Liver Biopsy Leads to Serendipitous Diagnosis of Glycogen Storage Disease Type IX in a Patient With Fontan-Associated Liver Disease

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Abstract: Fontan-associated liver disease (FALD) is a form of congestive hepatopathy resulting from Fontan palliation procedures in patients with single ventricle physiology. Although there is variation between pediatric centers, the surveillance for FALD may include liver biopsies for assessment of degree of fibrosis. Our report describes a 7-year-old girl with hypoplastic left heart syndrome who underwent Fontan palliation at age 2, and presented with disproportionate hepatomegaly, elevated liver enzymes, and increased stiffness on liver elastography. Liver biopsy showed diffuse hepatocellular cytoplasmic glycogenation, leading to the diagnosis of glycogen storage disease IX. This case demonstrates the importance of investigating unexpected physical exam findings and the potential for serendipitous benefit of liver biopsy in FALD.

Key Words: hypoplastic left heart syndrome, Fontan-associated liver disease, glycogen storage disease type IX, hypoglycemia

INTRODUCTION

The Fontan procedure directs venous blood flow directly to the pulmonary circulation. This palliative procedure allows children with single ventricle physiology to survive to adulthood but causes passive venous congestion of the liver. This in turn results in chronic congestive hepatopathy and gradual accumulation of fibrosis termed Fontan-associated liver disease (FALD). Common early findings on liver biopsy include sinusoidal congestion with sinusoidal and perivenular fibrosis, later advancing to bridging fibrosis, and ultimately cirrhosis (1,2). The approach to monitoring at our center is to use blood testing and imaging to assess hepatic injury, function, and fibrosis. In most cases, 10 to 15 years after the completion of the Fontan circuit, we perform a liver biopsy, as liver enzymes are normal or only slightly elevated and are not predictive of degree hepatic fibrosis on liver biopsy (3,4). Typical progression of FALD varies by patient with cirrhosis and HCC being the most serious adverse outcome of FALD in adulthood (5). However, histological fibrosis is universal even in pediatric age (4). In this case report, we describe a child with Fontan physiology who had marked hepatomegaly within 4 years of completion of her circuit, prompting earlier evaluation for the presence of FALD.

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CASE REPORT

A 7-year-old girl, with hypoplastic left heart syndrome 4 years postcompletion Fontan procedure, was referred to the Children's Hospital of Philadelphia for evaluation of junctional cardiac rhythm with fluctuating liver enzymes and marked hepatomegaly. She underwent staged palliation with a stage 1 Norwood with right modified Blalock-Taussig shunt at 6 days of age, right bidirectional Glenn at 5 months, and an extracardiac fenestrated Fontan was completed at 35 months. Her postoperative course was complicated by recurrent obstruction of her neoaortic arch, which was treated with balloon angioplasty and by recurrent post-Fontan pleural effusion in the early postoperative period.

As part of her routine visit, she underwent a physical exam, echocardiogram, and Acoustic radiation force impulse (ARFI) shear wave elastography of liver. On physical examination, she was generally well appearing though mildly cyanotic. Her vital signs were notable for SpO_2 89%, which was expected for her physiology, weight 19.7 kg (15th %ile for age), height 115 cm (10.6th %ile for age), and body mass index 14.9 (35th %ile for age). The abdomen was notable for soft liver edge 4 cm below the right costal margin crossing the midline below the xiphoid without prominent abdominal vessels or ascites. Echocardiogram showed low-normal RV function with trivial tricuspid regurgitation, unobstructed atrial septum and aorta, and patent Fontan fenestration. Her EKG was notable for junctional rhythm. Serum chemistry analysis revealed increased liver enzymes including alanine aminotransferase (ALT) 44 U/L (ULN 35), aspartate aminotransferase (AST) 68 U/L (ULN 40), and gamma-glutamyl transferase 53 U/L (ULN 21). Liver ultrasound was notable for liver span of 13.8 cm, which is was unexpected 4 year post-Fontan palliation (in our center's cohort, we reported a mean of 15.1 cm at 14.9 years post Fontan) (4). ARFI shear wave elastography of the liver demonstrated increased liver stiffness with median 3.66 m/s (pediatric normal 1.16 m/s).

Given the disproportionate hepatomegaly and liver stiffness post Fontan, she underwent cardiac catheterization to evaluate her hemodynamics and liver biopsy to assess hepatic fibrosis. Cardiac catheterization was notable for elevated Fontan pressures (13 mmHg) with normal cardiac index. With atrial pacing at 110 bpm, the Fontan, pulmonary artery, and pulmonary capillary wedge pressures all decreased. Her liver biopsy demonstrated findings of a GSD, including diffuse cytoplasmic and nuclei glycogenation within the hepatocytes (Figs. 1 and 2).

The patient was referred for further endocrine evaluation. Genetic analysis found the presence of a heterozygous PHKA2 variant consistent with X-linked glycogen storage disease (GSD) type IX, a deficiency of the enzyme phosphorylase kinase in the liver, needed to break down glycogen (3,6). She underwent X-inactivation studies that showed 85% skewing, which explained her phenotype

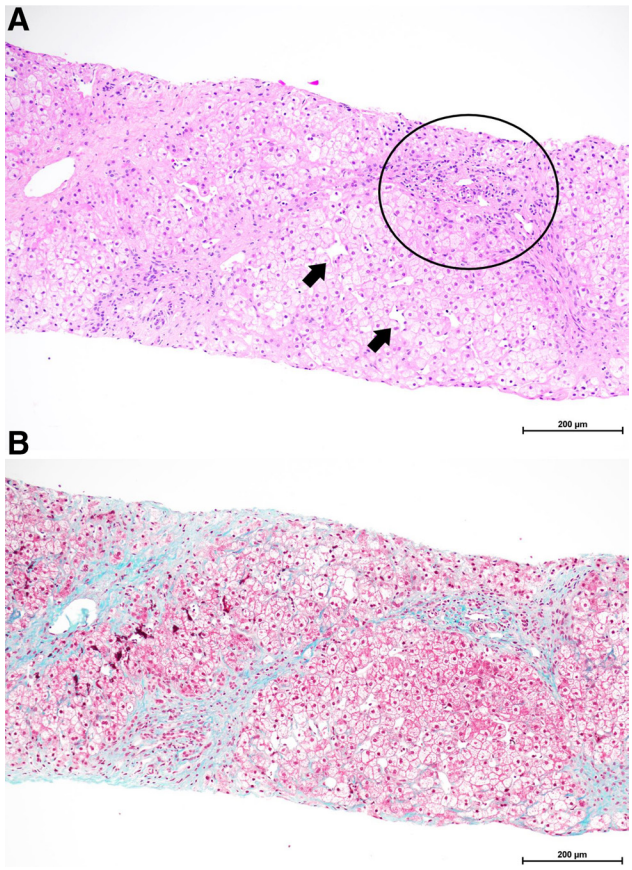

FIGURE 1. (A) Hematoxylin and eosin staining showing changes compatible with prior Fontan procedure: sinusoidal dilation (arrows), portal and perivenular fibrosis with areas of bridging fibrosis, and minimal chronic portal inflammation (circled) (100× original magnification). (B) Gomori Trichome staining delineating the areas of fibrosis (green) (100× original magnification).

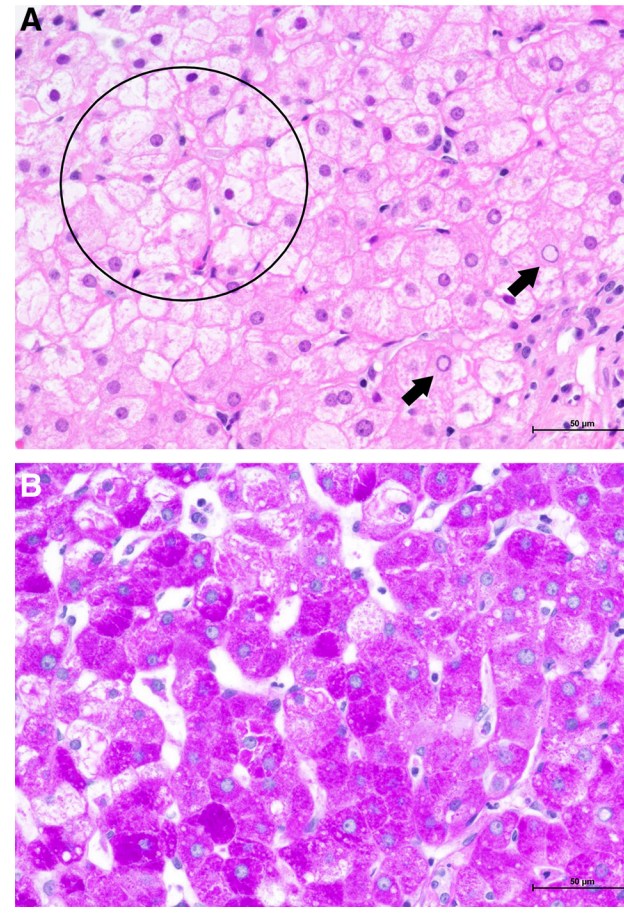

FIGURE 2. (A) Diffuse hepatocellular cytoplasmic clearing (circled) and occasional glycogenated nuclei (arrows) (hematoxylin and eosin, 400× original magnification). (B) Cytoplasmic glycogen within hepatocytes appears magenta on periodic acid-Schiff staining (400× original magnification).

despite neither parent suffering from X-linked GSD type IX. Her endocrinologist prescribed cornstarch nightly. At 2 years postdiagnosis, her growth has improved from Z score –2.74 to –2.03 and her liver enzymes normalized.

DISCUSSION

This case exemplifies the overlapping signs and symptoms between FALD and GSDs and shows the utility of liver biopsy particularly in atypical presentation of patients with FALD. There are conflicting guidelines in the literature for FALD imaging and liver biopsy surveillance (5,7–10). The American Heart Association and European Society of Pediatric Radiology both recommend noninvasive surveillance with ultrasound, elastography, and if indicated cross sectional imaging starting in childhood. Both organizations consider liver biopsy investigational at this point (9,10). In addition to routine imaging as recommended by American Heart Association, our clinical team routinely obtains liver biopsy 10 to 15 years after completion of palliation when liver fibrosis is universal. This helps risk stratify adolescent patients for possible complications of FALD before their transition to an adult congenital heart disease program (2,4). Our team prioritizes obtaining a liver biopsy earlier to assess for fibrotic changes in patients with abnormal noninvasive evolution-hepatomegaly disproportionate to time since Fontan, abnormal ALT, AST, and gamma-glutamyl transferase or disproportionate elevated liver stiffness in elastography for time since Fontan. When the biopsy results arrived, the disproportionate hepatomegaly found on physical exam began to unfold into a whole new clinical picture (3).

GSD type IX has many variations in phenotype due to its X-linked inheritance with clinical features overlapping with FALD (3). Depending on lyonization in biological females, the phenotype may range from asymptomatic to severe (3,6). The PHKA2 pathogenic variant present in this patient is liver specific and is commonly associated with hepatomegaly, growth delay, and hypoglycemia (3,6). Biochemical analysis in these patients also typically illustrate elevated liver transaminases, hypercholesterolemia, and hypertriglyceridemia (3). Although this patient had elevated transaminases and moderate growth delays, there were only 2 episodes of blood glucose levels below 60 that were documented and were not accompanied by symptoms of hypoglycemia. The most prominent evidence of her GSD was hepatomegaly, which overlapped with the expected findings from FALD. The serendipitous finding on histology led to a targeted evaluation and treatment plan. Based on our literature search, this would be the first reported case of a patient presenting with hypoplastic left heart syndrome and GSD type IX. This case demonstrates the importance of physical examination in patients with FALD and use of additional testing (in this case liver biopsy) when there are unexpected or disproportionate findings that require explanation. As next

generation sequencing becomes more readily available, a universal screen for disorders that may exacerbate FALD, such as in this case, may be useful in the future. However, this cannot replace a focused history, physical exam, and interdisciplinary discussion as the main tool in clinical assessment of patients with FALD.

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