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CASE REPORT

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False-negative Hepatobiliary Scintigraphy for Biliary Atresia

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Abstract

We present the case of a patient with biliary and duodenal atresia who showed false-negative hepatobiliary scintigraphy results. The patient was born at 37 weeks and 2 days of gestation. Her mother had undergone amnioreduction after detection of a double-bubble ultrasound sign in the fetal abdomen. At 2 days of age, total serum bilirubin level was elevated. On hepatobiliary scintigraphy 4 days later, the gallbladder was visualized from 30 min and it showed duodeno-gastric reflux at 240 min. After 24 h, the radiotracer was almost washed out in the hepatic parenchyma, but there was retention in the gastroduodenal junction. Because the biliary to duodenal transit was visible, biliary atresia seemed unlikely. Abdominal ultrasonography at 7 days of age showed a small dysmorphic gallbladder, but triangular cord sign was not definite. Magnetic resonance cholangiography revealed atretic gallbladder. Although cystic and common bile ducts were visible, the proximal common hepatic bile duct was not visible. The next day, serum total bilirubin levels remained elevated (17.1 mg/dl) with direct bilirubin level of 1.2 mg/dl. Kasai portoenterostomy with duodeno-duodenostomy was performed at 10 days of age. Histopathological evaluation showed a fibrous obliteration of the common bile duct, consistent with that of biliary atresia.

Keywords Neonatal jaundice · Biliary atresia · Hepatobiliary scintigraphy · Mebrofenin

Introduction

Biliary atresia is a destructive inflammatory obliterative cholangiopathy in neonates that affects both intrahepatic and extrahepatic bile ducts of varying lengths [1] and manifests as cholestatic jaundice, acholic stools, and hepatomegaly. If untreated, biliary atresia can cause progressive liver cirrhosis and liver failure. The disease is classified according to the predominant atresia site. Type I showing obliteration of the common bile duct (about 5% of cases). Type II shows patency to the level of the common hepatic duct (about 2% of cases) and divided into type IIa, which have a patent cystic duct and common bile duct, and type IIb, which showed obliterated common hepatic duct, cystic duct, and common bile duct. Type III showing obliteration of the left and right main hepatic ducts at the level of the porta hepatis (> 90% of cases) [2]. However, residual but microscopic biliary ductules maintain continuity with the intrahepatic biliary system in all three types.

Failure to establish bile flow is an indication for liver transplantation. Biliary atresia remains the most common indication for liver transplantation in children, accounting for about 75% of transplantations in those < 2 years of age (European Liver Transplant Registry 2005) [3]. Kasai portoenterostomy is a palliative surgical treatment for bile drainage. Early diagnosis of biliary atresia is critical because Kasai portoenterostomy is recommended within the first 60 days of life to prevent irreversible liver failure.

Hepatobiliary scintigraphy in patients with biliary atresia typically shows good hepatic uptake but with absent excretion into the intestine within 24 h. Although the procedure's pooled sensitivity goes up to 98.7% [4, 5], the probability of false-negative results exists, which is a limitation that should be considered by nuclear physicians to make valid interpretations. Herein, we report the case of an infant with biliary and duodenal atresia who showed false-negative hepatobiliary scintigraphy results.

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Case Report

Our patient was born at 37 weeks and 2 days of gestation by cesarean section. The mother of the infant had undergone amnioreduction at 34 weeks and 2 days of gestation due to the presence of a double-bubble sign in the fetal abdomen and polyhydramnios on ultrasonography. The patient's body weight was 2120 g at birth, and her Apgar score was 8/9. Vital signs were stable, and her physical exam was unremarkable except for the presence of a distended abdomen. She was kept under observation in the neonatal intensive care unit. On the day of her birth, abdominal ultrasonography (US) revealed signs of duodenal atresia with dilated stomach and proximal duodenum and collapsed distal duodenum and small bowels. While the common bile duct was present, the gallbladder was not visible. A nasogastric tube on low intermittent suction (pressure, 15 cmH_2O) was inserted.

Routine hematology tests performed the next day were unremarkable; however, her serum total bilirubin level was 4.4 mg/dl (normal range, 0.2–1.2 mg/dl) with direct bilirubin level of 0.5 mg/dl (normal range, 0–0.5 mg/dl). Therefore, for further evaluation, the infant underwent hepatobiliary scintigraphy at 6 days of age. Anterior images were obtained at 5, 30, 60, and 90 min after intravenous injection of 1 mCi ^{99m}Tc–mebrofenin, which revealed diffusely decreased hepatic uptake at 5 min. The gallbladder was visualized from 30 min; however, bowel activity was not visualized until 90 min. Moreover, hepatic parenchymal excretion was markedly delayed showing only 17.8% excretion until 90 min. We obtained delayed images to evaluate the biliary to enteric tract transit. In a delayed 240-min image, curvilinear retention of radiotracer was shown in left side abdomen which means tracer activity in the gallbladder passes into the stomach through the duodenum. Due to duodenal atresia of this patient, radiotracer activity showed duodeno-gastric reflux instead of migration to the small bowel. After 24 h, hepatic parenchymal activity was almost washed out. Retention of radiotracer was noted in the gastroduodenal junction, which cannot be migrated to the small bowel due to duodenal atresia (Fig. 1). Because we observed biliary to duodenal transit, biliary atresia seemed unlikely. However, the patient's clinical course deteriorated with greenish discoloration of the nasogastric drain. A follow-up serum total bilirubin level at 8 days of age revealed elevated levels (17.1 mg/dl) with direct bilirubin level of 1.2 mg/dl.

A follow-up abdominal ultrasonography at 7 days of age showed the presence of a small dysmorphic gallbladder. The intrapancreatic portion of the common bile duct was present and the anterior wall of the right portal vein showed increased echogenicity, but a triangular cord sign was not definite (Fig. 2a); normal liver parenchymal echogenicity without focal lesions was observed. Magnetic resonance cholangiography (MR cholangiography) revealed the possible presence of an atretic gallbladder, which cystic and common bile ducts were visible, but not the proximal common hepatic bile duct which suggests type IIa biliary atresia (Fig. 2b). Duodenal atresia was suspected because the focal proximal duodenum and the stomach were dilated, duodenal second portion near the ampulla showed abrupt discontinuation, and other imaging results were also consistent with that of duodenal atresia.

Based on this evidence, we diagnosed the patient with biliary atresia and recommended the need for a Kasai type II procedure. At 10 days of age, the patient underwent Kasai portoenterostomy with duodeno-duodenostomy. An intraoperative cholangiography was not performed because we did not identify the bile duct hole. During the procedure, an atresia of the porta hepatis to the common hepatic duct was evident which confirms type IIa biliary atresia. Histopathological evaluation revealed a fibrous obliteration of the common bile duct, a finding consistent with that of biliary atresia (Fig. 3). The bile duct luminal diameter was 20 μm, 1 mm in length in diameter with a slit-like pattern. The infant was diagnosed with an atretic gallbladder with the absence of gallbladder mucosa. Bile ductular proliferation with fibrosis also showed at the gallbladder specimen.

After the operation, the patient's clinical course became stable, and the serum total bilirubin level decreased to 0.5 mg/dl on the day of discharge.

Discussion

Herein, we described the case of an infant who presented with progressive hyperbilirubinemia with a greenish nasogastric drain. Hepatobiliary scintigraphy showed gallbladder and duodenal activity on delayed images; nevertheless, the patient was diagnosed with biliary atresia. Serial ultrasonography and MR cholangiography revealed the possible presence of an atretic gallbladder. The common bile duct, but not the common hepatic duct, was visualized. However, during surgery, the surgeon could not identify the bile duct hole, and the pathological specimen revealed a fibrous obliteration of the common bile duct.

Although while performing hepatobiliary scintigraphy, hepatic excretion was severely delayed until 90 min, the gallbladder was visualized at 30 min. Considering the location in the gallbladder fossa above the lower margin and the round-shaped homogeneous radiotracer retention, we excluded the possibility of confusing the right kidney with the gallbladder (Fig. 1). In a delayed 240-min image, curvilinear radiotracer retention activity was shown in left side abdomen which location corresponds with stomach in MR cholangiography on

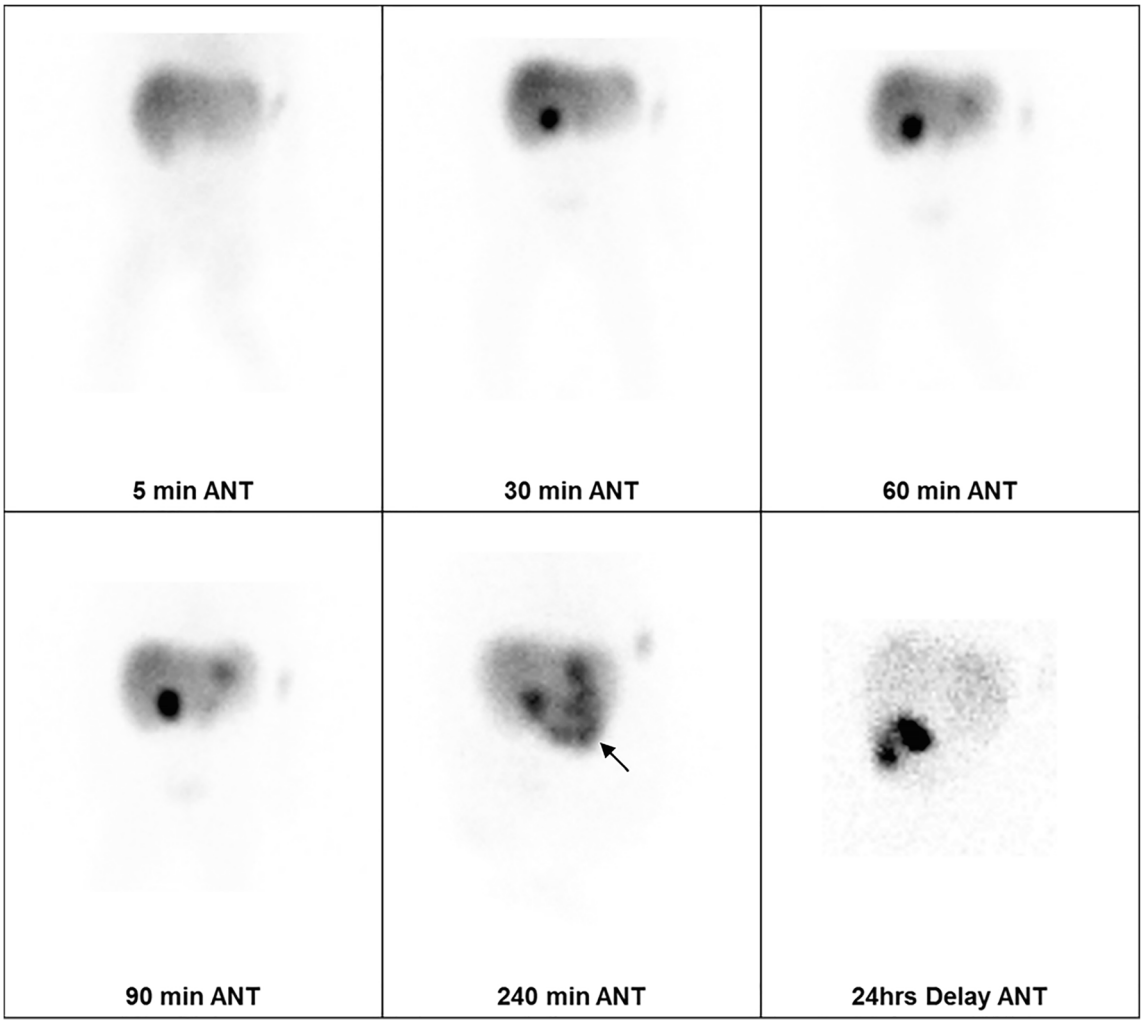

Fig. 1 ^{99m}Tc–Mebrofenin hepatobiliary scintigraphy in the anterior projection showing delayed hepatic parenchymal excretion with gallbladder filling starting at 30 min. A 240-min image showing duodeno-gastric reflux (arrow). A 24-h image showing almost complete lack of hepatic parenchymal activity and retention radiotracer in the gastroduodenal junction

Fig. 2b. It means tracer activity in the gallbladder passes into the stomach through the duodenum. It proves transit of the radiotracer into the bowel, which can exclude biliary atresia on hepatobiliary scintigraphy [6].

Imaging 24 h after radiotracer injection revealed that the hepatic parenchymal activity was almost washed out, and the distinct retention of the radiotracer at the gastroduodenal junction, which also can exclude biliary atresia. Due to duodenal

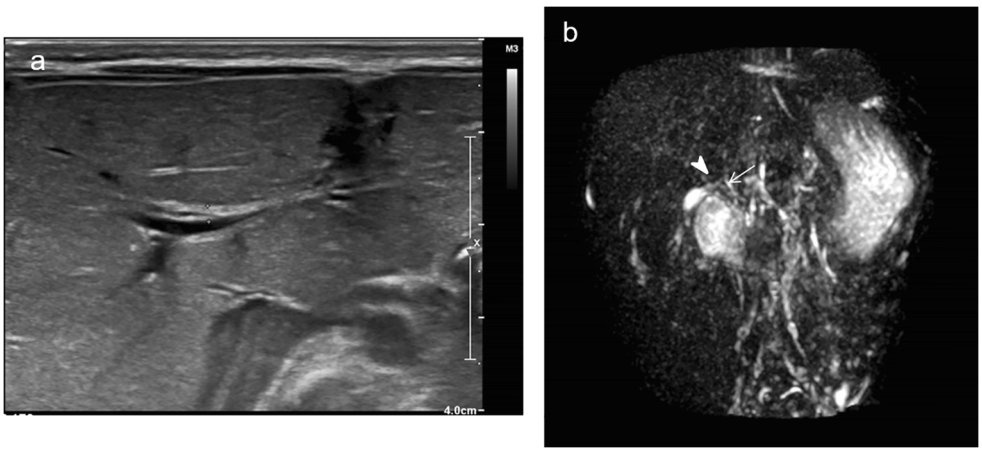

Fig. 2 **a** Ultrasonography showing increased echogenicity in the anterior wall of the right portal vein but no definite triangular cord sign. **b** Magnetic resonance cholangiography with 3D maximum intensity projection (MIP) reconstruction image showing suspicious visible cystic duct (arrow head) and common bile duct (arrow) but absence of proximal common hepatic bile duct images

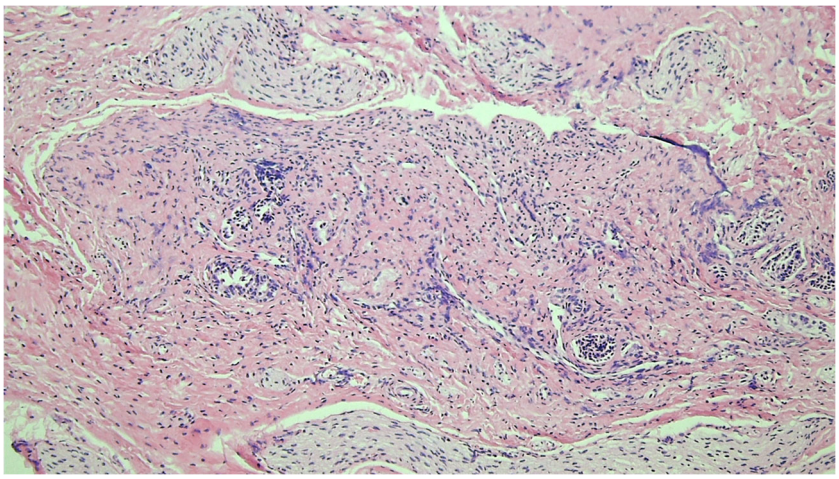

Fig. 3 Common bile duct at the site of fibrous obliteration, which is nearly occluded by fibrosis and only small slit-like lumens remain (original magnification × 100)

atresia of this patient, radiotracer activity was not seen in the small bowel distal to the duodenum.

Among the various methods used to diagnose biliary atresia, US is recommended as a screening test because of its cost-effectiveness and no ionizing radiation and sedation. Presence of sonographic gallbladder abnormalities, including absence of the gallbladder, abnormal wall feature and small size, and "triangular cord" sign (triangular or tubular echogenic density due to fibrous tissue in the bifurcation of the portal vein at the porta hepatis), are the key indicators of biliary atresia. When both signs are visible, they carry high sensitivity and specificity (up to 95% and 89%, respectively) [7]; however, ultrasonographic diagnoses remain subjective tasks. In our study, ultrasonography revealed a small dysmorphic gallbladder, but only showed slightly increased echogenicity in the portal vein, which is not definite for a triangular cord sign. In summary, the ultrasonographic features present in our patient were not sufficient for diagnosis of biliary atresia, warranting the need for further evaluation.

MR cholangiography is another noninvasive imaging modality used for diagnosis of biliary atresia; however, high cost and the need for sedation negate its routine use. Nonvisualization of the extrahepatic bile ducts during MR cholangiography reveals biliary atresia [8] with 90% sensitivity and 77% specificity [9]. False-positive results are due to motions resulting in poor visual quality, insufficient bile production, or visibility of only the common bile ducts with the absence of images of the right, left, and common hepatic ducts. In our study, the cystic and common bile ducts were visible, but the proximal common hepatic duct was not, which is a characteristic feature of type IIa biliary atresia. However, the possibility of false-positive results is a weakness of MR cholangiography.

Hepatobiliary scintigraphy is a noninvasive and objective diagnostic test for biliary atresia with high sensitivity (98.7%) and specificity (93%) [10]. High sensitivity is more important than the specificity for the diagnosis of biliary atresia because early diagnosis is crucial for appropriate treatment and also because false-negative results (excretion of the tracer into the bowel despite biliary atresia) are extremely rare. Therefore, hepatobiliary scintigraphy is widely used as a single test for detecting biliary atresia.

Misinterpretations of scintigraphy, such as confusing kidney or urinary bladder for bowel activity from true false-negative results, should be considered. For example, Verreault et al. [5] had reported two false-negative results caused by urine being interpreted as bowel excretion; however, the possibility of actual false-negative scintigraphy results is evident because Lee et al. had also reported that all but one patient (1.6% of 61 patients) with pathologically confirmed biliary atresia showed nonvisualization of the gallbladder without bowel activity [11]. The patient in our study represents a true false-negative case revealed by hepatobiliary scintigraphy, which may be attributed to the presence of a remnant slit-like lumen functioning as a passage, despite the pathological results. Diagnosis of fibrous obliteration with the biliary tree through the Kasai specimen is the final confirmation of biliary atresia [12]. Only 20% of biliary atresia showed complete fibroinflammatory obliteration [13]. However, while the common bile duct in our patient was nearly occluded by fibrosis, it was not completely obstructed. Presumably, the bile could pass through slit-like but patent lumen, which was found in the specimen. Relatively short segment of obliterated common hepatic duct in type IIa biliary atresia makes possible to bile transit in to the duodenum in this patient.

In conclusion, hepatobiliary scintigraphy has a high sensitivity and specificity and is an objective diagnostic tool that can enable clinicians to take objective decisions for a definite treatment. However false-negative results, as demonstrated in this study, are possible. Therefore, despite its high sensitivity, clinical course and other diagnostic modalities should be considered when interpreting the findings of hepatobiliary scintigraphy of patients with neonatal jaundice.

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Compliance with Ethical Standards

Conflict of Interest Hyunji Kim, Sujin Park, Sejin Ha, Jae Seung Kim, Dae Yeon Kim, and Minyoung Oh declare that they have no conflicts of interest.

Ethical Statement All procedures performed in this study involving human participants were in accordance with the ethical standards of the respective institutional research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. For this type of study, formal consent was not required.

Informed Consent The institutional review board at our institute approved this retrospective study, and the requirement to obtain informed consent was waived.

References

1. Sokol RJ, Mack C, Narkewicz MR, Karrer FM. Pathogenesis and outcome of biliary atresia: current concepts. J Pediatr Gastroenterol Nutr. 2003;37:4–21.
2. Wildhaber BE. Biliary atresia: 50 years after the first Kasai. ISRN Surg. 2012;2012:132089.
3. Hartley JL, Davenport M, Kelly DA. Biliary atresia. Lancet. 2009;374:1704–13.
4. Wang L, Yang Y, Chen Y, Zhan J. Early differential diagnosis methods of biliary atresia: a meta-analysis. Pediatr Surg Int. 2018;34(4):363–80 1–18.
5. Kianifar HR, Tehranian S, Shojaei P, Adinehpoor Z, Sadeghi R, Kakhki VRD, et al. Accuracy of hepatobiliary scintigraphy for differentiation of neonatal hepatitis from biliary atresia: systematic review and meta-analysis of the literature. Pediatr Radiol. 2013;43:905–19.
6. Tulchinsky M, Ciak BW, Delbeke D, et al. SNM practice guideline for hepatobiliary scintigraphy 4.0. J Nucl Med Technol. 2010;38:210–8.
7. Zhou L, Shan Q, Tian W, Wang Z, Liang J, Xie X. Ultrasound for the diagnosis of biliary atresia: a meta-analysis. AJR Am J Roentgenol. 2016;206:W73–82.
8. Han SJ, Kim MJ, Han A, Chung KS, Yoon CS, Kim D, et al. Magnetic resonance cholangiography for the diagnosis of biliary atresia. J Pediatr Surg. 2002;37:599–604.
9. Chavhan GB, Babyn PS, Manson D, Vidarsson L. Pediatric MR cholangiopancreatography: principles, technique, and clinical applications. Radiographics. 2008;28:1951–62.
10. Kwatra N, Shalaby-Rana E, Narayanan S, Mohan P, Ghelani S, Majd M. Phenobarbital-enhanced hepatobiliary scintigraphy in the diagnosis of biliary atresia: two decades of experience at a tertiary center. Pediatr Radiol. 2013;43:1365–75.
11. Lee H, Kang J, Kim KM, Jang JY, Jang S-J, Yu E. The clinicopathological parameters for making the differential diagnosis of neonatal cholestasis. Korean J Pathol. 2009;43:43–7.
12. Van Eyken P, Fanni D, Faa G. Extrahepatic bile duct atresia from the pathologist's perspective: pathological features and differential diagnosis. J Pediatr Neonatal Individ Med. 2014;3(2):e030247.
13. Muthukanagarajan SJ, Karnan I, Srinivasan P, Sadagopan P, Manickam S. Diagnostic and prognostic significance of various histopathological features in extrahepatic biliary atresia. J Clin Diagn Res. 2016;10:Ec23–7.