Paroxysmal Nocturnal Hemoglobinuria (PNH)- Introduction to PNH

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Paroxysmal Nocturnal Hemoglobinuria (PNH) is an acquired clonal chronic hemolytic anemia, often severe. PNH is a rare disease (estimated population frequency less than 10 per million) without age or gender predilection. The clinical picture of PNH is unique: intravascular hemolysis (with hemoglobinuria), high risk of thrombosis and pancytopenia (underlying some degree of bone marrow failure). PNH results from the expansion of a hematopoetic stem cell (HSC) carrying a somatic mutation of the X-linked PIGA gene. The HSC carrying the mutated PIGA gene and all its mature progeny are defective in the biosynthesis of the glycosylphosphatidylinositol (GPI) molecule that anchors various proteins to the cell membrane. Currently, the diagnosis of PNH is based on the flow cytometry demonstration of significant proportions of granulocytes and red cells with the GPI deficient phenotype. The complement system plays a central role in the pathogenesis of PNH: the hemolysis of PNH red cells, mostly intravascular, results from the activation of complement that is not blocked on their surface because the deficiency in two GPI-linked complement regulatory proteins (CD55 and CD59). This impaired regulation of complement on PNH blood cells accounts., very likely, also for the thrombosis. However, the deficiency of GPI-linked proteins does not explain neither the pancitopenia nor the expansion of PNH (GPI-negative) blood cells. In fact, the inactivation of the PIGA gene in mice do not provide growth advantage to the PIGA-mutated HSC. Moreover, very small PNH blood cell populations exist in almost all healthy people. In order to explain the paradoxical expansion of PNH populations in a context of bone marrow failure, a reasonable model is that the mutated HSC expands by escaping the attack of autoreactive T cells against normal (GPI-positive) hematopoiesis. In keeping, it has been found that in PNH patients there are deranged T cells and that a specific population of CD8+ T cells can react against the GPI molecule when presented by the CD1d, suggesting that in PNH patients the more likely target of the autoimmune attack is the GPI anchor itself.

The most important advance in the clinical management of PNH has been the introduction of a human monoclonal antibody (eculizumab) directed against the component 5 of complement (C5). This targeted therapy abrogates intravascular hemolysis by preventing C5 activation and the subsequent formation of the lytic complex on the membrane of PNH red cells. Eculizumab has proven to be safe and clinically effective in reducing the blood transfusion requirement, in improving the quality of life and in reducing the risk of thrombosis in most of the patients with hemolytic PNH. Despite the clinical effectiveness of eculizumab, a small proportion of patients remain transfusion-dependent, likely because a fraction of PNH red cells become coated with C3 and, subsequently, can undergo phagocytosis resulting in extravascular hemolysis. Further progress in knowledge about the diverse pathogenetic mechanisms involved in PNH will help in improving the treatment of PNH patients, especially of those that benefit partially of eculizumab.