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Atypical Cholecystitis after Bone Marrow Transplantation : Gallbladder Wall Thickening due to Cyclosporine A

Yoshitaka Nakamori,[1] *Kohei Ueda,*[2] *Toru Takahashi,*[1] *Masaaki Toyosawa,*[3] *Yusuke Inoue,*[4] *Eiichi Oeda,*[5] *Yutaka Sato*[6] *and Yukio Tanizawa*[1]

[1] Division of Molecular Analysis of Human Disorders, Department of Bio-Signal Analysis, Yamaguchi University School of Medicine, 1-1-1, Minami-Kogushi, Ube, Yamaguchi 755-8505, Japan
[2] Health Service Center, Organization for University Education, Yamaguchi University, 2-16-1, Tokiwadai, Ube, Yamaguchi 755-8611, Japan
[3] Department of Internal Medicine, Shin Mizumaki Hospital, 1-2-1, Tateyashiki, Mizumaki-cho, Onga-gun, Fukuoka 807-0051, Japan
[4] Division of Hematology, Department of Internal Medicine, Hikari Municipal Yamato General Hospital, 974, Iwata, Hikari, Yamaguchi 743-0192, Japan
[5] Department of Internal Medicine, Hofu-Onsen Hospital, 1634-1, Daido, Hofu, Yamaguchi 747-1232, Japan
[6] Division of Hematology, Department of Internal Medicine, Kanmon Medical Center, 1-1-1, Nochida, Shimonoseki, Yamaguchi 751-8501, Japan
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Abstract A 16-year-old Japanese male with acute mixed lineage leukemia in the second remission underwent allogeneic bone marrow transplantation from a HLA-identical sibling donor. Atypical cholecystitis developed three weeks after transplantation. Abdominal ultrasound examination revealed marked thickening of the gallbladder wall without biliary sludge or gallstones. Cholecystitis was treated by the cessation of cyclosporine A three days after symptoms development. To our knowledge, this is the first report of a patient with cyclosporine A induced cholecystitis, that may have been due to direct injury to the gallbladder wall and not a cholestatic mechanism.

key words: cholecystitis, gallbladder wall thickening, bone marrow transplantation, cyclosporine A

Introduction

Acute cholecystitis, which is a rare complication of bone marrow transplantation,[1)2)] and is commonly caused by biliary sludge,[3)] cytomegalovirus[4)] and fungal[5)] infection, and leukemic relapse with gallbladder involvement.[6)] We present a patient with atypical cholecystitis after bone marrow transplantation, with marked thickening of the gallbladder wall that was probably caused by cyclosporine A.

Case report

16-year-old Japanese boy with acute mixed lineage leukemia in the second remission underwent allogeneic bone marrow transplantation from a HLA-identical sibling donor in May, 2000. He received cytarabine 2 g/m^2 twice daily on day -5 and once daily on days -4 and -3, cyclophosphamide 2.5 g/body once daily on days -4 to -3, and total body irradiation (4 Gy) on days -3 to -1, as conditioning

regimen. Cyclosporine A and methotrexate as graft versus host disease (GVHD) prophylaxis were started on day +1 at a daily dose of 3.0 mg/kg and at a daily dose of 10 mg/m2 on days +1, +3, and +6, respectively.

On day +6, the serum concentration of cyclosporine A had increased to be 459 ng/ml (normal trough level: 200～300 ng/ml), but no abnormalities in blood chemistry or abdominal ultrasound examinations had developed. Alkaline phosphatase and lactate dehydrogenase started to increase on day +16, as did aspartate and alanine aminotransferases on day +20. Abdominal ultrasound examination, which was performed on day +21, revealed marked thickening (12 mm) of the gallbladder wall, with no evidence of biliary sludge or gallstones in the gallbladder or the bile ducts. The bile ducts were not dilated (Fig.1a), and the liver and spleen were not enlarged. Even though a low grade fever developed, the patient still did not develop any other symptoms or signs, including nausea, vomiting, right upper quadrant pain, and jaundice. Sonographic Murphy's sign was negative. Blood counts on day +21 were: hemoglobin 8.2 g/dl, leukocytes 3.5 x 10^9/L, and platelets 10 x 10^9/L. Blood chemistry tests revealed: aspartate aminotransferase 77 IU/L (normal range: 12-34 IU/L), alanine aminotransferase 69 IU/L (normal range: 5-43 IU/L), alkaline phosphatase 449 IU/L (normal range: 114-358 IU/L), lactate dehydrogenase 372 IU/L (normal range:115-217 IU/L), and C-reactive protein 8.41 mg/dl (normal range: 0.0-0.25 mg/dl). Serological tests for IgM antibodies to Epstein-Barr, herpes simplex, and herpes zoster viruses were all negative. Cytomegalovirus antigenemia was negative, and serum β-D-glucan was within the normal range. The serum concentration of cyclosporine A was still elevated (319.8 ng/ml on day +21). As there was no evidence of bacterial, viral, or fungal infection, he was treated without changes to his medications. On day +25, hyperkalemia and acidosis developed, the diagnosis of renal tubular acidosis due to cyclosporine A was made, and cyclosporine A was discontinued. Soon after the cessation of the drug, hepatobiliary function tests improved and abdominal ultrasound examination revealed a rapid reduction in the degree of the gallbladder wall thickening. By day +27, 2 days after cyclosporine A administration was ceased, the wall thickness had decreased to 5 mm (Fig.1b), and the serum concentration of cyclosporine A had decreased to 94.0 ng/ml. Most of the blood chemistry tests returned to within normal ranges by day +27: aspartate aminotransferase 67 IU/L, alanine aminotransferase 102 IU/L, alkaline phosphatase 621 IU/L, and lactate dehydrogenase 230 IU/L. By day +39, the wall thickness has returned to a normal size of 4 mm.

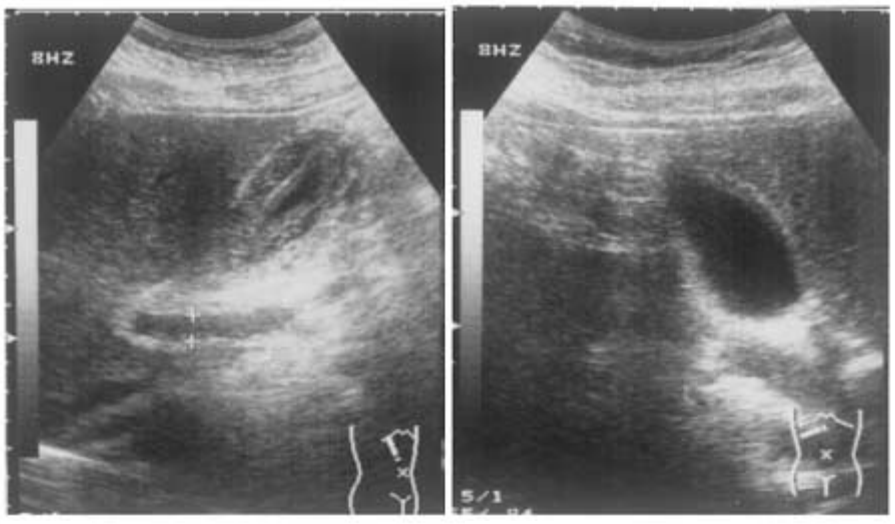

Fig. 1a Fig. 1b

Fig. 1a Abdominal ultrasound examination on day +21 revealed marked thickening of the gallbladder wall to 12 mm. Diameter of the common bile duct (+)was 8 mm.
Fig. 1b Abdominal ultrasound examination performed 2 days after the cessation of cyclosporin A. Wall thickness of the gallbladder was reduced to 5 mm.

Discussion

Several etiologies have been suggested to cause hepatobiliary dysfunction in the early post-transplantation period.[7] One such etiology includes bacterial, viral, or fungal infection, all of which were excluded in our patient by clinical and laboratory examinations. Total parenteral nutrition may contribute to cholestasis, biliary sludge and acalculous cholecystitis after transplantation. However, in our patient, abdominal ultrasound examination revealed marked thickening of the gallbladder wall without the accumulation of biliary sludge, that improved without the cessation of parenteral nutrition. Other common causes of gallbladder wall thickening, including hypoalbuminemia, hepatitis, right heart failure, pericholecystic fluid, incomplete gallbladder distention, adenomyomatosis, gallbladder carcinoma, and infiltration of leukemic cells, were not observed in this patient. In addition, hepatic GVHD was also not likely, because no evidence of GVHD was found in other organs, and because the cholecystitis improved without administration of immunosuppressive drugs. As cholecystitis developed about 20 days after transplantation, regimen related toxicity was considered and was supported by the immediate reduction in the gallbladder wall thickening after the cessation of cyclosporine A. Hepatobiliary abnormalities, as revealed by blood chemistry analysis, improved simultaneously. From these observations, we consequently concluded that the gallbladder wall thickening was induced by cyclosporine A. The hepatobiliary toxicity of cyclosporine A is caused by dose-related inhibition of canalicular bile transport by the drug that causes cholestatic liver injury with mild increases in the serum bilirubin concentration.[7] As jaundice was not exhibited by our patient, we speculate that cyclosporine A directly induced the inflammatory and edematous changes in the gallbladder wall, but not by a cholestatic mechanism. Cyclosporine A is metabolized in the liver, small intestine, and kidney to more than 30 metabolites that are mainly excreted through the bile ducts.[8] We propose that the most likely mechanism of the gallbladder wall thickening in our patient was direct chemical stimulation of the mucosal membrane of the gallbladder by some of the cyclosporine A metabolites. This is the first report of this atypical form of the hepatobiliary toxicity with gallbladder wall thickening caused by cyclosporine A. The effect of this drug must be considered when aseptic cholecystitis with gallbladder wall thickening develops after bone marrow transplantation.

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