MEDICINE

432 Team

33 Leukemia (Acute and Chronic)

Done By:
May H. Alorainy

Reviewed By:
Abdulrahman Alakeel

جامعة الملك سعود
King Saud University

COLOR GUIDE: • Females' Notes • Males' Notes • Important • Additional

Objectives

1. Define the meaning of leukemias and determine acute and chronic.
2. Identify the pathophysiology & etiology of leukemia.
3. Describe the diagnosis and prognostic features of leukemia.
4. Explain how the management of leukemia.

Text in orange is from Davidson's.

The (Approach) part just below the summery is add by the team leaders. It is taken from (*Approach to Internal Medicine*) by David Hui

Leukemias

Leukemias are a group of cancers of the blood/bone marrow and are characterized by an abnormal proliferation (production by multiplication) of blood cells, usually white blood cells (leukocytes). Leukemia is a broad term covering a spectrum of diseases. Any of various acute or chronic neoplastic diseases of the bone marrow in which unrestrained proliferation of white blood cells occurs and which is usually accompanied by anemia and thrombocytopenia.

Leukemic cells infiltrate the bone marrow leading to suppression of normal hematopoiesis and subsequently bone marrow (BM) failure.

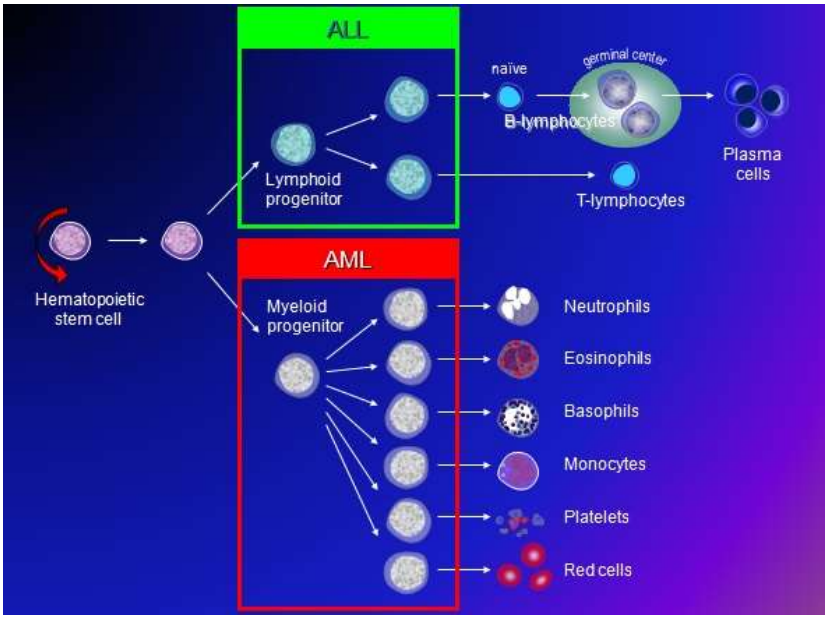
Classification of leukemias

Two major types (4 subtypes) of leukemias: With different prognosis and treatment

- **Acute leukemias**
  - Acute lymphoblastic leukemia (ALL)
  - Acute myelogenous leukemia (AML) (also "myeloid" or "nonlymphocytic")

- **Chronic leukemias**
  - Chronic lymphocytic leukemia (CLL)
  - Chronic myeloid leukemia (CML)

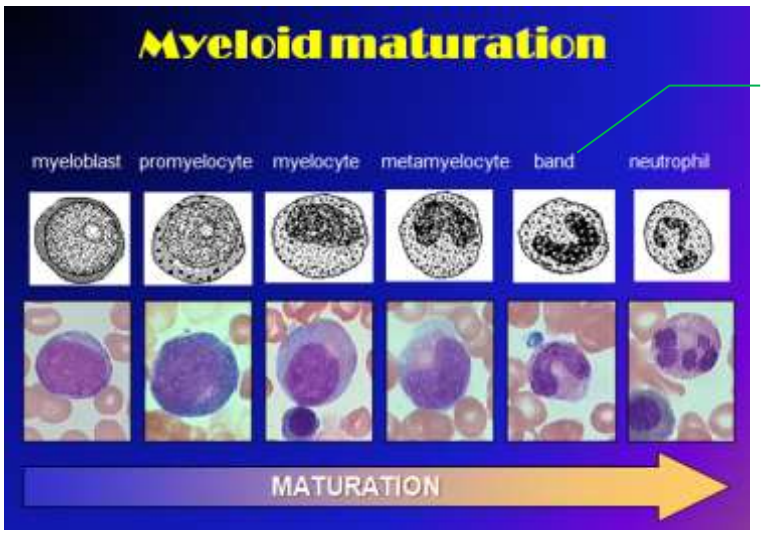
(Within these main categories, there are typically several subcategories)



- Any disease that arises from the myeloid elements (white cell, red cell, platelets) is a myeloid disease → AML, CML.
- Any disease that arises from the lymphoid elements is a lymphoid disease → ALL, CLL.

Acute vs. Chronic leukemia

	Acute	Chronic
Cell type	Young, immature, blast cells in the bone marrow (and often blood)	Accumulation of mature, differentiated cells in bone marrow and blood.
Presentation	More fulminant presentation Short history	Often subclinical or incidental presentation
Course	More aggressive course	In general, more indolent (slow) course
Extramedullary manifestations	Occasionally blast cells may form a tumor-like mass anywhere in the body termed "myeloid sarcoma","chloroma" or "granulocytic sarcoma". This is especially true for AML.	Frequently splenomegaly
CBC	Predominance of blasts in blood WBC count is usually high due to blast cells (NOT mature WBCs) but occasionally it may be normal or low because BM can be tightly packed and cells are unable to pass into peripheral blood.	• Leukocytosis with mature lymphocytosis → CLL • Leukocytosis with mature neutrophilia → CML



To recap, leukemias are classified according to cell of origin:

Lymphoid cells

- ALL - lymphoblasts
- CLL – mature appearing lymphocytes

Myeloid cells

- AML – myeloblasts
- CML – mature appearing neutrophils

Remember! WBC, RBC and platelets have the same origin, which is myeloid.

Acute leukemia

Definition: Disorders with clonal expansion of precursor cells (myeloid or lymphoid) with reduced capacity to differentiate. There is maturation arrest at the blast stage and bone marrow infiltration by blast cells causing suppression of normal precursors (bone marrow failure). (> 20% blast cells in the bone marrow)

- Normal blast cell count in BM should be less than 5%.
- If blast count falls between 5-20% → Myelodysplastic syndromes (MDS), which is a group of pre-leukemic conditions usually presenting with refractory anemia and excess blast count.

Types:

1. Acute Myeloid Leukemia (AML)

2. Acute Lymphoblastic leukemia (ALL)

Note(s):

ALL is the most common cancer in children, it is highly curable (almost 85% of patients).

Age Groups:

Childhood (< 15)	> 80%	ALL
Adult (> 15)	> 80%	AML
Elderly (> 60 years)		

AML is about four times more common than ALL in adults. In children, the proportions are reversed, the lymphoblastic variety being more common.

Etiology:

- Mostly unidentifiable cause i.e., de nove (≥80%)
- Drugs & chemicals: One of the side effect of chemotherapy is secondary malignancy such as AML.
  - Alkylating agents (Chlorambucil, N mustard, Melphalan)
  - Topoisomerase inhibitors (Etoposide) Also called VP-16
  - Benzene
- Ionizing radiation. Best evidence that radiation causes cancer is the famous atomic explosion in Japan.
- Myelodysplastic syndrome.
- Myeloproliferative disorders → (CML, polycythemia vera, essential thrombocythemia, myelofibrosis)
- Genetic disorders: All characterized by some DNA damage and inefficient repair mechanisms making them prone to leukemia
  - Down's syndrome
  - Bloom syndrome
  - Faconi anemia
  - Wiskott Aldrich syndrome

Clinical presentation

Symptoms

- Usual 1-3 Month History : MDS – 1yr
- Features of BM failure.
- Fatigue, malaise, dyspnea (anemia).
- Bleeding. e.g. after dental procedure.
  - Easy bruisability
  - Severe epistaxis
  - Patients with low platelet count develop muco-cutaneous type of bleeding.
- Fever (infections). → Low neutrophil count predisposes to recurrent bacterial and fungal infections.
- Bone Pain due to infiltration of bone marrow, press over the sternum or the shin.

Signs

- Pallor.
- Hemorrhage from the gums, epistaxis, skin, fundus, GI tract, urinary tract, menorrhagia is common in females.
- Hepato-splenomegaly.
- Enlarged lymph nodes. Mostly in ALL.
- Gum (hypertrophy) or skin infiltration (M5). Because leukemic cells infiltrate gum tissue.
- Fever (sepsis, pneumonia, peri-rectal abscess).

Diagnosis

- **CBC:**
  - Anemia
  - Thrombocytopenia
  - WBC count
    - **High** (chronic/acute)
    - Normal (acute) or
    - Low (acute)
- **Coagulation Studies:** Acute promyelocytic leukemia (M3) is associated with DIC
- **Biochemical Studies (Urea and electrolytes, liver function test).**
- **Peripheral Blood smear:** shows blasts in almost all cases
- **Bone Marrow Examination & Romanowsky stain:**
  - Enumeration of blasts, maturing cells, recognition of dysplasia. >20% blasts → here you can establish the diagnosis of acute leukemia.
  - **Types of bone marrow biopsies:**

    1. Aspirate, for cytology → useful for examination of cellular details.

    2. Tissue, for histology → most useful in cases of aplastic anemia or to see infiltration by tumor or fibrosis.

- **Flow cytometry (Surface immunophenotype of blast cells):**
  - Defines blast cell lineage commitment as myeloid, lymphoid or biphenotypic.
  - Immunophenotyping detects the presence or absence of white blood cell (WBC) antigens.
  - Most of the antigens that immunophenotyping detects are identified by a CD (clusters of differentiation or cluster designation) number, such as: CD1a, CD2, CD3, CD4, CD8, CD13, CD19, CD20, CD33, CD61, etc.
  - Flow cytometry is performed by processing blood or marrow samples and adding specific antibodies tagged with fluorescent markers. These antibodies attach to corresponding antigens on the WBCs when the antigens are present, and are analyzed.
  - Results are then graphed and compared to "normal" results and to patterns that are known to be associated with different leukemias

- **Cytogenetics (chromosomal analysis) & molecular studies (FISH, PCR):** Detect clonal chromosomal abnormalities, including those of prognostic importance.
- **CSF analysis:** (all ALL patients, some AML).
- **Cytochemistry:** Myeloperoxidase, Sudan Black B, esterases to determine involved lineages Cytochemistry is becoming obsolete and is less used nowadays.

Differential diagnosis

1. Aplastic anemia.
2. Myelodysplastic syndromes (MDS).
3. Multiple myeloma. → Plasma cell malignancy (B lymphocytes)
4. Lymphomas. → Can infiltrate BM causing a drop in cell counts.
5. Severe megaloblastic anemia. → May result in low cell counts however, BM biopsy will look normal, folic acid deficiency.
6. Leukemoid reaction. → WBC count is about 50,000
   *If WBC count is > 100,000 = hyperleukocytosis, it raises the suspicion of leukemia.

Epidemiology of AML

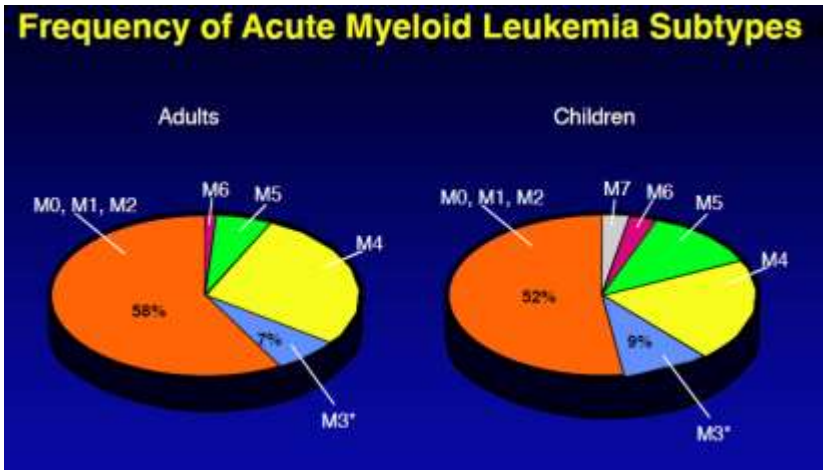
- Incidence – 2.7 per 100,000
  - 12.6 per 100,000 in those over 65 yrs
  - median age of presentation : 67 yrs
- More prevalent in:
  - Males
  - European descent
  - Hispanic/Latino background (promyelocytic leukemia, AML-M3)

FAB (French American British) Classification of AML

- **M0** undifferentiated acute myeloblastic leukemia (5%)
- **M1** AML with minimal maturation (20%)

- **M2** AML with maturation (30%) → t(8;21) associated with a good prognosis
- **M3** Acute promyelocytic leukemia (5%) → t(15;17) PML/RARA gene fusion
- **M4** Acute myelomonocytic leukemia (20%)
- **M4** eos Acute myelomonocytic leukemia with eosinophilia (5%) → inv (16)
- **M5** Acute monocytic leukemia (10%) → t(9;11)
- **M6** Acute erythroid leukemia (3%)
- **M7** Acute megakaryoblastic leukemia (3%)

M6 & M7 are rare.



WHO Classification of AML

- **AML with recurrent genetic abnormalities:**
  - t(8;21), t(16), inv(16), chromosome 11 changes
  - t(15;17) as usually seen with AML M3
- **AML with multilineage dysplasia (more than one abnormal myeloid cell type is involved).** Likely to have evolved from MDS → worse prognosis and difficult to treat
- **AML related to previous chemotherapy or radiation. (secondary AML)**
- **AML not otherwise specified**
  - undifferentiated AML (MO)
  - AML with minimal maturation (M1)
  - AML with maturation (M2)
  - Acute myelomonocytic leukemia (M4)
  - Acute monocytic leukemia (M5)
  - Acute erythroid leukemia (M6)
  - Acute megakaryoblastic leukemia (M7)
  - Acute basophilic leukemia (M8)
  - Acute panmyelosis with fibrosis
  - Myeloid sarcoma (also known as granulocytic sarcoma or chloroma)
- **Undifferentiated or biphenotypic acute leukemias:** leukemias that have both lymphocytic and myeloid features. Sometimes called ALL with myeloid markers, AML with lymphoid markers, or mixed lymphoid lineage leukemias, it is difficult to diagnose and to treat.

Treatment of acute leukemias

1. Specific therapy (chemotherapy): Which includes 3 stages

a) Induction: In this phase, the bulk of the tumor is destroyed

- Obtained by using high doses of chemotherapy causing severe bone marrow hypoplasia thus, allowing regrowth of normal residual stem cells to regrow faster than leukemic cells.
- **Remission** is defined as < 5% blast in the bone marrow + normal neutrophil and platelet count and normal hemoglobin level.

b) Consolidation: If remission has been achieved, residual disease is attacked in this phase.

- Repeated cycles of different or same drugs to those used during induction.
- Higher doses of chemotherapy.
- Advantage: Delays relapse and improved survival.
- In poor prognosis leukemia, this may include hematopoietic stem cell transplantation.

c) Maintenance: For ALL patients only, it is not benefit with AML

- Smaller doses for longer period
- Produce low neutrophil counts & platelet counts
- Objective is to eradicate progressively any remaining leukemic cells.

***Note:** Treatment of acute promyelocytic leukemia M3 includes ATRA (all transretenoic acid) which has greatly reduced induction deaths from bleeding in this good-risk leukemia.

2. Supportive treatment:

- Vascular access (Central line) because these patient need to have their blood drawn frequently for tests + chemotherapy + IV fluids and drug administration + blood transfusions. So it is more convenient for both the doctor and the patient to get a central line.
- Prevention of vomiting
- Blood products (Anemia, ↓Plat)
- Prevention & treatment of infections (antibiotics)
- Management of metabolic complications

ALL vs. AML regarding treatment

ALL	AML
Induction	Induction
Consolidation	Consolidation
Maintenance	**No** maintenance
CNS prophylaxis for all patients	CNS – Selected group only

*In patients with ALL, it is necessary to give CNS prophylactic treatment as this is a sanctuary site where standard therapy does not penetrate. This usually consists of a combination of cranial irradiation, intrathecal chemotherapy and high dose methotrexate, which crosses the blood brain barrier.

Prognosis *important*

Prognostic factors in AML:

- **Age**: Above the age of 50 years, the complete remission rate falls progressively.
- **Cytogenetics**: Three risk groups defined
  - Good risk: patients with t(8;21), t(15;17) and inv/t(16).
  - Intermediate risk: Normal, +8, +21, +22, 7q-, 9q-, abnormal 11q23, all other.
  - Poor risk: patients with -7, -5, 5q-, abnormal 3q and complex karyotypes.
- **Treatment response:**
  - Patients with >20% blasts in the marrow after first course of treatment have short remissions (if achieved) and poor overall survival.
  - If they promptly clear the leukemia → good sign
  - If on day 15-20 of chemotherapy and they still have blast cells in blood or BM → bad sign. Inadequate response to therapy.
- **Secondary AML:** Patients with AML following chemotherapy or myelodysplasia respond poorly (bad prognosis).
- **myelodysplasia:** Patients with trilineage myelodysplasia have a lower remission rate.

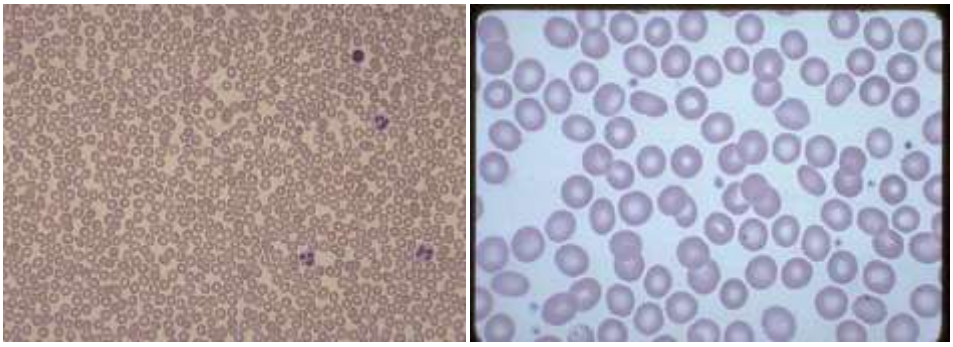
Treatment and prognosis of AML

- **Intensive chemotherapy**
  - Patients < 55 years old: 80% remissions
  - Patients > 55 years old: progressive reduction in remission rate
- **Bone marrow (stem cell) transplantation**
  - Autologous and allogeneic transplants reduce the relapse rate.
  - In acute leukemia, the immune system fails to recognize and fight abnormal cancerous cells.
  - Allogeneic BM transplant enhances their immunity to eradicate leukemic cells. (Graft vs. leukemia effect).
- **Importance of cytogenetics for prognosis in children and adults < 55 years old**
  - Good risk cytogenetic group: 91% remissions, 65% five year survival

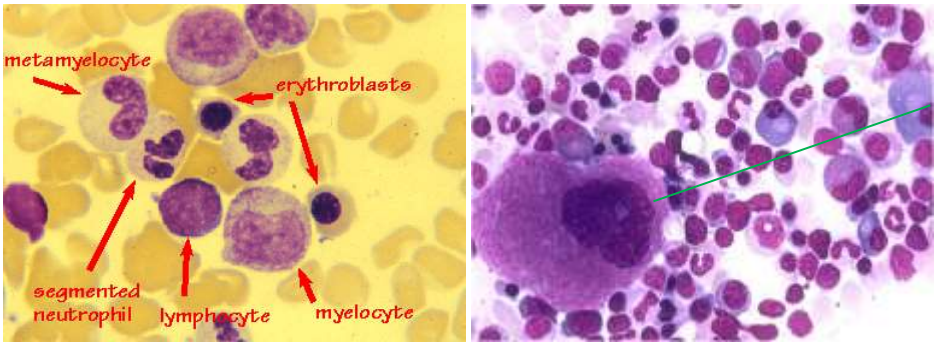
Prognostic factors in ALL

Poor Prognostic Factors:

- Age < 2 yrs and > 10 yrs best prognosis between 2-10 yrs old
- Male sex
- High WBC count (> 50 $x10^9$/L)
- Presence of CNS disease
- Bone Marrow: Blasts present on day 14
- Day 28: No complete response
- Cytogenetics:
  - Hyperdiploid (>50 ch) → Good risk.
  - Hypodiploid, t(9:22), t(4:11) → Poor risk.

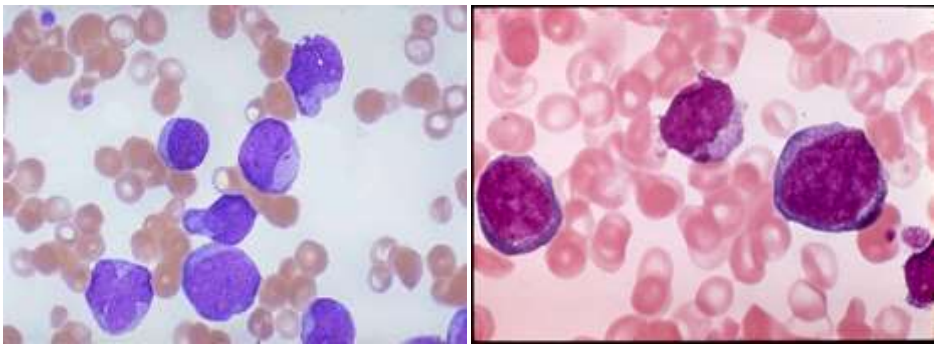


Normal blood film



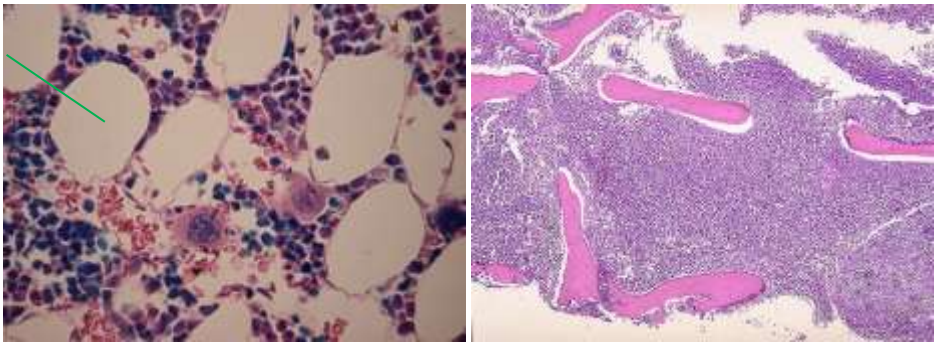
Megakaryococyte

Normal bone marrow



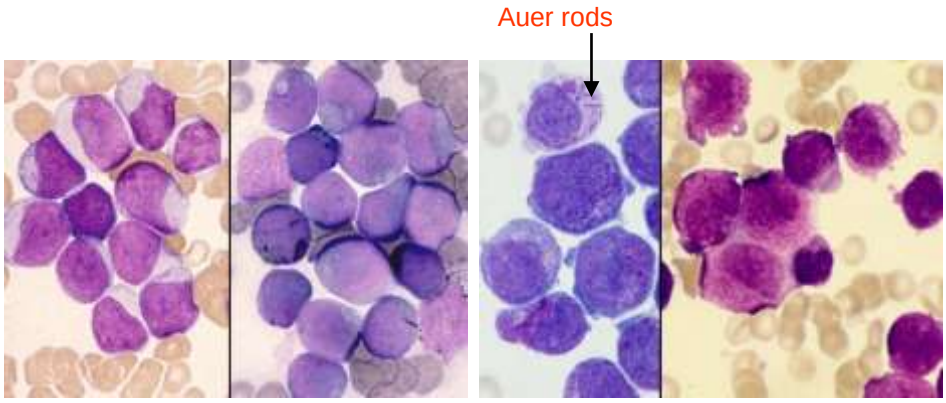
Blast cells

Fat cell



Normal BM biopsy

BM biopsy in AML (hypercellular)



Sudan black stain positive in AML

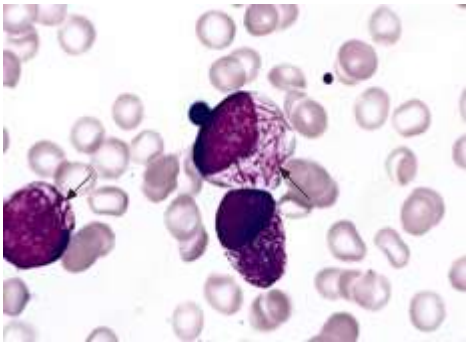


Figure 1

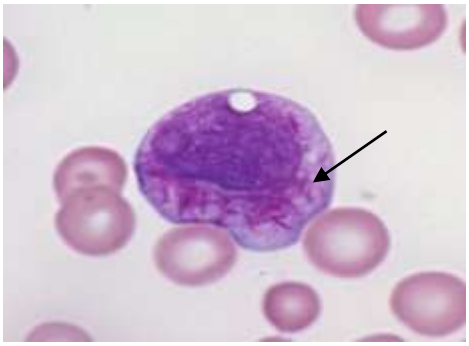
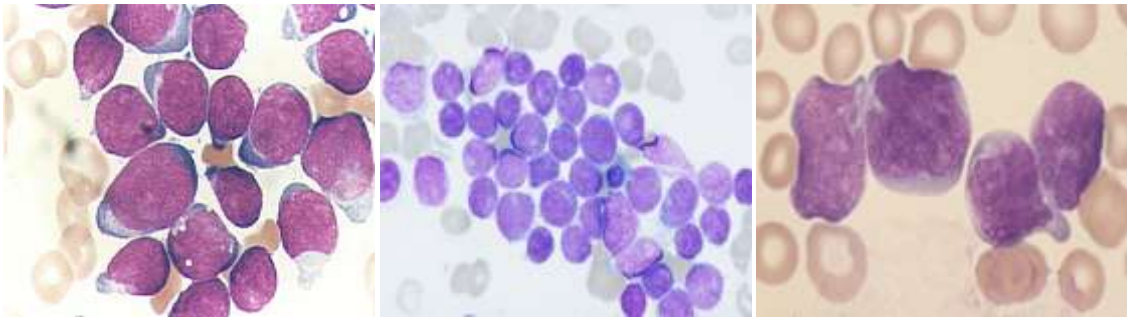


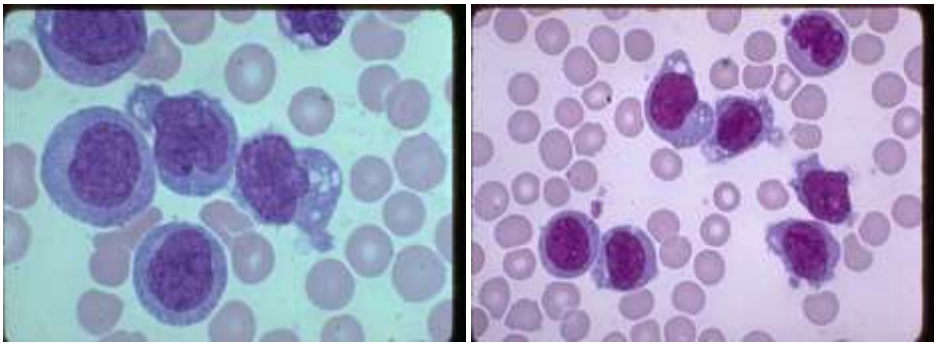
Figure 2

AML

Arrows pointing at Auer rods in figure 1 and 2, which are eosinophilic granules forming a line (Auer rods). They can be seen in AML but NOT in ALL.



ALL



Budding out of blast cells → most likely to be megakaryocytic

Chronic Leukemias

Definition: Neoplastic proliferations of mature haemopoeitic cells.

Types:

1. Chronic lymphocytic leukemia (CLL)
2. Chronic myeloid leukemia (CML)

Chronic Lymphocytic Leukaemia (CLL)

- Neoplastic proliferations of mature lymphocytes.
- Distinguished from ALL by:
  - Morphology of cells.
  - Degree of maturation of cells.
  - Immunologically immature blasts in ALL.
  - CLL affects mainly elderly.

Clinical presentation

Symptoms: Symptoms are similar to lymphoma

- May be entirely absent in 40%.
- Weakness, easy fatigue, vague sense of being ill.
- Night sweats.
- Feeling of lumps.
- Infections especially pneumonia.
- Presence of B symptoms (fever, night sweats, weight loss) is an indication to treat.

Physical examination:

- Pallor.
- Lymphoadenopathy:
  - Cervical, supraclavicular nodes more commonly involved than axillary or inguino-femoral.
  - Non-tender, not painful, discrete, firm, easily movable on palpation.
- Splenomegely, mild to moderate.
- Hepatomegaly.

Clinical staging: *important*

- **Stage 0-I →** lymphocytosis ± Lymph nodes (LNS).
- **Stage II →** above + hepatosplenomagely.
- **Stage III →** Anaemia. Hb< 10 g/l
- **Stage IV →** Thrombocytopenia. Platelet count : $<100x10^9/L$.

Laboratory Tests

- CBC
  - Lymphocyte count > 5 x 10^9/L (5 -500 x 10^9/L).
  - Platelets may be decreased
  - Hb may be low
- Blood film.
- PB immunophenotyping.
- Bone marrow biopsy (needed before starting treatment) to have a baseline and follow up with treatment.
- Imaging is needed occasionally if there is an enlarged lymph node.

Treatment

- **Observation.** In early stages of CLL, you don't have to treat you can wait and observe because studies showed no benefit nor change in outcome from treating them earlier.
- **Chemotherapy**.
  - Oral chlorambucil
  - Fludarabine, Cyclo
- **Immunotherapy**
  - Anti-CD 20 (Rituximab) Treats both lymphoma and CLL.
  - Anti-CD 52 (Alemtuzumab)
- **FC-R (**Fludarabine, Cyclo and Rituximab**) is the current standard**
- **Indications for starting chemotherapy**
  - Progressive Symptoms
  - Progressive Anemia or Thrombocytopenia
  - Bulky LN, large spleen
  - Recurrent Infections

Chronic Myeloid Leukemia (CML)

- CML is a clonal stem cell disorder characterised by increased proliferation of myeloid elements at all stages of differentiation.
- Incidence increases with age, M > F.
- **CML is characterised by 3 distinct phases:**
  1. **Chronic Phase:** Proliferation of myeloid cells, which show a full range of maturation. Here the disease is reposnisve to treatment and easily controlled (Early phase).
  2. **Accelerated Phase:** A decrease in myeloid differentiation occurs.
  3. **Blast crisis** in wich the disease transforms into an acute leukemia, either myeloid (70%) or lymphoblastic (30%) which is relatively refractory to treatment (difficult to treat). This is the cause of death in the majority of patients.
- Most patients present in the chronic phase. If untreated, they progress to accelerated phase or even worse, blast crisis.

Clinical features

Symptoms

- Asymptomatic (50% of patients)
- Fatigue
- Weight loss
- Abdominal fullness and anorexia
- Abdominal pain, esp splenic area
- Increased sweating
- Easy bruising or bleeding

Signs

- Splenomegaly (95%) (50% of patients have a palpable spleen ≥ 10 cm BCM, usually firm and non tender). Patients with CML typically have a huge (massive) spleen reaching the midline and umbilicus.
- Hepatomegaly (50%)
- Sternal tenderness is a reliable sign of disease. Is usually limited to a small area, most commonly the midbody. (Fifth intercostal disease).

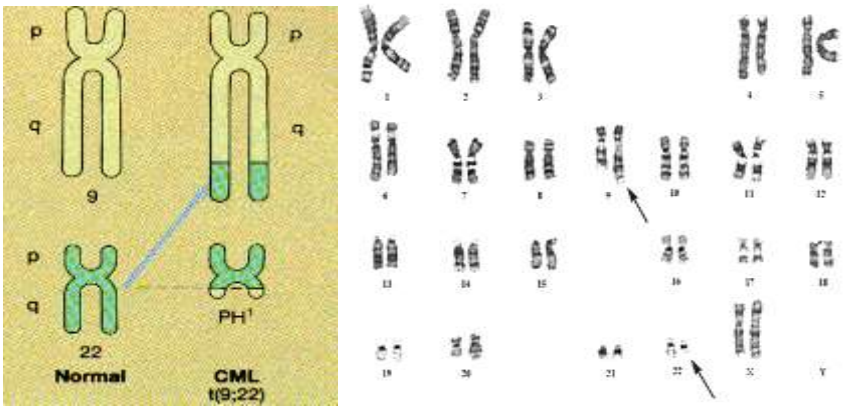
Diagnosis

Blood picture in chronic phase:

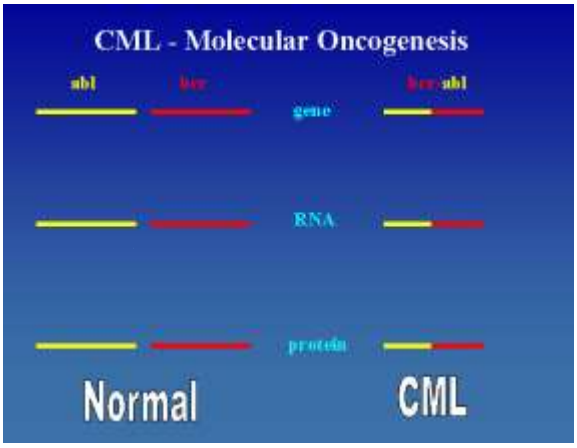
- Neutrophil leukocytes 20,000 - >500, 000/μ L High WBC count
- Basophilia → tends to increase as the disease progresses.
- Low LAP score
- Blasts < 5%
- Nucleated RBCs
- Thrombocytosis→ High platelet count may persist during treatment, in both chronic and accelerated phases but usually drops dramatically at blast transformation.
- Anaemia

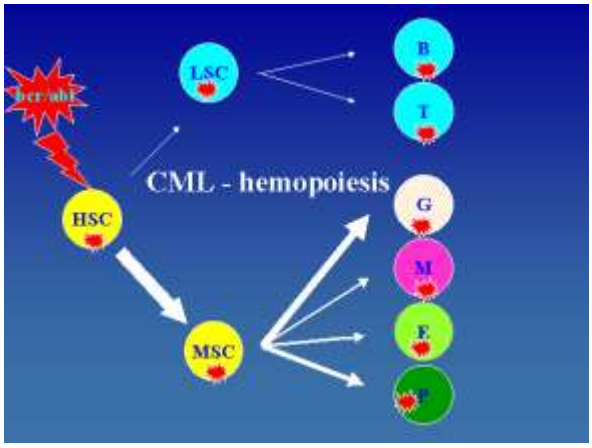
Cytogenetics of CML:

- Philadelphia (Ph) chromosome is an acquired cytogenetic abnormality in all CML cells.
- Reciprocal translocation of chromosomal material between chromosome 22 and chromosome 9. **t(9;22)**
- Diagnostic test for CML → if you don't have a positive Ph chromosome, it's not CML



Karyotype 46,XX,t(9;22)(q34;q11.2) -- Ph chromosome





- ABL & BCR are two separate normal genes present in chromosomes 9 & 22 respectively. They are called proto-oncogenes. When they combine together in chromosome 22 they form a hybrid "fusion" gene which is the Ph chromosome → becomes an oncogene → simulation of cell production by inducing tyrosine kinase.
- In some patients in whom conventional chromosomal analysis does not detect a Ph chromosome, BCR ABL gene product is detectable by molecular technique.

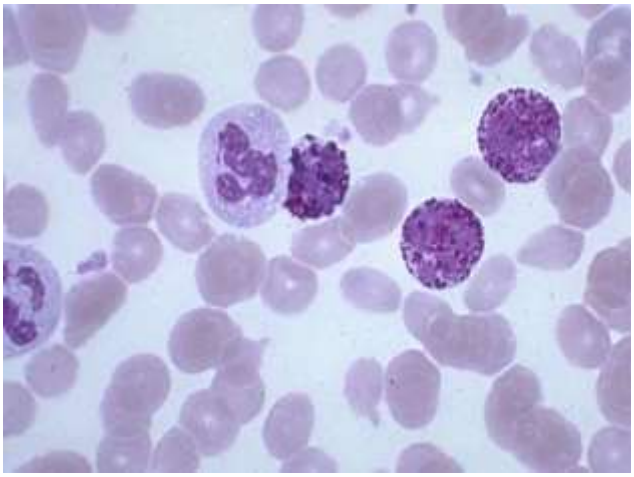
Treatment

Treatment response criteria:

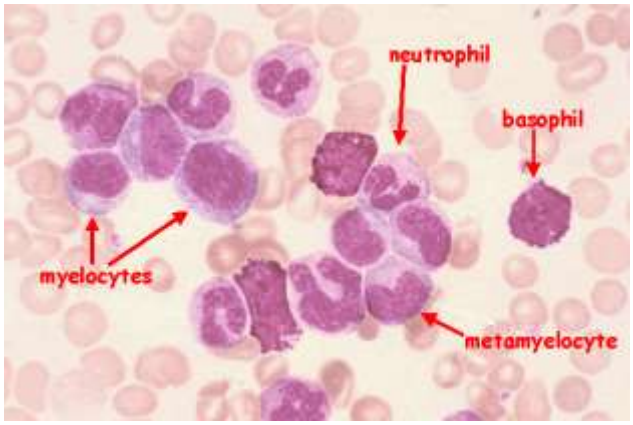
- **Hematological response:** Normalization of blood count.
- **Cytogenetic response:** Ph chromosome should disappear in response to therapy. Therefore, its presence should be tested repeatedly to monitor response to treatment.
  - Major cytogenetic response → 1-35% Ph +ve cells in metaphase
  - Minor cytogenetic response → 36-65% Ph +ve cells in metaphase
- **Molecular response**, a simple PCR quantitative test**:** Absence of BCR/ABL gene

Principles of treatment:

- **Control & prolong chronic phase (non-curative)**
  - Tyrosine kinase inhibitors-Imatinib (Glivec): First line treatment
  - In resistant cases 2nd line TKIs (Nilotinib, Dasatinib, Bosutinib) are very useful (approved as 1st line)
  - Alpha-Interferon: used previously as 1st line and had many side effects including flu-like symptoms and depression.
  - Oral chemotherapy (Hydroxyurea, ARA-C)
- **Eradicate malignant Clone (curative)**
  - Allogeneic BM/stem cell transplantation: can be curative in pts resistant to TKIs but has significant complications & mortality.
  - Alpha Interferon?
  - Imatinib? 2nd line TKIs
- **Accelerated and blast phase**
  - Imatinib, 2nd line TKIs
  - Treat like AML or ALL followed by BMT



CML. 1 mature neutrophil and 3 Basophils

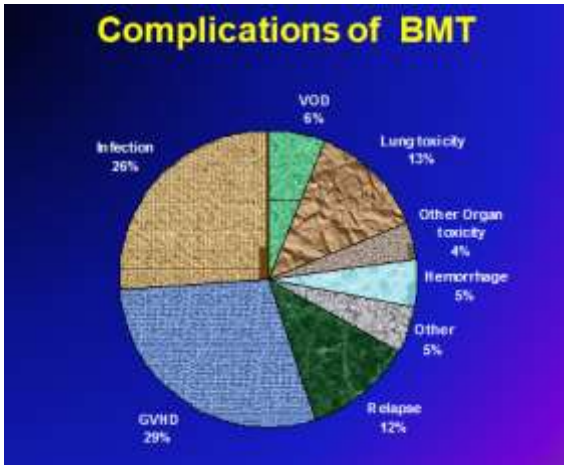


CML vs. Leukemoid Reaction

1. LAP Score
2. Philadelphia Chromosome
3. Basophilia
4. Splenomegaly

Bone marrow or PBSC transplantation in leukemias

- **Types of transplant**
  - Autologous transplant. Patient's own stem cells are first harvested and frozen. After conditioning therapy, the autologous stem cells are reinfused.
  - Allogeneic Transplant. Healthy marrow or blood stem cells from a donor are infused intravenously into the recipient.
- **Purpose of transplant**
  - Autologous: To deliver a high dose of chemo to kill any residual cancer (lymphoma, multiple myeloma)
  - Allogeneic: To eradicate residual leukemia cells. Graft vs leukemia effect.



- **Technique of transplantation**
  - MHC + HLA matching
  - Chemotherapy
  - Total body irradiation
  - GVHD prophylaxis

- **Complications of transplantation**
  - Prolonged BM suppression (graft failure)
  - Serious infections
  - Mucositis
  - Graft versus host disease (GVHD); Graft-versus-host disease (GVHD) is caused by the cytotoxic activity of donor T lymphocytes which become sensitized to their new host, regarding it as foreign.

SUMMARY

1. If mature differentiated cells are proliferating, the cells will have low growth fraction and produce indolent neoplasms. E.g. Chronic leukemia
2. If more primitive stem cells are involved, the cells have the highest growth fraction of all human neoplasms, producing rapidly progressive, life-threatening illnesses like acute leukemia.
3. In general, hematological malignancies are diseases of elderly patients, the exception being ALL which predominantly affects children, and Hodgkins lymphoma, which affects people aged 20-40 years.
4. The diagnosis of leukemia is usually suspected from abnormal blood count, often a raised white count, and is confirmed by examination of the bone marrow.
5. Classification and prognosis of acute leukemia is determined by immunophenotyping, chromosome and molecular analysis.
6. Aggressive and potentially curative therapy which involves periods of severe bone marrow failure would not be possible without appropriate supportive care.
7. CML is a myelproliferative stem cell disorder resulting in proliferation of all hematopoietic lineages but manifesting predominantly in the granulocytic series.
8. The defining characteristic of CML is the chromosome abnormality known as Philadelphia chromosome.
9. The diagnosis of CLL is based on the peripheral blood findings of a mature lymphocytosis (> 5 x 109/L) with characteristic morphology and cell surface markers.
10. In CLL treatment is only required if there is evidence of bone marrow failure, massive or progressive lymphadenopathy or splenomegaly, systemic symptoms such as weight loss or night sweats, a rapidly increasing lymphocyte count or autoimmune hemolytic anemia or thrombocytopenia.
11. Imitinib is current standard of care for CML.

IMPORTANT NOTES FROM EXTERNAL RESOURCES

	Notes
Name of 1st book	Davidson's Principles and Practice of Medicine
Question book	Rubin's Pathology Q&A

Approach to Leukemia

HEMATOLOGIC MALIGNANCIES OVERVIEW

I. **MYELO** bone marrow. Myeloproliferative disorders (PRV, CML, ET, and MF) involve cell accumulation, while myelodysplastic disorders involve abnormal bone marrow cell growth. Both disorders have risk of transformation to acute myeloid leukemia.
II. **MYELOID** neutrophils, monocytes, macrophages, eosinophils, basophils, mast cells, erythrocytes, platelets, and their precursors. Myeloid malignancies include AML and CML.
III. **LYMPHOID** B cells, T cells, natural killer cells. Lymphoid malignancies include ALL, CLL, and all lymphomas.
IV. **LEUKEMIA** malignant cells in blood and/or bone marrow. May be myeloid (AML, CML) or lymphoid* (LL/ALL, SLL/CLL) in origin. Myeloid leukemia seldom presents in lymph nodes.
    - ACUTE LEUKEMIA involves immature blast cells. More aggressive course
    - CHRONIC LEUKEMIA involves mature differentiated cells. More indolent course
V. **LYMPHOMA** malignancy of lymphoid origin and presents more in lymphoid organs.
    - HODGKIN'S LYMPHOMA B cell (Reed Sternberg cell)
    - NON-HODGKIN'S LYMPHOMA B, T, or NK cell.

*lymphoblastic lymphoma (LL) = acute lymphoblastic leukemia (ALL). Small lymphocytic lymphoma (SLL) = chronic lymphocytic leukemia (CLL)

CLINICAL FEATURES

- ✓ **PANCYTOPENIA** weakness, fatigue, infections, gingival bleed, ecchymosis, epistaxis, menorrhagia
- ✓ **BONE PAIN** ribs, sternum, long bones
- ✓ **CUTANEOUS LESIONS** leukemic cutis (especiallyM4,M5), chloromas (skin local collection of blasts, granulocytic sarcoma especially M2), gum hypertrophy (M5)
- ✓ **CNS LEUKEMIA** (especially M4, M4EO, and M5)
- ✓ **DIC** associated with M3 subtype
- ✓ NOTE: lymphadenopathy, hepatosplenomegaly not common

For more details go throw **(Approach to Internal Medicine)** starting from **page 166**

Questions

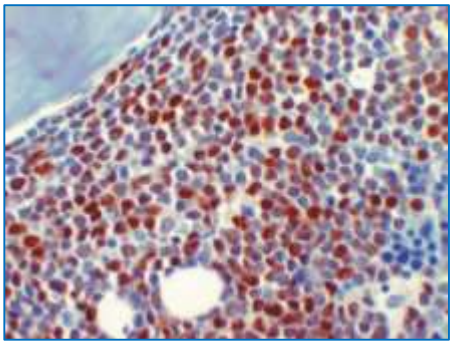
1) A 60-year-old man complains of night sweats, weight loss, easy fatigability, and discomfort in the left upper abdominal quadrant. Physical examination reveals splenomegaly. Laboratory studies show leukocytosis (40,000/mL). A peripheral blood smear demonstrates mature and maturing granulocytes, myelocytes, basophils, and occasional myeloblasts. The bone marrow is hypercellular and dominated by WBC precursors. Megakaryocytes are numerous, and RBC precursors are less prominent. A smear of the bone marrow aspirate is shown in the image. Cytogenetic studies disclose a monoclonal population of abnormal cells with a t(9;22)(q34;q11) chromosomal translocation. What is the appropriate diagnosis?

a. Acute lymphoblastic leukemia
b. Acute myeloid leukemia
c. Chronic lymphocytic leukemia
d. Chronic myelogenous leukemia
e. Myelodysplastic syndrome

2) Which oncogene is located at the t (9;22) chromosomal breakpoint in the patient described in Question 1?

a. abl
b. erb
c. myb
d. myc
e. neu

3) A 6-year-old boy presents with fatigue, fever, and night sweats. Physical examination reveals marked pallor. Palpation of his sternum demonstrates diffuse tenderness. Laboratory studies disclose anemia, thrombocytopenia, and leukocytosis. The WBC differential count shows that 90% blasts. A bone marrow biopsy stained immunohistochemically for terminal deoxynucleotidyl transferase (TdT) is shown in the image. Which of the following is the appropriate diagnosis?



a. Acute lymphoblastic leukemia
b. Acute myelogenous leukemia
c. Acute promyelocytic leukemia
d. Chronic lymphocytic leukemia
e. Chronic myelogenous leukemia

432 Medicine Team Leaders

Raghad Al mutlaq & Abdulrahman Al Zahrani
For mistakes or feedback: *medicine341@gmail.com*

Answers:

1st Questions: D

2nd Questions: A

3rd Questions: A