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Scintigraphic progress of the liver in a patient with Alagille syndrome (arteriohepatic dysplasia)

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We encountered a 9-year-old Japanese girl with Alagille syndrome. Her scintigraphic examinations of the liver were performed at the ages of 16 months and 9 years. ^{99m}Tc-PMT, a hepatobiliary imaging agent, was distributed homogeneously in the liver at the younger age, but unevenly produced an area of focally increased uptake in the medial segment of the liver surrounded by peripheral atrophy at the older age. ^{99m}Tc-GSA, a hepatoreceptor binding agent, was highly accumulated in the area, corresponding to the focally increased uptake of ^{99m}Tc-PMT. These imaging findings suggest that the pathophysiological and morphological changes of the liver occurred in our patient during the clinical course.

Key words: Alagille syndrome, ^{99m}Tc-GSA, ^{99m}Tc-PMT, bile stasis, large regenerative nodule

INTRODUCTION

ALAGILLE SYNDROME (arteriohepatic dysplasia) is a rare autosomal dominant disorder characterized by chronic cholestasis due to intrahepatic duct hypoplasia, cardiovascular abnormalities and other multi-system congenital abnormalities.[1–3]

Scintigraphic examinations with ^{99m}Tc-pyridoxyl-5-methyl-tryptophan (^{99m}Tc-PMT) and ^{99m}Tc-galactosyl serum albumin (^{99m}Tc-GSA) were performed to assess the liver condition of our patient with Alagille syndrome. There are some reports about this disorder assessed by radionuclide imaging examinations.[4–9] To our knowledge, this is the first report describing the change of the ^{99m}Tc-PMT imaging findings in a patient with Alagille syndrome. The change of scintigraphic findings in our case may be due to the pathophysiological changes in the liver of a patient with Alagille syndrome in the different stages of the disease.

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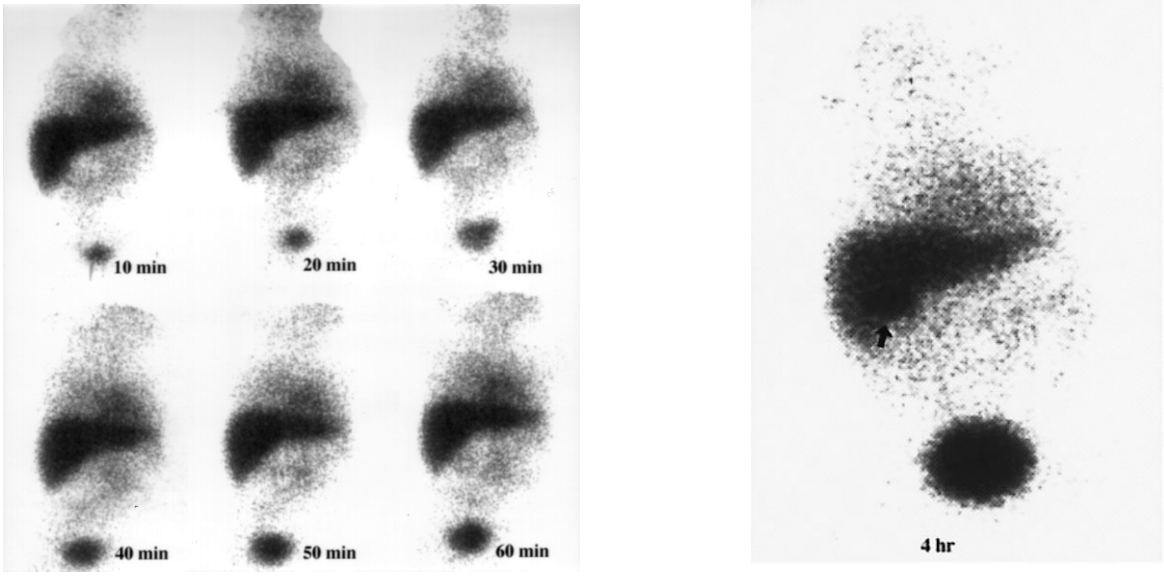
CASE REPORT

A 9-year-old girl underwent ^{99m}Tc-PMT hepatobiliary imaging and ^{99m}Tc-GSA hepatoreceptor imaging, to evaluate her liver condition in January, 1999. She was born at the 38th weeks of pregnancy in 1989. She had gray feces and heart murmur at the examination of the age of one month. She was referred to our hospital and underwent cholangiography and liver biopsy under the laparotomy at the 49th day after her birth. The cholangiography showed intrahepatic duct hypoplasia and a liver biopsy revealed intrahepatic bile duct stasis.

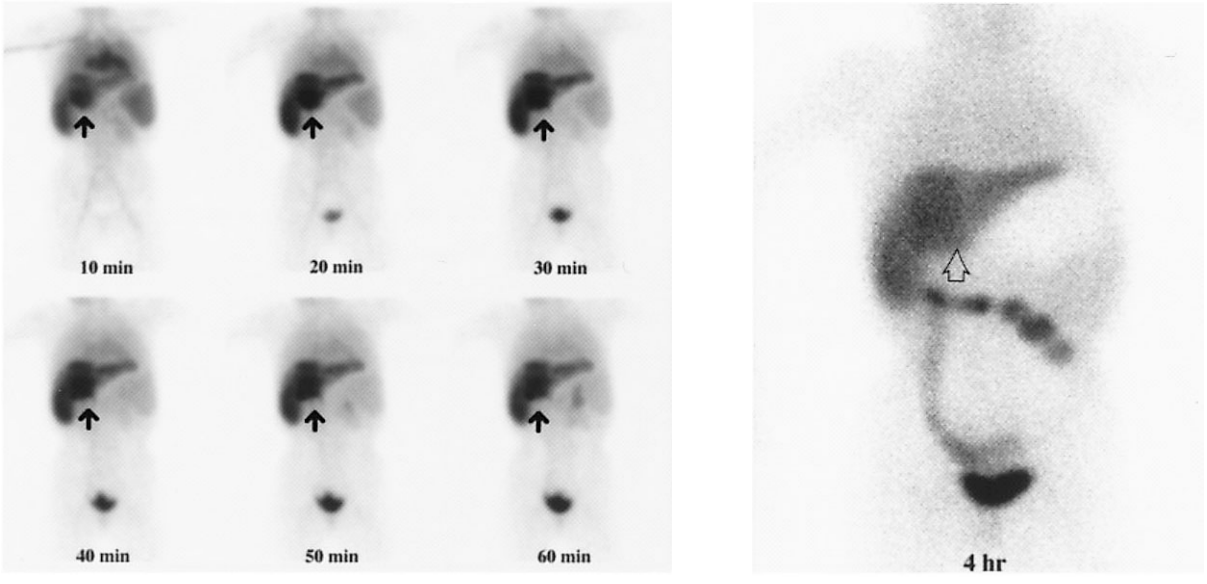
She also had characteristic facial features and peripheral pulmonary artery stenosis. Thus the partial Alagille syndrome was diagnosed. Since then, she had been followed up and received the treatments for biliary cirrhosis, lack of fat-soluble vitamins and recurrent pathologic fractures. She had a sister who also had intrahepatic duct hypoplasia and died after operation of aortic valve stenosis.

When she was at the age of 16 months, hepatobiliary imaging was performed with 74 MBq of ^{99m}Tc-PMT using a gamma camera (RC-1C-1635LD; HITACHI). The serial 10 min anterior images were obtained at 10, 20, 30, 40, 50, 60 min and 4 hr after the intravenous injection. The images showed the liver uniform in accumulation of



A B

Fig. 1 Serial ^{99m}Tc-PMT 10-minute images for 60 minutes at the age of 16 months (A) demonstrate persistent appearance of cardiac blood pool activity, uniform distribution of activity throughout the liver, no visible clearance of tracer from the entire liver, and no visualization of the bile ducts, gallbladder, or gut. The 4-hour image (B) has the same findings as (A), except for decreased cardiac blood pool activity and visualization of the gallbladder (*arrow*).



A B

Fig. 2 Serial ^{99m}Tc-PMT 10-minute images for 60 minutes at the age of 9 years (A) demonstrate slow clearance of cardiac and enlarged splenic blood pool activity, uneven distribution of activity in the atrophic liver with a round high activity in the medial segment of the liver (*closed arrows*), no visible clearance of tracer from the liver, and no visualization of the bile ducts, gallbladder, or gut. However the 4-hour image (B) shows no visible blood pool activity, relatively decreased activity of the medial segment (*open arrow*), and visualization of the colon.

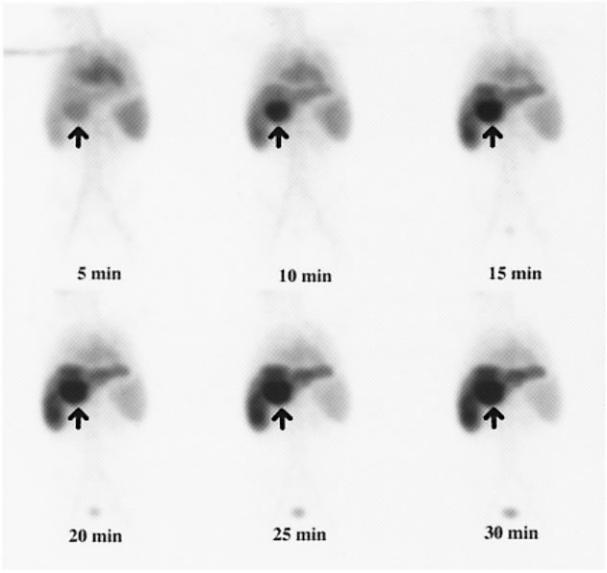


Fig. 3 Serial ^{99m}Tc-GSA 5-minute images for 30 minutes at the age of 9 years demonstrate slow disappearance of cardiac and splenic blood pool activity, relatively high and rapid uptake of tracer in the middle segment (*arrows*).

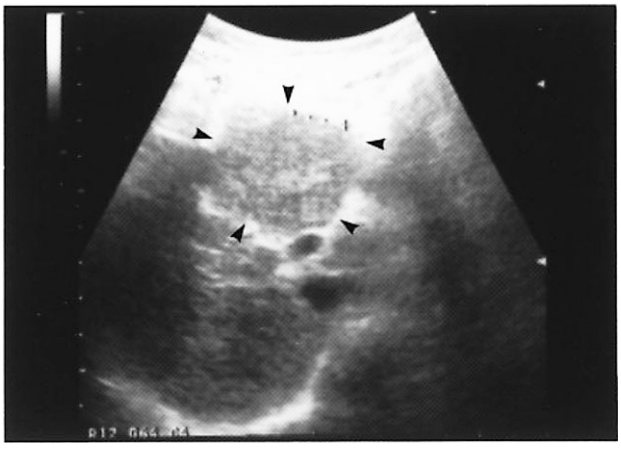


Fig. 4 Ultrasound sonography shows the enlarged medial segment of the liver (*arrowheads*).

the tracer (Fig. 1A). The 4-hour image showed persistent tracer accumulation throughout the liver, appearance of the gallbladder and no apparent visualization of the gut (Fig. 1B). Serum total bilirubin was elevated to 25.7 mg/d*l* with its direct bilirubin level of 18.1 mg/d*l*. Serum total cholesterol was also elevated to 706 mg/d*l*.

Eight years later, the dynamic hepatobiliary and hepatoreceptor scans were performed with ^{99m}Tc-PMT and ^{99m}Tc-GSA, respectively, using a gamma camera (PRISM2000; SHIMADZU). Dynamic ^{99m}Tc-PMT imaging was performed after injection of 74 MBq of ^{99m}Tc-PMT in the same way as before. The findings of dynamic images were quite different from the previous ones and

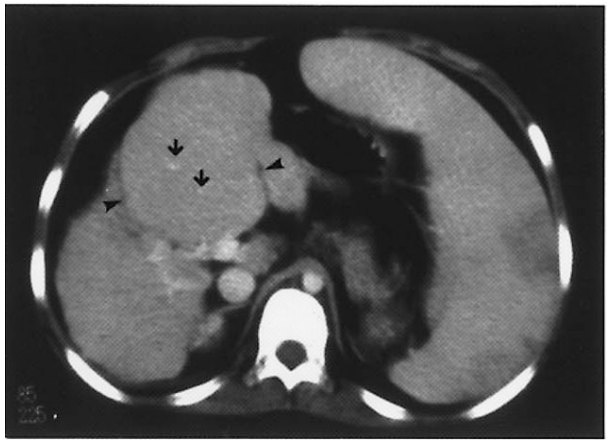


Fig. 5 Contrast-enhanced CT shows enlargement of the medial segment (*arrowheads*) with penetration of vessels (*arrows*) and shrinkage of other segments of the liver. Splenomegaly is also demonstrated.

showed an atrophic liver with dull edges and splenomegaly. In addition, an area of increased focal uptake was observed in the central portion of the liver, in which the activity gradually decreased (Fig. 2A). The 4-hour image demonstrated the colon, but the gallbladder was not depicted (Fig. 2B).

Six days later, the serial hepatoreceptor images were obtained for 30 min following an intravenous bolus injection of 111 MBq of ^{99m}Tc-GSA. The ^{99m}Tc-GSA images demonstrated significant tracer accumulation in the medial segment of the liver (Fig. 3), corresponding to the lesion of focally increased uptake observed on the ^{99m}Tc-PMT images. Ultrasound sonography (Fig. 4) and contrast enhanced CT (Fig. 5) demonstrated enlargement of the medial segment of the liver, which corresponded to the area of high accumulation on both ^{99m}Tc-GSA and ^{99m}Tc-PMT images. CT demonstrated the enlarged medial segment of the liver showing the similar homogeneous enhancement as the other segments, with the normal penetration of vessels and an atrophic gallbladder.

At this time, the levels of serum total bilirubin (11.8 mg/d*l*), direct bilirubin (9.7 mg/d*l*), and total cholesterol (183 mg/d*l*) were lower than those at the age of 16 months.

She underwent liver transplantation on Jan. 10, 2001 at the age of 11 years at Kyoto university hospital. Histological examination of the resected liver demonstrated biliary cirrhosis with paucity of bile ducts. On the other hand, the structure of the liver parenchyma was relatively well preserved in the nodular lesion, 8 cm in diameter, of the medial segment. The nodule was composed of hyperplastic hepatocytes. In the nodule, there were portal tracts containing interlobular bile ducts as well portal veins with focal fibrous obliteration and dilated hepatic arteries. There was no atypia in the hepatocytes and a diagnosis of large regenerative nodule was made. At the present time, she is 14 years old and in good health.

DISCUSSION

Alagille syndrome is one of the causes of jaundice and cholestasis in the newborn period and at the older age, the patient may have chronic hepatic disease.[1–3] Both sexes were affected approximately equally.[1] The syndrome is characterized by peculiar facies, chronic cholestasis, posterior embryotoxon, butterfly-like vertebral arch defects, and peripheral pulmonary artery hypoplasia or stenosis.[1–3] The complete Alagille syndrome is diagnosed when all these five features are present. When only four or three features are present, it is the partial Alagille syndrome.[2] Our case had three of these features (chronic cholestasis, characteristic facial features and peripheral pulmonary artery stenosis). Thus the partial Alagille syndrome was diagnosed. There is an autosomal incidence pattern with variable penetrance.[2]

In our case, scintigraphic examinations with ^{99m}Tc-PMT were performed at the ages of 16 months and 9 years. The interesting point of this case is the change of ^{99m}Tc-PMT imaging findings in the first and second examinations. The first examination showed uniform distribution of the tracer throughout the liver with diffuse poor clearance during the 4-hr imaging time. The second examination showed the uptake in the central portion of the liver was initially higher than that in the periphery of the liver, and the activity in the central portion of the liver became less intense on the 4-hr image than on the 60 min or earlier images, which suggested faster clearance of ^{99m}Tc-PMT in the hypertrophic area than in the other areas.

Balich et al.[4] reported the pattern of ^{99m}Tc-mebrofenin, a hepatobiliary imaging agent, in a 7.5-week-old male infant with Alagille syndrome who showed similar uniform distribution of activity throughout the liver with slow disappearance of cardiac blood pool activity as our first images with ^{99m}Tc-PMT and the late appearance of the gallbladder on the 24-hours image. These findings suggest that the hypoplastic change of bile ducts may spread uniformly, resulting in low excretion capacity. Torizuka et al.[5] reported that both tracers of ^{99m}Tc-PMT and ^{99m}Tc-GSA accumulated significantly in the hyperplastic nodule in the central portion of the liver in a 6-year-old boy with Alagille syndrome. Tajima et al.[6] also reported that all tracers of ^{99m}Tc-PMT, ^{99m}Tc-GSA and ^{99m}Tc-phytate accumulated significantly in the hyperplastic nodule in the liver in a 10-year-old boy with Alagille syndrome. They called such a hyperplastic nodule focal liver hyperplasia[5] or hepatic nodular hyperplasia.[6] We would like to call ours a large regenerative nodule according to the report on terminology of nodular hepatocellular lesions.[10] The imaging findings of ^{99m}Tc-GSA and ^{99m}Tc-PMT in both cases were similar to those of our second images. Their histological examination also similar to ours; biliary cirrhosis with paucity of bile ducts with a large hypertrophic nodular lesion which contained hyperplastic hepatocytes. This suggests that compensatory hyperplasia arose in the medial segment of the liver which were less damaged as the cirrhotic change progressed in the periphery areas. Aburano et al.[7] described a scintigraphic pattern of hepatobiliary imaging with ^{99m}Tc-IDA in a 20-year-old woman with Alagille syndrome that the tracer showed normal clearance in the central portion of the liver while the persistent activity retained in the periphery of the liver, resulting in a photopenic center surrounded by a hot peripheral rim on the later images. This pattern is different from the second ^{99m}Tc-PMT imaging pattern in our patient, in which clearance of ^{99m}Tc-PMT from the central portion of the liver was slower than in the case of Aburano et al. The difference in findings of hepatobiliary imagings between the past reported cases of Alagille syndrome was regarded as various features in this disorder.[4]

However, the similarity in the scintigraphic pattern of our first images obtained at the age of 16 months to the case of a 7.5-week-old male infant by Balich et al.[4] and our second images obtained at the 9 years to the case of a 6-year-old boy by Torizuka et al.[5] and a 10-year-old boy by Tajima et al.[6] and the different pattern of the 20-year-old woman by Aburano et al.[7] seem to reflect the progressing features of this disorder with age. Therefore, the difference of patterns in the hepatobiliary scan in Alagille syndrome between the previous reports may be attributed to the pathological and functional changes with time rather than the intrinsic character of each case.

There are some reports of primary hepatocellular carcinoma developing in patients with Alagille syndrome.[3,8,9] We have to be careful to differentiate the focal nodular benign lesion from hepatocellular carcinoma in Alagille syndrome. Although ^{99m}Tc-GSA or ^{99m}Tc-PMT can be also taken up by hepatocellular carcinoma,[11,12] it is visualized as a hot area in the late (5 hr) ^{99m}Tc-PMT images and does not show increased uptake in the early (5–60 min) ^{99m}Tc-PMT images.[12] ^{99m}Tc-GSA can accumulate significantly in a hyperplastic nodule as shown in the cases reported by Torizuka et al.,[5] Tajima et al.[6] and ours because ^{99m}Tc-GSA imaging reflects the functional hepatocyte mass with asialoglycoprotein receptors. Thus, the hot nodular lesion on both the early (5–60 min) ^{99m}Tc-PMT and ^{99m}Tc-GSA images has little possibility to be hepatocellular carcinoma.

Radionuclide imaging studies with ^{99m}Tc-PMT and ^{99m}Tc-GSA can demonstrate diffuse and focal hepatic pathophisyological and morphological conditions and are useful to distinguish the focal nodular benign lesion from hepatocellular carcinoma in Alagille syndrome.

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