Introduction

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This focus section includes articles on three anemias associated with bone marrow failure: acquired aplastic anemia (AA), paroxysmal nocturnal hemoglobinuria (PNH), and refractory anemia (RA) and the myelodysplastic syndromes (MDS). These conditions are linked because of similarities in their presentation, laboratory findings, and pathophysiology.[1,2] The association among these diseases began in earnest in 1967, when Lewis and Dacie reported a combined AA-PNH syndrome, and Damashek speculated that a bone marrow insult may be a common factor in the pathophysiology of AA, PNH, and hypoplastic leukemia.[3,4] All three diseases are characterized by cytopenia affecting one or more cell lines. Bone marrow hypocellularity is a characteristic feature of AA, and although not typical, may also be found in MDS and PNH. Reticulocytopenia is characteristically found in AA and MDS, but can also be seen in PNH. This overlap in laboratory findings can cause difficulty in differential diagnosis and classification of these disorders.

A defect in the bone marrow stem cell compartment is another common factor in all three diseases, however different mechanisms are responsible for the cytopenias. In AA, the stem cells are depleted from the marrow by an autoimmune T-cell attack on the stem cell pool.[1] In PNH, a mutation occurs in a stem cell that results in circulating blood cells deficient in glycosylphosphoinositol-linked membrane proteins such as CD55 and CD59. The absence of these surface proteins leads to increased susceptibility to complement-mediated lysis and hemolytic anemia.[3] In MDS, clonal mutations in stem cells cause multi-lineage dysplasia and ineffective hematopoiesis.[2]

The exact relationship among the diseases is unclear. Patients presenting with primary AA can develop PNH or MDS during or after treatment. Mutant PNH clones occur in AA, and they can be selected for expansion due to their resistance to the immune attack experienced by the normal stem cells.[3] On the other hand, patients presenting with primary PNH can also evolve into AA as a late manifestation. AA and PNH may be a single entity that can present either as primary AA or a primary PNH.[4] Barrett suggests that the immune attack in AA causes genomic instability in the stem cell pool, and predisposes to mutations and clonal stem cell disorders leading to MDS.[2] Therefore, AA may be the first in a multistep process in the development of MDS. Also the increased T cell activation found in both AA and MDS provides support for an autoimmune pathophysiology in both conditions.[1,2] Further research will determine if these diseases are distinct entities or if they are related by a common pathophysiology or etiology.

The articles that follow will discuss each disease in detail and compare and contrast the similarities and differences among this group of bone marrow failure syndromes. The laboratory tests used for differential diagnosis, as well as the treatment and prognosis will also be covered.

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