

CASE REPORT

ADVANCED

CLINICAL CASE

Fontan Liver Lesions: Not Always HCC



Christiane Haeffele, MD, MPH,^{a,b} Avin Aggarwal, MBBS,^c Glen Lutchman, MD,^c Gruschen R. Veldtman, MD,^d Fred M. Wu, MD,^{e,f} George K. Lui, MD^{a,b}

ABSTRACT

A 24-year-old Fontan procedure patient underwent surveillance liver cardiac magnetic resonance imaging. Findings were suggestive of hepatocellular carcinoma (HCC). Currently, HCC is diagnosed based on imaging alone. Given her otherwise reassuring clinical profile, she underwent liver biopsy. Pathology demonstrated focal nodular hyperplasia. This raises concern for overdiagnosis of HCC in Fontan patients without tissue confirmation. (**Level of Difficulty: Advanced.**) (J Am Coll Cardiol Case Rep 2019;1:175-8) © 2019 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

HISTORY OF PRESENTATION

A 24-year-old female presented with a history of right-sided heterotaxy including asplenia, an unbalanced atrioventricular canal with hypoplastic left ventricle and double-outlet right ventricle, and pulmonary artery hypoplasia. She had undergone a Blalock-Taussig shunt procedure in infancy until adequate growth of the pulmonary arteries was achieved. A bidirectional Glenn operation was performed within her first year of life. The third stage of single-ventricle palliation was completed with a lateral tunnel Fontan procedure at age 12. She was then converted to an extracardiac Fontan procedure at 13 years of age.

LEARNING OBJECTIVES

- To recognize that Fontan-associated liver disease is a different disease entity from more prevalent types of cirrhosis.
- To highlight the need for more Fontan-specific imaging guidelines.
- To consider biopsy in the evaluation of lesions concerning for hepatocellular carcinoma in the Fontan patient.

In 2016, she presented for follow-up. She was assessed New York Heart Association functional class I, and her review of symptoms was negative, including any abdominal symptoms. An echocardiogram demonstrated a moderately dilated systemic right ventricle with mildly reduced systolic function. Her liver function test results were within normal limits, with a total bilirubin concentration of 0.7 mg/dl, an aspartate aminotransferase concentration of 19 IU/l, an alanine aminotransferase level of 42 IU/l, and an alkaline phosphatase level of 71 IU/l. Her alpha-fetoprotein level (AFP) was normal at 3 ng/ml. Review of her liver function test results dating back to 2009 showed normal values. Her hepatitis C antibody was negative, and her hepatitis B test results were consistent with immunization. Platelets were $286 \times 10^3/\mu\text{l}$, international standardize ratio was 1.0, and albumin concentration was 4.1 g/dl.

MEDICAL HISTORY

The patient was a nonsmoker and did not drink alcohol. Her medications included losartan, aspirin, and combined oral estrogen/progesterone contraceptive pills. She had no history of prior hepatotoxic medications or exposures.

From the ^aDepartment of Medicine, Division of Cardiovascular Medicine, Stanford University, Palo Alto, California; ^bDepartment of Pediatrics, Division of Pediatric Cardiology, Stanford University, Palo Alto, California; ^cDivision of Gastroenterology and Hepatology, Stanford University, Palo Alto, California; ^dCincinnati Children's Hospital Adolescent and Adult Congenital Heart Program, Cincinnati, Ohio; ^eDepartment of Cardiology, Boston Children's Hospital, Boston, Massachusetts; and the ^fDepartment of Medicine, Brigham and Women's Hospital, Boston, Massachusetts. The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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**ABBREVIATIONS
AND ACRONYMS****AASLD** = American Association
for Study of Liver Disease**AFP** = alpha-fetoprotein**ALT** = alanine aminotransferase**AST** = aspartate
aminotransferase**AV** = atrioventricular**CT** = computed tomography**FALD** = Fontan associated liver
disease**FNH** = focal nodular
hyperplasia**GS** = glutamine synthetase**HCC** = hepatocellular
carcinoma**INR** = international normalized
ratio**MRI** = magnetic resonance
imaging**US** = ultrasound

A routine liver cardiac magnetic resonance (CMR) performed to screen for cirrhosis showed evidence of fibrosis on the basis of hyperintense reticulations (Figure 1A) and elastography (Figure 1B). Two lesions (Figure 2) were visualized that exhibited arterial enhancement and delayed phase washout, findings believed to be consistent with hepatocellular carcinoma (HCC). One lesion measured 1.2 × 0.8 cm, and the second lesion measured 1.2 × 1.4 cm. Both lesions had a pseudocapsule.

According to current guidelines, in the setting of cirrhosis, HCC is diagnosed by imaging alone, due in part to the 2.7% risk of tumor seeding with biopsy (1). Following 2010 American Association for Study of Liver Disease criteria, if a lesion is >1 cm, has early post-contrast arterial enhancement, and has delayed phase washout, HCC can be diagnosed with a high pretest probability. Based on these guidelines, elective chemo-

embolization is generally recommended.

The patient underwent cardiac catheterization after the findings of the liver CMR images, which revealed normal Fontan hemodynamics. Cardiac index was 4.9 l/min per m² by the Fick method with a Fontan pressure of 8 mm Hg. Transpulmonary gradient was 4 mm Hg, and her right (systemic) ventricular pressure was 109/4 mm Hg. There were no significant gradients throughout the Fontan pathway or across her aorta. Her pulmonary vascular resistance was 0.8 WU. Her mixed venous saturation was 81% with a systemic saturation of 93%.

The patient's data were reviewed by a multidisciplinary and multi-institutional group of adult congenital heart disease and hepatology experts. Given the patient's unremarkable Fontan hemodynamics, her normal liver tests, and lack of cirrhosis history, the consensus recommendation was to take a biopsy of the liver lesions. The risks were discussed with the patient.

INTERVENTION

A CT-guided liver biopsy was performed. Fifteen core samples were taken from the right-sided hepatic lesion concerning in appearance for HCC. Histopathology was consistent with focal nodular hyperplasia (FNH). Tissue samples showed the characteristic fibrosis with ductules at the interface between hepatocytes and the fibrous region, and prominent arteries, all intrinsic to FNH (Figure 3A). Copper-binding protein, also expressed in FNH, was seen (Figure 3B).

Finally, staining for glutamine synthetase, which is overproduced in FNH in a "map-like" pattern, was also positive (Figure 3C). The other lesions were not biopsied.

DISCUSSION

Fontan circulations have obligatory venous hypertension and decreased cardiac output, given the reliance on a single ventricle for complete circulatory support. Venous hypertension has been associated with greater transmission of mechanical tension to the liver matrix, which is believed to then cause fibrosis. Depressed cardiac output and cyanosis are also likely to contribute to signaling for fibrosis through hypoxia-inducible factors. The net result is the development of Fontan-associated liver disease (FALD).

The process is insidious and may lead to overt cirrhosis and liver failure. Cirrhosis in this setting is associated with survival of 35% at 5 years after diagnosis (2). Additionally, HCC has been demonstrated in Fontan patients and presents significant concern for long-term prognosis.

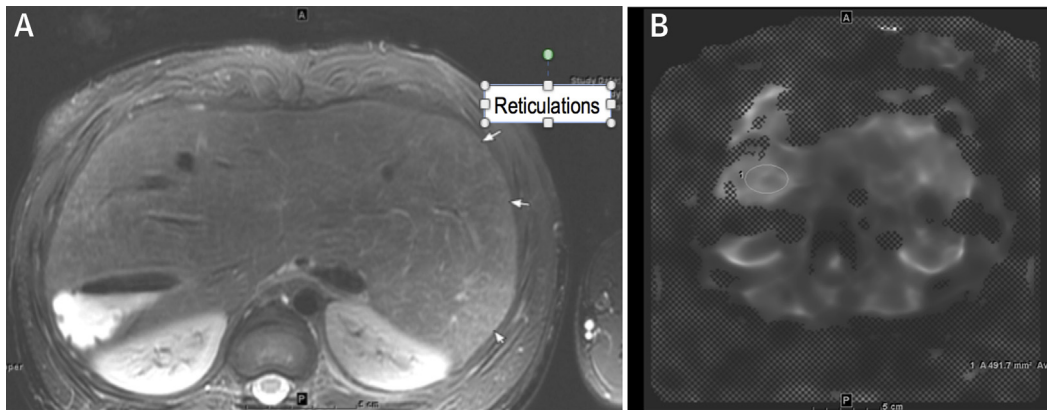
Routine screening for liver disease in Fontan patients remains a challenge. Noninvasive measurements of hepatic function remain intact until advanced stages of hepatic fibrosis. Hypervascular nodules are often present in Fontan patients (3,4). Determining which lesions are potentially benign, reactive lesions versus HCC is one of the difficulties in FALD evaluation. Case reports have been published documenting the presence of HCC in patients approximately 14 to 22 years after Fontan procedure (3). Most of these patients had documented cirrhosis and elevated AFP.

This patient did not have risk factors detailed in other case reports of HCC in Fontan patients (3). She had excellent Fontan pressures, serologic testing indicated good hepatic synthetic function, her cardiac index was normal, and her AFP levels were normal.

Current guidelines recommend diagnosing HCC by imaging alone in patients with cirrhosis or an otherwise high pre-test probability (5). The imaging guidelines for HCC screening and treatment are based primarily on patients with a history of chronic viral hepatitis or alcoholic cirrhosis, which are inflammatory states. In contrast, Fontan liver physiology is primarily a congestive state. Although there may be a final common pathway for these different disease states, in the absence of more definitive data, Fontan liver physiology cannot be treated using the same protocols.

In cases with atypical radiological features, tissue diagnosis by either fine needle aspiration or biopsy is

FIGURE 1 Hyperintense Reticulations Consistent With Fibrosis



(A) Axial T2, fine T2 hyperintense reticulations consistent with fibrosis. **(B)** MR elastogram, heterogeneous in distribution but highest area measured was 3.5 kPa. Elastography of 3.5 kPa has been demonstrated to correlate with stage F0 to F1 fibrosis.

recommended (6). Given that the long-term effects of FALD have not been well delineated, biopsy can aid in diagnosis and prognostication. Newer biopsy methods, such as the coaxial technique, have not resulted in tumor seeding along the biopsy track as seen with other methods (7).

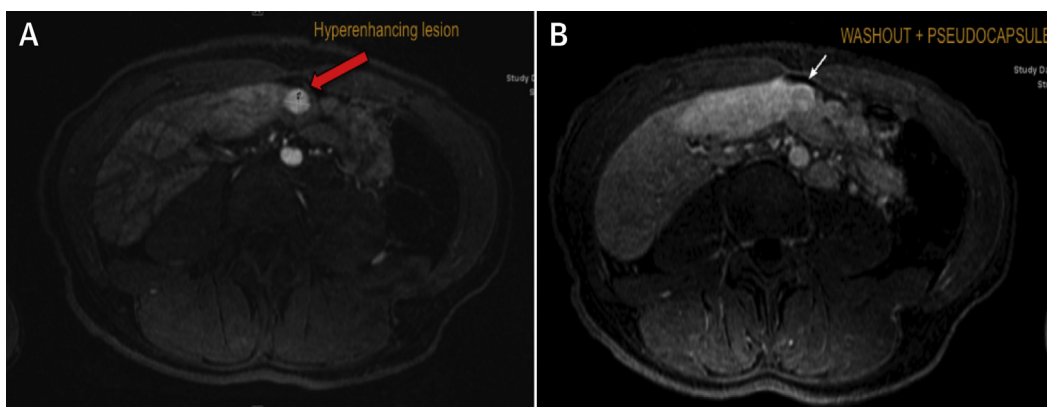
Currently, there are no guidelines regarding liver surveillance in Fontan patients. The American Association for the Study of Liver Disease recommends liver imaging every 6 months in patients with hepatitis B and C infection, alcoholic cirrhosis, and hemochromatosis (5). A recent FALD stakeholder meeting suggested liver imaging in Fontan patients every 6 months if cirrhosis is detected (8). There is no consensus as to when to start screening or which

imaging modality (ultrasonography, CMR, or CT) should be used.

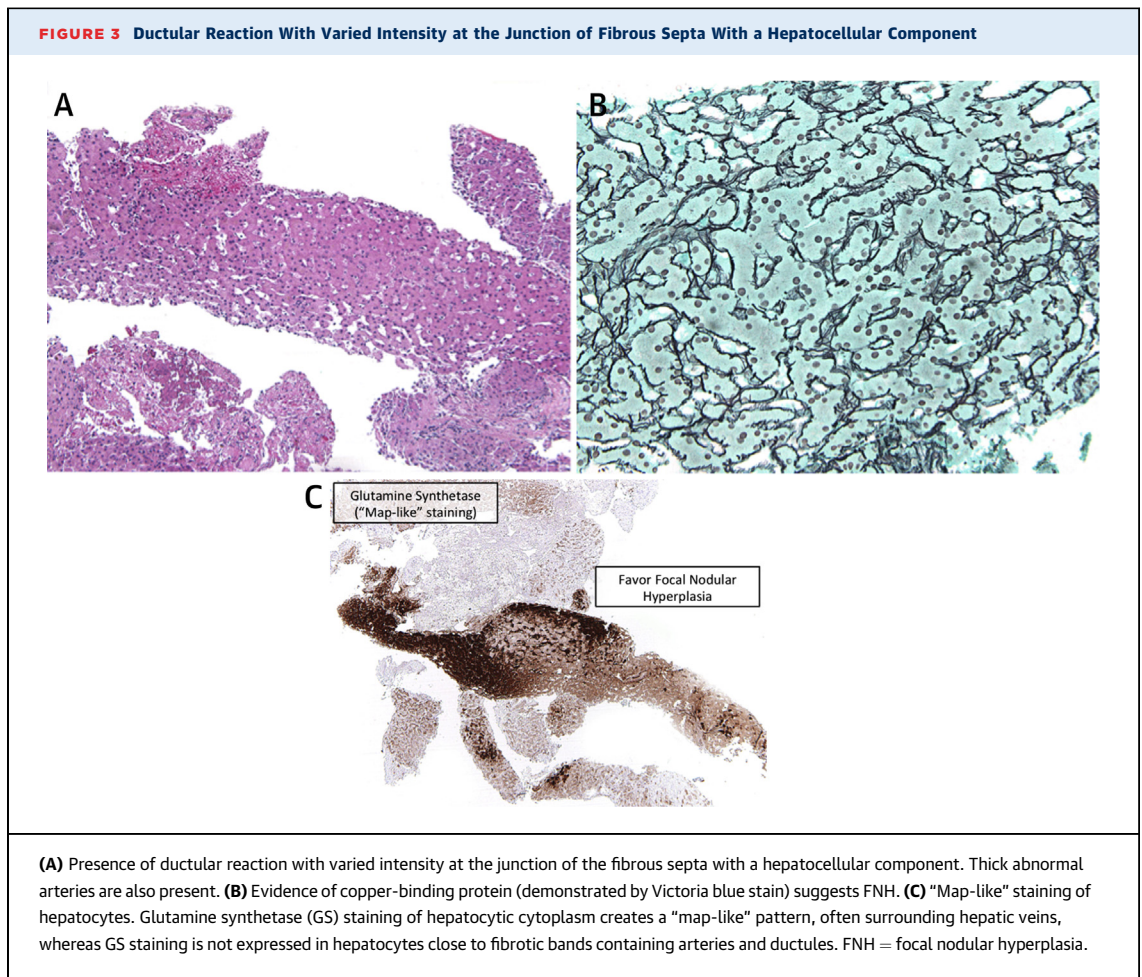
More study is needed to determine the utility of liver surveillance and biopsy in FALD. Overscreening may lead to unnecessary testing and invasive procedures. However, if recommendations are too conservative, early stage cancer or cirrhosis may be missed. The diagnosis of HCC has important implications, as the treatment of choice is liver transplantation. In Fontan patients, liver transplantation generally would only be considered as part of a combined heart-liver transplantation (9).

The present case suggests the importance of liver biopsy in the evaluation of liver lesions suspicious for HCC. The present authors believe a full hepatic

FIGURE 2 Arterial Phase Enhancement and Venous Phase Washout



(A) Arterial phase shows hyperenhancement. **Oval circle in A** indicates a nodule that shows hyperenhancement during the arterial phase of the scan. **(B)** Venous phase shows slightly hypointense/washout with a suggestion of pseudocapsule.



evaluation of the Fontan patient must include a biopsy if suspicious findings are present on imaging.

FOLLOW-UP

Our patient continues to be closely monitored. Serial repeat CMR studies have demonstrated stable liver

nodules without significant interval growth or the appearance of new lesions.

ADDRESS FOR CORRESPONDENCE: Dr. Christiane Haeffele, Stanford University, 870 Quarry Road Extension, Palo Alto, California 94304. E-mail: haeffele@stanford.edu.

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KEY WORDS awareness, congenital heart defect, cyanotic heart disease, imaging, treatment