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– CASE REPORT –

Sinusoidal Obstruction Syndrome after Autologous Stem Cell Transplant

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Abstract

Introduction: *Vaso-occlusive crisis or Sinusoidal obstruction syndrome (SOS) is a clinical entity generally observed after allogeneic stem cell transplant. Its classical form occurs typically after rescue stem cell infusion, and the risk is maximum till day +21 of the transplant. The etiopathogenesis includes the conditioning regimen that causes endothelial injury, the cytokines released from damaged tissue, and the immunosuppressive agents used to prevent graft rejection and graft-versus-host disease. It manifests as tender hepatomegaly, ascites, and deranged liver function tests. Occurrence during an autologous stem cell transplant is rare. Case- We describing a case of a 58-year-old male with multiple myeloma admitted for autologous hematopoietic stem cell transplant complicated by SOS. The patient's serum bilirubin level increased to 7.8mg/dl, accompanied by tender hepatomegaly and weight gain. Whole abdomen ultrasound examination showed hepatomegaly. The diagnosis was made using modified Seattle criteria and managed conservatively with diuretics, fluid restriction, and supportive treatment.*

Conclusion: *Sinusoidal obstruction syndrome can occur in an autologous stem cell transplant. Restricted fluid intake and supportive therapy can be sufficient to manage SOS.*

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Introduction

Stem cell transplantation is the modality for long-term disease control used in multiple myeloma. The procedure includes the collection of the patient's own stem cells, mobilised with granulocyte colony-stimulating factor (G-CSF), followed by a conditioning protocol with high-dose chemotherapy and stem cell rescue. The procedure is complicated by prolonged cytopenias and febrile neutropenia and is accompanied by various infections.[1] The vaso-occlusive crisis or sinusoidal obstruction

syndrome is one of the complications occurring during this period. The clinical manifestations include tender hepatomegaly, ascites, weight gain, and increased serum bilirubin above 2 mg/dl.[2] Various hypotheses have been proposed regarding the etiopathogenesis of SOS, including the conditioning regimen and the high-dose chemotherapy regimen used for myeloablation, which not only destroys the recipient's bone marrow but also damages other tissues. The tissue injury activates the pathogen associated molecular pattern and disease associated molecular patterns, which activate the cascade of reactions with activation of B cell, endothelial injury, change in the size of capillary endothelium mainly in the Liver, ultimately leading to slough off the endothelium, stasis of blood flow leading to retention of fluid in the liver and subsequently hepatomegaly, ascites due to increase in back pressure in circulation and weight gain due to third space edema.[3] The risk is higher with allogeneic stem cell transplant, particularly with haplo-identical matched transplant, due to a high amount of immune reactions and subsequent high damage to the endothelium.[4] Moreover, immunosuppression itself causes direct hepatic sinusoidal injury, with an increased incidence of SOS. [5] The rise in bilirubin secondary to sinusoidal injury also complicates the transplant, as SOS delay crucial engraftment.[6] Further, a series of changes leads to multi-organ failure and ultimately may lead to mortality. Prevention is the best strategy, which includes maintaining strict input-output balance, monitoring liver function tests, and performing regular clinical examinations. Despite prophylaxis, 13% of patients undergoing allogeneic stem cell transplant have SOS.[4] Data on autologous stem cell transplant are scarce, with only case reports.[7] However, SOS can occur in an autologous stem cell transplant with hyperbilirubinemia and clinical signs of SOS. In an autologous stem cell transplant, we should keep our differential diagnosis wide open, though it is rare. We are describing a case of a 58-year-old male undergoing an autologous stem cell transplant, complicated by SOS, monitored with weight and abdominal girth monitoring, and managed with fluid restriction and diuretics.

Case report

A 58-year-old male with no comorbidities complained of severe back pain for two months. He underwent magnetic resonance imaging (MRI) of the spine, which suggested lytic lesions in the lumbar spine, bilateral femori, multiple site pelvis, bilateral acetabulum, Sacrum. Baseline myeloma workup also showed anemia and renal dysfunction. The patient was diagnosed with multiple myeloma, ISS stage III. Patient received the Bortezomib, Cyclophosphamide, Dexamethasone (VCD) regimen, followed by radiotherapy (RT) of 8 Gy in 1 fraction to L2-4 vertebrae. After normalisation of serum Creatinine, the patient was started on Bortezomib, Lenalidomide, and Dexamethasone (VRD) (4 cycles) along with Daratumumab (8 doses). Further response evaluation revealed stable disease, and the patient was planned for autologous stem cell transplant.

Patient underwent an autologous stem cell transplant, with conditioning using intravenous Melphalan 200 mg/m2 after granulocyte colony-stimulating factor-induced stem cell mobilisation. The stem cell dose given was 9.2 × 10^6 cells/kg. On day +6 of transplant, the patient started having fever, diarrhea, and vomiting, in view of febrile neutropenia, injection Cefoperazone + Sulbactam and injection Amikacin was started along with anti-secretory agents. Patient on Day +7 continues to have fever and elevated serum bilirubin of 2.8 mg/dl. In view of increased bilirubin, N-acetyl Cysteine (NAC) infusion was started. In view of a further rise in serum Bilirubin to 4.2 mg/dl with direct bilirubinemia, tender hepatomegaly, and decreased urinary output, SOS was suspected. The patient was started on diuretics and restriction of intravenous fluids. The antifungal prophylaxis was changed to Injection Anidulafungin. Despite optimisation of fluid management, the patient's serum Bilirubin increased to 5.8mg/dl. Clinical diagnosis of SOS was made according to the modified Seattle criteria. Ultrasound abdomen showed hepatomegaly, 17cm. In subsequent days, serum Bilirubin rose to 7.7 mg/dl. (Image 1) Glutathione was started with strict intravenous or oral intake and diuretics were continued. Gradually, serum bilirubin decreased to 3.8 mg/dl, then to 2.7 mg/dl, and returned to normal in the subsequent week. Neutrophil engraftment was achieved on day +15, and platelet engraftment was achieved on day +16. Patient was discharged on day+ 18 of the transplant. A multidisciplinary team, including the Hepatology specialty, managed the case.

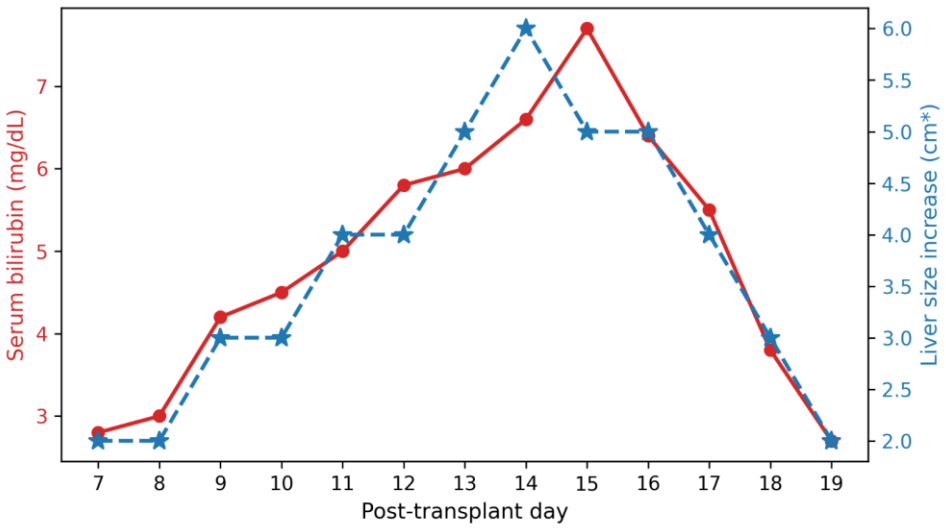

Image 1. *Trend of serum Bilirubin(mg/dl) and liver size(in cm) in post-transplant days [* below right costal margin in mid-clavicular line]*

Discussions

Sinusoidal obstruction syndrome generally occurs after allogeneic stem cell transplant; however, incidences have been reported after autologous stem cell transplant. In many cases, the conditioning regimen is the main cause of the SOS. Alkylating agents are associated with a higher risk of more severe Liver injury due to direct sinusoidal injury, and a higher risk of SOS.[8] In our case study, we used Intravenous Melphalan at a dose of 200mg/m2 as a conditioning regimen, followed by stem cell rescue. This conditioning damages hepatic sinusoids, leading to loss of sinusoidal fenestrations and accumulation of blood cells in the space of Disse; a higher dose causes a greater insult and results in SOS, as in our case.[9]

Treatment modalities, per se, can cause the SOS. The radiation therapy, prior therapy with alkylating agents, total body irradiation(TBI) based conditioning regimen, and use of Gemtuzumab Ozagamicin cause sinusoidal injury and contribute to the development of SOS.[2] Our patient has received 3 cycles of Bortezomib-Cyclophosphamide and dexamethasone (VCd) and 4 cycle of Bortezomib-Lenalidomide and dexamethasone (VRd), along with 8 doses of intravenous Daratumumab. Cyclophosphamide was given as a 300mg/m2 weekly dose, and none of the other medications received were implicated in the causation of SOS. The pre-existing liver injury is one of the factors involved in SOS; however, baseline liver function parameters were normal with mild transaminitis during the period of receiving Lenalidomide, which was stopped one month before taking the patient to the stem cell transplant. Older age is considered to be one of the risk factors for the SOS, however this relation is not always linear , with few studies mentioning age >60 years and age <1-2 years is associated with higher incidence of SOS , in contrast in one study all who aged > 25 years had increased incidences of SOS while other study showing older age is risk factor for the SOS with underlying comorbidities.[2,10,11] Our patient had received 8 Gy radiotherapy in single fraction to L2-4 vertebrae which was unlikely to contribute to SOS. Since our patient underwent an autologous stem cell transplant, HLA mismatch and immune suppression were not contributory. SOS itself delays platelet engraftment.[12] In our case, neutrophil engraftment was achieved on day +15 and platelet engraftment on day +16. During this time, the patient had an increased need for single donor platelet transfusion, requiring transfusions on alternate days, further indicating presence of SOS.

Conclusion

Sinusoidal obstruction syndrome can occur in an autologous stem cell transplant. Restricted fluid intake and supportive therapy can be sufficient to manage SOS.

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