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The presence of paroxysmal nocturnal hemoglobinuria in patients with idiopathic chronic renal failure

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ABSTRACT

Paroxysmal nocturnal hemoglobinuria (PNH) is an acquired clonal stem cell disease. Chronic renal failure (CRF) is defined as progressive deterioration in the regulation of fluid and electrolyte balance of the affected kidney due to a decrease in glomerular filtration rate resulting from various diseases. We also investigated the presence of PNH in follow-up patients diagnosed with end-stage renal failure (ESRD) of unknown etiology in this study.

This study was carried out at the Yuzuncu Yil University in Van, Turkey. Sixteen patients with end-stage renal failure who had unknown etiology from a total of 143 patients were included in the study. The patients' age, gender, hemogram, biochemical parameters, and percentage of PNH clone were examined. PNH clone was analyzed by the Fluorescein Aerolysin method.

Of the patients, 10 (62%) were female, 6 (38%) were male. Hemodialysis was performed in 15 patients (94%) as renal replacement therapy. Fourteen of the patients (88%) had anemia. LDH was elevated in 6 patients (38%), and those with high LDH also suffered from anemia. PNH clone was negative for all patients as determined by FLAER analysis.

A survey of the literature did not result in any study on the presence of paroxysmal nocturnal hemoglobinuria in idiopathic chronic renal failure. This is the first such study with this focus. Based on review of the cases described in the literature, PNH should be considered in the differential diagnosis of renal failure cases which are unexplained and especially those accompanied by hemolysis findings.

Key Words: Chronic renal failure, paroxysmal nocturnal hemoglobinuria, dialysis

Introduction

Paroxysmal nocturnal hemoglobinuria is a rare hematopoietic stem cell disease resulting from a somatic mutation in the PIG-A gene (phosphatidylinositol glycan-complementation class A gene) and characterized by chronic intravascular hemolysis, bone marrow failure, and thrombosis. Under normal conditions, proteins such as DAF (Decay accelerating factor, CD55) and MIRL (Membrane inhibitor of reactive lysis, CD59), which are located on the cell membrane and protect the cell from the effects of lysis by complement, are present. This mutation in the PIG-A gene disrupts the normal structure of glycosyl phosphatidylinositol (GPI), which binds various proteins to the erythrocyte cell membrane, leading to the absence of CD55 and CD59 proteins on the cell surface. As a result, erythrocytes become a clear target for the complement system and uncontrolled intravascular hemolysis occurs (1-4).

The prevalence of PNH disease is 2-5 1,000,000, with a mean age of 33, and is found in equal frequency in males and females (5). The most commonly used method of diagnosis is flow cytometry. With this method, the absence of CD55 and CD59 proteins bound to the membrane by GPI on erythrocytes, granulocytes, and lymphocytes containing the PNH clone on the peripheral side can be shown. One of the most effective methods for the detection of GPI antigens is the FLAER (Fluorescein Aerolysin) method. FLAER has high sensitivity and is able to detect as little as 0.01% of PNH clones (6). Screening for PNH is recommended in the presence of recurrent hemoglobinuria, coombs negative intravascular hemolysis, aplastic anemia, myelodysplastic syndrome (refractory anemia or multilineage dysplasia) and/or venous thrombosis in abnormal regions. PNH should be considered and screened for in cases of unexplained abdominal pain, fatigue, dysphagia, dyspnea, erectile dysfunction, iron deficiency, cytopenias, and renal insufficiency accompanied by hemolysis (6).

Recurrent acute renal damage due to pigmentation (pigment nephropathy) can be seen in the acute phase of chronic hemolysis in PNH. Renal involvement has been reported in advanced stages and may present with clinical manifestations

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ranging from chronic renal disease to end-stage renal failure (7). Renal involvement, such as chronic renal failure, is related to chronic tubular hemosiderin deposition, and most patients are clinically asymptomatic. As renal involvement can be observed in the course of PNH, PNH patients diagnosed with renal involvement have also been reported (8).

Chronic renal failure (CRF) is the progressive deterioration in the regulation of fluid-electrolyte balance of the affected kidney resulting from a decrease in glomerular filtration rate levels, due to various diseases. CRF is defined as a reduction in objective renal damage and/or the glomerular filtration rate (GFR) to below 60 ml/min 1.73 m^2 for a period of at least three months. A GFR rate below 15 mL/min/1.73 m^2 is defined as end-stage renal failure (ESRD). CRF may be related to a number of factors, and the frequency of these varies by country. In the United States, 39% of end-stage renal failure is caused by diabetes mellitus, 26% is due to hypertension, and 11% results from glomerulonephritis (9). In Turkey, the most reliable data on the causes of end-stage renal failure have been obtained by the Turkish Society of Nephrology. According to its 2015 Registry Report, chronic glomerulonephritis, diabetes, and hypertension were the most frequent causes of chronic renal failure in Turkey (Table 1). The report found no cause in 22% of diagnosed cases of CRF (10).

In the present study, we investigated the presence of paroxysmal nocturnal hemoglobinuria (PNH) in follow-up patients with an unexplained diagnosis of ESRD.

Materials and methods

Out of 143 patients diagnosed with ESRF, sixteen patients whose ESRF was of indeterminate etiology were enrolled in the study at the Department of Internal Medicine of Yuzuncu Yil University in 2016. The mean age, sex, hemogram parameters (hemoglobin, leukocyte count, platelet count, MCV), lactate dehydrogenase (LDH), indirect bilirubin, direct Coombs test, iron, total iron binding capacity (TDBC), ferritin, folate, vitamin B12 levels, history of thrombosis, peripheral blood smear, and PNH clone percentage were examined. The patients were screened for PNH by means of the Fluorescein Aerolysin (FLAER) test from peripheral blood.

Results

Ten of the patients (62%) were female and 6 (38%) were male; the mean age was 52 ± 8 (22-74). Three of the patients (19%) were younger than 40 years of age. Hemodialysis was performed in 15 patients (94%) and peritoneal dialysis in 1 patient (6%) as renal replacement therapy. The general characteristics of the patients are summarized in Table 2.

Regarding laboratory evaluations, all patients were found to have normal leukocyte counts and platelet counts. The mean hemoglobin level of the patients was 10.8 gr/dL (9.6 gr/dL - 12.2 gr/dL). Fourteen of the patients (88%) had anemia. Erythrocyte

Table 1. Causes of chronic renal failure (CRF) in Turkey

Etiologic cause	Frequency (%)
Chronic glomerulonephritis	21
Diabetic nephropathy	16
Hypertension, nephrosclerosis	16
Urological (stone, obstruction, etc.)	8
Chronic interstitial nephritis	7
Chronic kidney diseases	5
Others (of known cause)	6
Unknown	22

Table 2. General characteristics of the study patients

Characteristics	Number	Frequency (%)
Female	10	62
Male	6	38
Age		
<40 years	3	19
>40 years	13	81
Renal replacement modality		
Hemodialysis	15	94
Peritoneal dialysis	1	6
Total	16	

Table 3. Clinical and laboratory results of the study patients

Parameter	Number	Frequency (%)	(Lowest – highest level)
Low hemoglobin	14	88	(9.6 gr/dL -12.2 gr/dL)
Elevated LDH	6	38	(162 U/L - 348 U/L)
Elevated indirect bilirubin	3	19	(0.4 mg/dL -1.4 mg/dL)
Low haptoglobin	1	6	(20 mg/dL - 180 mg/dL)
Positive direct Coombs test	0	0	
History of thrombosis	0	0	
Unexplained cytopenia	0	0	
Positive PNH clone	0	0	

morphology was normal in the peripheral smears of patients with anemia. Levels of iron, vitamin B12, and folate were normal in all patients with anemia, while total iron binding capacity (TIBC) was low and ferritin was elevated. Patients with high ferritin were all receiving intermittent iron replacement. LDH was elevated in 6 patients (38%), all of whom also had anemia. Indirect bilirubin was elevated in 3 patients (19%) and haptoglobin was low in one patient (6%). All patients with indirect bilirubin elevation and/or low haptoglobin had anemia and underwent hemodialysis. All patients were PNH clone negative as indicated by FLAER. Clinical and laboratory findings for the study patients are summarized in Table 3.

Discussion

Paroxysmal nocturnal hemoglobinuria causes uncontrolled complement activation, resulting in the development of intravascular hemolysis, which in turn can lead to anemia, bone marrow failure, renal dysfunction, pulmonary hypertension, and thromboembolic complications (11). Initial PNH indicators are divided into 3 subgroups in terms of clinical findings and natural course of the disease. The first is classical PNH, which presents with intravascular hemolysis, the second is PNH associated with bone marrow deficiencies such as aplastic anemia and myelodysplastic syndrome, and the third is defined as subclinical PNH without clinical hemolysis (11). In the course of intravascular hemolysis, acute renal failure due to massive hemoglobinuria develops following severe hemolysis attacks. The main pathology in this case is acute tubular necrosis. Other scenarios encountered include chronic interstitial disease resulting from chronic renal failure, chronic hemosiderin accumulation, and chronic renal failure with arterial nephrosclerosis (12,13). Although renal involvement in paroxysmal nocturnal hemoglobinuria is rare, both acute and chronic renal failure have been identified (14,15). In one study, renal insufficiency developed in 64% of paroxysmal nocturnal hemoglobinuria patients, of whom 21% were reported to have end-stage renal failure at the 10-year follow-up (16). A review of the literature reveals only a limited number of case-based reports of chronic renal failure caused by paroxysmal nocturnal hemoglobinuria (7, 15-17). All cases in the present study consist of patients with end-stage renal failure of unknown etiology.

While LDH levels that we can evaluate as hemolytic findings may be higher than normal by several fold in classical PNH, in subclinical PNH accompanied by bone marrow deficiencies, LDH can be observed at normal levels (11). In the cases in the present study, LDH levels were up to 1.5 times higher than normal. There were no abnormal hemolysis findings suggesting severe hemolysis. As PNH patients undergo continuous intravascular hemolysis, hemoglobiuria and hemosiderinuria can lead to severe iron loss. Morphologically, normochromic normocytic anemia or hypochromic microcytic anemia develops (11). In the cases in the present study, anemia was normochromic normocytic and was accepted as an anemia of chronic disease related to CRF based on the study results.

The most important complication that develops in the course of PNH is thrombotic events, which affect the abdominal veins. Thrombotic events occur frequently in hepatic, splenic, mesenteric, renal, and portal veins (18). None of the patients in our study had a history of arterial or venous thrombosis. In PNH, indirect bilirubin increases as a result of intravascular hemolysis, and haptoglobin, which binds free hemoglobin, decreases (11). In our patients there was slight elevation of indirect bilirubin elevation and low haptoglobin, a situation attributed to the mechanical effect of hemodialysis. In PNH patients, especially in those with bone marrow failure such as platelet

anemia or myelodysplastic syndrome, cytopenias can be seen in one or more batches (11). In our cases, excepting anemia, there was no leukopenia or thrombocytopenia.

In summary, we did not find any study in the literature on paroxysmal nocturnal hemoglobinuria in idiopathic chronic renal failure, making ours the first such study. However, we believe that further studies involving many more patients are necessary in order to obtain the true incidence of PNH in idiopathic chronic renal failure. Based on our review of cases described in the literature, we recommend that paroxysmal nocturnal hemoglobinuria be considered in the differential diagnosis of renal failure cases of indeterminate etiology and accompanied by hemolysis findings.

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