Ischemic Cholangiopathy Post Liver Transplantation: A Clinical Case

Colangiopatia Isquémica Pós Transplante Hepático: Caso Clínico

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Abstract:

Ischemic cholangiopathy (IC) post liver transplant (LT) is not a rare condition, it should be suspected and treated, if possible, without delay. We report a case of a 69-year-old man who underwent LT without any instability, vascular, infectious or graft disorders, but 15 months after LT, had cholangitis with stenting of the biliary tract. One year later, he had a new episode of cholangitis, with stenosis of the left main duct and peripheral poverty of the biliary tract and developed graft failure. Despite optimal medical and endoscopic treatment, the patient died. This case illustrates how, sometimes, IC course can be asymptomatic and insidiously, with posterior graft failure even with appropriate endoscopic management. Early recognition and a prompt referral are essential because re-transplantation could be an option in this situation.

Keywords: Bile Duct Diseases; Ischemia; Liver Transplantation/adverse effects; Postoperative Complications.

Resumo:

A colangiopatia isquémica (CI) pós-transplante hepático (TH) não é uma situação rara, devendo ser diagnosticada e tratada, se possível, sem atraso. Apresentamos o caso de um homem de 69 anos que foi submetido a TH sem qualquer instabilidade, alterações vasculares, infeciosas ou do enxerto e que, após 15 meses, apresentou quadro de colangite com necessidade de colocação de stent na via biliar. Um ano depois, nova colangite com estenose do ducto principal esquerdo e pobreza periférica das vias biliares com falência do enxerto. O paciente foi submetido a todo o tratamento médico e endoscópico sem evolução positiva. Este caso ilustra o curso, por vezes assintomático e insidioso, da CI com subsequente falência do enxerto, apesar do tratamento endoscópico otimizado. O reconhecimento precoce e referenciação atempada são essenciais para que o retransplante seja uma opção a ser considerada.

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Palavras-chave: Complicações Pós-Operatórias; Doenças dos Ductos Biliares; Isquémia; Transplantação de Fígado/efeitos adversos.

Learning Points

1. Ischemic cholangiopathy should be considered in liver transplant recipients with cholestatic liver test abnormalities, recurrent cholangitis, or unexplained graft dysfunction, even in the absence of hepatic artery thrombosis.
2. Its clinical course may be insidious, with initially subtle biochemical or imaging abnormalities, and may progress despite apparently preserved vascular flow on Doppler ultrasound.
3. MRCP and ERCP are key tools for the diagnosis and characterization of non-anastomotic biliary strictures and associated peripheral biliary rarefaction in post-transplant ischemic cholangiopathy.
4. Early recognition, prompt biliary drainage, and timely referral to a transplant centre are essential, as some patients may ultimately require retransplantation despite optimal medical and endoscopic management.

Introduction

Liver transplantation is a life-saving treatment for patients with end-stage liver disease and selected other indications. Despite major advances in surgical technique, graft preservation, and post-transplant care, biliary complications remain an important source of morbidity after transplantation and may significantly affect graft and patient outcomes.[1,2]

Among post-transplant biliary complications, (NAS) represent a particularly challenging entity. Ischemic cholangiopathy refers to focal or diffuse bile duct injury caused by impaired blood supply, typically in the absence of hepatic artery thrombosis or stenosis.[2,3] This vulnerability is explained by the peculiar vascularization of the biliary tree, which depends almost exclusively on the peribiliary vascular plexus arising from the hepatic arterial circulation.[2,3] As a result, cholangiocytes are especially susceptible to ischemic injury, and damage to this microvascular network may lead to epithelial loss, biliary strictures, biliary casts, and impaired ductal regeneration.

The pathogenesis of ischemic cholangiopathy is complex and incompletely understood.[4-6] Ischemia-reperfusion injury, prolonged cold ischemia time, bile salt toxicity, and

immune-mediated mechanisms have all been implicated in its development.[2,3,7,8] Clinically, presentation may range from asymptomatic cholestatic liver enzyme abnormalities to recurrent cholangitis, jaundice, biliary pain, and, in severe cases, graft dysfunction or graft loss.[2,7,8] Imaging plays a central role in diagnosis, with magnetic resonance cholangiopancreatography being particularly useful for detecting intrahepatic strictures, biliary dilatation, biliary casts, and associated collections, while also helping to exclude other post-transplant biliary complications.[9,10]

Early recognition of ischemic cholangiopathy is essential because management is often complex and frequently requires a multidisciplinary approach involving medical, endoscopic, radiological, and sometimes surgical interventions. In more severe cases, re-transplantation may ultimately be required. We report a case of ischemic cholangitis in a liver transplant recipient, highlighting the diagnostic challenges and therapeutic implications of this uncommon but clinically significant post-transplant complication.

Case Report

A 69-year-old man with decompensated liver alcoholic cirrhosis, with 20 on MELD score, underwent orthotopic liver transplantation (LT) in 2016. 54 years old brain donor (DBD) from catastrophic haemorrhagic stroke, without any chronic disease, always stable in the intensive care unit (ICU) without any vasopressor support. Cold and warm ischemia time was 4 hours and 30 minutes, respectively. ABO isogrupal transplant was made with CMV positive donor/recipient (D+/R+). No blood transfusion was required, nor was reperfusion syndrome detected. He spent 48 hours at intensive care without a vasopressor. Doppler ultrasound documented a normal liver graft, with a normal hepatic artery and portal vein. The patient was transferred to the liver unit, with immunosuppressed drugs (corticosteroids and tacrolimus). Three weeks later, he was discharged, presenting normal liver enzymes and cholestatic parameters with 20 mg of oral prednisolone and 3 mg tacrolimus twice a day (tacrolimus level ~ 7 ng/mL). Serial Doppler ultrasound examinations were normal at first year post LT. CMV viral load always remained negative and adjusted prophylaxis was administered at the outpatient clinic. Fifteen months post LT, he developed progressive jaundice, pruritis and recurrent fever for 5 days. At the emergency room, he presented right upper pain and fever and he was hemodynamically stable. Lab analysis was: White blood cells (WBC) -15 000/uL; Total bilirubin 8 mg/dL, direct bilirubin 6 mg/dL, ALP- 540 U/L, gGT-223 U/L, AST/ALT -38/55 U/L, reactive -protein C (rPC)- 40 mg/L, INR-1.3, tacrolimus level- 6 ng/mL, DNA--CMV negative. Doppler ultrasound showed normal hepatic arterial flow velocity, patent portal vein and mild intrahepatic biliary dilation. At magnetic resonance cholangiopancreatography (MRCP), non-anastomotic strictures at main biliary duct were observed. Endoscopic retrograde cholangiopancreatography (ERCP) with biliary drainage was done with biliary stent. At hospital discharge, ursodeoxycholic acid was started. After 3 months, the stent was removed. Liver enzymes, cholestatic parameters and DNA-CMV load were normal during the outpatient clinical vigilance. Never had evidence clinical or analytical of alcohol recurrence. One year later, he presented with jaundice, pruritis, ascites and liver encephalopathy, with white blood cells (WBC) -3000/uL; total bilirubin 28 mg/dL, direct bilirubin 20 mg/dL, ALP-300 U/L, gGT-1120 U/L; AST/ALT -60/75 U/L, rP -3 mg/L, INR-2.1, tacrolimus level – 6.8 ng/mL, DNA-CMV negative. Ultrasound documented intrahepatic biliary dilation. MRCP confirmed NAS intrahepatic of the common bile duct (Fig. 1). ERCP confirmed the stricture and he was treated with

Figure 1: MRCP – non-anastomotic stricture left intrahepatic of the common bile duct (blue arrow).

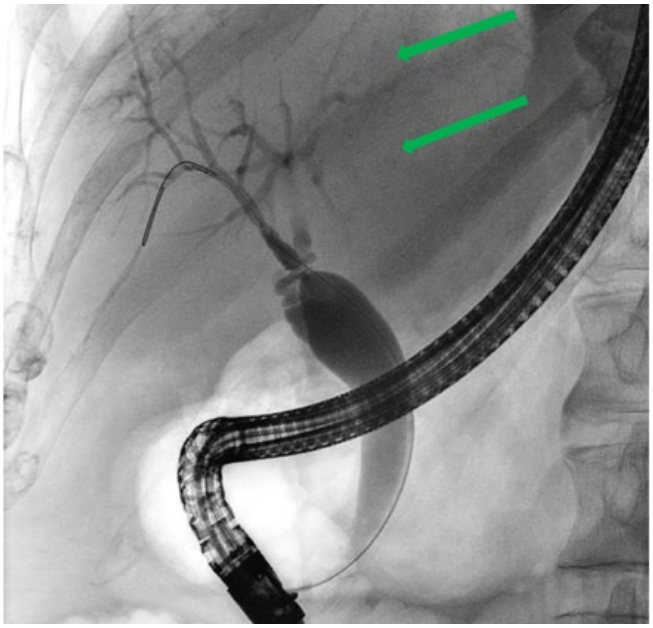

Figure 2: ERCP – Rarefaction of peripheral intrahepatic bile duct (green arrow).

stenting, without documentation of sludge but with rarefaction of peripheral intrahepatic bile duct (Fig. 2). Even with parenteral antibiotics, endoscopic decompression and optimal medical support, the patient at eighth day underwent septic shock with multiple organ system failure (MOSF) also with graft failure. He was supported in UCI but with no response to all standard care (Fig. 3). Due to this rapid and negative evolution re-transplantation was not possible to be considered. The patient died ten days after hospital admission.

Discussion

Liver transplant is a curative treatment for patients with end-stage liver disease but biliary complications are a major cause of morbidity or mortality with a negative impact on graft survival.[3,7,10] The frequency and severity of this pathology led some authors to name it the "Achilles heel" of liver transplantation, as the biliary system has only arterial supply.[3,11,12] The incidence of biliary complications range from 10%-15% in deceased donor liver transplantation and up 15% in living donor liver transplant settings.[13]

The biliary complications can be divided into anastomotic and non-anastomotic strictures. NAS is usually seen in association with ischemic cholangiopathy. The median time of NAS presentation is 6 months, although they can be present later on (10% at first year to 16% post LT at 10 years).[13,14] NAS can be divided due to biliary localization: main biliary duct branches (sub hilar or hilar) versus

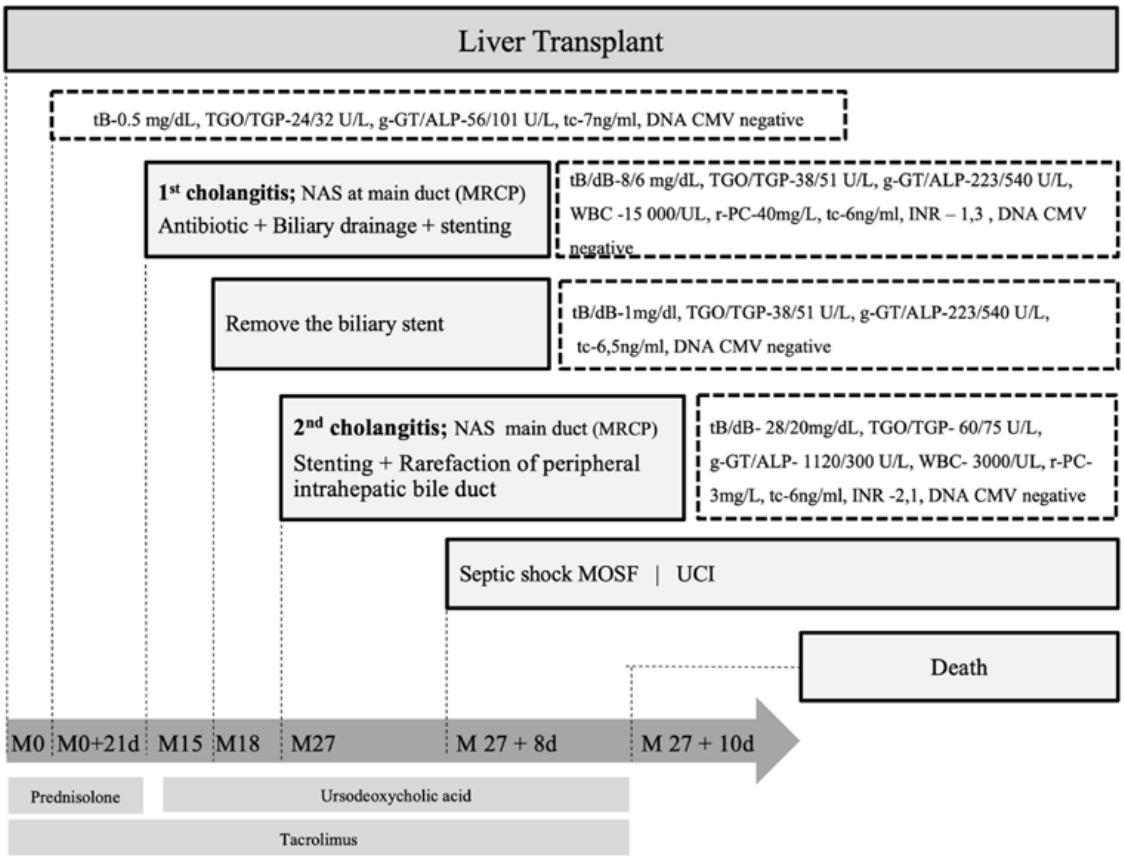

Figure 3: Case Report timeline.
M- month; d- day; tB- total bilirubin; dB- direct bilirubin; tc- tacrolimus level; MOSF - multiorganic systemic failure ; NAS- non-anastomotic stricture; UCI- intensive care unit.

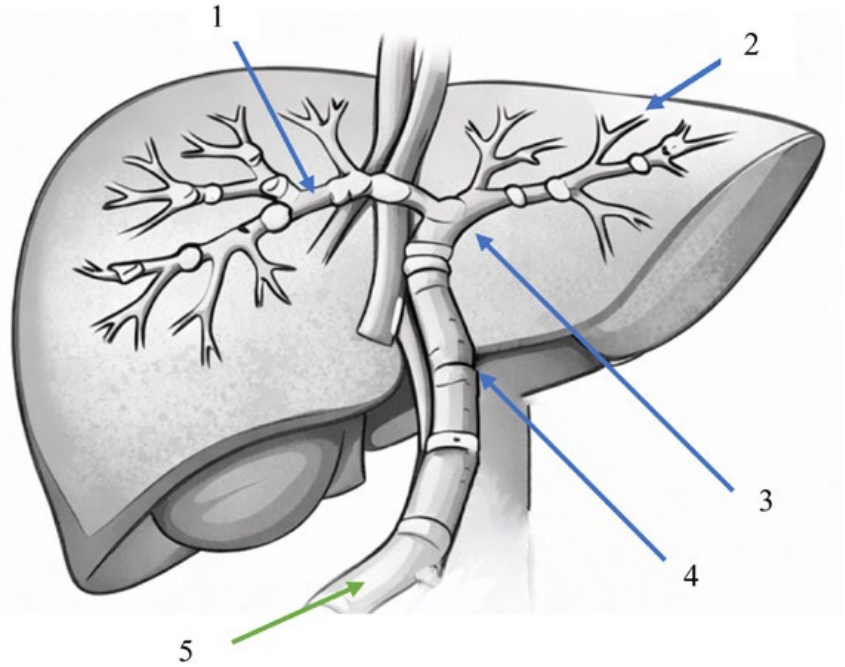

Figure 4: 1 - NAS intrahepatic duct; 2 - NAS peripheral biliar duct; 3 - NAS hilar duct; 4 - NAS extrahepatic main duct; 5 - AS.

peripheral intrahepatic duct (Fig. 4).[15] The majority of NAS occurs around the bifurcation or slightly below it. Early NAS, detected in the first year, are usually more central, whereas later NAS is more often detected in the liver periphery.[15]

For general physician or non-transplant hepatologist IC should be suspected in a liver transplant patient when there are subtle but progressive signs of biliary dysfunction. One of the earliest clues is a cholestatic pattern in liver tests, particularly a gradual rise in g-GT and alkaline phosphatase, without an elevation of transaminases. This may occur without jaundice in the early stages, which can delay recognition if one relies only on bilirubin value. As the disease progresses, patients may develop recurrent febrile episodes, usually reflecting intermittent bacterial cholangitis due to impaired bile drainage through damaged and strictured ducts. The patient can present jaundice, fever, right upper quadrant discomfort, bacteremia and an unexplained graft dysfunction. In the presence of unexplained graft dysfunction other causes must be ruled out, such as vascular complications (especially hepatic artery thrombosis), rejection, recurrent primary disease (PSC, PBC or IgG4 cholangitis), cholangiocarcinoma or CMV cholangiopathy.

IC is due to ischemic injury of the bile ducts, which depend almost entirely on the hepatic arterial blood supply, making them particularly vulnerable. IC often presents insidiously and asymptomatic. So, it is important to have a routine post-transplant surveillance even in patients without symptoms. US should be performed because it is an easy exam and can give indirect signs of IC. Further evaluation, particularly with MRCP, is essential to diagnosis and identification of the characteristic multifocal intrahepatic strictures.

Early recognition by a non-transplant hepatologist and rapid treatment of cholangitis can save the graft function and prevent its loss.[4] Urgent referral to a transplant centre is indicated in liver transplant recipients with established IC who demonstrate evidence of clinical, biochemical, or radiological progression, such as recurrency or severe episodes of cholangitis, particularly if with a poor response to antibiotics (it can suggest inadequate biliary drainage) and a high risk of sepsis, a rapid rise in cholestatic enzymes (ALP, GGT) or the development of jaundice (important warning sign), indicating progression of biliary injury.

Treatment of IC includes percutaneous drainage of biliary duct or biliary collection, antibiotics and antifungal treatments, endoscopic drainage with stenting, percutaneous transhepatic biliary drainage (PTBD) or a combination of both.[2,13] Unfortunately, IC strictures tend to be more diffuse, bilobar and with high predilection for smaller intrahepatic ducts, so it is more difficult to treat them with ERCP or PTBD.[4] Imaging findings such as multifocal intrahepatic strictures, biliary cast formation, or extensive ductal irregularity necessitate advanced endoscopic or percutaneous interventions that are typically available in specialized transplant centres. Failure of initial conservative or local management, as well as the development of systemic inflammatory response, sepsis, or organ dysfunction, must constitute also an indication for urgent referral. Early involvement of a transplant centre is essential to enable multidisciplinary management. This includes interventional biliary procedures, evaluation for potential re-transplantation and mitigating the risk of irreversible graft loss. An early communication and coordination with the transplant centre is crucial. A collaborative model of care facilitates the patient support as will improve graft and patient outcomes. ■

Contributorship Statement

DV – Study conceptualization, manuscript drafting, and critical revision.
MF – Critical revision and scientific contribution.
All authors approved the final version to be published.

Declaração de Contribuição

DV – Conceptualização do estudo, redação do manuscrito e revisão critica.
MF – Revisão critica e contribuição científica.
Todos os autores aprovaram a versão final a ser publicada.

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