PNH in bone marrow failure

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Paroxysmal nocturnal hemoglobinuria (PNH) is a hematopoietic stem cell disorder characterized by complement-mediated intravascular hemolysis caused by clonal expansion of hematopoietic stem cells (HSCs) with mutations in genes, including phosphatidylinositol glycan class A (PIGA), involved in GPI-anchor synthesis. The triad of PNH are ❶intravascular hemolysis (IVH) and hemoglobinuria, ❷thrombosis, and ❸bone marrow failure (BMF), and the degree of each sign and the overall clinical pictures are different from case to case. According to a comparative study between Japan and the U.S., hemolytic symptoms including thrombosis are prominent in Caucasian (U.S.) cases, whereas hematopoietic failure symptoms are prominent in Asian (Japanese) cases. Historically in 1961, Drs. Dacie and Lewis reported that 25% of patients who had PNH had significant bone marrow hypoplasia or had a history of it and that 15% of patients with aplastic anemia (AA) had a positive acidified serum lysis test. Using Kanazawa high-sensitivity flow cytometry, which can detect with a sensitivity of 0.003%, PNH-type granulocytes were detected in 57% of AA patients and 20% of low-risk myelodysplastic syndromes (MDS) patients. If PNH-type blood cells are detected, immunosuppressive therapeutic agents are highly recommended. For cases where a small PNH clone is detected by high-sensitivity flow cytometry, consider the possibility of future transformation to overt PNH. Whereas, to identify hemolytic PNH, the conventional methods are sufficient. If PNH-type blood cells are not detected by conventional methods, it is unlikely that PNH is the cause of hemolysis in most cases.

Although the mainstay of treatment for PNH is symptomatic therapy for these triads, the development of the anti-C5 antibody eculizumab has demonstrated a variety of benefits, including a reduction in the risk of thrombosis, relief of smooth muscle spasm-related symptoms associated with hemolysis, and improvement in quality of life and prognosis, in addition to marked hemolytic inhibition. Subsequently, a modified version of eculizumab, the recycling antibody ravulizumab, was developed, extending the dosing interval from 2 weeks to 8 weeks and improving convenience. Crovalimab, another recycling antibody, is currently in Phase III trials using the proprietary SMART technology to achieve low-dose subcutaneous injection. Treatment of PNH with terminal complement inhibitors, including eculizumab and ravulizumab presents a new challenge: extravascular hemolysis. To overcome this challenge, the proximal complement inhibitor, a C3 inhibitor pegcetacoplan was approved in the U.S. In addition, the amplification loop inhibitors, a factor B inhibitor iptacopan, and a factor D inhibitor danicopan, are under development. This presentation will provide an overview of the pathogenesis and treatment of PNH, focusing on BMF in PNH.