

Chronic Renal Failure Secondary to Paroxysmal Nocturnal Hemoglobinuria

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ABSTRACT

Paroxysmal nocturnal hemoglobinuria (PNH) is a rare and acquired stem cell disease which is characterized with chronic intravascular hemolysis and diffuse venous thrombosis. In PNH, renal failure is rare and acute renal failure, which is caused by hemolytic attacks that are usually triggered by infection and surgical intervention, may happen. A 48-year old male patient who had chronic renal failure (CRF) and has been hemodialysing for about 11 years was admitted to our hospital with the symptoms of pancytopenia. Although Ham's test and sugar water test of our patient were negative, with the results of bone marrow aspiration-biopsy, abdominal MRI and flow cytometry tests, we found out that pancytopenia was due to PNH with type II cells dominancy and CRF was due to hemosiderosis.

Key Words: Chronic renal failure, Paroxysmal nocturnal hemoglobinuria, Hemosiderosis

ÖZET

Paroksizmal Nokturnal Hemoglobinüriye Sekonder Gelişen Kronik Böbrek Yetmezliği

Paroksizmal nokturnal hemoglobinüri (PNH) kronik intravasküler hemoliz ve yaygın venöz trombozlarla karakterize yaygın, kazanılmış bir kök hücre hastalığıdır. PNH'de böbrek yetmezliği nadirdir ve genellikle enfeksiyonun ve cerrahi müdahalelerin tetiklediği hemolitik ataklar sonucunda gelişen akut böbrek yetmezliği görülmüştür. Kronik böbrek yetmezliği (KBY) olan ve yaklaşık 11 yıldır hemodiyalize giren 48 yaşındaki erkek hasta pansitopeni semptomlarıyla hastanemize başvurdu. Hastanın yapılan şeker su ve Ham's testleri negatif gelmesine rağmen, yapılan kemik iliği aspirasyon-biyopsisi, batin MR ve akım sitometri testleri neticesinde pansitopeninin, tip II hücrelerin çoğunlukta olduğu PNH'e ve KBY'nin ise hemosiderosise bağlı olduğu saptandı.

Anahtar Kelimeler: Kronik böbrek yetmezliği, Paroksizmal nokturnal hemoglobinüri, Hemosiderozis

INTRODUCTION

PNH is a rare acquired clonal disease of hematopoietic stem cells caused by an unusual susceptibility of erythrocytes to the lytic action of complement due to their membrane abnormalities and it is characterized by chronic intravascular hemolysis and thrombotic tendency. The absence of complement regulatory proteins CD55 and CD59 in the red cell membrane results in complement-mediated hemolysis and hemoglobinuria. Hemolysis is continuous but episodes of exacerbation of red blood cell lysis occur. Venous thromboses are frequent and usually involve mesenteric, portal, hepatic and cerebral veins. There is definite relationship with aplastic anemia and also with myelo-proliferative disorders (1).

In PNH, renal failure is rare and acute renal insufficiency has been recognized previously in association with an acute hemolytic crisis (2). However, kidney involvement is usually benign and secondary to chronic deposition of hemosiderin in the proximal convoluted tubule, that cause a mild tubular dysfunction manifest as a concentrating defect (3). In addition to this renal siderosis leading apparently to several tubular atrophy and interstitial fibrosis, recurrent microvascular thrombosis as a result of microinfarctions or direct nephrotoxicity of iron or repeated episodes of pyelonephritis may also has a role in progression to chronic renal insufficiency. We reported a case of CRF patient whose etiology was later determined as PNH.

CASE REPORT

A 48-years old male patient, who had chronic renal failure (CRF) and has been hemodialysing for about 11 years, was admitted to our clinic with the complaints of weakness and tiredness which was persisting for about two months. He had transfusi-

ons with frequent intervals and had no history of hypertension, diabetes mellitus and any other chronic diseases. In addition, there was also no history of drug usage. Physical examination of the patient was normal except pallor, pretibial edema and mild splenomegaly. His blood cell count showed pancytopenia with results Hgb: 7.16 g/dL, MCV: 92.5 fl, corrected reticulocyte: 3.4%, Plt: 550 x10⁹/L and Neu: 0.645 x10⁹/L. Increased biochemical parameters are indirect bilirubin: 1.1 mg/dl (N:0-0.8), BUN: 69 mg/dL (N:7-25), creatinin: 11.75 mg/dL (N:0.6-1.2) and ferritin: 964 ng/ml (N:22-232). Other parameters are serum iron: 116 µg/dL (N:25-160), total iron binding capacity: 246 µg/dL (N:250-425), and transferin saturation: 47%. The patient's LDH, Vitamin B₁₂, folic acid, prothrombin time and INR values were all in normal ranges. HBsAg, Anti-HCV and Anti-HIV were negative. Only once and very limited amount of urine sample could be taken owing to the patient's anuric situation and many bladder epithels were detected in urine sediment without any hemosiderin. With the suspect of PNH, Ham's test and sugar water test were done. Both Ham's test and sugar water test were negative. Blood marrow aspiration-biopsy revealed accelerated erythropoiesis with hypercellular, megaloblastoid and displastic characters and increased in number of hemosiderin granules and sideroblasts.

Flow cytometry analysis of peripheral blood demonstrated that erythrocytes with partial CD 55 and CD 59 expression were dominated (Table 1). The percentage of CD 55 and CD 59 negative granulocytes was 1.2% and 11.5% (Figure 1). This flow cytometry test was done four weeks after transfusion and as a result of this test, patient was diagnosed as PNH. Echocardiographic study of the patient was normal. In the patient's abdominal doppler ultrasonography (USG), hepatosplenomegaly was de-

Table 1. Flow cytometric analysis of erythrocytes of the peripheral blood

	Type I cell (normal expression)	Type II cell (partial defficiency)	Type III cell (total deficiency)
CD 55 expression	0.7%	86.9%	11.6%
CD 59 expression	1.1%	97.1%	1.6%

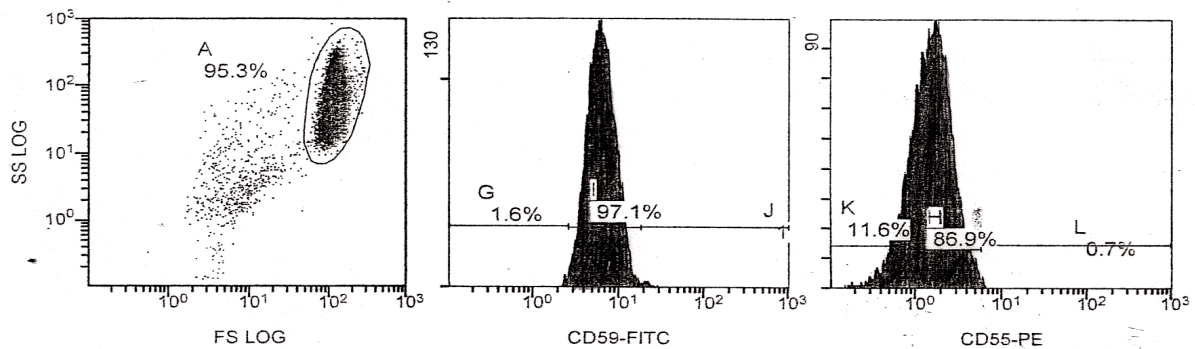


Figure 1. Schematic appearance of erythrocytes' flow cytometry investigation

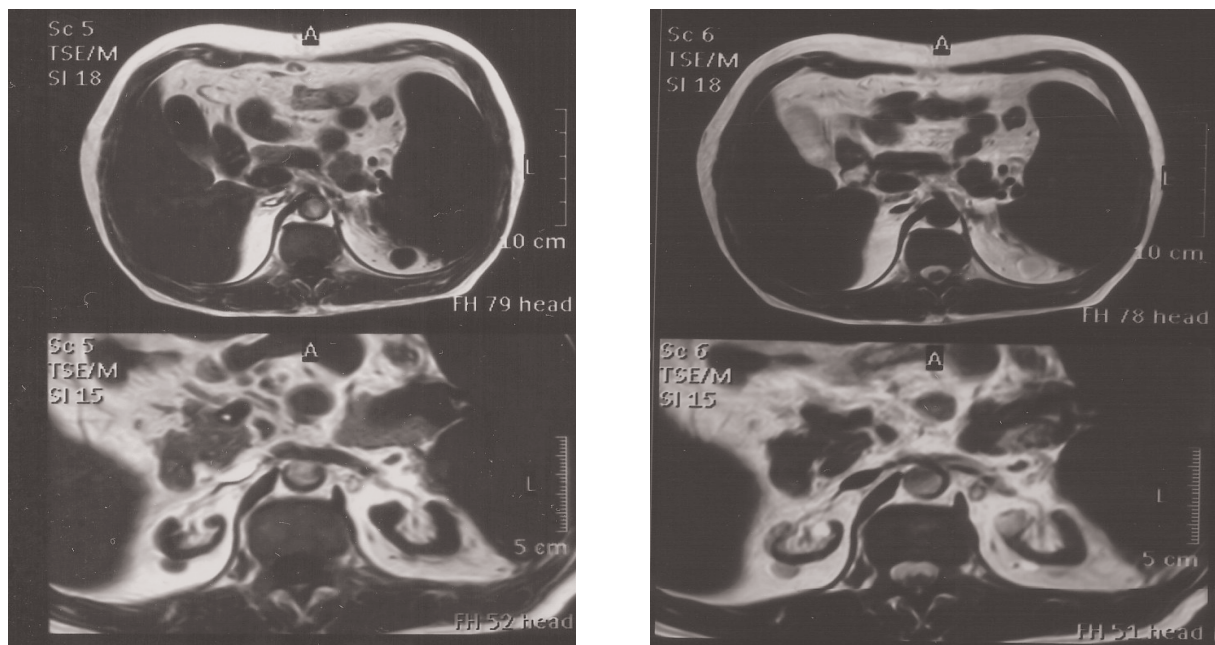


Figure 2. T1 and T2 weighted images showing hemosiderosis in liver, spleen and kidneys

tected without any ascites. In addition, portal and splenic veins were found as open. As a result of these findings, he was considered as cirrhosis in the compensated phase. The patient had a past medical history of liver biopsy in another center for about two years ago. However pathological result of this biopsy could not be achieved and one more biopsy was not accepted by the patient. After all, because of the high ferritin value, hepatosplenomegaly and increased hemosiderin staining in blood marrow, in order to investigate hemosiderin deposition in the renal cortex, abdominal magnetic resonance imaging (MRI) was applied due to its high imaging qu-

ality for searching hemosiderin deposition (Figure 2). Abdominal MRI showed low signal intensity of spleen, liver and bilateral renal paranchymas in T2 weighted images which was attributed to hemosiderosis (4).

DISCUSSION

PNH is a chronic condition with a median survival of 10-25 years after diagnosis. It is associated with venous thrombosis in at least one third of PNH patients, hemorrhage from thrombocytopenia and infection due to neutropenia (5). Azotemia has occa-

sionally been seen in patients with PNH. Acute renal failure may occur during severe hemoglobinuric crisis which may be precipitated by blood transfusions, infections, surgical procedures, contrast media, reaction to drugs, sleep and even exercise (6). By the effect of these stimulants, there is excess complement production resulting hemoglobinuria that acts as a tubular toxin and causes acute renal dysfunction. Microvascular thrombosis, thought to be due to abnormal platelet function, is also common in PNH and felt to contribute acute renal dysfunction during hemolytic crisis. The reduced renal function was short lived with return to normal in few weeks after the termination of crisis. However, in some severe hemolytic attacks, patients could require transient dialytic support for recovering their renal functions.

There are few case reports in literature search, concerning the association between PNH and chronic renal failure. It is obvious that renal hemosiderosis has been observed in chronic intravascular hemolysis. Renal siderosis leads apparently to severe tubular atrophy and interstitial fibrosis which causes renal insufficiency. However, some authors believe that PNH can cause renal failure mostly as a result of microinfarctions due to repeated episodes of microvascular thrombosis rather than to this hemosiderin deposition (7). Others stated that chronic renal failure was a consequence of repeated episodes of pyelonephritis. It is also suggested that iron might play an important role in the nephrotoxicity associated with hemoglobinuria. So, the authors believed a direct nephrotoxic effect of iron (3).

In our case, we described a patient who had chronic renal failure with an unknown etiology. He was admitted with symptoms of pancytopenia. At first sight, it was thought that pancytopenia was because of chronic hemodialysis complication. However, by the help of flow cytometry investigation, PNH was diagnosed even if the Ham's test was negative (8). Flow cytometric analysis, in which antibodies are directed against complement regulatory proteins CD55 and CD59, is the most informative and sensitive assay available for diagnosis of PNH. This analysis identify a population of CD55 and CD59 deficient cells. In addition, it can both evaluate the percentage of abnormal cells and identify discrete populations with different degrees of deficiency particularly on erythrocytes. Erythrocytes with nor-

mal expression are called PNH I, those with subnormal expression having usually 10% of normal expression are called PNH II, those with complete deficiency are called PNH III. As transfusion will increase the proportion of cells with normal expression of CD55 and CD59, flow cytometric assay will be affected by recent red blood cell transfusion. Therefore, to detect accurate information, analysis should be performed at least 1 month before the transfusion or during a transfusion absent period. In order to obtain additional information, analysis of expression of CD55 and CD59 on granulocytes may be useful. The life span of PNH granulocytes is normal in contrast to CD55 and CD59 deficient red blood cells. Therefore, the proportion of abnormal granulocytes is unaffected by red blood cell transfusion and more accurately detects the PNH clone size. Patients with subclinical symptoms have little or no clinical evidence of hemolysis. Because of having small PNH clones, most of these patients have refractory anemia or aplastic anemia. For this reason, both at diagnosis and yearly after treatment, even in the absence of biochemical or clinical evidence of hemolysis, high sensitive flow cytometric analysis is recommended for these patients (9). Ham's test does not detect small populations of abnormal cells which results in a decrease in sensitivity. The degree of lysis does not accurately reflect the proportion of abnormal cells and the degree of abnormality of the abnormal cells cannot be assessed. The sucrose lysis test is technically easier to perform but has a higher rate of false-positive results thus decreasing its specificity. Although it more accurately detects the proportion of PNH-type III red blood cells than the Ham's test, it likewise does not delineate the abnormality of these cells and does not quantitatively delineate the number of PNH-type II cells. Further, flow cytometry distinguishes much better the cells of intermediate abnormality of PNH cells (10).

After all, because the patient had chronic compensated hemolysis and had a history of multiple blood transfusions owing to his low hemoglobin value, hemosiderosis was suspected for the etiology of his renal insufficiency. So, we had two main opportunities in order to demonstrate hemosiderosis. One is renal biopsy which seems unnecessary because of being end stage renal failure and the other method is MRI which shows the renal cortical hemosiderosis.

Abdominal MRI was done to study the iron deposition and revealed low signal intensity not only in renal paranchymas but also in liver and spleen, on T2 weighted images. On MRI, normal kidneys show low or medium signal intensity on T1 weighted images and the renal cortex being slightly hyperintense with respect to the medulla causing a relatively good differentiation. In normal kidneys, on T2 weighted images, the cortex and medulla have a very similar and moderately high signal intensity causing no distinction between them (3). When hemosiderin deposition occurs in the renal cortex, it becomes darker than renal medulla reversing their differentiation on T1 weighted images. Hemosiderin contains ferric iron and deposits of hemosiderin explain low signal intensity of the renal cortex depicted in T2 weighted images which is also a characteristic finding in our patient's MRI. When transfusional siderosis is absent, low signal intensity confined to the kidney suggests PNH, whereas low signal intensity limited to the spleen and liver is characteristic of transfusional hemosiderosis and hemochromatosis (7). However, iron deposits were demonstrated not only in kidneys but also in liver and spleen depending on receiving multiple blood transfusions and resulting decreased signal intensity on MRI (3,11).

In summary, this a case of chronic renal failure who has been hemodialysing for years with an unknown PNH etiology. Chronic renal failure in PNH is a diagnosis of exclusion so that careful diagnostic workup is mandatory (12). In fact, very little is known about the mechanism leading to renal failure in PNH. The role of hemosiderosis in chronic renal failure may be more significant and postmortem studies of patients with PNH suggested that hemosiderosis contributes to nephrosclerosis, even among the relatively asymptomatic patients (4). Here, we noninvasively showed hemosiderosis which is caused by both chronic compensated hemolysis due to clinically mild PNH and multiple blood transfusions, by MRI findings.

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