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2. Neoplastic Proliferations of White Cells

~ Myeloid Neoplasms II

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The 2016 WHO Classification of MPN
Chronic myeloid leukemia, *BCR-ABL1*–positive
Chronic neutrophilic leukemia
Polycythemia vera
Primary myelofibrosis (PMF) Primary myelofibrosis, prefibrotic/early stage Primary myelofibrosis, overt fibrotic stage
Essential thrombocythemia
Chronic eosinophilic leukemia, not otherwise specified (NOS)
Myeloproliferative neoplasm, unclassifiable

Myeloproliferative Neoplasms (MPN)

Myeloproliferative Neoplasms

Its a hallmark of neoplasm

Very common in proliferation

- A group of disorders characterized by the presence of **mutated, constitutively activated tyrosine kinases** or other related molecules in signaling pathways → lead to growth factor independence.

Problem is with proliferation not differentiation so it can be differed from the previous diseases

- **Tyrosine kinase** Mutations do not impair differentiation.
- So the most common consequence is increase in production of one or more mature blood elements

Myeloproliferative Neoplasms

- The neoplastic progenitors tend to seed secondary hematopoietic organs (spleen, liver, & LNs) → hepato-splenomegaly (**neoplastic** extramedullary hematopoiesis).
- MPNs often transform to AML

Myeloproliferative Neoplasms

- Four major diagnostic entities are recognized:

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

Myeloproliferative Neoplasms

Chronic because its a mature cell

Associated with worse prognosis

- CML is separated from the others by its characteristic BCR-ABL1 fusion gene → produces a constitutively active BCR-ABL1 tyrosine kinase.
- The most common genetic abnormalities in “BCRABL–negative” MPNs are activating mutations in the tyrosine kinase JAK2.
- all MPNs have variable propensities to transform to:

The mutation will transfer it into continuously active

1) a “spent phase”: resembling primary myelofibrosis
2) a “blast crisis” identical to AML

- Both triggered by the acquisition of other somatic mutations

Chronic Myeloid Leukemia (CML)

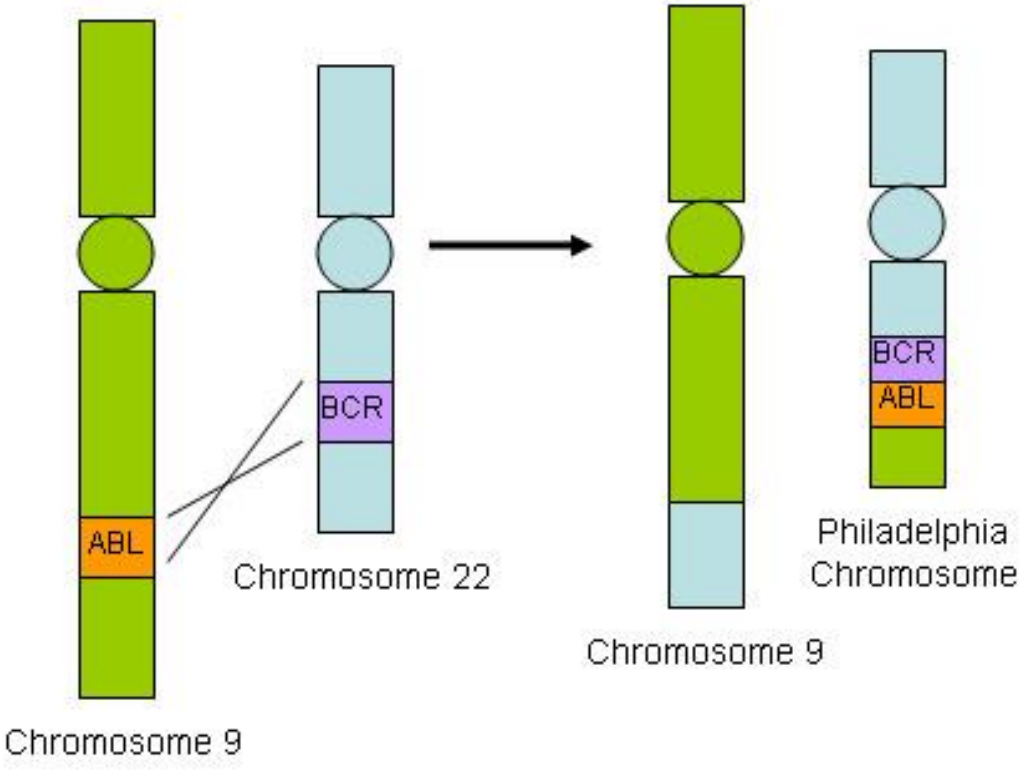
Pathogenesis

- CML is distinguished from other MPN by the presence of a chimeric BCR-ABL gene, derived from portions of the BCR gene on chr.22 & the ABL gene on chr.9
- 95% of cases, the BCR-ABL gene is the product of a balanced t(9;22) translocation that moves ABL from chr.9 to a position on chr.22 adjacent to BCR.
- Translocation identified in some B-ALL.

Gene fused with each other that have different sources and are different from each other

Continuous uncontrolled proliferation

CML – Pathogenesis



Chronic Myeloid Leukemia (CML)

Pathogenesis

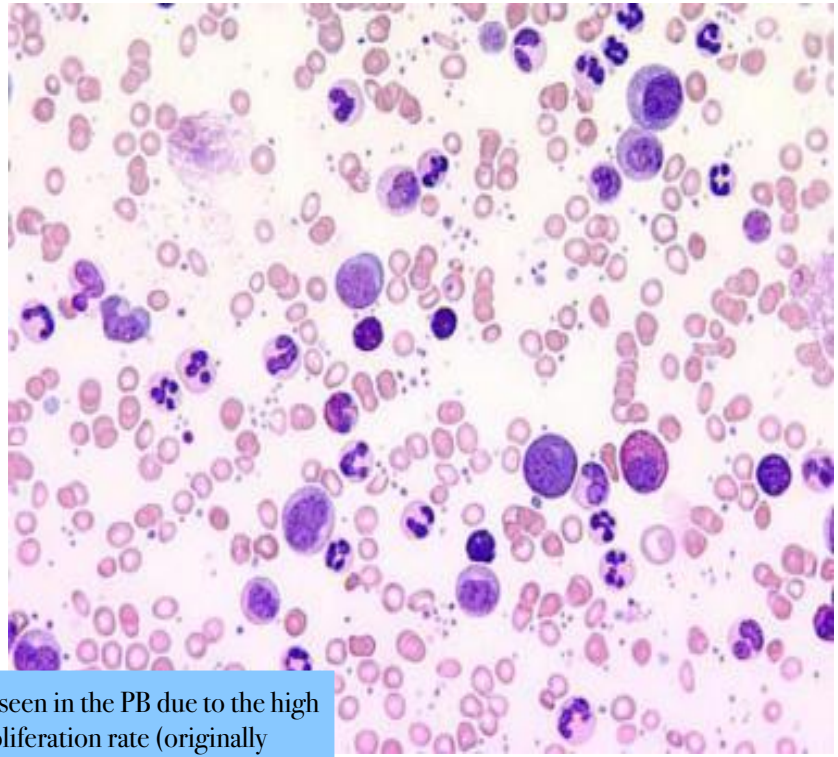
- The growth factor dependence of CML progenitors is greatly decreased by constitutive signals generated by BCR-ABL → mimic the effects of growth factor receptor activation.
- Because BCR-ABL does not inhibit differentiation, the early disease course is marked by excessive production of relatively normal blood cells, particularly granulocytes & platelets.

CML – Morphology

Peripheral blood

Leukocytosis

- Leukocyte count is ↑↑ (often >100,000 cells/µL).
- Circulating cells are predominantly neutrophils, metamyelocytes & myelocytes.
- Basophils, eosinophils & platelets are increased



Its seen in the PB due to the high proliferation rate (originally shouldn't be seen there)

CML - Morphology

BM

- The bone marrow is hypercellular , ↑ numbers of maturing granulocytic & megakaryocytic precursors.

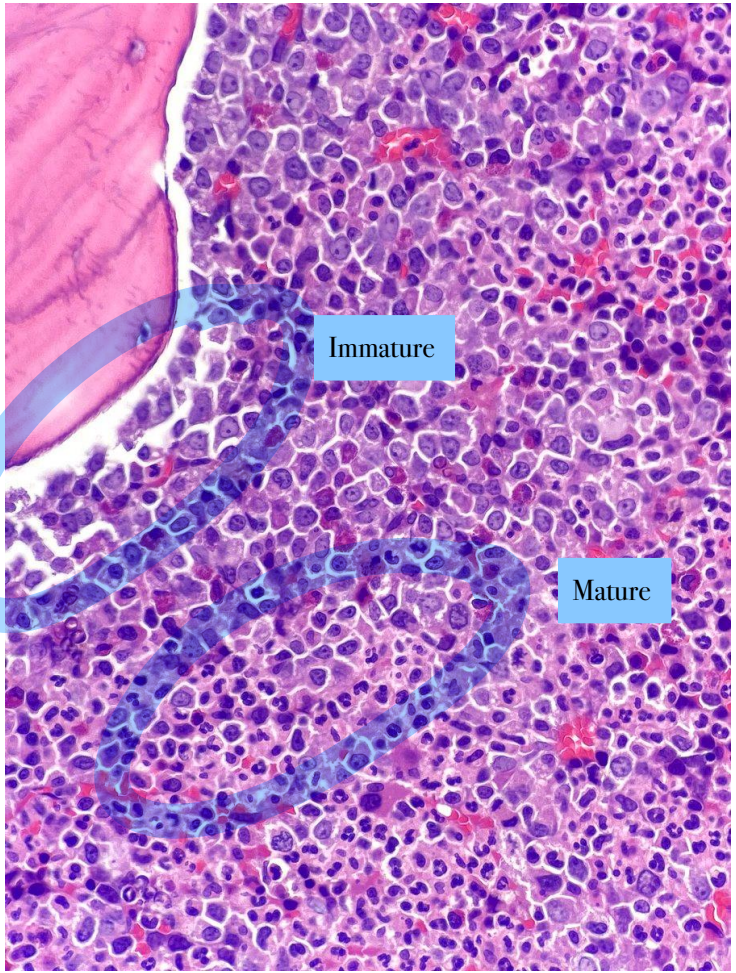
Will be less in size

And decreased nucleus

Cellurality in the BM examples

~10 y → 90.

~20 y → 70~80.

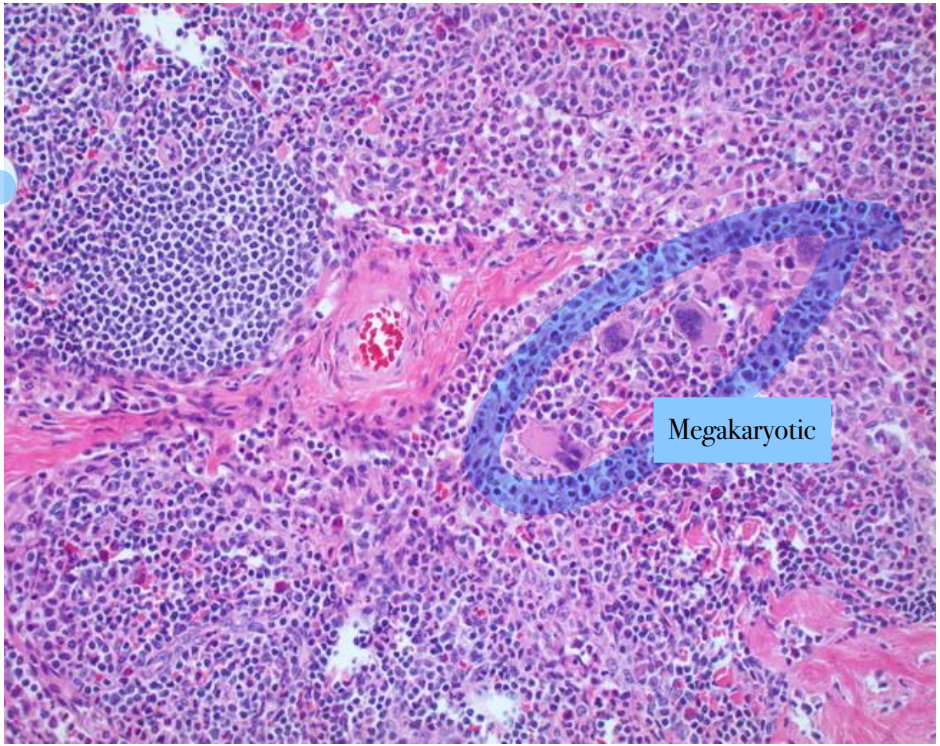


@LucasMassoth

CML – Morphology

Spleen

- Spleen resembles BM → extensive extramedullary hematopoiesis.



CML - Clinical features

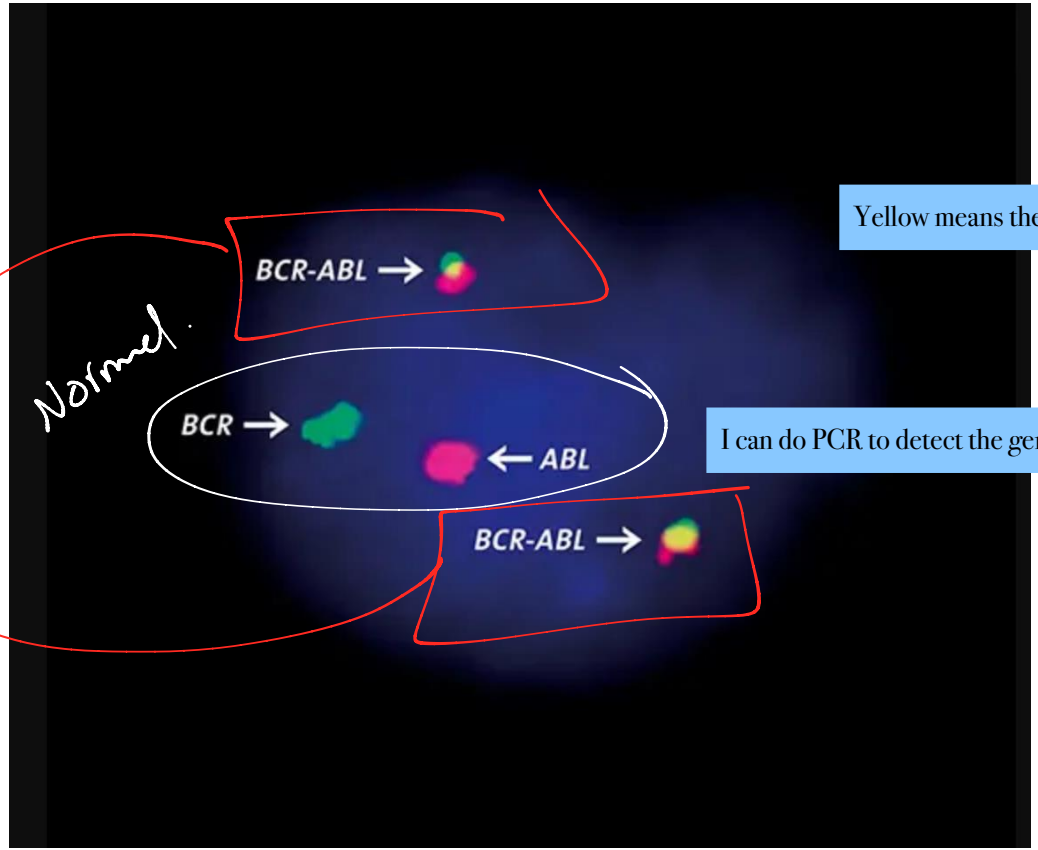
- Peaks in 4th & 5th decades.
- Initial symptoms usually are nonspecific (e.g., easy fatigability, weakness, weight loss)
- Sometimes the 1st symptom is a dragging sensation in the abdomen → splenomegaly.
- Necessary to distinguish CML from a leukemoid reaction (infection, stress, chronic inflammation..)

Due to the neoplastic cells consuming of the body nutrients

White blood cells will be increased to 80,000....

Clear Lift shift will be seen

Fluorescence in situ hybridization (FISH) for the BCR-ABL translocation



Yellow means they have a mixed gene

I can do PCR to detect the gene

Upnormal.

https://www.ganeshdiagnostic.com/

CML - Clinical features

- Slowly progressive disease: Median survival is 3 years without treatment.
- progress to accelerated phase

Less than 5 is the normal range

5-19

Anemia, new thrombocytopenia (additional genetic mutations).

- Progress to blast phase:

1) 70% AML
2) 30% ALL

Due to its affect to the progenitor cells

- Rarely progresses to spent phase with fibrosis.

↳CML.

CML – Treatment

- Tyrosine kinase inhibitors, like Imatinib, induces sustained remissions with manageable toxicity and prevents progression to blast crisis, particularly in patients with early disease. (an example of targeted therapy)

Didn't go to the accelerated phase

- It suppress the proliferative drive that leads to the acquisition of additional mutations

Polycythemia Vera (PCV)

The smocking
high altitude
Chronic obstructive pulmonary disease
It will have high level of erythropiotin cells

- Excessive proliferation of erythroid, granulocytic, and megakaryocytic elements → **panmyelosis**

Due to the increase of all cell types in marrow

- Most clinical signs & symptoms are related to an absolute increase in red cell mass.
- Must be distinguished from:

1. relative polycythemia →results from hemoconcentration.
2. Unlike reactive absolute polycythemia→ PCV is associated with low serum erythropoietin → a reflection of growth factor–independent growth of the neoplastic clone.

If i have the gene

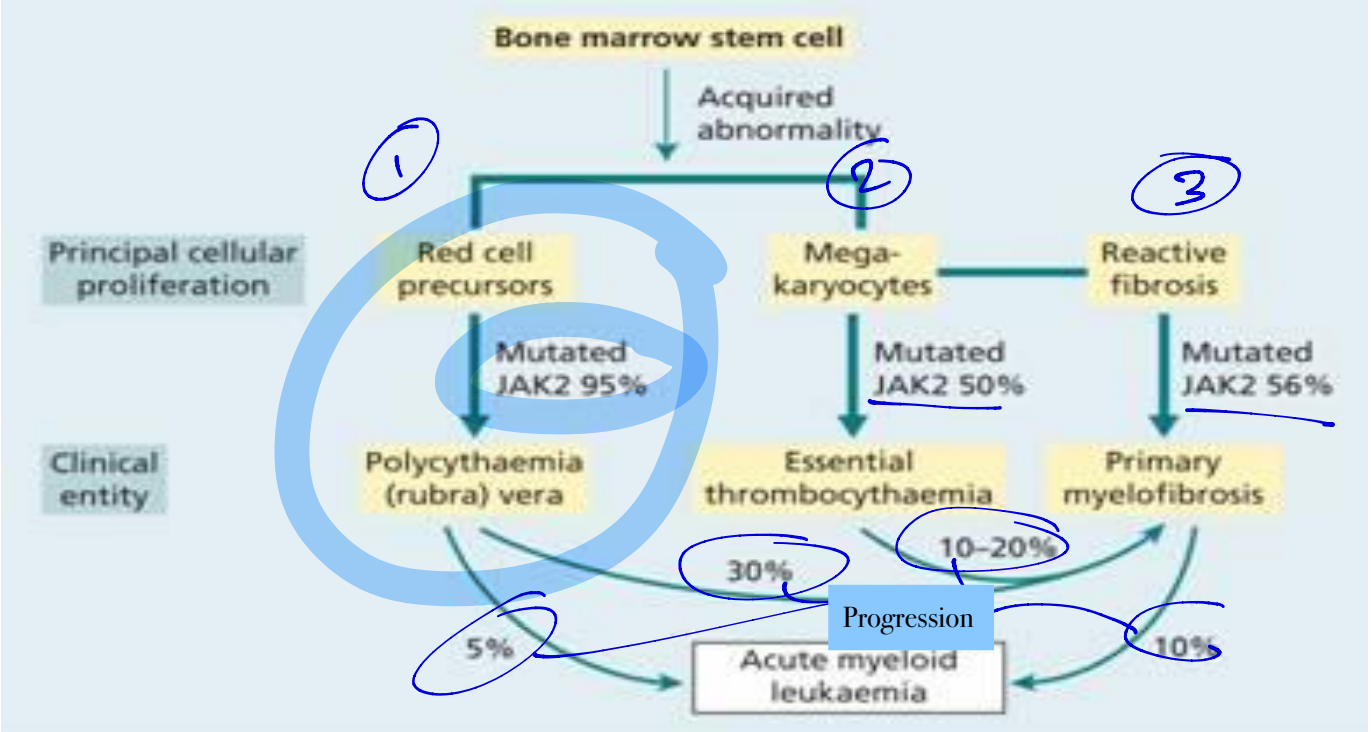
PCV

PCV – Pathogenesis

Base is differed

- Strongly associated (> 97%) with activating point mutations in the tyrosine kinase JAK2.
- JAK2 normally acts in the signaling pathways downstream of the erythropoietin receptor.
- The most common JAK2 mutation → lowers the dependence of hematopoietic cells on growth factors for growth and survival.

PCV – Pathogenesis



PCV - Morphology

- The major anatomic changes in PCV stem from increases in blood volume and viscosity. Increase in RBCs ⇒ ↑ Viscosity that will affect the flow and perfusion
- Hemoglobin levels (Hb > 16,5 g/dl (♂), > 16 g/dl (♀))
- **Congestion** of many tissues is characteristic.
- Hepatomegaly & small foci of extramedullary hematopoiesis.
- Spleen usually is slightly enlarged → vascular congestion.

Due to high number of RBC

PCV – Morphology

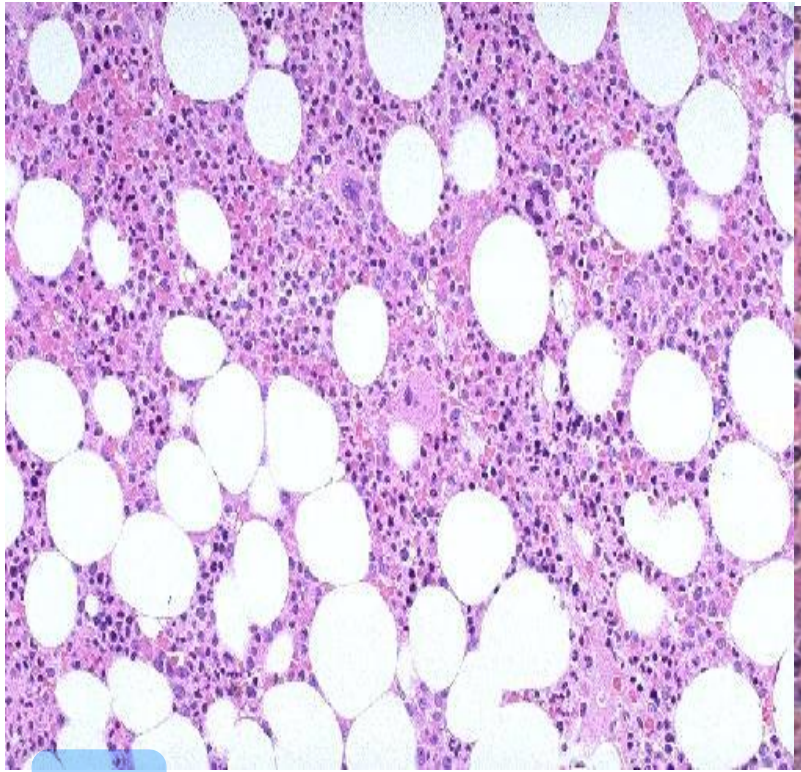
- Thromboses & infarctions are common → the increased viscosity and vascular stasis.
- Platelets produced from the neoplastic clone often are dysfunctional → elevated risk of thrombosis and bleeding Hemorrhages; often in GIT, oropharynx or brain.
- The peripheral blood often shows **basophilia**.

Worse picture in CNS

PCV – Morphology

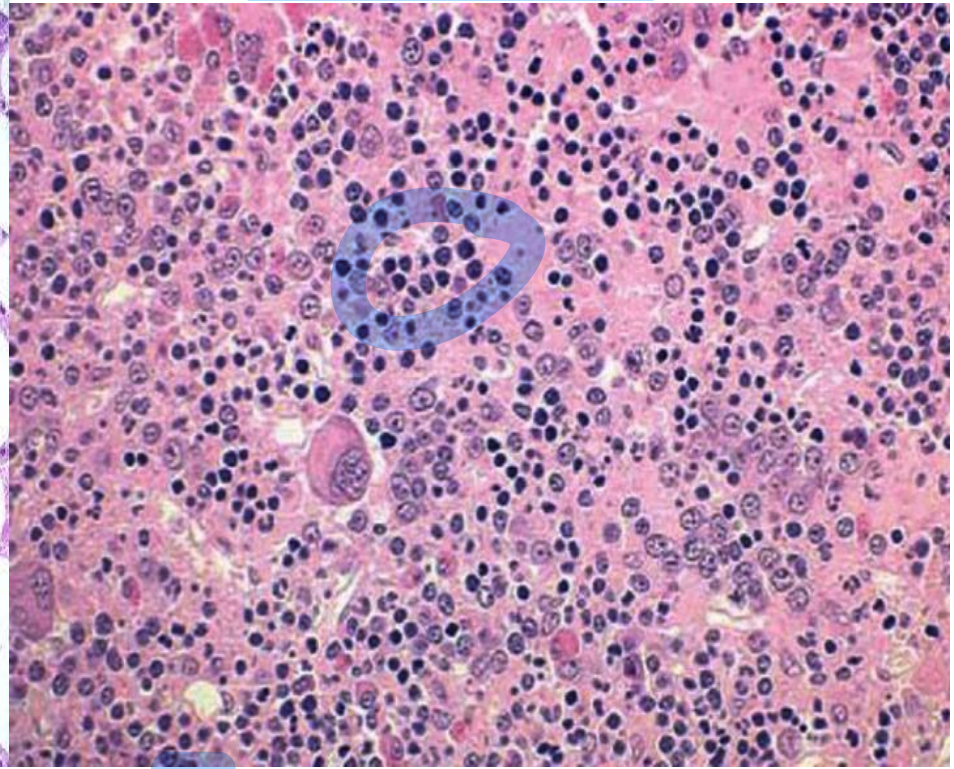
- The bone marrow is hypercellular owing to increased numbers of erythroid, myeloid, and megakaryocytic forms.
- PCV often progresses to a spent phase where the marrow is largely replaced by fibroblasts & collagen → increase extramedullary hematopoiesis.

PCV – Morphology



Normal

Islands of erythropoiesis very dark



PCV

PCV – Clinical features

- Insidious, usually in late middle age.
- Patients are plethoric & often cyanotic. Congested colour of the face
- Pruritus → Histamine released from the neoplastic basophils.
- Thrombotic and hemorrhagic tendencies & hypertension. Headache, dizziness, GIT (hematemesis &melena) common. Due to the sluggish blood flow

PCV – Prognosis

- Without treatment, death occurs from vascular complications within months.
- The median survival is increased to about 10 years by lowering the red cell count to near normal → repeated phlebotomy. سحب من الدم بالأوردة
- Prolonged survival → a propensity to evolve to a "spent phase" (resembling PM) ~10 years.
- Extensive marrow fibrosis, hematopoiesis shifts to the spleen, which enlarges markedly. Drive shift by the growth factor