[CASE REPORT]

Hepatocellular Carcinoma in a Patient with Tetralogy of Fallot: A Case Report and Literature Review

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Abstract:
We herein report a 34-year-old woman born with tetralogy of Fallot who had undergone 5 cardiac repair procedures. She developed liver nodules with congestive cirrhosis secondary to severe mitral regurgitation and an atrial septal defect. A percutaneous liver biopsy showed hepatocellular carcinoma with liver fibrosis, which was treated using transarterial chemoembolization.

Key words: Hepatocellular carcinoma, Tetralogy of Fallot, mitral regurgitation, atrial septal defect, transarterial chemoembolization

(Intern Med Advance Publication) (DOI: 10.2169/internalmedicine.7827-21)

Introduction

With recent advances in congenital heart surgery and intensive care medicine, many patients with congenital heart disease are now reaching adulthood. As a result, late complications are becoming more frequent clinical problems in such patients, and one of those complications is progressive liver disease. There are several reports of hepatocellular carcinoma (HCC) in patients after the Fontan operation (1). In addition, since HCC development was reported after the Mustard operation in 2005 (2), it has also been shown that patients with a history of congenital heart disease who undergo non-Fontan surgery can develop HCC (2-5). However, there are only a few reports on HCC management in patients with cirrhosis following repair of tetralogy of Fallot (TOF).

We herein report a case of HCC in a 34-year-old woman with a history of TOF and 5 cardiac repair procedures, managed with transarterial chemoembolization (TACE).

Case

A 34-year-old woman with a history of TOF and a persistent left superior vena cava was referred to the hepatology department because of high alpha-fetoprotein (AFP) levels, and abdominal ultrasonography detected a mass at the right hepatic lobe. She had undergone right ventricular outflow tract reconstruction 5 times over 15 years until the age of 16, and a pacemaker had been implanted due to complete atroventricular block at the age of 6. At 27 years old, cardiac catheterization identified a high central venous pressure (CVP) (23 mmHg), and the liver enzyme levels had gradually increased. During follow-up, right heart failure worsened with a gradual increase in CVP associated with R-L shunt of the atrial septal defect (ASD). Subsequently, the total bilirubin values, gamma guanosine triphosphate (GTP), and alkaline phosphatase level were elevated, and the platelet counts were decreased.

At her first visit, the laboratory data revealed high values of AFP, lens culinaris agglutinin-reactive fraction of AFP (AFP-L3), des-γ-carboxy prothrombin, hyaluronic acid, and type IV collagen 7S, along with a low platelet count (Table 1). Abdominal ultrasonography showed a 15-mm nodule on the right hepatic lobe, and ultrasonography indicated the presence of chronic liver disease with a nodular surface, a dull edge of the liver, and a dilated hepatic vein (Fig. 1A). The Child-Pugh score was 6 due to ascites controlled by...
Table 1. Laboratory Data.

| Test     | Value       | Test     | Value       |
|----------|-------------|----------|-------------|
| WBC      | 4.550 μL    | Na       | 137 mEq/L   |
| RBC      | 4.63×10^12/μL | K       | 4.5 mEq/L   |
| Hb       | 15.2 g/dL   | Cl       | 101 mEq/L   |
| Ht       | 46 %        | BUN      | 19 mg/dL    |
| Plt      | 10.7×10^11/μL | Cr     | 0.77 mg/dL  |
| PT activity | 61 %       | cGFR     | 69.4 mL/min/1.73 m² |
| PT-INR   | 1.32        | TP       | 7.8 g/dL    |
| AST      | 25 U/L      | Alb      | 4.1 g/dL    |
| ALT      | 19 U/L      | T-Chol   | 128 mg/dL   |
| γ-GTP    | 123 U/L     | Hba1c    | 6.2 %       |
| ALP      | 175 U/L     | BTR      | 3.62        |
| LDH      | 170 U/L     | BCAA     | 235 μmol/L  |
| T-Bil    | 2.0 mg/dL   | TYR      | 65 μmol/L   |
| D-Bil    | 1.0 mg/dL   | IgG      | 1,484 mg/dL |
| CRP      | 1.09 mg/dL  | IgM      | 124 mg/dL   |

WBC: white blood cell, RBC: red blood cell, Hb: hemoglobin, Ht: hematocrit, Plt: platelet, PT: prothrombin time, PT-INR: prothrombin time international normalized ratio, AST: aspartate aminotransferase, ALT: alanine aminotransferase, γGTP: γ-glutamyl transpeptidase, ALP: alkaline phosphatase, LDH: lactate dehydrogenase, T-Bil: total bilirubin, D-Bil: direct bilirubin, CRP: C-reactive protein, Na: sodium, K: potassium, Cl: chlorine, BUN: blood urea nitrogen, eGFR: estimated glomerular filtration rate, TP: total protein, Alb: albumin, T-Chol: total cholesterol, Hba1c: hemoglobin A1c, IgG: Immunoglobulin G, IgM: Immunoglobulin M, M2BPgi: mac-2-binding protein glycosylation isomer, FIB4-index: Fibrosis-4 Index, AFP: α-fetoprotein, ALP: third electrophoretic form of lentil lectin-reactive AFP, DCP: des-γ-carboxy prothrombin, CEA: Carcinoma embryonic antigen, CA19-9: Carbohydrate antigen 19-9, BTR: ratio of total branched-chain amino acid, BCAA: branched chain amino acid, TYR: tyrosine, HBsAg: hepatitis B surface antigen, Anti-HBs: antibody to hepatitis B surface antigen, Anti-HBe: antibody to hepatitis B core antigen, Anti-HCV: antibodies against hepatitis C virus, ALBI: albumin bilirubin, N.D.: not detected

diuretics. She had no other causes of liver disease, including viral hepatitis, alcohol consumption, autoimmune antibodies, or metabolic factors, such as diabetes mellitus, obesity, or fatty liver.

Contrast-enhanced ultrasonography revealed a 15-mm nodule at segment (S) 8 with enhancement in the early phase, washout in the vascular phase, and a defect pattern in the post-vascular phase (Fig. 1B). On dynamic computed tomography (CT) of the abdomen, the lesion showed arterial enhancement (Fig. 1C) and washout in the portal phase (Fig. 1D). She did not undergo gadolinium-ethoxybenzyl diethyleneetramine pentaaetetic acid-enhanced magnetic resonance imaging (EOB-MRI) as she had a pacemaker. A percutaneous ultrasound-guided needle biopsy targeting the liver nodule at S8 was performed using a 21-gauge sonopsy needle (Hakko, Nagano, Japan). The histological examination confirmed well- to moderately differentiated HCC (Fig. 2A) with fibrosis around the portal vein area and bridging fibrosis in the liver section (Fig. 2B).

The HCC was considered a candidate for surgical resection or radiofrequency ablation (RFA) according to the clinical guideline. Therefore, her cardiac function was evaluated. An echocardiogram showed right ventricular enlargement and interventricular septal flattening during systole with an R-L shunt of the ASD, indicating a stage of pressure overload. She received furosemide (60 mg), spironolactone (75 mg), and tolvaptan (7.5 mg), and her systolic blood pressure was maintained at 90 mmHg. Since she had a mixed ventricular defect (vital capacity, 59%; forced expiratory volume in 1 s, 31%) with an R-L shunt of the ASD, a constant oxygen supply (1 L/min) was needed.

Considering her decreased cardiac function, surgical resection of the HCC was impossible, and RFA was avoided because the HCC nodule was in contact with the diaphragm. Therefore, TACE was selected as locoregional therapy after obtaining informed consent from the patient. Abdominal angiography detected another HCC near the known HCC at S8 (Fig. 3A, B). TACE treatment with epirubicin (5 mg) and lipiodol (0.5 mL) plus 1-mm gelatin sponge particles (2 mg) was performed from the S8 hepatic artery for each lesion, followed by confirmation of lipiodol deposits by non-contrast-enhanced CT (Fig. 3C, D). The liver and cardiac function were maintained after TACE, and the patient was discharged without any complications on day 15. Five months after TACE, the levels of AFP, AFP-L3, and DCP were normalized (AFP, 6 ng/mL; AFP-L3, less than 10%; DCP, 14 mAU/mL), and no recurrence of HCC was seen on abdominal imaging.

**Discussion**

TOF is the most common and fatal congenital cyanotic heart condition. The first surgical repair of TOF was reported in 1954 in a cohort of 106 patients, with a 30-year survival rate of 77% (6, 7). Currently, the proportion of patients who survive into adulthood has increased by more than 90% due to advances in surgical techniques and medications (8, 9). TOF repair diverts blood from the right ventricle to the pulmonary arteries, thereby increasing the survival in infants with hypoxia (10). However, a prolonged
survival after TOF repair leads to elevated pulmonary and right-sided heart pressures, which then cause chronic passive hepatic congestion (11). Prolonged passive chronic hepatic venous congestion leads to chronic centrilobular hypoxia (12) and the formation of regenerative nodules and eventual cirrhosis, also known as cardiac cirrhosis (13). There have been several reports about HCC related to cardiac cirrhosis, which developed in Fontan patients (14). Since 2005, it has been reported that HCC can also develop in patients with congenital heart disease with non-Fontan surgery (2-5). As shown in Table 2, recent studies identified two cases of TOF who were diagnosed with HCC (4, 5)

**Figure 1.** Abdominal ultrasonography showing a hepatic nodule 15 mm in size at the right lobe, a dull edge in the liver, and a dilated hepatic vein (A). Contrast-enhanced ultrasonography showed a lesion 15 mm in size with enhancement in the early phase, washout in the vascular phase and a defect pattern in the post-vascular phase (B). Dynamic computed tomography of the abdomen showed a round lesion 15 mm in size at segment 8 that had arterial enhancement (C) and washout in the portal phase with delayed peripheral enhancement and a non-homogeneous pattern of hepatic enhancement in the portal vascular phase due to congestive liver (D).

**Figure 2.** Histological findings showing that the nuclear/cytoplasmic ratio was increased with atypical cells aggregated with irregular trabecular patterns (A). Contrast findings showing increased fibrosis around the portal vein area and bridging fibrosis in the liver section (B).
two cases diagnosed with combined hepatocellular-cholangiocarcinoma (15, 16). Although our patient showed a high level of AFP and several images indicated typical HCC, we performed a histological examination to rule out combined hepatocellular-cholangiocarcinoma. The age at the HCC diagnosis ranges from 24 to 54 years old, and the time elapsed since surgical repair is generally between 21 and 47 years. In the present case, HCC was diagnosed at 34 years old, which was 18 years after surgical repair. Therefore, we recommend that early follow-up for congestive hepatopathy and liver tumor be considered in such patients.

Regarding the background liver, Fig. 2B shows fibrosis around the portal vein area and bridging fibrosis with sinusoidal dilatation. However, in our case, fibrosis markers were not markedly increased (Table 1). Noninvasive serologic biomarkers are unlikely to effectively predict the fibrosis risk in congestive hepatopathy (17), probably due to non-inflammatory liver disease of congestive hepatopathy. Further studies are needed to identify a noninvasive fibrosis markers for estimating liver fibrosis in congestive hepatopathy.

Chronic elevation of CVP due to congenital heart disease, as observed in this case, leads to congestive hepatopathy and hepatic fibrosis. Following the cardiac repair procedure, patients with TOF can develop cirrhosis and HCC. These patients require lifelong follow-up with both a pediatric cardiologist and a hepatologist. As patients with congenital heart diseases may not be good candidates for surgical resection of HCC due to a decreased heart function, other treatment options should be considered. Our patient had a decreased cardiac function, indicating that surgical resection of the HCC was impossible. One HCC nodule was in contact with

**Figure 3.** Abdominal angiography showing sub-diaphragm hepatocellular carcinoma at segment 8 (A, B). Non-contrast-enhanced computed tomography after transarterial chemoembolization (C, D).

**Table 2.** Characteristics of the Five Patients with Tetralogy of Fallot Diagnosed with Hepatocellular Carcinoma.

|   | Gender | Age at diagnosis of HCC, years | Age at surgical repair, years | Time elapsed since the surgical repair, years | AFP level (ng/mL) | Pathology                        |
|---|--------|--------------------------------|-------------------------------|---------------------------------------------|------------------|----------------------------------|
| 1  | Male   | 45                             | N.A.                          | N.A.                                        | 79.4             | Hepatocellular carcinoma         |
| 2  | Female | 24                             | 3                             | 21                                          | 99               | Hepatocellular carcinoma         |
| 3  | Female | 27                             | 3                             | 24                                          | 55.9             | Hepatocellular-cholangiocarcinoma |
| 4  | Female | 54                             | 7                             | 47                                          | 16,208           | Hepatocellular-cholangiocarcinoma |
| Our case | Female | 34                             | 2                             | 32                                          | 792              | Hepatocellular carcinoma         |

HCC: hepatocellular carcinoma, AFP: alpha-fetoprotein, N.A.: not available
the diaphragm, which required artificial ascites for percutaneous radiofrequency ablation. However, artificial ascites sometimes causes iatrogenic pleural effusion, which can carry a risk of severe respiratory disorders in patients who require a constant oxygen supply due to an impaired cardiac function. Radiation therapy was not selected because we worried about radiation lung injury. Therefore, TACE was selected as a local treatment for our patient with HCC.

We herein report an HCC patient with severe cardiopulmonary dysfunction following TOF repair that was managed with TACE. As there have been several cases of HCC with congestive hepatopathy after the Fontan procedure for single-ventricle physiology, congestive hepatopathy with Fontan-associated liver disease (FALD) is recognized as a risk factor of HCC. However, there are few reports of the outcomes of HCC after cardiac repair of TOF. We should pay attention to the development of HCC in cases with congestive liver disease other than FALD.

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

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