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Case Report

The First Case of Coexistence of Cystic Fibrosis and Biliary Atresia (BA) in a Neonate and a Literature Review and a Novel BA Mutation

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Abstract

Background: The coexistence of CF and BA in a neonate is exceedingly rare, adding complexity to both diagnosis and management.

Objective: This is the first case report of CF and BA in a neonate in the Middle East with Novel BA mutation and literature review.

Case Presentation: A four-week-old Saudi male neonate was referred for evaluation of cholestasis, suspected BA due to clinical signs and family history. The initial workup revealed elevated liver function tests and characteristic imaging findings consistent with BA, confirmed by liver biopsy and cholangiogram. The patient underwent a successful Kasai procedure. In light of the history of recurrent cough and loose bowel movements, the Whole-exome sequencing was dose which identified a pathogenic homozygous CFTR mutation (c.2988+1G>A), confirming CF, alongside VUS in the LARS1 and RINT1 genes, associated with infantile liver failure syndromes. He was started on supportive therapies for CF, and showed marked improvement on symptoms and growth. The VUS findings necessitate long-term monitoring due to their potential impact on liver function.

Conclusion: This case underscores the diagnostic and therapeutic challenges posed by the rare co-occurrence of CF and BA in a neonate, which is further complicated by additional genetic findings.

Keywords: *Biliary Atresia; Cystic Fibrosis; Neonate; Cholestasis; Whole-Exome Sequencing; Genetic Variants; LARS1; RINT1; Kasai Procedure*

Introduction

Persistent neonatal jaundice, particularly beyond the first weeks of life, often raises concerns about underlying hepatobiliary or metabolic disorders [1,2]. Among these, biliary atresia (BA) stands as a critical pediatric condition, involving the progressive obstruction of the bile ducts, leading to cholestasis and, if untreated, cirrhosis and liver failure [3]. BA typically presents within the first few weeks of life with symptoms like jaundice, pale stools, and hepatomegaly, requiring timely intervention to prevent irreversible liver damage [3].

The primary surgical treatment for BA, the Kasai procedure, offers an opportunity for bile drainage by creating a conduit between the liver and intestine [4]. However, BA is complex, with multifactorial origins, and early diagnosis is essential for optimal outcomes, underscoring the need for specialized assessment and management in suspected cases [5].

Cystic fibrosis (CF) is a hereditary disorder caused by mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene, leading to dysregulation of chloride and sodium transport across epithelial cells [6]. While CF is widely recognized for its respiratory manifestations, it also significantly impacts the gastrointestinal and hepatobiliary systems [7].

The disease is often diagnosed in the neonatal period due to symptoms such as meconium ileus or failure to thrive [7]. However, hepatic manifestations like biliary obstruction and liver disease are also well- documented in CF and can complicate management when they overlap with other hepatobiliary conditions [8]. In neonates presenting with cholestasis, distinguishing between CF related liver manifestations and primary biliary disorders like BA can be challenging but crucial for appropriate therapeutic intervention [9].

The case presented here involves a four-week-old Saudi male with a complex clinical picture of concurrent BA and CF, highlighting the intersection of genetic and hepatobiliary pathologies. Genetic testing further identified variants of uncertain significance (VUS) in the LARS1 and RINT1 genes, both associated with autosomal recessive liver failure syndromes.

Methodology

The study collected the following data from medical records: demographics, medical history, presentations, genetic findings, growth data, management, biochemical data, and complications. Genetic testing was conducted as part of routine clinical practice. DNA extraction from peripheral blood samples was performed, and whole exome sequencing was carried out for all included patients. Additionally, the Varsome database was reviewed to check the latest ACMG class for the report variants in table 1 [10].

Location	Gene(transcript): change at the DNA level	Change at the protein level	Type	Coding impact	ACMG class	Autosomal Recessive	Zygosity	dbSNP
Intron 18	*CFTR*(NM_000492.4):c.2988+1G>A	p.?	SNV	Non-coding	P	Yes	Homo	rs75096551
Exon 6	*LARS1*(NM_020117.11):c.536A>T	p.(His179Leu)	SNV	Missense	VUS	Yes	Homo	rs1581072394
Exon 12	*RINT1*(ENST00000257700.7):c.1693G>A p	.(Ala565Thr)	SNV	Missense	VUS	Yes	Homo	Not available

Table 1: *Genetic findings of the index case.*

ACMG: American College of Medical Genetics and Genomics; P: Pathogenic; VUS: Variant of Uncertain Significance; SNV: Single Nucleotide Variant; Homo: Homozygous, dbSNP: A Unique Identifier Prefixed by 'rs' Assigned by the dbSNP Database to Each Variant.

Case Presentation

A four-weeks-old Saudi male was referred from a local hospital in Al-Ahsa (a city in Eastern Province Saudi Arabia) to the pediatric surgery section for the management of biliary atresia. Prenatal history was unremarkable except for an antenatal ultrasound showing echogenic bowel. He is a product of pre-term (36 weeks), spontaneous vaginal delivery (SVD) following a premature rupture of membranes (PROM), with meconium-stained amniotic fluid. With a birth weight of 2.6 kg and initially required a Neonatal Intensive Care Unit admission for 1 month.

During his NICU stay, an abdominal x-ray revealed dilated bowel loops (Figure 1), which were subsequently ruled out for obstruction. Additionally, the baby had a history of passage of thick stool and had gram-negative sepsis, which resolved after antibiotic course. Cholestasis also noted after a few days with elevated gamma-glutamyl transferase (GGT), pale stools, and slightly elevated liver function tests (LFTs) for which he was started on Ursodeoxycholic acid. Abdomen US Findings were suggestive of biliary atresia by the combination of a non-visualized gallbladder, thickened structures (CORD sign), and mild dilation of the hepatic arteries. He then was referred to our hospital (King Faisal Specialist Hospital and Research Centre) in Riyadh for further investigation for the management of his biliary atresia.

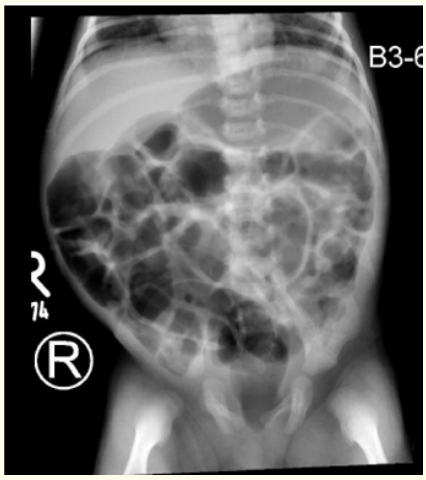

Figure 1: *Abdomen X ray at presentation. Abdomen X ray showing mild gastric air distension, mild to moderate air distended bowel loops mostly distal with an intraluminal air extension including the rectum up to the anal verge are noted. No abnormal air lucencies suggestive of pneumatosis or suspicious of free air identified.*

Evaluation at our center upon arrival, the baby was in a stable condition except for jaundice. The following investigations were initiated: blood workup including comprehensive liver function tests, Gama-glutamyl transferase (GGT), bilirubin levels, and other markers of cholestasis (Table 2). Screening for infectious causes of neonatal jaundice revealed a positive urine culture for *Klebsiella pneumonia* and *Citrobacter freundii*, both of which were treated with meropenem. Blood and stool cultures were negative.

Bilirubin (Total)	114.4	108.8	103.2	92.0	81.3
Bilirubin (Direct)	100.2	N/A	N/A	N/A	N/A
GGT	114.0	N/A	N/A	N/A	N/A
AST	353.0	370.0	N/A	235.0	201.0
ALT	319.9	258.3	N/A	198.3	146.4
ALP	294.0	256.0	N/A	235.0	284.0

Table 2: *Laboratory results.*

GGT: Gama-Glutamyl Transferase; AST: Aspartate Transaminase Test; ALT: Alanine Aminotransferase Test; ALP: Alkaline Phosphatase; N/A: Not available.

Abdominal ultrasound and US Hepatic/Portal vein duplex scan were done and revealed a diffuse increase in hepatic parenchymal echogenicity without evidence of intrahepatic biliary duct dilation. A small gallbladder was visualized, which could be attributed to recent feeding. However, the possibility of a small atretic gallbladder could not be excluded. The hepatic vasculature was patent, and mild left hydronephrosis was noted. Skeletal survey showed no evident skeletal dysplastic findings indicative of specific dysplasia or suggestive of Alagille syndrome identified. The pediatric gastroenterology and surgery teams recommended a laparoscopic cholangiogram and liver biopsy (Figure 2) which confirmed a non-fibrotic liver with an atrophied gallbladder and biliary system, consistent with biliary atresia. Consequently, the baby underwent a successful Kasai procedure.

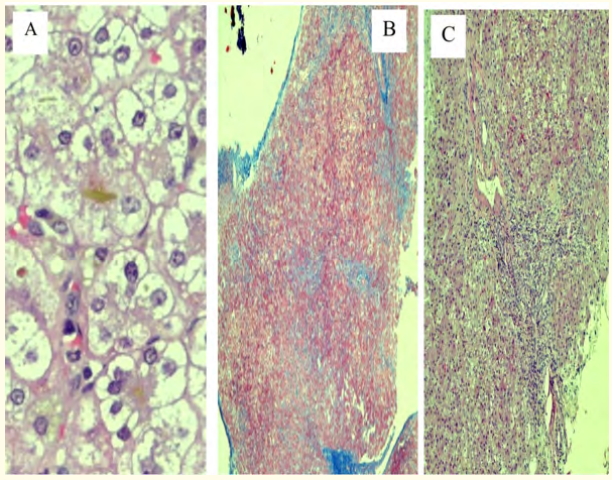

Figure 2: *Pathology results.*

A: Hepatocyte ballooning with cholestasis, B: Capsular fibrosis with portal tract fibrosis with no cirrhosis, C: Hematoxylin and Eosin (H&E) of liver with portal tract showing ductopenia and ductular proliferation.

Initial chest x ray showed Normal heart size and central pulmonary vascularity. Mild bilateral perihilar bronchial wall thickening. No focal airspace disease or significant pleural effusion on either side. The fecal fat test was positive, > 60 fat globules seen, normal low < 60 fat globules), low vitamins, vitamin A 96 ug/L (Normal range 343 - 838 ug/L), vitamin E 4 mg/L (Normal range 5.5 - 15.5 mg/ L), vitamin D 9 nmol/L (Normal range 60 - 100 nmol/L), zinc level 7.4 umol/L (Normal range 10.6 - 19), indicating malabsorption. Alpha fetoprotein test was high 22.40 ug/L (Normal range 0 - 7 ug/L), Ferritin 1,840.0 ug/L normal range (30 - 400 ug/L), thyroid function test, TSH 4.980 mU/L, (Normal range 0.270 - 4200 mu/L), T4 156.0 nmol/L (Normal range 66 - 181), anti SSA Ro antibody 5.1 units (1 - 19 units), anti SSB La antibody 2.9 units (0 - 19.9 units), antinuclear antibody screen was positive, anti gliadin IgG 6.2 U/Ml, anti gliadin IgA 3.2 U/mL, anti-nuclear antibody quantitative: Speckled 1:80 (Negative 1:40), negative anti reticulin and endomysium IgA, anti tissue transglutaminase IgA < 1.2 Units/Ml, organic acids GCMS urine not remarkable, L- carnitine, total 31.7 umol/l (38.1 - 68), L-carnitine, free 27.8 umol/l (26.9 - 49), L-carnitine total/L-carnitine free ratio 1.1, A ratio of > 1.6 is suspicious for a secondary disturbance in carnitine metabolism. sweat chloride test could not be performed due to the absence of sufficient sweat production.

In reviewing the history, Patient had loose bowel motion, recurrent cough and history of death sibling. Whole exome sequencing (Table 1), revealed a homozygous pathogenic mutation in the CFTR gene (c.2988+1G>A), confirming the diagnosis of cystic fibrosis, an autosomal recessive disorder. This mutation is classified as pathogenic based on ACMG guidelines.

In addition, a homozygous variant in the LARS1 gene (c.536A>T, p.His179Leu) was detected, which is classified as a variant of uncertain significance (VUS). The LARS1 gene is associated with infantile liver failure syndrome 1, an autosomal recessive disorder. Although the clinical significance of this mutation is uncertain, it occurs in a critical region of the gene (PM1).

Another homozygous variant in the RINT1 gene (c.1693G>A,p.Ala565Thr) was identified, which is also classified as a variant of uncertain significance (VUS). The RINT1 gene is associated with infantile liver failure syndrome 3, an autosomal recessive condition. Although the pathogenicity of this variant is not fully established, it occurs in a mutational hotspot (PM1).

Hospital course: After confirming the diagnosis of cystic fibrosis, the patient started on pancreatic enzyme replacement and vitamins, resulting in a good clinical response, no cough or exacerbation, with regular bowel movements, no more steatorrhea, he has adequate feeding with gradual weight gain, no more jaundice, stable from a pediatric surgery team standpoint.

Discussion

This case highlights the unusual coexistence of biliary atresia (BA) and cystic fibrosis (CF) in a neonatal patient, a combination seldom documented in clinical literature. Both BA and CF independently present complex diagnostic and therapeutic challenges, especially when overlapping hepatic complications are involved. Although BA is the leading cause of pediatric liver transplantation globally, affecting approximately 1 in 8,000 to 18,000 live births [11], CF is more frequently associated with pulmonary complications but also affects the gastrointestinal and hepatobiliary systems [7]. The concurrent presentation of these two conditions is not only rare but also complicates clinical management, as they can both independently lead to significant liver dysfunction if not promptly addressed [12].

Genetic testing played a crucial role in this case, confirming CF through the identification of a homozygous pathogenic mutation in the CFTR gene [13]. The mutation (c.2988+1G>A) has been classified as pathogenic according to the American College of Medical Genetics (ACMG) guidelines and has been reported in cases of CF in the literature [13]. Whole-exome sequencing (WES) also identified two variants of uncertain significance (VUS) in LARS1 and RINT1 genes, both associated with autosomal recessive infantile liver failure syndromes. Though these variants lack well-established pathogenicity, their presence in this neonate suggests a potential contribution to hepatic abnormalities, warranting ongoing clinical monitoring. The identification of VUS in cases with known genetic disorders complicates clinical management and emphasizes the need for precision medicine in pediatric hepatology [14,15].

The successful Kasai procedure underscores the importance of timely intervention for BA to improve bile flow and prevent liver cirrhosis, especially critical in neonates with comorbid conditions [16]. However, long-term outcomes for BA patients remain variable, with many requiring liver transplantations in early childhood, especially in cases of cirrhosis or portal hypertension [17]. CF- related hepatobiliary complications further compound these risks, as hepatic manifestations in CF, including steatosis, focal biliary cirrhosis, and multilobular biliary cirrhosis, are well-documented and contribute to morbidity in these patients [18]. The management strategy in this case focused on addressing BA surgically while providing pancreatic enzyme supplementation and antibiotic therapy for CF, showcasing the importance of a comprehensive approach to complex neonatal presentations [19].

The discovery of VUS in the LARS1 and RINT1 genes poses further challenges to this patient's long- term management. The LARS1 gene variant, associated with infantile liver failure syndrome 1, is located in a critical region and may have implications for liver function, although its clinical significance remains uncertain [20]. Similarly, the RINT1 variant, located in a mutational hotspot linked to infantile liver failure syndrome 3, requires further clinical observation due to its possible association with hepatobiliary disease [21]. In cases such as this, where pathogenic and uncertain genetic findings coexist, there is a need for ongoing liver function monitoring and potential early intervention if liver dysfunction is observed. Recent studies highlight the importance of cautious interpretation of VUS and recommend further genetic counseling and potential family screening to clarify the potential risks associated with these variants [15].

Our case aligns with other reports where CF and BA coexist, yet presents unique aspects not commonly observed in comparable cases. Greenholz., *et al*. (1997) [22] identified infants with cystic fibrosis and biliary atresia with striking cholestasis resistant to conventional treatments and a reliance on the Kasai procedure for bile drainage, similar to our case. However, in contrast to the cases they reported, our patient had additional variants of uncertain significance (VUS) in the LARS1 and RINT1 genes, which introduce complexities regarding liver function monitoring.

Ang., *et al*. (2023) [12] also reported a dual diagnosis of BA and CF, emphasizing the challenge of treating persistent jaundice and nutritional deficiencies particularly pancreatic insufficiency in such infants. Unlike our case, their patient faced early Kasai failure, necessitating transplant consideration, while our patient's post-operative course was comparatively stable. This stability may be attributed to early intervention and an integrated approach to pancreatic enzyme replacement, though continued vigilance is warranted due to the potential impact of the VUS on liver health.

Eminoglu., *et al*. (2012) [23] described neonatal cholestasis due to a novel CFTR mutation that mimicked BA without evident bile duct obstruction, allowing for resolution of symptoms through supportive treatments. In contrast, our case demonstrated significant obstruction requiring Kasai surgery, aligning more with cases involving anatomical biliary abnormalities. Additionally, Shapira., *et al.* (1999) [24] and Lykavieris., *et al.* (1996) [25] documented cases of CF-associated liver disease presenting as cholestasis but without severe outcomes or liver failure in most patients, suggesting a relatively stable prognosis when CF-related liver disease manifests without structural biliary atresia (Table 3).

Study	Patient Demographics	Genetic Findings	Primary Diagnoses	Intervention(s)	Outcomes
Greenholz et al., 1997 [22]	Neonatal patients (3 cases)	Cystic fibrosis-related gene abnormalities	CF-associated bile duct obstruction, biliary atresia	Kasai procedure, biliary irrigation	cases 2 resolved jaundice, 1 had liver failure
Ang et al., 2023 [12]	month-old-2 female	CFTR mutations	Biliary atresia, cystic fibrosis	Kasai procedure, pancreatic enzyme replacement	Referred for liver transplant evaluation
Eminoglu et al., 2012 [23]	day-old-63 male	Novel CFTR mutation (p.G1247X)	Neonatal cholestasis mimicking BA	Pancreatic enzyme replacement, ursodeoxycholic acid	Jaundice resolved by 7 months
Shapira et al., 1999 [24]	infants 12 (retrospective)	Cystic fibrosis	CF-associated liver disease, hyperbilirubinemia	Varies; liver biopsy, cholangiography	cases 11 had short- to medium-term liver stability
Lykavieris et al., 1996 [25]	Neonatal (9 out of 1474)	CFTR mutations and other comorbidities	Neonatal cholestasis, biliary atresia mimicry	Various supportive treatments, liver biopsy	case of 1 cirrhosis; others stable short-term
Agawu et al., 2019 [26]	Preterm infant male	No CF-specific mutation	TPN-associated cholestasis	TPN, biliary surgery	Normalized bilirubin by 3 months post-op
The current Case	week-old-4 male, Saudi	CFTR mutation, LARS1, RINT1 VUS	Biliary atresia, cystic fibrosis	Kasai procedure, enzyme therapy, antibiotics	Stable post-surgery; ongoing monitoring

Table 3: *Literature review of neonatal cases with cystic fibrosis and biliary atresia.*

CFTR: Cystic Fibrosis Transmembrane Regulator Gene Mutation; TPN: Total Parenteral Nutrition.

Conclusion

This case emphasizes the diagnostic complexity and clinical implications of concurrent BA and CF in neonates. The involvement of VUS in LARS1 and RINT1 genes highlights the role of precision medicine in understanding the genetic landscape of pediatric liver disease, especially when considering long-term prognosis and follow-up care. Moving forward, further research is warranted to elucidate the impact of VUS on clinical outcomes in neonatal hepatobiliary disorders, guiding therapeutic strategies and optimizing care for patients with multifactorial genetic and metabolic liver conditions.

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