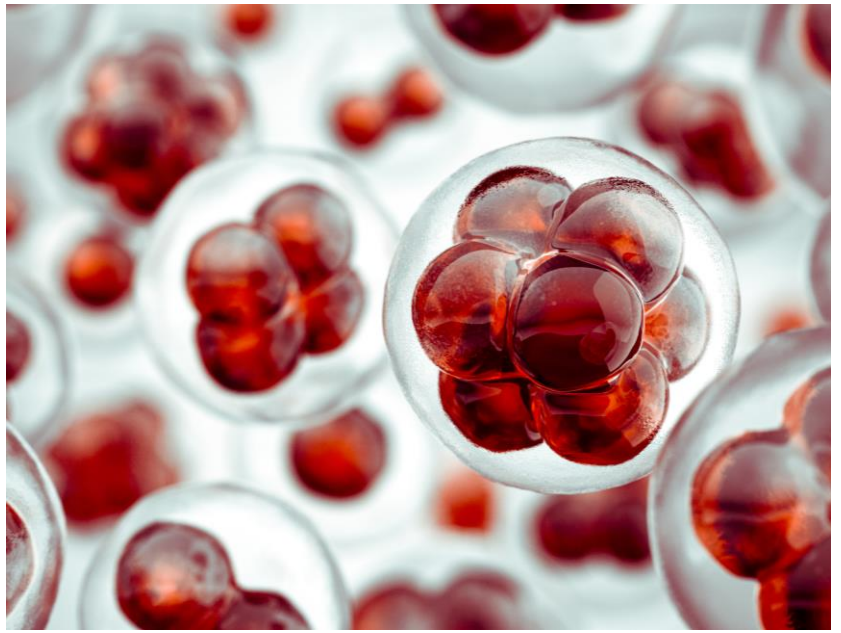


Acute Myelogenous Leukemia : FOCUS on Acute Promyelocytic Leukemia (APL)

Sara Tinsley- Vance PhD, APRN, AOCN

MAY 13, 2023

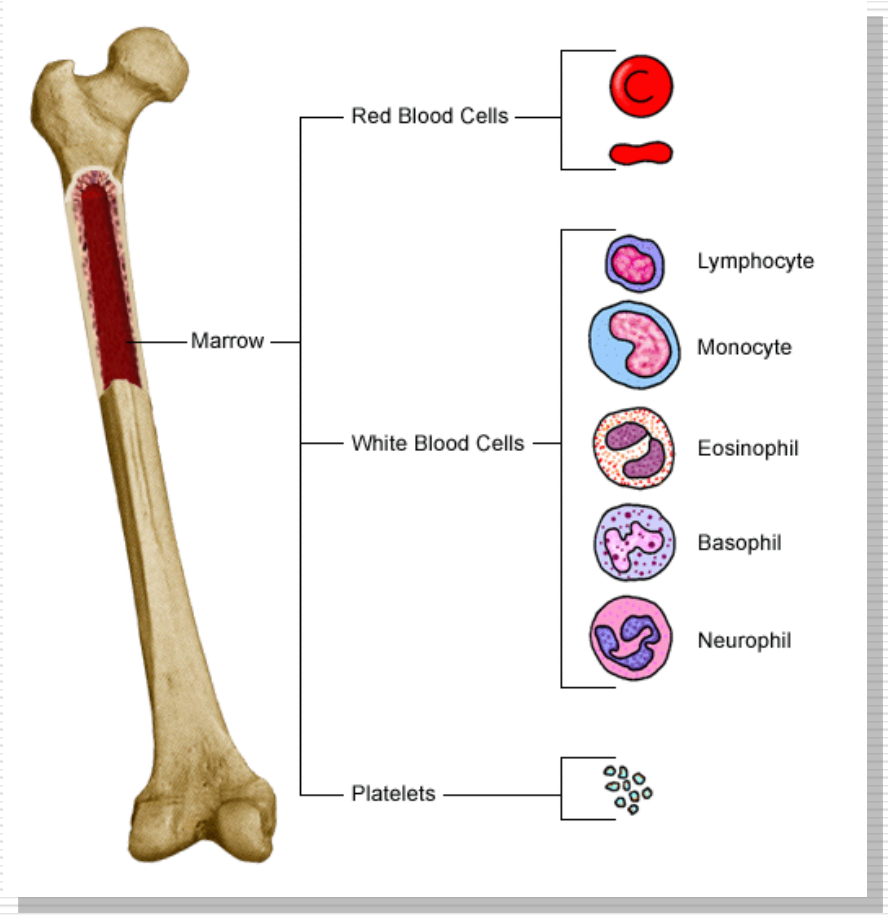
Disclosures

- Sara Tinsley-Vance is on the speaker's bureau for Astellas; consultant for Novartis; consultant and on the speaker's bureau for Bristol Myers Squibb, Incyte, Jazz, CTi
- Relevant financial relationships have been mitigated

Objectives

- Review epidemiology, etiology, pathophysiology of AML
- Identify risk categories of AML according to European Leukemia Net
- Discuss clinical presentation of AML
- Recognize the latest updates in management of acute promyelocytic leukemia (APL)
- Outline critical aspects of treatment for induction of APL

Leukemia



- Group of hematologic malignancies affecting the bone marrow and lymphatic system
- 1847 German pathologist Virchow "leukemia" or white blood
- Abnormalities of proliferation of lymphoid and myeloid cell lines
- Acute versus chronic

Piccaluga, Pier Paolo. "Introductory Chapter: A Brief History of Acute Leukemias Treatment." *Acute Leukemias*. IntechOpen, 2021.

Epidemiology for Acute Myelogenous Leukemia (AML)

- 20,380 new cases projected
- 11,310 deaths projected
- Slightly more men than women diagnosed
- Median age at diagnosis of 69 years
- 5-year relative survival rate of ~ 30%

Siegel, RL, Miller, KD, Wagle, NS, Jemal, A. Cancer statistics, 2023. CA Cancer J Clin. 2023; 73(1): 17- 48. doi:10.3322/caac.21763

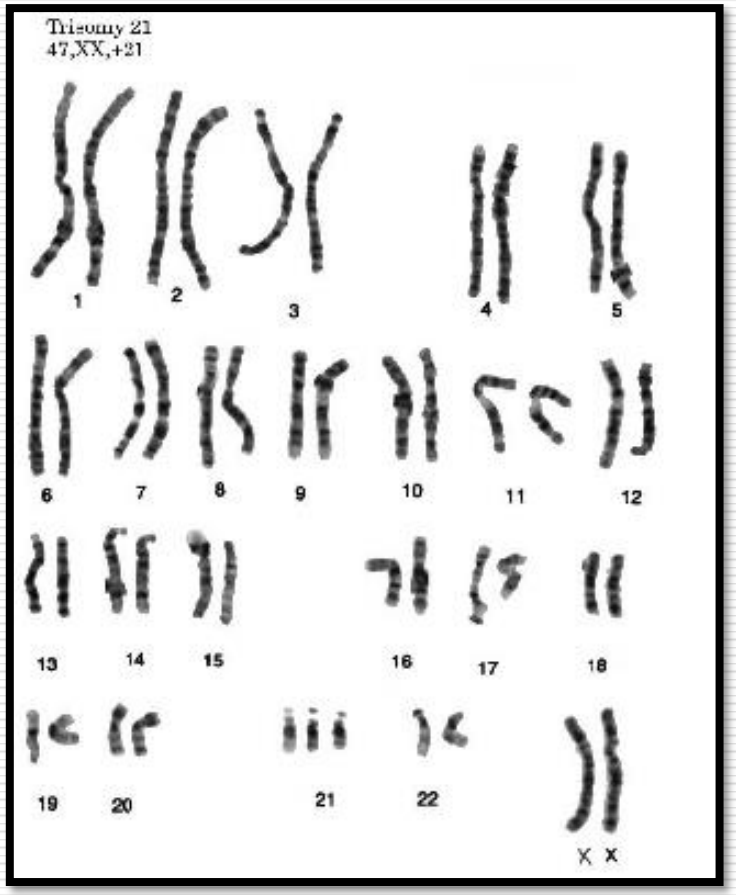
Epidemiology for Acute Promyelocytic Leukemia

- Makes up between 7-8% of adult AML cases
- Median age at diagnosis of 47 years
- Slightly more men than women
- Rarely diagnosed prior to the age of 20
- Survival rates > 90%
- More common among Hispanics

Cingam SR, Koshy NV. Acute Promyelocytic Leukemia. [Updated 2022 Jun 27]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK459352/

Etiology | Genetic Factors

- Evidence of familial clustering
- Genetic disorders
  - Down's syndrome
  - Bloom's syndrome
  - Fanconi's anemia
  - Klinefelter's syndrome
- Acquired chromosomal abnormalities
  - 55-78% of adult patients with acute leukemia
- Most commonly evolve from MDS



Nickels EM, Soodalter J, Churpek JE, Godley LA. Recognizing familial myeloid leukemia in adults. Ther Adv Hematol. 2013 Aug;4(4):254-69. doi: 10.1177/2040620713487399. PMID: 23926458; PMCID: PMC3734901

Etiology-Chemicals

- Alkylators
- Antibiotics
  - Chloramphenicol
  - Phenylbutazone
- Chemotherapy
  - Etoposide
  - Topoisomerase II inhibitors
  - Therapy related leukemia is 20-25%

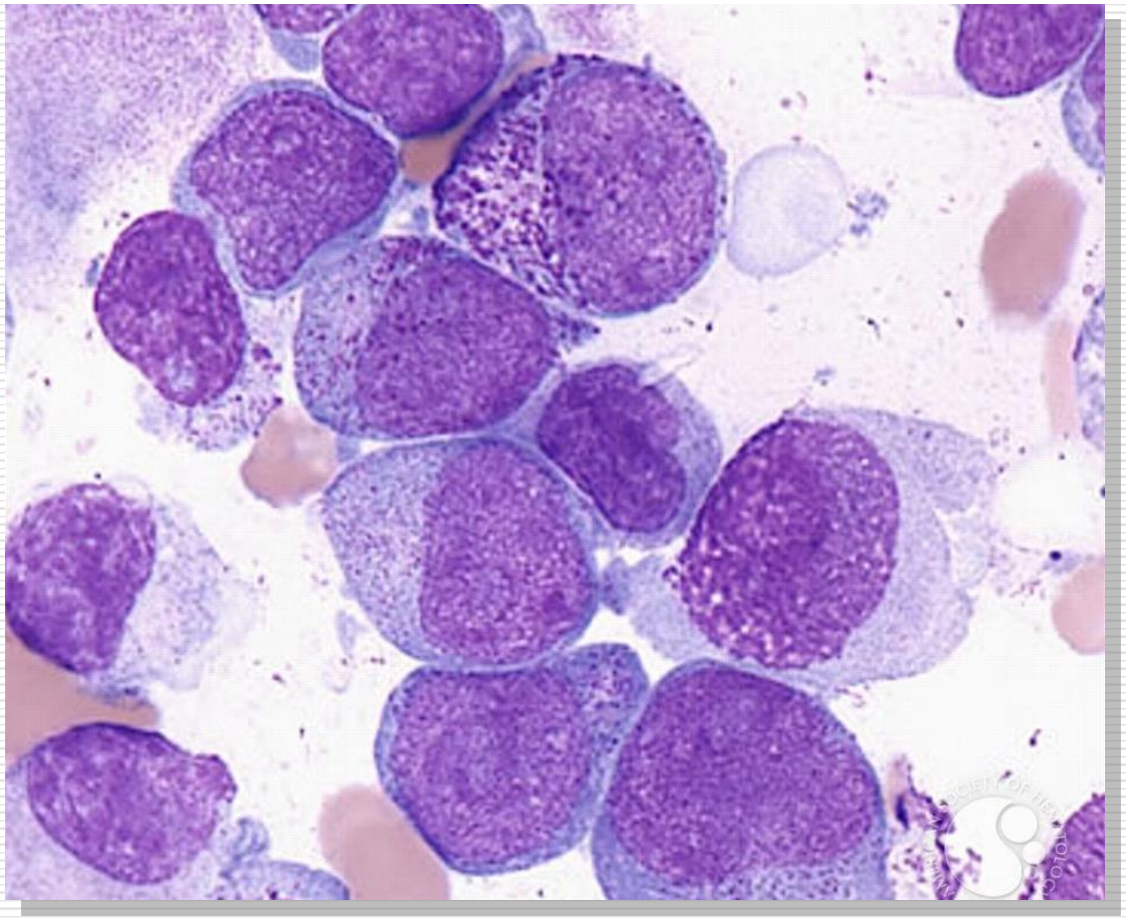
Döhner H, et al. Diagnosis and management of AML in adults: 2022 recommendations from an international expert panel on behalf of the ELN. Blood. 2022 Sep 22;140(12):1345-1377. doi: 10.1182/blood.2022016867.

Etiology-Radiation

- Most conclusively identified leukemogenic factor in humans
  - Japanese survivors of atomic bomb
  - Early radiologists

Iliakis G, Wang Y, Guan J, et al. DNA damage checkpoint control in cells exposed to ionizing radiation. Oncogene. 2003;22(37):5834–47.References go here.

Etiology

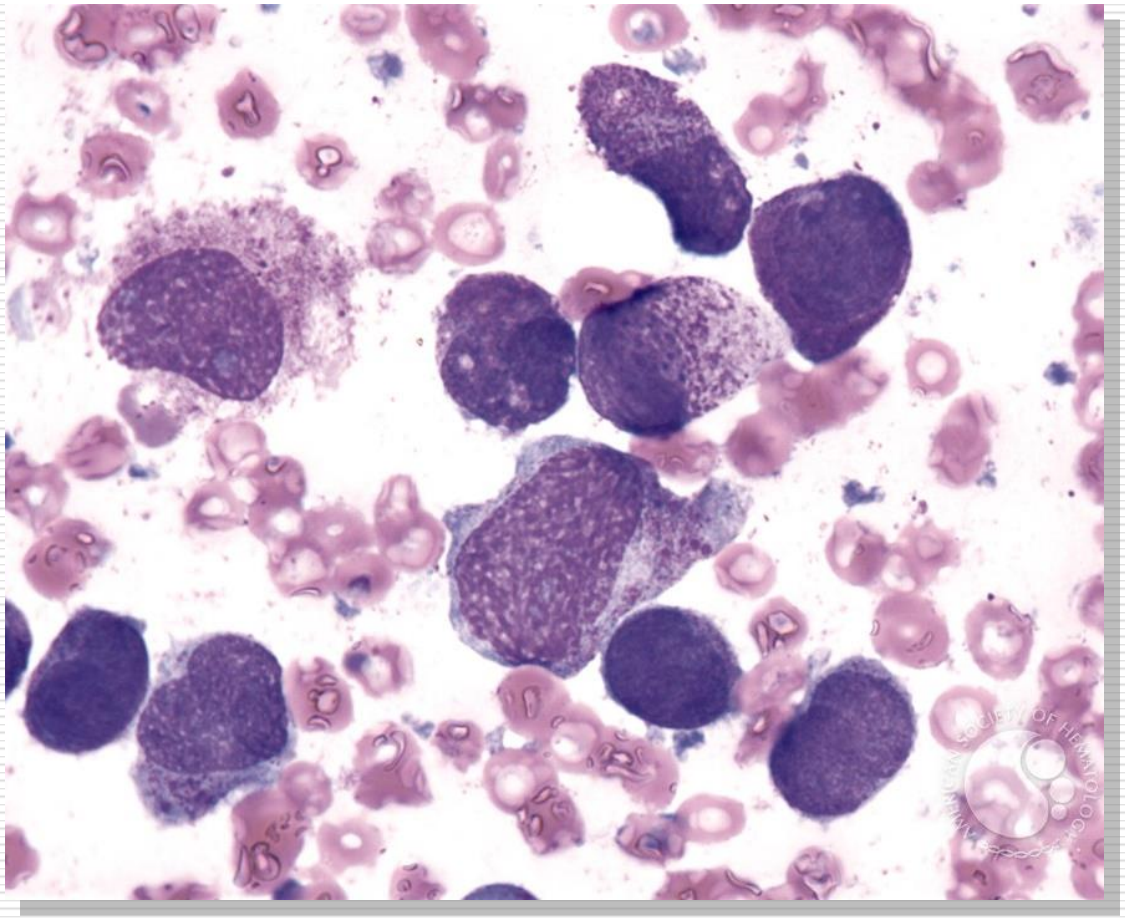


- Most often, the cause of acute myelogenous leukemia is unknown
- Older age
- Germline mutations

Shallis, Rory M., et al. "Epidemiology of acute myeloid leukemia: Recent progress and enduring challenges." Blood reviews 36 (2019): 70-87.

Pathophysiology

- Normal regulatory mechanisms for cell proliferation and maturation are missing or abnormal.
  - Arrest of the cell in an early phase of maturation causes accumulation of immature cells
  - Abnormal proliferation of these immature cells
  - Crowding of other marrow elements
- Driven by germline and acquired somatic mutation



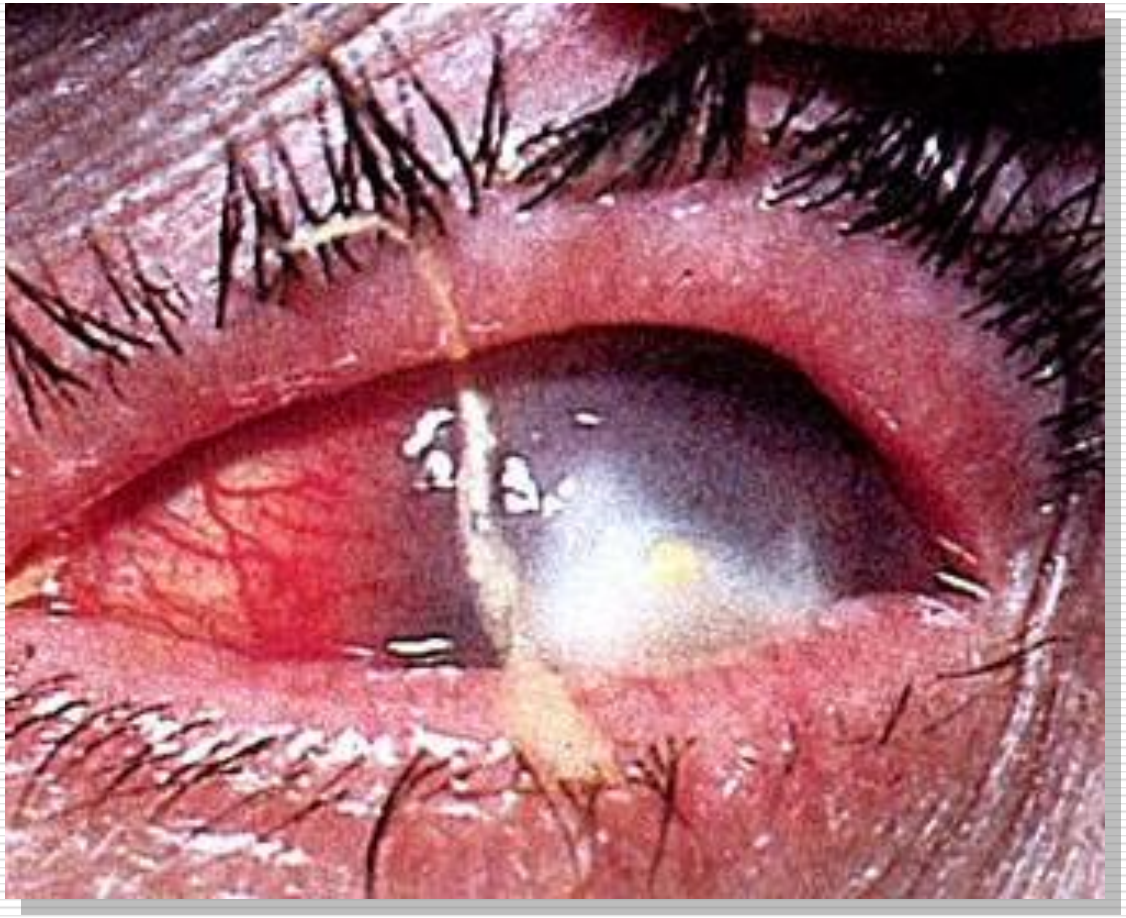
Vakiti A, Mewawalla P. Acute Myeloid Leukemia. [Updated 2022 Aug 15]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK507875/

CLINICAL MANIFESTATIONS OF AML

- Driven by the cytopenia
  - Anemia
  - Thrombocytopenia
  - Neutropenia
- Subtype of AML
- Comorbidities
- Frailty

Liesveld JL, Lichtman MA. Acute myelogenous leukemia. In: Kaushansky K, Lichtman MA, Prchal JT, et al., editors. Williams Hematology. 9th ed. . United States of America: McGraw-Hill Education; 2016.

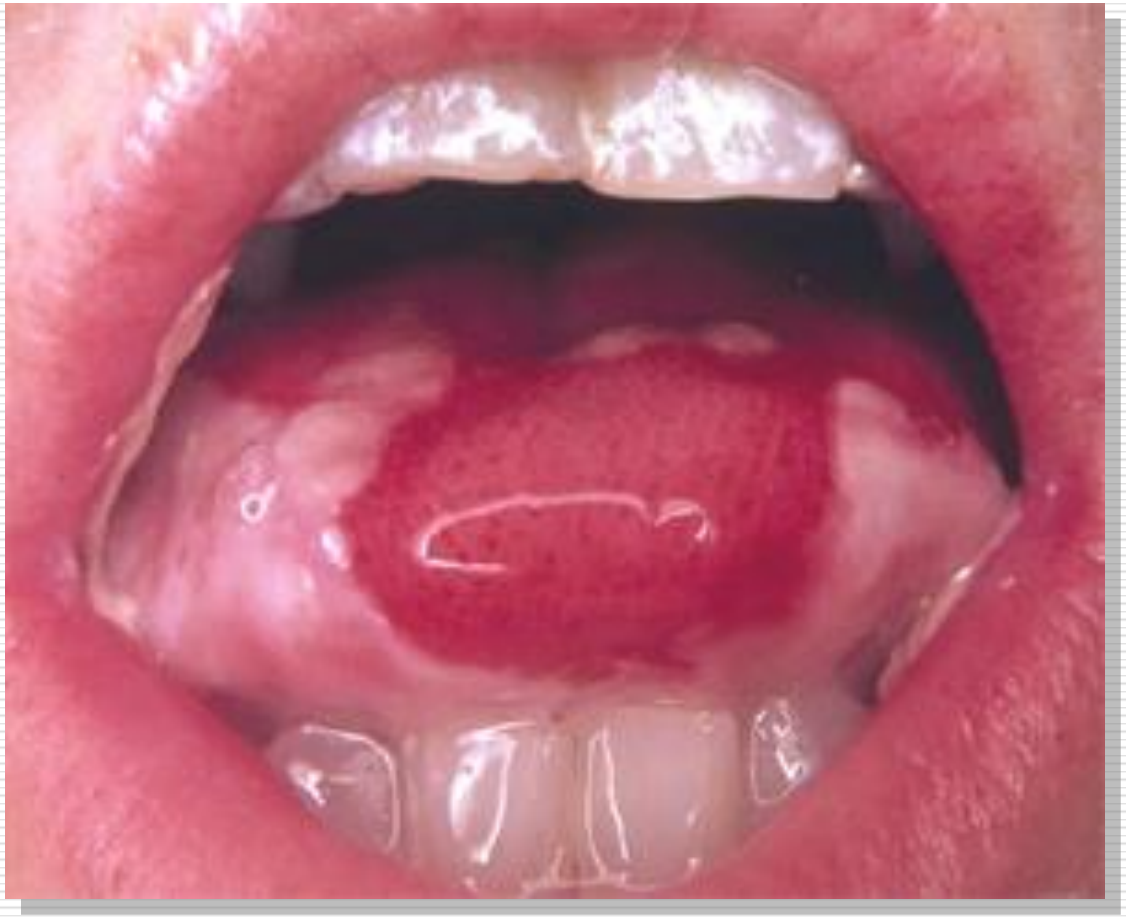
Clinical Manifestations



- Neutropenia
  - Fever
  - Abdominal pain
  - Respiratory infection
  - Perirectal abscess
  - Adenopathy

Liesveld JL, Lichtman MA. Acute myelogenous leukemia. In: Kaushansky K, Lichtman MA, Prchal JT, et al., editors. Williams Hematology. 9th ed. . United States of America: McGraw-Hill Education; 2016.

Clinical Manifestations



- Neutropenia
  - Mucositis
- Fungal invasions with prolonged neutropenia

Liesveld JL, Lichtman MA. Acute myelogenous leukemia. In: Kaushansky K, Lichtman MA, Prchal JT, et al., editors. Williams Hematology. 9th ed. . United States of America: McGraw-Hill Education; 2016.

Clinical Manifestations

- Anemia
  - Fatigue or malaise
  - Pallor
  - Dyspnea

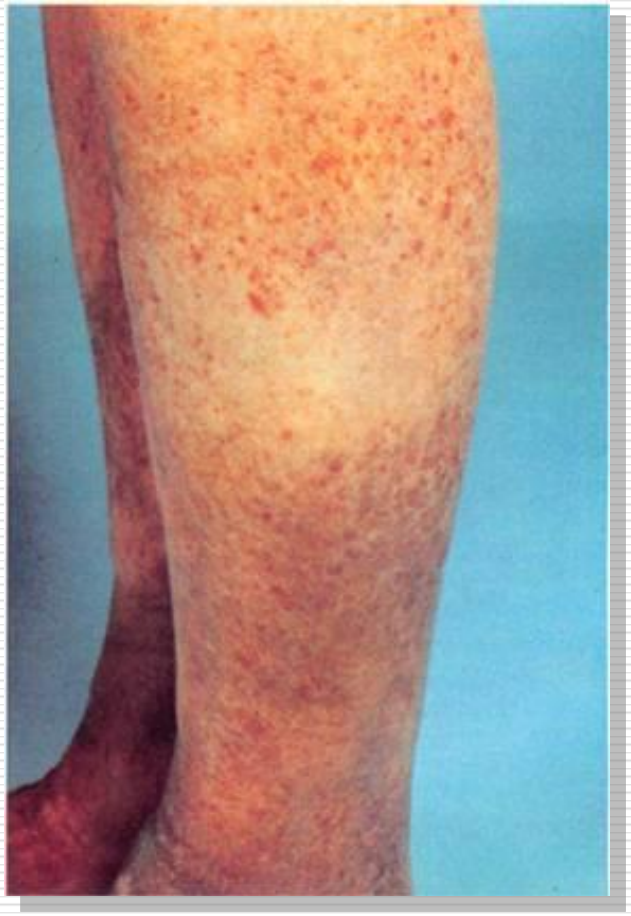
Liesveld JL, Lichtman MA. Acute myelogenous leukemia. In: Kaushansky K, Lichtman MA, Prchal JT, et al., editors. Williams Hematology. 9th ed. . United States of America: McGraw-Hill Education; 2016.

Clinical Manifestations

- **Leukemic infiltrates**
  - Pain or swelling in bones and joints
  - Hepatomegaly
  - Splenomegaly

Liesveld JL, Lichtman MA. Acute myelogenous leukemia. In: Kaushansky K, Lichtman MA, Prchal JT, et al., editors. Williams Hematology. 9th ed. United States of America: McGraw-Hill Education; 2016.

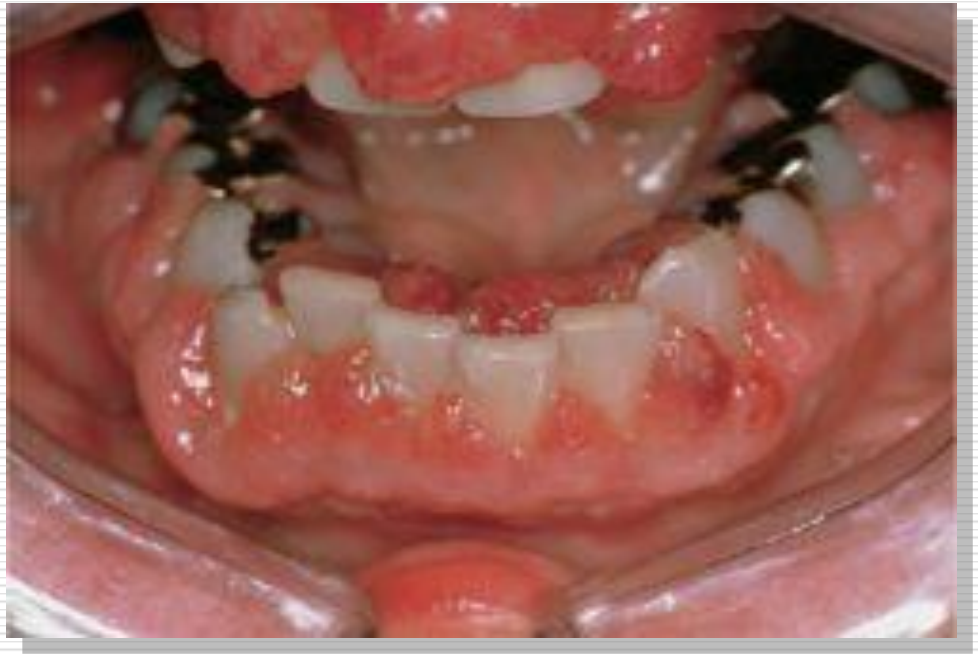
Clinical Manifestations



- **Thrombocytopenia**
  - Purpura, petechiae, ecchymoses
  - Bleeding gums
  - Epistaxis
  - Retinal hemorrhage
  - Intracranial bleeding

Liesveld JL, Lichtman MA. Acute myelogenous leukemia. In: Kaushansky K, Lichtman MA, Prchal JT, et al., editors. Williams Hematology. 9th ed. United States of America: McGraw-Hill Education; 2016.

Assessment of Acute Leukemia



- Physical symptoms and findings influenced by:
  - Type of leukemia cell
  - Degree of leukemic cell burden
  - Involvement of organs and systems outside the bone marrow or circulation
  - Depression of normal marrow elements by leukemic process

Liesveld JL, Lichtman MA. Acute myelogenous leukemia. In: Kaushansky K, Lichtman MA, Prchal JT, et al., editors. Williams Hematology. 9th ed. United States of America: McGraw-Hill Education; 2016.

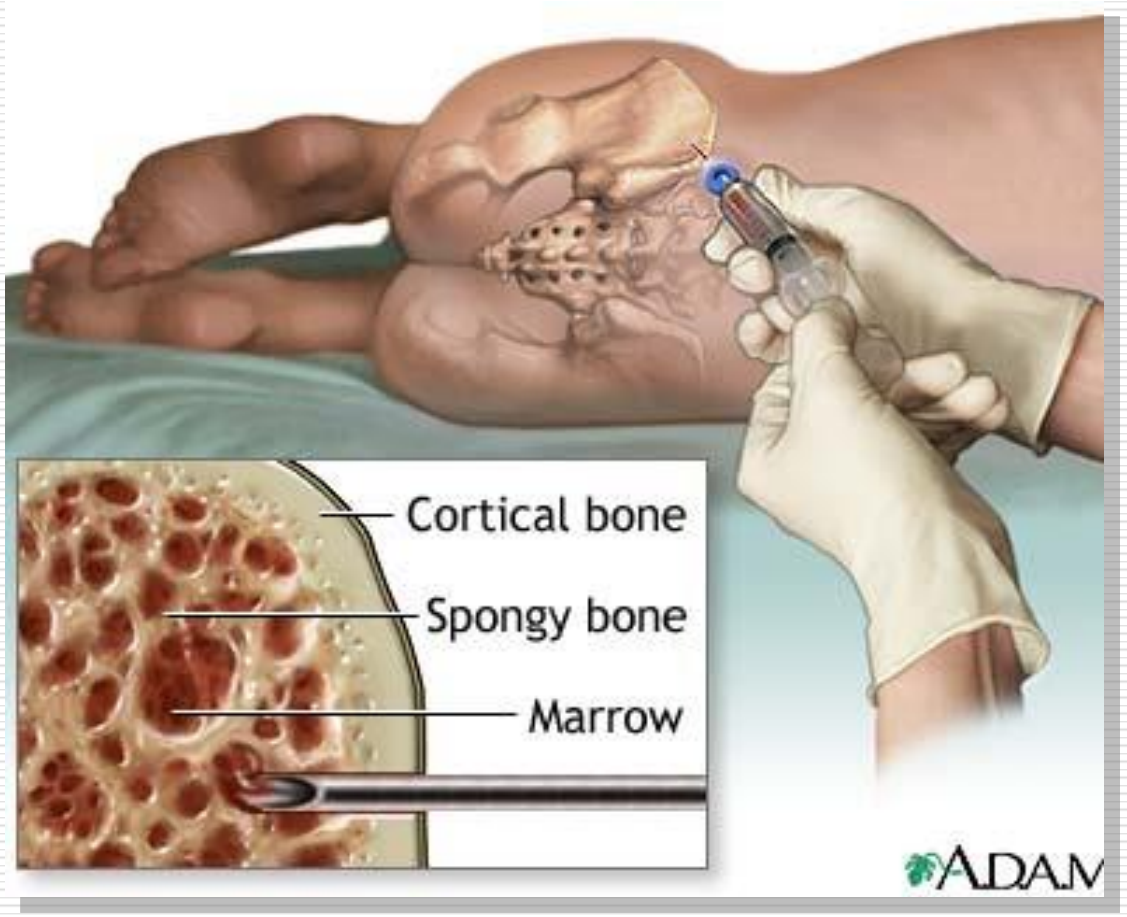
Clues from Patient History

- Signs and symptoms normally present for less than three months
- Most complaints are nonspecific
  - Common symptoms include fatigue, weight loss, infections, unexplained bleeding, bone pain, and shortness of breath

Liesveld JL, Lichtman MA. Acute myelogenous leukemia. In: Kaushansky K, Lichtman MA, Prchal JT, et al., editors. Williams Hematology. 9th ed. United States of America: McGraw-Hill Education; 2016.

Diagnostic studies for AML

- AML versus ALL
  - Suggested by peripheral smear
  - Bone marrow biopsy and aspiration
    - Normally hypercellular
    - Auer rods diagnostic of AML
  - 90% have blast cells present in the peripheral blood work



Narayanan, D., & Weinberg, O. K. (2020). How I investigate acute myeloid leukemia. International journal of laboratory hematology, 42(1), 3-15.

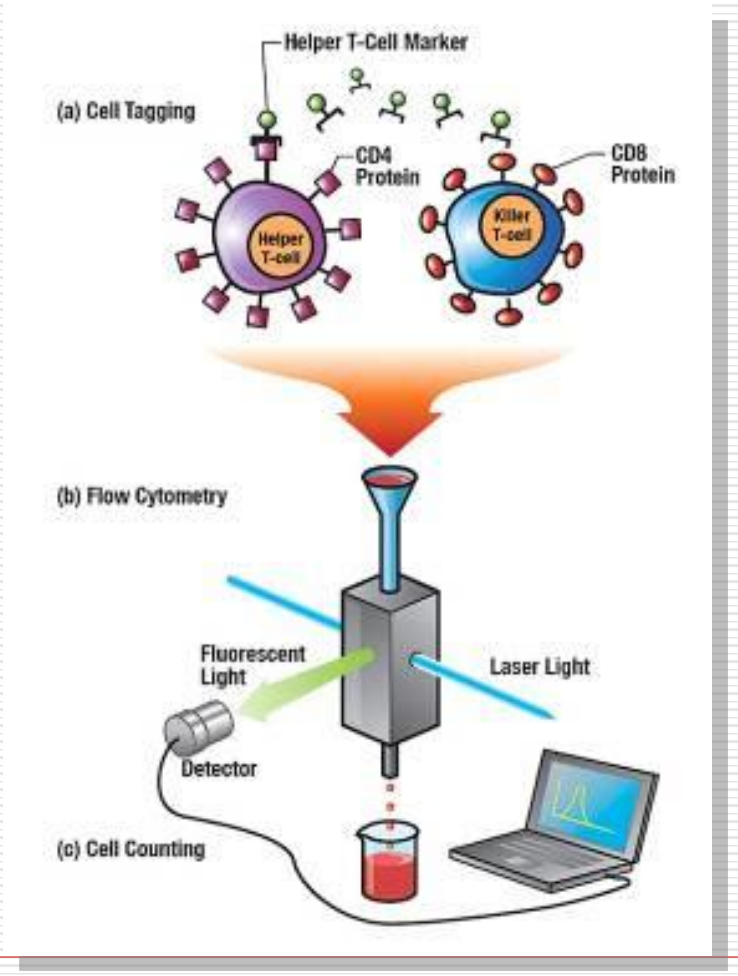
Diagnostic studies

- Cytogenetic analysis
  - Confirm diagnosis
  - More than 2/3 of patients have nonrandom chromosomal abnormalities
  - Translocations, inversions, or loss or gain in chromosome number
  - Prognostic indicators

Narayanan, D., & Weinberg, O. K. (2020). How I investigate acute myeloid leukemia. International journal of laboratory hematology, 42(1), 3-15.

Diagnostic Studies - Flow cytometry

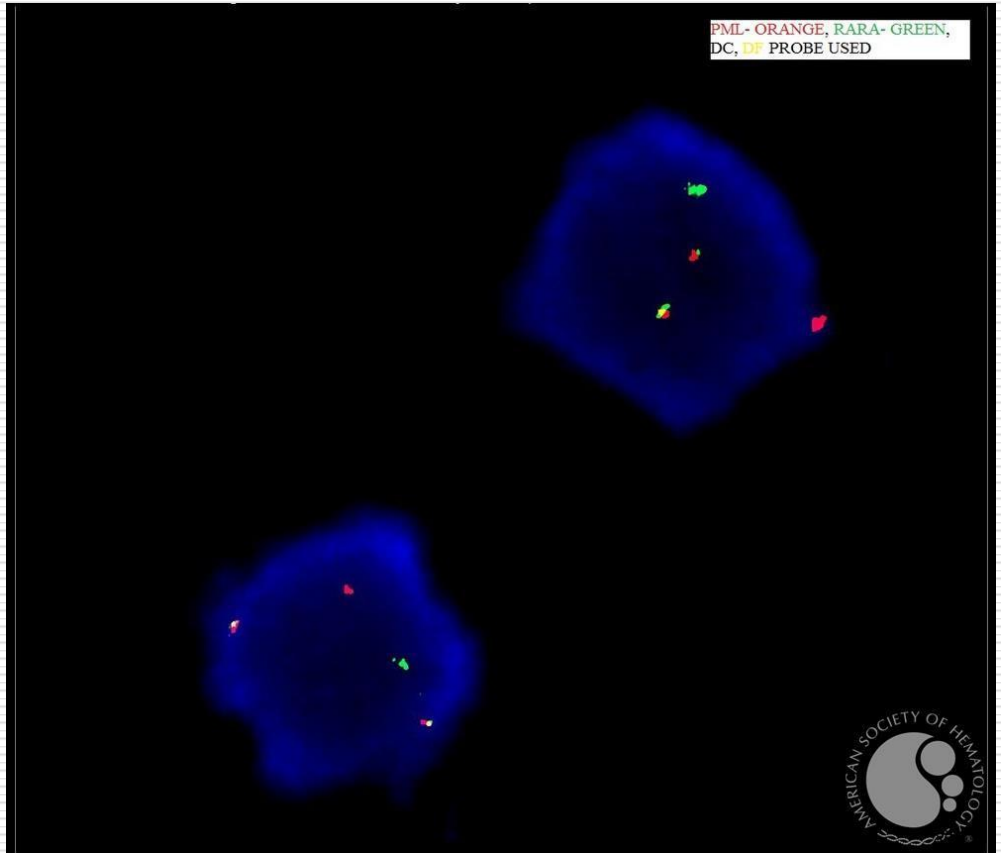
- Immunologic studies
  - Clusters of differentiation
    - Reside on surface of hematopoeitic cells
  - Assist with distinguishing between AML and ALL
    - Some patients have markers for both lymphoid and myeloid leukemia or leukemia of ambiguous lineage (21%)



Narayanan, D., & Weinberg, O. K. (2020). How I investigate acute myeloid leukemia. *International journal of laboratory hematology*, *42*(1), 3-15.

Diagnostic Studies: Fluorescence In Situ Hybridization (FISH)

- Used for detecting cytogenetic abnormalities
- Useful when metaphases are not available from traditional karyotyping
- Must identify what you are “FISHing" for from the specimen



Shakoori AR. Fluorescence In Situ Hybridization (FISH) and Its Applications. Chromosome Structure and Aberrations. 2017 Feb 10:343–67. doi: 10.1007/978-81-322-3673-3_16. PMCID: PMC7122835.

Diagnostic Studies: Reverse Transcriptase Polymerase Chain Reaction (PCR)

- High specificity and sensitivity
- Used to measure minimal residual disease in certain subtypes of AML, including APL
  - PML-RARA
  - BCR/ABL
  - RUNX1

Qin D. Molecular testing for acute myeloid leukemia. Cancer Biol Med. 2021 Aug 4;19(1):4–13. doi: 10.20892/j.issn.2095-3941.2020.0734.

2022 ELN AML RISK CLASSIFICATION

Three Risk Categories

Based on Genetic and molecular Abnormalities

Guides Treatment recommendations

Risk category	Genetic abnormality
Favorable	t(8;21)(q22;q22.1)/*RUNX1*::*RUNX1T1*
	inv(16)(p13.1q22) or t(16;16)(p13.1;q22)/*CBFB*::*MYH11*
	Mutated *NPM1* without *FLT3*-ITD
	bZIP in-frame mutated *CEBPA*
Intermediate	Mutated *NPM1* with *FLT3*-ITD
	Wild-type *NPM1* with *FLT3*-ITD
	t(9;11)(p21.3;q23.3)/*MLLT3*::*KMT2A*
	Cytogenetic and/or molecular abnormalities not classified as favorable or adverse
Adverse	t(6;9)(p23;q34.1)/*DEK*::*NUP214*
	t(v;11q23.3)/*KMT2A*-rearranged
	t(9;22)(q34.1;q11.2)/*BCR*::*ABL1*
	t(8;16)(p11;p13)/*KAT6A*::*CREBBP*
	inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2)/*GATA2*, *MECOM(EVI1)*
	t(3q26.2;v)/*MECOM(EVI1)*-rearranged
	−5 or del(5q); −7; −17/abn(17p)
	Complex karyotype, monosomal karyotype
	Mutated *ASXL1*, *BCOR*, *EZH2*, *RUNX1*, *SF3B1*, *SRSF2*, *STAG2*, *U2AF1*, or *ZRSR2*
	Mutated *TP53*

Döhner H, Wei AH, Appelbaum FR, et al. Diagnosis and management of AML in adults: 2022 ELN recommendations from an international expert panel. 2022. Online ahead of print. DOI: 10.1182/blood.2022016867

Emergency Management of APL

- Individuals with suspected APL should be immediately hospitalized and managed as a medical emergency
- Even before confirmation:
  - ATRA
  - Measures to counteract the coagulopathy should be initiated immediately
    - Based solely on the clinical suspicion of APL
    - Review of the peripheral blood (PB) smear

Miguel A. Sanz, et al. ; Management of acute promyelocytic leukemia: updated recommendations from an expert panel of the European LeukemiaNet. Blood 2019; 133 (15): 1630–1643.

Latest Updates in Management of APL

- Diagnosis should be confirmed by molecular detection of PML-RARA fusion (or rare molecular variants)
  - PCR for PML/RARA
  - FISH for PML/RARA (quicker turn around time)
- Management of coagulopathy
  - Treatment with ATRA should be started immediately
  - Transfusions of fibrinogen and/or cryoprecipitate, platelets, and fresh-frozen plasma should be given immediately
  - And daily or more than once a day if needed, to maintain the fibrinogen concentration above 100-150 mg/dL, the platelet count above 30×10^9/L to 50×10^9/L, and the INR below 1.5

Miguel A. Sanz, et al. ; Management of acute promyelocytic leukemia: updated recommendations from an expert panel of the European LeukemiaNet. Blood 2019; 133 (15): 1630–1643.

Latest Updates in Management of APL

- Monitor at least daily and more frequently if required, until all clinical and laboratory signs of the coagulopathy disappear
  - Platelet counts
  - Routine coagulation parameters
    - Prothrombin time
    - Activated partial thromboplastin time
    - Thrombin time
    - Fibrinogen
    - Fibrinogen-fibrin degradation products

Miguel A. Sanz, et al. ; Management of acute promyelocytic leukemia: updated recommendations from an expert panel of the European LeukemiaNet. Blood 2019; 133 (15): 1630–1643.

Latest Updates in Management of APL

- Recommend avoiding the following during remission induction
  - Central venous catheterization (except PICC)
  - Lumbar puncture
  - Other invasive procedures (eg, bronchoscopy) due to high risk of hemorrhagic complications
- Determine clinical risk versus benefit of hemorrhagic events

Miguel A. Sanz, et al. ; Management of acute promyelocytic leukemia: updated recommendations from an expert panel of the European LeukemiaNet. Blood 2019; 133 (15): 1630–1643.

Treatment options

- Non–high-risk patients (WBC count ≤10 × 10^9/L)
  - ATRA plus ATO for induction (daily until complete remission [CR] or for a maximum of 60 days)
  - Consolidation therapy (ATO 5 days per week, 4 weeks on 4 weeks off, for a total of 4 courses and ATRA 2 weeks on and 2 weeks off for a total of 7 courses)
  - EKG at the beginning of each treatment week to monitor for QTc prolongation
  - Keep magnesium at 2.0 and potassium at 4.0
  - Monitor medication lists carefully and avoid other QTc prolonging medications
    - Such as certain antiemetics and antifungals

Miguel A. Sanz, et al. ; Management of acute promyelocytic leukemia: updated recommendations from an expert panel of the European LeukemiaNet. Blood 2019; 133 (15): 1630–1643.

Treatment options

- Non–high-risk patients (WBC count ≤10 × 109/L)
  - ATRA plus ATO was associated with:
    - Significantly less myelosuppression
    - Fewer infections
  - more frequent increases in:
    - Liver enzymes
    - QTc prolongation
    - Reversible and manageable with temporary drug discontinuation
    - Dose adjustment is sometimes necessary

Miguel A. Sanz, et al. ; Management of acute promyelocytic leukemia: updated recommendations from an expert panel of the European LeukemiaNet. Blood 2019; 133 (15): 1630–1643.

Treatment options

- For high-risk APL patients (WBC count >10 × 10^9/L)
  - ATRA plus ATO with the addition of some cyto-reductive chemotherapy
    - A single dose of GO (6 mg/m^2)
  - ATRA plus chemotherapy
    - 90% to 95% CR rates
    - 85% to 90% rates of long-term survival
    - ATRA plus daunorubicin and cytarabine
    - ATRA plus idarubicin alone
    - Consolidation therapy should entail administration of at least 2, and possibly 3, further cycles of ATRA plus anthracycline–containing chemotherapy.

Miguel A. Sanz, et al. ; Management of acute promyelocytic leukemia: updated recommendations from an expert panel of the European LeukemiaNet. Blood 2019; 133 (15): 1630–1643.

Thank you for your attention!