Chronic Leukemia

Objectives:

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

Dr's notes
Important
Extra notes
** Only in girls slide
** Only in boys slide

Revised & Approved

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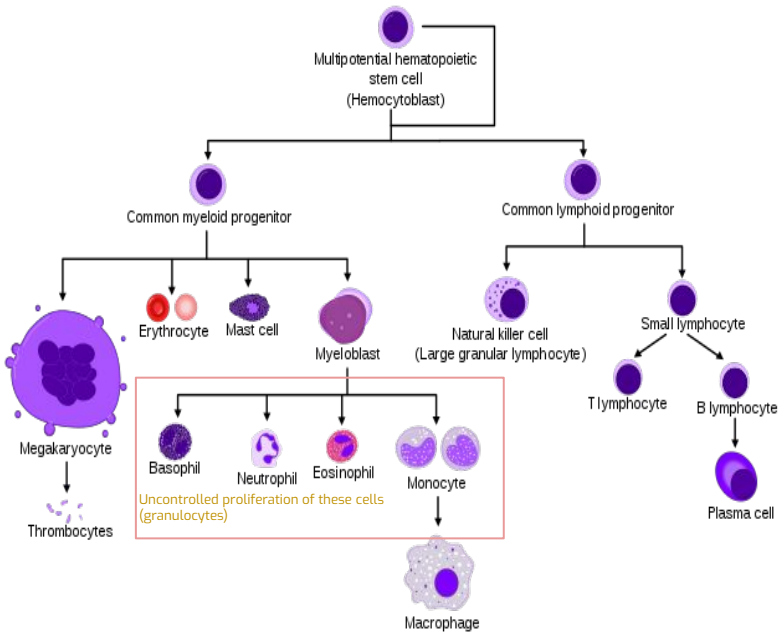
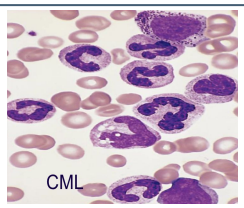
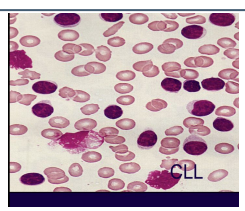
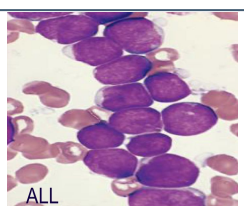
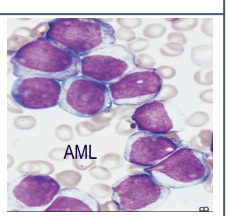
Editing file

Chronic Leukaemias

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



Main types of leukemia

	Chronic	Acute
Lymphoid	**LPN (CLL)**	**ALL**
Myeloid	**MPN/MDS (CML)**	**AML**
Mixed	There's no chronic mixed because it is purely stem cell disease	**Acute biphenotypic**
none	**————————**	**Acute**
	  • cytes (mature) (lymphocytes: right) • (Neutrophils :left) • Months/ years	  • Blasts • Short period of time/ Weeks

Chronic Leukaemias

Well explained by female doctor but she said just read it | Males doctor : what I want you here to know that BCR-ABL must be positive to diagnose the patient with CML

classification of myeloid neoplasms according to 2008 world health organization classification scheme

1.myeloproliferative neoplasm (MPN)
1.1 chronic myelogenous leukemia, BCR-ABL1-positive (CML)
1.2 polycythemia Vera (PV)
1.3 Essential thrombocythemia (ET)
1.4 primary myelofibrosis
1.5 chronic neutrophilic Leukaemia (CNL)
1.6 chronic eosinophilic Leukaemia, not otherwise specific (CEL-NOS)
1.7 Mast cell disease (MCD)
1.8 MPN, unclassifiable

- 8 Types
- each peripheral blood cells has its own disease

2.myeloid and lymphoid neoplasms with eosinophilia and abnormalities of PDGFRA, and FGFR1
3.MDS/MPN mixed type
3.1 chronic myelomonocytic leukemia (CMML)
3.2 juvenile myelomonocytic leukemia (JMML) children
3.3 Atypical chronic myeloid leukemia, BCR-ABL-negative (aCML) same as CML but negative BCR-ABL
3.4 MDS/MPN, unclassifiable
4. Myelodysplastic syndrome (MDS)
5.Acute myeloid Leukaemia (AML)

Myeloproliferative neoplasm

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

MPN features

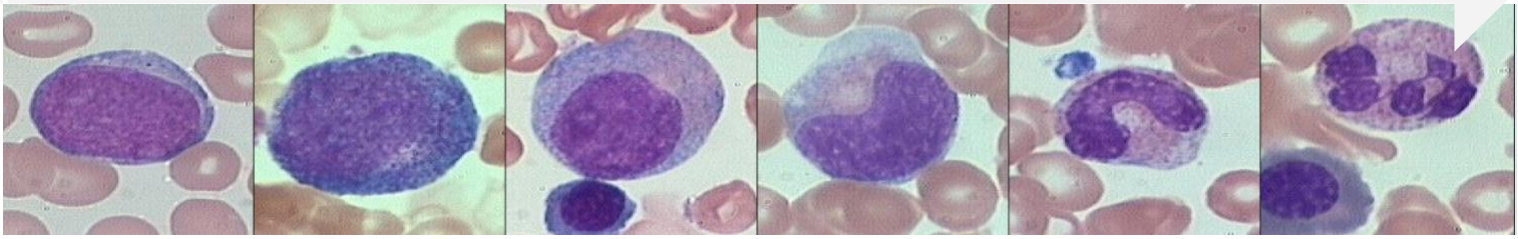
- Cytosis increase in blood cells (unlike pancytosis which was decrease in blood cells)
- Organomegaly (mainly splenomegaly)
- High uric acid Because of destruction of cells
- Hypercellular bone marrow
- Progression to acute leukaemia (mainly AML)

Chronic Myeloid Leukemia (CML)

- Stem cell MPN myeloproliferative neoplasms
- 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) .

I can diagnose CML by the presence of BCR-ABL1

Maturation



Myeloblast | **Promyelocyte** | **Myelocyte** | **Metamyelocyte** | **Band** | **Neutrophil**

Found in peripheral
Pre-neutrophils

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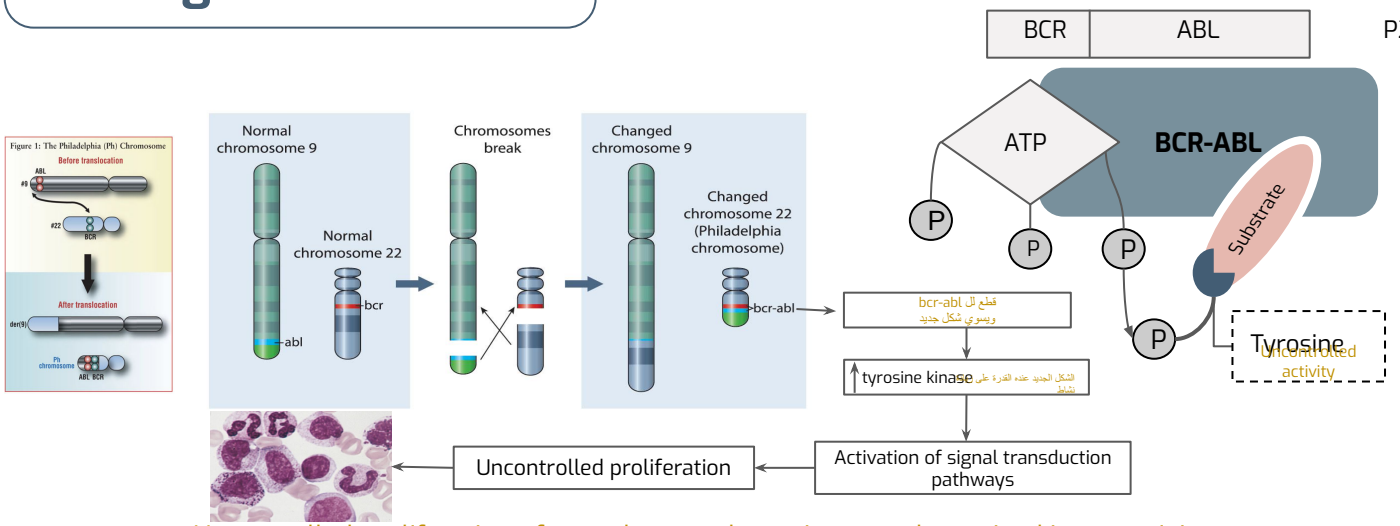
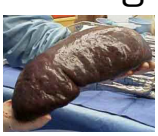
Pathogenesis of CML



Uncontrolled proliferation of granulocytes due to increased tyrosine kinase activity

Clinical features

- Asymptomatic presentation(20-40%):
- Routine CBC : marked **leukocytosis**
- Common symptoms : Fatigue ,weight loss or night sweating
- Abdominal discomfort due to splenomegaly
- **Splenomegaly (Massive)** →  تقريبًا 3Kg

Chronic Myeloid Leukemia (CML)

Main differential diagnosis ★

1 - Chronic myelomonocytic leukemia (monocytosis , **BCR-ABL –ve**).

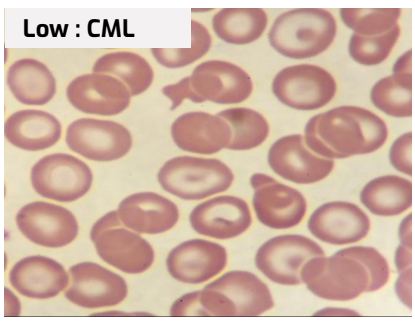
CML : + to ABL- BCR ll CMML : - to ABL-BCR

2 - Leukemoid reaction: Leukocytosis due to physiological response to stress or infection.

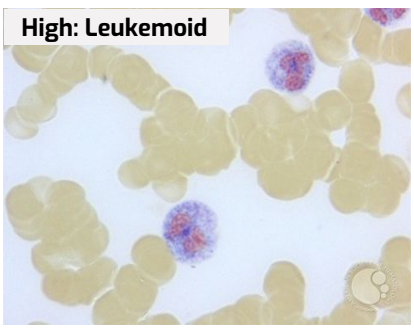
	CML	Leukemoid
Age	Adult	Any age
WBC count	High	High but <100,000
Differential	Mainly myelocytes and segmented Males doctor add. (Neutrophils)	Mainly Bands Pre-neutrophil
Morphology	Hypogranular	Toxic
Splenomegaly	+	-/+
NAP score	Low	High
BCR/ABL imp	+ve	-ve
Onset	Chronic	Acute

Neutrophil Alkaline Phosphatase (NAP) score :

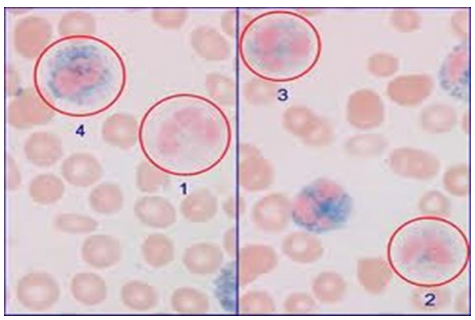
Cytochemical stain that estimate the amount of alkaline phosphatase enzyme in neutrophils .



Low = you are dealing with malignancy



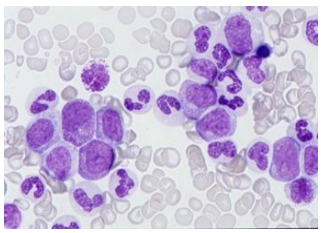
High = you are dealing with leukemoid reaction



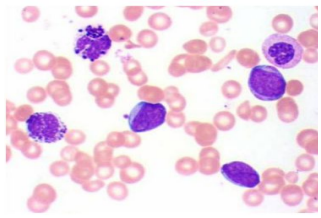
Chronic Myeloid Leukemia (CML)

CML phases

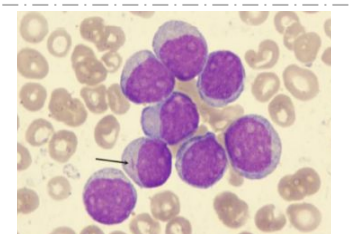
Chronic phase:
- Leukocytosis (12-1000×10^9/L)
- Mainly neutrophils & myelocytes
- Blasts ≤ 10% ,Basophils ≤ 20%
- Stable course (years)



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 or Anti-BCR-ABL1) like Imatinib
- Excellent response (5y overall survival≥ 90%)
- If no response ; stem cell transplantation best treatment

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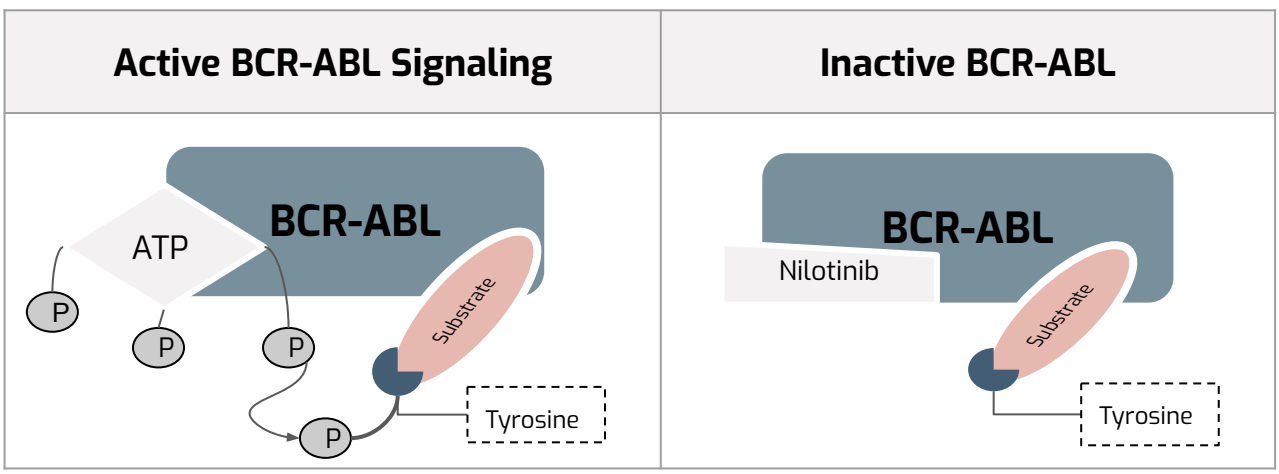
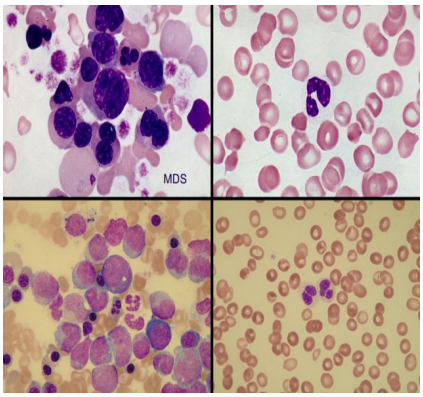


Myelodysplastic Syndromes MDS

MDS characterized by :

- **Peripheral cytopenia** (**Low HB ± Low WBC & Low PLT**) not cytosis
- Dysplasia (abnormal morphology)
- Ineffective hematopoiesis (**hypercellular marrow**)
- Progression to AML (preleukemic disease 1)
- Enhanced apoptosis
- Variable genetic abnormalities mainly -5, -7
- Treatment : supportive +/- chemotherapy

  Elderly patients (50-70)



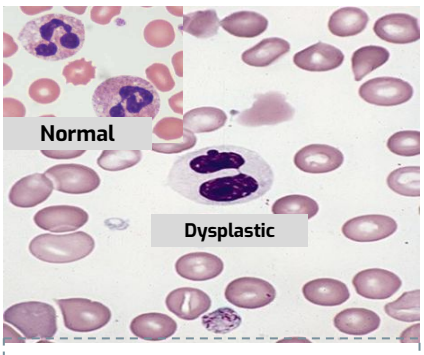
Many subtypes according to:

1 - Blast count (MDS related to AML)

2 - Degree of dysplasia

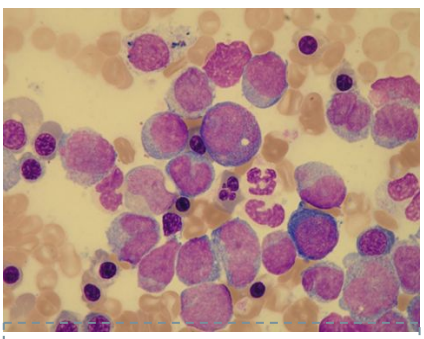
3 - Genetics

↑ Proliferation + ↑ Apoptosis in the BM
= Ineffective Hematopoiesis
Very little cells(abnormal) enter the circulation



Blood: peripheral
Pancytopenia with dysplasia

Normal neutrophil: 3-4 lobes with granulation
MDS : hypogranular cytoplasm(agranular), bi-lob, Less cell count



BM:
Hypercellular with dysplasia

1- MDS are considered preleukemias, so patients are at increased risk for developing acute leukemia.

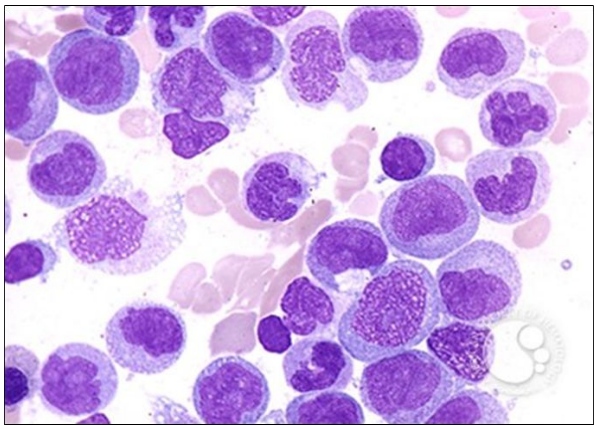
Chronic Myelomonocytic Leukemia (CMML)

Myelo: granulocytes = neutrophils
Monocytic :monocytes (only in CMML not in CML)

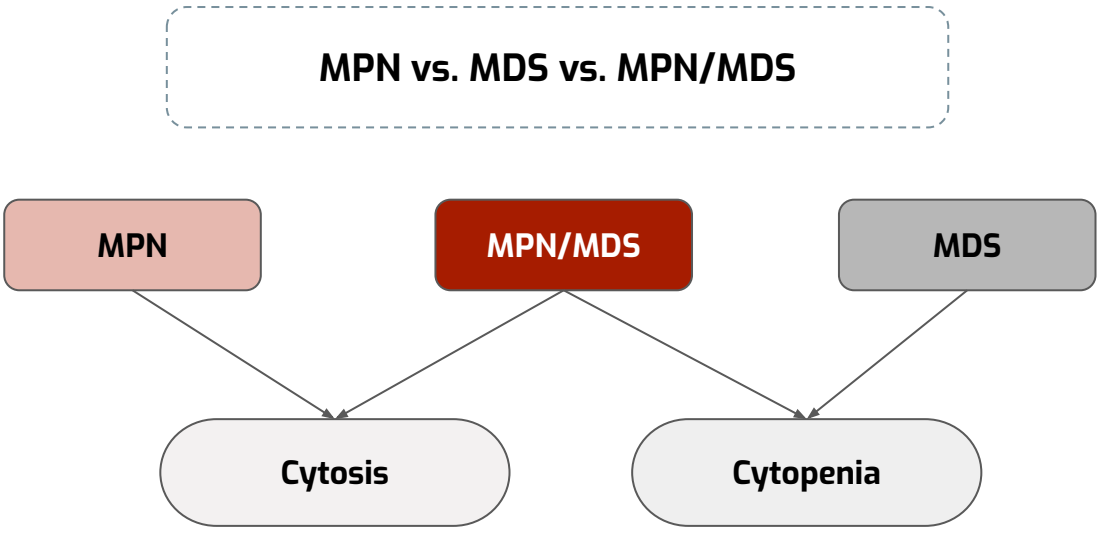
- Clonal Hematopoietic malignancy characterized by

★ **Proliferation of <u>BOTH</u> monocytes and neutrophils (Granulocytes)**

- **MDS/MPN disease:** mixed features
  - Features of MDS (dysplasia & enhanced apoptosis).
  - Features of MPN (marked proliferation).
- **Philadelphia** (BCR-ARB) **chromosome must be negative**
- **Blast must be less than 20%** chronic , BUT In acute more than 20%
- Aggressive course (survival rate around 2.5 y)
- Treatment : Chemotherapy ± SCT stem cell transmission

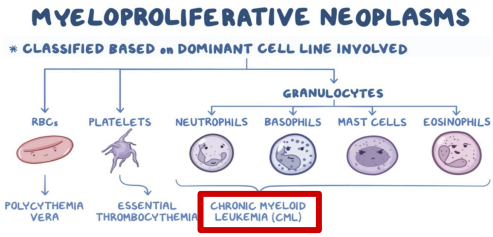


Bone marrow: Increasing in **both** monocytes and granulocytes



Summary

Chronic leukemias are heterogeneous group of hematopoietic neoplasms characterized by uncontrolled proliferation and decreased apoptotic activity with variable degrees of differentiation. Composed of relatively **mature cells** (cytes).



Chronic Myeloid Leukemia (CML)
+ve BCR-APL1

Characteristics	• Consistently associated with **BCR-ABL1** fusion gene located in the **Philadelphia (Ph) chromosome** which results from **t(9;22).** • Predominant proliferation of **granulocytic cells**. • It is a stem cell MPN. Myeloproliferative neoplasm features: Cytosis, hypercellular bone marrow, splenomegaly
Pathogenesis	**BCR-ABL1** fusion gene→ inc. tyrosine kinase activity → uncontrolled proliferation of granulocytes
Clinical Features	• Marked leukocytosis • Massive splenomegaly • Abdominal discomfort • Weight loss • Night sweats • Fatigue
Phases of CML	1. Chronic phase: blasts ≤ 10%, present with **leukocytosis, neutrophil, myelocytes** 2. Accelerated phase: 10-19% blasts 3. Blastic phase: ≥ 20% blasts → Acute Leukemia
Main differential diagnosis	• Chronic **myelomonocytic** leukemia (**monocytosis** , **BCR-ABL –ve**). • Leukemoid reaction: Leukocytosis due to physiological response to stress or infection (BCR-ABL –ve). ○ Under microscope: mainly myeolcytes, segmented & neutrophils
Treatment	Tyrosine kinase inhibitors (anti-BCR-ALB1)

Myelodysplastic Syndromes (MDS)

Characteristics	• **Peripheral cytopenia** • **Dysplasia** • Ineffective hematopoiesis (hypercellular marrow) • Enhanced apoptosis ★ Has many subtypes according to: 1. **Blast count** 2. **Degree of dysplasia** 3. **Genetics**

Chronic Myelomonocytic Leukemia (CMML)
-ve BCR-ABL1; philadelphia chromosome negative.

- Clonal Hematopoietic malignancy characterized by **Proliferation of BOTH monocytes and neutrophils**
- Characterized by mixed features of **MDS/MPN disease**:
  - Features of **MDS** (dysplasia & enhanced apoptosis)
  - Features of **MPN** (marked proliferation).
- Blasts must be **less than 20%**

Myelo: granulocytes=neutrophils
Monocytic: monocytes (only in CMML not in CML)

DR Mansoor: CML is characterized by proliferation of **granulocytes** and is consistently associated with **BCR-ABL1** fusion gene located in the Philadelphia (Ph) chromosome which results from **t(9;22). However, this Philadelphia chromosome is not specific to CML.** BCR-ABL1 with t(9,22) is associated with **BOTH** ALL and CML. We differentiate between them based on the cells seen, lymphoblasts or granulocytes?

Quiz

Q1) Which of the following is associated with the BCR-ABL1 fusion gene?							
A	AML	B	CML	C	ALL	D	CMML
Q2) Neutrophil Alkaline Phosphatase (NAP)score Is high in?							
A	CML	B	CMML	C	Leukemoid reaction	D	MDS
Q3) Clonal Hematopoietic malignancy characterized by proliferation of **both** monocytes and neutrophils ; is known as?							
A	CMML	B	MDS	C	AML	D	CML
Q4)A 55 year old patient came to the clinic for a regular check up. He does not of complain any symptoms. His results are as follows: High WBC count, Mainly bands, High NAP score. What is the most likely diagnoses:							
A	CML	B	CMML	C	AML	D	infection
Q5) Which one of the following genes Must be positive in CML?							
A	APC	B	BCR-ABL	C	REKA-B	D	P53
Q6) The most important characteristic for CMML							
A	Basophil proliferation	B	Monocyte proliferation	C	B lymphocyte proliferation	D	Eosinophil proliferation

Q1	Q2	Q3	Q4	Q5	Q6
B	C	A	D	B	B

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