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Diagnosis and Treatment in Pediatric Acute Lymphoblastic Leukemia for General Pediatricians

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Foreword

The treatment results of pediatric acute lymphoblastic leukemia (ALL), the most prevalent pediatric cancer in most countries, have been improved greatly with cure rate approaching 90% [1-4]. To a pediatrician, the diagnosis or at least the suspicion of ALL is sometimes difficult, may be missed, or be misleading, especially when a pediatrician first sees a patient at outpatient clinic or emergency service. A good guidance to overcome these difficulties may be practically helpful.

Diagnosis

Symptoms

Nonspecific symptoms

The effects of cytokines and the wide leukemic infiltration such as to gastrointestinal tract cause fever, malaise, anorexia, mood change, growth stop, or body weight loss. The fever is mostly low-grade, or middle-grade, occasionally high-grade, can be misdiagnosed as a viral infection at the beginning. The fever, usually off and on, can be long for weeks or even months until a diagnosis of ALL is made. The frequency of fever ranges from 30 to 50%.

Specific symptoms

At diagnosis, lymphoblasts have heavily infiltrated bone marrow so that the normal hematopoiesis is suppressed to cause anemia, thrombocytopenia, and decreasing production of competent white cells. Pallor may be felt by the parents or guardians. Easy bruise--petechiae and ecchymoses, and epistaxis are often. Frequent infections may occur as the immunity has been weakened. Bone pain caused by stretching of periosteum, occurring less frequently than fever, is very annoying. However, it predicts a very good outcome. Headache and vomiting urge a suspicion of CNS leukemia.

* ALL vs juvenile rheumatoid arthritis

15 % of ALL bone pain have mild swelling on joint, a diagnosis of juvenile rheumatoid arthritis may be made. Nevertheless, the other symptoms and signs including the complete blood counts (CBC) can favor a diagnosis of ALL. In "juvenile rheumatoid arthritis" esp. with a lower white count, following CBC is mandatory to avoid overlooking the diagnosis of ALL.

*Growth pain vs bone pain of ALL

Growth pain in rapid growing children is common. As compared to bone pain of ALL, growth pain is mild and without presenting symptoms/signs of ALL. A CBC can promptly exclude ALL.

Signs

Pallor can occur in weeks. Lymph node enlargement and hepatosplenomegaly are common but not of prognostic value.

* Differential diagnosis on lymph node enlargement:

Normal enlargement of lymph nodes in infants and children occurs exclusively on posterior neck and inguinal areas, appears small, movable and elastic. The lymph node enlargement of malignancy locates widely, large, fixed and firm. The locations may include anterior neck, supraclavicle, and/or axilla. If needed, a CBC promptly differentiates.

Special signs

A mediatinal mass, esp. frequent in T-ALL, may cause dyspnea and/or superior vena cava syndrome and is a medical emergency. At diagnosis, testicular involvement occurs in 0.5 % of boys. Hypopyon, leukemic involvement in anterior chamber of eye, is rare. Telangiectasis on bulbar conjunctiva in child with B-precursor ALL and ataxia telangiectasia warrants special caution since the patient tolerates chemotherapy, esp. radiotherapy poorly. Unlike AML, spinal cord compression by an epidural mass is rare [5].

The complex of symptoms and signs will urge a suspicion of acute leukemia. Actually, every patient with ALL has at least one symptom/sign.

Differential diagnosis:

1. AML: Usually can at least be distinguished by immunophenotyping and/or myeloperoxidase stain if morphological judgement is equivocal.
2. Aplastic anemia: Usually without organomegaly, with a very low reticulocyte count, can be easily distinguished by a bone marrow smear. While a bone marrow biopsy is not needed in acute leukemia, it is absolutely required in aplastic anemia.
3. Infectious mononucleosis: Atypical lymphocytes occasionally resemble lymphoblasts. However, specific upper eyelid swelling/antibodies reactions lead to diagnosis of mononucleosis. A bone marrow aspiration is occasionally needed to differentiate diagnoses.
4. Immune thrombocytopenic purpura (ITP): Only when blood loss produces anemia, and viral infection produces leucopenia or concurrence of antibodies-mediated anemia and neutropenia, an ITP may mimic ALL. However, reticulocytes are high in a bleeding ITP without organomegaly. Giant platelets can be seen on a blood smear. Bone marrow examination is rarely needed.

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Work-up

A CBC is the first step for diagnosis and differential dignosis. In ALL, the WBC counts vary from 500 to 2,000,000/mm3 with a median of 22,000/mm^3. Thirty % of patients have leukopenia. The presence of blasts are very helpful, however, in leukopenic state, the blasts are often not present on blood smear. Anemia and thrombocytopenia each are present in 97 % of patients. Unless there is hyperleukocytosis, a bone marrow aspiration is mandatory for a morphological subtyping, immunophenotyping, chromosomal analysis, molecular subclassification, and search of leukemia-associated antigens which is crucial for the subsequent minimal residual disease (MRD) monitoring by flow cytometry. Dry tapping may occur but an experienced hand usually can still get some aspirate for laboratory examinations. At diagnosis, cautions should be paid to: (1) a fever? If so, works up for sepsis and gives empiric antibiotics first, (2) tumor lysis? Renal insufficiency and hyperphosphatemia are usually preceeded by hyperuricemia. Hyperuricemia alone responds briskly to urate oxidase (Rasburicase) and now can be easily managed. However, if aggressive hyperphosphatemia and / or renal failure occur, hemodialysis will be life-saving.

The smear observation by an expert can differentiate ALL from acute myeloid leukemia (AML) in more than 90 % of patients, but not 100%. The traditional FAB classification delineates that nearly 90 % of patients is L1, 11 % L2 and less often L3. However, the concordant rate between experts is not high, moreover, the recent tools have accurately subgrouping ALL so successfully, that omission of FAB classification is acceptable.

Treatment

Immunophenotyping, which also differentiate ALL and AML, can divides ALL patients to B-precursor (precursor B, B-cell precursor, precursor B-cell, B-lineage, and B-cell, etc.), T-cell and mature B cell. Mature B subtype is usually <= 1 % and can be successfully treated as advanced non-Hodgkin lymphoma and is not discussed here.

In general, patients of B-precursor have a better outcome than those of T-cell. Genetic (molecular + cytogenetic) abnormalities [6,7] define subtypes with favorable outcome include *TEL-AML1(ETV6-RUNX1) / t(12:21)* which comprises around 25% of ALL, hyperdiploidy (+51) which comprises around 25% of ALL, and *TCF3-PBX1*/t(1:19) which comprises 5-6% of ALL [should be treated with high-risk (HR) protocol]. The subtypes with poorer prognosis include hypodiploidy 3% with chromosome number < 44, *BCR-ABL1*/t(9:22) <4%, and MLL gene rearrangement 5%, esp. *MLL-AF4*/t(4:11) in infants. Those with genetic abnormalities comprised 64% of ALL in Caucasian. In Far East, however, the frequencies of *TEL-AML1* fusion and hyperdiploidy (+51) are only half of the Caucasian's [8]. Provisionally, patients at diagnosis with ages 1-9 years, and white count <50,000, and those with TEL-AML1 fusion or hyperdiploidy will be tentatively considered as standard (SR, low) risk. These patients who can have MRD on D15-19 of induction therapy < 1% and MRD at the end of induction <0.01%, will then classified as definitive SR and will treated not heavily. Otherwise, the patients will be treated with HR or very high risk (VHR) protocol [9]. MRD can define the risk group so that patients can be adequately treated, can predict outcome, and can help to decide change treatment such as hematopoietic stem cell transplantation (SCT).

The contemporary treatment of ALL starts with a 5-week induction therapy. After attaining a complete remission, consolidation therapy followed, and continued by a long maintenance therapy. In the early period of maintained therapy, there are re-induction(s) or re-intensificatio(s). The additions of consolidation and re-induction have very effectively enhanced the outcome. CNS prophylaxis is crucial and for a long time has been mainly relied on cranial radiation. However, it has been proven that CNS prophylaxis can be successful with triple intrathecal therapy alone, without cranial radiation, so that the adverse sequels from cranial radiation can be avoided [9-11]. The use of Dasatinib or imatinib in Ph (+) ALL may improve outcome. Prophylaxis with antibacterial and antifungal agents to patients with profound neutropenia in the early phase of therapy can decrease severe infections [12]. Overall, 6-7% of ALL patients need SCT, including those who relapses early.

Further improvement may need identifying new leukemic cell genetic lesions to for target therapy, and optimizing treatment based on host pharmacodynamics and pharmacogenomics, and delineating drug resistance [13]. Deeper characterization of leukemic cell genetic abnormalities has found new subtypes such as early T-cell precursor ALL [14] and Philadelphia chromosome-like ALL [15,16] which could be treated according to MRD level [17] and could be responsive to target therapy [18]. Genome-wide analyses have also revealed the role of inherited cancer predisposing genes and small nucleotide polymorphisms of several genes in the development of childhood ALL. These advances promise to lead to better personalized treatment strategies in the near future [13].

Contributions from every pediatric specialist, nursing staff, laboratory medicine, imaging medicine, pathology, blood bank, surgery ,social worker, and other colleagues are very important. A satisfactory diagnosis and treatment of pediatric ALL is a result of coordinated cooperation.

Competing Interests

The authors have declared that no competing interests exist.

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