

Taylor & Francis
Taylor & Francis Group

Biotechnology & Biotechnological Equipment

ISSN: 1310-2818 (Print) 1314-3530 (Online) Journal homepage: https://www.tandfonline.com/loi/tbeq20

Paroxysmal nocturnal haemoglobinuria: a case presenting with isolated thrombocytopenia

Mustafa Yilmaz, Beyhan Guvercin & Ceren Konca

To cite this article: Mustafa Yilmaz, Beyhan Guvercin & Ceren Konca (2016) Paroxysmal nocturnal haemoglobinuria: a case presenting with isolated thrombocytopenia, Biotechnology & Biotechnological Equipment, 30:2, 332-334, DOI: 10.1080/13102818.2015.1112750

To link to this article: https://doi.org/10.1080/13102818.2015.1112750

© 2016 The Author(s). Published by Taylor & Francis.

Published online: 08 Feb 2016.

Submit your article to this journal

Article views: 1563

View related articles

View Crossmark data

Full Terms & Conditions of access and use can be found at
https://www.tandfonline.com/action/journalInformation?journalCode=tbeq20

BIOTECHNOLOGY & BIOTECHNOLOGICAL EQUIPMENT, 2016
VOL. 30, NO. 2, 332–334
http://dx.doi.org/10.1080/13102818.2015.1112750

Taylor & Francis
Taylor & Francis Group

ARTICLE; MEDICAL BIOTECHNOLOGY

OPEN ACCESS

Paroxysmal nocturnal haemoglobinuria: a case presenting with isolated thrombocytopenia

Mustafa Yilmaz[a], Beyhan Guvercin[b] and Ceren Konca[b]

[a]Division of Hematology, Department of Internal Medicine, Karadeniz Technical University, Trabzon, Turkey; [b]Department of Internal Medicine, Karadeniz Technical University, Trabzon, Turkey

ABSTRACT

Paroxysmal nocturnal haemoglobinuria (PNH) is a rare disease characterized by intravascular haemolysis, haemoglobinuria and thrombosis. The present study reported PNH patients presenting with isolated thrombocytopenia. A 31-year-old male patient was referred to haematology outpatient clinic because of thrombocytopenia detection. Initially, there was no anaemia, but apparent haemolytic anaemia occurred in the patient within a year. The PNH was diagnosed by using fluorescently labelled inactive variant of the protein aerolysin test. Anaemia, jaundice, thrombosis, fatigue, dyspnoea, dark urine, abdominal or gastric pain, dysphagia and erectile dysfunction are primary symptoms of PNH, leading to diagnosis. This is an atypical PNH case presenting with isolated thrombocytopenia, which led to difficulty and delay in diagnosis.

ARTICLE HISTORY
Received 19 July 2015
Accepted 22 October 2015

KEYWORDS
Paroxysmal nocturnal haemoglobinuria; thrombocytopenia; diagnose

Introduction

Paroxysmal nocturnal haemoglobinuria (PNH) is a clonal hematopoietic stem cell disease which manifests itself by chronic intravascular haemolysis findings, bone marrow failure and thrombosis.[1,2] From a pathophysiological point of view, a somatic mutation in the phosphatidylinositol *N*-acetylglucosaminyltransferase subunit A (*PIG-A*) gene, located on the X chromosome, is the cause of the disease. The *PIG-A* gene is involved in the encoding of the glycosylphosphatidylinositol (GPI) protein. In PNH, some complement inhibitory proteins, including CD55 and CD59, which bind to the cell membrane by GPI-anchoring proteins, are missing in mature cells which are generated from mutated hematopoietic stem cells.

The CD55 protein (decay accelerating factor) expressed by normal hematopoietic cells inhibits the activation of the complement system. The CD59 protein (membrane inhibitor of reactive lysis) inhibits the cytolysis function of the complement system. Since CD55 and CD59 proteins are missing from the blood cells of PNH patients, complement activation is not blocked and haemolysis occurs. The defect in proteins binding to the cell membrane via the GPI-anchoring proteins is measured by using flow cytometry. This is referred as the golden standard in the diagnosis of PNH. Anaemia, fatigue, dyspnoea, dark urine, abdominal or gastric pain, dysphagia, erectile dysfunction, jaundice and thrombosis are the primary symptoms. To date, PNH has not been listed among the primary causes of isolated thrombocytopenia.

The present study is a case report of a PNH patient, presenting only with isolated thrombocytopenia that was not accompanied by the typical clinical and laboratory symptoms of PNH.

Materials and methods

The present study is a clinical case presentation. It was a unique case, because it had a status of atypical presentation with isolated thrombocytopenia, which caused difficulty and delay in diagnosis.

Laboratory analyses

All laboratory analyses were performed in the clinical laboratory of Karadeniz Technical University Hospital. Blood samples were collected in ethylenediaminetetraacetic acid containing tubes. Anti-coagulated whole blood and plasma samples were obtained for full blood analysis. Complete blood count analyses were performed by using the AU 5800 Autoanalyzer (Beckman Coulter, Clare, Ireland) according to the manufacturer's instructions.

CONTACT Mustafa Yilmaz mustafa.yilmaz@ktu.edu.tr

© 2016 The Author(s). Published by Taylor & Francis.
This is an Open Access article distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/4.0/), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Fluorescent aerolysin (FLAER)-based flow cytometry assay

Samples were processed according to the protocols described previously [3] and were analysed on FC-500 flow cytometer (M/S Beckman Coulter, Brea, CA, USA).

Case presentation and laboratory results

A 31-year-old male patient was referred to another haematology outpatient clinic because of detection of thrombocytopenia during a routine complete blood count. The laboratory findings were as follows: haemoglobin −13.7 g/dL, mean corpuscular volume (MCV) −90.7 fL, leukocyte count −5400 mm^{-3} and platelet count −52.000 mm^{-3}. The clinical examination revealed normal findings. Peripheral blood smear and biochemistry showed normochromic, normocytic red blood cells (RBCs); 69% neutrophils; 22% lymphocytes; 6% monocytes; 3% eosinophils; platelets count: an average of 5 platelets were seen under 10 successive 100× objective fields; 3% reticulocytes; 602 IU/L (<248 IU/L) lactate dehydrogenase (LDH); 20 IU/L (0−45 IU/L) alanine transaminase; 19 IU/L (0−35 IU/L) aspartate transaminase; 0.2 mg/dL (0.2−1.2 mg/dL) total bilirubin; 0.1 mg/dL (0−0.25 mg/dL) direct bilirubin. The activated thromboplastin time was 28.1 s (22−40 s), the prothrombin time was 12.7 s (11−14 s), the level of d-dimers was normal. The tests for hepatitis B surface antigen, hepatitis C virus, human immunodeficiency virus and antinuclear antibody were negative. The possible aetiology of thrombocytopenia was further assessed by abdominal ultrasonography which revealed normal findings. The patient was diagnosed as having idiopathic thrombocytopenic purpura (ITP) and this was followed by three months of regular check-ups. Within a year, the haemoglobin was reduced to 9.4 from 13.7 g/dL; leucocytes were reduced to 3800 from 4900 mm^{-3} and the platelets were between 50.000 and 54.000 mm^{-3}.

The patient was referred to our University Hospital clinic after the occurrence of anaemia and there were no significant findings, except pallor, during the physical exam. Peripheral blood smear results were as follows: 59% neutrophils, 35% lymphocytes, 4% monocytes, 2% eosinophils, 12.2% reticulocytes. RBCs showed anisocytosis and polychromasia, which were microcytic and hypochromic: (MCV: 78.6 fL), iron: 36 μg/dL (50−170 μg/dL), iron binding capacity: 504 μg/dL (228−428 μg/dL), ferritin: 13.2 ng/mL (23.9−336.2 ng/mL), LDH: 1360 IU/L, haptoglobulin < 29 mg/dL (30−200 mg/dL), direct bilirubin: 0.1 mg/dL, total bilirubin: 0.9 mg/dL. The direct Coombs test was negative. Iron replacement was performed for the treatment of accompanying iron deficiency anaemia. PNH was suspected, and flow cytometric analysis was performed for this reason. By applying the FLAER test, PNH clone was detected in 34% of the RBCs, in 89% of the granulocytes and in 67% of the monocytes. Methylprednisolone (20 mg in every other day) was initiated in addition to the daily iron therapy. One month after the diagnosis, the white blood cells (WBCs) were 4700 mm^{-3}, the haemoglobin was 12.6 g/dL, the MCV was 90.3 fL and the platelets were 92.000 mm^{-3}. The haemoglobin level was significantly increased. Haemolysis parameters were as follows: reticulocytes ratio of 15% and LDH of 1,253 IU/L. This therapeutic regimen provided a significant restoration of the haemoglobin levels, but the status of haemolysis was aggravated and thus eculizumab therapy was initiated. Under the eculizumab therapy, the WBCs were 4200 ins_start> mm^{-3}, the haemoglobin was 12.6 g/dL, the platelets were 144.000 mm^{-3}, the LDH was 298 IU/L, the total bilirubin was 1.1 mg/dL and the direct bilirubin was 0.18 mg/dL, which indicated a successful haemolysis control.

Case discussion

PNH is a rare blood disease, affecting 8000−10,000 patients in North America and Europe.[4] In PNH, the most common finding is a slight-severe normo-macrocytic anaemia. If there is an iron loss due to chronic haemoglobinuria, then microcytic anaemia may be accompanying the iron deficiency. Haptoglobulin is low and unconjugated bilirubin may be slightly high. Typically, LDH is high in almost all cases. PNH may affect myeloid and megakaryocytic series, with the exception of erythroid series. Usually, erythroid hyperplasia is found in the bone marrow. Venous thrombosis may be observed in 30%−40% of the PNH patients. The presence of thrombocytopenia may increase the risk of thrombosis. The prominent symptoms were as follows: fatigue, dark urine, abdominal or stomach pain, dysphagia, erectile dysfunction, dyspnoea, jaundice and thrombosis. These symptoms may vary between patients, thus causing difficulty in diagnosing the disease.

There are reports of PNH cases presenting with pancytopenia that were being followed up because of recurrent acute renal failure, superior sagittal sinus thrombosis and Budd−Chiari syndrome, intra-abdominal bleeding due to splenic rupture, central retinal artery occlusion and cerebral venous sinus thrombosis, acute tubular necrosis and systemic lupus erythematosus (SLE). Chen et al. [5] have presented a PNH patient, who was followed up because of aplastic anaemia, but then manifested itself by symptoms such as reduction in urine output, discoloration of urine and recurrent acute renal failure. Sharma et al. [6] have presented a 26-year-old

PNH patient with hepatic venous thrombosis after superior sagittal sinus thrombosis. Nakamura et al. [7] have presented a 29-year-old female with PNH case presenting with profound pancytopenia, who was followed for SLE. An atypical PNH case presenting with splenic infarct followed by massive intra-abdominal bleeding due to splenic rupture, was also presented.[8] Yang et al. [9] have presented another example of atypical PNH case with isolated central retinal artery occlusion. There is also a report of PNH cases presented with cerebral sinus thrombosis and acute tubular necrosis.[10–12] To the best of our knowledge, there has not been any cases of PNH presenting with isolated thrombocytopenia in the available literature in English.

Conclusions

In this case report, we presented an atypical PNH patient, who was initially diagnosed with ITP due to the presence of isolated thrombocytopenia; however, after one year of follow up, because of overt anaemia, haemolysis and reticulocytosis, PNH was suspected. A FLAER test was performed and a PNH clone was detected. This report implied that PNH should be suspected if a patient with isolated thrombocytopenia without anaemia shows even a slight increase in LDH. It should also be noted that the disease may present itself just by isolated thrombocytopenia.

Disclosure statement

No potential conflict of interest was reported by the authors.

References

[1] Hillmen P, Lewis SM, Bessler M, et al. Natural history of paroxysmal nocturnal hemoglobinuria. N Engl J Med. 1995;333:1253–1258.

[2] Brodsky RA. Paroxysmal nocturnal hemoglobinuria: stem cells and clonality. Hematology Am Soc Hematol Educ Program. 2008;2008(1):111–115.

[3] Sutherland DR, Kuek N, Azcona-Olivera J, et al. Use of a FLAER-based WBC assay in the primary screening of PNH clones. Am J Clin Pathol. 2009;132:564–572.

[4] Living with PNH. Understanding the treatment options for paroxysmal nocturnal hemoglobinuria [Internet]. [cited 2015 Jul 19]. Available from: http://www.pnhdisease.org/html/files/pnh_patient_brochure_v1.pdf

[5] Chen SC, Hung CC, Hsu CP, et al. Recurrent acute renal failure in a patient with aplastic anemia-paroxysmal nocturnal hemoglobinuria syndrome: a case report. Kaohsiung J Med Sci. 2007;23:579–583.

[6] Sharma A, Itha S, Baijal SS, et al. Superior sagittal sinus thrombosis and Budd–Chiari syndrome due to paroxysmal nocturnal hemoglobinuria managed with transjugular intrahepatic portosystemic shunt: a case report. Trop Gastroenterol. 2005;26:146–148.

[7] Nakamura N, Sugawara T, Shirato K, et al. Paroxysmal nocturnal hemoglobinuria in systemic lupus erythematosus: a case report. J Med Case Rep. 2011;5:550.

[8] Uzun S, Alpay N, Ozturk GB, et al. A case of paroxysmal nocturnal hemoglobinuria presenting with intra-abdominal bleeding due to splenic rupture, developing renal infarct. Int J Lab Hematol. 2008;30:248–253.

[9] Yang HS, Park SH, Choi JR, et al. Isolated central retinal artery occlusion as an initial presentation of paroxysmal nocturnal hemoglobinuria and successful long-term prevention of systemic thrombosis with eculizumab. Jpn J Ophthalmol. 2008;57:424–428.

[10] Misra UK, Kalita J, Bansal V, et al. Paroxysmal nocturnal haemoglobinuria presenting as cerebral venous sinus thrombosis. Transfus Med. 2008;18:308–311.

[11] Memon AR, Khan R, Rauf MU, et al. Paroxysmal nocturnal hemoglobinuria presenting as cerebral venous sinus thrombosis: a case report. Int Arch Med. 2014;7:39.

[12] Wijewickrama ES, Gooneratne L, De Silva C, et al. Acute tubular necrosis in a patient with paroxysmal nocturnal hemoglobinuria. Saudi J Kidney Dis Transpl. 2013;24:105–108.