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Surveillance for hepatocellular carcinoma secondary to cardiogenic cirrhosis in patients with congenital heart disease

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Sirs:

Cyanotic congenital heart diseases (CHD), including tetralogy of Fallot (TOF), were previously fatal diseases. Surgical advancements such as the Blalock–Taussig shunt and the Fontan procedure have improved the outlook of patients diagnosed with CHD, such that patients can expect a 20-year survival rate approaching 90 % [1]. The improved survival of children with CHD is now affecting adult medicine. An estimated 1.3 million adults now live in the USA with CHD and that number is expected to increase by 5 % per year [2]. Patients with CHD are predisposed to developing hepatic dysfunction as a result of either the primary cardiac defect or surgical palliation, or both. As the CHD population ages, particular attention must be paid to hepatic surveillance to identify patients with cardiogenic cirrhosis, as there is an increased incidence of subsequent development of HCC over time.

To illustrate the complex and chronic nature of HCC development in patients with congenital heart disease, we present the case of a 24-year-old female born with TOF who underwent three separate cardiac procedures and developed cardiogenic cirrhosis secondary to a regurgitant pulmonic valve. Interval imaging and subsequent biopsy identified a lesion within the right lobe of the liver, consistent with HCC. In addition to this report, we review

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the relevant literature and provide recommendations for surveillance in the adult CHD patient population.

Our patient was born cyanotic with TOF and critical pulmonary artery stenosis dependent on ductal pulmonary blood flow. Repair took the form of three surgeries: emergently after birth, a central shunt was placed to circumvent the stenosis; at age 3, a pulmonary valve homograft was placed, the atrial-septal defect was repaired, and the right pulmonary artery was reconstructed to the level of the hilum; and at age 12, due to significant pulmonary valve regurgitation and sonographic evidence of right ventricle (RV) dysfunction, our patient underwent replacement of the pulmonary homograft with a Synergraft extending into the distal left pulmonary artery. Echocardiography performed 5 years after pulmonic valve replacement demonstrated no evidence of intracardiac shunting, but identified a dilated RV with significantly increased systolic pressures secondary to continued pulmonary valve regurgitation. Magnetic resonance imaging (MRI) of the chest identified a hypokinetic and dilated RV with a regurgitant fraction of 31 %. A diagnosis of decompensated congestive heart failure was made by complete heart catheterization. Following identification of the diagnosis of right heart failure, the patient was administered low-dose diuretics, but lost to follow-up due to socioeconomic reasons.

At the age of 24, our patient became symptomatic with new-onset abdominal pain, abdominal ascites, and lower extremity edema. Computed tomography of the abdomen demonstrated heterogenous hepatic nodularity consistent with cardiogenic cirrhosis with features suggesting portal hypertension. Laboratory findings demonstrated no evidence of viral hepatitis or abnormal liver function and, except for an elevated serum alpha-fetoprotein (AFP) level of 99 ng/ml, were within normal limits. In addition, there was no history of alcohol intake or features of metabolic syndrome including hypercholesterolemia, morbid obesity, or diabetes mellitus. Additional dynamic contrasted abdominal MRI demonstrated a 2.0 cm hypervascular mass in the right lobe of the liver with washout on delayed imaging. These imaging findings were consistent with HCC (Fig. 1).

Segmental resection (segment 7) of the HCC lesion was completed after cardiac catheterization confirmed optimization for operative intervention. Resection was considered the best option due to minimal portal hypertension evident by a platelet count of 186,000. The abdominal ascites and peripheral edema were felt to be secondary to right heart failure and were not seen during operative exploration that followed a fairly aggressive diuretic regimen. Other curative therapies including ablation and liver transplantation were not considered due to location of the liver lesion and lack of insurance, respectively. Intraoperative examination of the liver revealed extensive hepatic cirrhosis and one solitary mass lesion in the right lobe of the liver. Intraoperative central venous pressure (CVP) monitoring confirmed significant right-sided cardiac dysfunction with initial CVP readings of 35 mmHg. The resected tumor specimen was a moderately differentiated HCC with negative margins in the background of a cirrhotic liver (Fig. 2). The patient tolerated the procedure well, was discharged on hospital day 5, and remains free of recurrence more than 2 years after the initial resection. Six months following the operative resection, the patient underwent percutaneous pulmonary valve replacement.

The majority of cases of HCC arise secondary to chronic liver injury from viral hepatitis B or C, excessive alcohol intake, non-alcoholic fatty liver disease, and more rarely from genetic causes such as hemochromatosis, Wilson's disease, and others [3]. Due to improved care, patients undergoing CHD repairs as infants have significantly increased survival and no longer succumb to acute cardiac issues; however, these patients can demonstrate increased sequelae of longstanding cardiac insufficiency such as right heart failure with progression to cardiogenic cirrhosis over time. This is evident in the increase of reported cases of cardiogenic cirrhosis as the underlying etiology of HCC over the last two decades [4–8]. Asrani et al. describe four patients with univentricular CHD who underwent Fontan repair with subsequent identification of HCC and suggest cirrhosis develops within 11–15 years post-procedure in patients under the age of 25 years, with an estimated incidence of HCC of 1–5 % per year, similar to other etiologies of chronic liver disease producing cirrhosis [8]. An improvement in CHD survival obviates the need for improved cancer monitoring in this population.

Despite surgical resection of HCC, our patient, due to her cirrhosis, maintains a 5-year recurrence rate of approximately 50 % [9]. Liver transplantation is another curative modality for patients with HCC; however, liver shortages in the region where this patient was treated necessitate surgical resection rather than orthotopic liver transplantation as the first curative therapy offered.

Guidelines need to be established for HCC surveillance in patients with decompensated congestive heart failure in the setting of repaired congenital heart disease. Although cirrhosis is difficult to distinguish from chronic right heart failure, any consequence of portal hypertension such as thrombocytopenia should be enough to warrant surveillance for HCC. Transient elastography may be a useful modality to screen for cirrhosis in the future, but is currently not widely used outside of the research setting in the majority of high-volume centers. In high-risk patients with established chronic liver disease and cirrhosis, the National Comprehensive Cancer Network recommends abdominal ultrasonography and serum AFP every 6–12 months [10]. The American Association for the Study of Liver Diseases (AASLD) suggests HCC surveillance for patients with chronic liver disease and an annual incidence rate that exceeds 1.5 % for patients with hepatitis C and 0.2 % for patients with hepatitis B [11]. Based on currently available patient data, HCC incidence in patients with CHD who developed cirrhosis is between 1 and 5 %, exceeding the chronic liver disease surveillance cutoff suggested by the AASLD [8]. By extension, annual or bi-annual ultrasonography and serum AFP levels should be performed on patients with previously repaired CHD who demonstrate evidence of hepatic cirrhosis.

The patient presented above provides an important lesson in proper health management during the transition from pediatric care to adult care, a shift that all patients with CHD must face. Continuity of care is a critical factor in identifying, preventing, and/or significantly delaying the development of chronic liver disease in this patient population. These patients require multidisciplinary medical management that includes (but is not limited to) cardiologists, hepatologists, and social workers that can help identify barriers to regular treatment access. Due to the expanding adult population of patients with surgically repaired

CHD, we are beginning to understand the longterm clinical consequences and unique manifestations of disease secondary to the surgical repair process.

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Fig. 1. Magnetic resonance images demonstrating evidence of a 2.0 cm nodule in segment 7 at the dome of the liver. The mass displayed arterial enhancement and washout with delayed peripheral enhancement, which is consistent with a diagnosis of hepatocellular carcinoma

Fig. 2. Histopathologic analysis of the surgical specimen. a Moderately differentiated hepatocellular carcinoma with adjacent non-neoplastic liver parenchyma (40× magnification). b Trabecular and solid pattern, 4+ cells thick (100× magnification). c Large tumor cells with eosinophilic cytoplasm, distinct nucleoli and mitotic figures (200× magnification). d Background cirrhotic liver with nodule formation surrounded by fibrous tissue (40× magnification)