Clinical Case Report

Medicine®

OPEN

Hepatocellular carcinoma after the Fontan procedure in a 16-year-old girl

A case report

Chaeyoun Oh, MD[a], Joong Kee Youn, MD[a], Ji-Won Han, MD[a], Gi Beom Kim, MD, PhD[b], Hyun-Young Kim, MD, PhD[a,*], Sung-Eun Jung, MD, PhD[a]

Abstract

Introduction: The Fontan procedure (FP) has become the standard operation for patients with single ventricle physiology. However, a long period of elevated systemic venous pressure and low cardiac output after the procedure result in chronic inflammation and liver cirrhosis, which may eventually lead to the occurrence of hepatocellular carcinoma (HCC).

Clinical Findings: We described the case of a 16-year-old female who developed HCC after the FP. At 21 months, the patient received a lateral tunnel FP, and 14 years later, she began complaining of abdominal distension, telangiectasia, and fatigue. Imaging studies revealed a large hepatic mass involving most of the right lobe and multiple masses in the left lobe. Evidence suggested severe liver cirrhosis, and the presence of ascites, hepatosplenomegaly, paraesophageal gastric varices reflecting the severity of the disease. In addition, tumor thrombosis was found in the right hepatic vein, middle hepatic vein, and inferior vena cava, as well as multiple metastatic nodules in both lungs. The patient received an incisional biopsy and the diagnosis of HCC was pathologically confirmed. After treatment with 1 cycle of systemic chemotherapy, she received ongoing supportive care for disease-related complications, and died 2 months after chemotherapy due to hematemesis.

Conclusion: With the advances in medicine, the incidence of Fontan physiology-related complications is likely to increase, and the incidence of HCC will also increase accordingly. As early diagnosis of HCC results in better patient outcomes, a surveillance guideline for HCC after the FP should be developed.

Abbreviations: AFP = alpha-fetoprotein, CT = computed tomography, FP = Fontan procedure, HCC = hepatocellular carcinoma, PA = pulmonary artery, TACE = transcatheter arterial chemoembolization.

Keywords: case report, Fontan physiology, Fontan procedure, hepatic complication, hepatocellular carcinoma

1. Introduction

The Fontan procedure (FP) is a palliative surgical procedure used in children with single ventricle physiology. It involves diverting the venous blood from the right atrium to the pulmonary arteries without passing through the morphologic right ventricle.[1] Since first described in 1971, the Fontan procedure has become the standard operation for patients with single ventricle physiology.[2] Despite saving numerous lives for the past 45 years, the Fontan circulation is often associated with long-term complications such as heart failure, pleural effusion, hypercoagulability, portal hypertension, and atrial fibrillation.[3] Among these, long-term elevated systemic venous pressure and low cardiac output may lead to the development of liver cirrhosis, and such a progression may eventually result in the incidence of hepatocellular carcinoma (HCC) in some patients.[4]

In this study, we presented the case of a 16-year-old female patient who developed HCC at a young age after receiving the FP. Informed consent was written by the patient and her parents.

2. Case report

This female patient was born full-term at 2.6 kg with an unremarkable perinatal history. At 3 months of age, she was evaluated for a heart murmur, and after receiving a diagnosis of tricuspid atresia with double outlet right ventricle, she was admitted to our hospital for treatment and further evaluation. At 5 months, she received a pulmonary artery banding operation, at 21 months she underwent bilateral bidirectional cavopulmonary shunt, and at 21 months, finally underwent a lateral tunnel FP. At 6 years of age, the patient began complaining of dizziness, and evaluation findings were consistent with sinus bradycardia. While receiving follow-up care for this condition, she was also diagnosed with a moderate degree of aortic regurgitation. The patient received a pacemaker insertion and an aortic valve replacement at the age of 10 years to treat sinus bradycardia and aortic regurgitation, respectively. At 9 years of age, the patient was evaluated for gait ataxia and developmental delay. Magnetic resonance imaging of her brain revealed a small lacunar infarction and cerebellar atrophy.

Editor: Wenyu Lin.

The authors have no conflicts of interest to disclose.

[a] Department of Surgery, [b] Department of Pediatrics, Seoul National University College of Medicine, Seoul, Korea.

[*] Correspondence: Hyun-Young Kim, Department of Pediatric Surgery, Seoul National University Children's Hospital, Seoul, Korea (e-mail: spkhy02@snu.ac.kr).

Medicine (2016) 95:41(e4823)

Received: 5 June 2016 / Received in final form: 28 July 2016 / Accepted: 18 August 2016

http://dx.doi.org/10.1097/MD.0000000000004823

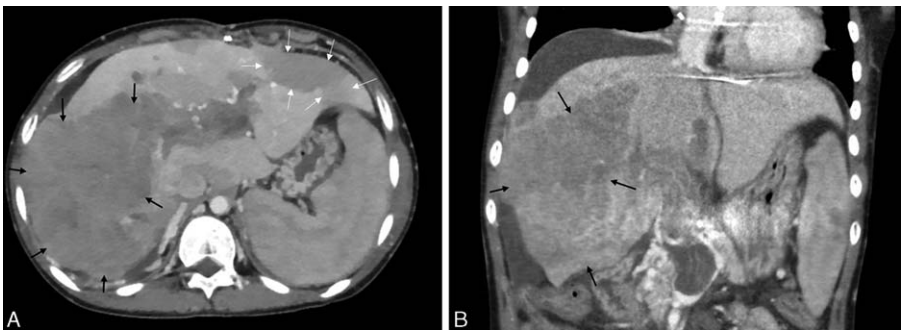

Figure 1. Abdominal CT images show a large mass in the right hepatic lobe (black arrow, 12.5 × 10.5 × 7.5 cm) and multiple masses in the left lobe (white arrow): (A) axial view, (B) coronal view. CT = computed tomography.

At 15 years of age, the patient developed peripheral edema and an abdominal ultrasound was performed. The ultrasound revealed mild hepatic lobulations with no signs of ascites or liver cirrhosis. Laboratory evaluations showed normal liver enzyme levels, and alpha-fetoprotein (AFP) levels were not measured.

One year later, the patient was readmitted to our hospital because of abdominal distension, telangiectasia, and fatigue. The liver, on abdominal ultrasound imaging, showed a heterogeneous echotexture, warranting the need for further evaluation studies. A computed tomography (CT) of the abdomen showed a large mass involving most of the right hepatic lobe, as well as multiple masses in the left lobe (Fig. 1). This image also revealed signs of progressive liver cirrhosis, such as ascites, hepatosplenomegaly, paraesophageal varicies, along with evidence of tumor thrombosis in the inferior vena cava and right and left hepatic veins. On laboratory evaluations, blood test results were as follows: aspartate transaminase (AST) 82 IU/L(normal range; 1–40), alanines transaminase (ALT) 28 IU/L(normal range; 1–40), gamma-glutamyl transaminase (GGT) 123 IU/L(normal range; 8–35), total bilirubin 1.8 mg/dL(normal range; 0.2–1.2), and AFP and protein induced by vitamin K absence or antagonist-II (PIVKA-II) levels were measured at 211,580 ng/mL(normal range; 0.89–8.78) and 35,721 mAU/mL(normal range; 0–40), respectively. The patient was seronegative for hepatitis B and C and reported no history of alcohol consumption. Her body mass index was 15.11 kg/m^2. She had a Child–Pugh score of 8. Echocardiography revealed that ejection fraction of left ventricle was 59%. A chest CT performed on the same day showed multiple metastatic nodules in both lungs (Fig. 2).

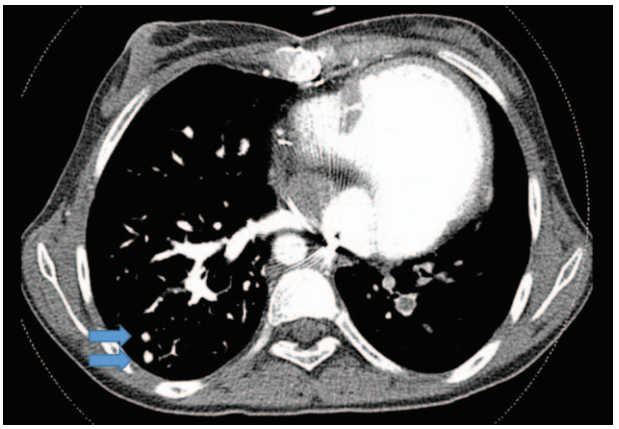

Figure 2. Chest CT reveals multiple metastatic nodules in right lung (arrow). CT = computed tomography.

Three days later, the patient began experiencing hematemesis and hematochezia and an endoscopic variceal ligation was performed. Due to the presence of large volume ascites, peritoneal seeding could not be excluded and a percutaneous liver biopsy was not done. An incisional biopsy was obtained from segments 4 and 5 of the liver, and a diagnosis of HCC was pathologically confirmed (Fig. 3). The patient received 1 cycle of cisplatin-based chemotherapy. She received 3 subsequent endoscopic variceal ligations. Currently, the patient is no longer taking warfarin for her underlying heart conditions, and as she is not a candidate for a liver transplantation, she receives supportive care for disease-related complications. After 2 months of chemotherapy, she died at home with hematemesis, possibly due to variceal bleeding.

3. Discussion

In the United States, ~650,000 to 1.3 million people are born with congenital heart diseases, and this number continues to show 5% increases every year.[5,6] Warnes et al[5] reported that with successful surgery, 85% of these cases survive to adulthood. Since first described in 1971, the FP has been used to treat various congenital heart diseases with single ventricle physiology.[2] Forty-five years after receiving this operation, some patients have experienced Fontan physiology-related complications. The postoperative circulatory changes result from the following 4 major changes: (1) single ventricle circulation, (2) nonpulsatile pulmonary perfusion, (3) systemic venous hypertension, and (4) intracardiac scarring.[3,4]

Chronic elevation of central venous pressure and tissue hypoxia are associated with hepatic complications. After the FP (with the exception of the atrioventricular Fontan), blood flow into the superior vena cava bypasses the right ventricle by going directly into the pulmonary artery (PA) or into the right atrium that is connected to the PA. Due to this configuration, the central venous pressure is not reflective of the intracardiac preload, but is instead representative of the chronically elevated PA pressure. Such mechanisms cause repetitive mechanical stretch and compression via passive congestion on hepatocytes.[3,4,7] In addition, high systemic venous pressure results in low cardiac output, which, in turn, causes low hepatic perfusion and chronic tissue hypoxia. Passive congestion and tissue hypoxia cause repetitive hepatocyte injury and inflammation, leading to the progression of liver cirrhosis, ultimately resulting in the development of HCC.[4,8,9]

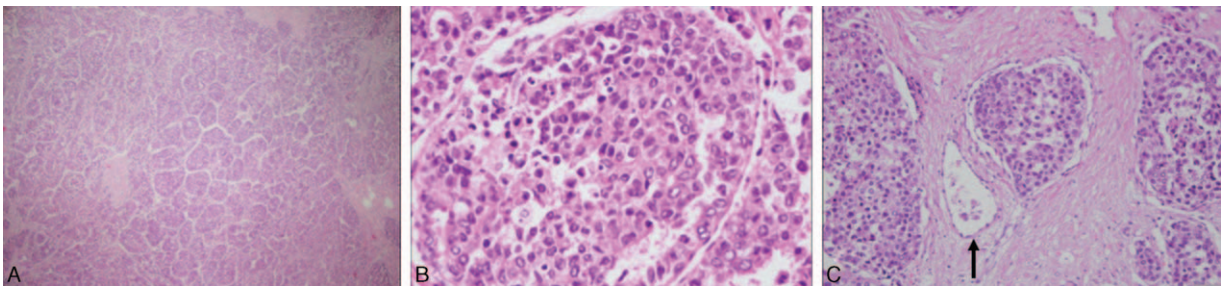

Figure 3. Histologic appearance of the HCC: (A) histologic pattern: compact and trabecular, (B) Edmondson–Steiner nuclear grade II/IV, (C) presence of vascular invasion (arrow). HCC = Hepatocellular carcinoma.

Cardiac cirrhosis-related HCC was first reported by Ho et al[10] in 1990. There are 10 published PubMed case reports of HCC after the FP, and with the addition of our case, this number has increased to a total of 11 (Table 1).[9,11–15] HCC incidence after the FP has not been frequently reported. The incidence of hepatic complications including HCC are correlated with the duration of elapsed time since the initial FP.[7,16] According to Baek et al[16], the odds of hepatic complications were 4.4 times higher in patients belonging to a group with a postoperative duration of 11 to 15 years compared to patients with a postoperative duration of 5 years or less. The odds were even higher (OR 9.0) for patients belonging to a group with a postoperative duration of 16 to 20 years. Patients belonging to a group with a median postoperative duration of 11.5 years showed signs of hepatomegaly (53%), splenomegaly (9%), abnormal transaminases (30%), elevated GGT (61%), elevated biliruibin (32%), and coagulopathy (58%).[17]

A study conducted by Kiesewetter et al[7] in 2007 focused on patients with a mean postoperative duration of 14.1 years (range: 6.9–26.4 years); they reported that 58.3% of patients belonging to this group had developed liver cirrhosis. Although subsequent studies failed to report postoperative duration, the authors reported that 15% of patients with a mean age of 26±9 years showed signs of liver cirrhosis.[18] For patients with liver cirrhosis, the risk of HCC increases annually by 1.5 to 5.0%.[9] However, screening guidelines for subsequent HCC after the FP have yet to be made. Both our case and the case reported by Yamada et al[14] described patients who developed HCC 14 years after receiving the FP. In addition, another case of a 13-year-old female patient who developed HCC after cardiac surgery has been reported; although this patient did not receive an FP, she did receive palliative surgery at 7 months of age for pulmonary atresia with an intact ventricular septum.[19] Although AFP levels were not checked 1 year prior to the diagnosis, abdominal ultrasound images revealed no signs of liver cirrhosis and liver enzyme levels were within normal limits. The patient unfortunately showed rapid disease progression, and developed HCC within only 1 year. Thus, we propose that patients who have received the FP 10 years ago or earlier should receive AFP and abdominal ultrasound screening tests at 6 month intervals as part of an HCC surveillance program.

4. Conclusion

Patients who have previously received the FP experience long-term Fontan physiology-related complications in adulthood. In this study, we reported a case of a 16-year-old female who developed HCC 14 years after receiving the FP. With continued medical advancements, we expect the number of Fontan physiology-related complications to increase, and the incidence of HCC in these patients will also increase accordingly. Early diagnosis of HCC results in better patient outcomes, as many treatment modalities remain viable. Therefore, we conclude that a HCC surveillance guideline should be developed for patients who have undergone the FP.

Table 1

Reported cases of HCC after the Fontan procedure.

Reference (year)	Age at diagnosis of HCC	Duration from FP to HCC (years)	Other risk factor for HCC	Treatment	Outcome
Ghaferi and Hutchins (2005)	24	18	None	–	Died, ruptured hematoma
Saliba et al (2010)	26	22	None	Chemo therapy	Died 1 year later
	28	18	None	Sorafenib	Died 1 year later
Asrani et al (2012)	32	–	None	TACE[1]	Waiting CHLT[2]
	24	–	None	–	Died, metastasis
	33	–	None	Radioembolization	Died, bleeding from a hepatic artery pseudoaneurysm
	42	–	Hepatitis C	TACE[1]	Waiting CHLT[2]
	51	28	None	local ablation	Cancer free
Yamada et al (2015)	15	14	None	TACE[1]	Died 2 year later
Kwon et al (2015)	32	23	None	Liver resection	Cancer free
Present case (2016)	16	14	None	Chemo therapy	Died 2 months later

CHLT = combined heart and liver transplantation, FP = Fontan procedure, HCC = hepatocellular carcinoma, TACE = transcatheter arterial chemoembolization.

References

[1] Wu FM, Ukomadu C, Odze RD, et al. Liver disease in the patient with Fontan circulation. Congenit Heart Dis 2011;6:190–201.

[2] Fontan F, Baudet E. Surgical repair of tricuspid atresia. Thorax 1971;26:240–8.

[3] McRae ME. Long-term issues after the Fontan procedure. AACN Adv Crit Care 2013;24:264–82. quiz 283-264.

[4] Asrani SK, Asrani NS, Freese DK, et al. Congenital heart disease and the liver. Hepatology 2012;56:1160–9.

[5] Warnes CA, Williams RG, Bashore TM, et al. ACC/AHA 2008 guidelines for the management of adults with congenital heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Develop Guidelines on the Management of Adults With Congenital Heart Disease). Developed in Collaboration With the American Society of Echocardiography, Heart Rhythm Society, International Society for Adult Congenital Heart Disease, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. J Am Coll Cardiol 2008;52:e143–263.

[6] Marelli AJ, Mackie AS, Ionescu-Ittu R, et al. Congenital heart disease in the general population: changing prevalence and age distribution. Circulation 2007;115:163–72.

[7] Kiesewetter CH, Sheron N, Vettukattill JJ, et al. Hepatic changes in the failing Fontan circulation. Heart 2007;93:579–84.

[8] Jolley M, Colan SD, Rhodes J, et al. Fontan physiology revisited. Anesth Analg 2015;121:172–82.

[9] Asrani SK, Warnes CA, Kamath PS. Hepatocellular carcinoma after the Fontan procedure. N Engl J Med 2013;368:1756–7.

[10] Ho SS, Brown R, Fitzgibbon B. Hepatocellular carcinoma with cardiac cirrhosis. Med J Aust 1990;152:553–4.

[11] Ghaferi AA, Hutchins GM. Progression of liver pathology in patients undergoing the Fontan procedure: chronic passive congestion, cardiac cirrhosis, hepatic adenoma, and hepatocellular carcinoma. J Thorac Cardiovasc Surg 2005;129:1348–52.

[12] Saliba T, Dorkhom S, O'Reilly EM, et al. Hepatocellular carcinoma in two patients with cardiac cirrhosis. Eur J Gastroenterol Hepatol 2010;22:889–91.

[13] Elder RW, Parekh S, Book WM. More on hepatocellular carcinoma after the Fontan procedure. N Engl J Med 2013;369:490.

[14] Yamada K, Shinmoto H, Kawamura Y, et al. Transarterial embolization for pediatric hepatocellular carcinoma with cardiac cirrhosis. Pediatr Int 2015;57:766–70.

[15] Kwon S, Scovel L, Yeh M, et al. Surgical management of hepatocellular carcinoma after Fontan procedure. J Gastrointest Oncol 2015;6: E55–60.

[16] Baek JS, Bae EJ, Ko JS, et al. Late hepatic complications after Fontan operation; non-invasive markers of hepatic fibrosis and risk factors. Heart 2010;96:1750–5.

[17] Camposilvan S, Milanesi O, Stellin G, et al. Liver and cardiac function in the long term after Fontan operation. Ann Thorac Surg 2008;86: 177–82.

[18] Pike NA, Evangelista LS, Doering LV, et al. Clinical profile of the adolescent/adult Fontan survivor. Congenit Heart Dis 2011;6:9–17.

[19] Rosenbaum J, Vrazas J, Lane GK, et al. Cardiac cirrhosis and hepatocellular carcinoma in a 13-year- old treated with doxorubicin microbead transarterial chemoembolization. J Paediatr Child Health 2012;48:E140–3.