CASE REPORT

Surgical Resection for Hepatocellular Carcinoma with Cardiac Cirrhosis after the Fontan Procedure

Yoshitaka Takuma¹, Yuji Fukada¹, Shota Iwadou¹, Hirokazu Miyatake¹, Shuji Uematsu¹, Ryoichi Okamoto¹, Daisuke Sato², Hiroyoshi Matsukawa³, Shigeihiro Shiozaki², Masahiro Kamada¹, Toshiaki Morito¹, and Yasuyuki Araki¹

Abstract

A 29-year-old woman who underwent the Fontan procedure at 10 years of age had an incidental finding of liver masses on abdominal ultrasonography. Subsequent gadolinium ethoxybenzyl diethylenetriamine pentaacetic acid magnetic resonance imaging showed a 15 mm hypervascular mass with washout in the hepatobiliary phase in liver segment 4 (S4), and an 18 mm hypervascular mass without washout in the hepatobiliary phase in liver segment 2 (S2). The S2 liver mass was pathologically diagnosed to be a regenerative nodule by an ultrasound-guided needle biopsy, and the S4 liver mass was pathologically diagnosed as a poorly differentiated hepatocellular carcinoma after partial hepatectomy.

Key words: hepatocellular carcinoma (HCC), Fontan, cardiac cirrhosis, surgical resection

(Intern Med 55: 3265-3272, 2016) (DOI: 10.2169/internalmedicine.55.6869)

Introduction

The Fontan procedure is used to separate the systemic and pulmonary circulations in patients with various forms of functionally univentricular hearts. In the Fontan circulation, systemic venous return is sent to the pulmonary arteries without passage through a ventricle. The Fontan procedure can result in various late complications, including central venous hypertension, diminished oxygen delivery, reduced cardiac output, venous thrombosis, and arrhythmia (1, 2). These complications caused by central venous hypertension lead to parenchymal injury, fibrosis, and cirrhosis of the liver (2, 3). Cardiac cirrhosis is a serious late complication of congenital heart disease and can cause hepatocellular carcinoma (HCC) (4, 5). However, the prevalence and risk factors of cirrhotic changes and HCCs have not been clearly identified. Furthermore, non-invasive diagnostic tools for hepatic fibrosis and the management of HCC in patients after undergoing the Fontan procedure have not yet been clearly established.

We herein report a case of HCC with cardiac cirrhosis treated with surgical resection.

Case Report

A 29-year-old woman with a history of a univentricular heart had undergone a Fontan operation 10 years of age. She also had situs inversus. She was followed-up at the department of pediatric cardiology in our hospital, and regularly underwent blood examinations without alpha-fetoprotein (AFP) at 2- or 3-month intervals. The results showed that the transaminase level was within the normal range. On a routine follow-up day, she experienced slight abdominal discomfort and received abdominal ultrasonography (US). She had an incidental finding of liver masses and was referred to our department.

B-mode conventional US showed a 15 mm hypoechoic mass in liver segment 4 (S4) (Fig. 1a), and an 18 mm hyperechoic mass in liver segment 2 (S2) (Fig. 2a). Furthermore, the liver parenchyma had a coarsened appearance consistent with cirrhosis, and ascites and splenomegaly were
We next performed contrast-enhanced US (CEUS) using a bolus injection of 0.015 mL/kg Sonazoid (perfluorobutane; Daiichi-Sankyo, Tokyo, Japan). The mass lesion in S4 was homogeneously enhanced in the arterial dominant phase (from 10 to 30 seconds) (Fig. 1d). The lesion became progressively hypochoic relative to the adjacent liver parenchyma during the portal dominant phase (from 30 to 120 seconds) (Fig. 1e), and provided a contrast defect with a clear border in the postvascular phase (10 minutes later) (Fig. 1f). The mass lesion in S2 was homogeneously enhanced in the arterial dominant phase (Fig. 2b). The lesion became isoechoic mass relative to the adjacent liver parenchyma during the portal dominant phase (Fig. 2c) and provided no defects in the postvascular phase (10 minutes later) (Fig. 2d).

We subsequently performed magnetic resonance imaging (MRI) with conventional T1- and T2-weighted imaging (WI) before and after contrast media administration, including diffusion imaging. The contrast media used was hepatocyte-specific Primovist [gadolinium ethoxybenzyl diethylenetriamine pentaacetic acid (Gd-EOB-DTPA); Bayer Schering Pharma, Berlin, Germany]. There was radiographic evidence of liver cirrhosis with portal hypertension, including a nodular surface, a coarse texture, ascites, and splenomegaly on MRI (Fig. 3a and b).

This imaging revealed a mass lesion in S4 with a moderately low intensity in T1-WI (Fig. 3c) and moderately high intensity in T2-WI (Fig. 3d). In diffusion imaging, the lesion showed a moderately high intensity (Fig. 3e). In the postcontrast phases, the lesion revealed homogeneous enhancement in the arterial phase at 20 seconds (Fig. 3b and f), and washout in the portal phase at 70 seconds and interstitial phase at 180 seconds. At 20 minutes (hepatobiliary phase) after the contrast uptake the lesion showed washout (Fig. 3g). According to these findings, a final diagnosis of HCC was made. In addition, MRI imaging revealed a mass lesion in S2 with a moderately high intensity in T1-WI (Fig. 4b) and moderately low intensity in T2-WI (Fig. 4c). In diffusion imaging, the lesion showed a moderately low intensity (Fig. 4d). In the postcontrast phases, the lesion revealed a homogeneous enhancement in the arterial phase (Fig. 4a and e), an isoenhancement relative to the adjacent liver parenchyma in the portal and interstitial phases, and a high intensity in the hepatobiliary phase (Fig. 4f).

The laboratory data are given in Table 1. Her liver func-

Figure 1. Ultrasonography findings (arrows). B-mode conventional ultrasonography showed a 15 mm hypoechoic mass in liver segment 4 (S4) (a), the liver parenchyma had a coarsened appearance consistent with cirrhosis, and ascites and splenomegaly were observed (b, c). CEUS using Sonazoid showed a homogeneously enhanced mass in the arterial dominant phase (d), a hypoechoic mass relative to the adjacent liver parenchyma during the portal dominant phase (e), and a contrast defect with a clear border in the postvascular phase (f).
Figure 2. B-mode conventional ultrasonography showed an 18 mm hyperechoic mass in liver segment 2 (S2) (a); and CEUS showed a homogeneously enhanced mass in the arterial dominant phase (b), isoechoic mass relative to the adjacent liver parenchyma during the portal dominant phase (c), and no defects in the postvascular phase (d).

Figure 3. There was radiographic evidence of liver cirrhosis with portal hypertension, including a nodular surface, a coarse texture, ascites, and splenomegaly on MRI (a, b). Gd-EOB-DTPA MRI showed a 15 mm S4 mass with a moderately low intensity in T1-WI (c), moderately high intensity in T2-WI (d), moderately high intensity in diffusion (e), homogeneous arterial enhancement (b, f), and complete washout in the hepatobiliary phase (g).
Figure 4. Gd-EOB-DTPA MRI showed an 18 mm S2 mass with a moderately high intensity in T1-WI (b), moderately low intensity in T2-WI (c), moderately low intensity in diffusion (d), homogeneous arterial enhancement (a, e), and high intensity in the hepatobiliary phase (f).

Table 1. Results of Blood Tests.

| Hematology      | Blood biochemistry    | Serology          |
|-----------------|-----------------------|-------------------|
| WBC 3.0 ×10^3/μL| TP 7.7 g/dL           | HBsAg (+)         |
| RBC 494×10^6/μL | Alb 4.9 g/dL          | HBsAb (+)         |
| Hb 9.5 g/dL     | ChE 166 IU/L          | HBeAb (+)         |
| Hct 32.7%       | T.Bil 1.0 mg/dL       | HCV-Ab            |
| PLT 12.5×10^4/μL| D.Bil 0.5 mg/dL       | ANA (-)           |
|                 | AST 23 IU/L           | AMA-M2 (-)        |
|                 | ALT 13 IU/L           | IgG 1,267 mg/dL   |
|                 | LDH 226 IU/L          | IgA 233 mg/dL     |
|                 | ALP 163 IU/L          | IgM 231 mg/dL     |
|                 | γ-GTP 47 IU/L         | AFP 117.1 ng/mL   |
|                 | ZTT 8.5 KU            | AFP-L3 46.8 %     |
|                 | TTT 4.6 KU            | CEA 0.4 ng/mL     |
|                 | BUN 19 mg/dL          | CA19-9 5.1 ng/mL  |
|                 | Cr 0.79 mg/dL         |                  |
|                 | CRP 0.010 mg/dL       |                  |
|                 | hyaluronic acid 53 ng/mL |               |
|                 | type IV collagen 8.5 ng/mL |         |
|                 | ICG-R15 19.9%         |                  |

WBC: white blood cells, RBC: red blood cells, Hb: hemoglobin, Hct: hematocrit, PLT: platelets, PT: prothrombin time, INR: international normalized ratio, TP: total protein, Alb: albumin, ChE: cholinesterase, T.Bil: total bilirubin, D.Bil: direct bilirubin, AST: aspartate aminotransferase, ALT: alanine aminotransferase, LDH: lactate dehydrogenase, ALP: alkaline phosphatase, γ-GTP: γ-glutamyltransferase, ZTT: zinc sulfate turbidity test, TTT: thymol turbidity test, BUN: blood urea nitrogen, Cr: creatinine, CRP: C-reactive protein, ICG-R: indocyanine green retention, HBsAg: hepatitis B surface antigen, HBeAb: hepatitis B surface antibody, HBeAb: hepatitis B core antibody, HCV: hepatitis C virus antibody, ANA: antinuclear antibodies, AMA-M2: anti-mitochondrial M2 antibody, AFP: alpha-fetoprotein, AFP-L3: Lens culinaris agglutinin-reactive fraction of AFP, CEA: carcinoembryonic antigen, CA: carbohydrate antigen.

tion was well preserved with the Child-Pugh classification A, and her international normalized ratio was low (the patient was on warfarin for atrial arrhythmia). Other lab findings included a high AFP level [normal less than 40 nanograms/milliliter (ng/mL)], high Lens culinaris agglutinin-reactive fraction of AFP (AFP-L3) (normal less than 10%), low platelet count (normal greater than 150,000/microliter), high hyaluronic acid (normal less than 50 ng/mL), and high
Discussion

In the present case, there were no known etiological factors such as hepatitis viral infection, alcoholic liver disease, autoimmune liver diseases, autoimmune hepatitis, primary biliary cirrhosis, metabolic liver diseases [such as non-alcoholic steatohepatitis (NASH)], or medication with hepatotoxic drugs (such as amiodarone). Moreover, significant hepatic inflammation or fat deposition was not seen as a result of processes such as hepatitis viral infection or NASH. On histology in the present case, hepatic sinusoidal fibrosis extending from centrlobular areas toward the portal tract without inflammation were observed. Schwarz et al. discussed that hepatic fibrosis after the Fontan procedure was a mixed disease that affects both the portal and centrlobular areas in liver biopsy and autopsy specimens (6, 7). Sinusoidal fibrosis is believed to result from an increase in central venous pressure transmitted to hepatic cells that surround the central veins, because the extent of cirrhosis is strongly correlated with elevated hepatic venous pressures and a low cardiac index in patients after undergoing the Fontan procedure (8). After Fontan palliation, a significant liver disease can result in central venous congestion and hypoxia resulting from a low cardiac output, however, little is known regarding fibrogenic mechanisms independent of the inflammation-mediated pathway in congestive liver disease (CLD). In CLD, mechanotransduction associated with stretching and compression of hepaticstellate cells may be a potent inducer of hepatic fibrosis (9, 10). Using a newly characterized murine CLD model, sinusoidal thrombosis and mechanical stretching of adjacent hepatic stellate cells caused by sinusoidal dilatation was shown to induce the release of fibronectin by hepatic stellate cells, and both fibrin and stretching stimulated fibronectin fibril assembly through a β1-integrin and actin-dependent mechanism (11).

In addition, hepatic complications after the Fontan proce-
Figure 6. A macroscopic appearance of the resected S4 specimen revealed a yellowish-white encapsulated solid tumor measuring 15 mm in size (a). Microscopically, the growth pattern of the S4 liver tumor showed expansive growth with extracapsular invasions (b, Hematoxylin and Eosin (H&E) staining with a low-power field). Tumor cells had an increased nuclear/cytoplasmic ratio, polymorphic, and chromatin-rich nuclei, and the pathological diagnosis was poorly differentiated HCC (c, H&E staining with a high-power field).

procedure are associated with the duration of follow-up (8, 12). Progression to cirrhosis may even be observed within 10 years after the initial Fontan procedure (13). In 34 patients with a median follow-up of 11.5 years after the Fontan procedure, 30% experienced abnormal transaminases, 61% abnormal γ-GTP, 32% abnormal bilirubin, and 58% coagulopathy (14). As compared to a duration of 0-5 years, the odds ratio of hepatic complications was 4.4 for a post-Fontan duration of 11-15 years and 9.0 for a duration of 16-20 years, respectively (12).

Liver cirrhosis is a potential prerequisite for HCC; however, the prevalence and progression of cirrhotic changes in the Fontan population have not been clearly identified. Non-invasive diagnostic tools for hepatic fibrosis are needed, because a liver biopsy, the golden standard for diagnosing liver cirrhosis, is difficult to perform in Fontan patients due to prophylactic anticoagulation. Similar to the present case, a radiological assessment of liver fibrosis using various methods such as US, CT, or MRI may be useful.

There are several reports of HCC in patients with CLD following the Fontan procedure. As shown in Table 2, a recent PubMed search identified 12 cases of HCCs among published reports. The publications described the use of surgical resection, transcatheter arterial chemoembolization, radioembolization, local ablation, or sorafenib therapy (15-22). In previous reports, two patients were treated with surgical resection (20, 21). For early stage HCC, surgical resection provides curative treatment with a long-time survival, however, hepatectomy is rarely performed following the Fontan procedure because it is difficult to detect early stage HCCs. Although the present patient did not receive periodic surveillance for HCC, such as US and AFP, it is fortunate that early stage HCC was incidentally detected. HCC detected after the onset of symptoms has a poor prognosis (5-year survival rate of 0-10%). In contrast, early stage HCCs detected by surveillance can be cured with both surgical resection and liver transplantation (5-year disease-free survival rate >50%) (23).

Thus, surveillance for HCC may be necessary in patients with CLD who undergo the Fontan procedure because cirrhosis is a high-risk factor for HCC. However, the screening interval for liver disease after the Fontan procedure has not yet been established. Surveillance is based on an ultrasound examination, and the recommended screening interval is 6 months according to the American Association for the Study of Liver Diseases (AASLD) practice guidelines on the man-
The non-cancerous area of the resected specimen revealed bridging fibrosis without fat deposition, and the patient was diagnosed with liver cirrhosis [silver impregnation (a)]. Fibrosis was observed in both the portal and pericellular areas, the sinusoidal structure was maintained, and significant inflammation was not seen [silver impregnation (b, c) with a high-power field].

Table 2. Reported Cases of Hepatocellular Carcinoma after Fontan Procedure.

| Reference | No. of cases | Age(y) | Sex | AFP (ng/mL) | Size (mm) | Treatment          | Outcome |
|-----------|--------------|--------|-----|-------------|-----------|--------------------|---------|
| 15        | 1            | 24     | M   | ND          | 40        | ND                 | Died    |
| 16        | 2            | 27     | F   | 162.7       | 22.1      | Systemic chemo     | Died    |
|           |              | 28     | F   | 788         | 40        | Sorafenib          | Died    |
| 17        | 4            | 32     | F   | 700         | ND        | TACE               | Alive   |
|           |              | 24     | M   | 5,000       | ND        | ND                 | Died    |
|           |              | 33     | M   | 630         | ND        | Radioembolization   | Died    |
|           |              | 42     | F   | 106         | ND        | TACE               | Alive   |
| 18        | 1            | 51     | M   | ND          | 10        | Local ablation     | Alive   |
| 19        | 1            | 19     | F   | ND          | ND        | Sorafenib          | Died    |
| 20        | 1            | 23     | F   | ND          | 148       | Surgical resection | Alive   |
| 21        | 1            | 32     | M   | 13          | 40        | Surgical resection | Alive   |
| 22        | 1            | 15     | M   | 2           | ND        | TAE                | Died    |
| Our case  | 1            | 29     | F   | 117.1       | 15        | Surgical resection | Alive   |

F: female, M: male, ND: not described, TACE: transarterial chemoembolization, TAE: transarterial embolization

The authors state that they have no Conflict of Interest (COI).
References

1. Kendall TJ, Stedman B, Hacking N, et al. Hepatic fibrosis and cirrhosis in the Fontan circulation: a detailed morphological study. J Clin Pathol 61: 504-508, 2008.

2. Wanless IR, Liu JJ, Butany J. Role of thrombosis in the pathogenesis of congestive hepatic fibrosis (cardiac cirrhosis). Hepatology 21: 1232-1237, 1995.

3. Kaulitz R, Luhmer I, Bergmann F, Rodeck B, Hausdorff G. Sequelae after modified Fontan operation: postoperative haemodynamic data and organ function. Heart 78: 154-159, 1997.

4. 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 52: e143-e263, 2008.

5. Asrani SK, Asrani NS, Freese DK, et al. Congenital heart disease and the liver. Hepatology 56: 1160-1169, 2012.

6. Schwartz MC, Sullivan L, Cohen MS, et al. Hepatic pathology may develop before the Fontan operation in children with functional single ventricle: an autopsy study. J Thorac Cardiovasc Surg 143: 904-909, 2012.

7. Schwartz MC, Sullivan LM, Glatz AC, et al. Portal and sinusoidal fibrosis are common on liver biopsy after Fontan surgery. Pediatr Cardiol 34: 135-142, 2013.

8. Kiesewetter CH, Sheron N, Vettukattil JJ, et al. Haptic changes in the failing Fontan circulation. Heart 93: 579-584, 2007.

9. Rockey DC. Current and future anti-fibrotic therapies for chronic liver disease. Clin Liver Dis 12: 939-962, xi, 2008.

10. Goto T, Mikami KI, Miura K, et al. Mechanical stretch induces matrix metalloproteinase 1 production in human hepatic stellate cells. Pathophysiology 11: 153-158, 2004.

11. Simonetto DA, Yang HY, Yin M, et al. Chronic passive venous congestion drives hepatic fibrogenesis via sinusoidal thrombosis and mechanical forces. Hepatology 61: 648-659, 2015.

12. Baek JS, Bae EJ, Ko JS, et al. Late hepatic complications after Fontan operation: non-invasive markers of hepatic fibrosis and risk factors. Heart 96: 1750-1755, 2010.

13. Pike NA, Evangelista LS, Doering LV, Koniak-Griffin D, Lewis AB, Child JS. Clinical profile of the adolescent/adult Fontan survi-