Pediatric preleukemic disorders

J.G. van den Tweel

Universitair Medisch Centrum Utrecht, The Netherlands.

For many pathologists, diagnosing preleukemic disorders is often a difficult diagnostic problem, not least because the incidence of these diseases is very low. Diagnosing preleukemic disorders in children is even more difficult. Bone marrow biopsies in these situations are usually seen only by pathologists in specialized centers. Nevertheless, every pathologist should know about preleukemic situations in childhood. The situation is not only complicated by the fact that most pathologists have little experience with pediatric bone marrow but also because there is little information about the normal histology of bone marrow in newborn and young children. Another complicating factor is the large spectrum of diseases that can develop into leukemia, many of which are very rare. A final complicating factor is that the diagnosis of these diseases is often based on very subtle and difficult to diagnose bone marrow changes.

Pediatric preleukemic disorders can be divided into three main groups: i) hereditary preleukemic disorders, clinically manifested by single-cell cytopenias as well as by pancytopenias; ii) primary myelodysplastic syndromes, including juvenile chronic myeloid leukemia and infantile monosomy-7; and iii) secondary myelodysplasia as a late complication of radiotherapy and/or chemotherapy.

Hereditary preleukemic disorders

Most syndromes involving bone marrow failure (single-cell cytopenias and pancytopenias of both the inherited and the acquired type) are, in at least a few patients, associated with the subsequent appearance of leukemia. These disorders involve the red cell series, the granulocytic series as well as lymphopoiesis abnormalities. In a number of cases all cell lines are involved. The most important single-cell cytopenias with an increased risk of development of leukemia are pure red cell aplasia, Kostmann's syndrome and Shwachman's syndrome. Pancytopenias with an increased risk of developing leukemia are Fanconi's anemia, Bloom's syndrome, aplastic anemia, and familial bone marrow failure. Other disorders with increased risk are trisomy-21 and ataxia telangiectasia.

Single cell cytopenias

Pure red cell aplasia

Pure red cell aplasia (Diamond-Blackfan anemia) is a severe macrocytic or normocytic anemia characterized by an isolated depletion of erythroid precursors. The disease is usually seen in the first year of life.

The pathogenesis of the disease is probably an intrinsic defect of the erythropoietic precursor cells. Histologically, most bone marrow shows erythroid hypoplasia or aplasia. Many congenital abnormalities are seen in children with pure red cell aplasia among which abnormalities of the head and upper limbs are prevalent. There is a slightly increased risk of acute myelogenous leukemia (AML) and myelodysplastic syndromes (MDS).

Kostmann's syndrome

Kostmann's syndrome is a rare disease, also known as infantile genetic agranulocytosis. It is also referred to as severe chronic neutropenia. Usually, children with this disease develop severe pyogenic infections and extreme neutropenia in the first half-year of life. Histologically, the bone marrow shows an absence or markedly decreased number of myeloid precursors. Most patients die of infections and some develop AML.

Shwachman's syndrome

Shwachman's syndrome is a rare multiorgan disorder characterized by a variable neutropenia in patients with a large number of other abnormalities. Disease symptoms may resemble those of cystic fibrosis. Approximately 25% of the patients develop aplastic anemia. The bone marrow is histologically usually hypocellular. Occasionally MDS or AML is seen.

Pancytopenias

Fanconi's anemia

Fanconi's anemia is the most common inherited form of congenital pancytopenia. It may take years before the hematological abnormalities reveal themselves. Bone marrow examination shows hypocellular or aplastic bone marrows, often with dyserythropoiesis.

Bloom's syndrome and ataxia telangiectasia are characterized by pancytopenic marrow failure.

Primary myelodysplastic syndromes

Primary myelodysplastic syndromes are characterized by maturational disturbances resulting in ineffective hematopoiesis, morphological abnormalities in one or more cell lines and an increased chance of developing acute leukemia. The different MDS subgroups of the French-American-British (FAB) classification apply also to children.

In addition, juvenile chronic myeloid leukemia and the infantile monosomy-7 syndrome are incorporated in the pediatric MDS group.

Juvenile chronic myeloid leukemia

Juvenile chronic myeloid leukemia is a chronic myeloid leukemia without the Philadelphia chromosome. It is characterized by a marked monocytosis and high fetal hemoglobin levels. The peripheral blood and the bone marrow cells show dysplastic features and the prognosis of this disease is poor.

Infantile monosomy-7

The prominent feature of this disease is monosomy or partial deletion of chromosome-7. The histology of this disease is the same as that of the other myelodysplastic diseases. Since monosomy-7 is also seen in other myelodysplastic and leukemic disorders, infantile monosomy-7-related MDS is only diagnosed in children under 3 years of age. The prognosis is relatively good with 40% of the patients surviving 5 years.
Secondary myelodysplastic syndrome

Secondary myelodysplastic syndrome is seen as a complication of radiotherapy and/or chemotherapy. Several papers have reported the development of MDS post-therapy in children. Juvenile chronic myeloid leukemia and infantile monosomy-7 do not occur as secondary myelodysplastic disorders.

References


Bone marrow involvement in non-Hodgkin’s lymphoma according to the REAL classification

G. de Wolf-Peeters

Dept. of Pathology University Hospitals KU Leuven, Leuven, Belgium.

Introduction

The Revised American European Lymphoma (REAL) classification, a proposal by the International Lymphoma Study Group, was published in 1994. This classification was an attempt to simplify the existing plethora of lymphoma classifications, to update them with recent phenotypical and genotypical data and, most importantly, to offer a reproducible classification acceptable to both Europeans and Americans. While the Working Formulation published in 1982 was indeed meant to serve as a translation system between the various classifications, it became very popular in the United States as “a classification on its own”; in contrast, European pathologists continued to use the Kiel classification. Moreover, it should be noted that both classification systems were based on pure morphology as cases were studied on hematoxylin and eosin or Giemsa stained sections only. To complicate the situation even more, lymphomas presenting with blood and/bone marrow involvement were identified as lymphoid leukemias but were separately subtyped according another classification, which was proposed by the French American British (FAB) group. As immunohistochemistry and flow cytometry for phenotyping lymphomas became widely performed and as genotyping on these neoplasms by karyotyping and molecular techniques became available, these lymphoid malignancies were better understood and “new” lymphoma-entities were identified. As the lymphoma classifications used until then needed to be revised, a new proposal was necessary. Bone marrow examination is a routine procedure in the staging post-therapy follow-up of patients with non-Hodgkin’s lymphoma. In addition, this investigation may serve as “the” diagnostic tool in certain subtypes of lymphoma and in clinical settings in which enlarged peripheral nodes are absent or splenomegaly is the sole presenting finding. Bone marrow investigation should include trephine biopsy sections (and trephine imprints) as well as aspirate smears and may be completed by the examination of blood smears. All these specimens contribute to the final diagnosis and frequently complement one another.

Traditionally, the morphological evaluation of a bilateral trephine biopsy is the method of choice in assessing bone marrow involvement in lymphoma. In view of the REAL classification, the use of previously defined criteria, such as the number and growth pattern of the lymphoid infiltrates and/or the cytological features of the lymphoid cells in the trephine, is not always helpful in identifying the biological meaning of these infiltrates or in subtyping the lymphoma.

Identification of the biological meaning of lymphoid infiltrates in the trephine

The usefulness of phenotyping on paraffin-embedded trephine sections is limited; frozen sections theoretically allow for a more extended panel of antibodies to be applied but this technique is more demanding and difficult to incorporate in a routine practice. Moreover, incorrect interpretation of the staining results may occur. Alternatively, immunophenotyping may be performed on bone marrow aspirate samples but may give discordant results due to sample variation between the trephine biopsy and the bone marrow aspirate.

With the development of molecular biological techniques such as the polymerase chain reaction (PCR), it has become possible to recognize the clonal character of lymphoid infiltrates by analyzing the presence of lymphoma-specific genetic translocations or clone-specific antigen receptor gene rearrangements. In addition, due to its increased sensitivity, the PCR technique offers the potential to detect small numbers of malignant cells, allowing the monitoring of minimal residual disease.

Detection of minimal residual disease is mostly performed in peripheral blood and bone marrow aspirate samples because these samples can be freshly processed. Bone marrow trephine biopsies, which have been fixed and decalcified, are more problematic but they may be analyzed with some PCR techniques. However, in our experience as well as in that of others, the analysis on bone marrow sections of IgH gene rearrangements with the PCR technique works well and this technique may be more sensitive than morphological and immunohistochemical analysis.

Subtyping non-Hodgkin’s lymphomas

Whether a correct subtyping of the lymphoma is possible using the previously described growth pattern and/or the cytological features of the trephine infiltrate is debatable. A reevaluation of these morphological parameters, based on a detailed analysis of fully documented cases and taking the REAL classification into account, seems to be mandatory. At present we have such a study underway, including more than 300 cases documented by phenotypical and genotypical data. Our first results indicate that in comparison with blood smears and bone marrow smears, the study of bone marrow trephines offers the most sensitive technique for detecting lymphomatous infiltrates. Nevertheless, preliminary results indicate that the various growth patterns as defined in the past (nodular, interstitial, massive and paratrabecular) are not specific to all lymphoma subtypes and that cytological features of the lymphomatous infiltrate may be misleading. While this phenomenon has been described for nodal large cell lymphomas, as they may present with a small cell component in the trephine, it is less well known that the cytological features of the lymphomatous infiltrate in the trephine do not always allow the various subtypes of small cell lymphomas to be cor-