EJCRIM
European Journal
of Case Reports
in Internal Medicine

HEPATIC SINUSOIDAL OBSTRUCTION SYNDROME (SOS) ASSOCIATED WITH CHECKPOINT INHIBITOR THERAPY

Marianna Litterio[1], Nicole Marchetti[2], Francesco Carubbi[1], Marianna Tudini[2], Luciano Mutti[2,3,4], Claudio Ferri[1]

[1] Department of Life, Health & Environmental Sciences, University of L'Aquila, L'Aquila, Italy
[2] Department of Biotechnological and Applied Clinical Sciences, University of L'Aquila, L'Aquila, Italy
[3] Center of Biotechnology, College of Science and Technology, Temple University, SHRO, Philadelphia, USA
[4] Italian Group for Mesothelioma, Italy

Corresponding author's e-mail: marianna.litterio@graduate.univaq.it

Received: 10/09/2024
Accepted: 24/09/2024
Published: 13/12/2024

Conflicts of Interests: The Authors declare that there are no competing interests.
Patient Consent: Written informed consent was obtained from the patient.

How to cite this article: Litterio M, Marchetti N, Carubbi F, Tudini M, Mutti L, Ferri C. Hepatic sinusoidal obstruction syndrome (SOS) associated with checkpoint inhibitor therapy. *EJCRIM* 2024;**11**:doi:10.12890/2024_004885

ABSTRACT

Sinusoidal obstruction syndrome (SOS) is a distinctive and potentially fatal form of hepatic injury that mainly occurs after hematopoietic-stem cell transplantation but also due to many other conditions including drug or toxin exposure. Recently, immune checkpoint inhibitors (ICIs) have revolutionised the treatment of many solid organ malignancies. Furthermore, as their use has become more widespread, rare toxicities have emerged. The difficulty lies in diagnosing these unusual toxicities with an incidence of as low as less than 1% hence defined as SOS. The development of the disease can be rapid and unpredictable. The severe forms of SOS may result in multi-organ dysfunction with a high mortality rate (>80%).

We present the case of a patient with metastatic lung adenocarcinoma treated with the ICI pembrolizumab who developed SOS with marked portal hypertension as a rare severe, toxic side effect of immunotherapy. This report highlights the importance of considering SOS in patients who develop liver dysfunction and/or portal hypertension during or after immunotherapy for neoplastic disease. Early identification and severity assessment is crucial in facilitating prompt diagnosis and timely treatment, improving the prognosis of our patients.

KEYWORDS

Sinusoidal obstruction syndrome, SOS, pembrolizumab, immune checkpoint inhibitors

LEARNING POINTS

- Understand less common side effects of immunotherapy, now used in daily clinical practice.
- Consider sinusoidal obstruction syndrome (SOS) in patients who develop liver dysfunction and/or portal hypertension during or after immunotherapy for neoplastic disease.
- Early identification and severity assessment is crucial in facilitating prompt diagnosis and timely treatment, improving the prognosis of patients.

EFIM
European Federation of Internal Medicine

Publisher
smc media srl

INTRODUCTION

Hepatic sinusoidal obstruction syndrome (SOS) is characterized by damage to small hepatic vessels mainly affecting sinusoidal endothelium. Although this syndrome is typically associated with allogenic haematopoietic stem cell transplants (HSCT), a number of toxins and drugs, including chemotherapies and immunosuppressive therapies, as well as total body or liver irradiation and ABO mismatch platelet transfusion can also cause it[1]. Recently, SOS has been described also within the spectrum of rare immune-related adverse events (irAEs) occurring in patients treated with immune checkpoint inhibitors (ICIs) *(Table 1)*. The clinical presentation of SOS includes jaundice, abdominal right upper-quadrant pain and tender hepatomegaly, ascites, and unexplained weight gain. Imaging may demonstrate a pattern of heterogenous enhancement in the portal phase and magnetic resonance imaging (MRI) can be helpful in the assessment of this condition. Elevated portal pressures can be observed upon invasive measurement and histological examination reveals non-fibrous portal areas with sinusoidal dilation and perisinusoidal fibrosis and lobular veins occluded with fibrous tissue.

We describe the case of a patient with metastatic lung adenocarcinoma treated with the ICI pembrolizumab, who developed portal hypertension secondary to SOS as a rare severe toxic side effect of immunotherapy.

CASE DESCRIPTION

In 2020, a 67-year-old man was diagnosed with metastatic non-oncogene-addicted left lung adenocarcinoma. Immunohistochemistry examinations detected a programmed death-ligand 1 (PD-L1) expression of 30%, so he started first line therapy with pembrolizumab-pemetrexed-carboplatin (4 cycles) in December 2020 followed by maintenance therapy with pembrolizumab-pemetrexed from March 2021 (35 total cycles), and pembrolizumab monotherapy until August 2023 when it was eventually discontinued due to immune-related symptomatic hypothyroidism. His medical background also included dyslipidaemia, type 2 diabetes, systemic arterial hypertension, peripheral artery disease, paroxysmal atrial fibrillation with previous pulmonary embolism, chronic obstructive pulmonary disease, benign prostatic hyperplasia and hepatitis B virus (HBV) infection. In November 2023, he was admitted to the hospital due to progressive increase of the abdominal circumference, weight gain (9 kg) and stinging pain in the lower abdominal quadrants. In the emergency room, blood tests showed microcytic hypochromic anaemia (Hb 10.3 g/dl, MCH 22.1 pg, MCV 69.4 fl), neutrophilic leukocytosis (leucocytes 12.8 $\times 10^3$/µl, neutrophils 8.8 $\times 10^3$/µl), hyperglycaemia (192 mg/dl) and increased values of alkaline phosphatase (ALP, 320 IU/l), gamma-glutamyltransferase (GGT, 144 IU/l), aspartate transaminase (AST, 230 IU/l), alanine transaminase (ALT, 266 IU/l), direct bilirubin (0.46 mg/dl) and C-reactive protein (CRP, 10.6 mg/dl). Ultrasound scan revealed an enlarged liver with polilobulated margins and a non-homogeneous finely thickened echo-structure, without evidence of focal parenchymal lesions. It also highlighted the presence

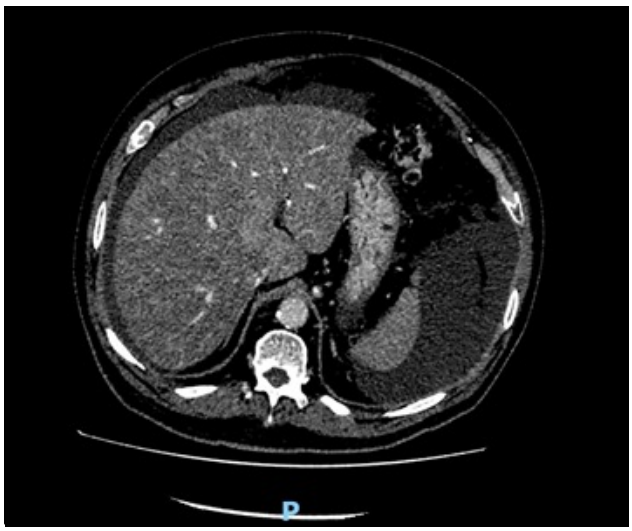

Figure 1. Computed tomography scan (portal phase). Hepatomegaly with a non-homogeneous intrahepatic vascularization and abundant intra-abdominal effusion.

Haematopoietic stem cell transplants	
ABO mismatch platelet transfusion	
Cancer chemotherapeutic agents	Cyclophosphamide, 6-mercaptopurine, azathioprine, actinomycin D, melphalan, oxaliplatin, dacarbazine, cytarabine, fluorouracil, carboplatin, busulfan, cytosine arabinoside, melphalan, urethane
Chemotherapy for acute myeloid leukaemia	Gemtuzumab ozogamicin
Immune checkpoint inhibitors	Nivolumab, pembrolizumab, gemtuzumab ozogamicin
Pyrrolizidine alkaloid	Bush tea, herbs (Symphytum officinale, Echinacea)
Radiation-induced liver disease	>30 grays
Liver transplantation	

Table 1. Common causes of hepatic sinusoidal obstruction syndrome.

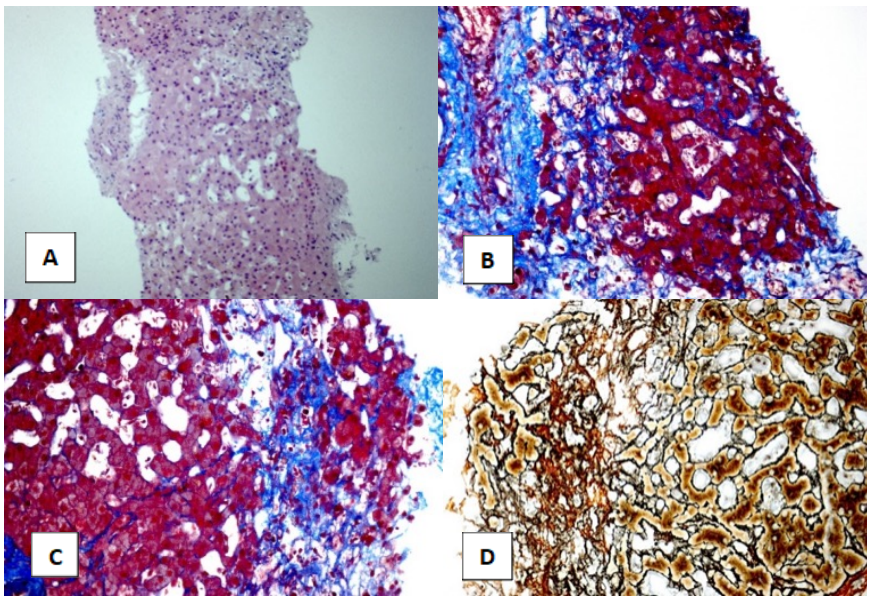

Figure 2. Dilatation and congestion of sinusoids are located in centrilobular zones around the terminal hepatic vein. Endothelial cells of veins and sinusoids are damaged, leading to hematic deposition in the space of Disse and to hepatocyte necrosis around the central veins. A) Haematoxylin and eosin (H&E) stain; B e C) Masson's trichrome stain; C) Silver stain.

of abundant free intra-abdominal effusion. Ascitic fluid microbiology and cytology were negative. To exclude acute right heart failure underlying ascites, cardiac ultrasound was performed. HBV-DNA was not detected, ruling out HBV infection. Test results for other hepatotropic viruses, including hepatitis A and hepatitis C, herpes simplex, cytomegalovirus, Epstein-Barr, human immunodeficiency, and parvovirus B19 were negative. Antinuclear antibodies and other autoimmune hepatitis serologic markers were also negative. Full body computed tomography (CT) scan with contrast showed mild hepatomegaly with inhomogeneity of the intrahepatic vascularization, a slight reduction in the calibre of portal branches, supra-hepatic veins and intrahepatic vena cava along with initial oesophageal distal varices and abundant intra-abdominal effusion *(Fig. 1)*. Esophagogastroduodenoscopy (EGD) documented Candida oesophagitis and confirmed distal oesophageal varices. Histological examination of tissue biopsied with ultrasound-guided of liver segments II-IV showed signs of centrilobular congestion, diffuse sinusoidal ectasia with minimal and focal centrilobular hepatocellular necrosis, and collagen deposition tissue architecture without significant fibrosis and portal inflammation *(Fig. 2)*. During hospitalization, intravenous diuretic and steroid therapy was started. Over a period of 3 weeks, there was a clinical improvement with decrease of body weight (7 kg) and abdominal circumference and resolution of the abdominal pain. In addition, at the time of patient's discharge there was a clear reduction in the following laboratory values: AST 27 UI/l, ALT 48 UI/l, GGT 114 UI/l, ALP 206 UI/l and direct bilirubin 0.31 mg/dl. One month after discharge, neither signs of ascites nor worsening of liver function were observed.

DISCUSSION

Sinusoidal obstruction syndrome (SOS) is a rare liver injury characterized by damage of small hepatic vessels. The risk factors include older age, female sex, specific types of conditioning regimen (e.g., myeloablative therapy), pre-existing liver diseases, antithrombin III defects, and thalassemia. In particular, patients with a serum transaminase level of >2.5 times the upper normal limit, a serum bilirubin level of >1.5 times the normal limit, liver cirrhosis, hepatic irradiation, and active viral hepatitis are considered to be at risk of SOS. The previous use of hepatotoxic drugs is also a risk factor[2]. Our patient was a 67-year-old man with previous HBV infection and chemoprophylaxis interrupted due to drug intolerance. Furthermore, his serum transaminase level progressively increased in the previous few months until reaching a value >5 times the normal limit and he had undergone treatment with multiple drugs including immunotherapy (pembrolizumab) for his cancer.

The advent of ICIs has revolutionised the treatment landscape across a variety of solid tumours, with high rates of sustained responses. As the indications for ICI monotherapy, doublet therapy and combinations with other targeted and chemotherapeutic agents expand, and these compounds are increasingly used in earlier lines of treatment, clinicians frequently deal with a wide spectrum of irAEs. These events occur due to loss of self-tolerance, with a wide array of inflammatory syndromes and involvement of a range of immune cells and mechanisms. The most common irAEs are myocarditis, pneumonitis, neurological toxicity, haematological toxicity, cutaneous effects. In SOS, cholangitis, hypoparathyroidism, non-infectious cystitis have been observed[3]. SOS results from the activation of the sinusoidal endothelial cells (SECs) by chemotherapy and radiotherapy, resulting in the sustained and intense production of cytokines (interleukin-1, IL-6, and tumour necrosis factor-α) that induce endothelial damage and sinusoidal endothelial swelling. The progression of SOS involves the depletion of glutathione and nitric oxide from the SECs, the increased expression of intrahepatic matrix metalloproteinases and vascular endothelial growth factor, and the activation of clotting factors. This results in the leakage of blood cells and cellular debris, leading to the obstruction of sinusoids[4]. The main clinical features of

SOS include rapid weight gain, tendentially unresponsive to diuretics, painful hepatomegaly, ascites and alterations of liver function tests, in the absence of other explanations for these signs and symptoms. In transplanted patients SOS generally occurs within the 20 days following the procedure[5]. ICIs can induce a specific immune-mediated hepatitis, which it often presents as a hepatocellular or mixed hepatitis that usually arises within 2 to 12 weeks after the start of therapy. The challenge arises when SOS becomes evident long after the administration of the causative agent. Our patient started a first line therapy with pembrolizumab-pemetrexed-carboplatin in December 2020, but side effects of the treatment only appeared when he started monotherapy with pembrolizumab in March 2023. Treatment was stopped due to evidence of immune-related symptomatic hypothyroidism and of interstitial pneumonia in August. The patient also had an increase in abdominal circumference and body weight which worsened over the weeks prior to admission. Taking together all the above, we can conclude that this was a case of late-onset hepatotoxicity, not explained by other possible causes.

The gold standard for diagnosis of SOS remains liver biopsy. Histologically, SOS can present in an acute, subacute or chronic form. As a result of exposure to toxic agents (acute), endothelial cells damaged round off and detach from the sinusoidal wall, obstructing blood flow. This is accompanied by extravasation and accumulation of red blood cells and cellular debris in the terminal hepatic vein. In the subacute phase (after days or weeks) collagen is deposited in and around the affected hepatic venula leading to progressive obliteration of the venule. With the persistence of the SOS lesions into weeks to months (chronic), dense perivenular fibrosis develops and radiates into parenchyma. There may be severe destruction of lobular parenchyma, and rarely evolution to cirrhosis[6]. Our patient's liver biopsy showed signs of chronic liver disease associated with a subacute form of SOS.

Current management of SOS primarily consists of supportive care (fluid management, oxygenation, blood transfusions) and avoidance of hepato/nephrotoxins. Patients with evidence of moderate SOS should be treated with mild diuretics or paracentesis, if ascites occurs. Patients with severe SOS require treatment with defibrotide. For clinically significant irAEs management involves withholding the ICI (temporarily or permanently) and administering corticosteroids[7].

CONCLUSIONS

This report highlights the importance of considering SOS in patients who develop liver dysfunction and/or portal hypertension during or after immunotherapy for neoplastic disease. Early identification and severity assessment is crucial in facilitating prompt diagnosis and timely treatment, improving the prognosis of our patients.

REFERENCES

1. Mavrikou I, Chatzidimitriou D, Skoura L, Nikolousis E, Sakellari I, Gavriilaki E. Molecular Advances in Sinusoidal Obstruction Syndrome/Veno-Occlusive Disease. *Int J Mol Sci* 2023;**24**:5620.
2. Corbacioglu S, Jabbour EJ, Mohty M. Risk Factors for Development of and Progression of Hepatic Veno-Occlusive Disease/Sinusoidal Obstruction Syndrome. *Biol Blood Marrow Transplant* 2019;**25**:1271-1280.
3. Javaid A, Bennett C, Rao A, Spain L. Rare Immune-Related Adverse Events (irAEs): Approach to Diagnosis and Management. *Pharmaceut Med* 2024;**38**:25-38.
4. Sakumura M, Tajiri K, Miwa S, Nagata K, Kawai K, Miyazono T, et al. Hepatic Sinusoidal Obstruction Syndrome Induced by Non-transplant Chemotherapy for Non-Hodgkin Lymphoma. *Intern Med* 2017;**56**:395-400.
5. Bonifazi F, Barbato F, Ravaioli F, Sessa M, Defrancesco I, Arpinati M, et al. Diagnosis and Treatment of VOD/SOS After Allogeneic Hematopoietic Stem Cell Transplantation. *Front Immunol* 2020;**11**:489.
6. Fan CQ, Crawford JM. Sinusoidal obstruction syndrome (hepatic veno-occlusive disease). *J Clin Exp Hepatol* 2014;**4**:332-46.
7. Aziz MT, Kakadiya PP, Kush SM, Weigel K, Lowe DK. Defibrotide: An Oligonucleotide for Sinusoidal Obstruction Syndrome. *Ann Pharmacother* 2018;**52**:166-174.