Case Report

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Website: www.ijhonline.org

DOI: 10.4103/ijh.ijh_2_19

A female with classical paroxysmal nocturnal hemoglobinuria misdiagnosed as megaloblastic anemia

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Abstract:

Paroxysmal nocturnal hemoglobinuria (PNH) is a rare acquired disorder of the hematopoietic stem cells, which manifests as bone marrow failure, hemolytic anemia, and thrombosis. PNH affects both sexes equally and may present at any age, although it is most often diagnosed in young adulthood. Here, we report a case of a middle-aged woman, presented with one and a half year history of anemia, significant fatigue, backache, and persistent high erythrocyte sedimentation rate. The patient has no organomegaly and did not give a history of thrombotic events previously. She was considered as a case of megaloblastic anemia at another center and treated accordingly. Her full blood count showed mild macrocytic anemia with slight polychromasia. The hemolytic anemia workup revealed slightly raised serum bilirubin (unconjugated) and undetectable haptoglobin with hemosiderin in urine. Ham's test was positive, and the diagnosis of PNH was confirmed by flow cytometry. The patient was treated with short-course steroids and folic acid, and her general condition has become stable.

Keywords:

Ham's test, hemolytic anemia, paroxysmal nocturnal hemoglobinuria

Introduction

Paroxysmal nocturnal hemoglobinuria (PNH) is an acquired disorder characterized by chronic hemolytic anemia. The defect is intrinsic to the red cells and results from somatic mutation of a gene known as phosphatidylinositol glycan anchor biosynthesis Class A (PIG-A) on chromosome X.[1] Cells having PIG-A mutations are deficient in a class of protein called glycosylphosphatidylinositol (GPI) anchor. Consequently, the PNH stem cells and their progeny lack the GPI-anchored proteins, some of which protect red blood cells from destruction; some are involved in blood clotting while others are involved in protection against infection. Of these, the deficiency of CD55 and CD59 GPI-anchored complement regulatory proteins leads to complement-mediated intravascular hemolysis. The identification of the genetic defects responsible for PNH may give insight for developing more effective therapies.[2]

PNH has an incidence of 1.3–1.5 new cases per million populations per year and is primarily a disease of younger adults. Males and females are both affected equally.[3]

A wide spectrum of symptoms is associated with PNH; the most common include significant fatigue, hemolysis, aplasia, and thrombosis. The disease has three major subtypes: classical PNH, which includes patients who have evidence of PNH in the absence of another bone marrow (BM) failure disorder; PNH in the context of other primary BM disorders, like aplastic anemia or myelodysplastic syndrome; and subclinical PNH, where patients have small PNH clones with no clinical or laboratory evidence of hemolysis or thrombosis.[4]

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Submission: 15-02-2019
Accepted: 08-03-2019
Published: 17-10-2019

How to cite this article: Jalal SD, Saeed SM, Rashid NG, Saeed AS. A female with classical paroxysmal nocturnal hemoglobinuria misdiagnosed as megaloblastic anemia. Iraqi J Hematol 2019;8:81-3.

Several tests exist for PNH including sucrose lysis test and Ham's test which demonstrate the increased sensitivity of PNH red blood cells (RBCs) to complement mediated lysis. Flow cytometry, however, has become the gold standard for making the diagnosis, using antibodies against GPI-anchored proteins deficient on peripheral blood cells.[5,6]

Case Report

A 55-year-old female presented to Sulaimani Public Health Laboratory Hematology Department, Sulaimani-Iraq, with one and a half year history of anemia. She suffers from weakness and lower back pain. On examination, the patient was pale with no organomegaly. She was treated with iron supplements, folic acid tablets, and B12 injection over the last period, and she was even transfused twice (the last one was three months from her recent presentation). Her relative stated that she was diagnosed as a case of megaloblastic anemia. The result of the full blood count at the time of presentation is as follows: Hb 8.7 g/dl, MCV 103 fl, MCH 34.4 pg, WBC 4 × 10^9/l, and Plt 170 × 10^9/l. Corrected reticulocytes = 9% and erythrocyte sedimentation rate = 96 mm/h. The blood film did not reveal any significant finding apart from mild polychromasia and increased rouleaux formation. Coombs test was negative, total bilirubin was 1.7 mg/dl (unconjugated = 1.5 mg/dl), and ferritin was 30 ng/ml. Due to the patient's complaints of fatigue and backache, protein electrophoresis was arranged, and the result was normal. The patient has already done a number of serological tests, and all turned to be normal including anti-*Brucella* IgM/IgG, latex agglutination, antinuclear Abs anti-dsDNA, anti-cyclic citrullinated peptide, and anti-cardiolipin IgM/IgG Ab. On BM aspirate, erythroid hyperplasia was evident with generally normoblastic maturation. To investigate this case further, haptoglobin was performed, and interestingly, it was undetectable (normal range 30–200 mg/dl). Hemosiderin in urine was positive. The patient was referred by her physician for dynamic abdominal magnetic resonance imaging (MRI) (at Shorsh hospital-Sulaimani-Iraq) to exclude the possibility of parenchymal iron overload as the patient has chronic hemolytic anemia, and surprisingly, both kidneys revealed an abnormal cortex signal intensity that favors iron overload.

The MRI findings encouraged us to exclude the possibility of PNH, and Ham's test was performed first as screening, which turned to be positive results. Thereafter, we moved further to confirm the diagnosis using flow cytometry markers: CD59, CD24, CD14, and FLAER as GPI-linked Abs and CD45, CD15, CD33, and glycophorin A for gating purposes. The results were as follows: no PNH clone was identified among the RBCs, while Type III deficiency (severe deficiency) of FLAER and CD14 was evident among monocytes (90%) while 93% of granulocytes displayed Type III of FLAER and CD24 deficiency [Figure 1].

She is now under regularly 2-month follow-up at Hiwa Hematology-Oncology Hospital, Sulaimani, Iraq, with only folic acid tablets supplementation. Fortunately, she is stable with the Hb around 11 g/dl, without overt hemolysis.

Discussion

PNH is a rare acquired hematopoietic stem cell disorder with quite unusual constellation of clinical findings. The rarity of the disease and nonspecific clinical features may result in potential delays in diagnosis. The value of a prompt and accurate diagnosis has increased as effective therapies have become available.[7] This case was misdiagnosed as megaloblastic anemia, and PNH was not considered as a potential diagnosis since reticulocyte percentage was not estimated at first neither bilirubin. In addition, the patient did not give a history of previous attacks of thrombosis or passing red

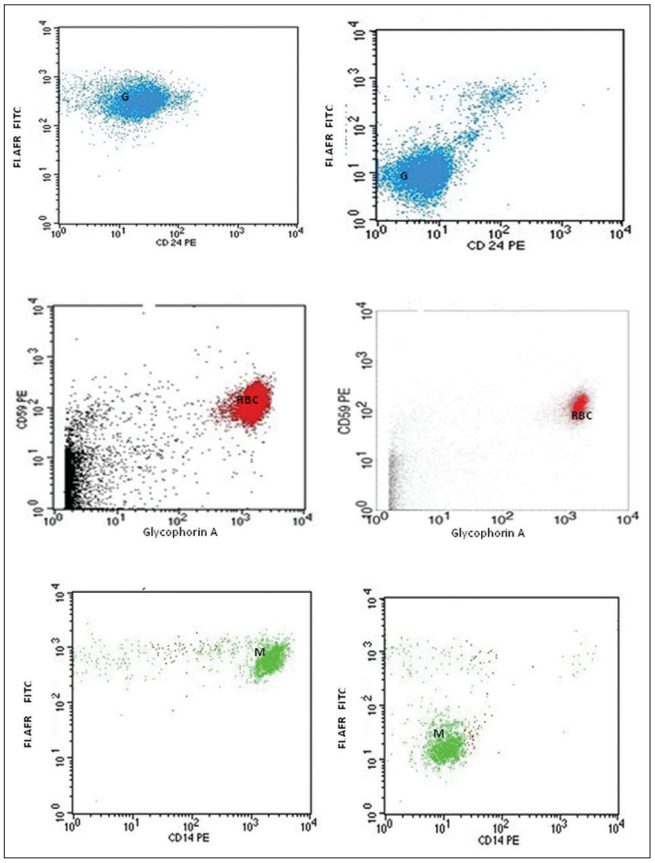

Figure 1: Illustration of the patient peripheral blood sample (right-side flow cytometry plots) with a normal blood sample (left-side plots). The patient's RBC expresses CD59 at a comparable intensity to the control's RBC, while her granulocytes (G) and monocytes (M) lacked CD24 and CD14 expression, respectively. FLAER was absent on both granulocytes and monocytes of the patient sample in comparison to the control which showed normal expression pattern of each of CD24, CD14, and FLAER. RBC = Red blood cell

urine, both of which might have driven the differential diagnosis towards hemolytic anemia and PNH. The patient was referred to Sulaimani Public Laboratory to investigate for the underlying causes of her anemia. Once a hemolytic anemia was suspected, we went into the hemolytic anemia workout to find the pathology for her intravascular hemolysis. The appropriate treatment for PNH depends on the severity of symptoms. This patient experienced few symptoms and did not require treatment other than folic acid and sometimes iron supplementation to increase red blood cell production.

In our opinion, it is paramount to stress on the proper laboratory evaluation of patients with anemia and considering PNH among the list of differential diagnoses even if the clinical findings were unusual.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

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