



CASE REPORT

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Congenital hepatic fibrosis with novel mutations in PKD1 gene masquerading as early cryptogenic cirrhosis: a rare case report

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Abstract

Background: Congenital hepatic fibrosis (CHF) is a rare disorder of the porto-biliary system occurring due to the defective remodeling of ductal architecture leading to progressive fibrosis of the portal tract. Though classically, CHF has been reported to be associated with autosomal recessive polycystic kidney disease (ARPKD), there have been only a few reports associating CHF with autosomal dominant polycystic kidney disease (ADPKD). Also, there is a lack of proper sequencing panels and gene database covering CHF-related genes in the medical literature. CHF often presents with features of portal hypertension without overt signs or symptoms of liver disease. However, often due to lack of awareness among radiologists and physicians, such cases might get labeled as early stage of cryptogenic cirrhosis.

Case presentation: Here, we report a 17-year-old boy who presented with a portal hypertensive bleed. Though initially an early phase of cirrhosis was suspected, no identifiable cause was found. Though he had grade IV esophageal varices, the liver function was absolutely normal with no signs of liver failure. This further leads to subsequent cross-sectional imagings which lead to the diagnosis of CHF. Further genetic analysis revealed it to be a rare case of CHF associated with ADPKD, with some novel mutations in the PKD1 gene.

Conclusion: CHF is a rare disorder needing a high index of suspicion and awareness. The presence of classic radiological morphological features of left lobe hypertrophy and right lobe atrophy with the tell-tale histopathological findings, fibrous enlargement of the portal tract, and irregularly shaped proliferating bile ducts often clinches the diagnosis.

Keywords: Congenital hepatic fibrosis, Portal hypertension, Polycystic kidney disease, Case report

Background

Congenital hepatic fibrosis (CHF) is a rare congenital disease of the liver's porto-biliary system caused as a result of a faulty remodeling of the ductal plate architecture leading to progressive fibrosis of the portal tract [1]. Classically, CHF has been reported to be associated with autosomal recessive polycystic kidney disease (ARPKD); however, there is a lack of proper sequencing panels and

gene database covering CHF-related genes in the medical literature [2]. It generally presents with features of portal hypertension without any apparent signs or symptoms of liver disease. However, often due to lack of awareness among radiologists and physicians, such cases might get labeled as “idiopathic or cryptogenic early cirrhosis.”

Case presentation

A 17-year-old boy presented to the surgical emergency with massive bouts of hematemesis. He gave a similar history of hematemesis episodes twice, 4 years back, which were conservatively managed, without any

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intervention. There was no history of alcohol abuse. His parents gave no history suggestive of poor developmental delay or neuropsychiatric abnormalities. At presentation, he was alert and conscious. On examination, he was severely pale, tachycardic (150 bpm), and hypotensive (80/40 mmHg). Abdominal examination revealed massive splenomegaly reaching down to the umbilicus. There was no ascites, no dilated/prominent veins, or other stigmata of chronic liver disease. Laboratory parameters showed severe anemia (Hb 4.8), leucopenia (TC WBC 2.8 G/l), thrombocytopenia (40,000/dl), and normal liver function.

After initial resuscitation and hemodynamic stability, upper GI endoscopy was done, which revealed grade IV esophageal varices with no gastric varices. Band ligation was done in the same setting. He was further investigated to look for the cause of portal hypertension. An abdominal ultrasound showed multiple bilateral renal cysts with altered liver echoes, splenomegaly (18 cm), a patent portal vein of diameter 10 mm with hepatopetal flow, and high Acoustic Radiation Force Impulse (ARFI) values (1.7) suggestive of chronic liver disease. Wilson's disease, glycogen storage disorders, hemochromatosis, autoimmune hepatitis, viral hepatitis, and cystic fibrosis were ruled out with subsequent investigations. Due to the presence of grade IV varices with a very well-

preserved liver function and no identifiable cause of liver disease, further cross-sectional imaging was planned to identify any non-cirrhotic pathology.

A contrast-enhanced computed tomography (CECT) showed dysmorphic liver (hypertrophic left lateral and medial segments and atrophic right lobe), splenomegaly, and multiple small bilateral renal cysts (Fig. 1a–c). With a high index of suspicion for CHF based on existing literature, a T2-weighted magnetic resonance imaging (MRI) was also done, which showed high periportal signal intensity (Fig. 1d). Thereafter, to decrease his dependence on endoscopy sessions, prevent further bleeding episodes, and to address the hypersplenism features, he was taken up for splenectomy and proximal splenorenal shunt (PSRS). He had an uneventful post-surgical recovery. A liver biopsy was taken intra-operatively which showed ductal plate malformation and periportal fibrosis suggestive of congenital hepatic fibrosis (Fig. 2). Due to the disease's inherited nature, a genetic evaluation was done. The genomic DNA was extracted from the peripheral blood and using targeted next-generation gene sequencing, seven genes commonly associated with fibropolycystic diseases of kidney and liver (PKHD1, PKD1, PKD2, MUC1, GANAB, UMOD, DZIP1L) were analyzed. Results showed two heterozygous missense mutations in the PKD 1 gene suggestive of autosomal

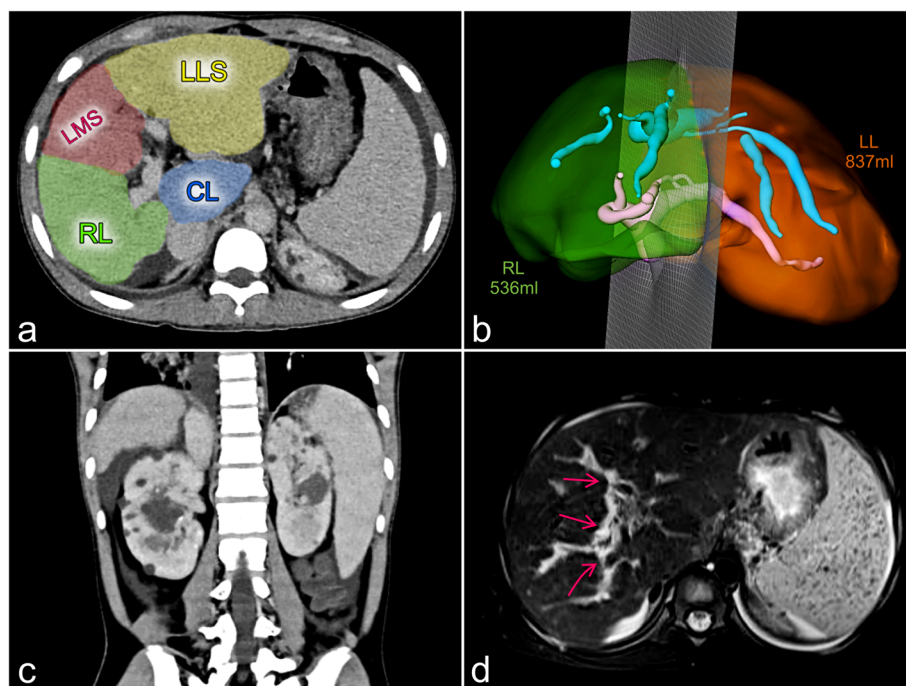


Fig. 1 **a** Contrast-enhanced computed tomography (CECT) portal phase (axial section at the level of portal vein bifurcation) showing hypertrophic left lateral (yellow) and medial (red) segments, hypertrophic caudate lobe (blue), and atrophic right lobe (green). LLS—left lateral segment, LMS—left medial segment, RL—right lobe, CL—caudate lobe. **b** Three-dimensional virtual liver segmentation showing hypertrophied left lobe (837cc) vs small right lobe (536cc). RL—right lobe, LL—left lobe. **c** Coronal section in CECT showing multiple cysts in bilateral kidneys. **d** T2-weighted magnetic resonance imaging showing high periportal signal intensities with widened portal tracts (red arrows).

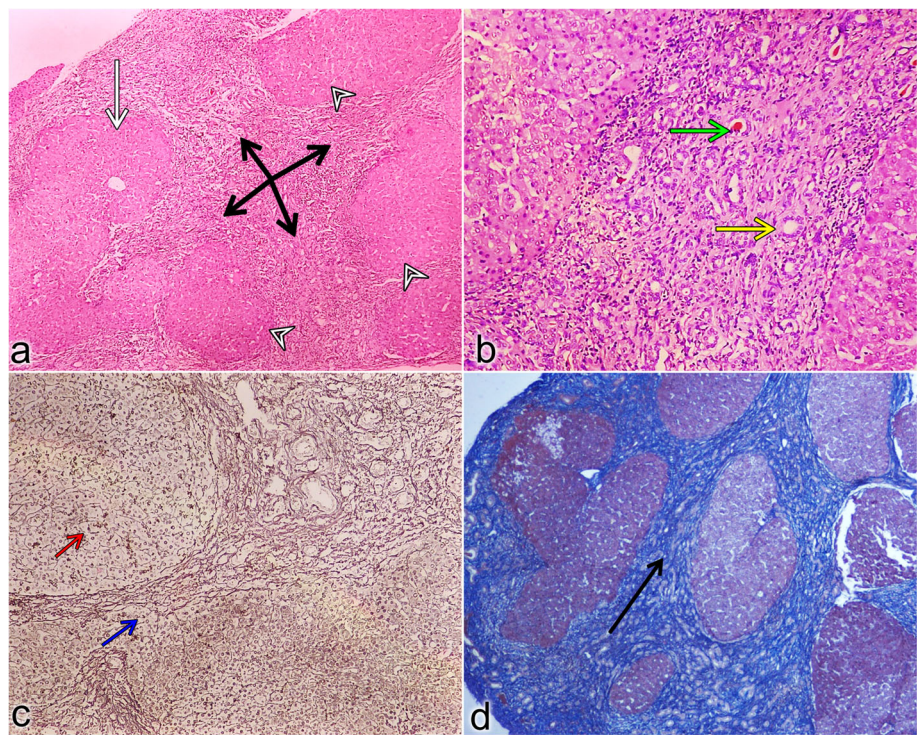


Fig. 2 Sections from the wedge biopsy of liver showing **a** loss of normal architecture with irregular bridging fibrosis (black arrows) separating the liver parenchyma into lobules (white arrow) and irregular nodules (white arrow heads) (H&E, × 40). **b** Bile ductular proliferation (yellow arrow) and bile plugging (green arrow) (H&E, × 200). **c** Reticulin stain has highlighted the fibrosis (blue arrow) outlining a nodule and the nodule shows maintained reticulin framework (red arrow) (reticulin stain, × 100). **d** Masson's trichrome stain has highlighted the irregular fibrosis (black arrow) between islands of liver parenchyma imparting a jigsaw-puzzle pattern (MT, × 40)

dominant polycystic kidney disease (ADPKD). The genetic variations seen in the patient are summarized in Table 1. These mutations have been described in the PKD1 gene database panel as likely pathogenic but have not been reported in any case of CHF earlier. The patient's father though asymptomatic, was screened with an abdominal ultrasound, which showed bilateral multiple renal cysts, but the liver was morphologically normal. No other first or second-degree relatives could be clinically or genetically evaluated due to financial constraints.

Discussion

CHF is a rare progressive fibrotic process involving the liver that results from a malformation of the ductal plate. Though the existence of such a disease process was first described in 1856 [3], it was much later in 1960 and 1961 when the term “congenital hepatic fibrosis” came into existence with more elaborated clinical descriptions

[4, 5]. A ductal plate is the embryological precursor of intrahepatic bile ducts and is formed by a cylindrical layer of epithelial cells that surrounds a branch of the portal vein [6]. Maturation arrest and the lack of remodeling of the ductal plate can occur resulting in the persistence of an increased number of immature embryological ductal structures, which stimulates excessive periportal fibrosis, giving rise to the various clinical manifestations [7].

Though CHF has been mostly associated with ARPKD, there have been a few reports associating CHF with ADPKD [8–11] like our present case, but the mutations described in this case are novel and have not been described for CHF previously. Other rare syndromic associations with CHF are with Joubert syndrome, Senior-Loken syndrome, COACH syndrome, and Cogan syndrome [7].

The clinical presentation and severity of symptoms in CHF are very variable. It usually presents in the

Table 1 The summary of the novel mutations in PKD1 gene in this patient with congenital hepatic fibrosis

Gene	Exon location	Nucleotide change	Amino acid change	Zygosity
PKD 1	Exon 15	c.6223C>T	p.Arg2075Cys	Heterozygous
PKD 1	Exon 11	c.2534T>C	p.Leu845Ser	Heterogenous

childhood or early adulthood as one of the four broad types: portal hypertension, cholestatic, mixed, and latent [12]. Due to its rarity, if CHF diagnosis is not established during childhood, it can be easily missed or unrecognized in adult patients who present with an upper GI bleed, and they often get labeled as early cirrhotics or non-cirrhotic portal hypertension.

Diverse radiological modalities are present to detect this disease. Ultrasonography with a splenoportal Doppler is usually the first investigation for such a patient with portal hypertension. Although challenging experienced radiologists can pick up the morphological changes of liver lobes, biliary dilatations and cysts, portal vein changes, and cystic changes in kidneys on ultrasonography. Cross-sectional imaging modalities like CECT or MRI can show changes in the gross morphology of the liver with accurate volume measurements. T2-weighted MRI would also show high signal intensity in the periportal regions suggesting periportal fibrosis and proliferating small biliary ductules [13]. A high index of suspicion for CHF should be there in patients with imaging features like hypertrophy of the left lateral segment and caudate lobe, normal or hypertrophic left medial segment, atrophic right lobe, presence of splenomegaly, and other portal hypertensive features and cystic renal abnormalities [14]. In CHF, the left medial segment is usually normal or enlarged, while in liver parenchymal cirrhosis, atrophy of the medial segment is seen [15]. There might be other associated features of ductal plate malformation such as biliary hamartomas or Caroli's disease, cavernoma formation, or benign regenerative nodules, but their presence is not mandatory for the diagnosis of CHF.

Although a liver biopsy clinches the diagnosis of CHF unequivocally, findings might be often mistaken for a cirrhotic liver. Widened fibrous bands in the portal tract with an increased number of irregularly shaped proliferating bile ducts, lined by normal cuboidal epithelium, is the hallmark of CHF. Hepatic lobules with hepatocyte morphology usually stay normal, unlike a cirrhotic liver [7]. Role of genetic evaluation is not for the diagnosis, but in the fact that CHF is a rare inherited disease associated with several genetic syndromes which might have other systemic involvement later in the course and therefore, influence the treatment strategies as a whole. Also, like in this case, the presence of an autosomal dominant mutation can help us do genetic counseling of the patient and the family members.

There is no treatment modality shown till date, to stop or reverse the fibrotic pathological process in congenital hepatic fibrosis. Treatment mainly involves managing the complications, like portal hypertension, as in this case. Though endoscopic therapies such as band ligation or glue injection are the mainstay for an acute bleeding episode or primary and secondary prophylactic

management of esophageal and gastric varices, surgical portosystemic shunts provide long-term relief and decrease the dependence on repeated endoscopy sessions [2, 16]. For patients who present at later stages with the signs of liver failure or extensive hepatic fibrosis, liver transplantation remains the only treatment option [17].

Conclusion

CHF is a rare disorder needing a high index of suspicion and awareness. Despite characteristic morphologic features in cross-sectional imaging or biopsy, a multidisciplinary approach by clinicians, pathologists, and radiologists is crucial for an accurate diagnosis. The management is directed toward supportive treatment and relieving complications, including interventions for portal hypertension.

Abbreviations

ADPKD: Autosomal dominant polycystic kidney disease; ARFI: Acoustic radiation force impulse; ARPKD: Autosomal recessive polycystic kidney disease; CECT: Contrast-enhanced computed tomography; CHF: Congenital hepatic fibrosis; MRI: Magnetic resonance imaging; PSRS: Proximal splenorenal shunt

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Authors' contributions

Concept and design: SD, VPNR. Data acquisition and analysis, manuscript preparation: SD, BHS. Critical revision and finalizing of the manuscript: SD, AJ, RA, VPNR. All authors contributed to the conceptualization and design of the case report. All authors have read and approved the final manuscript.

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Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Declarations

Ethics approval and consent to participate

The study was approved by the Institutional Ethics Committee of Jawaharlal Institute of Postgraduate Medical Education and Research, Puducherry, India (JIP/IEC/2021/168). Written informed consent to participate was obtained from the patient's father.

Consent for publication

Written informed consent was obtained from the patient's father for publication of this case report and the accompanying images.

Competing interests

The authors declare that they have no competing interests.

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