

Fatigue Improvement after Eculizumab in Paroxysmal Nocturnal Hemoglobinuria: Apropos of a Case

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Abstract

A 54-year-old male presented with shortness of breath and was diagnosed with pulmonary emboli. Laboratory studies revealed hemolytic anemia. Flow cytometry showed a prominent white blood cell clone without CD59 in 85% (NV 0-3.0) and red blood cells with 8.5% CD59 absence (NV 0-3.0) confirming a diagnosis of paroxysmal nocturnal hemoglobinuria. Eculizumab was started to decrease the possibility of a thrombotic recurrence, with incidentally, a marked subjective improvement of symptomatology, as fatigue, was seen. We reviewed current literature regarding the improvement in fatigue seen in patients with paroxysmal nocturnal hemoglobinuria treated with eculizumab.

Fatigue Improvement after Eculizumab in Paroxysmal Nocturnal Hemoglobinuria: Apropos of A Case

A 54-year-old male presented with shortness of breath and was diagnosed with acute pulmonary emboli for which anticoagulation was started. Complete blood count showed normocytic anemia (8.3 K/uL), thrombocytopenia (66 K/uL), and elevated white blood cells (15.1 K/uL), thus a peripheral blood smear (*panel A*) was obtained which revealed reticulocytes. Lactate dehydrogenase (LDH) was high at 1,437 IU/L, haptoglobin was low, Coombs test was negative and fibrinogen was normal. Cytogenetic studies revealed trisomy 8 suspicious for the possibility of an accompanying myeloid disorder, nevertheless bone marrow biopsy was negative for myelodysplastic syndrome and only showed reactive erythroid hyperplasia (*panel B low power and panel C, high power*) which would be expected in a hemolytic process. Platelet count normalized shortly afterwards and it was likely initially diminished secondary to consumption in the setting of an acute thromboembolic event. Flow cytometry showed a prominent white blood cell clone with absence of CD59 in 85% (NV 0-3.0) and red blood cells with absence of CD59 in 8.5% (NV 0-3.0) confirming a diagnosis of paroxysmal nocturnal hemoglobinuria. Eculizumab was started to decrease the possibility of thrombotic recurrence, with a marked subjective improvement of symptoms as fatigue was seen. Hemoglobin and LDH were borderline normal. The patient was vaccinated against *Neisseria meningitidis* prior to starting eculizumab therapy as per standard guidelines.

Paroxysmal nocturnal hemoglobinuria is a rare clonal hematological condition of unchecked complement activation characterized by a multipotent hematopoietic stem cell progenitor that acquires a mutation in the class A phosphatidylinositol glycan (PIG) gene or PIG-A gene, which governs the production of glycosyl-phosphatidyl-inositol (GPI) anchors [1]. The selected abnormal clone ultimately expands bearing a mutation that renders multiple cells in the body, including red blood cells, deficient of GPI anchored proteins, as the complement-mediators CD55 and CD59, which in turn make cells susceptible to complex activation and membrane attack complex with subsequent chronic intravascular hemolysis and anemia [1]. The latter was initially felt to be the main culprit for many of the associated symptoms seen in paroxysmal nocturnal hemoglobinuria, including fatigue and decreased quality of life, nevertheless improvements in the degree of fatigue seem to be independent of the hemoglobin levels. Recently, it has been suggested that the release of free hemoglobin into the vasculature due to hemolysis, leads to nitric oxide depletion which might contribute to the development of fatigue and smooth muscle dystonias [2].

The different phenotypes seen in patients with paroxysmal nocturnal hemoglobinuria might be explained by selection and expansion of the abnormal clone which would render a population of cells into a heterogeneous combination of normal and abnormal cells. As an example, type I red blood cells are normal, type II red blood cells are partially deficient in GPI-proteins, and type III red blood cells are completely deficient in GPI-proteins [3]. The larger the number of type III red blood cells present, the worse the hemolysis seen in a particular patient. The fact that our patient's CD59 was lower in red blood cells than in white blood cells might be counterintuitive; nevertheless a reasonable explanation would be that while both red and white blood cells carry the abnormality, red blood cells might be more prone to complement induced attack than white blood cells thus, when testing is performed, the CD59 red blood cell population has already been diminished due to hemolysis.

Eculizumab is an anti-C5 humanized monoclonal antibody which inhibits terminal complement mediated intravascular hemolysis in GPI-defective cells and is the first targeted disease-modifying therapy for paroxysmal nocturnal haemoglobinuria [4]. This antibody binds to the complement protein C5, halting the attachment of the terminal complement complex cascade (C5b-9). In clinical trials of eculizumab compared with baseline and placebo, eculizumab was well tolerated and increased health-related quality of life and fatigue scores and decreased intravascular hemolysis, levels of LDH, stabilizing hemoglobin and reaching packed red cell transfusion independence in more patients [5]. The pivotal study by Hillmen et al. [6] revealed significant improvements ($p < 0.001$) in the quality of life of patients receiving eculizumab. The seminal trials that evaluated the safety and efficacy of eculizumab, TRIUMPH and SHEPHERD, noted statistically significant improvement in the Functional Assessment of Chronic Illness Therapy (FACIT) Fatigue instrument scores, by week 3 with $p=0.009$ and by week

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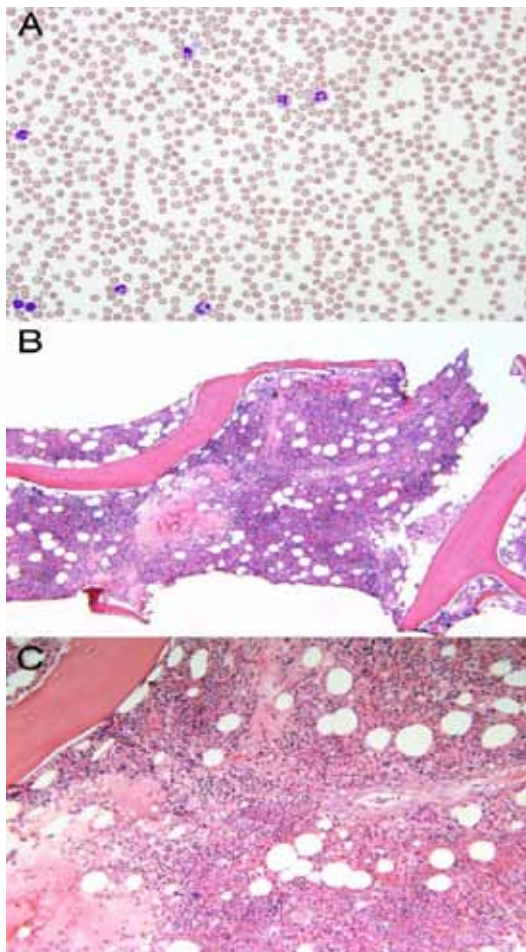


Figure 1: Panel A: Peripheral blood smear showing normochromic anemia, thrombocytopenia and reticulocytes. Panel B: Bone marrow biopsy showed reactive erythroid hyperplasia (low power). Panel C: Bone marrow biopsy showed reactive erythroid hyperplasia (high power).

1 with $p < 0.001$ respectively [7], which was subsequently confirmed by smaller trials. The scores seen in the Fatigue instrument may range from 0 to 52; where higher scores point towards improvement in fatigue. López Rubio et al. [8] found that fatigue resolved in 96% of 25 patients with paroxysmal nocturnal hemoglobinuria that were treated with eculizumab. Kim et al. [9] saw improvement in fatigue 4 out of 6 patients treated with eculizumab. Kanarura et al. [10] reported similar findings and, independent of hemoglobin level variations, fatigue improved within 2 weeks of commencing eculizumab. In a placebo-controlled trial, adverse reactions reported in 5% or more of 43 patients that received eculizumab included headache 19 (44%), nasopharyngitis 10 (23%), back pain 8 (19%), nausea 7 (16%), cough 5 (12%), sinusitis 3 (7%), respiratory tract infection 3 (7%), myalgia 3 (7%), influenza-like illness 2 (5%), among others. Although relatively well tolerated, the burdensome constitutional toxicity that develops in patients exposed to eculizumab makes more surprising the fact that some patients have an improvement in their fatigue and strengthens the point of our case [11]. Alfinito et al. [12] documented that eculizumab treatment alters the immune profile of patients with PNH. In untreated PNH, Treg, IFN- γ and IL-17 production are reduced; whereas CXCR4 expression, NKTi and IL-4 secretion are increased [12]. Whether or

not the interaction between PNH and the immune system explains the improvement on fatigue remains to be seen [12]. Until the development of eculizumab, the management of PNH has mainly been symptomatic with transfusion support, folic acid nutritional support, anticoagulation after thromboembolic disease ensued, and allogeneic stem cell transplantation for selected cases. Eculizumab, despite the fact that it is not a curative therapy, provides a statistically significant improvement in fatigue and quality of life which are so critically important for patients with paroxysmal nocturnal hemoglobinuria.

References

1. Pu JJ, Brodsky RA (2011) Paroxysmal nocturnal hemoglobinuria from bench to bedside. *Clin Transl Sci* 4: 219-224.
2. Brodsky RA (2008) Advances in the diagnosis and therapy of paroxysmal nocturnal hemoglobinuria. *Blood Rev* 22: 65-74.
3. Kelly R, Richards S, Hillmen P, Hill A (2009) The pathophysiology of paroxysmal nocturnal hemoglobinuria and treatment with eculizumab. *Ther Clin Risk Manag* 5: 911-921.
4. McKeage K (2011) Eculizumab: a review of its use in paroxysmal nocturnal haemoglobinuria. *Drugs* 71: 2327-2345.
5. Röth A, Dührsen U (2011) Treatment of paroxysmal nocturnal hemoglobinuria in the era of eculizumab. *Eur J Haematol* 87: 473-479.
6. Hillmen P, Young NS, Schubert J, Brodsky RA, Socié G, et al. (2006) The complement inhibitor eculizumab in paroxysmal nocturnal hemoglobinuria. *N Engl J Med* 355: 1233-1243.
7. Schubert J, Hillmen P, Röth A, Young NS, Elebute MO, et al. (2008) Eculizumab, a terminal complement inhibitor, improves anaemia in patients with paroxysmal nocturnal haemoglobinuria. *Br J Haematol* 142: 263-272.
8. López Rubio M, Morado M, Gaya A, Alonso Rosa D, Ojeda E, et al. (2011) [Paroxysmal nocturnal hemoglobinuria therapy with eculizumab: Spanish experience]. *Med Clin (Barc)* 137: 8-13.
9. Kim JS, Lee JW, Kim BK, Lee JH, Chung J (2010) The use of the complement inhibitor eculizumab (Soliris®) for treating Korean patients with paroxysmal nocturnal hemoglobinuria. *Korean J Hematol* 45: 269-274.
10. Kanakura Y, Ohyashiki K, Shichishima T, Okamoto S, Ando K, et al. (2011) Safety and efficacy of the terminal complement inhibitor eculizumab in Japanese patients with paroxysmal nocturnal hemoglobinuria: the AEGIS clinical trial. *Int J Hematol* 93: 36-46.
11. http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/125166s172lbl.pdf.
12. Alfinito F, Ruggiero G, Sica M, Udhayachandran A, Rubino V, et al. (2012) Eculizumab treatment modifies the immune profile of PNH patients. *Immunobiology* 217: 698-703.