Introduction to Acquired and Inherited Bone Marrow Failure

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KEYWORDS

• Aplastic anemia • Inherited bone marrow failure • Germline mutations
• Somatic mutations

KEY POINTS

- Acquired aplastic anemia and inherited bone marrow failure syndromes both can present with pancytopenia and must be distinguished at presentation because they have important differences with respect to critical treatment decisions as well as specific continued monitoring requirements.
- The rapid recent advances in the genetic interrogation of patient samples have led to the identification of new inherited germline diseases and the appreciation that patients with classic inherited bone marrow failure disorders may be normal in appearance with few if any of the expected clinical clues.
- Somatic mutations in aplastic anemia may have prognostic value although there is considerable variation at the individual level.
- Hematopoietic stem cells from several inherited marrow failure diseases can correct the proliferative defect and may then still develop further somatic mutations that can progress to myelodysplastic syndrome or acute myeloid leukemia.

INTRODUCTION

Bone marrow failure (BMF) disorders are characterized by presentation with pancytopenia or single-lineage cytopenias. Although acquired aplastic anemia (AA) is the most common BMF disease at all ages, children and adults may have an inherited BMF (IBMF) disease that must be diagnosed if present, because this is critically important not only for treatment choices but also to monitor for progression to myelodysplastic syndrome (MDS) or acute myeloid leukemia (AML). MDS and AML occur with increased frequency through acquisition of somatic mutations in medically treated patients with acquired AA but have a much greater likelihood in patients with germline

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IBMF.[1] Many of the germline mutations diagnostic of IBMF set the stage for additional somatic mutations and cytogenetic changes that account for this increased risk. In this article and other articles in this issue, acquired AA and IBMF are discussed with respect to management challenges and to the recent exciting wealth of genetic information that has accrued with the advances in the ability to interrogate the genome by next-generation techniques in the clinic, at an ever-declining cost.

ACQUIRED APLASTIC ANEMIA

AA is the most frequent cause of pancytopenia at all ages but still rare, with an annual incidence of 2 cases per million in developed countries to 4 cases per million to 7 cases per million in Asia. There are 2 age peaks, 15 to 25 years and greater than 60 years,[2] which may suggest differences in etiology between these 2 groups, because germline IBMF syndromes are more frequently diagnosed in younger patients. AA is usually idiopathic but sometimes secondary to infection (eg, hepatitis and Epstein-Barr virus), drugs (chloramphenicol and others), or toxins (benzene, insecticides). Although acquired AA usually occurs in normal children and adults with no previous history of growth failure or congenital abnormalities that suggest an IBMF syndrome, recent genetic studies have shown that IBMF disorders can present without any of these telling clinical clues and, therefore, must be excluded. As might be expected, AA that occurs in infants and young children is more likely due germline mutations.[3,4]

Pathophysiology

Although the pathophysiology of AA is unknown, several lines of evidence support a role for the immune system (see Schoettler and Nathan's article, "The Pathophysiology of Acquired Aplastic Anemia: Current Concepts Revisited," in this issue). Evidence supporting this mechanism comes from identical twin transplants, two-thirds of whom require immunosuppressive pretransplant conditioning for sustained engraftment. These data could also indicate, however, an underlying stem cell defect, because a significant proportion of twin transplants require no conditioning, suggesting that replacement of stem cells is sufficient to cure the disease. Other lines of evidence for an immune mechanism include the greater likelihood of developing AA in individuals with certain HLA alleles and the body of evidence that demonstrates an activated immune system (see Schoettler and Nathan's article, "The Pathophysiology of Acquired Aplastic Anemia: Current Concepts Revisited," and Mufti and Marsh's article, "Somatic Mutations in Aplastic Anemia," in this issue). Immunological evidence includes the oft-cited data of response to treatment with antithymocyte globulin (ATG) and cyclosporine (CsA), but it should borne in mind that the mechanism by which these medications work is unknown. The observation that AA patients with short telomeres respond as well to treatment with ATG and CsA as patients with normal-length telomeres emphasizes that how precisely these agents work is still unknown; ATG has stimulatory (low-concentration) as well as inhibitory (high-concentration) effects on colony formation of $CD34^+$ bone marrow cells from normal, AA, and MDS individuals,[5,6] which raises questions about the conclusion that their use supports an immunosuppressive mechanism of action. Furthermore, more intense and specific immunosuppression, such as rabbit ATG and alemtuzumab, does not improve the results. In addition, one of the hallmarks of autoimmune disease is the identification of self-antigens to which the immune attack is directed, and such an antigen expressed on hematopoietic stem cells (HSCs) has never been identified.

The presence of a dysregulated activated immune system is important to the pathophysiology of acquired AA, and the finding of HLA loss of heterozygosity (6pLOH) is a