Received: 10 September 2018 | Revised: 24 October 2018 | Accepted: 22 November 2018

DOI: 10.1111/chd.12730

ORIGINAL ARTICLE

WILEY Congenital Heart Disease

Focal liver lesions following Fontan palliation of single ventricle physiology: A radiology-pathology case series

Emily M. Engelhardt BS[1] | Andrew T. Trout MD[2,3] | Rachel M. Sheridan MD[4] | Gruschen R. Veldtman MBChB[5] | Jonathan R. Dillman MD, MSc[2,3]

[1]University of Cincinnati College of Medicine, Cincinnati, Ohio

[2]Department of Radiology, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio

[3]Department of Radiology, University of Cincinnati College of Medicine, Cincinnati, Ohio

[4]Division of Pathology and Laboratory Medicine, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio

[5]Adult Congenital Heart Disease Program, Heart Institute, Department of Pediatrics, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio

Correspondence
Andrew T. Trout, MD, Department of Radiology, MLC 5031, Cincinnati Children's Hospital Medical Center, Cincinnati, OH 45229. Email: andrew.trout@cchmc.org

Abstract

Purpose: Patients who have undergone Fontan palliation of single ventricle physiology congenital heart disease are prone to developing focal liver lesions. In our experience, the variety of lesions occurring in this population is greater than that described in the literature. The purpose of this study was to describe the breadth of biopsy-proven liver lesions in patients post–Fontan palliation of single ventricle physiology cared for at our institution.

Methods: We retrospectively identified patients who had previously undergone the Fontan operation and had a focal liver lesion biopsied between January 2000 and June 2018. Medical records were reviewed for lesion pathology, background liver findings, pertinent laboratory data, and demographic data. CT and MRI images were reviewed to describe imaging findings of the reported lesions.

Results: Twelve patients met inclusion criteria; 58% (7/12) of which were female. Fifteen lesions were biopsied including four macroregenerative/benign hepatocellular hyperplastic nodules, two hepatocellular adenomas, two hepatocellular carcinomas, two intrahepatic cholangiocarcinoma (in the same patient), one venous malformation, and one focus of vascularized scar tissue. Two additional lesions in patients postcardiac transplant were posttransplant lymphoproliferative disorder.

Conclusion: Patients who have undergone Fontan palliation of single ventricle physiology are prone to develop a variety of liver lesions, both benign and malignant.

KEYWORDS

congenital heart disease, Fontan operation, histopathology, imaging features, liver lesion

1 | INTRODUCTION

The Fontan operation involves connecting the inferior vena cava (via an extracardiac conduit or intracardiac lateral tunnel) to the pulmonary arteries, in addition to directly anastomosing the superior vena cava to the pulmonary arteries. This channels systemic venous blood directly to the lungs without first going through a subpulmonary ventricular chamber. The Fontan operation has been an effective palliative procedure for patients born with single ventricle physiology congenital heart disease.[1] However, the procedure causes a sustained increase in central venous pressure (CVP) with dynamic augmentation of CVP during exertion. These pressures are directly transmitted to the liver and other end organs. As a result, hepatic complications, among other systemic complications, are increasingly being identified in patients who have undergone Fontan palliation.[1,2]

The cause of hepatic complications following Fontan is likely multifactorial, including CVP elevation with associated chronic hepatic congestion, increased mesenteric vascular resistance, and oftentimes inadequate cardiac output, which may lead to intermittent hypoxemic insults.[1] These physiologic consequences ultimately

may result in hepatic fibrosis, cirrhosis, portal hypertension, and focal liver lesions.[1,3] Increasingly, focal liver lesions, including hepatocellular neoplasms, are being identified in Fontan patients. Lesions that have been described in patients post-Fontan include hepatocellular carcinoma, hepatocellular adenomas (rare), intrahepatic cholangiocarcinoma, and most often regenerative and focal nodular hyperplasia (FNH)-like hypervascular nodules.[2,4-6]

The purpose of this study was to add to the existing literature regarding focal liver lesions in patients after the Fontan operation by reporting our single-center experience with biopsy-proven focal liver lesions in this population. We have deliberately limited this report to lesions diagnosed on the basis of histopathologic sampling, as liver lesions in this population may have atypical imaging appearances which can lead to incorrect diagnoses.[2]

2 | METHODS

Our institutional review board approved this single-institution retrospective review and waived the requirement for informed consent. All study activities complied with the Health Insurance Portability and Accountability Act (HIPAA, USA 1996).

Using an electronic search tool (Illuminate InSight; Softek, Overland Park, Kansas), we identified all patients (no age cutoff as liver disease in this population occurs across a broad age range from childhood to adulthood) at Cincinnati Children's Hospital Medical Center with a history of single ventricle physiology congenital heart disease palliated with the Fontan operation that had undergone biopsy of one or more focal liver lesions between January 1, 2000 and June 15, 2018.[7] Our search tool allows a query of both imaging and pathology records. Examples of search terms used included: Fontan, congenital heart disease, cavopulmonary anastomosis, liver, mass, lesion, biopsy, hepatocellular, hepatocellular carcinoma, and adenoma. Furthermore, an institutional database of all patients with a history of the Fontan operation was reviewed for patients who met inclusion criteria. Identified patients' electronic medical records were searched to assess for focal liver lesions identified by imaging with histopathologic correlation.

A single reviewer (EME), under the supervision of two board certified Pediatric Radiologists (JRD and ATT) reviewed pertinent electronic medical records (EPIC, Verona, Wisconsin) of all patients identified to confirm a history of single ventricle physiology status post–Fontan operation and history of one or more focal liver lesions than underwent biopsy. Medical records also were reviewed for: age at biopsy, interval from Fontan operation to biopsy, lesion histopathologic diagnosis, and laboratory values closest prior to biopsy (aspartate aminotransferase [AST], alanine aminotransferase [ALT], total bilirubin, direct bilirubin, gamma-glutamyl transferase [GGT], alkaline phosphatase, alpha-fetoprotein [AFP]).

The most recent CT and/or MRI examination preceding the biopsy for each patient was reviewed by a single board-certified pediatric radiologist (ATT) in order to document: total number of focal liver lesions, size (greatest transverse dimension) of the biopsied lesion, and imaging features (signal intensity or attenuation characteristics, enhancement pattern) of the biopsied lesion.

Descriptive statistics were performed, with continuous data summarized using medians and ranges and categorical data summarized using counts and percentages (Microsoft Excel; Microsoft Corp., Redmond, Washington).

3 | RESULTS

Twelve patients met inclusion criteria; 58% (7/12) of which were female. Median age at the time of liver biopsy was 19 years 11 months (range: 10 years 9 months-33 years 9 months). The median time interval between the Fontan operation and liver biopsy was 14 years (range: 7-30 years). Specific palliated cardiac lesions in the study population are detailed in Table 1. Thirty-three percent (4/12) of patients had a lateral tunnel Fontan pathway, with the remaining 67% (8/12) having an extracardiac Fontan pathway.

3.1 | Biopsied liver lesions

Fifteen lesions were targeted for biopsy, all via an image-guided percutaneous approach (Tables 1 and 2). The indications for biopsy varied and are detailed in Table 2. Three patients each had two lesions targeted for biopsy, while all other patients had a single lesion targeted. Two lesions biopsied were in patients with history of Fontan palliation of single ventricle physiology who had subsequently undergone heart transplant. One patient had undergone heart transplant 11 years 7 months after the Fontan operation and underwent lesion biopsy 5 months after heart transplant. The other patient had undergone heart transplant 4 months after the Fontan operation and underwent lesion biopsy 15 years 9 months after heart transplant. These patients were included in the cohort because patients with a history of Fontan palliation may have liver lesions that developed under the influence of the Fontan circulation that persist after cardiac transplantation.

Eighty-seven percent (13/15) of lesions targeted for biopsy were in the right lobe of the liver. One lesion was located in the left lobe and one lesion was in the caudate. The median number of core biopsies obtained was three (range: 1-8). Lesional tissue was not obtained for 1 lesion, suggesting the lesion was not adequately sampled at biopsy. Biopsies of background liver (nonlesional) tissue were obtained in 11 patients.

3.2 | Histopathology of liver lesions

Four of 15 (27%) biopsied lesions were described as macroregenerative/benign hepatocellular hyperplastic nodules (Figure 1). Two (13%) lesions were hepatocellular adenomas, one of the inflammatory subtype and the other of a mixed subtype (hepatocyte nuclear factor 1α [HNF1α] inactivated with beta-catenin activation) (Figure 2). Two (13%) lesions were hepatocellular carcinomas, one of which was of the fibrolamellar subtype (Figure 3).

TABLE 1 Patient details including specific heart condition, Fontan type, and lesion diagnosis

Patient #	Palliated cardiac lesion(s)	Type of Fontan operation	Interval since Fontan operation (years)	Age at biopsy (years)	# Lesions on imaging	Histopathology of biopsied lesion(s)
1	Hypoplastic left heart syndrome	Lateral tunnel	19.8	22.3	>10	Macroregenerative/benign hyperplastic nodule
2[a]	Hypoplastic left heart syndrome and malposed great vessels	Extracardiac	28.5	32.3	2	Intrahepatic cholangiocarcinoma
			29.3	32.5	Occult	Intrahepatic cholangiocarcinoma
3	Tricuspid atresia	Extracardiac	7.3	10.8	>10	[b]
4	D-transposition of the great arteries with pulmonary stenosis and multiple ventricular septal defects	Extracardiac	26.2	30.2	1	Venous malformation
5	Double-inlet left ventricle	Extracardiac	11.5	15.7	>10	Benign hepatocellular hyperplastic/macroregenerative nodule Benign hepatocellular hyperplastic/macroregenerative nodule
6	L-transposition of the great vessels with hypoplastic left-sided systemic right ventricle	Extracardiac	11.9	16.2	>10	Adenoma, inflammatory subtype Macroregenerative nodule
7	Heterotaxy with unbalanced atrioventricular canal defect and hypoplastic left ventricle	Lateral tunnel	~11[c]	17.1	>10	Adenoma, mixed HNF1α-inactivated and beta-catenin activated
8	Unbalanced atrioventricular canal	Extracardiac	13.6	19.9	2	Vascularized scar tissue
9	Tricuspid atresia	Lateral tunnel	11.2	15.0	1	Hepatocellular carcinoma, fibrolamellar type
10	Double-out right ventricle[d]	Extracardiac	16.1	20.7	3	Possible posttransplant lymphoproliferative disorder
11	Hypoplastic left heart syndrome[d]	Extracardiac	12.0	15.8	3	Posttransplant lymphoproliferative disorder
12	Double-inlet left ventricle	Lateral tunnel	~30[c]	33.7	3	Hepatocellular carcinoma

Abbreviation: HNF1α, hepatocyte nuclear factor 1α.
[a]Previously reported in Wang et al.[6]
[b]Diagnosis provided did not report a focal lesion, suggesting lesional tissue was not obtained.
[c]Exact date of Fontan Operation not known (only year known).
[d]Patient's status post-heart transplant.

One lesion (7%) was a venous malformation. Two (13%) lesions, both from the same patient, one at diagnosis and one at recurrence 10 months later, were intrahepatic cholangiocarcinoma. This case has been previously reported.[6] Posttransplant lymphoproliferative disorder (PTLD) was confirmed in one of the patients with history of cardiac transplant and is suspected in the other posttransplant patient. One lesion that appeared distinct by imaging (7%) was diagnosed as vascularized scar tissue by histopathology. Imaging features for each of the biopsied lesions are detailed in Table 2.

TABLE 2 Pertinent laboratory values and imaging features for the biopsied lesions

Patient #	Indication for biopsy	Histopathology of biopsied lesion(s)	Serum AFP (normal < 8 ng/mL)	Size of biopsied lesion	Imaging modality	Imaging description
1	New lesion heterogeneity in the hepatocyte phase	Macroregenerative/benign hyperplastic nodule	23.7↑	1.1 cm	MRI	Precontrast: T1-W isointense T2-W isointense DWI isointense Postcontrast: Arterial phase hyperintense Portal venous phase hyperintense Equilibrium phase hyperintense Hepatocyte phase heterogeneously hyperintense
2[a]	Imaging concern for malignancy	Intrahepatic cholangiocarcinoma	37.9↑	4.7 cm	CT	Postcontrast: Arterial phase hypoattenuating Portal venous phase hypoattenuating w/enhancing rim
	Imaging concern for tumor recurrence	Intrahepatic cholangiocarcinoma	24.1↑	Occult	CT	Occult (detected by FDG PET)
3	Listing for cardiac transplant	[b]	2.2	0.8 cm	MRI	Precontrast: T1-W isointense T2-W isointense DWI isointense Postcontrast: Arterial phase hyperintense Portal venous phase hyperintense Equilibrium phase hyperintense Hepatocyte phase hyperintense
4	Indeterminate lesion by CT, contraindication to MRI	Venous malformation	2.3	1.7 cm	CT	Postcontrast: Portal venous phase hypoattenuating with nodular internal foci of enhancement
5	Clinical concern for hepatocellular carcinoma	Benign hepatocellular hyperplastic/macroregenerative nodule	8.5↑	2.2 cm	MRI	Precontrast: T1-W heterogeneously hypointense T2-W heterogeneously hyperintense DWI isointense Post contrast: Arterial phase hyperintense Portal venous phase isointense Equilibrium phase hyperintense Hepatocyte phase heterogeneously hyperintense
	Clinical concern for hepatocellular carcinoma	Benign hepatocellular hyperplastic/macroregenerative nodule		1.4 cm	MRI	Precontrast: T1-W isointense T2-W heterogeneously hypointense DWI hypointense Postcontrast: Arterial phase hyperintense Portal venous phase isointense Equilibrium phase isointense Hepatocyte phase heterogeneously hyperintense

(*Continued*)

TABLE 2 (*Continued*)

Patient #	Indication for biopsy	Histopathology of biopsied lesion(s)	Serum AFP (normal < 8 ng/mL)	Size of biopsied lesion	Imaging modality	Imaging description
6	Imaging suspicion for hepatocellular adenoma (T1-W hyperintensity)	Adenoma, inflammatory subtype	1.9	1.4 cm	MRI	Precontrast: T1-W hyperintense T2-W hyperintense DWI obscured by artifact Postcontrast: Arterial phase hyperintense Portal venous phase isointense Equilibrium phase isointense
	Imaging suspicion for hepatocellular adenoma in another lesion	Macroregenerative nodule		1.5 cm	MRI	Precontrast: T1-W isointense T2-W hypointense DWI obscured by artifact Postcontrast: Arterial phase hyperintense Portal venous phase isointense Equilibrium isointense
7	Imaging concern for hepatocellular neoplasm (T1-W hyperintense, hepatocyte phase hypointense)	Adenoma, mixed HNF1α-inactivated and beta-catenin activated	2	2.7 cm	MRI	Precontrast: T1-W hyperintense T2-W hypointense DWI isointense Postcontrast: Arterial phase hyperintense Portal venous phase hyperintense Equilibrium phase hyperintense Hepatocyte phase hypointense
8	Imaging concern for atypical lesion (hepatocyte phase hypointense)	Vascularized scar tissue	1.9	1.9 cm	MRI	Precontrast: T1-W isointense T2-W hyperintense DWI isointense Postcontrast: Arterial phase hyperintense Portal venous phase hyperintense Equilibrium phase hyperintense Hepatocyte phase hypointense
9	Imaging concern for malignancy	Hepatocellular carcinoma, fibrolamellar type	1.6	8 cm	CT	Postcontrast: Arterial phase heterogeneously hyperattenuating
10	Imaging concern for atypical lesion	Suspected posttransplant lymphoproliferative disorder	4.4	2.6 cm	MRI	Precontrast: T1-W isointense T2-W hyperintense DWI hyperintense Postcontrast: Arterial phase hyperintense Portal venous phase hyperintense Equilibrium phase hyperintense Hepatocyte phase isointense

(*Continued*)

TABLE 2 (*Continued*)

Patient #	Indication for biopsy	Histopathology of biopsied lesion(s)	Serum AFP (normal < 8 ng/mL)	Size of biopsied lesion	Imaging modality	Imaging description
11	Imaging concern for malignancy	Posttransplant lymphoproliferative disorder	0.9	3.1 cm	CT	Ill-defined margins Postcontrast: Portal venous phase hypoattenuating
12	Imaging concern for malignancy	Hepatocellular carcinoma	849.5↑	3.6 cm	MRI	Precontrast: T1-W hypointense T2-W hyperintense DWI hyperintense Postcontrast: Arterial phase rim hyperintense, central hypointense Portal venous phase rim hyperintense, central hypointense Equilibrium phase rim hyperintense, central hypointense Hepatocyte phase rim isointense, central hypointense

↑ indicates elevated value.

Abbreviations: T1-W, T1-weighted; T2-W, T2-weighted; DWI, diffusion weighted imaging (b800).

[a]Previously reported in Wang et al.[6]

[b]Diagnosis provided did not report a focal lesion, suggesting lesional tissue was not obtained.

Biopsy of background (nonlesional) liver tissue showed changes consistent with Fontan pathophysiology in 11 cases, including sinusoidal dilatation and portal and pericentral fibrosis. Macrovesicular steatosis was observed in two patients, in one of whom this was believed to be related to corticosteroid therapy following cardiac transplant.

3.3 | Serum biochemical markers (Table 2)

Eleven of 12 (92%) patients with focal liver lesions had an elevated serum GGT (range: 27-312 unit/L). The only patient that had a normal serum GGT was the patient who had undergone cardiac transplant at age 4 years 11 months, 4 months after the Fontan operation. Two patients had mildly elevated AST and ALT values, one of whom had a hepatic adenoma (Patient 7; AST = 136, ALT = 167) and the other who had fibrolamellar hepatocellular carcinoma (Patient 9; AST = 126, ALT = 90). The same patients had elevated alkaline phosphatase values (289 and 695, respectively) as did the patient with vascularized scar tissue (Patient 8; alk phos = 214). Serum alpha-fetoprotein (AFP) levels were elevated in 4/12 patients (33.3%). Marked elevation was observed in the patient with conventional hepatocellular carcinoma (serum AFP was normal in the patient with fibrolamellar hepatocellular carcinoma). Mild elevation in serum AFP was observed in the one patient with intrahepatic cholangiocarcinoma (AFP = 37.9 at diagnosis, 24.1 at recurrence) and in one patient with a macroregenerative nodule (Patient 1, AFP = 23.7). AFP levels were only minimally above the upper limit of normal in the fourth patient who had two separate macroregenerative nodules, biopsied and confirmed on histopathology.

4 | DISCUSSION

Liver damage after Fontan palliation of single ventricle physiology congenital heart disease may be much more common than originally thought.[8] Congestive hepatopathy is the initial and primary manifestation followed by the development of fibrosis, but focal liver lesions inclusive of benign nodules and cancers, most often hepatocellular carcinoma, are being increasingly reported.[6] The literature on lesion development in the Fontan population remains sparse. To add to the existing literature, we report a series of 12 patients with 15 biopsied lesions from our institution, three of whom had malignant tumors including two hepatocellular carcinomas (one fibrolamellar type) and an intrahepatic cholangiocarcinoma. Two of these patients with malignant tumors were young adults, ages 32 and 33, 29 and 30 years post–Fontan operation, respectively. However, one patient presented with fibrolamellar hepatocellular carcinoma at age 15, only 11 years post-Fontan. This younger patient emphasizes the importance of early liver screening in this specific patient population.

The risk of development of hepatic malignancy in patients after the Fontan operation has been discussed in the literature. Nandwana et al reported their single institution experience with 113 patients, 5

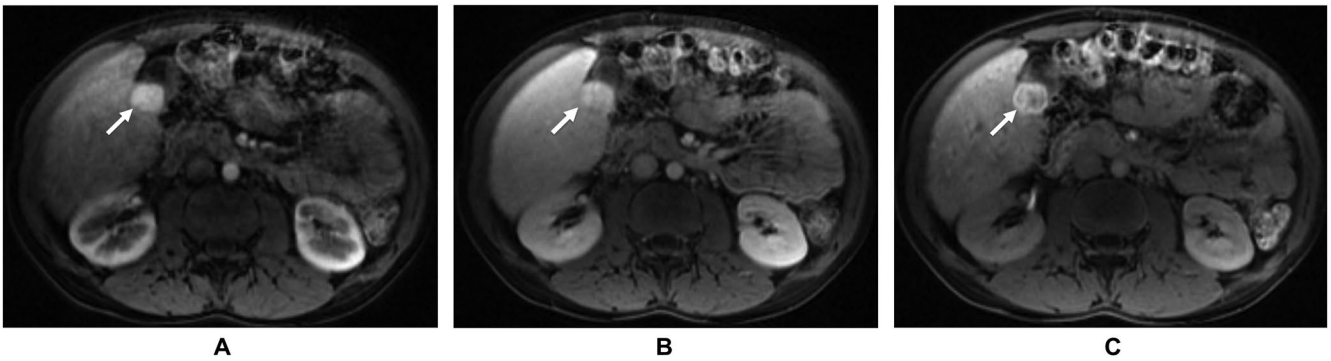

FIGURE 1 A 15-year-old girl (Patient 5) status post–Fontan operation with benign focal nodular hyperplasia (FNH)-like lesion arising from the inferior aspect of the right hepatic lobe. A, Postcontrast (gadoxetate disodium) arterial phase T1-weighted image shows that the lesion hyperenhances relative to background liver. B, Equilibrium phase image shows that the lesion remains hyperintense to background liver. C, Hepatocyte phase image shows heterogeneous retention of contrast material

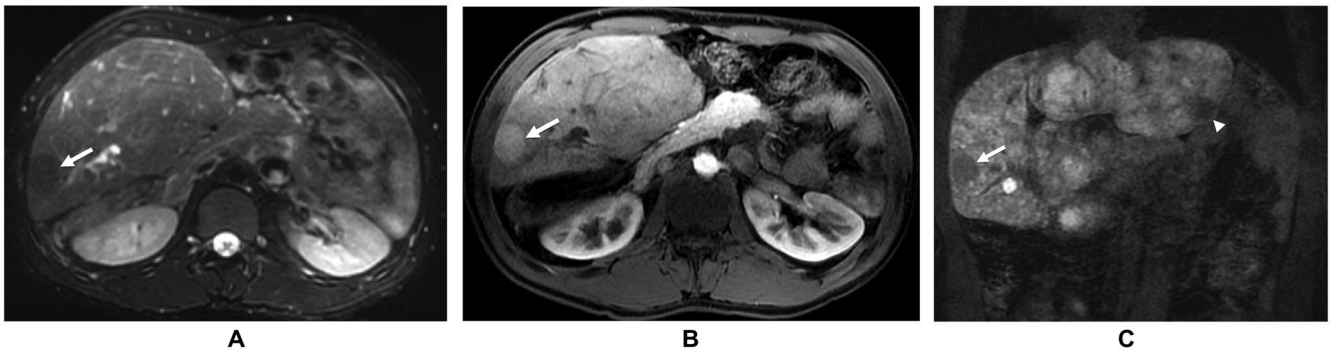

FIGURE 2 A 17-year-old boy (Patient 7) status post–Fontan operation with biopsy proven mixed HNF1 A-inactivated, beta-catenin activated subtype hepatocellular adenoma. A, Axial T2-weighted fat-saturated image shows an ovoid hypointense lesion in the right hepatic lobe (arrow). B, Postcontrast (gadoxetate disodium) arterial phase T1-weighted image shows that the lesion hyperenhances relative to background liver. C, Coronal hepatocyte phase image shows that the lesion is hypointense compared to background liver. Another lesion with similar signal characteristics (not biopsied) is seen in the left lobe (arrowhead). Numerous additional lesions retaining contrast material (not biopsied) are present throughout the liver

(4%) of whom developed hepatocellular carcinoma during follow-up. In the same study, 81% of patients who were imaged within 20 years after the Fontan operation had imaging findings consistent with chronic liver disease.[9] To date, the prevalence of hepatic malignancy in the Fontan population has not been defined. It has been suggested that serum AFP levels might be a valuable screening tool for malignancy in the Fontan population.[2] The single conventional hepatocellular carcinoma in our series was associated with a markedly elevated serum AFP while the intrahepatic cholangiocarcinoma was associated with a mild elevation in AFP. However, the other hepatic malignancy (fibrolamellar type hepatocellular carcinoma) described here was not associated with an elevated serum AFP. Notably, both of these lesions had concerning imaging features demonstrating the additive value of serum AFP and imaging surveillance in the Fontan population.

As in prior series, the majority of biopsied liver lesions in our series were benign, including hypervascular regenerative (macroregenerative or FNH-like)-type nodules and a venous malformation.[2] In their 2017 study of 30 patients post–Fontan palliation with hyperenhancing liver nodules, Wells et al reported 215 out of 245 total nodules to be FNH-like lesions based on imaging features (though few were biopsy-confirmed). The other 30 nodules were considered atypical based on imaging features. Of these atypical nodules, biopsy was obtained in six with three reflecting hepatocellular carcinoma and three reflecting FNH-like lesions.[2] Our series is somewhat unique in that we report a wider variety of hepatic lesions in patients following the Fontan operation. We report not only benign FNH-like/regenerative-type nodules and hepatocellular carcinoma but also other hepatic malignancies (fibrolamellar-type hepatocellular carcinoma, intrahepatic cholangiocarcinoma), hepatic neoplasms (hepatocellular adenomas), and lymphoproliferative processes. In our series, hepatocellular adenomas were identified in 2 of 12 patients, adding this diagnosis to the list of differential diagnoses that must be considered for hypervascular nodules in patients post-Fontan. To our knowledge, development of hepatocellular adenomas in this population has not been extensively reported. Babaoglu et al reported a single case of hepatic adenomatosis in a 7-year-old girl after Fontan and Ghaferi and Hutchins reported a single 14-year-old

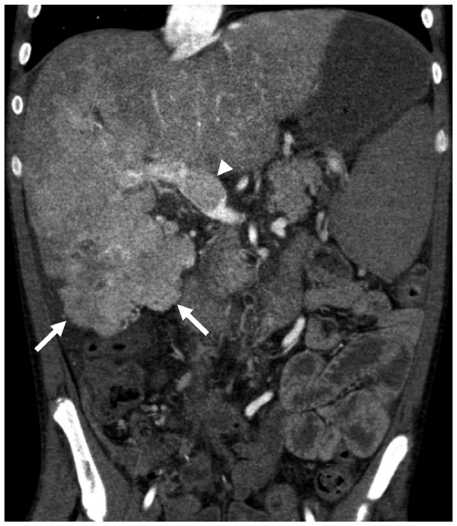

FIGURE 3 A 15-year-old- boy (Patient 9) status post–Fontan operation with fibrolamellar hepatocellular carcinoma with tumor thrombus in the main portal vein. Contrast-enhanced coronal CT image in the arterial phase shows a large, heterogenously hyperenhancing, lobulated, partly exophytic mass arising from the inferior aspect of the right hepatic lobe (arrows). Enhancing tumor thrombus is seen expanding the main portal vein (arrowhead)

patient with a single hepatocellular adenoma, subtype unspecified.[4,10] Recognizing that hepatocellular adenomas are among the lesions that can develop in patients after the Fontan operation is important as a subset of these lesions can either hemorrhage or undergo malignant transformation.[11]

Interestingly, the variety of lesions identified in patients following the Fontan operation and reported in both in the literature and our series is similar to what has been reported in the presence of congenital vascular anomalies of the liver, particularly Abernethy malformations.[12] In both cases, abnormal hepatic vascularity generates a diffuse abnormal hepatic milieu that seems to stimulate development of liver lesions of multiple histologic subtypes. The specific processes that contribute to lesion development in patients following the Fontan operation, and in patients with other hepatic vascular abnormalities are incompletely defined. In our series, biopsies of background liver showed sinusoidal dilation and portal and pericentral fibrosis with steatosis is a minority of patients. Prior series including that by Ghaferi and Hutchins have shown chronic passive congestion, centrilobular necrosis, and cardiac cirrhosis.[4,10]

In our population, there is an apparent predilection for biopsied lesions to be in the right hepatic lobe. Eighty-seven percent in our series were in the right hepatic lobe. The right lobe comprises a larger portion of the total liver bulk which may, in part account for a greater number of liver lesions on the right. Beyond this, however, the significance of this finding is uncertain given the small sample size and potential sampling bias. We are not aware of other studies describing such a predilection and while potentially interesting, we do not want to place too much weight on this finding at this time.

As demonstrated by our case series and reports from other authors, routine liver screening for focal lesions is probably indicated in patients following the Fontan operation.[8] Currently, there is incomplete consensus about liver surveillance in the Fontan population in terms of timing, frequency, and method(s). In their recent consensus document, the American College of Cardiology recommended that baseline liver assessment, including labs, ultrasound with Doppler and possibly elastography should be obtained 5 years after Fontan completion with repeat surveillance every 1-3 years in adolescents and adults.[13] Institutional practices, however, remain variable. In their 2016 publication, Josephus Jitta et al suggested that for the general Fontan population, fibrosis and cirrhosis screening by a hepatologist should begin 10 years after Fontan completion with annual liver laboratory tests and imaging of the liver with ultrasound or MRI every 2 years.[14] In the subset of patients with severe fibrosis or cirrhosis, the authors suggested that screening for hepatocellular carcinoma should be conducted every 5-12 months, similar to what is done for the hepatitis C population.[14] At our institution, our current protocol for Fontan patients is to perform a screening MRI every other year beginning at age 13 with ultrasound in the years between the MRI exams. If a suspicious lesion is found (ie, the lesion shows findings atypical for an FNH-like lesion, such as T1-weighted signal hyperintensity, T2-weighted hypointensity or heterogeneity, postcontrast "washout," and/or hepatocyte phase hypointensity) then the patient will be either sent for biopsy or referred for short-term follow-up MRI.

The post-Fontan, postcardiac transplant population, two of whom are represented in our series, and both of whom were diagnosed with PTLD, reflects a unique population as it relates to liver screening. These patients are at risk for PTLD at a frequency of approximately 5%.[15] Despite this, we are not aware of accepted guidelines for screening for PTLD in these patients. Additionally, the natural history of liver lesions postcardiac transplant that may have initially developed in the environment of the Fontan circulation is not known and therefore the ongoing risk associated with these lesions, particularly in the context of necessary immunosuppression is uncertain. Clearly, further study of this likely growing patient group is necessary to define optimal screening algorithms.

While our study adds to the literature concerning focal liver lesions in patients post-Fontan, it has limitations. First, it is a small retrospective case series with only 14 pathology-proven liver lesions. While this is a small series, the strength of this series lies in the fact that all lesions were pathologically proven. This is in contrast to some series in the literature that relied on imaging diagnosis and is particularly important given the growing recognition of atypical imaging features for some hypervascular liver lesions.[16] Second, our data are limited to a single institution that serves as both a primary and a tertiary referral center for Fontan patients and thus might not reflect the distribution of disease seen elsewhere.

5 | CONCLUSION

Patients post-Fontan can present with multiple types of liver lesions. These lesions may arise over a wide range of time after the Fontan procedure and may have atypical imaging features.

CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest with the contents of this article.

AUTHOR CONTRIBUTIONS

Data collection, data analysis/interpretation, drafting article, approval of article: Emily M. Engelhardt.
Concept/design, data collection, data analysis/interpretation, drafting article, critical revision of article, approval of article: Andrew T. Trout
Data collection, critical revision of article: Rachel M. Sheridan
Concept/design, critical revision of article: Gruschen R. Veldtman
Concept/design, data analysis/interpretation, critical revision of article: Jonathan R. Dillman

ORCID

Andrew T. Trout https://orcid.org/0000-0003-1431-4054

REFERENCES

1. Hilscher MB, Johnson JN, Cetta F, et al. Surveillance for liver complications after the Fontan procedure. *Congenit Heart Dis*. 2017;12(2):124-132.
2. Wells ML, Hough DM, Fidler JL, Kamath PS, Poterucha JT, Venkatesh SK. Benign nodules in post-Fontan livers can show imaging features considered diagnostic for hepatocellular carcinoma. *Abdom Radiol*. 2017;42(11):2623-2631.
3. Pundi K, Pundi KN, Kamath PS, et al. Liver disease in patients after the Fontan operation. *Am J Cardiol*. 2016;117(3):456-460.
4. Babaoglu K, Binnetoglu FK, Aydogan A, et al. Hepatic adenomatosis in a 7-year-old child treated earlier with a Fontan procedure. *Pediatr Cardiol*. 2010;31(6):861-864.
5. Conroy MR, Moe TG. Hepatocellular carcinoma in the adult Fontan patient. *Cardiol Young*. 2017;27(2):407-409.
6. Wang D, Marshall D, Veldtman G, et al. Intrahepatic cholangiocarcinoma after Fontan procedure in an adult with visceral heterotaxy. *Pathol Res Pract*. 2018;214(6):914-918.
7. Rychik J, Veldtman G, Rand E, et al. The precarious state of the liver after a Fontan operation: summary of a multidisciplinary symposium. *Pediatr Cardiol*. 2012;33(7):1001-1012.
8. Wolff D, van Melle JP, Dijkstra H, et al. The Fontan circulation and the liver: A magnetic resonance diffusion-weighted imaging study. *Int J Cardiol*. 2016;202:595-600.
9. Nandwana SB, Olaiya B, Cox K, Sahu A, Mittal P. Abdominal imaging surveillance in adult patients after fontan procedure: risk of chronic liver disease and hepatocellular carcinoma. *Curr Probl Diagn Radiol*. 2018;47(1):19-22.
10. 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(6):1348-1352.
11. Stoot JH, Coelen RJ, De Jong MC, Dejong CH. Malignant transformation of hepatocellular adenomas into hepatocellular carcinomas: a systematic review including more than 1600 adenoma cases. *HPB*. 2010;12(8):509-522.
12. Ghuman SS, Gupta S, Buxi TB, et al. The Abernethy malformation-myriad imaging manifestations of a single entity. *Indian J Radiol Imaging*. 2016;26(3):364-372.
13. Daniels CJ, Bradley EA, Landzberg MJ, et al. Fontan-associated liver disease. *J Am Coll Cardiol*. 2017;70(25):3173-3194.
14. Josephus Jitta D, Wagenaar LJ, Mulder BJ, Guichelaar M, Bouman D, van Melle JP. Three cases of hepatocellular carcinoma in Fontan patients: review of the literature and suggestions for hepatic screening. *Int J Cardiol*. 2016;206:21-26.
15. Kumarasinghe G, Lavee O, Parker A, et al. Post-transplant lymphoproliferative disease in heart and lung transplantation: defining risk and prognostic factors. *J Heart Lung Transplant*. 2015;34(11):1406-1414.
16. Trout AT, Towbin AJ, Smith EA, Gupta A, Dillman JR. Hepatocyte-specific contrast media: not so simple. *Pediatr Radiol*. 2018;48(9):1245-1255.

How to cite this article: Engelhardt EM, Trout AT, Sheridan RM, Veldtman GR, Dillman JR. Focal liver lesions following Fontan palliation of single ventricle physiology: A radiology-pathology case series. *Congenital Heart Disease*. 2019;14:380–388. https://doi.org/10.1111/chd.12730