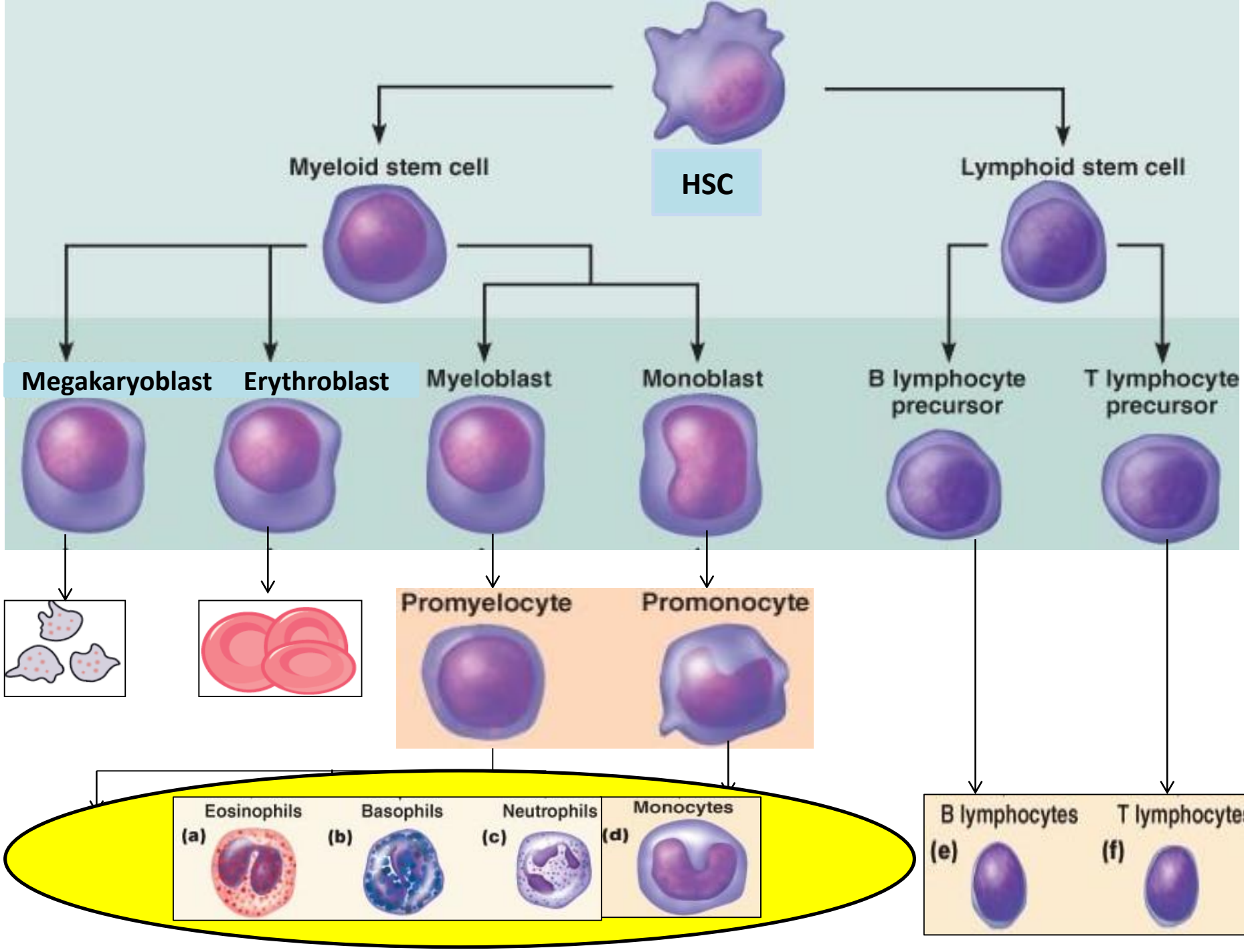
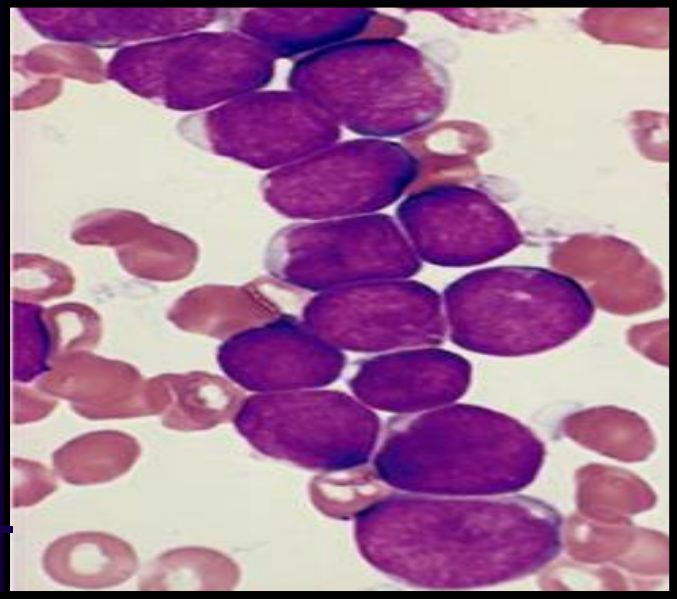
Chronic Leukaemias

- **Heterogeneous group of hematopoietic neoplasms**
- **Uncontrolled proliferation and decreased apoptotic activity with variable degrees of differentiation**
- **Composed of relatively mature cells**
- **Indolent. (If untreated, the course is in months or years)**
- **Occurs mainly in adults**

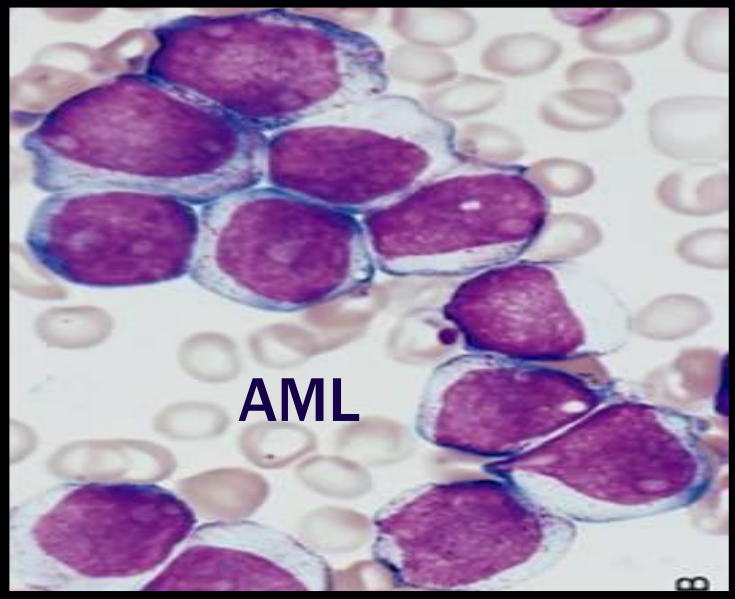

HSC
Myeloid stem cell
Lymphoid stem cell
Megakaryoblast
Erythroblast
Myeloblast
Monoblast
B lymphocyte precursor
T lymphocyte precursor
Promyelocyte
Promonocyte
Eosinophils
(a)
Basophils
(b)
Neutrophils
(c)
Monocytes
(d)
B lymphocytes
(e)
T lymphocytes
(f)

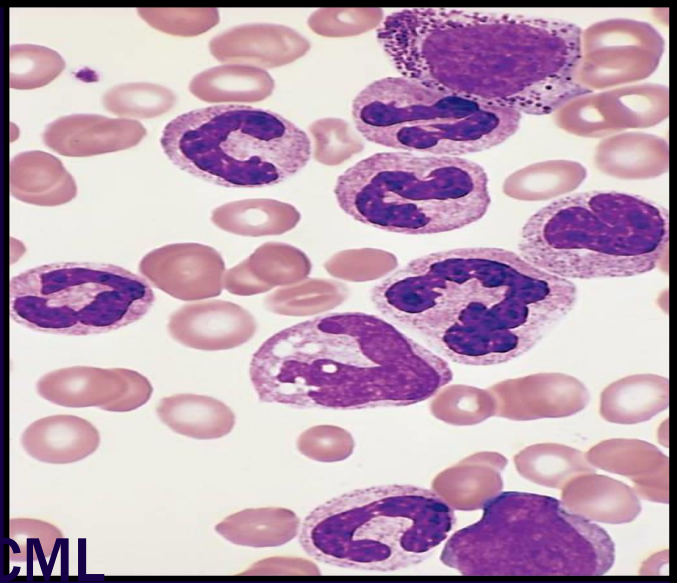
Main Types of Leukemia

	Acute	Chronic
Lymphoid	ALL	LPN(CLL)
Myeloid	AML	MPN/MDS (CML)
Mixed	Acute Biphenotypic	
Non	Acute Undifferentiated	

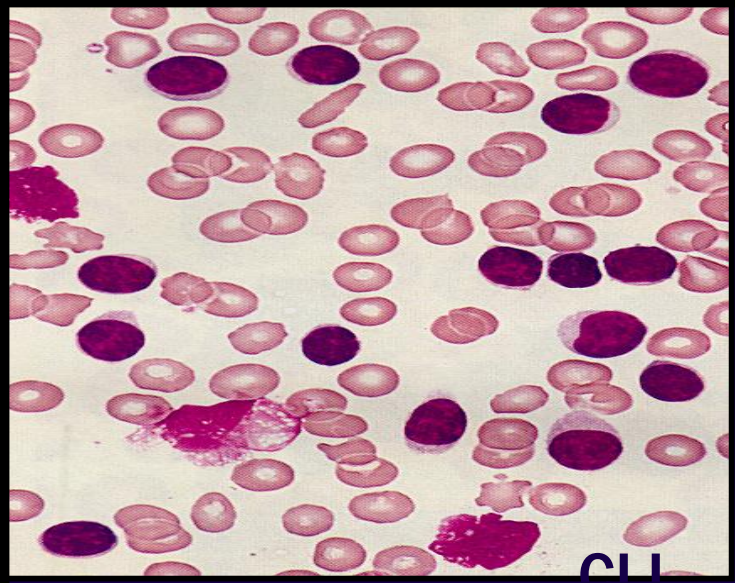


ALL





CML



CLL

Table 1. Classification of Myeloid Neoplasms According to the 2008 World Health Organization Classification Scheme

1. **Myeloproliferative neoplasms (MPN)**
   - 1.1. Chronic myelogenous leukemia, *BCR-ABL1*–positive (CML)
   - 1.2. Polycythemia vera (PV)
   - 1.3. Essential thrombocythemia (ET)
   - 1.4. Primary myelofibrosis (PMF)
   - 1.5. Chronic neutrophilic leukemia (CNL)
   - 1.6. Chronic eosinophilic leukemia, not otherwise specified (CEL-NOS)
   - 1.7. Mast cell disease (MCD)
   - 1.8. MPN, unclassifiable
2. **Myeloid and lymphoid neoplasms with eosinophilia and abnormalities of *PDGFRA*, *PDGFRB*, and *FGFR1***
3. **MDS/MPN**
   - 3.1. Chronic myelomonocytic leukemia (CMML)
   - 3.2. Juvenile myelomonocytic leukemia (JMML)
   - 3.3. Atypical chronic myeloid leukemia, *BCR-ABL*–negative (aCML)
   - 3.4. MDS/MPN, unclassifiable
4. **Myelodysplastic syndromes (MDS)**
5. **Acute myeloid leukemia (AML)**

Myeloproliferative Neoplasms

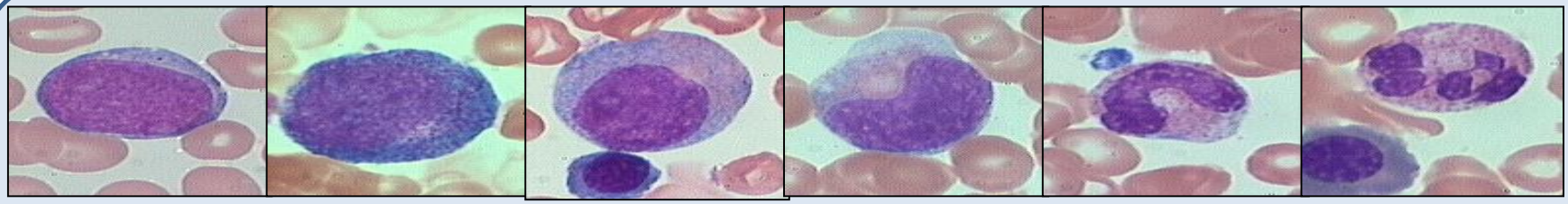
- **Malignant proliferation of myeloid cells (maturing cells) in blood and bone marrow.**
- **Occur mainly in adults**
- **Slow onset and long course**

MPN features

- Cytoses
- Organomegaly (mainly splenomgaly)
- High uric acid
- Hypercellular bone marrow
- Progression to acute leukaemia (mainly AML)

Chronic Myeloid Leukemia (CML)

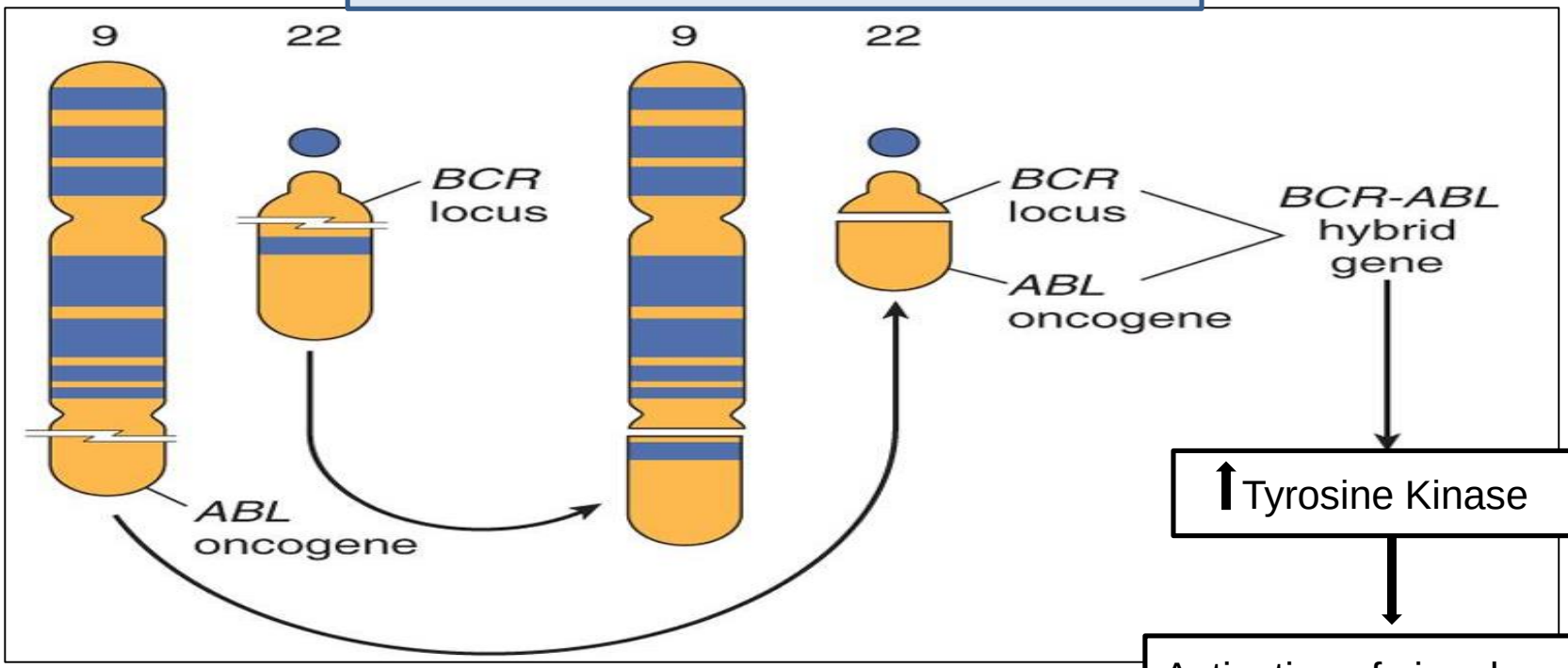
- Stem cell MPN.
- Predominant proliferation of granulocytic cells.
- Consistently associated with the *BCR-ABL1* fusion gene located in the Philadelphia (Ph) chromosome which results from t(9;22) .



myeloblast promyelocyte myelocyte metamyelocyte band neutrophil

MATURATION

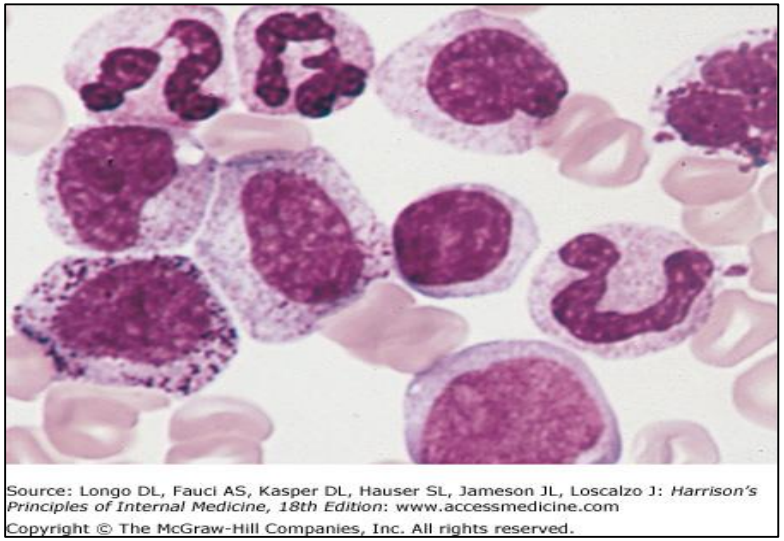
Pathogenesis of CML



↑ Tyrosine Kinase

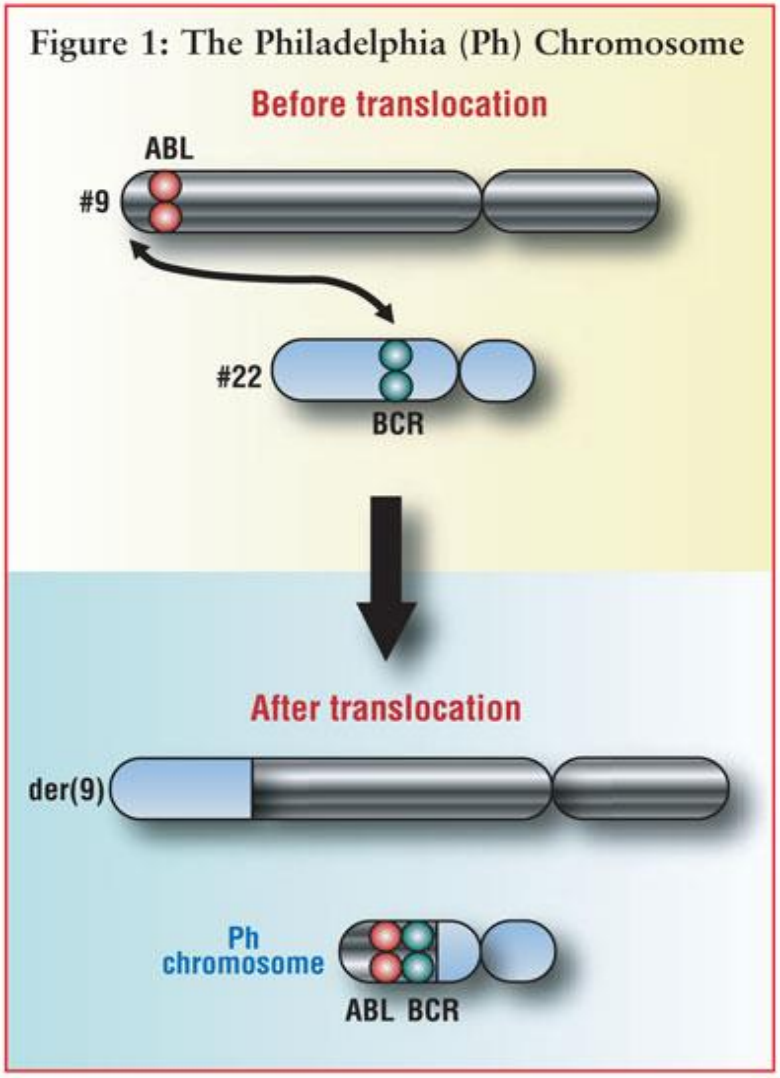
Activation of signal transduction pathways

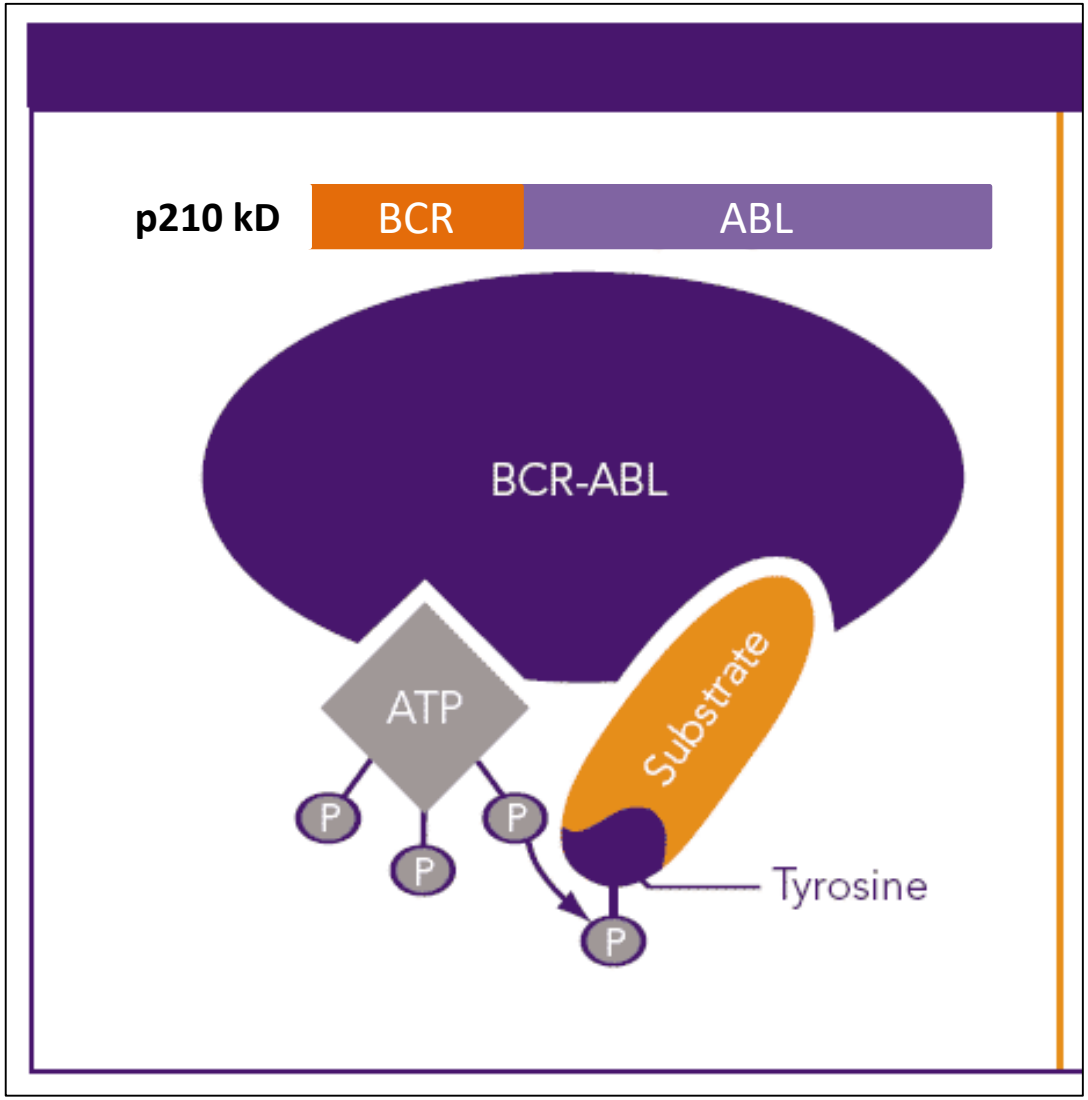
Uncontrolled proliferation



Source: Longo DL, Fauci AS, Kasper DL, Hauser SL, Jameson JL, Loscalzo J: *Harrison's Principles of Internal Medicine, 18th Edition*: www.accessmedicine.com

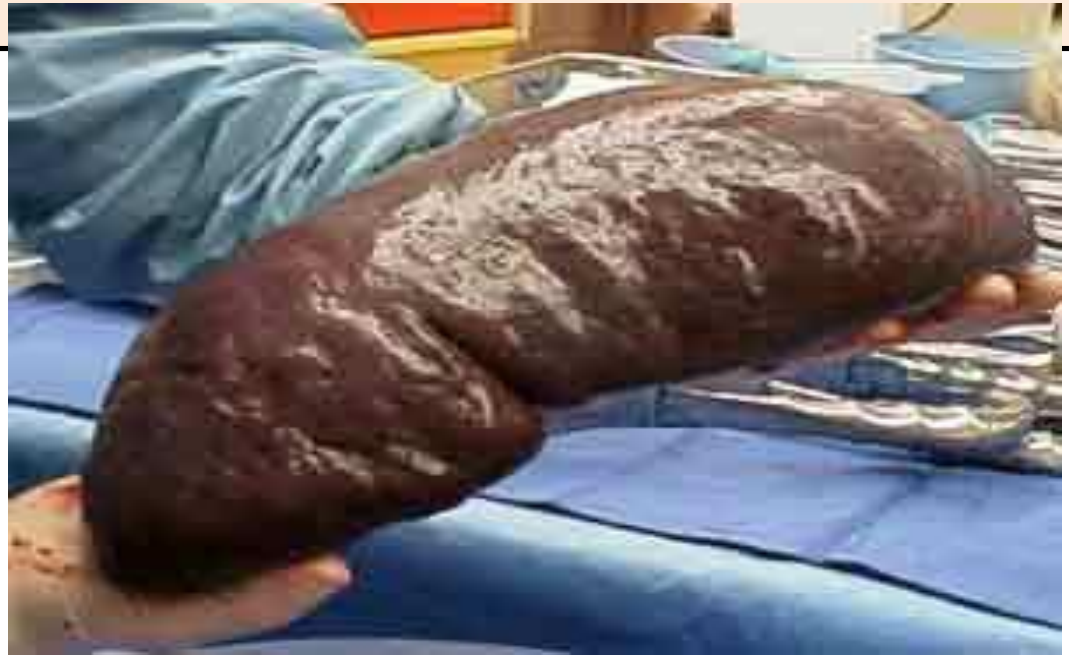
Pathogenesis of CML





Clinical Presentation

- Asymptomatic presentation(20-40%):
- Routine CBC : marked leukocytosis
- Common symptoms : Fatigue ,weight loss or night sweating
- Abdominal discomfort due to splenomegaly
- Splenomegaly (Massive)



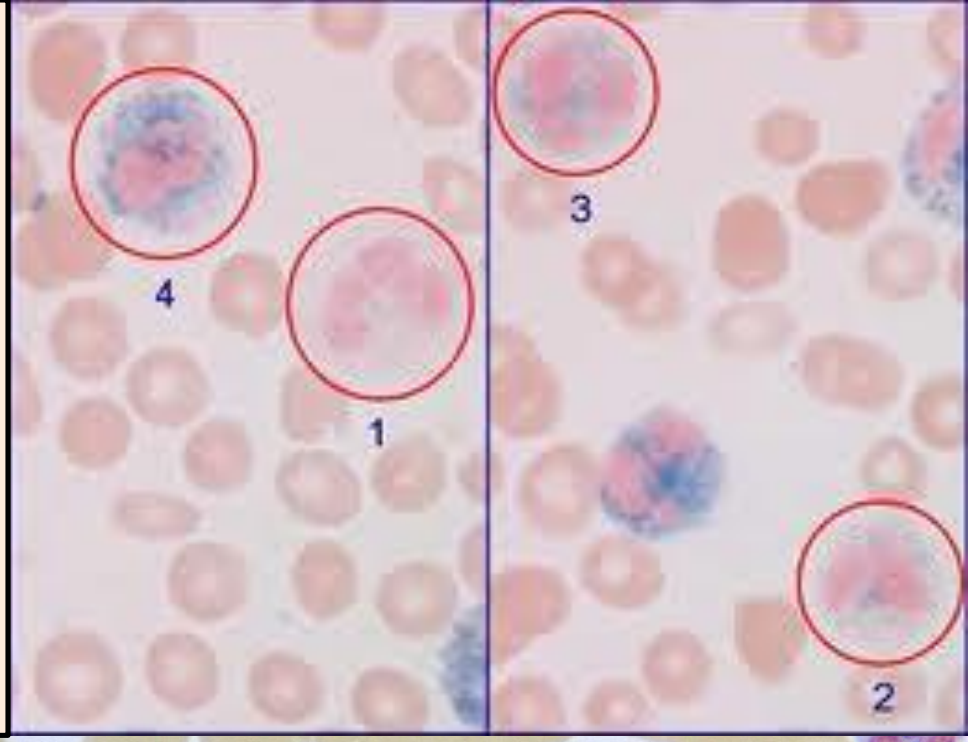
Main Differential Diagnosis

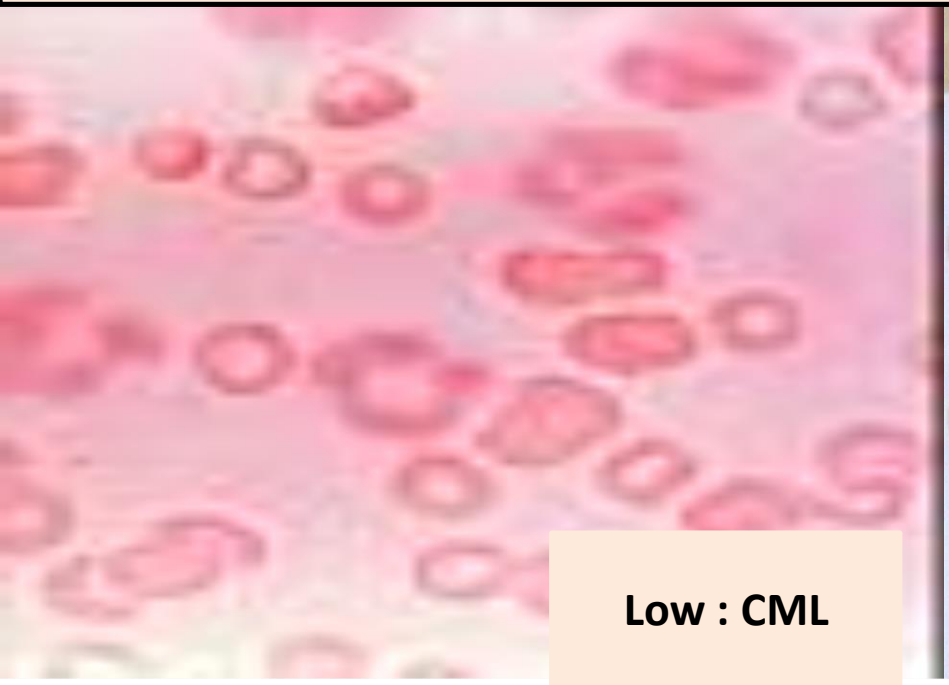
1- Chronic myelomonocytic leukemia (monocytosis ,BCR-ABL –ve) .
2-Leukemoid reaction: Leukocytosis due to physiological response to stress or infection

	CML	Leukaemoid
Age	Adult	Any age
WBC count	High	High but <100,000
Differential	Mainly myelocytes and segmented	Mainly Bands
Morphology	Hypogranular	Toxic
Splenomegaly	+	-/+
NAP score	Low	High
BCR/ABL	+ve	-ve
Onset	Chronic	Acute

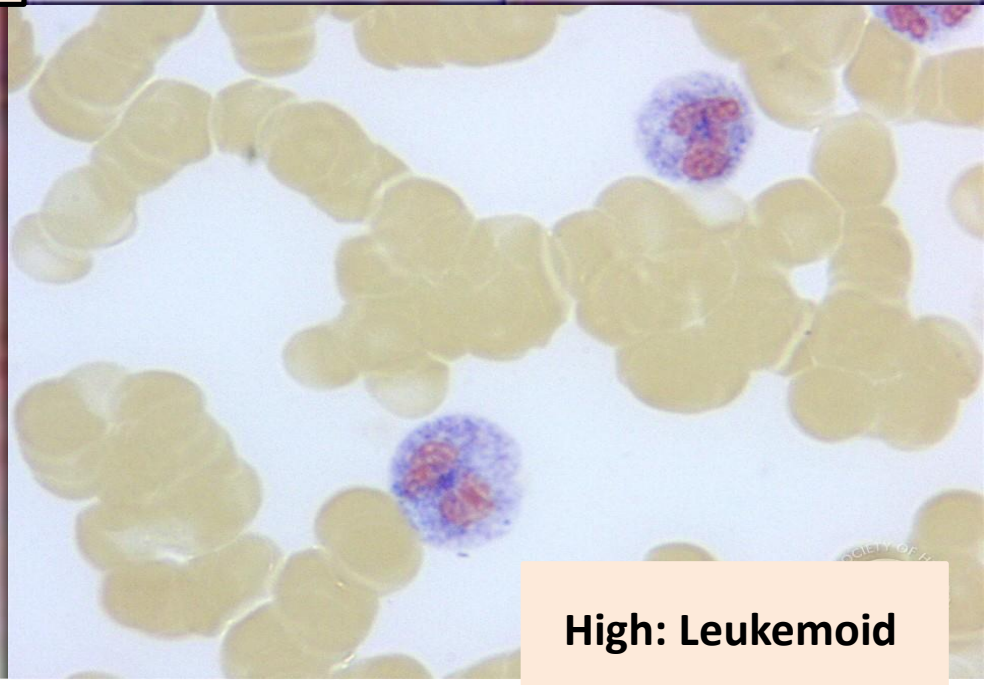
Neutrophil Alkaline Phosphatase (NAP)score :

•Cytochemical stain that estimate the amount of alkaline phosphatase enzyme in neutrophilis .





Low : CML

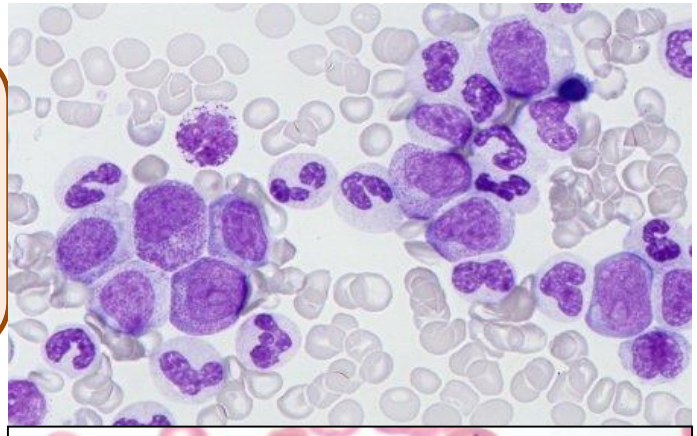


High: Leukemoid

CML Phases

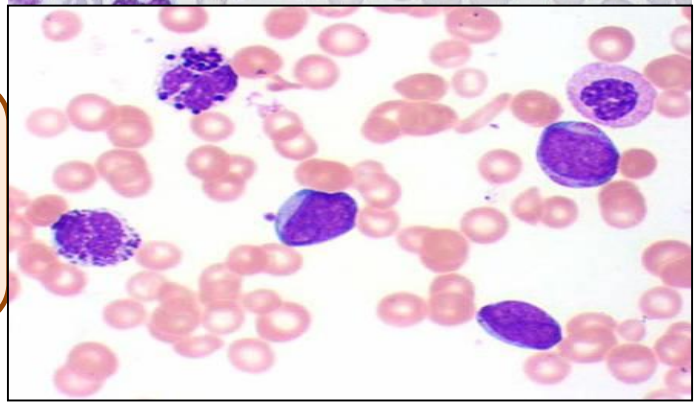
Chronic phase

- Leukocytosis (12-1000×10^9/L)
- Mainly neutrophils & myelocytes
- Blasts ≤10% ,Basophils≤ 20%
- Stable course (years)



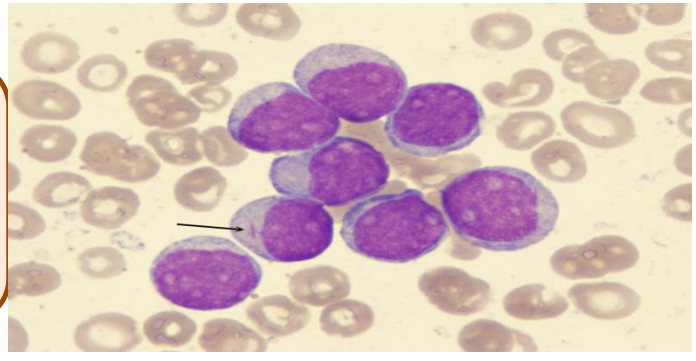
Accelerated phase

- Increasing counts
- 10-19% blasts (basophils ≥20%)
- Unstable course (months)

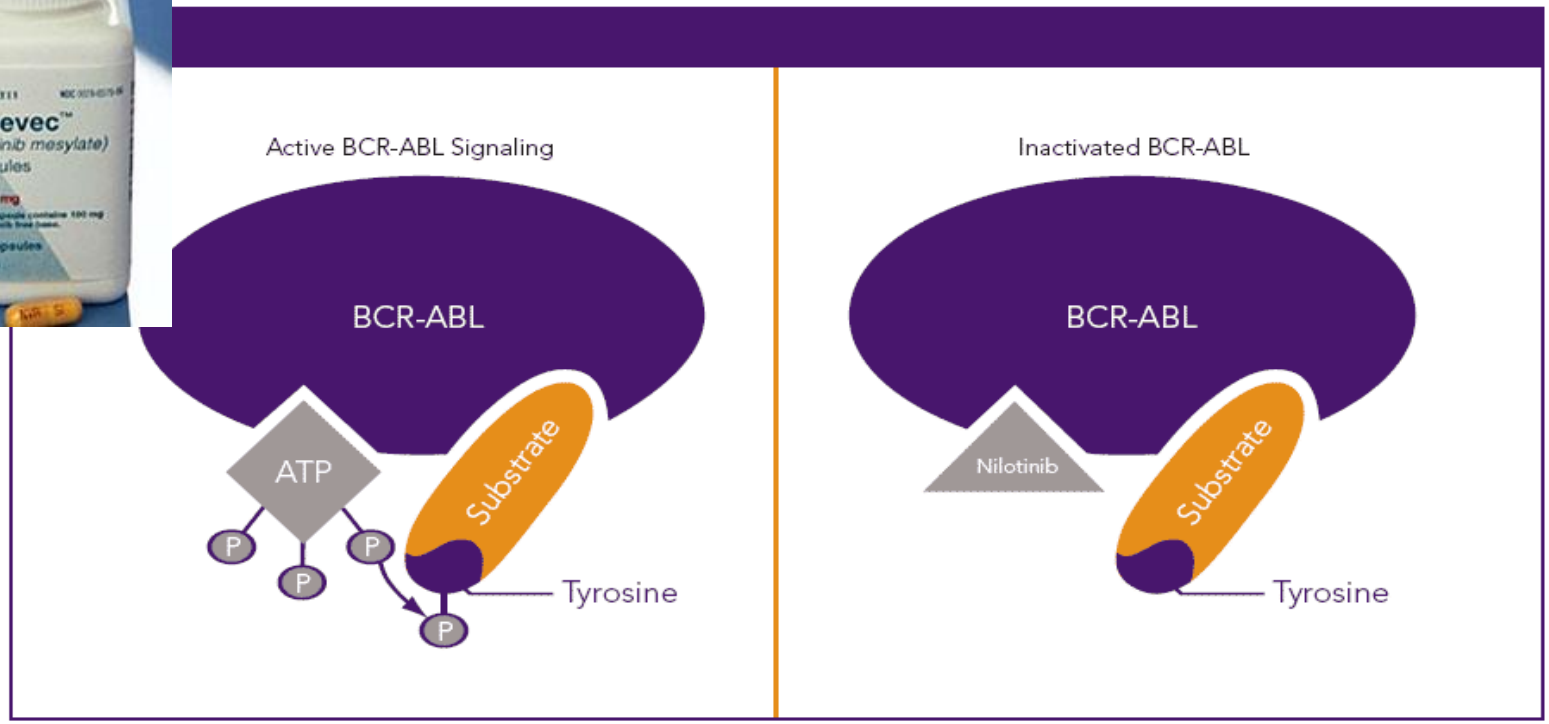


Blastic phase

- ≥20% blasts = Acute Leukemia
- 80% AML & 20% ALL
- (coarse: Weeks)



CML Treatment



- Targeted therapy (tyrosine kinase inhibitors like Imatinib)
- Excellent response (5y overall survival≥ 90%)
- If no response ; stem cell transplantation

Myelodysplastic Syndromes MDS

- **Group of myeloid neoplasms characterized by:**

  1-Peripheral cytopenia (Low HB ± Low WBC & Low PLT)

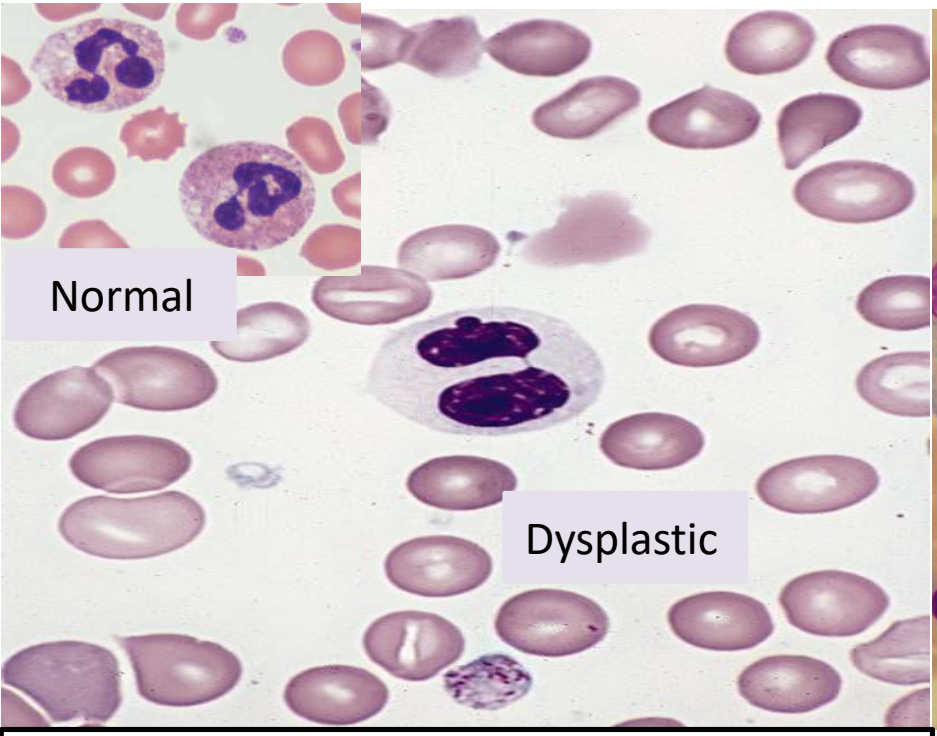
  2- Dysplasia (abnormal morphology)

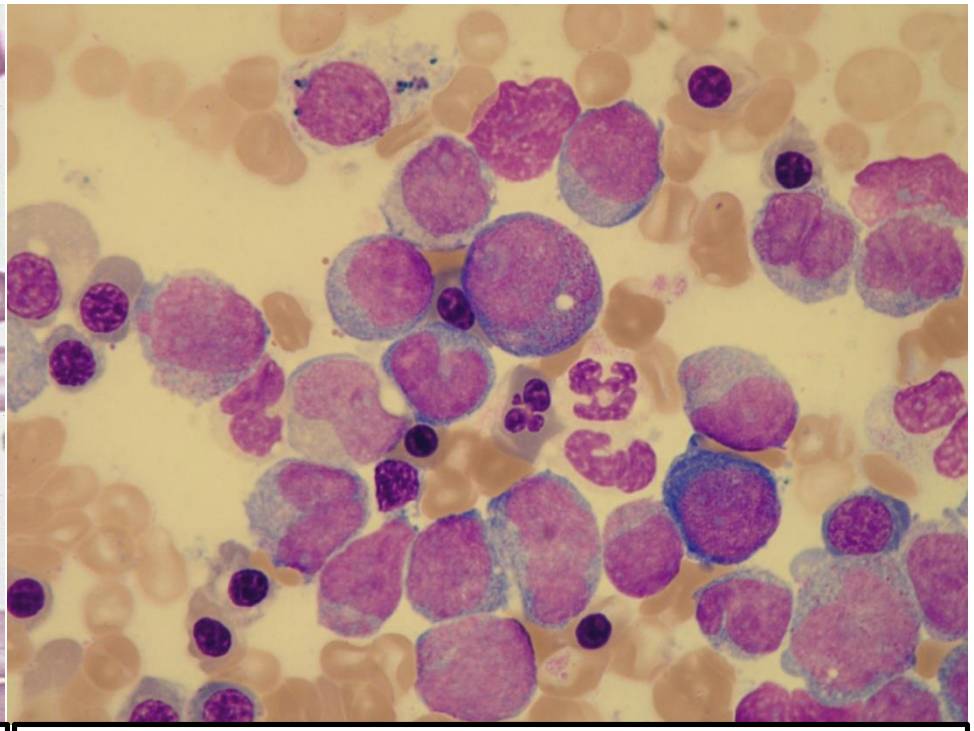
  3- Ineffective hematopoiesis (hypercellular marrow)

  4-Progression to AML (preleukaemic disease)

  5-Enhanced apoptosis

Myelodysplastic Syndromes MDS

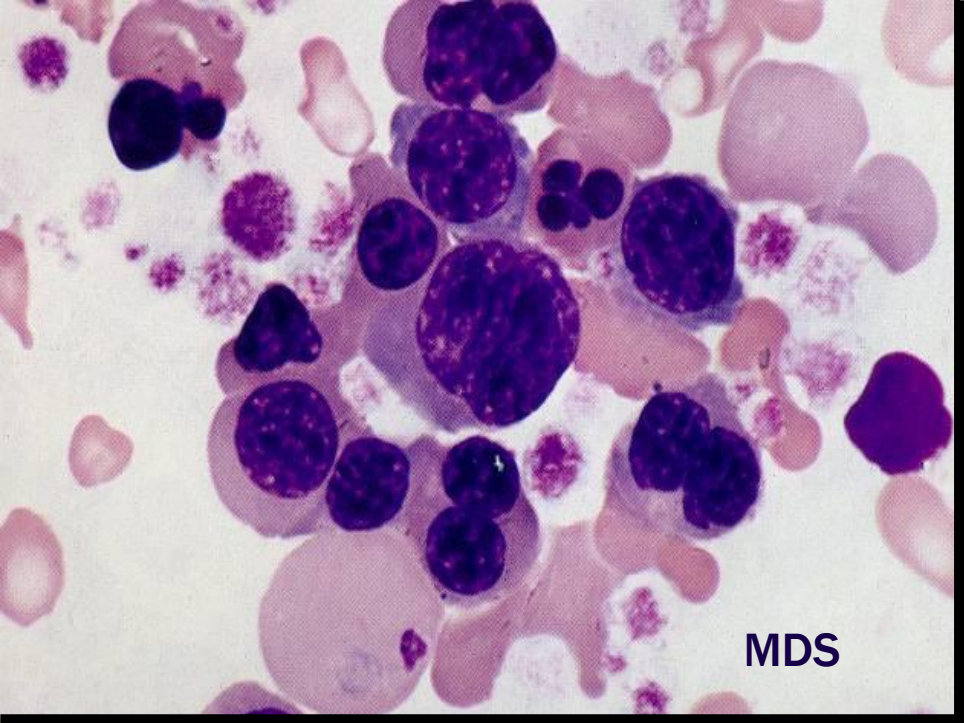
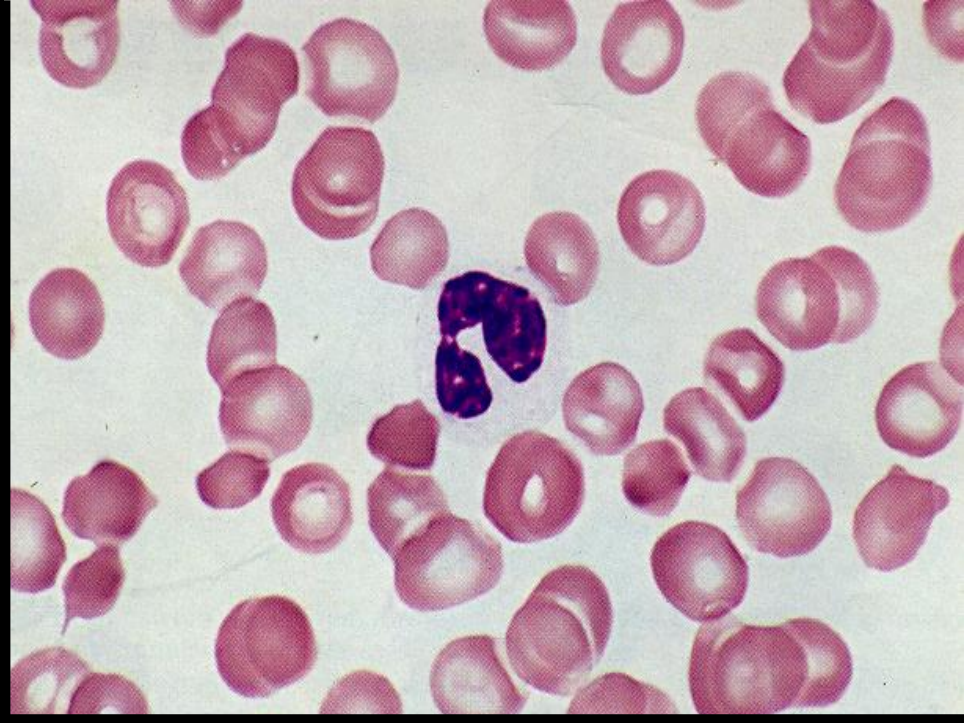
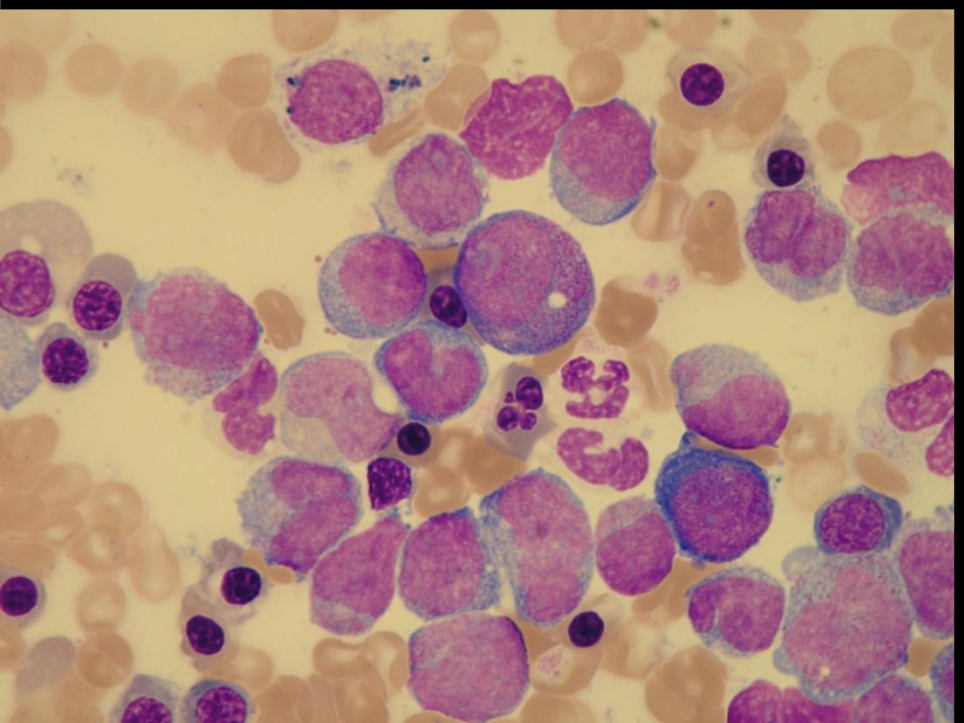
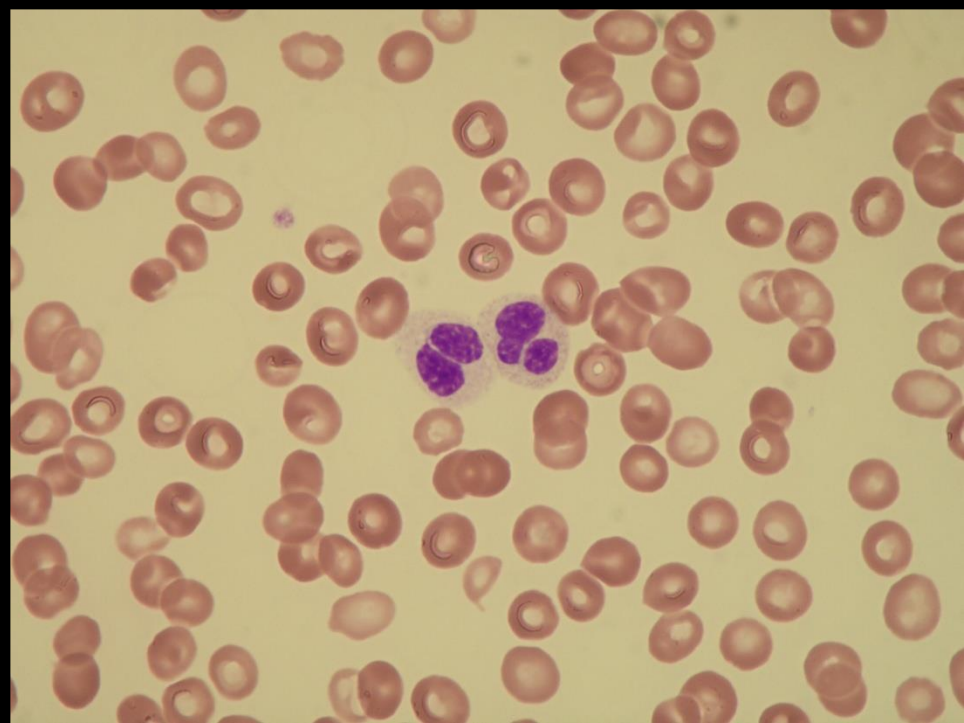




Blood: Pancytopenia with dysplasia

BM: Hypercellular with dysplasia

↑ Proliferation — ↑ Apoptosis = Ineffective Hematopoiesis


MDS




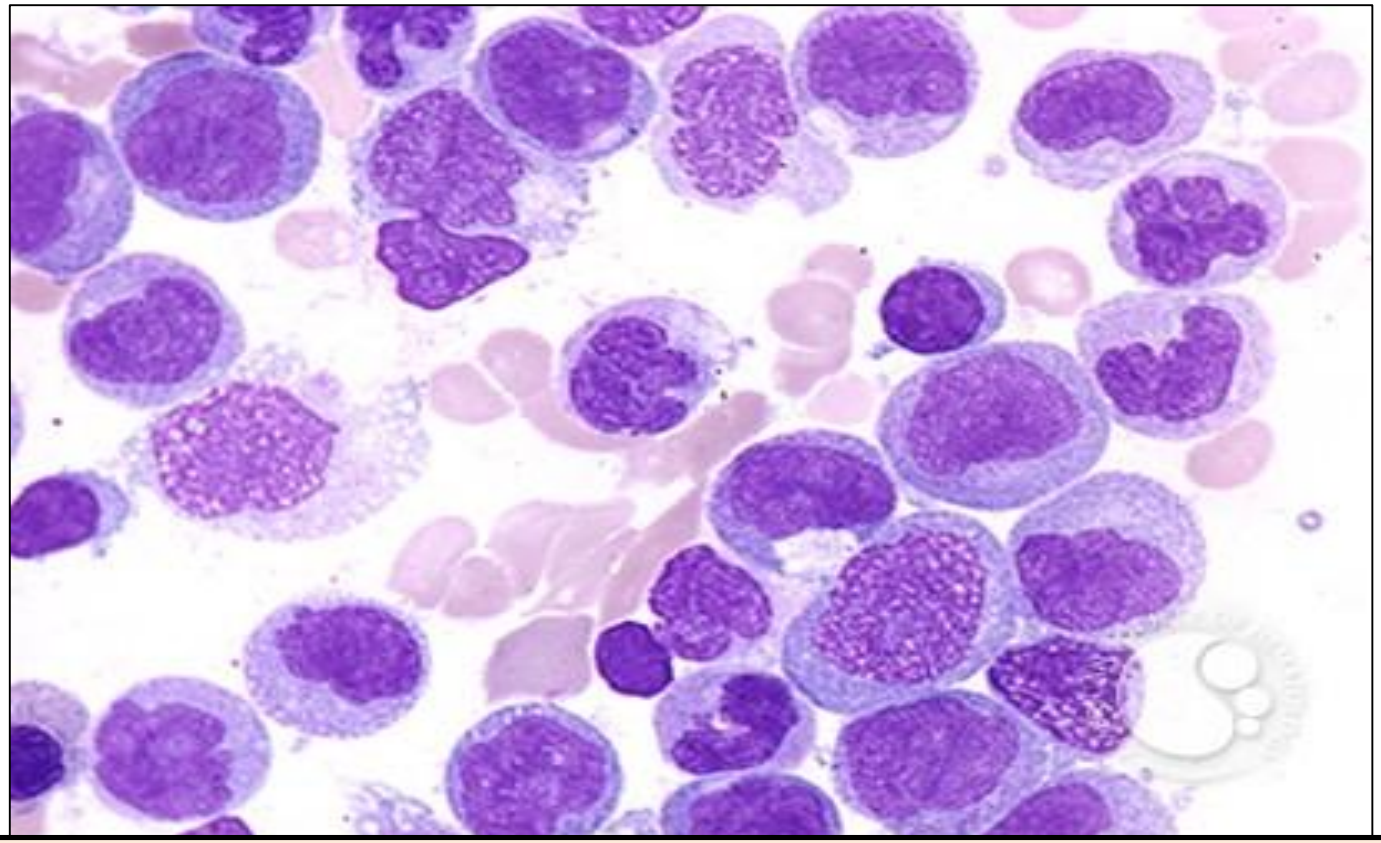
Myelodysplastic Syndromes MDS

- **Many subtypes according to:**
  - **1-Blast count**
  - **2-Degree of dysplasia**
  - **3-Genetics**
- **Variable genetic abnormalities mainly -5, -7**
- **<u>Treatment</u> : supportive +/- chemotherapy**

Chronic Myelomonocytic Leukemia (CMML)

- **Clonal Hematopoietic malignancy characterized by proliferation of both monocytes and neutrophils.**
- **MDS/MPN disease:**
  - *** Features of MDS (dysplasia& enhanced apoptosis)**
  - ***Features of MPN (marked proliferation)**
- **Philadelphia chromosome must be negative**
- **Blast must be less than 20%.**

CMML



- Aggressive course (survival rate around 2.5 y)
- Treatment : Chemotherapy ±SCT

MPN vs. MDS vs. MPN/MDS