Letter to the Editor

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Portal vein thrombosis as the first presentation of paroxysmal nocturnal hemoglobinuria

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SUMMARY Paroxysmal nocturnal hemoglobinuria (PNH) is a rare, acquired clonal hematopoietic stem cell disorder, characterized by hemolytic anemia, bone marrow failure and thrombosis. Portal vein thrombosis (PVT) is relatively rare in patients with PNH. In this paper, we reported PVT as the first clinical presentation of PNH in a female patient. PVT related symptoms resolved after anticoagulation therapy.

Keywords paroxysmal nocturnal hemoglobinuria, portal vein thrombosis, anticoagulation therapy

Letter to the Editor:

Paroxysmal nocturnal hemoglobinuria (PNH) is a rare, life-threatening, clonal hematopoietic stem cell disorder (*1*). PNH arises from a somatic mutation in the phosphatidylinositol N-acetylglucosaminyltransferase subunit A (*PIG-A*) gene located on chromosome X (*1*). It is characterized by a deficiency of glycosylphosphatidylinositol (GPI) anchored proteins, including CD55 and CD59, leading to complement-mediated hemolysis (*2*). The incidence of PNH is approximately 1-1.5 per 1,000,000 individuals worldwide with a 5- and 10-year mortality of 35% and 50%, respectively (*3-5*). Thrombosis, is a common complication of PNH, however, the most commonly involved site of thrombosis is hepatic vein, portal vein thrombosis (PVT) is rarely reported (*6*). Herein, we describe the disease course of and anticoagulation treatment for PVT in a PNH patient. Notably, no obvious clinical symptom was observed during a 15-year history of PNH. Abdominal pain secondary to PVT should be considered as the first presentation of PNH in this patient and was soon resolved after anticoagulation therapy.

A 55-year-old woman presented with fever and right upper abdominal pain for 30 days. She was accidentally diagnosed with PNH 15 years ago. Because she had not suffered any significant clinical symptoms potentially related to PNH, no specific medical treatment had been given for PNH. Neither regular medications nor family history of thrombosis was reported. On August 5, 2021, the patient was admitted to our hospital. On laboratory tests, hemoglobin was 84 g/L (reference range: 115-150 g/L), mean corpuscular volume was 107.6 fL (reference range: 82.0-100.0 fL), and platelets count was 38 × 10^9 cells/L (reference range: 125-350 × 10^9 cells/L), white blood cell was 3.3 × 10^9 cells/L (reference range: 3.5-9.5 × 10^9 cells/L) with 68.4% granulocytes, 8.7% monocytes, and 21.8% lymphocytes, lactate dehydrogenase (LDH) was elevated at 642 U/L (reference range: 109-245 U/L), total bilirubin level was 24.1 μmol/L (reference range: 5.1-22.2 μmol/L), alkaline phosphatase level was 269.28 U/L (reference range: 35-135 U/L), and γ-glutamyl transferase level was 245.3 U/L (reference range: 7-45 U/L). The Coombs test was negative, and the D-dimer was 3.71 mg/L (reference range: 0.00-0.55 mg/L). On August 6, contrast-enhanced abdominal computed tomography (CT) revealed portal vein, superior mesenteric vein, and splenic vein thrombosis with portal cavernoma (Figure 1). Endoscopy demonstrated mild varices on gastric fundus. On August 6, she received anticoagulation therapy of PVT at our department. Low molecular weight heparin (LMWH) was given at a dosage of 5,000 IU subcutaneously twice a day. Three days later, abdominal pain and fever completely disappeared. Fourteen days later, a repeat CT was performed, and showed that portal vein, superior mesenteric vein, and splenic vein thrombosis remained, but inflammatory exudate around the superior mesenteric vein was resolved (Figure 2). On November 20, follow-up CT still showed portal vein thrombosis, and superior mesenteric vein thrombosis with portal cavernoma. LMWH was converted to rivaroxaban (Figure 3). At the last follow-up on April 15, 2022, her general condition was stable without any complaints.

PNH can be characterized as hemolytic anemia, bone marrow failure, renal dysfunction, erectile dysfunction, pulmonary hypertension, infection, and unexplained

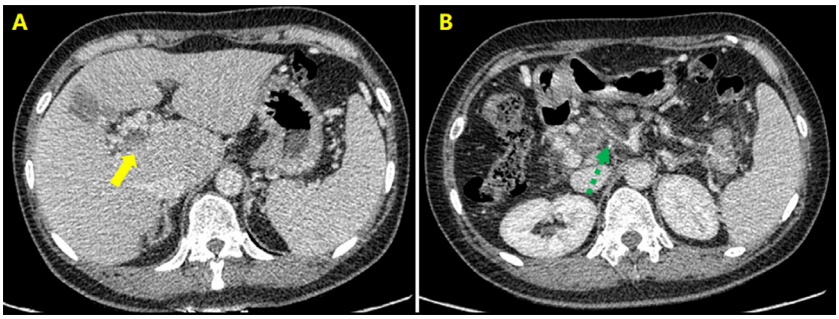

Figure 1. Computed tomography scans performed on August 6, 2021, at admission. Computed tomography showed portal vein thrombosis (solid arrow) **(A)** and superior mesenteric vein thrombosis (dotted arrow) **(B)**.

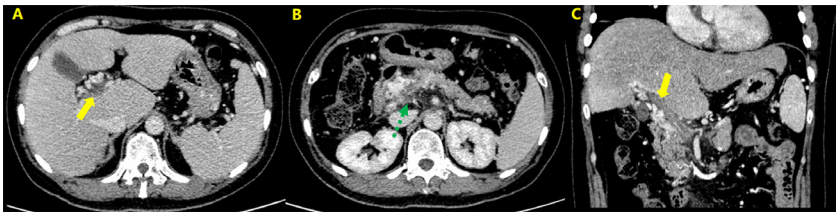

Figure 2 Computed tomography scans performed on August 20, 2021, after anticoagulation. Axial computed tomography scans showed portal vein thrombosis (solid arrow) **(A)** and superior mesenteric vein thrombosis (dotted arrow) **(B)**. Coronal computed tomography scans showed portal vein thrombosis (solid arrow) **(C)**.

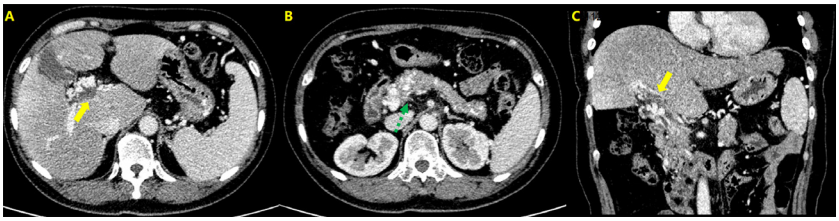

Figure 3. Computed tomography scans performed on November 20, 2021, during follow-up. Axial computed tomography scans showed portal vein thrombosis (solid arrow) **(A)** and superior mesenteric vein thrombosis (dotted arrow) **(B)**. Coronal computed tomography scans showed portal vein thrombosis (solid arrow) **(C)**.

thrombosis (*7*). However, some PNH cases do not have any clinical presentations (*8*). Similarly, despite PNH was diagnosed 15 years ago, our case did not have any classical manifestations until abdominal pain secondary to PVT developed as the first clinical presentation.

There are some possible mechanisms of thrombosis in patients with PNH. 1) PNH clone. The risk of thrombotic events appears to be directly associated with the size of PNH clone, especially the percentage of GPI protein-free granulocytes (PNH granulocytes > 50%). The 10-year cumulative thrombosis rate was 34.5% for PNH granulocytes > 50%, but only 5.3% for PNH granulocytes < 50% ($p < 0.01$) (*9*). The International PNH Registry analysis, the largest PNH study to date, also found that the incidence of thrombotic events was significantly higher in patients with PNH granulocytes > 50% than those with PNH granulocytes < 10% and PNH granulocytes within 10-50% (*10*). 2) Endothelial cell (EC) damage. EC damage can occur during any thrombotic event. In PNH patients, the free hemoglobin released from lysed PNH erythrocytes and its breakdown oxidative product heme can directly activate EC, increase the production of tissue factors, and further promote inflammation and coagulation (*11,12*). 3) Platelets activations. The absence of CD59 in PNH patients makes platelets vulnerable to complement attack, resulting in complement-mediated activation and disruption (*13*). Activated platelets also interact with neutrophils to promote thrombosis through the release of serine proteases and nucleosomes from neutrophils, which synergistically activate factor X to initiate coagulation primarily through the extrinsic pathway (*14*). 4) Intravascular hemolysis. Elevated hemoglobin from intravascular hemolysis may lead to nitric oxide depletion, which has also been reported to contribute to thrombosis (*11*).

Thrombosis is the leading cause of death in PNH patients. A thrombotic event increases the relative risk of death in PNH patients by 5- to 10- fold (*15,16*). There are some risk factors that help identify thrombosis in PNH patients, including LDH level ≥ 1.5 times the upper limit of normal (ULN), high PNH symptom burden,

ethnicity, and infection. In a Korean registry study of patients with PNH, LDH ≥ 1.5 times ULN at diagnosis was independently associated with increased odds of thrombotic events after adjusting for age, gender, and bone marrow failure (odds ratio 7.0; 95% confidence interval 1.5-32; $p = 0.013$) (17). In our case, the LDH level was 642 U/L, which is 2.6 times of the ULN. PNH symptom burdens include abdominal pain, fatigue, dyspnea, hemoglobinuria, and dysphagia. Higher PNH symptom burdens had a positive correlation with the GPI-deficient granulocyte clone size, and was also recognized as a risk factor for thrombosis (*10,17*). Ethnicity may be another risk factor for the development of thrombosis in PNH patients, because the incidence of thrombotic events was 13-17% in Asian PNH patients (*17,18*) and 29-44% in Western PNH patients (*5,8*). Taken together, venous thrombosis should be regularly observed in PNH patients, especially those with above-mentioned risk factors. On the other hand, Western studies have also suggested that routine screening for PNH should be considered in PVT patients (*19*). However, there was a very low prevalence of PNH in Chinese patients with PVT (*19,20*), which did not support the necessity of routine screening for PNH in such patients.

In PNH patients with acute thrombosis, eculizumab and anticoagulation should be given immediately with a duration of 3-6 months, and anticoagulation can be discontinued if thrombotic symptoms are resolved (*1*). Eculizumab is recommended as the first-line therapy for PNH, can improve long-term survival and quality of life, and reduce hemolysis and thrombotic events (*21-24*). However, high costs and difficulty to access limit the use of eculizumab in China (*25*). Additionally, anticoagulation can reach an overall response rate of more than 70% in patients with acute non-cirrhotic, non-malignant PVT (*26*). In a systematic review, complete or partial portal vein recanalization was observed in 38.3% and 14% of cases after initiation of anticoagulation therapy, respectively, but in 16.7% of cases without anticoagulation (*27*). Direct oral anticoagulants, such as rivaroxaban, are likely equivalent, but have not been well studied in PNH (*28*). Notably, anticoagulation also potentially increases the morbidity of variceal bleeding. A risk-benefit ratio of anticoagulants in non-cirrhotic PVT may be evaluated based on grade of gastroesophageal varices, recent bleeding events, prothrombotic disorders, and thrombocytopenia (*29*). Our case had PNH as a permanent thrombotic risk factor with low-risk varices without any previous bleeding events, so anticoagulation might be less risky. Alternative treatments would be considered if anticoagulation failed or was not feasible. Transjugular intrahepatic portosystemic shunt can be considered for the treatment of portal hypertension in patients with non-malignant and non-cirrhotic portal vein thrombosis (*30*), even those with portal cavernoma (*31*).

In conclusion, thrombosis should be routinely screened in patients with PNH, especially in high-risk patients. It is probable that PVT should be the first clinical presentation of PNH. Early anticoagulation therapy may be preferred in PNH patients with PVT.

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