J Surg Med. 2018;2(2):190-192.
DOI: 10.28982/josam.411600

Case report
Olgu sunumu

Journal of Surgery and Medicine

e-ISSN: 2602-2079

Paroxysmal nocturnal hemoglobinuria case presenting as cerebral venous sinus thrombosis

Serebral venöz sinüs trombozu ile başvuran paroksismal noktürnal hemoglobinüri vakası

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Abstract

Venous thromboembolism (VTE) is the leading cause of morbidity and mortality in paroxysmal nocturnal hemoglobinuria (PNH). Between 29% and 44% of PNH patients experience a clinically evident VTE that affects the liver, brain, gut or kidney. Cases of VTE have been reported in all major organs except the spinal cord and bone marrow. Cavernous venous sinus thrombosis (CVST) is rare, but it has been reported previously to occur late in the course of PNH. Here we describe a case of CVST in a 34-year-old female admitted to our hospital with severe left sided temporal headache, double vision and malaise as an initial manifestation of PNH. This is a rare case of CVST as a presenting manifestation of PNH. This case along with two other recent reports of CVST accompanied by haemolytic anaemia in patients with PNH encourages increased vigilance for PNH in patients without an associated thrombophilic condition.

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

Öz

Venöz tromboembolizm (VTE), paroksismal nokturnla hemoglobinuri'de (PNH) morbidite ve mortalitenin önde gelen nedenidir. PNH hastalarının %29 ila %44'ü, karaciğer, beyin, bağırsak veya böbrekleri etkileyen ve klinik olarak belirgin bir VTE deneyimi yaşamaktadır. Bugüne kadar, omurilik ve kemik iliği dışındaki tüm ana organlarda VTE vakaları bildirilmiştir. Kavernöz venöz sinüs trombozu (KVST) nadirdir, ancak daha önce PNH seyrinde geç ortaya çıktığı bildirilmiştir. Burada, hastanemize ciddi sol taraflı temporal başağrısı, çift görme ve başlangıçta PNH'nin ilk belirtisi olarak görülen halsizlik, kırgınlık şikâyeti ile başvuran 34 yaşında bir kadın hastada bir KVST vakasını sunduk. Vakamız PNH'ın klinik tabloları içinde nadir görülen bir KVST hastasıdır. Bu vaka, PNH'lı hastalarda hemolitik aneminin eşlik ettiği diğer iki KVST vakası gibi PNH ilişkili sık gözlenen trombofilik durumu olmayan hastalarda PNH için farkındalığı teşvik etmektedir.

Anahtar kelimeler: Paroksismal nokturnal hemoglobinuria, Kavernöz venöz sinüs trombozu, Eculizumab

Introduction

Paroxysmal nocturnal hemoglobinuria (PNH) is an acquired clonal hematopoietic stem cell disorder. Clinical manifestations of the disease can be defined as thrombophilia broadly, intravascular hemolysis, smooth muscle dystonia and bone marrow failure [1]. PNH arises because of the nonmalignant clonal expansion of one or several hematopoietic stem cells that have acquired a somatic mutation of the X chromosome gene PIGA, which is required for synthesis of the glycosyl phosphatidylinositol moiety that anchors some proteins to the cell surface [2].

Venous thromboembolism (TE) is the leading cause of morbidity and mortality in PNH. Between 29% and 44% of PNH patients experience a clinically evident VTE affecting the liver, brain, gut or kidney. To date, venous thrombosis has been reported in all major organs except the spinal cord and bone marrow [3], and is particularly common in the hepatic, portal, splenic and cerebral venous system. Cavernous venous sinus thrombosis (CVST) is rare, but when it does occur in PNH patients it has previously been reported to appear late on in the disease course [3-5]. Here we describe a case of CVST as an initial manifestation of PNH [3,4].

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Informed Consent: The author stated that the written consent was obtained from the patient presented in the study.
Hasta Onamı: Yazar çalışmada sunulan hastadan yazılı onam alındığını ifade etmiştir.

Conflict of Interest: No conflict of interest was declared by the authors.
Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemişlerdir.

Financial Disclosure: The authors declared that this study has received no financial support.
Finansal Destek: Yazarlar bu çalışma için finansal destek almadıklarını beyan etmişlerdir.

Received / Geliş tarihi: 01.04.2018
Accepted / Kabul tarihi: 11.04.2018
Published / Yayın tarihi: 11.04.2018

How to cite / Atıf için: Sümbül HE, Büyükşimşek M, Sümbül MS, Güvenç B. Paroxysmal nocturnal hemoglobinuria case presenting as cerebral venous sinus thrombosis. J Surg Med. 2018;2(2):190-192.

Case presentation

A 34-year-old female admitted to our hospital for severe left sided temporal headache, double vision and malaise. Physical examination revealed mild tachycardia (heart rate: 104 beats per minute) and lethargy as well as pain in right upper quadrant. Cranial nerve examination showed no paralysis and ophthalmological examination indicated bilateral advanced papilledema.

Laboratory test findings included: leucocyte count 7800/mm^3; hemoglobin 5.26 g/dl; hematocrit 16.3%; differential leucocyte count 88% neutrophils, 11% lymphocytes and 1% monocytes; platelet count 180,000/mm^3; C-reactive protein 15.0 mg/dL; d-dimer 54.8 mg/dL. Liver function tests showed elevated total and direct serum bilirubin (3.09/1.23 mg/dL), lactate dehydrogenase (LDH; 1281 U/L), and alanine/aspartate aminotransferases (AST/ALT; 204/191 IU), while alkaline phosphatase was within normal range. The total serum protein level was 4.9 g/dl, and serum albumin was 2.9 g/dl. Serum electrolytes and renal function tests were within normal limits; serum uric acid was 4.9 mg/dl.

Abdominal ultrasonography revealed mild hepatosteatosis, calculous cholecystitis and splenomegaly. A lateral sub capsular splenic infarct measuring 2.5 x 2.0 cm was also detected. Cerebral venography identified a filling defect consistent with a partially recanalized or small thrombus (Figure 1). Cerebral magnetic resonance imaging revealed focal ischemic focus in the left cerebellar hemisphere (Figure 2). Color Doppler studies of the carotid, vertebral, hepatomesenteric and portal vessels gave normal findings.

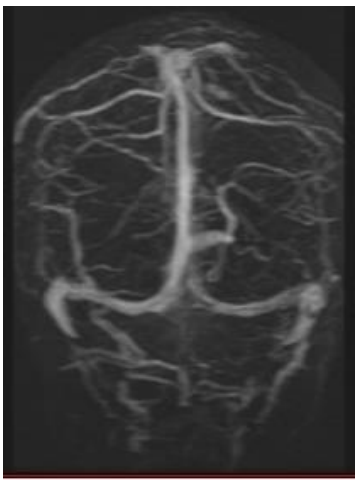

Figure 1: Cerebral venography: filling defect

The patient initially received enoxaparin 0.6 cm^3 twice daily. A peripheral blood smear revealed hemolysis. Negative findings were detected by direct and indirect Coombs testing, and we looked for thrombophilia based on the apparent thrombosis. Factor 5 homozygous Leiden mutation was normal; antithrombin 3, and Protein-C and -S levels were within normal limits. Anti-nuclear antibody was negative the reticulocyte count was 1.4%. We therefore suspected PNH based on the presence of Coombs-negative hemolytic anemia and VTE. FLARE-based (Fragment Length Analysis using Repair Enzymes) assays revealed a PNH clone size of 85% in granulocytes and 80% in monocytes.

The patient's abdominal pain decreased, and after 48 hours she was able to tolerate oral intake; her bowel sounds returned to normal. Enoxaparin was later switched to warfarin. However, her clinical picture was complicated by right hemiplegia, central facial paralysis and aphasia after 5 days under enoxaparin and warfarin therapy. Cerebral CT revealed a suspicious ischemic focus at the internal capsule and putamen (Figure 3). During follow up, right hemiplegia and aphasia regressed. Eculizumab was initiated. The patient was discharged from the hospital on day 27 with oral warfarin. Eculizumab therapy, 600 mg IV infusion for the first 4 weeks after 1 week 900 mg for the fifth dose then 900 mg for every 2 weeks was started at outpatient clinic. At the last outpatient clinic visit she is on eculizumab and warfarin therapy with no thrombotic events during 9 months of follow up. Her general health status has quietly improved with only a slight anemia and no need for any blood transfusions; she currently receives eculizumab every other week. Her plasma LDH at the time of writing is 160U/L, and the patient has gained weight. Written informed consent is obtained from the patient who participated in this study.

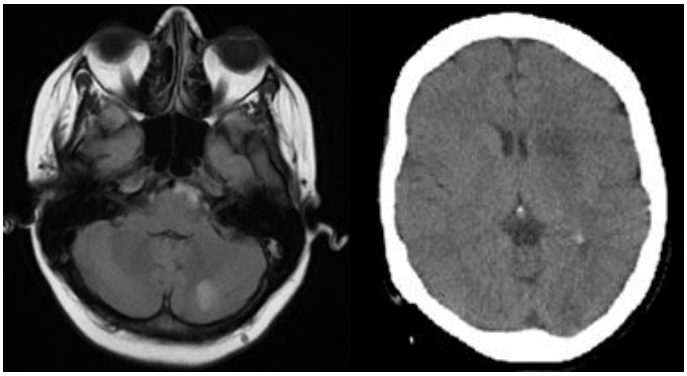

Figure 2: Cerebral MRI: partially re-canalized or small thrombus

Figure 3: Cerebral CT: ischemic focus at the internal capsule and putamen

Discussion

To the best of our knowledge, this is among the few cases of PNH in which the patient has presented with CVST as an initial disease manifestation. Two other cases of CVST in PNH have been described recently. Sharma et al described a patient with PNH who presented with thrombosis of the superior sagittal and right sigmoid sinuses, who was diagnosed 9 months later when the patient developed hepatic venous thrombosis [4]. More recently, the diagnosis of a patient 11 months after an initial episode of cerebral venous sinus thrombosis was described in India [3].

It is recommended that patients with a Coombs-negative hemolytic anemia, aplastic anemia, refractory anemia, and unexplained thrombosis in conjunction with cytopenias or hemolysis should be screened for PNH [6]. VTE merits special attention as it is considered the leading cause of PNH-related death, accounting for two-thirds of all mortalities in patients with this disease [2]. VTE is a relatively common complication during the course of PNH, with 29–44% of patients experiencing a clinically evident embolic event affecting the liver, brain, gut or kidney [2]. Among these sites, the hepatic vein is the most frequent location of thrombosis in PNH, accounting for the majority of deaths. CVST is the second most common type of thrombosis. There is a particular propensity for involvement of

hepatic and cerebral veins but the reason for this is not fully understood [7].

Hall et al reported that risk factors for thrombosis in patients with PNH include hemolytic anemia and hemoglobinuria, and PNH granulocyte clones >60% [7]. A more recent data from a Korean Registry showed that LDH≥1.5 ULN combined with clinical symptoms such as abdominal pain, chest pain, dyspnea or hemoglobinuria would be a better risk predictor for VTEs than clone size [8].

The exact pathophysiologic mechanism of VTE associated with PNH is yet to be clarified. A number of potential mechanisms include platelet activation by complement due to nitric oxide consumption because of intravascular hemolysis and endothelial damage by the intravascular hemolysis. Complement activation is recognized as a major contributor to vascular inflammation and is known to play a role in ischemia/reperfusion injury [9].

In the present case, PNH was suspected due to recurrent VTE, despite the absence of any other hereditary or acquired thrombophilic disorder. Moreover, the presence of hemolytic anemia, which was initially considered as a consequence of menorrhagia, also led to diagnosis of PNH.

VTE is a significant complication that constitutes an indication for the treatment of PNH in an otherwise asymptomatic patient [7]. Since thrombosis occurs frequently in visceral veins where morbidity and mortality is significant, careful anticoagulation is essential in such cases. Based on a retrospective study of 67 patients with PNH who did not receive prophylactic anticoagulation, Hall et al reported a VTE rate of 3.7 events per 100 patient-years, while no single VTE event was observed in 117.8 patient-years in 39 patients with PNH treated with anticoagulants (as primary prophylaxis) [9]; there were two serious hemorrhages in more than 100 patient-years of warfarin therapy in this study. The authors concluded that primary prophylaxis with warfarin in PNH prevents VTE with acceptable risks. However new VTE events or progression of initial VTE events have been reported in patients who are currently on anticoagulation in other reports [10-13]. Moreover, frequent occurrence of thrombocytopenia can increase the risk for fatal hemorrhage in patients with PNH [12,13].

Eculizumab is a humanized monoclonal antibody that specifically targets the terminal complement protein C5 [2]. It is the first treatment for PNH that effectively inhibits complement-mediated intravascular hemolysis, thereby preventing subsequent morbidities such as VTE. In a study by Hillmen et al. 2013, the reduction of the incidence of VTE from 11.3 events per 100 patient-years to 2.14 events per 100 patients-years, a relative risk reduction of 81.8% [14]. Our patient received eculizumab along with oral warfarin for 9 months. Follow up at 3-month intervals showed significant reduction in hemolysis, and there were no new VTE events or hemorrhages.

In conclusion, this is a rare case of CVST as a presenting manifestation of PNH. This case along with two other recent reports of CVST accompanied by hemolytic anemia in patients with PNH encourages increased vigilance for PNH in patients without an associated thrombophilic condition.

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