Familial Intrahepatic Cholestatic Cirrhosis With Positive Antimitochondrial Antibody

Familial Primary Biliary Cirrhosis

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Abstract
We present three siblings (out of four) with intrahepatic cholestatic disease and cirrhosis. Two of the siblings, a 33-year-old woman and a 34-year-old man had advanced liver disease— with the liver histology showing established cirrhosis with chronic cholestasis and excess copper accumulation. Both died two years later due to hepatic encephalopathy. The third sibling, a 37-year-old man on routine check-up was found to have abnormal liver functions. The liver biopsy showed marked bile ductular proliferation with bridging fibrosis, reduction in interlobular bile ducts, and excess copper accumulation. The presence of antimitochondrial antibody in the serum in 1 in 320 dilutions in all three patients and 1 in 80 dilutions in the oldest healthy sibling and hypergammaglobulinemia in all the siblings confirmed the diagnosis of familial primary biliary cirrhosis. Antinuclear and smooth muscle antibodies were not present. Clinical and biochemical improvement has been noted in the third sibling after therapy with ursodeoxycholic acid.
Key Words: Primary biliary cirrhosis—Familial—Antimitochondrial antibody—Copper—Copper associated protein.

CASE REPORTS

Case 1
The youngest sibling, a 33-year-old woman, was admitted in August 1993 with jaundice, pale colored stools, high colored urine, and itching during pregnancy. She delivered normally in December 1993. She had no previous history of jaundice, blood transfusions, or drug intake. Physical examination showed icterus, enlarged liver and spleen, and no free fluid. Investigations results are summarized in Table 1.
The liver biopsy in January 1994 showed cirrhosis with hepato cytic and canalicular cholestasis, some inflammatory cells in the septa, ballooning degeneration of hepatocytes, Mallory's hyaline, focal absence of interlobular bile ducts, and excess accumulation of copper and copper associated protein (CAP) (Figs. 1A–1C). She was managed conservatively. Her health deteriorated rapidly from October 1995 and presented in December with bleeding gums, fluid overload, and hepatic encephalopathy and died.

Autopsy showed a shrunken liver weighing 605 g, with a finely nodular surface. Bile sludge was present in hepatic ducts but there were no gall stones. The extra hepatic biliary system was patent. Histological features were similar to that of the biopsy. Sections showed established micronodular cirrhosis with features of chronic cholestasis and patchy loss of interlobular bile ducts. Epithelioid granulomas or concentric periductal fibrosis were not present. Stainable copper and CAP deposits were present in several hepatocytes.

Case 2
The 34-year-old man, brother of patient 1, developed xanthelasma and was detected to have hyperlipidemia in 1993 (serum cholesterol 304 mg%; triglycerides 178 mg%). He was treated with bezofibrate for two months. In February 1994, he developed jaundice associated with pale colored stools and high colored urine, and in August 1994, he developed itching. He used to consume alcohol once every 2–3 weeks for five years but stopped after developing jaundice. There was no past history of jaundice or blood transfusions.
Physical examination revealed icterus and xanthelasma. Liver and spleen were enlarged. There was no ascites. Investigations results are given in Table 1.
The liver biopsy obtained by transjugular route showed small fragmented pieces of liver tissue, some of which were partially

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rimmed by fibrous tissue and contained focal aggregates of inflammatory cells. Other features were hepatic cystic ballooning, Mallory's hyaline, focal canalicular cholestasis with bile plugs, and excess accumulation of copper and CAP (Figs. ID-1P).

He was treated with ursodeoxycholic acid (UDCA) for one month but treatment was discontinued because there was no improvement. He presented in November 1995 with bleeding gums and fluid overload, developed hepatic encephalopathy in December, and died three days prior to his sister. An autopsy was not done.

**Case 3**

The 37-year-old man, brother of patients 1 and 2, was detected to have deranged liver functions in 1994 on routine check-up. He was asymptomatic. He used to consume alcohol occasionally but stopped six years back. There was no significant past history.

Physical examination showed an enlarged, firm, and smooth liver (4 cm). Spleen was palpable 3 cm below the costal margin. There were no ascites. Investigation results are given in Table 1.

He was also found to have had eosinophilia (16-30%) since 1994. A liver biopsy was done in February 1996, following his siblings' death. The biopsy showed expansion of the portal tracts with marked bile ductular proliferation, reduction in interlobular bile ducts, mild inflammation, bridging fibrosis with focal nodularity, and excess accumulation of copper and CAP (Figs. 1G and 1H). Epithelioid granulomas were not present.

He was advised to begin treatment with UDCA but he did not take it. He has been on regular follow-up since then. In July 1997, he developed bleeding from esophageal varices, which was managed by endoscopic variceal ligation. He was then started on UDCA 300 mg B.I.D. with which his liver functions have normalized (Table 1) and hepatosplenomegaly has regressed. He had three sessions of endoscopic variceal ligation, and has not had any rebleeding so far. He was also being treated with propranolol and isosorbide mononitrate to reduce the portal pressure. At the last follow-up on July 24, 1998, he had just palpable liver and spleen. The children of all patients have normal liver functions and they are doing well.

**Case 4**

The 39-year-old woman, the eldest sibling, had jaundice when she was 12 years old. She is asymptomatic at present. Her physical examination, liver functions, and lipid profile were all within normal limits (Table 1). A liver biopsy was not done. She has no children.

There were no congenital anomalies or dysmorphic features of Alagille syndrome in these patients. The parents of these patients were of nonconsanguineous marriage. The father died at the age of 62 years. He never had jaundice. The mother is 66-years-old and is doing well. The family members have been living far apart for many years.

Hepatitis B surface antigen and hepatitis C antibody were not present in the sera of all the siblings. Work-up results for Wilson disease were negative.

The sera were subsequently tested for antimitochondrial antibodies (AMAs) by the fluorescent antibody technique. AMAs were present at a 1 in 320 dilution in all three patients and a 1 in 80 dilution in the healthy sibling. Hence, a diagnosis of familial PBC was made. Antinuclear antibodies (ANAs) and antismooth muscle antibodies were not present. Endoscopic retrograde cholangiogram was normal in all three patients studied.
DISCUSSION

PBC is very rarely reported from the Indian subcontinent. We are aware of only a few individual case reports\textsuperscript{11-13} that have preceded this one. It is of added interest that, in this situation of paucity, we found a family where three out of four siblings were affected by the disease, two of them were men. The clinical symptoms and presentation of the disease were characteristic of chronic cholestatic liver disease. The liver histology in two of the deceased siblings showed established cirrhosis with features of long-standing cholestasis. In the third sibling, the liver biopsy showed marked bile ductular proliferation with reduction in interlobular bile ducts, bridging fibrosis, and excess accumulation of copper and CAP. The normal cholangiogram in all three patients and the absence of any characteristic histological findings excluded primary sclerosing cholangitis. None of these cases showed epithelioid granulomas or bile duct epithelial damage. Hence, histologically, familial intrahepatic cholestatic cirrhosis due to idiopathic adult ductopenia was considered. The presence of AMAs in the sera of all four siblings was the test that confirmed the diagnosis of familial PBC. Studies have shown that the presence of AMA is virtually diagnostic of PBC.\textsuperscript{14,15} The concomi-
tant absence of ANA and antismooth muscle antibodies or the markers of viral infection aided this diagnosis. The presence of AMAs in the sera of unaffected siblings, though at much lower dilutions than in patients, has been reported before. Also consistent with the diagnosis was the presence of hypergammaglobulinemia in both the patients and unaffected sibling and the rapid deterioration in health once jaundice started.

UDCA is the most effective therapy now available for patients with PBC. Clinical and biochemical improvement has been shown with UDCA therapy in PBC, as seen in the third case presented in this series. When data from three of the studies using 13–15 mg/kg/d of UDCA was combined, there was significant improvement in survival, free of transplantation, in the group receiving UDCA.

Epidemiological studies have reported a prevalence of familial PBC in 1.33% of the families of probands in the United Kingdom and in 5.5% of the families of probands in New York. This suggests a genetic predisposition to the disease. However, there has also been evidence of a common exposure to environmental agents. The affected siblings of this report lived their adult lives far away from each other; therefore, it appears likely that they had similar genes. It is also possible that they came in contact with the environmental agent that provoked the disease very early in their life.

REFERENCES