

Unusual early bile excretion from the liver in patients with fulminant hepatic failure as detected by Tc-99m-PMT hepatobiliary scintigraphy; Comparison with Tc-99m-GSA scintigraphy

Shin MATSUOKA,* Katsuhiko UCHIYAMA,* Yoshio KUNIYASU,** Yasuo NIIO,** Shin HASEBE,** Hideki SHIMA,* Sonomi OISHI,* Youko NOJIRI* and Hitoshi OGATA*

*Department of Radiology, Teikyo University School of Medicine, Ichihara Hospital

**Department of Radiology, Showa University, Fujigaoka Hospital

In two females (58 and 14 years old) with fulminant hepatic failure, Tc-99m-PMT hepatobiliary scintigraphy was used to evaluate intrahepatic bile stagnation, and Tc-99m-GSA scintigraphy to evaluate hepatic functional reserve. In both patients, Tc-99m-PMT hepatobiliary scintigraphy showed unusual early bile excretion into the extrahepatic bile duct and small intestine within the first 30 min of imaging. These findings contradicted typical findings of intrahepatic bile stagnation of fulminant hepatic failure. The receptor index and blood clearance index determined from dynamic acquisition data on Tc-99m-GSA scintigraphy suggested a markedly decreased hepatic functional reserve. These findings were compatible with fulminant hepatic failure. A discrepancy was observed between the findings of hepatobiliary scintigraphy and those of Tc-99m-GSA scintigraphy. The pathological state of early bile excretion from the liver into the bile duct should be considered in fulminant hepatic failure.

Key words: fulminant hepatic failure, technetium-99m PMT, hepatobiliary imaging, technetium-99m GSA, asialoglycoprotein receptor

INTRODUCTION

FULMINANT HEPATIC FAILURE is characterized pathophysiologically by massive necrosis of hepatocytes and marked intrahepatic bile stagnation as well as by a poor prognosis and low survival rate.¹ Because an appropriate management approach is essential to improve the survival rate, early diagnosis and prospective evaluation of the prognosis are important.² Various blood biochemical examinations have historically been used for early diagnosis of fulminant hepatic failure, but their results are not always meaningful because patients with fulminant hepatic failure may be treated by plasmapheresis and blood product supplementation.

Radionuclide examination techniques such as Tc-99m-N-pyridoxyl-5-methyl-triptyophan (PMT) hepatobiliary scintigraphy and Tc-99m diethylenetriamine pentaacetic acid galactosyl human serum albumin (GSA) have been applied for the determination of the severity of fulminant hepatic failure.^{3,4} In patients with fulminant hepatic failure, marked intrahepatic bile stagnation on hepatobiliary scintigraphy and a markedly decreased hepatic functional reserve on Tc-99m-GSA scintigraphy are common findings.

We present two patients with fulminant hepatic failure who showed unusual early bile excretion from the liver on Tc-99m-PMT scintigraphy and severely impaired hepatic functional reserve on dynamic data in Tc-99m-GSA scintigraphy.

CASE REPORTS

Two patients with fulminant hepatic failure underwent both Tc-99m-PMT hepatobiliary scintigraphy and Tc-99m-GSA scintigraphy. In hepatobiliary scintigraphy,

Received October 23, 2000, revision accepted December 18, 2000.

For reprint contact: Shin Matsuoka, M.D., Department of Radiology, Teikyo University School of Medicine, Ichihara Hospital, 3426-3, Anesaki, Ichihara, Chiba 299-0111, JAPAN.
E-mail: shinma@med.teikyo-u.ac.jp

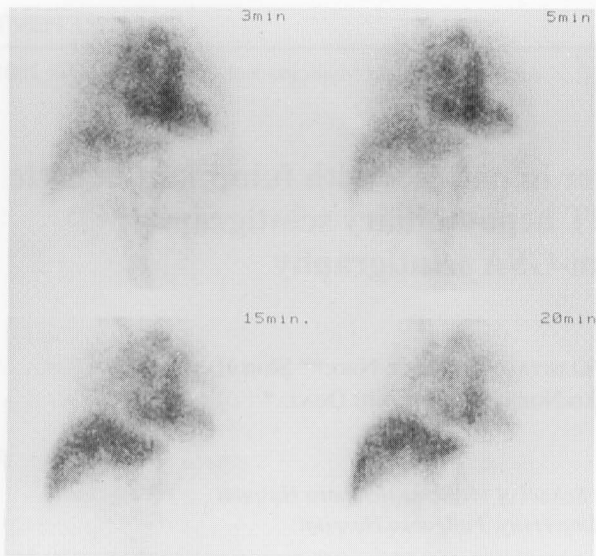


Fig. 1 Serial hepatic receptor imaging with Tc-99m-GSA in a 58-year-old woman with a fulminant hepatic failure. A marked cardiac pool is observed even after 20 minutes.

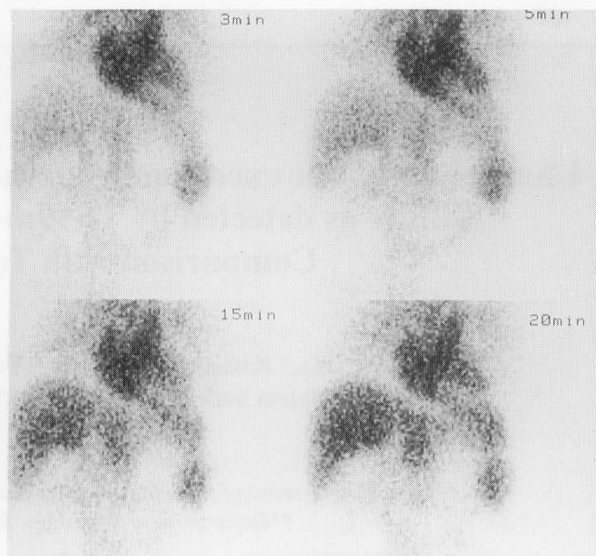


Fig. 3 Serial hepatic receptor imaging with Tc-99m-GSA in a 14-year-old girl with fulminant hepatic failure. A persistent cardiac pool is observed even after 20 minutes.

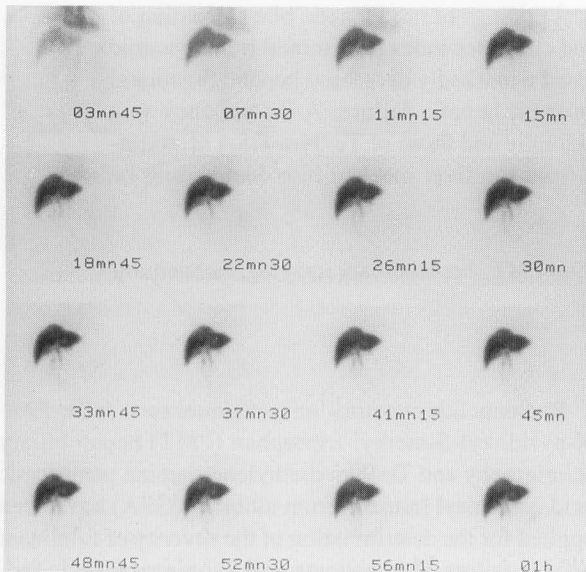


Fig. 2 Serial Tc-99m-PMT hepatobiliary scintigraphy in a 58-year-old woman with fulminant hepatic failure, after 3 min to 60 min. The duodenum was visualized 26 minutes after initial injection. The cardiac pool image disappeared after 14 minutes. Residual intrahepatic radioactivity was prominent even after 60 minutes.

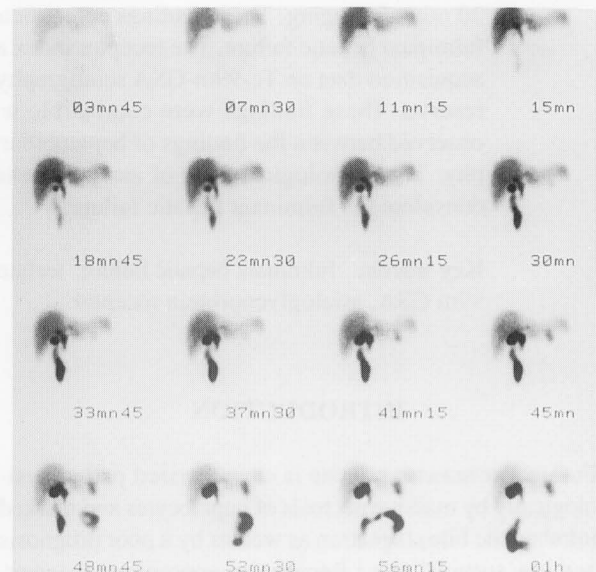


Fig. 4 Serial Tc-99m-PMT hepatobiliary scintigraphy in a 14-year-old girl with fulminant hepatic failure after 3 min to 60 min. The common bile duct and duodenum were visualized 15 minutes after initial injection.

after a bolus intravenous injection of Tc-99m-PMT (185 MBq), sequential dynamic images were obtained with a gamma camera (Sophy DHD, Sopha Medical, Buc, France) at the rate of 2 sec/frame for the first 60 seconds and 30 sec/frame for the next 60 minutes. Whenever necessary delayed images were obtained 24 hours after the first injection. In Tc-99m-GSA scintigraphy, after a bolus

injection of Tc-99m-GSA (185 MBq), serial dynamic images were taken with a gamma camera (STARCAM 3000XR/T, GE Medical Systems, Milwaukee, Wis) at the rate of 3 sec/frame for the first 60 seconds and 15 sec/frame for the next 20 minutes. According to a report by Kudo et al.,⁵ the time-activity curves for the heart and liver were generated from regions of interest (ROIs) placed

over the left ventricle and the whole liver. The receptor index (LHL15) was calculated by dividing the radioactivity counts of the liver ROI by the radioactivity counts of the liver plus heart ROI at 15 min after injection. The index of blood clearance (HH15) was calculated by dividing the radioactivity count of the heart ROI 15 min after the initial injection by the radioactivity count of the heart ROI 3 min after the initial injection.

Case 1

A 58-year-old woman was hospitalized with a 7-day history of jaundice and acute aggravation of liver function. The initial blood biochemical analysis showed marked hyperbilirubinemia (total serum bilirubin 15.9 mg/dl, direct bilirubin 10.8 mg/dl). Prothrombin time was noticeably reduced (24.0%). Her hepatic coma scale was grade 2. No history of hepatotoxic drugs, blood transfusions or other hepatitis-inducing factors was noted, and serologic tests for hepatitis A, B and C were negative. Tc-99m-GSA scintigraphy was performed one day after admission. A remaining noticeably cardiac pool and hepatic atrophy were recognized (Fig. 1). LHL15 and HH15 were 0.66 and 0.87, respectively, indicating greatly decreased hepatic functional reserve. Tc-99m-PMT hepatobiliary scintigraphy was performed 3 days after admission. The cardiac pool image disappeared 14 minutes after the first injection and the bile duct and small bowel appeared after 18 minutes and 26 minutes after it, respectively (Fig. 2). The early appearance of the bile duct and small bowel suggested little impairment of bile excretion, whereas a large degree of intrahepatic radioactivity remained even after 60 minutes, suggesting serious intrahepatic cholestasis. During the examination period of both scintigraphic techniques, no notable changes in clinical or blood biochemical examination data occurred. This patient underwent intensive therapy including fourteen plasmapheresis sessions, but died 38 days after admission due to liver failure.

Case 2

A 14-year-old girl developed appetite loss and abdominal distention as initial symptoms and was admitted with jaundice and rapid progression of liver dysfunction. Laboratory investigation showed slightly increased total serum bilirubin (2.1 mg/dl) and noticeably decreased prothrombin time (17.8%). The hepatic coma scale indicated grade 2. Tc-99m-GSA scintigraphy was performed 2 days after admission. A very persistent cardiac pool was observed (Fig. 3). The receptor index and blood clearance index were 0.57 and 0.87, respectively, demonstrating greatly decreased liver functional reserve. Tc-99m-PMT hepatobiliary scintigraphy was performed 4 days after admission. The bile duct and the duodenum appeared 15 minutes after the first injection (Fig. 4). These findings did not suggest impaired bile excretion. During the examination period with both scintigraphic techniques, no re-

markable changes in blood biochemical examination data or clinical findings were observed. Despite plasma exchange and plasma filtration dialysis, this patient died 51 days after onset due to hepatic failure and multiple organ failure.

DISCUSSION

The prognosis of fulminant hepatic failure is very poor with a survival rate of less than 50%. Steroid therapy and gulcagon-insulin therapies have traditionally been performed, but mortality remains high. In recent years, treatment with interferon, cyclosporin and plasma exchange have been positively applied, and these treatments have proved effective.⁶ Furthermore, auxiliary partial orthotopic liver transplantation, in which the native liver is left partially in place and a donor liver fragment is added, is a promising, recently developed therapy for patients with fulminant hepatic failure.⁷ To select the optimal treatment, early diagnosis of fulminant hepatic failure and evaluation of its prognosis are clinically important. In addition to blood biochemical examinations, CT⁸ and liver scintigraphy^{3,4,9,10} have recently been useful imaging methods to diagnose fulminant hepatic failure and to evaluate its severity.

Fulminant hepatic failure is characterized not only by extensive hepatocyte necrosis but also by intrahepatic bile stagnation. Yoshida et al.¹¹ analyzed the direct serum bilirubin/total serum bilirubin ratio, and showed that intrahepatic cholestasis in fulminant hepatic failure is due to impaired conjugation of bilirubin. Another study with Tc-99m-PMT hepatobiliary scintigraphy also showed greatly impaired bile excretion and a high mortality rate in fulminant hepatic failure.³ It reported that half of all patients without delineation of the small intestine within 24 hours in the Tc-99m-PMT hepatobiliary scintigraphy died. But in this study hepatobiliary scintigraphy of the two patients showed bile excretion into the extrahepatic bile duct and small intestine in the early phase. A possible reason for these findings is in the pathological state of bile transportation in fulminant hepatic failure. Although electron microscopic studies were not performed in these patients, the findings would likely have been as follows: 1) formation of shunts between blood and the biliary tract due to loosening of the intercellular tight junction, 2) destruction of pre-existing intracellular structures such as the cytoskeleton, and 3) collateral excretion into the extrahepatic bile ducts through a pseudo-bile duct.

Tc-99m-GSA scintigraphy is a new method for estimating of hepatic functional reserve on the basis of specific binding of hepatocytes to asialoglycoprotein receptor.¹² Shiomi et al.,⁴ who performed Tc-99m-GSA scintigraphy in 8 patients with acute hepatitis and 12 with fulminant hepatic failure, reported retrospectively that the receptor index was less than 0.83 in all patients with fulminant hepatic failure, whereas it was over 0.83 in all

patients with acute hepatitis. In addition, all survivors of fulminant hepatic failure had a receptor index of 0.58 or higher. Tc-99m-GSA scintigraphy was considered to be useful for diagnosing fulminant hepatic failure and evaluating its prognosis. In our patients, the Tc-99m-GSA scintigraphy index showed a marked decrease, which is consistent with fulminant hepatic failure according to Shiomi's criteria.

In this paper a discrepancy was observed between the findings of Tc-99m-PMT hepatobiliary scintigraphy and those of Tc-99m-GSA scintigraphy in two patients with fulminant hepatic failure. The results demonstrated the possibility of a pathological state in fulminant hepatic failure, which is characterized by early bile excretion from the liver into the bile duct and small intestine.

REFERENCES

1. Sherlock S. Fulminant hepatic failure. *Adv Intern Med* 1993; 38: 245–267.
2. Trey C, Davidson C. The management of fulminant hepatic failure. *Prog Liver Dis* 1970; 3: 282–298.
3. Uchiyama K, Kuniyasu Y, Nii Y, Hasebe S, Shinohara H, Matsuoka S, et al. Clinical evaluation of the scoring of optical findings with technetium-99m-N-pyridoxyl-5-methyl-tryptophan (PMT) hepatobiliary scintigraphy for fulminant hepatitis. [Thesis in Japanese] *Nihon Gazou igaku zasshi* 1998; 16: 349–356.
4. Shiomi S, Kuroki T, Kuriyama M, Takeda T, Nishiguchi S, Nakajima S, et al. Evaluation of fulminant hepatic failure by scintigraphy with Technetium-99m-GSA. *J Nucl Med* 1997; 38: 79–82.
5. Kudo M, Todo A, Ikekubo K, Hino M. Receptor index via hepatic asialoglycoprotein receptor imaging: correlation with chronic hepatocellular damage. *Am J Gastroenterol* 1992; 87: 865–870.
6. Yoshida M, Sekiyama K, Iwamura Y, Sugata F. Development of reliable artificial liver support (ALS)-Plasma exchange in combination with hemodiafiltration using high-performance membranes. *Dig Dis Sci* 1993; 38: 469–476.
7. Devlin J, Wendon J, Heaton N, Tan KC, Williams R. Pretransplantation clinical status and outcome of emergency transplantation for acute liver failure. *Hepatology* 1995; 21: 1018–1024.
8. Itai Y, Sekiyama K, Ahmadi T, Obuchi M, Yoshida M. Fulminant hepatic failure: observation with spiral CT. *Radiology* 1997; 202: 379–382.
9. Waxman AD. Scintigraphic evaluation of diffuse hepatic disease. *Semin Nucl Med* 1982; 12: 75–88.
10. Shiomi S, Ikeoka N, Minowa T. Diagnostic value of liver scintigraphy in fulminant hepatitis and severe acute hepatitis. *Acta Hepatol Jpn* 1985; 26: 592.
11. Yoshida M. Acute hepatitis, fulminant hepatitis, and jaundice. [Thesis in Japanese] *Nippon Naika Gakkai Zasshi* 1997; 86: 544.
12. Stadalnik RC, Vera DR, Woodle ES, Trudeau WL, Porter BA, Ward RE, et al. Technetium-99m-NGA functional hepatic imaging: preliminary clinical experience. *J Nucl Med* 1985; 26: 1233–1242.