

Spontaneous Remission of Paroxysmal Nocturnal Hemoglobinuria During Eculizumab Treatment

Fahri Sahin^{a, d}, Asu Fergun Yilmaz^a, Melda Comert^a, Fusun Ozdemirkiran^b,
Nihal Mete Gokmen^c, Guray Saydam^a

Abstract

Paroxysmal nocturnal hemoglobinuria (PNH) is a very rare acquired disease which is characterized by increased sensitivity to complement proteins. The only curative treatment option for PNH has been still allogeneic stem cell transplantation from HLA-matched donor. Eculizumab, which is a monoclonal antibody, has been established as the effective approach not only for prevention of hemolysis, but also for prevention of potential organ damages such as thromboses and failure of target organs. But eculizumab does not have any impact on, or may increase, clone status and nature of the disease. We, hereby, report a case whose disease undergone spontaneous remission under treatment of eculizumab treatment.

Keywords: Paroxysmal nocturnal hemoglobinuria; Spontaneous remission; Eculizumab

Introduction

Paroxysmal nocturnal hemoglobinuria (PNH) is an acquired clonal disorder of the hematopoietic stem cells caused by a mutation in X-linked phosphatidylinositol glycan class A (PIG-A) gene. It results in partial or complete absence of certain GPI-linked proteins. As a result, increased sensitivity of red blood cells to complement system, intravascular hemolysis and generation of inflammatory mediators occur. Especially the absence of CD55 (decay accelerating factor) and CD59 (membrane inhibitory of reactive lysis) proteins which are linked to the membrane by GPI anchor proteins leads to intravascular hemolysis, generation of inflammatory

mediators and the other symptoms of the disease [1, 2].

The clinical manifestations and presenting symptoms are diverse at the presentation and during the course of the disease due to the effected organs and systems. Hemolysis, bone marrow failure with cytopenias and life-threatening thrombotic episodes are the most common clinical manifestations. Myelodysplastic syndrome and acute leukemias can also be seen in the course of the disease. One of the most common causes of mortality and morbidity in PNH patients is thromboembolism. Other causes of death are hemorrhage, renal and cardiac problems which can be related to thrombosis and intravascular hemolysis, infections, transformation to myelodysplastic syndrome or aplastic anemia [3-5]. During the course of the disease, spontaneous remission is a rare entity. A retrospective analysis consisted of 80 patients, and 12 patients had spontaneous clinical remission [6].

Eculizumab, a complement inhibitor, is a monoclonal antibody which decreases risk of thrombosis and hemolysis in patients with PNH by inhibiting complement system [7-9]. In the era of eculizumab, although the complications such as hemolysis and thrombosis can be taken under control, cure and the remission of the disease is still a rare entity.

This report describes a case of spontaneous PNH remission during eculizumab treatment.

Case Report

A 27-year-old male was admitted to hospital due to bilateral bruising in the arm. The physical examination was normal except ecchymoses. The complete blood count revealed low platelet ($13,000/\text{mm}^3$) and hemoglobin/hematocrit (Hb/Hct: $68\text{g/L}/19.8\%$) with normal leukocyte (WBC: $4,600/\text{mm}^3$) levels. Initial diagnosis was idiopathic thrombocytopenic purpura and the patient received intravenous immunoglobulin plus corticosteroids. Following an increase in the platelet count, the therapy was maintained with cyclosporine. Six months later, the patient has presented with thrombocytopenia once again and transferred to Ege University Hospital after an initial red blood cell and platelet transfusions. On admission, the platelet count was $20,600/\text{mm}^3$, Hb/Hct $95\text{g/L}/28.7\%$. Biochemistry tests were normal but high lactate

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^aDepartment of Hematology, Ege University, Izmir, Turkey

^bDepartment of Hematology, Izmir Katipcelebi University, Izmir, Turkey

^cDepartment of Immunology, Ege University, Izmir, Turkey

^dCorresponding author: Fahri Sahin, Department of Hematology, Ege University School of Medicine, Bornova, Izmir 35100, Turkey.
Email: fahri.sahin@ege.edu.tr

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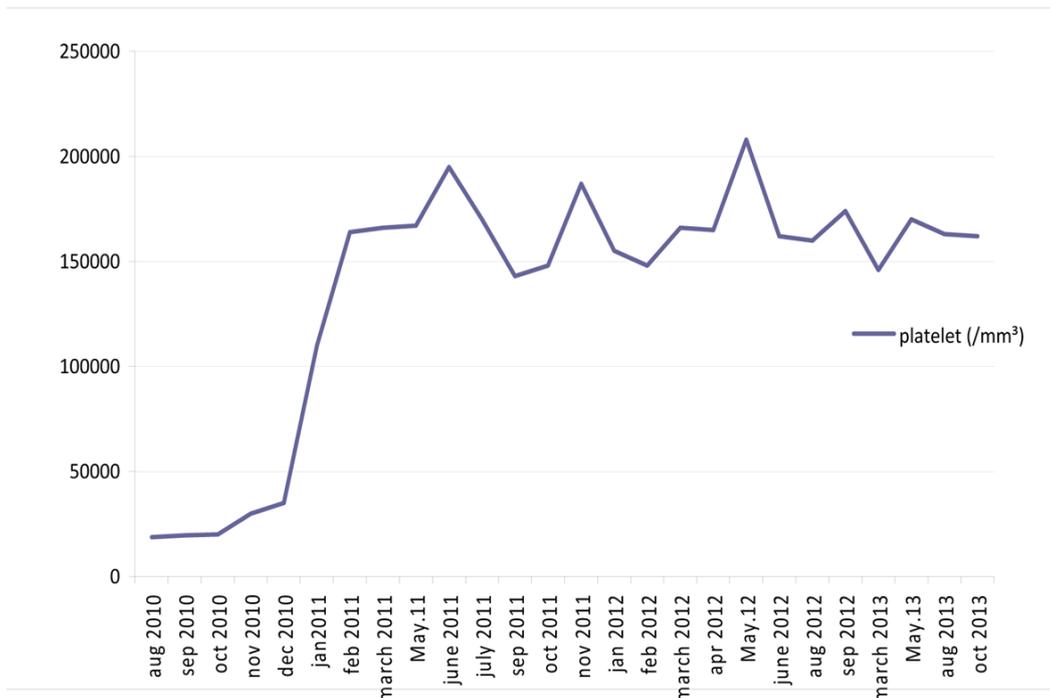


Figure 1. Platelet results during and after the end of eculizumab treatment.

dehydrogenase (LDH: 629 IU/L) level was remarkable. His vitamin B12, folic acid and serum iron parameters were all normal. Hemolysis was prominent with low haptoglobin, high LDH and reticulocyte levels. Both direct and indirect combs tests were negative. His medical history was insignificant except for the prior thrombocytopenia/bruising episode. He was diagnosed as non-immune hemolytic anemia and thrombocytopenia. Bone marrow aspiration and biopsy was

reported as normocellular with dyserythropoiesis. PNH was suspected due to cytopenias with hemolysis. Flow cytometry showed a PNH clone of granulocytes 25% with CD55, CD59 and the clone size was increased up to 69% next month. The eculizumab treatment was initiated. Eculizumab rapidly improved platelet count, Hb values and normalized LDH levels of the patient (Fig. 1, 2). Approximately 15 months after eculizumab therapy, flow cytometry results showed a

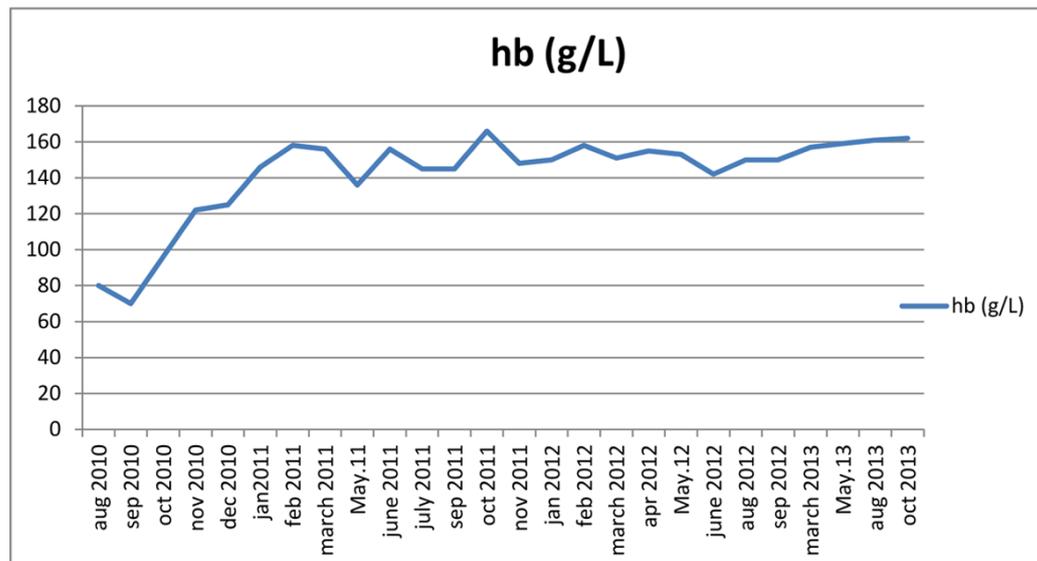


Figure 2. Hemoglobin results during and after the end of eculizumab treatment.

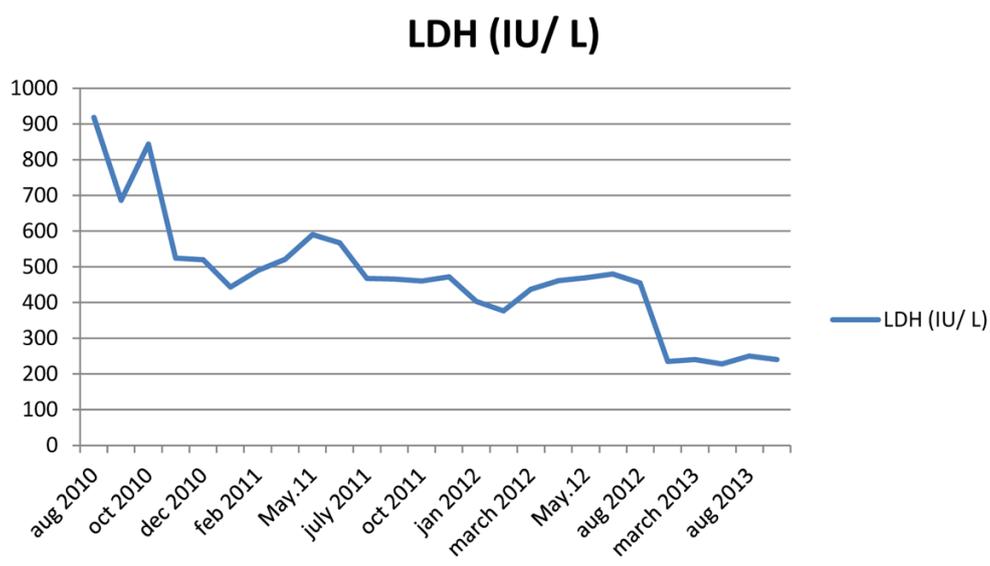


Figure 3. Lactate dehydrogenase results during and after the end of eculizumab treatment.

granulocyte clone of 6.2%. Considering a PNH clone < 10% suggested spontaneous remission and we have discontinued eculizumab therapy. The patient has been closely monitored after eculizumab discontinuation, most recently at 4 months following the last dose. During the follow-up period LDH and Hb levels were stable and normal. Flow cytometry revealed a granulocyte PNH clone of 6.65% at December 2012. No thrombosis or other complications have occurred. Platelets, Hb and LDH results before, during and after the end of eculizumab treatment are shown in Figures 1-3.

He is still followed up with normal Hb, platelet and leucocyte counts in remission without any complication.

Conclusion

PNH is a clonal hematopoietic stem cell disease which is characterized by hemolysis, thrombosis and cytopenias. Before the treatment with eculizumab, a monoclonal antibody which inhibits the terminal complements activation [10], there is not much treatment option for PNH patients. Supportive cares like platelet and red blood cell transfusions, folic acid and vitamin B12 supplementations, treatment of thrombosis with warfarin and low molecular weight heparin and immunosuppressive therapies like cyclophosphamide are the only treatment options before the era of eculizumab [5].

Treatment with eculizumab decreases mortality and morbidity and improves the quality of life by diminishing the rate of hemolysis, need for transfusions and thrombosis without any evidence of cumulative toxicity and serious side effects. But it does not cure the disease [10-15], since this agent does not cure the disease and does not affect the clonal

stem cells in the marrow; the size of the clone is not affected or even can expand during the treatment with eculizumab [13]. But in our case, the size of the PNH clones decreased during the treatment less than 10% and the treatment with eculizumab was stopped.

Allogenic stem cell transplantation is the only curative treatment option in PNH patients but it is associated with a substantial risk of graft-versus-host disease, mortality and morbidity [16].

Spontaneous remissions are rare in PNH patients. It is documented that in a retrospective study consisting of 80 patients only 12 PNH patients achieved clinical remission. In nine of these patients, the remission was documented with historical Hams test. Normal levels of GPI-linked proteins can be demonstrated in only five of these patients and only four of these patients had no neutrophils of PNH clone. In this historical series, spontaneous remission was achieved between 10 and 20 years after the diagnosis [6]. Socie et al also demonstrated spontaneous remission in 11 patients among 220 PNH patients in France [17]. A spontaneous remission was reported in a case report of a Japanese girl. She achieved clinical and hematological remission without decreasing the clonal size of PNH cells in the first years which indicates that clonal regression is not a rule for normalization of complete blood count levels [18]. Another case report from China also demonstrates the same hypothesis that it is not essential to eliminate all abnormal clones to get a clinical remission with decreasing the level pancytopenia [19]. In these case reports, the clonal size regression did not accompany the clinical remission. By contrast with this in our case, the size of the PNH clone also diminished with recovering of hemolysis and pancytopenia. We could not find a case of

remission under the treatment of eculizumab.

Allogenic stem cell transplantation, the only curative treatment of PNH, should be reserved for imminently life-threatening cytopenias since even spontaneous remissions can be achieved during the course of the disease. Eculizumab should be considered before SCT to support improved quality of life, survival and allow for potential remission.

Conflict of Interest

The authors declare no competing financial interests.

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