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A Rare Case Mimicking Congenital Hepatic Fibrosis

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Short Title: A Case Mimicking Congenital Hepatic Fibrosis

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Abbreviations: American College of Medical Genetics and Genomics (ACMG); anti-RNP ribonucleoprotein/Smith (anti-RNP/SM) antibody; complex A (IFT-A); congenital hepatic fibrosis (CHF); controlled attenuation parameter (CAP); Cytokeratin 7 (CK7); ductal plate malformation (DPM); endoscopic band ligation (EBL); epithelial cell adhesion molecule (EpCAM); estimated glomerular filtration rate (eGFR); gamma-glutamyltransferase (GGT); gastrointestinal (GI); Genome Aggregation Database (gnomAD); Hematoxylin and eosin (H&E) stain; immunoglobulin G (Ig G); intraflagellar transport (IFT); magnetic resonance cholangiopancreatography (MRCP); neural tube defects (NTDs); nonselective beta-blocker (NSBB); porto-sinusoidal vascular disease (PSVD); transjugular intrahepatic portosystemic shunt (TIPS); transthoracic echocardiogram (TTE); upper GI hemorrhage (UGIH); Whole exome sequencing (WES);

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Keywords: liver fibrosis; non-cirrhotic portal hypertension; ciliopathy; ductal plate malformation

A 50-year-old Asian woman presented with a five-year history of abdominal distension. She denied dyspepsia, regurgitation, belching, nausea, vomiting, hematemesis, melena, constipation or weight loss. An upper gastrointestinal (GI) endoscopy conducted two years ago revealed mild esophageal varices without red signs. Abdominal contrast-enhanced computed tomography scan performed at the local hospital indicated liver cirrhosis, splenomegaly, and portal hypertension (Figure *A*). The patient's blood routine test results showed leucopenia (2.1*10^9 /L), mild anemia (106 g/L), and thrombocytopenia (122*10^12/L). Blood coagulation tests and liver biochemistries were normal except for a slightly elevated gamma-glutamyltransferase (GGT) level (62 U/L). When inquired about past history, she reported a history of elevated GGT levels for nearly ten years. Additionally, during a cardiovascular assessment prompted by chest discomfort four years ago, splenomegaly and thrombocytopenia were once noted. She denied any history of parasitic infection or alcohol consumption, but mentioned a two-week course of traditional Chinese medicine of unspecified composition three years earlier. Regarding family history, to the best of her knowledge, there was no consanguineous marriage in her family, however, she had a younger brother who had been diagnosed with liver cirrhosis and chronic kidney disease for more than two decades and died of liver and kidney failure at the age of 43.

Physical examination on presentation showed an enlarged spleen without ascites or abdominal wall varices. Further laboratory tests indicated an elevated antinuclear antibody titer (1:80), a positive anti- ribonucleoprotein/Smith (anti-RNP/SM) antibody and a relatively high immunoglobulin G (Ig G) level (18.0 g/L). Antibodies

for hepatitis virus B and C were negative, and tumor markers remained within normal limits. Ultrasound liver elastography showed a moderate liver stiffness value of 11.4 kPa (IQR/M 24%), with a normal controlled attenuation parameter (CAP) of 223 dB/m. Magnetic resonance cholangiopancreatography (MRCP) did not reveal any biliary tract abnormalities. A repeat upper GI endoscopy disclosed severe esophagogastric varices with red signs (Figure *B*, *C*). Subsequently, a transjugular liver biopsy was performed. The Hematoxylin and eosin (H&E) stain (Figure *D*) exhibited swollen hepatocytes in the lobules, occasional punctate necrosis and mild dilatation of the hepatic sinusoids. In addition, numerous uniform and small bile ducts interruptedly encircled the portal tracts, accompanied by mild portal lymphocytic inflammation. Periportal and portal-portal septa were observed on Masson stain (Figure *E*). Cytokeratin 7 (CK7) immunostaining demonstrated a ductular reaction (Figure *F*), while expression of epithelial cell adhesion molecule (EpCAM) was detected on the bile ducts (Figure *G*).

What is the cause of the portal hypertension?

Answer: Hepatorenocardiacdegenerative Fibrosis Affected by *TULP3* Mutation

Establishing the Diagnosis： Based on the patient's radiographic findings, we initially suspected that her portal hypertension was secondary to cirrhosis. However, the results of her liver biochemistry and ultrasound liver elastography were not consistent with this hypothesis, raising the possibility of non-cirrhotic portal hypertension. Consequently, the liver biopsy was performed and confirmed the absence of cirrhosis. The patient's remarkably rapid progression of portal hypertension reminded us of porto-sinusoidal vascular disease (PSVD), but the liver biopsy did not correspond to the histological lesion of PSVD, instead, it revealed a conspicuous ductal plate malformation (DPM). This, together with the patient's family history and MRCP results, led to the diagnosis of portal hypertensive congenital hepatic fibrosis (CHF). Whole exome sequencing (WES) was therefore conducted to ascertain the PKHD1 mutation. Beyond expectation, WES identified bi-allelic genetic variants in *TULP3* (GenBank: NM_003324.5), resulting in hepatorenocardiacdegenerative fibrosis, which belongs to ciliopathy. The results were verified via Sanger sequencing. The newly reported mutation (c.253+1G>A) is a canonical +1 splice site mutation with an extremely low frequency in the Genome Aggregation Database (gnomAD), thus can be classified as likely pathogenic according to the joint consensus recommendation of the American College of Medical Genetics and Genomics (ACMG)[1]. No other clinically relevant variants were detected. Subsequently, blood samples from her family members were sent for Sanger sequencing as well. The patient's father, surviving brother, son and daughter were all found to be variant carriers, suggesting an autosomal recessive

inheritance pattern, as illustrated in the pedigree (Figure *H*).

Review： Hepatorenocardiacdegenerative fibrosis is a type of ciliopathy first described by Devane et al. in 2022[2], characterized by progressive degenerative liver fibrosis, fibrocystic kidney disease and hypertrophic cardiomyopathy. It is affected by homozygous or compound heterozygous bi-allelic variants in *TULP3* and is inherited in an autosomal recessive pattern. *TULP3* encodes Tubby-like protein 3, a 442-amino acid protein that participates in intraflagellar transport (IFT) by binding to complex A (IFT-A) and plays a key role in cilium assembly and maintenance[3,4]. *TULP3* mutations contribute to impaired trafficking of ARL13B, INPP5E, and GPR161[2,5], resulting in dysregulated WNT and TGF-β signaling pathways. Furthermore, these variants may diminish SIRT1 modulation of profibrotic signaling pathways, consequently promoting the progression of fibrosis[2].

Patients with hepatorenocardiacdegenerative fibrosis initially present with abnormal liver function tests, particularly elevated markers of cholestasis. Symptoms may appear at various ages, with the earliest onset being in infancy. The most prominent manifestation is severe non-cirrhotic portal hypertension, which can present as thrombocytopenia, splenomegaly, ascites, and even esophagogastric variceal hemorrhage. Hepatosplenomegaly, inhomogeneous liver parenchyma and signs of portal hypertension can be observed on abdominal imaging. The histopathological results of the liver are variable, commonly paucicellular portal fibrosis with minimal portal inflammatory infiltrate and moderate unspecific ductular reaction. Biliary type fibrosis without DPM was reported on the explant liver of one patient[2]. In contrast to

previous reports, our patient's liver biopsy exhibited a typical histological pattern of CHF, which highlights the importance of genetic testing for precise diagnosis and treatment. Management aimed at reducing portal pressure, such as nonselective beta-blocker (NSBB) therapy or transjugular intrahepatic portosystemic shunt (TIPS), are essential. Prior to the development of medications capable of reversing fibrosis, liver fibrosis in these patients would progress continuously to cirrhosis, and they may ultimately require liver transplantation[2].

Renal manifestations exhibit heterogeneity, with a decline in estimated glomerular filtration rate (eGFR) typically following hepatic manifestations, while hypertrophic non-obstructive cardiomyopathy may not manifest until the patient's sixth or seventh decade of life. Although it has been suggested that heterozygous variants of *TULP3* may contribute to human neural tube defects (NTDs)[6], none have been found in this patient's family. It remains unknown whether *TULP3* variants would cause other comorbidities such as retinal degeneration or diabetes as observed in other ciliopathies[7]. Therefore, regular and comprehensive assessments, especially of the heart and kidneys, are imperative for the management of these patients.

Patient Outcome： Following the initial examination, the patient underwent renal and cardiac evaluations. Despite her brother's history of kidney disease indicating potential renal involvement due to *TULP3* mutations, the patient exhibited normal kidney function and no renal lesions were detected on abdominal imaging. A transthoracic echocardiogram (TTE) revealed mildly decreased diastolic function of the left ventricle without evidence of left ventricular hypertrophy, which matches previous reports that

the cardiac presentation is relatively age-related. Besides, the serum IgG level descended to the normal range on subsequent retesting without specific treatment. Carvedilol was administered to decrease portal pressure and endoscopic band ligation (EBL) was postponed as she had not experienced upper GI hemorrhage (UGIH) yet. Genetic counseling was provided to her family members by a specialist. To date, the patient has not experienced UGIH, reduced eGFR or manifestations of hypertrophic nonobstructive cardiomyopathy, and the follow-up is ongoing.

References

1. Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med 2015;17:405-424.

2. **Devane J, Ott E, Olinger EG**, et al. Progressive liver, kidney, and heart degeneration in children and adults affected by TULP3 mutations. Am J Hum Genet 2022;109:928-943.

3. **Hesketh SJ, Mukhopadhyay AG,** Nakamura D, et al. IFT-A structure reveals carriages for membrane protein transport into cilia. Cell 2022;185:4971-+.

4. Jiang MQ, Palicharla VR, Miller D, et al. Human IFT-A complex structures provide molecular insights into ciliary transport. Cell Research 2023;33:288-298.

5. **Khamirani HJ, Palicharla VR**, Dastgheib SA, et al. A pathogenic variant of TULP3 causes renal and hepatic fibrocystic disease. Frontiers in Genetics 2022;13.

6. Kuang L, Jiang Y, Chen S, et al. Rare variants in TULP3 abolish the suppressive effect on sonic hedgehog signaling and contribute to human neural tube defects. Genes Dis 2022;9:1174-1177.

7. Hildebrandt F, Benzing T, Katsanis N. Ciliopathies. N Engl J Med 2011;364:1533-43.

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