Focal Liver Hyperplasia in Alagille Syndrome: Assessment with Hepatoreceptor and Hepatobiliary Imaging

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A child with Alagille syndrome, characterized by intrahepatic bile duct paucity, developed severe liver cirrhosis and was referred for liver transplantation. In the pre-transplantation evaluation, scintigraphic scans were performed using $^{99m}$Tc-galactosyl serum albumin ($^{99m}$Tc-GSA) as a hepatoreceptor binding agent and $^{99m}$Tc-pyridoxyl-5-methyl-tryptophan ($^{99m}$Tc-PMT) as a hepatobiliary agent. These studies demonstrated severe hepatobiliary dysfunction with an area of increased focal uptake in the liver. Histological examination at surgery confirmed that this focal lesion was an area of compensatory hyperplasia in advanced biliary cirrhosis. We present the usefulness of these tracers for detecting the focal hyperplasia of the liver.

Key Words: Alagille syndrome; focal liver hyperplasia; hepatoreceptor imaging; hepatobiliary imaging


Alagille syndrome is an uncommon disorder that causes chronic cholestasis from the neonatal or early infancy period (1,2). The characteristic pathological features of this disease are marked hypoplasia or agenesis of the interlobular bile ducts with multisystem congenital anomalies. It has previously been reported that 12% of patients develop cirrhosis and that approximately 20% require liver transplantation, either for hepatic failure or refractory pruritus and severe malnutrition (3–5).

This report describes a child with Alagille syndrome who developed severe cirrhosis and an unusual nodular lesion in the liver. Radionuclide imaging studies using $^{99m}$Tc-galactosyl serum albumin ($^{99m}$Tc-GSA), which is a hepatoreceptor binding agent, and $^{99m}$Tc-pyridoxyl-5-methyl-tryptophan ($^{99m}$Tc-PMT) were performed to evaluate hepatobiliary function and the nodular lesion. These images showed severe hepatobiliary dysfunction with an area of increased focal uptake in the liver. Surgical and pathological evaluations at transplantation revealed that the focal uptake was an area of focal compensatory hyperplasia in a background of severe biliary cirrhosis.

CASE REPORT

A 6-yr-old boy was referred to Kyoto University Hospital for evaluation for liver transplantation. The child was suffering from severe cirrhosis associated with Alagille syndrome. He was born at full term and had an uneventful delivery. There were no documented prenatal infections, such as rubella, influenza or herpes simplex, during pregnancy. As a neonate, the patient had persistent jaundice and a heart murmur, and congenital biliary atresia was suspected. A laparotomy was performed at the age of 1 mo, and liver biopsy revealed intrahepatic duct hypoplasia. When the patient was 1 yr old, pulmonary stenosis was suspected due to right cardiac catheterization. The patient exhibited the typical physical manifestations of Alagille syndrome, including hypertelorism, broad forehead, high nose and pointed chin. The patient’s mother did not have the same facial features.

Cholecystectomy was performed for cholestasis when the patient was 5 yr old. At 6 yr, severe liver cirrhosis was suspected based on serum biochemical data. The serum direct bilirubin value was 21.5 mg/dl. Jaundice and marked venous dilatation on the abdominal wall were observed. X-ray CT images revealed liver atrophy with splenomegaly and a high density nodular lesion in the medial right lobe of the liver (Fig. 1).

The patient underwent dynamic $^{99m}$Tc-GSA imaging under a rotating gamma camera. Following a bolus injection of 74 MBq $^{99m}$Tc-GSA, dynamic images were obtained in the anterior projection (including the liver and heart in the field of view) for 30 min. Images were obtained for 5 sec/frame for 1 min, 20 sec/frame for 2 min and 60 sec/frame for 27 min. Tomographic scans were soon obtained after the dynamic study. The tracer slowly accumulated in the liver and the image at 30 min postinjection showed poolings of $^{99m}$Tc-GSA in the heart and an enlarged spleen, indicating severe liver dysfunction (Fig. 2A). In addition, a region of significantly increased activity was noted in an area similar to the abnormality on the CT scan, SPECT images subsequently confirmed this observation (Fig. 2B).

Two days after $^{99m}$Tc-GSA imaging, dynamic hepatobiliary SPECT scans were obtained with $^{99m}$Tc-PMT. Following a bolus injection of 74 MBq $^{99m}$Tc-PMT, dynamic SPECT images were acquired with a multidetector SPECT scanner, at a rate of 5 min/frame for 60 min. The dynamic images (Fig. 3) revealed that tracer uptake was decreased and hepatic biliary excretion was delayed, suggesting biliary cirrhosis. An area of increased focal uptake was also detected in the middle of the liver, similar to the hot lesion observed on the $^{99m}$Tc-GSA images.

Living related liver transplantation was performed 2 days after the dynamic hepatobiliary SPECT scan. The donor was the patient’s father and surgery was uneventful. At surgery, the native liver appeared cholestatic and atrophic, but the nodular lesion in the medial right lobe was hypertrophic and clearly distinguished from the surrounding tissue (Fig. 4A). Histological examination revealed severe liver cirrhosis with a paucity of intrahepatic bile ducts, consistent with Alagille syndrome (Fig. 4B). On the other hand, the hepatic lobules were less damaged and some bile ducts and vessels were seen in the hypertrophic nodular lesion. The appearance was similar to focal nodular hyperplasia. There was no evidence of malignancy (Fig. 4C).

DISCUSSION

Alagille syndrome is a rare disorder characterized by chronic cholestasis due to intrahepatic duct hypoplasia (1,2). In addition to cholestasis, other manifestations include characteristic facial qualities, pulmonary artery stenosis, ocular posterior embryotoxon, vertebral malformation and retardation of physical and
FIGURE 1. Plain transverse CT image reveals hepatic atrophy and splenomegaly. A high density nodular lesion (arrowhead) is observed in the medial right lobe of the liver.

FIGURE 2. Technetium-99m-GSA images. (A) Anterior images at 3, 15, 20 and 30 min after injection. A region of high activity is detected in the liver (L). Prolonged blood-pool activity on the heart (H) and spleen (S) indicates severe liver dysfunction. (B) Serial axial SPECT image (from top to bottom). The high activity region of the liver corresponds to the nodular lesion on the CT image.

FIGURE 3. Technetium-99m-PMT images. Dynamic SPECT images (5 min/frame, from top to bottom) disclose severe biliary dysfunction. A region of high activity (arrow) is detected in the middle of the liver, corresponding to the nodular lesion on the CT image. The activity remains high at 60 min (arrowhead).

mental development. This syndrome has generally been thought to have a benign clinical course (5); however, recently it has become clear that patients with this syndrome are at risk for several serious clinical problems, including heart failure, liver failure and hepatocellular carcinoma (7–9). When liver cirrhosis becomes critical, liver transplantation is the treatment of choice. Transplantation in a patient with malignant liver tumor, however, has little likelihood of success. Most patients die within 3 yr as a result of tumor recurrence (10). Therefore, assessment of liver dysfunction and early detection of liver tumors are critical in the treatment of this disease.

Technetium-99m-GSA is a recently developed analog ligand to asialoglycoprotein receptor (ASGP-R), which is a hepatocyte
Cirrhosis. It is similar to technetium-99m-galactosyl neoglycoalbumin (99mTc-NGA). Kudo et al. (12,13) described the usefulness of 99mTc-GSA in assessing hepatocyte mass function. They observed that the concentration of ASGP-R in the liver is decreased and can be associated with the degree of hepatocellular damage. In evaluating hepatic tumors, cold defects are seen in primary malignant tumors because surface ASGP-R has been lost during malignant dedifferentiation (14). A compound of technetium-99m iminodiacetic acid (99mTc-IDA) may also be used to evaluate the severity of diffuse hepatic diseases (15). Aburano et al. (16) recently described a characteristic pattern of 99mTc-IDA uptake in intrahepatic bile duct hypoplasia. The specificity for the hot spots has not been determined, however, because 99mTc-IDA compound may highly accumulate in hepatocellular carcinoma as well as focal nodular hyperplasia (17,18).

In the present patient, the nodular lesion on the CT image showed markedly increased 99mTc-GSA uptake, whereas decreased activity was observed in the surrounding liver. These findings suggest that the liver was severely cirrhotic and that the nodular lesion was a compensatory hyperplasia of the liver, not a primary malignant liver tumor. Thus, 99mTc-GSA may be valuable for differentiating between these two disorders. Technetium-99m-PMT uptake was also higher in the nodular lesion; however, 99mTc-GSA accumulated more significantly in the nodular lesion. This may be due to the fact that as a hepatoreceptor-binding agent, 99mTc-GSA reflects the functional hepatocyte mass more closely than does 99mTc-PMT. Histological results were consistent with these scintigraphic findings.

Previous reports have described nodular lesions in the liver associated with Alagille syndrome. They include hepatocellular carcinoma (19–21) and hamartomatous nodule (22), which were detected by x-ray CT or MRI and later verified by liver biopsy or autopsy. We believe this represents the first report of Alagille syndrome assessed with 99mTc-GSA and 99mTc-PMT. In this patient, both radiotracers revealed the pathophysiological conditions accurately, although 99mTc-GSA may be more useful in characterizing focal hyperplasia of the liver in severe cirrhosis.

**REFERENCES**