بسم الله الرحمن الرحيم

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Leukemia

- Leukemia is the most common neoplasm in childhood. It represents about 41% of all malignancies < 15 yrs of age.
- Genetic & environmental factors predispose to childhood malignancies:
- **Genetic**: identical twins, Down syndrome, fancony anemia…
- **Environmental:** ionizing radiation, drugs, alkylating agents, benzene, advanced maternal age, EBV, etc…

Types

1. Acute lymphoblastic leukemia (ALL): 77% of the total.
2. Acute myelogenous leukemia (AML): 11%
3. Chronic mylogenous leukemia (CML: 2-3%
4. Juvenile CML (JCML): 1-2%
5. Undefined leukemia: 7-9%

Acute Lymphoblastic Leukemia (ALL)

- It is the most common type of childhood leukemia (77% of the total).
- Sex incidence: male:female = 1.2 : 1.

Clinical presentations

- The initial presentations are usually non-specific as anorexia, fatigue, irritability, & intermittent low grade fever. There may be bone or joint pain especially in lower extremities.

Bone marrow infiltrations with blast cells & subsequent failure of hematopoiesis:
- Anemia: pallor, tiredness, headache, dizziness…
- Thrombocytopenia: bruising, bleeding, retinal hemorrhage…
- Neutropenia: pyrexia, infections…

Organs infiltrations:
- Lymphadenopathy & hepatosplenomegaly
- There may be bone tenderness & joint swelling.
- Rarely, there is ↑ intracranial pressure (ICP): papillidema, retinal hemorrhage, cranial nerve palsies, etc…

- There may be respiratory distress (usually due to anemia but may be due to large mediastinal mass)
- There may be skin infiltrate (especially in infants).
- There may be testicular infiltrations (rare at presentation).

Diagnosis

- Anemia & thrombocytopenia are seen in most patients.
- Leukemic cells are often not observed in the routine peripheral blood film.
- Most patients with ALL present with total WBC count of <10,000/ μL. WBC count may be normal, ↑, or ↓.
- The leukemic cells are often initially reported to be atypical lymphocytes which need further evaluation.
- There may be no blast cells on blood film (aleukemic leukemia).

Bone marrow examination:

- Leukemia is diagnosed when the hemogenous population of lymphoblasts represent > 25% of bone marrow cells.

1. Morphology: Blasts cells are classified according to the French-American-British (FAB) classification into: • L1 (80-85%) • L2 (10-15%) • L3 (2-3%)
2. Cytochemistry: Special stains which distinguish ALL & AML.
3. Immunophenotypes: Monoclonal antibodies differentiate cells of lymphoid or myeloid origin or subtypes of lymphoid origin.
4. Cytogenetics: Number of chromosomes & structural changes (translocations) & chromosomal abnormalities which are found in most patients with ALL.

- **Lumbar puncture**: to assess cell count & blast cells.
- **Biochemistry:** blood urea & electrolytes, liver functions tests, immunoglobulns…
- **Viral serology**: baseline chickenpox & measles titers…
- **Radiology**: CXR (mediastinal mass & pleural effusion), Abdominal U/S (organomegaly , abdominal mass).

Differential diagnosis:

AML, Neuroblastoma, Rhabdomyosarcoma. Ewing sarcoma, Retinoblastoma, Causes of 1ry bone marrow failure (aplastic anemia, myelofibrosis, ITP, neutropenia…), Infectious mononucleosis (fever + lymphadenopathy) & Rheumatoid arthritis (fever + joint swelling)

Treatment

- The single most important prognostic factor in ALL is the treatment.

Supportive care

- IV hydration + allopurinol before starting treatment.
- RBC^s & platelets transfusions.
- Antibiotics for febrile neutropenia.

Chemotherapy

1. Remission induction: to eradicate the disease from the bone marrow, usually for 4 weeks using a combination of Vinicristine, Corticosteroids (dexamethasone or prednisone) & Asparginase ± intrathecal Cytarabine or Methotrexate ± Danorubicin. This leads to 98% remission.

2. CNS therapy: to ↓ risks of CNS relapses, as intrathecal methotrexate, intensive systemic chemotherapy, & cranial irradiation (only for CNS leukemia).
3. Intensification / consolidation therapy: A combination therapy to prevent drug resistance (for 14-28 wks).
4. Maintenance therapy (for 2-3 years): daily 6-Mercaptopurine, weekly Methotrexate & four weekly Vinicristine + Dexamethasone
- Co-trimoxazole is given during therapy as a prophylaxis against pneumocystic carinii pneumonia.
Bone marrow transplantation: for small number of patients with particularly poor prognosis especially those with Philadelphia chromosome (t (9;22) translocation)
Relapse
- It is the major impediment to the successful outcome :
1. Bone marrow relapse (15-20%): most serious complications.
2. CNS relapse.
3. Testicular relapse (1-2% in boys).

Prognosis

- Most children with ALL can be expected to have a long term survival with a rate of > 80% after 5 years.
- Less favorable factors include :
1. Age < 1 yr or > 10 yr at the time of diagnosis.
2. WBC count > 100.000/μL at the time of diagnosis.
3. Slow response to the initial therapy.
4. Chromosomal abnormalities including hypodiploidy & Philadelphia chromosome.
5. Other parameters to assess prognosis as immunophenotype & cytogenetics.

Acute Myelogenous Leukemia (AML)

- It represents 11% of the total cases of childhood leukemia.
- There are several chromosomal abnormalities associated with AML, but there are no predisposing genetic or environmental factors.
- The most common classification of the subtypes of AML is the FAB system which divides AML into 7 types (M1, M2……M7).
Clinical presentations: may include any or all of the findings associated with bone marrow failure in ALL + signs & symptoms infrequently occur in ALL like subcutaneous nodules, infiltrations of the gingival, DIC, &discrete masses called chloroma.
Diagnosis: Bone marrow analysis.
Treatment: Chemotherapy or may be bone marrow or stem cells transplantation.

Chronic Myelogenous Leukemia (CML)

- It represents 2-3% of the total cases of childhood leukemia.
- About 99% of cases are characterized by Philadelphia chromosome.
- It may be associated with the exposure to the ionizing radiation.

Clinical presentations: They are non-specific as fever, fatigue, weight loss, & anorexia. The spleen is often greatly enlarged causing pain in the left upper quadrant area of the abdomen.

- Typically, the chronic phase is terminated 3-4 yrs after the onset to the " blast crisis" phase (dramatic ↑ of blood count, hyperuricemia, & neurologic symptoms).

Diagnosis: Bone marrow analysis (↑ myeloid cells) + cytogenic studiess (Philadelphia chromosome).

Treatment: It may include chemotherapy (Hydroxyurea or Interferon), but the optimum treatment is the allogenic bone marrow or stem cells transplantation (cure rate is up to 80%).

Lymphoma

- There are 2 common types of lymphoma :

1. Hodgkin disease (HD)

2. Non-Hodgkin lymphoma (NHL)

- Lymphoma is the 3rd most common neoplasm in children.
- NHL is more common & more serious than HD.
- HD is almost always a nodal disease (arise from lymph nodes in 99% of cases).
- NHL has 3 sites of origin (which → wide range of presentations) :

1. Extra-nodal lymphatic tissues as lung & GIT (most common)
2. Nodal disease (next common)
3. Extra-lymphatic tissue (least common)

Peak incidence

- HD: It is rare below 5 years of age. The peak age incidence is from 15-30 yr & >50 yr.

- NHL: It can occur at any age. Generally, most cases of lymphoma below 10 yr of age are NHL.

Clinical presentations

Lymphoma usually present with one or more of the following presentations (some presentations as abdominal mass & 1ry bone disease are peculiar to NHL) :

1. Lymphadenopathy: It is the most common presentation. Cervical lymph nodes are the most common 1ry site. Occasionally, supra-clavicular, axillary, or inguinal nodes are the 1ry site. The nodes are significantly or hugely enlarged. They are firm, discrete, non-tender without

regional inflammation. Single or multiple groups can be involved. The enlargement is usually discovered by the patient or his/her parents. Splenomegaly may be present.

2. Mediastinal mass: Mediastinal lymph node enlargement can be the presentation of HD or NHL. It presents clinically with progressive dyspnea & features of superior vena cava obstruction (dilated veins over the upper part of the anterior chest wall with neck or facial edema). CXR clearly demonstrates the mediastinal widening.

3. Malignant malaise: Prolonged fever, anorexia, malaise, night sweating & weight loss can be the presentation of both HD & NHL.

4. Abdominal mass: Big intra-abdominal or retro-peritoneal mass can be the main presentation of NHL. Ascites may be present.

5. Primary bone disease: It can be the initial presentation of NHL. Progressive spinal cord compression (paraplegia) should always arise suspicion.

6. Pancytopenia: It is usually a manifestation of an advanced disease. It occurs due to either bone marrow infiltration or immuno-destruction of the 3 blood elements leading to anemia, purpura, & increase susceptibility to infection.

Diagnosis

1. Nodal biopsy: It is the most reliable method for diagnosis & identification of the pathological type , especially incases presented with lymphadenopathy.

2. Bone marrow biopsy: It may reveal the characteristic cells when the bone marrow is involved.

3. Radiological studies: CXR, skeletal survey, CT-scan, MRI.

Types

HD: The characteristic malignant cell is the "Reed-Sturnberg cell". HD is histologically divided int 4 subtypes with variable incidence & prognosis: Nodular sclerosis (50% of cases), Mixed cellularity (30%), Lymphocyte predominance (15%) & Lymphocyte depletion (5%)

NHL: The malignant cells can be classified in different ways as follows :

1. According to the grade of malignancy : as low grade or high grade. Most childhood NHL are of the high grade type.
2. Histologically : as lymphocytic type (more common) or histiocytic type.
3. Immunologically *:* as T-cell type (as in mediastinal masses) or B-cell type (as in abdominal masses).

Treatment: Chemotherapy

Prognosis : This depends on the following parameters :

1. Type: HD has much better prognosis than NHL. With HD, more than 90% of cases go into long remission with treatment, while with NHL, only 50% of cases can achieve such long remission.

2. Subtype: In HD, lymphocyte predominance has the best prognosis, followed by nodular sclerosis, mixed cellularity & lymphocyte depletion, respectively. In NHL, T-cell type has better prognosis than B-cell type.

3. Stage: Proper staging requires careful clinical evaluation & laboratory investigations & some times laprotomy. There are 4 stages according to the degree of spread of the disease (stage 1 has the best prognosis & stage 4 has the worst one).