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Case Report

Biopsy Proven Late-Onset Sinusoidal Obstruction Syndrome Successfully Treated With Defibrotide

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Abstract

We report an unusual case of a patient who developed a biopsy-proven Sinusoidal Obstruction Syndrome (SOS) more than 4 months after a nonmyeloablative allogeneic sibling transplant. The patient responded to defibrotide treatment with clear improvement in liver function and normalization of radiologic findings. Although a few cases of late-onset SOS have been reported in the literature, we describe, to the best of our knowledge, the first case of late-onset SOS successfully treated with defibrotide after allogeneic hematopoietic stem cell transplantation.

Keywords: Sinusoidal Obstruction Syndrome; Veno-Occlusive Disease; Allogeneic Transplant; Late Complications

Introduction

Despite decreasing incidence, sinusoidal obstruction syndrome (SOS; formerly veno-occlusive disease, VOD) remains one of the most serious complications after Hematopoietic Stem Cell Transplantation (HSCT) [1-4]. Characterized by a triad of painful hepatomegaly, hyperbilirubinemia and otherwise unexplained fluid retention, SOS typically occurs within 21 days of transplant. However, SOS has been observed later and should be included in the differential diagnosis of liver abnormalities beyond 3 weeks of transplant [5,6]. We describe the outcome of an allogeneic transplant recipient presenting with clinical signs of SOS more than 4 months after transplant; diagnosis was proven by biopsy and liver function recovered with defibrotide treatment.

Case Presentation

The patient was a 67 year old male initially diagnosed with stage IV follicular lymphoma. He was first treated with six cycles of chlorambucil and prednisone with partial response. Disease progression occurred approximately 2 years later; he then received 6 cycles of rituximab, cyclophosphamide, vincristine and prednisone (R-CVP). Two months after the last cycle, disease progressed clinically and radiologically; an inguinal lymph node biopsy revealed transformation into diffuse large B-cell lymphoma. The patient then received 2 cycles of salvage chemotherapy including rituximab, etoposide, methylprednisolone, arabinoside-C, prednisone (R-ESHAP regimen), followed by a nonmyeloablative allogeneic stem cell transplant from a matched sibling donor. Cytomegalovirus (CMV) status of both donor and recipient were positive and there was no ABO mismatch. All CT scans were normal prior to transplant.

Conditioning regimen consisted of ibritumomab tiuxetan (Zevalin®), fludarabine and cyclophosphamide as part of an experimental protocol. The patient received a peripheral blood stem cell graft containing 5.3 x 10^6 CD34+ cells/kg. Graft-Versus-Host Disease (GVHD) prophylaxis included tacrolimus and mycophenolate mofetil. Platelet and neutrophil engraftment occurred promptly. On day +30, the patient developed mild hepatic cytolysis, with Aspartate Aminotransferase (AST) and Alanine Aminotransferase (ALT) values less than twice the upper limit of normal with normal bilirubin. CMV reactivation was identified by polymerase chain reaction assay and rapidly controlled with valganciclovir.

On day +90 after allogeneic HSCT, the patient was hospitalized for respiratory infection. Shortly after admission, he developed abdominal discomfort with an erythematous skin rash involving 60% of his body surface. Upper gastro-intestinal endoscopy revealed a bulboduodenitis macroscopically compatible with upper gastro-intestinal GVHD but biopsy was not performed due to refractory thrombocytopenia (15 x 10^9/L). Initiation of oral prednisone 1 mg/kg led to rapid skin improvement and hospital discharge.

On day +114, the patient was readmitted for abdominal pain without diarrhea and rapid worsening of liver function tests. There were no signs of GVHD clinically and abdominal exam was unremarkable. ALT and AST increased up to 725 and 808 U/L (both normal <40 U/L) respectively, with a bilirubin up to 257 µmol/L (normal <21 µmol/L). At that time, an abdominal ultrasound showed a normal size homogeneous liver, a patent portal vein with normal blood flow, no biliary tract dilatation and absence of ascites. The abdominal CT scan was also unremarkable. Bone marrow biopsy showed a cellularity of 50% with no lymphoma infiltration. Because of high clinical suspicion of acute GVHD, the patient was treated with ursodeoxycholic acid, intravenous steroids and mycophenolate mofetil. Tacrolimus was discontinued due to probable microangiopathic anemia with secondary thrombocytopenia. The patient's clinical condition improved and bilirubin level decreased to 80 µmol/L. A repeat abdominal CT scan revealed distal small bowel thickening with trace amount of ascites.

Two weeks later, on day +133, the patient complained of progressive abdominal discomfort and swelling; weight increased from 75 to 80 kg (a 7% increase). Physical examination revealed new onset of enlarged abdominal girth without right upper quadrant tenderness and lower limb peripheral edema. An abdominal Magnetic

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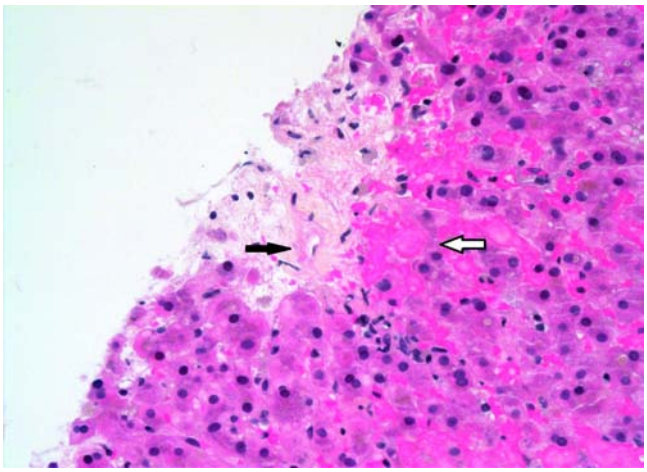

Figure 1: Terminal hepatic venule showing intimal obliteration of lumen (black arrow) with associated venous outflow obstruction of hepatic parenchyma (white arrow; hematoxylin-phloxin-safran stain).

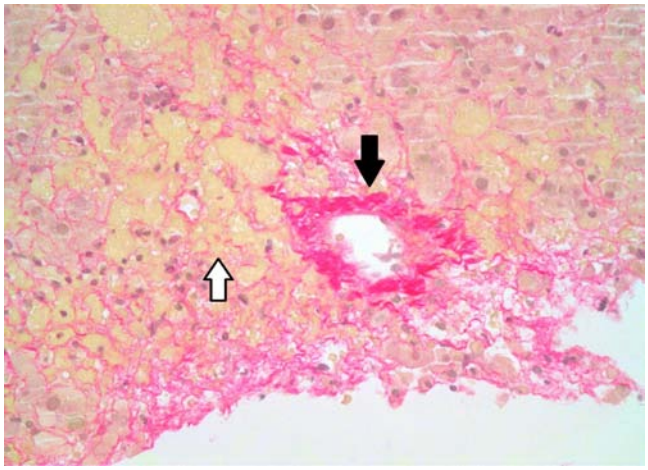

Figure 2: Shown is fibrous thickening and narrowing of a terminal hepatic venule (black arrow) with secondary congestion of hepatic lobule (white arrow; Sirius Red stain).

Resonance Imaging (MRI) showed both homogeneously enlarged liver (18 cm) and spleen (13 cm) with moderate ascites. There were no radiologic signs of nodular regenerative hyperplasia. A liver Doppler ultrasound showed a large amount of ascites, hepatomegaly and patent portal and hepatic veins with signs of revascularization of the para-umbilical vein suggesting portal hypertension. There were no signs of right cardiac failure or pulmonary hypertension on echocardiogram.

On day +161, the patient's clinical condition was stable on furosemide, prednisone and mycophenolate mofetil with a weight of 68 kg. However, liver function tests worsened, with elevated levels of AST (66 U/L), ALT (105 U/L) and bilirubin (144 µmol/L; conjugated 120) but without renal dysfunction. A trans-jugular liver biopsy was performed and pathologic examination revealed a mild portal lymphocytic infiltrate with bile duct damage along with lobular subacute cholestasis suggestive of toxic drug reaction or, less likely, GVHD. Terminal hepatic veins were the site of mild fibrous intimal obliteration and associated sinusoidal and liver cell plate congestion consistent with SOS (Figure 1,2). Finally, the hepatic parenchyma showed regenerative nodules without fibrosis compatible with Nodular Regenerative Hyperplasia (NRH).

Because of deteriorating liver function tests, weight gain and persistent ascites despite aggressive use of furosemide and spironolactone, treatment with IV defibrotide 6.25 mg/kg every 6 hours was started on day +172. In all, the patient received 35 days of treatment. His weight decreased from 72 kg to 61.5 kg. Liver function significantly improved, with bilirubin levels decreasing from 122 µmol/L before defibrotide to 88, 78, 72 and 40 (normal <21) µmol/L after 1, 2, 3 and 8 weeks after start of treatment, respectively. The patient left the hospital 5 weeks after initiating defibrotide in good clinical condition with only furosemide 20 mg daily. A repeat abdomen ultrasound 2 weeks after defibrotide showed a normal spleen, an enlarged liver (19 cm) and mild ascites; another one, performed 11 weeks later, showed normal liver and spleen, with trace ascites. Finally, the abdominal ultrasound performed 24 weeks after start of defibrotide initiation was completely normal.

On day +237, the patient was admitted to our intensive care unit with Pseudomonas aeruginosa pneumonia and septic shock; he unfortunately died from multi-organ failure and permission for autopsy was not granted.

Discussion

We report an unusual case of a patient who developed a 7% weight gain, worsening hyperbilirubinemia and ascites 133 days after a nonmyeloablative allogeneic sibling transplant. A transjugular liver biopsy revealed sub-acute cholestasis, NRH and vascular changes consistent with SOS. The patient's bilirubin level decreased from 122 to 40 µmol/L after receiving defibrotide as single treatment, with a completely normal abdominal ultrasound 6 months later. Prior to defibrotide, the patient had no improvement with increased immunosuppression and diuretics.

SOS diagnostic criteria developed by the Seattle and Baltimore teams both require occurrence of hyperbilirubinemia, abdominal pain and weight gain within 20 or 21 days of transplant, respectively [1-4]. Excluding time of clinical presentation, our patient met all SOS criteria except right upper quadrant pain. Although rare, cases of late SOS have been reported 24 to 57 days after autologous HSCT [5-8] and 69 days after exposure to gemtuzumab ozogamicin [9]. More recently, Pai et al. have reported 8 allogeneic transplant recipients who have developed SOS 33 to 77 (median 52) days after transplant, none of them being treated with defibrotide [10]. In another report, Platzbecker et al. have observed 6 cases of SOS (median time of occurrence 32 days, range 10 to 51) following a conditioning regimen with busulfan and fludarabine; no details of treatment were included [11]. Our patient did not receive busulfan or gemtuzumab ozogamicin and, to the best of our knowledge, is the first allogeneic transplant recipient reported to have developed SOS after day +100.

Of interest, the liver biopsy obtained revealed more than histologic features of SOS. Sub-acute cholestasis was most likely the sign of previous liver involvement by drug toxicity or acute GVHD. The small regenerative nodules without fibrosis were compatible with NRH, an entity which has been associated with chronic venous congestion as seen in this case, lymphoproliferative disorders and

drugs including cyclophosphamide [12]. However, the clinical course of our patient was inconsistent with NRH, which usually presents with normal size liver on radiologic exams, normal to mildly elevated serum transaminases, preserved hepatic function (albumin, prothrombin time) and normal to mildly elevated bilirubin. Hepatomegaly and splenomegaly at initial presentation, absence of nodularity on liver MRI, response to defibrotide with a normal abdominal ultrasound without ascites make NRH less likely to have caused the clinical picture seen in this patient.

SOS remains a variable clinical entity with an incompletely understood pathophysiology. Diagnosis is mainly clinical, although levels of plasminogen activator inhibitor-1 can help distinguish SOS from other causes of liver disease [1-4]. While mild cases usually resolve spontaneously, severe cases are associated with a mortality rate as high as 90% by day +100 following HSCT [1]. Defibrotide, a polydisperse mixture of oligonucleotides with antithrombotic and fibrinolytic effects on the microvascular endothelium, has emerged as an effective and safe treatment for patients with severe SOS with complete response rate in 30-40% of cases [3,4,13-15]. Excluding our patient, only 2 cases of late SOS successfully treated with defibrotide have been published thus far [8, 9], none having received allogeneic transplant.

In summary, patients who develop clinical and biological features of SOS later than day +21 should be investigated aggressively including a transjugular liver biopsy. Those with severity criteria and histologic features consistent with SOS should be considered for treatment with defibrotide.

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