Case Report

Reevaluating cholestasis: a case of PFIC3 diagnosed through whole genome sequencing after initial miss on cholestasis genetic panel

Abstract

Progressive Familial Intrahepatic Cholestasis (PFIC) 3 is a genetic condition caused by disruption of transportation of bile acids across hepatocytes resulting in bile acid buildup leading to cholestasis, liver dysfunction, and potentially liver failure. Our patient is an 18-year-old female with scoliosis and Bertolotti syndrome status-post left periacetabular osteotomy who presented with jaundice, scleral icterus, pruritis, elevated transaminases, cholestasis, and elevated gamma-glutamyl transferase (GGT). Evaluation revealed a negative cholestasis genetic panel with whole genome sequencing finding an ABCB4 gene mutation confirming PFIC3 diagnosis. She was started on ileal bile acid transporter (IBAT) inhibitors with clinical improvement.

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Introduction

Cholestasis can be caused by a variety of mechanisms including obstructive (biliary atresia, biliary cysts), infectious (cytomegalovirus, sepsis), genetic or metabolic disorders (Alagille syndrome, PFIC, alpha-1 antitrypsin deficiency), and toxic (drug-induced hepatitis, intestinal failure-associated liver disease) etiologies.[1] PFIC is a rare autosomal recessive disorder that has a variety of subtypes depending on the defect involved, occurring either at the level of production, transportation, or excretion of bile acids.[2,3] Uniquely, PFIC3 is caused by a defect in the ABCB4 gene on chromosome 7 which encodes for a translocator protein known as the multi-drug resistant (MDR) 3 P-glycoprotein, involved in phosphatidylcholine excretion.[1,2] MDR3 glycoprotein expression supports the transport of phosphatidylcholine flippase from the hepatocyte to the biliary canaliculi.[1-3] ABCB4 gene mutations lead to decreased MDR3 glycoprotein expression and accumulation of toxic free bile acids damaging hepatocytes resulting with increased risk of hepatocellular carcinoma and cholangiocarcinoma.[1-3] Studies reveal that MDR3 expression levels correlate with positive response to medical therapy, including ursodeoxycholic acid and rifampin.[3] Biliary diversion may not be effective with severe presentations, but liver transplantation is curative.[3,4]

We report a novel case of PFIC3 that was initially missed by a cholestasis genetic panel but later diagnosed through whole genome sequencing, showing improvement with IBAT inhibitors.

Case report

An 18-year-old Puerto Rican lean female with scoliosis and Bertolotti syndrome status-post left periacetabular osteotomy presented with jaundice, scleral icterus, and pruritis. Laboratory evaluations included elevated transaminases (aspartate aminotransferase [AST] 94 U/L, alanine transaminase [ALT] 145 U/L), elevated alkaline phosphatase [ALP] (468 U/L), elevated GGT (251 U/L), total hyperbilirubinemia (2.4 mg/dL) with mildly elevated direct bilirubin fraction (1.1 mg/dL) in the setting of normal albumin levels (4.2 g/dL), mild elevation of serum bile acids (15.6 umoL/L), hypertriglyceridemia, and hyperlipidemia. Additional laboratory evaluations for infectious hepatitis, autoimmune liver disease, and metabolic disorders were negative as shown in Table 1. Family history of PFIC3 was reported in the mother's two siblings. Due to high suspicion for PFIC3, a cholestasis genetic panel (Prevention Genetics®, Marshfield, WI) was completed; however, it was negative. Right upper quadrant abdominal ultrasound showed hepatomegaly (with liver size measuring 20.1 cm) with fatty infiltration and cholelithiasis without evidence of cholecystitis or common bile duct dilation. She underwent laparoscopic cholecystectomy with liver wedge biopsy which revealed an intact lobular structure and sinusoidal meshwork with no evidence of iron deposition, fibrosis, or steatosis (Figure 1). There was a mild mixed chronic inflammatory infiltrate of predominantly lymphocytes, rare eosinophils, and plasma cells suggesting a diagnosis of autoimmune hepatitis with the presence of plasma cells even though autoimmune hepatitis laboratory evaluation was negative.

After her surgery, she did well for a few months with resolution of her pruritis and jaundice along with normalizationof her liver enzymes and serum bilirubin. Unfortunately, her symptoms (pruritus) and laboratory abnormalities returned six months after surgery (repeat serum bile acids was elevated [42.2 umoL/L]). Repeat abdominal ultrasound and magnetic resonance cholangiopancreatography (MRCP) to assess for common bile duct stones or dilation was negative. Due to high suspicion for PFIC, genetic testing (GeneDx®, Elmwood Park, NJ) was sent and identified the patient as a G6PD carrier. This did not correlate with patient clinical findings. Further testing

with (Variantyx®, Framingham, MA) whole genome sequencing identified an autosomal recessive ABCB4 homozygous variant of uncertain significance. Repeat analysis of the original cholestasis genetic panel approximately 1 year after initial testing confirmed the findings on whole genome sequencing. This variant had recently been identified as a novel mutation in the Puerto Rican population to be associated with cholestatic jaundice and PFIC3. She was treated with Ursodiol, Atarax, Odevixibat, and fat-soluble vitamins with clinical improvement.

Table 1 Additional Laboratory Values in the Patient

Laboratory Parameters	Values
Infectious	
Strep A PCR	Negative
Urinalysis	Positive for bilirubin, urobilinogen
Autoimmune	
Anti-smooth muscle antibody	Negative
Liver/Kidney Microsome Type 1 Antibody	Negative
Antimitochondrial Antibody	Negative
Other	
Cholesterol	370 mg/dL (elevated
HDL	16 mg/dL (low)
LDL	306 mg/dL (elevated)
Triglycerides	267 mg/dL (elevated)
Ferritin	56 ng/mL
Ceruloplasmin	59 mg/dL
Thyroid studies (TSH/FT4)	Normal
IgA, IgG, IgM	Normal
IgG 1, 2, 3, and 4	Normal
Alpha 1-Antitrypsin Phenotype	MM Phenotype – Normal
Lysosomal Acid Lipase Activity	Normal
Bile Acids	15.6 umol/L -> 42.2 umol/L (elevated)
GGT	251 U/L -> 920 U/L (elevated)
aPTT	37.8 seconds (elevated)
PT/INR	Normal
CK	27 U/L (low)
CRP	Normal
ESR	Normal

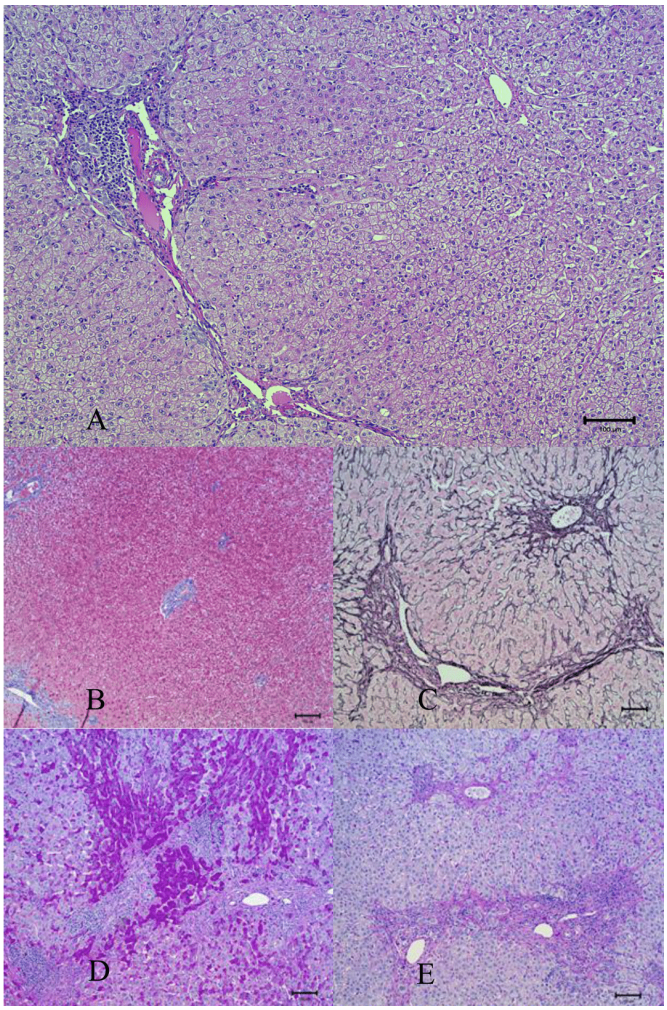

Figure 1 Liver biopsy. A) Mild, mixed chronic inflammatory infiltrate consisting of predominantly lymphocytes, rare eosinophils and plasma cells. B) The trichrome stain is negative for fibrosis. C) The reticulin stain shows an intact sinusoidal mesh work. D) Periodic Acid Schiff (PAS) stain highlights glycogen within the hepatocytes and no evidence of steatosis. E) The PAS with diastase stain is negative for large intracytoplasmic globules. All images taken at 100x magnification. Electron micrography images are not available.

Discussion

Diagnosis of PFIC3 is typically started with laboratory evaluation demonstrating elevated liver enzymes, conjugated bilirubin, and bile acids. Genetic testing is confirmatory. Management with medications like ursodiol and ileal bile acid transporter (IBAT) inhibitors are used to improve bile flow, reduce liver damage, and relieve pruritis.

Although liver biopsy was suggestive of autoimmune hepatitis (AIH) and family history was concerning for PFIC3 in our patient, AIH markers were negative twice. Additionally, the homozygous variant reported in our patient is found in 0.0058% of alleles in individuals of Latino descent specifically in the Puerto Rican population.[2]

Multiple cases have described liver disease that have later been found to be due to PFIC3. Ramraj et al. described two cases where the patients were thought to have Wilson's disease due serum ceruloplasmin level abnormalities, however with the chronicity and persistence of liver disease, full exon sequencing found ABCB4 gene mutations confirming the diagnosis.[5] Lipinski et al. documented four clinical cases with novel ABCB4 variants found by early next-generation sequencing.[6] Another case revealed the importance of early diagnosis when a 17-year-old female required liver transplantation for cryptogenic cirrhosis was retrospectively found to have PFIC3 by genetic analysis and immunohistochemistry in the setting of chronic rejection.[7] Our patient had an ABCB4 mutation not found on the cholestasis genetic panel likely due to a novel mutation resulting in diagnosis delay. Similar novel ABCB4 gene mutations have been reported in the literature leading to diagnosis delay and clinical variation.[8]

In conclusion, our report illustrates the potential to miss the rare diagnosis of PFIC3 if workup was suspended after initial genetic testing for PFIC3 was normal. In addition, this case highlights the value of thorough evaluation of suspected disease while demonstrating genetic expression of disease may manifest in different forms.

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The patient of the case report and their parents are aware of the intent to publish and have agreed to it. Signed informed consent was obtained for publication of the case details.

Conflicts of interest

None declared from all authors. No conflict of interest was reported.

Informed consent

The patient of the case report and their parents are aware of the intent to publish and have agreed to it. We have obtained signed informed consent and have archived it.

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