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Single Case

An Emphasis on Screening to Detect Liver Cirrhosis and Hepatocellular Carcinoma in Patients Having Undergone the Fontan Procedure in Early Childhood

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Fontan procedure · Hypoplastic left ventricle · Fontan-associated liver disease

Abstract
The Fontan procedure is a surgical procedure for patients with single-ventricle anatomy that results in the flow of systemic venous blood to the lungs without passing through a ventricle. Before the 1970s, most children with single-ventricle anatomy failed to survive into adulthood. With the introduction of the Fontan procedure, and its many modifications, the survival rate of these patients improved exponentially. With patients surviving longer, complications from this procedure are being documented for the first time. Cardiovascular complications are expected early on and are well studied. More serious are the non-cardiovascular complications in patients who survive into adulthood. The biggest entity is Fontan-associated liver disease (FALD) which needs thorough monitoring to screen for hepatocellular carcinoma (HCC). FALD includes

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chronic passive congestion, liver cirrhosis, and HCC. Once cirrhosis develops, monitoring with annual liver function tests, AFP, and abdominal ultrasonography need to occur to screen for HCC. Patients may need to be evaluated for combined heart-liver transplantation. Strict guidelines need to be developed for monitoring and surveillance of these patients to prevent late-stage complications. Herein, we report a unique case of FALD in a young female presenting two decades after the procedure with variceal bleeding.

Introduction

The Fontan procedure was first performed in 1968 by Dr. Francois Marie Fontan but reported in 1971. The procedure was performed for tricuspid atresia and was expanded later for patients with single-ventricle anatomy. Prior to the development of this procedure, single-ventricle anatomy was universally lethal [1]. The 10-year survival rate for single-ventricle anatomy post-Fontan procedure is about 79% [1]. These patients experience severe hypoxemia at birth due to the mixing of arterial and venous circulation. The Fontan procedure separates these two circuits and allows systemic venous return directly to the pulmonary arteries, avoiding the right ventricle altogether. Several revisions were made over the years to this procedure, with The Modified Fontan Repair being the most commonly used. The concept is to direct venous blood from superior vena cava (SVC) and inferior vena cava (IVC) directly into right pulmonary artery thus bypassing the right ventricle altogether. The procedure is done in two stages to avoid complications like pulmonary lymphatic congestion, pleural effusions due to sudden increase in circulation to the lungs. The first stage or hemi-Fontan procedure involves connecting SVC to pulmonary artery. Patient remains cyanotic after the hemi-Fontan procedure as blood from IVC is not directed to the lungs yet. During second stage, SVC is connected to IVC through a conduit completing the Fontan procedure. Thereafter, right ventricle takes over the function of pumping blood to rest of the body [2].

With the modified Fontan procedure, more children are surviving into adulthood, thus unveiling late complications in multiple organ systems. Such complications include heart failure, arrhythmias, thromboembolic events, pleural effusions, and Fontan-associated liver disease (FALD) which includes portal hypertension, hepatic fibrosis, and ultimately hepatocellular carcinoma (HCC) [3, 4]. We present the case of a 27-year-old female who underwent modified Fontan procedure at 5 years of age and subsequently developed FALD.

Case Description

A 27-year-old female with history of congenital heart disease (CHD) with single-ventricle anatomy, underwent modified Fontan procedure at the age of 5 years presented to the hospital with sudden onset of abdominal pain, coffee ground emesis, and black tarry stools. She was born with a double outlet right ventricle, a straddling mitral valve, a hypoplastic left ventricle, and pulmonary atresia. Her condition was diagnosed in early infancy due to cyanosis. She

underwent a right modified Blalock-Taussig shunt in early infancy and a hemi-Fontan procedure with atrial septectomy at the age of 2 years. She then underwent completion of Fontan at the age of 3 years, and placement of epicardial ventricular lead pacemaker due to bradycardia at the age of 5 years. Due to a transient ischemic attack, the Fontan fenestration was closed at the age of 20. At this time, she was lost to follow up and stopped taking her warfarin.

At the age of 27 years, she presented to the hospital with sudden-onset abdominal pain, coffee ground emesis, and black tarry stool of a few hours' duration. Her pain was localized to the epigastric area, dull aching in nature, non-radiating, 8/10 in intensity, constant, with no aggravating or relieving factors. She denied alcohol or NSAID use and was not on anticoagulation or antiplatelet drugs at the time of presentation. She denied having a similar episode in the past.

On arrival, her blood pressure was 90/50 mm Hg, heart rate 100 beats/min, afebrile, saturating 92% on room air. Her body mass index was 26.6. On abdominal examination, she had tenderness in the mid-epigastric region, positive bowel sounds, no distention, and no guarding or rigidity. Rectal examination revealed tarry black stool. Laboratory studies are mentioned in Table 1. Urine pregnancy test was negative.

After stabilizing the patient with intravenous fluids and intravenous proton pump inhibitors, emergent endoscopy was done revealing single 10-mm clean based nonbleeding ulcer in the antrum, 1 cord of grade III varices were seen in the lower third of the esophagus as shown in Figure 1. There were stigmata of recent bleeding (red wale sign), so three bands were applied for endoscopic variceal ligation to achieve hemostasis. The patient was subsequently treated for variceal bleeding with octreotide, and her bleeding resolved. An abdominal ultrasound showed a heterogenous appearance of the liver with nodular contour. Computed tomography (CT) of the abdomen with IV contrast showed a nodular liver with heterogenous enhancement and splenomegaly with no evidence of focal liver lesions as shown in Figure 2. Chronic liver disease workup was negative for viral hepatitis panel and autoimmune liver diseases. Right hepatic lobe core biopsy was performed which showed cirrhosis, chronic passive congestion with sinusoidal dilatation and sinusoidal fibrosis consistent with FALD as shown in Figure 3–5. Hepatocytes are well preserved. Periportal and centrilobular sclerosis was seen. No lobular inflammation or hepatocyte necrosis was seen. Her MELD score was 9 and Child-Pugh score was 5. Echocardiogram showed moderately enlarged right ventricle with right-sided aortic arch indicating transposition of great vessels. A shunt was noted in the right atrium indicating atrial septal defect. She was subsequently discharged from the hospital to follow up with the Hepatology Clinic for surveillance of esophageal varices and HCC.

Discussion

Single ventricle defects are rare and occur in about 5 out of every 100,000 live births [5]. Incidence of liver disease is almost universal. FALD is a hepatic disorder arising from hemodynamic changes following the Fontan procedure performed for single-ventricle anatomy. The main predictor of FALD is the time since surgery. Patients are 4.4 and 9 times at risk of having hepatic complications 11–15 years and 16–20 years after surgery, respectively [6]. In

our case, patient first developed FALD manifestations at the age of 27 years. Age at onset, clinical manifestations, and the nature of presentation are highly variable. Manifestations range from liver fibrosis to cirrhosis to HCC. Cases of HCC were recorded as early as 16 years of age [7].

The pathogenesis of liver fibrosis in this population is believed to be multifactorial: (i) birth-related injury from single ventricle, and (ii) low cardiac output leading to chronic hypoxic injury which may trigger inflammation and subsequent damage leading to fibrosis, (iii) after the Fontan procedure, systemic venous pressures increase 3–4-fold that of normal leading to elevated central venous pressures and mesenteric vascular resistance. These elevated pressures prevent the liver from draining effectively which leads to chronic venous congestion, sinusoidal dilation, and ultimately, hypoxia of the centrilobular hepatocytes [8]. At the molecular level, hepatic stellate cells and fibroblasts are activated, and TGF-beta drives the process forward leading to liver fibrosis [9]. Centrilobular fibrosis and sinusoidal fibrosis are pathognomonic liver histologic findings in FALD patients [10]. In our case, the liver biopsy demonstrated sinusoidal dilatation and fibrosis due to chronic congestion. Ghaferi and Hutchins [11] demonstrated that chronically elevated right heart pressures are the only common findings in patients who die post-Fontan procedure.

As increasing numbers of Fontan procedure survivors are reaching adulthood, a greater number of complications is expected. Guidelines must be established for the screening of liver fibrosis and HCC in this population. What makes assessment of liver dysfunction so difficult in this population is that these patients usually have only mild abnormalities in their lab work, even when with advanced disease [4]. As in our case, patient had changes of hepatic damage in the form of sinusoidal dilation, fibrosis and cirrhosis with no significant lab abnormalities. However, despite its limited utility, experts agree that aminotransferases, alkaline phosphatase, gamma-glutamyl transferase, bilirubin, coagulation studies, albumin, and total protein should still be assessed. In addition, a screening test for hepatitis B and hepatitis C should also be performed. Liver biopsy is the gold standard for diagnosis of FALD.

For patients who already developed cirrhosis, platelet count less than 150,000/μL, low serum albumin, and MELD score are some indicators of poor prognosis. As most of the Fontan patients are on anticoagulation, MELD score can be an overestimate. MELD-XI has been created to overcome this problem which excludes INR in MELD score calculation [12]. In the VAST study, a retrospective cohort study on 73 patients, the authors demonstrated a relationship between VAST score (1 point each for varices, ascites, splenomegaly, thrombocythemia), indicating features of portal hypertension and risk of major adverse events. Patients with a VAST score ≥2 have 9-fold increased risk of having a major event like death, organ transplant, or HCC [13]. Our patient presented with VAST score 2 and is considered high risk for major events according to this study.

In addition to being at increased risk for chronic passive congestion leading to cardiac cirrhosis, hepatic adenoma or portal hypertension, patients who underwent the Fontan procedure are also at increased risk for malignant liver lesions based on autopsy findings from patients who died after the Fontan procedure [11]. Therefore, additional screening with a serum alpha fetoprotein and liver imaging, either with ultrasound, elastography, CT, or magnetic resonance, is required. Approximately 98% of patients exhibit abnormal liver enhancement

on imaging like CT or MRI. Screening with imaging every 4–12 months is proven to be cost effective. Despite multiple improvisations in the Fontan procedure, patients tend to develop ventricular failure needing cardiac transplantation. Considering the increasing number of patients developing liver failure and malignant liver lesions, certain patients might be candidates for combined heart liver transplant. Patients with low Child-Pugh class A score and MELD score (<12) with failing Fontan circulation must be referred for combined heart liver transplantation. Liver transplant alone is to be considered in patients with cirrhosis and MELD score ≥15 or those with complications like ascites, variceal bleeding, or hepatic encephalopathy [10]. One-year mortality after combined heart liver transplant are very promising [14].

There are now more adults living with CHD than children living with CHD [15]. This has been made possible through life-saving surgeries such as the Fontan procedure. Adults living with the Fontan procedure are a unique population. As more adults are reaching adulthood, liver complications are being increasingly recognized like liver cirrhosis, complications from portal hypertension, HCC. Regular monitoring and surveillance are necessary to prevent late-stage complications, and further research is needed in order to establish guidelines and better manage care of these patients.

Statement of Ethics

Written informed consent was obtained from the patient to publish the case.

Conflict of Interest Statement

The authors certify that they have NO affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge, or beliefs) in the subject matter or materials discussed in this work.

Author Contributions

Madala S. followed the patient and drafted the manuscript. MacDougall K. helped draft the manuscript. Morvillo G. provided the images of liver biopsy. Gurala D., Gumaste V., and Polavarapu A. corrected, read, and approved the final manuscript.

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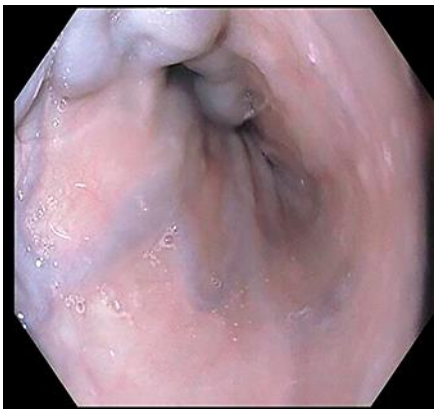

Fig. 1. Upper endoscopy image showing one cord of grade III esophageal varix.

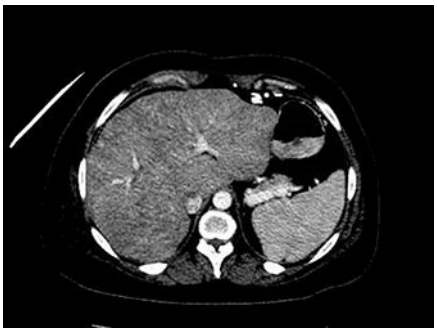

Fig. 2. Axial section of CT abdomen with IV contrast showing nodular contour of the liver with heterogeneous enhancement and mild splenomegaly.

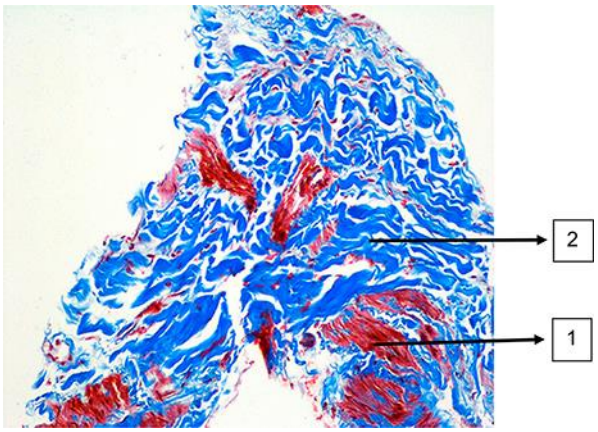

Fig. 3. Picture of liver biopsy showing hepatic nodule (1) surrounded by fibrosis (2). Magnification ×200.

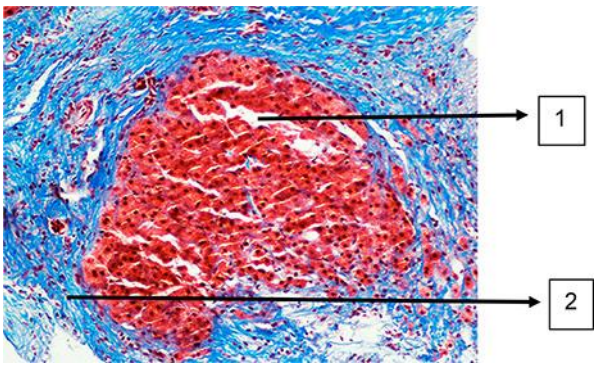

Fig. 4. Sinusoidal dilation (1) and sinusoidal fibrosis. Masson's trichome stain highlights perisinusoidal fibrosis (2). Magnification ×200.

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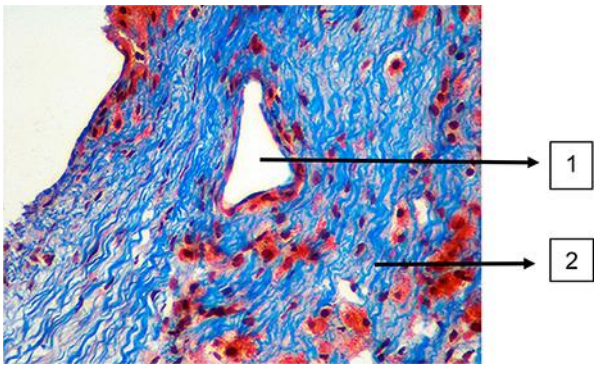

Fig. 5. Trichrome stain demonstrating central vein (1) with extensive surrounding fibrosis (2). Magnification ×400.

Table 1. Laboratory data on admission

WBC	6.49	K/μL	PT	14.60	s
RBC	4.94	M/μL	PTT	35.9	s
Hb	13.1	g/dL	INR	1.27	ratio
Hct	41.2	%			
PLT	196	K/μL			
Na	141	mEq/L	Total protein	6.7	g/dL
K	4.2	mEq/L	Albumin	3.8	g/dL
Cl	103	mEq/L	Total bilirubin	0.9	mg/dL
BUN	9	mg/dL	Alk phos	69	U/L
Cr	0.8	mg/dL	AST	13	U/L
Glucose	65	mg/dL	ALT	15	U/L
Ca	9.6	mg/dL			