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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

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Myeloproliferative Neoplasms (MPN)

Myeloproliferative Neoplasms

- ▶ 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.
- ▶ **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) → hepatosplenomegaly (**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

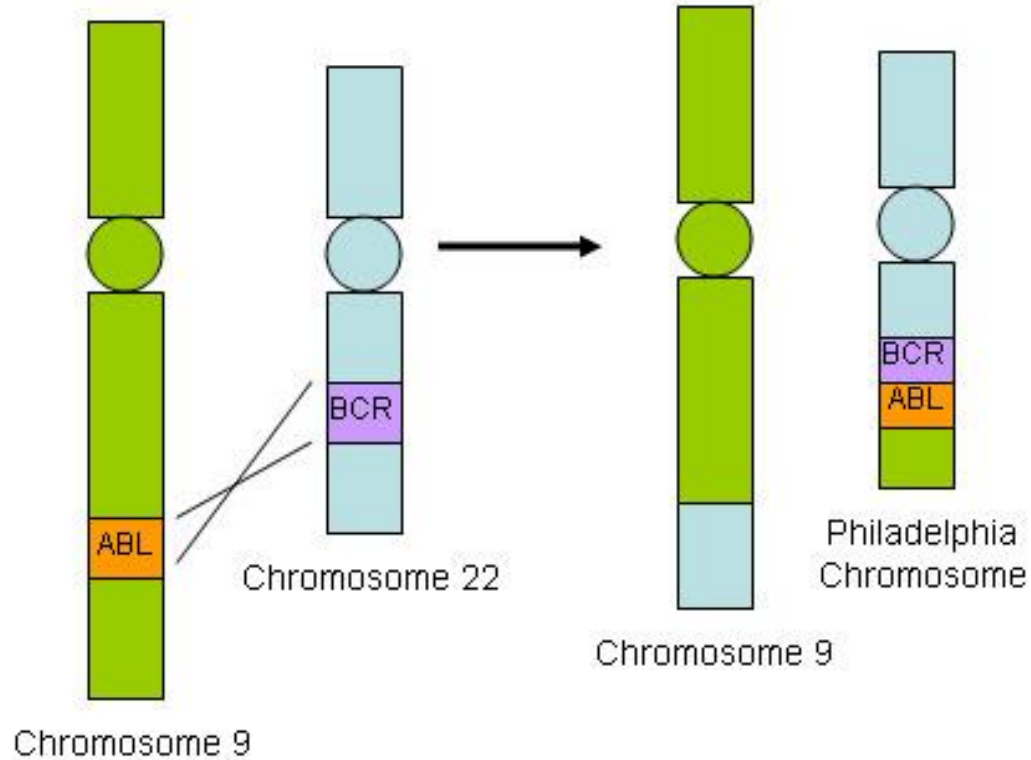
- ▶ CML is separated from the others by its characteristic BCR-ABL1 fusion gene → produces a constitutively active BCR-ABL1 tyrosine kinase.
- ▶ The most common genetic abnormalities in “BCRABL–negative” MPNs are activating mutations in the tyrosine kinase JAK2.
- ▶ all MPNs have variable propensities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

CML - Pathogenesis



Chronic Myeloid Leukemia (CML)

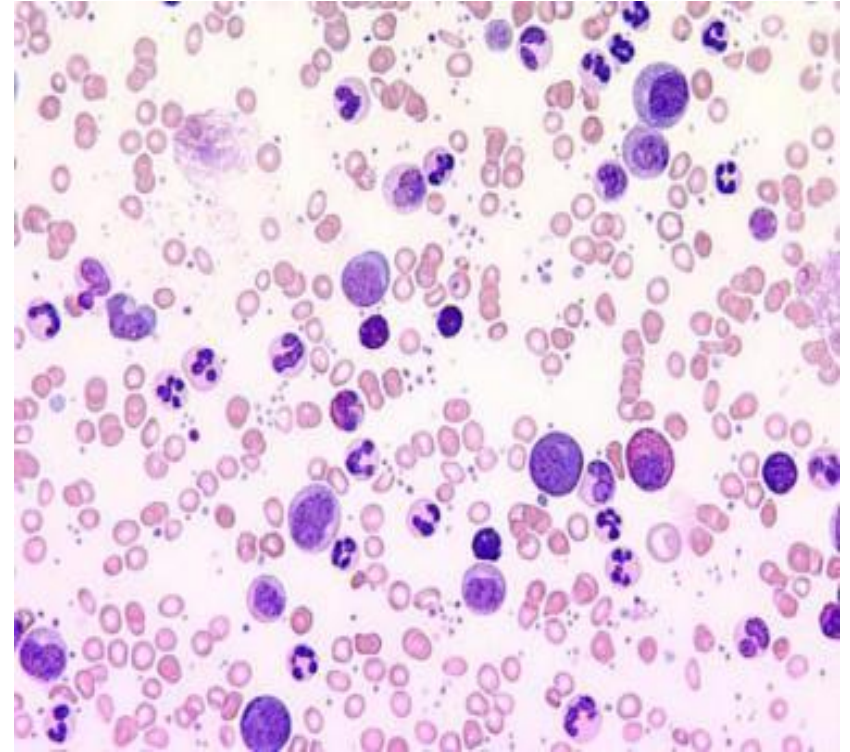
Pathogenesis

- ▶ 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

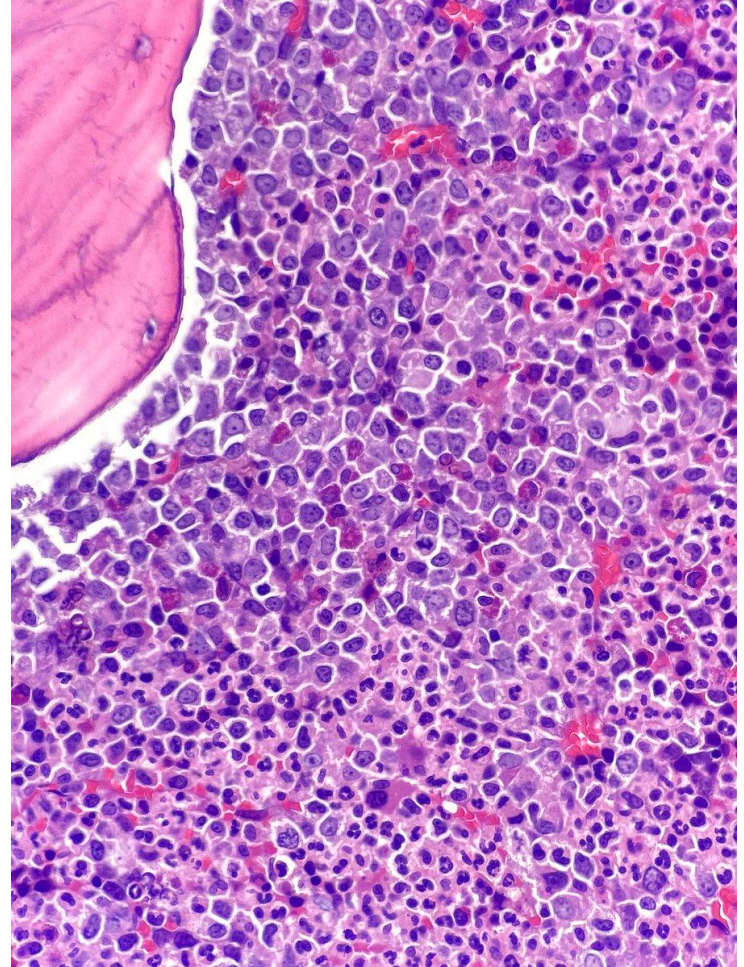
- ▶ Leukocyte count is $\uparrow\uparrow$ (often $>100,000$ cells/ μL).
- ▶ Circulating cells are predominantly neutrophils, metamyelocytes & myelocytes.
- ▶ Basophils, eosinophils & platelets are increased



CML - Morphology

BM

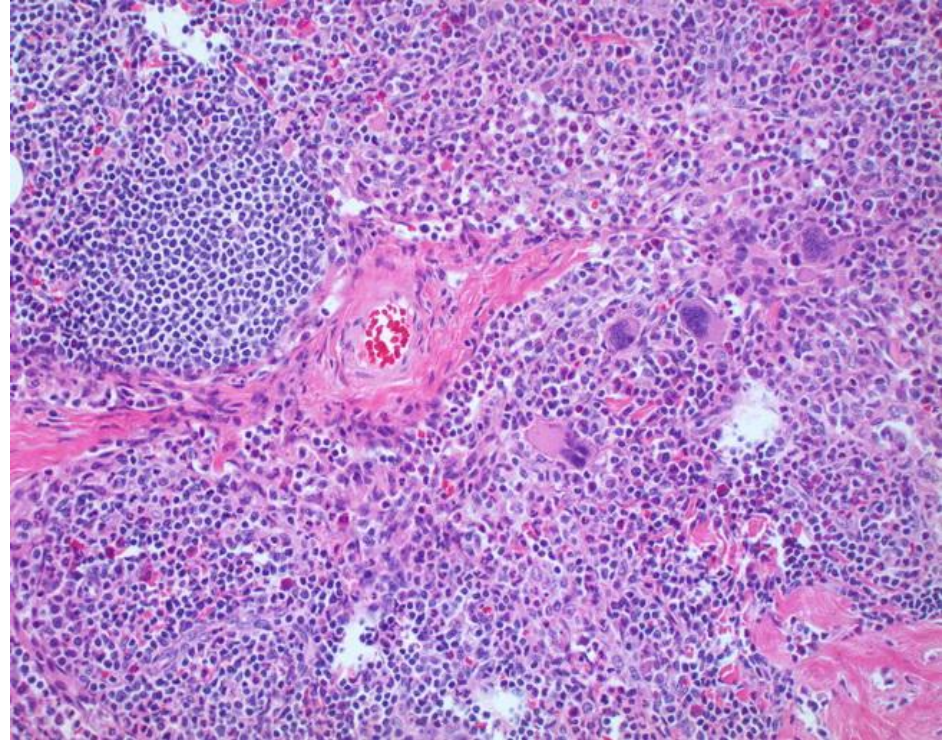
- ▶ The bone marrow is hypercellular , ↑ numbers of maturing granulocytic & megakaryocytic precursors.



CML - Morphology

Spleen

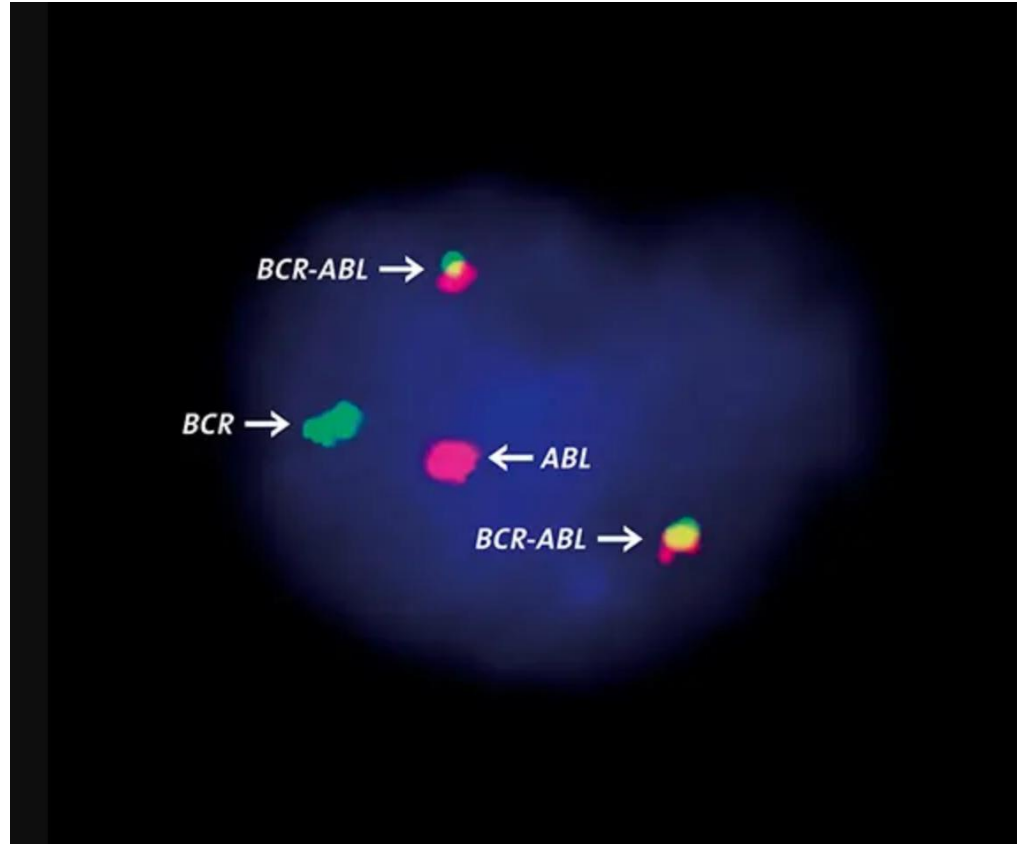
- ▶ Spleen resembles BM → extensive extramedullary hematopoiesis.



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..)

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



CML - Clinical features

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

Anemia, new thrombocytopenia (additional genetic mutations).

- ▶ Progress to **blast phase**:
 - 1) 70% AML
 - 2) 30% ALL
- ▶ **Rarely** progresses to **spent phase** with fibrosis.

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

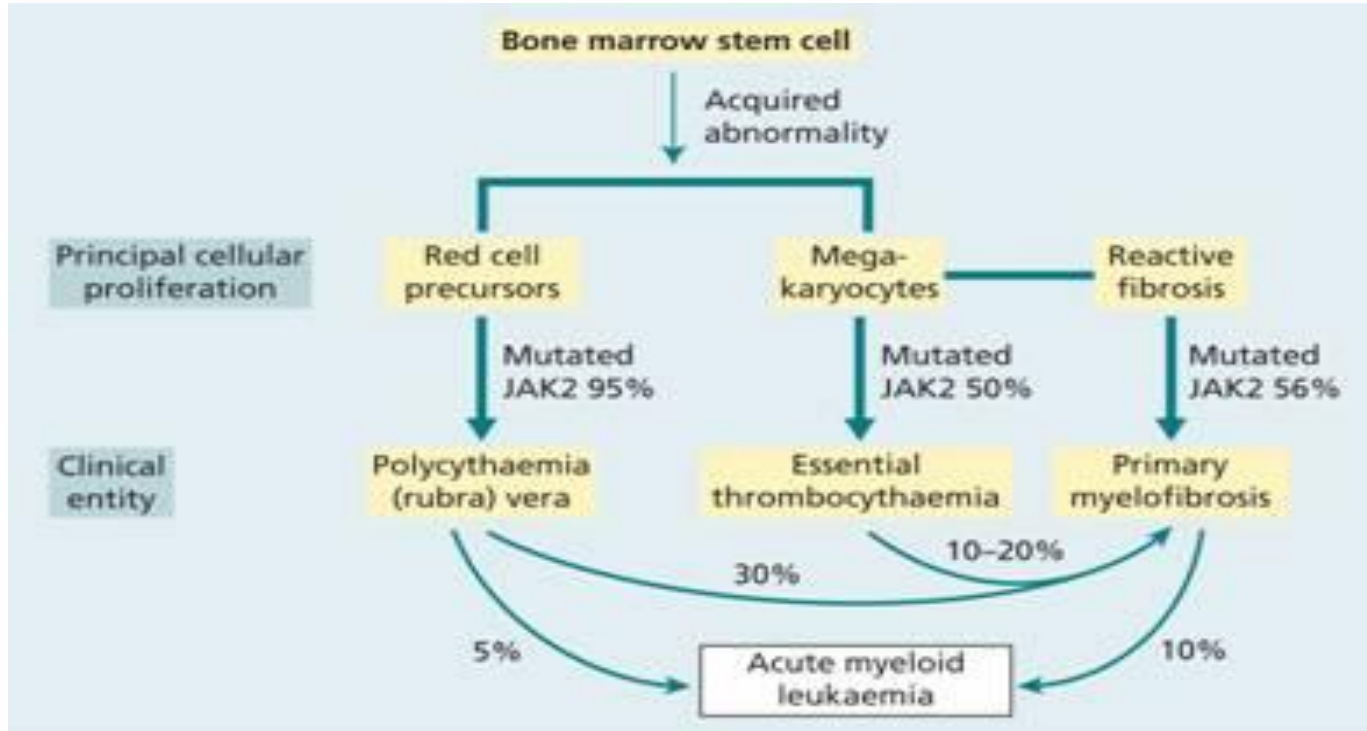
Polycythemia Vera (PCV)

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

PCV – Pathogenesis

- ▶ 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.
- ▶ 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.

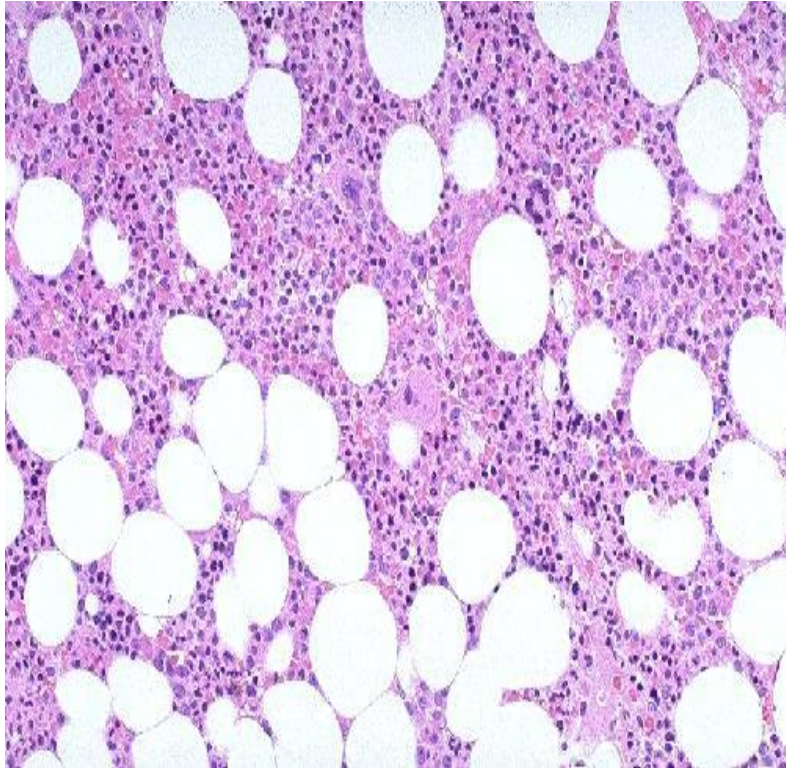
PCV – Morphology

- ▶ 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**.

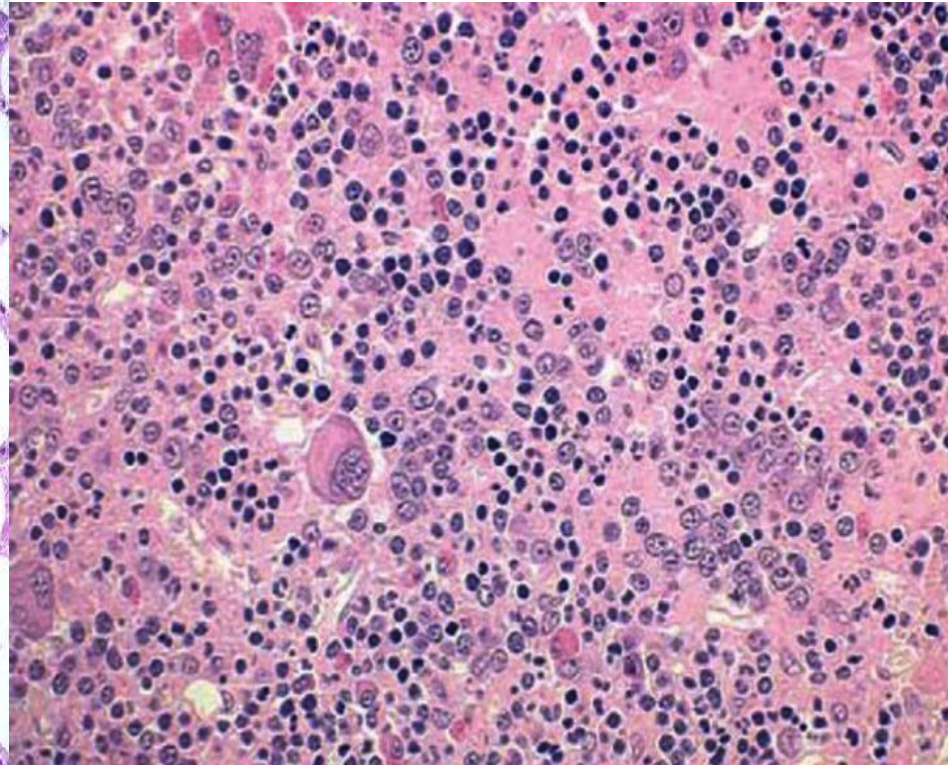
PCV – Morphology

- ▶ 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



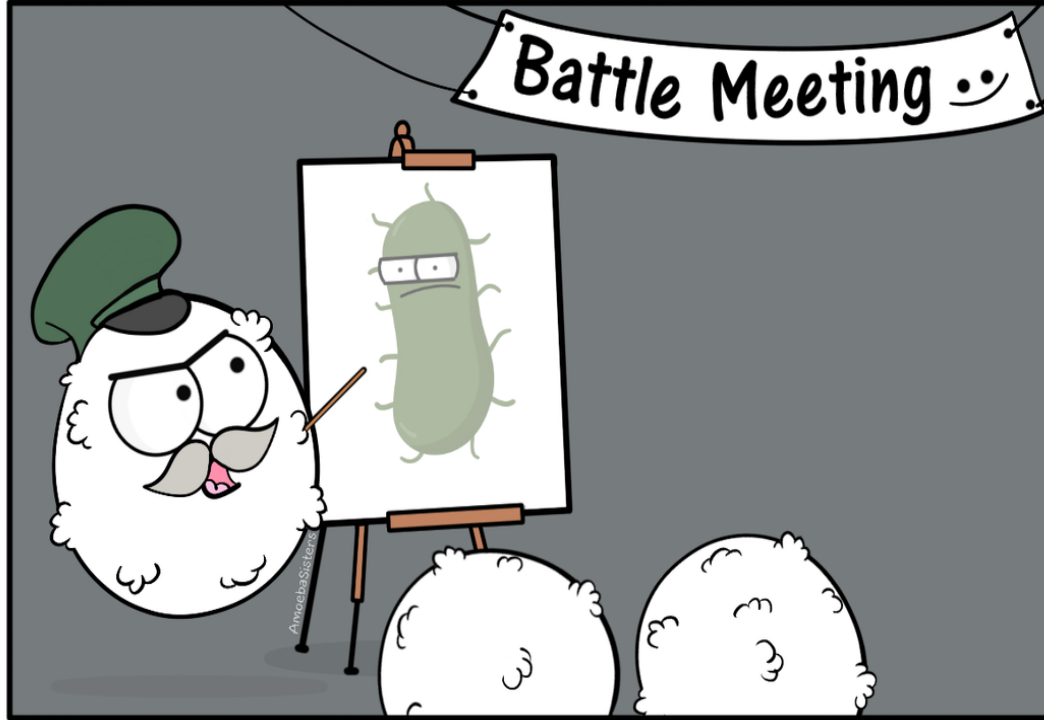
PCV

PCV – Clinical features

- ▶ Insidious, usually in late middle age.
- ▶ Patients are plethoric & often cyanotic.
- ▶ Pruritus → Histamine released from the neoplastic basophils.
- ▶ Thrombotic and hemorrhagic tendencies & hypertension. Headache, dizziness, GIT (hematemesis & melena) common.

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.
- ▶ 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.



White blood cells: waging war with pathogens
while you're watching cat videos.

