Case Report

Stem Cell INVESTIGATION

Acute myeloid leukemia and fatal *Scedosporium prolificans* sepsis after eculizumab treatment for paroxysmal nocturnal hemoglobinuria: a case report

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Abstract: Eculizumab has become the standard of care for patients with paroxysmal nocturnal hemoglobinuria (PNH). As more patients are treated, the long-term outcomes of these patients will become apparent. We recently treated a patient who developed PNH in the setting of aplastic anemia. The patient developed acute myeloid leukemia less than three years after initiating eculizumab. The patient also died suddenly from Scedosporium sepsis during induction therapy. This patient's course seemed more aggressive than would be expected. The possible effect of complement blockade is discussed.

Keywords: Eculizumab; hemoglobinuria; paroxysmal; leukemia; myeloid; acute; *Scedosporium*

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Introduction

Paroxysmal nocturnal hemoglobinuria (PNH) is a clonal hematopoietic stem cell disorder caused by a somatic mutation in phosphatidylinositol N-acetylglucosaminyltransferase subunit A (*PIGA*), whose gene product is required for the synthesis of glycosyl-phosphatidyl inositol (GPI) anchors (1). Loss of GPI anchors results in a deficiency of the protective complement inhibitors CD55 and CD59 on erythrocytes, thus making them susceptible to complement-mediated lysis. The clinical hallmarks of PNH include acquired hemolytic anemia, bone marrow failure and life-threatening thrombosis (2). Eculizumab, a monoclonal antibody that binds to the complement protein C5, protects PNH red cells from complement mediated intravascular hemolysis by inhibiting the formation of the membrane attack complex (C5–C9) (3,4). In two double-blind, randomized, placebo-controlled trials, eculizumab reduced intravascular hemolysis and improved quality of life in patients with PNH who received the drug (5,6). Although eculizumab has immunosuppressive properties, there is only one published case report of a malignancy (melanoma) developing on eculizumab (7). Although it is difficult to assess causality from individual case reports, it is helpful to see the spectrum of malignancies that occur in these patients.

Case presentation

Currently we describe a patient who developed acute myeloid leukemia while on treatment with eculizumab. This case received a waiver of consent from the Institutional Review Board of New York Medical College, Valhalla, NY, USA.

A 71-year-old male with no significant past medical history presented to his primary care doctor in December 2013 with complaints of fatigue and dyspnea on exertion. A complete blood count (CBC) showed a white blood count (WBC) of 5.8×10^9/L, hemoglobin of 13.1 gm/dL and a platelet count of 60×10^9/L. The patient was initially observed, however follow-up laboratories in February 2014 showed marked deterioration. The white blood count was 3.3×10^9/L with 40% neutrophils, 56% lymphocytes and 4% monocytes, the hemoglobin was 7.7 gm/dL and the platelet count was 8×10^9/L. The patient was referred to our center at that time. A bone marrow biopsy was hypoplastic (cellularity 10%) with normal myeloid and megakaryocytic morphology.

There was a rare dysplastic erythroid cell (<10%) and a blast count of less than 1%. Flow cytometry and cytogenetics were normal, as was a myelodysplastic syndrome (MDS) FISH panel. An MDS next-generation sequencing panel that included *ASXL1*, *RUNX1*, *EZH2*, *ETV6*, and *TP53* showed no mutations. Other laboratories, including reticulocyte count, Coombs, LDH, haptoglobin, folate, iron studies, hepatitis panel, and human immunodeficiency virus (HIV), parvovirus and Lyme serologies were unremarkable. His initial B12 level was low, however, he had no response to B12 injections. PNH testing showed that 0.1% of red cells lacked CD59 expression, and 5% of monocytes and 2% of granulocytes showed downregulation of CD59 and lack of FLAER expression.

In March 2014, the patient was treated for aplastic anemia with anti-thymocyte globulin, 40 mg/kg daily for 4 days, steroids and cyclosporin. Only 2 months later the patient developed clinical evidence of intravascular hemolysis with rapid expansion of his PNH clone (red cells 0.25%, granulocytes 22%, monocytes 27%). After vaccination, he began therapy with eculizumab in July of 2014. He received ongoing therapy with eculizumab combined with cyclosporine and became transfusion in dependent with a normal WBC, hemoglobin of 11 gm/dL and peak platelet count of 71×10^9/L.

In May of 2017, the patient was referred back to us for evaluation of worsening pancytopenia. His WBC was 4.1×10^9/L with 23% neutrophils, 53% lymphocytes, 16% monocytes, 1% eosinophils, 1% basophils, and 6% blasts. The hemoglobin was 9.4 gm/dL, and the platelet count was 19×10^9/L. A bone marrow biopsy showed acute myeloid leukemia with 55% blasts that expressed CD34, CD117, partial CD33, dim CD13, and HLA-DR. Cytogenetics demonstrated 46,XY,del[7](q22q34)[2]/46, XY[18]. Next-generation sequencing revealed mutations in *PALB2* (c.311C>T; p.P104L, 50%), *PHF6* (c.834+2T>G, 52%), and *RUNX1* (c.967_967+1insA, 10%, and c.593A>G; p.D198G, 22%).

The patient was treated with CLAG-Ida (cladribine, cytarabine, granulocyte colony stimulating factor and idarubicin). On day 7 the patient developed neutropenic fever and received cefepime and vancomycin. A urine culture grew *E. coli*. On day 14 the patient suddenly developed septic shock and required intubation and pressor. Blood cultures grew vancomycin-resistant enterococcus and mold that was subsequently identified as *Scedosporium prolificans*. Despite maximal support the patient expired on day 17 of therapy.

Discussion

Eculizumab has changed the outcome of patients with PNH (8). In a report of the long-term results of eculizumab in 195 PNH patients who were treated over a 66-month period, only four deaths occurred, resulting in an estimated 3-year survival rate of 97.6% (9). All patients demonstrated a reduction in LDH, and 96.4% of patients remained free of thromboembolic events.

Eculizumab is a powerful inhibitor of the complement pathway. It is thus expected that immunological pathways that rely on complement activation could be adversely affected. For example, it is well documented that patients treated with eculizumab are at increased risk of infections, particularly *Neisseria meningitidis* infections (10). In the long-term study, 40 patients reported a total of 67 serious infections, including two cases of meningococcal sepsis (9). These infections can occur even after appropriate vaccination and are similar to those seen in patients with hereditary disorders of complement (11).

Classically, T-cell immunity is thought to be the primary host defense mechanism preventing the development and propagation of malignant diseases. More recently, a relationship between imbalanced complement activation in the tumor microenvironment and suppression of antitumor immune responses has been discovered (12). Despite these findings, there are only limited reports of malignancies occurring in patients treated with eculizumab. In the long-term study, one patient developed MDS and was taken off study to pursue a stem cell transplant (9). Manganoni *et al.* reported a patient who developed two melanomas simultaneously after having received eculizumab for 6 years as treatment of PNH (7). There was no family history of skin cancers and no prior dysplastic nevi in this patient. Further post marketing studies are needed to determine the incidence of malignancies in patients treated with eculizumab.

Progression to acute myeloid leukemia is a known complication of aplastic anemia in patients treated with immunosuppressive therapy. On average, the incidence of MDS and acute myelocytic leukemia (AML) after immunosuppressive therapy ranges from 5–15% after a follow-up of 5–11 years (13,14). In our case, the presence of a PNH clone at diagnosis was evidence of clonal disease from the start, even though the patient did not meet diagnostic criteria for MDS at that time. It is unknown if eculizumab could have influenced the rapidity with which our patient progressed to AML.

Our patient expired from *Scedosporium* sepsis very early into his treatment course. Although there are many reports of *Scedosporium* infection occurring in leukemia patients undergoing induction therapy or allogeneic stem cell transplantation, these life threatening fungal infections are more common in patients with multiply-relapsed disease, and in those who have either been neutropenic for prolonged periods of time, or in those receiving T-cell suppressing therapies after transplant (15). It is unknown whether pretreatment with eculizumab increased our patient's risk of developing a relatively rare disseminated fungal infection so early in his treatment course.

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None.

Footnote

Conflicts of Interest: K Seiter is on the speaker's bureau of Alexion Pharmaceuticals. The other authors have no conflicts of interest to declare.

Informed Consent: Written informed consent was obtained from the patient for publication of this manuscript and any accompanying images.

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