CASE REPORT

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A Rare Association: Cystic Fibrosis and Congenital Cystic Adenomatoid Malformation

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ABSTRACT Cystic fibrosis (CF) is the most common severe autosomal recessive disorder in Caucasians. A homozygous change of the CF transmembrane regulator gene causes viscosity in pancreatic and bronchial secretion. Obstruction of secretion is responsible for liver and biliary tract symptoms. Congenital cystic adenomatoid malformation (CCAM) is a rare lung disorder of unknown etiology affecting the distal bronchi. It is important because of the risk of recurrent lung infections and malignancy. A 3-month-old female patient was brought to our hospital with symptoms of insufficient weight gain and pale appearance. The patient was hospitalized with a pre-diagnoses of malnutrition, hemolytic anemia, and cholestasis. She was diagnosed with CF liver disease and congenital adenomatoid malformation following thorough evaluation. Our patient with CF liver disease and pancreatic involvement was found to have a deltaF508 homozygous change. Our case is reported because of the rare association of hereditary CF disease and CCAM of unknown cause.

Keywords: Cystic fibrosis; congenital cystic adenomatoid malformation; liver

Cystic fibrosis (CF) is a multisystemic disease caused by CF transmembrane regulator (CFTR) gene changes. It occurs at an average of 1 in 3,000 live births. It is the most common autosomal recessive disorder and can be fatal in the Caucasian race.[1] CFTR gene was the first identified pathogenic gene of CF in 1989, and more than 2,000 mutations have been reported to date. DeltaF508 is the most commonly found change, accounting for more than two-thirds of the CF alleles.[2] CFTR protein is found in secretory epithelial cells in the lung, liver, pancreas, intestines, reproductive tracts, and sweat glands. It regulates chloride and bicarbonate secretion and as a result the fluidity and alkalinity of the secretions. A homozygous change of the CFTR gene causes viscosity and acidity in the pancreas and bile secretion. Partial or complete obstruction of the secretion is responsible for digestive system, liver, and biliary tract symptoms.[3]

Congenital cystic adenomatoid malformation (CCAM) is a rare structural lung disorder of unknown etiology that affects the distal bronchi. It constitutes 25% of all congenital lung structural disorders. It causes formation of multiple cysts in different locations, with pressure on the lung tissue on the same side or mediastinum. Diagnostic clinical findings are respiratory distress and recurrent lung infections.[4] Although almost all reported cases have been in Caucasians, no relationship has been found with sex, weight, gestational week, and the number of births of the mother.[5]

Our case is presented because the association of CF and CCAM is rare in the literature.

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A 3-month-old female patient was referred to our hospital with the diagnosis of cholestasis and anemia made in the health institution, which she has admitted with symptoms of inability to gain weight, pale appearance, fever and cough. In her physical examination, her anthropometric measurements were as follows: Weight: 3650 g (<3 percentile), height: 52 cm (<3 percentile), head circumference: 36 cm (<3 percentile). Her skin was icteric, respiratory sounds were rough, and her liver (102 cm, 40-90 cm) and spleen (84 cm, 30-70 cm) were palpable. The cardiovascular system examination and neuromotor development were normal. Eye examination by an ophthalmologist found a cataract on the right side (Figure 1).

FIGURE 1: The punctate cataract on the right side.

She was born by cesarean section from a 29-year-old healthy mother and a 33-year-old healthy father, who had a distant consanguineous marriage, at the 38th week of gestation, weighing 3500 g. She had a healthy 8-year-old sister. It was reported that her father's female cousin had a history of recurrent pulmonary infections (Figure 2).

Nasopharyngeal swab specimen of our patient indicated influenza B infection, and oseltamivir treatment was administered because it caused lower respiratory tract infection (LRTI). Possible etiology of cholestasis was investigated in detail: Infection panel was negative (TORCH infections, viral hepatitis), hypopituitarism was ruled out, and metabolic tests, concerning galactosemia, tyrosinemia, cerebrotendinous xanthomatosis, and other metabolic disorders gave no specific findings. Ultrasound showed normal hepatic bile ducts and hepatosplenomegaly. She had normochromic anemia and alloimmunization was thought to be the cause of anemia because of normal bone marrow examinations performed due to Rh incompatibility and a history of blood transfusion before admission, and a positive direct Coombs test in the fourth month.

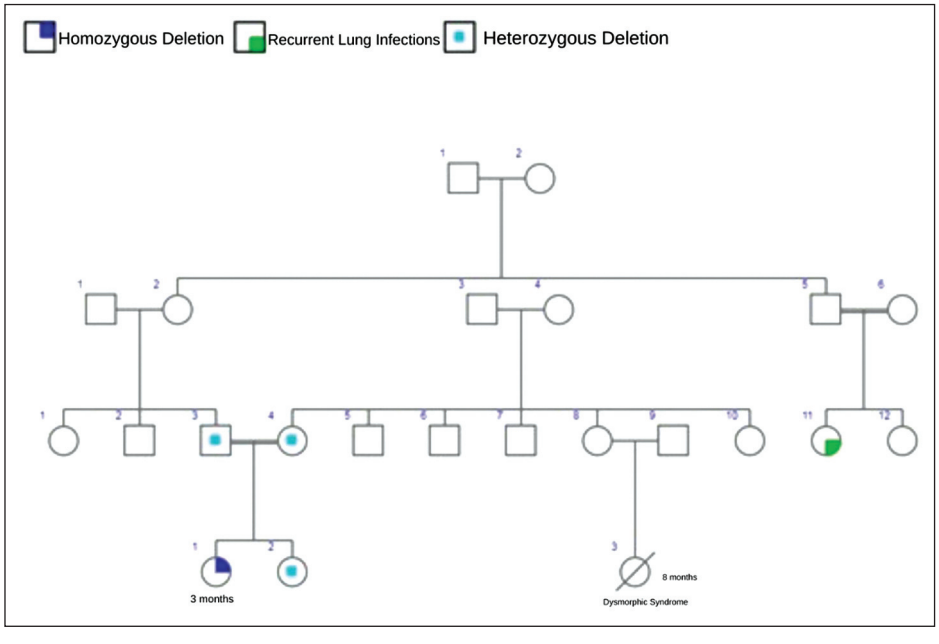

FIGURE 2: Family tree: Homozygous deletion detected in the female child, and heterozygous deletion in her mother, father and sister.

Vitamin A, D, E, K replacements and pancreatin (pancreatic enzyme replacement therapy) were given because of cholestasis and exocrine pancreatic insufficiency. Insufficient weight gain despite adequate breast milk suggested digestive disorders. Extensive hydrolyzed formula containing medium-chain triglycerides was initiated.

After influenza B treatment, despite experiential antibiotherapy, pulmonary tomography was requested and CCAM was detected, as respiratory findings and suspicious consolidation in the right upper lobe continued on chest radiography (Figure 3). For the treatment of cystic adenomatoid malformation, thoracoscopy was delayed due to the conditions of the case and the nature of the lesion, and follow-up was preferred due to its morbidity.

Due to the frequent and prolonged diseases involving the lower respiratory tract, no specificity was found in immunodeficiency examinations. Despite adequate nutrition, signs of exocrine pancreatic insufficiency such as growth retardation, light and fatty stools, and CF disease findings such as lung infection were detected. DNA sequence analysis was performed because sweat testing was not available. As a result of examining the relevant exon regions of the CFTR gene, a homozygous deletion of the c.1521_1523delCTT (p.Phe508delPhe) (delta F508) mutation was detected. In the family screening, heterozygous delta F508 deletion was detected in the patient's mother, father, and sister (Figure 4).

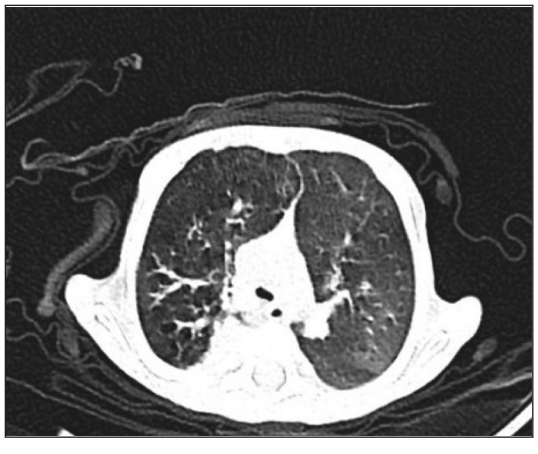

FIGURE 3: Congenital cystic adenomatoid malformation image in lung computed tomography (cystic structures in the upper lobe of the right lung, the largest of which is 5 mm in diameter).

The patient was treated with recombinant human deoxyribonuclease 1 (dornase alfa) therapy and chest physiotherapy. No colonization was detected in deep tracheal culture. Growth retardation was compensated through rapid weight gain.

The principles stated in the Declaration of Helsinki were adhered to and consent was obtained from the patient's parents.

DISCUSSION

CF is a multisystemic disease caused by CFTR gene changes. A homozygous CFTR gene change causes viscous and acidic bile secretions due to an exocrine secretion disorder and insufficient bicarbonate secretion. Viscous and acidic bile content is expected to cause inflammation and development of fibrosis and cirrhosis by causing ductal obstruction and hepatotoxicity.[1,3] In most patients, the disease causes focal changes of no clinical significance. However, multilobular cirrhosis may develop in a small subset of patients leading to the development of portal hypertension, splenomegaly and hypersplenism.[6]

Cystic fibrosis liver disease (CFLD) has been increasingly reported with survival in patients with CF. The most common manifestation of CFLD, ranging from mildly asymptomatic hypertransaminasemia to liver cirrhosis, may be splenomegaly, jaundice, biliary colic, and hepatomegaly alone, together with or incidentally with abnormal liver function tests.[7]

In a multi-center study conducted in France in 2017, it was stated that severe CFLD was very rare under the age of five years, and male sex, meconium ileus, and homozygous mutations were risk factors for severe CFLD. The most common findings of CFLD are clinical and biochemical abnormalities. Fifty percent of the patients were diagnosed as having hepatosplenomegaly and cholestasis.[8] In our patient, hepatic involvement manifested as hepatosplenomegaly and cholestasis, as expected in infants with CF, differed with age at diagnosis and progressed clinically well despite having a homozygous mutation.

Cholestasis usually resolves spontaneously in the first few months of life, but in some cases, it may progress to liver fibrosis.

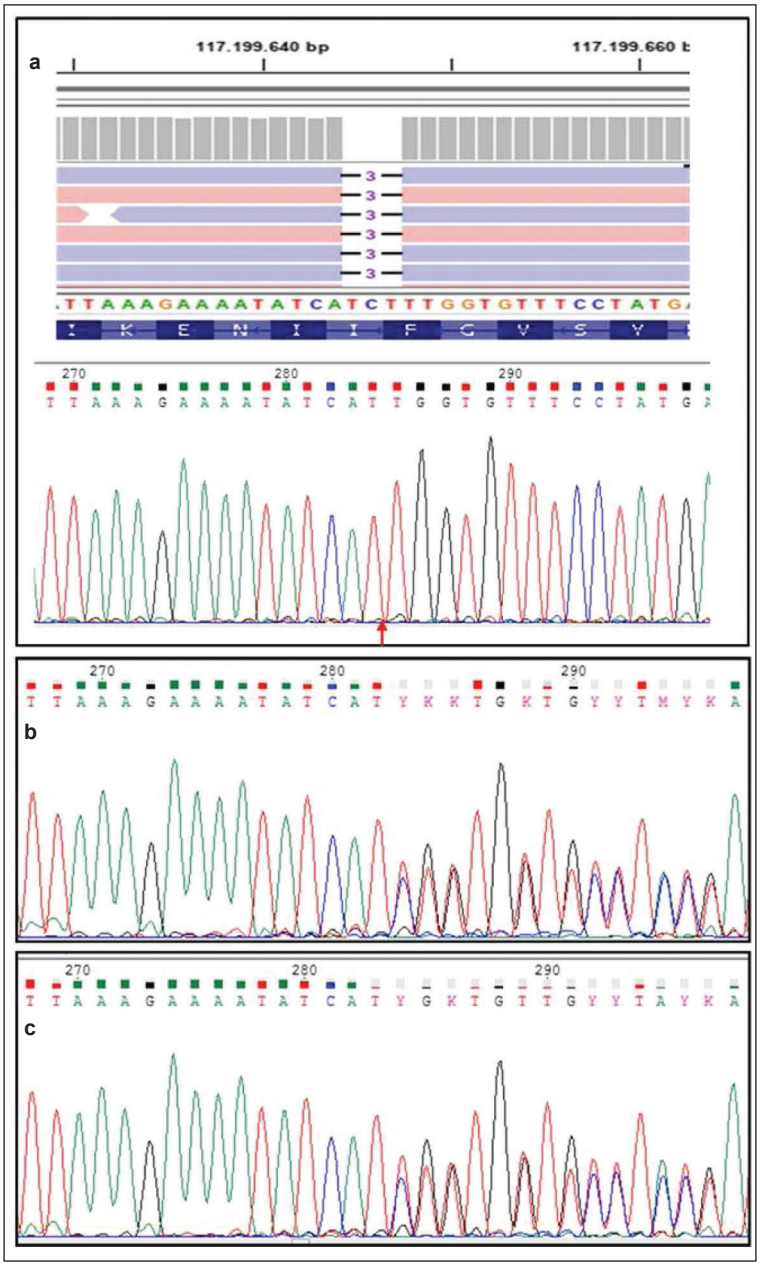

FIGURE 4: a) Image of the IGV mutation region as a result of next generation sequencing (upper panel) and electrophoregram image of the case as a result of sanger sequencing (lower panel) for verification. The presence of Delta F508 mutation in the homozygous state in the CF transmembrane regulator gene was confirmed in the case. b) and c) sanger sequencing electrophoregrams of the mother and father of the case, respectively. Delta F508 mutation was present in heterozygous state in both parents.

In older children, CFLD may present as hepatic steatosis with or without hepatitis, focal biliary cirrhosis, and multilobular cirrhosis.[9] Early diagnosis of CFLD is important because symptoms may occur late with advanced hepatic bile duct involvement.[10] Although cholestasis in our patient regresses considerably, it continues. Interestingly, Pierre Yves Boëlle et al. reported that liver disease was associated with poorer lung function and nutritional status.[8]

CF has been included in newborn screening in Turkey since 2015. Although our patient is a Turkish citizen, she was born in Iraq due to her parent's work commitments, which meant her newborn screening was delayed. This emphasizes the importance of newborn screening.

CFLD is recognized after other factors of liver disease have been ruled out. Ultrasonography plays a very important role in the diagnosis of CFLD by evaluating liver parenchymal changes such as fibrosis, cirrhosis, steatosis, bile duct abnormalities, and portal vein blood flow abnormalities. Liver biopsy is the gold standard for CFLD diagnosis, involvement type, severity, and staging. There are no existing evidence-based guidelines or specific recommendations for the prevention or management of CFLD. Therefore, CFLD treatment is aimed at reducing the impact of additional problems. For CFLD management, adequate calorie intake is limited to fat-soluble vitamin supplementation, pancreatic enzyme replacement, and avoidance of hepatotoxic drugs. Ursodeoxycholic acid (UDCA) is the only drug available that can prevent the progression of CFLD.[11] UDCA aims to improve bile flow and non-CFTR bile chloride ducts and protects hepatocytes from the toxicity of accumulating bile acids. It has been reported that liver functions and liver histology improve in patients with CFLD after the initiation of UDCA.[12] In a study conducted on patients with CFLD between January 2004 and 2017, it was reported that patients who were given UDCA treatment did not have severe liver disease.[8] In our patient, there were no cirrhotic changes in the liver and we observed that UDCA treatment improved clinical and laboratory findings during a one-year follow-up.

A vital aspect of CFLD management is nutritional support. Nutritional therapy aims to increase energy intake to 150% of the requirement. Patients with CF and other exocrine pancreatic insufficiency require fat-soluble vitamins A, D, E and K. In patients with anorexia, enteral tube feeding may be required. Feeding in our patient was oral, and adequate weight gain was observed.

CCAM is a rare (1: 25,000) structural lung disorder, the cause of which is not clearly known. It is thought to be a transient and focal lung development anomaly secondary to airway obstruction, and it has been reported that lung development is caused by the incompatibility in the pseudoglandular stage before the 16th gestational week.[13] It can be detected prenatally with imaging methods. It is usually asymptomatic, when complicated with additional problems, it becomes symptomatic and may present as fever, cough, or respiratory distress associated with emphysema, pulmonary hypoplasia or respiratory infection.[12] In addition to these additional problems, CCAMs are important because of the risk of developing bronchioloalveolar carcinoma or other types of malignant transformation (e.g. sarcoma or blastoma).[14] Conforti et al. recommended early surgery even if a CCAM was asymptomatic because of frequent infections, the difficulty of surgery after infections, and the risk of malignancy.[15] Our patient was not diagnosed prenatally, instead diagnosis was made following inadequate response to LRTI and suspicious finding in her chest X-ray and due to malnutrition, follow-up was preferred due to morbidity concerns.

Two rare diseases, one autosomal recessive and the other non-hereditary, causing irreversible progressive lung disease, were found together in our patient, and a good response was obtained through supportive treatment. While there is a defect in chromosome 7 in cystic fibrosis, there is no hereditary defect in CCAM. Although both diseases increased the risk of LRTI, our patient had a good prognosis.

This case has been reported because the coexistence of CF and CCAM has not been reported in the literature, and in the light of our case, it should be kept in mind that effective treatment management can be achieved with early diagnosis of CFLD.

Source of Finance

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Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Arzu Aras;* ***Design:*** *Reha Artan;* ***Control/Supervision:*** *Reha Artan;* ***Data Collection and/or Processing:*** *Banu Nur;* ***Analysis and/or Interpretation:*** *Reha Artan;* ***Literature Review:*** *A. Esra Manguoğlu;* ***Writing the Article:*** *Arzu Aras;* ***Critical Review:*** *Reha Artan;* ***References and Fundings:*** *Reha Artan;* ***Materials:*** *Ayzen Bingöl.*

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