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CASE REPORT

Severe takotsubo cardiomyopathy following orthotopic liver transplantation: A case series

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Summary
Introduction: Acute decompensated heart failure is a known complication following orthotopic liver transplant. Among those, there are some cases of takostubo type cardiomyopathy (TC), commonly referred to as ''broken heart syndrome''. While the exact mechanism of TC is unknown, it frequently proceeds a physical or emotional stressor. Here we present a series of seven cases of TC following orthotopic liver transplant.
Methods: A retrospective chart review was conducted on 454 patients were identified as having post-operative cardiac dysfunction in the setting of orthotopic liver transplantation. Of those, seven were identified as having TC based on apical ballooning, acute heart failure without evidence of coronary artery disease. All seven underwent pre-operative cardiac evaluation per protocol. Extensive chart review was performed on the seven patients to identify pre and post-operative qualities.

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Results: At this single institution, TC affected 7/454 patients, reflecting an incidence of 1.5% over the eight year study period. Of the seven patients affected, one expired. Patients represented a mix of emergent and scheduled transplantation in the setting of end stage liver disease (ESLD). Patients had a mix of etiologies related to their ELSD including hepatitis C, alcoholic cirrhosis, and non-alcoholic steatohepatitis.
Discussion: It is important to recognize TC as a potential complication following liver transplantation so as to detect cases earlier in the disease course and begin early goal-directed care.

Introduction

As liver transplantation has become a more common procedure, new and unknown complications are presenting themselves. One such complication is acutely decompensated heart failure, which affects approximately 3—7% of patients undergoing liver transplant in the post-operative period and results in a nearly 45% mortality [1,2]. Retrospective and prospective studies have described decompensated heart failure as a complication in individuals without previous cardiac history [3,4,5,1,2]. Among cases of acutely decompensated heart failure, there have been several case reports of takotsubo type cardiomyopathy within the first two weeks post liver transplant [6,7]. Takotsubo cardiomyopathy is defined as an acute, and frequently reversible, heart failure syndrome without obstructive coronary disease [8].

In the evaluation for liver transplantation, patients undergo an extensive cardiac workup not only for pre-operative risk stratification, but also because this population has a higher than average risk of cardiac complications following surgery [9]. Interestingly, many patients who have normal cardiac evaluations — including echocardiogram and cardiac catheterization — develop heart failure in the post-transplant period [2]. Liver transplantation induces stress on the body, leading to the release of catecholamines and inflammatory mediators, which may lead to a decompensation of a cardiovascular system with already diminished reserves [1].

The aim of this series is to present seven cases of acutely decompensated heart failure leading to cardiogenic shock attributed to takotsubo cardiomyopathy in post liver transplant patients at a single center.

Methods

A total of 454 patients were identified who underwent liver transplant in a single center from 2006 to 2014 and met the following inclusion criteria: age greater than 18-years old, liver transplantation, and post-operative cardiac dysfunction. Cardiac dysfunction was defined as suffering from cardiogenic shock, hypotension, or cardiomyopathy following transplantation during the same hospitalization. An echocardiogram ejection fraction of 35% or less was used to identify cardiomyopathy. Takotsubo was identified based on apical ballooning seen on either echocardiogram or cardiac catheterization in the absence of coronary artery disease. Of the 454 patients meeting inclusion criteria, seven were identified as having takotsubo type cardiomyopathy as the etiology of their cardiogenic shock based on the above criteria. Extensive chart review was conducted on these patients through the system-wide electronic medical record. Pre and post-operative cardiac function and liver transplant indications were identified as seen in Table 1.

Case 1

Patient One is a 59 year-old male with a history of hepatitis C cirrhosis and alcohol use complicated by hepatocellular carcinoma who underwent scheduled orthotopic liver transplantation (OLT) at a Model for End Stage Liver Disease (MELD) Score of 28. On pre-transplant evaluation, a Cardiolite stress test was performed, which was negative for ischemia; a transthoracic echocardiogram at this time showed an ejection fraction of 55—60% with mild global chamber dilatation. Shortly after transplantation, the patient developed a hepatic artery thrombosis and sepsis due to abscess formation requiring re-transplantation. After the second liver transplant, he suffered from post-operative hypotension and ventricular ectopy and subsequently went into heart failure requiring inotropic support. A repeat echocardiogram at this time showed an EF of 20—25% with apical-septal and apical-lateral wall segment hypokinesis. In addition, he had a troponin elevation with peak of 0.43 mg/dL. He underwent ischemic workup in the form of a nuclear stress test, which showed left ventricular dilatation and fixed reduction of activity of the lateral wall of LV without reversible abnormalities. This patient was started on goal-directed heart failure medications (beta-blocker, ACE inhibitor). Follow-up echocardiography demonstrated an EF of 55—60% two weeks later without residual structural changes.

Case 2

Patient Two is a 55 year old female with end stage liver disease (ESLD) secondary to hepatitis C who underwent liver transplantation at a MELD of 31. She was found to have an ejection fraction of 65% with severe left ventricular hypertrophy on pre-operative echocardiogram. She had no

Table 1 Patient characteristics.

Case No.	Age	Gender	Date of Tx	Death	Etiology of liver Ds	MELD	Urgency	Pre-transplant EF	Post-transplant EF	Follow-up EF	Outcome
1	59	M	5/15/2009, 7/19/2009	N	Hepatitis C, Etoh, HCC	28	Scheduled	55—60	20	60	Recovery
2	55	F	12/16/2008	N	Hepatitis C	31	Scheduled	65 LVH	25—30	50—55	Recovery
3	47	F	3/31/2010	N	Autoimmune	8	Scheduled	65	15—20	60	Recovery
4	51	F	05/28/10, 06/01/10	Y- 14 days	Alcoholic	28	Scheduled	50, valvular dysfn	10—15	10—15	Death
5	49	M	7/26/2010	N	Hepatitis C	30	Emergent	55-60	20—25	55—60	Recovery
6	68	F	4/6/2012	N	Hepatitis C	29	Emergent	65	25	55	Recovery
7	51	M	8/12/2012	N	NASH	28	Scheduled	60—65	10	50—55	Recovery

immediate post-operative complications and was discharged to an acute rehabilitation facility. She was subsequently re-admitted for an acute kidney injury and dyspnea. An echocardiogram was obtained, which revealed an ejection fraction of 10% along with severe global hypokinesis, moderate to severe mitral regurgitation, moderate tricuspid regurgitation, and moderate pulmonic regurgitation. A left heart catheterization showed an ejection fraction of 20% with non-obstructive coronary artery disease. An endometrial biopsy was obtained, which showed evidence of iron overload and fibrosis despite a normal serum ferritin. This patient was started on goal-directed heart failure medication and ultimately sent for further genetic workup for hemochromatosis. Follow-up echocardiogram demonstrated an EF of 50-55% with no wall motion or valvular abnormalities.

Case 3

Patient Three is a 47 year old female with past medical history of primary biliary cholangitis and Sjrogrens disease who underwent scheduled liver transplantation with a MELD of eight. Transplant was indicated for cirrhosis due to primary biliary cholangitis complicated by autoimmune hepatitis and hepatocellular carcinoma. Cardiac history is significant only for one episode of chest pain for which she had a negative Cardiolite stress test. Her ejection fraction was 65% with normal chamber sizes and moderate tricuspid regurgitation on pre-operative echocardiogram. On post-operative day one, she developed shortness of breath, hypotension, and chest pain. A repeat echocardiogram at this time showed an EF of 15—20%, severely dilated left ventricle, and severe global hypokinesis of the left ventricle. In addition, she had a troponin elevation to 0.44 ng/dL. She underwent left heart catheterization, which showed no evidence of coronary artery disease, but rather yielded severe apical hypokinesis in all segments. She recovered quickly from the liver transplant and was discharged home. On follow-up echocardiogram, ejection fraction was 60% without any wall motion abnormalities. Seven years after transplantation, she has had no recurrence of chest pain or heart failure symptoms and continues to have a grossly normal echocardiogram.

Case 4

Patient Four is a 51 year old female with alcoholic cirrhosis with MELD Score of 28 who underwent scheduled liver transplantation. She had no known cardiac history prior to transplantation. On pre-operative evaluation, her ejection fraction was found to be low-normal at 45—50% with aortic cusp sclerosis and moderate mitral regurgitation; she had no symptoms of heart failure. Within 24 hours of transplantation, she showed signs of graft failure and subsequently went into fulminant liver failure necessitating a second emergent transplant. After her second transplant, she did well for approximately 10 hours before becoming hypotensive. Repeat echocardiogram at this time showed an ejection fraction of 10—15% with global hypokinesis and biventricular dilatation. At this time, she was noted to have elevated central venous pressure (CVP) and associated end-organ failure as manifested by hepatic congestion, encephalopathy, and anuric renal failure in addition to heart failure in the setting of cardiogenic shock. As such, she was emergently placed on veno-arterial extracorporeal membrane oxygenation (ECMO) along with intra-aortic balloon pump support. ECMO support was complicated by bleeding, and she was de-cannulated with continuation of the intra-aortic balloon pump and aggressive presser support. After several days of no improvement, supportive measures were withdrawn and she expired.

Case 5

Patient Five is a 49 year old gentleman with end stage liver disease secondary to hepatitis C with a MELD Score of 29 who underwent emergent transplantation. On pre-operative evaluation, his ejection fraction was 55—60% without significant motion or valvular abnormalities. Several days after transplantation, he became hypotensive and he had yet to regain consciousness following the procedure. An echocardiogram was obtained with ejection fraction of 20—25% with dilated right and left ventricles. He required presser support during this time for persistent hypotension. He continued to have altered mental status, which was attributed to central pontine myelinolysis. He was discharged to a long-term care facility where he ultimately regained consciousness.

Shortly thereafter, he was transferred to acute rehabilitation, where he was re-admitted secondary to increased ascites and volume overload. On repeat echocardiogram, he was found to have an EF of 30—35% with a moderately dilated left ventricle. Repeat echocardiograms over the subsequent six months showed an EF of 55-60%; he has had no further heart failure symptoms.

Case 6

Patient Six is a 68 year old woman with history of diabetes mellitus and cirrhosis secondary to Hepatitis C with a MELD Score of 29 who underwent urgent liver transplantation in the setting of acute decompensated liver failure. As part of the pre-transplant work up, she underwent right and left heart catheterization, which showed no evidence of flow- limiting coronary artery disease and low pulmonary vascular resistance. Her ejection fraction was 65%. Her post-operative course was complicated by biliary strictures and choledocolithiasis requiring multiple procedures. Within a week of transplant, she developed increased shortness of breath and volume overload leading to respiratory distress necessitating emergent intubation. An echocardiogram was obtained that showed an EF 25—30% with moderate global hypokinesis of the left ventricle and ballooning. She was treated conservatively with beta blockade. Follow-up echocardiography showed slow resolution of cardiomyopathy with return to normal EF of 55% without residual wall motion abnormalities; the patient had no further symptoms of heart failure following discharge.

Case 7

Patient Seven is a 51 year old male with past medical history significant for diabetes mellitus type II and COPD who underwent scheduled transplantation due to liver failure secondary to non-alcoholic steatohepatitis (NASH) at a MELD of 28. Pre-operative left heart catheterization showed no obstructive coronary artery disease and an EF of 60%. He initially did well after transplantation and was able to be extubated. The following day, however, he became hypotensive and hypoxic requiring emergent intubation. Shortly thereafter, he became fluid overloaded with cool extremities. An echocardiogram was obtained, which showed an EF of 10%, a restrictive left ventricular diastolic filling pattern with an enlarged right ventricle, and mild to moderate mitral regurgitation. In addition, he had a troponin leak with peak levels at 2.0 ng/dL. He underwent right and left heart catheterization at this time, which showed no evidence of coronary artery disease, but with severe LV dysfunction consistent with stress- induced cardiomyopathy. He went into cardiogenic shock requiring presser support with end-organ damage as evidenced by acute renal failure and encephalopathy. He was evaluated for ECMO, but was perfusing well and ultimately recovered from the shock state without external support. Repeat echocardiograms within the month following transplant showed normalization of the ejection fraction without residual wall motion abnormalities.

Discussion

Out of 454 patients who underwent liver transplantation, seven were complicated by post-operative takotsubo cardiomyopathy, representing an incidence of 1.5% over the eight year time period. Patients represented a variety of etiologies of ESLD as well as timing of surgery. Patients' baseline characteristics and post-operative findings are summarized in Table 1. Of the seven patients, one expired.

Our case series demonstrates seven cases of acute decompensated heart failure post liver transplantation. Six of seven transplant recipients developed a classic presentation of takotsubo cardiomyopathy following OLT and the seventh seems to have been complicated by infiltrative disease, though there was no follow-up. All patients underwent thorough pre-transplant work up, many of them undergoing left and/or right heart catheterization. Spare one patient with mild valvular dysfunction, all patients had normal echocardiograms prior to transplantation. All patients were ruled out for ischemia as the cause of cardiac dysfunction and through process of exclusion, were diagnosed with takostubo type cardiomyopathy as the cause of their cardiogenic shock. This case series represents a variety of patients including both patients requiring emergent transplantation in the setting of fulminant liver failure as well as those on whom the procedure was done as they came up on the transplant list. This finding suggests that the urgency of the procedure does not correlate with post-procedure cardiomyopathy.

A review of the literature yields few reports of takotsubo cardiomyopathy following liver transplant. Lee et al. published the first case report in 2007, with cardiogenic shock presenting several hours after transplantation attributed to takostubo cardiomyopathy [10]. Of the subsequent reports, one resolved with the use of left ventricular assist device (LVAD) [11]. One presented as cardiac arrest immediately after transplantation [12]. Two cases at Albert Einstein Hospital presented as cardiac arrest following transplantation, subsequently noted to have apical ballooning on echocardiography, which resolved completely [13]. Two cases were described in patients with lobe transplantation, and both resulted in death [14]. One case reports intra-operative apical ballooning, which has been commonly reported in other vascular procedures [15]. Gaivan et al. (2018) have reported the most comprehensive series of patients with Takotsubo cardiomyopathy following solid organ transplant at two transplant centers, and again propose the use of ventricular assist devices in the acute setting of cardiogenic shock [16]. Our series, however, presents the first single-center compilation of cases with similar diagnoses.

While our series is unique in that we describe seven distinct cases of cardiogenic shock, all attributed to takotsubo, and all in the setting of liver transplantation, it is not without limitations. Data reviewed only spans 12 years during the growth of a transplant program. In addition, we do not have access to significant amounts of follow-up data, as patients frequently went to cardiologists outside of the hospital's electronic medical record system. The number of cases as compared to the total number of transplants,

however, remains noteworthy and certainly warrants further investigation. At present, there is no standardized post-transplant evaluation of cardiac function at this institution. Given the findings of this study as well as a review of the literature, it begs the question of the utility of routine post-transplant echocardiography to evaluate cardiac function so as to better identify patients who are at risk of developing cardiogenic shock in the post-transplant period. A future study implementing post-transplant echocardiography and evaluating its' potential risks and benefits would help to clarify whether or not it aids in early detection and improves patient outcomes. Regardless, we believe that early echocardiography in presence of a new shock state following OLT is imperative to help guide early therapies.

The pathophysiology of takotsubo cardiomyopathy is not firmly established, but evidence suggests it is multifactorial and directly related to catecholamine excess and a hyperstimulation of the sympathetic nervous system [17]. The diagnosis of this condition is based on clinical manifestations, ECG, and echocardiogram findings [6]. Optimal management of takotsubo cardiomyopathy in the acute setting is similar to that of patients with acute coronary syndrome (ACS) 13 so as to not miss an MI. Current long-term options include beta-blockers, ACE inhibitors, and diuretics [17]. For sub-acute and long-term care, the recovery time can vary between several days to several weeks [17]. Anticoagulation therapy should be considered in patients with severe hypokinesis that persists after two to three days due to reports of thromboembolism in this condition [17]. Other long-term treatment strategies include beta-blockade and combined alpha and beta blockade due to the relationship between this condition and a catecholamine surge, but there is scant data demonstrating the efficacy of these options [17].

The relationship between takotsubo cardiomyopathy and liver transplantation remains just as vague. Leading hypotheses revolve around the concept of ''hyperdynamic circulation:'' increased cardiac output coupled with decreased systemic vascular resistance [5,7]. A cirrhotic patient requiring liver transplantation has been subject to drastic physiologic cardiovascular changes, which leads to a form of cardiac remodeling termed ''cirrhotic cardiomyopathy'' as the cirrhotic liver augments blood flow, thus affecting both preload and afterload. It has been shown in animal models that a cirrhotic heart has less cardiac preload reserve, which reflects contractility [22]. Humans with cirrhosis have been shown to have an increased prevalence of both diastolic and systolic dysfunction, which is associated with the cirrhosis in the absence of alcoholic cardiomyopathy and ischemic cardiomyopathy [22]. What remains curious is the manifestation of takotsubo following transplantation, when blood flow is theoretically improved. This may indicate that the operation itself is the stressor that brings on takotsubo cardiomyopathy.

In conclusion, takotsubo cardiomyopathy represents 1-2% of patients who present with ACS, [17] but there are very few reports of this condition occurring among post-operative liver transplantation patients. Takotsubo cardiomyopathy must be considered as a possible cause of heart failure in liver transplant patients. With increased awareness, diagnosis of this condition and early intervention with goal-directed therapies can lead to improved clinical management and long-term prognosis

Disclosure of interest

The authors declare that they have no competing interest.

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