

Two Roads Diverge: Treatment Choice in Coexisting Severe Aplastic Anemia and Paroxysmal Nocturnal Hemoglobinuria

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Abstract

Aplastic anemia (AA) is a bone marrow failure syndrome of pancytopenia due to impaired hematopoiesis. It is strongly associated with paroxysmal nocturnal hemoglobinuria (PNH). Each condition can cause the other, or occur simultaneously. There are no guidelines for treating concomitant AA and PNH; immunosuppressive therapy (IST) or hematopoietic stem cell therapy (HSCT) is first-line for the former, and ecilizumab is first-line for the latter. New studies suggest that treating AA/PNH together versus sequentially should depend on AA severity. We report the case of a previously healthy male (31-year-old, Nigerian immigrant) who developed jaundice, scleral icterus, easy fatigability, and epistaxis. He was diagnosed with AA on bone marrow biopsy and with PNH on flow cytometry. He initially underwent chemotherapy due to increased infection risk with ecilizumab in a neutropenic patient; however, he showed minimal response and thus began ecilizumab pending allogeneic stem cell transplant. There are no guidelines for treating patients with both AA and PNH, and clinical decision making is generally individualized based on disease severity. Only one prior publication reported simultaneous treatment with ecilizumab and chemotherapy, due to stated concern for pancytopenia, especially neutropenia, being the most immediate cause of morbidity/mortality. This demonstrates the individualized decisions that must be made when treating simultaneous PNH and AA, and the importance of PNH/severe AA patients as a separate subpopulation.

Keywords: Aplastic anemia; Paroxysmal nocturnal hemoglobinuria; Immunosuppressive therapy; Chemotherapy

Introduction

Aplastic anemia (AA) is a bone marrow failure syndrome in

which the hematopoietic stem cell pool is severely diminished, causing pancytopenia. Severe AA is defined as marrow cellularity < 25% (or 25-50% with < 30% residual hematopoietic cells), plus at least two of the following: 1) neutrophils < $0.5 \times 10^9/L$; 2) platelets < $20 \times 10^9/L$; or 3) reticulocyte count < $20 \times 10^9/L$. It has a very poor prognosis if untreated [1]. AA can result from autoimmune factors, drugs, viruses, or other exposures. It is also strongly associated with paroxysmal nocturnal hemoglobinuria (PNH) [2]. The relationship between the two conditions is complex: each can develop into the other, or occur simultaneously. There are no definitive guidelines for treating concomitant AA and PNH; immunosuppressive therapy (IST) or hematopoietic stem cell therapy (HSCT) is first-line for the former, and the monoclonal antibody ecilizumab is first-line for the latter. Administering them together versus sequentially remains a matter of clinical discretion. Here, we report a patient with severe AA secondary to PNH and review the literature regarding the best treatment approach for such patients.

Case Report

Our patient is a 31-year-old man without significant past medical history who recently emigrated from Nigeria. He presented with a history of jaundice and scleral icterus for a few months, and a 1-year history of easy fatigability, dyspnea/palpitations on exertion, and epistaxis. Initial labs showed pancytopenia and hemolytic anemia. Bone marrow biopsy revealed hypocellularity to < 5% with almost no hematopoiesis, consistent with severe AA. He was admitted for transfusions and further workup.

Infectious workup and heavy metal screen were negative. Peripheral smear was remarkable only for hypocoellularity. Flow cytometry eventually confirmed PNH, with 73% of granulocytes, glycosphosphatidylinositol (GPI)-deficient.

The patient was started on chemotherapy for AA with anti-thymocyte globulin (ATG), prednisone, and cyclosporine (CsA). He also received eltrombopag and neutropenic prophylaxis. After PNH was diagnosed, we debated treating it with ecilizumab. However, because ecilizumab increases risk of infection and our patient was neutropenic, we chose to continue ATG/CsA and defer ecilizumab until his cell counts improved.

Unfortunately, he has shown minimal response to chemotherapy after 4 months of treatment. He has achieved transfusion independence, but remains pancytopenic and icteric with ongoing hemolysis. Repeat bone marrow biopsy after 6 weeks

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of chemotherapy showed a stable PNH clone with 72% of granulocytes and 69% of monocytes GPI-deficient. It was then decided to pursue allogeneic stem cell transplant. In the interim, he has been started on eculizumab and is continuing CsA.

Discussion

PNH is a rare hemolytic anemia caused by complement-mediated attack on erythrocytes. It occurs due to acquired somatic mutations in *PIGA*, an X-linked gene that encodes a catalytic subunit crucial to the biosynthesis of GPI [2]. GPI is a glycolipid involved in post-translational modification of protein precursors. Another function is to “anchor” signaling proteins to the membranes of hematologic cells [3].

Due to loss of the GPI anchor, PNH patients cannot retain the surface proteins cluster of differentiation 55 (CD55) (decay-accelerating factor) and CD59 (membrane inhibitor of reactive lysis). These proteins protect red blood cells from complement-mediated degradation [2, 4, 5]. Specifically, CD55 accelerates degradation of membrane-bound C3 convertase, thus preventing it from activating the alternative complement cascade; CD59 inhibits polymerization of C9 and its subsequent formation into the membrane attack complex (MAC) [2, 5]. Consequently, *PIGA*-mutant erythrocytes are susceptible to attack by the innate immune system. Once sufficient clonal expansion of the mutated progenitor cell takes place, the disease becomes irreversible.

The symptoms of PNH are sequelae of hemolytic anemia, most classically the red morning urine for which the disease is named. Rarely, hemolysis generates more free hemoglobin than haptoglobin and hemopexin can clear, causing it to bind nitric oxide to depletion. This results in symptoms of smooth muscle deregulation, including esophageal spasms, dysphagia, and erectile dysfunction [2]. Thrombophilia is also common, due to increased release of prothrombotic cytokines and defective fibrinolysis [4]. PNH patients have elevated risk of venous thrombosis and a six-fold increased incidence of chronic kidney disease compared to the general population [2].

The relationship between PNH and AA is well described but still little understood. AA can develop secondary to PNH or *vice versa*. Furthermore, idiopathic AA patients are much more likely to carry an incidental PNH clone than the general population. In fact, 68% of AA patients in one study tested positive for a PNH clone on flow cytometry [6]. PNH is thought to cause AA because complement attack targeting CD55/CD59-deficient erythrocytes also causes collateral damage to normal hematopoietic precursor cells. Conversely, it is thought that idiopathic AA predisposes to PNH clones because autoimmune attack against hematopoietic cells spares pre-existing CD55/CD59-deficient erythrocytes. This causes a relative increase in their percentage of total erythrocyte volume, but they do not proliferate further [6].

PNH as the cause of AA can be distinguished from idiopathic AA with a subclinical PNH clone by the presence of symptoms specific to PNH, such as thrombosis or hemolytic anemia (as was the case with our patient). Patients with AA secondary to PNH have a better prognosis than patients with

idiopathic AA. However, PNH patients with severe AA have a much worse prognosis than patients with classic PNH [7].

Treatment for patients with both AA and PNH is not standardized, but is generally based on severity of AA. Historically, PNH was treated with corticosteroids, with bone marrow transplant required for total cure. Now, first-line treatment is eculizumab, a monoclonal antibody to the complement intermediary C5. Disease refractory to eculizumab treatment may still require transplantation. Similarly, AA is treated with IST consisting of horse ATG and CsA, but HSCT is the only cure and is recommended in young patients who would tolerate it well [8].

A 2017 prospective study in a Korean cohort demonstrated equal efficacy of eculizumab in PNH/AA patients compared to classic PNH patients, with almost all subjects in both groups achieving decreased hemolysis and transfusion independence within 36 months [9]. However, this study did not stratify the PNH/AA patients by severity of AA. Another Korean study did separately analyze PNH/severe AA patients, and found that their much higher mortality rate resulted from major bleeds and infections resulting from cytopenias [7]. Given that pancytopenia is a much more immediate cause of morbidity/mortality than hemolysis, and that eculizumab does not improve pancytopenia in PNH/severe AA patients, the study authors recommended HSCT or IST for all PNH/severe AA patients before initiating eculizumab. Alashkar et al report the only known case of a patient already on eculizumab for PNH, who then progressed to severe AA and began concurrent ATG/CsA [10]. This patient achieved restoration of cell counts with continued suppression of hemolysis, suggesting that eculizumab and IST can be used together safely and effectively.

In our patient’s case, we independently reached the same conclusion as Kim et al [7], namely that treating his severe AA was more pressing than treating his PNH, as his most likely cause of short-term mortality was infection. However, as he responded poorly to IST alone, we ultimately added eculizumab. He continues to receive close outpatient follow-up to monitor cell counts. It remains to be seen how he responds to this treatment plan as he awaits HSCT. Regardless, this case demonstrates the individualized decisions that must be made when treating patients with simultaneous PNH and AA. In particular, it emphasizes the importance of treating patients with PNH/severe AA as a separate subpopulation, a nuance that has previously received limited attention as per literature review.

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None to declare.

Financial Disclosure

None to declare.

Conflict of Interest

None to declare.

Informed Consent

The informed consent was obtained from patient whose case is presented above.

Author Contributions

Aamina Shakir was the primary author; Austin LaGrow and Sunny Narulsa assisted with writing; and Sanobar Nusrat assisted with editing.

Data Availability

Any inquiries regarding supporting data availability of this study should be directed to the corresponding author.

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