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Alagille Syndrome
- A Case Report -

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Alagille syndrome is a rare autosomal dominant disorder showing complicated systemic manifestations, although the hepatic manifestations are predominant in many patients. We report a case of Alagille syndrome in a male baby who presented with a heart murmur at 2 days old and his echocardiography showed aortic stenosis. He presented with acholic stool and jaundice at 3 months old and a liver biopsy revealed paucity of the interlobular bile duct in the portal tract. This progressed to cirrhosis, for which a liver transplantation was performed at 10 months old. The explanted liver showed biliary-type cirrhosis with severe cholestasis. There was an absence of the interlobular bile ducts on microscopic examination. Bile duct paucity, associated with cholestasis, a peculiar face (prominent forehead, deep-set eyes, pointed mandible and bulbous nasal tip), and cardiac anomaly were observed, which were consistent with Alagille syndrome. He died of heart failure.

Key Words : Alagille Syndrome – Intrahepatic Bile Duct – Heart Disease

Alagille syndrome is an autosomal dominant disorder, involving abnormalities of varying severity in multiple organ systems.[1,2] The diagnosis of Alagille syndrome has traditionally been based on the finding of paucity of the interlobular bile ducts, associated with three to five major features: chronic cholestasis, cardiac disease, skeletal anomalies, ocular abnormalities and a characteristic facial phenotype (prominent forehead, deep-set eyes, pointed mandible and bulbous nasal tip). To our knowledge, eleven cases were reported in the Korean literature.[3,4] We report a 10 month old male baby with Alagille syndrome, who received a liver transplantation.

CASE REPORT

A 2-day-old male baby presented with a heart murmur. After admission, dextrocardia and situs inversus totalis were detected, and an echocardiography showed aortic stenosis (Fig. 1). He had a prominent forehead, deep-set eyes, pointed mandible and bulbous nasal tip. At 3 months old, he was readmitted to the hospital due to acholic stools and jaundice. Laboratory tests were performed, with the following results; Alkaline phosphatase 840 IU/L, GOT 424 IU/L, GPT 495 IU/L, γ-GTP 945 IU/L, total bilirubin 11.17 mg/dL and direct bilirubin 8.61 mg/dL. The viral marker study for HBs Ag was negative, anti-HBs positive, anti-HCV negative and anti-HAV IgM negative. A blood test for the cytomegalovirus IgM antibody was positive. An open cholangiogram and a liver wedge biopsy were performed to evaluate the extra-and intrahepatic bile ducts. The open cholangiogram showed a patent extrahepatic bile duct, but the microscopic finding from the biopsy specimen showed lobular necroinflammation, with giant cell formation, and cholestasis. There were five portal tracts in the biopsied liver and no interlobular bile ducts were found in all portal tracts (Fig. 2). The immunohistochemical staining for cytokeratin 7 confirmed a loss of the interlobular bile ducts, and the staining for the cytomegalovirus was negative.

Follow-up revealed the progression to liver cirrhosis, so a liver transplantation was performed at 10 months old. The explanted liver weighed 378 gm (the weight of normal liver; 213-330 gm

at 6-12 months old) and measured 14×8×6 cm. The external surface showed vague micronodularity and severe cholestasis with firm consistency grossly (Fig. 3A). On microscopic examination, there was micronodular cirrhosis, with a paucity of the interlobular bile ducts (Fig. 3B, C). The immunohistochemical staining for cytokeratin 7 and 19 confirmed a loss of the interlobular bile ducts (Fig. 3D). The patient died of heart problem the following day.

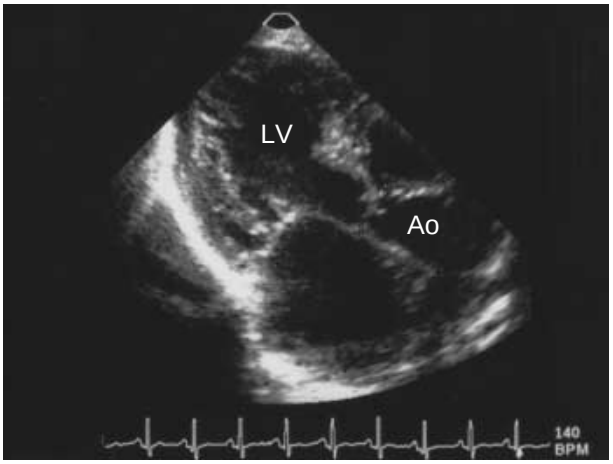

Fig. 1. The echocardiography shows aortic stenosis and post-stenotic dilatation, measuring 1 cm and 1.74 cm, respectively. Ao, aorta; LV, left ventricle.

The patient had paucity of the interlobular bile ducts, associated with cholestasis, heart disease and a peculiar face, which were consistent with Alagille syndrome.

DISCUSSION

Bile duct paucity is defined histologically, in a full-term or older infant, as a ratio of the bile duct to the portal tract less than 0.5.[5] In normal children this ratio lies between 0.9 and 1.8. Bile duct paucity has been classified into syndromic and nonsyndromic paucity. Syndromic paucity has also been called arteriohepatic dysplasia, intrahepatic atresia, biliary hypoplasia, intrahepatic biliary dysgenesis and Watson-Alagille syndrome. Currently, the term Alagille syndrome has virtually achieved uniform acceptance in the literature. Alagille syndrome was first described

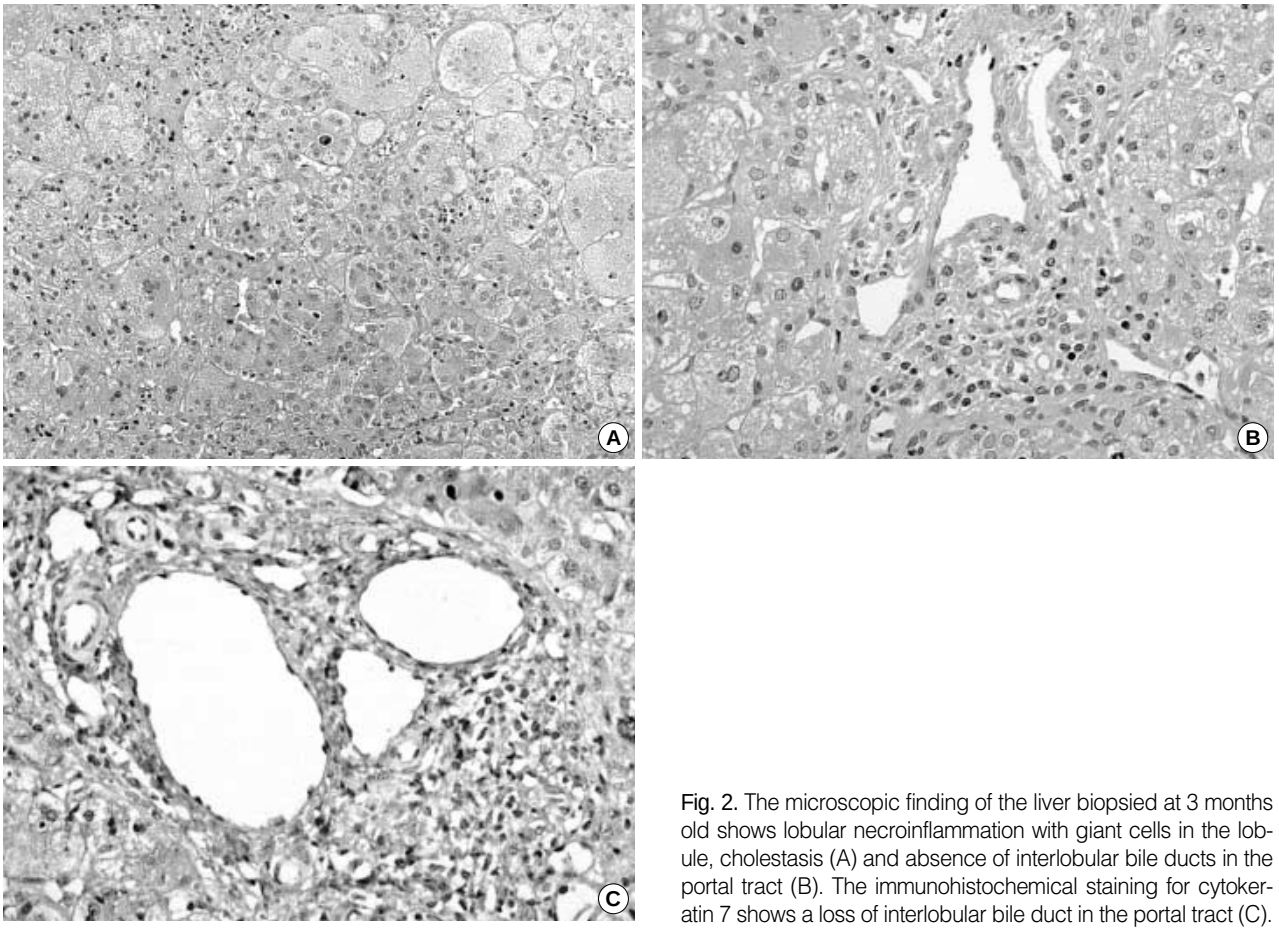

Fig. 2. The microscopic finding of the liver biopsied at 3 months old shows lobular necroinflammation with giant cells in the lobule, cholestasis (A) and absence of interlobular bile ducts in the portal tract (B). The immunohistochemical staining for cytokeratin 7 shows a loss of interlobular bile duct in the portal tract (C).

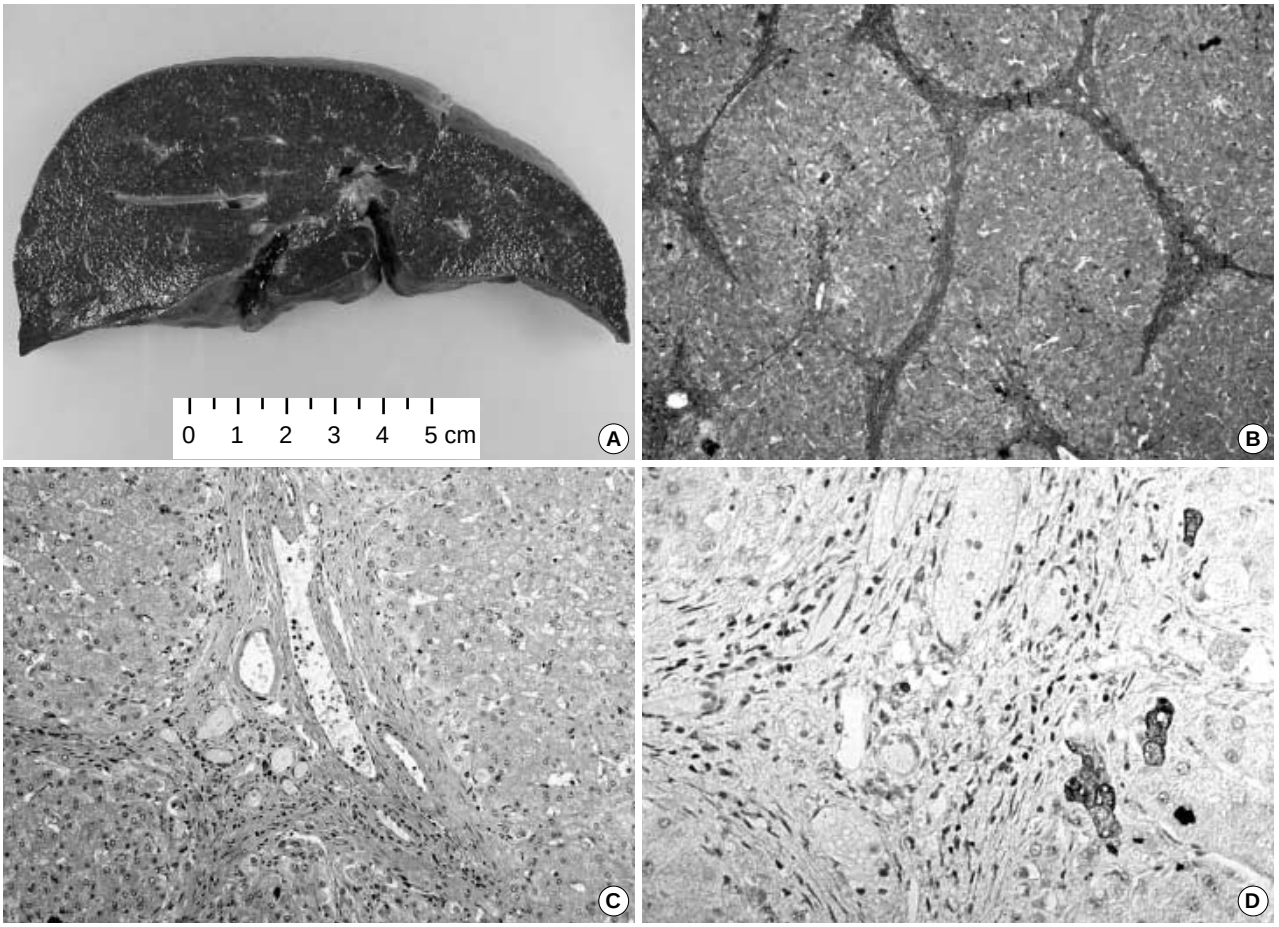

Fig. 3. The pathologic features of the explanted liver at 10 months old. Grossly the explanted liver shows vague micronodularity with severe cholestasis (A). The trichrome stain shows biliary cirrhosis with cholestasis (B). The portal tracts reveal an absence of interlobular bile ducts (C). The immunohistochemical staining for cytokeratin 7 shows a loss of interlobular bile duct in the portal tract. The positive cells are hepatocytes with biliary metaplasia (D).

by Alagille and colleagues in 1969. They recognized that some patients with idiopathic bile duct paucity had similar clinical features, and extended these observations in 1975. Since that time, a large series of patients with Alagille syndrome have been reported. They demonstrated differing frequencies of the manifestations. However, the diagnosis of Alagille syndrome has traditionally been based on the findings of paucity of the interlobular bile ducts, associated with three to five major features: chronic cholestasis, cardiac disease, skeletal anomalies, ocular abnormalities and a characteristic facial phenotype (prominent forehead, deep-set eyes, pointed mandible and bulbous nasal tip). According to these criteria, our patient's features were consistent with Alagille syndrome.

The presence of a heart murmur is the most common manifestation of Alagille syndrome.[6] The majority of these murmur are caused by pulmonic stenosis. Intracardiac lesions (such as tetralogy of Fallot) and extracardiac vascular lesions (such as coarctation of the aorta, patent ductus arteriosus) may be present. Our patient had an aortic stenosis, which is rare in Alagille syndrome.

Recently, the Jagged 1 gene, at chromosome 20 p11.23-p12.1, was identified as being responsible for Alagille syndrome.[7] Jagged 1 encodes a conserved transmembrane protein, which is a ligand of the Notch receptor. The Notch signaling pathway has been shown to play an important role in the determination of a cells fate and differentiation. Mutations in Jagged 1 can be identified in 70% of Alagille syndrome patients, and they are inherited in 30-50% of cases. As molecular testing has become more readily available, the identification of Jagged 1 mutations have been proposed as new entities of the diagnostic criteria.[6] According to the revised diagnostic criteria, patients with isolated manifestations in extrahepatic organs are diagnosed as having Alagille syndrome if Jagged 1 mutations are identified. This has served to shift the focus from the liver to the complicated systemic manifestations, although the hepatic manifestations are predominant

in many patients. Molecular genetic testing of the Jagged 1 was not performed on our patient.

Of the patients presenting with liver disease in infancy, 10 to 50% eventually go on to develop intractable portal hypertension, cirrhosis or liver failure.[2,6] Liver transplantation is eventually necessary in 21 to 31% of these patients. The post-transplant survival rates have ranged from 79% to 100%, and the factors contributing significantly to the mortalities were predominantly cardiovascular complications.[2,6] Our patient expired due to a cardiac problem.

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