GE – Portuguese Journal of Gastroenterology

Clinical Case Study

GE Port J Gastroenterol 2024;31:437–442
DOI: 10.1159/000536535

Received: October 10, 2023
Accepted: December 30, 2023
Published online: March 14, 2024

Transjugular Liver Biopsy: The Key to a Rare Etiology of Cholestatic Hepatitis after Bone Marrow Transplantation

Inês Pestana[a] Juliana Pedro[b] Carolina Simões[c] Carlos Noronha Ferreira[b, d] Sara da Mata[e] Isabel Claro[c]

[a]Serviço de Gastrenterologia, Hospital Amato Lusitano ULSCB, Castelo Branco, Portugal; [b]Serviço de Gastrenterologia e Hepatologia, Centro Hospitalar Universitário Lisboa Norte, Lisboa, Portugal; [c]Serviço de Gastrenterologia, Instituto Português de Oncologia de Lisboa Francisco Gentil, Lisboa, Portugal; [d]Clínica Universitária de Gastrenterologia, Faculdade de Medicina de Lisboa, Universidade de Lisboa, Lisboa, Portugal; [e]Serviço de Anatomia Patológica, Instituto Português de Oncologia de Lisboa Francisco Gentil, Lisboa, Portugal

Keywords

Transjugular liver biopsy · Liver graft-versus-host disease · Hepatic sinusoidal obstruction syndrome · Hematopoietic stem cell transplantation

Abstract

Introduction: Hematopoietic stem cell transplantation (HSCT) is associated with multiple complications, such as sinusoidal obstruction syndrome (SOS) (hepatomegaly, ascites, jaundice, and thrombocytopenia) and graft-versus-host disease (GVHD) (with the skin, gastrointestinal tract, and liver being the main targets). These entities may present overlapping clinical findings, being considered differential diagnoses, but their coexistence is rare. ***Case Presentation:*** A 29-year-old male with acute myeloid leukemia underwent HSCT. On day (D)+20, he developed hyperbilirubinemia, pleural effusion, ascites, and painful hepatomegaly. Abdominal ultrasound was suggestive of SOS, and defibrotide was initiated. On D+44, acute cutaneous, intestinal, and hepatic GVHD developed which improved after treatment with methylprednisolone. On D+132, there was worsening cholestasis and abdominal pain. MRCP revealed strictures in several segments of the intrahepatic bile ducts and irregularity of the main bile duct. Due to aggravation of liver enzyme changes and clinical worsening, he was admitted to the Intensive Care Unit. Due to persistence of severe hyperbilirubinemia (30 mg/dL) and thrombocytopenia (30,000 cell/uL), he underwent a hepatic hemodynamic study which revealed a hepatic venous pressure gradient of 10 mm Hg. The transjugular liver biopsy revealed canalicular hepatic cholestasis, bile duct injury, and focal hepatocellular necrosis suggestive of GVHD as well as injury to centrilobular veins and centrilobular necrosis compatible with possible SOS. Mycophenolate mofetil was started, but on D+195, the patient died of septic shock. ***Discussion/Conclusion:*** This case is notable for its complexity and for demonstrating the rare coexistence of histological features of SOS and GVHD. Although the clinical and laboratory findings may be sufficient for the diagnosis, it is important to highlight the importance of liver hemodynamic study and transjugular liver biopsy in these patients who often have severe thrombocytopenia, for the characterization and histological confirmation of cholestatic hepatitis, especially when the etiology may be multifactorial.

karger@karger.com
www.karger.com/pjg

Correspondence to:
Inês Pestana, ines_pestana15@hotmail.com

Biópsia hepática transjugular: a chave para uma rara etiologia de hepatite colestática após transplante de progenitores hematopoiéticos

Palavras Chave
Biópsia hepática transjugular · Doença do enxerto contra hospedeiro hepática · Síndrome de obstrução sinusoidal hepática · Transplante de progenitores hematopoiéticos

Resumo
Introdução: O transplante de progenitores hematopoéticos (HSCT) está associado a múltiplas complicações, como Síndrome de Obstrução Sinusoidal hepática (SOS) (hepatomegalia, ascite, icterícia e trombocitopenia) e Doença do Enxerto contra Hospedeiro (GVHD) (pele, tracto gastrointestinal e fígado como principais alvos). Estas entidades podem apresentar quadros clínicos sobreponíveis, sendo consideradas diagnósticos diferenciais mas a coexistência é rara. ***Caso Clínico:*** Um homem de 29 anos com leucemia mieloide aguda foi submetido a HSCT. No dia (D)+20, apresentou hiperbilirrubinemia, derrame pleural, ascite e hepatomegalia dolorosa. Ecografia foi sugestiva de SOS e foi iniciado defibrotido. No D+44, desenvolveu GVHD cutânea, intestinal e hepática aguda, com melhoria após tratamento com metilprednisolona. No D+132, agravamento de colestase e dor abdominal. A CPRM revelou estenoses em vários segmentos das vias biliares intra-hepáticas e irregularidade da parede da via biliar principal. Devido ao agravamento clínico e analítico, foi internado na Unidade de Cuidados Intensivos. Por manter hiperbilirrubinemia (30 mg/dL) e trombocitopenia (30.000 células/uL), foi submetido a estudo hemodinâmico hepático que revelou gradiente de pressão venosa hepática de 10 mm Hg. A biópsia hepática transjugular revelou colestase hepática canalicular, lesão dos ductos biliares e necrose hepatocelular focal sugestivos de GVHD, assim como e lesão de veias centrolobulares e necrose centrolobular compatível com possível SOS. Iniciou micofenolato de mofetil, mas em D+195 faleceu no contexto de choque séptico. ***Discussão/Conclusão:*** Este caso destaca-se pela sua complexidade e por demonstrar a rara coexistência de aspectos histológicos de SOS e GVHD. Embora o quadro clínico e analítico possa ser suficiente para o diagnóstico, é de relevar a importância da biópsia hepática transjugular em doentes imunossuprimidos com trombocitopénia grave para caracterização e confirmação histológica de quadros de hepatite colestática, sobretudo quando a etiologia pode ser multifactorial.

Introduction

In patients undergoing hematopoietic stem cell transplantation (HSCT), adverse events may develop in up to 80% of patients, and these include Graft-versus-host disease (GVHD) and sinusoidal obstruction syndrome (SOS) which result in significant morbidity and mortality [1–3]. Early diagnosis is essential to guide treatment [1, 3]. SOS results from chemotherapy or radiation-induced destruction of hepatic microvasculature during conditioning of the bone marrow [1, 3–7], and results in reduced hepatic outflow and post-sinusoidal portal hypertension [1, 5, 7].

Clinical and laboratory features of SOS usually develop ≤3 weeks after HSCT [1, 3, 6, 7]. SOS represents the most common cause of liver disease (10–60%, depending on risk factors and conditioning regimen) during the first 20 days after HSCT, although it may also present later (15–20%) [1, 3, 6, 7]. SOS may progress to systemic vasculitis and multi-organ failure [3, 4]. Severe SOS is associated with a mortality rate of up to 85% [4, 6–8].

Acute GVHD is a frequent immune-mediated adverse event after HSCT and is associated with high morbidity and mortality [9, 10]. It develops due to destruction of the recipient tissues and organs by the donor immune effector cells [9, 10]. It usually occurs ≤3 months after HSCT but may occur later [10]. Acute GVHD most frequently affects the skin, liver, and gastrointestinal tract [2, 3, 9, 10].

Gastrointestinal involvement occurs in 30–75% of cases and its diagnosis is based on clinical features, imaging tests, and histopathology [3]. The diagnosis of liver GVHD is often challenging [6, 10]. Usually, cutaneous and gastrointestinal manifestations are present when jaundice develops, but liver involvement may be the presenting feature [6].

Chronic GVHD can affect any organ without a defined time limit and develops in 40–73% of patients [2, 3, 10]. It is characterized by progressive destruction of small intrahepatic bile ducts, leading to vanishing bile duct syndrome and end-stage liver disease [10]. Although SOS and GVHD represent different entities, clinical manifestations may overlap or resemble other adverse events, which can be an important diagnostic challenge which potentially influences their timely management [3].

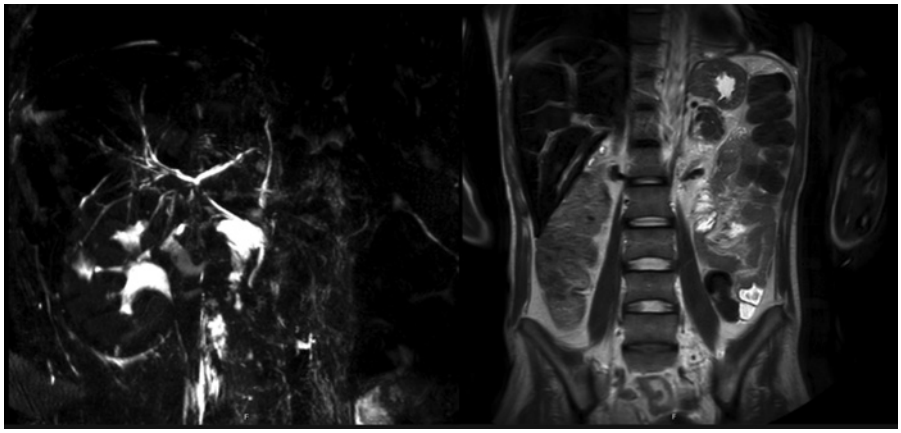

Fig. 1. MRCP-revealed segmental strictures in the intrahepatic bile ducts and irregularity of the main bile duct.

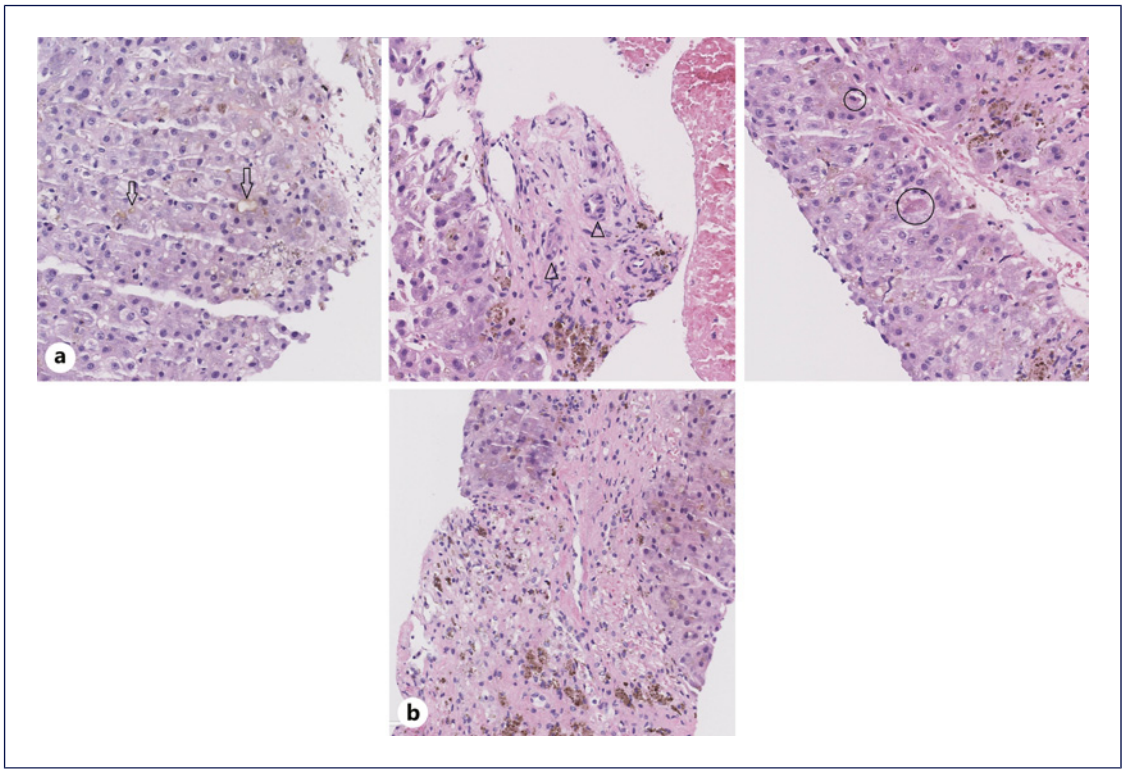

Fig. 2. Histological features of TJLB. **a** Features of GVHD: liver tissue biopsy with canalicular cholestasis (arrow), small bile duct injury (arrowhead), and focal hepatocellular necrosis (circle). **b** Features of SOS: liver tissue biopsy with central vein narrowing and extravasated erythrocytes.

Case Report

A 29-year-old male patient with bone marrow aplasia since 2014 underwent HSCT in August 2022 for acute myeloid leukemia. Prophylaxis against GVHD (anti-thymocyte globulin from day (D)-3 to D-1, total dosage 378.7 mg; tacrolimus from D-2; mycophenolate mofetil from D-0 to D+56, 1000 mg 12/12 h) and against SOS (ursodeoxycholic acid 500 mg 8/8 h; acetylcysteine 300 mg 12/12 h during the entire hospital stay) was done. The donor was unrelated, with HLA correspondence of 9/10 and major AB0 incompatibility.

On D+20 after HSCT, he developed liver enzyme changes with cytolysis, which evolved to cholestasis, as well as weight gain, pleural effusion, ascites, and painful hepatomegaly. Ultrasound (US) findings of homogeneous hepatomegaly, thickening of the gallbladder wall, ascites, and bilateral pleural effusion without vascular hemodynamic changes were suggestive of late hepatic (severe) SOS. The patient was administered defibrotide

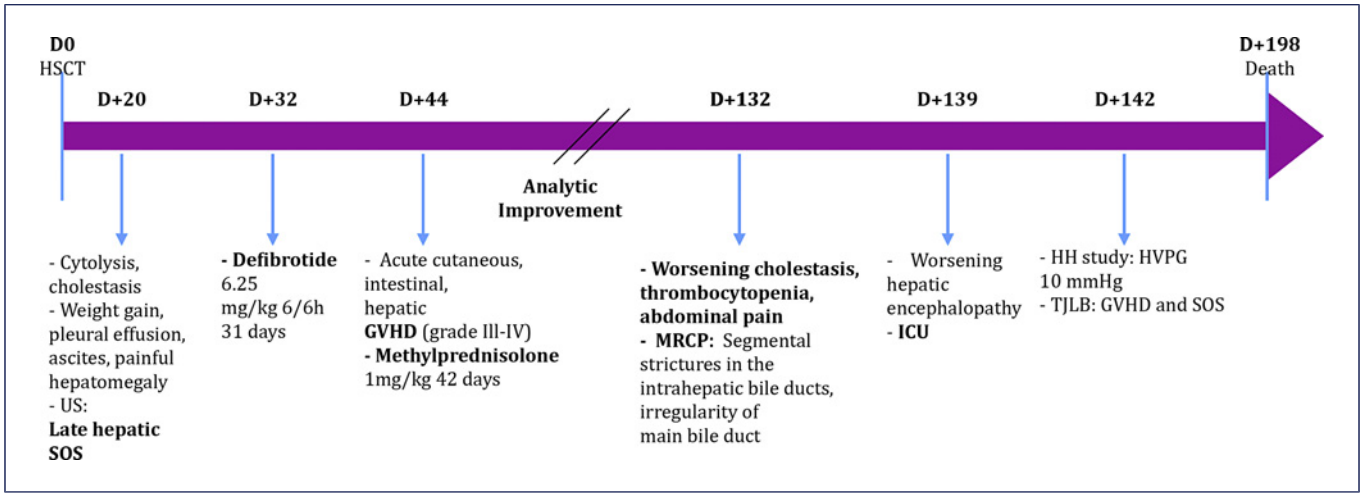

Fig. 3. Timeline of patient evolution. D, day; GVHD, graft-versus-host disease; HH, hepatic hemodynamic; HVPG, hepatic venous pressure gradient; ICU, intensive care unit; MRCP, magnetic resonance cholangiopancreatography; SOS, sinusoidal obstruction syndrome; TJLB, transjugular liver biopsy; US, ultrasonography.

Table 1. Summary of the liver enzyme changes along the clinical course of the patient

	Platelets, 10^9/L/μL	PT, s	INR	Total bilirubin, mg/dL	AST, UI/L	ALT, UI/L	ALP, UI/L
D+20	26	16.5	1.5	2.17	36	74	206
D+32	71	20	1.8	5.02	480	945	188
D+44	82	14.8	1.3	17.00	119	175	285
D+132	18	11.1	1.0	11.75	198	1,028	379
D+139	30	10.8	0.9	30.00	137	359	359
D+142	39	10.4	0.9	29.19	129	407	284

(6.25 mg/kg 6/6 h) on D+32, this was maintained for 31 days, and it resulted in clinical improvement and a significant improvement of cholestasis (total bilirubin 1.15 mg/dL, ALP 206 U/L).

On D+44, the patient developed acute cutaneous, intestinal, and hepatic GVHD [grade III-IV – total bilirubin of 17 mg/dL, AST 119 UI/L, ALT 175 UI/L, prothrombin time (PT) 14.8 s]. He was started on methylprednisolone (1 mg/kg for 42 days), and there was a progressive improvement of cholestasis. On D+132, in the context of worsening cholestasis (total bilirubin 11.75 mg/dL, AST 198 UI/L, ALT 1028 UI/L, ALP 379 U/L, PT 11.1 s), thrombocytopenia, and abdominal pain, an MRCP was performed, and it revealed segmental strictures in the intrahepatic bile ducts and irregularity of the main bile duct (shown in Fig. 1).

Due to worsening hepatic encephalopathy, he was admitted to the intensive care unit (ICU). On D+139, despite treatment with steroids, there was progressive worsening of cholestasis (total bilirubin 30 mg/dL, ALP 359 U/L, AST 137 UI/L, ALT 359 UI/L, PT 11.3 s) and persistence of severe thrombocytopenia (30×10^9/L/uL). On D+142, a hepatic hemodynamic (HH) study was performed by the bedside in the ICU, and it revealed a hepatic venous pressure gradient (HVPG) of 10 mm Hg. The transjugular liver biopsy (TJLB) revealed canalicular cholestasis, bile duct injury, and focal hepatocellular necrosis suggestive of GVHD, as well as features suggesting injury to centrilobular veins and centrilobular necrosis, which are observed in SOS (shown in Fig. 2a, b). There was extensive hemosiderosis. Mycophenolate mofetil (1,000 mg 12/12 h) was started. However, due to chronic GVHD and consequent septic shock, the patient died on D+195 (timeline and laboratory values shown in Fig. 3 and Table 1, respectively).

Discussion

This case exemplifies the crucial role of HH studies and TJLB in determining the etiology of post-HSCT cholestasis with the rare coexistence of GVHD and SOS. The patient had risk factors for SOS and GVHD which were mainly transplant related (allogenic transplant, unrelated, and HLA-mismatched donor) [3, 10].

The revised European Group for Blood and Marrow Transplantation (EBMT) criteria in adults include: classical SOS (≤21 days after HSCT with bilirubin ≥2 mg/dL and two of the following: painful hepatomegaly, weight gain, ascites); late-onset SOS (>21 days: the same features as classical, histologically proven, and two of four criteria for classical SOS plus hemodynamic/US evidence of SOS) [4, 7].

US and Doppler US can be useful in distinguishing hepatic GVHD from SOS [3, 4] and can reveal nonspecific abnormalities (hepatomegaly, splenomegaly, gallbladder wall thickening [>6 mm], ascites, periportal cuffing, signs of portal venous flow abnormalities) [3, 4, 7]. The reversal of portal venous flow is more specific but often occurs late during the course of SOS [7]. CT features suggestive of SOS include periportal edema, ascites, and a right hepatic vein diameter <0.45 cm [3].

In GVHD, radiologic imaging is important for early diagnosis and treatment [2, 3]. Imaging findings are frequently nonspecific and include enhancement of the biliary tract, gallbladder wall thickening, dilatation of the common bile duct, pericholecystic fluid, and biliary sludge [2, 3].

The histologic confirmation of SOS is limited to some centers and is rarely performed early after HSCT due to concerns regarding the potential complications of percutaneous liver biopsy [4, 10]. This limitation also explains why the diagnosis of acute GVHD of the liver is often one of exclusion [10]. Due to its sensitivity and specificity, liver stiffness measurement can be useful for a preclinical diagnosis of SOS and in monitoring response to treatment [4, 7].

However, HH study with TJLB is the gold standard and is safe even in patients with thrombocytopenia. It can be performed by the bedside in severely ill and unstable patients in the ICU, as was the case with our patient. It allows the measurement of HVPG and adequate histology for diagnosis [4, 6, 10, 11]. A HVPG ≥10 mm Hg defines clinically significant portal hypertension [3, 4, 6, 7]. The prognosis is especially poor when the HVPG is ≥ 20 mm Hg [3].

The typical histopathological features of GVHD include bile duct damage which may be severe, active hepatitis, and venulitis [2, 4, 10]. Liver histology may also be evaluated for drug toxicity, bacterial, viral, and fungal infection, and iron overload [3].

HSCT patients often have iron overload due to ineffective erythropoiesis coupled with increased intestinal absorption and multiple transfusions [2, 12]. It may mimic GVHD exacerbation, resulting in unnecessary continuation/intensification of GVHD immunosuppressive therapy [12, 13].

In conclusion, this case highlights the importance of HH study and TJLB in a patient who developed cholestatic hepatitis and severe thrombocytopenia after HSCT. The TJLB performed by the bedside in the ICU revealed the rare coexistence of SOS and GVHD as the causes of the cholestatic hepatitis after HSCT.

Statement of Ethics

The authors declare that all ethical procedures and standards were followed. The patient gave consent to the publication of the case report and accompanying images.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

The authors do not have any financial disclosures to report.

Author Contributions

All authors fulfilled criteria of ICMJE for authorship: acquisition, analysis, or interpretation of data for the work; drafting the work or revising it critically for important intellectual content; final approval of the version to be published; agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

References

1 Vythoulkas D, Tsirigotis P, Griniezaki M, Konstantellos I, Lazana I. Endothelial dysfunction syndromes after allogeneic stem cell transplantation. Cancers. 2023;15(3):680.
2 Mihăilă RG. Liver graft versus host disease after allogeneic peripheral stem cell transplantation: update on etiopathogenesis and diagnosis. Rom J Intern Med. 2016;54(2):83–92.
3 Mahgerefteh S, Sosna J, Bogot N, Shapira M, Pappo O, Bloom A. Radiologic imaging and intervention for gastrointestinal and hepatic complications of hematopoietic stem cell transplantation. Radiology. 2011;258(3):660–71.
4 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 Apr3;11:489.
5 Özkan HA, Özkan SG. Hepatic veno-occlusive disease (sinusoidal obstruction syndrome) after hematopoietic stem cell transplantation in adult patients: diagnosis, incidence, prophylaxis, and treatment. Transfus Apher Sci. 2022;61(1):103372.

6 Arai S, Lee L, Vogelsang G. A systematic approach to hepatic complications in hematopoietic stem cell transplantation. Stem Cel Transplant. 2002;11(2):215–29.
7 Mohty M, Malard F, Alaskar AS, Aljurf M, Arat M, Bader P, et al. Diagnosis and severity criteria for sinusoidal obstruction syndrome/veno-occlusive disease in adult patients: a refined classification from the European society for blood and marrow transplantation (EBMT). Bone Marrow Transplant. 2023;58(7):749–54.
8 Chalandon Y, Mamez AC, Giannotti F, Beauverd Y, Dantin C, Mahne E, et al. Defibrotide shows efficacy in the prevention of sinusoidal obstruction syndrome after allogeneic hematopoietic stem cell transplantation: a retrospective study. TransplantCellTher. 2022;28(11):765.e1–765.e9.
9 Zeiser R, Teshima T. Nonclassical manifestations of acute GVHD. Blood. 2021;138(22):2165–72.
10 Malard F, Holler E, Sandmaier BM, Huang H, Mohty M. Acute graft-versus-host disease. NatRevDisPrimers. 2023;9(1):27.
11 Modi D, Ye JC, Surapaneni M, Singh V, Chen W, Jang H, et al. Liver Graft-Versus-Host Disease is associated with poor survival among allogeneic hematopoietic stem cell transplant recipients. Am J Hematol. 2019;94(10):1072–80.
12 Kambham N, Higgins J, Sundram U, Troxell M. Hematopoietic stem cell transplantation: graft versus host disease and pathology of gastrointestinal tract, liver, and lung. Adv Anat Pathol. 2014;21(5):301–20.
13 Kamble RT, Selby GB, Mims M, Kharfan-Dabaja MA, Ozer H, George JN. Iron overload manifesting as apparent exacerbation of hepatic graft-versus-host disease after allogeneic hematopoietic stem cell transplantation. Biol Blood Marrow Transplant. 2006;12(5):506–10.