CASE REPORT

Budd Chiari Syndrome and Intrahepatic Cholangiocarcinoma, An Unusual Combination: Case Report and Review of the Literature

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ABSTRACT

Introduction: Intrahepatic cholangiocarcinoma arising in the setting of Budd Chiari syndrome is uncommon and its prognostic and management implications differ from hepatocellular carcinoma.

Case Presentation: We report a case of intrahepatic cholangiocarcinoma in a patient with primary Budd Chiari syndrome. Hepatocellular carcinoma is known to occur with Budd Chiari syndrome. It was difficult to differentiate from hepatocellular carcinoma in the presence of increased alfa-fetoprotein levels. The contrast imaging showed features of progressive enhancement in the arterial, portal, and venous phases. A targeted liver biopsy showed histological features typical for cholangiocarcinoma. Immunostaining for cytokeratin 7 and cytokeratin 20 were positive, whereas that for arginase was negative, suggesting an intrahepatic cholangiocarcinoma. The patient was planned for inferior vena cava angioplasty followed by resection for intrahepatic cholangiocarcinoma.

Conclusion: Previously, only secondary Budd Chiari syndrome developing in the background of primary liver tumor has been described; no report exists of intrahepatic cholangiocarcinoma arising in background of primary Budd Chiari syndrome.

INTRODUCTION

Budd Chiari syndrome (BCS), or hepatic vein outflow tract obstruction, is characterized by obstruction anywhere from the hepatic veins (HV) to the inferior vena cava (IVC) outflow.[1] BCS can be subdivided into primary, characterized by HV stenosis secondary to thrombotic obstruction or phlebitis, or secondary, due to compression of the HV by tumors, cysts, or abscesses.[2] BCS is a risk factor for the development of hepatocellular carcinoma (HCC), with a reported prevalence of 1.9% and cumulative 10-year incidence of 3.5%[3]; however, cholangiocarcinoma has rarely been reported in patients with BCS, and only a few case reports exist. To the best of our knowledge, of the existing case reports, most (5) of them reported the development of secondary BCS with cholangiocarcinoma,[4–7] and there is only a single case report of cholangiocarcinoma developing on a background of primary BCS.[8] Hereby, we report a case of primary BCS presenting as intrahepatic cholangiocarcinoma (ICC), probably only the second case in the English literature and the first from the East.

CASE REPORT

A 42-year-old gentleman presented to the outpatient department with a recent onset of pain in the epigastric region over the past 3 months and noncholestatic jaundice for 15 days (Table 1: Timeline). There was an associated loss of appetite and a weight loss of 3 kg since the onset of symptoms. There was no history of prodromal symptoms, history of jaundice in the past, hematemesis, melena, or altered sensorium. There was a history of tobacco chewing for the past 10 years. He denied a history of chest pain, palpitations, focal neurological deficit, limb pain and swelling, and vision loss in the past. He denied prior blood transfusion, surgery, tattooing, high-risk behavior, family history of liver disease, and injecting drug or alcohol use. The examination was positive for icterus and a palpable firm mass in the epigastric region that was nontender to touch. There were no prominent abdominal veins.

His liver function tests revealed bilirubin of 5.6 mg/dL (normal <1 mg/dL) with a direct fraction of 4.1 mg/dL. Aspartate aminotransferase level was 75 IU/L (normal <40 IU/L), alanine aminotransferase levels 53 IU/L (normal <40 IU/L), and alkaline phosphatase level 595 IU/L (normal <240 IU/L), with a normal total protein and albumin level of 7.3 g/dL and 4.0 g/dL, respectively. Serological tests hepatitis B surface antigen and anti–hepatitis C virus were negative. His alfa-fetoprotein (AFP) was significantly raised, 2500 ng/mL (normal <4 ng/mL), and cancer antigen (CA)-19.9 was 12.9 U/mL (normal <37 U/mL).

Multiphasic magnetic resonance imaging (MRI) (Figure 1) revealed a large multilobulated mass of approximate size 10 cm × 8 cm × 10 cm involving segments III and IV, on the background of a cirrhotic liver. The mass was T1 hypointense, T2 hyperintense, showing patchy heterogeneous arterial enhancement that showed progressive enhancement on portal, hepatic venous, and subsequent 3-minute delayed phase. The areas showing enhancement also showed restriction on diffusion-weighted imaging. In addition, there was splenomegaly (spleen size 15 cm), and the main portal vein diameter was 12 mm. The left portal vein and left hepatic artery were involved by the tumor, and there was left-sided intrahepatic biliary radical dilatation. The MRI also showed nonvisualization of right and middle HVs

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Table 1. Timeline

Date	Clinical Details	Investigations	Interventions/advise
October 2018	Presented with right upper quadrant pain for 3 months and jaundice since 15 days.	Liver function tests: bilirubin (total/direct) 5.6/4.1 mg/dL, SGOT/SGPT 75/53 IU/L, ALP 595 IU/L	Multiphase MRI to characterize liver lesion
	No previous decompensation	HBsAg and anti-HCV Ab: negative	
	Examination revealed icterus and epigastric mass arising from liver	AFP: 2500 ng/mL	
		CA 19.9: 12.9 U/mL	
November 2018	Progressive jaundice	Multiphase MRI: a large mass in the background of a cirrhotic liver with feature of hepatic venous outflow obstruction	Biopsy from mass
December 2018		Biopsy from mass: tumor with cholangiolar differentiation Doppler: Inferior vena cava and hepatic venous obstruction	Offered IVC angioplasty followed by tumor resection
			Patient declined therapy

48-year-old gentleman, chronic tobacco chewer, Non-smoker, non-alcoholic, no previous comorbidities.

and distal most intrahepatic and suprahepatic. The hemiazygous vein appeared enlarged. A subsequent Doppler showed evidence of IVC occlusion and nonvisualization of all the HVs with no ascites and a mass lesion in left lobe, as demonstrated on MRI. The patient underwent a targeted biopsy from the mass lesion, which showed cholangiolar differentiation (Figure 2a) with positivity for cytokeratin (CK) 7 (Figure 2b) and CK 20 (Figure 2c) and no evidence of hepatocyte differentiation with negative arginase (Figure 2d), overall consistent with an ICC. Upper gastrointestinal tract endoscopy showed evidence of portal hypertension in the form of severe portal hypertensive gastropathy with no esophageal varices. The patient was planned for IVC angioplasty followed by resection of the left lobe mass lesion. The patient was offered IVC angioplasty for management of BCS followed by curative resection for ICC, which he declined and was lost to follow-up.

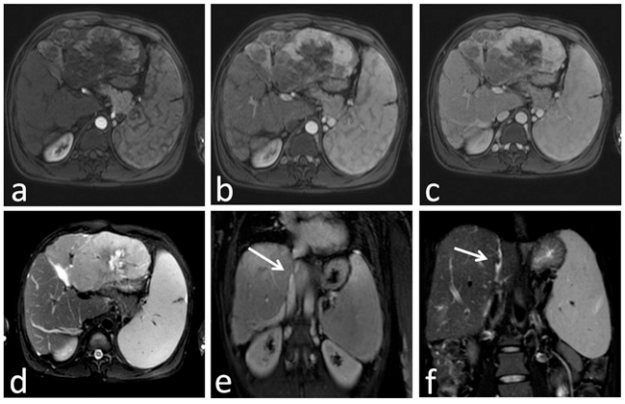

Figure 1. Multiphasic magnetic resonance imaging of the abdomen shows a large mass lesion in segments III and IV, on the background of a cirrhotic liver. The mass shows progressive enhancement on (a) arterial, (b) portal, and (c) venous phases on contrast imaging. The stenotic intrahepatic and suprahepatic part of the inferior vena cava also can be visualized: arrows in (e) and (f).

CONCLUSION

We hereby describe a case of mass-forming ICC in a patient with primary BCS. BCS is a risk factor for HCC; cholangiocarcinoma has been rarely described in patients with BCS. Our patient presented with a mass lesion in a cirrhotic liver background with high levels of AFP, raising the possibility of HCC, which has an association with BCS. However, the findings on multiphasic contrast MRI showed progressive enhancement with no washout and left-sided intrahepatic biliary radical dilatation suggestive of ICC. These findings led us to do a liver biopsy that showed features of cholangiolar differentiation and no hepatocellular differentiation.

Our case had primary BCS with the involvement of both HVs and IVC, which is a common site of block in patients with BCS.[9]

Only 10% of cholangiocarcinomas have an established risk factor.[10] On evaluation for these factors, our patient

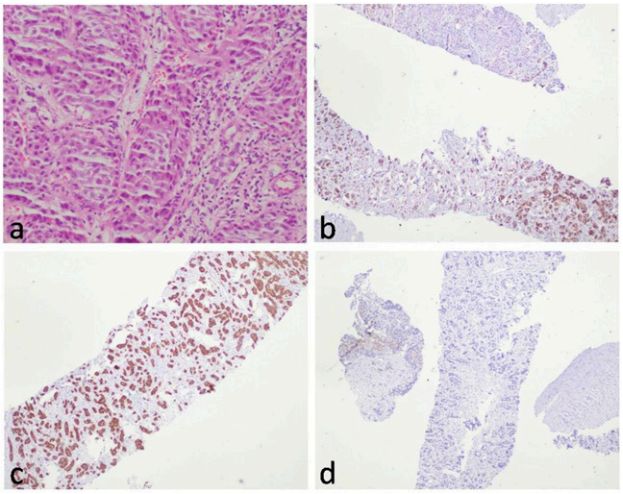

Figure 2. Cholangiocarcinoma. (a) Section stained with hematoxylin and eosin shows clusters of cells with large nuclei showing occasional gland formation on a background of fibrous stroma. (b) CK 7 positivity, (c) CK 20 positivity, (d) arginase is negative. CK = cytokeratin.

had only cirrhosis and tobacco use as evident risk factors. Cirrhosis has been shown to be associated with the development of cholangiocarcinoma, whereas the strength of association with tobacco use is questionable.[11] The possibility of a combined hepatocellular-cholangiocarcinoma (combined HCC-CC) was also contested. Per Park and colleagues,[12] "The World Health Organization (WHO) classification defines combined HCC-CC, classical type as a tumor containing unequivocal elements of both HCC and cholangiocarcinoma (CC), which are intimately admixed, this tumor should be distinguished from separate HCC and CC arising in the same liver."Our patient's biopsy sample did not show any evidence of hepatocyte differentiation, thus questioning the preceding possibility of combined HCC-CC. Combined HCC-CCs are difficult to diagnose preoperatively because of a risk of sampling error (sampling only the area of a single phenotype). Thus, most of the literature reports on combined HCC-CC are based on resected surgical specimens.

Our patient also had a significantly raised AFP level of 2500 ng/mL, which is atypical for cholangiocarcinoma. A study of primary liver cancers in Japan,[13] had shown that 19.2% of cholangiocarcinomas had elevated AFP levels (>200 ng/mL). An exceptionally elevated level of AFP of 12,310.7 ng/mL has been reported as a case report in a histologically proven cholangiocarcinoma.[14] In our case, the exceptionally elevated AFP levels can be explained by the common stem cell origin of both HCC and cholangiocarcinoma.

Our case is also unique in that the patient had a normal CA-19.9 level of 12.9 IU/mL, which can be explained by the fact that the sensitivity of CA-19.9 >37 IU/mL for diagnosing cholangiocarcinoma is only 77.1%.[15]

A diagnosis of ICC, instead of HCC, has prognostic and management implications because of poor median survival of 3 years only with ICC, and also because only a minority (15%) present with resectable disease at the time of presentation.[16] Surgical resection with curative intent is probably the only potentially curative treatment in ICC. Even after a curative intent resection, the probability of cure is only 10%.[17]

The development of secondary BCS due to a primary liver cancer containing a cholangiocarcinoma component has been described previously. Of the 5 case reports in the literature, 4 have reported the primary liver tumor as cholangiocarcinoma,[5-7] and the fifth has reported the tumor to be a combined HCC-CC.[4] All of these reports have shown tumor extension through the HVs leading to tumor thrombus in the IVC and secondary BCS. A single case report previously has described the development of a combined HCC-CC on the background of primary BCS.[8]

Our case was unique in that this is probably the second case in the international literature that describes development of ICC on a background of BCS-related cirrhosis. ❖

Disclosure Statement

None for all authors.

How to Cite this Article

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