Case Report

Congenital cardiac liver cirrhosis with combined hepatocellular-cholangiocarcinoma—a case report

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Background: Cardiac liver cirrhosis secondary to Fontan procedure has been associated with hepatocellular carcinoma at a younger age. However, Fontan associated liver disease and combined hepatocellular-cholangiocarcinoma has not been previously reported. Combined hepatocellular-cholangiocarcinoma is a rare cancer that accounts for 2–5% of primary liver tumors and poses significant diagnostic and treatment challenges. This case highlights these needs and potential screening and treatment considerations. Herein we describe a case of combined hepatocellular-cholangiocarcinoma in a patient with autism, congenital heart disease, and Fontan procedure.

Case Description: The patient is a 27-year-old male who presented with a liver mass detected on MRI performed in the context of a rising alpha-fetoprotein during a screening visit. Biopsy of the mass revealed a combined hepatocellular-cholangiocarcinoma which was staged as localized. Due to the COVID-19 pandemic and subsequent halt of all elective surgeries, the patient received local therapy with chemoembolization followed by pembrolizumab. The disease progressed though, and therapy was changed to gemcitabine plus cisplatin. Patient received 2 cycles of therapy, after which he and his family decided to transfer medical care to Memorial Sloan Kettering. Next generation sequencing of the tumor revealed *TP53* and *FGFR2* mutations. By then patient was also found to have lung metastasis. To help address the hepatocellular carcinoma, lenvatinib was added. Patient had sustainable disease control for about a year, yet eventually developed thrombocytopenia complicated by an episode of gastrointestinal bleeding. With a worsening performance status, adverse events of the treatment, and recurrent hospitalizations, a goals of care discussion with his family led to the discontinuation of active cancer therapy and patient was started on best supportive care. Patient remained in active follow-up until the time of this report and passed away less than a year from initiating best supportive care alone.

Conclusions: This challenging case raises awareness towards screening and monitoring all patients with Fontan procedure for Fontan associated liver disease and liver cancers, including combined hepatocellular-cholangiocarcinoma. To the best of our knowledge, this is the first description of combined hepatocellular-cholangiocarcinoma occurring in the context of cardiac cirrhosis. The management difficulties that led to altering the goals of care, is another reminder of the dynamic nature of the care oncologists would provide.

Keywords: Fontan; cardiac cirrhosis; combined hepatocellular-cholangiocarcinoma; case report

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Introduction

This is the case of combined hepatocellular-cholangiocarcinoma secondary to cardiac cirrhosis. This is the first case report of such occurrence. This report highlights the rarity of the disease, need for screening and increased awareness among clinicians who treat patients with congenital heart disease, and highlights the need for additional therapeutic interventions for combines hepatocellular-cholangiocarcinoma and the need for multidisciplinary approach in managing these complex cases. We present the following case in accordance with the CARE reporting checklist (available at https://jgo.amegroups.com/article/view/10.21037/jgo-21-878/rc).

Case presentation

This is a male patient who was 27-year-old at time of initial presentation. Patient was born with congenital heart disease and situs ambiguous. Anomalies included atrioventricular canal defect, heterotaxia (dextrocardia, situs inversus of the stomach, and malrotation of the bowels), and asplenia. Patient required a Blalock surgery in the neonatal period, a bidirectional Glenn (BDG) shunt procedure at the age of 3, and a Fontan (1) procedure at the age of five. Each successive procedure directed more venous blood flow directly into the pulmonary circulation to improve oxygenation. Patient's past medical history is significant for autism and impaired decision-making capacity. He was living with his parents who acted as his healthcare proxy.

His family history was negative for cardiac, liver diseases, or malignancies. At age 23 and 18 years since the Fontan procedure, the patient was found to have signs of cirrhosis. Of note patient had no known history of hepatitis B or C infection. At age 24, a liver mass was found. The mass measured 3.8 by 4.2 cm, there was no evidence of vascular invasion or metastatic disease. This was stage IB. At this point, the serum alpha fetoprotein (AFP) was up to 100 ng/mL from a baseline of normal, 2 years prior. At time of presentation patient had no symptoms of concern and he had preserved liver function with Child Pugh score of A.

Biopsy of the mass showed a primary hepatic carcinoma with features consistent with combined hepatocellular-cholangiocarcinoma. As illustrated in *Figure 1*, the tumor's hepatic origin was confirmed by the presence of albumin as detected by an *in situ* hybridization assay. The tumor had areas with gland formation and stromal desmoplasia, morphologically compatible with intrahepatic cholangiocarcinoma. In other areas, the tumor appeared more hepatocellular with a nested growth pattern and expresses glypican 3 on immunohistochemistry.

An elective planned surgical resection was aborted in view of the COVID-19 pandemic. Patient instead had a trans-arterial chemoembolization with doxorubicin beads (DEB-TACE) that was followed by pembrolizumab (240 mg every 3 weeks administered intravenously), what was defined by the caring team as adjuvant therapy. Therapy with pembrolizumab was complicated by hypothyroidism despite a total of two doses. AFP decreased to a nadir of 28.7 ng/mL after TACE and the limited course of pembrolizumab.

Repeat imaging after 3 months of TACE revealed evident progression of disease radiologically, add to an increased AFP level close to 200 ng/mL. Patient was started on gemcitabine (800 mg/m^2 administered intravenously on days 1 and 8 of 21-day cycle) and cisplatin (20 mg/m^2 administered intravenously on days 1 and 8 of 21-day cycle).

By the time patient received 2 cycles of chemotherapy, his care was transferred care to Memorial Sloan Kettering as per the family wishes. On physical examination, patient was well appearing, alert and oriented, interactive with limited engagement, hemodynamically stable. No abdominal masses or tenderness, no lower extremity swelling. Add to the elevated AFP, CA19-9 were within the normal range. A CT scan of the chest, abdomen, and pelvis, with intravenous iodine contrast helped detail the extent of disease in the liver against a background of cirrhosis. Scattered small pulmonary nodules were found, suggestive of metastatic disease in addition to the situs ambiguous within the abdomen (right stomach, mid liver, malrotation of the intestines) (*Figures 2,3*). Biopsy of the lung lesion was performed, and it revealed a carcinoma that had features consistent with metastatic combined hepatocellular-cholangiocarcinoma. At this time patient had confirmed stage IV disease. Patient's therapy of gemcitabine plus cisplatin was thus continued, and lenvatinib 8 mg orally

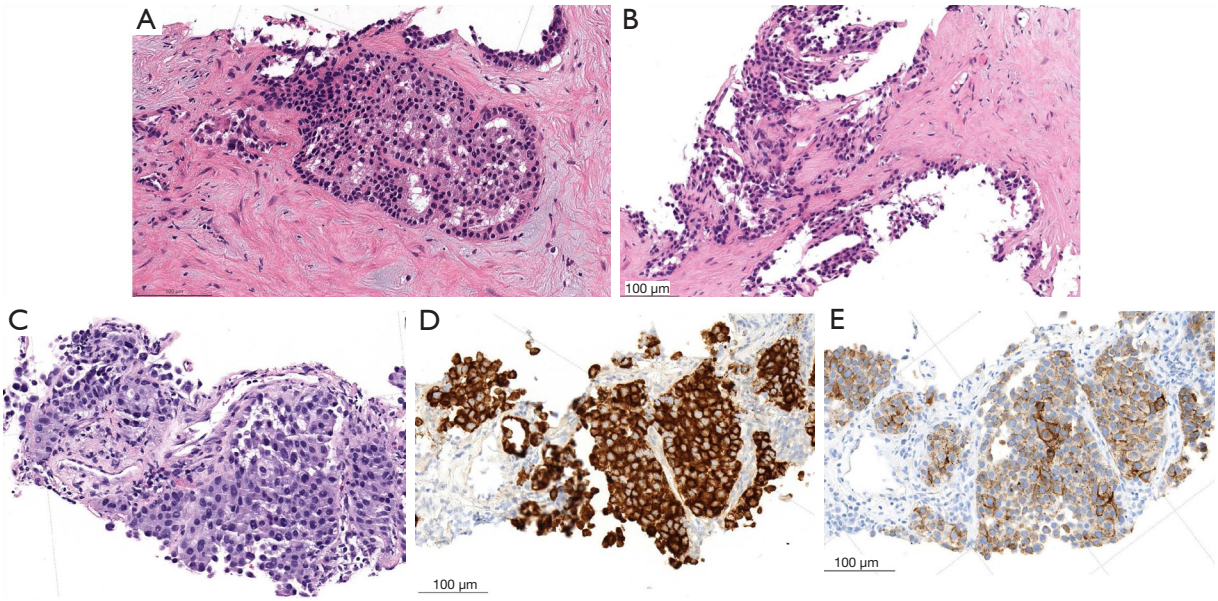

Figure 1 Pathological findings of the combined hepatocellular-cholangiocarcinoma. Hematoxylin & Eosin staining demonstrating some portions of tumor having gland formation and stromal desmoplasia (A,B), indicative of cholangiolar differentiation, while other portions having a more nested or trabecular pattern of growth with cytologic features suggestive of hepatocellular differentiation (C). The tumor is positive for albumin by in situ hybridization (D) and focally positive for glypican-3 by immunohistochemistry (E). Magnification times: 100×.

once daily was added to help address the hepatocellular carcinoma component of the disease. The therapy was fairly well tolerated as patient was followed with regular clinical assessments and blood work.

The course of the disease was complicated by several episodes of hypoxia; during the most drastic one, oxygen saturation was around 75% compared to patient's baseline of around 85% on room air. CT angiogram of the chest was performed, and patient was found to have pulmonary embolism (PE). Patient was started on therapeutic anticoagulation with low molecular weight heparin at 1 mg/kg twice daily subcutaneously, with improvement in symptoms and later near resolution of PE on subsequent imaging.

Later on, patient developed seizure and lower extremity weakness, prompting workup. MRI brain showed new foci of cortical and leptomeningeal enhancement and scattered punctate foci of hypo-intensity throughout the cerebrum and cerebellum (*Figure 4*). Lumbar puncture cerebrospinal fluid (CSF) cytology was negative for malignant cells. Electroencephalogram (EEG) was performed and showed no evidence of epileptic activity. MRI total spine did not show leptomeningeal disease either. A repeat MRI brain at a 1-month interval showed that the previously identified multifocal leptomeningeal enhancement/disease had nearly resolved. Patient's symptoms resolved, he was treated with antiepileptics sodium vakproate ER 1,000 mg daily and levetiracetam 500 mg twice daily with no further recurrence in these symptoms. Patient continued to be followed closely with high adherence to therapy and clinical appointments.

Patient continued to receive his anti-cancer systemic therapy with disease control for around one year. However, patient developed gastrointestinal bleed in the context of anticoagulation and low platelets. Nine months into therapy, patient developed a thrombocytopenia that became persistent. A bone marrow biopsy followed, and showed a normocellular marrow with trilineage maturing hematopoiesis, dysmegakaryopoiesis, and no increase in blasts. The degree of dysmegakaryopoiesis seen was concerning and raised the possibility for a Therapy-Related Myeloid Neoplasm (t-MN), including Myelodysplastic Syndrome (MDS) or Chronic Myelomonocytic Leukemia (CMML) (*Figure 5*).

With a worsening performance status, adverse events of the treatment, and recurrent hospitalizations, a goals of care discussion with the patient's family led to the discontinuation of active cancer therapy and patient was started on supportive care with the goal to maximize

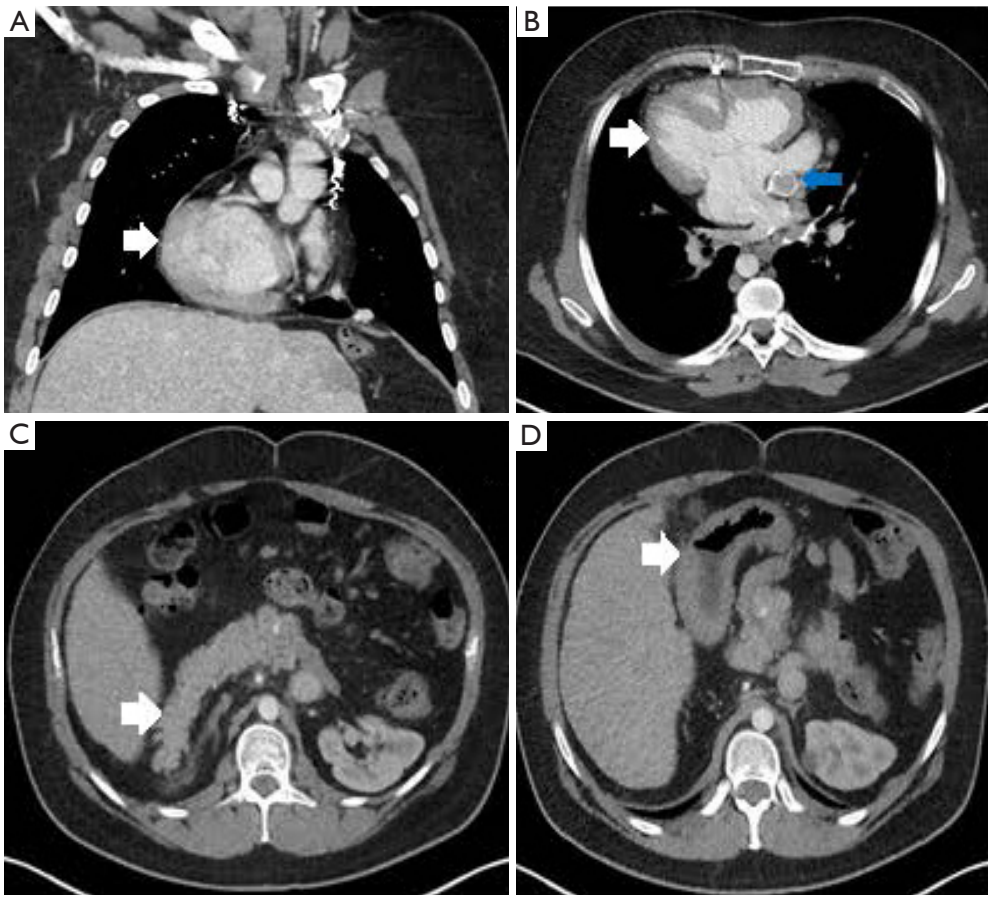

Figure 2 Congenital heart disease. Heterotaxia with asplenia. (A,B) Dextrocardia (white arrows) partially visualized Fontan repair (blue arrow). (C,D) Pancreas and stomach (white arrows) extending to the right of the midline.

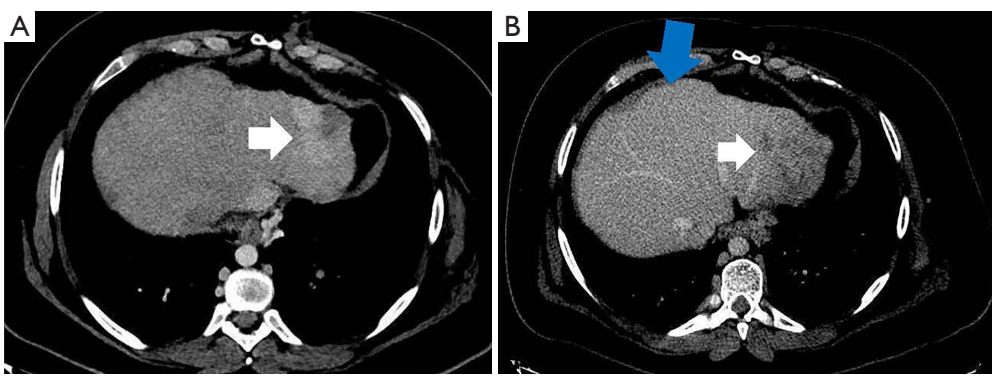

Figure 3 CT abdomen and pelvis. (A) Arterial phase. Partly hypervascular, heterogeneously enhancing mass in hepatic segment two (white arrow). (B) Portal venous phase. Hepatic contour nodularity, consistent with cirrhosis (blue arrow). Partial washout of the mass in keeping with pathological diagnosis of hepatocellular carcinoma-cholangiocarcinoma (white arrow).

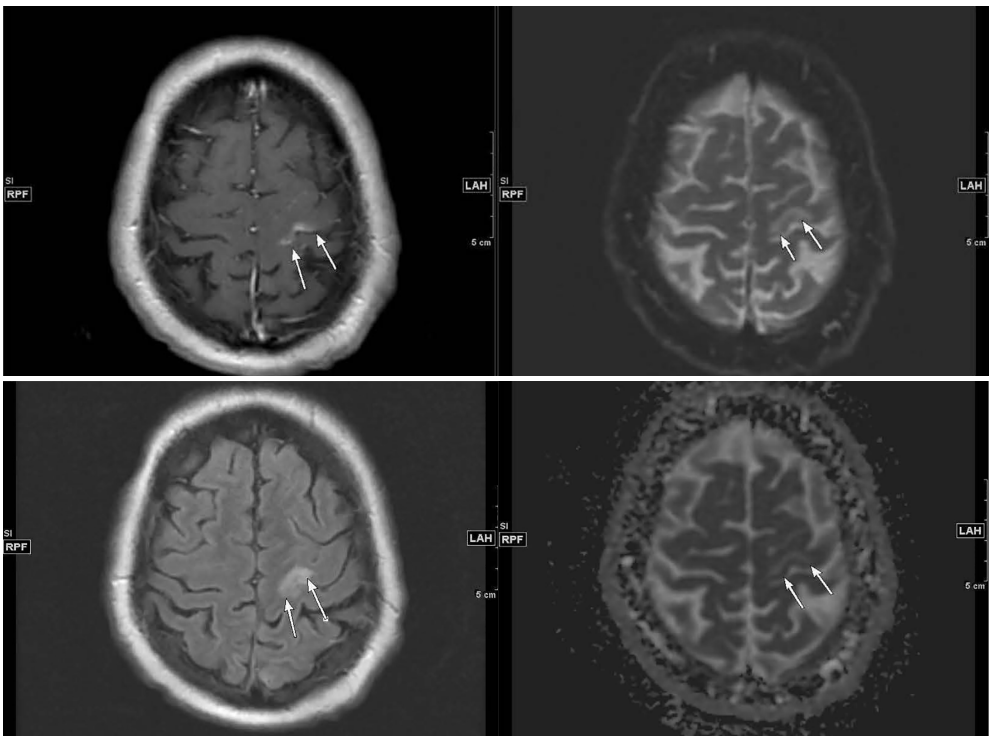

Figure 4 Brain MRI showing suspected leptomeningeal disease and left pre-central gyrus. The arrows point at the leptomeningeal disease.

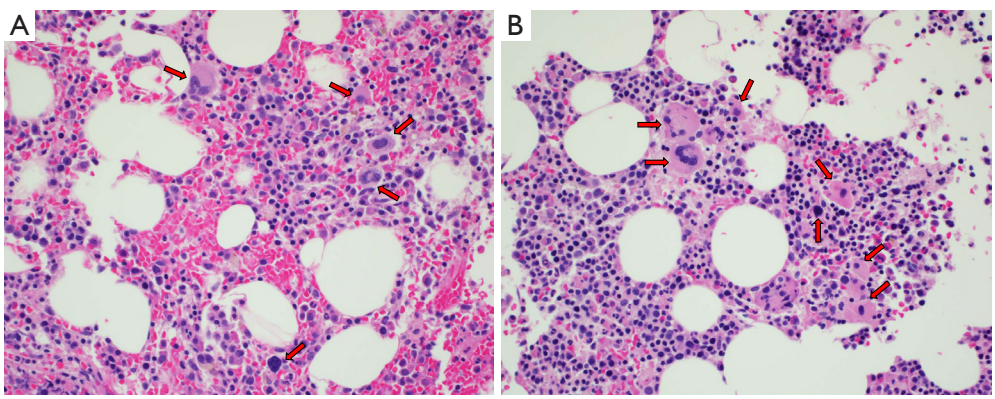

Figure 5 Hematoxylin & Eosin slide of the bone marrow core biopsy at 400× magnification. The red arrows point to megakaryocytes with frequently atypical morphology.

quality of life and maintain dignity. Patient continued to be followed closely and he passed away peacefully several months later.

All procedures performed in the study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Verbal informed consent was obtained from the patient's guardians in view of the patient autistic medical status, for publication of this case report and accompanying images.

Discussion

We report herein a case of combined hepatocellular-cholangiocarcinoma in a patient with liver cirrhosis following Fontan procedure. To the best of our knowledge,

this is the first reported case of cardiac liver cirrhosis leading to hepatocellular-cholangiocarcinoma or intrahepatic cholangiocarcinoma alone to that effect. This case brings up several multidisciplinary learning points. During clinical course, the patient developed a PE, which is a serious concern in the setting of Fontan procedure, in view of the low pulmonary arterial pressures critical to maintain cardiac output. Patient also experienced one episode of seizure. The causes of seizure may have been multifactorial, including history of autism, the state of cardiac ischemia that might happen which decreases the seizure threshold, and hypoxia. Of note, patients with cardiac condition and Fontan procedure tend to have a lower-than-normal oxygen saturation (2).

This case also illustrates the significant impact of COVID-19 pandemic on access to healthcare, particularly for cancer patients. Initially, patient's tumor was amenable to surgical resection, but surgery was deferred given the substantial risks during the pandemic and the need to prioritize the limited resources in treating the increasingly high numbers of severe and complicated cases of COVID-19 infections.

The Fontan procedure has improved the chances of survival of patients born with single ventricle congenital heart disease. This significant impact is associated with several physiological changes in patients manifested early on and in the later years after the surgery. Hemodynamic changes associated with the new circulation generated by the Fontan procedure include elevated central venous pressure (CVP), up to 6 times higher than the usual pressure, and diminished cardiac output, responsible for the development of Fontan-associated liver disease (FALD). There is currently an increased recognition of FALD and other late complications of Fontan surgery. Liver fibrosis is a universal side-effect of the Fontan operation. The incidence of both liver cirrhosis and hepatocellular carcinoma increases with the duration of the Fontan circulation (3). In FALD, the liver is exposed to chronic and repeated insults from the time of birth. Liver damage may occur prior to the formation of the Fontan circulation due to the effects of abnormal fetal circulation and cyanosis on the liver, or following the Fontan procedure, due to the exposure to elevated CVP and diminished cardiac output. Chronic venous hypertension is transmitted to the hepatic sinusoids and may promote liver fibrosis (4).

Cases of cardiogenic cirrhosis and hepatocellular carcinoma association have been previously described and reported in the literature (5). Author GAA and colleagues reported on two cases of female patients with congenital heart disease treated with Fontan procedure who developed HCC in their twenties in the setting of cardiac cirrhosis.

HCC secondary to Fontan-associated liver cirrhosis was observed in patients as young as sixteen years old (6). In a retrospective series of patients undergoing surveillance imaging after Fontan procedure, the prevalence of HCC was 5 of 145 patients (3.4%) (7).

The American College of Cardiology (ACC) meeting in 2015 discussed the current state of FALD with the goal of developing a multidisciplinary approach to preventing, screening, and treating this subgroup of patients (8). This emphasizes the importance of collaboration between pediatric and adult cardiologists, heart failure specialists, pediatric and adult hepatologists, and liver transplant specialists. Recommended steps to prevent and slow down the progression of FALD included optimizing the anatomy and physiology of the Fontan circulation, avoiding hepatotoxic injuries, preventing obesity and nonalcoholic steatohepatitis (NASH), hepatitis vaccination, and early hepatology referral. Screening for FALD was recommended for children and young adults with labs and imaging. Frequency of imaging should be no less than every 3–5 years for children less than 12 years old and every 1–3 years for adolescents and adults.

The diagnosis of combined hepatocellular-cholangiocarcinoma is dependent on evidence of both hepatocellular and biliary epithelial features within the same tumor, hence the absolute importance of a biopsy (9). Its true incidence may be higher than that reported due to historical diagnostic difficulties and in some instances lack of biopsy (10). Combined hepatocellular-cholangiocarcinoma is a challenging entity to describe; it is a rare finding and accounts for around 2–14% of primary liver tumors with notable variation across references (11). There are no clear guidelines for treatment of combined hepatocellular-cholangiocarcinoma. Beyond surgical resection for early-stage disease, systemic treatment of mixed tumors remains undefined and usually geared to the predominant component of the tumor, when identifiable. The combination of gemcitabine, cisplatin, plus sorafenib has been evaluated in a study of patients with biliary cancers, including a few cases with mixed histology (12). Given this safety data, and the more recent data on lenvatinib efficacy in HCC (13), along with the overlap in sorafenib and lenvatinib toxicity profile, we chose this combination in this case.

Historically, prior to the advances in HCC systemic

therapies, treatment of advanced/metastatic combined hepatocellular-cholangiocarcinoma was mostly directed at the cholangiocarcinoma component, in the form of cytotoxic chemotherapy by default of the response of the cholangiocarcinoma component to chemotherapeutic interventions and a possible perspective of further aggressivity of this component of the disease. With the current advent of novel combinations and more successful HCC treatments (14-16), a more current approach is needed.

For early-stage disease, surgery and local therapies are the most considered and applicable interventions (17). In the setting of Fontan associated liver disease, surgery would be associated with higher risks though. There is also limited data on liver transplant in combined hepatocellular-cholangiocarcinoma (18).

This case also illustrates the value of tumor biopsy in the setting of liver cirrhosis and liver tumors, where the diagnosis of HCC is usually made based on radiological criteria, to establish histopathological diagnosis given the possibility of combined hepatocellular-cholangiocarcinoma.

Strengths and limitations

The case has several strengths. We benefited from the expertise of pathology, radiology, cardiology, hematology, neurology, and psychiatry disciplines in providing valuable input caring for this patient and writing this manuscript. The case is the first reported combined HCC-cholangiocarcinoma secondary to cardiac cirrhosis and raises awareness for importance of screening in this population and the need for collaboration among pediatricians, cardiologists, and hepatologists at the early stage. The case describes several treatment modalities for this rare cancer with unmet therapeutic needs. Limitations include the lack of large studies/data on this disease, which increases the value of such reports to spread knowledge and raise awareness to include rare cancers in research.

Conclusions

We report herein the first case of combined hepatocellular-cholangiocarcinoma in a young patient with FALD. This rare and diagnostically challenging cancer occurring at this young age is linked to the congenital heart disease and Fontan complications. Liver biopsy should be done universally when diagnosing primary liver tumor. Patients with Fontan related liver disease or cardiac liver cirrhosis should undergo screening for liver cancers at an early age. A broad perspective in a complex medical situation may dynamically alter the medical priorities from a complex medical intervention perspective to a more robust and caring best supportive caring one.

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Footnote

Reporting Checklist: The authors have completed the CARE reporting checklist (available at https://jgo.amegroups.com/article/view/10.21037/jgo-21-878/rc).

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available a https://jgo.amegroups.com/article/view/10.21037/jgo-21-878/coif). DM reports that she received honoraria from Astra Zeneca for lectures, presentations, and educational events. WB reports that he received royalties from Oxford University Press Royalty textbooks and Kluwer Publishing, consulting fees from Blue Note Therapeutics, and honoraria from Kubler Ross Foundation of Argentina for lecture, GKA reports that he received support from Adicet, Alnylam, AstraZeneca, Autem, Beigene, Berry Genomics, Boehringer Ingelheim, Celgene, Cend, CytomX, Eisai, Eli Lilly, Exelixis,Flatiron, Genentech/Roche, Genoscience, Helio, Helsinn, Incyte, Ipsen, Merck, Nerviano, Newbridge, Novartis, QED, Redhill, Rafael, Servier, Silenseed, Sobi, Vector, Yiviva for consultancy and from Arcus, Astra Zeneca, BioNtech, BMS, Celgene, Flatiron, Genentech/Roche, Genoscience, Incyte, Polaris, Puma, QED, Silenseed, Yiviva for institutional grants. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in the study were in accordance with the ethical standards of the institutional and/or national research

committee(s) and with the Helsinki Declaration (as revised in 2013). Verbal informed consent was obtained from the patient's guardians in view of the patient autistic medical status, for publication of this case report and accompanying images.

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