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REVIEW

Liver Transplantation and Budd-Chiari Syndrome: When the Cause Becomes the Solution

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ABSTRACT

Budd-Chiari syndrome consists a rare medical entity which has an estimated incidence of 0.1 to 10 people per million every year. It is defined by the obstruction of the flow in the inferior vena cava or the hepatic veins. Various classifications have been proposed. So, it can be acute or chronic and primary or secondary. Iatrogenic, a subtype of secondary Budd-Chiari syndrome, is caused by various medical interventions, including liver transplantation. On the other hand, liver transplantation is the ultimate therapeutic management of Budd-Chiari syndrome. Finally, a medical paradox and a vicious circle has been created. Liver transplantation can potentially be both the cause and treatment of Budd-Chiari syndrome. Budd-Chiari syndrome is simultaneously the cause and complication of liver transplantation. Our aim is to describe this double role of liver transplantation in Budd-Chiari syndrome and to acknowledge that a high degree of clinical suspicion is necessary for the proper recognition and management of this life-threatening condition.

Keywords: liver; transplantation, Budd-Chiari, paradox.

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INTRODUCTION

Budd-Chiari syndrome (BCS) is a rare medical entity with an estimated incidence of 0.1 to 10 people *per* million every year (1). It is defined by the obstruction of the flow in the inferior vena cava (IVC) or the hepatic veins (HV) (2, 3).

Various classifications have been used for this syndrome. It can be either acute or chronic. The chronic form is more frequent and is characterized by signs of portal hypertension. On the other hand, the clinical presentation of acute BCS includes ascites, hepatomegaly and acute liver failure. The morphological division of BCS is truncal, radicular or veno-occlusive, which means that obstruction of the flow occurs in IVC, HV or small centrilobular veins, respectively (1). Finally, BCS is classified as either primary or secondary. Primary BCS is mostly a result of hematological disorders and hypercoagulable conditions. Secondary BCS appears due to invasion or extrinsic pressure of the veins from various reasons, including hepatocellular carcinoma (HCC), liver abscesses and cysts (1, 4).

Iatrogenic BCS can be described as secondary BCS and is caused by various medical interventions, of which hepatectomy seems to be the most common (5). It should be mentioned that orthotopic liver transplantation (OLT) also has been reported in the literature as a cause of this entity. Aucejo et al described three patients who underwent OLT due to HCC, primary biliary cirrhosis and hepatitis C (Table 1). The piggyback technique, which is used in OLT, seems to be responsible for the development of BCS. This happens when only two out of three recipient HV are used (6). It should be highlighted that the right HV (RHV) was the occluded vessel in all patients. The same location of the lesion was probably a result of the surgical technique. All patients in this case series manifested ascites. Diagnosis of BCS was conducted postoperatively by the use of ultrasonography, computed tomography and angiography. Treatment included angioplasty and stent placement. If left untreated, serious complications can occur, including graft failure, rejection and even death (7). Close attention is necessary concerning the anatomical and surgical features of caval anastomosis in order to prevent this rare complication (6).

Being a life-threatening medical condition, BCS treatment requires a multidisciplinary approach stepwise in order to control the clinical symptoms and the venous thrombosis, and to reestablish the liver venous drainage. The treatment varies from the conservative approach to surgical intervention. In the absence of contraindications, all patients should receive anticoagulation therapy even after radiological or surgical interventions (8). Initially, low molecular weight heparin is preferred, followed by vitamin K antagonists. Anticoagulation is considered to be sufficient controlling the mild type of BCS (9).

Vascular interventions aim to restore the blood flow, correcting the obstruction or creating a bypass. Percutaneous angioplasty with or without stenting is a viable treatment option for patients who have stenosis or occlusion of the HV or IVC. Several authors have found a satisfactory long-term efficacy and survival rate of this specific procedure, while the absence of anticoagulation therapy is related with higher rates of stenting occlusion (10, 11).

Compared to the above procedure, transjugular intrahepatic portosystemic stent shunt (TIPSS) is most frequently indicated for BCS in patients with acute liver failure, Rotterdam class III, or those who have failed medical therapy, previous hepatic venous stenting or diffuse HV thrombosis due to technical difficulty in maintaining venous patency. Given that BCS is a very

TABLE 1. Characteristics of patients presenting Budd-Chiari syndrome after liver transplantation

Study	Patient	Budd-Chiari syndrome					
		Cause	Symptom	Location	Diagnosis	Treatment	Recurrence
Aucejo *et al*, 2006 (6)	52y / M	LT for HCV, with Piggyback technique	Abdominal pain, distention, ascites	RHV	Vena cavography	Stent	Yes. Finally, free
	51y / F	LT for PBC, with Piggyback technique	Ascites, pleural effusions	RHV	US, CT	Angioplasty and stent	Yes. Finally, free
	54y / M	LT for HCC, with Piggyback technique	Ascites	RHV	CT	Angioplasty twice	Yes. Finally, free

M: male; LT: liver transplantation; HCV: hepatitis C virus; RHV: right hepatic vein; F: female; PBC: primary biliary cirrhosis; US: ultrasonography; CT: computed tomography; HCC: hepatocellular carcinoma.

TABLE 2. Characteristics of patients with Budd-Chiari syndrome who underwent liver transplantation

Study	Patient	Budd-Chiari syndrome					
		Cause	Symptom	Location	Diagnosis	Treatment	Recurrence
Yamada *et al*, 2006 (13)	3-39 y / 8 M, 1 F	Six patients had idiopathic BCS, one BCS due to lupus anticoagulant, one MPD, one hypereosinophilic syndrome	NR	NR	Doppler-US, CT, cavography	Four patients had non-surgical treatment with balloon dilatation, interventional thrombectomy and/or TIPSS before LT. Finally, all nine underwent LT	Two patients had metallic stent placement following balloon dilatation and interventional thrombectomy, one thrombolysis with local infusion of urokinase
Shimoda *et al*, 2007 (14)	40 y / F	HCC	NR	IVC, HV	Cavography	Multiple interventional procedure with stents. Finally, LT	No
Choi *et al*, 2010 (15)	41-50 y / 1 M, 3 F	Three patients had HCC, one had idiopathic BCS	Variceal bleeding. Uncontrolled ascites	IVC, HV	Doppler-US, CT, MRI	One patient had undergone mesoatrial 10 years before LT. Finally, all four underwent LT	One patient had biliary stricture treated with ERCP with dilatation and stent placement and one CMV infection
Sakçak *et al*, 2012 (16)	12 y / F	Hydatid cyst	Recurrent ascites and deterioration of liver function	IVC	NR	Stent. Finally, LT	No
Fukuda *et al*, 2013 (17)	34 y / F	Occlusion of mesoarial shunt	Fatigue, ascites, GI bleeding	IVC	CT, venography	LT	No
Yakci *et al*, 2015 (18)	12-32 y / 2 M, 2 F	NR	NR	IVC	Doppler-US, CT	LT	NR. 2 patients died in 5 m after biliary complications
Ara *et al*, 2016 (19)	Mean age 28.6±12.5 y / 18 M, 21 F	31 patients had idiopathic BCS, two echinococcus cysts, two HCC, one MPD, one hemangioendotheliom, one paroxysmal nocturnal hemoglobinuria, and one alveolar echinococcosis	Clinical manifestations of acute or chronic BCS, specific signs NR	NR	Doppler-US, CT	LT	No
Yang *et al*, 2017 (20)	10 y / M	After hepatectomy and biliary fistula	Ascites, esophageal varices, splenomegaly	MHV	Interventional angiography	Stent and hepatectomy. Finally, LT	No
Yagi *et al*, 2018 (21)	51 y / F	NR	Massive ascites	RHV, LHV, MHV	CTA, venography	TIPSS. Finally, LT	No
Yoon *et al*, 2019 (22)	36-53 y /1 M, 4 F 1 M	Idiopathic BCS. Two patients had also membranous obstruction of VC	Recurrent hepatic encephalopathy, variceal bleeding, ascites and hydrothorax	IVC	NR	LT	No
Aktas *et al*, 2021 (23)	Mean age 54,01±11,3 y / 18 M, 15 F	Three patients had MPD, 23 prothrombotic disorders, seven idiopathic	Recurrent hepatic encephalopathy episodes, refractory ascites, hepatorenal syndrome	25 patients in HV, seven PV thrombosis, one SIV obstruction	Doppler-US, CTA	20 patients had anti-coagulant therapy, two also TIPSS, 13 no therapy. Finally, all 33 underwent LT	No
Rocha-Santos *et al*, 2021 (24)	35 y / M	HCC	Ascites and hematemesis due to esophageal varices, mild jaundice	IVC	CT	TACE twice. Finally, LT	No

y: years, M: male; F: female; BCS: Budd-Chiari syndrome; MPD: myeloproliferative disorder; NR: not reported; US: ultrasonography; CT: computed tomography; TIPSS: transjugular-intrahepatic portosystemic stent shunt; LT: liver transplantation; HCC: hepatocellular carcinoma; IVC: inferior vena cava; HV; hepatic veins; MRI: magnetic resonance imaging; ERCP: endoscopic retrograde cholangiopancreatography; CMV: cytomegalovirus; GI: gastrointestinal; m: months; MHV: middle hepatic vein; RHV: right hepatic vein; LHV: left hepatic vein; CTA: computerized tomography angiography; VC: vena cava; PV: portal vein; SIV: small intrahepatic veins; TACE: transarterial chemoembolization.

rare entity, there is not enough consensus describing the five-year survival rate and mortality, which varies between 56.1% to 88% and 0% to 26.2%, respectively (12).

Finally, OLT is the ultimate therapeutic management of BCS (1, 13-24). Orthotopic liver transplantation was performed in patients with progressed liver failure, chronic or acute, due to

prothrombotic conditions (V Leiden mutation, protein c/s deficiency, antiphospholipid syndrome, etc), Myeloproliferative disease and lupus can occur due to space-occupying lesions such hydatid or echinococcus cyst, HCC, pericardial post-operative complications, or abscess; and bronchobiliary fistula (Table 2) (13-24). Their clinical presentation demonstrated signs of portal hypertension, such as ascites, esophageal varices or splenomegaly. Previous therapies such as hepatectomies and stents had been proved unsuccessful. Orthotopic liver transplantation should be considered when all other therapeutic approaches have failed. It is urgent in patients with fulminant hepatic failure. However, various complications can occur. These include graft failure or rejection, bleeding, renal failure and vascular disorders (25). In addition, these patients require chronic immune-suppressive and anticoagulant therapy (1). In the context of the anticoagulation therapy, Aktas et al reported that 13 patients who did not receive anti-coagulants prior to liver transplantation (LT) had bleeding complications, but the authors could not give further information (23). Patients with BCS who underwent OLT had an estimated five-year survival of 90% (26). Also, comparing patients who underwent LT due to BCS and those who underwent LT due to other etiologies, there is no statistical difference between the two groups (23).

Based on the rarity of the nature of post-transplantation BCS, there are no clear data regarding the preventive measures. Interpreting the aforementioned data we can assume thrombophilia investigation, long-term anticoagulation therapy, the type of the anastomosis as well as stenting at the area of the anastomosis could lead to limited rates of stenosis or occlusion of the HV avoiding post-transplantation BCS. Several authors proposed heparin in the early post-operative period, followed by warfarin, acetylsalicylic acid, clopidogrel or combination of them (19, 23). Identifying the underlying disease is mandatory to determine the proper anticoagulant therapy. To avoid post-LT thrombosis, Ara *et al* reported that the INR should kept between 1.5 and 2, especially in patients with prothrombotic factors. Besides patients' thrombotic tendency, Yamada et al reported that BCS recurrence was related to the surgical technique. In addition, once BCS occurs after transplantation, treatment options such as percutaneous catheterization with thrombolytic agents, *e.g.*, urokinase, percutaneous balloon angioplasty, use of stenting and TIPSS have been described in the literature, but there was not enough consensus regarding their clinical value (13). Certainly, early recognition of the potential stricture and possible BCS recurrence is the most crucial factor. Consequently, further clinical trials should be performed elucidating the preventive factors and interventional techniques as well as their outcome. ❑

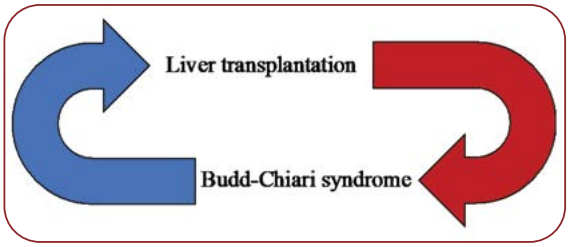

FIGURE 1. Medical paradox as a vicious circle between liver transplantation and Budd-Chiari syndrome (BCS). Liver transplantation may potentially be both the cause and treatment of BCS, and Budd-Chiari syndrome may simultaneously be the cause and complication of liver transplantation

CONCLUSION

In conclusion, a medical paradox and a vicious circle has been created. As aforementioned, OLT can potentially be both the cause and treatment of BCS. Budd-Chiari syndrome is simultaneously the cause and complication of OLT (Figure 1). It would be even more interesting if this happened to the same patient, that is, appearance of BCS after OLT and re-transplantation due to the BCS. To date, no such cases have been reported. Thus, great attention should be given to the techniques which are being used in OLT, in order to prevent BCS development. High clinical suspicion is necessary for the proper recognition and management of this life-threatening condition. ❑

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