Chapter 7
Diagnostic Approach to Aplastic/Hypoplastic Bone Marrow Disorders

ABSTRACT

Bone marrow aplasia is a hypofunctional HSC disorder with variable etiology. The term encompasses both acquired and hereditary types. Patients with marrow aplasia often present with single or multiple cytopenias, age-related marrow hypocellularity, with or without other organ abnormalities, and a variable risk of clonal evolution. The pathogenic mechanisms of acquired and hereditary marrow aplasia involve immunologic and germline gene abnormalities of stem cells. Clonal evolution often occurs due to the acquisition of somatic and germline mutations. Recently, hematopoietic stem cell transplantation using fludarabine-based protocols significantly improved outcomes, particularly for patients with FA and DC. New and potentially more efficacious therapies may improve patient outcomes, including hematopoietic gene therapy and drugs, e.g., transforming growth factor (TGF)-beta inhibitors for FA and PAPD5, a human poly(A) polymerase, inhibitors for DC that target disease-specific defects.

INTRODUCTION

Aplastic and hypoplastic marrow disorders are a spectrum of clinically and pathogenically overlapping hypofunctional HSC diseases with variable etiology, including hereditary and acquired causes, a risk of clonal evolution, and are often life-threatening. They also overlap with other bone marrow failure conditions, e.g., hypoplastic myelodysplastic syndrome, and familial predisposition hemopoietic malignancies.

Cytopenia and age-related marrow hypocellularity, with or without other abnormalities are often the presenting features. Accurate diagnosis is crucial for optimal management but may be challenging. Their pathogenesis highlights the overlapping nature of hematological (BMF, MDS, and AML) and extra-hematological phenotypes produced by germline genetic variants.

A multidisciplinary systematic approach is necessary for diagnosis, with early consideration of a comprehensive genetic analysis to avoid overlooking rare entities and delaying therapy.

This chapter highlights aplastic and hypoplastic bone marrow disorders in terms of:

A. The phenotypes and pathogenesis
B. The diagnostic approach to a hypoplastic marrow

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C. The mimics and differential diagnosis of hypoplastic marrow disorders

THE PHENOTYPES AND PATHOGENESIS OF HYPOPLASTIC BONE MARROW DISORDERS

Acquired and inherited pathogenic mechanisms lead to qualitative and quantitative dysfunction of HSCs or progenies. Persistent cytopenia of one or more blood elements is often the first presentation that brings a patient to medical attention. The age of presentation varies with the type; inherited forms are more frequent in childhood but have variable penetrance and phenotype that may delay presentation to adulthood or the elderly. Acquired forms can occur at any age.

Acquired Aplastic Anemia (AAA)

The AAA has a bimodal age incidence in adolescents and the elderly but can present at any age. Cases are often sporadic due to extrinsic direct or indirect HSC injury, most frequently due to iatrogenic causes, such as chemotherapy and radiation. Chemical agents, drugs, and viruses can also induce direct HSC damage (Young, 2018). However, most cases (about 70%) have no identifiable cause and are classified as idiopathic. Most idiopathic cases result from immunological damage of stem cells triggered by extrinsic factors such as viruses (Giudice et al.,2021). The immune effector mechanisms often involve cytotoxic T cells (CTLs) producing type 1 cytokines, which induce apoptosis via Fas/FasL.

About 10-15% of patients with AAA have a loss of the chromosome 6 segment carrying the HLA alleles (6PLOH), representing potential high-risk alleles implicated in the immune pathogenesis of AAA. The “escape clones,” sustain hematopoiesis by clonal expansion (Betensky et al., 2016) of cells deficient in glycosyl phosphoinositol (GPI)-anchored proteins, resulting from an acquired mutation in PIG-a and are probably a target of the immune response (young, 2018)

Somatic mutations in the STAT3 signaling pathway may play a role in some cases of AAA. A rare acquired somatic mutation in the UBA1 gene underlies the VEXAS syndrome, causing a range of immunologic and hematologic symptoms, and often presents with cytopenia and hypoplastic marrow with cell vacuolations in an adult. (Babushok et al., 2017)

Short telomeres also occur in immune aplastic anemia due to increased mitotic demand on a limited pool of stem cells. Accelerated telomere attrition precedes progression to monosomy 7 (Young, 2018; Choijilsuren et al., 2021).

Inherited Bone Marrow Failure Syndromes (IBMFS)

The inherited bone marrow failure syndromes (IBMFS) constitute a group of syndromic and non-syndromic diseases caused by loss-of-function germline mutations inherited from parents or de novo soon after fertilization (Keino et al., 2017).

Germline mutations involve basic cell survival functions and genetic modifying processes. In addition, constitutional gene defects may indirectly damage hematopoietic stem cells in syndromes affecting immune regulation, such as Cytotoxic T-lymphocyte-associated Protein 4 (CTLA-4) or deficiency of the enzyme ADA2 (Adenosine Deaminase 2) (DADA2) mutations (Young, 2018)