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LEUKEMIAS

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Leukemias arise from malignant transformation of hematopoietic cells and proliferate primarily in the bone marrow. In general, leukemias are classified as:

- Acute based on rapidity of presentation and progression
- Chronic

In addition, acute leukemias are often morphologically poorly differentiated while chronic leukemias show a more normal differentiation pattern of the malignant cells.

Leukemias are further classified by the cell of origin being either myeloid or lymphoid.

AML

- AML is a clonal disorder of a primitive stem cell that result in excess proliferation of immature cells and suppression of normal hematopoiesis
- Leukemic cells infiltrate organs and suppress other cell lines, resulting in cytopenias.
- Classification of AML has traditionally relied on **morphology** to break this group of disorders into 8 types according to the French-American-British (FAB) classification system. Recently, this has undergone changes – the so called (WHO) classification system- based on new **molecular characteristics** of the individual disorders within AML

AML FAB CLASSIFICATION

- M0: minimal differentiation
- M1: without differentiation
- M2: with maturation
- M3: acute promyelocytic leukemia APL
- M4: myelomonocytic
- M5: monocytic
- M6: erythroblastic leukemia
- M7: megakaryocytic

- Epidemiology
  - median age: 62 – 65 years
  - 5 cases per 100,000 at age 60 years
  - 1% of cancer deaths
- Risk factors
  - exposure to ionizing radiation
  - exposure to chemicals: benzene
  - exposure to drugs:

* alkylating agents (cyclophosphamide, chlorambucil, melphalan)

* topoisomerase II inhibitors (etoposide)

- genitic factors

* identical twins of leukemic patients have higher rates of leukemia

* increased rates of leukemia in Down's syndrome, Bloom's syndrome, Fanconi's anemia, Klinefelter's syndrome

- myelodisplastic syndrome

- Prognostic factors: generally,

  -worse prognosis if age over 60 years,

  - poor functional status,

  - AML secondary to prior chemotherapy or myelodisplastic syndrome

  - WBC greater than 20.000/mL

- Cytogenitics are the most critical prognostic factor

CLINICAL PRESENTATION

- The main presenting symptoms are caused by decreased production of normal cells
  - pallor, fatigue, and dyspnea from anemia
  - petechiae, hematoma, and bleeding (oral, GI) from thrombocytopenia
- Splenomegaly is **uncommon**
- Individual types may have unique features

- Leptomeningeal involvement is common in late stages
  - headache and altered mental status are the most common symptoms
  - cranial nerve palsies are the most common signs
- Hyperleukocytosis is seen when increased WBC (common if WBC > 100,000/mL) results in obstruction of capillaries and small blood vessels causing widespread ischemic changes, which can result in:
    - stroke
    - pulmonary congestion
- Tumor lysis syndrome

DIAGNOSIS

- Diagnosis depends on identification of myeloblasts in peripheral blood smear or bone marrow preparations

- peripheral smear may vary from pancytopenia without circulating blasts to marked blastocytosis

- AUER RODS are cytoplasmic inclusions of aggregated lysosomes and are considered pathognomonic for myeloid leukemia

- Morphology and immunologic / cytologic markers define the AML subtypes
- Other laboratory features

  - hematologic :

  - WBC can be low or high
  - blast count may be low or high
  - hematocrit usualy in the 20s
  - platelet count usualy low

  - increased cell turnover can increase serum potassium, phosphate, and uric acid

- spurious abnormalities are related to utilization (oxygen, glucose) by the high WBC count or excessive cell death (potassium) in the phlebotomy tube.

TREATMEN

- Chemotherapy treatment consists of 2 parts:

  - induction

  - consolodiation

- Induction chemotherapy is based on a combination of an anthracycline and cytarabine and has a GOAL of stabilizing the sick patient and restoring bone marrow function

- In patient with APL, all – trans retinoic acid (ATRA) IS ADDED TO INDUCTION PHASE
- CONSOLODIATION (or intensification) consists of either several additional cycles of intensive cytarabine –based chemotherapy or stem cell transplant and has a GOAL of curing the patient of AML

- Bone marrow transplant (BMT) can be curative but is usually reserved for younger patients (< 55 years) and those considered incurable by routine chemotherapy(i.e., those patients with poor risk cytogenitics or leukemias related to previous therapy or arising from previous bone marrow disorders)
- Hyperleukocytosis is treated with leukophoresis and emergent lowering of counts

- Result of treatment
- 35% to 40% of patients will be alive and free of disease at 5 years
- The relapse rate declines sharply after 4 to 5 years

ALL

- Mainly occurs in children
- Worse prognosis with:
  - increasing age,
  - Philadelphia chromosome
  - WBC greater than 30,000/mL
- Recently classification has been updated by WHO

- ALL FAB classification
- ALL L1: fine to slightly condensed chromatin
- ALL L2: variable nuclear size, moderate amount cytoplasm
- ALL L3: homogenous, round nucleus, deeply basophilic, highly vacuolated

CLINICAL PRESENTATION

- Usually acute onset of symptoms (less than 2 weeks)
- Presents with fatigue, pallor, bleeding or bruising or infection
- 50% present with fever, because of either pyrogenic cytokine release or concurrent

  infection
- 50% have lymphoadenopathy and splenomegaly on examination
- Anterior mediastinal mass is common with T – cell infiltration of the thymus
- CNS involvement is common in all types of ALL

DIAGNOSIS

- Lymphoblasts are seen on peripheral smear and bone marrow preparation

  -may be difficult to differentiate from myrloblasts

  - flow cytometry is helpful in distinguishing ALL from AML
- Evaluation always includes analysis of CSF for CNS involvement

TREATMENT

- Standard treatment is a multiple agent chemotherapy and require maintenance therapy for at least 2 years
- CNS chemoprophylaxis with methotrexate +/- CNS radiation may be given to prevent CNS relapse
- BMT may be performed if there are poor prognostic factors if the disease progresses

CHRONIC MYELOGENOUS LEUKEMIA

- CML is a malignant clonal disorder that is classified as one of the myeloprolifrative syndromes
- CML has been well characterized
  - 9;22 translocation (the philadelphia chromosome) produces a Bcr:Abl gene fusion
  - Protein product is a constitutively active tyrosine kinase causing uncontrolled cell proliferation and decrease apoptosis

- Better prognosis with:
  - age younger than 40 years,
  - low percentage of blasts
  - the absence of thrombocytopenia
  - mild splenomegaly
- Natural progression is from a benign chronic phase to fatal blast crisis in 3 to 5 years
  - blasts typically myeloids (70%), but can be lymphoblastic (20%) or undifferentiated
  - prognosis after blast crisis is very poor, with median survival of a few months

CLINICAL PRESENTATION

- Early satiety and left upper quadrant fullness, fatigue
- Splenomegaly on examination seen in 50%
- CBC typically shows WBC count greater than 100,000/mL, anemia, and thrombocytosis
- Blast crisis may present as fever, night sweats, bone pain, and easy bruising

DIAGNOSIS

- Peripheral smear typically shows the presence of virtually all cells of neutrophilic series, from mature neutrophils to myeloblast
- Diagnosis is established by demonstration of the **philadelphia chromosome** or by PCR detection of the Bcr:Abl fusion gene

TREATMENT

- Allogeneic BMT remains the only known curative therapy
  - cure rate is 70%
  - Graft versus leukemia effects are critical for success; however, benefits of this must be weighed against the risk of GVHD which is the critical component of morbidity and mortality
  - Require HLA matched donor
  - In general, transplantation has better outcome when done on patient early in the course of their disease and/or during chronic phase

- Medical management considered the standard first line in most patients (exception being younger patients with a high risk presentation)
- Imatinib mesylate (Gleevec) is a tyrosine kinase inhibitor that blocks the effect of Bcr:Abl on the cell and results in marked clinical improvements
- Complete hematologic remission in over 90% of patients treated upfront
- Complete cytogenitics remission in 60% to 70% of patients treated upfront

Thank you ☺