leukemia

Introduction:

- Acute leukemia is a hematologic malignancy characterized by infiltration of the bone marrow, blood, and other tissues by uncontrolled proliferation and abnormal delayed differentiation of clonal myeloid or lymphoid precursor cells, exceeding 20% of the bone marrow or blood.
- The word leukemia comes from the Greek Leukos (white) and aima (blood)
- In adults, AML (acute myeloid leukemia) is more common than ALL (acute lymphoblastic leukemia).

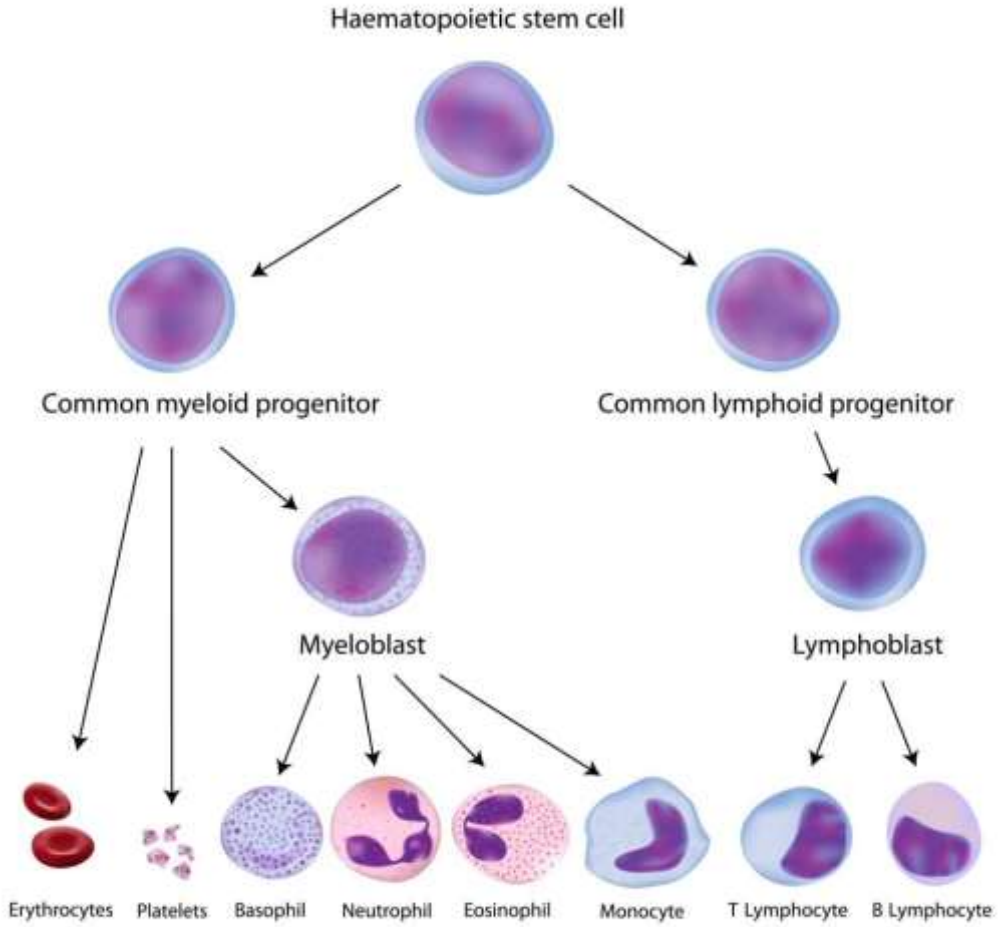
Cont. Introduction:

- Acute leukemias occur when cells of either the early myeloid (AML) or early lymphoid (ALL) lines lose their ability to differentiate, while retaining their ability to replicate.
- These blast cells accumulate in the bone marrow and crowd out normal hematopoiesis. The blast cells often spill out into the peripheral circulation but may be contained within the marrow.

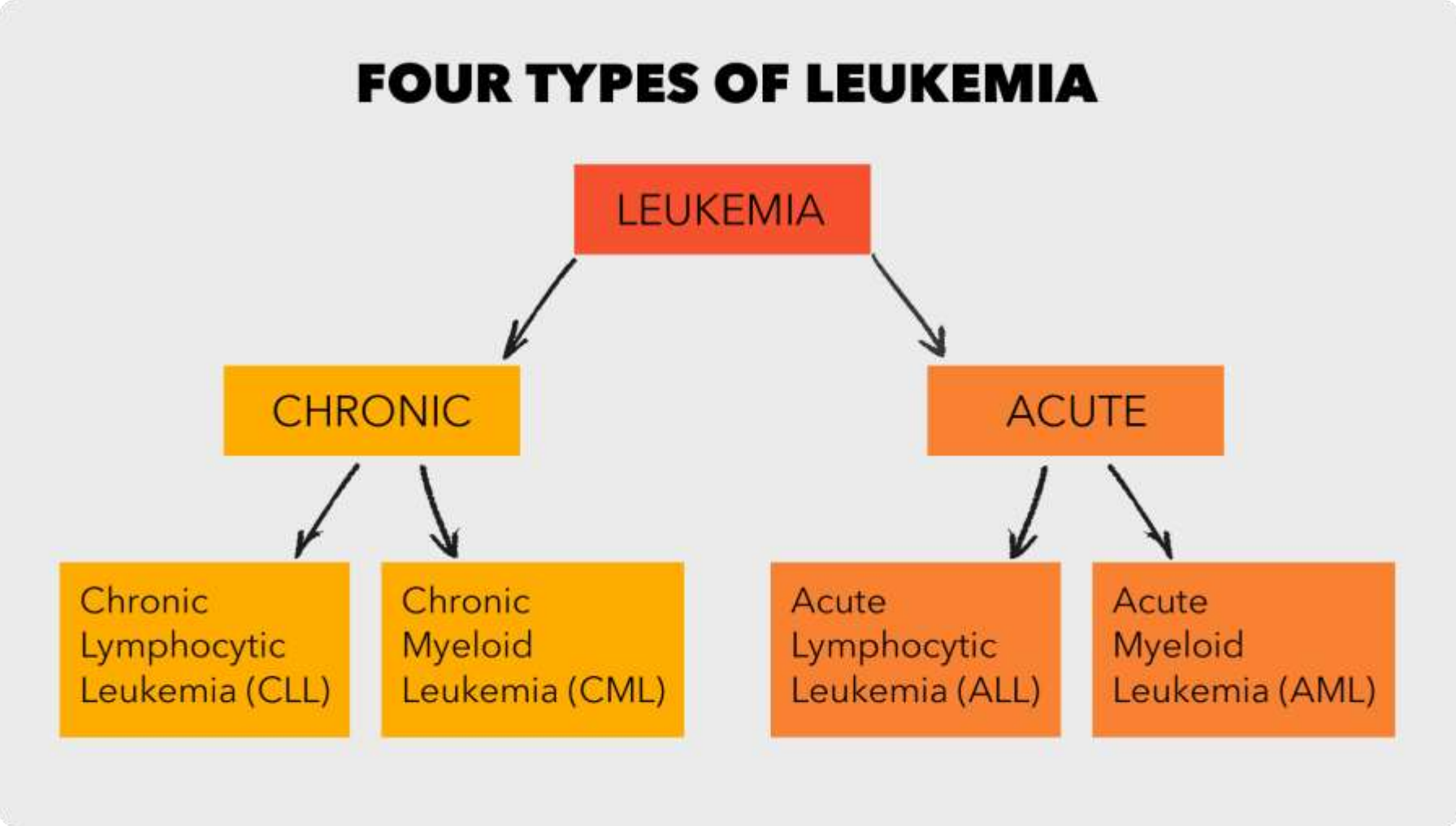
Cont. Introduction:

- Suspect acute leukemia when blasts (immature cells) are seen in the peripheral blood smear, without mature cells. Note that chronic leukemias have overproduction of 1 or more developing cell lines but not of blasts.
- Patients present with symptoms related to cytopenias (infections, fatigue, mucosal bleeding).
- Diagnosis and prognosis are made using morphologic analysis, cytogenetic studies (karyotype), cytochemical analysis (PAS, peroxidase, esterase, Sudan black), molecular markers, and cell surface markers (flow cytometry and immunophenotyping for CD

Pathophysiology



Types of leukemia



Acute leukemias:

Acute Myeloid Leukemia:

During normal hematopoiesis, myeloid blast cells differentiate into granulocytes, monocytes, erythrocytes, or megakaryocytes. AML is a clonal disorder of the early myeloid cells where there is overproduction of myeloblasts with reduced production of red cells, platelets, and mature granulocytes.

Cont. Acute Myeloid Leukemia

Presentation:

- AML typically manifests with anemia, thrombocytopenia, or functional neutropenia secondary to bone marrow replacement with abnormal myeloblasts.
- Petechiae, epistaxis, and other mucosal hemorrhages occur when the platelet count dips below 20,000/µL.
- Symptoms of anemia vary more with the patient's age and comorbidities.
- Although the leukocyte count is typically elevated, the absolute neutrophil count tends to be low which confers an increased risk of infection.
- When fever is present, it's usually from infection; this leukemia rarely involves the CNS.
- Bone pain is uncommon.

Cont. Acute Myeloid Leukemia

Etiology:

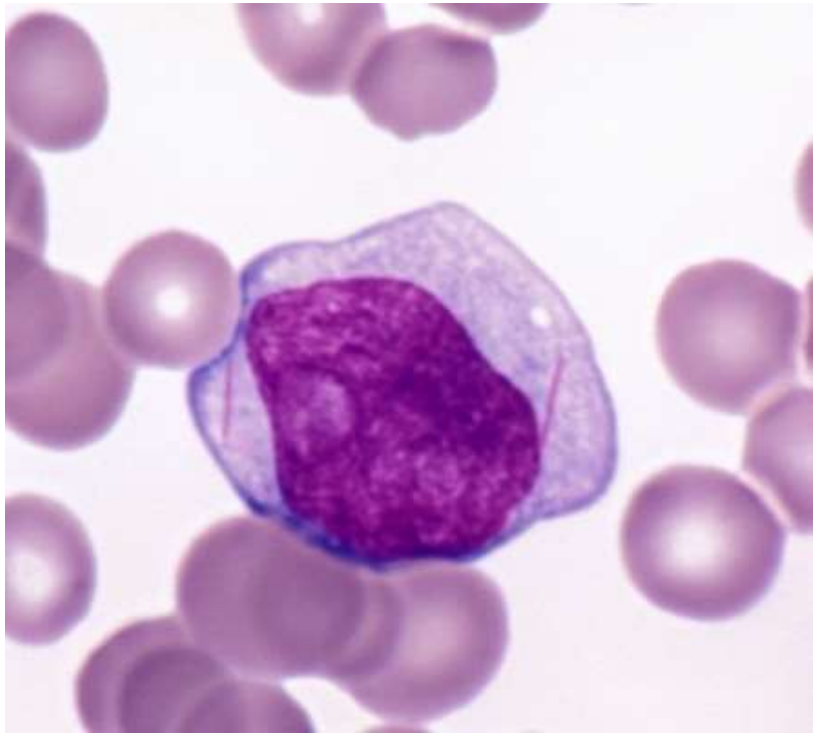
The disorder can develop from exposure to **chemicals** such as benzene and certain **chemotherapeutic agents.** It may also arise after **transformation from myeloproliferative disorders,** myelodysplastic disorders, aplastic anemia, and PNH.

Typically, these secondary leukemias have a worse prognosis than de novo AML.

Cont. Acute Myeloid Leukemia

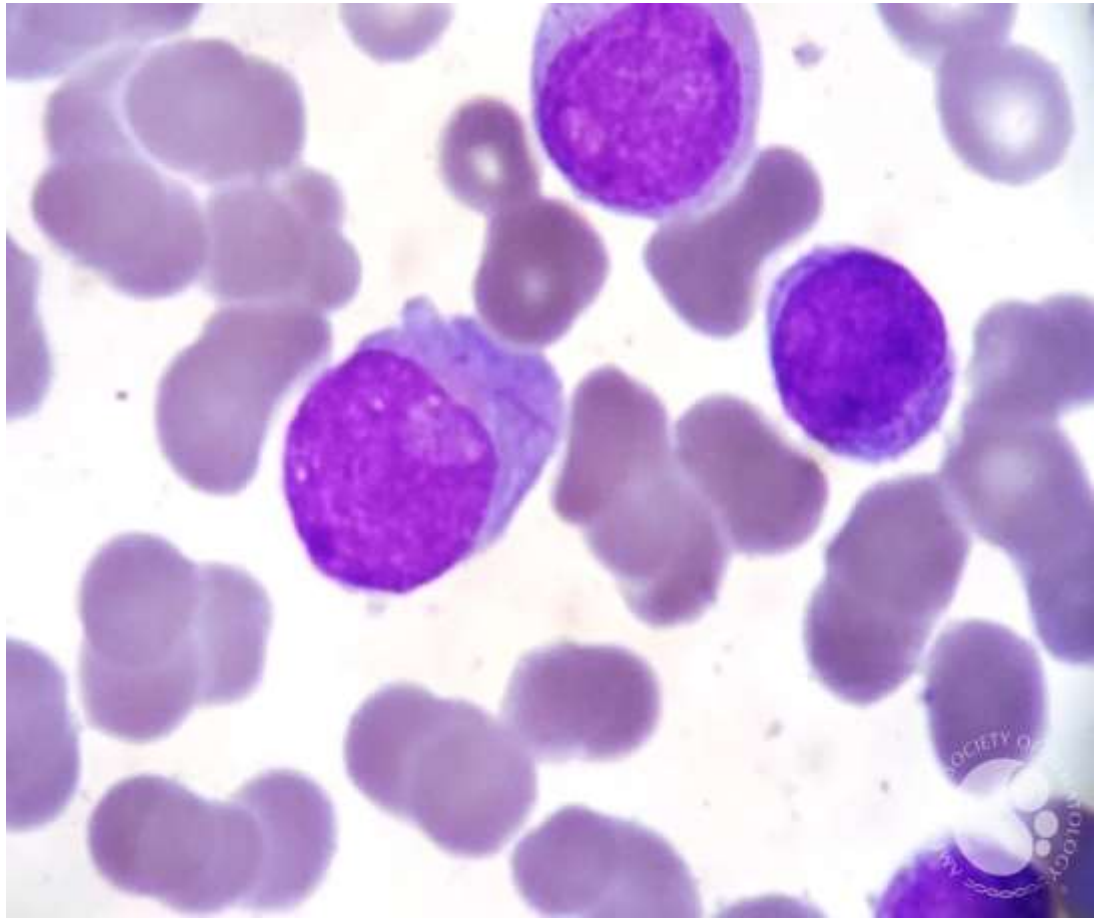
Diagnosis:

- Diagnose AML by bone marrow biopsy if blasts are seen in the peripheral blood: Marrow blasts ≥ 20% is acute leukemia.
- Commonly, the blasts of AML and ALL look alike, and you cannot tell the type of leukemia by observation alone, so cytochemical tests, immunophenotyping, and chromosomal analysis are performed on marrow cells.
- However, finding Auer rods inside peripheral blood blast cells makes the diagnosis of AML. Auer rods are



Cont. Acute Myeloid Leukemia

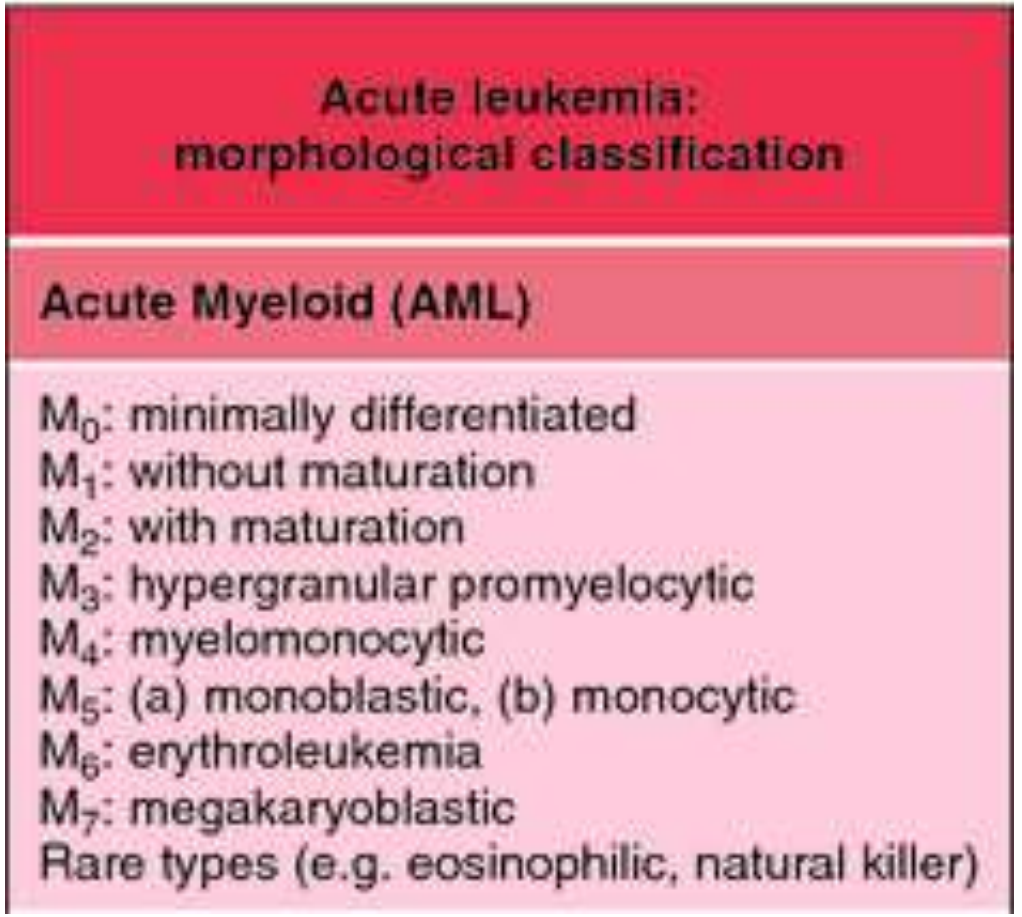
Myeloblasts are usually seen in the **peripheral blood smear** but may be absent despite unequivocal bone marrow infiltration.



Cont. Acute Myeloid Leukemia

Classification of AML:

- Cytogenetic and molecular classification of AML is increasingly important.
- Acute promyelocytic leukemia, characterized by immature leukocytes with distinctive primary granules that contribute to coagulopathy and chromosomal translocation t(15;17)



Cont. Acute Myeloid Leukemia

Prognosis

Currently, several factors are used to establish AML prognosis.

Cytogenetic findings represent one of the most powerful prognostic indicators.

The karyotype can be used to classify patients into different risk groups:

- Favourable karyotype → t(8;21), t(15; 17), or inv(16)
- Intermediate karyotype → normal karyotype or t(19; 11)
- Unfavourable karyotype → inv (3), 5/del(5q), monosomy 7, or a more complex karyotype (3 or more aberrations)

Other unfavourable prognosticators for AML include:

- Age> 60
- Poor performance status
- WBC count> I OO,OOO/mm3
- Prior disease of the bone marrow (myelodysplasia or myeloproliferative disorder)
- Mutations in FLT3 (a receptor tyrosine kinase), found in 20-30% of

Cont. Acute Myeloid Leukemia

AML M3:

- Translocation between chromosomes 15 and 17, involving the promyelocytic leukemia gene and retinoic acid receptor a gene (PML-RARα).
- Prognosis for aPML is very favorable, and therapy is associated with a remission rate of > 80% and a cure rate of > 70%.
- Treatment includes all-trans retinoic acid (ATRA), which is used to induce differentiation, along with daunorubicin.
- Patients with aPML are also at increased risk for developing DIC due to release of procoagulants from cytoplasmic granules. The diagnosis of aPML needs to be made quickly because DIC can change aPML from a curable disease into a fatal one within hours.

Cont. Acute Myeloid Leukemia

Treatment:

- Chemotherapy:
  - Standard induction therapy for AML (non-aPML) is a combination of anthrarycline (daunorubicin) and infusional cytarabine.
  - Consolidation therapy can take the form of further chemotherapy with the same agents as above.
  - With standard therapy, for patients > 60 years of age, remission is achieved in 40-50%, but long-term, event-free survival is achieved in < 10%. For patients < 60 years of age, long-term survival, on average, is 20-30%.
- stem cell transplantation
  - Allogeneic stem cell transplantation is an important treatment option in patients with AML. It is typically reserved for patients < 60 years of age.

Cont: acute leukemia:

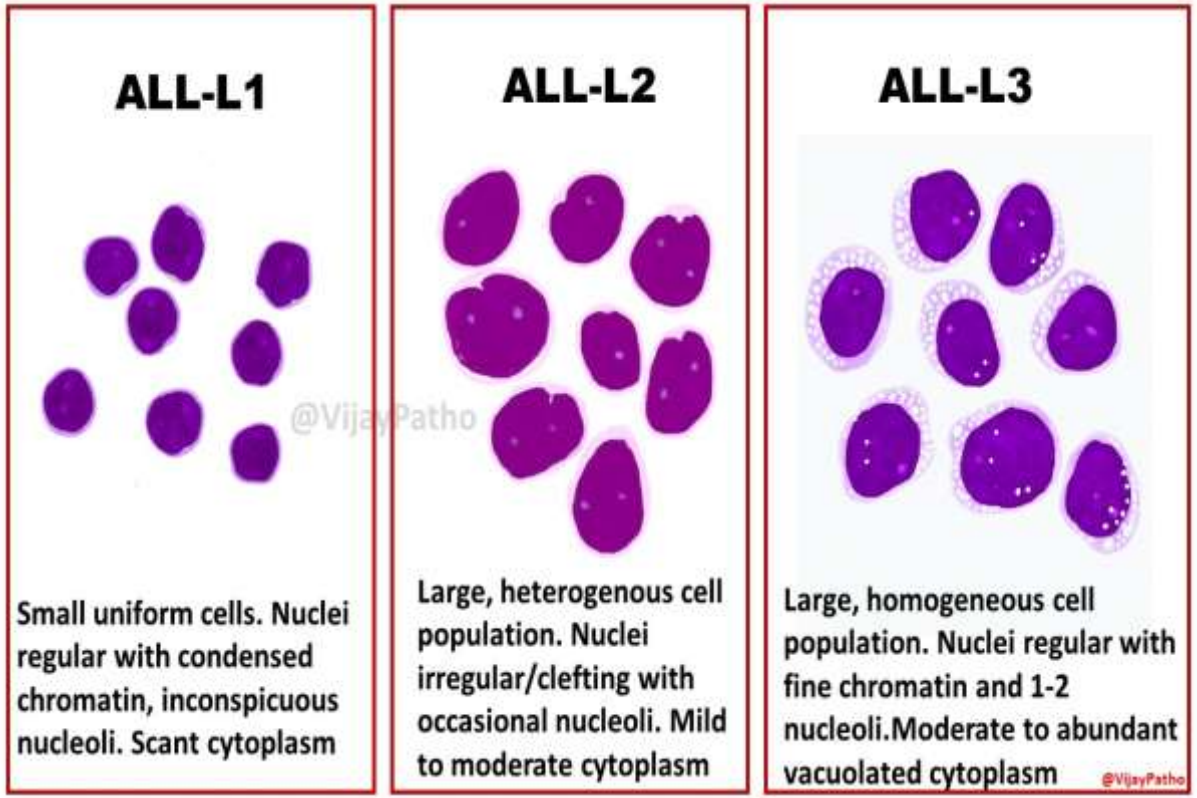
Acute Lymphoblastic Leukemia:

Acute lymphoblastic leukemia (ALL) is a clonal disorder of early lymphocytic precursors. The blasts of ALL may be of B- or T-cell lineage. While ALL is primarily a disorder of children, there is a bimodal age distribution with increased incidence also in older patients. ALL represents 20% of adult leukemias.

Cont. Acute Lymphoblastic Leukemia

The WHO classification divides ALL into 3 categories:

- precursor B-cell (frequency 70-75%),
- precursor T-cell (frequency 20-25%),
- mature B-cell ALL (Burkitt lymphoma/leukemia, frequency 5%).



Cont. Acute Lymphoblastic Leukemia

- Patients with ALL present with malaise, bleeding, infections, bone pain, or a combination of these symptoms, with a small subset (<10%) having symptomatic central nervous system involvement (e.g., cranial nerve and/or retinal abnormalities and symptoms of meningeal irritation) at diagnosis.
- In adults, 75% of ALL is of B-cell lineage; mature B-cell ALL can manifest as extramedullary disease, including gastrointestinal or testicular involvement.
- A mediastinal mass with wheezing and stridor or

Cont. Acute Lymphoblastic Leukemia

- Definitive diagnosis and important prognosticators are made by immunophenotyping and chromosomal analysis of the leukemic cells.
- Similar to AML, ALL is classified by immunophenotype, cytogenetics, and molecular abnormalities.
- The most important cytogenetic abnormality in adult ALL is the Philadelphia chromosome, found in 20% to 30% of patients.
- Historically, Philadelphia chromosome-positive ALL had a poor prognosis.

Cont. Acute Lymphoblastic Leukemia

Prognosis:

Unfavourable prognostic factors in ALL:

- Age > 60
- WBC > 1OO,OOO/mm3
- Mature B- or early T-cell types
- Persistent minimal residual disease, as detected by flow cytometry after remission is achieved
- t (9;22) translocation= Philadelphia chromosome (unlike in CML, where the translocation is favourable)
- t(4;11) = MLL-AF 4 fusion gene

Cont. Acute Lymphoblastic Leukemia

Treatment:

- Regimen backbones include vincristine, anthracycline, corticosteroids, and l-asparaginase.
- Induction therapy is followed by intensification and consolidation.
- Central nervous system prophylaxis is essential during ALL therapy, and a maintenance phase of oral mercaptopurine (daily) and methotrexate (weekly) can last up to 2 years.
- L-asparaginase have unique toxicities such as allergic reactions, hypofibrinogenemia, thrombosis, and hypertriglyceridemia with
- For patients with 1 or more unfavourable

Cont. Acute Lymphoblastic Leukemia

Complications:

- Adult survivors of childhood leukemia face higher risks of secondary cancer, cardiovascular disease, and the metabolic syndrome (high BMI, elevated waist circumference, dyslipidemia, elevated fasting glucose, and hypertension) compared with age matched controls.
- The cumulative incidence of secondary cancer after radiation therapy for childhood ALL reaches 11% at 30 years; tumours include skin cancer, thyroid and parotid tumours, sarcomas, and brain tumours.
- Echocardiography to screen for left ventricular dysfunction should be performed at intervals of 3 to 5 years, particularly if anthracycline exposure was high or if chest radiation was used.

Chronic leukemia

Chronic Myeloid Leukemia:

- CML is a clonal process resulting in abnormal production and proliferation of granulocytes, generally with normal differentiation.
- Patients may present with asymptomatic neutrophil elevation on routine laboratory testing, but many have weight loss, abdominal fullness (splenomegaly), fatigue, or fever.
- The neutrophilia associated with CML is often accompanied by a left shift, with bands, meta-myelocytes, myelocytes, promyelcytes, and even myeloblasts
- A left shift with basophilia or eosinophilia without a clinical reason for a leukemoid reaction

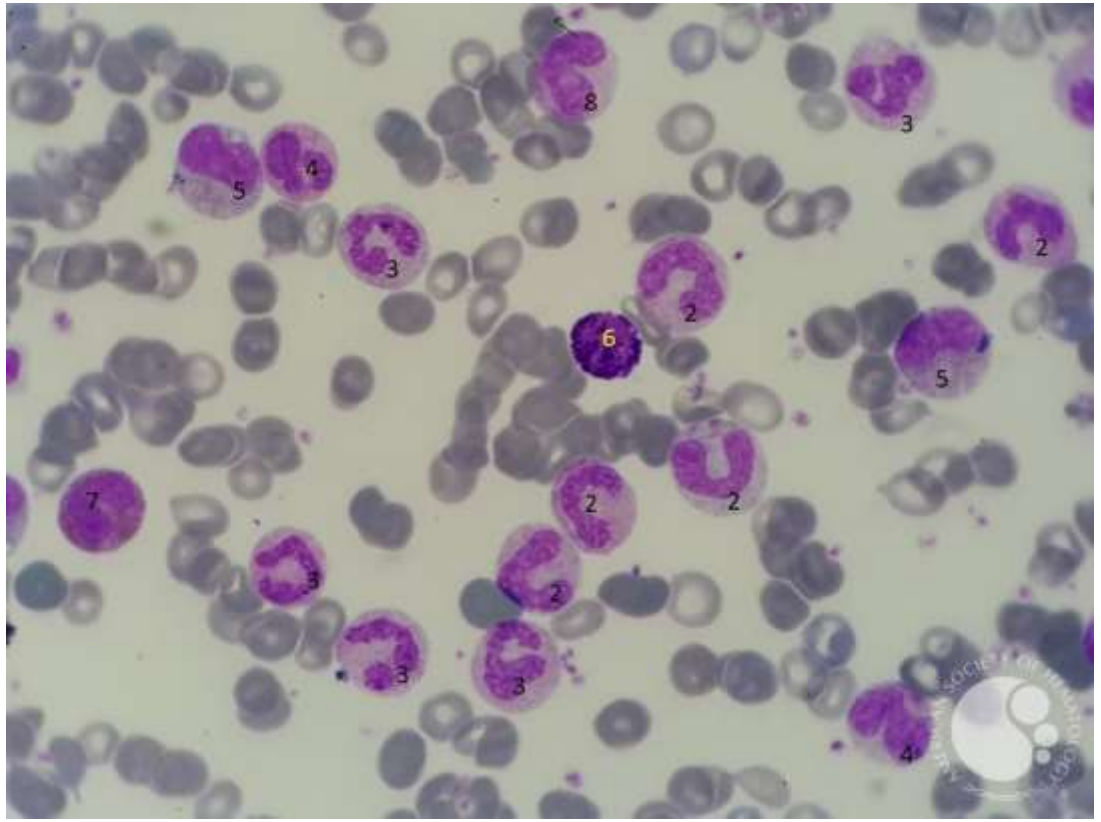
Cont. Chronic Myeloid Leukemia

- CML is defined by the presence of the Philadelphia chromosome, a reciprocal trans location of the ABL gene on chromosome 9, to the BCR gene on chromosome 22.
- The Philadelphia chromosome can be detected with routine cytogenetics, fluorescence in situ hybridization, and screening for the BCR-ABL transcript through reverse transcriptase polymerase chain reaction.

Cont. Chronic Myeloid Leukemia

Peripheral blood smear:

At diagnosis, testing peripheral blood is as accurate as bone marrow samples.



Cont. Chronic Myeloid Leukemia

- CML has three phases:
  - chronic (<10% myeloblasts),
  - accelerated (10% -19% myeloblasts),
  - blast (>20%, myeloblasts).
- Most patients present in the chronic phase, which is more indolent but quite responsive to therapy.
- The blast phase is technically a secondary acute myeloid leukemia (AML).

Cont. Chronic Myeloid Leukemia

Treatment:

- Treatment is necessary at diagnosis for all patients.
- Tyrosine kinase inhibitors (TKIs) have revolutionized the treatment and outcomes of CML.
- TKIs (imatinib, dasatinib, nilotinib, bosutinib, ponatinib) target the BCR-ABL oncoprotein and prevent downstream signaling.
- They have resulted in excellent **long term control** of CML, **improved survival**, and **decreased the need for HSCT**

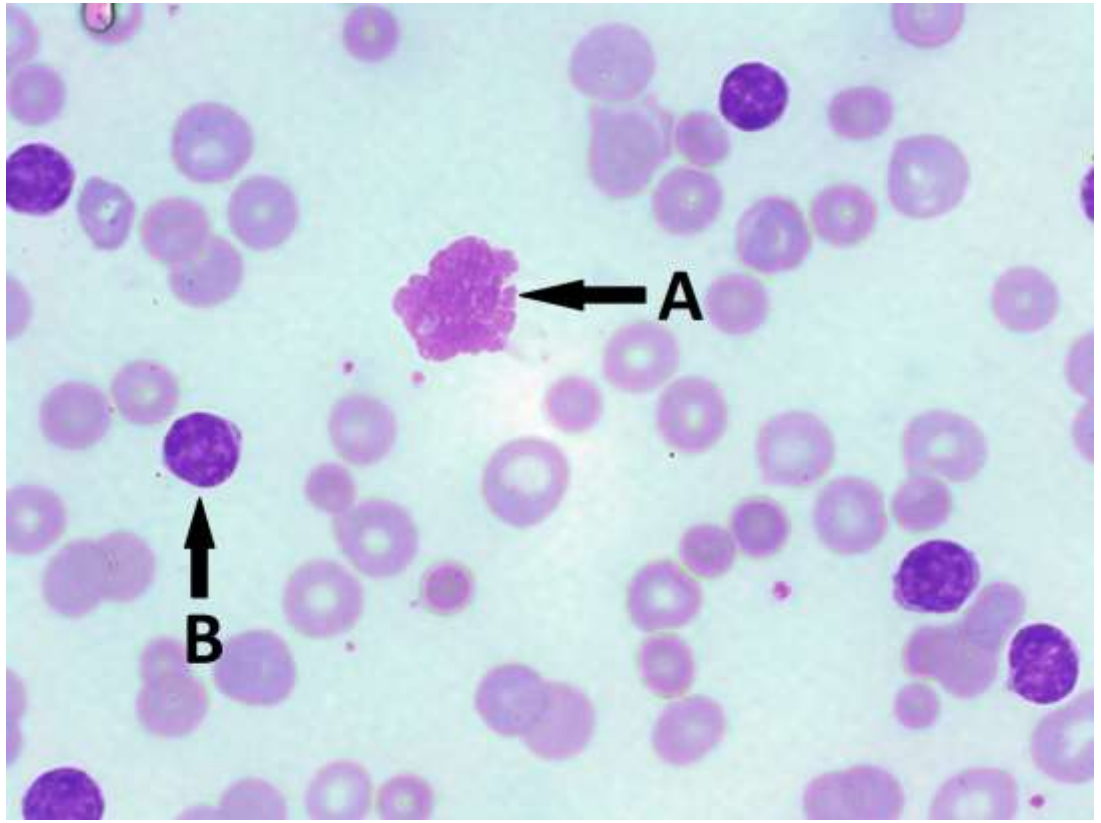
Cont. chronic leukemia:

Chronic lymphocytic leukemia:

- CLL is generally readily diagnosed as an increase in absolute lymphocytes on complete blood count
- Flow cytometry using peripheral blood smear is essential in establishing the diagnosis and will reveal B-cell antigens (CD19, CD20, CD23) and co-expression of CD5
- Bone marrow aspiration and biopsy are not necessary to diagnose and stage most patients with CLL

Cont. chronic lymphocytic leukemia

- Lymphocytes are predominantly small and mature appearing (B), although they may be fragile and form “smudge” cells (A) on peripheral blood smear



Cont. chronic lymphoacytic leukemia

- CLL is typically an indolent disease and many patients require no therapy for many years.
- Prognosis can relate to the extent of cytopenias, organomegaly and degree of nodal involvement but also on cytogenetics and molecular genetic characteristics
- Poor prognostic cytogenetics:
  - 17p deletion
  - 11 q deletion

Cont. chronic lymphoacytic leukemia

Treatment:

- Treatment of CLL is mainly a "watch and wait" strategy like other indolent lymphomas.
- Several treatment options are available, however:
  - Young patients: multiple agents (fludarabine and rituximab) with the goal of a prolonged remission (risks immunosuppression). Stem cell transplant is under investigation.
  - Elderly patients: chlorambucil (gentle, single-agent therapy) and rituximab with goal of symptom palliation. Bendamustine (an alkylating agent) is gaining increased use in both elderly and younger

Cont. chronic lymphoacytic leukemia

Complications:

- Patients with CLL are prone to infections, in part related to commonly associated hypogammaglobulinemia (treated with IVIG to reduce infectious events)
- Patients may also develop autoimmune cytopenias such as ITP, AIHA.
- Transformation to a large cell lymphoma (Richter transformation) occurs in about 5% of patients, and is generally associated with poor prognosis and refractory disease.

Thank you!