CASE REPORT

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A Rare Association between Left Lobe Secondary Biliary Cirrhosis and Budd-Chiari Syndrome Secondary to Hepatocellular Carcinoma in the Non-Cirrhotic Right Liver Lobe

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ABSTRACT

Liver cirrhosis is a diffuse chronic liver disease affecting the entire liver. The fibrosis accumulation and distribution in the liver are known to be heterogeneous. „Localized" or „focal" cirrhosis is only anecdotically reported. Acute hepatitis E virus (HEV) infection is uncommon in western countries, especially in temperate climate areas and is very often missed or underdiagnosed. However, it may be responsible of up to 15% of acute-on-chronic liver failure cases. We present the case of a 35-year-old patient with a very uncommon association of Budd-Chiari syndrome secondary to hepatocellular carcinoma (HCC) developed on a non-cirrhotic right liver lobe and secondary biliary cirrhosis of the left liver lobe, that further complicated with acute HEV infection leading to acute-on-chronic liver failure and death.

Key words: autochthonous HEV infection – single liver lobe cirrhosis – secondary biliary cirrhosis – secondary Budd-Chiari syndrome – hepatocellular carcinoma.

Abbreviations: Alb: Albumin; AFP: alpha feto-protein; ALP: alkaline phosphatase; ALT: alanine aminotransferase; AST: aspartate aminotransferase; BCS: Budd-Chiari syndrome; CK7: cytokeratin 7; CMV: cytomegalovirus; EBV: Epstein-Barr virus; GGT: gamma glutamyl transpeptidase; HBV: hepatitis B virus; HCV: hepatitis C virus; HEV: hepatitis E virus; HSV: hepes simplex virus; HCC: hepatocellular carcinoma; IVC: inferior vena cava; MELD: model for end-stage liver disease; (MD)CT: (multi-detector) computer tomography; PT: prothrombin time; TB: total bilirubin.

INTRODUCTION

Hepatocellular carcinoma (HCC) is the third leading cause of cancer-related death worldwide [1], and mostly arises in the setting of underlying cirrhosis (90% of the cases) regardless of its etiology [2]. Rarely it may also occur in a non-fibrotic liver [3]. Although portal vein invasion is not unusual, only approximately 10% of the patients with HCC develop secondary obstruction of the hepatic venous outflow (presence of thrombus or extrinsic compression), known as secondary Budd-Chiari syndrome (BCS) [4].

Hepatitis E virus (HEV) is an enteral transmitted infection, that in industrialized countries has been until recently regarded as a rare, imported disease from endemic tropical regions (Asia, Africa) [5]. However, there is new evidence to support the opinion that HEV represents a greater problem than previously thought, especially for patients with underlying chronic liver disease [6]. Of the four human HEV-genotypes, in developed regions genotypes 3 and 4 are considered pathogenic, with zoonotic transmission, predominantly after ingestion of infected pork meat [5, 7]. While HEV infection may be responsible for up to 40% of acute liver failure cases in endemic areas [8], in western countries its involvement has been proved in only 10-15% cases [9].

Further, we will present a rare association of acute-on-chronic liver failure caused by HEV infection in a patient with HCC related secondary Budd-Chiari syndrome.

CASE PRESENTATION

A 35-year-old male patient was transferred to our tertiary health care center for aggravation of liver failure manifested by severe ascites, jaundice and grade 2 hepatic encephalopathy. Relevant information from the patient's history was biliary tree surgery performed in infancy, for biliary hypoplasia.

Laboratory examinations evidenced severe alteration of the liver function (serum albumin 2.9 g/dl, total bilirubin 35 mg/dl; prothrombin time 36.1 sec; INR 2.47), low platelets count ($76*10^{-3}$/μL), as well as alteration of liver enzymes (aspartate aminotransferase, AST 263 U/L; alanine aminotransferase, ALT 285 U/L; gamma glutamyl transpeptidase, GGT 187 U/L; alkaline phosphatase, AK 1,661 U/L). Child-Pugh score was calculated at 13 points and MELD score was 40 points.

Neither abdominal US, nor multi-detector contrast enhanced CT showed biliary tree dilatations, but revealed signs of decompensated advanced chronic liver disease and multiple hyperenhancing nodules in the right liver lobe. Moreover, MDCT showed specific Budd-Chiari syndrome (BCS) changes: a giant thrombus extended to the hepatic veins, inferior vena cava (IVC), right atrium, external iliac veins and left femoral vein (Fig. 1); caudate lobe hypertrophy; left lobe atrophy; inhomogeneous hepatic structure due to perfusion alterations. Serum alpha-fetoprotein (AFP) was moderately elevated (107.9 ng/mL).

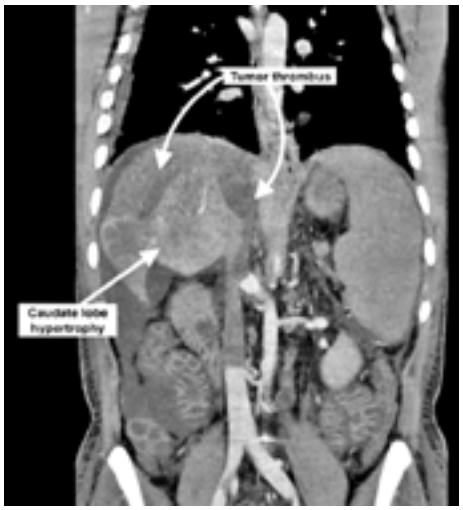

Fig. 1. Budd-Chiari modifications: giant thrombus extended to hepatic veins, IVC and right atrium.

Additionally, the acute-on-chronic liver failure workup revealed positive IgM anti-HEV, while other acute viral (HBV, HCV, CMV, EBV, HSV), bacterial (leptospirosis) or parasitic (toxocariosis) infections, as well as autoimmune conditions, were excluded.

Due to uncontrolled variceal bleeding, the patient died 10 days after admission.

PATHOLOGICAL EXAMINATION

Post-mortem pathological examination was carried out and highlighted a rare association of particular liver lesions (Table I). The left liver lobe (which had been primarily affected by biliary hypoplasia in infancy) had a macroscopic hypoplastic appearance. At microscopy, it contained changes suggestive for secondary biliary cirrhosis: fibrous septa containing mild lymphocytic infiltrate which joined incomplete portal spaces (ductopenia), sinusoidal and pericentrolobular fibrosis, acute ischemia (centrilobular hepatocytes with necrosis) and cholestasis (Fig. 2a). Moreover, CK7 staining confirmed the absence of bile ducts (Fig. 2b).

The right lobe contained nodular lesions represented by a proliferation of tumor cells resembling hepatocytes with mild to moderate nuclear atypia arranged in thick plates consistent with a moderately differentiated hepatocellular carcinoma (HCC) (Edmondson and Steiner grading system) (Fig. 3). Adjacent liver parenchyma showed massive hepatocellular necrosis and hemorrhages in zone 3 extending also in zone 2, hepatocyte atrophy, sinusoidal dilatation and centrilobular veins' dilatation and thrombosis (Fig. 4), changes that are suggestive for BCS. There were also intracanalicular cholestasis and a mild portal lymphocytic infiltrate, histopathological modifications consistent with hepatitis E. Masson trichrome staining revealed mild portal fibrosis but no fibrous septa, demonstrating the absence of cirrhosis.

DISCUSSION

The present case exemplifies a rare association between secondary biliary cirrhosis on the left liver lobe and HCC complicated with secondary BCS on the non-cirrhotic right liver lobe. The hepatic lesions described on both lobes led to severe parenchymal injury and chronic liver insufficiency. Furthermore, acute HEV infection precipitated the acute-on-chronic liver failure and finally led to death.

Usually, HCC arises in a cirrhotic liver, being the most common primary hepatic tumor [3]. However, it can also develop in the absence of cirrhosis, but different carcinogenetic mechanisms seem to be involved and the etiology often remains unidentified [3]. Chronic HBV infection is most frequently associated with HCC in the absence of cirrhosis, but this was not the case in this patient. The fibrolamellar type of HCC is a rare condition usually arising in younger patients without hepatitis/cirrhosis [18], but the pathologic examination excluded this disease in our 35-year-old patient. Chronic

Table I. Summary of the pathology findings in this patient

	Localization	Pathology findings
LEFT LOBE	Secondary biliary cirrhosis	(i) fibrous septa; (ii) sinusoidal fibrosis; (iii) pericentrolobular fibrosis; (iv) ductopenia; (v) cholestasis and microvesicular steatosis; (vi) absence of bile ducts at CK7 staining.
RIGHT LOBE	Hepatocellular carcinoma	(i) irregular cells with large nucleus, scarce cytoplasm, focal prominent nucleoli; (ii) nodular lesions: moderately differentiated HCC with extensive areas of tumor necrosis and vascular tumor invasion; (iii) tumor embolus.
	Secondary Budd Chiari syndrome	(i) centrilobular zone necrosis and hemorrhages; (ii) neutrophilic infiltrates (mild/moderate); (iii) hepatocyte atrophy; (iv) sinusoidal dilatation; (v) cholestasis; (vi) centrilobular veins dilatation and thrombosis.

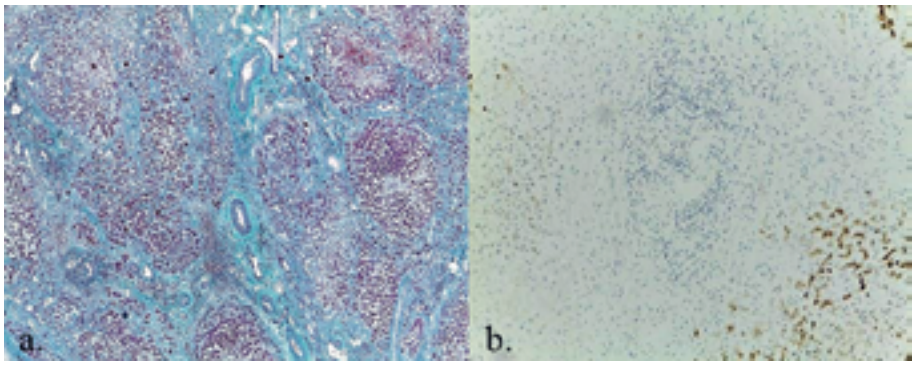

Fig. 2. Left liver lobe. a) Trichrome Masson staining, x100: fibrous septa; b) CK7 staining (x100): absence of bile ducts.

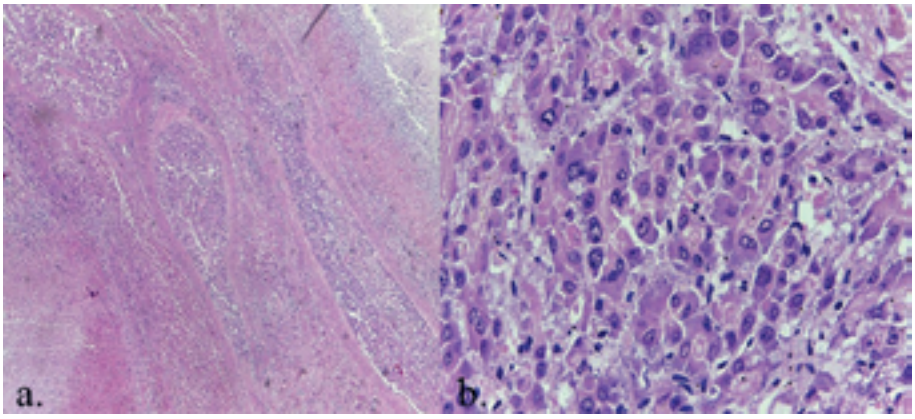

Fig. 3. Right liver lobe sections. a) (H&E stain, x 100) nodular lesion: moderately differentiated HCC; b) (H&E stain, x 400) malignant cells: irregular cells with large nucleus, scarce cytoplasm, focal prominent nucleoli.

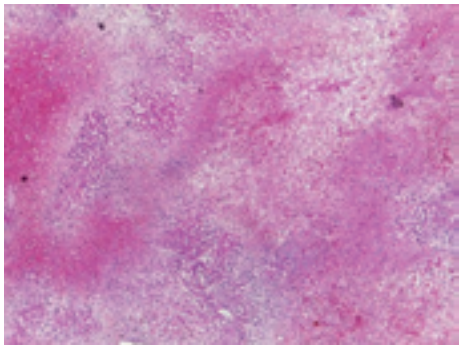

Fig. 4. Right liver lobe section (H&E, x40). Secondary BCS: no fibrous septas; centrolobular hepatocytes with necrosis; bleedings.

aflatoxin exposure is also associated with HCC development in the absence of cirrhosis, especially in (sub)tropical areas [19]. A full toxicology screening was not performed in this case; therefore, we cannot totally exclude this particular situation, especially because the patient was a carpenter and aflatoxin may develop beneath the wet sawdust.

Secondary BCS is a rare disease, mainly caused by the obstruction of the hepatic venous outflow in the presence of compressive lesions or malignant invasion [10]. Pathology in the reported case confirmed the existence of tumor invasion in the hepatic veins and up to the entrance of IVC in the right atrium, linking the rare association between HCC and secondary BCS [11, 12].

Due to the large tumor, the portal hypertension syndrome is more likely to be explained by secondary BCS than by cirrhosis limited to the left lobe. Despite the long-term evolution of secondary BCS, abundant fibrosis was not found at the pathological examination. To the best of our knowledge, there are no cited publications regarding cirrhosis affecting a single liver lobe.

Biliary atresia is a rare congenital condition, which is associated with ductopenia and leads to secondary biliary cirrhosis, carrying poor life expectancy in the absence of a Kasai portoenterostomy, followed by liver transplant [13, 14]. However, the extent of biliary atresia may vary, both in terms of severity and extension; therefore, biliary hypoplasia may also be diagnosed in newborns with persistent jaundice. In this particular case, the pathologic findings from the left liver lobe (ductopenia and cirrhosis) may be the consequence of either a strictly localized form of biliary hypoplasia, that was not influenced by the atypical surgical solution in infancy, or (more likely) a postsurgical biliary damage that led to secondary biliary cirrhosis.

The incidence of autochthonous HEV infection in high-income countries has risen in the past few years, mainly caused by genotypes 3 and 4, transmitted by infected pork meat, while genotypes 1 and 2 are endemic in the tropics and are transmitted by contaminated drinking water [15]. Although it is a common cause of self-limited acute viral infection, HEV infection is often unrecognized or misdiagnosed with drug-induced liver injury [16]. Hepatitis E virus infection may

cause decompensation in patients with underlying chronic liver disease, in whom the prognosis is poor [6, 16], and is responsible for up to 10-15% of cases of acute liver failure. A recent study shows that from five HEV infected patients with underlying chronic liver injury, three died of acute-on-chronic liver failure [6]. Treatment with ribavirin may be effective for these patients [17]. In the current case, however, ribavirin therapy was not initiated due to severe anemia and thrombocytopenia.

CONCLUSION

Here we reported the case of a young adult in whom we found an unusual association of secondary biliary cirrhosis of the left hepatic lobe developed years after biliary tree surgery, and an advanced HCC of the right lobe (in the absence of cirrhosis), with vascular invasion which caused secondary BCS. In addition, autochthonous acute HEV infection precipitated acute-on-chronic liver failure that led to severe complications and death.

Conflicts of interest: No conflict to declare.

Authors contribution: A.F. gathered relevant data and drafted the manuscript. O.F., H.S. and B.P. managed the case during admission; A.M.F. and I.R. performed the pathology examination; H.S. and B.P. critically reviewed the manuscript.

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