Paroxysmal Nocturnal Hemoglobinuria

A Complement-Mediated Hemolytic Anemia

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KEYWORDS

• Paroxysmal nocturnal hemoglobinuria • Hemolytic anemia
• Alternative pathway of complement • Humanized anti-C5 monoclonal antibody
• Eculizumab • C3 blockade • C1 inhibition • Bone marrow failure

KEY POINTS

- Paroxysmal nocturnal hemoglobinuria (PNH) is a rare, clonal, hematopoietic stem cell disorder with 3 clinical features: hemolytic anemia from uncontrolled complement activation, thrombosis, and bone marrow failure.
- Eculizumab is a humanized monoclonal antibody that binds to C5 in complement system and decreases intravascular hemolysis, reduces thrombosis risk, and improves quality of life.
- Persistent extravascular hemolysis in PNH while on eculizumab remains a relevant clinical issue and multiple therapies are being examined to improve this.

INTRODUCTION

Paroxysmal nocturnal hemoglobinuria (PNH) is a rare, clonal, hematopoietic stem cell disorder that manifests with a hemolytic anemia from uncontrolled complement activation, bone marrow failure, and a propensity for thrombosis.[1–3] It is the chronic hemolytic anemia in PNH, largely mediated by the alternative pathway of complement (AP), from which the disease derives its descriptive moniker.[2] PNH is a unique disease whose clinical manifestations have been linked to the deficiency in glycosylphosphatidylinositol-anchored proteins (GPI-APs). These manifestations include a lack of the complement regulatory proteins CD55 and CD59.[4] CD55 regulates the formation and stability of the C3 and C5 convertases,[1] whereas CD59 blocks the formation of the membrane attack complex (MAC).[2,5]

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Hematol Oncol Clin N Am 29 (2015) 479–494
http://dx.doi.org/10.1016/j.hoc.2015.01.005 hemonc.theclinics.com
0889-8588/15/$ – see front matter

The bone marrow failure component of the disease is well-appreciated. The mechanism of the thrombophilia is less well-described. Historically, PNH is among the first diseases in which the role the complement cascade plays in the pathogenesis is well-elucidated. This review focuses on the dysregulation of the complement cascade, leading to the hemolytic anemia in PNH as well as its other clinical manifestations and the therapies available presently and possibly in the future for the disease.

THE PATHOPHYSIOLOGY OF THE COMPLEMENT DYSREGULATION IN PAROXYSMAL NOCTURNAL HEMOGLOBINURIA

The complement system is our host defense system that protects the intravascular space through opsonizing and lysing bacteria. The complement system consists of plasma proteins that interact via 3 major pathways: the classical, alternative, and lectin binding.[6,7] This system encompasses these distinct cascades with individual functions, which all converge into a common final effector mechanism—the MAC (Fig. 1). These 3 pathways independently lead to activation of C3 and C5 convertases.[6] Although the classical and the lectin pathways require specific triggers to be activated—usually infection—it has been known for years that the AP exhibits low-grade continuous activation owing to spontaneous hydrolysis of C3 (called the "tick-over" phenomenon).[8–10] In addition, some components of the AP constitute an

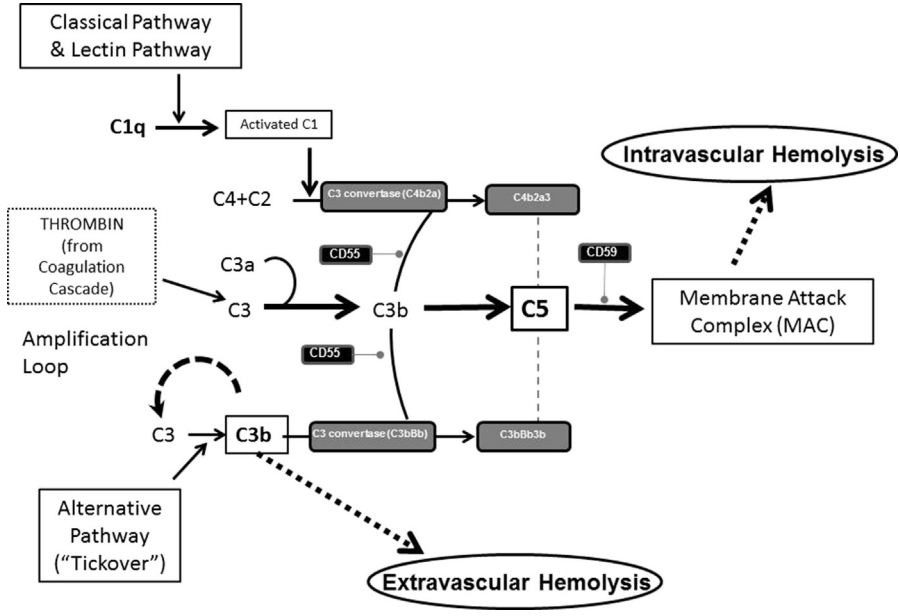

Fig. 1. The complement cascade. The complement cascade is activated via the classical, lectin or alternative pathways. C3 is activated via C3 convertases. This step is regulated by the action of CD55, a glycosylphosphatidylinositol (GPI)-anchored protein. Subsequently, C5 is cleaved into C5a and C5b. C5a mediates a number of biological processes and C5b begins the terminal pathway of complement and the assembly of the membrane attack complex (MAC). The formation of the MAC is regulated by CD59, another GPI-anchored protein. Thrombin interacts with the complement cascade where it can directly cleave C3. Thrombin can also cleave C5 into C5a, which occurs independently of C3 and therefore represents a bypass of the 3 traditional complement activation pathways.