Primary biliary cirrhosis and hemolytic anemia confusing serum bilirubin levels

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M Brackstone, CN Ghent. Primary biliary cirrhosis and hemolytic anemia confusing serum bilirubin levels. *Can J Gastroenterol* 2000;14(5):445-447. Hemolysis is observed in more than 50% of patients with cirrhosis. However, there has been little documentation of the association of primary biliary cirrhosis with autoimmune hemolytic anemia. Two cases, found within a single practice, of primary biliary cirrhosis coexisting with autoimmune hemolysis and a third case coexisting with hereditary spherocytosis are presented. Anemia in such patients is commonly attributed to chronic disease, and hyperbilirubinemia is attributed to primary biliary cirrhosis. These patients were considered for liver transplantation until the diagnosis of a comorbid hemolytic process was established. This association may be more prevalent than previously recognized. A diagnosis of comorbid hemolysis must always be considered in context with anemia and serum bilirubin levels that rise out of proportion to the severity of the primary biliary cirrhosis.

Key Words: Hemolytic anemia; Primary biliary cirrhosis; Serum bilirubin levels

Cirrhose biliaire primitive, anémie hémolytique et taux de bilirubine sérique

RÉSUMÉ : Plus de 50 % des patients souffrant de cirrhose présentent aussi de l'hémolyse. Cependant, il existe peu de documentation sur la concomitance de la cirrhose biliaire primitive et de l'anémie hémolytique auto-immune. Voici deux cas, observés dans un même cabinet, de cirrhose biliaire primitive associée à une hémolyse auto-immune et un troisième cas de même maladie associée à une microsphérocytose héréditaire. L'anémie est généralement attribuée à la maladie chronique, et l'hyperbilirubinémie, à la cirrhose biliaire primitive. Les patients dont le cas est exposé ci-dessous étaient candidats à une transplantation du foie jusqu'à ce qu'un diagnostic de processus hémolytique comorbide fût posé. Ce type d'association est peut-être plus fréquent qu'on le pense. Il faut donc toujours envisager la possibilité d'hémolyse comorbide dans les cas où l'anémie et les taux de bilirubine sont hors de proportion par rapport à la gravité de la cirrhose biliaire primitive.

Primary biliary cirrhosis (PBC) is a chronic cholestatic disease, characterized by progressive fibrosis with septal and interlobular duct destruction (1). PBC is most common in women and is often associated with other autoimmune diseases such as scleroderma, rheumatoid arthritis, thyroiditis and polymyalgia rheumatica, and consequently is considered a prototypical autoimmune disease (1).

Hemolysis is observed in more than half of all patients with cirrhosis, regardless of their disease etiology (2). However, little literature is available regarding any association

between PBC and autoimmune hemolytic anemia, or other severe hemolytic states (3).

Two patients seen within a single practice, a case of hereditary spherocytosis coexisting with PBC and a literature review to suggest that autoimmune hemolytic anemia may be considered another autoimmune disease associated with PBC are presented. The relevance of this association lies in the effect of the comorbid hemolysis that raises serum bilirubin levels, such that missing the hemolysis diagnosis may confuse the physician into thinking that the PBC is more se-

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Figure 1 Serum bilirubin ($\mu\text{mol/L}$) and hemoglobin ($10^{-9}/\text{L}$) levels before, during and after treatment for hemolytic anemia in patients with primary biliary cirrhosis

vere than it actually is. The case of hereditary spherocytosis is presented to illustrate further this problem.

CASE PRESENTATIONS

Patient 1: A 49-year-old woman presented in 1988 with general fatigue and pruritus. The diagnosis of PBC was confirmed by a positive test for mitochondrial antibodies and a liver biopsy that showed stage IV PBC. She was treated with cholestyramine and ursodiol. Her disease was considered to be stable (alanine aminotransferase 168 $\mu\text{mol/L}$, aspartate aminotransferase 157 $\mu\text{mol/L}$, alkaline phosphatase 551 $\mu\text{mol/L}$ and bilirubin 17 $\mu\text{mol/L}$). Her course was complicated by hypothyroidism and osteodystrophy. In February of 1997, her jaundice had worsened (bilirubin 235 $\mu\text{mol/L}$) without any appreciable change in liver enzyme levels. Abdominal ultrasound showed no dilation of the bile ducts. She complained of dark urine and pale stools, and her jaundice was considered to reflect her worsened cholestasis. Her physical examination confirmed palpable splenomegaly, without lymphadenopathy or palpable hepatomegaly. However, her lactic dehydrogenase (LDH) level was greater than 1000 and her hemoglobin level fell to 82 g/L with a mean corpuscular volume of 113 fL and a reticulocyte count of 693.

A direct antiglobulin test was positive for immunoglobulin G. It was determined that she had cold type autoimmune hemolytic anemia. Because of concerns about the predictable negative effects of steroids on her osteodystrophy, liver transplantation for PBC combined with splenectomy for the hemolytic anemia was considered. However, a trial of prednisone 50 mg/day was elected, with ursodiol 1 g/day, alendronate 10 mg/day, thyroxine 100 $\mu\text{g/day}$, folic acid 10 mg/day and cholestyramine 4 g bid to maintain therapy. Her serum bilirubin level promptly fell from 235 to 45 $\mu\text{mol/L}$, and her hemoglobin level rose from 82 g/L to 119 g/L (Figure 1). After six months of prednisone treatment, steroids were withdrawn and she maintained pretreatment levels of hemoglobin and bilirubin for the subsequent year.

Patient 2: A 66-year-old woman presented in 1991 with a 13.6 kg weight loss over 12 months, with worsening pruritus and fatigue over six months. Her history included osteoarthritis and a cholecystectomy, but no risk factors for chronic liver disease and no known autoimmune diseases. She tested positive for mitochondrial antibodies, and her immunoglobulin M level was 9.5 g/L. She was shown to have stage III PBC on liver biopsy and was treated with cholestyramine and ursodiol. In 1993, she developed dyspnea and pallor, and was found to be anemic with a hemoglobin level of 58 g/L. Her bilirubin level rose from 7 to 26 $\mu\text{mol/L}$ (Figure 1). A direct antiglobulin test was positive for warm type hemolytic anemia. Treatment with prednisone 20 mg/day was elected; azathioprine 100 mg/day was started after she responded to prednisone. The prednisone dose was tapered and discontinued after one year. She remained on azathioprine 100 mg/day with normal blood counts in the subsequent three years of follow-up.

Patient 3: A 35-year-old woman was referred for liver transplantation assessment for PBC of 30 months. She was obviously icteric and had a palpable spleen 6 cm below the costal margin, without palpable hepatomegaly or other signs of portal hypertension. Upper gastrointestinal endoscopy showed no signs of portal hypertension. Review of a previous liver biopsy showed stage 1 PBC and normal liver function (albumin 41 g/L, international normalized ratio 1.0). Alkaline phosphatase was 161 $\mu\text{mol/L}$, bilirubin 49 $\mu\text{mol/L}$ and anti-mitochondrial antibody was positive at one to 64 dilution. Her serum hemoglobin level was 111 g/L, and review of a blood film showed microspherocytes. Further investigation of her family history confirmed splenomegaly, anemia and spherocytosis in the patient's father. Splenectomy was performed to treat her hereditary spherocytosis. The liver appeared grossly normal to the surgeon, and her serum bilirubin level fell to 15 $\mu\text{mol/L}$ postoperatively (Figure 1).

DISCUSSION

An association between PBC and various other autoimmune conditions has been described clearly (1-5). In addition, the presence of reduced red blood cell survival with all types of cirrhosis, including PBC, has been well documented (1). The mechanism for this is not clear and may involve intracorporeal or extracorporeal mechanisms (1). Because of

the common association between PBC and other autoimmune conditions, it is logical to consider that autoimmune hemolysis may be another condition seen in association with PBC, and creates more potential for confusion in recognizing and characterizing anemia, and/or hyperbilirubinemia in this setting.

This case series presents two patients with autoimmune hemolysis, and one with hereditary spherocytosis that demonstrate the diagnostic problems arising when PBC and hemolysis coexist. One patient had cold type and another had warm type autoantibodies to red blood cells; both patients experienced autoimmune hemolysis to steroid treatment with resolution of jaundice and anemia. It is surprising that both patients were able to have steroid treatment withdrawn without a relapse of hemolysis. The patient with hereditary autoimmune hemolytic anemia illustrates that similar confusion about serum bilirubin elevations can arise with other causes of hemolysis in patients with PBC, and that hyperbilirubinemia resolves with appropriate treatment of the hematological disorder. Gilbert's syndrome may likewise produce a confusing, disproportionate elevation of serum bilirubin levels in early PBC but was not present in any of our cases. It should not be associated with anemia and can be readily diagnosed by using bilirubin fractionation and reticulocyte counts.

Surprisingly, there have been few case reports of autoimmune hemolytic anemia associated with PBC (2,6-8). The first report of warm type hemolysis was in a study of red blood cell survival (2). Subsequent case reports (6-8) documented an association between autoimmune hemolytic anemia and PBC. One case report documented autoimmune hemolytic anemia and autoimmune myocarditis in a patient with PBC (9). The remaining literature reports that the attempts made to demonstrate an association between PBC and autoimmune hemolysis were complicated by histories of use of medications that may induce autoimmune hemolytic anemia (8,10-12). This raises concerns that the association may be with the medication rather than with the disease. Two of the patients discussed above illustrate that autoimmune hemolysis is possibly secondary to rifampin for treatment of tuberculosis (8,11). The third patient report discussed autoimmune hemolytic anemia and tiopronin, although hemolysis began before the use of tiopronin (12). Only one case of cold type autoimmune hemolytic anemia and PBC appeared to be without other autoimmune comorbid conditions or drug induction (7). This patient presented with hemolytic anemia four years after PBC was diagnosed. This patient was enrolled in a study to determine the effect of plasma exchange on hemolytic anemia, but died shortly after the study was initiated.

The present cases demonstrate that the onset of autoimmune hemolytic anemia may occur after the diagnosis of PBC. This raises some clinical dilemmas for following the clinical course of PBC with serum bilirubin levels. Unless

the possibility of a secondary diagnosis of some form of hemolysis is considered, the PBC may be considered to be solely responsible for the elevated serum bilirubin level. It is then easy to conclude erroneously that the PBC is advanced and to recommend an inappropriate therapy, as shown in the patient with autoimmune hemolytic anemia. Serum bilirubin levels have long been known to be important in assessing the prognosis of PBC (13,14), and confounding hemolysis may lead to erroneous conclusions about the severity of the disease. Therefore, we recommend that patients with PBC whose serum bilirubin levels are disproportionate to the apparent stage of their disease or whose serum bilirubin levels rise suddenly undergo screening for associated hemolysis.

CONCLUSIONS

The intent of this report is to demonstrate that the association between PBC and autoimmune hemolytic anemia is real and must always be considered, especially in the setting of anemia and serum bilirubin levels that rise disproportionately to the patient's stage of PBC. The literature review documents a number of such cases described in isolation, but the frequency of the association may be higher than previously appreciated.

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