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Case report:

Primary Biliary Cirrhosis associated with rheumatoid arthritis : two case reports in China

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ABSTRACT

Primary biliary cirrhosis(PBC) is a slowly progressive autoimmune disease of the liver which mainly affects women aged between 35 and 45 years.Prolonged liver inflammation can cause scarring, leading to cirrhosis. Although 50 to 60 percent of patients are asymptomatic at diagnosis, they will develop symptoms later. PBC can be associated with arthralgia and other non-hepatic autoimmune diseases, such as Sjögren's syndrome, sicca syndrome, thyroiditis and scleroderma. PBC and rheumatoid arthritis (RA) have been suggested to coexist in 1.8 to 5.6% of patients with PBC, but data supporting this association are scarce. We report two cases of such an association and discuss how to improve threapy.

Keywords: primary biliary cirrhosis, rheumatoid arthritis, ursodeoxycholic acid, methotrexate

INTRODUCTION

Primary biliary cirrhosis is a slowly progressive autoimmune disease of the liver that primarily affects women. Its peak incidence occurs in the fifth decade of life, and it is uncommon in persons under 25 years of age (Kaplan and Gershwin, 2005).

50 to 60 percent of patients are asymptomatic at diagnosis (Pares and Rodes, 2003; Prince et al., 2004). However, most asymptomatic patients, over time, will develop symptoms and hepatic disease will progress (Metcalf et al., 1997). Fatigue and pruritus are the most common presenting symptoms (Bergasa et al., 2003).

Other common findings in PBC include Sjögren's syndrome, sicca syndrome, thyroiditis and scleroderma (Watt et al., 2004). The co-existence of PBC and RA is well known with a frequency ranging from 1.8 % to 5.6 % (Pares and Rodes, 2003; Marasini et al., 2001). As far as we know there is no data of PBC frequency in large cohort of patients with RA.

Ursodeoxycholic acid (UDCA) is the only approved drug for PBC. However, the beneficial effect of UDCA in PBC patients is uncertain.

As we know the co-existence is rare and may occur concomitantly or serially. Clinicians must be aware of the possibility of liver disease so that it can be treated as soon as possible. We report two cases of such an association in China.

CASE 1

In 2004, a 62-year-old woman presented with inflammatory arthralgia of the metacarpophalangeal,interphalangeal and left knee joints. She was negative for rheumatoid fac-

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tor. She was treated with Tripterygium wilfordii (Chinese crude drug).

In 2006, the disease flared up with pruritus and jaundice. Her urine presents dark brown. She was treated with amino acids drugs.

Three months later, the patient developed fatigue. Jaundice and pruritus became active again. Laboratory findings on admission are summerized in Table 1. Alkaline phosphatase (ALP), γ-glutamyltranspeptidase (GGT), aspartate aminotransferase (AST), alanine aminotransferase (ALT), γ-globulin, IgG, and IgM were elevated, but the level of serum bilirubin was normal. Viral markers were still negative. Liver ultrasound was normal, showing no biliary duct dilatation and no biliary sludge. The presence of anti-mitochondrial antibodies (AMA M2 type, 1/320) led to the diagnosis of PBC. A liver biopsy confirmed the diagnosis and revealed stage II histology.

X-ray revealed bilateral and symmetrical erosion of the metacarpophalangeal joints. She was positive for rheumatoid factor and anti-CCP antibodies. She received 10 mg/kg of ursodeoxycholic acid per day, which improved the pruritus and biological hepatic abnormalities.

Table 1
Patients characteristics and laboratory data on admission

	Case 1	Case 2
Age	62	41
Sex	Female	Male
Histologic stage of PBC	II	IV
ALP (IU/L)	767	598
GGT (IU/L)	172	562
ALT (IU/L)	68	25
AST (IU/L)	104	98
TBIL (mmol/L)	7.8	51.5
ANA	Positive (1:640)	Positive (1:320)
AMA	Positive (1:320)	Positive (1:640)
Ig G (g/L)	18.5	11.0
Ig M (g/L)	2.42	0.685
Anti-HAV antibody	Negative	Negative
Anti-HBV antibody	Negative	Negative
Anti-HCV antibody	Negative	Negative
RF (IU/mL)	17.4	20.4
hs-CRP (mg/L)	15	19
ESR (mm/hr)	25	50

ALP: Alkaline Phosphatase, GGT: gamma-glutamyl transferase, ALT: alanine aminotransferase, AST: aspartate aminotransferase, TBIL: Total Bilirubin, AMA: antimitochondrial antibodies, ANA: antinuclear antibodies, Ig: immunoglobulin, RF: rheumatoid factor, ESR: erythrocyte sedimentation rate, CRP: C-reactive protein

CASE 2

In 2001, a 41-year-old man presented with fatigue all of the body. Hepatic tests showed elevated aminotransferase. He was not taking any drugs.

In 2002, he developed symmetrical arthritis of the knees. He was treated with penicilin, but the disease got worse and worse. The patient got fever and jaundice quickly. He was negative for rheumatoid factor and hand X-rays were normal. Serological tests

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were negative for hepatitis A, B and C. Biological investigations revealed that he was negative for other antibodies such as antinuclear antibodies (ANA), anti-neutrophil cytoplasmic antibodies (ANCA), smooth muscle and liver-kidney microsomal antibodies (LKM1). He was treated prednisone (30 mg per day).

In 2004, he presented symmetrical inflammatory arthralgia of the hands and knees (metacarpophalangeal and proximal interphalangeal joints) once again. X-ray showed bilateral femoral heads aseptic necrosis. Then the disease was controlled with prednisone (30 mg per day) and methotrexate (15 mg per week).

In 2005, he was diagnosed with PBC. The diagnosis was based on the discovery of elevated ALP and GGT level, but normal values for transaminase and bilirubin during a blood test (Table1). The liver ultrasound revealed hepatic cirrhosis and hypersplenotrophy. Further biological investigations revealed that she was positive for AMA type. A liver biopsy revealed signs of non-suppurative cholangitis with fibrosis or cirrhosis. X-ray showed bilateral femoral head aseptic necrosis. She was positive for rheumatoid factor and anti-CCP antibodies; she was treated with ursodeoxycholic acid (10 mg/kg per day) and methotrexate (15 mg per week). Methotrexate and ursodeoxycholic acid released the symptoms and hepatic tests' value.

DISCUSSION

Primary biliary cirrhosis is a chronic cholestatic disease, which leads to progressive fibrosis of the liver and sometimes to cirrhosis. Most cases are currently diagnosed in asymptomatic patients (Pares and Rodes, 2003). Primary biliary cirrhosis (PBC) and rheumatoid arthritis (RA) are chronic medical conditions in which, although the etiology is uncertain, autoimmune features predominate. Both of these conditions are fairly rare, with RA being found in approximately 1 % of the population and PBC being found in approximately 20/100,000 women and 2/100,000 men (Gabriel et al., 1999; Kim et al., 2000). The likelihood of these uncommon conditions occurring in the same patient is very rare and unusual.

It has been well established that patients with PBC (case 2) may have musculoskeletal complaints and patients with RA (case 1) may have evidence of hepatic dysfunction. RA did not show specificity in our two patients; in one patient, articular involvement occurred before PBC and in the other, it occurred subsequently. Interestingly, it is reported that most of patients were diagnosed with RA years before PBC was diagnosed (Siegel et al., 2003). More data are required to determine which one is the predominant disease. It should be noticed in case 2 that the destructive arthropathy of the bilateral femoral heads contrasted with other mild erosive lesions of the wrist. Such rapidly destructive arthropathies have already been described in PBC, involving notably the hip (Bourgeois et al., 1981). Our findings, together with previous findings, suggest that the discovery of abnormal hepatic tests (mainly elevated ALP concentrations) should lead to AMA measurement in patients with RA and that patients with PBC presented joints erosion should consider RA.

Ursodeoxycholic acid (UDCA) is the only approved drug for PBC. However, the beneficial effect of UDCA in PBC patients is uncertain. An updated systematic review did not demonstrate any benefit of UDCA on mortality and mortality or liver transplantation in patients with PBC (Gong et al., 2007).

Articular involvement occurred before PBC in case 1,which raised questions about hepatotoxicity of RA drugs. In fact, methotrexate (MTX) has been tested as a treatment for PBC, especially when classical UDCA monotherapy is ineffective (Lindor et al., 1995; Kaplan et al., 2004). Conflicting data have been reported, but a recent ten-year follow-up study suggested that MTX plus UDCA was not more effective than UDCA alone in terms of survival free of liver trans-

plantation. In addition, adverse events associated with methotrexate treatment have been reported in 24.5 % of PBC patients (Lindor et al., 1995). Other data showed that the coexistence of these two diseases does not seem to modify the course of either disease and we can suggest that methotrexate can be choosen as a treatment of both of them without scare of hepatotoxicity, in association with ursodeoxycholic acid (Siegel et al., 2003).

In conclusion, if PBC patients can be controlled with ursodeoxycholic acid, we recommend UDCA monotherapy. However, if UDCA is ineffective, MTX plus UDCA may be an alternative. A high risk of drug-induced hepatotoxicity should be considered, when PBC is associated with RA. The association between PBC and RA is rare. However, recognition of the correct diagnosis can have a tremendous impact on therapy and possibly on prognosis of such patients.

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