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CASE REPORT PEER REVIEWED | OPEN ACCESS

Paroxysmal nocturnal hemoglobinuria with sagittal vein thrombosis as the initial presentation

Shreyaska Dahal, Mazhar Soufi, Sayali Kulkarni, Jamshed Zuberi

ABSTRACT

Introduction: Paroxysmal nocturnal hemoglobinuria is a rare disease that presents with a variety of symptoms including hematuria, thrombosis, and other non-specific symptoms. Venous thrombosis is not uncommon in paroxysmal nocturnal hemoglobinuria (PNH). However, a thromboembolic event as the presenting symptom of PNH is rare and can be life-threatening, when affects the sagittal veins in the brain.

Case Report: A 28-year-old female presented to the facility with left-sided hemiparesis. Initial workup revealed a right-sided subacute hemorrhagic infarct of the parietal lobe, and magnetic resonance imaging (MRI) venography demonstrated extensive venous thrombosis involving the sagittal, straight, and transverse sinuses, with secondary edema in the involved hemisphere. Thrombotic events may affect up to 50% of PNH patients and account for at least one-third of mortality in PNH. Although disease presentation in PNH is variable, cerebral venous sinus thrombosis as the first thrombotic event in disease presentation along with the absence of hematuria makes this case unique. High suspicion of thrombosis and a differential diagnosis of PNH should be considered in young patients presenting with these symptoms, even in the absence of hematuria. Ravulizumab has significantly reduced thrombotic events, and these therapies should be immediately commenced upon high suspicion of thrombosis. Allogeneic hematopoietic stem cell transplantation offers the only curative approach for PNH to date.

Conclusion: Paroxysmal nocturnal hemoglobinuria is a very rare and life-threatening disease. Hematuria is not always present in this disease. Complement inhibitor therapy should be started immediately upon confirmation of the diagnosis to decrease future thrombotic events. Paroxysmal nocturnal hemoglobinuria patients may need allogeneic hematopoietic stem cell transplantation, which is the only curative approach available today.

Keywords: Cerebral venous sinus thrombosis, Eculizumab, Paroxysmal nocturnal hemoglobinuria

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INTRODUCTION

Paroxysmal nocturnal hemoglobinuria is a rare life-threatening disease of the blood with an incidence rate estimated to be around 1 in a million. The disease primarily affects younger adults and is characterized by hemolytic anemia, thrombosis, and impaired bone marrow function in the late stages. However, the disease may present with a variety of non-specific symptoms such as fatigue (80%), shortness of breath (64%), and renal insufficiency (62%).

There are three subtypes of PHN: the classical PNH, which has no bone marrow involvement, PNH

with primary bone marrow dysfunction (such as myelodysplastic syndrome and aplastic anemia), and subclinical PNH, in which patients have clones with no clinical or laboratory evidence of hemolysis or thrombosis [1]. In fact, bright red blood in the urine (hemoglobinuria), a classic symptom of PNH, is seen in only less than 50% of patients [1]. While hemoglobinuria may be an intermittent phenomenon, it is now evident that hemolysis is thought to be ongoing throughout the day and during night and is often accompanied by abdominal, as well as back pain [2].

Venous thrombosis is not uncommon in PNH, as coagulopathies arise from destruction of red blood cells (RBCs) and intravascular hemolysis. However, a thromboembolic event as the presenting symptom of PNH is rare and is estimated to occur in less than 5%, or an incidence rate of 1 in 20 million [3]. Throughout the course of the disease, thrombotic events may affect up to 50% of PNH patients and can significantly impact survival, accounting for at least one-third of mortality [4].

Here we present a rare case of PNH in a young female who had extensive venous thrombosis involving the draining system of the brain. Although the presentation is not unique to the disease due to the hypercoagulability known to these patients, the rarity of cerebral vascular sinus thrombosis in the absence of hematuria (1 in 2 million), as well as the challenging location of the first thrombotic event, made this case unique and worth reporting.

CASE REPORT

A 28-year-old female, with a past medical history of hyperlipidemia and a hemorrhagic stroke in 2019, presented to our facility with left-sided hemiparesis. Her initial workup included a computed tomography (CT) scan of the brain, which revealed a right-sided subacute hemorrhagic infarct of the parietal lobe. Subsequently, MRI venography demonstrated extensive venous thrombosis involving the sagittal, straight, and transverse sinuses, with secondary edema in the involved hemisphere (Figures 1 and 2). She was started on a heparin drip with therapeutic goals and was admitted to the neurologic intensive care unit (ICU) for close monitoring. Her initial diagnostic workup included flow cytometry, which detected the absence of CD55 and CD59 confirming the diagnosis. During her second day of ICU stay, an acute change in mental and functional status prompted a repeat head and neck computer tomography with angiography (CTA), which demonstrated evidence of left internal jugular vein thrombosis with minimal hemorrhagic conversion. Two hours after the event, the patient regained motor function with residual subjective weakness mainly impacting the left upper extremity. She remained in the ICU for one week, during which repeat head CT showed no additional changes, and the patient was monitored until her treatment with Ravulizumab commenced and appropriate prophylactic vaccinations were administered. The patient never experienced hematuria.

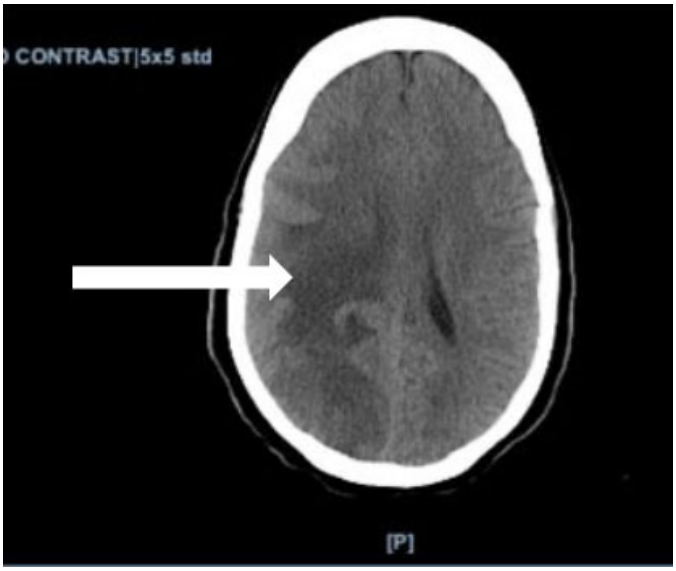

Figure 1: CT without contrast showing right-sided subacute hemorrhagic infarct of the parietal lobe.

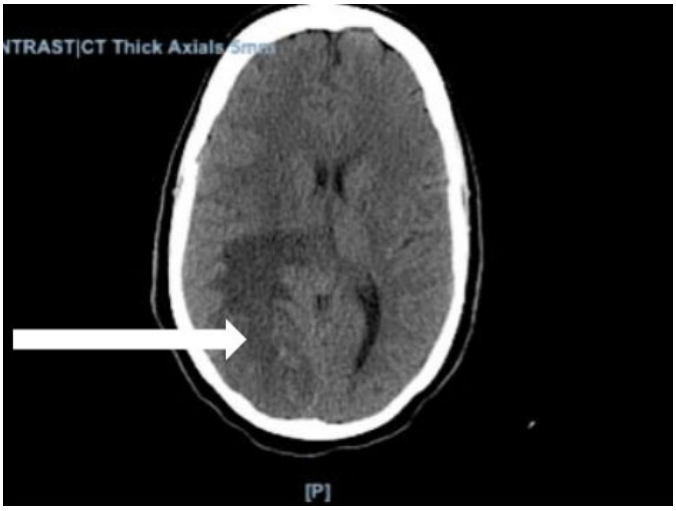

Figure 2: CT without contrast showing right-sided subacute hemorrhagic infarct of the parietal lobe with slight midline shift.

DISCUSSION

The mechanism in which PNH results in a hypercoagulable state remains unclear [5], however, pathophysiology is thought to originate from a deficiency in complement regulators on platelets surface, along with the increased tendency of these regulators to activate and aggregate, which leads to increased clot formation and thromboembolism in these patients. Paroxysmal nocturnal hemoglobinuria is an acquired genetic defect

in the PIGA gene [2]. In PNH, mutation of a single stem cell in the bone marrow clones itself. This stem cell has diminished expression of complement proteins CD55 and CD59, glycosylphosphatidylinositol-anchored surface proteins, that inhibit the formation of C3 convertases and prevent polymerization of the membrane attack complex (MAC), which is the terminal complex in the complement cascade. In turn, this leads to uncontrolled MAC assembly resulting in intravascular hemolysis and destruction of leukocytes [6].

An average of 36% patients experiences at least one thromboembolic event during the disease process, with the most common sites being hepatic, mesenteric, portal, splenic, and inferior vena cava (IVC) thrombosis. In 19% of patients' visceral thrombosis occur before the diagnosis of PNH is established, and it accounts for 40–67% of deaths from the disease. For the remaining patients, thrombosis occurs within five years after diagnosis and is associated with poor survival especially if it embolizes to the brain or liver. Although thrombosis occurs in only 16% of PNH cases, it is the most common cause of mortality as patients with thrombosis only have a 40% survival rate at four years [7].

The hepatic vein is a common site for thrombosis (7.5–25% of patients) leading to Budd-Chiari syndrome, hepatic failure, and eventual mortality. The sagittal vein of the brain is another common site, although any vein can be affected. Multiple sites are involved in more than one-fifth of cases [1, 4]. The most frequent neurologic complication is superior sagittal vein thrombosis which results in death in more than one-third of cases with a large tendency for hemorrhagic conversion. Thromboses in the lateral, cavernous, sigmoid, and sagittal sinuses will result in severe headaches, vomiting, seizures, altered mental status, and/or papilledema. It can also cause cranial nerve palsies (6, 7 specifically), central retinal vein thrombosis, and even cerebellar or lower cranial nerve signs if there is sigmoid sinus thrombosis [7].

Cerebral venous sinus thrombosis (CVST) occurs when a blood clot forms in the brain's venous sinuses [8]. The obstruction of the venous system by the thrombus results in buildup of pressure leading to secondary brain edema (Figure 1) and in some cases even hemorrhagic conversion. Cerebral venous sinus thrombosis is a rare form of stroke which has an annual incidence rate of around five in a million [8]. Risk factors for CVST include hypercoagulable states such as pregnancy, the use of oral contraceptive pills (OCPs), antithrombin III deficiency, lupus anticoagulant, factor V Leiden mutation, or any malignancy, among others including PNH [8] as was the case for our patient.

Historically, the management of PNH was mostly supportive, however, the development of complement inhibitors like Eculizumab and Ravulizumab has decreased the risk of thrombotic effects, as well as adverse vascular complications. Eculizumab and Ravulizumab are monoclonal antibodies that inhibit the MAC assembly decreasing hemolysis. Before Eculizumab was made available, PNH patients had a median survival of between 10 and 22 years, with thrombosis accounting for 22–67% of deaths. An average of 30% patients had at least one thrombosis [3]. Pooled data from three original clinical trials have concluded that the use of Eculizumab had a risk reduction of thrombotic events estimated at around seven-fold; and these estimates were sustained on long-term follow-up with an ongoing relative risk reduction of thrombotic events estimated at around 82% [3]. However, in times of breakthrough hemolysis triggered by an infection, retrospective trials still show that patients are at a risk of thrombosis even if they are receiving Eculizumab [3].

Ravulizumab is another drug developed and approved by the FDA in 2018. It has 3–4 times longer half-life, requires dosing every eight weeks, is more cost-effective, and has fewer breakthrough hemolysis episodes. In countries where Eculizumab is not available, patients should be treated with long-term therapeutic anticoagulation. Finally, due to the inhibitory effect of these agents on complement cascade, meningococcal vaccination is highly recommended before the start of therapy.

Currently, allogeneic hematopoietic stem cell transplantation offers the only curative approach for PNH. Although alternative strategies like cell therapy and gene therapy are available, these experimental efforts have not been able to deliver promising results. There are also many novel-therapy developmental projects focused on inhibiting targets upstream in the complement pathway, but all are still in preliminary stages and will not likely be available soon.

CONCLUSION

Paroxysmal nocturnal hemoglobinuria is a very rare and life-threatening disease. Unlike what the name implies, hematuria is not always present. High index of suspicion should be sought in young adults with thrombosis in an unusual location as was the case for our patient. Complement inhibitor therapy should be started immediately upon confirmation of the diagnosis to decrease future thrombotic events. Although no consensus exists for primary prophylaxis to manage thromboses, due to their unpredictable nature it is important to initiate therapy especially in the group of patients who have high recurrence rates, including clones of more than 50%, or increased genetic risk for thrombosis. Controversy surrounds lifelong anticoagulation for secondary prophylaxis. However, individual patient risk factors, as well as specific PNH symptoms such as anemia should be considered when determining the need for anticoagulation therapy, as well as the therapeutic ranges of therapy, which all add challenges to the management of PNH. When Eculizumab treatment is initiated, frequent dosing

requirements and breakthrough hemolysis can result in poor quality of life, therefore, dosing and symptomatic monitoring should be followed throughout the course of the disease. Eventually, PNH patients may need allogeneic hematopoietic stem cell transplantation, which is the only curative approach available today.

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Author Contributions

Shreyaska Dahal – Conception of the work, Design of the work, Drafting the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Mazhar Soufi – Conception of the work, Design of the work, Drafting the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Sayali Kulkarni – Conception of the work, Design of the work, Drafting the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Jamshed Zuberi – Conception of the work, Design of the work, Drafting the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Guarantor of Submission

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Written informed consent was obtained from the patient for publication of this article.

Conflict of Interest

Authors declare no conflict of interest.

Data Availability

All relevant data are within the paper and its Supporting Information files.

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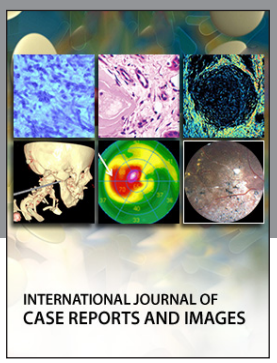

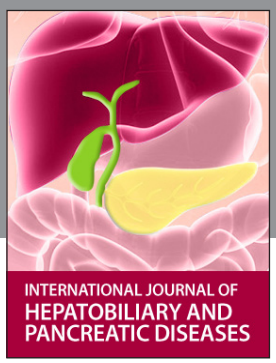

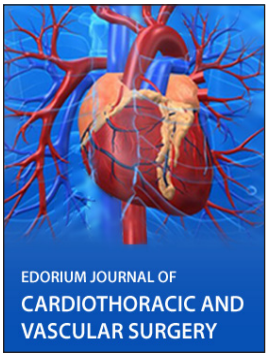

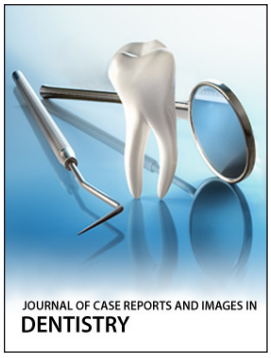

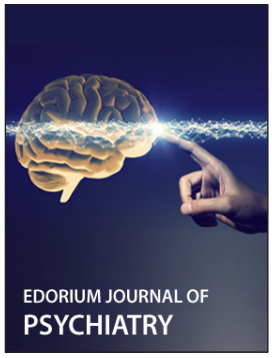

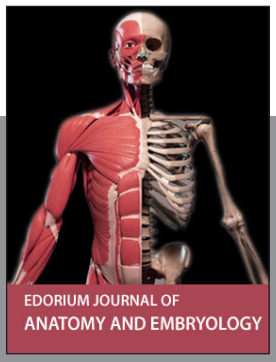

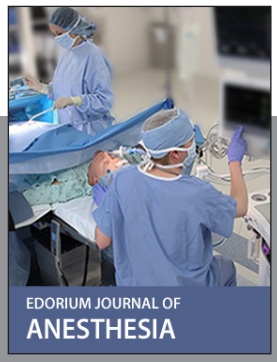

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