Bone Marrow Failure Syndromes: Paroxysmal Nocturnal Hemoglobinuria

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KEYWORDS

- Hemolysis • Aplastic anemia • Myelodysplasia
- Bone marrow failure • Bone marrow transplant
- Eculizumab

Speaking in London as President of the Section of Pathology of the Royal Society in March 1963, Professor John V. Dacie (1912–2005) gave a prescient review of paroxysmal nocturnal hemoglobinuria (PNH), which he regarded as *the* blood disease.[1] Dacie's review focused on the following five central problems connected with PNH that were unresolved at the time:

1. The nature of the red cell defect
2. The nature of the factors in normal plasma that bring about hemolysis of the PNH red cell
3. Whether the patient's leukocytes and platelets are abnormal
4. The relationship between PNH and thrombosis
5. The ultimate problem—the etiology of the disease and its relationship to marrow hypoplasia

In the ensuing 45 years, Dacie's first,[2,3] second,[4] and third[5–7] central problems have been solved. The fourth central problem, the basis of the thrombophilia of PNH, remains largely speculative.[8] Dacie's ultimate problem, the etiology of the disease and its relationship to marrow hypoplasia, is the subject of this article.

AN OVERVIEW OF PAROXYSMAL NOCTURNAL HEMOGLOBINURIA

PNH is an acquired disease that results from nonmalignant clonal expansion of one or more hematopoietic stem cells[9] that have undergone somatic mutation of the X-chromosome gene *PIGA*.[6,7,10] The protein encoded by *PIGA* is essential for synthesis of the glycosyl phosphatidylinositol (GPI) moiety that serves as the membrane anchor

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for a functionally diverse group of cellular proteins.[3] As a consequence of mutant *PIGA*, all GPI-anchored proteins (GPI-APs) are deficient on affected stem cells and their progeny. Two proteins, CD55 (decay accelerating factor, DAF)[11–13] and CD59 (membrane inhibitor of reactive lysis, MIRL)[14,15] that inhibit the activation and cytolytic functions of complement are among the GPI-APs normally expressed by hematopoietic cells. The Coombs-negative intravascular hemolysis (and the resultant hemoglobinuria) that are the clinical hallmarks of classic PNH are a direct consequence of the deficiency of CD55 and CD59, because peripheral blood erythrocytes derived from the mutant clone lack the capacity to restrict cell-surface activation of the alternative pathway of complement and to block formation of the cytolytic membrane attack complex.[4]

Thromboembolism is the leading cause of morbidity and mortality in PNH.[8,16–19] Unusual sites of involvement, including hepatic vein thrombosis (Budd-Chiari syndrome) and thrombosis of mesenteric, cerebral, and dermal veins, characterize the thrombophilia of PNH.[20] In contrast to the present thorough understanding of the complement-mediated hemolytic anemia of PNH,[4] however, the pathobiology of the thrombosis of PNH is largely speculative.[8]

An association between PNH and acquired aplastic anemia has been recognized for more than 50 years,[1,21–23] and all patients who have PNH have evidence of bone marrow dysfunction.[24] Understanding the association between PNH and aplastic anemia seems to be a key to unlocking the complex pathophysiology of this eccentric disease. The close association of PNH with an immune-mediated bone marrow failure syndrome (ie, aplastic anemia) suggests that hematopoietic stem cells with mutant *PIGA* have a conditional growth or survival advantage in the setting of a specific type of bone marrow injury with subsequent independent, nonmalignant expansion of the *PIGA*-mutant clone in some (but not all) cases. In this view of PNH, acquired deficiency of one or more GPI-APs in hematopoietic stem cells through somatic mutation of *PIGA* is seen as nature's approach (by way of natural selection) to treatment of immune-mediated bone marrow injury.

THE CLINICAL PROBLEM

The peripheral blood of patients who have PNH is a mosaic of normal and abnormal cells (**Fig. 1**), and the percentage of abnormal cells varies widely among patients. For example, hypothetical patient A may have 90% abnormal, GPI-AP–deficient cells with 10% of the cells showing normal expression of GPI-APs (based on flow cytometric analysis of peripheral blood neutrophils or erythrocytes), whereas hypothetical patient B may have 10% abnormal cells and 90% phenotypically normal cells. The degree of mosaicism among different patients is determined by the extent to which the *PIGA*-mutant clone expands, but the factors that determine clonal expansion in an individual patient are largely speculative.[25] *PIGA*-mutant stem cells seem to have no intrinsic growth or survival advantage,[26,27] suggesting that clonal expansion is driven by factors that are distinct from but that work in concert with mutant *PIGA*.[3] Although the clinical manifestations of PNH depend in large part on the size of the clone, the extent of the associated bone marrow failure also contributes significantly to disease manifestations. Thus, PNH is not a binary process; based on the clinical features, bone marrow characteristics, and the size of the mutant clone (based on the percentage of GPI-AP–deficient PMNs), the International PNH Interest Group recognizes three disease subcategories (**Table 1**).

Although the bone marrow of patients who have classic PNH appears fairly normal morphologically (**Table 1**), numerous in vitro studies have shown that the growth characteristics of marrow-derived stem cells are aberrant.[24] Moreover, when stem cells