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TEACHING CASE

# Hepatocellular carcinoma occurring in Alagille syndrome

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## Abstract

Hepatocellular carcinoma only rarely occurs in Alagille syndrome. Here, we report on three cases of hepatocellular carcinoma associated with Alagille syndrome. All three patients were boys and presented with jaundice. In addition, they had the characteristic facial appearance of Alagille syndrome with cardiac, vertebral, and eye anomalies, and all had passed acholic stools from the neonatal period. Liver biopsies were diagnosed as bile duct paucity, compatible with Alagille syndrome in two cases, but the third case showed marked bile duct proliferation at the initial liver biopsy when 7 months old, which made diagnosis difficult. Eventually, all three cases progressed to biliary cirrhosis and hepatocellular carcinoma, which occurred at 17 months, 4 years, and 7 years, respectively. Because of the unusual liver histology and early onset of hepatocellular carcinoma, careful clinicopathologic correlations and close monitoring are required for the diagnosis of Alagille syndrome and for the early detection of hepatocellular carcinoma.


***Keywords:*** Alagille syndrome; Bile duct disease; Hepatocellular carcinoma

## Introduction

Alagille syndrome is an autosomal dominant multisystem disorder involving the liver, heart, skeleton, eyes and face, which is caused by mutations in *Jagged1*. [5,9,11,14]. The diagnostic criteria of Alagille syndrome are a histologic finding of bile duct paucity and a ratio of bile ducts to portal tracts of $\leqslant 0.4$ [1,2,6,14,16], in combination with three of the following five major clinical features: cholestasis, a cardiac defect (most commonly stenosis of the pulmonary valve, pulmonary artery, and its branches), skeletal abnormalities (most commonly ''butterfly vertebrae''), ophthalmologic abnormalities (most commonly posterior embryotoxon), and characteristic facial features [2]. Less commonly, there may be abnormalities of the kidneys, neurovasculature, or pancreas. However, even when a patient cannot meet these full criteria if there is a family history of similar symptoms, the diagnosis should be considered because of the highly variable expression shown by this syndrome [2].

Hepatic diseases in Alagille syndrome are known to have a benign clinical course. However, 12–14% develop into biliary cirrhosis [9] and rarely into hepatocellular carcinoma [2,6,7,10]. Here, we report on three cases of Alagille syndrome associated with hepatocellular carcinoma, with some emphasis on the unusual bile duct

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pathology, duct proliferation rather than paucity, and on the early development of hepatocellular carcinoma.

## Case report

### Case 1

A 4-month-old boy was transferred to our hospital because of jaundice, which developed 20 days postpartum. He had a unique facial appearance, i.e., hypertelorism, deep-set eyes, and abnormal ear lobes (Fig. 1). His eyes had posterior embryotoxon in the cornea. Mild hepatosplenomegaly was noted by abdominal ultrasonography, but vertebrae were normal on spine radiographs. Technetium-99m-DISIDA scintiscan findings were within normal limits. Left pulmonary arterial and aortic stenosis were found by echocardiography. Laboratory tests showed total bilirubin 10.4 mg/dL, direct bilirubin 7.4 mg/dL, aspartate aminotransferase 420 U/L, alanine aminotransferase 358 U/L, alkaline phosphatase 427 U/L, gamma glutamyl transpeptidase (GGT) 616, and total protein 7.4 g/dL (Table 1). A needle biopsy of the liver at the age of 7 months revealed the features of cholestatic hepatitis with interlobular bile duct proliferation, canalicular bile plugging, moderate porto-periportal inflammatory cell infiltration, and periportal fibrosis, suggesting extrahepatic biliary obstruction. Bile duct remodeling and proliferation were well shown by CK7 immunostaining (Fig. 1).

When he was 17 months old, fever developed, and he was admitted with an impression of ascending cholangitis. Ultrasonography and CT revealed a $6 \times 6.5$ cm exophytic mass in the dome of the right liver lobe. The mass contained irregular cysts on ultrasonograms and a hyperattenuated area on CT scans before contrast administration (Fig. 1), suggestive of tumor necrosis or bleeding. Free fluid was observed around the mass. Hepatosplenomegaly and diffuse nodularity of the liver suggested hepatic cirrhosis by ultrasonography. Serum α-fetoprotein was elevated at 289,000 ng/dL, but HBsAg and anti-HCV were negative. No metastatic lesions were found by bone scan or chest X-ray. One month later, a liver transplantation was performed. The resected liver showed a hepatocellular carcinoma of a single nodular, cirrhotomimetic, and macro-trabecular type with massive central hemorrhage. The surrounding liver tissue showed biliary cirrhosis. After liver transplantation, total bilirubin decreased to 1.4 mg/dL, and he was healthy 20 months posttransplantation.

### Case 2

A 4-month-old boy was transferred to our hospital for evaluation of generalized jaundice and the passing of acholic stools since the neonatal period. He was the product of a normal full-term spontaneous delivery. He, too, had a characteristic facial appearance–frontal bossing, mild hypertelorism, low-set ears, and flat nasal bridge. Ventricular septal defect with pulmonary stenosis was found by echocardiography, which was performed because of systolic murmur.

Total bilirubin was 17.2 mg/dL, direct bilirubin 12.2 mg/dL, aspartate aminotransferase 388 U/L, alanine aminotransferase 395 U/L, alkaline phophatase 632 U/L, and γ-glutamyltransferase 184 U/L (Table 1). HBs Ag and anti-HCV were negative. Abdominal ultrasonography showed a small gallbladder with a thick wall and irregular lumen. No hepatosplenomegaly was noted. Radiographs of the spine showed multiple "butterfly" deformities of the dorsal vertebrae (Fig. 1). However, an ophthalmic examination revealed no abnormal findings. Percutaneous needle biopsy of the liver at 4 months of age showed a paucity of interlobular bile ducts with some remodeling of the ductal plates at the periphery of the portal tracts without definite lumen formation. When he was 4 years old, he suffered from malaise, poor oral intake, and sudden distension of the abdomen over a few days. His symptoms then escalated to respiratory difficulties and melena. Abdominal ultrasonography showed multiple variably sized (0.7–6.2 cm) hyperechoic nodules or masses in the liver, some of which enhanced well in the arterial phase CT scans (Fig. 2). Splenomegaly and massive ascites were seen, but no portal vein thrombosis was found. His serum α-fetoprotein was 41,400 ng/dL, and viral hepatitis markers were all negative. A liver biopsy of the masses showed hepatocellular carcinoma of cirrhotomimetic, mixed macro- and micro-trabecular type (Fig. 2). Treatment options were limited. The patient was discharged home and died.

### Case 3

A boy born at full-term by vaginal delivery presented with jaundice with generalized itching and also had passed acholic stools since birth. His face showed a broad, protruding forehead, a pointed chin, deep-set eyes, and corneal opacity of the left eye. A liver biopsy at 3 months of age revealed paucity of interlobular bile ducts. When he was 7 years old, he had a short stature with an icteric appearance. Multiple bean to small pea-sized lymph nodes were palpated in his neck, and abdominal ultrasonography showed a large hypoechoic mass (7 cm in diameter) in the right lobe of the liver. The diffuse liver nodularity and splenomegaly suggested underlying liver cirrhosis. On a radiograph of the spine taken at this age, a "butterfly" vertebra was noted at T7. Moreover, multiple metastatic pulmonary nodules were observed on the chest radiograph. No biliary tract