جامعة الملك سعود
King Saud University
1957

Chronic Leukemia

Dr. Mansour Aljabry MD,MSHA,KSUF

Chairman of Pathology Department

Head of Academic guidance Unit

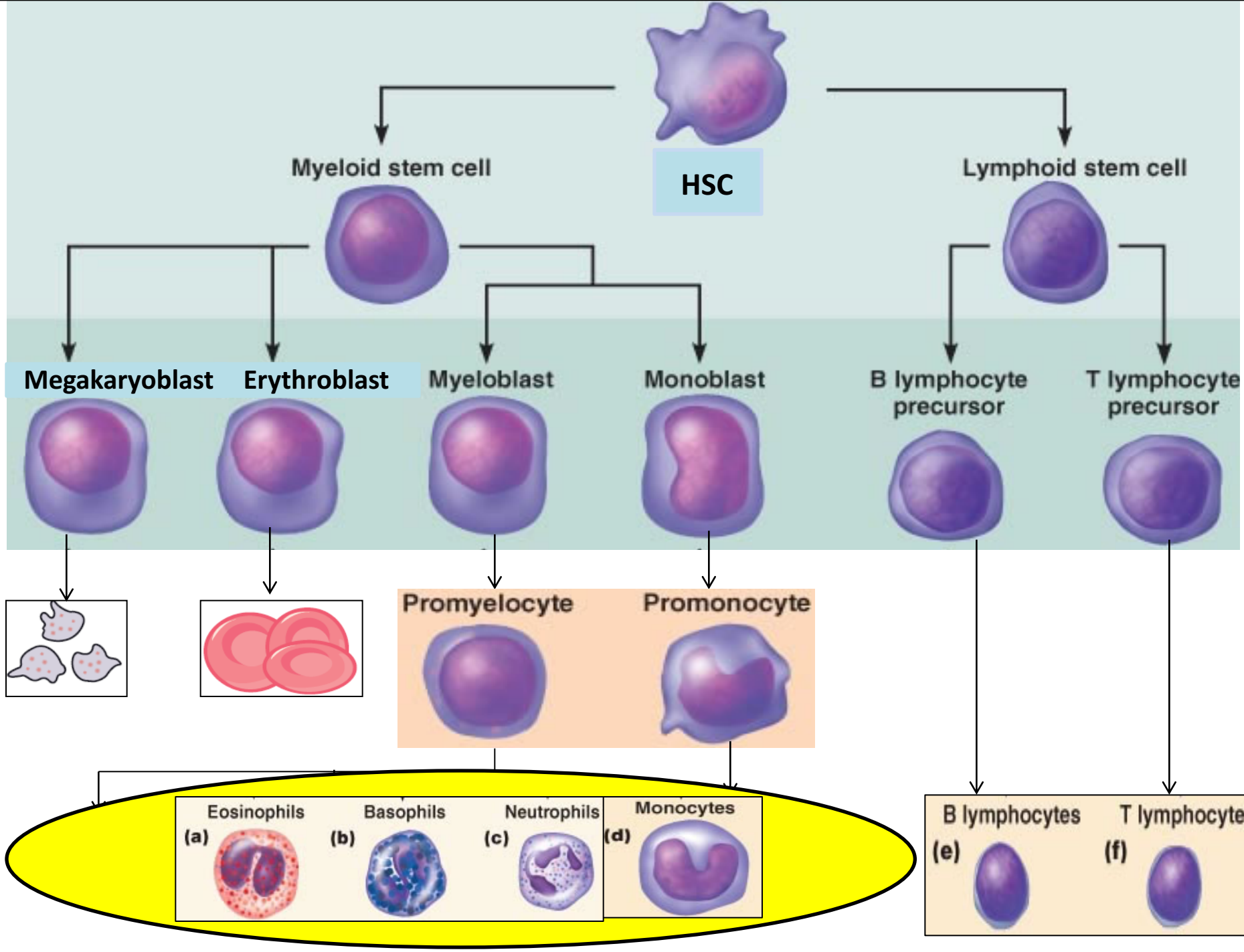
Associate Professor & Consultant Hematologist

Objectives

1. To understand the general features of Myeloproliferative neoplasms
2. To understand the clinicopathological differences between AML and CML)
3. To understand the diagnostic approach for chronic leukemia and the major differential diagnosis of CML
4. To recognize the importance of genetic study in diagnosis and treatment of CML.
5. To understand the general aspect of myelodysplastic syndrome (MDS) including definition , pathogenesis , clinical features and prognosis
6. To understand the general aspect of chronic myelomonocytic leukemia CMML including definition , pathogenesis , clinical features and prognosis

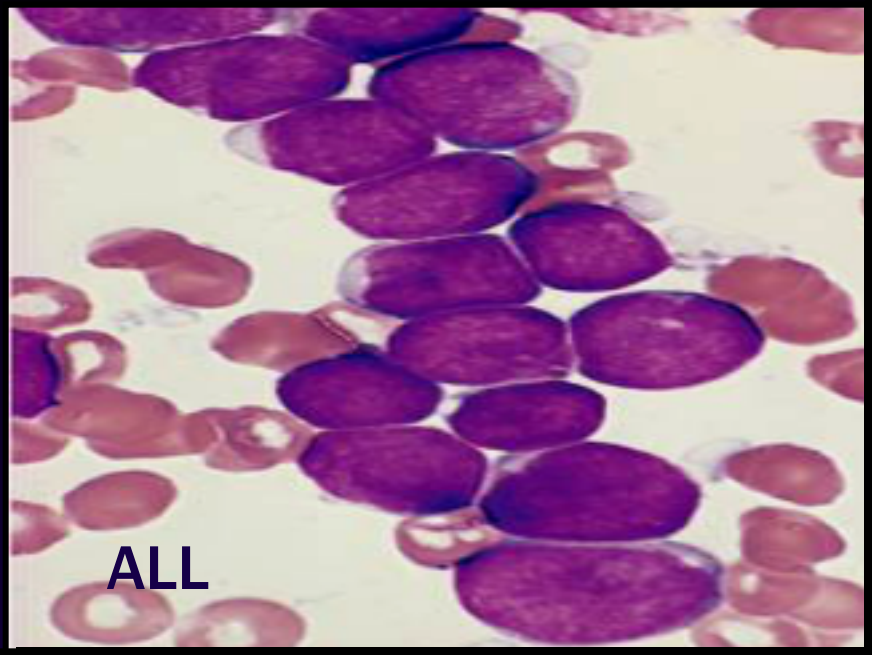
Chronic Leukaemias

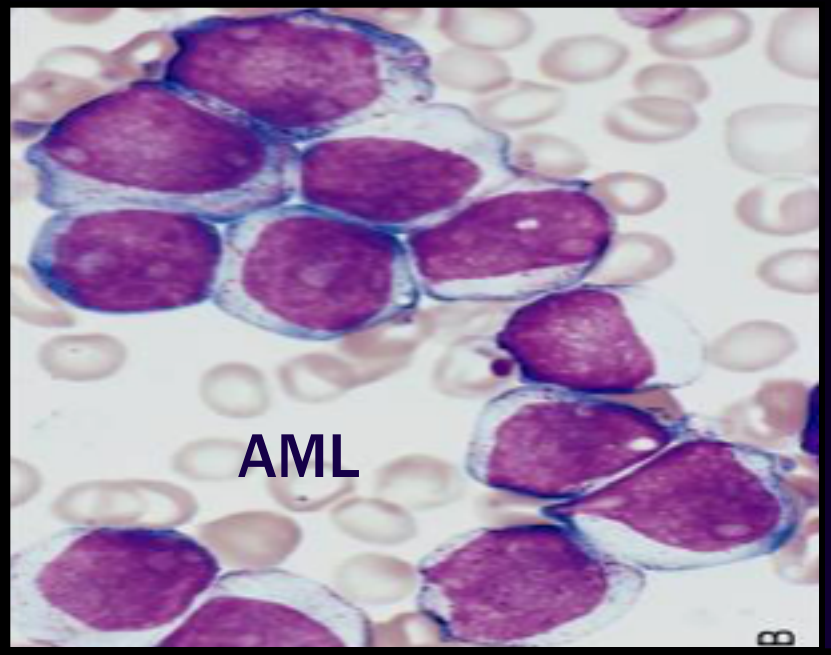
- Heterogeneous group of hematopoietic neoplasms
- Uncontrolled proliferation and decreased apoptotic activity with variable degrees of differentiation
- Composed of relatively mature cells
- Indolent. (If untreated, the course is in months or years)
- Occurs mainly in adults

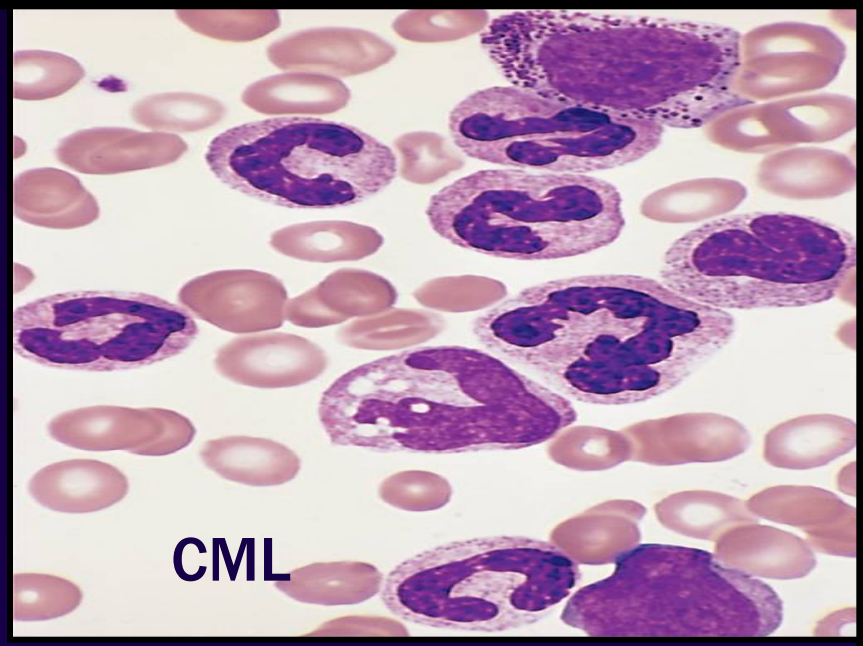

HSC
Myeloid stem cell
Lymphoid stem cell
Megakaryoblast
Erythroblast
Myeloblast
Monoblast
B lymphocyte precursor
T lymphocyte precursor
Promyelocyte
Promonocyte
Eosinophils
(a)
Basophils
(b)
Neutrophils
(c)
Monocytes
(d)
B lymphocytes
(e)
T lymphocytes
(f)

Main Types of Leukemia

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


ALL


AML


CML

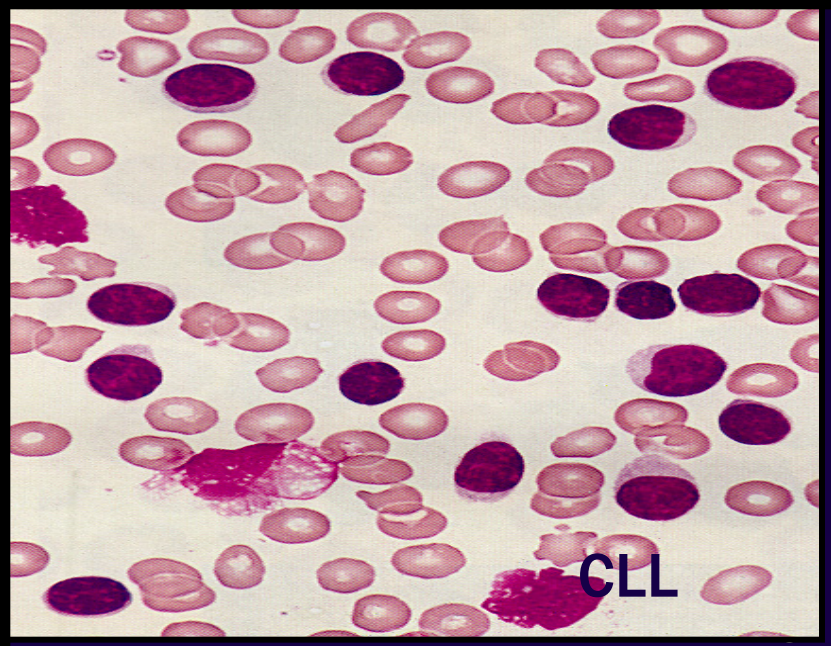

CLL

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

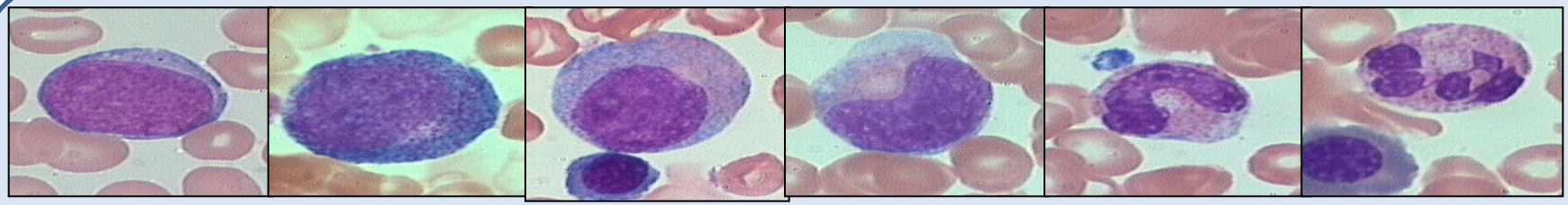
- Malignant proliferation of myeloid cells (maturing cells) in blood and bone marrow.
- Occur mainly in adults
- Slow onset and long course

MPN features

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

Chronic Myeloid Leukemia (CML)

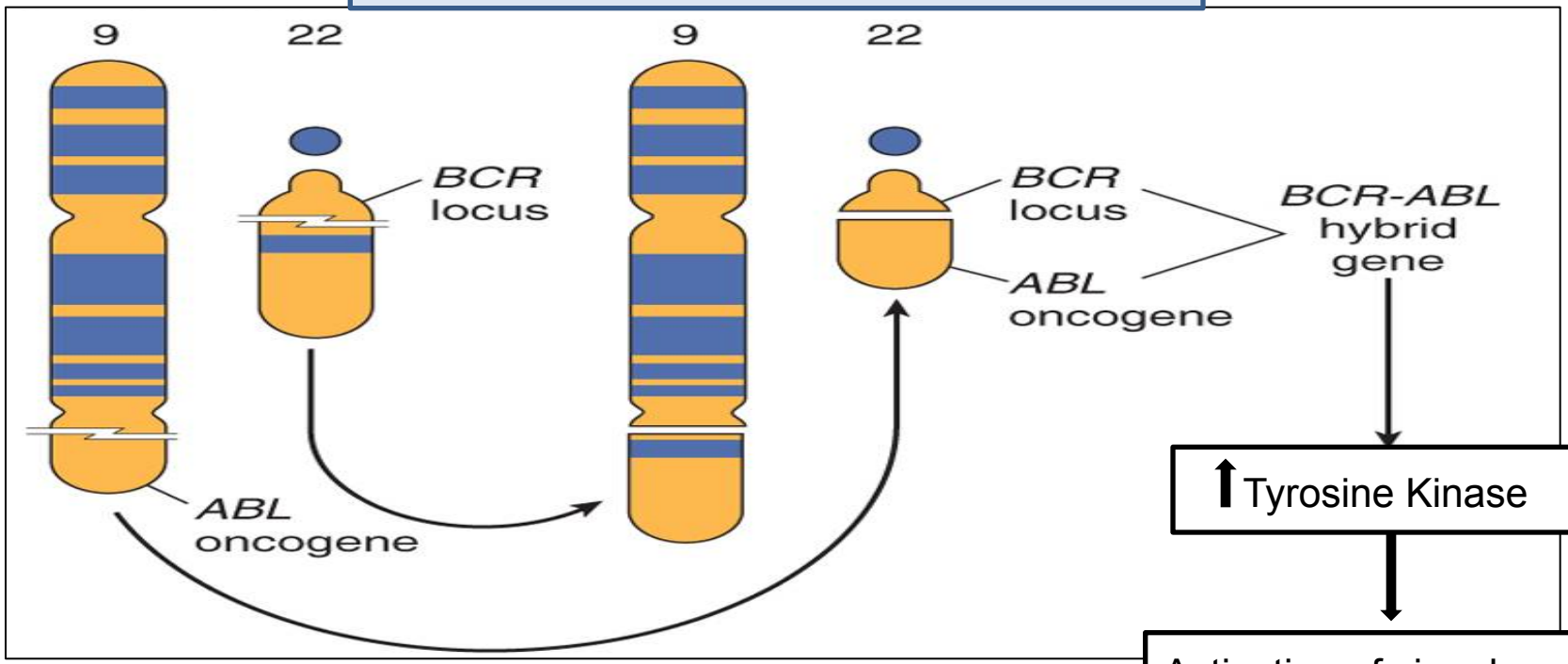
- Stem cell MPN.
- Predominant proliferation of granulocytic cells.
- Consistently associated with the *BCR-ABL1* fusion gene located in the Philadelphia (Ph) chromosome which results from t(9;22) .



myeloblast promyelocyte myelocyte metamyelocyte band neutrophil

MATURATION

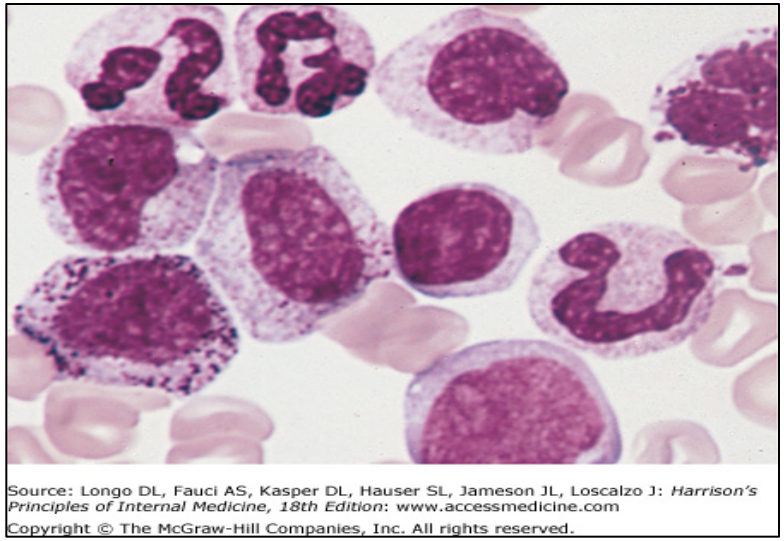
Pathogenesis of CML



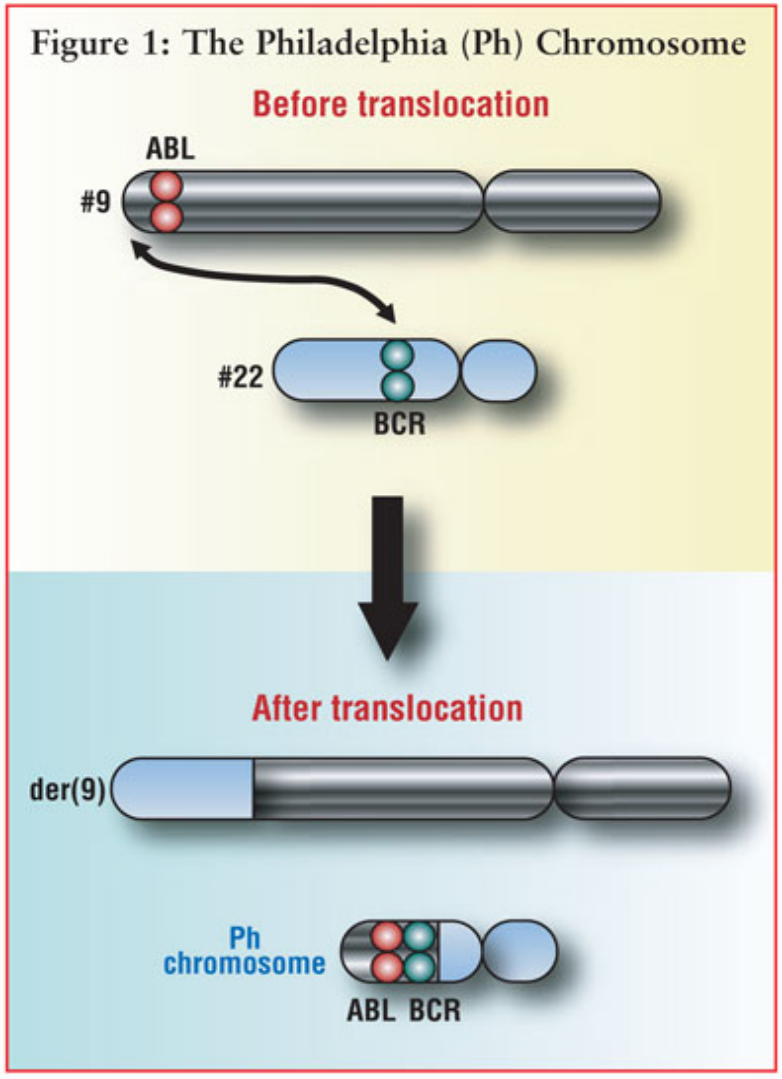
↑ Tyrosine Kinase

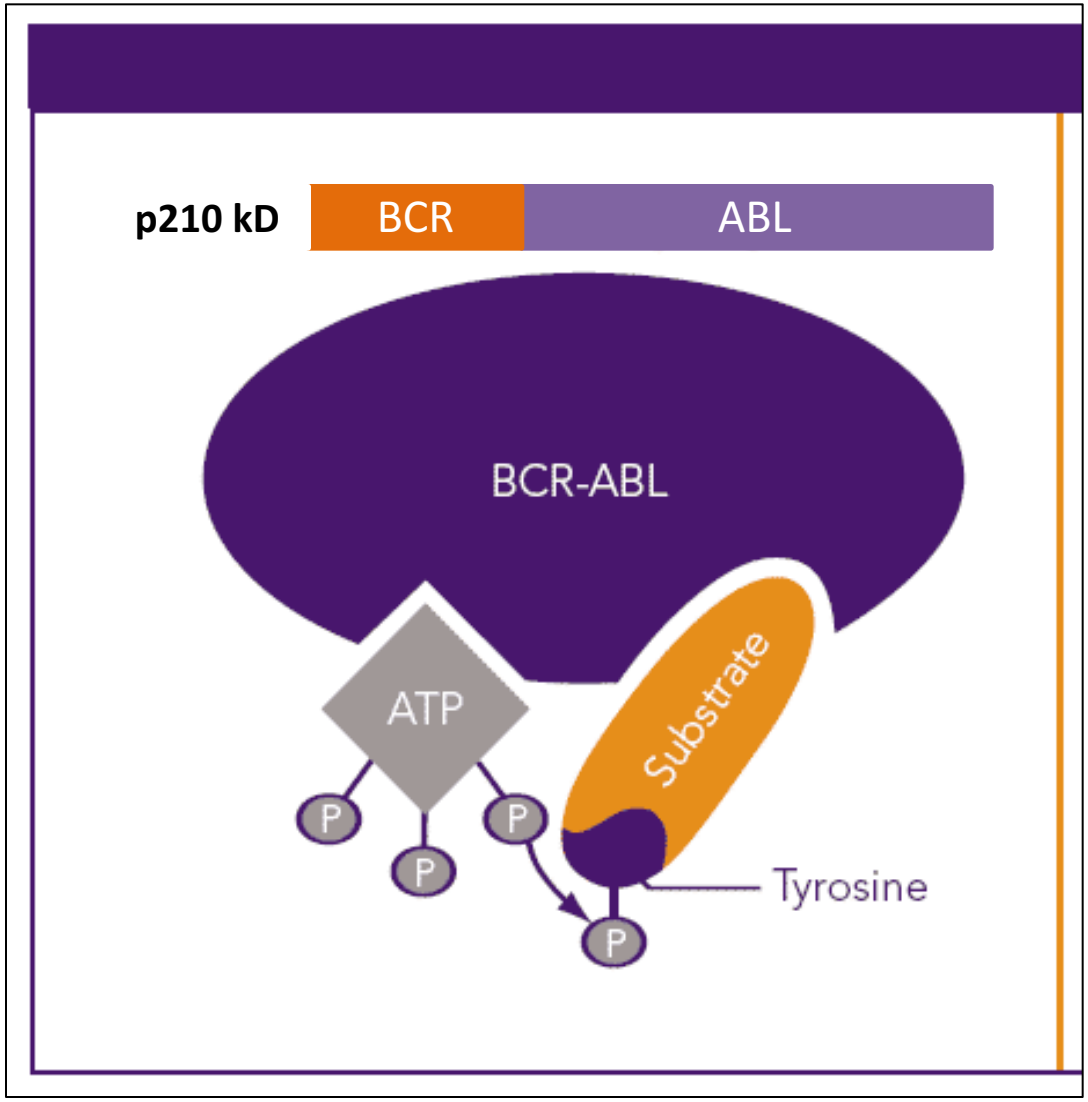
Activation of signal transduction pathways

Uncontrolled proliferation



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)

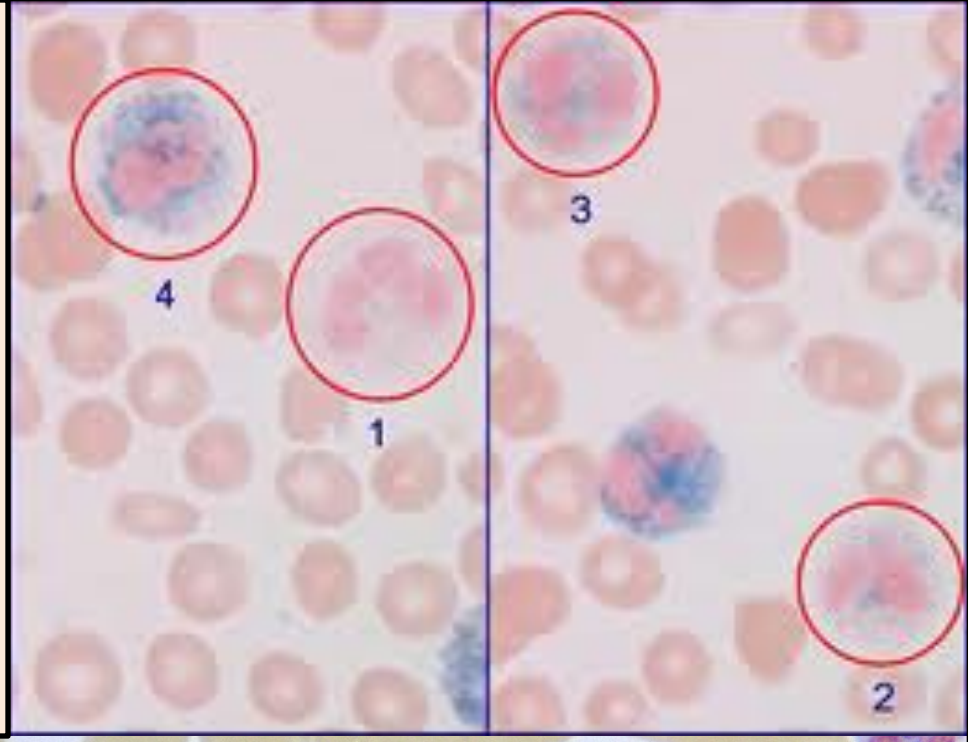
Main Differential Diagnosis

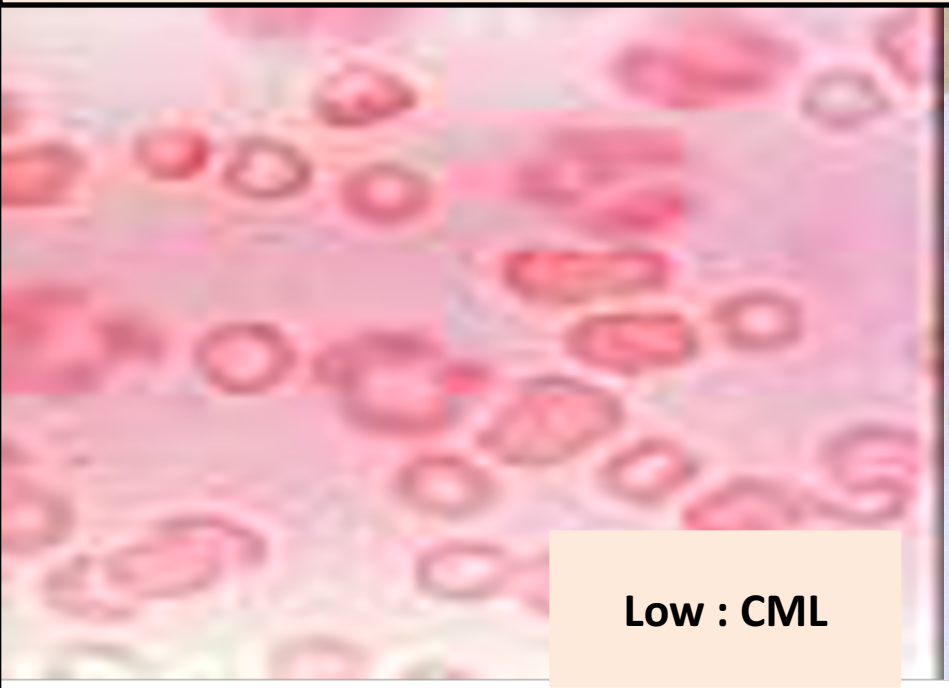
1- Chronic myelomonocytic leukemia (monocytosis ,BCR-ABL –ve) .
2-Leukemoid reaction: Leukocytosis due to physiological response to stress or infection

	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

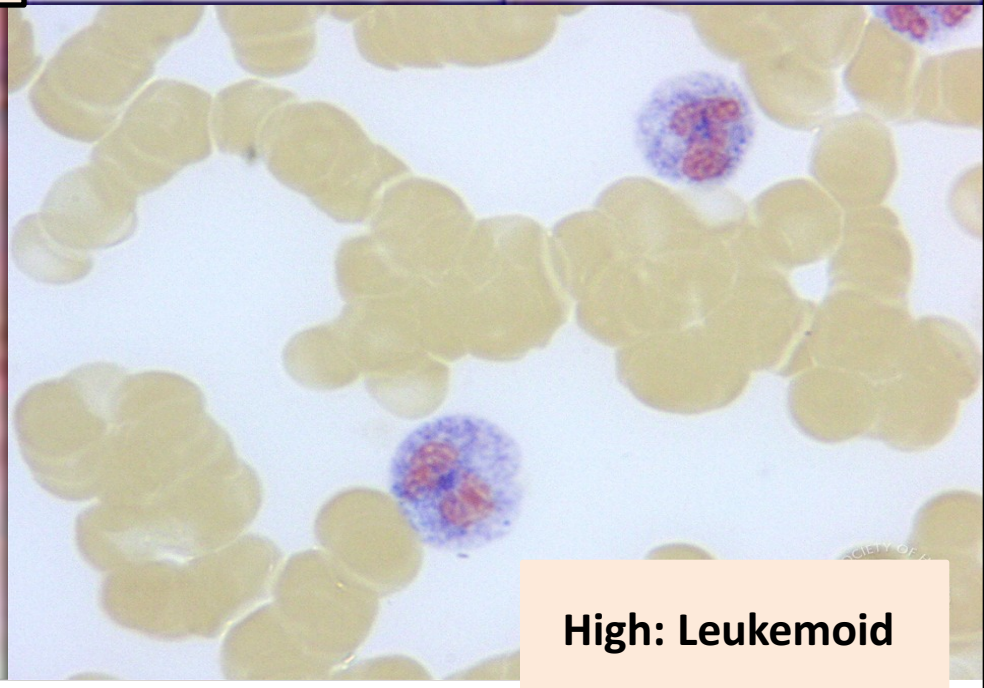
Neutrophil Alkaline Phosphatase (NAP)score :

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





Low : CML

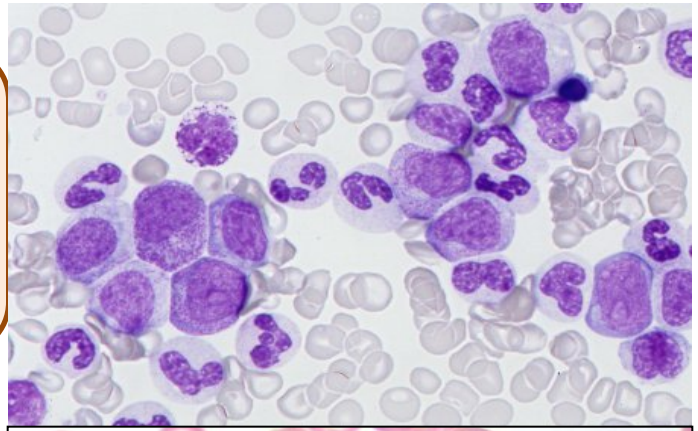


High: Leukemoid

CML Phases

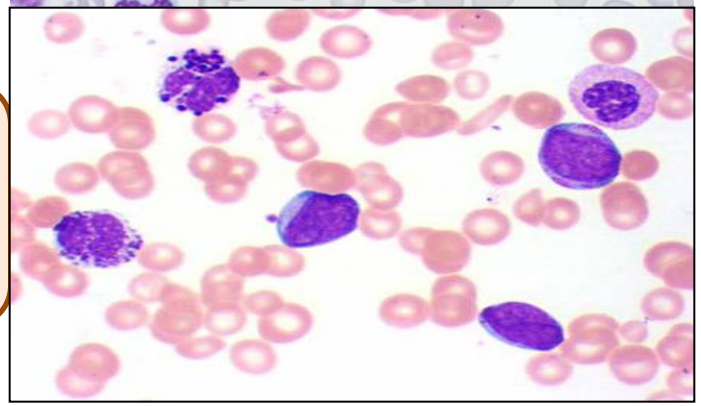
Chronic phase

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



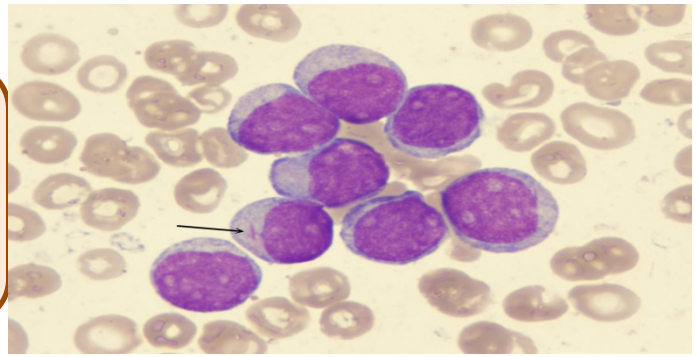
Accelerated phase

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

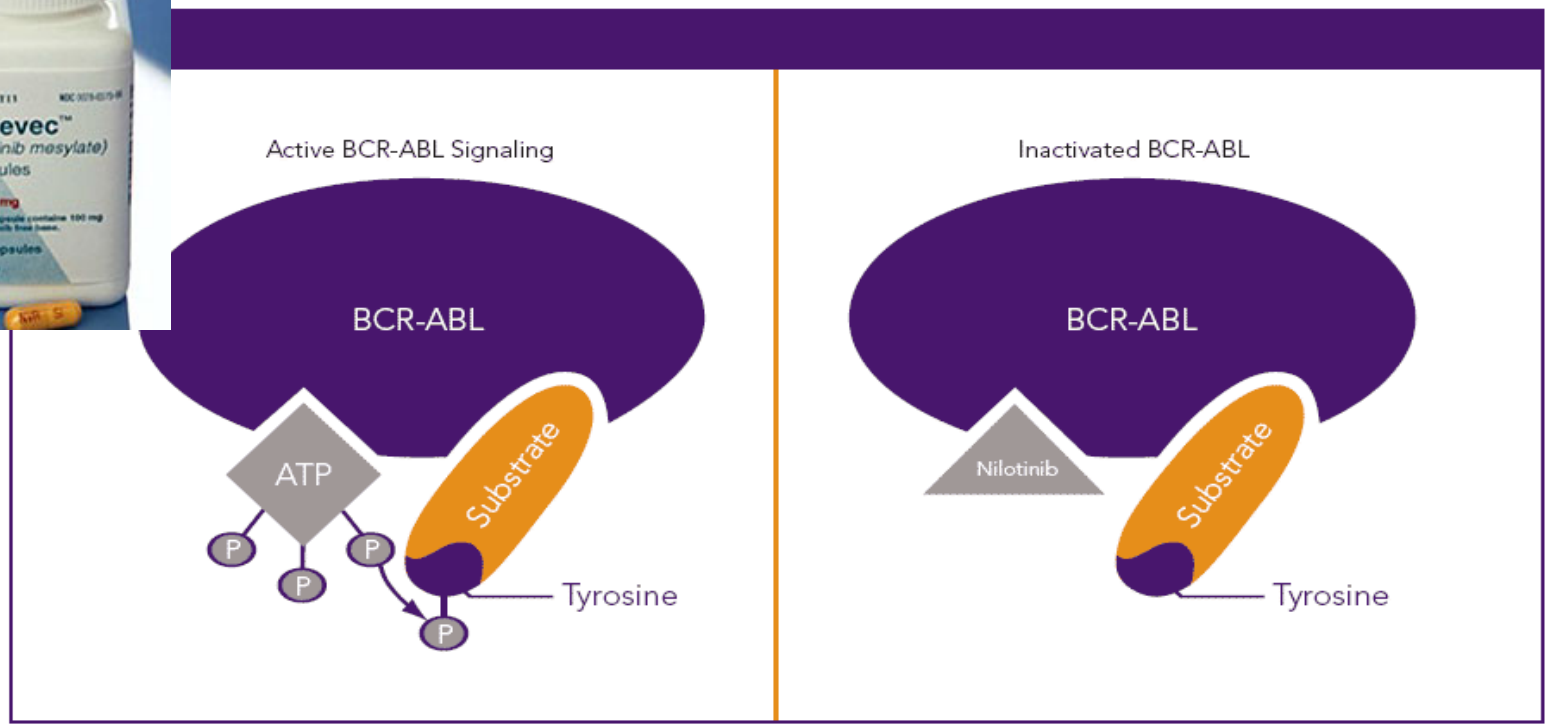


Blastic phase

- ≥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)

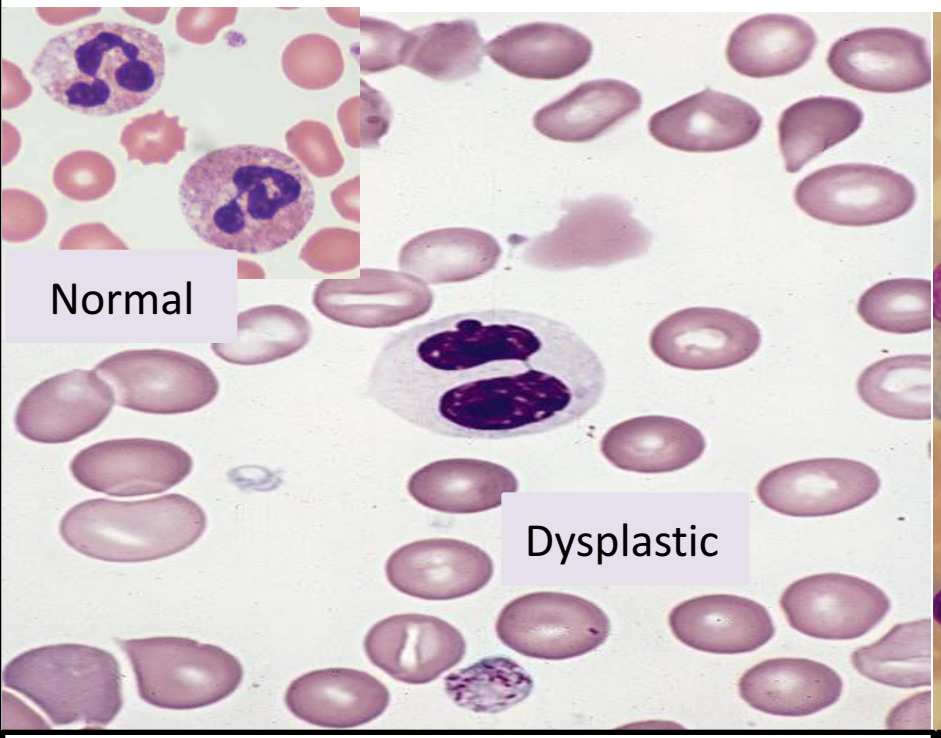
  2- Dysplasia (abnormal morphology)

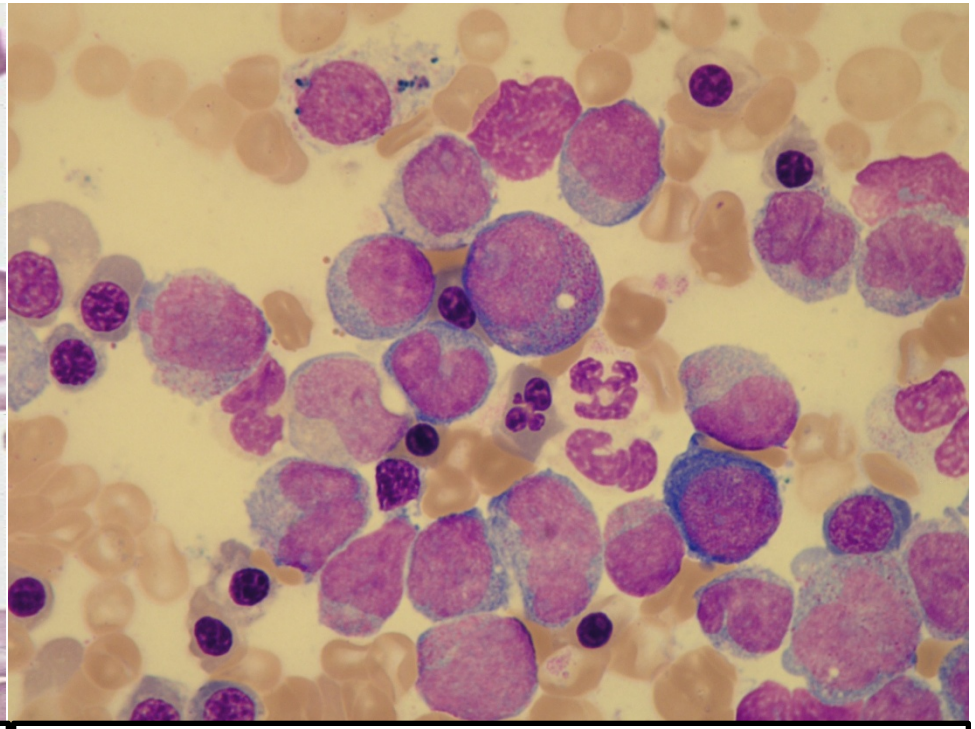
  3- Ineffective hematopoiesis (hypercellular marrow)

  4-Progression to AML (preleukaemic disease)

  5-Enhanced apoptosis

Myelodysplastic Syndromes MDS

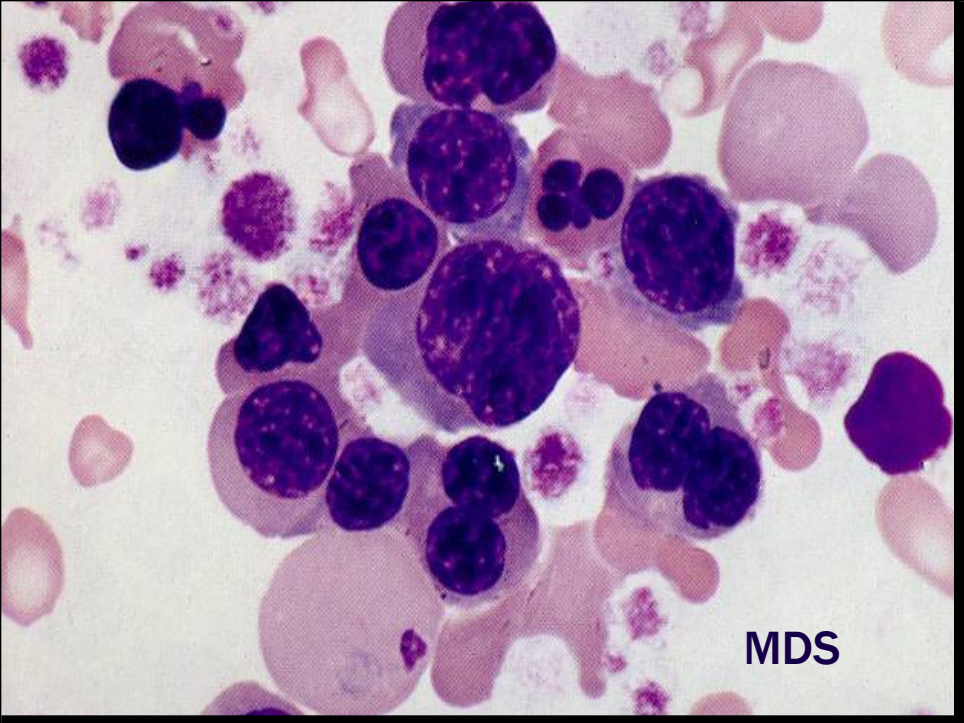


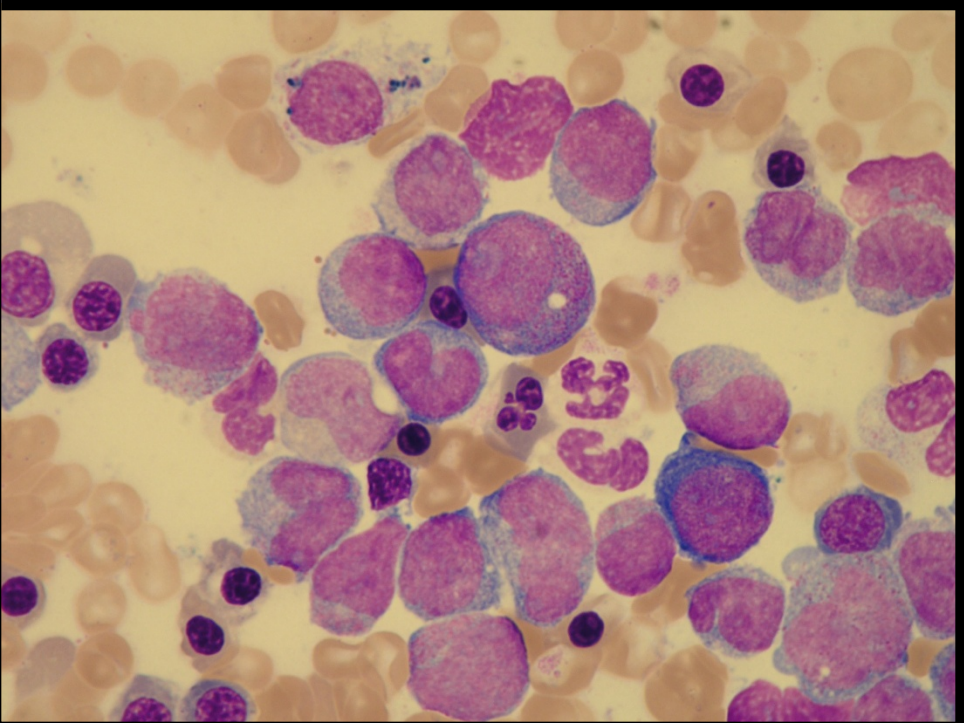
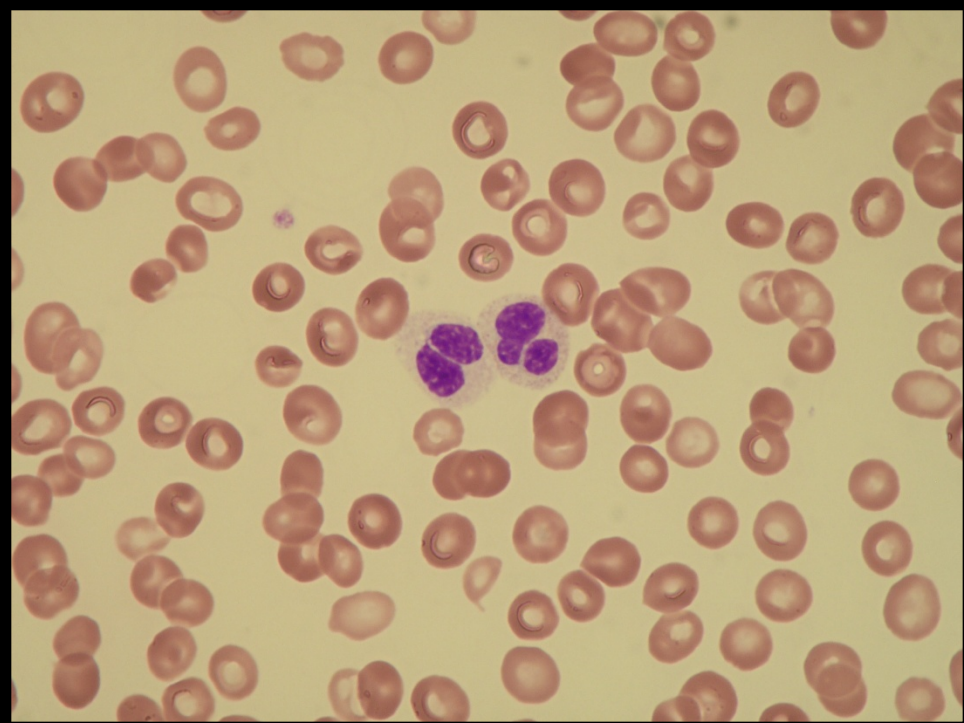


Blood: Pancytopenia with dysplasia

BM: Hypercellular with dysplasia

↑ Proliferation — ↑ Apoptosis = Ineffective Hematopoiesis


MDS

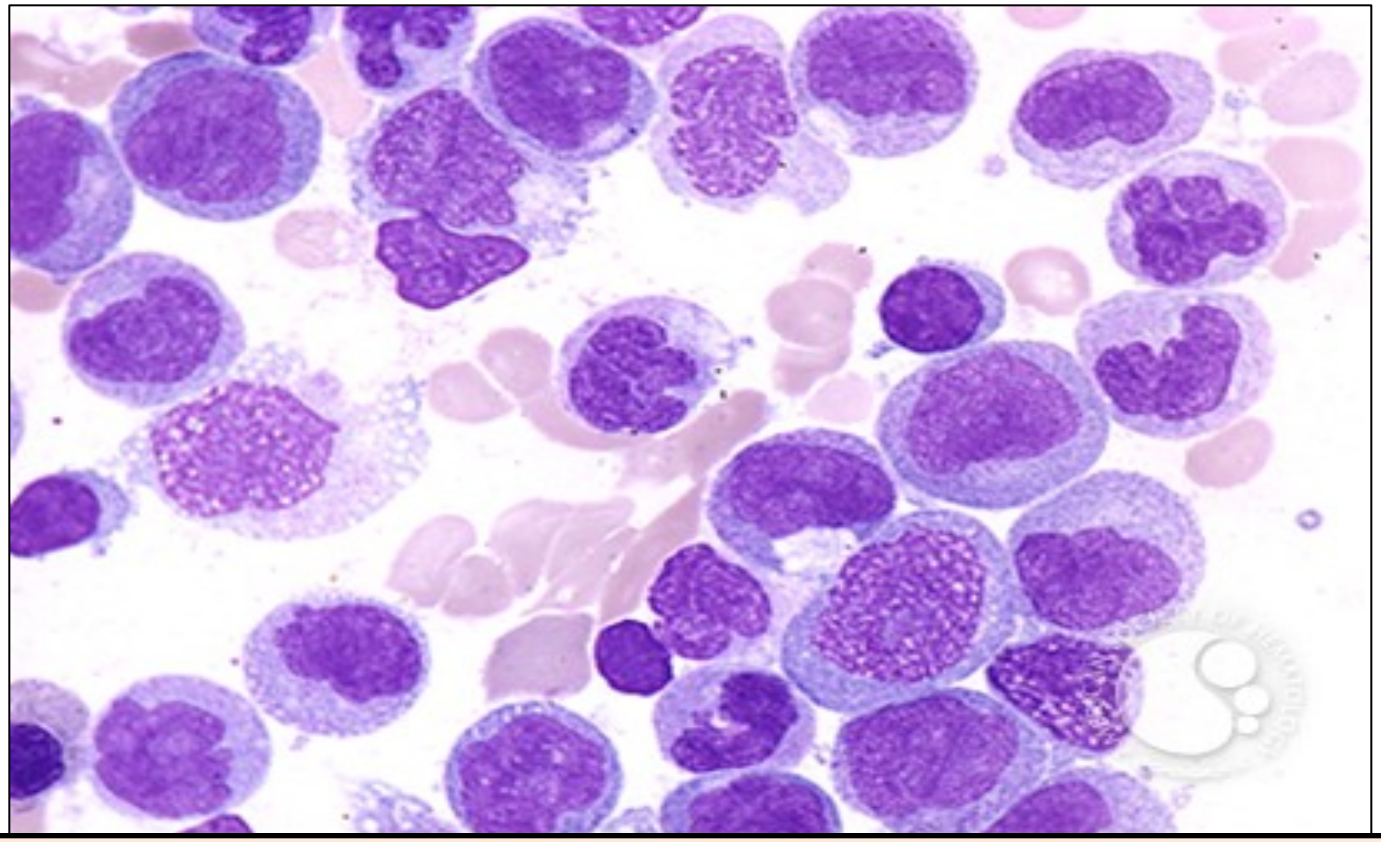
Myelodysplastic Syndromes MDS

- **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)

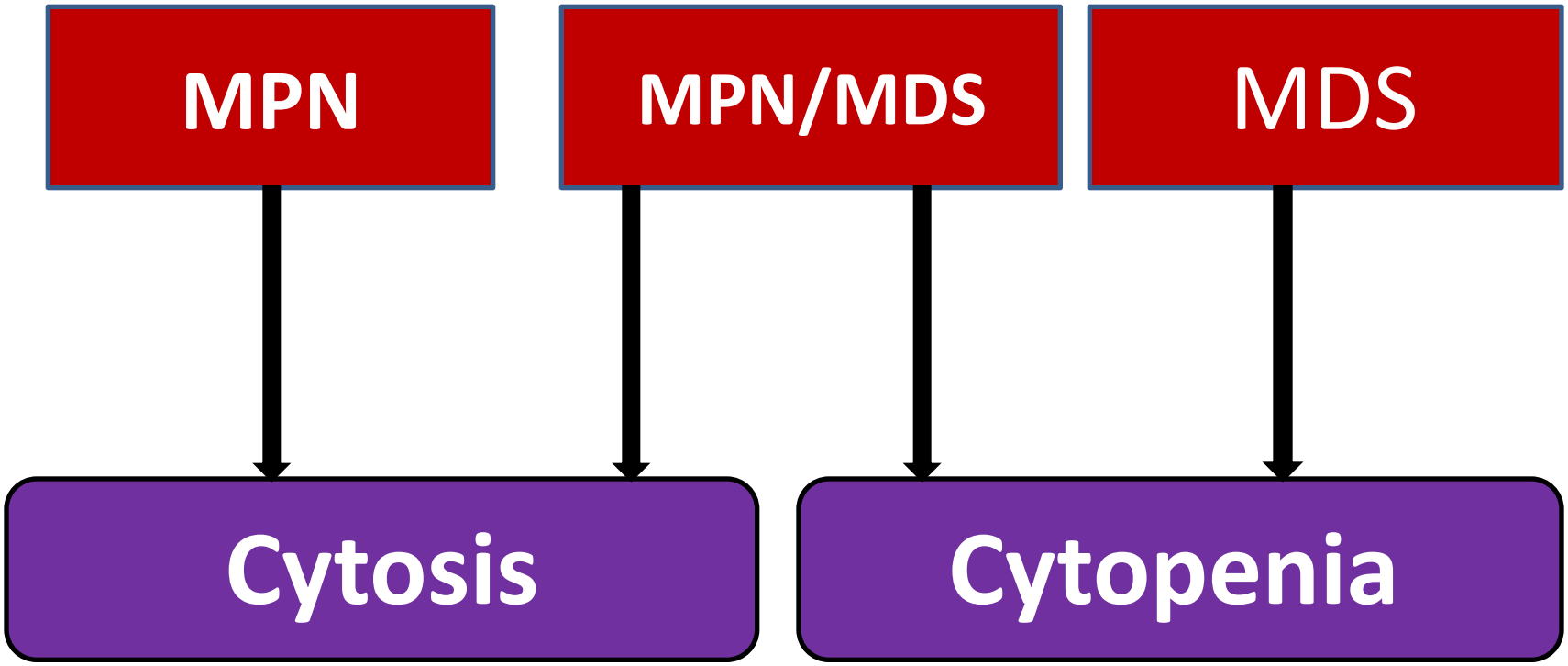
- Clonal Hematopoietic malignancy characterized by proliferation of both monocytes and neutrophils.
- MDS/MPN disease:
  - * Features of MDS (dysplasia& enhanced apoptosis)
  - *Features of MPN (marked proliferation)
- Philadelphia chromosome must be negative
- Blast must be less than 20%.

CMML



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

MPN vs. MDS vs. MPN/MDS



??