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Paroxysmal Nocturnal Hemoglobinuria Following Alemtuzumab Immunosuppressive Therapy for Myelodysplastic Syndrome and Complicated by Recurrent Life-Threatening Thrombosis Despite Anticoagulation: Successful Intervention with Eculizumab and Fondaparinux

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Abstract

The pathogenesis of paroxysmal nocturnal hemoglobinuria (PNH) is not fully understood. We report a patient with myelodysplastic syndrome who developed symptomatic PNH following treatment with alemtuzumab. A small PNH clone, identified prior to alemtuzumab, expanded resulting in hemolytic anemia and recurrent CNS thromboses despite anticoagulation. Remission was achieved with eculizumab and fondaparinux therapy. Alemtuzumab has been associated with the development of glycosylphosphatidylinositol negative cells, but its clinical significance has been unclear. Our case emphasizes its potential clinical importance. Future studies are necessary to expand our understanding of this rare disease entity and improve its management.

Introduction

Paroxysmal nocturnal hemoglobinuria (PNH) is a rare disease occurring in patients who have expansion of an abnormal hematopoietic clone characterized by mutations in the PIG A gene.

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This gene is necessary for the synthesis of an important protein anchor, glycosylphosphatidylinositol (GPI) [1]. Although PIGA gene mutations are common and can be found in the general population, it is not well understood how some abnormal PIGA mutated clones are able to preferentially multiply and cause PNH [1]. We report a case of a patient with myelodysplastic syndrome (MDS) who developed PNH following therapy with alemtuzumab and whose course was complicated by multiple recurrences of cerebral thrombosis despite anticoagulation.

Case Report

A 56 year-old male had been diagnosed with idiopathic thrombocytopenic purpura in 1998 and had been treated with steroids, intravenous gamma globulin (IVIG), azathioprine, rituximab and splenectomy. By 2005, he was no longer responding to steroids nor IVIG treatment, had become anemic, and was dependent on packed red cell and platelet transfusion. His bone marrow aspirate was noted to have erythroid predominance, dyserythropoiesis, and markedly decreased megakaryocytes. Bone marrow biopsy revealed 30% cellularity with erythroid predominance, interstitial lymphocytosis, and absent megakaryocytes. These findings were consistent with MDS. Cytogenetic analysis revealed presence of a minor population of clonally proliferating cells with loss of chromosome 18. He was noted to be HLA DR 15 positive. He continued to be transfusion dependent and developed gastrointestinal bleeding in May 2005. In November 2005, he was enrolled in a clinical trial at the National Institutes of Health (protocol 05-H-0206) utilizing alemtuzumab (a monoclonal antibody against CD52; CAMPATH®) as immunosuppressive therapy for his MDS. Baseline screening done at the NIH revealed a PNH clone consisting of 4% of neutrophils. Two months after beginning alemtuzumab, he was noted to be anemic with hemoglobin of 10.5 g/dL. Evaluation for hemolytic anemia revealed Coombs negative hemolysis with an elevated lactate dehydrogenase level of 1665 U/L and an elevated total bilirubin of 3.61 mg/dL. PNH clone was now noted to comprise 90% of neutrophils and 58% of red blood cells by CD59 screening. He also had thrombocytopenia with platelets of 19,000/ μ L. Rituximab therapy was utilized to treat the thrombocytopenia.

In September 2006, the patient developed severe persistent headache. An MRI/MRA of the brain revealed a right internal jugular thrombosis. With his platelet count at 133,000/ μ L, he was anticoagulated with warfarin. He remained asymptomatic until his headaches returned one month later. Follow-up MRI/MRA of the brain revealed a new transverse and sigmoid sinus venous thrombosis despite therapeutic INR of 2-3. Anticoagulation was switched to enoxaparin, a low molecular weight heparin (LMWH). In January 2007, he developed recurrent frontal headache and hemoglobinuria. Platelet count was 127,000/ μ L, PT 15.2 seconds, and APTT 30.8 seconds. Repeat MRI/MRA revealed evidence of a new thrombosis in the left transverse and superior sagittal sinuses. Evaluation for heparin-induced thrombocytopenia (HIT) was negative. His neurologic exam was non-focal. Anticoagulation was changed to a direct factor Xa inhibitor, fondaparinux 10 mg subcutaneous daily, with resolution of his symptoms. In February 2007, rituximab 375 mg/m² intravenous weekly $\times$ 4 and prednisone 60 mg daily were instituted for hemoglobinuria with thrombocytopenia (platelets 18,000/ μ L). Hemoglobin was initially 13 g/dL and LDH 1197 U/L. He was concurrently entered into a clinical trial, C06-002 EMBRACE, utilizing eculizumab (a monoclonal antibody directed at the terminal complement activation complex) to control his PNH. Following the initiation of eculizumab, steroids were tapered and discontinued. By March 2007, hemolysis had completely resolved with hemoglobin 14.5 g/dL, reticulocytes 93,600/ μ L, and LDH 200 U/L. Platelet count stabilized at 191,000/ μ L by April 2007. He has been continued on fondaparinux anticoagulation plus eculizumab maintenance at 900 mg IV every 2 weeks and remains in remission.

Discussion

PNH has been associated with the bone marrow failure syndromes aplastic anemia and MDS. These patients often lack clinical evidence of hemolysis since patients with MDS or aplastic anemia usually have a small PNH clone size. Clone size can be ascertained by the amount of GPI deficient cells detected by flow cytometry. PNH cells lack GPI, which functions as an anchor for many membrane-stabilizing proteins including CD55 and CD59. CD55 regulates complement C3 convertase and CD59 inhibits reactive membrane lysis [1]. Without these proteins, red blood cells are susceptible to complement-mediated lysis. As a result, patients experience hemolysis. Thrombosis not only occurs through complement activation, but also from activation by ADP released by intravascular lysis of red cells. The balance between thrombosis and fibrinolysis is further disrupted in patients with PNH since they have decreased amounts of another GPI linked protein, urokinase plasminogen activator receptor, found on monocytes which attack thrombi and initiate fibrinolysis.

Eculizumab has been shown to block terminal complement activation resulting in decreased hemolysis and improved overall quality of life [2,3]. It has also been shown to decrease thrombosis by blocking complement activation of platelets and preserving nitric oxide levels by decreasing intravascular hemolysis [2]. Intravascular hemolysis leads to increased free hemoglobin, which depletes nitric oxide. Nitric oxide plays a vital role in preventing platelet aggregation and down-regulating the coagulation cascade [3]. Eculizumab decreases thrombosis rates, even in patients on antithrombotic therapy, with a relative reduction of 94% [2].

Thrombosis is a major cause of mortality in patients with PNH. Of the patients who develop thrombosis, most will do so within the first year following diagnosis of PNH, as occurred in our patient. Thrombosis risk is increased in patients with PNH clones greater than 50%, with the risk of thrombosis over 10 years estimated to be up to 44% [4]. Management may include prophylaxis with warfarin or other anticoagulants in patients lacking contraindications to anticoagulation. In a long term follow-up of 103 patients with large PNH clones anticoagulated with warfarin or other anticoagulants, anticoagulant failure was frequent with an observed thrombotic event rate of 10.6 events per 100 patient-years [2]. Furthermore, life-threatening hemorrhage has been observed in patients with PNH treated with anticoagulation [1]. The patient reported here was not offered prophylactic anticoagulation following the diagnosis of PNH due to past gastrointestinal bleeding and low platelet count.

CD55 and CD59 deficient cells have been detected in 9 to 16% of patients with lymphoproliferative disease [5,6]. These patients had small populations of PNH-like cells. It was hypothesized that additional mechanisms were required to cause the development of clinical PNH [6]. Immune selection for PNH stem cell proliferation seems to play an important role since PNH has been associated with aplastic anemia, MDS, and immunosuppressive treatments such as alemtuzumab [5,7]. Since PIG A mutated clones lack CD52, they would have a survival advantage during treatment with alemtuzumab. While emergence of GPI-negative cells following alemtuzumab therapy has been reported, a relation to the development of clinical PNH has not been previously reported. These PNH-like clones have been noted to resolve after cessation of alemtuzumab treatment [5]. Our patient may have had a small PNH clone due to his MDS that was unmasked and permitted to proliferate by his treatment with alemtuzumab. It has been suggested that PNH clone size be evaluated prior to the institution of alemtuzumab treatment [5,7]. More studies need to be done to clarify how certain PNH clones multiply and under what conditions.

At the time of our patient's initial thrombotic event, he was anticoagulated with warfarin. Following recurrent thrombosis despite therapeutic anticoagulation with warfarin, he was

switched to enoxaparin. Nevertheless, he had recurrent thrombosis four months later. There have been no published reports regarding long-term anticoagulation of patients with both warfarin and LMWH failure. Fondaparinux is a selective factor Xa inhibitor that can be administered subcutaneously in the outpatient setting. It does not bind to platelet factor 4 and has only been associated with one case of heparin-induced thrombocytopenia [8]. While there are ongoing studies on the long-term safety of fondaparinux administration, safety data for up to 32 days use have been reported in perioperative deep vein thrombosis prophylaxis. A concern with fondaparinux use is that there is no available antidote to reverse factor Xa inhibition in the event of trauma or bleeding episodes. The patient has been monitored closely and has shown no evidence of bleeding on fondaparinux.

Conclusion

This case exemplifies treatment challenges that may arise in this rare disease. The significant mortality of thrombosis coupled with the risk of anticoagulation in PNH patients who have thrombocytopenia underscores the importance of close monitoring. Targeted therapy utilizing eculizumab permits control of the underlying cause of both hemolysis and thrombosis.

Fondaparinux is an alternative means of chronic anticoagulation for patients who have failed warfarin and LMWH therapy. Further study will be necessary to ascertain long-term safety and efficacy in this subgroup of patients.

The use of alemtuzumab as immunosuppressive therapy for MDS may have permitted a small pre-existing PNH clone to expand and become clinically significant. No clear correlation has been previously established between alemtuzumab therapy and the emergence of PNH. Our case illustrates the potentially life-threatening consequences that can ensue. Recognition of this phenomenon coupled with further clinical experience will establish its significance. Vigilance is warranted when alemtuzumab is utilized in subsets of patients at particular risk for PNH.

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