Idiopathic Adulthood Ductopenia Long-Term Follow-up After Liver Transplantation

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In 1988, Ludwig et al proposed the term idiopathic adulthood ductopenia (IAD) for the condition of chronic cholestatic liver disease associated with loss of intrahepatic bile ducts of unknown etiology with clinical onset in adulthood (1).

In recent years, several cases of idiopathic biliary ductopenia in adulthood have been described. This disease is severe in most cases and can progress to cirrhosis. For progressive IAD, orthotopic liver transplantation (OLT) has been the only successful treatment. There are only a few cases reported of OLT for IAD and no information is available about the prognosis of these patients in the long term after OLT. In the present report, we describe the long-term follow-up after OLT in one patient fulfilling IAD criteria.

CASE REPORT

A 44-year-old female patient was referred to our institution in 1992 for OLT. She was otherwise healthy until 1989, when she started to have progressive symptoms of fatigue, pruritus, jaundice, dark urine, and pallor of the stools. She had no history of neonatal jaundice or liver disease in infancy or blood transfusions. There was no familial history of cholestasis.

The only relevant findings on physical examination were severe jaundice, moderate hepatomegaly, and splenomegaly.

Laboratory studies revealed the following findings: hemoglobin, 11 g/dl; white blood count, 6.1/pl; platelets, 199/pl; ALT, 133 IU/L; AST, 222 IU/L; GGT, IU/L; alkaline phosphatase, 2400 IU/L; total bilirubin, 31.94 mg/dl; conjugated bilirubin, 22.59 mg/dl; albumin, 3.36 g/dl; prothrombin time, 84%; cholesterol, 858 mg/dl; and triglycerides, 189 mg/dl. Serum iron, transferrin saturation, ferritin, a-1-antitrypsin, and ceruloplasmin were normal. Serological tests for anti-smooth muscle, anti-neutrophil–cytoplasm, antinuclear, antimitochondrial, and anti-liver– kidney microsome antibodies, hepatitis B surface antigen, and hepatitis C virus serology were negative. Serological tests for infection by cytomegalovirus (CMV), Epstein–Barr virus (EBV), and Herpes virus were as follows: CMV IgM, negative; CMV IgG, 715 U/ml; EBV VCA, 1/160; EBV, EA, 1/40; and herpes virus, 2.06 U/ml. a-Fetoprotein was normal. Serological test for HIV antibodies was negative.

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An ultrasound study demonstrated hepatomegaly. No evidence of cholelithiasis or biliary dilation was noted. The spleen measured 14.5 cm and there was no ascites. The portal blood flow was hepatopetal. An endoscopy retrograde cholangiopancreatography demonstrated completely normal extrahepatic bile ducts and minimal irregularities of the intrahepatic bile ducts in the left lobe. A colonoscopy revealed no evidence of inflammatory bowel disease. Two percutaneous liver biopsies performed at another hospital showed severe cholestasis.

OLT was performed in February 1993. An end-to-end choledochocholedochostomy was performed over a T-tube. Immunosuppressive therapy was begun with cyclosporine, methylprednisolone, and azathioprine. The native liver weighed 2120 g and measured 19.5 x 24 x 10.2 cm. The specimen had smooth, green light outer surfaces. After the cut, the surface was green with white areas. The gallbladder measured 7.5 x 2.5 cm. Microscopically the liver showed cholestasis with bile plugs (Figure 1), fibrosis, and a reduction in the number of interlobar bile ducts (Figure 2). In 37 portal tracts, only two bile ducts were found. An orcein stain for copper-associated protein was negative. There were no granulomas or infiltration with inflammatory cells. In the described clinical setting, these pathological findings confirmed the diagnosis of IAD.

One episode of acute cellular rejection occurred on day 5 after OLT, which was reversed with steroid bolus therapy. Following this episode, the patient's clinical course was uneventful. From 1993 to 2000 liver function tests have been obtained at our center each year and no abnormal liver function tests have been observed. Steroid therapy was discontinued by September 1998 and azathioprine by November 1998. At this time, the patient is on cyclosporine monotherapy. A follow-up percutaneous liver biopsy performed in 1998 showed mild nonspecific findings (mild lymphocytic infiltrate in all portal tracts and minimal centrilobular cholestasis). In four portal tracts, four bile ducts were observed (Figure 3). Liver function tests at the time of liver biopsy were as follows: AST, 16 IU/L; ALT, 18 IU/L; GGT, 22 IU/L; alkaline phosphatase, 138 IU/L; total bilirubin, 0.6 mg/dl; and conjugated bilirubin, 0.18 mg/dl.

DISCUSSION

Idiopathic adulthood ductopenia (IAD) is a term that describes a chronic cholestatic liver disease of unknown etiology which has its clinical onset in adulthood and is associated with loss of intrahepatic bile ducts. Clinical onset consists in jaundice, pruritus, and hemorrhage by portal hypertension, and elevated levels of alkaline phosphatase and hyperbilirubinemia are revealed in blood tests (2).

Several groups have reported patients with idiopathic adulthood ductopenia. Of a total of 57 patients described so far (3), few patients, including our case, are more than 40 years of age at the onset of the symptoms.

In our case the clinicopathologic findings are quite similar to those described by other authors. The most prominent feature of the histological examination of the native liver was ductopenia, defined as the presence of identifiable bile duct in less than 50% of portal tracts. According to established criteria (3) our case can be classified as adulthood ductopenia.

Although most cases are sporadic, familial cases have been described (4). The clinical course of IAD is variable. Frequently some patients have progressive cholestasis leading to biliary cirrhosis (5), while others have stable disease (6). Moreno et al. reported on 24 patients with an asymptomatic

elevation in liver enzymes and ductopenia with an apparent nonprogressive course. The beneficial effect of treatment with ursodeoxycholic acid has been suggested (6, 7). When progression to liver failure occurs, OLT is indicated. Its evolution after OLT is unknown.

IAD is considered a syndrome with several possible causes such as late-onset nonsyndromic paucity of intrahepatic bile ducts, small-duct primary sclerosing cholangitis, viral cholangitis, autoimmune hepatitis, and cholangitis (3), hence the possibility of recurrent disease after liver transplantation should be considered. In fact, recurrence of primary disease in patients undergoing liver transplantation due to chronic cholestatic conditions such as primary biliary cirrhosis (8), autoimmune hepatitis (9), and primary sclerosing cholangitis (10) is a widely reported event.

The evolution after OLT is unknown. As far as we know, only seven patients have received OLT for IAD (1, 11–14). Only three of these patients have been reported to be alive and well 1 to 2 years after OLT (11, 13) and liver function tests are reported to be normal in only one case (11).

In our case no clinical or biochemical indicating recurrent cholestasis have developed 7 years after transplantation. A liver biopsy performed 6 years after transplantation revealed only a mild inflammatory infiltrate and minimal centrolobular cholestasis. These findings may be considered nonspecific and are frequently found in liver grafts, with otherwise normal function several years after transplantation. In addition, all portal tracts showed the presence of a bile duct.

In conclusion, this is the first report of the longterm evolution of IAD after OLT in one case in which no signs of disease recurrence have been noted 7 years after OLT.

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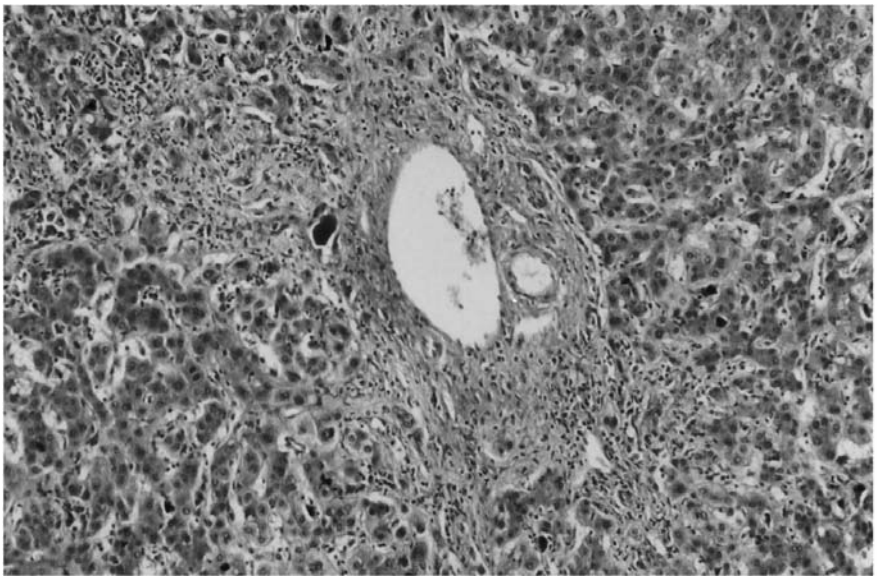

Fig 1. Section of the explanted liver showing intense cholostasis with bile plug formation and rosetoid transformation of the hepatocytes. HE; original magnification, X450.

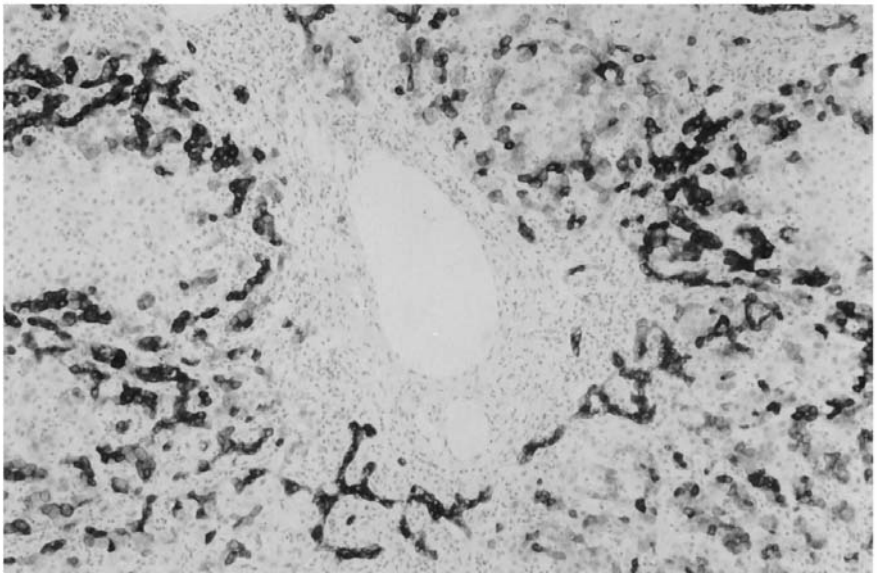

Fig 2. Portal tract without interlobular bile ducts. Immunohistochemical stain with cytokeratin (AE3–AE1) failed to show epithelial bile cells. Note the intense ductular transformation of the peripheral hepatocytes. AE3–AE1, DAB; original magnification, X200.

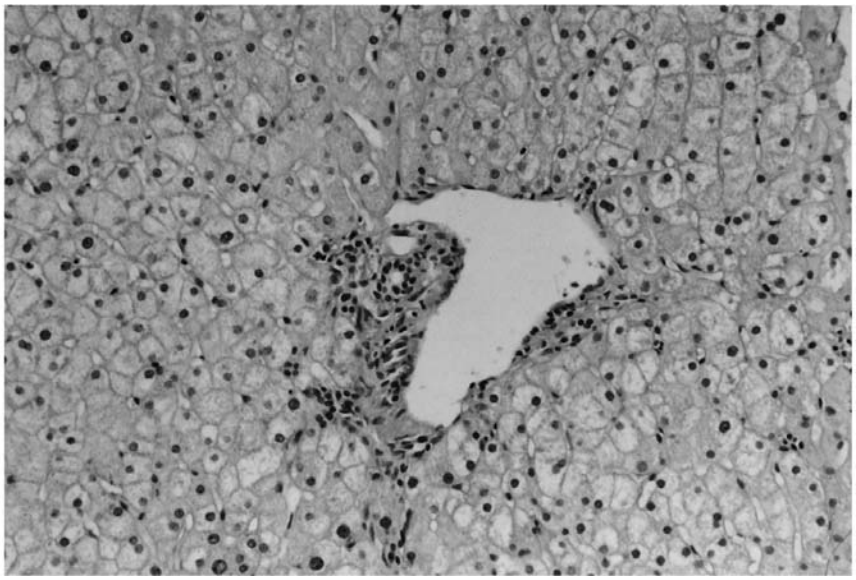

Fig 3. Four-year-posttransplant biopsy showing only mild nonspecific changes, scattered portal lymphocytes, and minimal hepatocyte cholestasis.