Acute Lymphoblastic Leukemia: Symptoms, Diagnosis and Treatment

Leukemia is a group of neoplastic disorders characterized by clonal proliferation of hematopoietic cells in the bone marrow, with abnormal cells spilling into the peripheral blood.

Classifications of Leukemia:

1. Based on Clinical Course:

- **Acute Leukemia:**
  - Rapid onset and progression.
  - Predominance of immature “blast” cells.
  - Fatal within weeks to months without treatment.
- **Chronic Leukemia:**
  - Insidious onset, slower progression.
  - Presence of more mature cells alongside blasts.
  - Survival for months to years without treatment.

2. Based on Cell Line Involved:

- **Myeloid Lineage:** Myelocytic/Granulocytic leukemia.
- **Lymphoid Lineage:** Lymphocytic leukemia.

Four Main Types:

1. **Acute Myeloid Leukemia (AML)**
2. **Acute Lymphoblastic Leukemia (ALL)**
3. **Chronic Myeloid Leukemia (CML)**
4. **Chronic Lymphocytic Leukemia (CLL)**

Etiology of Leukemia

Host-Related Risk Factors:

- Genetic syndromes (e.g., Down syndrome, Fanconi anemia)
- Hereditary chromosomal instability
- Immunodeficiency syndromes
- Pre-existing marrow disorders (e.g., MDS, aplastic anemia)

Environmental Risk Factors:

- Exposure to ionizing radiation
- Mutagenic chemicals (e.g., benzene)
- Certain chemotherapeutic agents

- Oncogenic viruses (e.g., HTLV-1, EBV)

Acute Lymphoblastic Leukemia (ALL)

Pathophysiology:

- Uncontrolled proliferation of lymphoid precursor cells (T or B lineage).
- Arrest in differentiation ? accumulation of lymphoblasts.
- Bone marrow failure: anemia, thrombocytopenia, neutropenia.
- Extramedullary infiltration: liver, spleen, lymph nodes, CNS, testes.

Epidemiology:

- **Most common pediatric cancer.**
- Peak age: 2–5 years.
- Slight male predominance.
- Less common in adults; adult prognosis poorer.

Clinical Presentation

Bone Marrow Failure:

- **Anemia:** Fatigue, pallor, dyspnea.
- **Thrombocytopenia:** Petechiae, ecchymoses, bleeding.
- **Neutropenia:** Recurrent infections, fever.

Organ Infiltration:

- **Hepatosplenomegaly**
- **Lymphadenopathy**
- **Bone pain:** Especially in long bones (due to marrow expansion).
- **CNS involvement:** Headache, vomiting, cranial nerve palsies (in advanced disease).
- **Mediastinal mass:** More common in T-cell ALL (? respiratory symptoms, SVC syndrome).
- **Testicular enlargement:** Occasional in boys due to leukemic infiltration.

Diagnosis of ALL

Initial Laboratory Findings:

- CBC: Variable WBC count, anemia, thrombocytopenia.
- Peripheral blood smear: Presence of lymphoblasts.
- Coagulation profile (to assess for DIC).

Definitive Diagnosis:

- **Bone Marrow Aspiration and Biopsy:**

- 20% lymphoblasts (WHO criteria for ALL).

Cytochemical Staining:

- **TdT+ (Terminal deoxynucleotidyl transferase):** Positive in 90% of cases.
- **PAS+ (Periodic acid–Schiff):** Characteristic block positivity.
- **MPO & Sudan Black B:** Negative (differentiates ALL from AML).

Immunophenotyping (Flow Cytometry):

- Determines lineage:
  - **B-cell ALL:** CD10, CD19, CD22.
  - **T-cell ALL:** CD2, CD3, CD7.

Cytogenetic and Molecular Studies:

- t(12;21): Favorable prognosis (common in children).
- Philadelphia chromosome (t(9;22)): Poor prognosis (common in adults).
- Other poor prognostic abnormalities: t(4;11), hypodiploidy.

Imaging and Other Tests:

- Chest X-ray: To assess mediastinal mass.
- Lumbar puncture: To assess CNS involvement.
- Testicular ultrasound (in males with testicular signs).

Prognosis and Risk Stratification

Favorable Prognostic Factors:

- Age 1–10 years
- WBC <50,000/?L at diagnosis
- B-cell subtype
- Good initial response to chemotherapy
- Specific genetic translocations (e.g., t(12;21))

Poor Prognostic Indicators:

- Age <1 year or >10 years
- High WBC count (>50,000/?L)
- T-cell ALL or Philadelphia chromosome-positive
- CNS/testicular involvement
- Poor response to induction therapy

Treatment of ALL

Phases of Chemotherapy:

1. **Induction:** Goal is remission (<5% blasts)
    - Vincristine, corticosteroids, anthracyclines, asparaginase.
2. **Consolidation (Intensification):**
    - Methotrexate, cytarabine, 6-MP.
3. **Maintenance:**
    - 6-MP, methotrexate ± vincristine/prednisone.
4. **CNS Prophylaxis:**
    - Intrathecal methotrexate ± cranial irradiation.

Targeted Therapy:

- **Tyrosine kinase inhibitors (e.g., imatinib)** for Ph+ ALL.

Hematopoietic Stem Cell Transplant (HSCT):

- Considered in high-risk patients or those with relapsed disease.

Complications

Disease-Related:

- Anemia, infections, bleeding
- CNS involvement
- Tumor lysis syndrome

Treatment-Related:

- Myelosuppression
- Secondary malignancies
- Organ toxicities (hepatotoxicity, neurotoxicity)
- Growth retardation in children

Key Takeaways for Exam:

- ALL is the most common leukemia in children.
- Presents with bone marrow failure, organ infiltration, and high lymphoblast count.
- TdT+ and PAS+ are hallmark features.
- Diagnosis confirmed via bone marrow biopsy.
- Favorable prognosis in children with good risk factors.
- CNS prophylaxis is essential due to risk of leukemic spread to the CNS.