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Case Report

The coexistence of two rare diseases thought to use the same pathologic pathway: cystic fibrosis and Niemann-Pick disease

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ABSTRACT

Background. Cystic fibrosis (CF) is a multisystemic, autosomal recessive disease, which is caused by a mutation in the transmembrane conduction regulator protein (CFTR) gene. We present a patient who was diagnosed with CF and later diagnosed with Niemann-Pick type-A (NPA) disease, which is an autosomal recessive lysosomal lipid storage disease.

Case. A 2-month-old Syrian refugee patient was diagnosed with CF due to a high sweat test and two homozygous CFTR-related pathogenic gene mutations in our pediatric pulmonology clinic, where she was referred due to a high immunoreactive trypsinogen (IRT) value as a result of newborn screening. As the patient had neurological symptoms and hepatosplenomegaly that could not be explained by CF in the clinical follow-up, the patient was diagnosed with NPA was made with a cherry red spot on eye examination, foam cells in the bone marrow, and low sphingomyelinase activity, in addition to CF.

Conclusions. Although CF and NP have common systems of involvement in both diseases, pathological symptoms have different origins. If a patient with CF has simultaneous neuromotor delay, other autosomal recessive diseases that may accompany it should be suspected. In studies, similar pathological pathways related to abnormal cholesterol accumulation in the cell were detected between NP type C and CF. But our case was NPA. As case reports on the coexistence of the two diseases increase, we believe that a better understanding of similar pathological pathways may lead to new therapeutic targets for both diseases.

Key words: cystic fibrosis, pathological pathway, Niemann-Pick, autosomal recessive diseases.

Cystic fibrosis (CF) is an autosomal recessive disease caused by mutations in the gene encoding the cystic fibrosis transmembrane conductivity regulator (CFTR). CFTR is a chloride channel located mainly in the apical membrane of epithelial cells, affecting salt and fluid transport.[1] Niemann-Pick (NP) is an autosomal recessive lysosomal lipid storage disease and organomegaly and neurological retardation are seen due to lipid storage.[2]

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In animal experimental studies, although CF and NP type-C (NPC) diseases contain different genetic defects, similar cholesterol processing defects and abnormal accumulation of free cholesterol in the perinuclear membrane compartments have been shown. Cholesterol storage affects many cellular functions and signaling pathways. It was hypothesized that both CFTR activation and expression and NPC protein expression were regulated by the cyclic adenosine monophosphate (cAMP) pathway, and a feedback response involving this pathway might play a role in the cholesterol accumulation phenotype.[3,4]

In our patient, CF and Niemann-Pick type-A (NPA) coexistence were detected.

The aim of this case report is to increase the number of CF and NP case reports, to better elucidate the pathological pathway and thus to reach common therapeutic goals.

Case Report

A 2-month-old male Syrian refugee patient was referred to the pediatric pulmonology clinic due to an immune reactive trypsinogen (IRT) level of 135.1 ng/mL at the first measurement and 93.7 ng/mL at the second measurement. His general condition was good, his body weight was 4000 g (< 3p) standard deviation score (SDS): -1.9, his height was 53 cm (10-25 p) SDS: -1.76, and his head circumference was 38.5 cm (3-10p) SDS: -0.86. His parents were second-degree relatives, and the mother lost her first pregnancy due to anencephaly. There was no family history of disease suggestive of CF or metabolic disease. The patient's history was unremarkable other than a one-day hospitalization and phototherapy due to jaundice. His complete blood count was as follows: white blood cell (WBC): 13,300/µL, absolute neutrophil count (ANC): 3400/µL, absolute lymphocyte count (ALC): 8200 /µL, hemoglobin (Hgb): 11 g/dL, platelet count (PLT): 247,000/µL, alanine aminotransferase (ALT): 208 U/L, aspartate aminotransferase (AST): 137 U/L, sodium (Na): 133 mmol/L, potassium (K): 4.9 mmol/L, chloride (Cl): 99 mmol/L, gamma-glutamyl transferase (GGT): 142 U/L, direct bilirubin: 0.5 mg/dL, indirect bilirubin: 0.61 mg/dL, total protein: 56.5 g/dL, albumin: 4.2 g/dL, total cholesterol: 169.4 mg/dL, and triglyceride: 335 mg/dL. His fecal fat test was positive, his sweat chloride test result was 89 mEq/L, and a genetic examination revealed compound heterozygosity for c.328G>C (D110H mutation)/c.274-8T>C, leading to a diagnosis of CF for which treatment was started. Hypotonicity and hepatomegaly developed in the second month and so a further evaluation was planned. A neurologic examination revealed a lack of head control, and an abdominal examination revealed the liver to be palpable 3 cm below the costal margin. An eye examination revealed bilateral cherry-red spots. Abdominal ultrasonography revealed grade-I increased echogenicity in the liver and diffuse hepatosplenomegaly, and a bone marrow aspirate showed NP foam cells (Fig. 1). Cranial magnetic resonance (MR) revealed a thin corpus callosum and a slightly increased subarachnoid distance. The sphingomyelinase (SM) activity measured from bone marrow aspiration findings was found as 1.7 nm/hr/mg protein (normal: 52-173 nm/hr/mg protein), and the patient was reported as homozygous c.1430C>T. Based on these clinical and examination findings, the patient was diagnosed as having NPA in addition to CF. At follow-up, the patient's liver and spleen continued to increase in size. The patient experienced increased respiratory distress due to diaphragmatic compression and developed a recurrent pulmonary infection, so a tracheostomy was performed. Respiratory support was given to the patient with a home-type mechanical ventilator. Over a year, the patient's throat cultures revealed the growth of *Pseudomonas aeruginosa* eight times, thus the patient was started on treatment for Pseudomonas colonization; he did not have CF-related pulmonary parenchyma involvement. In the pediatric intensive care unit (PICU) follow-up, the patient had ascites and required frequent paracentesis. The patient, who was followed up by the departments of Pediatric

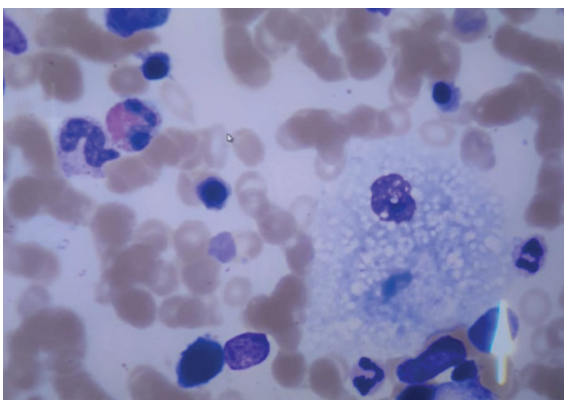

Fig. 1. Typical foam cell (arrow) from the marrow aspiration of the patient.

Pulmonology and Gastroenterology for CF and NP, died during PICU follow-up for respiratory distress and sepsis. Written informed consent was obtained from the family for this case report.

Discussion

Cystic fibrosis is an autosomal recessive disorder that presents with different clinical symptoms due to the involvement of multiple systems. Early diagnosis and appropriate treatment are important for the reduction of long-term morbidity, for which IRT newborn screening programs have been developed and are used in our country.[1] Pulmonary symptoms are the most common of all symptoms in all age groups, followed by gastrointestinal symptoms. This leads to such manifestations as fat-soluble vitamin deficiencies, calorie starvation, and growth and developmental retardation. The typical lesions in liver disease that develop in one-third of patients with CF include biliary obstruction, focal biliary cirrhosis due to progressive periportal fibrosis, and hypersplenism.[5] Our patient was referred to our clinic with a high IRT identified during newborn screening and was found to have fat malabsorption, growth retardation, elevated liver enzymes, hepatosplenomegaly, and hypotonicity at follow-up. The diagnosis of CF was confirmed through a sweat chloride test and from the identification of a genetic mutation, but the patient had unexplained neurological symptoms and organomegaly.

NP disease is a rare, autosomal recessive lysosomal lipid storage disorder that is characterized by visceromegaly and neurologic changes that occur due to the excessive storage of lipids, sphingomyelin, and cholesterol. It often presents with neurologic symptoms, gastrointestinal symptoms such as hypersplenism and cirrhosis, growth retardation-developmental delay, ocular symptoms, and pulmonary involvement. There are six clinical subgroups of NP, among which types A, B, and C are the most common.[2] Type A is the most common acute form with neurologic involvement, the course of which is fatal. In this form, symptoms start within the first 5 months of life, with the most prominent symptoms in infancy being hepatosplenomegaly, feeding difficulties, abdominal distension, frequent pulmonary infections, progressive retardation of early motor functions, macular degeneration, and convulsions. Patients rarely survive beyond the age of 2 years. Sphingomyelinase activity is almost totally reduced or absent. In type B, which occurs in infancy or early childhood, symptoms progress slowly, and patients often survive into adulthood.[2,6] The clinical spectrum of type C ranges from a neonatal rapidly fatal disorder to an adult-onset chronic neurodegenerative disease. The most characteristic symptom is vertical supranuclear gaze palsy.[7] Our patient was evaluated for neurologic diseases because he had hepatosplenomegaly and neurologic findings that could not be explained by CF alone, which was detected at the age of 2 months. An eye examination and cranial MR imaging were performed. The eye examination revealed bilateral cherry-red spots. The patient was diagnosed with NPA because of the marked decrease in SM activity, genetic mutation, and foam cells on the bone marrow aspiration material.

Significant differences in NP compared with CF are excessive lipid deposition in the liver and spleen leading to hepatosplenomegaly and progressive liver failure, in addition to neurologic symptoms.

Cystic fibrosis and NP disease have many common signs, such as gastrointestinal symptoms growth retardation-developmental delay, and pulmonary involvement. In the literature, this co-existants has been explained through the similar pathological pathways between NPC and CF. In a study by Kelley et al.[3] NPC and CF cell models shared a series of cell regulatory changes, including reduced nitric oxide synthase 2 (NOS2), high sterol-sensing domain (STAT1), Ras Homology Family Member A (RhoA) expression, and they reported that NPC-fibroblasts were similar to CF cells in

terms of altered expression of various signaling proteins. In another study, it was shown that both CFTR activation and expression were regulated by the cAMP pathway, and a feedback response involving this pathway played a role in the cholesterol accumulation phenotype in CF cells. The similarity between the two diseases is that cholesterol accumulation in dysfunctional NPC cells occurs with the same cAMP-mediated response. The diagnosis of our patient was NPA. To the best of our knowledge, there is no report on the similarity between NPA and CF in the literature. Considering the similar metabolic pathways between NPC and CF, and the co-occurrence of NPA and CF in our patient, it suggests that a similar pathway may also cause NPA and CF.[4] It is also believed that the F508del mutation, which is the most common cause of CF, causes misfolding of the CFTR protein by impairing the efficient exit signal of the CFTR protein from the endoplasmic reticulum (ER), and NPC1 mutations are believed to cause the same defective protein response from the ER by causing protein misfolding. Our patient did not have a F508del mutation, but the coexistence of NPA and CF suggests that other CFTR mutations should also be investigated in this respect.[3]

In conclusion, if a patient's presentation cannot be explained by CF alone, other rare autosomal recessive diseases such as storage disorders should also be considered. There are articles about the similarity of pathologic metabolic pathways between NPC and CF, but our case was NPA. We believe that as the relevant case reports in the literature increase, the similar pathologic pathway relationship between them will be better understood.

Ethical approval

Written informed consent was obtained from the family for this case report.

Author contribution

The authors confirm contribution to the paper as follows: study conception and design: AİY, SP; data collection: AİY, BU, GÜ, HT; analysis and interpretation of results: SP; draft manuscript preparation: AİY, BU, SP. All authors reviewed the results and approved the final version of the manuscript.

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Conflict of interest

The authors declare that there is no conflict of interest.

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