A Case of Cemiplimab Associated Sinusoidal Obstruction Syndrome

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ABSTRACT

Background:
Hepatic veno-occlusive disease (VOD) or sinusoidal obstruction syndrome (SOS), is a clinical syndrome characterized by hepatomegaly, right-upper quadrant pain, and ascites that occurs most commonly in the setting of high-dose chemotherapy or hematopoietic stem cell transplantation (HSCT). The diagnosis can be confirmed on biopsy. Cemiplimab is an immune checkpoint inhibitor recently approved for the treatment of cutaneous squamous cell carcinoma. There are currently no known reports of Cemiplimab associated VOD/SOS.

Case Summary:
A 58-year-old female with a history of locally advanced basal cell carcinoma of the left eye treated with six months of Cemipilimab presented with ascites. On admission, labs were notable for a total bilirubin of 1.2, mildly elevated liver function tests, alkaline phosphatase 884, and international normalized ratio 2.1. A diagnostic tap revealed a high SAAG ascites that was negative for infection. A comprehensive serological workup for viral, metabolic and autoimmune causes was unrevealing. A transjugular liver biopsy demonstrated a hepatic venous pressure gradient of 18 mmHg, nodular regenerative hyperplasia (NRH), and portal venopathy. The patient was discharged on steroids but returned one month later for recurrent ascites and worsening bilirubin of 12.6 (direct 7.3). COVID PCR was negative. A full rheumatologic and vasculitis workup was unremarkable. Repeat biopsy demonstrated moderate NRH changes, prominent central vein sclerosis with fibrous obliteration, signs of VOD/SOS and central venulitis with fibrotic changes with sinusoidal portal hypertension.

Discussion
VOD occurs most often with hematopoietic stem cell transplantation and chemotherapeutic agents. Here we present the first case of Cemiplimab associated VOD/SOS. Despite discontinuation of the offending agent and a trial of steroids, the patient's clinical course continued to deteriorate. She eventually developed refractory ascites and portosystemic encephalopathy. She was deemed to not be a candidate for liver transplant given her underlying malignancy. She was transitioned to home hospice before further treatment, such as defibrotide, was pursued. VOD associated with immune checkpoint inhibition should be considered in the differential diagnosis of patients who develop new onset liver dysfunction and ascites while receiving these medications.

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INTRODUCTION

- Hepatic veno-occlusive disease (VOD), also known as sinusoidal obstruction syndrome (SOS), is a clinical syndrome characterized by hepatomegaly, right-upper quadrant pain, and ascites that can occur after high-dose chemotherapy, hematopoietic stem cell transplantation (HSCT), or liver transplantation.
- In VOD, sinusoidal endothelium injury leads to sinusoidal microcirculation disturbances, sinusoidal congestion, and alterations in normal blood flow resulting in activation of hepatic stellate cells which deposit collagen in the space of Disse.
- The diagnosis of VOD can be made via the European Bone Marrow Transplantation (EBMT) criteria in adults which requires the following:
  - Classical SOS beyond day 21 (this includes bilirubin greater than or equal to 2mg/mL and two of following: painful hepatomegaly, weight gain, and ascites)
  - Histologically proven SOS
  - Or two or more of the classical criteria and ultrasound or hemodynamic evidence of SOS
- Defibrotide, is the only studied drug used for the treatment of moderate and severe VOD/SOS.
- Cemiplimab is a programmed cell death protein 1 (PD-1) checkpoint inhibitor, recently approved for the treatment of cutaneous squamous cell carcinoma (SCC) and basal cell carcinoma (BCC).
- This case documents a patient with a diagnosis of VOD/SOS following the initiation of Cemiplimab.

Case Study

58 year old woman with a past medical history of locally advanced basal cell carcinoma treated with six months of Cemipilimab presenting with new-onset ascites one month after discontinuation of the drug.

- **Case workup:**
  - Diagnostic Paracentesis: SAAG >1.5. No culture growth. <250 polymorphonuclear neutrophils (PMNs)
  - Lab Results: Sodium 129, Creatinine 0.7, Albumin 3.0, Total Bilirubin 12.6 (direct 7.3), Alanine Transaminase 220, Aspartate Aminotransferase 147, Alkaline Phosphatase 2025, White Blood Cell 11.1, Hemoglobin 14.5, INR 1.6.
  - Erythrocyte Sedimentation Rate (ESR) and C-Reactive Protein (CRP) normal
  - Autoimmune workup:
    - Complement C3 and Complement C4 normal
    - Negative Anti-Nuclear Antibody, Anti-Mitochondrial Antibody, Anti-Smooth Muscle Antibody, Cryoglobulin, Anti-Proteinase 3, Myeloperoxidase Antibody, Beta-2 Glycoprotein, Anticardiolipin IgG
  - COVID negative/ Influenza negative
  - Lyme serology negative
  - Blood cultures no growth
  - Herpes Simplex Virus (HSV) and Epstein-Barr Virus (EBV) negative
  - Quantitative CMV PCR was 330,573 IU/mL.
  - CT Abdomen and Pelvis: Diffuse heterogenous enhancement of the liver parenchyma
  - Computed Tomography Angiography (CTA) of Abdomen: no evidence of inflammation in large vessels
  - Transjugular Liver Biopsy: moderate nodular regenerative hyperplasia (NRH) changes, prominent central vein sclerosis with fibrous obliteration, signs of SOS/VOD and central venulitis with fibrotic changes and sinusoidal portal hypertension.
  - A CMV immunohistochemical stain was negative.
- Patient was briefly treated with 100mg prednisone daily for one week then transitioned to 40mg daily for weeks with no improvement

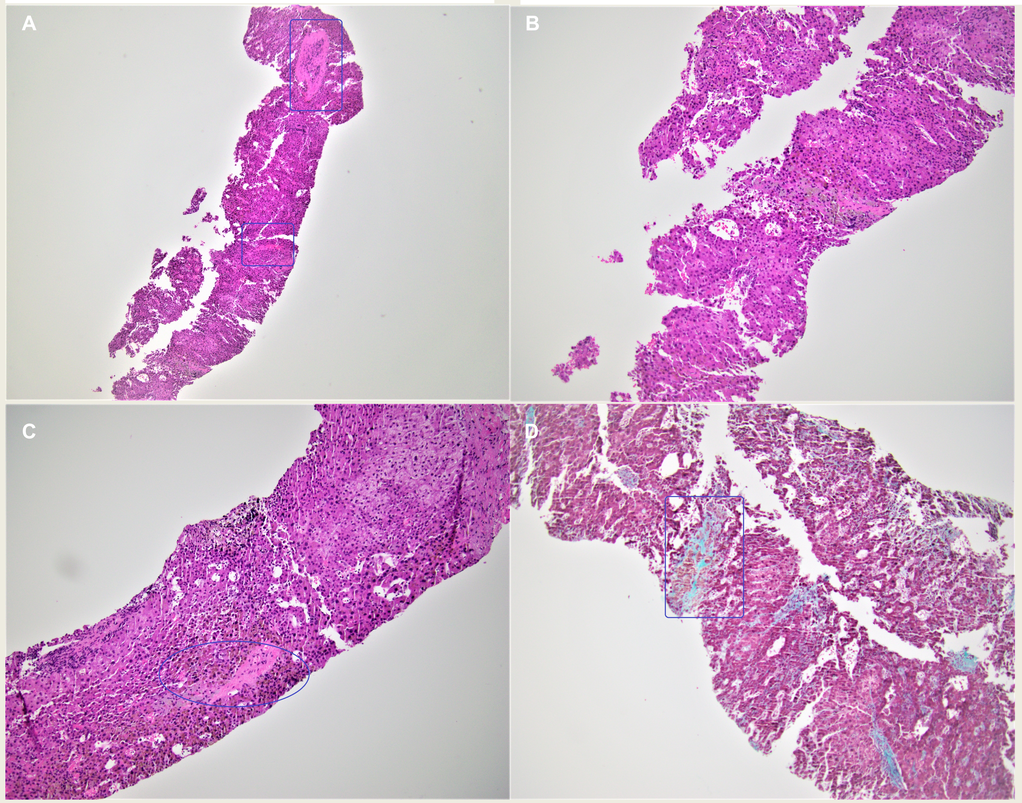
Results

A. Moderate nodular regenerative hyperplasia (NRH) of previously normal hepatic parenchyma

B. Prominent central veins sclerosis with fibrous obliteration.

C. Centrizonal sclerosis with ceroid laden macropahges
- Ceroid laden macrophages are a well recognized pathologic feature of liver injury commonly seen in AI-DILI (autoimmune drug induced liver injury).
- Ceroid contains modified lipoproteins (such as MDA-LDL), which are generated as a consequence of chronic oxidative stress.

D. Elastic trichrome with centrizonal sclerosis
- Elastic trichrome highlights pathologically increased fibrosis



DISCUSSION

- Our patient met EBMT criteria for VOD/SOS given her positive biopsy, elevated total bilirubin, and ascites refractory to diuretics.
- Full diagnostic work-up was all negative along with no response to a prolonged steroid course ruling out all other etiologies of VOD/SOS.
- Onset of symptoms and VOD were preceded by a six-month course of anti-PD1 therapy for the treatment of BCC.
- Given the morbidity and mortality of VOD/SOS, immediate cessation of the offending agent occurred, however, the patient was transitioned to hospice and died before further treatment could be pursued.
- VOD/SOS is often associated with chemotherapy drugs and T cell-mediated destruction associated with GVHD, however, in our patient we present a report of checkpoint inhibitor-induced VOD/SOS.
- Hepatic veno-occlusive disease associated with immune checkpoint inhibition should be considered in a differential diagnosis of liver dysfunction in patients receiving these medications.

REFERENCES

1. Bonifazi F, Barbato F, Ravaioli F, et al. Diagnosis and Treatment of VOD/SOS After Allogeneic Hematopoietic Stem Cell Transplantation. Front Immunol. 2020;11:489. doi:10.3389/fimmu.2020.00489
2. DeLeve LD, Wang X, Kuhlenkamp JF, Kaplowitz N. Toxicity of azathioprine and monocrotaline in murine sinusoidal endothelial cells and hepatocytes: the role of glutathione and relevance to hepatic venoocclusive disease. Hepatology. 1996;23(3):589-599. doi:10.1002/hep.510230326
3. Fuste B, Escolar G, Marin P, Mazzara R, Ordinas A, Diaz-Ricart M. G-CSF increases the expression of VCAM-1 on stromal cells promoting the adhesion of CD34+ hematopoietic cells: studies under flow conditions. Exp Hematol. 2004;32(8):765-772. doi:10.1016/j.exphem.2004.05.023
4. Mercanoglu F, Turkmen A, Kocaman O, et al. Endothelial dysfunction in renal transplant patients is closely related to serum cyclosporine levels. Transplant Proc. 2004;36(5):1357-1360. doi:10.1016/j.transproceed.2004.05.073
5. Zoja C, Furci L, Ghilardi F, Zilio P, Benigni A, Remuzzi G. Cyclosporin-induced endothelial cell injury. Lab Invest. 1986;55(4):455-462.
6. Mohty M, Malard F, Abecassis M, et al. Revised diagnosis and severity criteria for sinusoidal obstruction syndrome/veno-occlusive disease in adult patients: a new classification from the European Society for Blood and Marrow Transplantation. Bone Marrow Transplant. 2016;51(7):906-912. doi:10.1038/bmt.2016.130
7. Mohty M, Battista ML, Blaise D, et al. A multicentre, multinational, prospective, observational registry study of defibrotide in patients diagnosed with veno-occlusive disease/sinusoidal obstruction syndrome after haematopoietic cell transplantation: an EBMT study. Bone Marrow Transplant. 2021;56(10):2454-2463. doi:10.1038/s41409-021-01265-2
8. Perrier A, Didelot A, Laurent-Puig P, Blons H, Garinet S. Epigenetic Mechanisms of Resistance to Immune Checkpoint Inhibitors. Biomolecules. 2020;10(7):E1061. doi:10.3390/biom10071061
9. Kida A, Matsuda K, Matsuda M, Sakai A. Hepatobiliary and Pancreatic: Biliary injury related to checkpoint inhibitor "pembrolizumab." J Gastroenterol Hepatol. 2019;34(9):1478. doi:10.1111/jgh.14677
10. LoPiccolo J, Brener MI, Oshima K, Lipson EJ, Hamilton JP. Nodular Regenerative Hyperplasia Associated With Immune Checkpoint Blockade. Hepatology. 2018;68(6):2431-2433. doi:10.1002/hep.30157