A Patient With Primary Biliary Cirrhosis Accompanied by Wilson's Disease

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Abstract

Introduction: Both primary biliary cirrhosis (PBC) and Wilson's disease (WD) can cause copper retention in the liver, which is an important factor for liver cellular damage. Copper chelation may preserve liver cell function. It is challenging to distinguish WD from copper accumulation in patients with PBC. There have been few case reports of PBC co-occurrence with WD.
Case Presentation: Here we report a case of PBC with WD in a 55-year-old Chinese male. In addition to the typical pathological characteristics of PBC and a large number of copper depositions in the liver, the patient showed *WD ATP7B* gene mutations.
Conclusions: Co-occurrence of PBC with WD is rare, which can cause diffusely intrahepatic copper deposition. Early liver biopsy and genetic testing are necessary for the diagnosis. The combination of ursodeoxycholic acid with zinc and sodium dimercaptopropane sulfonate is effective.

Keywords: Primary Biliary Cirrhosis, Wilson's Disease, Copper

1. Introduction

Primary biliary cirrhosis (PBC) is an autoimmune disease characterized by chronic progressive cholestasis with the destruction of the intrahepatic small bile ducts that can lead to liver cirrhosis. It can be accompanied or preceded by various autoimmune disorders. Antimitochondrial antibody (AMA) is considered a specific biomarker of PBC and some authors describe it as the serologic signature of the disease (1).

In PBC, in addition to the primary pathogenic process that directed against small intrahepatic bile ducts, copper overload can be seen in liver cells, which occurs as a complication of impaired copper excretion in bile. It has been suggested that similar to liver damage of Wilson's disease, an excess of liver copper in PBC is an important factor causing hepatic injury, and copper chelation may alleviate it.

Wilson's disease (WD) is an autosomal recessive disorder characterized by copper accumulation in the liver, brain, kidneys, and cornea due to inadequate biliary copper excretion (2). Initial findings may indicate the presence of a chronic or fulminant liver disease, progressive neurologic disorder without clinical liver dysfunction, isolated acute hemolysis, and psychiatric disorders. Clinical presentation of the disease can be variable, and different types of parenchymal changes of the liver can be seen on imaging modalities.

High concentrations of hepatic copper had been report-ed in PBC, extrahepatic biliary obstruction, biliary atresia, cryptogenic cirrhosis with cholestasis, WD, and Indian childhood cirrhosis (ICC), as well as in normal neonatal livers (3). However, co-occurrence of two of them in a patient is rare. Here we report a case of PBC with WD in a 55-year-old male.

2. Case Presentation

A 55-year-old male was admitted to our hospital due to yellow urine for 15 years and elevated transaminase of 3-year duration. Three years ago, the patient was clinically diagnosed with drug-induced liver injury in other hospital (Figure 1 A). The liver biopsy demonstrated changes, including hepatocellular swelling and less commonly focal hepatocellular necrosis with a sparse lymphocytic infiltrate and cholestasis, glycogenated nuclei and hepatic steatosis. Abdominal ultrasonographic findings were not compatible with liver cirrhosis.

At admission, vital signs were blood pressure 155/90 mmHg, pulse 60 beats per minute, respiration 15 per minute, body temperature 36.1°C. He was a nonsmoker and nondrinker and had no prior or family history of PBC or WD.

Laboratory examination results showed serum albumin 36.5 g/L, total bilirubin (TB) 73.7 μmol/L (3 - 20 μmol/L), direct bilirubin (DB) 60.3 μmol/L (2 - 6 μmol/L), alanine ami-

notransferase (ALT) 61 U/L (0 - 40 U/L), aspartate aminotransferase (AST) 84 U/L (0 - 40 U/L), alkaline phosphatase (ALKP) 522 U/L (80 - 128 U/L), gamma-glutamyl transpeptidase (r-GT) 445 U/L (0 - 40 U/L), AMA 1: 10000, and antinuclear antibodies (ANA) 1: 320. Hepatitis B surface antigen (HBsAg), anti-hepatitis C virus (HCV), antismooth muscle actin (SMA) and anti-liver-kidney-microsome (LKM) were negative. To clarify diagnosis, the second liver biopsy was carried out. Variable hepatocellular ballooning degeneration and binucleated hepatocytes were seen. Also, increased pigment deposition, intrahepatic bile duct proliferation, fibrosis, and cirrhosis were present (Figure 2 A). Copper deposition was detectable in both periseptal and intranodular areas; the latter is a less common finding in other types of cholestatic copper deposition, such as PBC. The pathologic diagnosis was PBC with elevated liver copper (Figure 2 B). However, there were no other typical pathological features of WD. Slit-lamp examina-

tion revealed no Kayser-Fleischer ring. Serum ceruloplasmin and 24-hour urinary copper excretion were 0.35 g/L (normal 0.22 ~ 0.58 g/L), and 145 μg/L (normal 0 - 40 μg/L), respectively. We detected the copper in liver in the first biopsy. Copper accumulation in liver was found (Figure 1 B). Then the exons 2, 7, 8, 11, 12, 13, 14, 15, 16, and 18 of the *WD ATP7B* gene were tested. The results showed mutations including exon 12 of AGA - AAA, ArgLys (G/A rs732774 SNP, heterozygosity, polymorphism), exon 16 of GTC - GCC, Val 1140Ala (T/C hybrid, CM044579, abnormal) and exon 18 of 3903 + 6C > T, Splice (C/T hybrid, CS067807, abnormal). So, the patient's final diagnosis was PBC and WD. He was treated with ursodeoxycholic acid (UDCA), zinc and sodium dimercaptopropane sulfonate. The lasting 3-month successful treatment resulted in improvement in liver function, clinical signs and symptoms, as well as liver function: serum albumin 38 g/L, TB 29.0 μmol/L, DB 16 μmol/L, ALT 38 U/L, AST 41 U/L, ALKP 300 U/L, r-GT 220 U/L.

Figure 1. Histological Changes and Copper in the First Liver Biopsy
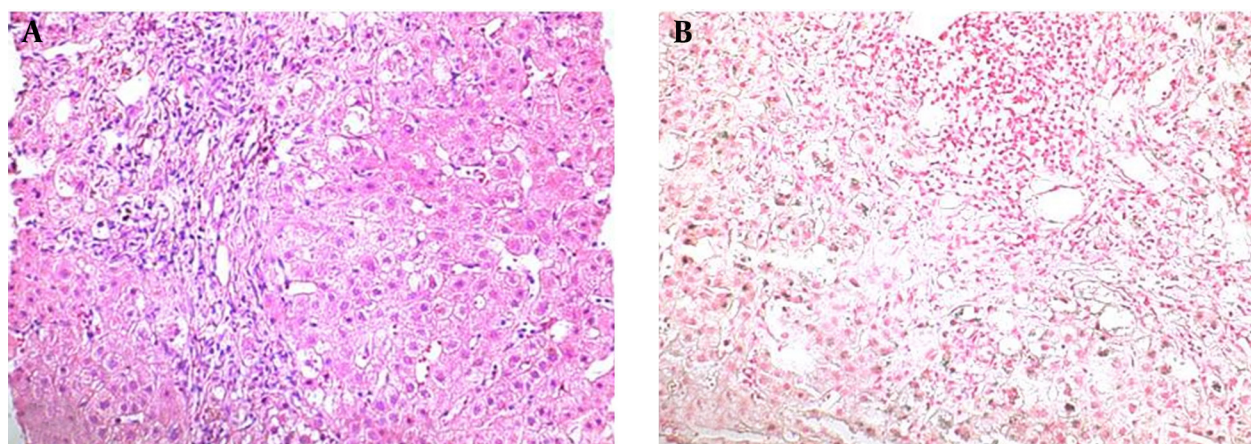
A, Hematoxylin and eosin staining; and B, Rubeanic acid copper staining.

Figure 2. Histological Changes and Copper in the Second Liver Biopsy
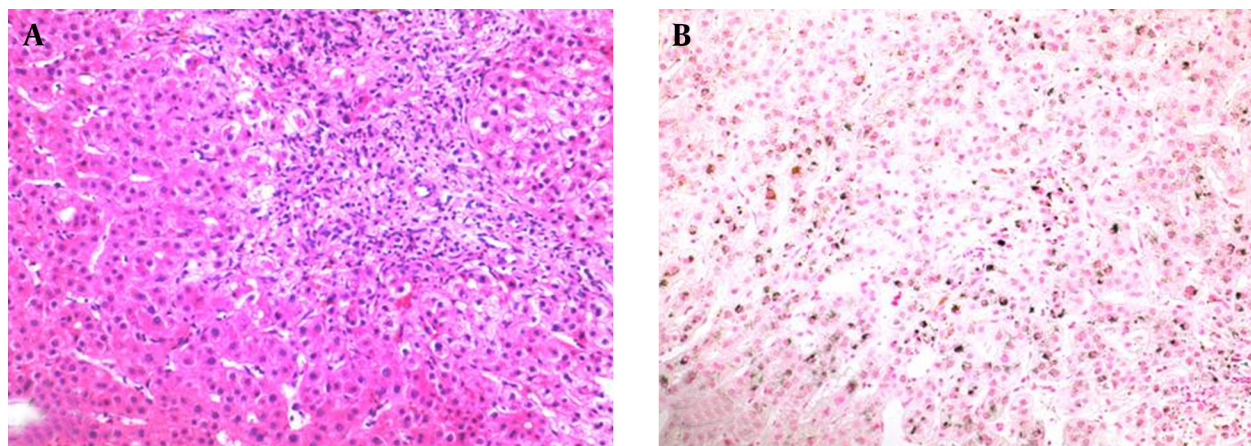
A, Hematoxylin and eosin staining; and B, Rubeanic acid copper staining.

3. Discussion

The diagnosis of PBC is generally based on the following criteria (4): biochemical evidence of cholestasis with elevated serum alkaline phosphatase, presence of AMA and histopathologic evidence of nonsuppurative cholangitis and destruction of small or medium-sized bile ducts if a biopsy is performed. The patient in this study accorded with the characters mentioned above, with elevation of ALKP, positive AMA and typical pathological features, should be definitely diagnose with PBC.

However, the patient's liver histology showed diffusely deposition of copper throughout the hepatic lobule, which was more than most of PBC patients. In generally, copper retention is a phenomenon secondary to PBC, the metal being confined to the periportal region of the liver lobules. At the time of diagnosis, 55% of patients with PBC have liver copper concentrations below the range occurring in WD. So, WD must be considered in the differential diagnosis.

Typically, the combination of Kayser-Fleischer (K-F) rings and a low serum ceruloplasmin (< 0.1 g/L) level is sufficient to establish a diagnosis of WD (5). However, WD could not be ruled out in this patient though there was no K-F rings and with normal ceruloplasmin. Other assay for diagnosing WD such as measurement of serum ceruloplasmin oxidase activity, which was superior to immunologic assays, was generally not available in routine labs (6). Thus, the combination of tests reflecting disturbed copper metabolism may be needed for many patients. Additionally, for diagnostic purposes, a liver biopsy is required if the clinical signs and noninvasive tests do not allow a final diagnosis of WD or if there is suspicion of other or additional liver pathologies. Think back of this patient's first liver biopsy, it indeed showed several features suggesting the early histologic abnormalities of WD, including mild steatosis (both microvesicular and macrovesicular), glycogenated nuclei in hepatocytes, and focal hepatocellular necrosis. However, with progressive parenchymal damage, biliary fibrosis even subsequently cirrhosis and diffusely copper deposition were showed in the liver.

Furthermore, We got the powerful evidence of WD in this patient by using the Wilson's disease scoring system, which was based on all available tests and proposed by the Working Party at the 8th International Meeting on Wilson's disease (Table 1) (7). A score of greater than or equal to four establishes a diagnosis of WD. The score of this patient is 7, clearly indicating a diagnosis of WD.

It should be noted that copper deposition in the liver is not the specific feature of WD or PBC. There were different mechanisms for them. Wilson's disease is an inborn error of copper metabolism, whereas in PBC, cholestasis and biliary cirrhosis dominate the clinical and biochemical evolution of the disease, with liver copper retention occurring as a complication of cholestasis. Also, several non-Wilson's diseases of copper overload have been described, idiopathic copper toxicosis (ICT), primary sclerosing cholangitis, and endemic Tyrolean infantile cirrhosis (ETIC), which share the common end point of cirrhosis due to excessive copper accumulation. Therefore, when there is copper deposition in the liver, many diseases have to be identified.

Table 1. Scoring System Developed at the Eighth International Meeting on Wilson's Disease, Leipzig, 2001

Clinical Tests and Evaluations	Score
Typical Clinical Symptoms and Signs	
Kayer-Flesicher rings	
Present	2
Absent[a]	0
Neurologic symptom[b]	
Severe	2
Mild	1
Absent[a]	0
Serum ceruloplasmin, g/L	
Normal, > 0.2[a]	0
0.1 - 0.2	1
< 0.1	2
Coombs-negative hemolytic anemia mutation analysis	
Present	1
Absent[a]	0
Other Tests	
Liver copper (in absence of cholestasis), μmol/g	
> 5 × ULN, (> 4)	2
0.8 - 4	1
Normal, (< 0.8)	-1
Rhodamine-positive hepatocyte on biopsy[a]	1
Urinary copper (in absence of acute hepatitis)	
Normal	0
1 - 2 × ULN	1
> 2 × ULN[a]	2
Normal, but > 5 × ULN after D-penicillamine	2
Mutation analysis	
Two chromosome mutations[a]	4
One chromosome mutation	1
No mutations detected	0
Evaluation[c]	
Diagnosis highly likely	≥ 4
Diagnosis probable, more tests needed	3
Diagnosis very unlikely	≤ 2

[a]Diagnostic scoring of Wilson's disease in this case; ULN, upper limit of normal range.
[b]Typical abnormalities at brain MRI.
[c]Evaluations based on total scores.

In conclusion, co-occurrence of PBC with WD is rare. Patients with WD who concurrently have other liver diseases, particularly PBC, hepatitis C viral infection, hemochromatosis, hemochromatosis heterozygote, or primary sclerosing cholangitis may present with more severe hepatic injury and show greater mortality (8). Often the WD diagnosis is delayed in these individuals as other disease entities are considered first. Early liver biopsy and genetic mutation analysis are necessary and helpful for the final diagnosis. Fortunately, treatment with UDCA, zinc and sodium dimercaptopropane sulfonate is effective for this patient.

Footnotes

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