Autoimmune hemolytic anemia as a complication of primary biliary cirrhosis

Carlos R de MEDEIROS, Daniela C SETÚBAL

Hematology and Bone Marrow Transplantation Service, HC-UFPR, Curitiba, PR, BRAZIL

Turk J Haematol 2004;21(3): 153-155

Received: *06.05.2004* ***Accepted:*** *17.05.2004*

ABSTRACT

Primary biliary cirrhosis (PBC) is characterized by a continuous T-lymphocyte mediated attack on small intralobular bile ducts, with their gradual destruction. Patients with PBC often exhibit concomitant autoimmune conditions, and autoimmune hemolytic anemia (AIHA), that is idiopathic in 50% of cases, has rarely been associated to PBC. Ursodeoxycholic acid (UDCA) has been considered the main treatment to PBC patients through a decrease in the detergent effect of endogenous bile acids, concomitantly reducing the hemolytic process. We report the case of a female patient with AIHA complicating PBC, treated with short course prednisone and UDCA, with good response.

Key Words: Primary biliary cirrhosis, Anemia, Hemolytic, Autoimmune, Ursodeoxycholic acid.

ÖZET

Primer biliyer sirozun komplikasyonu olarak otoimmün hemolitik anemi

Primer biliyer siroz (PBS), küçük intralobuler safra yollarına sürekli T-lenfosit aracılıklı bir saldırı sonucu, bunların hasarlanması ile karakterize bir hastalıktır. PBS'li hastalar, hastalıklarının seyri sırasında başka otoimmün hastalıklarla karşılaşabilirler. Otoimmün hemolitik anemi ile PBS birliği çok nadir bildirilmiştir. Ursodeoksikolik asit (UDCA), endojen safra asitlerinin deterjan etkisini azaltarak, birlikte olan hemolitik süreci de azaltır. Bu yazıda PBS seyri sırasında otoimmün hemolitik anemi görülen; UDCA ve kısa süreli prednizon ile iyi yanıt alınan bir kadın hasta bildirilmektedir.

Anahtar Kelimeler: Primer biliyer siroz, Anemi, Hemolitik, Otoimmün, Ursodeoksikolik asit.

INTRODUCTION

Autoimmune hemolytic anemia (AIHA) is characterized by a positive Coombs' test, and may be classified in "warm" and "cold" type, if the antibodies react better with red cells at 37°C or at 4°C. Primary biliary cirrhosis (PBC) mainly affects middle-aged women and is characterized by progressive cholestasis. Up to 80% of PBC patients have one associated autoimmune condition (mainly collagen and thyroid immune diseases), and almost 40% have two or more. However, AIHA has rarely been described in association with PBC. To our knowledge, only 11 cases of PBC associated to AIHA have been reported in literature[1]. We report a case where the association of PBC and AIHA was diagnosed, with the AIHA responding to a short course of prednisone and remaining stable with ursodeoxycholic acid (UDCA) as maintenance therapy.

A CASE REPORT

A 50-years old asymptomatic female patient was referred to our service because of anemia and leukopenia. She had no history of recent use of medications, but had a severe retinal illness, that caused her a lost of 60% of visual acuity in both eyes, on last four years. The rest of physical examination was normal except for a discrete hepatic enlargement. Hemoglobin was 110 g/L, reticulocyte count 30 x 10^9/L, normochromic and normocytic red blood cells (RBC). White blood cell count was 3 x 10^9/L, with normal differential count. A positive antinuclear antibody (1: 640), as well as elevation of alkaline phosphatase and gammaglutamyl transpeptidase, was detected. Following, the presence of antimitochondrial antibodies strongly suggested the diagnosis of PBC. She went to a percutaneous liver biopsy, where inflammation and fibrosis confined to portal space and focal granulomas were demonstrated (stage I PBC). Surprisingly, after the biopsy the patient hemoglobin importantly decreased to 70 g/L, and large polychromatophilic red blood cells with increase of reticulocyte count were present on blood smear. Then, a positive direct antiglobulin test (Coombs' test) for IgG and C3d was found, confirming the diagnosis of "warm" AIHA complicating PBC. The treatment was started on with prednisone (1 mg/kg day) and UDCA (13 mg/kg day). After a short course (two weeks), we rapidly decreased the prednisone dose, in an attempt to avoid more collateral effects of the drug on the retinal illness, but maintaining UDCA at same dose. Two months later, the patient had no evidence of hemolysis, with normal hematocrit and a negative Coombs' test.

DISCUSSION

AIHA is idiopathic in 50% of cases, or secondary to medication (methyldopa, quinidine, penicillin), viral infections (usually in children), hematological malignancies (chronic lymphoid leukemia, lymphoma and myeloma) and reumathological disorders (lupus and rheumatoid arthritis)[2]. PBC is characterized by a continuous T-lymphocyte mediated attack on small intralobular bile ducts, leading to their gradual destruction and eventual disappearance. The sustained loss of intralobular bile ducts results in cirrhosis and liver failure. Secondary damage to hepatocytes may occur from the accumulation in the liver of increased concentrations of potentially toxic substances, such as bile acids. The naturally occurring bile acids (as cholic acid, chenodeoxycholic acid and deoxycholic acid) are all detergents and can dissolve cell membranes[3]. In vitro, they have also been shown to damage red cell membrane. So, the expositions of "hidden" red cells antigens probably lead to the hemolytic process[4].

Treatment of PBC has two goals: to control symptoms and complications of chronic cholestasis and to cease the destruction of bile ducts. The latter goal has been difficult to achieve. Immunosuppression (glucocorticoids, azathioprine, and cyclosporine) barely decreases some enzymatic levels of PBC patients, but survival free of liver transplantation is not prolonged. However, UDCA delays the progression to end-stage liver disease,

enhances survival and is well tolerated. Despite the incomplete understanding of UDCA mechanism of action, it apparently decreases the endogenous bile acid (and its detergent effect) and the immune-mediated destruction of hepatocytes[5]. Therefore, it may also reduce the hemolytic process.

So, the association of UDCA to prednisone used to treat our patient showed us an interesting result: fast resolution of hemolysis followed by a negative Coombs' test, and possibility of short term use of prednisone in a dose capable of provoke more intense collateral effects to our patient.

REFERENCES

1. Nakasone H, Sakugawa H, Fukuchi J, Miyagi T, Sugama R, Hokama A, Nakayoshi T, Kawakami Y, Yamashiro T, Kinjo F, Saito A, Taira N, Toda T, Kan I. A patient with primary biliary cirrhosis associated with autoimmune hemolytic anemia. J Gastroenterol 2000;35:245-9.
2. Gehrs BC, Friedberg RC. Autoimmune hemolytic anemia. Am J Hematol 2002;69:258-71.
3. Kaplan MM. Primary biliary cirrhosis. N Engl J Med 1996;335:1570-80.
4. Fuller SJ, Kumar P, Weltman M, Wiley JS. Autoimmune hemolysis associated with primary biliary cirrhosis responding to ursodeoxycholic acid as sole treatment. Am J Hematol 2003;72:31-3.
5. Poupon RE, Bonnand AM, Chretien Y, Poupon R. Ten-year survival in ursodeoxycholic acid treated patients with primary biliary cirrhosis. The UDCA-PBC study group. Hepatology 1999;29:1668-71.

Address for Correspondence:

Carlos R de MEDEIROS, MD

Hematology and Bone Marrow
Transplantation Service, Hospital de Clinicas
UFPR, Rua General Carneiro 181
80060-900, Curitiba, PR, BRAZIL

e-mail: *crdemedeiros@hotmail.com*