CASE REPORT

Treatment of a patient with classical paroxysmal nocturnal hemoglobinuria and Budd-Chiari syndrome, with complement inhibitor eculizumab: Case Report

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Abstract

Background. Paroxysmal nocturnal haemoglobinuria (PNH) is a rare acquired clonal disorder of hematopoietic stem cells involving all blood cells. Erythrocytes have increased susceptibility to complement-mediated haemolysis. Thrombosis is the leading cause of mortality and follows episodes of acute hemolysis. Eculizumab, a monoclonal antibody blocking activation of complement C5 is currently used in the treatment of PNH. Recent results demonstrated that eculizumab effectively reduces thrombosis.

Description of case. We present a 30-year-old male patient admitted with abdominal and lumbar pain. Thorough investigation revealed severe hemolytic anemia requiring transfusions and hepatosplenomegaly. Imaging findings were compatible with a Budd-Chiari syndrome. Flow cytometry confirmed the PNH diagnosis. Due to refractory ascites he underwent a transjugular intrahepatic portal-systemic shunt (TIPS) and eculizumab administration was started.

Results. He has already completed three years of eculizumab treatment and he is transfusion independent. There is also a significant reduction in fatigue with improvement in his quality of life. Doppler scans of his TIPS persistently show it to be patent.

Conclusions. Classical PNH patients with thrombosis and severe intravascular hemolysis are particularly challenging to manage. For these patients, eculizumab is a reasonable therapeutic option, expecting that by decreasing the risk for thrombosis, life expectancy may be increased.

Key words: Paroxysmal nocturnal haemoglobinuria (PNH), Budd-Chiari syndrome, eculizumab

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Introduction

Paroxysmal nocturnal haemoglobinuria (PNH) is a rare acquired clonal disorder of hematopoietic stem cells, related to a somatic mutation in the PIG-A gene that involves all blood cells. Erythrocytes have increased susceptibility to terminal complement-mediated haemolysis. PNH is characterized by intravascular haemolysis, thromboembolic episodes and variable degrees of bone marrow failure[1]. Thromboembolism (TE) is a serious and life-threatening complication which occurs in approximately one-third of PNH patients[1-3]. The cumulative incidence of this complication was nearly 37% in classical PNH, 10 years after diagnosis[3]. An initial TE increases the relative risk of death 5- to 10-fold and represents the single most frequent cause of mortality in PNH patients. Sites affected are manifold and often at atypical localization. They most commonly involve abdominal veins such as hepatic, splenic, mesenteric veins, portal and inferior vena cava, and cerebral veins[1,2,4].

Clinical manifestations of hepatic venous outflow obstruction, from hepatic veins to the junction of inferior vena cava and right atrium is defined as Budd-Chiari syndrome. Portal hypertension typically develops. Imaging studies combined with clinical information are essential for a definitive diagnosis[5]. Most patients have an underlying thrombotic diathesis. Its aetiology is multifactorial including myeloproliferative disorders, antiphospholipid antibody syndrome, PNH and inherited thrombophilia (FV Leiden, prothrombin mutation G20210A, antithrombin, protein C and protein S deficiency)[6]. Pregnancy and postpartum, oral contraceptives, chronic infections, chronic inflammatory diseases and tumors may also cause Budd-Chiari syndrome[7,8].

Eculizumab, a humanized monoclonal antibody that blocks activation of terminal complement C5 components is currently used in the treatment of PNH patients. Treatment with eculizumab reduces transfusion requirements, ameliorates anemia and markedly improves quality of life by resolving the constitutional symptoms associated with chronic intravascular hemolysis[9,10]. Thrombosis in PNH frequently follows episodes of acute hemolysis suggesting that inadequate complement inhibition or hemolysis

might be an important underlying factor contributing to the thrombophilia seen in these patients. Recent results from the International Trial using eculizumab demonstrated that inhibition of complement activation and intravascular hemolysis effectively reduces thrombosis in these patients. Considering that thrombosis has been demonstrated to cause the majority of deaths in PNH, it is reasonable to expect that eculizumab treatment may increase the life expectancy, by decreasing the risk of thrombosis[11].

Aim of this study is the presentation of eculizumab treatment in a patient with classical PNH and Budd-Chiari syndrome.

Description of case

A 30-year-old male was admitted to the hospital for diffuse abdominal and lumbar pain. Clinical findings: pallor and hepatosplenomegaly. Laboratory findings included: WBC 7300/μl (Neutro 72%), Hb 9.8 g/dl, Ht 31.8%, MCV 82.4 fl, plt 146·10^3/μl, ESR 24 mm, CRP normal. Biochemistry findings were: elevated liver enzymes, AST: 57 IU/l, ALT: 48 IU/l, ALP: 160 IU/l, γ-GT: 91 U/l, high LDH levels (1587 IU/l, normal range 240-480 IU/l), billirubin total 1,6 mg/dl, billirubin direct 0,5 mg/dl, glucose, urea, creatinine, electrolytes normal, ferritin 27 ng/ml (normal range 10-291 ng/ml), direct Coombs negative, HBV, HCV, HIV negative, other virology tests negative. Imaging studies of the chest (X-ray and CT) were normal. Abdomen CT and upper abdomen MRI depicted entire liver enlargement, caudate lobe enlargement, splenomegaly with splenic infarcts and lack of visualization of hepatic veins in their junction with inferior vena cava. There was no thrombus in the portal vein, splenic and superior mesenteric vein. Ascites and dilatation of azygous vein was evident. MRA of inferior vena cava-hepatic veins revealed stenosis of the intrahepatic part of inferior vena cava and the proximal part of hepatic veins. Liver-spleen scintiscan also demonstrated caudate lobe enhancement, pathognomonic of the Budd-Chiari syndrome. The above findings were compatible with the diagnosis of a Budd-Chiari syndrome. Further thorough investigation for thrombophilia including levels of antithrombin, Protein C and Protein S, the Factor V Leiden mutation, and Prothrombin mutation G20210A, was negative. PCR-JAK2V617F for myeloproliferative neoplasms was negative, antiphospholipid antibodies (lupus anticoagulant, anticardiolipin antibodies and anti-beta2GPI), antinuclear antibodies, anti-dsDNA and anti-ENAs antibodies were negative, serum immunoglobulin levels were normal. Bone marrow aspirate biopsy showed: hypercellular marrow with erythroid hyperplasia. Echocardiographic study revealed good biventricular function, no valvulopathy, no evidence either of constrictive pericarditis or pulmonary hypertension, no depiction of right atrial myxoma. Coexistence of hemolytic anemia with a Budd-Chiari syndrome were taken into account for a possible PNH diagnosis. High sensitivity flow cytometry confirmed the PNH diagnosis[12], as four negative markers were identified, one on peripheral blood red cells CD59 21.8% and three on polymorphonuclears CD55 67.8%, CD59 67.9% and CD16 90%.

Antithrombotic therapy with LMWH was administered, followed by anticoagulation with acenocoumarol. The patient's clinical condition progressively deteriorated the months following PNH diagnosis. He developed worsening of anaemia, jaundice, fatigue and severe ascites. He underwent new MRI-MRA that depicted further increase in liver and caudate lobe size, stenosis of inferior vena cava and hepatic veins, dilated portal, splenic and mesenteric veins, splenomegaly and severe ascites (Figure 1). Signs of new thromboses were not found. The patient was confronted with supportive treatment and frequent large-volume paracentesis. Antithrombotic therapy was continued. Despite treatment, patient deteriorated due to refractory ascites and frequent hemolytic crises requiring symptomatic treatment with transfusions and corticosteroids. Finally, one and a half year after PNH diagnosis he underwent orthotopic liver pre-transplantation evaluation and placement of a TIPS (Transjugular Intrahepatic Portal-Systemic Shunt)[13]. At the same time, patient was vaccinated against meningococcal infection and two weeks later eculizumab was started by IV infusion, 600 mg every 7 days for the first 4 weeks, followed by 900 mg for the fifth dose, 7 days later and 900 mg every 14 days thereafter. He has already completed three years of treatment with eculizumab. This resulted in a dramatic reduction of hemolysis markers, as documented by a sharp drop in LDH levels and significant hemoglobin increase (Figure 2). He is independent from transfusions and corticosteroids. There is also a significant reduction in PNH symptoms, such as fatigue, resulting in a signifi-

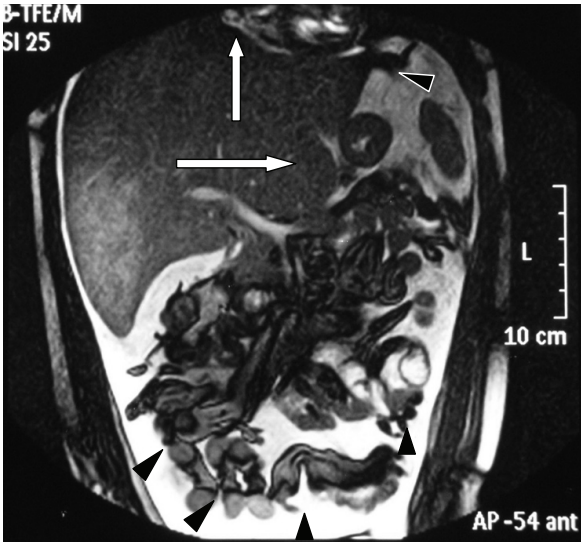

Figure 1: Magnetic Resonance Images acquired with T2-weighted sequences: hepatomegaly, caudate lobe enlargement (horizontal white arrow), lack of visualization of hepatic veins outflow (vertical white arrow), absence of thrombus within portal, splenic and mesenteric veins, splenomegaly and severe ascites (black arrowheads).

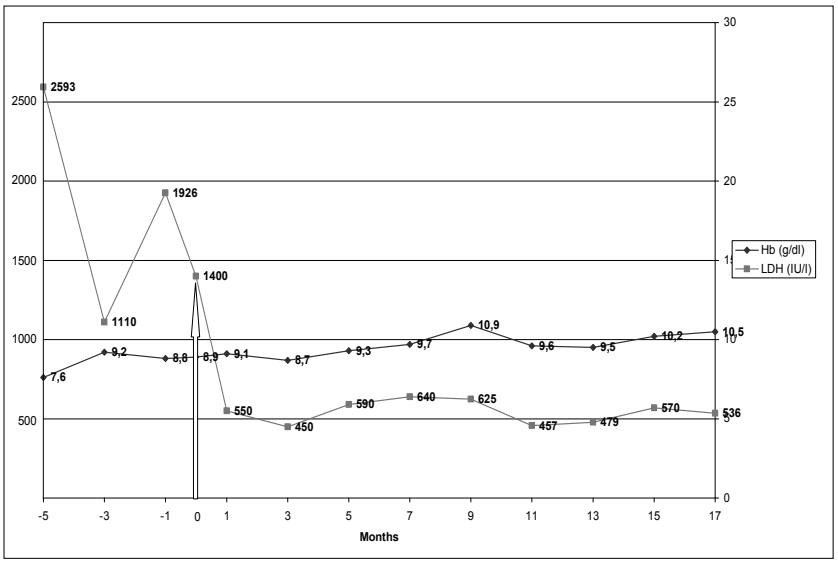

Figure 2. Mean levels of LDH and Hb before and during eculizumab treatment.
Time zero: first eculizumab administration.

cant improvement in his quality of life. His latest LDH is normal, Hb 12.5 g/dl, Ht 37.0%. His liver tests and renal function are within normal limits. Ultrasound Doppler scans of his TIPS performed every six months, persistently show it to be patent, without any evidence of thrombosis. MRI depicted absence of ascites.

Discussion

PNH is a rare, serious disease affecting an estimated 8,000 to 10,000 people in North America and Europe[1]. Median age of diagnosis is early 30's[2,14]. It is a chronic and life threatening disorder. Thrombosis is the leading cause of mortality in these patients. Median survival is 10-15 years following initial diagnosis[1,14].

Mechanism of thrombosis in PNH is not entirely understood. It is probably multifactorial. Hemolysis contributes to TE and TE events are temporally associated with increased hemolysis[15]. Intravascular hemolysis releases free plasma Hb, which scavenges nitric oxide. Nitric oxide depletion is associated with increased platelet aggregation, adhesion and accelerated clot formation[16]. Additionally, PNH platelets undergo exocytosis of the complement attack complex. Formation of microvesicles with phosphatidylserine externalization, is a potent in-vitro procoagulant. Prothrombotic microvesicles are detected in PNH blood[16]. Fibrinolysis is also perturbed and PNH blood cells lack the GPI-anchored urokinase receptor. Tissue factor pathway inhibitor (TFPI) requires a GPI-anchored co-receptor for trafficking to endothelial cell surface[17]. There is no correlation between inherited thrombophilia and thrombosis in PNH [18].

Age at presentation of the Budd-Chiari syndrome is usually the third or fourth decade of life. PNH is frequently affecting young individuals of the same age and thrombosis, which occurs in 40% of them with haemolytic disease[1,4] shows a predilection for the intra-abdominal veins, especially the hepatic, suggesting that the majority of patients in whom the aetiology of the Budd-Chiari syndrome is not apparent, may have an undiagnosed PNH. It is likely that many PNH cases still remain undiagnosed worldwide. Patients with Budd-Chiari syndrome in whom after thorough clinical and laboratory investigation no other etiological factor is identified, should be tested for PNH with high sensitivity flow cytometry, as well.

Allogeneic hematopoietic stem cell transplantation (HSCT) was considered as a potentially curable treatment option in our patient. At the same time, eculizumab had received marketing approval from the U.S. Food and Drug Administration (FDA) for PNH, so we could have access to this therapy. Eculizumab has proven to be a safe and effective therapy for PNH in three multi-national clinical studies, TRIUMPH, a placebo-controlled, 26 weeks, Phase 3 study, involving 87 PNH patients[10], SHEPHERD, an open-label 52 week Phase 3 trial involving 97 PNH patients[19] and E05-001, a long term extension study[11].

The standard of care after venous thrombosis in PNH has been life-long full anticoagulation. Thrombolysis should be considered in a PNH patient who develops Budd-Chiari syndrome acutely[20]. However, anticoagulation is only partially effective in preventing thrombosis in PNH. Pathophysiology of thrombosis in PNH is complement related. Therefore, anti-complement therapy with eculizumab should prevent the occurrence of thrombosis[11]. Nowdays, thrombosis is an absolute indication for initiating treatment with eculizumab. Our patient has already completed a period of three years on eculizumab. TIPS is the method of choice in most patients with Budd-Chiari syndrome with fewer complications than surgical shunt, may serve as a bridge to liver transplantation, but shunt thrombosis occurs in the long term[13]. In our patient TIPS is functioning perfectly, probably due to targeted anti-complement therapy. A controversial issue is whether PNH patients on eculizumab, with a prior thrombus, need to remain on anticoagulation. As data are insufficient to make strong recommendations[21], we continue anticoagu-

lation. Recent Phase III studies of eculizumab in PNH patients demonstrate that eculizumab markedly reduces the thrombosis risk, regardless of whether or not patients are receiving anticoagulation [11,19,22]. Thus, a question of major clinical importance is whether lifelong anticoagulation is necessary for PNH patients, who are well controlled on eculizumab therapy. It may be safe to withdraw anticoagulation in PNH patients on eculizumab[23]. However, more experience and longer follow-up is necessary before recommending withdrawal of anticoagulation in all PNH patients.

Conclusively, classical PNH patients with thrombosis and severe intravascular hemolysis are particularly challenging to manage. For these patients, eculizumab is a reasonable therapeutic option, expecting that by decreasing the risk for thrombosis, life expectancy may be increased.

Conflicts of interest

Authors declare no conflict of interest.

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