Two difficulty diagnosis cases of severe veno-occlusive disease

Background: The occurrence of Hepatic veno-occlusive disease (VOD) is rare liver disease. However, severe VOD is often lethal and one of the most common causes of death following stem cell transplantation (SCT).

Case Reports: Case 1 was a 30-year-old woman who was diagnosed as Budd-Chiari syndrome with liver failure. She was admitted to our department to undergo liver transplantation. Four days after admission, she underwent liver transplantation. Her liver explant showed VOD. Case 2 was a 74-year-old woman who was admitted to a community hospital for further examination. Her condition continued to deteriorate with liver failure, and she died 39 days after admission. Liver autopsy also showed VOD. Either of the patients had difficulty in diagnose as VOD. Neither of the patients had a history of SCT.

Conclusions: VOD should be considered as a cause of acute hepatic failure, even if the patient has no history of SCT.

Key words: veno-occlusive disease • liver failure • stem cell transplantation

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Background

Hepatic sinusoidal obstruction syndrome (SOS) was formerly known as veno-occlusive disease (VOD), but recent studies have shown hepatic sinusoid injury as primary pathological events before injury to the hepatic venules [1–4]. The most common cause of VOD is stem cell transplantation (SCT). Prognosis of VOD or SOS is variable, with mortality rates ranging from 7% to 50% [5]. However, progressive VOD was shown to have poor prognosis in some series, with up to 100% mortality [6,7]. Herein, we report the cases of 2 patients with no history of SCT having hepatic failure due to VOD and discuss the pathophysiology of VOD.

Case Reports

Case 1

A 30-year-old woman was admitted to a community hospital for examination because of massive ascites. Four months before admission, she had taken birth control pills for 1 month. Computed tomography (CT) showed narrowing of the inferior vena cava (IVC). Histological examination of the liver showed dilatation of the sinusoid and sinusoidal congestion. On the basis of these findings, we diagnosed her condition as Budd-Chiari syndrome and administered warfarin and a diuretic. However, no remarkable improvement was obtained. Chest CT after 4 months revealed a mediastinal tumor, and she was diagnosed with malignant lymphoma. She received ABVD (adriamycin, bleomycin, vinblastine, and dacarbazine) therapy. The physician discontinued the 1.5 course of ABVD therapy because of an abnormal liver test. Next, she received radiation therapy (36 Gy) and achieved remission. One month after radiation, her laboratory data showed elevated levels of total bilirubin and ammonia. Two months after radiation, the patient’s clinical course continued to deteriorate with worsening ascites and encephalopathy, progressing to renal insufficiency, and CT imaging revealed massive ascites and a high-density nodule in liver segment 8 (Figure 1). This nodule showed enhancement in the arterial and portal phases, suggesting a hyperplastic nodule (Figure 1). Therefore, she was admitted to our department to undergo liver transplantation. Upon examination, her temperature was 36.4°C, her blood pressure was 118/78 mmHg, and her pulse was 111/min. She presented with grade III hepatic encephalopathy. Laboratory tests showed the following results: red blood cell count, 365×10⁴/mm³; hemoglobin level, 10.5 g/dL; prothrombin time (PT), 17%; PT-INR, 3.91; total bilirubin level, 3.2 mg/dL; ammonia level, 400 µg/dL; aspartate aminotransferase (AST) level, 54 IU/L; alanine aminotransferase (ALT) level, 29 IU/L; blood urea nitrogen (BUN) level, 102 ng/dL; and creatinine level, 4.81 mg/dL. Four days after admission, she underwent liver transplantation. The liver explants showed congestive liver and swelling. We observed exclusion of IVC by the swollen caudate lobe, but no stenosis of the large IVC or hepatic vein (Figure 2). Histological examination of the liver explant showed centrilobular hepatocyte necrosis with stasis. In the center of these areas, concentric narrowing of the terminal hepatic venules or sublobular hepatic veins caused obstruction of the lumen (Figure 3). These findings were suggestive of veno-occlusive disease (VOD). A liver
nodule found in S8 showed a slightly increased cell density, but no cellular atypia. Therefore, this nodule was diagnosed as hyperplastic nodule (Figure 4). Two years after transplantation, she is alive without major complications.

Case 2

A 74-year-old woman was admitted to a community hospital for common cold symptoms. She was received an oral antibiotics (Cefaclor) for 5 days because of fever and elevated levels of AST (115 IU/L) and ALT (44 IU/L). After 7 days, she presented with right flank pain and ascites and was admitted to a community hospital for further examination. She had hypertension, hyperlipidemia, and gallstone. Upon examination, her temperature was 36.6°C, blood pressure was 120/70 mmHg, and pulse was 90/min. She presented with jaundice and general edema. Laboratory tests showed the following results: AST level, 96 IU/L; ALT level, 35 IU/L; alkaline phosphatase level, 552 IU/L; gamma-glutamyl transpeptidase level, 68 IU/L, total bilirubin level, 7.8 mg/dL; and prothrombin time, 47%. CT imaging showed hepatomegaly, massive ascites, and multiple low-density nodules. These nodules showed enhancement on early and delayed phase scans, which suggested hyperplastic nodules. After admission, the patient was diagnosed with cryptogenic hepatic failure with infection and was administered antibiotics, a branched-chain amino acid solution and glucagon-insulin therapy. Her fever was ameliorated; however, her liver function worsened. Fourteen days after admission, the total bilirubin level increased to 15.3 mg/dL, levels of prothrombin time increased to 34%, and creatinine level increased to...
3.4 mg/dL. Her systemic condition worsened and 39 days after admission, she died.

Liver autopsy revealed swelling of the right lobe but showed no stenosis of the IVC or large hepatic vein. Microscopic examination indicated that the sinusoid was markedly dilated (Figure 5). Severe congestion and necrosis were present surrounding the central vein area. Hepatic venules showed obstruction of the lumen. Thus, she was diagnosed with VOD. Multiple small nodules mimicking nodular regenerative hyperplasia were also observed in the liver.

Discussion

VOD is related to specific drugs. Pyrrolizidine alkaloids were the first identified agents causing sporadic or epidemic occurrence [8]. VOD has been frequently reported as a complication of SCT. This is thought to be because of pretreatment with chemotherapy and radiation agents or radiation. Moreover, VOD has been reported in users of oral contraceptives [9,10]. In case 1, the patient had taken oral contraceptives before symptoms appeared. Oral contraceptives are also known to cause Budd–Chiari syndrome. Taken with imaging findings, this patient was diagnosed as Budd–Chiari syndrome. VOD should be considered as a differential diagnosis. On the diagnosis of Budd–Chiari syndrome, this patient received chemotherapy and radiation for malignant lymphoma, which may have worsened the patient’s disease.

In case 2, the patient had not previously taken any medication and the cause of her VOD was unclear. Two VOD cases in infants who had not taken any medication have been previously reported [11]. Meanwhile, adult VOD cases as complications of thrombotic thrombocytopenic purpura (TTP) and hemophagocytic syndrome (HPS) without taking medication have been reported [12,13].

Recently, clinical criteria for diagnosing VOD have been formalized as the Baltimore and Seattle criteria [8,14]. These criteria include hepatomegaly, weight gain, and liver failure. In our patients, imaging modalities showed hepatomegaly, rapid body weight increase, jaundice, and laboratory data showed mild elevation of transaminase. Therefore, our patients met these criteria. Additionally, these criteria were based on patients who received SCT. Our patients were not diagnosed with VOD when they underwent liver transplantation or at autopsy. Therefore, it is difficult to diagnosis these patients with VOD given that they had no history of SCT.
Most patients with mild VOD survive, while severe VOD typically results in a fatal outcome.

A previous large cohort study showed that acute renal failure is a universal complication (6). Our patients also showed acute renal failure. This pathophysiology is a consequence of both sinusoidal hypertension and renal tubular injury [15].

Recently, VOD (SOS) was thought to originate from swelling of endothelial cells, leading to destruction of the endothelial cell line, which embolizes and blocks microcirculation. These events have been associated with abnormalities in factors such as VII, protein C levels, and plasminogen activator inhibitor. These findings indicate administration of infusion of low-dose heparin, recombinant tissue plasminogen activator (t-PA), and prostaglandin E1 (PGE1) as innovative therapies [16–18]. However, patients with severe SOS fail to respond to these therapies. In patient 1, warfarin was used to treat Budd-Chiari syndrome, but no improvement was observed.

Liver transplantation as salvage therapy for severe VOD is controversial and is based on the cause of SOS. Though the outcome of transplantation for VOD is not clear, poor prognosis is typically reported. Most of these poor prognosis cases were patients in which liver transplantation after SCT has been performed [19]. In case 1, the patient had received chemotherapy and radiation therapy for malignant lymphoma, and had achieved remission state. If severe VOD is diagnosed in patients who have not received SCT, liver transplantation should be considered.

Conclusions

Here, we present 2 FHF patients with severe VOD. Severe VOD is a life-threatening disease, and diagnosis of VOD at an early stage is important. VOD should be considered as a cause of FHF, even if the patient has no history of SCT.

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