Diffuse hepatocellular carcinoma secondary to cardiac cirrhosis in heterotaxy syndrome

Akash Mathavan [1], Akshay Mathavan [1], Keegan Hones,[1] Ellery Altshuler [2]

[1]College of Medicine, University of Florida, Gainesville, Florida, USA
[2]Internal Medicine, University of Florida College of Medicine, Gainesville, Florida, USA

Correspondence to
Akash Mathavan;
amathavan2496@ufl.edu

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SUMMARY

Heterotaxy syndrome is a rare congenital defect of left-right laterality of major visceral organs, often categorised by the presence of symmetric left or right atrial heart chambers with a single effective ventricle. Known as left or right atrial isomerism, these conditions may present with a distinct pattern of extracardiac anomalies. Heterotaxy is often palliated with the Fontan procedure and is suggested to be subject to similar long-term sequelae of congestive hepatopathy and ischaemia, increasing the risk for hepatocellular carcinoma. Few works document primary, localised hepatocellular carcinoma in patients with heterotaxy syndrome. We present a case of diffuse, multifocal metastatic hepatocellular carcinoma in a young patient with left atrial isomerism and dextrocardia. We also review suggested guidelines of surveillance for liver disease and hepatocellular carcinoma in this patient population.

BACKGROUND

Heterotaxy is defined as a defect in left-right laterality and the normal assembly of visceral organs (situs solitus) that does not satisfy their complete, mirrored rearrangement (situs inversus). While the prevalence of both heterotaxy and situs inversus is roughly 0.01% of live births, those with situs inversus do not often experience fatal organ dysfunction when compared with heterotaxy due to conserved organ-vessel morphology.[1] In patients with heterotaxy syndrome, abnormal developmental symmetry may be described by the presence of two same-sided, or isomeric, atria and atrial appendages in the cardiac anatomy, known as left or right atrial isomerism.[2] Variations in cardiac position—levocardia, mesocardia, dextrocardia—are frequently observed but malposition does not correlate with the type of isomerism. Early embryological disruption of laterality classically produces distinct patterns of extracardiac anomalies observed in left or right atrial isomerism, including the presence of varying lung lobulation and accessory spleens; however, a great degree of incongruence in this development exists, generating a spectrum of presentations in heterotaxy syndrome.[3] Heterotaxy is often palliated with the Fontan procedure. When compared with right atrial isomerism, left atrial isomerism is more often associated with chronic heart failure and systemic venous hypertension leading to hepatomegaly. Moreover, several works have described Fontan-associated liver disease via long-term congestive hepatopathy, termed cardiac cirrhosis, contributing to onset of hepatocellular carcinoma.[4–6] Two of these reports detail localised hepatocellular carcinomas in patients with heterotaxy syndrome.[7 8] We report a case of diffuse, multifocal hepatocellular carcinoma in a patient with heterotaxy syndrome palliated with the Fontan procedure.

CASE PRESENTATION

A man in his 20s with complex heterotaxy syndrome (left atrial isomerism and dextroposition of the heart) presented to an outpatient cardiology evaluation with 2 months of abdominal distention and worsening constant pain localised to the umbilicus. Extensive cardiac history consisted of transposition of great arteries with right atrioventricular valve atresia, bilateral superior vena cava with interrupted right-sided inferior vena cava, and a single, double outlet primitive ventricle with severe subpulmonic stenosis. Congenital anomalies were palliated with a series of procedures, including the Fontan, maze completion for sinus node dysfunction and atrial flutter, and pacemaker implantation. Routine evaluation of Fontan physiology consistently noted elevated central venous pressures of 18 mm Hg (normal <12 mm Hg), indicating longstanding systemic venous hypertension. On presentation, the patient also reported intermittent orthopnea, nausea and vomiting and denied exertional dyspnoea, lower extremity oedema, chest pain or diaphoresis. The patient's medications consisted of digoxin 0.25 mg one time a day, furosemide 40 mg one time a day, lisinopril 20 mg one time a day, sotalol 80 mg two times a day, and aspirin 81 mg one time a day; however, he had been unable to maintain this regimen for 7 months prior to presentation.

The patient was afebrile with a blood pressure of 135/83 mm Hg, heart rate of 82 beats/min, and oxygen saturation of 92% on room air. Physical examination was notable for marked hepatomegaly with liver edge palpable 8 cm below the costal margin, ascites with fluid wave, symmetrically clear lung fields, and the absence of arrhythmia or new heart murmur. Laboratory tests revealed an elevated haemoglobin of 17.6 g/dL with normal leucocyte count of 5.8×10^9/L and platelet count of 299×10^9/L. ECG exhibited an atrial paced rhythm, a QR pattern consistent with severe right ventricular hypertrophy, and a corrected QT interval (QTc) of 444 ms. Chest X-ray exhibited a normal cardiac silhouette positioned in the right hemithorax and no evidence of an acute chest process. Transthoracic echocardiogram demonstrated Fontan circulation in the superior and inferior vena cava, dilated left-sided atrium, and moderate right atrioventricular

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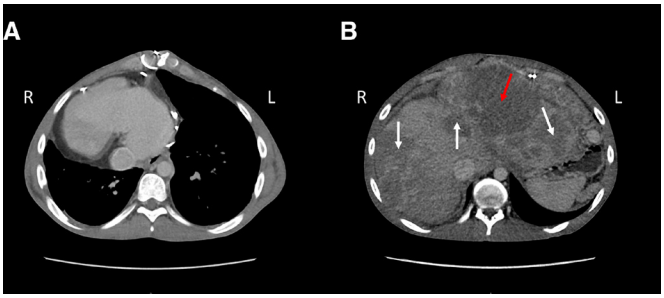

Figure 1 Axial CT image of (A) dextrocardia with single effective ventricle and (B) multifocal, diffuse hepatocellular carcinoma (white arrows), with the largest mass measuring 12×8 cm (red arrow).

valve regurgitation. Single ventricle systolic function appeared intact. Due to concerns of deteriorating single ventricular function, the patient was admitted for diuresis and sotalol initiation with monitoring of QTc.

INVESTIGATIONS

The patient was initially managed with intravenous furosemide 40 mg one time a day and sotalol 80 mg two times a day, experiencing no symptomatic improvement. Due to continued hepatomegaly with prominent ascites, the possibility of a pathological liver process was explored. Liver function tests showed elevated total bilirubin of 1.6 mg/dL, direct bilirubin of 0.4 mg/dL, alkaline phosphatase of 138 IU/L, and aspartate aminotransferase of 97 IU/L with normal levels of alanine aminotransferase of 18 IU/L. Serologies for viral hepatitides were negative. Beta-human chorionic gonadotropin levels were within normal limits. Significantly elevated levels of lactate dehydrogenase of 325 IU/L and alpha-fetoprotein (AFP) of >60 000 ng/mL were observed.

Ultrasound of the abdomen visualised multiple hyperechoic masses in the liver. With concomitantly elevated AFP, hepatocellular carcinoma and extragonadal germ cell tumour were considered for primary aetiology. Ultrasound of scrotum exhibited normal echogenicity of testicles with no evidence of mass. CT of chest and abdomen affirmed dextrocardia with monoventricle and demonstrated an enlarged liver essentially entirely replaced by multiple masses, concerning for multifocal hepatocellular carcinoma (figure 1). Tumorous implants along the mesentery superior to the liver and in the pelvis as well as innumerable pulmonary nodules suggested metastatic disease. A focal obstructive thrombus within the main portal vein and findings of pulmonary hypertension including splenomegaly (16 cm) and multiple varices were observed. Subsequent liver biopsy revealed poorly differentiated tumour with abundant mitosis, pleomorphic nuclei and necrosis. Immunohistochemistry exhibited strong reactivity for glutamine synthetase, alpha-1 antitrypsin, SALL-4, glypican-3, and AFP with focal reactivity for cytokeratin AE1/AE3, CDX-2, CK19, CD10 and Hep-par. Cells were negative for CD30, CEA-P, p63, TTF-1, PLAP and OCT 4. Under the setting of clinical presentation, radiographic findings and biopsy results, the patient was diagnosed with stage III hepatocellular carcinoma.

TREATMENT

The patient experienced symptomatic relief with paracentesis, removing 4.5 L of fluid. Sorafenib 400 mg two times a day was initiated on the recommendation of oncology evaluation. Pain was managed with hydromorphone. He was also referred to hepatology for a workup under consideration of transarterial chemoembolisation but was unable to attend evaluation.

OUTCOME AND FOLLOW-UP

Two weeks following initiation of oral sorafenib, the patient presented to the emergency department with acute hypoxic respiratory distress, initially requiring non-invasive ventilation that was weaned to nasal canula. Significant ascites and jaundice were observed. He endorsed severe, diffuse abdominal pain refractory to hydromorphone, prohibiting ambulation. CT of abdomen and pelvis showed increased expansion of the liver capsule via mass effect and CT of chest demonstrated enlargement of pulmonary nodules, development of new nodules, and presence of new lytic lesions on the sternum. Given the advancement of the disease and resulting comorbidities, the patient and his family values aligned on prioritising pain control and time with one another; thus, they requested discontinuation of sorafenib and transitioned to hospice care. This young man returned home and passed 2 days later, a little over 1 month following initial discovery of the hepatocellular carcinoma.

DISCUSSION

The prognosis for patients with heterotaxy syndrome is significantly varied. Major sources of morbidity include respiratory distress due to susceptibility to infections, decompensated heart failure from deterioration of single ventricle, or sepsis secondary to functional asplenia. Outcomes for left atrial isomerism are typically superior; survival to 18 years of age for right atrial isomeric patients is roughly 50% compared with 74% in those with left atrial isomerism.[9] Extracardiac anomalies typically associated with left atrial isomerism include polysplenia, bilobed one-sided liver, symmetric bilobed lungs and higher likelihood of arrhythmias whereas presentation in right atrial isomerism consists of asplenia, symmetrical horizontal liver, bilateral trilobed lungs and predominance of single ventricle physiology.[10] However, variations and incongruence in these combinations of anomalies are common. Some reports have demonstrated upwards of 20% discordance between atrial isomerism and expected lung lobulation or splenic status.[11]

The Fontan procedure is the standard palliative surgical intervention in congenital univentricular hearts, primarily indicated for atrioventricular valve atresia, left or right hypoplastic heart syndromes, and complex congenital heart diseases including those seen in heterotaxy syndrome.[12 13] It involves diverting systemic venous return to the pulmonary arteries, bypassing the morphologic right ventricle. Specifically, blood flow from the superior vena cava and inferior cava is directed to the right and left pulmonary arteries, respectively, re-establishing a series circuit between the systemic and pulmonary circulations with the single effective ventricle. While Fontan circulation improves arterial saturation, venous hypertension and decreased cardiac output are well-described consequences. Additionally, there are numerous reports illustrating Fontan-associated liver disease—chronic liver inflammation, hepatic fibrosis and cirrhosis. Congestive hepatopathy and intermittent ischaemia result in recurrent liver insults, referred to as cardiac cirrhosis.[14] Venous congestion secondary to chronic heart failure has been shown to inflict liver injury via similar pathology. In both instances, liver biopsy supports cardiac dysfunction as the aetiology of liver disease through evidence of centrilobular fibrosis and necrosis.

Hepatocellular carcinoma is an increasingly recognised sequalae of Fontan-associated liver disease.[6 15 16] Compared with hepatocellular carcinoma due to alternative aetiologies, those

with a history of Fontan procedure have similar mortality rates with a 1-year survival of less than 50%. However, the median age of onset is in the early second decade compared with early sixth decade and there is a higher rate of underlying cirrhosis prior to diagnosis. The presentation of hepatocellular carcinoma in post-Fontan patients with heterotaxy syndrome is less documented. A PubMed search for 'Fontan procedure', 'heterotaxy' and 'hepatocellular carcinoma' yields two reports. Cases with no established atrial isomerism and no evidence of history of Fontan procedure were excluded. The patients were a 19-year-old young man with left atrial isomerism and midline liver and a 27-year-old woman with left atrial isomerism and right-sided liver presenting with haematemesis and elevated AFP on surveillance following observed hepatomegaly, respectively. The former was found to have a localised 2.0 cm hepatocellular carcinoma and was successfully treated with transarterial chemoembolisation with no documented follow-up, and the latter had a 2.2 cm hepatocellular carcinoma treated with proton beam therapy, surviving for 38 months without recurrence. In both cases, radiofrequency ablation and surgical resection were dismissed due to proximity of the lesions to the inferior vena cava.

Our patient presented with diffuse hepatocellular carcinoma, with the largest mass measuring 12×8 cm. While hepatomegaly was noted on evaluation several years prior, surveillance was not pursued. Sorafenib was prescribed for treatment but only initiated for 1 week before repeat visit to the emergency department. Indeed, standard therapies for hepatocellular carcinoma of common aetiologies, including liver transplantation, are suggested to be equally efficacious in treatment of those with hepatocellular carcinoma due to Fontan-associated liver disease. Of equal but as of yet undetermined significance is the role and algorithm of surveillance of post-Fontan patients for Fontan-associated liver disease, including hepatocellular carcinoma.[17] Extensive investigations suggest over 25% of patients with a history of Fontan procedure have an incidence of observable cardiac cirrhosis, exceeding the high-risk cut-off for hepatocellular carcinoma surveillance indicated for patients with chronic liver disease established by the American Association for the Study of Liver Diseases.[18] This would consist of routine abdominal ultrasonography and serum AFP measurements. Due to low prevalence and limited availability of data, what is also unknown is if the risk and course of Fontan-associated liver disease vary by the initial indication, from atretic atrioventricular valve to complex congenital heart disease such as heterotaxy syndrome.

Patient's perspective

When our son was first born, and we learned about his heart conditions, I couldn't believe it at first—none of us could. It made me wonder, as a mother, if I had done something wrong. We were not prepared for all of the treatment, the surgeries, and the changes that would come out of it. Still, we tried to not let it affect our family. As he grew up, there were times where he would be at the hospital for months and the other children would be left with the grandparents, but we made it work. We tried to keep his life as normal as possible. When our son started to complain about his stomach pain, we thought it was another problem with his heart. Then the doctors told us it was in fact not his heart but something else. I remember feeling shocked. Nothing but shock. Total shock. We were always prepared to lose him, always knowing that his heart was weak. We thought that was how he would go. But we never would have thought he would be diagnosed with cancer, and we never thought we would lose him to that. In the end, I don't wish that anything had been done differently for him. Nothing. I think the team did what they could with the information they had, and they were phenomenal. Ultimately, I hope that his memory and his experience can be used to let others know and be aware that something like this can happen. It would be amazing if his experience could provide more for others out there that might be in similar circumstances. Years later, and I still think about him. I hope some other family may be spared that. I just want everyone to know it's a possibility and, regardless of whatever caused it, which I truly will never know, it's something everyone should be on the lookout for. And I hope it can lead to some changes in order to catch these things sooner for kids with syndromes like my son.

Learning points

- Heterotaxy syndrome is a defect of asymmetric visceral organ left-right laterality that is often palliated with the Fontan procedure.
- A significant portion of patients with a history of the Fontan procedure develop Fontan-associated liver disease, with an increased risk for liver cirrhosis and hepatocellular carcinoma.
- The course of Fontan-associated liver disease and hepatocellular carcinoma in patients with heterotaxy syndrome is poorly understood.
- There are no established surveillance guidelines for Fontan-associated liver disease, but routine abdominal ultrasonography and serum alpha-fetoprotein measurements may be effective.

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Case reports provide a valuable learning resource for the scientific community and can indicate areas of interest for future research. They should not be used in isolation to guide treatment choices or public health policy.

ORCID iDs
Akash Mathavan http://orcid.org/0000-0003-3496-2542
Akshay Mathavan http://orcid.org/0000-0002-3850-834X
Ellery Altshuler http://orcid.org/0000-0003-1811-317X

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