



# Leukemia

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Objectives:

- **Not given yet**

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References:

**Slides - Black**

**Doctor's notes - Red**

**Step up /cecil / davidson - Blue**

**Extra explanation - Grey**

Optional:



[Editing file](#)

# Leukemia

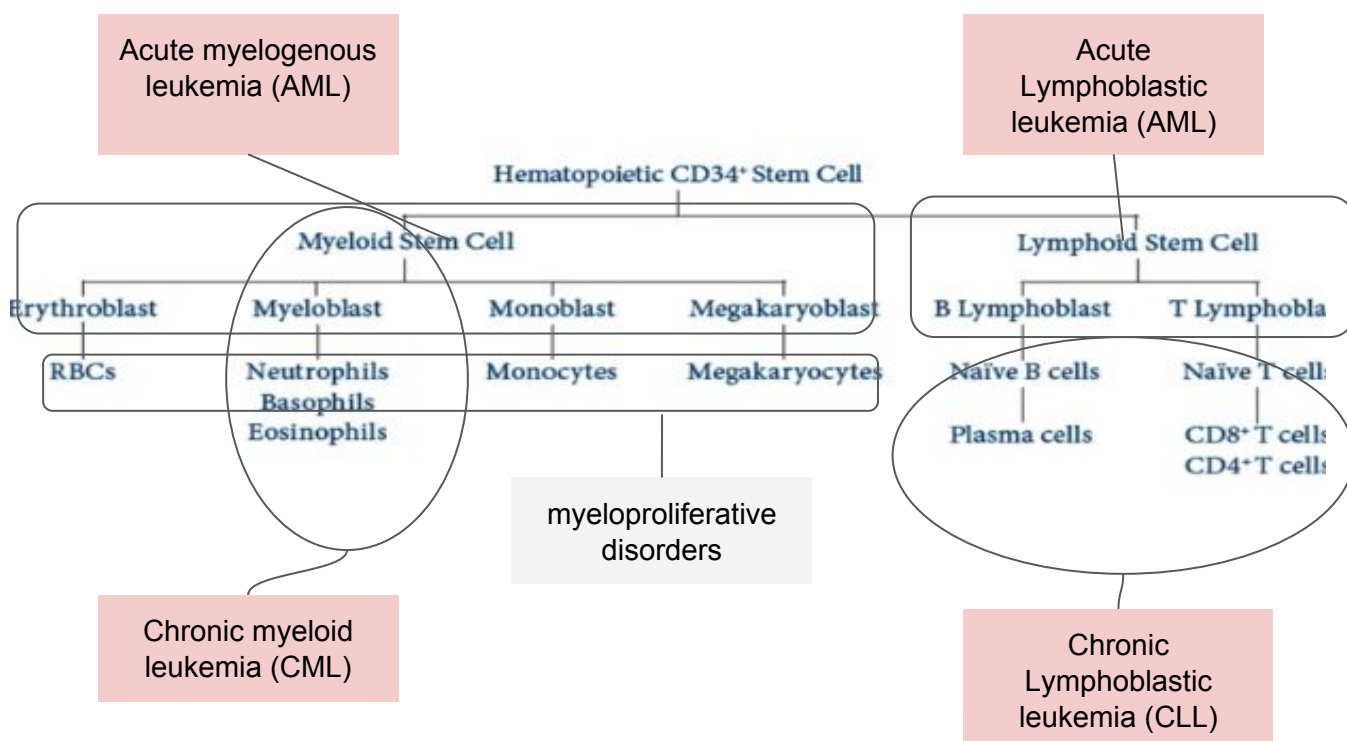
A group of malignant disorders affecting the blood and blood-forming tissues of, bone marrow, lymph system and spleen. Results in an accumulation of **dysfunctional** cells because of a loss of regulation in cell division for unknown reason. Progressive, fatal if untreated.

- As we discussed earlier in “introduction to oncology” lecture that the cancer starts by any mutation could happen to a cell which will result in unregulated division of the mutated cells. The same concept is applied here.
- Cellular components of blood are: RBCs, WBCs, Platelets all are derived from bone marrow through hematopoiesis system.
- In the pic you see down is the hematopoietic system including different lineages and as you see all are originated from the Hematopoietic stem cell.
- Now, leukemia is a result of a defect “mutation” in these lineage and depending on different lineage we have different types of leukemia (See picture below).
- Leukemia can be divided into four subtypes:-
  - Acute myelogenous leukemia (AML) → A defect in myeloid stem cell with ceased maturation of cells
  - Acute lymphoblastic leukemia (ALL) → A defect in lymphoid stem cell with ceased maturation of cells
  - Chronic myeloid leukemia (CML) → A defect in myeloid stem cell with maturation of cells
  - Chronic lymphocytic leukemia (CLL) → A defect in lymphoid stem cell with maturation of cells
- Each one of them has special features as we will discuss later

**Etiology**:- No single causative agent. Most from a combination of factors.

## Genetic and environmental influences

- *Associated with the development of leukemia*
  - Chemical agents
  - Chemotherapeutic agents
  - Viruses
  - Radiation
  - Immunologic deficiencies. especially: AIDS.



## Classification of leukemias

- **Acute leukemia:**

Acute lymphoblastic leukemia (ALL)

Acute myelogenous leukemia (AML)

- **Chronic leukemia:**

Chronic lymphocytic leukemia (CLL)

Chronic myeloid leukemia (CML)

(Within these main categories, there are typically several subcategories)

the classifications according to the cell maturity

Acute	Chronic
Accumulation of immature cells	Accumulation of dysfunctional mature cells
Younger age group (can occurs in all age groups)	Older age group
Fatal if untreated	Sometimes you don't have to treat (Watch & Wait).
discovered in the ER	discovered incidentally

! any secondary leukemia: the prognosis is poor

## Myelogenous Leukemia

- Leukemia characterized by proliferation of myeloid tissue (as of the bone marrow and spleen) and an abnormal increase in the number of granulocytes, myelocytes, and myeloblasts in the **circulating blood (the first step in diagnosis)**.
- Myeloid tissue is a biologic tissue with the ability to perform hematopoiesis. It is mainly found as the red bone marrow in bones, and is often synonymous with this. However, **myeloid can also be present in the liver and spleen only without involving the bone marrow**.  
A myelocyte is a young cell of the granulocytic series, occurring normally in bone marrow, but not in circulating blood (except when caused by certain diseases).
- Granulocytes are a category of white blood cells characterized by the presence of granules in their cytoplasm. They are also called **polymorphonuclear leukocytes**(PMN or PML) because of the varying shapes of the nucleus, which is usually lobed into three segments.
- The myeloblast is a unipotent stem cell, which will differentiate into one of the actors of the granular series.

## Acute Myelogenous Leukemia(AML)

Leukemia characterized by proliferation of myeloid tissue (as of the bone marrow and spleen) and an abnormal increase in the number of granulocytes, myelocytes, and myeloblasts in the circulating blood. One fourth of all leukemias.

– 85% of the acute leukemias in adults

Abrupt, dramatic onset



AML patients will present with occluded vessels manifestations, because of the myeloblast large size

patients mostly have **complications** related to

### 1- **cytopenia:**

- Serious infections due to leukopenia, abnormal bleeding due to thrombocytopenia or shortness of breath or fatigue due to anemia.(why they usually not come with severe anemia? Because there is extramedullary hematopoietic system \*RBC's can be produced by other lymphoid tissues\*)

### 2- **Uncontrolled proliferation of myeloblasts:**

Leukostasis : High level of circulating blasts( >80,000 to 100,000) leads to :

- pulmonary edema and hemorrhage.
- CNS complications such as intracranial bleeding or thrombosis, cranial nerve invasion, and leukemic meningitis.
- Heart failure.
- Treated by leukapheresis.



Leukopheresis:

a laboratory procedure in which blood is drawn and white blood cells are separated from the blood and the red blood cells are returned to the patient

### 3- **Hyperplasia of bone marrow and spleen**

### 4- **Tumor lysis syndrome:**

High blast cell numbers result in the release of cellular breakdown products, leading to hypokalemia, acidosis and hyperuricemia with resultant renal failure.

Diagnosis:

### 1- Lab findings:

- The WBC count is variable (from 1,000/mm<sup>3</sup> to 100,000/mm<sup>3</sup>) with >20% blast cells(immature cells) in the circulatory blood.
- Cytopenia.
- Electrolytes disturbance.

### 2- Bone marrow biopsy: Auer rods.



## Nutshell

- ◆ AML is common in adult
- ◆ It's characterized by accumulation of immature myeloid cells in BM (>20)
- ◆ Circulating myeloblast are seen in peripheral smear
- ◆ Positive Myeloperoxidase
- ◆ Auer rods in blood film
- ◆ Clinical finding include:- Anemia, recurrent infection, and bleeding
- ◆ Acute promyelocytic leukemia (APL) is a subdivision of AML and it's characterized by DIC; it's immediate emergency that can be treated by Vitamin A

### **Acute promyelocytic leukemia:**

APL is formerly known as the FAB M3 subtype of AML characterized by a chromosomal translocation t(15;17).

Patient with APL often exhibit life-threatening bleeding caused by disseminated intravascular coagulation.

## Acute Lymphocytic Leukemia (ALL)

- **Most common type of leukemia in children.** (15% of acute leukemia in adults)
- Immature lymphocytes proliferate in the bone marrow
- It is the leukemia most responsive to therapy.
- Poor prognostic indicators are as follows:  $<2$  or  $>9$ ;  $WBC > 10^5/mm^3$  and/or CNS involvement.

### Signs and symptoms may appear abruptly

- Fever, bleeding. "Insidious with progressive"
- Weakness, fatigue

Sometimes the patient present with weakness/fatigue without fever or bleeding, why? because of the release of the many inflammatory mediators (Ex: TNF)

- Central nervous system manifestations and testicular involvement **WHY? (Lymphocytes can cross the blood-brain barrier and sertoli cell barrier because it's smaller).**
- anterior mediastinal mass



## Nutshell

- ◆ ALL is common in children
- ◆ Increased lymphoblasts in peripheral smear and BM
- ◆ Can be present as mediastinal mass
- ◆ CNS and Testicular involvement → A prophylactic radiation and/or chemotherapy to CNS
- ◆ Has a better response to therapy compared to AML

## Chronic leukemia

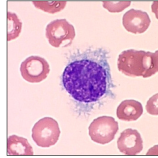
Chronic Myelogenous Leukemia(CML)	Chronic Lymphocytic Leukemia(CLL)
<ul style="list-style-type: none"> <li>• the comments</li> <li>• Excessive development of mature neoplastic granulocytes in the bone marrow               <ul style="list-style-type: none"> <li>– Move into the peripheral blood in massive numbers</li> <li>– Ultimately infiltrate the liver and spleen. → (Splénomegaly&amp;Hepatomegaly)</li> </ul> </li> <li>• <b>Philadelphia chromosome</b> <ul style="list-style-type: none"> <li>– The chromosome abnormality (mutation or translocation) that causes chronic myeloid leukemia (CML) (9 &amp;22)</li> </ul> </li> <li>• Genetic marker Chronic, stable phase followed by acute,aggressive (blastic) phase.</li> <li>• CML is considered as a myeloproliferative disorder, so the platelet count and erythrocyte count are usually normal or even increased.</li> <li>• <b>granulocytosis:</b> <ul style="list-style-type: none"> <li>↑↑↑ Neutrophils</li> <li>↑ basophils &amp; eosinophils</li> </ul> </li> <li>• Can progress and transform into Acute leukemia (AML or ALL)</li> <li>• can be missed as a leukemoid reaction</li> <li>• Imatinib is mainstay treatment</li> </ul>	<ul style="list-style-type: none"> <li>• is the most common leukemia that occurs after age 50</li> <li>• Production and accumulation of functionally inactive but <b>long-lived</b>, mature-appearing lymphocytes               <ul style="list-style-type: none"> <li>B cell involvement</li> <li>Lymph node enlargement is noticeable throughout the body</li> </ul> </li> <li>• <b>↑ incidence of infection (Because dysfunctional lymphocytes).</b></li> <li>• Complications from early-stage CLL is rare</li> <li>• May develop as the disease advances– Pain, paralysis from enlarged lymph nodes causing pressure.</li> <li>• The management is <b>watch&amp;wait.</b></li> <li>• Usually asymptomatic and diagnosed incidentally</li> </ul>

## Hairy Cell Leukemia

- **Rare form of leukemia due to neoplastic transformation of a subset of B lymphocyte**
- 2% of all adult leukemias, Usually in males > 40 years old
- Chronic disease of lymphoproliferation
  - B lymphocytes that infiltrate the **bone marrow** and **liver**.

It differs from CLL in gene expression.

- Cells have a “**hairy**” appearance



- Symptoms from ( **Splenomegaly**, pancytopenia, infection, vasculitis

Treatment: cladribine (gold standard).



Q: what is leukemoid reaction?

leukemoid reaction is acute inflammatory response to infection with increased in white blood cell count, or leukocytosis, and sometimes blasts may present

Q: How can I differentiate between CML and Leukemoid reaction?

1-History

2-Leukocyte alkaline phosphatase (LAP)

↑ in Leukemoid reaction

↓ in CML

3-No splenomegaly in leukemoid reaction

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## Unclassified (ambiguous) Leukemias

- Subtype cannot be identified
- Malignant leukemic cells may have lymphoid, myeloid, or mixed characteristics
- Frequently these patients do not respond well to treatment (**Poor prognosis**).

## Differential Diagnosis

1. Aplastic anemia (Pancytopenia but without blast) and RBC's are intact
2. Myelodysplastic syndromes (blast but not >20%)
3. Multiple myeloma (Pancytopenia)
4. Lymphomas
5. Severe megaloblastic anemia (Pancytopenia)
6. Leukemoid reaction (1- No splenomegaly. 2- increased leukocyte alkaline phosphatase. 3- Hx of infection or any precipitating event.)

## Clinical Manifestations

Relate to problems caused by

- Bone marrow failure
- Overcrowding by abnormal cells
- Inadequate production of normal marrow elements
- Anemia, thrombocytopenia, ↓ number and function of WBCs
- Leukemic cells infiltrate patient's organs
- Splenomegaly
- Hepatomegaly
- Lymphadenopathy
- Bone pain, meningeal irritation, oral lesions (chloromas)

## Diagnostic Studies for evaluation of leukemia:- “important”

1- **Peripheral blood evaluation** (CBC and blood smear)

Abnormal blasts & Cytopenia. → Acute leukemia

2- **Coagulation profile**: to exclude AML M3.

3- **Peripheral blood flow cytometry** → **to identify the cell type**

4- **Bone marrow biopsy** for:

Morphology, Cytogenetics, Flow Cytometry, Molecular.

## Collaborative Care

Goal is to **attain remission** (when there is no longer evidence of cancer cells in the body)

- **Remission induction:**

In this phase, the bulk of the tumour is destroyed by combination chemotherapy. The patient goes through a period of severe bone marrow hypoplasia, requiring intensive support and inpatient care from a specially trained multidisciplinary team

What is remission?

The main aim of treatment for acute lymphoblastic leukaemia is to give a remission. This means that the abnormal, immature white cells or blasts can no longer be detected in the blood or bone marrow, and normal bone marrow has developed again.

For many people with acute lymphoblastic leukaemia the remission lasts indefinitely and the person is said to be cured.

- **Remission consolidation:**

If remission has been achieved, residual disease is attacked by therapy during the consolidation phase. This consists of a number of courses of chemotherapy which has lower doses of the same drug, again resulting in periods of marrow hypoplasia. In poor-prognosis leukaemia, this may include haematopoietic stem cell transplantation.

- **Remission maintenance:**

If the patient is still in remission after the consolidation phase for ALL, a period of maintenance therapy is given, with the individual as an outpatient and treatment consisting of a repeating cycle of drug administration. This may extend for up to 3 years if relapse does not occur.

## Chemotherapy Regimens

Combination chemotherapy

### Mainstay treatment

– 3 purposes

- ↓ drug resistance
- ↓ drug toxicity to the patient by using

### multiple drugs with varying toxicities

- Interrupt cell growth at multiple points in the cell cycle.

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## Bone Marrow and Stem Cell Transplantation

### Goal

–Totally eliminate leukemic cells from the body using combinations of chemotherapy **قنبلة نووية** with or without total body irradiation

Eradicates patient's hematopoietic stem cells Replaced with those of an HLA-matched (Human Leukocyte Antigen) (especially ALL patients)

- Sibling (**is a brother or a sister**; that is, any person who shares at least one of the same parents ) because they have identical immune system
- Volunteer.
- Identical twin.
- Patient's own stem cells removed before.

**Case 1 17 ys lady presented to the Er with CBC : WBCs 50,000 HGB 10  
PLT 15000**

**Abnormal circulating blasts 30%**

**Now, how to approach this patient?**

Diagnosis and Risk stratification

1- Peripheral blood morphology

Abnormal blasts

2- Peripheral blood flowcytometry

30 % blasts with CD 33 , CD 34 +ve

3- Bone marrow biopsy (BMB)x for

Morphology (myeloblasts)

Cytogenetics( t 8:22) (**diagnostic and prognostic**)

Flow Cytometry (50% blasts express M antigens).

Molecular (mutational testing) (FLT 3 –ITD +ve)\*

Treatment Goals

1- Remission induction (chemo for 28 days)

2-Response assessment (day 28, why? to allow the bone marrow to recover)

3-Consolidation (chemo / SCT)

4- Maintenance.





# MCQ's

**Q1:** A 29-year-old woman complains of tiredness, especially during activity. On examination the patient appears pale. Auer rods and schistocytes can be seen on peripheral blood smear. The patient is referred for a bone marrow biopsy and the extracted cells are sent for cytogenetic analysis. The most likely results are:

- A. t(8:21)
- B. t(15;17)
- C. t(9:22)
- D. t(14;18)
- E. t(8;14)

**Q2:** A 50-year-old man comes to the physician because of gingival bleeding, epistaxis, and fever for 2 days. He appears acutely ill. His temperature is 39 c (102 F), blood pressure is 120/70 mmHg, pulse is 120/min, and respirations are 22/min. Bilateral rhonchi are heard on chest examination. He is admitted for further evaluation. Chest x-ray shows bibasilar infiltrates consistent with bronchopneumonia. Blood tests show 12,000 leukocytes/mm<sup>3</sup> with numerous myeloid blasts. Platelet count is 15,000/mm<sup>3</sup>. A bone marrow biopsy demonstrates hypercellular marrow, with 35% blasts. Elongated cytoplasmic inclusions consistent with Auer rods are appreciated in peripheral and marrow blasts. Which of the following is the most likely diagnosis?

- (A) Acute lymphocytic leukemia (ALL)
- (B) Acute myelogenous leukemia (AML)
- (C) Chronic myelogenous leukemia (CML)
- (D) leukemoid reaction
- (E) Myelodysplastic

**Q3:** A previously healthy, 48-year-old woman presents with easy fatigability, anorexia, and a 5-kg (11-lb) weight loss for 2 months. She also reports night sweats and occasional temperatures to 38 c (100 F). On examination, the spleen is palpable 4 cm below the left costal arch. Blood tests reveal a hemoglobin of 16 g/dL, 500,000 platelets/mm<sup>3</sup>, and 170,000 leukocytes/mm<sup>3</sup>. The differential count shows a left shift, with predominance of mature granulocytes, bands, and metamyelocytes. blasts are 3%. Serum chemistry is remarkable for low leukocyte alkaline phosphatase and high uric acid. Cytogenetic studies demonstrate the presence of the Philadelphia chromosome in white blood cells, which of the following is the most likely diagnosis?

- (A) Acute myelogenous leukemia (AML)
- (B) Chronic lymphocytic leukemia (CLL)
- (C) Chronic myelogenous leukemia (CML)
- (D) Leukemoid reaction
- (E) Myelofibrosis

**Q4:** A 5-year-old girl presents with her parents who have become concerned about the small petechiae and ecchymoses on her skin. An abdominal examination reveals hepatosplenomegaly. You suspect an acute leukaemia. The most appropriate initial investigation for diagnosis is:

- A. Chromosomal analysis of bone marrow cells
- B. Cytochemical analysis of bone marrow cells
- C. Direct microscopy of bone marrow cells
- D. Peripheral blood smear
- E. Flow cytometry

Answers: 1.B,2.B,3.C,4.D

**Thank you**

If you have any question please contact with us at:  
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