An infant with cholestasis, acholic stool and high GGT levels

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Cite this article as: *Sağ E, Işık G, Çebi AH, Kalyoncu M, Çakır M, Aydoğdu S. An infant with cholestasis, acholic stool and high GGT levels. Turk J Gastroenterol 2018; 29: 621-2.*

Dear Editor,

Neonatal cholestasis (NC) is a rare clinical condition characterized by decreased bile drainage and direct hyperbilirubinemia (1). Acholic stool and high gamma-glutamyl transferase (GGT) associated with cholestasis are specific findings for biliary atresia (BA). However, further etiologies must be investigated if operative cholangiography (OC) is not diagnostic.

A 3-month-old female patient was admitted with jaundice, hepatosplenomegaly, and pale stool. She was evaluated for NC; however, baseline tests were non-diagnostic. OC was performed to rule out BA due to persistent cholestasis, acholic stool, and elevated GGT (1150 U/L); however, the biliary tract was found to be intact. The patient was investigated for the presence of cholestasis and acholic stool by examination of neonatal sclerosing cholangitis (*DCDC2* gene), alpha-1 antitrypsin deficiency (A1AD; *SERPINA1* gene), Alagille syndrome (*JAG1* gene), progressive familial intrahepatic cholestasis type 3 (*ABCB4* gene), and cystic fibrosis (*CFTR* gene); no mutation was identified.

Abdominal ultrasound performed for distention at the age of 6 months revealed enlarged kidneys [right kidney was 72×40 (normal; 54.88±4.84) mm^2 and left kidney was 70×39 (normal; 55.83±5.6) mm^2], increased renal parenchymal thickness [both were 13 (normal; right kidney: 9.71±1.12, left kidney: 10.37±1.33) mm], and cystic dilations in the bilateral renal pyramids and collecting tubules.

On follow-up, she underwent liver transplantation from a living donor for the decompensation of liver functions. Explanted liver histology revealed congenital hepatic fibrosis (CHF). The final diagnosis was considered as CHF accompanied by autosomal recessive polycystic kidney disease (ARPKD). Homozygous c.10909C>T (p.Arg-3637Cys) mutation was found in the *PKHD1* gene. Parents were heterozygote for the mutation.

Evaluation of patients with negative cholangiography for BA is obscure. Some reports suggest evaluating for BA-mimicking conditions such as A1AD, PFIC3, and cystic fibrosis (2). Sira et al. (3) reported the causes of cholestasis that was misdiagnosed as BA and, they found that approximately 6.8% of the infants were misdiagnosed as BA and were diagnosed PFIC3, idiopathic neonatal hepatitis, cytomegalovirus hepatitis, Alagille syndrome, and CHF on the follow-up.

Autosomal recessive polycystic kidney disease, and associated CHF, is a developmental disorder of the kidneys and liver, caused by mutations in *PKHD1*. Fibrocystin/polyductin, encoded by *PKHD1*, is expressed on the primary cilia of the renal and bile duct epithelial cells and is believed to maintain the 3-dimensional tubular architecture. CHF results from malformation of the developing ductal plate. Approximately half of the patients with ARPKD present in the neonatal period with cystic kidneys, and pulmonary hypoplasia; presentation with NC is very rare (4). In a study with 1692 cases of NC, the rate of ARPKD associated CHF was reported to be 0.06% (5). Gunay-Aygun M et al. (4) reported the clinical manifestations of 73 patients with ARPKD with CHF and found that none of the patients presented with NC.

In conclusion, acholic stool and NC are unexpected findings of CHF. It may be related with agenesis/atresia of the intrahepatic bile ducts due to ductal plate malformation. CHF associated with ARPKD should be considered as differential diagnosis in patients with normal OC.

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Received: ***February 5, 2018*** *Accepted:* ***March 27, 2018*** *Available online date:* ***August 2, 2018***

DOI: ***10.5152/tjg.2018.18105***

Informed Consent: Informed consent was obtained from the patient who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - M.C.; Design - M.C.; Supervision - M.C.; Materials - M.C., M.K., S.A.; Data Collection and/or Processing - G.I., A.H.C., E.S.; Analysis and/or Interpretation - E.S., G.I., M.K., M.C.; Literature Search - G.I., E.S.; Writing Manuscript - G.I., E.S.; Critical Review - M.C.

Conflict of Interest: The authors have no conflict of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

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