CASE REPORT

Maintenance of renal function in a patient with a history of acute paroxysmal nocturnal hemoglobinuria-associated kidney injury

Francesca Re1,*, Ilenia Manfra1, Filomena Russo1, Caterina Plenteda1, Angelica Spolzino1, Elena Follini1, Maria Gullo1, Claudia Romano1, Maria Cristina Baroni2 and Franco Aversa1,3

1Haematology and Bone Marrow Transplant Unit, Parma General Hospital, 43123 Parma, Italy, 2Internal Medicine Unit, University of Parma, 43123 Parma, Italy, and 3Haematology and Bone Marrow Transplant Unit, University of Parma, 43123 Parma, Italy

*Correspondence address. Haematology and Bone Marrow Transplant Unit, Ospedale Maggiore di Parma, via Gramsci 14, 43123 Parma, Italy. Tel: +39-0521-703962; Fax: +39-0521-704820; E-mail: fRe@ao.pr.it

Abstract
Paroxysmal nocturnal hemoglobinuria (PNH) is a rare, life-threatening blood disorder characterized by intravascular hemolysis, thrombosis and bone marrow failure [1]. PNH arises from clonal expansion of hematopoietic stem cells with acquired somatic mutations in the X-linked PIG-A gene [2], producing a defect in glycosylphosphatidylinositol (GPI) anchor synthesis, leading to partial or complete absence of several specific GPI-linked proteins with complement-regulating activities, including CD59 (membrane attack complex inhibitory factor) and CD55 (decay accelerating factor) [3, 4]. Deficiency of these key complement-regulatory proteins in the RBC of patients with PNH renders them susceptible to terminal complement-mediated hemolysis.

Acute kidney injury (AKI) can be defined as a sudden decrease in kidney function that includes, while not being limited to, acute renal failure (ARF) [5]; cases of reversible ARF have been reported as a consequence of PNH [6, 7]. We report the case of a patient with PNH who developed AKI following an infection of undetermined diagnosis.

INTRODUCTION
Paroxysmal nocturnal hemoglobinuria (PNH) is a rare debilitating, life-threatening blood disorder characterized by intravascular hemolysis, thrombosis and bone marrow failure [1]. PNH arises from clonal expansion of hematopoietic stem cells with acquired somatic mutations in the X-linked PIG-A gene [2], producing a defect in glycosylphosphatidylinositol (GPI) anchor synthesis, leading to partial or complete absence of several specific GPI-linked proteins with complement-regulating activities, including CD59 (membrane attack complex inhibitory factor) and CD55 (decay accelerating factor) [3, 4]. Deficiency of these key complement-regulatory proteins in the RBC of patients with PNH renders them susceptible to terminal complement-mediated hemolysis.

Acute kidney injury (AKI) can be defined as a sudden decrease in kidney function that includes, while not being limited to, acute renal failure (ARF) [5]; cases of reversible ARF have been reported as a consequence of PNH [6, 7]. We report the case of a patient with PNH who developed AKI following an infection of undetermined diagnosis.
CASE REPORT

A 36-year-old African male was admitted in August, 2010 with high-grade fever and bloodstained urine of 7 days duration. He had a history of intermittent passage of dark-colored urine, which led to a diagnosis of PNH in 1999 in Senegal, Africa; pulmonary and mediastinal tuberculosis in 2001; and episodes of malaria. His symptoms included hyperpyrexia, vomiting and hematuria. He was febrile (38°C), with heart rate 110 bpm, BP 180/90 mmHg, oxygen saturation of 100%. Bilateral costovertebral angle tenderness was detected. Cardiac, pulmonary and abdominal examination was normal. As there were no details available of his original diagnosis of PNH, the patient was retested to rule out other causes of hemolysis.

Laboratory tests revealed estimated glomerular filtration rate <15 mL/min/1.73 m2, microcytic anemia with thalassemia trait (hemoglobin [Hb] 6.7 g/dL, mean corpuscular volume 73.7 femtolitre, ferritin 459 ng/mL, total iron binding capacity 222 μg/dL, serum iron 16 μg/dL), advanced azotemia (serum creatinine 16.2 g/dL, urea 210 mg/dL), hyperphosphatemia (6.8 mg/dL) and hyperuricemia (11 mg/dL). Although total bilirubin was normal, hemolysis was confirmed by high lactate dehydrogenase (LDH) levels (4233 U/L), high reticulocyte count (absolute number 99 290/mm3) and decreased haptoglobin value (17.9 mg/dL). White blood cell and platelet levels were 8150 and 252 000/mm3, respectively. Urinalysis showed pH 7, specific gravity 1008, trace proteinuria (21.2 mg/dL), microscopic hematuria (> 10 red blood cells [RBCs]/high-power field), without any casts and the presence of trace hemosiderin (0.60 mg/dL). Urine culture failed to show bacterial growth, despite leukocyte esterase of 125 C/uL and 50 white cells/high-power field.

Urinary tract ultrasound showed bilateral enlarged kidneys, with a pervasively hyperemic and thickened cortex; colored Doppler echography of the renal arteries and veins was normal. A peripheral blood smear showed fragmented RBCs, however, a diagnosis of thrombotic microangiopathy was ruled out by elimination. Indirect Coombs test was negative, while direct was slightly positive. Complement fractions C3 and C4 were normal and agglutinins were absent. G6PD level was normal. Malaria was ruled out as a cause of hemoglobinuria, given three negative blood samples; BK virus in urine was not detected. An in vitro indirect test for Mycobacterium tuberculosis based on measurement of a cell-mediated immune response to a peptide cocktail simulating mycobacterial proteins ESAT-6 and CFP-10 (Quantiferon-TB Gold Plus [QFT-Plus] test) suggested a probable diagnosis of tuberculosis. Chest X-rays and a high-resolution computed tomography scan were negative at the time of hospitalization and a repeat quantiferon test was negative. Kidney biopsy was not performed.

A diagnosis of PNH was confirmed by FLAER-based flow cytometry: the patient’s granulocytes were deficient in CD59, CD55 and CD16 with a clonality of 8% in the monocytic compartment and 8% in the myeloid compartment.

The patient was adequately hydrated with intravenous (IV) fluids and NaHCO3, and received a packed RBC transfusion. Levofloxacin and later prednisone were started empirically, aimed at controlling hemolysis. During hospitalization, renal function normalized without further intervention, serum creatinine level decreasing from 16.2 to 1.7 mg/dL. Hb gradually rose to 8.6 g/dL without further transfusions. LDH progressively decreased, to 1361 U/L, while haptoglobin level normalized. At discharge, after 15 days of hospitalization, the patient was asymptomatic, afebrile for 5 days, had a heart rate of 80 bpm, BP of 130/70, saturation of 100% while breathing ambient air. He continued regular follow-up and maintained normal renal parameters.

A low transfusional need was maintained from 2011 to 2012. However, from September 2013 due to recurrent episodes of hemolysis and hematuria (LDH progressively increasing to up to 2000 U/L; haptoglobin remained under normal value), Hb level decreased and required monthly RBC support. Given the high risk of thromboembolic events, a standard-dose eculizumab therapy was started in March 2015, consisting of eculizumab 600 mg via 25-45 min IV infusion every week for weeks 1-4, followed by 900 mg IV for the fifth dose 7 days later, then 900 mg IV every 14 days thereafter. The patient has been closely monitored during eculizumab therapy, and no thrombosis or other complications have so far occurred. LDH and Hb levels stabilized (>500 U/L and >15 g/dL, respectively) as well as the creatinine levels.

DISCUSSION

Patients with PNH are at higher risk of renal insufficiency, which is a common finding in patients with PNH [8]. Acute tubular necrosis is recognized as a complication of PNH-associated intravascular hemolysis [5, 7]. Kidney biopsies of PNH patients with AKI show common features of acute tubular necrosis, often against a background of moderate tubular atrophy with interstitial scarring and inflammation, with hemosiderin deposits in the proximal convoluted tubules [4]. These morphological findings suggest acute tubular injury superimposed on a chronic tubulointerstitial pathology. However, the exact mechanisms by which Hb promotes AKI are not fully known.

However, plasma haptoglobin, together with the haptoglobin-hemoglobin receptor CD163 (a Hb scavenger receptor), and the heme oxygenase-1 protein, is part of an important scavenging system normally responsible for the clearance and metabolism of free Hb, thereby counteracting the potentially harmful nitric oxide-scavenging effects of free Hb released during intravascular hemolysis, as well as eliciting an anti-inflammatory response [9]. In the presence of persistent intravascular hemolysis, plasma haptoglobin is consumed, leading to accumulation of free Hb as unbound dimers small enough to be filtered by the glomerulus and taken up by kidney tubular cells, leading to the accumulation of iron stored as hemosiderin, thought to be the mediator of proximal tubular cell injury, mostly through oxidative stress [3, 4].

Eculizumab (Soliris®) is a humanized monoclonal antibody that targets complement protein C5, thereby preventing production of the potent pro-inflammatory mediator C5a and the assembly of the terminal complement complex (membrane attack complex/MAC) during complement activation. Eculizumab is effective not only for the prevention of thromboembolism, the most common cause of mortality/morbidity in patients with PNH and chronic renal dysfunction, but also for reducing intravascular hemolysis, improving renal function and preventing end-organ damage [3, 10, 11]. Although these studies were in patients with chronic renal dysfunction, Ballarin et al. used eculizumab in a patient with ARF, resulting in a clear improvement in hematologic values, progressive resolution of discolored urine and rapid decline in serum creatinine over the following months. The patient’s ARF was shown to be associated with tubular hemosiderin deposits, local inflammation and oxidative stress, and CD163-positive macrophage-mediated activation of the anti-inflammatory response promoted improvement of renal
function and restoration of tissue integrity [7]. Additional evidence for the effects of eculizumab on renal function comes from a recently published retrospective real-world study of patients from the Spanish PNH Registry with a history of ARF or chronic renal failure (CRF) [8]. With the exception of one patient with sepsis, all patients with ARF (n = 22, 9 with ARF and CRF) treated with long-term eculizumab (mean: 3.5 ± 2.1 years) did not have new episodes of ARF. Two patients with CRF alone were treated with eculizumab without experiencing episodes of ARF. The authors concluded that clearance of iron from the kidney and inhibition of the production of anaphylatoxin C5a, together with decreased intravascular hemolysis and normalization of nitric oxide levels, was responsible for the improvement and maintenance of renal function with long-term sustained eculizumab treatment [8]. Their data support the beneficial effects of early eculizumab treatment in preventing the occurrence of ARF and reducing progression to CRF.

In conclusion, while early recognition of AKI and its immediate management with fluid administration and urine alkalization is crucial to reduce the risk of chronic kidney disease and end-stage disease, there is increasing evidence that treatment with eculizumab could substantially improve kidney function and reduce disease progression, by preventing the cascade of events that leads to recurrent and chronic intravascular hemolysis. In our patient with PNH-related AKI, eculizumab successfully improved hematologic values and renal function, and no thromboembolic events occurred.

CONFLICT OF INTEREST STATEMENT
The authors have no conflicts of interest to declare.

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ETHICAL APPROVAL
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CONSENT
Patient permission was obtained prior to writing this report.

GUARANTOR
Dr Francesca Re.

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