Pathology - Research and Practice xxx (xxxx) xxx–xxx

Contents lists available at ScienceDirect

Pathology - Research and Practice

journal homepage: www.elsevier.com/locate/prp

Intrahepatic cholangiocarcinoma after Fontan procedure in an adult with visceral heterotaxy

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ARTICLE INFO

Keywords:
Cholangiocarcinoma
Fontan palliation
Heterotaxy
Cholangiociliopathy
Atypical ductular proliferation
MYST3 mutation

ABSTRACT

Hepatic dysfunction, including development of hepatocellular carcinoma and other liver lesions has been increasingly reported following Fontan procedure for congenital heart disease. We report a unique case of intrahepatic cholangiocarcinoma 28 years after a Fontan procedure in a 31year old female with heterotaxy syndrome. The subcapsular mass-forming tumor was composed of poorly differentiated tumor cells arranged in small vague glandular or slit-lumen nests, and focally fused or anastomosing large trabecular patterns within the prominent fibrotic stroma. The tumor cells with immunoreactivity to CK7, CK19, Cam5.2, COX2, EMA, BCL-2, MOC-31 and AE1/AE3, supported a diagnosis of intrahepatic cholangiocarcinoma. Focal atypical ductular proliferation within the background liver may represent a precursor lesion to this tumor. Dysmorphic cilia observed by electron microscopy examination in the background liver may suggest cholangiociliopathy in heterotaxy. MYST3 mutation at Q1388H detected in intrahepatic cholangiocarcinoma is reported for the first time.

1. Introduction

The Fontan procedure, designed for staged surgical palliation of tricuspid atresia, has since been expanded to palliate all forms of single ventricle physiology. As surgical techniques and postoperative survival have improved, the management of these patients has progressively incorporated screening for, and management of chronic complications such as progressive hepatic fibrosis and hepatic neoplasms that develop in the context of congestive hepatopathy. Hepatocellular carcinoma (HCC) is the most commonly described hepatic malignancy in patients after Fontan palliation [1–3]. In this report, we describe a patient who developed peripheral intrahepatic cholangiocarcinoma 28 years following Fontan procedure.

2. Case report

2.1. Clinical history

A 31 year old female had complex congenital heart disease characterized by heterotaxy syndrome with left atrial isomerism, polysplenia and dextrocardia with surgical palliation including modified left Blalock–Taussig shunt on day 17 of life, followed by a Fontan procedure at 4 years of age. She subsequently required epicardial pacing with a dual chamber pacemaker for complete heart block. At age 32, she presented with shoulder pain, and non-specific right epigastric discomfort. Cardiac catheterization demonstrated good Fontan hemodynamics with no evidence of pathway obstruction and no abnormalities of pulmonary vascular resistance or ventricular function. Computed tomography (CT) of the abdomen showed an enlarged liver with subtle surface nodularity and a 5 cm, subcapsular mass in the right lobe (Fig. 1, anatomic left lobe in heterotaxy syndrome) that was hypoenhancing in both the arterial and portal venous phases. Initial alpha fetoprotein (AFP) was mildly elevated to 39 ng/ml (reference range: ≤8 ng/ml). The gallbladder was normal in appearance without wall thickening, cholelithiasis or pericholecystic fluid. Intrahepatic and extrahepatic bile ducts were not dilated. The kidneys, pancreas and spleen were normal. Clinical manifestations for primary ciliary dyskinesia (PCD) were absent. No history of alcohol intake, viral hepatitis, obesity or diabetes was recorded in the clinical notes. An ultrasound guided liver biopsy was performed, and the initial pathological findings were

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https://doi.org/10.1016/j.prp.2018.03.016
Received 10 December 2017; Received in revised form 28 February 2018; Accepted 13 March 2018

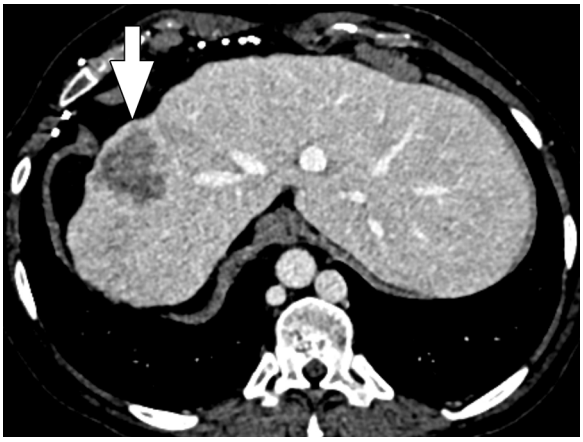

Fig. 1. Axial CT performed with intravenous contrast showed an irregular, hypoenhancing mass (arrow) in the right hepatic lobe (anatomic left lobe in heterotaxy syndrome) with overlying capsular retraction. The surface contour of the liver was nodular.

consistent with a poorly differentiated carcinoma favoring primary intrahepatic cholangiocarcinoma (ICC). Subsequent F-18 Fluorodeoxyglucose (FDG) PET/CT showed abnormal FDG uptake by the dominant liver mass (SUVmax = 4.8) as well as two smaller foci of abnormal increased metabolic activity adjacent to the dominant liver mass concerning for additional tumors. The patient underwent resection of the anatomic left lateral section of the liver.

2.2. Pathological findings and targeted next generation sequencing result

The liver specimen was serially sectioned perpendicular to the resection margin to reveal an irregular 6.3 × 5.6 × 3.1 cm tumor mass with firm grey-whitish cut surface (Fig. 2A), abutting the liver capsule. A 2.4 × 2.0 × 1.2 cm small nodule with similar gross findings was 0.5 cm away from the dominant mass. The resection margin was negative for the tumor. The background liver had a non-uniform vague or incomplete nodular appearance. No additional masses or lesions were identified.

The dominant tumor mass and the small nearby independent nodule were composed of poorly differentiated, small to medium-sized tumor cells which were occasionally pleomorphic. The tumor cells were arranged in small vague glandular or slit-lumen glandular nests, occasionally fused or anastomosed into large trabecular tumor nests within prominent fibrotic stroma (Fig. 2B–C). The infiltrating tumor cells entrapped adjacent hepatocytes (Fig. 2D, F) enveloping portal area structures such as small ducts/ductules (Fig. 2E) at the tumor periphery. The differential diagnoses included cholangiocarcinoma, hepatocellular carcinoma (HCC), combined hepatocellular-cholangiocarcinoma, metastatic adenocarcinoma and neuroendocrine tumor. The tumor cells were positive for CK7 (Fig. 2E), CK19 (Fig. 3A), Cam5.2 (Fig. 3B), COX2 (Fig. 3C), EMA, BCL-2, AE1/AE3 and MOC-31, an immunoprofile that supported a diagnosis of intrahepatic cholangiocarcinoma. These markers can also be positive in metastatic adenocarcinomas. Giving that the tumor cells were negative for CEA, CK20, CDX2, TTF1, ER, PR, GCDFP-15 and mammoglobulin, metastatic adenocarcinoma from GI, pancreas, breast, lung, kidney, ovary and thyroid were excluded. In the solid trabecular nests, the tumor cells were weakly positive for synaptophysin, a finding deemed insufficient for the diagnosis of neuroendocrine tumor, and interpreted as slight neuroendocrine differentiation in this tumor. Notably, immunoreactivity for synaptophysin has been reported in some cases of cholangiocarcinoma [4]. Although Glypican-3 immunoexpression within the tumor cells (Fig. 3D) raised the possibility of hepatocellular carcinoma or combined hepatocellular-cholangiocarcinoma, Glypican-3 has also been reported to be expressed in some cases of cholangiocarcinoma [5]. In addition, negativity for hepatic markers such as arginase (Fig. 3E), HepPar-1(Fig. 2F) and AFP excluded typical HCC. Compelling morphological evidence for combined hepatocellular-cholangiocarcinoma was lacking. However, some morphological feature of small duct or ductular-like tumor nests in this tumor may mimic combined hepatocellular-cholangiocarcinoma with stem-cell features, intermediate-cell subtype or cholangiocellular type. With the absent expression of hepatic markers and hepatic progenitor markers such as arginase, HepPar-1, AFP, CD10, CEA, c-kit (CD117), CD34, CD56 (NCAM) and vimentin, combined hepatocellular-cholangiocarcinoma is unlikely. The tumor cells were also negative for mucin by mucicarmine, Alcian blue and PAS after diastase treatment. Overall, macroscopic, morphological and immunohistochemical findings were most consistent with poorly differentiated intrahepatic cholangiocarcinoma, mass-forming type. The features of tumor infiltrating the periphery, fibrotic stroma and excessive tumor vasculature (Fig. 3F) were suggestive of subclassification as peripheral small duct type or ductular/cholangiolar type ICC recently proposed [6].

Background liver showed incomplete bridging stage 3 fibrosis (Fig. 4A), sinusoidal fibrosis, variable sinusoidal dilation, and mild macro/microvesicular steatosis in Zone 2 of hepatocellular lobules (Fig. 4B). Within the non-neoplastic background liver, we also found a few scattered microscopic foci of atypical ductular proliferation unrelated to overt fibrosis or vascular invasion by the main tumor. These lesions had nuclear atypia, forming compact ductules which mimicked tumor but were negative for the tumor markers such as Glypican 3 (Fig. 4C–E). Electron microscopy (EM) examination of the background liver showed dysmorphic cilia in the small bile ducts (Fig. 4F). Cytogenetic study showed a normal female karyotype with 46, XX [19].

To identify cancer-related mutations for therapeutic purposes, targeted next generation sequencing was performed on the paraffin-embedded tumor tissue at FoundationOne (Cambridge, MA). This assay is designed to include 315 genes as well as introns of 28 genes involved in rearrangements, known to be somatically altered in human solid tumors that are validated targets for therapy. Of unknown significance, a single genomic alteration, MYST3 mutation at Q1388H (at mutant allele frequency > = 10%) was identified in this tumor.

3. Discussion

Hepatic dysfunction after the Fontan operation is thought to be related to a combination of venous congestion of the liver and the relatively low cardiac output which chronically reduces hepatic arterial blood supply [2,7]. The creation of the Fontan circulation relieves the pulmonary overcirculation, systemic desaturation, and ventricular volume overload inherent to single ventricle physiology by redirecting returning systemic venous blood directly to the pulmonary circulation and allowing the single functional ventricle to solely pump oxygenated blood into systemic arterial circulation. The attainment of this physiologic relief comes with a trade-off as the achievement of a Fontan circulation produces novel pathophysiologic derangements, namely chronic elevation of central venous pressure (CVP) and a decrease in cardiac output; a dangerous combination that can portend end organ dysfunction [8]. The liver is unique in that it has a dual blood supply with about 20% of its blood supply coming from the systemic arterial system via the hepatic artery and the remaining 80% coming in the form of partially deoxygenated blood via the portal vein [9]. The elevated CVP seen in patients with a Fontan circulation is associated with a relative deprivation in portal venous inflow with a compensatory and relative increase in hepatic arterial blood supply to the liver, the so-called arterial buffer response. Hepatic arterial flow is vulnerable to the decreased cardiac output associated with the Fontan circulation limiting the extent to which the hepatic arterial buffer response can secure liver blood supply [10]. This combination of factors conspires to create a state of chronically decreased oxygen delivery to the liver which predisposes to organ damage. This hepatic injury can range from reversible fibrosis to irreversible cirrhosis and neoplasia.