Myeloproliferative Neoplasms (MPN)

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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

- There is a considerable degree of clinical and morphologic overlap among myeloproliferative neoplasms. The common features include:

• Increased proliferative drive in the bone marrow.

• Homing of the neoplastic stem cells to secondary hematopoietic organs, producing extramedullary hematopoiesis AND resulting in hepatosplenomegaly.

• Variable transformation to a spent phase characterized

by marrow fibrosis and peripheral blood cytopenias

• Variable transformation to acute leukemia

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

- Four major diagnostic entities are recognized:

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

Chronic myeloid leukemia (CML).

- CML is separated from the others by its characteristic BCR-ABL fusion gene → produces a constitutively active BCR-ABL 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
- 100% 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

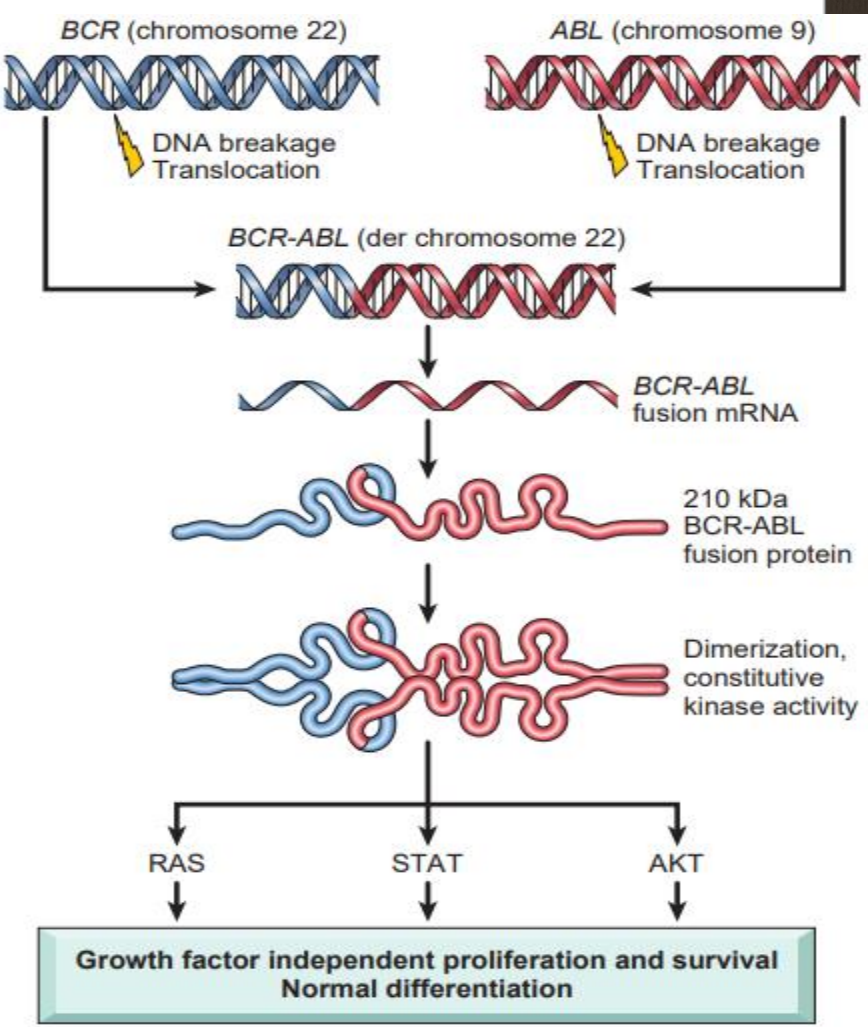


Figure 13.33 Pathogenesis of chronic myeloid leukemia. Breakage and joining of *BCR* and *ABL* creates a chimeric *BCR-ABL* fusion gene that encodes a constitutively active BCR-ABL tyrosine kinase. BCR-ABL activates multiple downstream pathways, which drive growth factor–independent proliferation and survival of bone marrow progenitors. Because BCR-ABL does not interfere with differentiation, the net result is an increase in mature elements in the peripheral blood, particularly granulocytes and platelets. *der,* Derivative chromosome.

Chronic Myeloid Leukemia (CML)

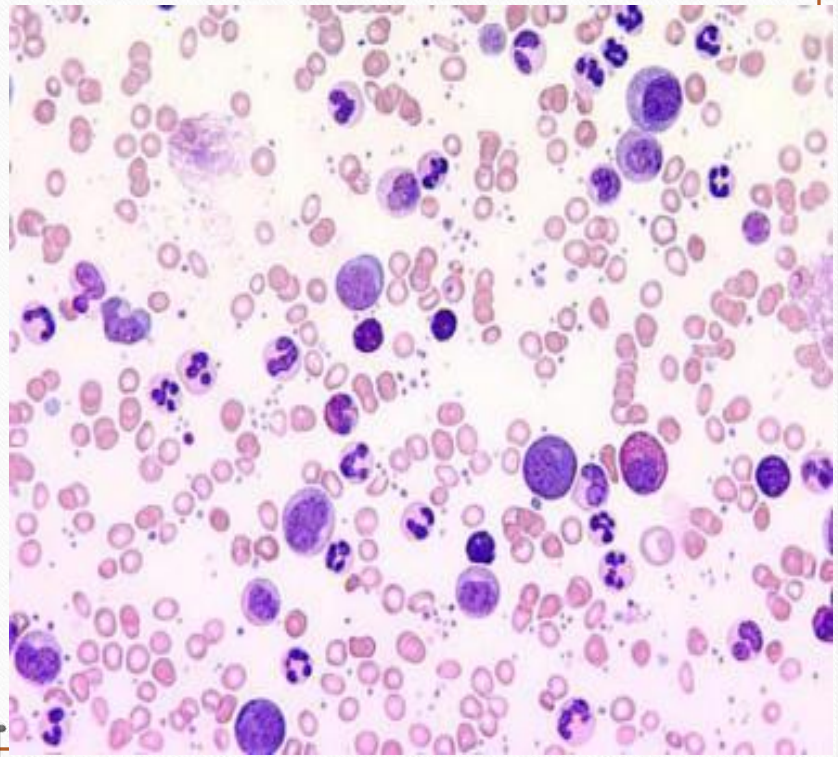
Pathogenesis

- 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

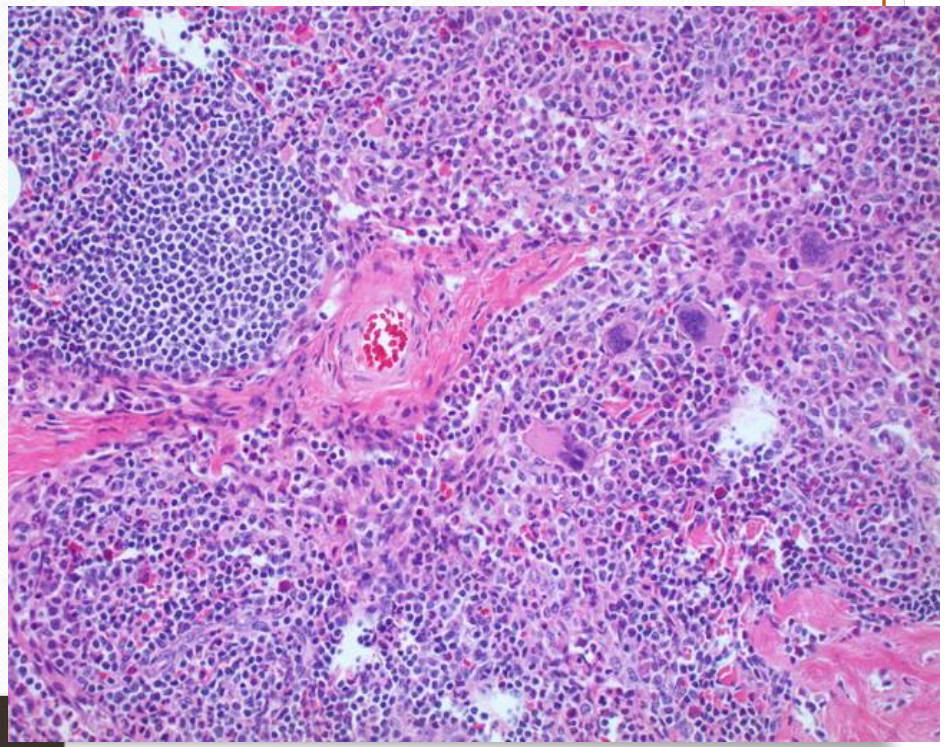
- Leukocyte count is ↑↑ (often >100,000 cells/µL).
- Circulating cells are predominantly neutrophils, metamyelocytes & myelocytes.
- Basophils, eosinophils & platelets are increased



CML - Morphology

BM & spleen

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

CML - Clinical features

- Slowly progressive disease

Median survival is 3 years without treatment

- Can progress to accelerated phase

Anemia, thombocytopenia & additional genetic mutations.

- Progress to blast phase:

1) 70% AML
2) 30% ALL

- Rarely progresses to spent phase with fibrosis.

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 relative polycythemia →results from hemoconcentration.
- Unlike secondary forms of polycythemia, in which erythropoietin levels are high, 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 - Morphology

- The major anatomic changes in PCV stem from increases in blood volume and viscosity.
- Hemoglobin levels (Hb > 18,5 g/dl (♂), > 16.5 g/dl (♀))
- **Congestion** of many tissues is characteristic.
- Hepatomegaly & small foci of extramedullary hematopoiesis.
- Spleen usually is slightly enlarged → vascular congestion.

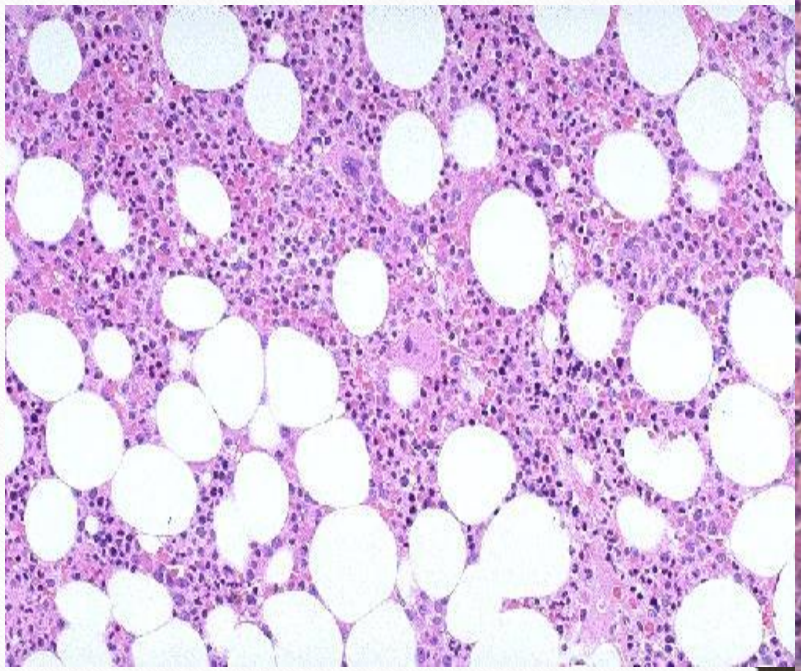
PCV - Morphology

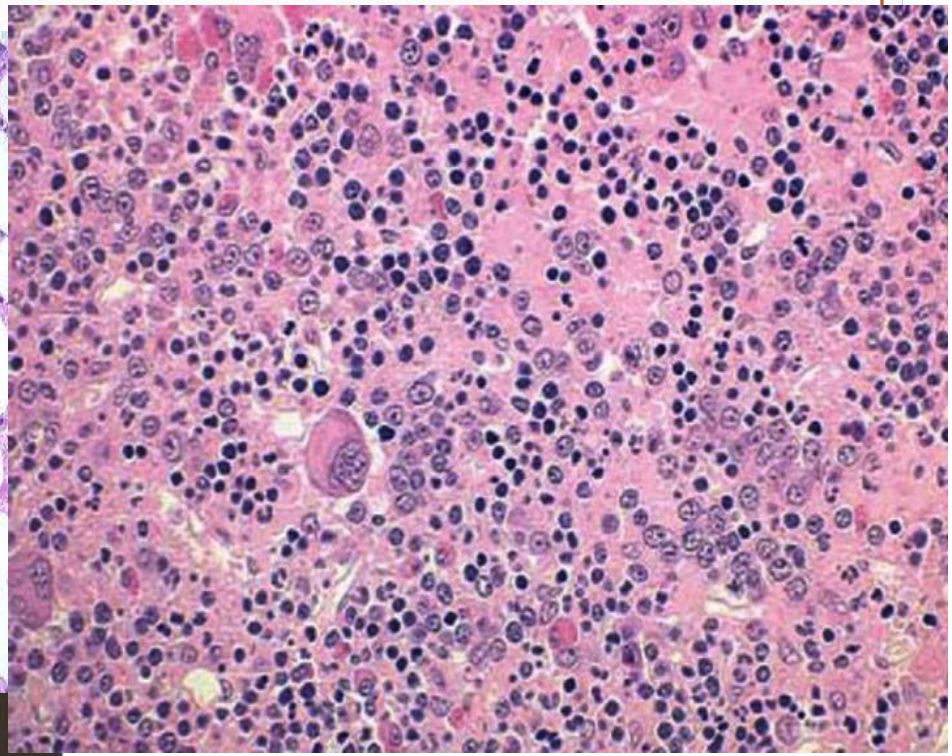
- Thromboses & infarctions are common → the increased viscosity and vascular stasis.
- Platelets produced from the neoplastic clone often are dysfunctional → elevated risk of thrombosis and bleeding Hemorrhages; often in GIT, oropharynx or brain.
- The peripheral blood often shows **basophilia**.

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





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.