Case Report

SAGE Open Medical Case Reports

Spontaneously ruptured hepatocellular carcinoma in Fontan-associated liver disease: A case report

SAGE Open Medical Case Reports
Volume 8: 1–5

DOI: 10.1177/2050313X20922030
journals.sagepub.com/home/sco
SAGE

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Abstract

The prognosis of congenital heart disease is dramatically improved by cardiac surgery. The Fontan procedure is the definitive palliative operation for patients with single-ventricle physiology. In parallel with the longer survival time achieved with the Fontan procedure, the incidence of Fontan-associated liver disease is increasing. A 40-year-old man who underwent Fontan procedures at the ages of 9 was referred to our hospital for further evaluation of multiple hepatic tumors. Enhanced computed tomography showed large hepatocellular carcinomas with portal thrombi (Vp3). Spontaneous hepatocellular carcinoma rupture occurred 2 weeks after the first visit to our hospital, and emergent transcatheter arterial embolization of the hepatic artery was performed. Three months later, the patient died of liver failure. Autopsy findings showed moderately differentiated hepatocellular carcinoma with a cirrhotic liver characterized by centrilobular fibrosis and sinusoidal dilation similar to that in Fontan-associated liver disease. We reported the first case of spontaneously ruptured hepatocellular carcinoma treated by emergent transcatheter arterial embolization in Fontan-associated liver disease. As the early diagnosis of liver cirrhosis and hepatocellular carcinoma results in better patients' outcome, cardiologists and hepatologists should be aware of Fontan-associated liver disease and advise patients to have regular follow-up of the liver.

Keywords

Fontan-associated liver disease, hepatocellular carcinoma, spontaneous tumor rupture, transcatheter arterial embolization, liver cirrhosis

Date received: 6 August 2019; accepted: 2 April 2020

Introduction

Hepatocellular carcinoma (HCC) is induced by continuous liver injury, particularly by fibrosis or cirrhosis of the liver. The main causes of continuous liver injury are hepatitis virus infection (types B and C), alcohol abuse, and metabolic diseases. However, congestive heart failure, including congenital heart disease (CHD), has also been shown to be a minor cause of continuous liver injury.[1,2] Hepatic complications are common in patients with CHD, nearly all of whom have hepatic fibrosis.[3] The prognosis of CHD is poor when treatment consists solely of palliative therapy; however, it is improved dramatically by the Fontan procedure, owing to recent medical advances and modifications to the surgical technique. The Fontan procedure diverts venous blood from the vena cava to the pulmonary arteries without passage through the morphologic right ventricle. Although the procedure improves the survival of patients with CHD, the incidence of a hepatic complication, known as Fontan-associated liver disease (FALD), is increasing. FALD was first reported in 1981, and the number of reports on this disease has been increasing since 2010. The mechanism of FALD-induced liver injury is suggested to be persistent chronic passive sinusoidal congestion. Recently, several investigators have reported on the development of HCC after the Fontan procedure.[4–6] However, only one case of spontaneously ruptured HCC in FALD has been reported in the literature.[7] In this case study, we report the first case of spontaneously ruptured HCC treated by emergent transcatheter arterial embolization (TAE) in an FALD patient.

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Table 1. The initial laboratory findings upon patient's arrival at our hospital.

Hematology		BUN (mg/dL)	32
WBC (/μL)	13,400	CRE (mg/dL)	1.17
HGB (g/dL)	11.6	IgM (mg/dL)	94.2
PLT (10^4/μL)	25.5	IgG (mg/dL)	1534.2
Coagulation		IgA (mg/dL)	267.6
PT (%)	17	Infection	
Biochemistry		HBsAb (–)	
CRP (mg/dL)	1.9	HBsAg (–)	
TP (g/dL)	5.9	HBcAb (–)	
Alb (g/dL)	3.1	HCVAb (–)	
AST (U/L)	136	Autoimmune	
ALT (U/L)	38	ANA (–)	
LDH (U/L)	247	AMA (–)	
ALP (U/L)	514	Markers of tumor	
GGP (U/L)	337	AFP (ng/mL)	538,882
ChE (U/L)	102	Seg.L3 (%)	29.8
T-Bil (mg/dL)	1.7	DCP (mAU/mL)	314,313

WBC: white blood cells; HGB: hemoglobin; PLT: platelets; PT: prothrombin time; CRP: C-reactive protein; TP: total protein; Alb: albumin; AST: aspartate aminotransferase; ALT: alanine aminotransferase; LDH: lactate dehydrogenase; ALP: alkaline phosphatase; GGP (U/L): gamma-glutamyltranspeptidase; ChE: cholinesterase; T-Bil: total bilirubin; BUN: blood urea nitrogen; CRE: creatinine ANA: antinuclear antibody; AMA: anti-mitochondrial; AFP: alpha fetoprotein; DCP: des-gamma-carboxy prothrombin.

Case presentation

Initially, a 40-year-old man was referred to our hospital in June 2015 for further evaluation of a large hepatic tumor ($63 \times 53\,mm^2$) that was identified using abdominal ultrasonography. He reported general fatigue, leg edema, appetite loss, and weight loss that began 1 month before his first visit to our hospital. Double-outlet right ventricle heart disease had been diagnosed in the patient at the age of 1 year. At 9 years of age, he underwent the Fontan procedure to connect the superior vena cava to the right pulmonary artery and the right atrial appendage to the main pulmonary artery. He had been receiving regular follow-up from only his cardiologist and not a hepatologist. He had not been diagnosed with liver dysfunction or chronic liver disease, prior to visiting our hospital. The initial laboratory findings upon his arrival at our hospital are shown in Table 1. The patient reported occasional alcohol consumption and no history of familial liver disease. He had no risk factors for ordinal liver diseases, such as viral infection, autoimmune disease, or metabolic disorders. Enhanced computed tomography (CT) showed that the hepatic tumors were enhanced in the arterial phase and washed out in the equilibrium phase, with Vp3 left portal vein tumor thrombosis (PVTT), metastasis to the left adrenal gland, splenomegaly, and no ascites were present (Figure 1). Magnetic resonance imaging was not performed. Esophagogastroduodenoscopy showed no esophagogastric varices. We diagnosed HCC due to FALD and recommended admission for TAE, to prevent rupturing of the HCC, followed by systemic chemotherapy with sorafenib. However, the patient chose not to be admitted to the hospital for treatment because of his employment obligations.

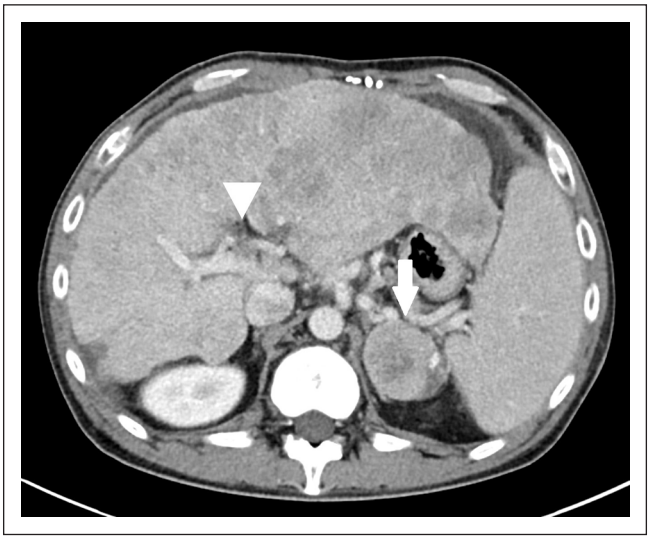

Figure 1. Enhanced CT imaging at the patient's first visit to our hospital. The results of CT showed a large hepatic tumor that occupied the liver, with left portal invasion (arrowhead) and metastasis of the left adrenal gland (arrow).

Two weeks later, he again was referred to our hospital due to concerns regarding his continuous upper abdominal pain. On his second arrival at our hospital, his blood pressure was 70/42 mmHg, and his heart rate was 96 beats/min. Enhanced CT showed intraperitoneal ascites, and high-density fluid pooled around the HCC within abnormal vessels in S3 (Figure 2(a)). We diagnosed hemorrhagic shock due to HCC rupture. In general, transcatheter arterial chemoembolization for HCC with PVTT (Vp3, 4) is contraindicated; however, in this case, to save this patient with hemorrhagic shock, emergent TAE for ruptured HCC was needed. Emergent TAE was performed via access of the right femoral artery. After assessment of the hepatic vasculature and portal circulation with an RC2 type catheter, a left hepatic angiogram showed a tumor that stained approximately 5.5 cm in size in the S2, and a tumor with abnormal blood vessels was suspected to have ruptured on the caudal side of S3 (Figure 2(b)). Selective TAE was performed, using a microcatheter (Toray Medical Co., Ltd, Tokyo, Japan). An embolic agent was used with the gelatin sponge cut into approximately 2 mm sections (Nippon Kayaku Co., Ltd, Tokyo, Japan), which were used without anti-cancer agents. After TAE, the extravascular leak had disappeared and the patient's vital signs improved. One month after HCC rupture, follow-up CT showed an enlargement of HCC, a PVTT, moderate ascites, and metastases in the bilateral lungs, left adrenal gland, and cerebral bones. As the patient's hepatic reserve worsened (Child C), best supportive care was selected by the physician. His ECOG performance status remained stable at grade 1 and he was discharged on the 70th day of hospitalization. However, 3 days after discharge, he experienced paralysis of his right

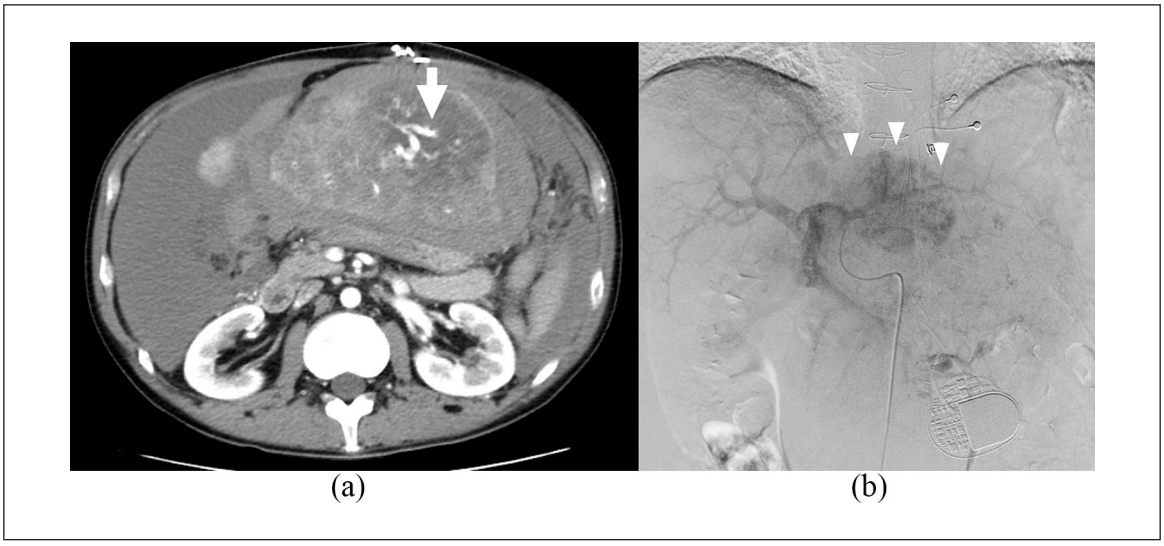

Figure 2. Enhanced CT imaging and angiography at the time of HCC rupture. (a) The results of enhanced CT showed intraperitoneal ascites and high-density fluid pooled around the HCC within strange vessels in segment 3 (arrow). (b) The results of emergent angiography showed multiple hepatic tumor stains and irregular vessels in segment 3 (arrowhead).

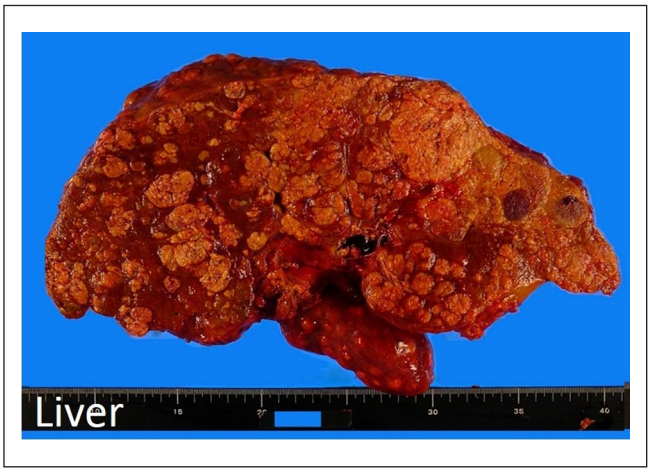

Figure 3. Macroscopic examination of the liver at autopsy. The liver was swollen and almost completely occupied by multiple tumors.

hand and leg that was caused by multiple bilateral hemorrhages in the cerebrum. Ten days after readmission, the patient died of liver failure. Informed consent for a full-body autopsy was obtained from the patient's family and an autopsy was performed. At autopsy, the liver weight was approximately 5000 g, and there were countless multifocal tumors (Figure 3) with moderate ascites. Metastases were observed in the lungs and adrenal glands. However, there were no intraperitoneal nodules. The hepatic tumors corresponded to moderately differentiated HCC because of their thick trabecular pattern, stratified appearance, and false duct structure of the cord-like type (Figure 4(a) and (b)). Noncancerous liver lesions showed sinusoidal dilatation, significant fibrosis, and marked central-to-portal bridging fibrosis, which is equivalent to liver cirrhosis (Figure 4(c) and (d)). However, centrilobular inflammation, bleeding in the vessels and necrosis, which typically occur in patients with acute heart failure, were not detected. In addition, there were no signs of piecemeal necrosis or interface hepatitis, which is indicative of viral hepatitis. We finally diagnosed the patient with FALD with advanced HCC.

Discussion

CHD occasionally causes liver cirrhosis, which is a condition called cardiac cirrhosis. Previous studies have reported that approximately 10% of deceased patients with congenital heart failure have liver cirrhosis.[8] The Fontan procedure necessitates a chronic elevation in central venous pressure to drive pulmonary circulation. After the procedure, patients have low hepatic perfusion pressure, chronic hypoxemia, and decreased cardiac output. These abnormal biological changes may lead to the development of liver cirrhosis. Hepatic complications caused by the Fontan procedure are called FALD. The known underlying causes of FALD are central venous hypertension, low cardiac output, and hypoxemia.[1] Hypoxia inducible factor 1 subunit alpha (HIF1α) is known to play an important role in the development of liver fibrosis.[9] Activation of HIF1α causes fibrosis through the activation and proliferation of hepatic stellate cells via cytokine signaling, such as vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF)-β, and fibroblast growth factor (FGF)-2. Recent studies show that the development of HCC in FALD patients is increasing. Egbe et al.[6] have shown that clinical features of HCC were found in 33 out of 2470 FALD cases (1.3%). The median age at the time of HCC diagnosis was 30 (range: 12–52) years and the median duration from Fontan operation to HCC diagnosis was 22 (range: 2–36) years. More than 50% of

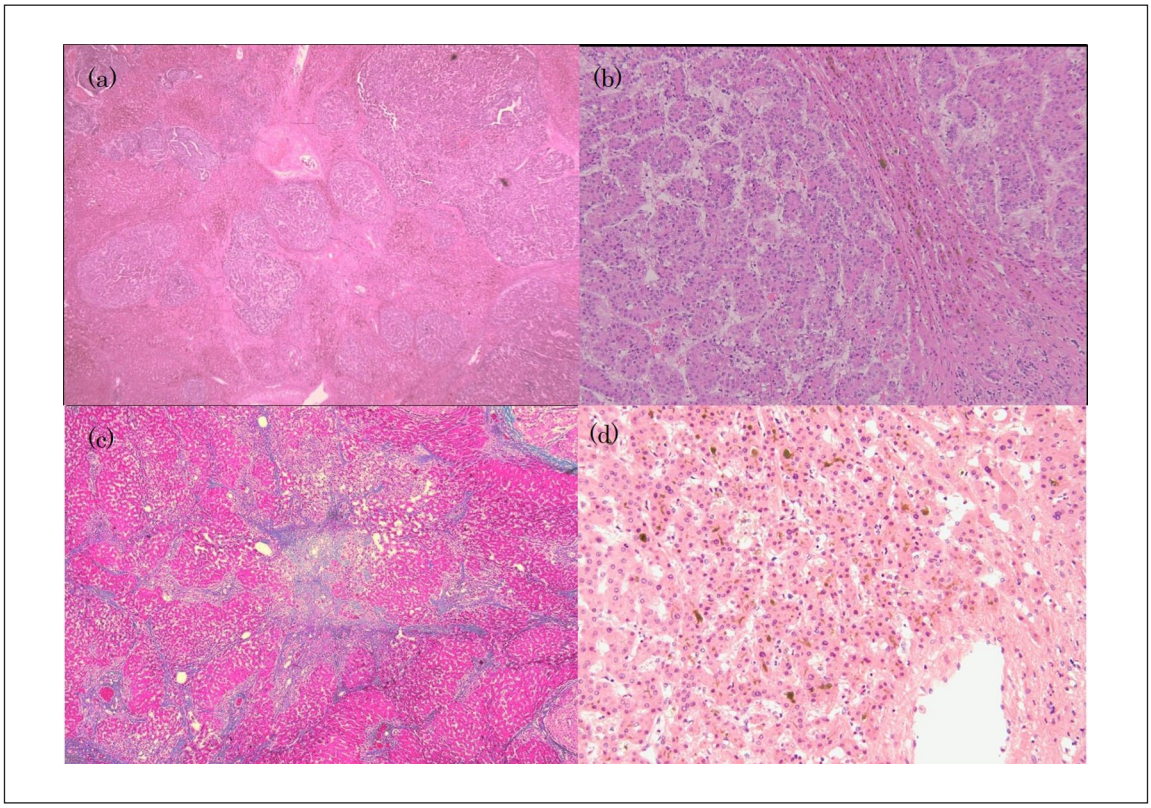

Figure 4. Histological examination of the liver tumor and non-cancerous lesions at autopsy. (a) Countless coated nodules occupied the liver (HE staining, 10-fold). (b) The moderately differentiated HCC showed a thick trabecular pattern, stratified appearance, and false duct structures of the cord-like type (HE staining, 100-fold). (c) Fibrosis around the central vein and developing bridging fibrosis were observed (Azan staining, 10-fold). (d) Sinusoidal dilation was apparent around the central vein. Interface hepatitis, hemorrhage, necrosis, and steatosis were not observed (HE staining, 40-fold).

HCC patients with FALD were diagnosed after the appearance of symptoms. The gold standard of assessment for liver fibrosis is a biopsy of the liver. After undergoing the Fontan procedure, patients usually require anticoagulant drugs, which make a biopsy of the liver difficult. Recent reports showed that non-invasive diagnostic tools, such as ultrasonographic elastography or magnetic resonance elastography (MRE), are useful for the detection of liver fibrosis. Each method has its own advantages and disadvantages. The most accurate diagnostic tool for fibrosis is MRE, but it is expensive, time-consuming, and contraindicated in pacemaker patients. Ultrasonographic elastography is easy and inexpensive, but its accuracy is inferior to that of its MRE counterpart.[10,11]

Although the degree of hepatic congestion is generally mild in FALD patients, the degree of fibrosis is considerably more severe than that in other congestive heart failure patients. This stark difference suggests that the development of liver fibrosis in FALD patients is more strongly influenced by hepatic hypoxia and low cardiac output rather than by hepatic congestion. Recent studies show that the characteristic histology of FALD includes sinusoidal dilation and fibrosis around the central hepatic vein; however, hepatic congestion, similar to Budd-Chiari syndrome, is rarely found in patients with FALD. In our patient, low-grade oxygen saturation (approximately 90% of normal) and mild sinusoidal dilation were observed. Therefore, we hypothesize that hypoxia may play a key role in the pathogenesis of hepatic fibrosis associated with FALD. In recent years, the incidence of HCC rupture had decreased due to earlier detection of HCC. In Asia, approximately 10% of patients with HCC die of HCC rupture each year.[12] Studies have demonstrated the efficacy of TAE in patients with ruptured HCC. In addition, in patients with ruptured HCC combined with PVTT, emergent TAE has a better prognosis than conservative therapies.[13]

To our knowledge, spontaneously ruptured HCC in FALD has only been reported in one case thus far. Here, we reported the first case of spontaneously ruptured HCC treated by TAE in a FALD patient. Reports of HCC after the Fontan procedure have been increasing and this might be due to an increased awareness of HCC development in these patients. The prevention of hepatic changes due to cardiac failure reportedly can keep the heart disease well controlled. Hepatologists should also follow up with patients after their Fontan procedures and cooperate with the patients' primary cardiologist so that liver cirrhosis or hepatic tumors can be identified and treated at an early stage. Further research on CHD-associated liver damage is required.

Conclusion

We report the first case of ruptured HCC treated by TAE 31 years after a Fontan procedure. Because the early diagnosis of liver cirrhosis and HCC results in better patient outcomes, clinicians—particularly cardiologists and hepatologists—should be aware of FALD and the annual surveillance required for its diagnosis.

Patient's perspective

> I have been diagnosed with a stable postoperative course of congenital heart disease, but accepted the possibility of shorter life span than others.
>
> I've been sad that my life would end because of other diseases, because I had thought my life would end because of heart disease. However, I heard this liver disease might be occurred from heart disease, so I can have accepted my current condition.

Authors' contributions

T.K. and Y.A. described the clinical case and assisted in data collection. H.K. coordinated and helped draft the manuscript. H.Y., A.M., R.N., and T.N. were responsible for the diagnosis, patient management, and review. All authors approved the final version of the text.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical approval

Our institution does not require ethical approval for reporting individual cases or case series.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

Informed consent

Written informed consent was obtained from a legally authorized representative for anonymized patient information to be published in this article.

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