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Please read this section first

The HPCSA and the Med Tech Society have confirmed that this clinical case study, plus your routine review of your EQA reports from Thistle QA, should be documented as a "Journal Club" activity. This means that you must record those attending for CEU purposes. Thistle will not issue a certificate to cover these activities, nor send out "correct" answers to the CEU questions at the end of this case study.

The Thistle QA CEU No is: MT-2015/009.

Each attendee should claim THREE CEU points for completing this Quality Control Journal Club exercise, and retain a copy of the relevant Thistle QA Participation Certificate as proof of registration on a Thistle QA EQA.

DIFFERENTIAL SLIDES LEGEND

CYCLE 47 SLIDE 1 – SEPTEMBER 2015

ACUTE LYMPHOBLASTIC LEUKEMIA

The leukemias are a group of disorders characterized by the accumulation of malignant white cells in the bone marrow and blood. These abnormal cells cause symptoms because of bone marrow failure (i.e. anaemia, neutropenia, and thrombocytopenia) and infiltration of organs (e.g. liver, spleen, lymph nodes, meninges, brain, skin or testes). Leukaemias are mainly classified into four types: acute and chronic leukaemia's, which are further subdivided into lymphoid or myeloid. Acute leukemias are usually aggressive diseases in which malignant transformation causes accumulation of blasts. The dominant clinical feature of these diseases is usually bone marrow failure caused by accumulation of blast cells although tissue infiltration also occurs. If untreated these diseases are usually rapidly fatal, but paradoxically are easier to cure than chronic leukemias. Acute leukemia is defined as the presence of over 30% blasts in the bone marrow at clinical presentation. It is further subdivided into acute myeloid leukaemia (AML) and acute lymphoblastic leukaemia (ALL) on the basis of whether the blasts are shown to be Myeloblasts or Lymphoblasts.

Acute lymphoblastic leukemia (ALL) is caused by an accumulation of lymphoblasts and is the most common malignancy of childhood. Its incidence is highest at 3-7 years, falling off by 10 years. The common (CD10+) precursor B type which is most usual in children has an equal sex incidence; there is a male predominance for T-ALL. There is a lower frequency of ALL after 10 years of age with a secondary rise after the age of 40.

Clinical features

Clinical features are secondary to the following:

- Bone marrow failure – anaemia (pallor, lethargy and dyspnoea); neutropenia (fever, malaise, features of mouth, throat, skin, respiratory, perianal or other infections) and thrombocytopenia (spontaneous bruising, purpura, bleeding gums and menorrhagia).
- Organ infiltration – tender bones, lymphadenopathy, moderate splenomegaly, hepatomegaly and meningeal syndrome (headache, nausea, vomiting, blurred vision and diplopia. Fundal examination may reveal papilloedema and sometime hemorrhage.

Diagnosis and Symptoms

Diagnosing ALL begins with a medical history, physical examination, complete blood count, and blood smears. Because the symptoms are so general, many other diseases with similar symptoms must be excluded. Hematological investigations may reveal a normochromic, normocytic anaemia with thrombocytopenia in most cases. The total white cell count may be decreased, normal or increased up to 200x 10^9/l or more. Blood film examination typically shows variable numbers of blasts cells. The bone marrow is hypercellular with 30% leukaemic blasts. The blasts are characterized by morphology, immunological tests and cytogenetic analysis and, for follow up, minimal residual disease analysis, by characterizing by PCR analysis the V gene or TCR gene clonal rearrangement of the particular patient. Cytogenetic analysis shows differing patterns in infants, children and adults which partly explains the different prognoses of these groups.

Lumbar puncture for CSF examination should be performed and may show that the spinal fluid has an increased pressure and contains leukemic cells. Biochemical tests may reveal a raised serum uric acid, serum LDH and less common hypercalcaemia. Liver and renal function tests are performed as a baseline before treatment begins. X-rays may reveal lytic bone lesions and a mediastinal mass caused by enlargement of the thymus and /or mediastinal lymph nodes characteristic of T-ALL.

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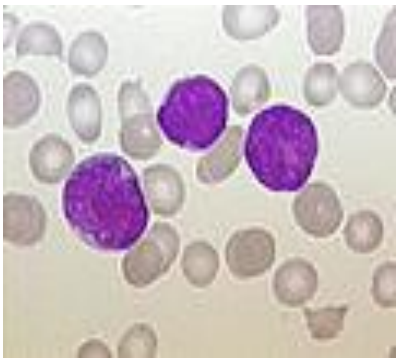
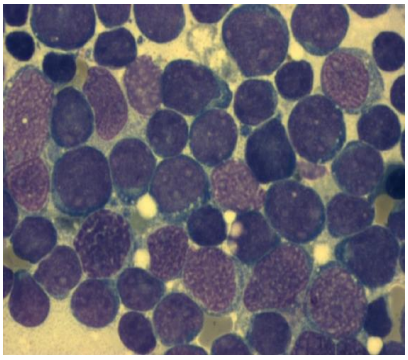
The differential diagnosis includes AML, aplastic anaemia, marrow infiltration with other malignancies, infections such as infectious mononucleosis and pertussis, juvenile rheumatoid arthritis and ITP.



ALL – Blood Smear



ALL – Bone Marrow

Cytogenetics

Cytogenetic translocations associated with specific molecular genetic abnormalities in ALL

Cytogenetic translocation	Molecular genetic abnormality	%
cryptic t(12;21)	TEL-AML1 fusion	25.4%
t(1;19)(q23;p13)	E2A-PBX (PBX1) fusion	4.8%
t(9;22)(q34;q11)	BCR-ABL fusion(P185)	1.6%
t(4;11)(q21;q23)	MLL-AF4 fusion	1.6%
t(8;14)(q24;q32)	IGH-MYC fusion	
t(11;14)(p13;q11)	TCR-RBTN2 fusion	

Prognosis

The survival rate has improved from zero, four decades ago, to 20-75 percent currently, largely due to clinical trials on new chemotherapeutic agents and improvements in stem cell transplantation (SCT) technology. Five-year survival rates evaluate older, not current, treatments. New drugs, and matching treatment to the genetic characteristics of the blast cells, may improve those rates. The prognosis for ALL differs between individuals depending on a variety of factors:

- Gender: females tend to fare better than males.
- Ethnicity: Caucasians are more likely to develop acute leukemia than African-Americans, Asians or Hispanics. However, they also tend to have a better prognosis than non-Caucasians.
- Age at diagnosis: children between 1–10 years of age are most likely to develop ALL and to be cured of it. Cases in older patients are more likely to result from chromosomal abnormalities (e.g., the Philadelphia chromosome) that make treatment more difficult and prognoses poorer.
- Cancer spread into the Central nervous system (brain or spinal cord) has worse outcomes.
- Morphological, immunological, and genetic subtypes
- Patient's response to initial treatment
- Genetic disorders such as Down's Syndrome

Cytogenetics is an important predictor of outcome. Some cytogenetic subtypes have a worse prognosis than others. These include:

- A translocation between chromosomes 9 and 22, known as the Philadelphia chromosome, occurs in about 20% of adult and 5% in pediatric cases of ALL.
- A translocation between chromosomes 4 and 11 occurs in about 4% of cases and is most common in infants under 12 months.

Not all translocations of chromosomes carry a poorer prognosis. Some translocations are relatively favorable. For example, Hyperdiploidy (>50 chromosomes) is a good prognostic factor.

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Cytogenetic change	Risk category
Philadelphia chromosome	Poor prognosis
t(4;11)(q21;q23)	Poor prognosis
t(8;14)(q24.1;q32)	Poor prognosis
Complex karyotype (more than four abnormalities)	Poor prognosis
Low hypodiploidy or near triploidy	Poor prognosis
High hyperdiploidy (specifically, trisomy 4, 10, 17)	Good prognosis
del(9p)	Good prognosis

Classification

The FAB classification

Subtyping of the various forms of ALL used to be done according to the French-American-British (FAB) classification, which was used for all acute leukemias.

- ALL-L1: small uniform cells
- ALL-L2: large varied cells
- ALL-L3: large varied cells with vacuoles

Each subtype is then further classified by determining the surface markers of the abnormal lymphocytes, called immunophenotyping. There are 2 main immunologic types: pre-B cell and pre-T cell. The mature B-cell ALL (L3) is now classified as Burkitt's lymphoma/leukemia. Subtyping helps determine the prognosis and most appropriate treatment in treating ALL.

WHO proposed classification of acute lymphoblastic leukaemia

The recent WHO International panel on ALL recommends that the FAB classification be abandoned, since the morphological classification has no clinical or prognostic relevance. It instead advocates the use of the immunophenotypic classification mentioned below.

1. Acute lymphoblastic leukemia/lymphoma - Former FAB L1/L2
   - Precursor B acute lymphoblastic leukemia/lymphoma. Cytogenetic subtypes:
     T (12; 21) (p12, q22) TEL/AML-1
     T (1; 19) (q23; p13) PBX/E2A
     t (9; 22) (q34; q11) ABL/BCR
     t (V, 11) (V; q23) V/MLL
   - ii. Precursor T acute lymphoblastic leukemia/lymphoma
2. Burkitt's leukemia/lymphoma - Former FAB L3
3. Biphenotypic acute leukemia

Treatment

The earlier acute lymphocytic leukemia is detected, the more effective the treatment. The aim is to induce a lasting remission, defined as the absence of detectable cancer cells in the body (usually less than 5% blast cells in the bone marrow). Treatment for acute leukemia can include chemotherapy, steroids, radiation therapy, intensive combined treatments (including bone marrow or stem cell transplants), and growth factors.

References

1. Essential Haematology , edition 5 , AV Hoffbrand, JE Petit, and PAH Moss
2. http://en.wikipedia.org/wiki/Acute_lymphoblastic_leukemia

Questions

1. Discuss the differences in the FAB versus the WHO classification of ALL.
2. Discuss the lab findings in a patient diagnosed with ALL.
3. Discuss the pathogenesis of ALL.