Adult Onset Progressive Familial Intrahepatic Cholestasis: A Rare Presentation

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ABSTRACT

Progressive familial intrahepatic cholestasis (PFIC) is a childhood genetic disease disrupting intrahepatic biliary secretion, and accounts for 15% of liver transplant in children. Although all patients will require liver transplant, early diagnosis and intervention can delay complications and transplantation. A 41-year-old male presented with cryptogenic cirrhosis and a MELD score of 35 for transplant evaluation. He had a childhood history of abnormal liver enzymes with a mixed pattern, and cholecystectomy due to recurrent gallstones. Prior liver biopsy showed autoimmune features, but he didn't respond to standard therapy. Re-evaluation of his biopsy was favoring biliary disease. However, MRCP with normal bile ducts. Given insidious onset of cirrhosis without an identifiable etiology and the suggestion of biliary cause, PFIC was considered during pre-transplant workup. Genetic testing for ABCB4 confirmed PFIC 3, and had underwent liver transplant with unremarkable complications. This case highlights the impact of exploring a diagnosis of PFIC in adults referred for liver transplantation with long standing cholestatic liver disease and negative initial workup,

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INTRODUCTION

- PFIC is a heterogeneous group of autosomal recessive childhood genetic disorders that disrupt intrahepatic biliary secretion.
- PFIC accounts for 10 to 15% of cholestatic diseases and liver transplantation indications in children.
- There are three main types of PFIC.
- PFIC 1, and 2 account for 2/3 of the cases, occur in early infancy, and are more aggressive in nature, while PFIC 3 accounts for 1/3 of the cases, occurs later in childhood, and is milder in nature and progression. However, all patients with underlying PFIC will ultimately require liver transplantation regardless of the type.
- The exact prevalence of PFIC remains unknown, but the estimated incidence ranges between 1/50,000 and 1/100,000 births per year.
- As of the 2018 literature review, the total reported PFIC1 and PFIC2 were less than 200, whereas the total reported cases of PFIC3, which is rarer, were less than 20.
- PFIC 3 is caused by a mutation of the ABCB4 gene, which encodes the human multidrug resistance 3 (MDR3) protein leading to impaired biliary phospholipid (PL) secretion and increased risk of hepatocytes injury and cholangitis.
- Herein we report a patient, who presented with decompensated cirrhosis due to PFIC 3 diagnosed at the age of 41 and ultimately required liver transplantation.

CASE PRESENTATION

We describe a 41-year-old male who presented with decompensated cryptogenic cirrhosis, and a MELD score of 35 for liver transplant evaluation.
He had a long history of liver enzymes abnormalities with a mixed pattern since being a teenager, along with cholelithiasis and recurrent gallstone pancreatitis requiring cholecystectomy at the age of 17.
Prior work-up at the age of 38 including a liver biopsy was suggestive of cirrhosis with autoimmune features. However, he did not respond to standard therapy of prednisone and azathioprine.
Re-evaluation of his liver biopsy during pre-transplant work-up demonstrated bile duct injury with cholestatic changes, and moderate periportal and focal bridging fibrosis. While it was difficult to determine the etiology of chronic liver disease on biopsy, the histologic findings favored biliary diseases.
Subsequent MRCP showed cirrhosis but normal bile ducts. He was briefly started on ursodiol but stopped due to side effects lack of clinical, and biochemical improvement.
Given the insidious onset of cirrhosis at a young age without an identifiable etiology and the suggestion of biliary etiology on biopsy with normal external bile ducts, although extremely rare, PFIC was considered during his pre-transplant work-up and a genetic testing panel was sent out.
Result however, was positive for ABCB4 gene, and had revealed heterozygous mutation at sequence variant c.2783+1G>T that is consistent with PFIC type 3.
He subsequently had a deceased donor liver transplantation with an unremarkable post-operative course.

DISCUSSION

- We describe a patient with PFIC3 who ultimately required liver transplantation at the age of 41.
- Diagnosis is typically based on combination of clinical picture, imaging, histopathology, and immunostaining. However, genotyping remains the gold standard.
- Looking at our patient's course retrospectively, the clinical picture with abnormal liver enzymes and cholestatic liver disease since adolescence were suggestive of PFIC syndromes. However, the condition's rarity along with his slow progressive course and atypical age of presentation with cirrhosis contributed to this delay in diagnosis.
- The diagnosis was confirmed eventually via gene testing that had shown heterozygous mutation at sequence variant c.2783+1G>T in the ABCB4 gene, which is first to be reported.
- This case highlights the potential impact of exploring a diagnosis of PFIC 3 in adults referred for liver transplantation with long standing cholestatic liver disease and negative initial workup by prompting for immunostaining and genetic testing.
- While currently liver transplantation is the main treatment option for end stage liver disease from PFIC, advances in gene therapy has led to potential curative treatments, and will be the therapy of the future as we better understand the genotype-phenotype correlation in PFIC syndromes.
- Ursodiol is the therapy of choice for patients with PFIC and is especially effective for PFIC 3. However, this was not the case with our patient, who did not show any clinical or biochemical response.
- As such, improved provider awareness and having a lower threshold for diagnostic testing may lead to earlier diagnosis which is critical for optimal management, delaying the onset of end-stage liver disease, and offering screening for family members.

CONCLUSION

- In a nutshell, this case report highlights the importance of exploring a diagnosis of PFIC 3 in adults referred for liver transplantation with liver cirrhosis of cholestatic picture, and negative initial hepatic workup by prompting for genetic testing.
- An early diagnosis is critical for optimal management, therapeutic intervention, avoidance of complications before the onset of end-stage liver disease and offering screening for family members in which a mutation has been identified.
- To this day, liver transplantation remains the ultimate treatment; however, gene therapy has been proposed to be the potential curative treatment in the near future based on ongoing experiments.

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