PEDIATRIC BONE MARROW INTERPRETATION

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KEYWORDS

• Bone marrow • Pediatric cancer • T cell • Marrow infiltrates • Genetic disorders

ABSTRACT

The evaluation of pediatric bone marrow poses specific challenges when compared with the general adult population. These challenges stem in part from the higher likelihood of congenital disorders with hematopoietic manifestations, some of which may give rise to hematologic malignancies. Familiarity with the spectrum of disorders seen in the pediatric age group allows for an appropriate and focused differential diagnosis. This review addresses the diagnostic workup of pediatric bone marrow samples, as directed by the peripheral blood and bone marrow findings in the context of the patient's clinical history. Recommendations for the appropriate use of ancillary studies in various scenarios are provided.

OVERVIEW

The evaluation of bone marrow samples obtained from children requires familiarity with the spectrum of hematologic diseases (including entities specific to this age group), as well as knowledge of the potential diagnostic pitfalls. First, it is important to realize that a large proportion of the benign and malignant disorders diagnosed during childhood are likely to be related to underlying genetic abnormalities, sometimes as the first manifestation of these defects. Another important consideration in children is that lymphoid progenitor cells (termed *hematogones*) normally present in the bone marrow are often increased in numbers as a reactive change to benign disorders or malignant neoplasms. These hematogone expansions overlap significantly with some of the most common leukemias seen in children, potentially misleading the observer toward an erroneous diagnosis of leukemia or the misclassification of a different neoplasm. Finally, certain types of malignant neoplasms with partially overlapping blastic morphologic features (so called "small blue-cell tumors"), but with vastly different biology requiring distinct therapeutic approaches, occur relatively frequently in young patients.

THE NORMAL PEDIATRIC BONE MARROW

The morphology of normal pediatric bone marrow overlaps significantly with that of adults. Two

Pathologic Key Features OF PEDIATRIC BONE MARROW INTERPRETATION

1. Interpretation of pediatric bone marrow samples requires that the pathologist integrate clinical, morphologic, and ancillary study results to arrive at the correct diagnosis.
2. Congenital syndromes and florid reactive processes must always be considered in the differential diagnosis of hematologic malignancies in the pediatric population.
3. Recognition of the general pathologic pattern (hypercellular, hypocellular, or single-lineage defect) aids in narrowing the differential diagnosis when interpreting bone marrow samples from pediatric patients.

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features are significantly different and may affect bone marrow interpretation: the overall cellularity and the presence of benign lymphoid precursors (hematogones), which may be markedly increased in some patients.

Most sources agree that bone marrow cellularity varies inversely with age, with a highly cellular marrow seen in very young patients and a gradual decrease seen with increasing age. Older studies using large wedge-shaped sections of bone obtained from sudden-death autopsy cases and the point-counting technique[1] reported an average cellularity of 78.8% (range 59% to 95%) in patients aged 1 to 9 years, and of 64.3% (range 41.5% to 86.6%) for patients in the second decade of life. More recent large-scale studies applied to biopsies obtained using a Jamshidi needle and direct visualization[2] have documented slightly lower marrow cellularities than previously accepted as normal values. In such studies, normal marrow cellularity was found to be about 80% in children younger than 2 years, declined to 60% to 70% by the age of 5 years, and remained relatively constant at about 60% in individuals aged 5 to 18 years.

Benign precursor B cells (also termed hematogones) are immature, often blastic-appearing lymphoid elements present in the marrow of all individuals, but particularly prominent in children.[3] These cells typically increase in number under a variety of reactive conditions, including both benign and malignant disorders. Hematogones encompass lymphoid cells with a spectrum of morphologic features, ranging from small lymphoblasts and larger blasts with homogeneous "smudgy" chromatin and cleaved nuclei, to mature-appearing lymphocytes; there are multiple intermediate forms with variable degrees of immaturity (**Fig. 1**A, B). When examined by flow cytometry, these cells show a characteristic pattern that mirrors their maturation sequence.[4] They include a minority of CD45dim+TdT+CD34+CD19+ CD10+CD20− early precursors, a majority of CD45stronger+ (but weaker than lymphocytes) TdT−CD34−CD19+CD10+CD20variably+ intermediate precursors, and a usually smaller subset of CD45 strong+CD20+ CD10+ more mature elements. These subsets vary in proportion depending on the clinical setting, with the early precursors predominating in the postchemotherapy recovery setting and the intermediate stage predominating in most other situations. These immunophenotypic profiles may also be demonstrated by immunohistochemical staining of biopsy samples. The spectrum of antigen expression in hematogones differs significantly from the strong and uniform pattern of antigen expression typically seen in B-lymphoblastic leukemia (B-ALL) (see **Fig. 1**C–F).

CLINICAL INDICATIONS FOR BONE MARROW EVALUATION IN CHILDREN

A variety of presenting clinical and laboratory findings, sometimes incidental in nature (such as extremely high, but asymptomatic leukocyte counts of chronic myeloid leukemia discovered on a routine blood examination in a primary physician's office) may trigger bone marrow evaluation in children. These findings are summarized in **Table 1**.

DIFFERENTIAL DIAGNOSIS: INTEGRATING CLINICAL AND MICROSCOPIC FEATURES AND ANCILLARY STUDIES

A combination of the clinical presenting features and peripheral blood and bone marrow morphology trigger specific diagnostic algorithms (including further ancillary studies). The following specific scenarios are discussed in the next sections, including the clinical and morphologic clues that help guide the use of ancillary studies and resolve the differential diagnosis particular to each scenario:

1. Hypercellular Bone Marrow
   - Infiltration by blastic neoplastic cells
   - Infiltration by histiocytic cells
   - Expanded hematopoiesis (with or without fibrosis or increased blasts)
2. Hypocellular Bone Marrow
3. Selective Defects of Single Cell Lineages
   - Erythroid
   - Myeloid
   - Megakaryocytic.

HYPERCELLULAR BONE MARROW

Much like in the adult population, the workup of a hypercellular bone marrow is guided by the morphologic features of the elements that accumulate to cause the observed increase in cellularity.

Infiltration by Blastic Neoplastic Cells

An increase in cellularity caused by sheets of blastic cells is typically related to one of the childhood hematopoietic blastic neoplasms. The distinction between these entities, which may be challenging at times, relies primarily on their morphologic and immunophenotypic features and to a lesser extent on their genetic features, as summarized in **Table 2**. Genetic features do play a major role in the subclassification of many of these neoplasms (most notably acute leukemias) into biologically