

Chronic Leukaemias

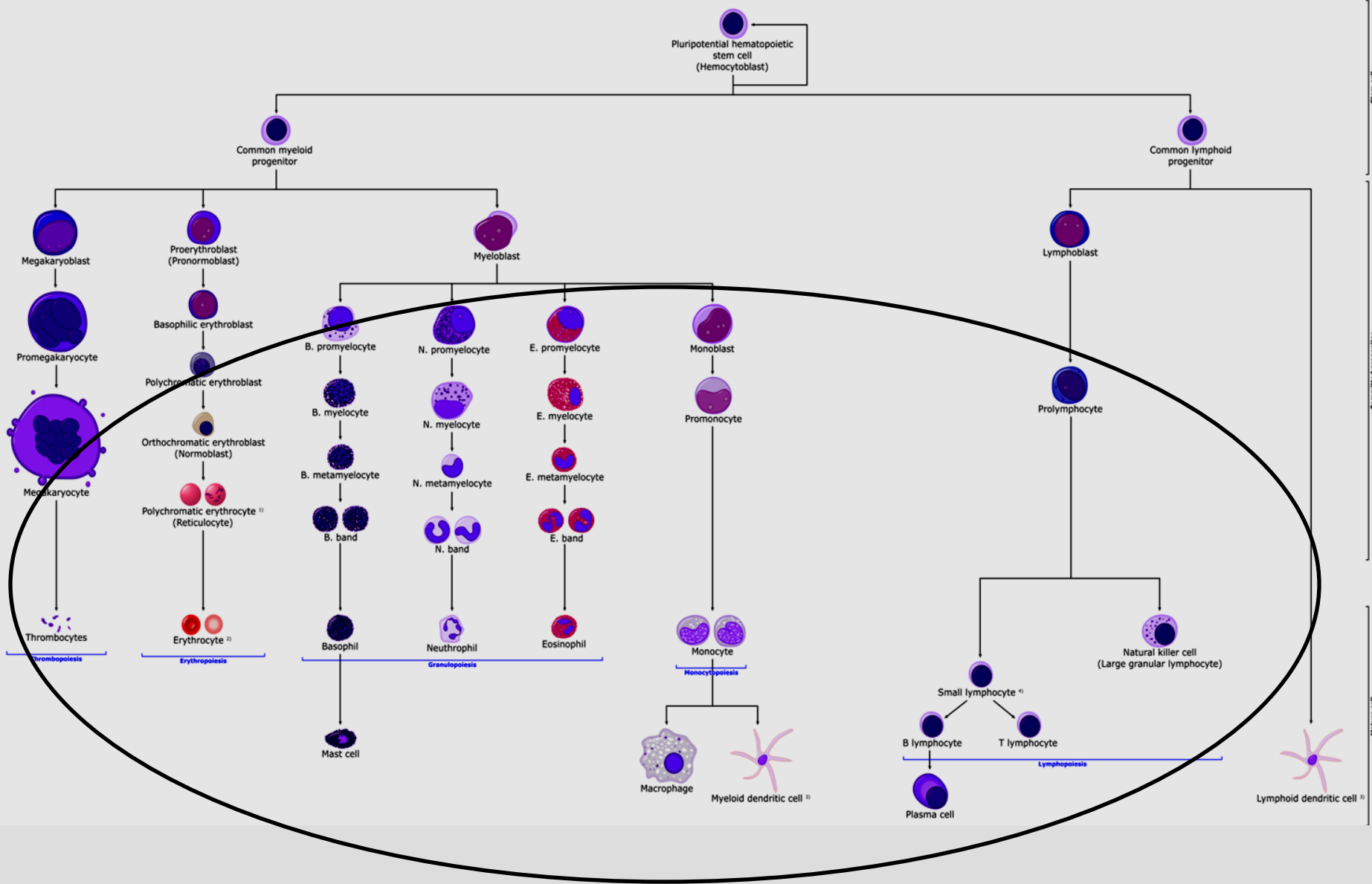
- **Heterogeneous group of hematopoietic neoplasms**
- **Uncontrolled proliferation and decreased apoptotic activity with variable degrees of differentiation**
- **Composed of relatively mature cells**
- **Indolent. (If untreated, the course is in months or years)**
- **Occurs mainly in adults**

Hematopoiesis in humans

Bone marrow

Blood

Tissue

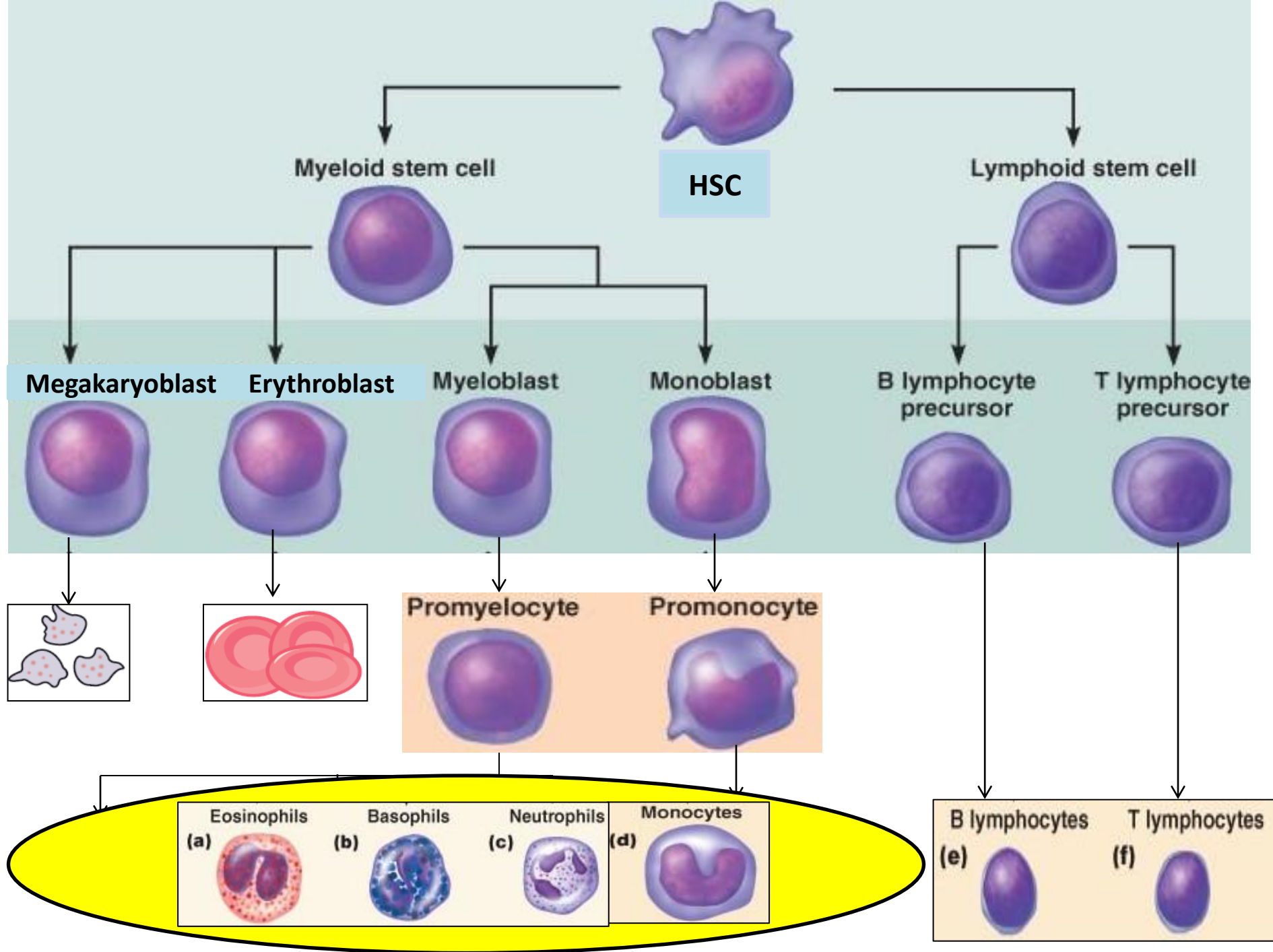


Chronic Leukaemia

Stem cell

Committed progenitor

Mature cell



Main Types of Leukemia

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

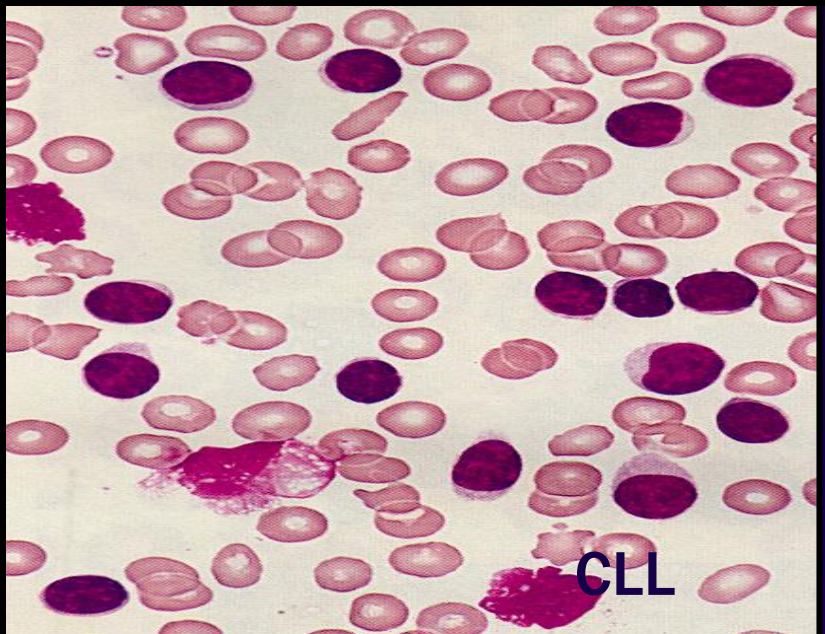
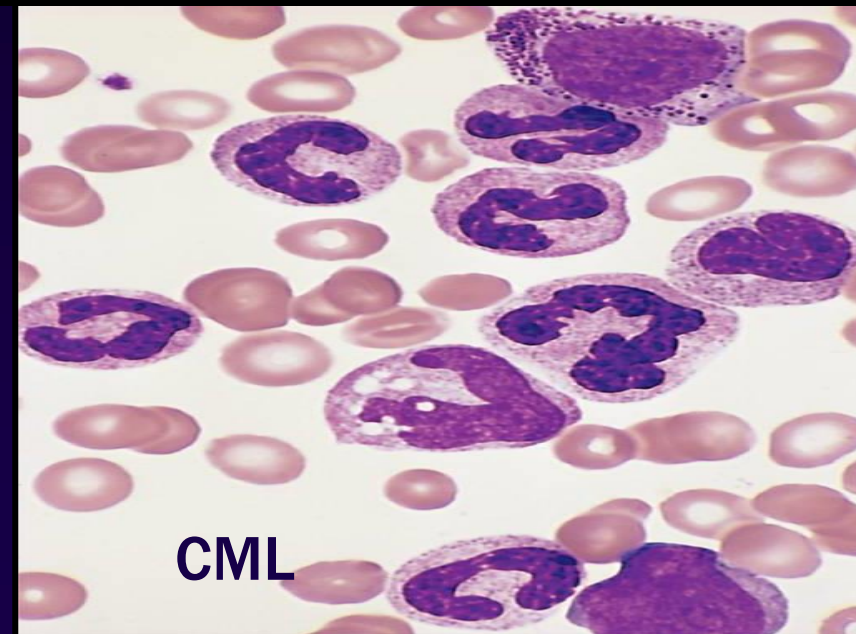
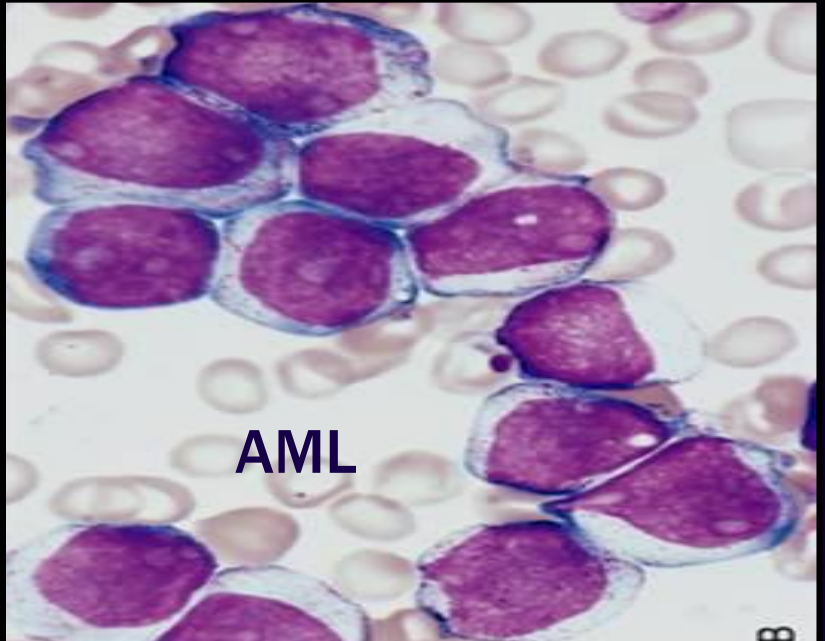
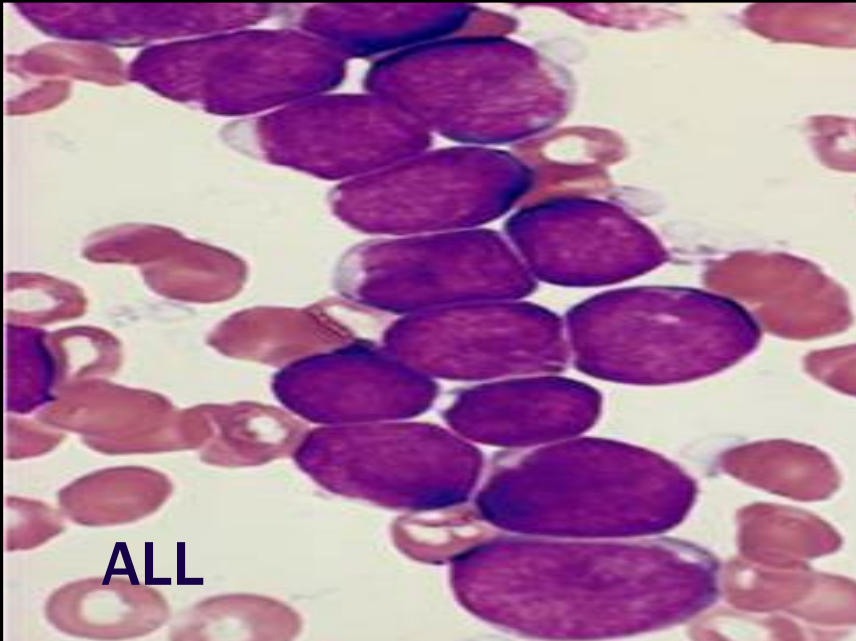


Table 1. Classification of Myeloid Neoplasms According to the 2008 World Health Organization Classification Scheme

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

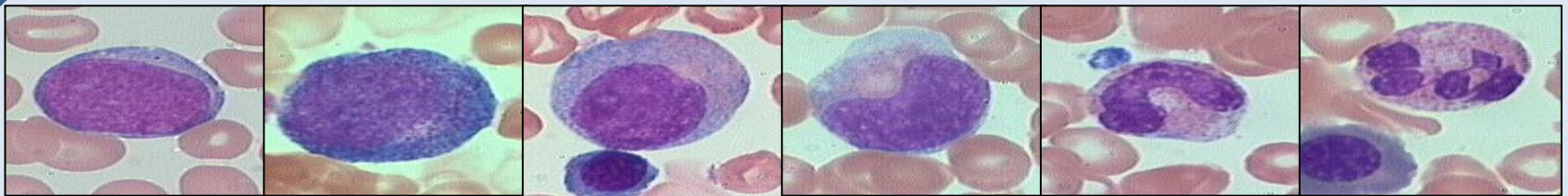
- **Malignant proliferation of myeloid cells (maturing cells) which are mainly granulocytes, in blood and bone marrow.**
- **Occur mainly in adults**
- **Slow onset and long course**

MPN features

- **Cytosis**
- **Organomegaly (mainly splenomegaly)**
- **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

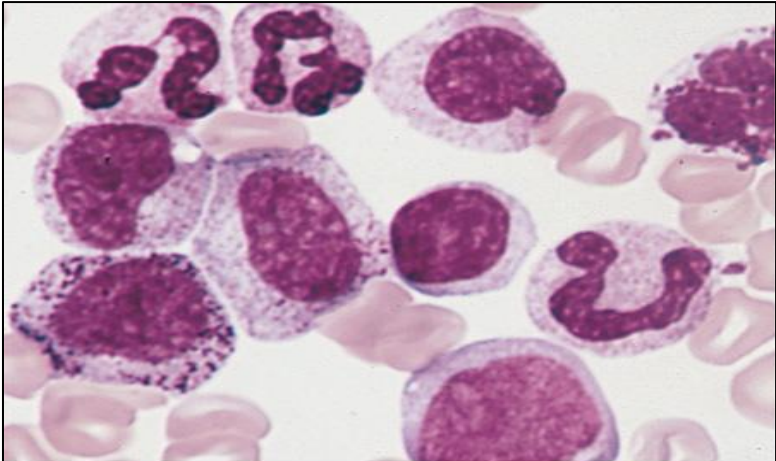
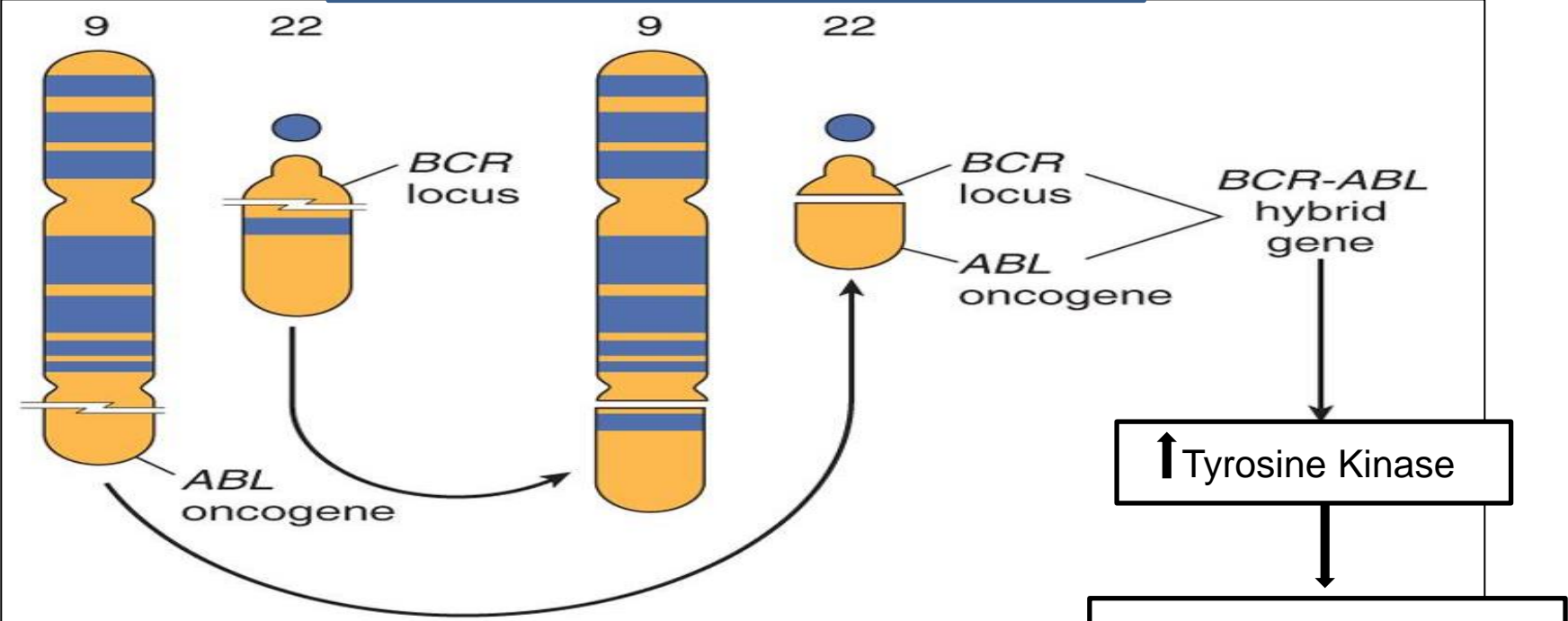
metamyelocyte

band

neutrophil

MATURATION

Pathogenesis of CML

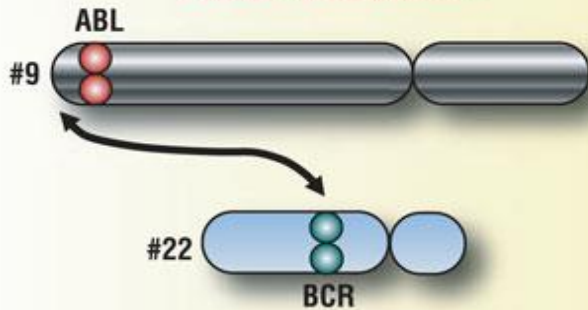


Source: Longo DL, Fauci AS, Kasper DL, Hauser SL, Jameson JL, Loscalzo J: *Harrison's Principles of Internal Medicine, 18th Edition*: www.accessmedicine.com
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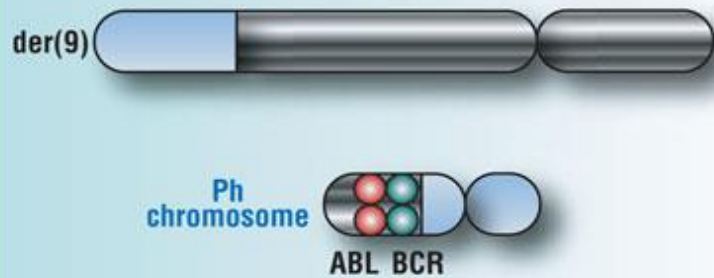
Pathogenesis of CML

Figure 1: The Philadelphia (Ph) Chromosome

Before translocation



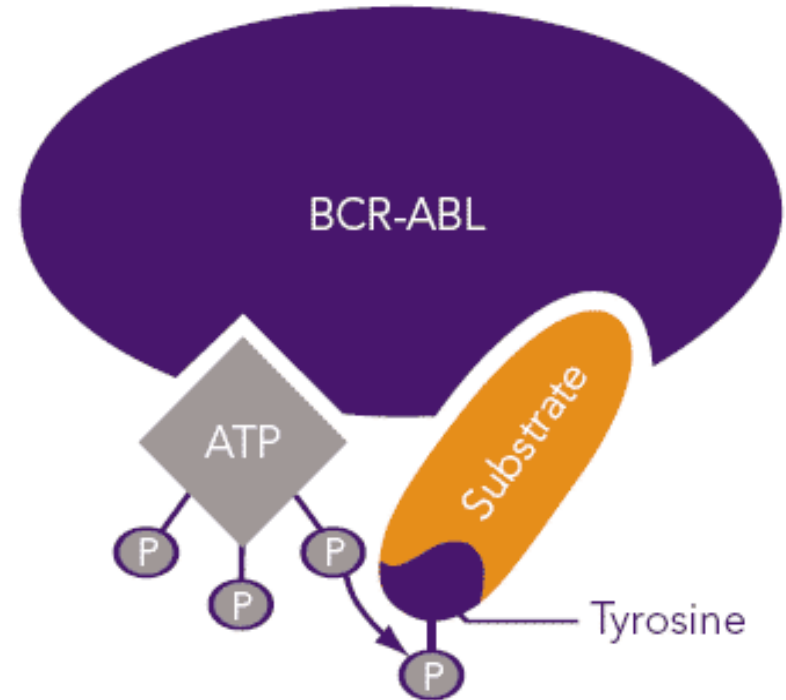
After translocation



p210 kD

BCR

ABL



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)**



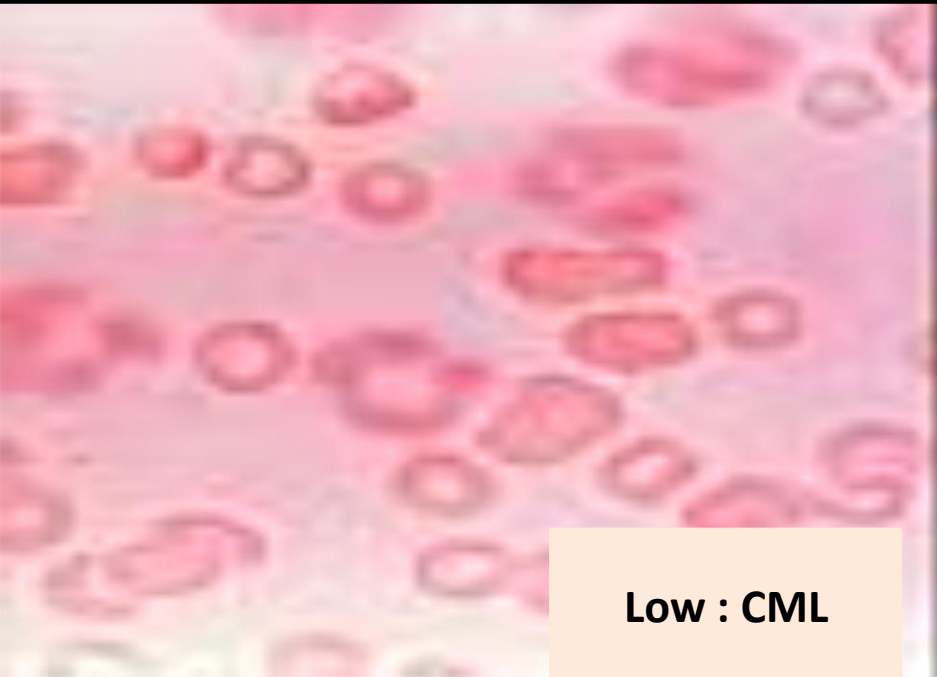
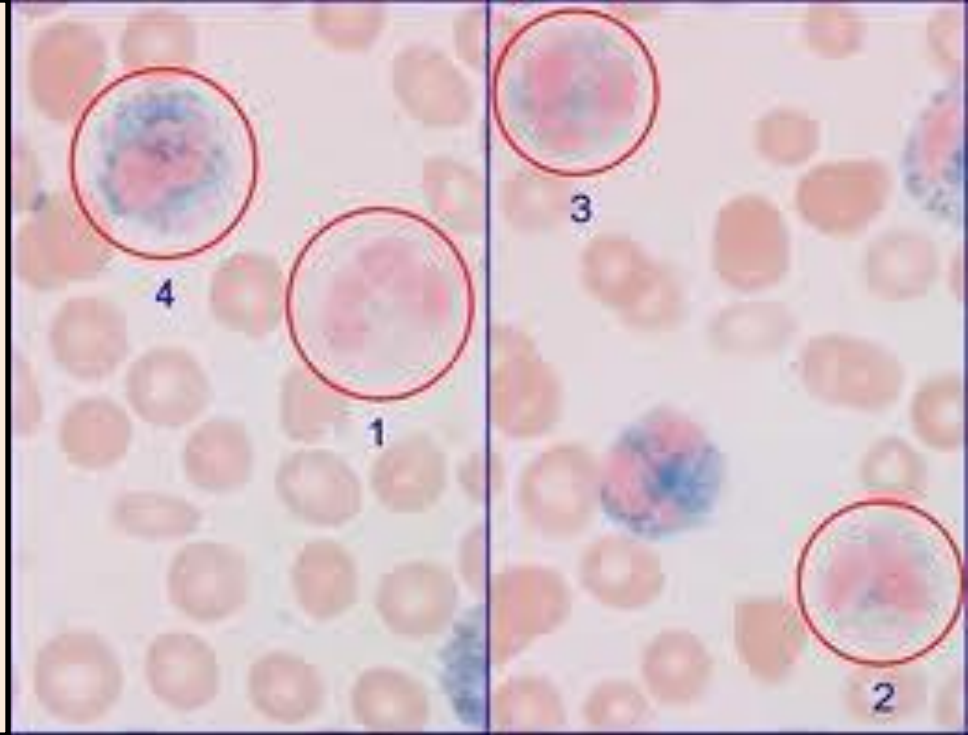
Main Differential Diagnosis

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

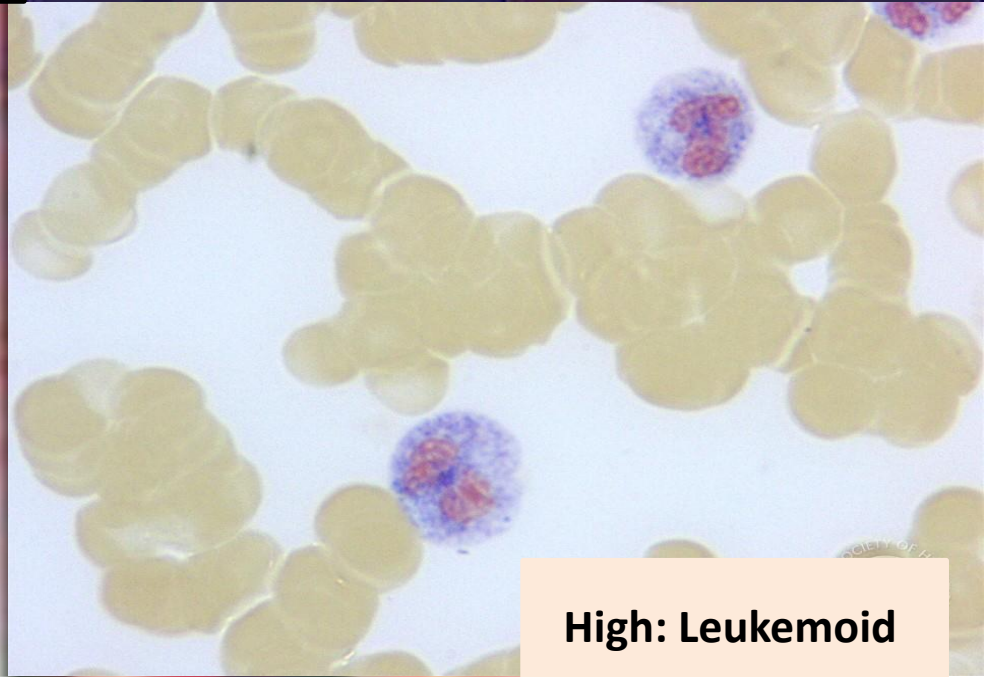
	CML	Leukaemoid
Age	Adult	Any age
WBC count	High	High but <100,000
Differential	Mainly myelocytes and segmented	Mainly Bands
Morphology	Hypogranular	Toxic
Splenomegaly	+	-/+
NAP score	Low	High
BCR/ABL	+ve	-ve
Onset	Chronic	Acute

Neutrophil Alkaline Phosphatase (NAP)score :

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



Low : CML

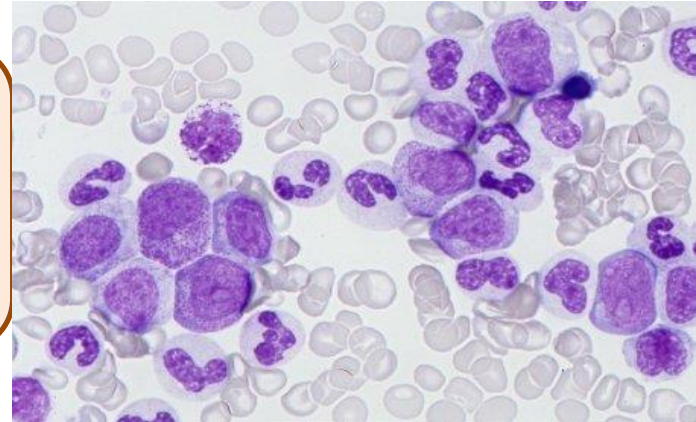


High: Leukemoid

CML Phases

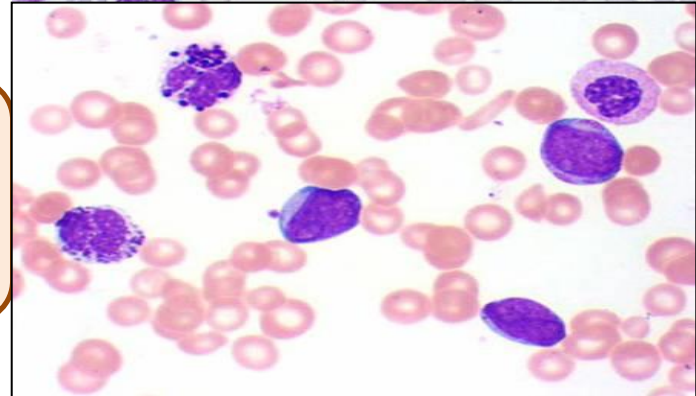
Chronic phase

- Leukocytosis ($12-1000 \times 10^9/L$)
- Mainly neutrophils & myelocytes
- Blasts $\leq 10\%$, Basophils $\leq 20\%$
- Stable course (years)



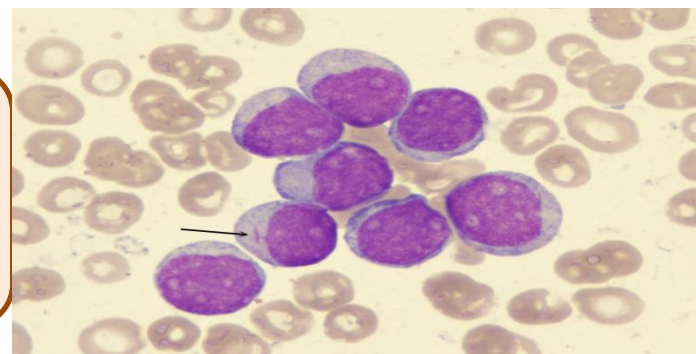
Accelerated phase

- Increasing counts
- 10-19% blasts (basophils $\geq 20\%$)
- Unstable course (months)

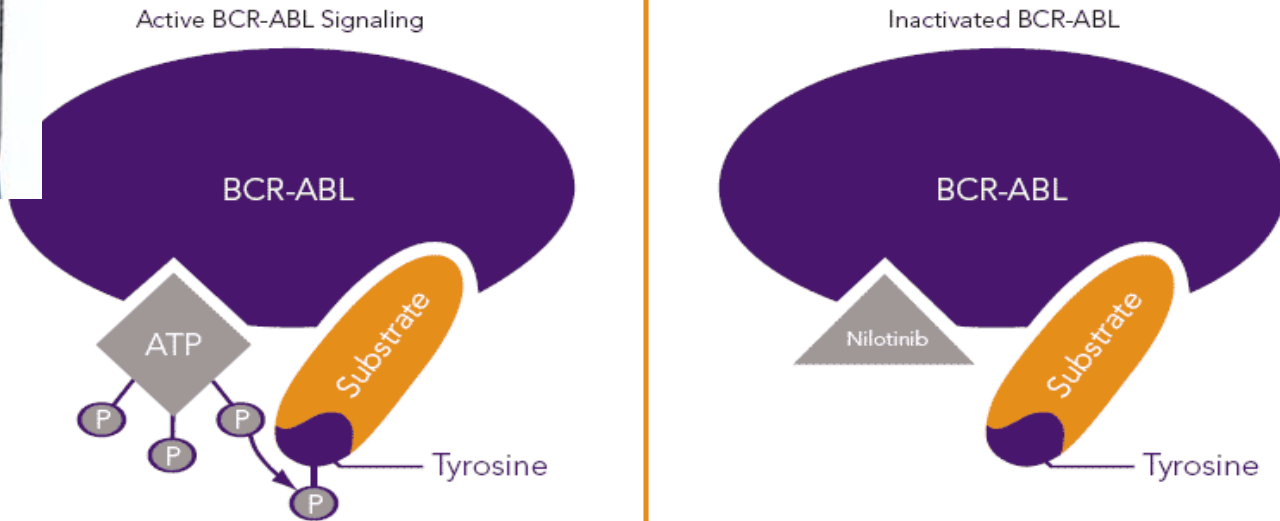


Blastic phase

- $\geq 20\%$ blasts = Acute Leukemia
- 80% AML & 20% ALL
- (course: Weeks)



CML Treatment

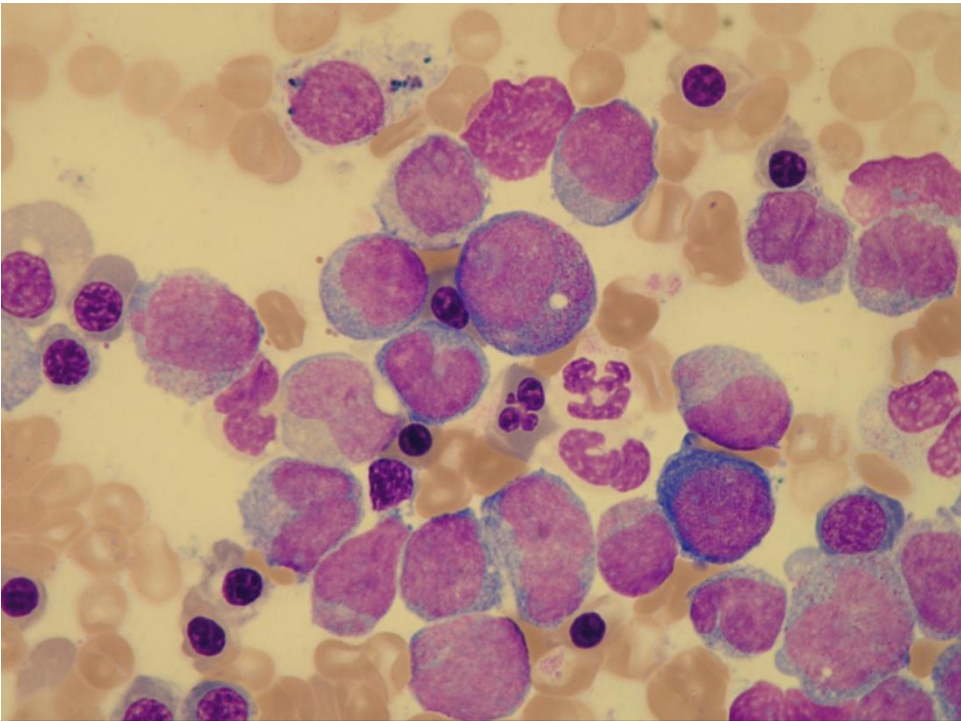
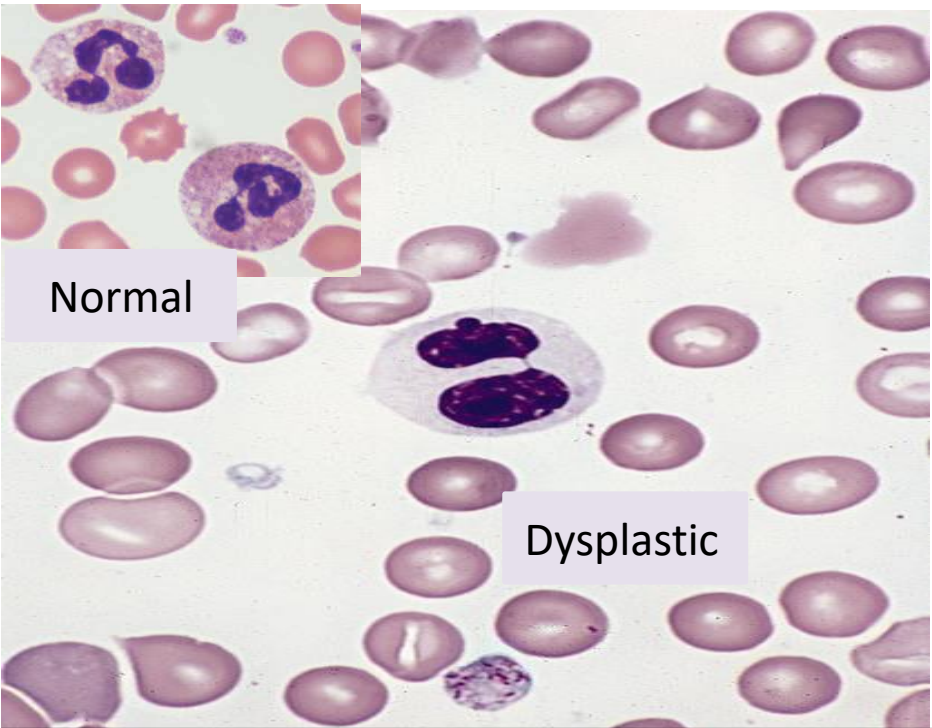


- Targeted therapy (tyrosine kinase inhibitors like Imatinib)
- Excellent response (5y overall survival $\geq 90\%$)
- If no response ; stem cell transplantation

Myelodysplastic Syndromes MDS

- **Group of myeloid neoplasms characterized by:**
 - 1-Peripheral cytopenia (Low HB \pm 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

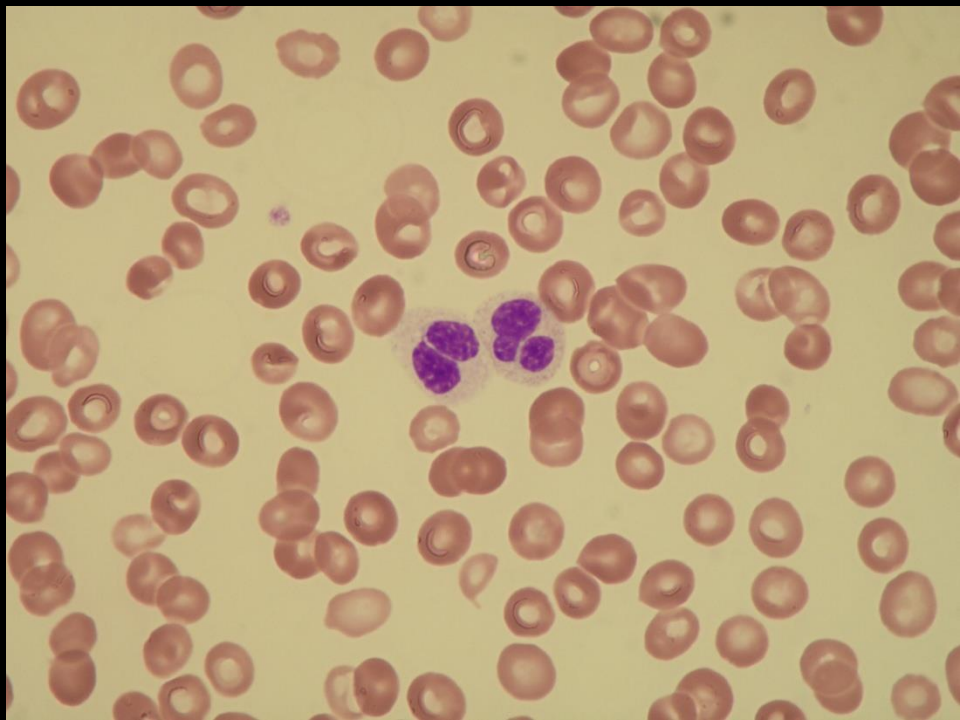
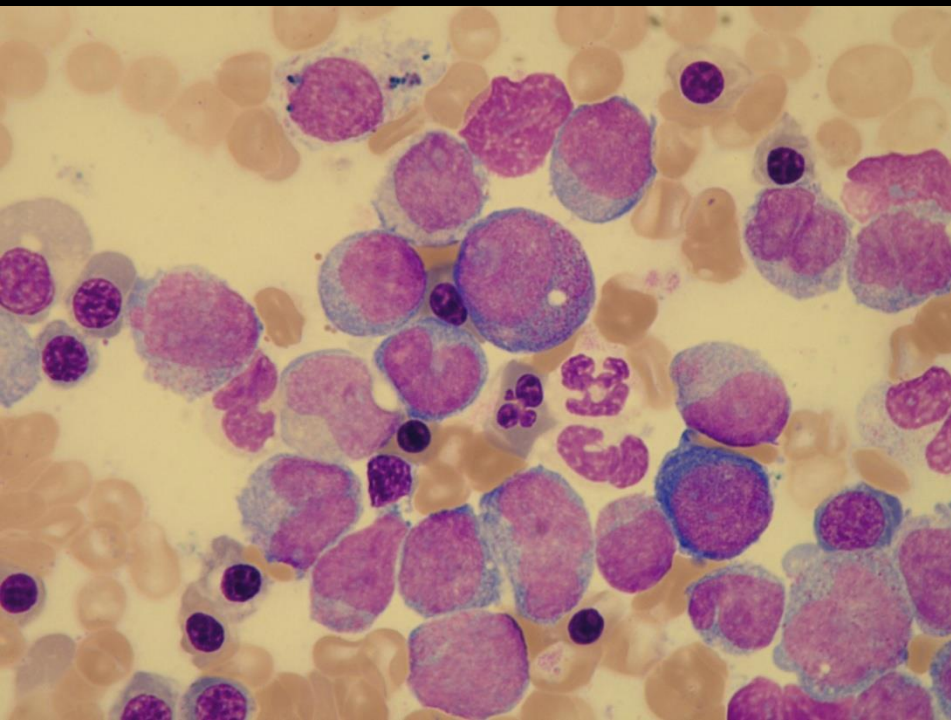
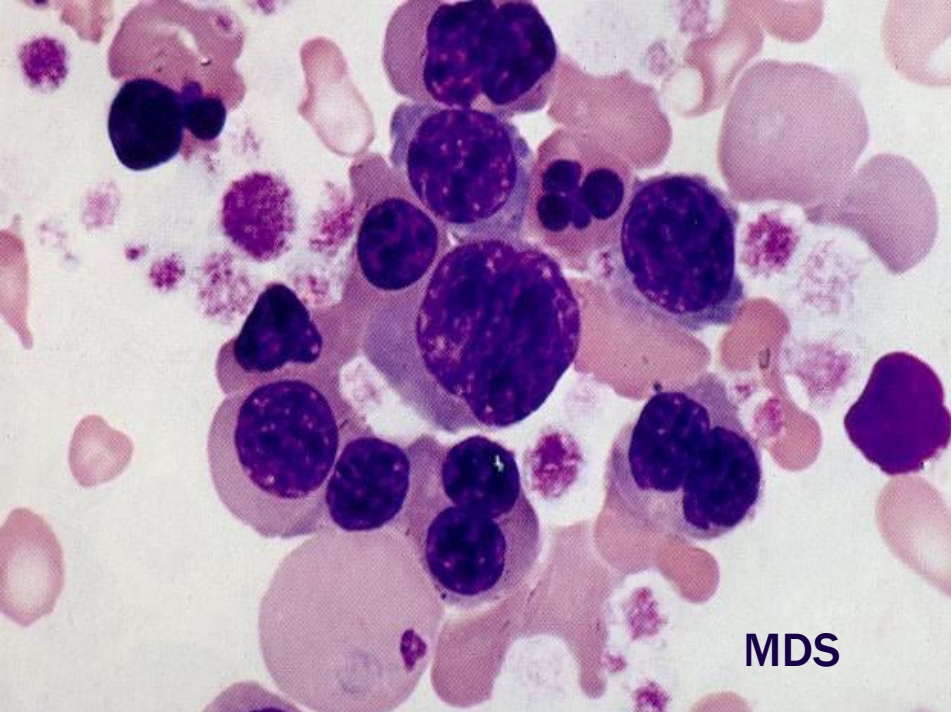
↑ Proliferation



↑ Apoptosis



Ineffective Hematopoiesis



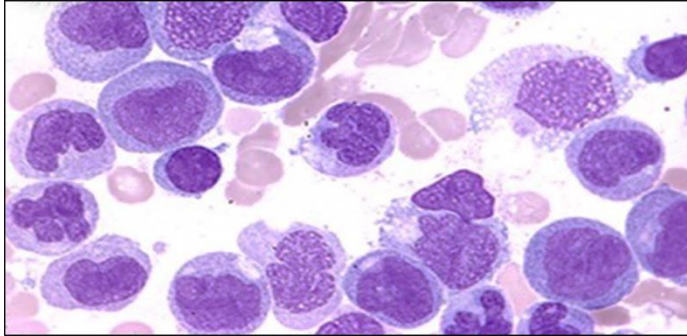
Myelodysplastic Syndromes MDS

- **Many subtypes according to:**
 - 1-Blast count**
 - 2-Degree of dysplasia**
 - 3-Genetics**
- **Variable genetic abnormalities mainly -5, -7**
- **Treatment : 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 \pm SCT

MPN vs. MDS vs. MPN/MDS

MPN

MPN/MDS

MDS

Cytosis

Cytopenia

Effective proliferation

Ineffective proliferation

