

# Paroxysmal nocturnal hemoglobinuria in the differential diagnosis of thrombocytopenia

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## Abstract

Paroxysmal nocturnal hemoglobinuria (PNH) is a disease which diagnosis may be delayed due to variable clinical findings. We describe herein a case of PNH in a 21 year old woman who admitted with complaints of chronic weakness, intermittent spontaneous ecchymoses, and an intermittent abdominal pain. On laboratory tests thrombocytopenia and iron deficiency anemia without any clinical findings were found. Flow cytometric evaluations showed a PNH clone of 15% for erythrocytes, 64% for monocytes, and 60% for granulocytes. The patient was diagnosed with PNH and an eculizumab therapy was initiated. Following initiation of eculizumab therapy, the frequency of abdominal pain attacks decreased, hemoglobin level normalized, and platelet values increased slightly. In patients submitting with a triad of symptoms such as thrombocytopenia, iron deficiency anemia, and abdominal pain attacks of unknown etiology we suggest considering PNH. We also encourage physicians to share their similar observations in order to raise the knowledge on infrequent presentations of PNH.

## Introduction

Paroxysmal nocturnal hemoglobinuria (PNH) is a rare, life-threatening, hematological disorder characterized by hemolysis of the red blood cells due to activation of the complement system.<sup>1</sup>

The prevalence of the disease is estimated as 1 to 5 cases per million worldwide. Clinical triad of hemolytic anemia, bone marrow failure and thrombophilia is typical for PNH.<sup>2</sup> The complex pathogenic mechanism of the disease is mostly discovered while some biological aspects are still under investigations. Clonal expansion of hematopoietic stem cells (HSCs) with a somatic mutation in X-linked phosphatidylinositol glycan class A (*PIG-A*) gene are considered to be the main cause of the disease.<sup>3</sup> Due to this mutation PNH is considered to be a genetic hematological disorder. However this genetic abnormality is insufficient to explain the pathogenesis of bone marrow failure and thromboembolism, therefore investigations and discussions are ongoing.<sup>4</sup> The absence of complement regulators on erythrocytes is the main reason of chronic hemolysis patients with PNH. Anemia, hemoglobinuria, fatigue, painful abdominal crises, dysphagia and erectile dysfunction are other symptoms related to intravascular hemolysis.<sup>5</sup> The thromboembolism is considered to be also linked to hemolysis however the true pathophysiology is not clear yet. Thrombosis and renal failure are leading causes of death in PNH patients.<sup>6</sup> Thrombocytopenia is a rare and unusual manifestation of PNH. In the literature there are insufficient data about the thrombocytopenia as initial presentation of PNH. Herein we report a 21 year-old woman with PNH presenting with thrombocytopenia misdiagnosed as immune thrombocytopenic purpura.

## Case Report

Twenty-one year-old woman was referred to our department at November 2014 from a medical center where she was followed for 2 years with diagnosis of immune thrombocytopenia and iron deficiency anemia. During that follow-up period she did not experience any bleeding and had moderate thrombocytopenia required not any treatment with anti-thrombotic drugs. However an oral iron supplementation on an occasional basis was given for anemia. Therefore she was referred to our clinic for further diagnosis and treatment. Her medical history showed that, she had been recovering while she was receiving oral iron supplementation; however her hemoglobin (Hb) levels were decreasing soon after cessation of treatment. Her thrombocytopenia (ranged from 45.000 to 55.000/mm<sup>3</sup>) persisted and there were no clinical findings

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consistent with blood loss that can explain a possible iron deficiency anemia. Also according to her anamnesis she reported complaints of chronic weakness, intermittent spontaneous ecchymoses, and an intermittent abdominal pain of unknown etiology. All necessary evaluations including abdominal ultrasound, and also assessments regarding thrombosis and FMF were performed however no clinical evidence was found for her abdominal pain.

Her thrombocytopenia (ranged from 45.000 to 55.000/mm<sup>3</sup>) persisted and there were no clinical findings consistent with blood loss that can explain a possible iron deficiency anemia. On physical examination, she was anemic (pale appearance of skin and mucous membranes), her spleen was slightly palpable (1 cm from 12<sup>th</sup> rib), and there were a few small (diameter <1 cm) ecchymosis at her lower extremity. During admission a series of laboratory tests and a bone marrow examination have been performed. Initial laboratory test showed a thrombocytopenia with a mild anemia and increased serum LDH levels (Table 1). Urine analysis showed hemosiderin cylinders. Bone marrow examination (both aspiration and biopsy)

revealed just a mild erythroid hyperplasia (normal cellularity: 60%). Hypersegmentation in megakaryocytes and slight dysplastic changes (multiple separated nucleus) were also observed. Cytogenetics was performed and result was 46,XX. Presence of iron deficiency was observed via bone marrow biopsy performed using iron staining. Therefore we performed fluorescein-labeled proaerolysin (FLAER) flow cytometric assay with the pro-diagnosis of non-immune mediated hemolytic anemia. Flow cytometric evaluations (with FLAER and/or CD16, CD24, CD66b) showed a PNH clone of 15% for erythrocytes, 64% for monocytes, and 60% for granulocytes. According to clinical, laboratory, and cytogenetic result the patient was diagnosed with PNH and eculizumab therapy was started. After initiation of eculizumab therapy, abdominal pain attacks disappeared, both hemoglobin and LDH levels normalized, and platelet values increased slightly as expected. Also no adverse reaction was seen due to eculizumab therapy.

## Discussion

Paroxysmal nocturnal hemoglobinuria is a rare, life-threatening, genetic hematological disorder characterized by hemolysis of the red blood cells. The classic manifestation of PNH is dark urine during the night with partial clearing during the day.<sup>7</sup> Its mostly present with hemolytic anemia usually in the form of intravascular hemolysis. The most common presentation is the presence of anemia associated with dark cola-

colored urine that is a manifestation of hemoglobinuria.<sup>8</sup> The latter may be confused with hematuria, and erroneous treatment could be given for urosepsis. Elevated reticulocyte count and serum LDH level with a low serum haptoglobin level in the absence of hepatosplenomegaly are the hallmarks of intravascular hemolysis. The bone marrow is usually markedly erythroid, with decreased or absent iron stores, depending on how long the patient has been losing iron in the urine.<sup>9</sup> Our case was interesting because of unusual presentation with thrombocytopenia. In the literature the frequency of PNH patients presenting with thrombocytopenia is relatively low. In this cases, it is consider that thrombocytopenia may be occur in a hypoplastic bone marrow similar to aplastic anemia (aplastic episodes). Our patient also presenting with recurrent abdominal pain. During diagnosis, 10% to 33% of patients with PNH may present with abdominal pain and other gastrointestinal disorders (dysphagia). These symptoms are more common for classical PNH patients.<sup>10</sup> Routine screening is not mandatory for all patients presenting with these symptoms. However if clinical and laboratory features of intravascular hemolysis and/or cytopenia are observed they should be screened for PNH.<sup>11</sup> In general clinical practice eculizumab treatment is recommended for PNH patients with thrombosis, portal hypertension or renal failure.<sup>12</sup> However some studies with aim to identify thromboembolism (TE) associated risk factors showed that, patients with elevated hemolysis (LDH levels  $\geq 1.5$  times the upper limit of normal [ULN]) at diagnosis were at significantly higher risk for TE than patients with LDH

$<1.5 \times \text{ULN}$ .<sup>13</sup> Brodsky *et al.* reported that patients with LDH levels  $>1.5 \times \text{ULN}$  are under great risk of thrombosis.<sup>14</sup> Furthermore the combination of LDH  $\geq 1.5 \times \text{ULN}$  with the clinical symptoms such as abdominal pain was associated with a greater increased risk for TE than elevated hemolysis or clinical symptoms alone. According to our patient's medical history she presented high LDH levels with fluctuating manner for the last 2 years. Therefore, we decided to start eculizumab therapy because of increased PNH clone size, increased serum LDH level and increased risk of thrombosis. This may prevented thrombosis and increase the quality of life of the patient. PNH is a paroxysmal disease, and it clinical and laboratory findings are not so prominent between attacks. Because of this it may be difficult to make the true diagnosis, and late or misdiagnosis is highly possible. PNH is a disease which diagnosis may be delayed due to variable clinical findings and this may lead to increase the risk of mortality and morbidity.<sup>15</sup> Early diagnosis is important for both to prevent the morbidity and to reduce the risk of mortality.

## Conclusions

In conclusion, we suggest considering PNH diagnosis in patients submitting with a triad of symptoms: thrombocytopenia, iron deficiency anemia, and abdominal pain attacks of unknown etiology. We also encourage physicians to share their similar observations in order to raise the knowledge on this unusual presentation of PNH.

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**Table 1. Laboratory results of the patient before and after Eculizumab treatment.**

Parameter	Pre-treatment	2 months post-treatment
White blood cells (/mm <sup>3</sup> )	4800	6700
Hemoglobin (g/dL)	10.1	12.0
Platelets (/mm <sup>3</sup> )	58,000	78,000
Reticulocyte (%)	5.9	3.2
Lactate dehydrogenase (U/L)	547	227
Direct Coombs test	(-)	(-)
Mean corpuscular volume (fl)	88	92
Haptoglobin (mg/dL)	12	42
Serum ferritin levels (ng/mL)	12	124
Antinuclear antibodies	(-)	(-)
Anti-dsDNA antibodies	(-)	(-)
HBsAg, Hepatitis C virus and HIV serology	(-)	(-)
Lupus anticoagulant (lupus antibody)	(-)	(-)

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