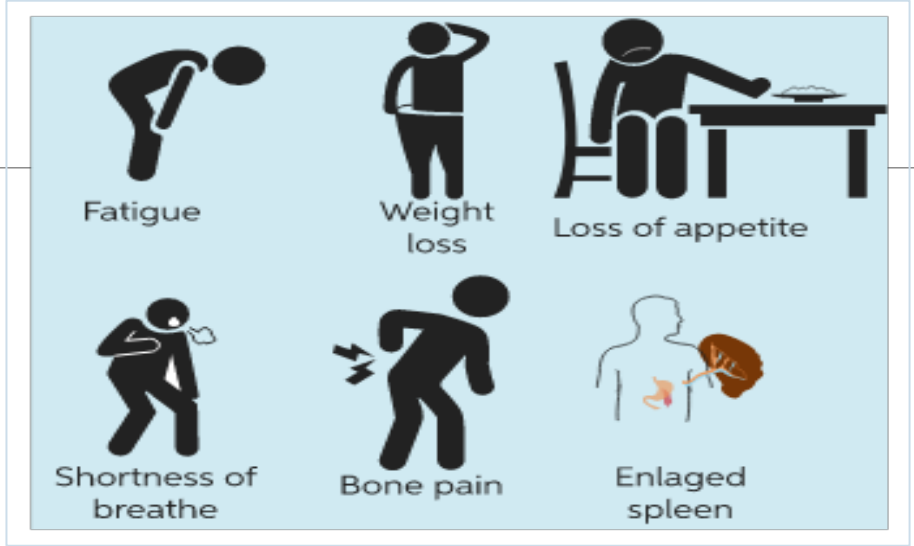
❑ Clinical Features

- Early: patients appear normal

- The onset is insidious.
  - The initial symptoms usually are nonspecific (e.g., anemia with fatigue, weakness, anorexia, weight loss)
  - Bleeding tendencies.
  - Infections.

- Dragging sensation in the abdomen caused by splenomegaly.

- Median survival of **3** years, even without treatment



❑ Laboratory Findings

مهم الزيادة بتكون في ال mature megakaryocytes and granulocytes

BP peripheral blood رح تطلع على bone marrow لانه حكينا الخلايا يلي تصنعت في ال

- The leukocyte count is elevated, often exceeding 100,000 cells/µL.

↑granulocytes

- The circulating cells are predominantly neutrophils, metamyelocytes, and myelocytes, but basophils and eosinophils are also prominent

– High platelet counts (early), thrombocytopenia (late)

↑megakaryocytes

-Mild to moderate anemia

-Low/absent leukocyte alkaline phosphatase (LAP) scores

❑ Pathology

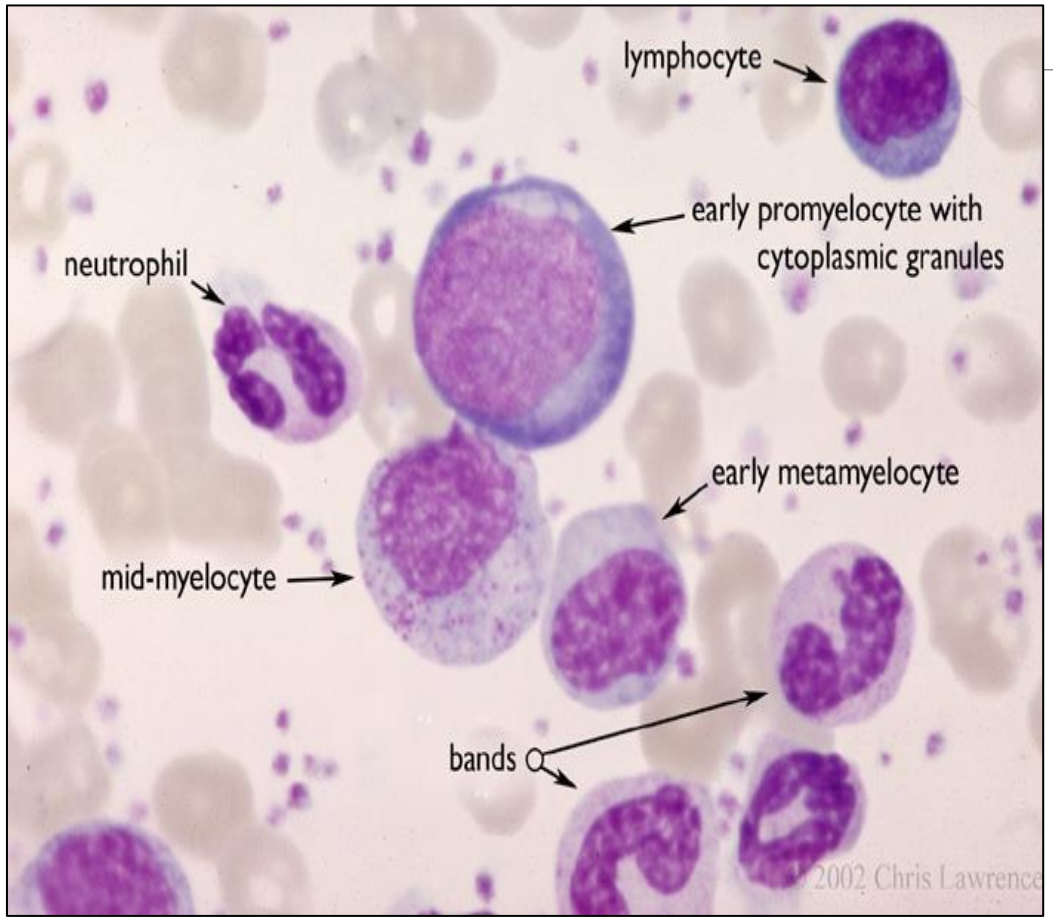
Bone marrow:

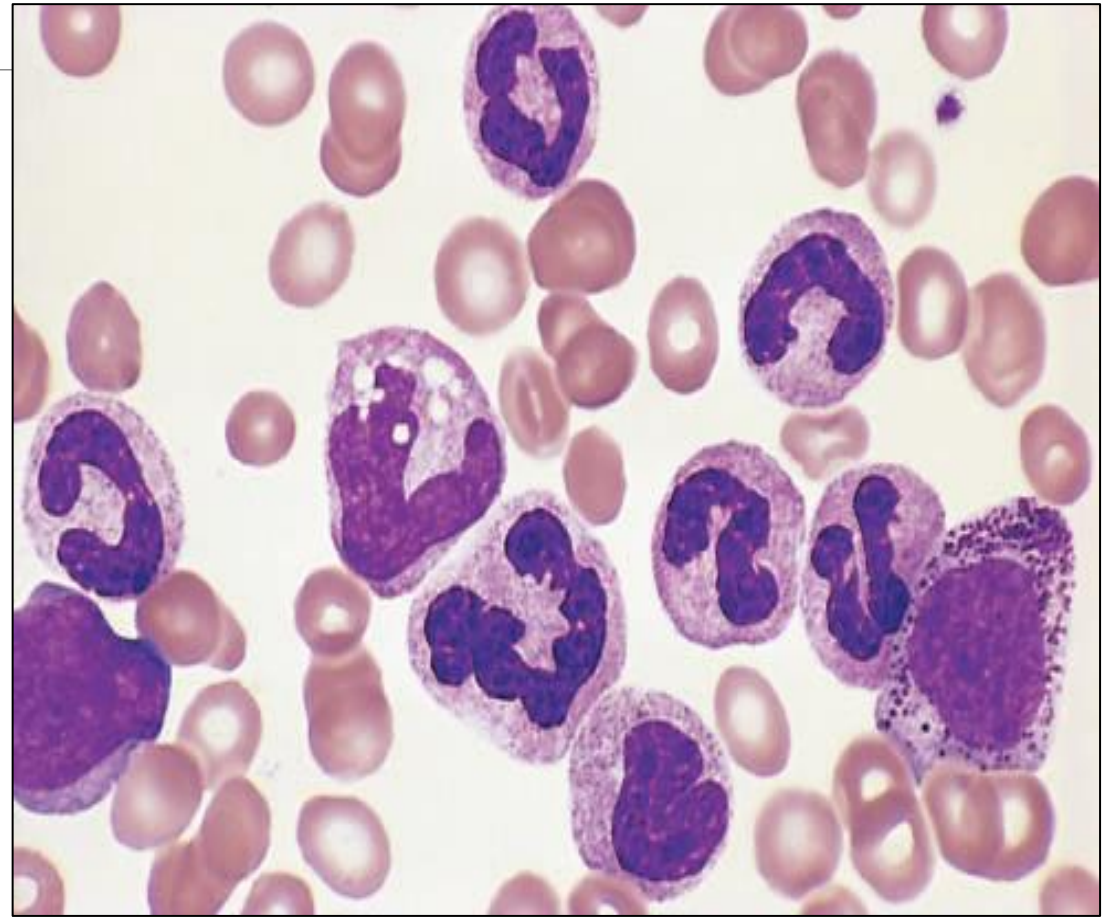
- Markedly hypercellular owing to increased numbers of maturing **granulocytic and megakaryocytic precursors.**
- Mild reticulin fibrosis
- Blasts <10%

Spleen

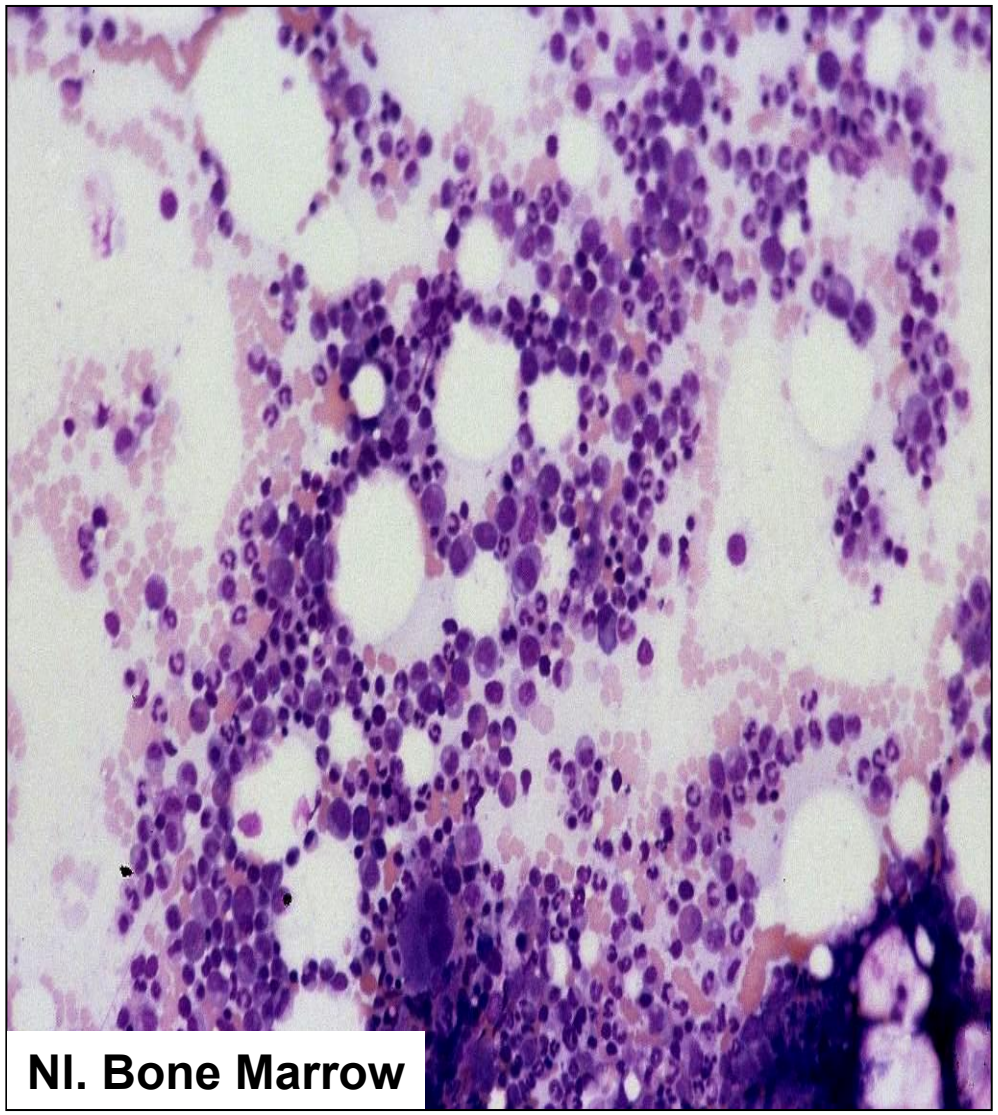
- Expanded red pulp with extramedullary hematopoiesis

CML—peripheral blood smear: Granulocytic forms at various stages of differentiation are present

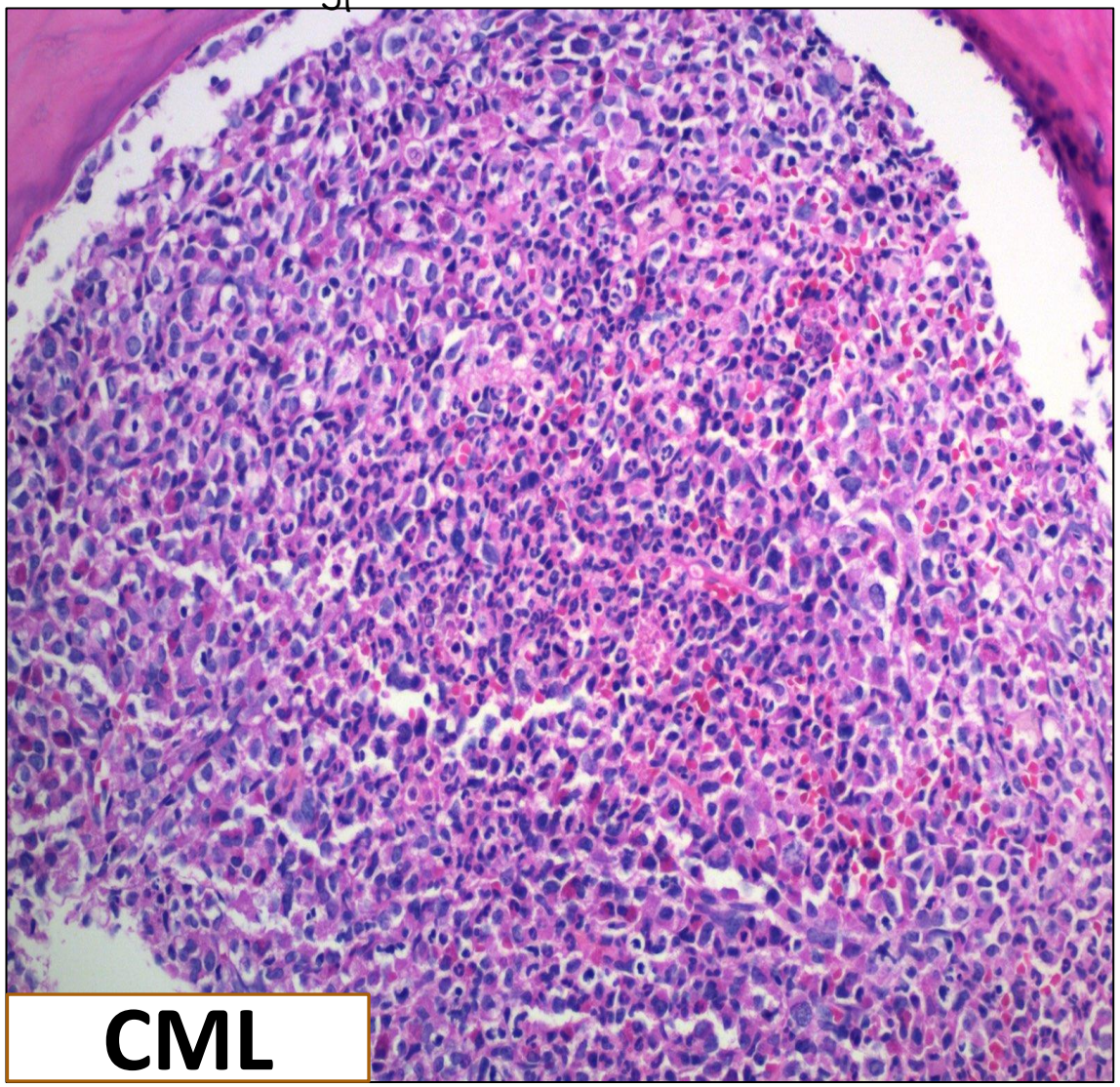




hypercellular



Nl. Bone Marrow



CML

❑ Course and Prognosis

- ***Slow progression of 3 phases (chronic, accelerated, and blast crises phases).***

Chronic phase

- 1-5 years
- Mild-moderate elevation of WBC
- Mild anemia
- Blasts <5% in BM
- Organomegaly, which responds to intermittent myelosuppression

Accelerated phase

وضع المريض رح يصير أسوء

- 50% of CML cases
- Increase WBC count despite treatment
- Increasing anemia
- New thrombocytopenia
- The appearance of additional cytogenetic abnormalities ال cancer cells ما بتوقف عند حد معين
- Increasing splenic size despite treatment
- 10 - 19% blasts in BM acute leukemia اقل من 20% لهيك بعدنا ما وصلنا لل

Blast crisis تحولنا من acute ل chronic

- ≥ 20% blasts (definition of acute leukemia) or extramedullary blast proliferation
- Abrupt or gradual over weeks (**Can occur abruptly without the previous accelerating phase**)
- **70%** are **myeloid** leukemia
- **30%** are **lymphoid** leukemia
- Associated with additional chromosomal abnormalities

لي في احتمال يكون lymphoid ؟؟؟

لانه ال mutations الأساسية صارت في stem cells

Polycythemia

increase in the concentration of red blood cells in the bloodstream due to a decrease in plasma volume, rather than an actual increase in the production of red blood cells by the bone marrow.

Causes of Polycythemia

- **Relative :** Reduced plasma volume(dehydration due vomiting or diarrhea): Hemoconcentration
- **Absolute:**
  - **Primary**: PV
  - **Secondary**: Increased Erythropoietin level:

- Adaptive: Lung disease, Smoking, cyanotic heart disease, high altitude living
- Paraneoplastic: Erythropoietin secreting tumors: RCC, HCC

2. Polycythemia Vera (PV)

إنزيم JAK2 بشتغل في ال pathway لل erythropoietin
و ال thrombopoietin و ال mutation في هذا الإنزيم
بزيد من ال proliferation في هاي الخلايا

- Insidious clonal disorder of pluripotential hematopoietic stem cells dominated by an expansion of the red cell mass.

- Strongly associated with activating mutations in the **tyrosine kinase JAK2**.

- This produces an excessive proliferation of erythroid, granulocytic, and megakaryocytic elements (**panmyelosis**).Poly = pan

- But most clinical signs and symptoms are related to an absolute **increase in red cell mass.**

كل الخلايا بيزيدوا لكن اكثر نوع هو ال erythroid cells
فالبتالي زيادة في الred mass لهيك اكثر الاعراض بتكون
مرتبطة بال red mass

- Associated with **low levels of serum erythropoietin**

If serum erythropoietin levels were high in a patient with polycythemia , it would be secondary polycythemia

معايير لتشخيص

2016 WHO Classification
1. Hb > 16.5 g/dL in men/Hb > 16.0 g/dL in women, or Hct > 49% in men/Hct > 48% in women, or increased RCM;
2. BM biopsy showing hypercellularity for age with trilineage growth (panmyelosis) including prominent erythroid, granulocytic, and megakaryocytic proliferation with pleomorphic, mature, megakaryocytes (differences in size);
3. Presence of *JAK2*V617F or *JAK2* exon 12 mutation %100
Subnormal serum EPO level
All 3 major or the first 2 major and the minor criterion

↑ Red mass

Major Criteria

لو ما عنا القدرة نعمل genetic testing ؟؟؟

↑ Red mass بكفي يكون عنا زيادة بال

+

↓ Erythropoietin

+ panmyelosis in BM

Minor Criteria

Criteria required for diagnosis

❖ Clinical Findings

- Appears insidiously, in late middle age.

↑RBCs

- Manifestations are related to expanded blood volume, increased blood viscosity, and thrombotic and hemorrhagic tendencies (Due to excessive distention of blood vessels and abnormal platelet function):

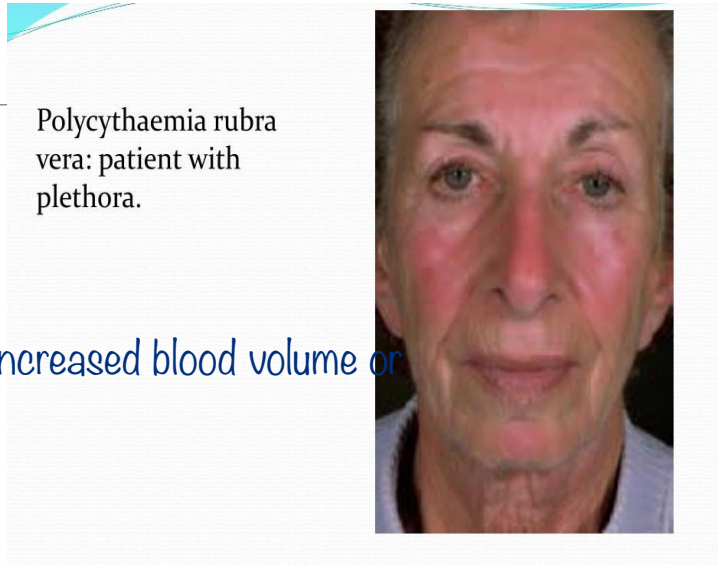
❖Patients are plethoric and somewhat cyanotic. plethoric: skin appears reddened due to increased blood volume or flow

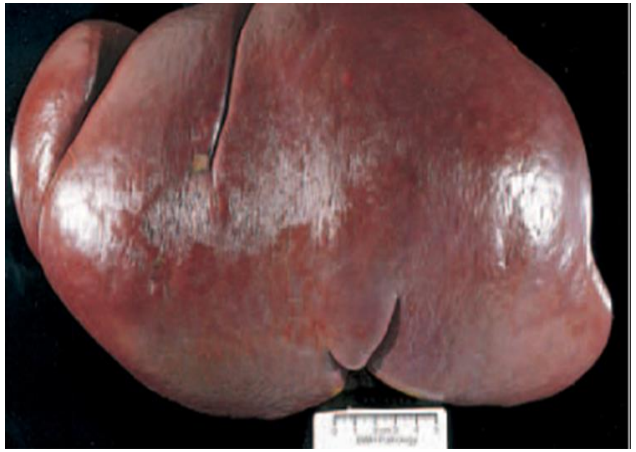
❖Thrombosis and infarction: Especially heart, spleen, and liver (Hepatic vein thrombosis called Budd-Chiari syndrome).

❖Headache, weakness, hypertension, GIT Sx, hematemesis, and melena are common

❖Pruritus.

❖Splenomegaly


Polycythaemia rubra vera: patient with plethora.



❖ Laboratory Findings

كله عالي بس نتذكر هاي الخلايا شكلاً mature

بس هي abnormalities functionally

- High red cell counts.

- High hematocrit

- High granulocyte count

- High platelet count (The platelets are functionally abnormal in most cases, and giant platelets and megakaryocyte fragments are often seen in the blood)

- Basophilia is common.

❖ Pathology

Bone marrow:

- Hypercellular owing to increased numbers of erythroid, myeloid, and megakaryocytic forms.

- Some degree of marrow fibrosis.

- Splenomegaly and enlarged liver

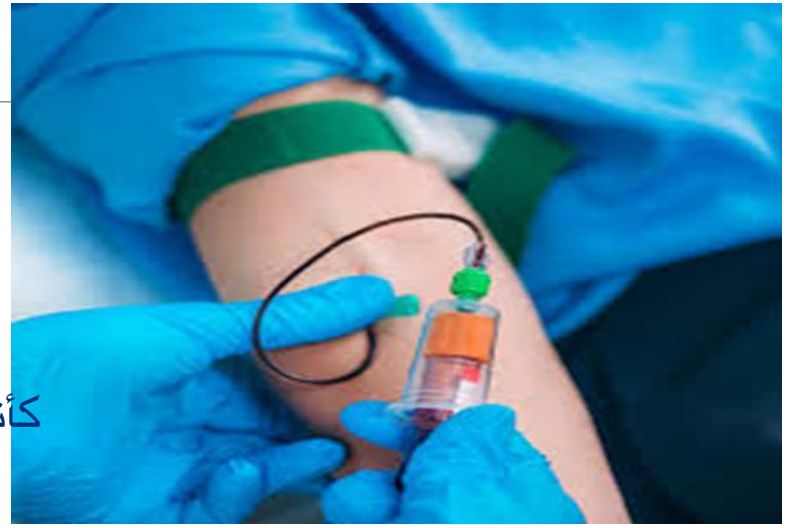
- Organs thromboses and infarctions

مهم نتذكر اي واحد من أنواع ال Chronic Myeloid Leukemia

ممكن المريض يدخل في مرحلة ال acute leukaemia

او ال spent phase

❖ PV Course & Prognosis



- **Proliferative phase**

  Erythroid proliferation

نستمر بسحب الدم من المريض

  Median survival –10 years (With repeated phlebotomy)

- **Spent phase**: 15-20% (marrow fibrosis) كأنه ال bone marrow استهلاك صار كله ألياف

- **AML**: 5-10%

ال survival يعتمد على ال treatment

- Without treatment, death occurs from vascular complications within months.
- With treatment, the median survival is increased.