433 Teams

MEDICINE

6 | Leukemia

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Objectives:

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

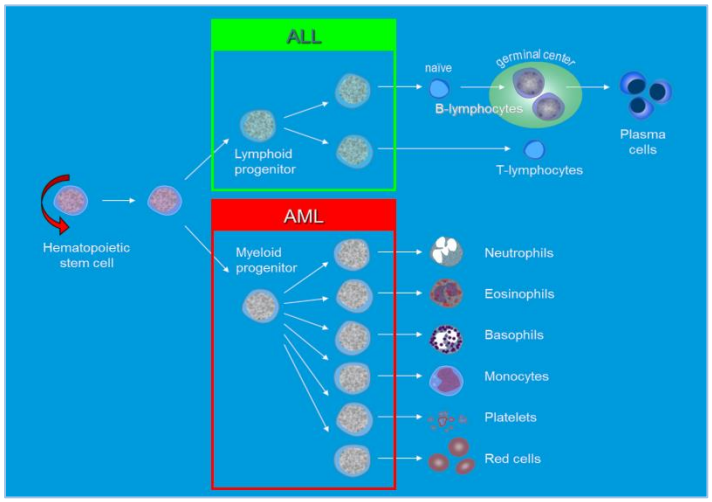
Leukemias

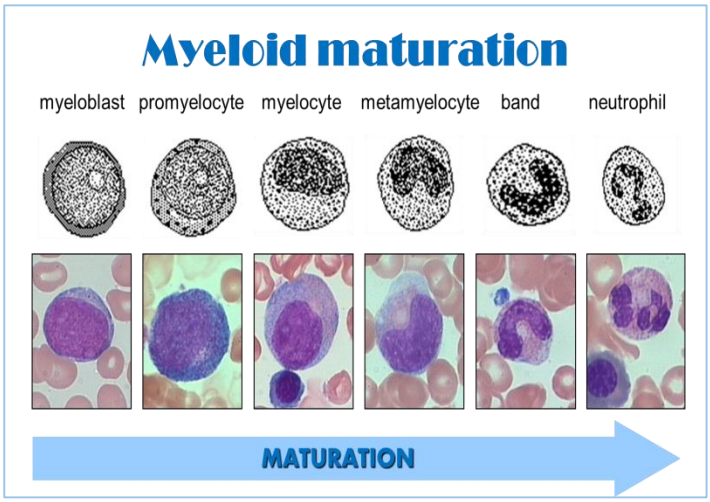
- **Leukemias** are a group of cancers of the blood/ bone marrow and are characterized by an abnormal proliferation (production by multiplication) of blood cells, usually white blood cells (leukocytes).
- **Leukemia** is a broad term covering a spectrum of diseases. Any of various acute or chronic neoplastic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

Classification of leukemias

Two major types (4 subtypes) of leukemias:

Acute leukemias	Chronic leukemias
Acute lymphoblastic leukemia **(ALL)**	Chronic lymphocytic leukemia **(CLL)**
Acute myeloid leukemia **(AML)**(also "myelogenous " or "nonlymphocytic")	Chronic myeloid leukemia **(CML)**





- 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).
- Leukemias are classified according to cell of origin:

Lymphoid cells	Myeloid cells
ALL - lymphoblasts	AML – myeloblasts
CLL – mature appearing lymphocytes	CML – mature appearing neutrophils

- The earliest cell that can be recognized in the bone marrow is the blast cell; so the feature of leukemia is increased number of blast cells.**(knowing the percentage of blast cells in bone marrow is important for diagnosis)**

Acute vs. chronic leukemia

	Acute leukemias	Chronic leukemias
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

! On a CBC, if you see:

- Predominance of **blasts** in blood → consider an **acute** leukemia.
- Leukocytosis with **mature** lymphocytosis → consider CLL.
- Leukocytosis with **mature** neutrophilia → onsider CML.

- Blasts → Acute
- Mature → Chronic
- **Acute promyelocytic leukemia**, the main cell type is promyelocytes with cytogenetic t(15;17) and the main clinical feature of the disease is **DIC** "disseminated intravascular coagulopathy" and it has a **very good prognosis.**

Acute Leukemia

Definition

- Disorders with clonal expansion of precursor (malignancies of immature hematopeotic cells) with reduced capacity to differentiate.
  1. Maturation arrest at the blast stage
  2. Bone marrow infiltration by blast cells causing suppression of normal precursors (bone marrow failure).

(> 20% blast cells in the bone marrow)

Groups

- Childhood (< 15 years) commonly (ALL)
- Adult (> 15 years) commonly (AML)
- Elderly (> 60 years)

Etiology

- **Mostly unidentifiable cause i.e., de nove (≥80%)**
- Drugs & chemicals
  - ✓ Alkylating agents (Chlorambucil, N mustard, Melphalan)
  - ✓ Topoisomerase inhibitors (Etoposide)
  - ✓ Benzene
- Ionizing radiation
- Myelodysplastic syndrome (MDS).

(Is a preleukemic state in which patient presents with cytopenia or anemia).

- Myeloproliferative disorders.

(is a malignant proliferation of myeloid cells, manly granulocytes and progresses to AML but never to ALL)

- Genetic disorders
  - ✓ Down's syndrome, Bloom syndrome, Faconi anemia, Wiskott Aldrich syndrome.

Symptoms

Usual 1-3 Month History : MDS – 1yr.

- ***Features of bone marrow failure:***
  1. **Anemia** (Fatigue, malaise, dyspnea).
  2. **Low platelets** (Bleeding e.g. after dental procedure, easy bruisability and Severe epistaxis).
  3. **Low neutrophils** → fever (bacterial & fungal infections).
  4. **Bone Pain**

Signs

- Pallor
- Hemorrhage from the gums, epistaxis, skin, fundus, GI tract, urinary tract
- Hepato-splenomegaly
- Enlarged lymph nodes
- **Gum (hypertrophy) or skin infiltration (M5)**
- Fever (sepsis, pneumonia, peri-rectal abscess)

Epidemiology	• 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)
Differential Diagnosis	1. Aplastic anemia. 2. Myelodysplastic syndromes. 3. Multiple myeloma (multiple myelomas arise from plasma cells). 4. Lymphomas. 5. Severe megaloblastic anemia. 6. Leukemoid reaction.
Diagnosis	• **Laboratory Tests** **1.** CBC → Anemia, Thrombocytopenia, normal or increased WBC. Despite an increase in white cell count, infection is a common presentation because leukemic cells (blasts) **do not function normally in controlling infection.** **2.** Peripheral Blood Smear → blasts in almost all cases. ✓ **M3 or acute promyelocytic** leukemia is most commonly associated with **Auer rods** also AML **3.** Bone Marrow Examination **(>20% blasts).**"the main technique to diagnose leukemias". **4.** Flow cytometry. Used to distinguish the different subtypes of acute leukemia by detecting the specific CD subtypes associated with each type of leukemia, myeloperoxidase is characteristic of acute myelocytic leukemia (AML). **5.** Cytogenetics (chromosomal analysis). **6.** CSF analysis (all ALL patients, some AML).

-The best initial test is a blood smear showing blast cells.

-The most accurate (gold standard) is flow cytometry.

Treatment of acute leukemias

1. Specific therapy (chemotherapy).

Stages of Therapy →	Induction	Consolidation	Maintenance

2. Supportive treatment:
   - ✓ Vascular access (Central line)
   - ✓ Prevention of vomiting
   - ✓ Blood products (Anemia, ↓Plat)
   - ✓ Prevention & treatment of infections**(antibiotics)**
   - ✓ Management of metabolic complications

✓ Stages of Therapy

1. Induction

- Obtained by using high doses of chemotherapy**(to achieve remession**
  1. Severe bone marrow hypoplasia
  2. Allowing regrowth of normal residual stem cells to regrow faster than leukemic cells.
- Remission (is achieved when the bone marrow is clear).
  - ✓ Normal neutrophil count
  - ✓ Normal platelet count
  - ✓ Normal hemoglobin level

Remission defined as < 5% blast in the bone marrow

2. Consolidation	• Repeated cycles of different or same drugs to those used during induction(repeated cycles of chemo to prevent relapse and kill all the malignant cells). • Higher doses of chemotherapy • Advantage: Delays relapse and improved survival
3. Maintenance	• Smaller doses for longer period • Produce low neutrophil counts & platelet counts • Objective is to eradicate progressively any remaining leukemic cells.

✓ Treatment (ALL vs AML)

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

Prognosis

The best indicator of prognosis in acute leukemia is cytogenetics

Table 9.20 Acute lymphoblastic leukaemia (ALL) risk factors

Risk factor	Good	Poor
Age	Younger age	Older age
WBC	<50×10⁹/L for B-lineage <100×10⁹/L for T-lineage	>50×10⁹/L for B-lineage >100×10⁹/L for T-lineage
Immunophenotype	CD10 + common ALL	Pro-B ALL
Cytogenetic aberrations	t(12;21) hyperdiploidy	t(9;22) or t(4;11) hypodiploidy
Time to response	Early clearance of blasts	Failure to achieve a CR within 3–4 weeks
Minimal residual disease	MRD negative	MRD positive
Extramedullary disease	CSF clear	CSF positive

- **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
- **Secondary AML**
  - Patients with AML following chemotherapy or myelodysplasia respond poorly
- **Trilineage myelodysplasia**
  - Patients with trilineage myelodysplasia have a lower remission rate

✓ WHO Classification of AML

- **AML with recurrent genetic abnormalities** → (Good prognosis)
  - t(8;21)M2, t(16) or inv(16)M, 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)** (poor prognosis)
- **AML related to previous chemotherapy or radiation** (poor prognosis)

• **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).**	

Chronic Leukemias

1. Chronic Lymphocytic Leukaemia (CLL)

Definition	• Neoplastic proliferations of mature lymphocytes. In chronic leukemias WBS's are so high where as in acute leukemias they're usually high, sometimes normal or even low in number. • Distinguished from ALL by a. Morphology of cells. b. Degree of maturation of cells. c. Immunologically immature blasts in ALL. d. CLL affects mainly elderly while ALL affects children .
Symptoms	• May be entirely absent in 40% • Weakness, easy fatigue, vague sense of being ill • Night sweats • **Feeling of lumps** "lymphadenopathy" • Infections especially pneumonia
Signs	• Pallor • **Lymphoadenopathy** A. Cervical, supraclavicular nodes more commonly involved than axillary or inguino-femoral. B. Non-tender, not painful, discrete, firm, easily movable on palpation. • Splenomegaly, mild to moderate. • Hepatomegaly
Clinical Staging	• (0-1) lymphocytosis ± lymph nodes. • (II) lymphocytosis ± lymph nodes + hepatosplenomagely. • (III) Anaemia. **(Hb< 10 g/l)** • (IV) Thrombocytopenia **(Platelet count : <100x109/L)**
Diagnostic Tests	• CBC ✓ **Lymphocytecount(> 5 x 10^9/L).** ✓ Platelets may be decreased ✓ Hb may be low

	✓ Blood film • PB immunophenotyping • Bone marrow biopsy (needed before starting treatment) • Imaging
Treatment	• For stage 0 and stage I →**there is no treatment.** • Stage II, stage III (anemia), and stage IV →treated with **fludarabine**. If there is a choice that lists fludarabine and rituximab, then this is the best initial therapy for advanced-stage disease (II, III, IV) or any patient who is symptomatic (severe fatigue, painful nodes).

2. Chronic Myeloid Leukemia (CML)

Tyrosine Kinase responses for the increase of proliferation in CML, because when BCR gene and ABL1 gene fused in Philadelphia chromosome "mutation in CML" leads to activate Tyrosine Kinase.

Definition	• CML is a **clonal stem cell** disorder characterised by increased proliferation of myeloid elements at all stages of differentiation. The clone is a group of cells that arise from a single cell; all cancers are clonal in nature. • Incidence increases with age, **M > F.**
Phases	• **Chronic Phase:** Proliferation of myeloid cells, which show a full range of maturation. • **Accelerated Phase** decrease in myeloid differentiation occurs. • **Blast crisis(acute leukemia)**
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) • Hepatomegaly (50%)
Diagnostic Tests	• **Chronic phase:** ✓ High WBC count that is **all neutrophils.** ✓ (After the high neutrophil count is found, you must determine if it is a reaction to another infection or stress (leukemoid reaction), or genuinely represents a leukemia). ✓ Leukocyte alkaline phosphatase score **(LAP) is low** in CML but high in reactive leukocytosis. ✓ The most accurate test is **BCR-ABL**," which can be done by PCR or FISH (fluorescent in-situ hybridization) on peripheral blood. ✓ Small numbers of **blasts**, but it should be **under 5%.** ✓ Basophils are increased. • **Cytogenetics:** ✓ **Philadelphia (Ph) chromosome** is an acquired cytogenetic abnormality in all leukaemia cells in CML, t(9;22). ✓ Reciprocal translocation of chromosomal material between chromosome 22 and chromosome 9.

Treatment	• **Tyrosine kinase inhibitors such as imatinib (Gleevec),** dasatinib, or nilotinib are the best initial therapy. • Only bone marrow transplantation can cure CML, but this should never be the first therapy.

✓CML vs leukemoid reaction:

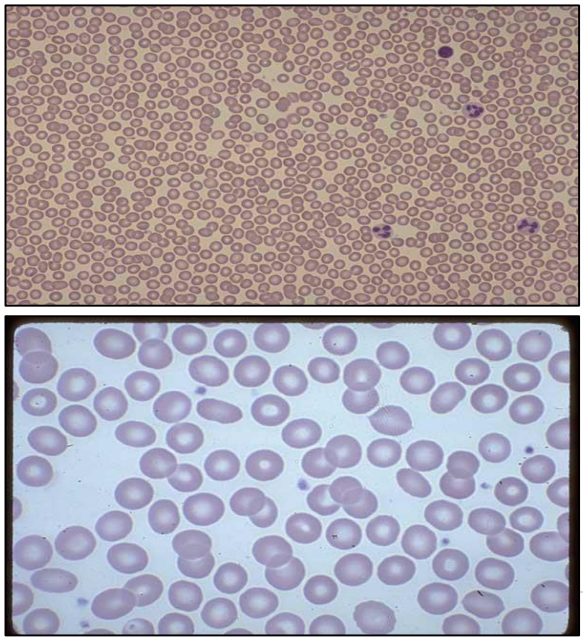
- ✓ LAP Score (low).
- ✓ Philadelphia Chromosome
- ✓ Basophilia
- ✓ Splenomegaly

leukemoid reaction is seen in cases of severe infection and stress in which WBS's are so high around 50,000.

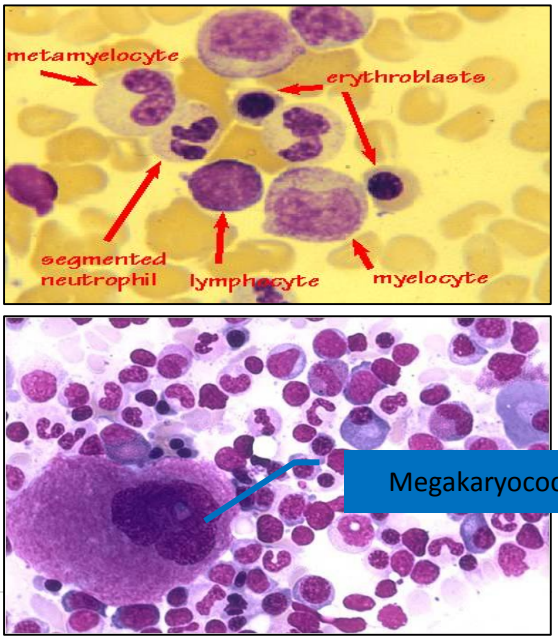
✓Transplantation in leukemias

Types of transplant	• Autologous transplant • Allogeneic Transplant
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
Signs	• Prolonged BM suppression (graft failure) • Serious infections • Mucositis • Graft versus host disease (GVHD)

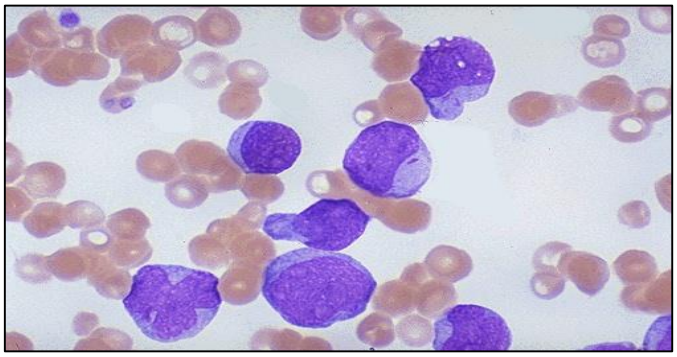
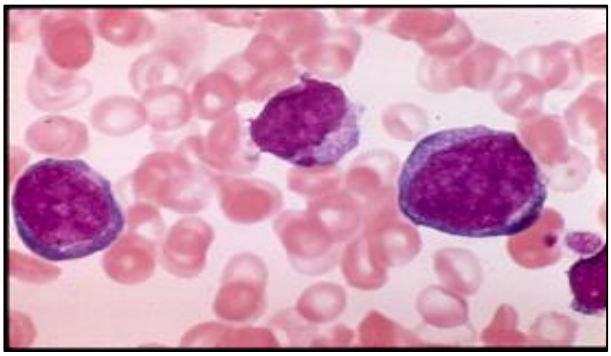
Blood Film-Normal



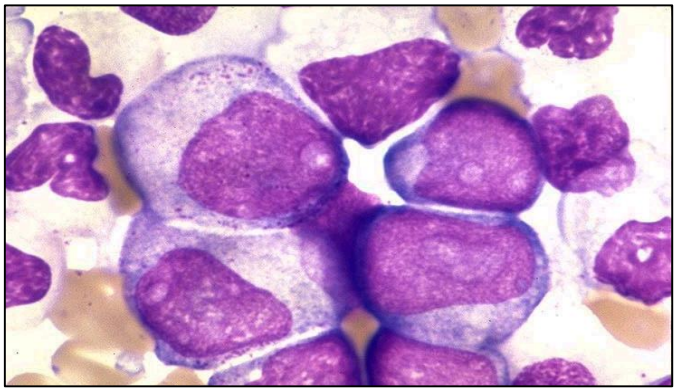
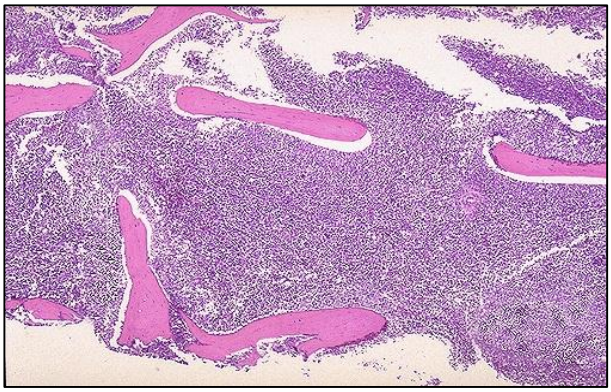
Normal BM cells



Acute leukemia

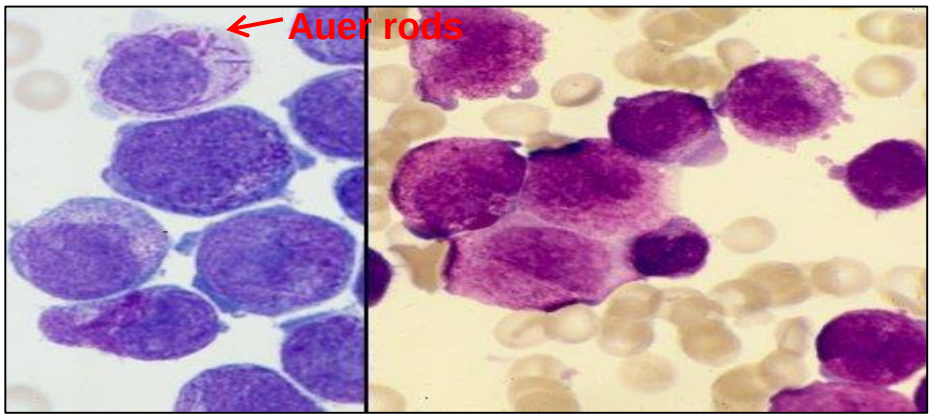



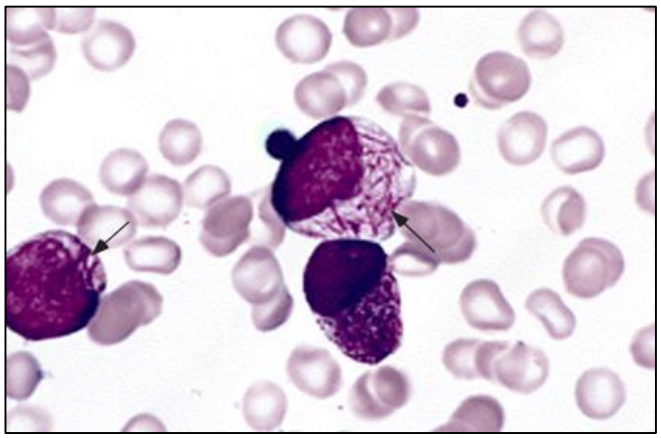
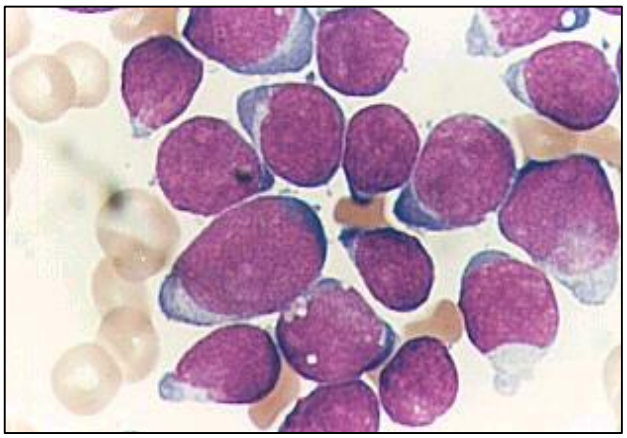
Blast cells

AML BM biopsy in AML (hypercellular)

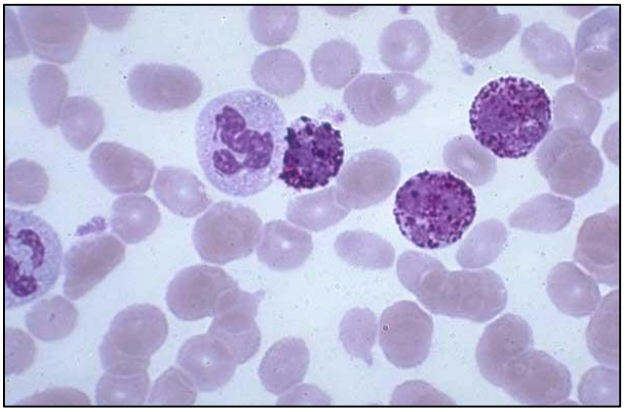
Q\ in which disease Aure Rods will be positive ?

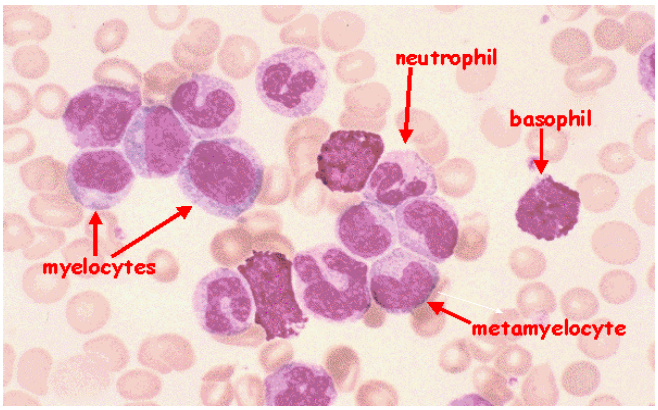


AML-M3 (Acute promyelocytic leukemia)

ALL





(CML) 1 mature neutrophil and 3 Basophils

Questions

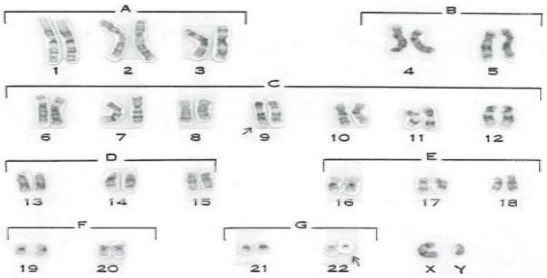
1-. A 60-year-old man presents with vague left upper quadrant abdominal fullness. He also has fatigue, malaise, and weight loss described as loosening of his pants. CBC shows Hgb: 12 g/dL (normal 14-18) Leukocytes: 40,000/µL (normal 4300-10,800) Platelet count: 500,000/µL (normal 150,000-400,000) Bone marrow biopsy shows hypercellular marrow. Chromosomal study is shown: Which of the following is the most likely diagnosis?

a. Acute myeloid leukemia

b. Chronic myelogenous leukemia

c. Chronic lymphocytic leukemia

d. Acute lymphocytic leukemia



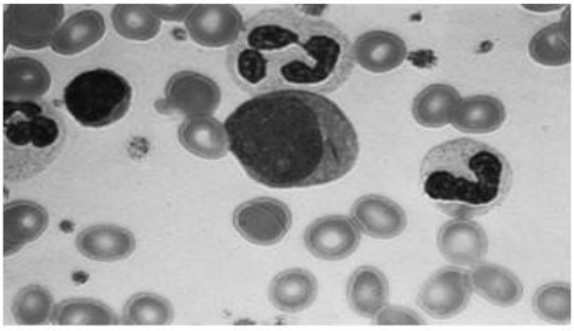
2-A 50-year-old man presents with 3 days of fever, diffuse bone pain, and extreme weakness. He denies any sick contacts. On examination, there is conjunctival pallor, dried blood on the nasal mucosa, and ecchymoses on both lower extremities. There is no lymphadenopathy or hepatosplenomegaly. Urinalysis and chest x-ray are normal. The peripheral blood smear is shown. What is the most likely diagnosis?

a. Multiple myeloma

b. Myelofibrosis

c. Acute myeloid leukemia (AML)

d. Chronic myelogenous leukemia (CML)



3- A 38-year-old woman presents with repeated episodes of sore throat. She is on no medications, does not use ethanol, and has no history of renal disease. Physical examination is normal. Hgb is 9.0 g/dL,MCV is 85 fL (normal), white blood cell count is 2000/µL, and platelet count is 30,000/µL. Which of the following is the best approach to diagnosis?

a. Erythropoietin level

b. Serum B12

c. Bone marrow biopsy

d. Liver spleen scan

e. Therapeutic trial of corticosteroids

4-327. A 47-year-old woman complains of fatigue, weight loss, and itching after taking a hot shower. Physical examination shows plethoric facies and an enlarged spleen, which descends 6 cm below the left costal margin. Her white cell count is 17,000 with a normal differential, the platelet count is 560,000, and hemoglobin is 18.7. Liver enzymes and electrolytes are normal; the serum uric acid level is mildly elevated. What is the most likely underlying process?

a. Myelodysplastic syndrome

b. Myeloproliferative syndrome

c. Paraneoplastic syndrome

d. Cushing syndrome

Answers: b, c, c, b.

Explanations

1. This patient has chronic myelogenous leukemia (CML).
Patients may be asymptomatic and diagnosed by abnormal CBC found incidentally, or patients may present with symptoms of fatigue, malaise, weight loss, early satiety or left upper quadrant pain due to splenomegaly. Patients with CML typically have a normocytic anemia, leukocytosis with mature cells more than immature cells, and thrombocytosis. Diagnosis can be confirmed with bone marrow biopsy and cytogenetic analysis. The cytogenetic hallmark is reciprocal translocation between chromosome 9 (Ablgene) and 22 (BCR gene) - t(9;22)(q34;q11.2), known as the Philadelphia chromosome. Thistranslocation results in an oncogenic gene (BCR-ABL gene). Treatment with the tyrosine kinase inhibitor imatinib has been shown to be effective in this condition. The Philadelphia chromosome is not specific to CML. Some patients, with acute lymphocytic leukemia (ALL) also have the BCR-ABL gene, but thesepatients do not have thrombocytosis. Acute myeloid leukemia and the lymphocytic leukemias are not associated with this chromosomal abnormality. None of the other choices are associated with thrombocytosis and the cytogenetic pattern shown.

2. Patients with acute myeloid leukemia (AML) usually present with nonspecific symptoms like fever, bone pain, headache, night sweats, and fatigue. Bone pain is attributed to the expansion of the marrow by leukemic cells. Laboratory abnormalities include anemia and thrombocytopenia. Patients with French American British (FAB) classification M3 variety (acute promyelocytic leukemia) of AML can also present with symptoms of disseminated intravascular coagulation (DIC) or can develop it during treatment. The blood smear in this patient shows a leukemic myeloblast containing an Auer rod. Auer rods are formed by fusion of lysosomal granules and appear as clumps of azurophilic, granular, needle-shaped material found in the cytoplasm of blast cells.Myelofibrosis would have a more insidious course and is usually associated with splenomegaly. Multiple myeloma can present with bone pain, but patients usually have chronic pain that is localized to the back or ribs. Acute lymphocytic leukemia (ALL) is less common in adults, and patients usually have generalized lymphadenopathy. Auer rods are found in myeloblasts but not in lymphoblasts of ALL. In ALL bone marrow biopsy would show a predominant lymphocytic pattern rather than myeloid predominance

3. The answer is c. (Fauci, pp 663-671.) This patient has an unexplained pancytopenia. If all three elements (red blood cells, white blood cells, and platelets) are affected, the cause is usually in the bone marrow (although peripheral destruction from hypersplenism can cause pancytopenia as well). In this patient without a history of liver disease or palpable splenomegaly on physical examination, a bone marrow production problem is the most likely culprit. Although B12 deficiency can cause pancytopenia, usually a macrocytic anemia is the most prominent feature; a serum B12 level would be reasonable, but the most productive approach would be to examine the bone marrow. Leukemia can present without leukocytosis (so-called aleukemic leukemia), but the most likely diagnosis would be aplastic anemia. In the elderly patient, myelodysplastic syndrome (MDS) may present with pancytopenia. Decreased levels of erythropoietin can cause decreased RBC production, but will not cause pancytopenia. A corticosteroid trial is not warranted until a diagnosis is established.

4. The answer is b. (Fauci, pp 671-677.) This patient has polycythemia vera, a clonal proliferative disorder of the bone marrow in which all three cell lines (red blood cells, platelets, and myelocytes) are overproduced. The other classic myeloproliferative disorders are chronic myelogenous leukemia,essential thrombocytosis, and myelofibrosis. It is important to distinguish myeloproliferative syndromes (where one or more cell lines proliferate) from myelodysplastic syndromes (where one or more cell lines—usually red cells—are deficient). In myelodysplastic disorders, white blood cells and platelets are normal, at least initially. These patients present with anemia, often in association with mild macrocytosis and other features of altered marrow maturation (ringed sideroblasts, hypolobulated polys, etc). Splenomegaly and cellular overproduction are not features of the myelodysplastic syndromes. Cushing syndrome can cause facial plethora but would not account for the splenomegaly or hematological changes. Gaisböck syndrome causes erythrocytosis with a normal red cell mass (resulting from diminished plasma volume) but does not cause splenomegaly, leukocytosis, or thrombocytosis. Polycythemia vera does not occur as part of a paraneoplastic process.

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