

A Diagnostic Quagmire: PFIC5 Presenting as a Rare Cause of Neonatal Cholestasis

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ABSTRACT

Progressive familial intrahepatic cholestasis is a heterogeneous group of autosomal recessive disorders defined by defects in bile excretion and transport. We describe a 6-week-old boy from Micronesia presenting with failure to thrive and jaundice. His diagnostic workup was remarkable for direct hyperbilirubinemia, hepatitis, and hepatic ultrasound with possible portosystemic shunting. The presence of toxoplasma IgG initially raised concern for congenital toxoplasmosis. Ultimately, the absence of bile salt export pump staining on liver histology and subsequent genetic studies confirmed a diagnosis of progressive familial intrahepatic cholestasis type 5, an exceedingly rare cause of neonatal cholestasis.

INTRODUCTION

Neonatal cholestasis has a broad differential including infectious, metabolic, genetic, structural, vascular, or toxin-related etiologies. A thorough evaluation, including imaging, laboratory testing, and liver biopsy, is often required to arrive at the correct diagnosis. We report a 6-week-old boy from Micronesia presenting with failure to thrive and jaundice and an initial workup indicative of toxoplasmosis. However, further history and diagnostic testing identified the true diagnosis: progressive familial intrahepatic cholestasis type 5 (PFSC5). This case highlights nuances that may contribute to diagnostic difficulties in the evaluation of neonatal cholestasis.

CASE REPORT

A 6-week-old weak boy born of consanguineous marriage to an O-positive, antibody-negative, direct Coombs-negative 38-year-old woman presented to the emergency department with a history of failure to thrive, direct hyperbilirubinemia, hepatitis, hypoglycemia, anemia, and coagulopathy. He was born in Micronesia, where his mother had minimal prenatal care. He did not receive vitamin K or hepatitis B vaccines after birth. He was initially exclusively breastfed, with the addition of formula supplementation after local hospitalization in Micronesia for poor weight gain.

On admission, the patient was 3.775 kg (birthweight 3.175 kg), at the 1.52 percentile for age. Physical examination was notable for a jaundiced, malnourished infant with hepatomegaly palpated 3–4 cm below the costal margin. Other than weak suck, neurological examination was normal. Laboratory analysis was notable for hepatitis with alanine transaminase 84 U/L, aspartate transaminase 244 U/L, normal gamma-glutamyl transferase test 34 U/L, albumin 3.1 g/dL, and alkaline phosphatase 300 U/L. Total bilirubin was 25.1 mg/dL with direct bilirubin 13.8 mg/dL. The complete blood count was unremarkable. There was mild coagulopathy with prothrombin time 65.6 seconds, international normalized ratio 1.49. Thyroid-stimulating hormone was mildly elevated at 7.63 U/mL with normal free thyroxine (FT4) 1.23 ng/dL. Infectious studies were positive for serum toxoplasma IgG; serology for other TORCH infections, hepatitises, cytomegalovirus, and parvovirus B19 was negative.

An abdominal ultrasound with Doppler showed increased pulsatility of the right and left portal veins, with prominent vasculature near the convergence of the portal and hepatic veins with concern for possible portosystemic shunting. An abdominal computed

tomography angiogram demonstrated a Budd Chiari-like appearance, suggesting possible hepatic venous outflow or sinusoidal obstruction. Again, the imaging raised concern for portosystemic shunting, but this was not definitively visualized. An echocardiogram showed a small patent foramen ovale and normal inferior vena cava.

To further evaluate for toxoplasmosis, cranial computed tomography was performed without evidence of intracranial calcifications. Ophthalmologic evaluation was negative for chorioretinitis or changes associated with Alagille syndrome. *Toxoplasma gondii* IgA and DNA by quantitative polymerase chain reaction was negative in blood and urine. Here, the medical team discovered that the patient had a history of blood transfusion while in Micronesia which could account for presence of toxoplasma IgG.

Ultimately, liver biopsy was performed with histology demonstrating intrahepatic cholestasis with giant cell transformation and absence of bile salt export pump (BSEP) staining along the canalicular membranes highly suggestive of PFIC. A cholestasis genetic panel showed that our patient was homozygous for the NR1H4 mutation 3c.911dupA, identified to be likely pathogenic for PFIC5. The patient underwent liver transplant at 3 months of age and is doing well at this time.

DISCUSSION

Congenital toxoplasmosis is an uncommon entity in the United States, occurring in 1 of 10,000 live births. However, its incidence around the world is much higher, and it is estimated that one-third of the world's population is infected with the parasite.¹ Positive serum toxoplasma IgG with negative IgM, as seen in our patient, may represent congenital toxoplasmosis without active infection, passive antibody transfer during gestation, or acquisition through blood transfusion. The gold standard for diagnosing congenital toxoplasmosis is toxoplasma IgA, IgG, and IgM serology on simultaneous samples from both the infant and mother. After unsuccessful attempts at contacting the biological parents, we proceeded with an alternative diagnostic option: *Toxoplasma gondii* polymerase chain reaction on urine and blood.² These were negative, rendering toxoplasmosis extremely unlikely.

PFIC is a heterogeneous group of autosomal recessive disorders defined by defects in bile excretion and transport.³ The genetic mutation causing PFIC5, the most recently classified of the PFIC disorders, occurs in the NR1H4 gene on 12q23.1. This gene encodes the farnesoid X receptor (FXR), a nuclear receptor regulating bile acid synthesis, transport, and conjugation. Bile acids serve as ligands to FXR, and increased binding activates molecular pathways leading to inhibition of bile acid synthesis, preventing overproduction. FXR's downstream targets include the genes responsible for PFIC 2 and 3—*ABCB11* encoding the BSEP and *ABCB4* encoding multidrug resistant protein 3, respectively. Variants in NR1H4 are associated with intrahepatic cholestasis of pregnancy.⁴

In a case series of 4 patients with PFIC5, 3 presented with neonatal jaundice and 1 with pleural effusions, ascites, and intraventricular hemorrhage. All had conjugated hyperbilirubinemia, hepatitis, prolonged PT, elevated INR, initially elevated alpha fetoprotein with subsequent downtrending, and low to normal gamma-glutamyl transferase. Two of the patients had worsening hyperammonemia, transaminitis, and hypoglycemia until liver transplant. As in our patient, histology revealed negative BSEP staining. Pathology also showed intrahepatic cholestasis with reactive proliferation of bile ducts, giant cell transformation, and fibrosis progressing toward micronodular cirrhosis. All patients rapidly progressed to hepatic failure by 2 years of age.^{5,6} Given the combination of severity and rarity of this condition, additional reporting and research is greatly needed. It is our hope that this case, especially as the presentation mimicked so many other, more common diseases, will help shed light on the diagnostic challenges inherent in neonatal cholestasis.

DISCLOSURES

Author contributions: S. Giang and RL Gordon wrote and edited the manuscript. KB Hass wrote and edited the manuscript and approved the final manuscript. S. Giang is the article guarantor.

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Informed consent was obtained for from the family of the patient despite several attempts. All identifying information has been removed from this case report to protect patient privacy.

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