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Review Article

Leukemia A Comprehensive Review of AML, CML – Causes, Diagnosis, and Emerging Trends and Treatment

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Abstract

Leukemia is a group of malignant disorders involving the uncontrolled proliferation of abnormal hematopoietic stem cells, leading to the accumulation of precursor cells immediately in the bone marrow and peripheral blood. This review focuses on two primary subtypes: Acute Myeloid Leukemia (AML) and Chronic Myeloid Leukemia (CML). In leukemia, immature cells such as myeloblasts and lymphoblasts dominate circulation, disrupting normal hematopoiesis. AML, mainly affecting adults, is a heterogeneous disease classified by FAB and WHO systems, with clinical features including bone marrow failure, organ infiltration, and distinct cytogenetic abnormalities like t (8;21), t (15;17), and inv (16). CML, typically seen in older adults, is driven by the Philadelphia chromosome translocation (t (9;22)), which forms the BCR-ABL fusion gene responsible for unchecked cell growth. It progresses through chronic, accelerated, and blast phases. Diagnosis involves clinical, hematological, and molecular assessments. Treatment includes supportive care, cytotoxic chemotherapy for AML, and targeted therapies like imatinib for CML. Emerging strategies emphasize personalized approaches.

Keywords: Leukaemia, AML, CML, Stem cells, Myeloblasts, BCR-ABL, Chemotherapy, Philadelphia chromosome

1. Introduction

Leukemia is a malignant disorder of the bone marrow marked by uncontrolled proliferation of hematopoietic stem cells. Under normal conditions, these cells mature into functional blood cells through various precursor stages. In leukemia, however, immature precursors like myeloblasts and lymphoblasts are released into the bloodstream, disrupting normal hematopoiesis. This review focuses on the two major types —myeloid and lymphoid leukemia—highlighting their pathogenesis, diagnostic features, and current treatment approach when the myeloblast of the bone marrow have uncontrolled mitosis due to genetic mutations that disrupt the normal cell cycle and growth regulation mechanism. This results in proliferation of abnormalities and spilled into blood finally result in the formation of myeloid

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Leukemia myeloblast replaces the cells like neutrophil, eosinophil, basophil due to abnormal proliferation.

Myeloid Leukemia is categorized into two types:

1. Acute Myeloid Leukemia (AML)
2. Chronic Myeloid Leukemia (CML)

ACUTE MYELOID LEUKEMIA (AML)

Introduction: Acute Myeloid leukemia (AML) is a heterogenous disease characterized by infiltration of malignant myeloid cells into the blood.

AGE: AML is primarily a disease of adults, approximately 65 years.

3. French-American-British (FAB) CLASSIFICATION

The FAB system of classification is a system to categorize AML into subtypes based on cell morphology and cytochemical characteristics

M0	AML is minimally differentiated	No auer rods (negative)
M1	AML without maturation	
M2	AML with maturation	Philadelphia translocation of t(8;21)
M3	Acute promyelocytic leukemia	Max auer rods t(15;17)
M4	Acute myelomonocytic leukemia	Inv(16) translocation
M5	Acute monocytic leukemia	
M6	Acute erythroleukemia	
M7	Acute megakaryocytic leukemia	Down syndrome

4. Why the FAB Classification Falls Short in Modern Leukemia Diagnosis?

The FAB system has limitations, as it doesn't account for genetic and molecular characteristics. The World Health Organization (WHO) classification has built upon the FAB system, incorporating additional features for more accurate diagnosis and treatment.
The FAB classification remains a fundamental part of understanding AML, providing a framework for diagnosis and classification.

5. Clinical features of AML

The clinical manifestations of AML arise primarily due to bone marrow failure and infiltration of leukemic blasts into various organs and tissues.

I. Bone Marrow Failure: Bone marrow suppression caused by the proliferation of leukemic blasts leads to a reduction in normal hematopoietic cells, resulting in:

- **Anemia** – leading to fatigue, pallor, and weakness
- **Thrombocytopenia** – causing bleeding tendencies and easy bruising
- **Increased susceptibility to infections** – due to neutropenia

II. Organ Infiltration:
Leukemic myeloblasts may infiltrate organs, causing various systemic signs and symptoms:

- **Bone pain and tenderness** – due to marrow expansion by blast cells
- **Lymphadenopathy** – resulting from infiltration of lymph nodes
- **Splenomegaly** – due to blast accumulation in the spleen
- **Hepatomegaly** – from infiltration of the liver
- **Gum hypertrophy** – especially in M4 and M5 subtypes, due to leukemic cell infiltration
- **Chloromas (granulocytic sarcomas)** – extramedullary tumors of myeloblasts, commonly seen in the skin
- **Orbital sarcomas** – when leukemic blasts infiltrate the orbital region

6. Laboratory Findings in Acute Myeloid Leukemia (AML)

Laboratory evaluation plays a crucial role in the diagnosis and classification of AML. Key investigations include complete blood counts, peripheral smear analysis, cytogenetic studies, immunophenotyping, and cytochemical staining.

A. Hematological Findings (Blood Picture)

- **Tests:** Complete Blood Count (CBC), Peripheral Blood Smear
- **Key Observations:**

Anemia: Typically, normocytic and normochromic, reflecting reduced red blood cell production.

Thrombocytopenia: Marked reduction in platelet count, leading to increased bleeding risk.

Leukocytosis: Elevated white blood cell (WBC) count, often exceeding 200,000/μL. Peripheral smears commonly show numerous immature cells, particularly myeloblasts.

B. Cytogenetic Abnormalities

Cytogenetic analysis helps classify AML subtypes and predict prognosis:

- **AML-M3:** Translocation t(15;17)
- **AML-M4:** Inversion inv(16)
- **AML-M2:** Translocation t(8;21)

C. Immunophenotyping

This method utilizes monoclonal antibodies to detect specific cell surface antigens, aiding in the precise identification of leukemia cell lineage and differentiation stage.

D. Cytochemistry

Cytochemical staining assists in differentiating AML from other hematologic malignancies:

Fig. 1. Showing Cytochemical staining

- **Myeloperoxidase (MPO):** Positive in myeloid blasts
- **Sudan Black B:** Positive, consistent with granulocytic lineage
- **Non-specific Esterase (NSE):** Helps identify monocytic differentiation, especially in M4 and M5 subtypes.

7. Current and Emerging Therapeutic Strategies in Acute Myeloid Leukaemia

The management of AML involves a combination of supportive care, targeted therapy, and cytotoxic chemotherapy. Treatment strategies are tailored based on the patient's age, overall health, genetic mutations, and disease subtype.

A. Supportive Care

Supportive treatment is essential to manage complications arising from bone marrow failure:

- **Anemia:** Managed with **fresh blood transfusions** to improve oxygen-carrying capacity.
- **Hemorrhage:** Treated using **platelet concentrates** to control bleeding and reduce the risk of hemorrhagic complications.

B. Targeted Therapy

While **Imatinib** is primarily used in Chronic Myeloid Leukemia (CML), it has limited use in AML unless BCR-ABL fusion is identified (a rare scenario in AML). Imatinib works by **inhibiting the BCR-ABL tyrosine kinase**, thereby blocking abnormal cell proliferation.

C. Emerging Trends in AML Treatment

Recent advances have shifted the treatment landscape towards **personalized and molecularly targeted therapies**. Notable developments include:

- **FLT3 inhibitors** (e.g., midostaurin, gilteritinib) for FLT3-mutated AML.
- **IDH1/IDH2 inhibitors** (ivosidenib and enasidenib) targeting isocitrate dehydrogenase mutations.
- **BCL-2 inhibitor venetoclax**, used in combination with hypomethylating agents for elderly or unfit patients.
- **Monoclonal antibodies** and **antibody-drug conjugates** (e.g., gemtuzumab ozogamicin) targeting surface markers like CD33.
- **CAR-T cell therapy** and **immune checkpoint inhibitors** are currently under clinical investigation, offering potential future treatment options.

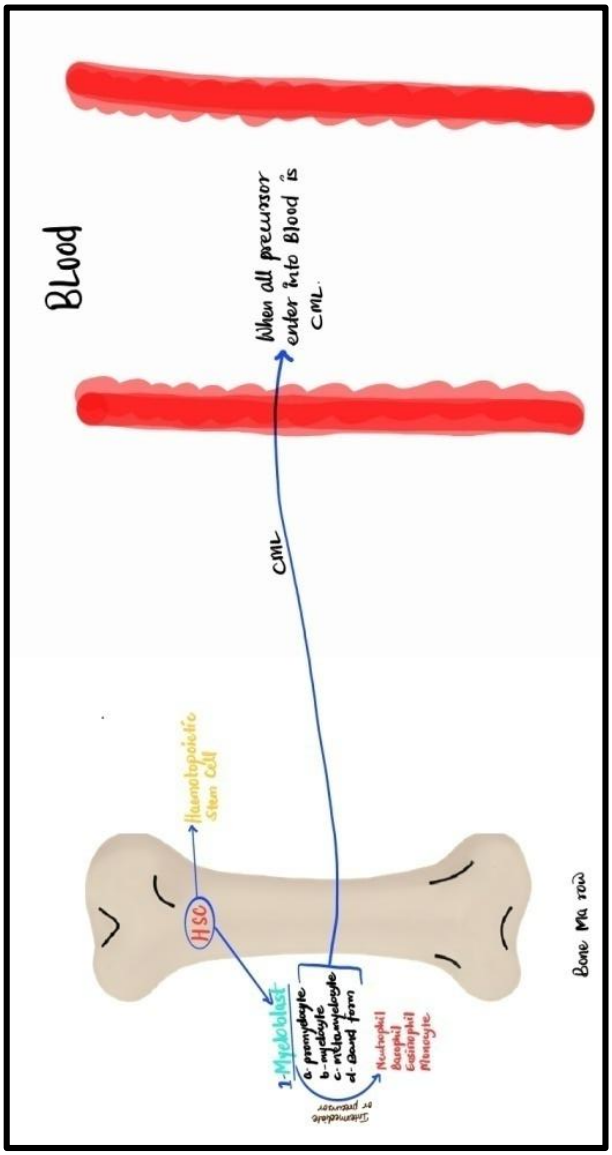
CHRONIC MYELOID LEUKEMIA (CML)

1. Introduction: Chronic myeloid leukemia is a acquired disease of haemopoetic stem cell that is characterized by

1. **Leucocytosis**: The number of WBCs increased as compare to their normal value.
2. **Basophilia:** the number of basophil cells get increased as compare to their normal value.
3. **Splenomegaly:** Enlargement of spleen.
4. **Distinct Chromosomal abnormality:** Translocation of t(9;12)

2. AGE: CML typically occurs in older adults, with the median age at diagnosis being over 50 years.

1. **Pathogenesis**: In CML, a genetic abnormality occurs where parts of chromosome 9 and chromosome 22 exchange places. The ABL gene from chromosome 9 fuses with the BCR gene on chromosome 22. This fusion creates the BCR-ABL gene, which produces an abnormal protein that functions as a tyrosine kinase enzyme. This enzyme causes uncontrolled cell division and mutation, leading to the development of CML. The BCR-ABL gene is a hallmark of CML.



4 Phases of CML:

Chronic phase	Accelerated phase	Blast phase
Less than 10% blast present in blood of bone marrow	10-19% blast is present in blood of bone marrow	More than 20% blast is present in the bone marrow of blood

2. Clinical features Chronic Myeloid Leukemia (CML)

I. Due to bone marrow failure

Bone marrow failure may cause diseases like-

a) Anaemia
b) Thrombocytopenia
c) Infection

II. Hypermetabolism: When mitosis taking place in bone marriow with high rate so it may cause weight loss, night sweats.

III. **Splenomegaly:** Excessive destruction of forming cells inside the spleen may cause enlagrment of spleen.

3. Laboratory Findings in Chronic Myeloid Leukemia (CML)

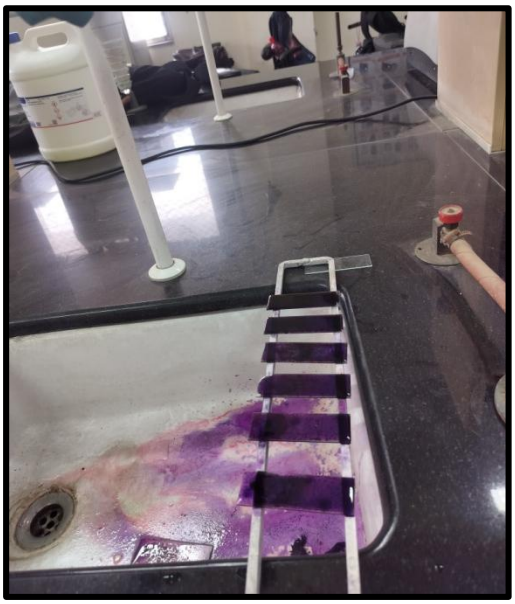
A. Blood Picture

Tests Performed:

- Complete Blood Count (CBC)
- Peripheral Blood Smear

Key Findings:

- **Anemia:** Typically normocytic and normochromic (normal size and hemoglobin concentration of red blood cells).
- **Thrombocytopenia:** Platelet count is reduced.
- **Leukocytosis:** Markedly elevated white blood cell (WBC) count, often exceeding 200,000/µL. Numerous immature WBCs are observed in the peripheral smear.



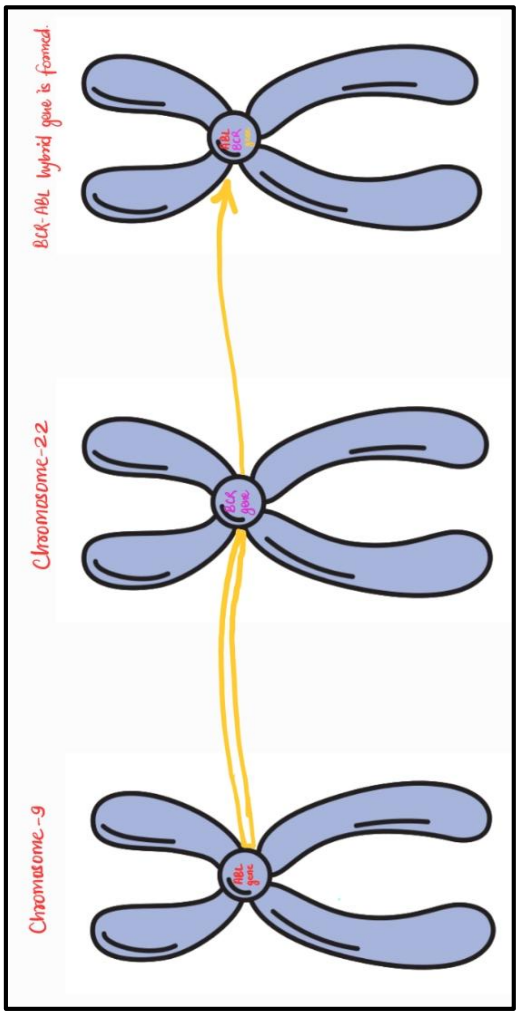
- **Common Cells Observed in the Blood Smear:**
  - MB – Myeloblast
  - PM – Promyelocyte
  - M – Myelocyte
  - MM – Metamyelocyte
  - B – Basophil
  - N – Neutrophil
  - E – Eosinophil
  - Band forms
  - M – Monocyte

B. Bone Marrow Examination

- **Cellularity:** The bone marrow shows hypercellularity due to excessive mitotic activity (hypermitosis).
- **Myeloid-to-Erythroid Ratio:** Increased, reflecting a predominance of white cell precursors over red cell precursors.
- **Erythropoiesis:** Decreased red blood cell production.
- **Megakaryocytes:** Reduced in number, contributing to thrombocytopenia.

C. Cytogenetics

- The **Philadelphia chromosome** [t(9;22)(q34;q11)] is detected in approximately 90–95% of CML cases.
- This translocation results in the **BCR-ABL fusion gene**, which produces an abnormal tyrosine kinase enzyme responsible for uncontrolled cell proliferation.



D. Cytochemistry

Neutrophil Alkaline Phosphatase (NAP) Staining:

In normal neutrophils, NAP levels are high.

In CML, NAP activity is significantly decreased.

This test helps differentiate CML from other causes of leukocytosis

7 Treatment of CML: From Supportive Care to Targeted Therapies The treatment of CML has evolved significantly over recent decades, moving from nonspecific supportive interventions to highly effective, targeted molecular therapies. Management is guided by the phase of the disease (chronic, accelerated, or blast crisis), patient age, comorbidities, and genetic findings.

A. Supportive Care

Supportive treatment is essential to manage complications resulting from impaired hematopoiesis, particularly in the early stages or in advanced disease phases:

- **Anemia:** Treated with **fresh blood transfusions** to restore hemoglobin levels and alleviate fatigue and pallor.
- **Hemorrhage:** Managed with **platelet concentrates** to control bleeding due to thrombocytopenia.

B. Targeted Therapy

A major breakthrough in CML therapy has been the development of **tyrosine kinase inhibitors (TKIs)** that target the **BCR-ABL fusion protein**, the product of the Philadelphia chromosome [t(9;22)].

- **Imatinib Mesylate** (first-generation TKI): Imatinib selectively inhibits the BCR-ABL tyrosine kinase, thereby halting the abnormal mitotic signaling that drives leukemic cell proliferation. It is the first-line therapy for chronic-phase CML and has significantly improved long-term survival and quality of life.

C. Emerging Trends and Next-Generation Therapies

While imatinib remains a cornerstone of CML treatment, resistance or intolerance may develop in some patients. To address this, **second- and third-generation TKIs** have been introduced:

- **Second-generation TKIs:**

  Dasatinib and **Nilotinib** offer increased potency and effectiveness in imatinib-resistant or intolerant patients.

- **Third-generation TKI:**
  - **Ponatinib** is effective even in cases with the T315I mutation, which confers resistance to earlier TKIs.
- **Treatment-Free Remission (TFR):** In selected patients achieving deep and sustained molecular remission, discontinuation of TKIs is being explored, allowing for periods without medication under careful monitoring.
- **Ongoing Research:** Novel agents including **asciminib** (a STAMP inhibitor targeting the ABL myristoyl pocket) and **immunotherapy approaches** are under investigation to overcome resistance and achieve more durable remissions.

Conclusion

Leukemia, particularly Acute Myeloid Leukemia (AML) and Chronic Myeloid Leukemia (CML), presents a significant clinical challenge due to its complex pathogenesis and variable presentation. Advances in diagnostic tools—ranging from cytogenetics to molecular profiling—have enhanced the precision of disease classification. The emergence of targeted therapies, such as tyrosine kinase inhibitors for CML and FLT3/IDH inhibitors for AML, marks a transformative shift toward personalized treatment. While supportive care remains foundational, modern approaches increasingly focus on molecular targets and immunotherapy. Continued research into resistance mechanisms and novel therapeutics is essential for improving patient outcomes and achieving long-term remission.

1. Conflict of Interest

Authors declare no conflict of interest.

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