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Caroli Syndrome Complicated with Intrahepatic Cholangiocarcinoma

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1. Abstract

Congenital hepatic fibrosis (CHF) and Caroli disease are two rare genetic diseases. When both conditions are present simultaneously, is known as Caroli syndrome. The main complications are cholangitis and those related to portal hypertension. An uncommon complication but devastating of this diseases is cholangiocarcinoma, with few cases reported in the literature. We present a case of an adult female with Caroli syndrome and polycystic renal disease who visited our emergency service referring abdominal pain. In the requested imaging studies a liver mass was observed and subsequently a biopsy of the lesion was taken for diagnosis. The pathologist reported intrahepatic cholangiocarcinoma. The risk of cholangiocarcinoma in congenital hepatic fibrosis is rare, but greater than in general population. The explanation of this increased risk is unknown. This is the youngest patient reported with this complication in CHF. Previously portal hypertension related complications and cholangitis were a main cause of mortality in patients with CHF or Caroli syndrome. Today many effective treatments exists for handle this complications. We expect to see more hepatobiliay malignancies in this cases. \

2. Introduction

Congenital hepatic fibrosis (CHF) and Caroli disease belongs to the group of hepatorenal fibropolycistic disorders. This group is characterized for be frequently associated with polycystic renal disease and other syndromes. CHF is a very rare disease caused by a genetic mutation resulting in ductal plate malformation with consequently periportal fibrosis. The exact prevalence and incidence of this disorder is unknown. The clinical picture is variable, some patients may have recurrent cholangitis and cholestasis, others portal hypertension related complications, but also both types could be present. Caroli syndrome is defined when both CHF and Caroli disease are present. A fearsome complication in this type of diseases are hepatobiliay malignancies, with a reported prevalence in 2%, and is more common in Caroli syndrome than in isolated CHF [1]. Because the lack of information, we don´t know if this group of patients may benefit of screening hepatobiliary malignancies.

3. Case Report

A 32 years old woman came to the emergency service of our hospital referring abdominal pain of recent onset that persist despite treatment with multiple analgesics drugs. Of relevant medical antecedents, she had Caroli syndrome diagnosed since childhood. No other members of her family have been affected of related diseases. At 8 years old, a Rex shunt surgery was done for treatment of portal hypertension related complications. Also at that time, polycystic kidney disease was discovered. She was referred to our hospital in her adult age to continue her medical attendance. After some years of missing her regular visits to our hospital, in one occasion she came to our emergency service for urgent dialysis and with acute variceal bleeding. She also had intracranial

arteriovenous malformations that were discovered in brain images requested for chronic headache. In this visit to our emergency service, we found her with normal vital signs and with moderate pain at the abdominal examination. She denied weight lost, fever, signs of gastrointestinal bleeding or another gastrointestinal complaint. The results of laboratories reported a creatinine in 8.73 mg/dL, BUN in 58 mg/dL, haemoglobin in 9.5 g/dL, platelets in 325× 10^9/L, total bilirubin in 0.69 mg/dL, albumin in 3.6 g/dL, alanine transferase in 28 U/L, aspartate transferase in 41 U/L, alkaline phosphatase in 386 U/L, lipase in 27 U/L and INR in 1.3. We performed an abdominal computed tomography to continue the approach of her abdominal pain (Figure 1A) that showed a liver lesion suspicious of malignancy and changes related to Caroli syndrome. Subsequently we requested a thorax computed tomography (Figure 1B) that revealed a suspicious nodule in one lung. For a definitive diagnosis, biopsy of the liver lesion (Figure 2) and the liver parenchyma were performed (Figure 3). In the liver lesion biopsy, the results were consistent with intrahepatic cholangiocarcinoma. The biopsy of liver parenchyma was consistent for congenital hepatic fibrosis. Tumoral markers were requested, resulting with afetoprotein in 1.55 ng/dL, carcinoembryonic antigen in 415 ng/ml and carbohydrate antigen 19-9 in 20,200 U/ml. She was discharged with the plan to receive systemic chemotherapy, unfortunately she developed cholangitis as complication, not amenable to endoscopic treatment. The patient and her family refuses active oncology treatment and was referred to palliative care service.

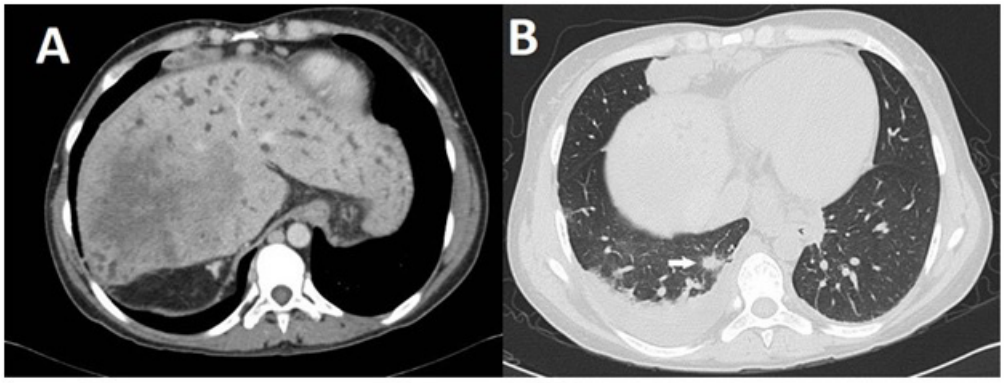

Figure.1. Abdominal and thorax computed tomography. (A) Liver with hypertrophy of the left lobe, with irregular borders and with a hypodense and heterogeneous lesion located in 8 and 7 segments. Dilatations of intrahepatic biliary ducts with saccular dilatations were also found. (B) Pulmonary nodule of 1.4 cm in the right inferior lobe (white arrow).

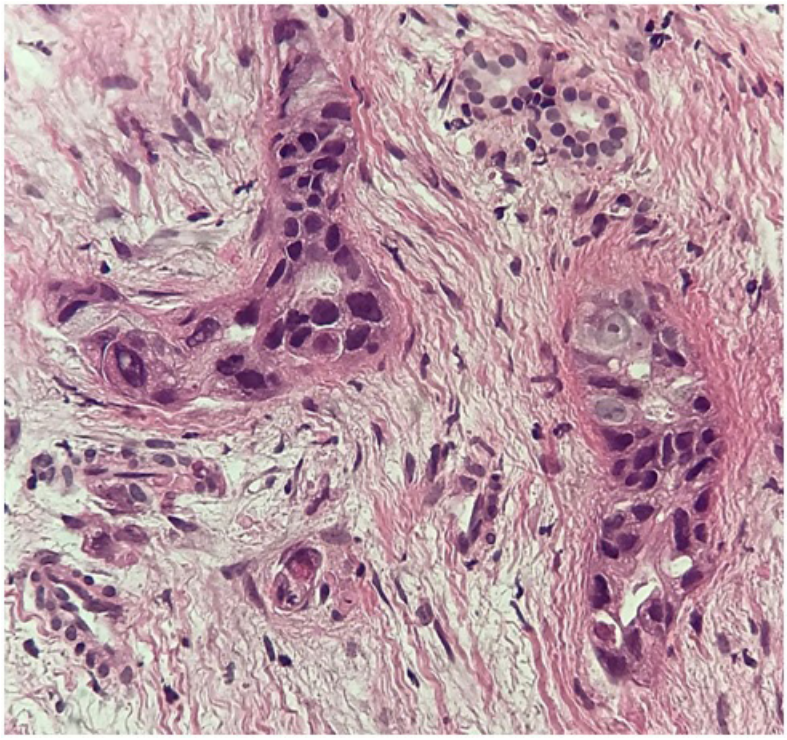

Figure 2: Biopsy of liver lesion showing malignant epithelial neoplasm conformed by glands with collapsed lumen coated with cubic cells, with hyperchromasia within a desmoplastic stroma consistent with cholangiocarcinoma.

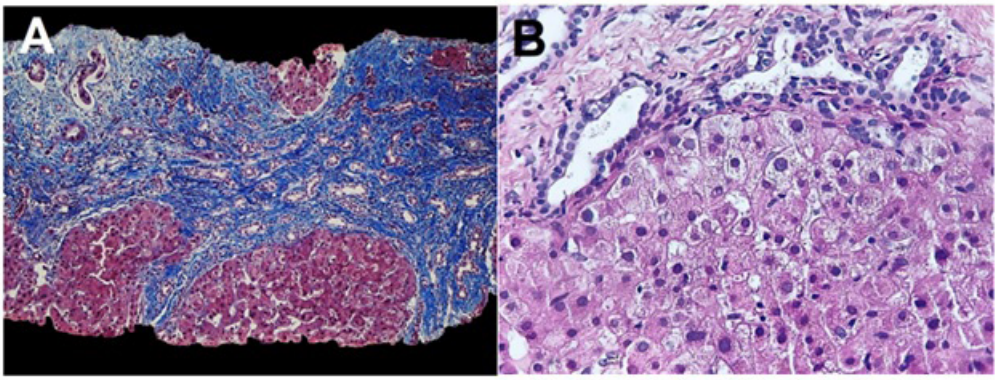

Figure 3: Biopsy of liver parenchyma (A) Masson trichrome stain shows extensive fibrosis (B) Portal expansion and ductular proliferation, with the lumens anastomosed and with centrifugal disposition that accommodate the limiting plaque, findings consistent with congenital hepatic fibrosis.

4. Discussion

CHF is an uncommon disorder that belongs to the group of fibropolicystic disease, a group that also include polycystic kidney diseases (PKD) and Caroli disease and is inherited in an autosomical recessive fashion. This disease was described by Dobbs 1960 and Kerr in 1961. The mutation in PKHD1, a gen that encodes fibrocystin/polycstin located in chromosome 6p21.1-p12, cause defective ciliary proteins required for normal development of biliary and portal system. The precise function of fibrocystin is unknown, but is thought to be involved in various cellular functions like regulation of prolifetation, secretion, differentiation, tubulogenesis, planar cell polarity and cell-matrix interactions. The most frequent pathogenic variants of PKHD1 gene are nonsense truncating mutation [2,13,16]. The ductal plate is a cylindrical layer of cells that surrounds a branch of portal vein and pass a process of remodelling and involution. Progressing remodelling initiate at 12 weeks of gestation and full maturation is completed at 20 weeks [3]. Imparied ciliary function during embryogenesis results in defective remodelling of the ductal plate, with persistence of immature embryonic duct structures that stimulates the formation of portal fibrosis and consequently portal hypertension. This process is caused by abnormal signals that leads to an imbalance between proliferation and apoptosis during ductal plate remodelling. Several pathophysiological mechanism have been proposed to explain this abnormal fibrosis in CHF. The progression of this disease is drive by processes of inflammation, fibrosis and cyst grow [4]. Portal vein branches anomalies are often present in conjunction with bile ducts defects. Almost a half of CHF cases have portal thrombosis with cavernomatous transformation. When the medium and large intrahepatic ducts are affected in CHF, they form cystic dilatations that could be seen in radiographic studies; this combination of liver fibrosis and biliary dilatations is known as Caroli syndrome, and differs from Caroli disease that in the latter there is no CHF. Different intrahepatic segments could be affected. Those who are diagnosed in the neonatal period more commonly have Caroli syndrome and develop more severe renal disease [5]. Other related ductal malformations are von Meyenburg complexes (bile duct hamartoma) and choledocal cyst. The estimated prevalence of CHF and related diseases are from 1: 10,000 to 20,000. The age of presentation is very variable, more often is discovered in childhood but cases in eldery patients have been reported [6]. Despite the mode of inheritance described, approximately half of cases may be sporadic [7]. In imaging studies, hypertrophy of the left lateral segment and caudate lobe with normal or hypertrophic left medial segment and atrophic right lobe have been described like distinct features of CHF. As a consequence of enhanced arterialization of the liver, enlarged hepatic artery could be seen [8]. Features of portal hypertension are also present. In case of Caroli syndrome, saccular dilatation of intrahepatic bile ducts communicating with biliary tree with a central dot sign make this diagnosis, also strictures or stones may be seen. Presence of renal cyst also should be evaluated, given the frequency of kidney involvement in this diseases. Ultrasound, computed tomography and magnetic resonance cholangiopancreatography (MRCP) have been used for diagnostic purpose and in an adequate context, CHF and Caroli syndrome diagnosis could be made without the risk of a liver biopsy. MRCP is the best method to evaluate de entire biliary system and is capable to demonstrate communications between dilates ducts and normal biliary tree, differentiating Caroli syndrome from other types of liver cyst [8]. For definitive diagnosis of CHF histopathologic evaluation of a liver biopsy is required. The more consistent features for CHF are hepatic fibrosis with nodular formation and irregulary shaped proliferating bile ducts, and in case of Caroli syndrome cystic dilatation of bile ducts are present. Persistence of CD56+ ductal plate remanents strongly suggests ductal plate malformation [3,13]. Normal hepatic lobes and hepatocytes are seen in CHF, this help to distinguish CHF and cirrhosis. Despite the similarities with cirrhosis, liver function is preserved in CHF, so liver test may be normal or mild altered. Progressive liver failure is rarely reported. This diseases are commonly diagnosed until complications are present [9,15]. The clinical manifestations are mainly related to portal hypertension complications, also organomegaly, cholestasis and cholangitis could be present. A large proportions of patients remains asymptomatic. In

case of the development of ascites, secondary causes for this must be searched. In Caroli syndrome the most important complications are cholestasis, hepatolithiasis and recurrent cholangitis. Chronic portal vein thrombosis is frequently present. Laboratories findings are non - specific [3,14]. Commonly CHF and related diseases are multisystemic disorders commonly associated with other ciliopathies like ARPKD, that could be underdiagnosed in children. Other forms of renal involvement and abnormalities in other organs had been described less frequently. Some of them are Joubert, Bardet–Biedl, Meckel–Gruber, and oral–facial–digital syndromes [3]. In our patient, many of the associations described in CHF like cerebral vascular malformations and polycystic renal disease with advance kidney failure were present. At this moment, there is no treatment to stop or reverse hepatic fibrosis. Many antifibrotic agents have been studied with variable results [3]. Management is focused in controlling of complications of cholestasis and portal hypertension. Endoscopic treatment is the main treatment for the treatment of esophageal and gastric varices and therapeutic endoscopic retrograde cholangiopantreatography for cholangitis in Caroli syndrome. Transyugular intrahepatic portosystemic shunt or surgery should be considered in refractory bleeding. In Caroli, partial syndrome liver resection could be an option in localized involvement. In cases of chronic liver failure or recurrent cholangitis despite endoscopic treatment, liver transplantation may be an option. Dual liver and kidney transplantation could be necessary when advanced kidney failure is present [9,10].

The risk of cholangiocarcinoma and other hepatobiliary malignancies, although relatively rare, are elevated in CHF compared to general population. Is not clear the cause of complication, but some theories are carcinogenic component of the bile with prolonged effect during biliary stasis, permanent stone irritation with formations of carcinogens and cellular predisposition for neoplasic change of the congenital cystic malformation [11]. In a metanalysis the prevalence of this malignancies were of 2% (21 patients), almost all were cholangiocarcinoma. 15% of deads in CHF patients were related to this malignancy (1). Cholangiocarcinoma is the most frequently hepatobilary malignancy described in fibropolicistic diseases, especially in Caroli syndrome, but in CHF alone hepatocarcinoma could be more prevalent. Only five cases of HCC arising for fibropolycitic disease have been reported and different modalities of treatment were used in each case. Partial hepatectomy and liver transplantation were some of the treatment options described. Radiofrecuency ablation under laparoscopy had also been reported as a therapeutic option in patient with hepatocellular carcinoma and could be considered in cases with controlled portal hypertension and no recurrent cholangitis [12]. Clinical features at the presentation of this malignancies are scarcely described in the literature. In a recent systematic review of twelve retrospective studies, patients were younger than other populations undergoing liver surgery. The overall incidence for cholangiocarcinoma was 6.6% and a high proportion were incidental findings. Disease duration was variable and most patients had episodes of cholangitis, sepsis, fever or abdominal pain [11]. In the case of our patient the only symptom referred that lead us to the diagnosis of cholangiocarcinoma was the new onset of an unspecific abdominal pain. Clinicians must have high suspicion index for hepatobiliary malignancies for any new or worsening symptom, since there are no studies or recommendations for screening in this context.

This is the youngest patient with Caroli syndrome with cholangiocarcinoma reported in the literature. Although this is a rare complication of fibrocystic diseases, the risk for hepatobiliary malignancies are incremented compared to general population. Today, cholangiocarcinoma and hepatocellular carcinoma are among one the main causes of mortality in this patients. The natural history of this diseases remains largely unknown. Today no treatment exists to reverse fibrosis in CHF and related diseases, so the management are focused in control portal hypertensive related complications and treat cholangitis episodes. No specific recommendations for hepatobiliary malignancies in CHF exists, but same interventions realized in other context could been used. The results in survival for each intervention depends on how early the detection of cholangiocarcinoma or hepatocellular carcinoma is made. When clinical manifestations are present this malignant complications are in advanced stages. Screening with different images modalities could employed for early diagnosis. The question if all patient with this conditions need to screened or only a subgroup of this patient benefits from it remains unknown. More studies are required to identify risk of factors and for methods for early diagnosis. For now, physician that follow patients with CHF and Caroli syndrome must be aware of this ominous complications and have high index suspicion in patients with worsening clinical condition.

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