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Case report

Two cases of paroxysmal nocturnal hemoglobinuria: clinical observations and treatment approaches

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ABSTRACT

Paroxysmal nocturnal hemoglobinuria (PNH) is a rare disorder associated with an acquired clonal defect of the hematopoietic stem cell. Abnormal expression of complement inhibitors results in hemolysis and thromboembolic complications. Here we present two pediatric cases of PNH. The first patient died due to progressive and nonspecific thromboembolic complications, particularly affecting the abdominal organs and vessels. Allogeneic bone marrow transplantation from a related donor, liver transplantation, and complement inhibitor therapy were not feasible. In the second patient, treatment with hematopoietic stem cell transplantation from an unrelated donor was successful, although complicated by episodes of graft-versus-host disease (GvHD) and recurrent viral infections. Considering the specific nature of PNH, early diagnosis and careful management of complications during treatment remain essential aspects.

KEYWORDS

paroxysmal nocturnal hemoglobinuria, hemolysis, bone marrow transplant, GvHD

INTRODUCTION

Paroxysmal nocturnal hemoglobinuria (PNH, also known as the Marchiafava-Micheli syndrome) is a rare, acquired disorder characterized by a non-malignant clonal expansion originating from an abnormal hematopoietic stem cell. The defect is most associated with a somatic mutation in the PIGA gene (phosphatidylinositol glycan class A) located on the short arm of the X chromosome. This gene encodes an enzyme responsible for the initial step in the biosynthesis of glycosylphosphatidylinositol (GPI) anchors. As a result, the synthesis of GPI-anchored membrane proteins is impaired, leading to a decreased or absent expression of complement regulatory proteins – primarily CD59 and CD55 – on the surface of myeloid lineage cells [1,2,3]. Uncontrolled complement activation causes intravascular (predominantly) and extravascular hemolysis [2]. Three clinical forms of PNH are recognized [1,2,4,5]. The disease occurs with equal frequency in males and females, most commonly around the age of 30 years [1,6]. In children, the classical form of PNH is very rare. Based on its pathophysiology, PNH is characterized by a classic triad of symptoms: hemolysis, thrombosis, and pancytopenia [7,8]. Hemolysis may lead to severe anemia, hyperbilirubinemia, and hemoglobinuria. Organ-related complications include chronic kidney disease and pulmonary hypertension. Additional symptoms may include fatigue, headache, abdominal pain, dysphagia, and exertional dyspnea [1,2,4,6]. The gold standard for the diagnosis and monitoring of PNH is flow cytometry [4]. The choice of therapeutic strategy depends on the clinical form of the disease and the severity of hemolysis [1,4,5]. Two particularly effective

approaches are currently recognized: complement inhibition therapy (targeting primarily complement component C5) and allogeneic hematopoietic stem cell transplantation (allo-HSCT) [4,5]. In this rare case report we highlight the possible consequences of delayed diagnosis and compare pre-complement inhibitor era management to currently available treatment options.

CASE REPORTS

Patient 1

A 12-year-old patient was admitted to the Department of Pediatric Hematology and Oncology in Zabrze in June 2008, secondary to overweight, body mass index = 23.2, delayed puberty and a drop in platelet count to 95 G/L. In April 2009, he was hospitalized due to abdominal pain. Laboratory tests revealed elevated transaminase levels (AST: 548 U/L, ALT: 262 U/L) without accompanying cholestasis, anemia (Hb: 8.6 g/dL) and thrombocytopenia (PLT: 59 G/L). Hepatitis B virus and hepatitis C virus infections, as well as autoimmune hepatitis were excluded, whereas Epstein-Barr virus (EBV) infection was confirmed. An abdominal ultrasound revealed fluid beneath the liver capsule (up to 7 mm). In January 2010, he was readmitted due to ascites with dilatation of the subcutaneous venous network of the trunk. A physical examination also revealed peripheral oedema and ulcers on the lower limbs. The patient was transferred to the Department of Gastroenterology “Children’s Memorial Health Institute” in Warsaw with suspected Budd-Chiari syndrome. Treatment with enoxaparin and alteplase was initiated, with subsequent improvement in the patient’s clinical condition. There was a reduction in oedema of the lower limbs, recanalization of the inferior vena cava and hepatic veins and ascites. Flow cytometry revealed a 97% subpopulation of granulocytes with complete absence of CD66b protein, a 76% subpopulation with complete absence of CD59 protein, and a very small subpopulation of erythrocytes with complete absence of expression of complement inhibitors CD55 (DAF) and CD59 (MIRL). The diagnosis of PNH was confirmed. Ongoing treatment with acenocumarol was initiated. The patient was readmitted to the hospital in April 2010 due to deterioration in his condition and thrombocytopenia. A physical examination revealed yellowing of the skin, post-inflammatory brown discoloration associated with healed lower-limb ulcers, dilated vascular network on the chest, petechiae and a palpable liver 10 cm below the right costal margin. Abdominal Doppler ultrasound confirmed hepatomegaly with no flow in the hepatic veins. Gastroscopy revealed oesophageal varices grade I/II. Prednisone was initiated at a dose of 1 mg/kg. The patient was initially considered for allogenic bone marrow transplantation from a family donor but was deferred because of liver failure risk. In September 2011, abdominal ultrasound showed signs of liver cirrhosis with regenerative nodules. Doppler ultrasound revealed hepatic vein thrombosis and

portal vein thrombosis. Pulmonary embolism and increasing ascites developed. Liver transplantation was deemed necessary. The patient underwent transplant qualification tests and oesophageal variceal banding was carried out. Laboratory tests revealed persistent anemia (Hb within 8 g/dL) and thrombocytopenia above 60 G/L, biochemical signs of liver failure, and high D-dimer levels. Anticoagulant therapy was modified: acenocumarol was replaced with low-molecular-weight heparin. In May 2013, the patient was readmitted urgently due to fever, diarrhoea, nosebleeds and low back pain requiring constant morphine therapy. Despite broad-spectrum antibiotics and antifungal treatment, increasing inflammatory parameters CRP (238.57 mg/L) were observed. Anticoagulant therapy and symptomatic treatment for the increasing ascites were intensified. The patient's clinical condition rapidly deteriorated, with increasing pain and hematemesis. He was transferred to the intensive care unit, where he died within 24 hours of cardiac arrest in the form of asystole. The clinical timeline of patient 1 is presented in Table I, and the patient's outcomes are summarized in Table II.

Table I. Clinical timeline of patient 1

Phase/Time	Presenting symptoms	Diagnostic procedures	Major complications	Therapeutic interventions	Outcomes
June 2008 – April 2009 (Age: 12–13)	thrombo-cytopenia, abdominal pain, anemia, elevated liver enzymes	complete blood count, liver function tests, viral and autoimmune hepatitis work-up, abdominal ultrasound	hematologic abnormalities, EBV infection	supportive treatment	persistent cytopenias with progressive disease
January 2010 (Age: 14)	ascites, abdominal wall collateral veins, peripheral oedema, lower limb ulcers	Doppler imaging, flow cytometry	Budd-Chiari syndrome	enoxaparin, alteplase, acenocoumarol	recanalization of hepatic veins and inferior vena cava with temporary clinical improvement, PNH diagnosis confirmed
April 2010 – September 2011 (Age: 14–15)	jaundice, hepatomegaly, portal hypertension	Doppler ultrasound, upper gastrointestinal endoscopy, abdominal ultrasound	persistent hepatic vein thrombosis, esophageal varices, liver cirrhosis, portal vein thrombosis	anticoagulation, prednisone, evaluation for allogeneic HSCT	HSCT ultimately abandoned because of advanced liver disease
March – May 2013 (Age: 17)	progressive ascites	liver transplantation work-up, laboratory	pulmonary embolism, progressive liver failure, portal hypertension	endoscopic variceal band ligation, low-molecular-weight heparin	qualified for liver transplantation

Table I. Clinical timeline of patient 1

		investigations, endoscopy			
May – July 2013 (Age: 17)	fever, diarrhea, severe back pain, epistaxis, worsening ascites	elevated inflammatory markers and D-dimers	progressive multiorgan deterioration	broad-spectrum antibiotics, antifungal therapy, intensified anticoagulation, analgesic	progressive clinical deterioration despite intensive therapy
25 July 2013 (Age: 17)	severe pain and hematemesis	intensive care assessment	terminal circulatory collapse (asystole)	intensive care support	death within 24 hours after ICU admission

Table II. Outcomes of patient 1

Age: 12 years old
Hematological status: active PNH, active hemolysis
Hemoglobin: drops to 8 g/dL
Platelets: 59 × 10^3/μL
LDH / Bilirubin: no data
AST / ALT: 262 / 548 U/L
Flow cytometry findings: PNH present a very small subpopulation of erythrocytes with complete absence of expression of complement inhibitors CD55 and CD5

Patient 2

A 10-year-old boy was hospitalized in October 2008 due to dark brown urine following treatment of a throat infection with amoxicillin. At that time, the patient was in good general condition, afebrile and without abnormalities on physical examination. Based on a positive Ham test, PNH was suspected, and the child was referred to the Department of Pediatric Hematology and Oncology in Zabrze for further diagnostic evaluation and treatment. Laboratory findings indicated hemolytic anemia. Autoimmune anemia and membranopathies were excluded, and borderline glucose-6-phosphate dehydrogenase (G6PD) activity was found. The bone marrow aspirate demonstrated an activated erythroblast lineage. Flow cytometry revealed 26% of red blood cells lacking CD55 and CD59 expression, 85% of granulocytes lacking CD16 and CD24 expression, and 81% of monocytes lacking CD14 expression. The diagnosis of PNH was established. Treatment with acenocumarol was initiated. The boy's condition remained stable. However, during infections, an

increase in hemolysis was observed, corticosteroids were used periodically, and the patient required red blood cell transfusions due to decreases in hemoglobin levels (Hb: 7.2 g/dL). In February 2011, the child underwent hematopoietic stem cell transplantation from an unrelated donor. Initially, post-transplant bone marrow reconstitution was normal, with marked stimulation of the myeloid lineage. On day 67 after transplantation, cutaneous changes characteristic of graft-versus-host disease (GvHD) were observed, presenting as a maculopapular rash involving the trunk and upper limbs. On day 71, diarrhoea and vomiting occurred, accompanied by severe general deterioration and markedly elevated inflammatory parameters. Stool PCR testing confirmed cytomegalovirus (CMV), and ganciclovir therapy was administered with good effect. In the following weeks, arterial hypertension and diabetes mellitus were diagnosed. In June 2011, exacerbation of cutaneous and intestinal GvHD occurred during CMV reactivation. Symptoms of upper respiratory tract infection developed, and *Aspergillus* sp. was cultured from sputum. Chest CT revealed nodular lesions in the left lung, and voriconazole therapy was administered, resulting in improvement. Subsequent hospitalizations were due to exacerbations of hemorrhagic diathesis, cutaneous rash, and gastrointestinal disturbances associated with recurrent CMV and EBV reactivations. Because of back pain, imaging studies were performed. Spinal CT revealed a compression fracture at Th7 and decreased bone mineralization. In subsequent examinations, a compression fracture of L2 was observed, along with anterior column height reduction of Th9 and Th10 vertebral bodies, and decreased height of Th2 and Th6 vertebral bodies. In June 2013, due to knee pain, magnetic resonance imaging of the knee joint was performed, revealing features of osteochondral necrosis of the femoral condyles with segmental marginal sclerosis. Throughout the course of treatment, immunosuppressive therapy was adjusted, and antiviral and antibacterial treatment and prophylaxis were applied. From June 2014 onward, the patient's condition remained stable. Orthopedic abnormalities and overweight remained ongoing issues. According to information obtained from the patient in 2022, he is ambulatory and hematologic remission of the underlying disease has been maintained. The clinical timeline of patient 2 is presented in Table III, and the patient's outcomes are summarized in Table IV.

Table III. Clinical timeline of patient 2 (pre- vs. post-transplantation)

Phase/Time	Presenting Symptoms	Diagnostic Procedures	Major Complications	Therapeutic Interventions	Outcomes
before allo-HSCT					
2008–2011 (Age: 10–12)	dark brown urine, active hemolysis	flow cytometry, Ham test, bone marrow biopsy	severe hemolytic crises	acenocoumarol, corticosteroids, packed red blood cells transfusions	transfusion dependency, unstable baseline status

2011 (Baseline) (Age: 12)	bone marrow failure	pre-transplant screen	severe pancytopenia	pre-transplant conditioning	prepared for transplant
after allo-HSCT					
2011–2014 (Age: 12–15)	cutaneous and gastrointestinal issues, severe back/knee pain	spinal and chest CT, knee MRI, sputum/stool PCR	acute GvHD, CMV/EBV reactivations, *Aspergillus* infection, vertebral fractures	allo-HSCT performed, immuno-suppression, ganciclovir, voriconazole, hypertension, diabetes	PNH clone eradicated, infections controlled, permanent orthopedic defect
2022 (Age: 24)	asymptomatic, chronic bone pain	flow cytometry, chimerism analysis	overweight / obesity, stable orthopedic issues	orthopedic and hematologic monitoring	complete remission, cured of PNH, transfusion independent

Table IV. Outcomes of patient 2

pre-transplantation (baseline)
Age: 10–12 years old
Hematological status: active PNH, active hemolysis
Hemoglobin: drops to 7.2 g/dL
Platelets: 115 × 10^3/µL
LDH / Bilirubin: no data
AST / ALT: no data
Transfusion requirement: multiple packed red blood cells transfusions (during infections)
Flow cytometry findings: PNH present; 26% of non-flagellated erythrocytes do not express CD55 and CD59 antigens
post-transplantation (follow-up / 2022)
Age: 13–16 years (complications) / 24 years old (2022)
Hematological status: stable hematological remission (PNH eradicated)
Hemoglobin: ~10 g/dL (current [2022]: no data)
Platelets: 204 × 10^3/µL
LDH / Bilirubin: 183 µmol/l / 22 U/L
AST / ALT: ~40 U/L / ~60 U/L
Transfusion requirement: multiple packed red blood cells transfusions (during infections)
Flow cytometry findings: no data

Discussion

PNH is a rare disease, particularly in children. The global prevalence of PNH is estimated at 10–20 cases/million, while the incidence is 1–1.5 cases/million. Diagnosis of PNH in pediatric patients is complicated. The delay in diagnosing PNH in patient 1 was due to the nonspecific clinical picture in

the early stage of the disease, which included thrombocytopenia, delayed puberty, and the absence of typical hemolysis. This could have suggested other hematologic causes, such as idiopathic immune thrombocytopenia or bone marrow aplasia, as well as endocrine disorders, such as constitutional delay of puberty or hypothyroidism. Additionally, the lack of intravascular hemolysis limited the suspicion of a clonal hematologic disease. Furthermore, coexisting EBV infection explained the cytopenias and elevated transaminases, masking the underlying disease. Ge et al. [9] found out, after conducting a retrospective analysis on 55 pediatric cases diagnosed with PNH in China, that thrombotic events were not observed in their patients. This observation may indicate possible population-related differences in clinical presentation; however larger studies are needed to confirm this hypothesis. The Ham test, used in the first diagnosis of patient 2, is currently not recommended due to its low sensitivity, specificity, and lack of prognostic significance. According to the recommendations of the Polish Pediatric Hematopoietic Cell Transplantation Group, testing for the presence of a PNH clone using flow cytometry (lack of CD55 [DAF] and CD59 [MIRL] expression in erythrocytes) should be performed in every child diagnosed with bone marrow aplasia, myelodysplasia, thrombosis, and hemolytic anemia with negative Coombs' tests [10]. Allo-HSCT is the only therapy with a possible cure. Indications for hematopoietic cell transplantation in children and adolescents with PNH are determined by conventional treatment results, and the procedure is justified only if it significantly increases the patient's chance of recovery. The preferred donor is the sibling of the patient. In patient 1, the risk of liver failure precluded the procedure. The most serious complication is GvHD. The disease is defined as acute when it occurs within the first 100 days. In patient 2 the first symptoms were visible on day 67 as characteristic skin lesions. In a study conducted by Kamranzadeh Fumani et al. [11], among 13 PNH patients who underwent transplantation, three developed GvHD, and the 5-year survival rate for the entire study group was 74.07%. Yılmaz et al. [12] analyzed sixteen patients with classic PNH and nineteen with PNH-AA (PNH associated with aplastic anemia) who received allo-HSCT and calculated a 2-year overall survival rate and GvHD-free survival rate of 81.2% and 78.1%, respectively. Six patients developed GvHD. In a study conducted by Markiewicz et al. [13] the incidence of acute GvHD grade II–IV was 23% and was lower in patients with classic PNH. No similar studies, including only a pediatric group, were found. The available data indicates the importance of an individualized clinical approach when deciding on transplantation, with clear benefits in patients with devastating and refractory hemolysis and bone marrow failure [14]. On this basis, we conclude that patient 2 would not be referred for a bone marrow transplant, because his health condition did not meet current standards and targeted therapies would be the preferred treatment method. Other treatment options previously used included anticoagulants

such as enoxaparin/acenocumarol, steroids and blood transfusions. These drugs are responsible for improving the symptoms of the disease, the most dangerous is thrombosis, which is the main cause of mortality. This is clearly illustrated by patient 1, who developed hepatic and portal vein thrombosis accompanied by pulmonary embolism and progressive ascites. The complexity of thromboembolic complications and their impact on mortality are characterized by high frequency occurrence, even in patients with small PNH clones, with low levels of hemolysis, and potential to develop in virtually any localization, in both arterial and venous vessels. Hemolysis releases free hemoglobin and its degradation product – heme, both endothelial-toxic and proinflammatory. Free hemoglobin induces endothelial activation/dysfunction with upregulation of procoagulant pathways. When scavenger proteins are saturated, nitric oxide (NO) is irreversibly bound with oxidized hemoglobin (methemoglobin formation), while hemolysis-derived arginase reduces arginine availability, limiting endothelial NO resynthesis. The resulting NO depletion promotes increased vascular smooth muscle tone, vasoconstriction effect, and endothelial proliferation. In addition to the presence of free hemoglobin, NO deficiency also contributes to enhanced platelet adhesion and aggregation. Moreover, complement dysregulation further drives inflammation via C5a release. Key cytokines (IL-6, IL-8, TNF-α) activate endothelium, monocytes, and granulocytes, inducing neutrophil extracellular traps, tissue factor expression, and plasminogen activator inhibitor upregulation [1,8]. The consequent thrombin generation establishes a 'vicious circle' effect, as thrombin can cleave C3 and C5 independently of convertases, activating complement and intensifying thromboembolic complications. Therefore, complement-targeted therapy is important to reduce mortality and can now be managed with eculizumab [1,15]. This first-line drug works by binding to the C5 protein and preventing breakdown into C5a and C5b. It has been proven to reduce LDH, increase hemoglobin levels, reduce the frequency of blood transfusions and intravascular hemolysis. This medication wasn't reimbursed during the treatment of both patients. It was reimbursed in Poland in 2018, although it was approved for treatment of PNH in 2007. In the pre-compliment era PNH was associated with high mortality. Terriou et al. [16] demonstrated that treatment with eculizumab significantly loweres risk of death compared to periods when complement inhibitors were not used. We hypothesize that, had patient 1 received this treatment, his chances of survival and prognosis might have improved. In comparison, patient 2 experienced excessive bone mass loss and vertebral body fractures that occurred probably because of high dose steroids which lead to reduced bone formation and increased bone resorption. The introduction of eculizumab allowed for the reduction or complete discontinuation of steroid therapy in most cases, which improved long-term results in terms of growth and bone density. Moreover, Cooper et al. [17] showed that eculizumab given before transplant was associated with

minimal GvHD. This suggests that prior inhibition of complement activation may reduce the risk of posttransplant alloimmunization. In our case, the lack of access to C5 inhibitor therapy may have been a factor contributing to the development of GvHD, although this relationship requires further study. In the recent years more drugs for PNH have been developed. Ravulizumab, approved by the EMA (European Medicines Agency) in 2019, is an IgG2/4K monoclonal antibody that specifically binds to the C5 protein of the complement system, but has a significantly longer half-life compared to eculizumab. It is recommended for the treatment of PNH in adults and children over 10 kg [6,18,19]. Chonat et al. [19] conducted a study on the efficacy of this drug in children. Although ravulizumab did not demonstrate superior efficacy compared to eculizumab, its improved pharmacokinetic profile translates into fewer hospital visits and a reduced treatment burden. Importantly, prior exposure to eculizumab did not negatively affect the efficacy or safety of ravulizumab. Patients who had not previously received eculizumab achieved clinical responses comparable to those of patients switching to ravulizumab, confirming its efficacy regardless of prior C5 inhibitor therapy. A further advance in the treatment of PNH was the development of danicopan. This oral complement factor D inhibitor is used as an adjunct to ravulizumab or eculizumab treatment. Its safety profile and efficacy in children are currently being evaluated in ongoing phase III clinical trials. Currently, the first reported cases of danicopan use in adolescent patients with PNH have been described, with promising results [20]. Pegcetacoplan is a cyclic peptide related to compstatin, which blocks C3 preventing the generation of C3b and subsequent C3b loading of the red blood cells [21]. The long-term safety profile is less established. In children there is a currently ongoing clinical trial using pegcetacoplan called PIONEER. Crovalimab is a humanized, anti-complement component C5 (anti-C5) recycling monoclonal antibody. It gained approval for adult and pediatric patients 12 years of age or older with a weight of 40 kg and above. It inhibits terminal complement activation and effectively controls intravascular hemolysis. Subcutaneous administration once every 4 weeks may improve patients' adherence and reduce treatment burden, which is particularly relevant in pediatric patients. Most common side effects include injection-site reactions, headache, pyrexia, and upper respiratory tract infections. In children, it has demonstrated effective control of intravascular hemolysis, significant reduction of LDH levels, reduced transfusion requirements and maintenance of stable hemoglobin levels during treatment [22].

CONCLUSIONS

This case report highlights the importance of early recognition and prompt diagnosis of PNH in pediatric patients. Timely identification allows for appropriate management and prevention of severe complications. Although hematopoetic stem cell transplantation remains the only curative

treatment, it carries a high risk of significant adverse events. Careful monitoring of presenting symptoms is essential, as pediatric PNH may differ in its clinical course and manifestations compared to adult cases. Continued awareness and individualized management are key to improving outcomes in this rare pediatric condition.

Authors' contribution

Study design – M. Kujawińska
Data collection – M. Kujawińska, M. Olek, M. Mielczarek, K. Osak, W. Matysiak
Manuscript preparation – M. Kujawińska, M. Olek, M. Mielczarek, K. Osak, W. Matysiak, T. Szczepański, A. Pobudejska-Pieniążek
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Final approval of the version to be published – M. Kujawińska, M. Olek, M. Mielczarek, K. Osak, W. Matysiak, T. Szczepański, A. Pobudejska-Pieniążek

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