Pictorial Essay

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Clinical and Imaging Features of Cystic Fibrosis in Korean Children

한국인 소아에서의 낭포성 섬유증의 임상 및 영상 소견

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Cystic fibrosis (CF) is a fatal hereditary disorder that primarily affects Caucasians and is rare in Asian populations, including Koreans. Diagnosing CF is often challenging and delayed owing to its rarity and its overlapping features with non-CF diseases, ultimately affecting the patient prognosis. Radiologists can provide initial clues for clinically unsuspected cases and play a crucial role in establishing an early childhood diagnosis. This pictorial essay reviews the clinical and imaging features of genetically confirmed CF in Korean children and increases awareness of this rare disease, thereby facilitating early diagnosis.

Index terms Cystic Fibrosis; Koreans; Children; Imaging

INTRODUCTION

Cystic fibrosis (CF) is an autosomal recessive disease caused by mutations in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene located on the long arm of chromosome 7 (1). The CFTR protein is an epithelial ion channel that plays a crucial role in water and salt secretion and absorption. Mutations in the *CFTR* gene lead to a reduced number and/or function of ion channels, resulting in the production of thickened mucus and secretion in organs where CFTR is highly expressed, such as the lungs, gastrointestinal tract, pancreas, and vas deferens (1). Radiological findings of CF are attributed to impaired mucus hydration and clearance, leading to airway or duct obstruction in the affected organs. This

obstruction results in organ destruction and the manifestation of radiological abnormalities. However, the phenotypic variability of CF in terms of severity and the organs involved is substantial, even with the same genotype mutation (1, 2). CF is a common genetic disorder in Caucasians, with a prevalence of 1 in 1353 in Ireland, whereas its prevalence is extremely low in East Asian countries, with an estimated prevalence of 1 in 350000 in a Japanese study (3, 4). In Korea, only 23 cases of CF have been reported, and the median age of diagnosis was 4.5 years, which is higher than those reported in Western populations (median age at diagnosis: 6 months) (5, 6). Most Korean patients present with respiratory symptoms (7). Meconium ileus and pancreatic insufficiency were reported in 47.8% and 57.9% of patients, respectively (6) which were lower than those in Western populations, where pancreatic insufficiency is reported in 80% of the patients, suggesting possible differences in clinical symptoms based on ethnicity and geography (6, 8).

Classic CF is diagnosed when patients have a sweat chloride concentration of > 60 mmol/L and one or more phenotypic characteristics (sinopulmonary disease, gastrointestinal or nutritional abnormalities, salt-loss syndrome, and male urogenital abnormalities resulting in obstructive azoospermia). Typically, disease-causing mutations can be identified in each *CFTR* gene. In contrast, non-classic CF refers to individuals who show CF phenotypes in at least one organ system with normal (< 30 mmol/L) or borderline (30–60 mmol/L) sweat chloride concentration (9). The diagnosis of CF in non-classic cases requires the detection of one disease-causing mutation in each *CFTR* gene or direct quantification of CFTR dysfunction using nasal potential difference or intestinal current measurement (9, 10). In Korea, the diagnosis of CF is often delayed owing to the low incidence of CF, unfamiliarity among physicians, and overlapping clinical and radiological features with non-CF disease.

Therefore, this case-based review discusses the clinical and imaging features of genetically confirmed CF in Korean children with respect to pulmonary and abdominal manifestations.

PULMONARY MANIFESTATIONS OF CF

CF is primarily associated with pulmonary disease, the leading cause of morbidity and mortality. Patients often present with respiratory difficulties during the neonatal period. Recurrent pneumonia, chronic cough, and sinusitis were the most common symptoms during the later stages (11, 12).

Mosaic attenuation is the most common finding in early stage CF on CT, with a reported incidence of 63%–100% (Figs. 1, 2B) (11, 13). Other frequent findings include bronchiectasis with upper zone predominance, tree-in-bud patterns, and mucus plugging with consolidation (Figs. 2C, 3) (11, 13). Because of the prevalence of tuberculosis in Korea, the presence of a tree-in-bud pattern in patients with CF may occasionally lead to a misdiagnosis of tuberculosis and the subsequent administration of anti-tuberculosis medications.

Other diseases, such as primary ciliary dyskinesia (PCD), immune deficiency disorders, infectious diseases, and aspiration pneumonia, can have overlapping clinical and imaging features. The combination of sinusitis and situs inversus suggests PCD (14). In the Western population, pulmonary lesions in PCD mainly affect the middle and lower lung zones compared to those in CF (13). However, Yang et al. (11) reported that the zonal predominance of pulmo-

Fig. 1. Pulmonary changes in a 6-year-old girl with cystic fibrosis.
A, B. Axial (A) and coronal (B) lung settings of a chest CT scan show mosaic attenuation, mild bronchiectasis, and bronchial wall thickening in both lungs.

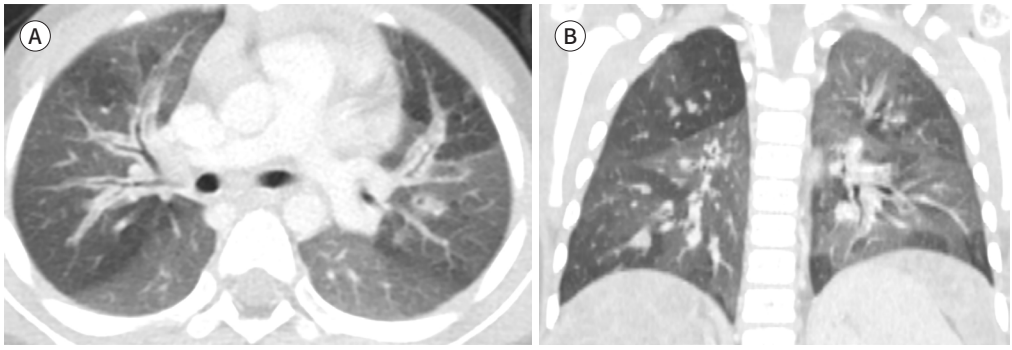


Fig. 2. Pulmonary and abdominal manifestations in a female patient with cystic fibrosis presenting with recurrent cough, diabetes mellitus, and lower abdominal pain. The patient had a history of preterm birth at a gestational age of 34 weeks and 5 days. Owing to the worsening abdominal distension despite conservative treatment, an ileostomy was performed.
A. Distal loopogram taken at 11 weeks after birth in a preterm baby shows impacted meconium pellets (arrows) as filling defects at the distal ileum with a small caliber of colon. This finding was initially misdiagnosed as meconium plug syndrome in neonates, considering the low incidence of cystic fibrosis in Korea and the history of preterm birth.
B. Coronal CT scan taken 10 months after birth shows mosaic attenuation in both lungs.
C. Follow-up chest CT at the age of 11 shows bronchiectasis, tree-in-bud appearance, and mucus plugging with upper zone predominance.
D. Axial CT scan at the age of 11 shows multinodular liver cirrhosis with fatty deposition, splenomegaly (not fully included), and fatty atrophy of the pancreas (arrows), which was not found in chest CT taken at the age of 10 months.

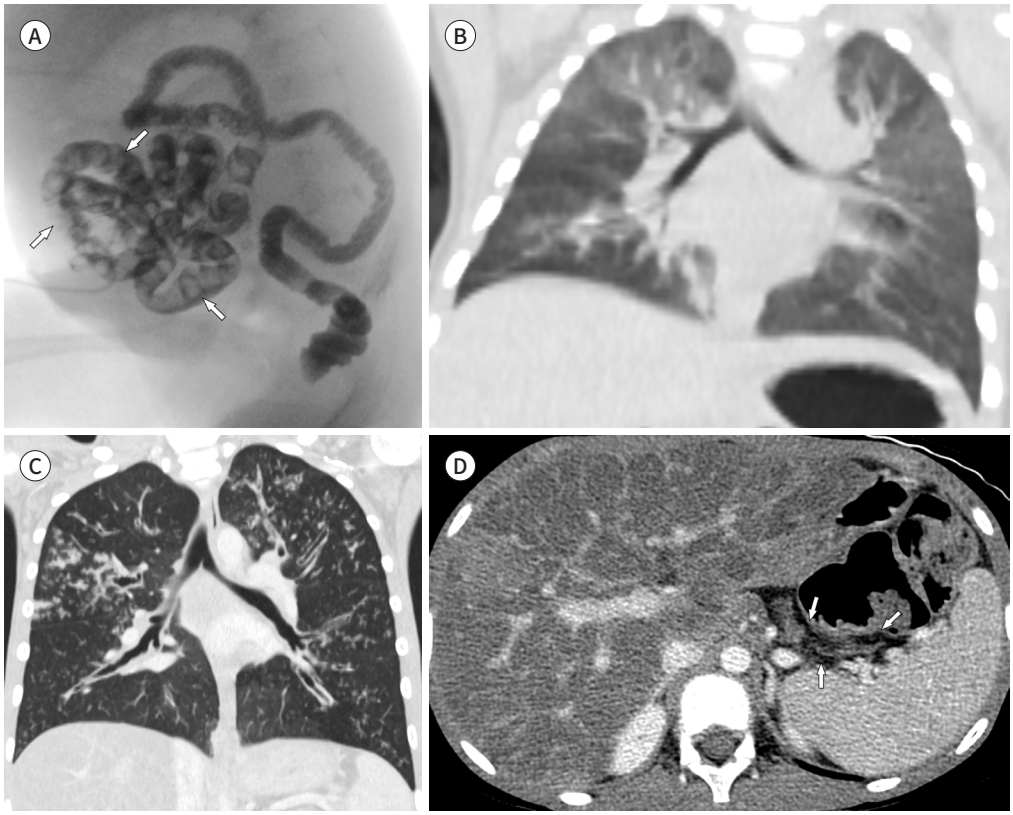


Fig. 3. Pulmonary changes in a 17-year-old female patient with cystic fibrosis who presented with chronic cough and sputum with a history of anti-tuberculous medication for one year.
A. Chest PA shows bronchovascular crowding with peribronchial thickening and ill-defined nodular opacities in both the upper and middle lung fields.
B, C. Axial (B) and coronal (C) CT scans show bronchiectasis and centrilobular nodules with a tree-in-bud appearance, mainly in the upper lung zones.

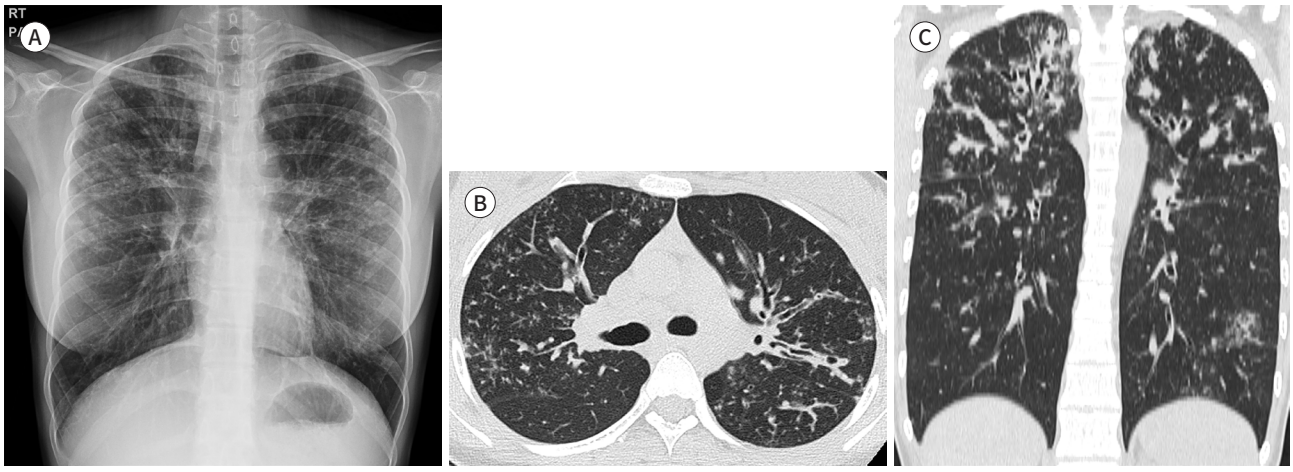
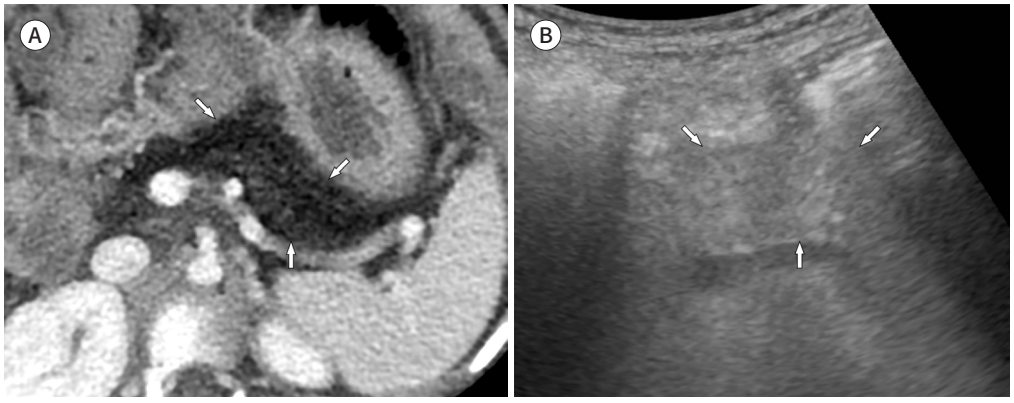


Fig. 4. Fatty replacement of the pancreas in a 6-year-old girl with cystic fibrosis.
A, B. Axial CT scan (A) and abdominal ultrasonography (B) show total fatty replacement of the pancreas (arrows).



nary lesions in patients with CF and PCD did not differ in the Korean population. It is unclear whether this discordant result was due to ethnic differences or the small sample sizes. Diffuse or lower lung zone predominance of bronchiectasis and absence of thymic tissue may support the diagnosis of immune deficiency disorders such as severe combined immunodeficiency and DiGeorge syndrome (15). A history of severe respiratory infection in a previously healthy patient and radiological findings of mosaic attenuation, bronchial wall thickening, and bronchiectasis without zonal predominance may suggest post-infectious bronchiolitis obliterans (16, 17). Aspiration pneumonia usually occurs in predisposing conditions such as gastroesophageal reflux disease, central nervous system problems, foreign body aspiration, or tracheoesophageal fistula affecting the posterior lungs (18).

ABDOMINAL MANIFESTATIONS OF CF

The pancreas is the most commonly affected abdominal organ in patients with CF, which manifests as exocrine or endocrine dysfunction (19). Associated symptoms include reduced growth, steatorrhea, and diabetes mellitus (1, 20, 21). The most common pancreatic manifestation is fatty replacement of the pancreas (Fig. 4), with a reported incidence of approximately 93%. Other manifestations include pancreatic calcification (Fig. 5) and cysts (19, 22, 23).

The hepatobiliary manifestations of CF include hepatic steatosis, varying degrees of fibrosis (Fig. 2D, 6), cholelithiasis, micro-gallbladder, and bile duct irregularity. Symptoms range from asymptomatic to fatal complications associated with liver cirrhosis and portal hypertension, including variceal bleeding, ascites, and coagulopathy associated with liver failure (22-24).

Meconium ileus (Figs. 2A, 7) is the earliest gastrointestinal manifestation of CF, with an in-

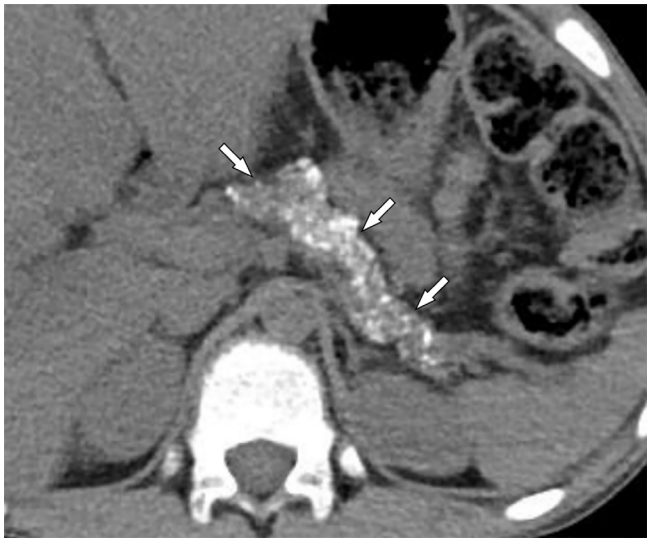


Fig. 5. Pancreatic calcification in an 8-year-old boy with cystic fibrosis who presented with chronic abdominal pain and steatorrhea.
Axial CT scan shows atrophic changes in the pancreas with extensive calcification (arrows) (Image courtesy: Dr. So Mi Lee, Kyungpook National University Hospital).

Fig. 6. Hepatic changes in a 6-year-old girl with cystic fibrosis who presented with abdominal distension and constipation.
A. Axial CT scan shows multinodular liver cirrhosis and left gastric varices (arrow).
B. Abdominal ultrasound of the left hemi-liver shows multiple echogenic nodules, suggesting uneven nodular fatty infiltration in the cirrhotic liver.
C. In and opposed-phase MR images confirm the fat component of the numerous hepatic nodular lesions, which are "pseudomasses" by periportal infiltration of fat in cystic fibrosis-associated hepatic steatosis.

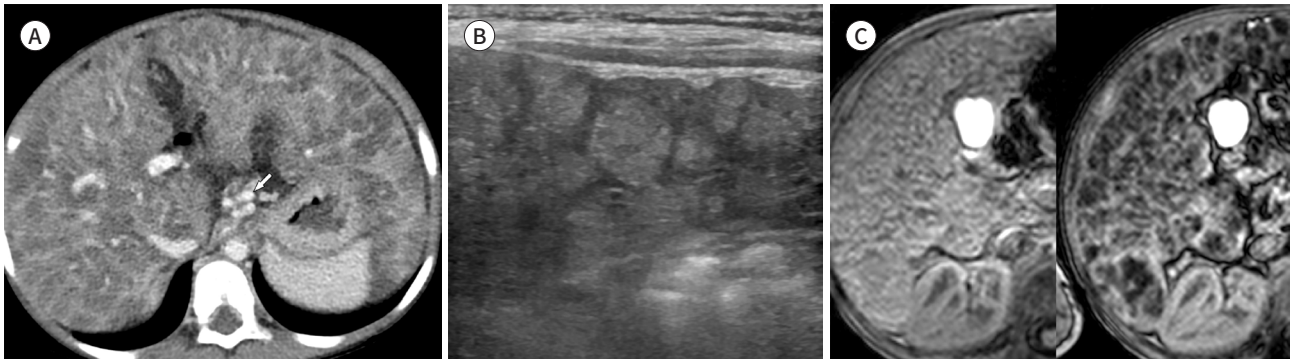


Fig. 7. Meconium ileus in a 1-day-old term neonate with cystic fibrosis who presented with bowel dilatation on fetal ultrasound.
A. Plain radiograph shows a distended abdomen and paucity of bowel gas, which is visible only at the stomach and proximal small bowels.
B. Abdominal ultrasound shows non-dilated small bowels (arrow) in the right lower quadrant and markedly dilated proximal small bowels filled with meconium (*). Under suspicion of ileal atresia or Hirschsprung disease, an explorative laparotomy was done with an ileostomy. No evidence of atresia. Pathology confirmed the presence of ganglion cell.
C. Distal loopogram performed before takedown surgery shows impacted meconium pellets (arrows) as multiple filling defects at the distal ileum.

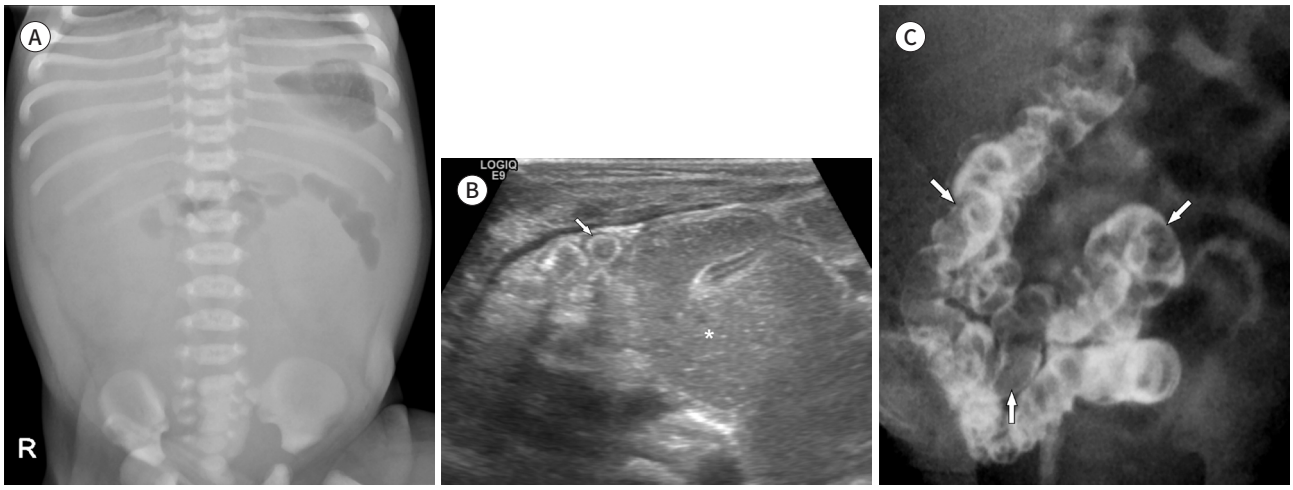
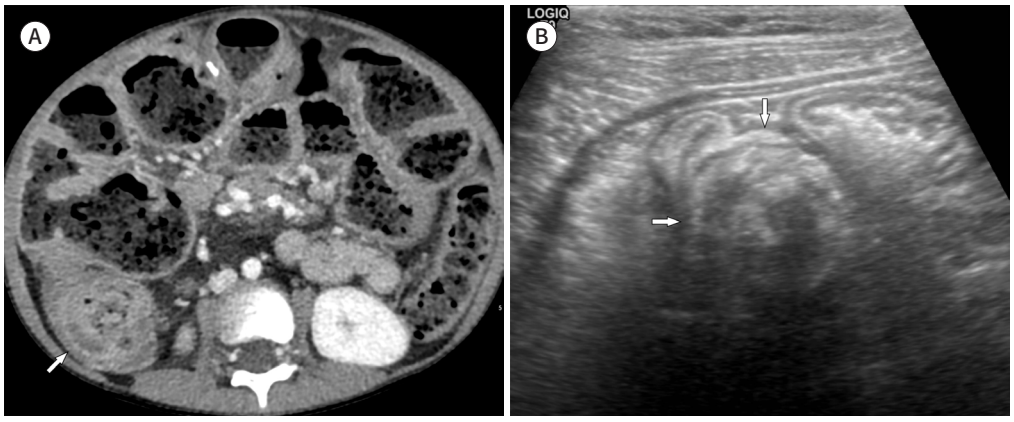


Fig. 8. Colonic manifestation of cystic fibrosis in a 6-year-old girl.
A, B. Ultrasound (B) taken one year after the axial CT scan (A) shows persistent wall thickening of the ascending colon, causing a wrinkled appearance simulating intussusception (arrows). Moreover, CT scan shows numerous fecal materials in the distended small bowel loops with diffuse wall thickening.



cidence of 10%–15% (25). This results from the impaction of an abnormally thickened meconium, which causes obstruction at the terminal ileum. Neonates with meconium ileus usually present with delayed passage of the meconium, abdominal distension, or vomiting after birth. These patients may also present with prenatal bowel dilatation (26). Although a previous study (27) reported that up to 90% of infants with meconium ileus have CF, in Korea, meconium-related obstruction (meconium plug syndrome) frequently occurs in preterm babies because of decreased intestinal motility caused by prematurity. Without a high index of suspicion, meconium-related obstruction in neonates can be mistakenly considered a motility problem. Although rare in Korea, concerns regarding CF should be addressed in term neo-

nates with meconium plug syndrome. Distal intestinal obstruction syndrome is equivalent to meconium ileus in older patients. Clinical manifestations include abdominal pain, a right lower quadrant mass, and vomiting (22, 23, 28). Radiographic evaluation shows dilated loops of the small bowel with or without an air fluid level and a bubbly soft tissue mass in the right lower quadrant (22). On ultrasound, a large amount of impacted fecal material can be observed in the ileocecal area (28). Approximately 50% of patients with meconium ileus have complications such as volvulus, perforation, and meconium peritonitis. CT can be used to assess these complications (22, 29).

Colonic abnormalities, including proximal colonic wall thickening (Fig. 8), infiltration, and pericolonic fat proliferation, have been reported as manifestations of CF (30, 31). Proximal colonic wall thickening is often associated with marked inner wall redundancy, which can be misinterpreted as colitis or intussusception but is persistently seen on follow-up imaging (32). Fibrosing colonopathy is diagnosed based on histological findings characterized by submucosal and lamina propria fibrosis combined with inflammatory changes. Presumably, pancreatic enzyme replacement therapy is associated with fibrosing colonopathy (33, 34), which manifests as mucosal irregularities, nodular wall thickening, colonic shortening, and segmental luminal narrowing (22, 29, 31).

CONCLUSION

In our case-based review, the diagnosis of CF was frequently delayed, with a median age at diagnosis of 13 years (interquartile range, 7–16 years). Furthermore, bronchiolitis and a tree-in-bud appearance simulated tuberculosis. Typical abdominal imaging findings such as fatty changes of the pancreas and a history of meconium ileus in neonates can provide clues for diagnosing this rare disease, while hepatic steatosis, cirrhosis, and proximal colonic wall thickening can present features of CF.

Although the incidence of CF is low in Korea, familiarity with these thoracic and abdominal manifestations allows for the early identification of patients with CF, thus facilitating timely diagnosis and management.

Author Contributions

Conceptualization, Y.S.; data curation, K.Y.J., Y.S.; formal analysis, K.Y.J., Y.S.; investigation, K.Y.J.; supervision, Y.S.; validation, Y.S., J.T.Y., K.J.H., P.J.E.; visualization, K.Y.J.; writing—original draft, K.Y.J.; and writing—review & editing, Y.S.

Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

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한국인 소아에서의 낭포성 섬유증의 임상 및 영상 소견

권용재 · 유소영* · 전태연 · 김지혜 · 박지은

낭포성 섬유증(cystic fibrosis)은 주로 백인에게 영향을 미치는 치명적인 유전 질환으로 한국을 포함한 아시아 인구에서는 드물다. 낭포성 섬유증의 진단은 질환의 희소성과 비 낭포성 섬유증과의 중복되는 특징으로 인해 종종 어렵고 지연되어 궁극적으로 환자 예후에 영향을 주게 된다. 영상의학과 의사는 임상적으로 의심되지 않는 경우에도 초기 단서를 제공할 수 있으며 조기 진단을 확립하는 데 중요한 역할을 한다. 본 임상화보는 국내 소아에서 유전적으로 확인된 낭포성 섬유증의 임상 및 영상 의학적 특징에 대해 알아보고 이 희귀 질환의 인식을 높여서 조기에 진단하는 데 도움을 주고자 한다.

성균관대학교 의과대학 삼성서울병원 영상의학과