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CASE REPORT | LIVER

Hepatic Sinusoidal Obstruction Syndrome in a Patient With Multiple Myeloma Treated With CyBorD

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ABSTRACT

Hepatic sinusoidal obstruction syndrome (SOS) is a life-threatening state generally occurring as a complication of conditioning regimens used for hematopoietic stem cell transplant. Hepatic SOS after a standard dose of chemotherapy in malignancies is rare, and there are only a few cases in pediatric literature. We report a 56-year-old man with multiple myeloma who experienced SOS after being initiated on chemotherapy including cyclophosphamide, dexamethasone, and bortezomib and who experienced a delay in treatment with defibrotide, because it is currently approved by the Food and Drug Administration for only patients who develop SOS after hematopoietic stem cell transplant.

INTRODUCTION

Sinusoidal obstruction syndrome (SOS), previously known as veno-occlusive disease (VOD), is a potentially serious complication of conditioning regimens used for hematopoietic stem cell transplant (HSCT) in the western world.[1] Presentation classically includes weight gain, painful hepatomegaly, ascites, and hyperbilirubinemia.[2] The underlying pathogenesis of SOS in the HSCT population involves enhanced radiation or chemotherapy-induced toxic injury to the sinusoidal endothelial cells and hepatocytes in zone 3 of the liver acinus. Subsequently, there is extensive cytokine production, depletion of cellular antioxidants, release of endothelial growth factors, and activation of clotting factors, which leads to sinusoidal obstruction and widespread liver disruption.[13] This same mechanism is suspected to occur in the non-HSCT population.[4] We represent a unique case of hepatic SOS in a patient with multiple myeloma after starting treatment with a standard dosage of cyclophosphamide.

CASE REPORT

A 56-year-old African-American man presented with progressive confusion, fatigue, right upper quadrant abdominal pain of 1-week duration. Two months earlier, the patient was diagnosed with kappa light-chain multiple myeloma (International Staging System, stage 3) and was initiated on CyBorD therapy (cyclophosphamide 300 mg/m^2, bortezomib 1.5 mg/m^2, and dexamethasone 40 mg). He had already developed end-stage renal disease from multiple myeloma, was anuric, and had been started on hemodialysis. He had completed day 1 of cycle 2 of CyBorD treatment regimen 14 days before presentation.

Physical examination revealed stable vitals, icteric sclera, tender hepatomegaly, and asterixis. There was no ascites appreciated. The patient had a weight gain of 4 kg from hospital measurement 2 weeks before, marking a 5.5% increase. Laboratory work revealed alanine transaminase 80 IU/L, aspartate transaminase 108 IU/L, alkaline phosphatase 432 IU/L, total bilirubin 10.5 mg/dL, international normalized ratio >10, and partial thromboplastin time 82.7. Abdominal ultrasound demonstrated mild hepatomegaly without ductal dilation or cholelithiasis, and there was no evidence of hepatic or portal vein thrombosis. Serologic testing for hepatitis B and C were negative. Ultrasound-guided percutaneous liver biopsy showed an increase in pericentral and sinusoidal collagen

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fibers, marked cholestasis, focal drop out of hepatocytes with fibrosis, and minimal inflammatory cells in the portal triad and pericentral veins consistent with SOS (Figure 1). Conservative management with vitamin K and lactulose for hepatic encephalopathy was administered.

The care teams involved decided that therapy with defibrotide was warranted and inquired about procuring this medication from specialty pharmacy and insurance before authorization. An extensive administrative review of this case was performed which lasted over 2 weeks before the medication was approved and administered to the patient. The delay was due to initial rejection of therapy based on the Food and Drug Administration (FDA) indication for the medication being strictly for treatment of pediatric and adult patients who received HSCT and developed hepatic VOD/SOS with concomitant renal or pulmonary dysfunction. After initiation of defibrotide, on day 5 of therapy, the patient developed significant lower gastrointestinal (GI) bleed, requiring blood transfusions and urgent endoscopic intervention. Unfortunately, defibrotide had to be discontinued due to the increased risk of GI hemorrhage and resultant unfavorable risk-benefit equation in this patient.

DISCUSSION

Hepatic SOS is primarily a clinical diagnosis observed in patients who present within 30 days of HSCT and exposure to high dose of immunosuppressive therapy. Two diagnostic criteria are in common use: the Baltimore Criteria and the Modified Seattle Criteria, which require 2 of the following to make the diagnosis of SOS—bilirubin of $\geq$2 mg/dL, hepatomegaly or right upper quadrant pain, and weight gain of $\geq$5%.[2,3]

Although the vast majority of patients who develop VOD/SOS are indeed HSCT patients, it is a syndrome that also occurs in non-HSCT patients treated with similar medications. Literature review revealed 3 major VOD/SOS cohorts: a Japanese cohort, the compassionate use program cohort, and the treatment-investigational new drug (T-IND) cohort.[5–7] The T-IND cohort has recently published a post-hoc analysis of its non–transplant-associated VOD/SOS patients. Of 1,137 patients enrolled in the T-IND cohort, 137 (12%) were identified as having VOD/SOS after non–HSCT-associated chemotherapy, 16 of which were adults (aged >16 years).[8] Similarly, non-HSCT patients made up 11% (79 of 710) of the compassionate use program cohort.[6]

In the non-HSCT setting, a number of inciting agents have been identified, including inotuzumab and gemtuzumab ozogamicin and vincristine.[9,10] Cyclophosphamide was part of our patient's treatment regimen, which was identified as the most common medication in the T-IND trial nontransplant subgroup.[8] Previous instances of suspected VOD/SOS involving cyclophosphamide were with high-dose therapy.[11] To the best of our knowledge, this is one of the very few cases describing hepatic SOS after conventional chemotherapy doses of cyclophosphamide in a patient with multiple myeloma. The higher doses of cyclophosphamide used for HSCT are associated with an array of toxicities, which include hemorrhagic cystitis, VOD, lung damage, and cardiac necrosis.

Cyclophosphamide is the inactive form of the drug which is activated by cytochrome P450 enzymes to form 4-hydroxycyclophosphamide and eventually phosphoramide mustard, the actual alkylating agent. Studies have shown that increased exposure and high local concentration of 4-hydroxycyclophosphamide may lead to damage to sinusoidal endothelial cells and ultimately VOD.[12] In our patient, the toxicity of cyclophosphamide could have been enhanced by drug-drug (dexamethasone and bortezomib) interactions or the underlying disease (multiple myeloma).

Defibrotide is the only FDA-indicated medication for VOD/SOS. The proposed mechanism of action of defibrotide involves reduction in endothelial cell activation and protection of endothelial cells from inflammatory and prothrombotic cascade. An early initiation of defibrotide therapy has demonstrated better clinical outcomes at +100 days and is now recommended in patients with VOD/SOS.[13] Hemorrhage, hypotension, and GI disturbances are some of the most common side effects associated with defibrotide treatment. Richardson et al showed that pulmonary hemorrhage was the most common type of hemorrhage, with GI hemorrhage being the second most

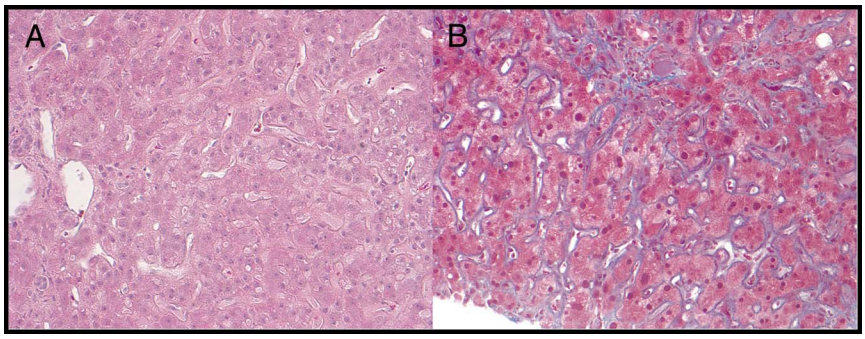

Figure 1. (A) Hematoxylin and eosin stain showing sinusoidal dilatation with atrophy and disruption of hepatocyte plates. (B) Trichrome stain showing perivenular and perisinusoidal fibrosis.

common type occurring in 3.3% of the patients who received defibrotide treatment.[14]

A study involving patients with severe SOS and multiorgan failure showed that the rates and types of adverse events among defibrotide-treated patients were similar to those in control subjects. However, it was noted that although the rates of hemorrhage were similar between the 2 groups, the rate of fatal hemorrhage was slightly higher in the defibrotide group.[15]

Within the United States, FDA indication for defibrotide is for the treatment of hepatic VOD/SOS in post-HSCT patients with renal or pulmonary dysfunction.[7] As evidenced by the T-IND trial, there is a non-negligible number of non-HSCT patients who develop VOD/SOS and strong consideration should be made to expand FDA indication to include non-HSCT patients with confirmed VOD/SOS.[8] Furthermore, physicians should be on the alert for hepatic SOS in patients receiving cyclophosphamide as it can be especially toxic in the presence of underlying hepatic disease and interaction with other drugs that increase its potency and toxicity.

This case report not only describes a rare case of VOD/SOS in a patient with multiple myeloma but also reports its development at a standard chemotherapy dosing of cyclophosphamide. Furthermore, broadened FDA indication for defibrotide therapy to include non-HSCT patients should be considered to prevent future treatment delays, such as that experienced by our patient.

DISCLOSURES

Author contributions: T. Tariq and J. Dawdy wrote the manuscript. S. Goyal, B. Mohamad, M. Singh, M. Mutchnick, and M. Ehrinpreis edited the manuscript. S. Goyal and T. Tariq are the article guarantors.

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