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Case Report

Crohn's Disease in Cystic Fibrosis

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Summary: We report on three patients suffering from cystic fibrosis (CF) who developed gastrointestinal symptoms of Crohn's disease (CD). Two patients developed enteroenteric or enterocutaneous fistulas. The diagnosis of CD is based on typical endoscopic, radiologic, and histological features of epithelioid granulomas in two children. **Key Words:** Cystic fibrosis—Crohn's disease—Coexisting cystic fibrosis and Crohn's disease.

Cystic fibrosis is the most frequent inherited metabolic disease in children (1,2). Although there are some reports of a coincidence with celiac disease, α_1-antitrypsin deficiency, and neuroblastoma (3–9), only three patients with both CF and inflammatory bowel disease (IBD) have been described so far (10–12). Among 120 CF patients under constant care at our CF clinic, we diagnosed Crohn's disease (CD) on three occasions over the last 5 years.

MATERIAL AND METHODS

Case 1

Although the patient's brother had died of this disease earlier, CF was diagnosed rather late, at 33 months (sweat chloride level, 100 mmol/L). Family history was negative with respect to inflammatory bowel disease. The patient developed pulmonary hypertension and failed to thrive. At 14 years, he developed recurrent abdominal pain, diarrhea, recurrent fever and weight loss, and arthralgia. Anal abscess formation by the age of 16 years was further complicated by a rectocutaneous fistula. At 16.5 years, he was physically retarded: less than 3rd percentile and pubertal stage II [all data according to Tanner and Davies (13)]. Basic laboratory data are given in Table 1. Endoscopy showed a markedly inflamed colonic mucosa with ulceration and extreme pseudopolyposis in the proximal transverse colon. Owing to luminal stenosis, a fistula at the right colonic flexure was not reached by the colonoscope but was visualized after a barium meal. In addition, a rectocutaneous fistula had already been seen by proctoscopy. Biopsy material showed a markedly inflamed colonic mucosa with lymphocyte infiltration and granulation tissue. No epithelioid granulomas were seen.

On the basis of these findings, in addition to CF, the diagnosis of CD was made.

The boy was treated with salazosulfapyridine (SASP, 1,500 mg/day), prednisolone (10 mg/day), and azathrioprine (50 mg/day). He also received an elemental diet intermittently over 6 weeks. On this regimen the boy's condition improved, and he showed a 6-kg weight gain over the next 18 months. The rectal fistula closed. Diarrhea, abdominal pain, and arthralgia subsided. However, 2 years later the patient's condition deteriorated and he died from pulmonary insufficiency.

Case 2

CF was diagnosed by the age of 6 months (sweat chloride level, 127 mmol/L) when this girl revealed mainly respiratory symptoms and had only mild pancreatic insufficiency. The clinical course of CF was characterized by mild recurrent pulmonary in-

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TABLE 1. *Basic laboratory data in three patients with cystic fibrosis and Crohn's disease*

	Case 1	Case 2	Case 3
ESR (mm/h)	65	50	76
Hemoglobin (g/dl)	11.6	10.8	11
WBC (10^3/mm^3)	7	18.9	10
Bands (%)	18	1	13
Platelets (10^3/mm^3)	333	488	639
IgA (mg/dl)	455	520	460
IgG (mg/dl)	1919	2408	1340
IgM (mg/dl)	221	198	125
Albumin (g/dl)	2.3	2.5	2.7
α_2-Globulin (g/dl)	1	1.1	1.1
γ-Globulin (g/dl)	2.6	2.1	1.5

fections. Family history was not contributory to CF and CD. Six months before the diagnosis of CD, the girl suffered from relapsing fever, with temperature up to 39°C, and from recurrent colicky abdominal pain. She appeared stunted and underweight (18.1 kg, 127 cm, under 3rd percentile) by the age of 12.3 years. A tender mass in the right lower abdomen showed thickened and rigid intestinal walls by ultrasonography. A marked inflammatory activity was indicated by a high white blood cell (WBC) with left shift and a high erythrocyte sedementation rate (ESR) (Table 1). Endoscopy showed mucosal ulceration, edema, and pseudopolyposis of the proximal part of the rectum with a narrow stenosis of the sigmoid colon. A barium enema study disclosed a fistula from the markedly altered ascending colon entering the sigmoid proximal to the stenosis mentioned earlier. Barium follow-through study showed additional fistulas in an extremely stenosed ileum with prestenotic dilatation. Biopsy specimen revealed massive inflammation of the entire mucosa and gave evidence of CD by the finding of epithelioid granulomas.

The girl was treated with SASP (1,500 mg/day), prednisolone (2 mg/kg body weight/day), and an elemental diet intermittently. Her condition improved, and there was relief from abdominal pain and fever. ESR decreased markedly. The child gained weight slightly (4.4 kg over the next 2 years) and reached menarche 3 months after initiating therapy. Unfortunately, pulmonary symptoms developed and an insulin-dependent diabetes complicated CF.

Case 3

In this boy, CF was diagnosed at 3 months of age (sweat chloride level, 92 and 119 mmol/L), and he had pulmonary and mild gastrointestinal symptoms. One older sister had died from CF. A few months before CD was diagnosed, he had diarrhea, failed to gain weight, and developed an anal abscess that had to be incised. By the age of 17.8 years the adolescent was malnourished and in poor general condition (44 kg, under 3rd percentile; 164 cm, 10th percentile). Basic laboratory data are given in Table 1.

Proctoscopy showed an anal fissure, abscess formation, and a long-standing anal fistula. Colonoscopy and barium enema were not done. At an upper gastrointestinal follow-through study of the terminal ileum showed cobblestone formation and a marked thickening of the intestinal wall. A highly altered ascending colon and cecum with ulceration and mucosal irregularity was suggestive of CD. Epithelioid granulomas from the anorectal regions confirmed the existence of CD.

The boy was treated with 5-aminosalicylic acid (5-ASA, 1,500 mg/day), prednisolone (20 mg on alternating days), metronidazole for therapy of the anal lesions (750 mg/day), and elemental diet for 6 weeks. His condition improved quickly, with healing of the anal abscess and the fistula. Abdominal pain improved and bowel motions normalized.

Unfortunately, the condition worsened 6 months later owing to an abdominal mass in the right lower abdomen, which caused intestinal obstruction. At laparotomy, a covered perforation in the cecal region, abscess formation, and numerous fistulas necessitated section and an ileocolostomy to the ascending colon. Transmural inflammation with numerous epithelioid granulomas in the resected bowel specimen gave further evidence of CD. The boy has done well so far with respect to both CD and CF.

DISCUSSION

Thus far, three publications have dealt with the simultaneous occurrence of CF and CD (10–12). In the girl described by O'Connor and Lawson (10), CF was diagnosed by the age of 1 year. Rectal bleeding, diarrhea, and an anal fistula resistant to therapy were the presenting symptoms of CD by the age of 9 years. At laparotomy the sigmoid colon was found to be thickened and ulcerated and showed cobblestoning with histological evidence of epithelioid granulomas without caseation. The diagnosis of CD of the descending and sigmoid colon with anorectal fistula formation was made.

Euler and Ament (11) reported a male CF patient

whose monozygotic twin died from meconium ileus at 6 days of age. This patient had developed a meconium ileus as well but recovered and thrived well until he was 6.5 years of age. He then suffered from relapsing fever, arthralgia, and weight loss over the next 2 years. Rheumatoid arthritis was diagnosed. At the age of 8.5 years, appendectomy was performed for a perforated appendix. Postoperatively, ileocolic and ileocutaneous fistulas developed. Relapsing fever continued. Another 2 years later, a conglomerate tumor in the right lower abdomen necessitated an ileocecal resection. Histopathologic study revealed transmural inflammation and polynucleated giant cells. The patient's course was complicated by additional enterocutaneous fistula formation at the site of the median laparotomy scar. He continuously lost weight and developed a malabsorption syndrome with deficiency of folic acid, vitamin B_{12}, and carotene. Radiologic studies revealed numerous ileocolic and ileocutaneous fistulas. There was only moderate peribronchitis by the age of 17 years, when CF was diagnosed (sweat chloride level, 95 mmol/L).

Ojeda and co-workers (12) reported on a 25-year-old man with both CF and CD. Except for two episodes of meconium ileus, CF was manifested mainly with respiratory symptoms. By the age of 23 years, the patient had weight loss, abdominal pain, diarrhea, intestinal bleeding, and anemia. Results of endoscopy of the upper and lower gastrointestinal and mesentericography were not conclusive. Massive bleeding necessitated emergency laparotomy with colectomy and ileostomy. An extremely fibrotic colon with extensive ulceration of both ascending and transverse segments had been the source of bleeding. Histopathologic findings were typical for CD, with fissures, discontinuous transmural inflammation including crypt abscesses, and giant cell granulomas. The diagnosis of CD was made. Increased sweat chloride levels in all these patients were seen in the first years of life. The finding of epithelioid granulomas in the three previously reported patients and in cases 2 and 3 of our series confirmed the presence of CD. In case 1, fistula formation, stenosis of the colon, and anorectal pathology is consistent with CD. The finding of epitheloid granulomas in five of six patients is high, as granulomas are found only in about 40% of rectal and colonic biopsy specimens on serial section (14).

In addition to local evaluation, all x-ray films have been seen by three other independent pediatric radiologists of the Pediatric Crohn's Disease Study Group. Tuberculosis, yersiniosis, salmonellosis, and campylobacter infection have been excluded in all our patients.

The combination of CF and CD does not predispose to an earlier onset of IBD. The age of presentation of our cases is in line with larger pediatric series (3,15) (Table 2). The interval between initial presentation and diagnostic proof of 6 months and 3 months, respectively, in cases 2 and 3 is short when compared with latencies of 18 to 31 months of larger series (10,11,15,16) (SW Bender, personal communication). This is surprising as many presenting symptoms of CD are rather unspecific and may well have been attributed to CF. This is true for abdominal pain, loose stool, fever, and arthralgia (observed in 8% of CF patients). The localization of CD mainly in the colon, with diarrhea and anorectal abscess and fistula formation, may have facilitated an early diagnosis of CD in our patients. In addition to the main involvement of the colon in CD, a high incidence of anorectal, enteroenteric, and enterocutaneous fistulas is seen in our patients, as in those

TABLE 2. *Clinical data of patients with cystic fibrosis and Crohn's disease from the literature and authors' own observations (cases 1–3)*

Source	Sex	Age at Diagnosis of CF (months)	Age at Presentation of CD (years)	Age at Diagnosis of CD (years)	Presenting symptoms of CD
O'Connor et al. (10)	F	12	9	10	Rectal bleeding, anal fistula, diarrhea
Euler et al. (11)	M	210	6.5	10.5	Fever, weight loss, arthralgia
Ojeda et al. (12)	M	4	23	25	Intestinal bleeding, diarrhea, abdominal pain, weight loss
Our case 1	M	33	14	16.5	Fever, abdominal pain, weight loss, arthralgia, anal abscess
Our case 2	F	6	11.7	12.3	Fever, abdominal pain, weight loss
Our case 3	M	3	17.5	17.8	Diarrhea, failure to thrive, anal abscess and fistula

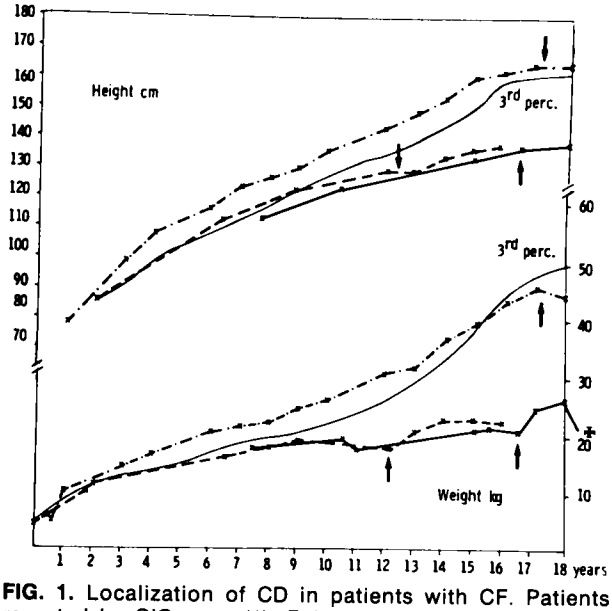

FIG. 1. Localization of CD in patients with CF. Patients reported by O'Connor (1), Euler (2), and Ojeda (3); (4) to (6) represent our own cases (4 = case 1; 5 = case 2; 6 = case 3).

reported by others (Fig. 1). These complications of CD developed early in the course of disease. With this presentation, CD should readily be suspected. Among 25 other children in our CD clinic enteroenteric fistulas were observed only twice. The latter frequency corresponds with data presented by others (17).

The cause of the simultaneous occurrence of CF and CD is unknown. Euler and Ament (11) and Ojeda et al. (12) postulate an incidental coincidence of both diseases, as Katz et al. (3) had suggested for the combination of CF and celiac disease. On the basis of our data, we suspect that the coexistence of CD and CF is not incidental. Poisson's curve for distribution of disease gives a probability of an incidental coincidence of CD and CF of 1 in 20,000. Our observations suggest a much higher frequency than calculated, and a manifestation of CD in the colon with frequent fistula formation.

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