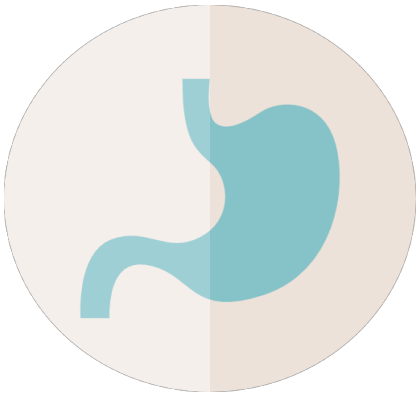
HAEMATOLOGY 436

MEDICINE
KING SAUD UNIVERSITY



تمت المراجعة
شوق الأحمري & عبدالعزيز العنقري

Chronic Leukemia

Objectives:

- To understand the general features of Myeloproliferative neoplasms
- To understand the clinicopathological differences between acute myeloid leukemia (AML) and chronic myeloid leukemia (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.

Color code:
Important.
Extra.
Doctor's Notes

References:

436 girls & boys' slides
435 teamwork slides

Editing file

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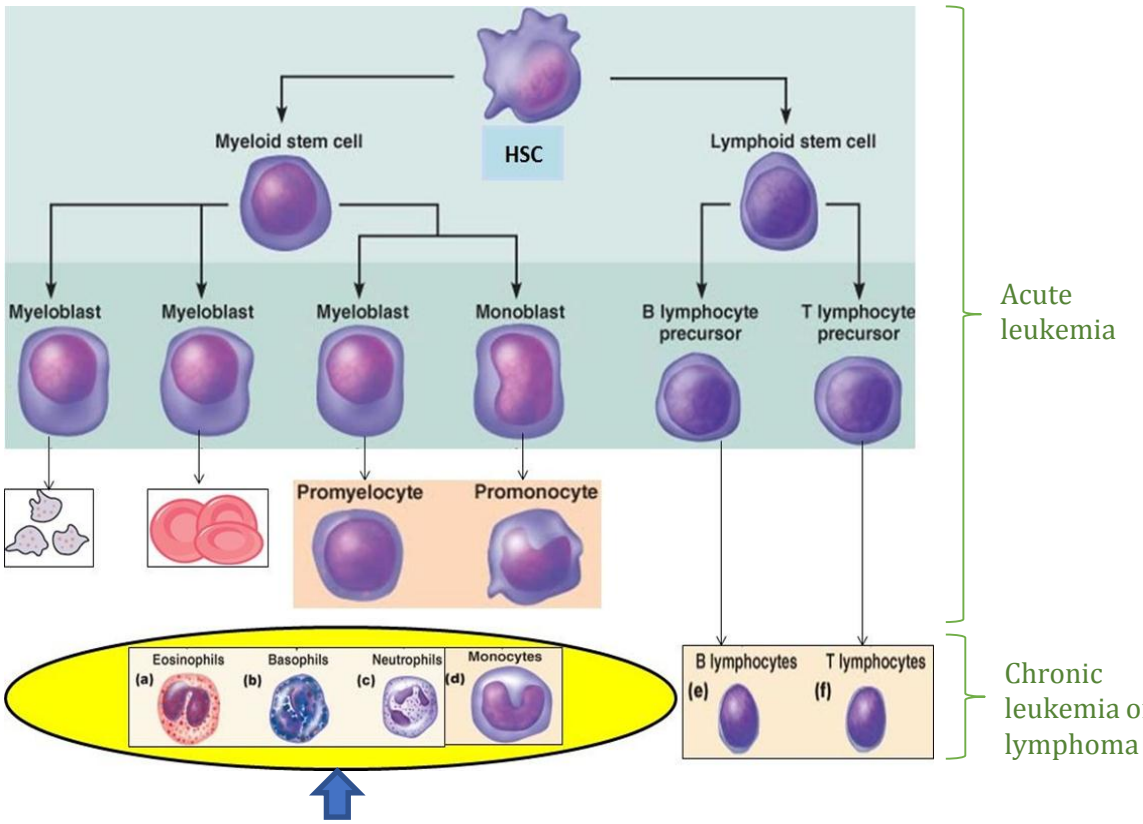
or simply use this form

Chronic leukemias

- Heterogeneous group of hematopoietic neoplasms
- Uncontrolled proliferation and decreased apoptotic activity with variable degrees of differentiation this the main difference between MPN and MDS where MDS there is proliferation but apoptosis is enhanced
- Composed of relatively mature cells the retain the ability to differentiate unlike AML
- Indolent (progress slowly)(If untreated, the course is in months or years, patient might be asymptomatic for years)
- Occurs mainly in adults

When we have **more than 20%** blasts it is **acute** leukemia, and when there is **less than 20%** it is **chronic** leukemia

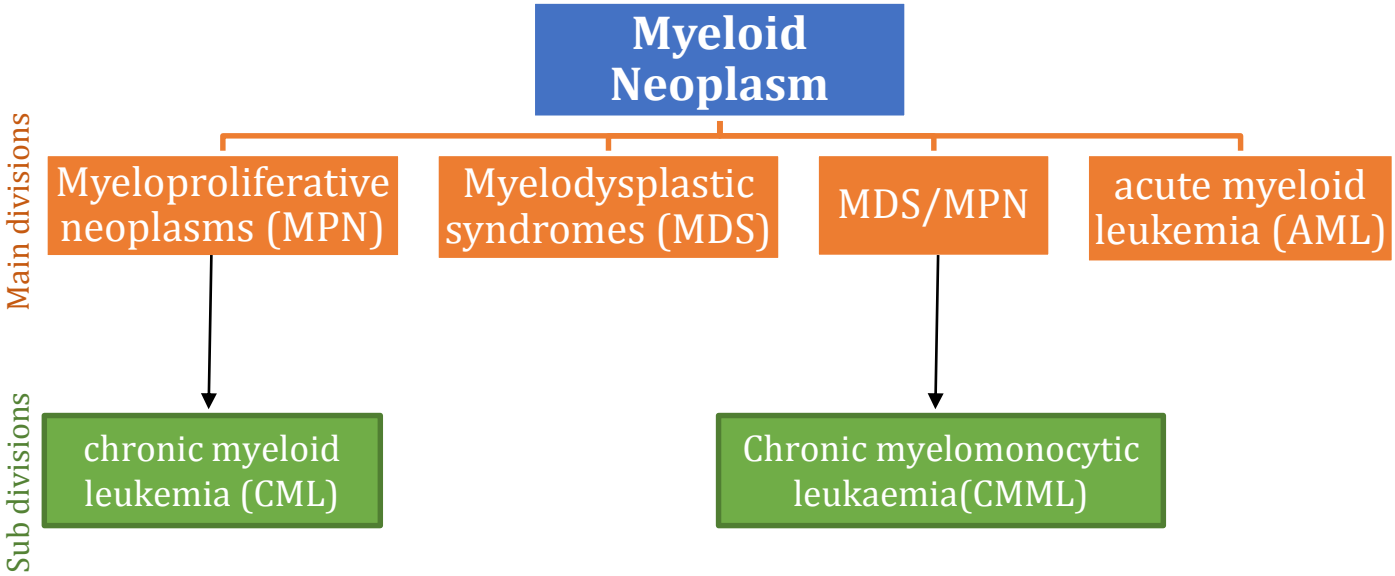


The cells affected or the disease manifestation is in this stage

-Main Types of Leukemia:-

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

-Before we start you have to know the classification of Myeloid Neoplasm According to WHO :-



-Myeloproliferative Neoplasms (MPN):-

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

MPN features:- important!

Cytoses increase in the number of cells (may be more than one lineage)

Organomegaly (mainly splenomegaly) due to accumulation of the cells and the extra hematopoietic role of the spleen

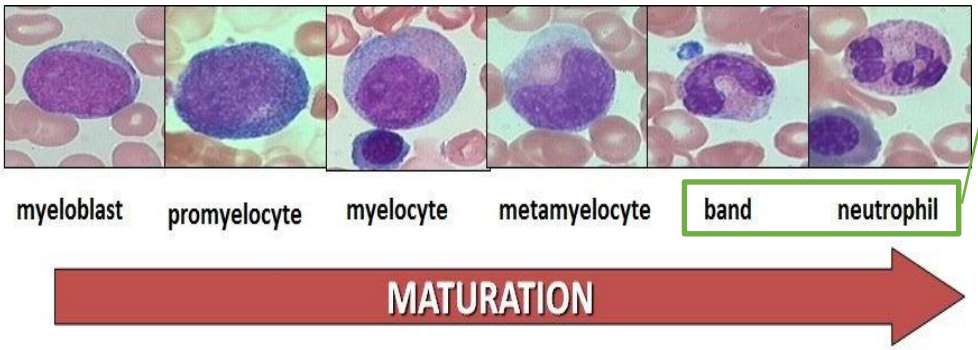
High uric acid the cells are defective and destroyed forming the uric acid from the purines of DNA

Hypercellular bone marrow the bone marrow is about 50% cellular but in case of MPN proliferation (malignancy) increases and could lead to fibrosis

Progression to acute leukemia (mainly AML) the parameter is blast count if above 20% it is considered as acute

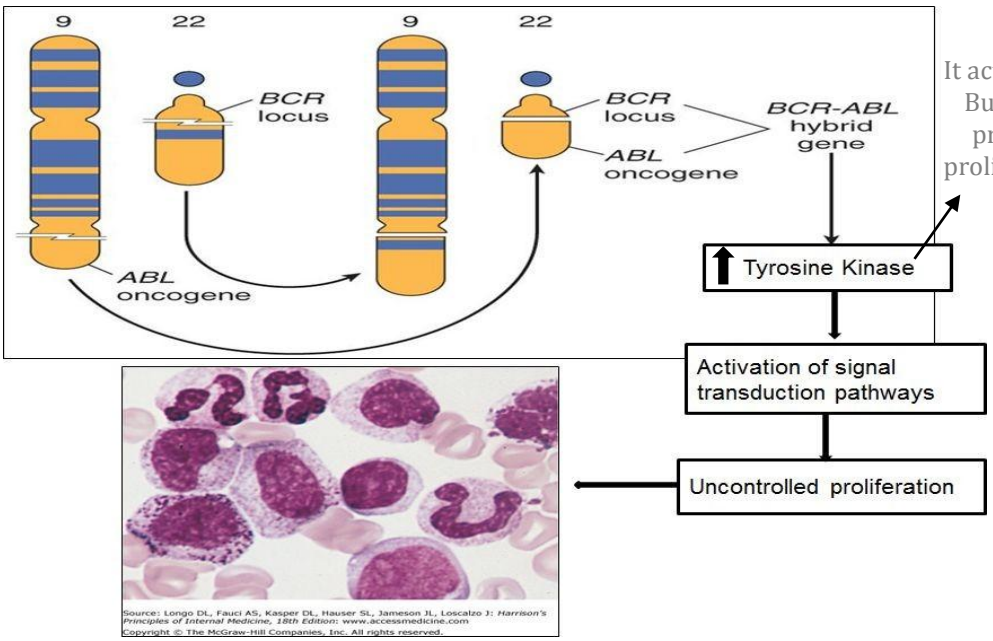
-Chronic Myeloid Leukemia (CML):

- Stem cell MPN.
- Predominant proliferation of granulocytic cells.
- Consistently associated with the BCR-ABL1 fusion gene (Most important feature of CML) located in the Philadelphia (Ph) chromosome (abnormal chromosome) which results from t(9;22)
- The main types of cells that found in CML are: Myelocyte & Neutrophils



These are normally present in the blood but if we find any of the precursors it is **abnormal.** How do they enter the blood? The bone marrow becomes hypercellular and the cells become crowded and start leaving and enter the blood.

-Pathogenesis of Chronic myeloid leukemia:

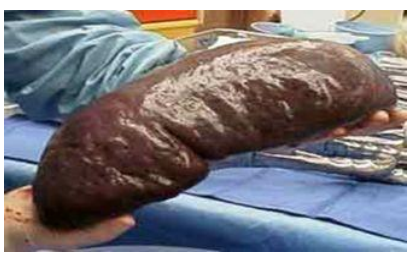


It acts like ON/OFF Button in many processes and proliferation is one of them

Translocation of the ABL segment on chromosome 9 to BCR locus on chromosome 22 fusing together in the chromosome the result is named Philadelphia chromosome 22 chromosome

This fusion gene has a binding site for ATP(the activity of Imatinib treatment is binding to this site and blocking it) that initiate the process of phosphorylation- activation- by tyrosine kinase of a substrate like JAK-2 involved in the transduction pathway that give rise to a state of uncontrolled proliferation

-Clinical Presentation:



Splenomegaly

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

-Main Differential Diagnosis: (كيف أفرق بين الكرونيك مايلويد لوكيميا والأمراض الثانية):-

1.Chronic myelomonocytic leukemia (CMML) (**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 and neutrophils.	Mainly Bands
Morphology	Hypogranular	Toxic
Splenomegaly	+ (massive)	-/+
NAP score هذا يفرق بينهم بسرعة	Low	High
BCR/ABL مكلف	+ve اذا كان بوسيتيف احلف لهم انه CML	-ve
Onset	Chronic	Acute

- Neutrophil Alkaline Phosphatase (NAP)score:

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

CML dysfunction cell do not have alkaline phosphate . But leukmoid is function cell

اللي يقتل البكتيريا هو هذا الانزيم فـ الخلايا الطبيعيه تحتوي هذا الانزيم اما الخلايا الغير طبيعيه لا تحتوي هذا الانزيم.

- **CML= Low**
- **Leukemoid = High**

- ## Chronic Myeloid Leukemia Phases:- المريض ينتقل من مرحلة لمرحلة اذا ما علجناه وكل مرحلة اخطر من اللي قبلها

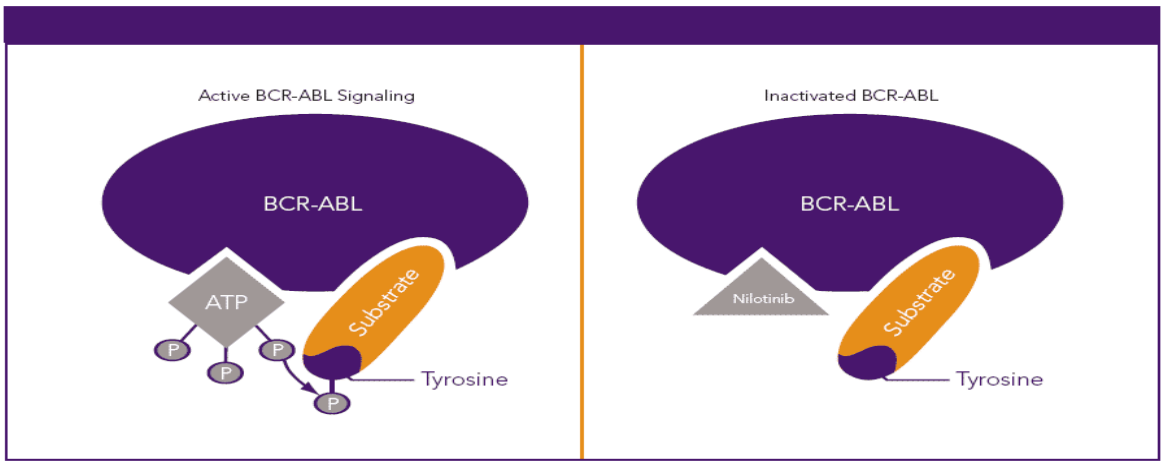
Chronic phase
- Leukocytosis (12-1000×10^9/L).
- Mainly neutrophils and myelocytes.
- Blasts ≤10% ,Basophils≤ 20%
- Stable course (years)

Accelerated phase
- Increasing counts
- 10-19% blasts (basophils ≥20%) (Why 19% ? because if it is 20 it will be AML)
- Unstable course (months)

Blastic phase (AML or ALL)
- (≥20% blasts = Acute Leukemia)
- (80% AML & 20% ALL)
- Coarse (Weeks)

- Treatment:

- 1st line **targeted** therapy (tyrosine kinase inhibitors like Imatinib)
  -Excellent response (5 years survival ≥ 90%) 2nd line therapy If **<u>no response</u>** : stem cell transplantation.
- This drug bind to ATP site of BCR-ABL competing with tyrosine kinase stopping its action



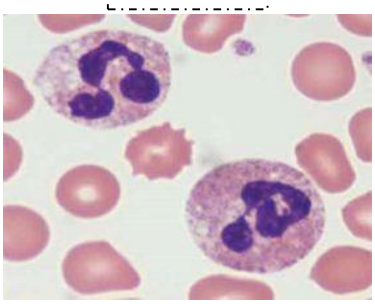
مثال لتسهيل المفاهيم: تخيل ان فيه مصنع سيارات صغير في مدينة صغيرة كان يصنع على قد حاجة المدينة ١٠ سيارات في اليوم مثلا (نورمال) فجأة جاء ميوتيشن داخل المصنع فـ زاد الإنتاج من ١٠ سيارات صار ينتج ١٠٠ سيارة في اليوم ، اولاً بتزدحم شوارع المدينة بالسيارات (Peripheral blood) وثانياً بيزدحم المصنع نفسه لأن الإنتاج فوق طاقته الاستيعابية (Bone Marrow) هذا هو اللي يصير في <u>CML</u> .
اما اللي يصير في <u>MDS</u> نفس مثال المصنع اللي فوق بس لما صار ميوتيشن هنا انهبلت المكائن وصارت تصنع سيارات مشوهة مثلاً تسوي سيارة بمكينتين أو سيارة بدون قير أو بدون كفرات فلما تطلع للشوارع بتخرب اول ما تطلع فبيجي المرور(Apoptosis) ويوقف هذي السيارات ويتلفها لأن ما منها فايدة فبيصير عندي مصنع قاعد يصنع سيارات خربانة ومزدحم من كثرتها(Bone Marrow)، أما الشوارع بتكون فاضية لأن المرور قاعد يتلف السيارات (Peripheral blood)

- Myelodysplastic syndromes (MDS):- ضروري تقرون المثال نهاية السلايد اللي قبل هذا

- Group of myeloid neoplasm's characterized by:

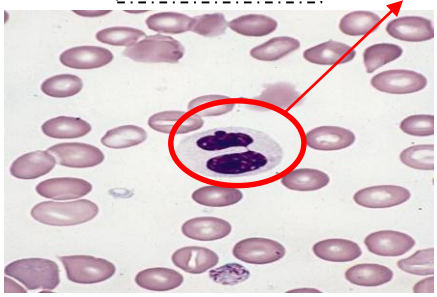
1- Peripheral cytopenia (low Hemoglobin ± low WBC & low PLT).
2- Dysplasia (abnormal morphology). خلايا مشوهة
3 Ineffective hematopoiesis (hypercellular bone marrow)
4 Progression to AML (preleukaemic disease).
5 Enhanced apoptosis. in the peripheral blood cause cytopenia

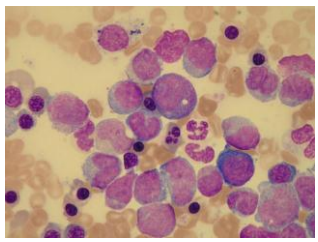
Normal



Dysplastic

No Granules! and ↓ number of lobes





Blood: Pancytopenia with dysplasia.

BM: Hypercellular with dysplasia

↑ proliferation - ↑ apoptosis = Ineffective hematopoiesis

- MDS subtypes classified according to:-

1- Blast count. prognosis depends on the number of blast the higher blast count prognosis is worse.
2- Degree of dysplasia.
3- Genetics: Variable genetic abnormalities mainly -5q (good prognosis more in female) , -7q (bad prognosis more in male)

- Treatment:

supportive +/- chemotherapy

- Chronic Myelomonocytic Leukemia (CMML)

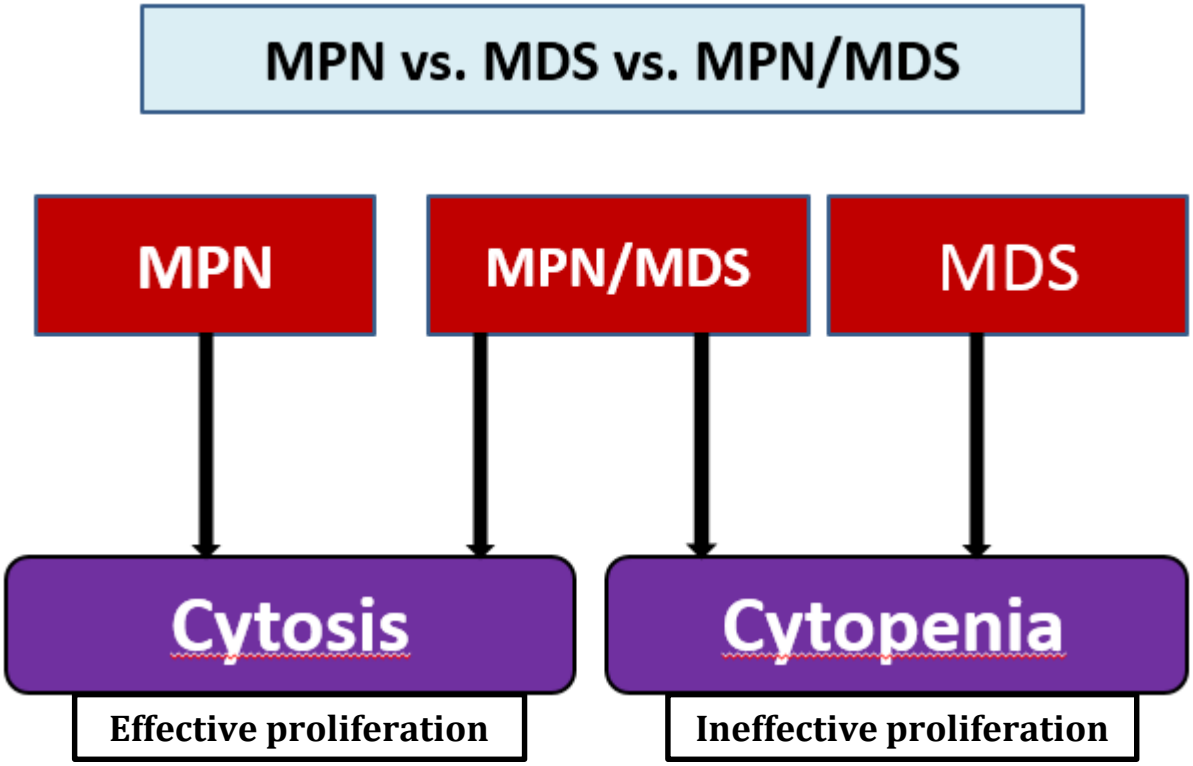
- Clonal Hematopoietic malignancy characterized by proliferation of both monocytes and neutrophils it is classified as MDS/MPN disease.

MDS/MPN disease: has both (takes features from both) **:-**

-Features of MDS (dysplasia & enhanced apoptosis).
-Features of MPN (marked proliferation).

- Philadelphia chromosome must be **negative.** (if it is +ve then it is CML)
- Blast must be **less than** 20%, (more than 20% → acute)
- Aggressive course (survival rate around 2.5y)

Treatment: Chemotherapy ±SCT



- Difference between Chronic Myeloid Leukemia & Acute Myeloid Leukemia

	CML	AML
onset	Indolent course . Symptoms appear after a long period	Rapid
phases	Three phases 1.Chronic phase 2.Accelerated phase 3.Blastic phase	No known phases
etiology	Gene mutation known as Philadelphia gene T(9;22)	Many mutations e.g. t(15;17)
hepatosplenomegaly	Marked (sometimes severe or massive especially spleen)	moderate
Blasts	Fewer than 20%	> 20%
Cell count	Cytosis	Cytopenia

MCQs:

1. The mutation responsible for the effects and manifestations of CML is :
A. t(15;17)
B. Philadelphia chromosome
C. Chromosome 5 monosomy
D. Chromosome 7 monosomy

2. The distinguishing feature of AML is:
A. Blast > 20%
B. Cytosis
C. bone marrow failure
D. Hepatomegaly

3. A 55 year old patient came to the clinic for a regular check up. He does not complain of any symptoms. His results are as follows:
High WBC count, Mainly bands, High NAP score. What is the most likely diagnoses:
A. CML
B. AML
C. CMML
D. infection

4. CMML is presented with cytopenia and decreased apoptosis:
A. True
B. False

5. Which one of the following genes Must be positive in CML?
A. APC
B. BCR-ABL
C. REKA-B
D. P53

Answers: 1. B , 2. A , 3. D , 4. B, 5. B

Good Luck !

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