Hematology

8/11

Chronic Leukemia

432 ***Hematology*** *Team*

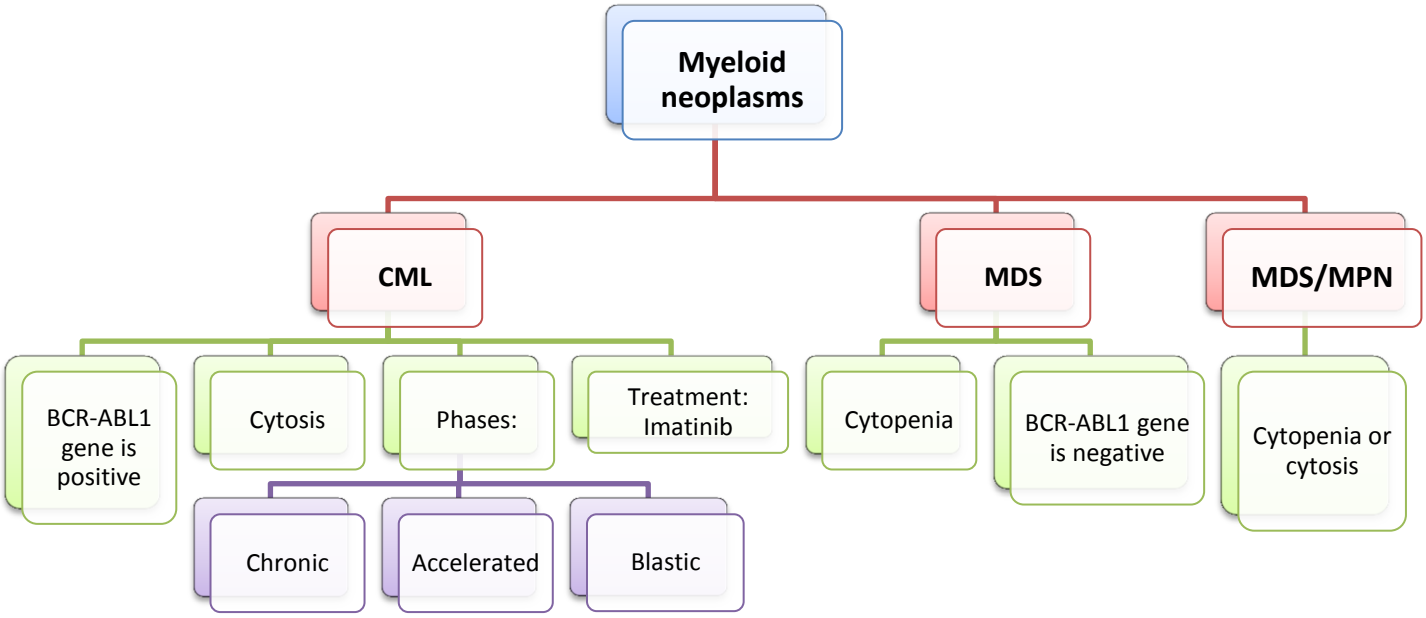
Done By: Zaina *Al-Sawah &* ***Reem*** *Al-Jubab*

Reviewed By: Abdulmohsen *Al-Meshari*

Color Index: Female notes are in Green. Male notes are in Blue. Red is important. Orange is explanation.

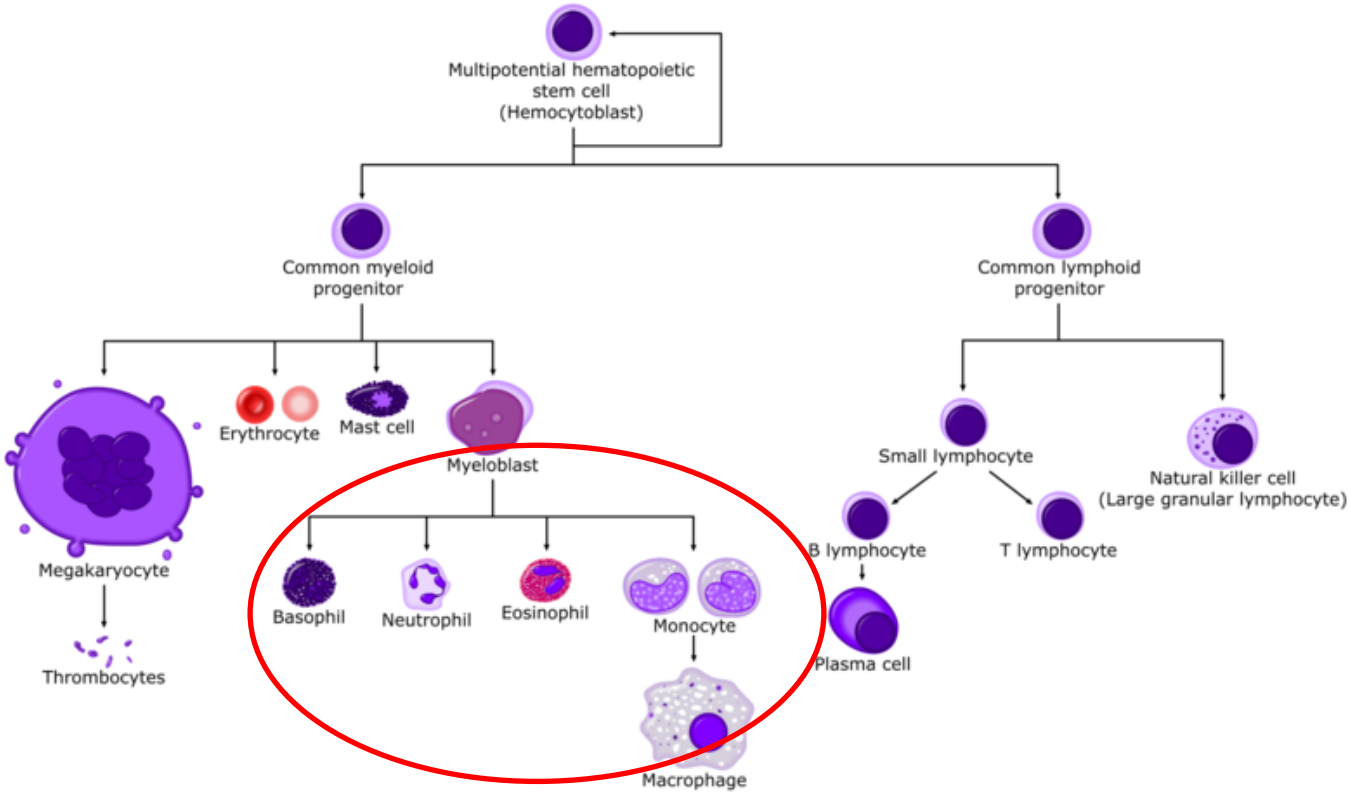
MPN

Mind Map:


Myeloid neoplasms
CML
MDS
MDS/MPN
BCR-ABL1 gene is positive
Cytosis
Phases:
Treatment: Imatinib
Chronic
Accelerated
Blastic
Cytopenia
BCR-ABL1 gene is negative
Cytopenia or cytosis

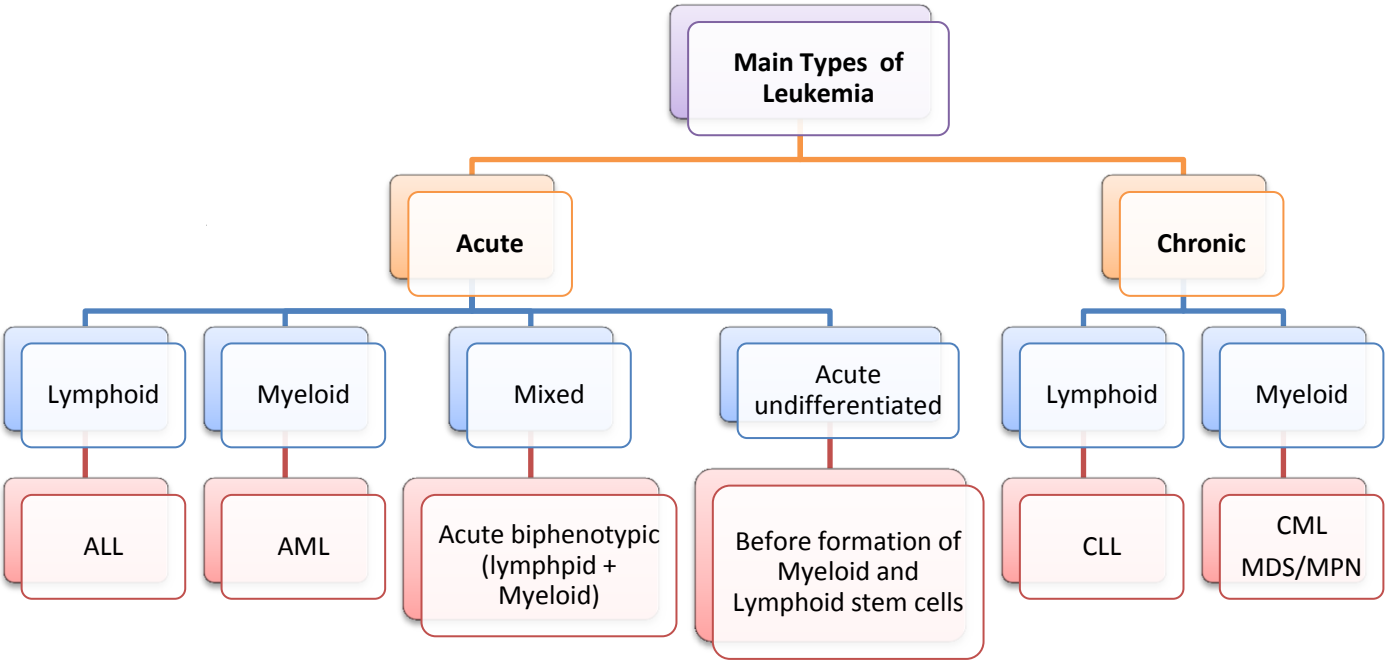
Chronic Leukemia

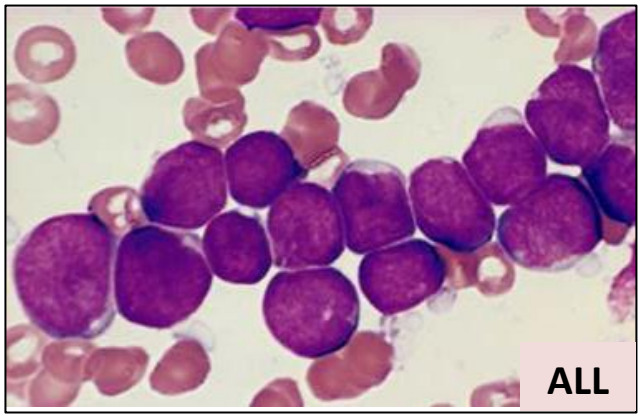
- Heterogeneous group of hematopoietic neoplasms.
- Uncontrolled proliferation and decreased apoptotic activity with variable degrees of differentiation **(unregulated growth of myeloid cells in bone marrow and their accumulation in blood).**
- Composed of relatively mature cells **(precursors are also present in circulation but mainly mature cells).**
- Indolent (If untreated, the course is in months or years) **(patient could be asymptomatic for years).**
- Occurs mainly in adults.

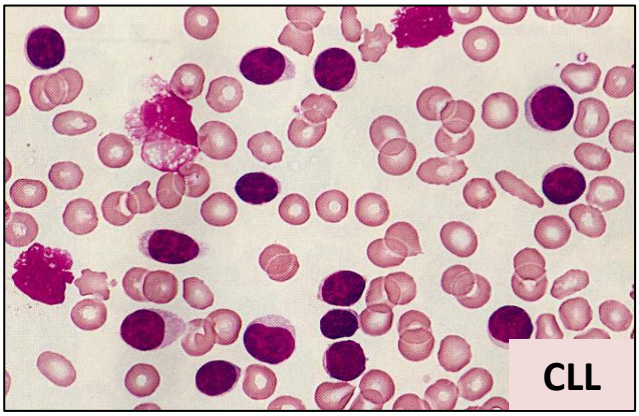


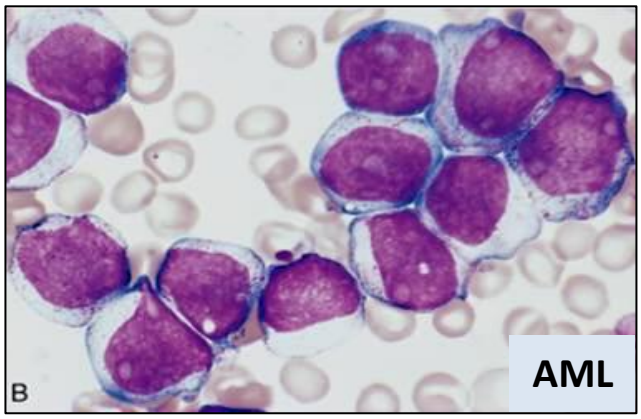
In Acute Leukemia: the proliferation is in the precursors, with reduced capacity to differentiate into mature cells (accumulation of blast cells in bone marrow and circulation)

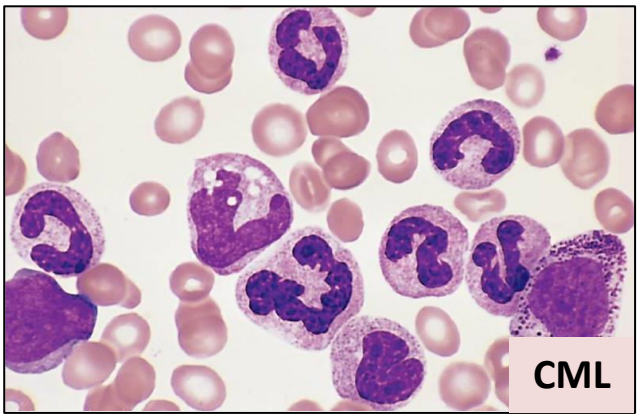
In Chronic Leukemia: the proliferation is mainly in mature cells











REMEMBER:

Leukemia can be divided on the basis of the speed of evolution of the disease into acute (rapid, weeks to months) and chronic (slow, asymptomatic for years).
Each of these is subdivided into myeloid and lymphoid according to the cell type involved.

Myeloproliferative Neoplasms:

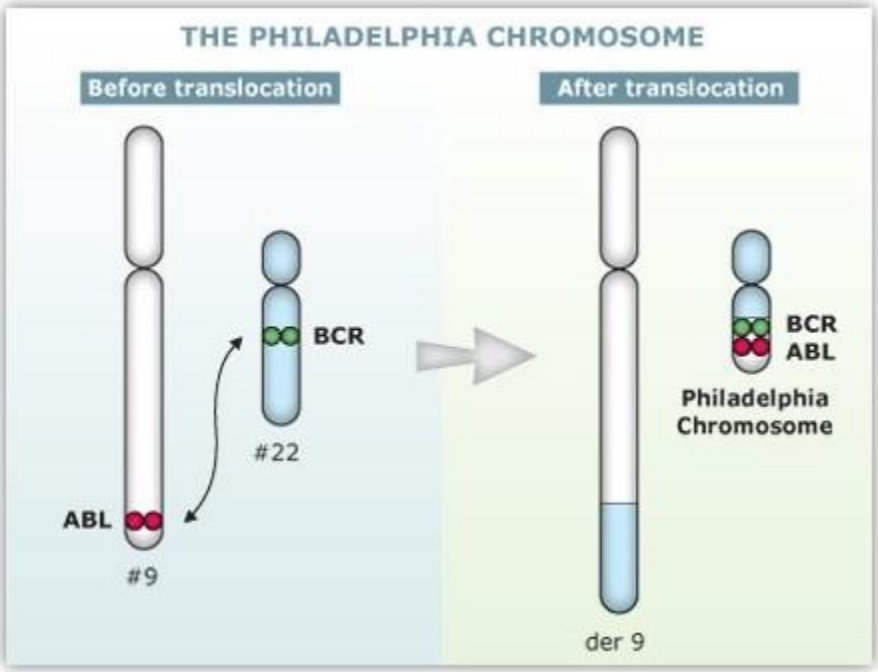
- Malignant proliferation of myeloid cells (maturing cells) which are mainly granulocytes, in blood and bone marrow.
- Occur mainly in adults.
- Slow onset and long course.

MPN Features:

- Cytosis (Increase in number of cells).
- Organomegaly (mainly splenomgaly) <- Constant feature.
- High uric acid **(patients might develop gout).**
- Hypercellular bone marrow.
- Progression to acute leukemia (mainly AML) **but never to ALL.**

Chronic Myeloid Leukemia:

- Stem cell MPN (Different from Acute Myeloid Leukemia. How? As mentioned in page #2, In AML, the pathogenesis is proliferation of Stem cells themselves (No differentiation) while in CML it leads to **increase in differentiation** of the stem cells = Mature cells.)
- Predominant proliferation of granulocytic cells.
- Associated with the BCR-ABL1 fusion gene located in the Philadelphia (Ph) chromosome which results from t(9,22).



REMEMBER:
The reciprocal translocation between chromosome 9 and 22 brings most of the ABL gene from chromosome 9 into the BCR region on chromosome 22 resulting in fusion of BCR-ABL on chromosome 22 and in this case ch. 22 is called Philadelphia chromosome. **(Its presence is a characteristic of CML and used for diagnosis).**

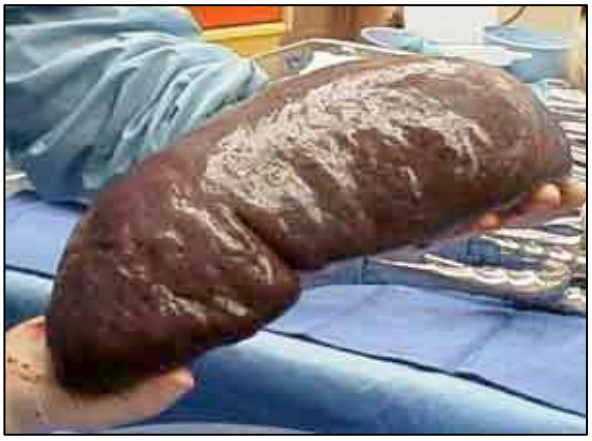
BCR-ABL hybrid gene has a tyrosine kinase activity and enhanced phosphorylating activity resulting in altered cell growth and uncontrolled proliferation

This hybrid gene BCR-ABL is absent in MDS and in MDS/MPN

Clinical presentation

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

  (Most common causes of Splenomegaly, in general, are: CML, Portal Hypertention and Leishmeniasis)



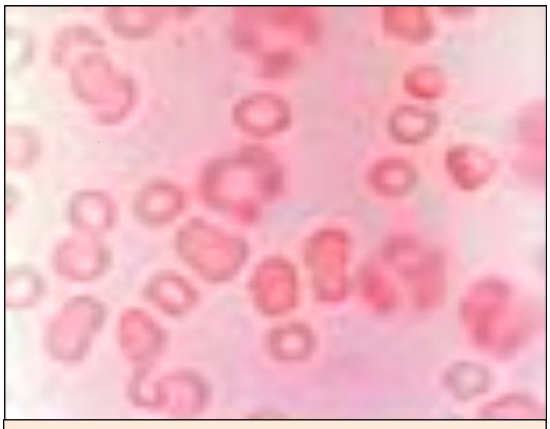
Main differential diagnosis

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

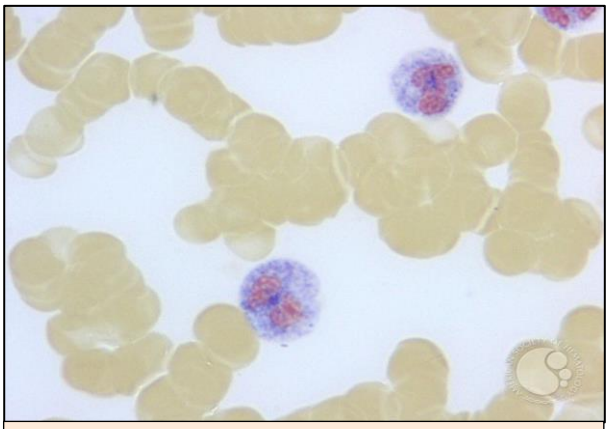
	CML	Leukemoid
Age	Adult	Any age
WBC count	High	High but <100,000
Differential	Mainly myelocytes and segmented	Mainly Bands
Morphology	Hypogranular	Toxic
Splenomegaly	+	-/+
NAP score	Low	High
BCR/ABL	+ve (disease)	-ve (normal)
Onset	Chronic	Acute

Neutrophil alkaline phosphate (NAP) score:

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



Low: CML (No stain)



High: Leukemoid

CML phases:

Chronic phase

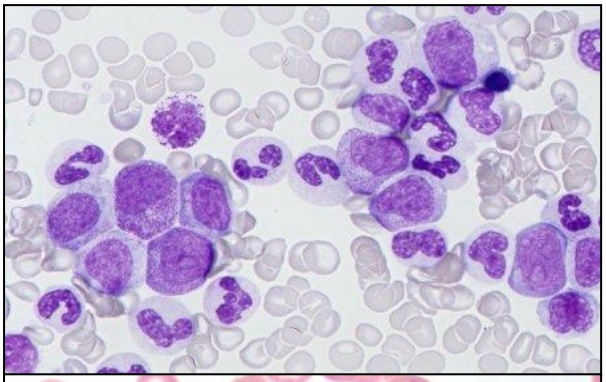
- Leukocytosis (12-1000×10^9/L)
- Mainly neutrophils & myelocytes
- Blasts ≤10% ,Basophils≤ 20%
- Stable course (years)

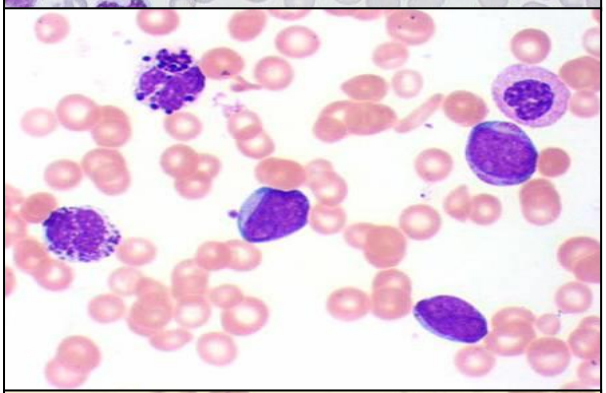
Accelerated phase

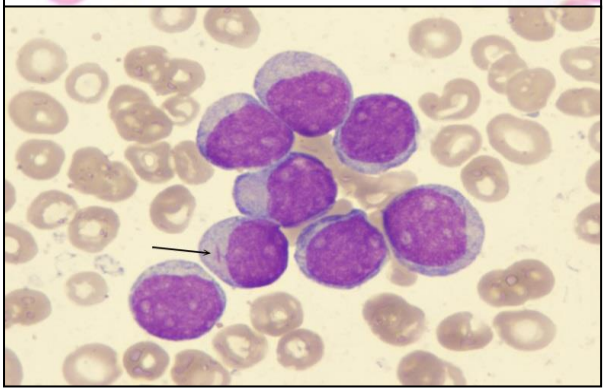
- Increasing counts
- 10-19% blasts (basophils ≥20%)
- Unstable course (months)

Blastic phase

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







CML treatment:

FIRST LINE OF TREATMENT:

Targeted therapy (tyrosine kinase inhibitors like **Imantinib (Trade name: Gleevec)**

Has excellent response (5 years overall survival ≥90%) => stops BCR-ABL

Second line therapy: If no response => stem cell transplantation

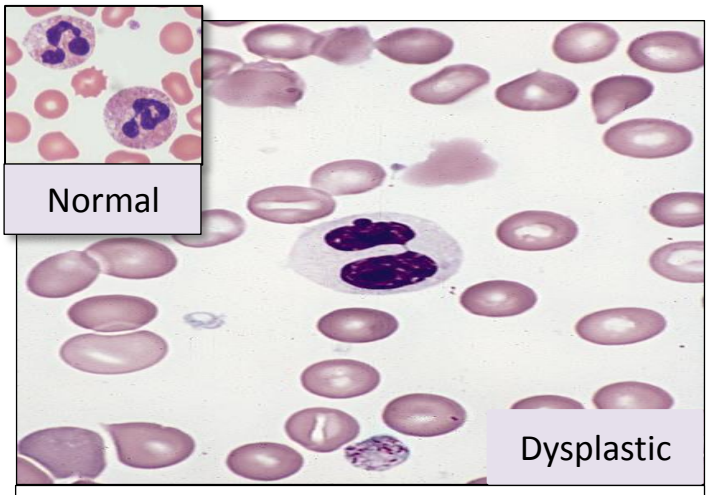
REMEMBER:

- Consistently associated with the BCR-ABL1 fusion gene located in the Philadelphia (ph) chromosome which results from t(9;22)
- First cause of massive splenomegaly is CML
- CML PHASES (chronic, accelerated, blastic)
- First and second line treatment

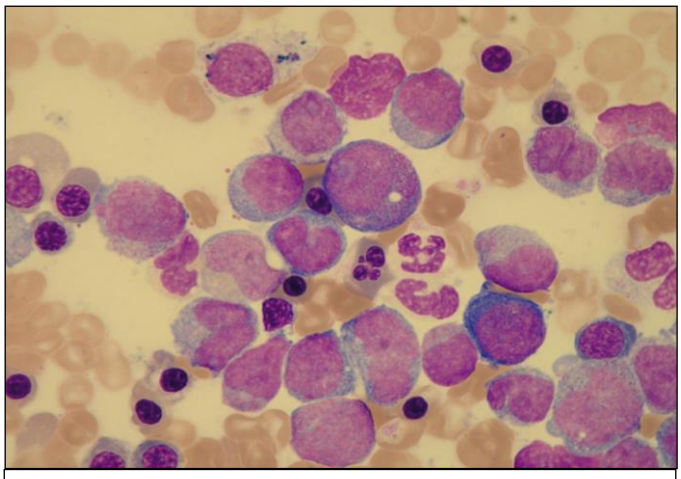
Myelodysplastic syndrome (MDS)

Group of myeloid neoplasms characterized by:

1- Peripheral cytopenia (low HB ± low WBC & low PLT).
2- Dysplasia (abnormal morphology).
3- Ineffective hematopoiesis (hyper cellular bone marrow).
4- **Progression to AML** (preleukaemic disease).
5- Enhanced apoptosis.



Blood: Pancytopenia with dysplasia



BM: Hypercellular with dysplasia

Proliferation — **Apoptosis** = **Ineffective Hematopoiesis**

NOTE: There won't be splenomegaly here because there are no cells in the peripheral blood

MDS has many subtypes according to:

1- Blast count
2- Degree of dysplasia
3- genetics

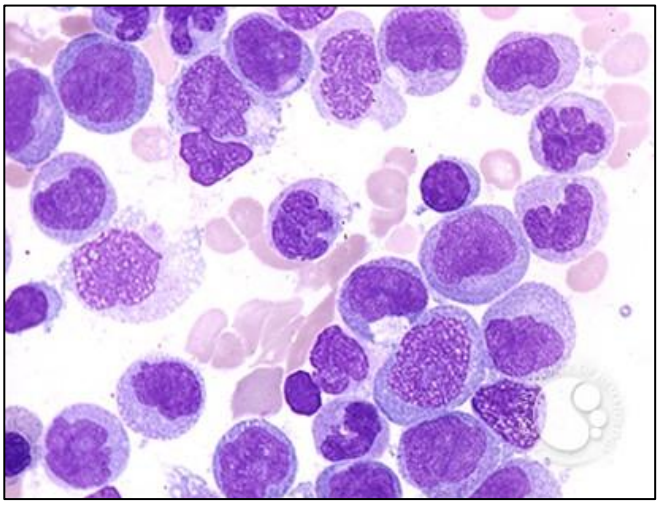
NOTE: variable genetic abnormalities mainly -5, -7

Treatment: Supportive +/- chemotherapy

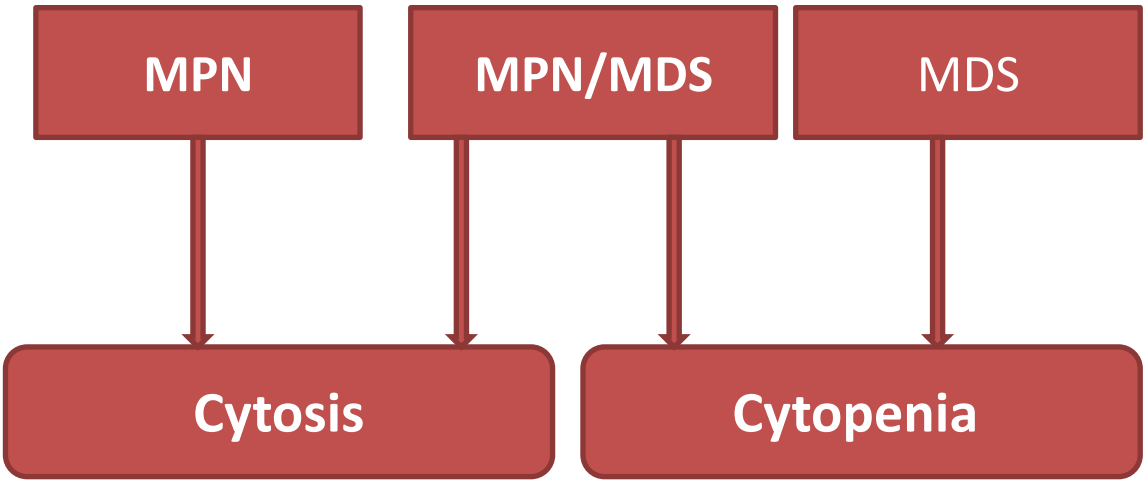
Chronic myelomonocytic leukemia (CMML)

- Clonal hematopoietic malignancy characterized by proliferation of both monocytes & neutrophils.
- MDS/MPN disease (Combination of both).
  - ❖ Features of MDS (dysplasia & enhanced apoptosis).
  - ❖ Features of MPN (marked proliferation).
- Philadelphia chromosome must be negative.
- Blast must be less than 20% if 20% and above => acute leukemia.

- Aggressive course: survival rate around 2.5 years.
- Treatment chemotherapy ± SCT (stem cell transplantation).



MPN vs. MDS vs. MPN/MDS



Summary

- **Chronic Myeloid Leukemia** is a clonal disorder of a pluripotent stem cell. The disease counts for around 15% of leukemias and may occur at any age but most frequently between the ages of 40 and 60.
- All cases of CML have a translocation between chromosome 9 and 22. This leads to the oncogene ABL1 being moved to BCR gene on chromosome 22 and generates the Philadelphia chromosome.
- The resulting chimeric BCR-ABL1 gene codes for a fusion of protein with tyrosine kinase activity.
- In most patients the Philadelphia chromosome is seen by karyotypic examination of tumor cells but the molecular rearrangement may sometimes only be detected by FISH or PCR
- The clinical features include anemia, bleeding and splenomegaly. There is usually a marked Neutrophilia with myelocytes and basophils seen in the blood film.
- Transformation to an accelerated phase or acute Leukemia may occur
- Treatment is with Tyrosine Kinase Inhibitors such as Imatinib (Glivec), dasatinib, nilotinib.
- Stem cell transplantation can be curative and may also be useful for advanced disease.
- The clinical outcome is now very good and patients can expect long term control of the disease.
- Chronic eosonophilic and neutrophil Leukemias are much rarer.

- **Myelodysplasia** includes a group of clonal disorders of of hemopoietic stem cells that lead to bone marrow failure and low blood cell counts. A hallmark of the disease is simultaneous proliferation and apoptosis of HSC leading to the paradox of a hypercellular bone marrow but pancytopenia in peripheral blood. There is a tendency to AML.
- In most cases, the disease is primary but it may be secondary to chemotherapy given for treatment of another malignancy.
- The main clinical features of anemia, infection, and bleeding are caused by reduction in the blood count. Most patients are over 70 years of age.
- Diagnosis is made by examination of the blood and bone marrow together with genetic studies of the tumor cells.
- They are classified into 8 major subtypes
- Scoring systems can divide patients in those with low grade or high grade disease.
- **MDS/MPN** neoplasms are a group of disorders classified between myelodysplasia and myeloproliferative disorders and show the presence of dysplastic features but also increased number of circulating cells.

Questions

1/ what chronic leukemia is most common in older people, ages >60?

A- CLL
B- CML
C- CMML

2/ what genetic change defines chronic myelogenous leukemia?

A- PH, t(9;22) BCR-ABL
B- t(8; 14)
C- t(14; 18) BCL-2

3/ main chromosomal abnormalities in MDS?

A- -6, -5
B- -5, -7
C- -6, -7

4/ chronic leukemia occur mainly in?

A- Infants
B- Children
C- Adults

5/ A 60-year-old man complains of night sweats, weight loss, easy fatigability, and discomfort in the left upper abdominal quadrant. Physical examination reveals splenomegaly. Laboratory studies show leukocytosis (40,000/mL). A peripheral blood smear demonstrates mature and maturing granulocytes, myelocytes, basophils, and occasional myeloblasts. The bone marrow is hypercellular and dominated by WBC precursors. Megakaryocytes are numerous, and RBC precursors are less prominent. Cytogenetic studies disclose a monoclonal population of abnormal cells with a t(9;22) chromosomal translocation. What is the appropriate diagnosis?

A- Acute lymphoblastic leukemia
B- Acute myeloid leukemia
C- Chronic lymphocytic leukemia
D- Chronic myeloid leukemia

6/ which oncogene is located at the t(9;22) chromosomal break- point in the patient described in Question 5?

A- ABL
B- ERB
C- MYB
D- MYC

Answers:

- 1- A
- 2- A
- 3-B
- 4-C
- 5-D
- 6- A

اللهم إني استودعك ما قرأت و ما حفظت و ما تعلمت فرده عليَ عند حاجتي إليه انك على كل شيء قدير

If there is any mistake or feedback please contact us on: 432PathologyTeam@gmail.com