CYSTIC FIBROSIS OF THE PANCREAS

Report of a Case

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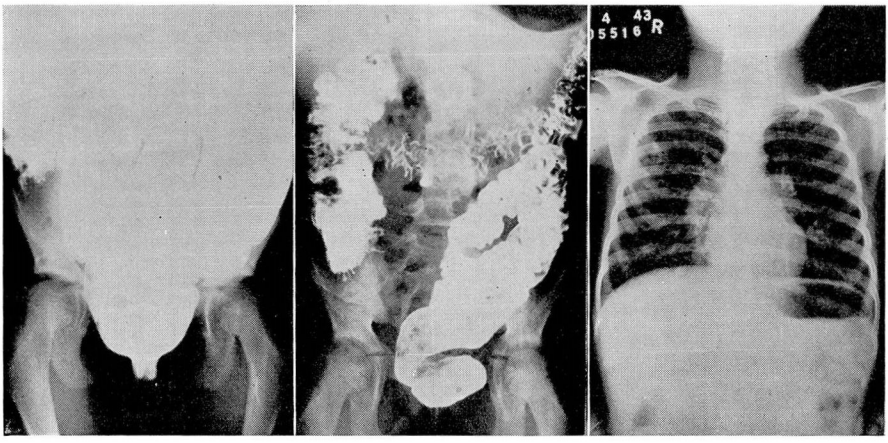
Cystic fibrosis of the pancreas is a fatal disease of infants and children characterized by a familial tendency, the celiac syndrome, and atypical bronchopneumonia. Prior to 1938 cystic fibrosis was confused with celiac disease but is now known to be one of a number of conditions which produce the symptom complex of the celiac syndrome. This case is reported because of the rareness of the condition.

CASE REPORT

A schoolgirl, aged 9, was admitted to the Cleveland Clinic Hospital on September 27, 1943.

She was hospitalized elsewhere at 1 year of age for malnutrition and again at the age of 6, when she had a chronic tracheobronchitis with a temperature of 104 F. A tentative diagnosis of celiac syndrome and pancreatic infantilism was made at that time. During the interval between admissions she averaged four stools a day but had eight large, foul, fatty stools when she included fats in her diet. She had a protuberant abdomen and moderate generalized adenopathy. The lungs were clear to percussion and auscultation. Laboratory examination revealed 4,210,000 erythrocytes and 69 per cent hemoglobin. The glucose tolerance curve was normal except for a rather low fasting sugar. Roentgenologic examination revealed pronounced increase in density of the right hilar shadow in the chest, opaque maxillary sinuses, and clouded ethmoid sinuses.



a. *b.* *c.*

FIG. 1. a. Large atonic colon filled with 1 gallon barium enema. b. Approximately 75 per cent expulsion of barium enema. c. Enlarged hilar glands and peribronchial infiltration.

Between her sixth and ninth years the patient averaged one to two stools daily but had constipation and pain just above the umbilicus. Her physician gave her liver injections and recommended a high protein, high carbohydrate, low fat diet.

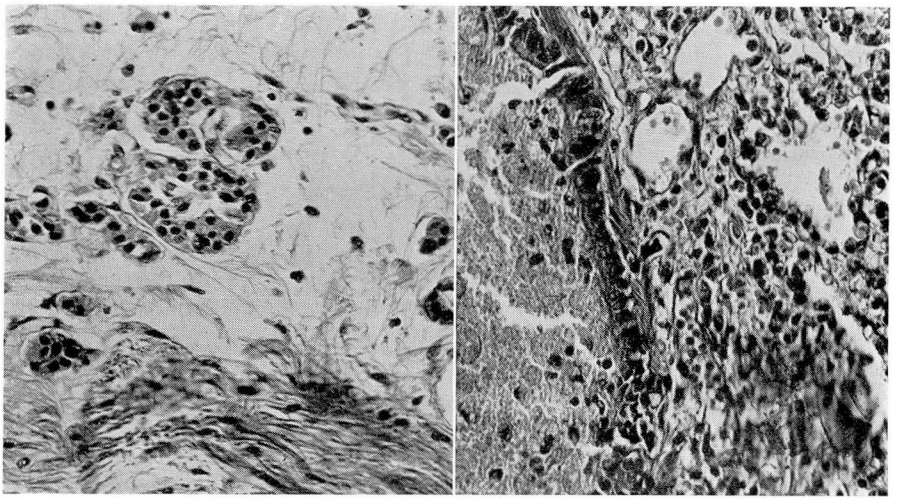
The child was admitted to the clinic at 9 years of age because of failure to gain weight, inability to digest food, attacks of abdominal pain, and a chronic morning cough. She was somewhat pale and had a rather protuberant abdomen. Her height was 49.5 inches and her weight 46 pounds. The tonsils were fairly large.

Chest examination revealed numerous moderately coarse, crepitant râles with increased breath sounds on the right to the fourth rib. A stereoroentgenogram revealed enlarged hilar glands and infiltration of the lungs (fig. 1c). The Mantoux test was negative, and no tubercle bacilli or fungi were found in three sputum specimens. No tubercle bacilli were found in the urine. The corrected sedimentation rate was 0.85 mm. per minute. Laboratory findings including blood calcium and blood phosphorus determinations were within normal limits.

Stool examination revealed numerous undigested meat fibers and slight increase in fatty acid crystals. Upon introduction of a 1 gallon barium enema a redundant atonic colon was found (fig. 1a). However, expulsion of 75 per cent of the barium was considered evidence against megacolon and was typical of celiac disease (fig. 1b).

During four months of observation the child's condition gradually became worse. Her temperature ranged from 100 to 101 F. daily, with increasing dyspnea and cough. At the last examination the right diaphragm was inactive.

The parents then took her to California, where she died suddenly about eight months after her first admission to the clinic. Postmortem examination was performed by Glen R. Halverson, M.D., of San Jacinto, California, who reported edema of the intes-



a. *b.*

Fig. 2. a. Cystic atrophy and fat infiltration. Almost total replacement of the glandular parenchyma by fatty tissue around normal islet tissue. b. Atypical bronchopneumonia with inflammatory infiltration. Bronchiole filled with purulent exudate.

tines and effusion of pleural, pericardial, and peritoneal cavities. The lungs were wet, and there was pus in the bronchioles. The pancreas was of average size, of lemon color, and cut as though it were fibrous tissue. Autopsy diagnosis was chronic bronchitis, metastatic calcification in kidneys, apparent congestive failure and cystic fibrosis of the pancreas.

C. S. Small, M.D., of Loma Linda, California and Harry Goldblatt, M.D., of Western Reserve University School of Medicine examined microscopic sections and agreed on the diagnosis of cystic fibrosis of the pancreas, although Dr. Goldblatt believed the case better called 'cystic atrophy and fat infiltration of the pancreas,' because there was no actual fibrosis in any of the sections examined (fig. 2a and b).

Because cystic fibrosis of the pancreas is a familial disease, it is important to note that a sister of the patient died of a similar disease at a much earlier age.

COMMENT

Although the celiac syndrome, or Gee-Herter disease, has been known since 1888, the first pathologic studies revealing the coexistence of fibrotic changes in the pancreas and the celiac syndrome were reported by Landsteiner[1] in 1905 under the heading of pancreatitis. In 1913 Garrod and Hurtley[2] reported a case of "congenital family steatorrhea," only one of two brothers having been observed. In 1925 Wolbach and Howe[3] demonstrated the presence of bronchiectasis in a high percentage of vitamin A deficient rats. In 1929 Kornblith and Otani[4] stated that both their reported case and that of Landsteiner represented inspissation of meconium into the pancreatic ducts, thus suggesting another possible cause for pancreatic fibrosis. In 1930 Harper[5] suggested that split fats in feces in celiac syndrome would differentiate the condition from pancreatic steatorrhea, because he thought that absence of pancreatic lipase resulted in unsplit fats in feces. This method of differentiation has been found unreliable, possibly because lipase of intestinal juice performs this function. In 1937 Sinclair and Smith[6] stated that fats are not absorbed until fatty acids undergo phosphorylation. Possibly exocrine pancreatic secretion is important in bringing about this phosphorylation, and therefore important in cystic fibrosis of the pancreas. In 1933 Ralli and others[7] demonstrated that pancreatectomized dogs fail to absorb vitamin A properly, a fundamental factor possibly related to the failure to absorb and utilize fats and in the production of symptoms and pulmonary changes in this disease.

Articles by Anderson[8], Thomas and Schlutz[9], and Harper[10] in 1938 pointed out the fact that some cases diagnosed celiac syndrome were actually cystic fibrosis of the pancreas. However, both conditions have many symptoms in common. In each the patient is young, usually has retarded physical development, passes large, foul, pale stools with intermittent diarrhea, and has a distended abdomen. According to Andersen[8], "Cystic fibrosis of the pancreas is a disease entity which

produces the celiac syndrome when the children survive the first year of life."

In 1939 Rauch and others[11] concluded that the pancreatic and pulmonary lesions are independent, but that they arise from a common congenital anomaly of the lungs and pancreas. In 1940 Cole and Howe[12] discussed six cases in adults of fatty liver with pancreatic atrophy. They considered these cases in adults to be similar to pancreatic fibrosis in children and pointed out that 60 per cent of Andersen's older group had fatty liver. They stated that it takes several weeks or months for pancreatic deficiency to produce a fatty liver. Experimental evidence indicates that survival and even weight gain are possible when only 10 per cent of pancreatic function is maintained.

The cause of this disease is not known, but Andersen[13] discussed (1) congenital defects, (2) inflammation of the pancreas in fetal life, and (3) vitamin A deficiency as possible causes. Atresia or even pseudoatresia of the pancreatic ducts[14,15], metaplasia of endothelial tissue in association with vitamin A deficiency, deposition of calcium in the pancreas, and the relative importance of disturbed metabolism have been discussed in recent years without the establishment of any definite etiologic factor. Snelling and Erb[16] recently queried whether vitamin A deficiency in the mother before childbirth might not be of etiologic importance.

The incidence may be as high as 3.3 per cent, reported by Andersen[8] in a careful survey of 605 microscopic sections of the pancreas at Babies Hospital in New York. That it is a disease of infancy is evidenced by the fact that 24 of her 49 patients died before 6 months of age. Andersen's oldest survivor lived until the age of 14½ years; the oldest of the 18 patients recorded by Menten and Middleton[17] was 10 years old. The patient presented in this article died at the age of 9.

That there is a strong familial tendency is demonstrated by our own patient, by Andersen (36 of 49 patients), and by Felsen and others,[18] who reported 4 instances with necropsy studies and 16 probable instances up to 1943. There seems to be no racial or economic group predilection, but 67 per cent of Andersen's patients were girls. We estimate that approximately 160 cases have been recorded to date.

Diagnosis. Although clinical diagnosis is difficult, differentiation of cystic fibrosis of the pancreas and the celiac syndrome has been made several times since 1938. Andersen said: "At present the differential diagnosis can be made with certainty only by examination of the duodenal juice for pancreatic enzymes or by microscopic examination of the pancreas. The best available proof of the diagnosis is the absence of

pancreatic trypsin and lipase in the duodenal juice." However, associated lesions such as chronic cough and roentgenologic evidence of bronchopneumonia or atypical pneumonia and occasionally bronchiectasis may suggest the possibility of pancreatic fibrosis. Chest symptoms may be the only or the primary presenting complaints. In a case reported by Mallory[19] chest lesions progressed from pneumonia, beginning with intersitial involvement of alveolar walls and peribronchial regions, to bronchiolectasis and bronchiectasis. Dilated bronchi and bronchioles become filled with purulent material caused by streptococci and secondary invaders such as staphylococci. Finally emphysema, atelectasis, and widespread lung fibrosis complicate the picture. A vitamin A tolerance test usually reveals a poor response both in cystic fibrosis of the pancreas and in the celiac syndrome. Attwood and Sargent[20] suggested that roentgenologic findings were in all lobes, as would be expected in a systemic disorder such as a vitamin A deficiency, but were more intense in the hilar regions. They also found disturbed intestinal motility and dilated loops of intestine with an occasional fluid level.

Fatty replacement of the pancreatic acinar parenchyma present in this case was observed in only 4 of Andersen's 49 cases. Dr. Small reported occasional spots of calcification in the epithelial linings of the kidney tubules of our case, a finding first recorded by Kennedy and Baggenstoss.[21] This may indicate some disturbance in the metabolism or excretion of calcium salts.

Salient differential points in distinguishing cystic fibrosis of the pancreas and the celiac syndrome have been compiled in the following table:

TABLE

CYSTIC FIBROSIS OF THE PANCREAS	Characteristics in Common	CELIAC SYNDROME
Familial tendency		
Onset usually in first year (insidious)		Onset rarely in first year
	Developmental retardation	
	Distended abdomen	
	Deficiencies: caloric, vitamin, and mineral	
Bulky stool (unsplit fat) Foul odor (putrefaction)	Diarrhea and constipation	Bulky, foul, and pale stool Frothy (fermentation)
Duodenal drainage Absent pancreatic enzymes		Normal
Abnormal x-ray of chest		Normal
Pathologic section, pancreas and lung, abnormal		Normal

Treatment. Because the disease is fatal, treatment is supportive. To supplement deficient pancreatic exocrine enzymes, pancreatin, lipocaic, or crude pancreatic extracts may be given in suitable quantities. In an attempt to limit metaplasia, vitamin A is given both orally and subcutaneously in therapeutic doses. Andersen suggested mother's milk and cod liver oil for infants in their first few months of life and the subsequent use of a high carbohydrate, high protein, low fat diet with caloric intake above the average requirement according to age.

SUMMARY

This case of cystic fibrosis of the pancreas reported with roentgenologic and necropsy findings was unusual in that the pancreatic acinar tissue was largely replaced with fat rather than fibrous tissue and that the patient lived an unusually long time. The disease was characterized by insidious onset of developmental retardation, diarrhea or bulky foul stools, and chronic respiratory infection. Although no clinical or pathologic studies were made on the patient's older sister, she reputedly died of a similar condition.

In infants with a feeding and developmental problem and an associated chronic pneumonic process or bronchiectasis, cystic fibrosis of the pancreas should be considered in the differential diagnosis.

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CYSTIC HYGROMA

Report of Three Cases

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Cystic hygroma is a benign disfiguring tumor of the neck, axilla, or chest wall and is thought to originate in anomalous development of the lymphatic system. Although the term *cavernous lymphangioma* is sometimes used, *hygroma*, derived from the Greek and meaning "moist tumor," is preferred.

EMBRYOLOGY

According to Jordan and Kindred[1] the lymphatic system develops in one of the two following ways:

"There has long been a question as to whether the lymphatic channels of the embryonic body develop as centrifugal endothelial sprouts from existing venous channels or by the fusion of isolated mesenchym-lined spaces, which upon fusion grow centripetally and transitionally