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CLINICAL BRIEF

Cystic Fibrosis Presenting with Neonatal Cholestasis Simulating Biliary Atresia in a Patient with a Novel Mutation

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Abstract Neonatal cholestasis is a rare presenting feature of cystic fibrosis which usually cannot be differentiated from other types of cholestasis. Herein, the authors report a 63 d-old boy with cystic fibrosis presenting with neonatal cholestasis mimicking biliary atresia. A new mutation in *CFTR* gene resulting in severe phenotype has been described. The cystic fibrosis patients with c.3871 G>T mutation may have acholic gaita mimicking biliary atresia in the absence of insipissated bile with minimal histologic findings in the liver.

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Introduction

Neonatal cholestasis is a rare presenting feature of cystic fibrosis (CF) [1]. Sometimes, the feces of the infant is acholic mimicking biliary atresia [2]. Here, the authors report a 63 d-old boy infant with CF presenting with neonatal cholestasis mimicking biliary atresia. A new mutation in *CFTR* gene resulting in severe phenotype has been presented. Pulmonary disease and hyponatremic dehydration were the most likely contributing factors to cholestasis. Albeit liver involvement is expected to be severe; histologic findings were not appreciated compared to the clinical picture. Cholestasis improved in due to course and he was anicteric by 7 mo of age.

Case Report

A 63 d–old boy was hospitalized for the etiologic investigation and treatment of cholestasis. Past history revealed that the baby had acholic stools and was hospitalized due to respiratory distress and hyponatremic dehydration at 30 d of age. He was born to consangineous parents. Prenatal and immediate postnatal periods were uneventful. Family history was unremarkable. Physical examination revealed jaundice as well as dry, loose and wrinkled skin with loss of subcutaneus tissue. Liver was 4 cm palpable below right costal margin. The rest of the examination was unremarkable. Blood biochemistry showed a total protein 3.1 mg/dl, albumin 1.4 mg/dl, total bilirubin 12.9 mg/dl, direct bilirubin 7.5 mg/dl, alkaline phosphatase 196 IU/L, alanine aminotransferase 32 IU/L, and gamma glutamyl transferase

49 IU/L. Prothrombin time was 19.6 s which is normalized after parenteral vitamin K. Metabolic studies including alfa-1 antitrypsin, urinary reducing substance, serum bile acids, hepatitis and TORCH screen were unremarkable. Pilocarpine sweat chloride iontophoresis test was unsuccesful on three occasions.

Abdominal ultrasound was normal. Hepatobiliary scintigraphy revealed a normal hepatic uptake of the tracer, retention of the radioactivity in the liver and lack of excretion to the small intestine up to 24 h post-infusion. Percutaneous liver biopsy showed canalicular cholestasis and extensive vacuolar degeneration in hepatocytes without appreciable inflammation and bile duct proliferation (Fig. 1). DNA sequence analysis of the exons and exon-intron boundaries of the *CFTR* gene revealed a homozygous nonsense mutation, c.3871 G>T (p.G1247X), in exon 23 (Fig. 2). The mutation is predicted to cause a premature stop in *CFTR* transcription and therefore be deleterious (Fig. 3). With supportive treatments including ursodeoxycholic acid and oral pancreatic enzyme replacement, the patient's jaundice gradually cleared and liver biochemistry returned to normal. The infant was anicteric by 7 mo of age.

Discussion

The prevalance of liver disease in CF was reported between 18 % and 41 % which increased with the age [3–5]. Liver disease has a wide spectrum including steatosis, focal and multilobulary cirrhosis, portal hypertension and gall bladder disease. Liver involvement as a consequence of CF rarely presents with neonatal cholestasis [2]. It is also rare as a cause of neonatal cholestasis with an overall prevalance of 0.67 % [1].

The etiology of neonatal cholestasis in CF is unknown but may be multifactorial. In some studies, an association between meconium ileus and neonatal cholestasis has been

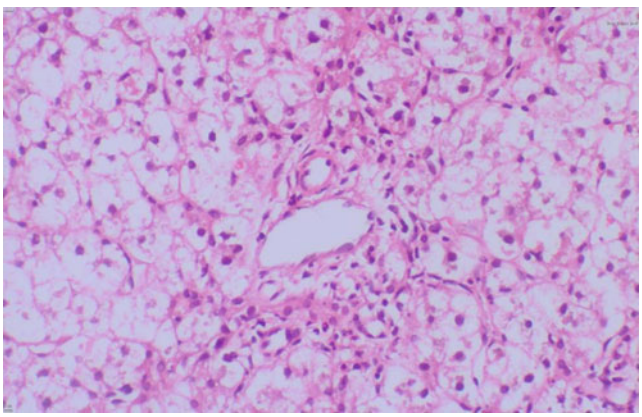

Fig. 1 Hepatocellular vacuolar degeneration and canalicular cholestasis (HEx400)

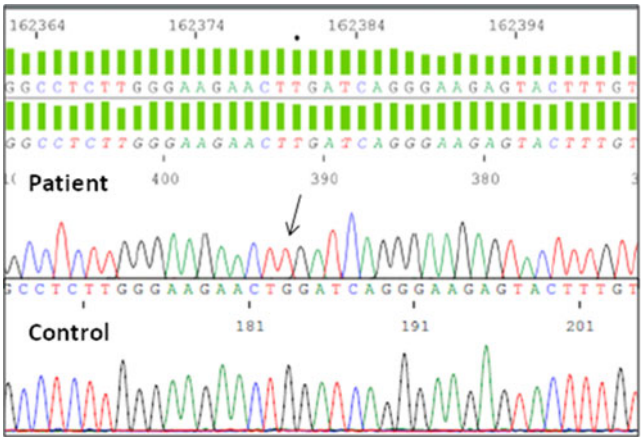

Fig. 2 The c.3871 G>T change leading to p.G1247X mutation in the patient

suggested in 25–50 % of patients [1, 6]. The complicated postnatal course requiring surgery, parenteral nutrition and infections may contribute to cholestasis. In the series Shapira R et al. [6], 10 out of 12 patients had an either clinical course complicated with meconium ileus, or coexisting condition such as respiratory disease. Of the nine patients reported by Lykavieris P et al. [1], six had an associated condition such as delay in meconium passage with or without intestinal obstruction, parenteral nutrition, homozygous PiZ alfa-1 antitrypsin deficiency or hypopituitarism. The pulmonary symptoms and dehydration with hyponatremic, hypocloremic metabolic alkalosis prior to cholestasis were the conditions complicating the clinical picture in the present case.

The liver disease appears to be associated with the severe genotype, although no mutation has been specifically linked to presence or severity of liver disease up to now. This is true for all types of liver disease including neonatal cholestasis. In the series by Shapira R et al. [6], on the other hand, genetic analysis demonstrated either homozygosity or heterozygosity for ΔF508 in 10 out of 11 patients with cholestasis. The mutation in the present case caused premature stop in *CFTR* transcription and therefore is expected to be associated with severe phenotype. This mutation is novel and has not been cited either in "Cystic Fibrosis Mutation Database" or in "Human Gene Mutation Database". Several other factors have been found to be significantly associated with development of liver disease, including pancreatic insufficiency, male sex, history of meconium ileus and early onset disease. The present case had all of the above risk factors but history of meconium ileus [7, 8].

Nonvisualization of intestine in hepatobiliary scintigraphy is a diagnostic dilemma and should be differentiated from biliary atresia. CF causes biliary stasis and inspissated bile syndrome resulting in acholic stools simulating bilary atresia. Most of the cases [5, 9] had moderate to severe focal fibrosis, variable portal inflammation, and some degree of

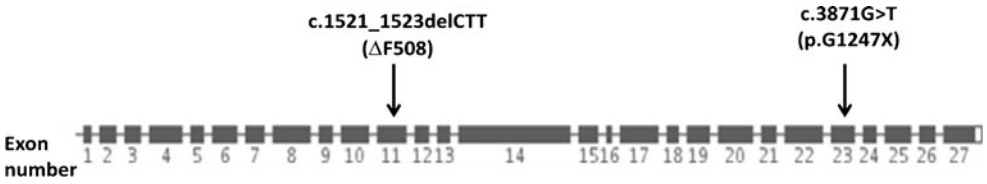

Fig. 3 Exonic location of the novel c.3871 G>T(p.G1247X) mutation with respect to the common c.1521_1523delCTT (ΔF508) mutation in the *CFTR* gene

ductular proliferation in liver biopsy. Although present case came to attention with the clinical picture and hepatobiliary scan resembling biliary atresia, he had only canalicular cholestasis without appreciable findings mentioned above in the liver biopsy. Similar cases are only rarely reported [10].

Conclusions

Thus, the authors report a case of CF-related neonatal cholestasis with a new CF mutation resulting in severe phenotype. It is a rare presentation type of CF-related liver disease. The authors also propose that patients with CF-related neonatal cholestasis may have acholic gaita mimicking biliary atresia in the absence of insipissated bile with minimal histologic findings.

Conflict of Interest None.

Role of Funding Source None.

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