Acute myeloid leukemia is due to a malignant transformation of the hematopoietic stem cells. It is predominantly seen in the age group of 50 - 60 years and is characterized by the arrest of leukocyte development in the early stage of development. Diagnosis is based on the presence of blast cells in the peripheral circulation. It is treated by chemotherapy, which includes treatment of remission and post-induction remission. Refractory cases of acute myeloid leukemia are treated by bone marrow transplants. Complications of AML include anemia, infections and bleeding, along with acute medical emergencies such as necrotizing enterocolitis, hyperleukocytosis and tumor lysis syndrome.

Definition of Acute Myeloid Leukemia

What is Acute Myeloid Leukemia?

Acute myeloid leukemia (AML) is a malignant disease arising due to a malignant transformation of the stem cells present in the bone marrow. It is characterized by the developmental arrest of the malignant cells in their primitive stage.
Epidemiology & Etiology of Acute Myeloid Leukemia

Higher Prevalence of Acute Myeloid Leukemia in Males
Males have more predominance when compared to females; it usually affects individuals above the age of 65 years.

Risk Factors in the Development of AML

- Hereditary causes
- Trisomy 21: Down syndrome
- Defective DNA repair: Bloom syndrome, Fanconi anemia and ataxia-telangiectasia
- Myeloproliferative syndromes: Polycythemia vera, and essential thrombocytosis
- Exposure to ionizing radiation (nuclear fallout) which involves an extremely high dose of radiation
- Exposure to chemicals like benzene, which is most commonly used in chemical industries
- Drugs: Chemotherapy drugs are the leading cause of drug induced AML
- Alkylating agent: Busulfan
- Topoisomerase inhibitors

Age-Based Presentation of leukemia

- 40—60 years: myeloid leukemia (AML & CML)
- 0—14 years: acute lymphocytic leukemia
- > 60 years: chronic lymphocytic leukemia

Classification of Acute Myeloid Leukemia

The FAB and the WHO Classification of AML

AML is classified according to the following standards:

- French-American-British (FAB) classification
- World Health Organization (WHO) classification

<table>
<thead>
<tr>
<th>Class</th>
<th>Definition</th>
<th>Morphology/Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>M0</td>
<td>Minimally differentiated AML</td>
<td>Absence of Auer rods and myeloperoxidase</td>
</tr>
<tr>
<td>M1</td>
<td>AML without maturation</td>
<td>Some blasts (≥ 3 %) are myeloperoxidase positive; Auer rods are seen</td>
</tr>
<tr>
<td>M2</td>
<td>AML with maturation</td>
<td>&gt; 20 % of marrow cells are myeloblasts, Auer rods are usually present Associated with t(8;21)</td>
</tr>
<tr>
<td>M3</td>
<td>Acute promyelocytic leukemia</td>
<td>Associated with cytoplasmic inclusions. Most cells are abnormal promyelocytes, often containing many Auer rods per cell; patients are younger on average (median age 35—40 yr); high incidence of DIC; strongly associated with t(15;17).</td>
</tr>
<tr>
<td>M4</td>
<td>Acute myelomonocytic leukemia</td>
<td>Myelocytic and monocyctic differentiation evident by cytochemical stains; monoblasts are positive for nonspecific esterase; myeloid cells show a range of maturation; Variable numbers of Auer rods; subset associated with inv(16).</td>
</tr>
<tr>
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</tr>
<tr>
<td>M5</td>
<td>Acute monocytic leukemia</td>
<td>Monoblasts and immature monocyctic cells (myeloperoxidase negative, nonspecific esterase positive) predominate; Auer rods are usually absent; older patients; more likely to be associated with organomegaly, lymphadenopathy, and tissue infiltration; the M5b subtype is defined by the predominance of mature-appearing monocytes in the peripheral blood, whereas only immature cells are seen in the M5a subtype.</td>
</tr>
<tr>
<td>M6</td>
<td>Acute erythroleukemia</td>
<td>Most commonly associated with abundant dysplastic erythroid progenitors; &gt; 20% of cells of the marrow non-erythroid cells are myeloblasts, which may contain Auer rods; usually occurs in advanced age or following exposure to mutagens (e.g. chemotherapy).</td>
</tr>
<tr>
<td>M7</td>
<td>Acute megakaryocytic leukemia</td>
<td>Blasts of megakaryocytic lineage predominate, as judged by expression of platelet-specific antigens; myelofibrosis or increased marrow reticulin often present; Auer rods are absent.</td>
</tr>
</tbody>
</table>

**WHO Classification of Acute Myeloid Leukemia**

- AML with recurrent genetic abnormalities
  - AML with t(8;21)(q22;q22)
  - AML with inv(16)(p13q22) or t(16;16)(p13;q22)
  - Acute promyelocytic leukemia with t(15;17)(q22;q12)
  - AML with t(9;11)(p22;q23)
  - AML with t(6;9)(p23;q34)
  - AML with inv(3)(q21q26.2) or t(3;3)(q21;q26.2)
  - AML (megakaryoblastic) with t(1;22)(p13;q13)
  - AML with mutated NPM1
  - AML with mutated CEBPA
  - AML with myelodysplasia-related features
  - Therapy-related AML and MDS
  - AML with minimal differentiation
  - AML without maturation
  - AML with maturation
  - Acute myelomonocytic leukemia
  - Acute monoblastic/acute monocytic leukemia
  - Acute erythroid leukemia (erythroid/myeloid and pure erythroleukemia variants)
  - Acute megakaryoblastic leukemia
  - Acute basophilic leukemia
  - Acute panmyelosis with myelofibrosis
  - Myeloid sarcoma
  - Myeloid proliferations related to Down syndrome
  - Transient abnormal myelopoiesis
  - Myeloid leukemia associated with Down syndrome
  - Blastic plasmacytoid dendritic cell neoplasm

**Pathophysiology of Acute Myeloid Leukemia**

**AML on a Cellular Level**
AML arises from stem cells of the hematopoietic system. They give rise to monoclonal proliferations and replace normal bone marrow cells.

In AML, there is developmental blockage of the myeloid cells in the earlier stage in contrast to chronic myeloid leukemia (CML) where there is a blockage in the later stage.

These immature myeloid cells (blast cells) are present in the bone marrow and enter the peripheral circulation. There should be a minimum of 20% blast cells to be diagnosed as an AML. These blast cells can fill the entire bone marrow and may result in dry tap and myelofibrosis.

Pathogenesis of AML

Chromosomal mutations also result in the arrest of the development. Translocation of
t(15 : 17 ) causes acute promyelocytic leukemia. This results in the fusion of the retinoic acid receptor on chromosome 17 with a PML gene on chromosome 15. The fusion product blocks the maturation in the promyelocytic stage resulting in acute promyelocytic leukemia. Administration of retinoic acid in acute promyelocytic leukemia can overcome this block and can be used in the treatment of acute promyelocytic leukemia.

Pathognomonic of AML

These are the intracytoplasmic rods seen in the myeloblasts. They have the following characteristics:

- Composed of abnormal lysosomes
- Stain with Sudan-black b stain
- Myeloperoxidase positive

Histochemistry

Myeloperoxidase positivity indicates the presence of granulocyte differentiation. Auers rods are typically positive for MPO. Non-specific esterase positivity indicates the presence of monocyte differentiation.

Immunohistochemistry

It indicates the presence of myeloid differentiation markers CD13, CD14, CD15, and CD64.

Clinical Examination and Symptoms of Acute Myeloid Leukemia

How to Recognize AML

Physical examination findings include the presence of increased oozing of blood from the intravenous line and ecchymosis. It indicates the presence of disseminated intravascular coagulation, in which there is a consumption of all the coagulation
factors necessary for the arrest of bleeding. The presence of papilledema, retinal infiltrates and cranial nerve palsy indicates the presence of CNS involvement. Monocytic leukemia most commonly presents with the gum hypertrophy and skin nodule formation. The presence of back pain indicates sarcomatous changes in the spine.

**Pancytopenia**

This is the predominant cause of the majority of the symptoms in AML. The symptoms include general weakness, increased infections and episodes of bleeding, especially from the gums and epistaxis. Increased fatigue and weakness is attributed to anemia and usually precedes AML. Bone pain in AML is due to the expansion of the medullary cavity in both the upper and lower extremities.

**Fever**

This symptom needs to be thoroughly evaluated as it is most commonly due to the neutropenia. Treatment with broad-spectrum empiric antibiotics is warranted, especially if the neutrophils count is < 1000.

**Skin**

Findings in the skin include the presence of petechiae ecchymosis due to thrombocytopenia and pallor due to anemia. It can result in leukocytoclastic vasculitis.

**Eyes**

Pale conjunctiva due to the presence of anemia and fundus examination shows the presence of hemorrhages.

**Central Nervous System**

The presentation includes complaining of the headache and cranial nerve palsies; acute monocytic and myelomonocytic leukemia has a greater predisposition for the development of CNS manifestations. Marked elevations of LDH is seen in CNS involvement.

**Oropharynx**

Monocytic subtypes typically show the presence of gingival hypertrophy.
Organomegaly

Lymphadenopathy is rare in AML. It is characterized by the absence of hepatomegaly and splenomegaly. Their involvement suggests the origin of AML as a result of a complication from a pre-existing myeloproliferative disorder. This may be due to the development of blast crisis in acute lymphoid leukemia.

Joint Pain

Joint pain occurs due to the presence of increased deposition of uric acid in the joints resulting in gout. There is also a feasibility of the joint synovial infiltration by the neoplastic cells, resulting in the joint pain.

Diagnosis of Acute Myeloid Leukemia

Lab Results for AML

Laboratory findings include:

- WBC count ranging from 10,000 cells/mm$^3$ to 100,000 cells/mm$^3$ along with the presence of blast cells
- Anemia: Usually normocytic or macrocytic in the presence of folic acid deficiency
- Thrombocytopenia
- Bone marrow findings show the presence of blast cells. The presence of “dry tap” indicates the presence of extensive fibrosis or hypercellular bone marrow.

The diagnosis of AML can be presumed by the presence of leukemic blast cells in the peripheral smear. Definitive diagnosis is based on the presence of bone marrow aspiration and biopsy. Immunophenotypic, morphologic and cytogenic studies are required for sub-classification of AML and accurate treatment.

The following two criteria are required for the accurate diagnosis:
- There should be a minimum of 20% blast cells in the bone marrow aspirate or peripheral blood; it is an absolute requirement for the diagnosis of AML. Exceptions include t(8;21), t(15;17) and inv(16).
- The documentation of the myeloid origin needs to be present, which can be done by the presence of the following:
  - Auer rods
  - MPO positivity
  - Myeloid markers

**Therapy of Acute Myeloid Leukemia**

**Possible Treatments for AML**

Remission induction therapy includes the initial course of intensive chemotherapy aimed at complete remission of leukemia. It is followed by post-induction chemotherapy. In chemotherapy, younger adults will have better survival rates when compared to older adults. Moreover, older adults are more likely to have chemotherapy complications when compared to their younger counterparts. Bone marrow transplant is used in resistant cases and on a case-by-case basis.

**Treatment of Younger Patients**

Remission induction therapy regimens for acute myeloid leukemia:

- Regimen 1: It includes cytarabine plus daunorubicin.
  - Standard 7+3 regimen: Administration of **cytarabine** for the first 7 days and **daunorubicin** for the first 3 days (daunorubicin is discontinued after the first 3 days). It achieves 60—80% remission with minimal toxicity.
- Regimen 2: It includes administration of cytarabine plus idarubicin. Dosing schedule for cytarabine includes twice daily dose for 12 doses along with idarubicin.

Idarubicin is administered immediately following idarubicin on the first 3 days. This regimen causes a 90% remission rate but has substantial toxicity. Cytarabine and idarubicin show higher rates of remission when compared to cytarabine and daunorubicin.

**Treatment of Older Patients**

Induction chemotherapy is performed with anthracycline and cytarabine when compared to other chemotherapy regimens.

**Post-induction Chemotherapy**

It is based on pre-treatment cytogenetics and molecular genetics. Favorable cytogenetics for post-induction chemotherapy include **t(8;21),inv16**. For patients with intermittent cytogenetics, treatment includes chemotherapy or bone marrow transplant. The treatment options are based on a case-by-case basis.

**Refractory cases:** **Hematopoietic bone marrow transplant** is the choice of treatment in refractory cases.

Monitoring during therapy is done by checking regular complete blood counts, and renal function tests. Liver function tests are performed weekly. Constant monitoring of the uric
Complications of Acute Myeloid Leukemia

Bleeding and Anemia alongside AML

The most common complications associated with AML include anemia, infection and bleeding while **neutropenic enterocolitis**, **DIC**, **hyperleukocytosis** and **tumor lysis syndrome** are medical emergencies.

**Anemia**

It is primarily a *normocytic normochromic anemia*, which typically increases on induction chemotherapy. It is to be managed with recurrent blood transfusion.

**Infection**

The presence of **neutropenia** will predispose to recurrent infections, which are to be managed with broad-spectrum antibiotics.

**Bleeding**

Bleeding is present due to the decreased platelet counts or due to DIC. DIC is predominantly seen in **acute promyelocytic leukemia** (M3). It is characterized by the rapid depletion of the coagulation factors and results in increased bleeding episodes. Treatment with platelet transfusions is indicated.

**Hyperleukocytosis**

It is a medical emergency which shows the presence of the increased total WBC count greater that $50 \times 10^9/L$. It presents with symptoms of **respiratory and neurological distress**.

**Tumor Lysis Syndrome**

It is a medical emergency which presents with acute renal failure due to massive tumor lysis. As a result of tumor lysis, there will be a significant release of potassium, uric acid, and phosphates into the systemic circulation. These, when obstructing the renal tubules, result in **acute anuric renal failure**.

A minimum of two criteria must be present in order to diagnose tumor lysis syndrome:

<table>
<thead>
<tr>
<th>Analyte</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uric acid</td>
<td>8 mg/dl</td>
</tr>
<tr>
<td>Potassium</td>
<td>6 mEq/L</td>
</tr>
<tr>
<td>Phosphorus</td>
<td>4.5 mg/dl</td>
</tr>
<tr>
<td>Calcium</td>
<td>7 mg/dl</td>
</tr>
</tbody>
</table>

There will be increased uric acid, potassium and phosphorus while a decreased calcium levels are seen in tumor lysis syndrome (as shown in the table). It can be prevented by prophylactic hydration and urinary alkalinization. **Allopurinol and rasburicase** can be used based on the risk factors.

**Neutropenic enterocolitis**: It is to be considered when the absolute neutropenic count is < 500/microL. It is usually diagnosed following chemotherapy. Clinical presentation involves lower quadrant abdominal pain associated with distension. Treatment is by providing supportive measures.
Prognosis of Acute Myeloid Leukemia and Survival Rate

Higher Chances for Younger AML-Patients

Factors which predict a favorable outcome in AML include the younger age of presentation with no previous history of chemotherapy and other hematological disorders.

The following table lists risk factors for the outcome in adults with acute myeloid leukemia:

<table>
<thead>
<tr>
<th>Favorable factors</th>
<th>Unfavorable factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &lt; 50</td>
<td>Age &gt; 60</td>
</tr>
<tr>
<td>Karnofsky score &gt; 60 %</td>
<td>Karnofsky score &lt; 60 %</td>
</tr>
<tr>
<td>MDR 1-negative phenotype</td>
<td>MDR 1-positive phenotype</td>
</tr>
<tr>
<td>No antecedent hematologic disorder or prior chemo/radiotherapy</td>
<td>Therapy-related AML, prior myelodysplastic syndrome, myeloproliferative or other hematologic disorder</td>
</tr>
<tr>
<td>t(8;21), inv(16)/t(16;16), t(15;17)</td>
<td>Complex karyotypic abnormalities,-5—7,3q26 aberrations, t(6;9), 11q23 aberrations</td>
</tr>
</tbody>
</table>

Review Questions

The correct answers can be found below the references.

1. Acute myeloid leukemia is a malignant transformation of hematopoietic stem cells. It usually affects the individuals above which age?
   A. 65 years
   B. 45 years
   C. 25 years
   D. 15 years
   E. 10 years

2. Which one of the following is the pathognomonic of acute myeloid leukemia?
   A. Nissl bodies
   B. Neurofibrillary tangles
   C. Howell-Jolly bodies
   D. Heinz bodies
   E. Auer rods

3. For the accurate diagnosis of acute myeloid leukemia, what is the minimum percentage of blast cells required in bone marrow or peripheral blood?
   A. 20 %
   B. 10 %
   C. 5 %
   D. 25 %
   E. 1 %
References


Tumor lysis syndrome: Prevention and treatment via upToDate.com. Date accessed: 29 Nov 2015.

Induction therapy for acute myeloid leukemia in younger adults via upToDate.com. Date accessed: 29 Nov 2015.

Treatment of acute myeloid leukemia in older adults via upToDate.com. Date accessed: 29 Nov 2015.

Overview of the complications of acute myeloid leukemia via upToDate.com. Date accessed: 29 Nov 2015.

Correct answers: 1A, 2E, 3A

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