Acquired Aplastic Anemia

What Have We Learned and What Is in the Horizon?

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KEYWORDS

• Acquired aplastic anemia • Hematopoietic stem cell • Autoimmunity
• Immunosuppressive therapy • Hematopoietic stem cell transplantation • Clonality
• Myelodysplastic syndrome

KEY POINTS

- Refractory cytopenias of childhood, inherited bone marrow failure syndromes, and familial disorders associated with myelodysplasia or immune dysregulation should be investigated during the diagnosis of acquired aplastic anemia.
- Although pancytopenia is the norm at diagnosis, it must be kept in mind that isolated cytopenias may be the predominant presenting symptom, along with milder decreases in other lineages in some cases.
- The role of autoimmune reaction targeting hematopoietic stem cells is well-understood in the pathogenesis of acquired aplastic anemia; however, alterations in stem cells leading to this response or, in other words, drivers of autoimmunity are not clearly identified.
- Although matched related donor hematopoietic stem cell transplantation is the treatment of choice with great outcomes, immunosuppressive therapy provides response in two-thirds of the patients who do not have matched family donors. Alternative donor transplants have been associated with much improved results in recent years.
- Acquired aplastic anemia can be associated with hematopoietic stem cell clonal disorders: paroxysmal hemoglobinuria can accompany at diagnosis or develop later. Clonal abnormalities leading to myelodysplasia and acute myeloid leukemia may follow immunosuppressive therapy.

Idiopathic acquired aplastic anemia (aAA) is a rare disorder with an estimated incidence of 300 to 600 cases in the United States annually; it is less frequent in children. It is characterized by peripheral pancytopenia and significantly decreased cellularity in the bone marrow (BM). Though isolated cytopenias may seem to be the only manifestation, all 3 lines are often affected at presentation. For instance, severe

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thrombocytopenia may be the prominent finding; however, an increased mean corpuscular volume and/or mild decrease in other counts may accompany the thrombocytopenia. Therefore, close monitoring and keeping the possibility of aAA in mind is prudent because therapeutic approaches to thrombocytopenia significantly depend on the underlying cause and delay in aAA diagnosis establishment may be very consequential. Infections and bleeding are the most common causes of morbidity and mortality in the very severe and severe forms of aAA. Severe aAA is characterized by peripheral blood absolute neutrophil count less than 0.5×10^9/L and the very severe form by less than 0.2×10^9/L, in addition to platelets less than 20×10^9/L and reticulocytes less than 20×10^9/L with decreased hematopoietic and overall cellularity in the BM.[1]

Although phenotypic findings in inherited BM failure syndromes (iBMFS) are not uncommon, some patients may not have any. Ruling out an underlying iBMFS is a prerequisite for establishing the diagnosis of aAA. Whereas lymphocyte chromosomal breakage testing is standard and practical in investigating underlying Fanconi anemia (FA), telomere length assessment is used for detecting disorders characterized by shortened telomeres in both myeloid and lymphoid cells in peripheral blood.[2] Telomere length in residual granulocytes are shortened in aAA. Not infrequently, there is a fine line between aAA and hypoplastic myelodysplastic syndrome (MDS) or refractory cytopenia of childhood (RCC) due to similarities in clinical presentation and laboratory findings.[3] In that regard, cytogenetic analysis of BM cells using karyotyping and fluorescence in situ hybridization (FISH) technique may provide some help, though they are not sensitive or specific enough.

Beyond the previously mentioned iBMFS, such as FA and short telomere disorders, BM aplasia may be in the spectrum of some inherited or familial conditions that are associated with immune dysregulation and/or tendency to develop myelodysplasia or myeloproliferation. It has become reasonable to run large gene panels to investigate for these underlying disorders at the time of diagnosis of BM failure.[4–6] Whether the utility of this approach can be justified is debatable; however, discovery of such genetic background may significantly affect treatment decisions. Paroxysmal nocturnal hemoglobinuria (PNH) is caused by an acquired hematopoietic stem cell (HSC) defect, leading to intravascular hemolysis, anemia, and thrombotic complications closely associated with aAA. Therefore, investigating for PNH is also a necessary step in patients with newly diagnosed aAA. Clinically evident PNH may be present around the time of aAA diagnosis and would require additional interventions.[7] Even flow cytometric detection of small clonal PNH populations may indicate the need for closer monitoring for the development of symptomatic PNH down the road and also points to possibility of a greater response to immunosuppressive therapy (IST).[8]

HISTOLOGY AND PATHOGENESIS

The BM tissue in acquired severe aplastic anemia (aSAA) displays severely decreased cellularity with some degree of reactive changes. There is no histologic evidence of acute inflammation at the time of diagnosis. As seen in tissue atrophy, blood supply to BM is diminished. Microvascular density and vascular endothelial growth factor (VEGF) expression were found to be lower in aSAA BM tissue, along with decreased serum levels of VEGF, which were substantially improved following successful IST.[9] Despite severely decreased hematopoiesis, typically there is no accompanying fibrosis in the BM. Space emptied by the elimination of hematopoiesis appears to have been partially filled by adipocytes. Relative lymphocyte predominance, primarily of T lymphocytes, is characteristic of BM histology. Additionally, relative increase in