






Hepatic venoocclusive disease/sinusoidal obstruction syndrome with normal portal vein flow mimicking aggravated chronic hepatic GVHD following inotuzumab ozogamicin salvage therapy: a case report of pathologic-radiologic discrepancy

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Abstract: Inotuzumab ozogamicin (INO) showed improved treatment outcomes for relapsed or refractory B-cell precursor acute lymphoblastic leukemia (BCP-ALL) but can induce hepatotoxic adverse events. Hepatic venoocclusive disease/sinusoidal obstruction syndrome (VOD/SOS) frequently develops after allogeneic hematopoietic cell transplantation (allo-HCT), and INO is a strong pretransplant risk factor. However, VOD/SOS can occur just after INO therapy. Here, we describe a BCP-ALL patient treated with INO for isolated extramedullary relapse after allo-HCT. The patient experienced elevated liver enzymes with ascites at 21 days from the last INO dose. Although she met the criteria for VOD/SOS, the diagnosis was challenging because of her ongoing hepatic graft-versus-host disease (GVHD) and normal portal vein flow on Doppler sonogram. The radiologist suggested liver cirrhosis based on computed tomography, with VOD/SOS, liver cirrhosis, and GVHD assumed to be differential diagnoses. She received supportive care with GVHD management; however, due to progressive hepatic failure, we conducted emergent deceased-donor liver transplantation, and the pathologic findings indicated VOD/SOS. Her leukemia was stable, but she died of sepsis after 3 months. INO use is a high-risk factor for VOD/SOS, but an accurate diagnosis can be challenging due to various hepatic complications. Early diagnosis and proper management for VOD/SOS is important for improved outcomes.

Keywords: acute lymphoblastic leukemia, case report, hematopoietic cell transplantation, inotuzumab ozogamicin, sinusoidal obstruction syndrome

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Main body

Inotuzumab ozogamicin (INO) is an antibody-drug conjugate composed of a humanized anti-CD22 monoclonal antibody conjugated to the cytotoxic calicheamicin. In a phase III trial that compared INO with standard intensive chemotherapy in relapsed or refractory B-cell precursor

acute lymphoblastic leukemia (R/R BCP-ALL), hepatic venoocclusive disease/sinusoidal obstruction syndrome (VOD/SOS) occurred in 23 of 164 patients (14.0%) in the INO arm which was higher than 3 of 143 patients (2.1%) in the standard arm.¹ Among them, VOD/SOS developed in 18 of 79 patients (22.8%) who underwent allo-HCT; of 5

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of 85 patients (5.9%) who developed VOD/SOS after treatment of INO, 2 had undergone allo-HCT before INO, while 3 had not. Although the incidence of VOD/SOS after INO is lower than after allo-HCT, it is important to consider VOD/SOS as it can occur at any time after hepatotoxic agent therapy, regardless of transplantation status.

In general, elevated liver enzyme pattern is so variable that hepatic dysfunction due to toxic anti-leukemic therapies can be challenging to diagnose. In addition, patients can present with non-specific signs or symptoms that can confuse the differential diagnoses, especially when the symptoms are related to allo-HCT complications.^{2,3} Here, we present a case of hepatic VOD/SOS that finally was diagnosed by pathologic findings after liver transplantation (LT) from a deceased donor. As the case was difficult to diagnose and manage, we are presenting a summary to inform future diagnoses and pathologic findings.

This research was conducted in accordance with the Institutional Review Board guidelines of the Catholic Medical Center (KC21ZISI0594) and Case Report (CARE) guidelines. A patient has provided written informed consent for the publication of information in the present manuscript.

Case presentation

A 49-year-old woman was diagnosed with Philadelphia chromosome-negative BCP-ALL with a karyotype of 45,XX,t(1;19;14;19)(q21;p13.1;q32;q13.1),-20[20]. She failed to achieve complete remission (CR) after initial modified hyper-CVAD (Hyper-fractionated Cyclophosphamide, Vincristine, Daunorubicin, and Dexamethasone) chemotherapy.⁴ After salvage chemotherapy using mitoxantrone plus high-dose cytarabine plus etoposide, she achieved delayed CR and underwent allo-HCT from a matched sibling donor. The conditioning regimen consisted of total body irradiation (330 cGy/day for 4 days, total 1320 cGy) and cyclophosphamide (60 mg/kg for 2 days, total 120 mg/kg). She suffered from moderate oral (score 2) and hepatic (score 2) chronic graft-*versus*-host disease (GVHD). At 25 months post-HCT, she complained of right shoulder pain, and imaging studies detected a pathologic fracture due to extramedullary relapse (EMR) that was confirmed by bone biopsy. Her bone marrow (BM) showed no evidence of leukemia with normal

cytogenetics. Positron emission tomography (PET) detected extensive EMR lesions including clavicle and humerus, abdominal wall, buttock, thigh, and lower leg lesions. Palliative radiotherapy was followed by four cycles of blinatumomab, and she showed partial remission with residual disease on the abdominal wall. Because her performance status was poor, she was switched to INO therapy (3 doses of 0.8, 0.5, and 0.5 mg/m² weekly) rather than intensive chemotherapy. After one cycle of INO, the remnant signal on abdominal wall was markedly decreased on PET evaluation (from 8.4 to 2.1 by standardized uptake value). Because she was suffering from chronic hepatic GVHD, her liver enzymes were fluctuating constantly with elevated total bilirubin level at a range of 1.8–3.0 mg/dl, and alkaline phosphatase and gamma glutamyl transferase values at a range of 3–8 times higher than the normal upper levels. At the time of INO, total bilirubin level was 2.1 mg/dl, and alkaline phosphatase and gamma glutamyl transferase was 537/588 U/L.

She started to complain about abdominal distension at 21 days from the last dose of INO, and we noticed a slightly increased total bilirubin level of 3.2 mg/dl. We first had suspicion of VOD/SOS and her increased bilirubin level and weight gain with ascites met the Baltimore and revised European Society for Blood and Marrow Transplantation (EBMT) diagnostic criteria. However, her bilirubin level had been already increased, and she complained no abdominal pain. Because the diagnosis was confusing, we planned further imaging studies for more information. Abdominal computed tomography (CT) and Doppler ultrasonography were performed to exclude VOD/SOS due to the variations in her symptoms (Supplement Table 1). The CT scan showed a shrunken liver without splenomegaly and a moderate amount of ascites (Figure 1(a)), which were interpreted as liver cirrhosis following chronic hepatic GVHD by the radiologist and hepatologist rather than the expected VOD/SOS findings. In addition, the Doppler ultrasonography indicated well-preserved triphasic portal vein flow with a velocity of 21.3 cm/s (Figure 1(b)). Although we had suspicion of VOD/SOS, the diagnosis was confusing and the severity grade was moderate based on revised EBMT criteria, we could not use defibrotide right away. Supportive care with fluid restriction was planned along with management for possible aggravation of hepatic GVHD with steroid and low-dose

mycophenolate mofetil. After these were implemented, she maintained a stable condition and stable bilirubin level for 2 weeks. However, her liver function suddenly deteriorated, she developed a large amount of ascites, and her total bilirubin level rose from 3.0 to 9.6 mg/dl within 1 week. Her liver function and hepatic encephalopathy continued to deteriorate, and consecutive CT scan showed more increased ascites and newly developed esophageal and gastric fundal varices. Therefore, emergency LT was planned from her initial sibling HCT donor. However, the sibling donor was in poor health condition, and a deceased donor became available, so an emergent deceased donor LT was conducted instead. The surgery was successful, and the final pathologic findings suggested diffuse sinusoidal dilatation with congestion and perisinusoidal hemorrhage which indicated hepatic VOD/SOS without evidence of fibrosis. We also observed some bile duct dystrophy and cholestasis which was considered findings of hepatic GVHD (Figure 2). Her liver function rapidly recovered without progression of leukemia, but she died of septic pneumonia at 3 months after LT.

Discussion

We report a case of an adult ALL patient who relapsed at 25 months after allo-HCT with extensive EM lesions without BM relapse. Recent data have shown that isolated EMR responds well to blinatumomab.⁵ However, in the presented case, the response to blinatumomab was not satisfactory, and INO was applied for residual leukemia. As she had experienced hepatic GVHD, INO use might not be appropriate for salvage treatment from the start of choice. She ultimately experienced hepatic dysfunction, and the diagnosis was challenging due to the varying clinical symptoms.

Although we initially suspected hepatic VOD/SOS, the ongoing hepatic GVHD confused our initial assessments, and the CT and Doppler ultrasonography results contributed to diagnostic confusion. Recent studies have shown that Doppler ultrasonography or liver stiffness measurement (LSM) by transient elastography (FibroScan, Echosens, France) were significantly used to identify the progression of VOD/SOS.⁶⁻⁸ The parameters in the scoring system using Doppler ultrasonography are portal vein flow <10 cm/s, hepatic artery resistive index (RI) ≥ 0.75

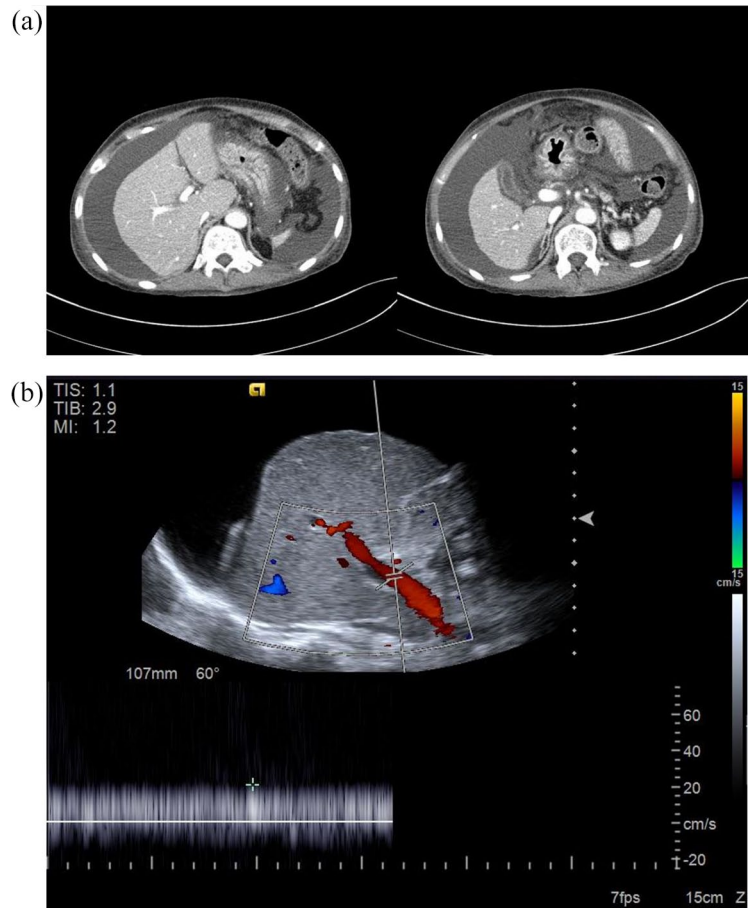


Figure 1. Imaging study. (a) Abdominal CT findings showing shrunken liver and gall bladder wall thickening with massive ascites. (b) Normal portal vein flow on Doppler ultrasonography (estimated velocity = 21.3 cm/s).

or peak systolic pressure (PSV) ≥ 100 cm/s, gallbladder wall thickening ≥ 4 mm, and presence of ascites; in this case, as we strongly depended on the result of normal portal vein flow, we decided with the low possibility of VOD/SOS initially. In this case, the PSV was 107.6 cm/s, and the RI value was 0.83, with moderate amount of ascites at the time of initial evaluation. The increment of liver stiffness value ≥ 10 kPa in post-HCT period compared with pre-HCT showed 100% sensitivity and 97% specificity for detection of VOD/SOS,⁸ and the value ≥ 21 kPa indicates clinically significant sinusoidal portal hypertension.⁹ Regrettably, we did not routinely check LSM by transient elastography in real-world practice and we did not expect the need for LSM at that time. Because our major diagnostic confusion was between the liver cirrhosis and the VOD/SOS, and both are related to portal hypertension. In addition, it should be considered that our patient was

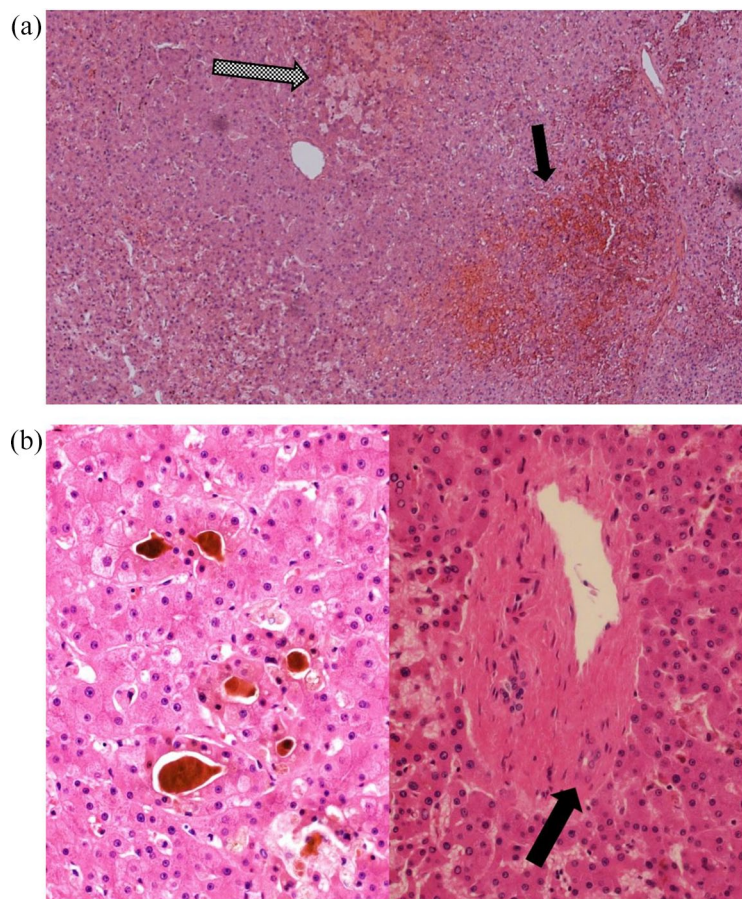


Figure 2. Post-hepatectomy histopathologic findings consistent with VOD/SOS and chronic hepatic GVHD. (a) Multifocal dilated sinusoids with hepatocyte atrophy (checked arrow) with extensive extravasation of red blood cells (solid arrow) showing hemorrhage ($\times 100$). (b) Cholestasis and bile duct dystrophy (arrow) without evidence of portal fibrosis ($\times 400$).

not a typical case of classic VOD/SOS, which had developed after 2 years post-HCT and after INO. Therefore, we could not make sure LSM would be helpful for the diagnosis in this case. If we routinely examined the stiffness of liver before the use of INO and after hepatic dysfunction, the results might be interesting. Although supportive care was attempted, the challenges for initial diagnosis delayed curative management using defibrotide, which could have aggravated the course of VOD/SOS. Moreover, we were not able to use defibrotide right away because defibrotide was only approved for severe to very severe grade of VOD/SOS according to insurance guidelines. Defibrotide is the only approved curative therapeutic agent for VOD/SOS¹⁰ and should be applied early before deterioration to achieve the best outcomes.¹¹

In patients who receive INO, prophylactic management and close monitoring of VOD/SOS are important.¹² Although the characteristics of VOD/SOS can be confused with those of other hepatic complications, diagnosis should be based on the exact evaluations, which will guide clinicians in determining appropriate treatment and improve patient outcomes.

Author contributions

JL and J-HY contributed to reviewing patients and writing the manuscript; GJM, DK, J-HL, TYK, S-SP, SP, S-EL, B-SC, Y-JK, and K-SE supported the treatment course of the patient; patient and the manuscript was critically reviewed by H-JK, C-KM, S-GC, and JWJ; SHL supported the pathology report; SL as a corresponding author, mainly charged in this patient and wrote the manuscript.

Conflict of interest statement

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Consent for publication

We confirm that a patient has provided written informed consent for the publication of patient information in the present manuscript.

Ethics approval and consent to participate

This research was conducted in accordance with the Institutional Review Board guidelines of the Catholic Medical Center (KC21ZISI0594).

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Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Supplemental material

Supplemental material for this article is available online.

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