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APPENDICITIS IN CYSTIC FIBROSIS: A CHALLENGING DIAGNOSIS

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Abstract: *Cystic fibrosis (CF) is the most frequent autosomal recessive chronic disease in Caucasians caused by defects in the Cystic Fibrosis Transmembrane Conductance Regulator (CFTR), that controls chloride and bicarbonate transport through cell membranes. CF is characterized by limited life expectancy due to multisystemic involvement, morbidity and mortality being influenced by progressive, obstructive lung disease, pancreatic insufficiency and associated comorbidities as diabetes and liver disease. Gastrointestinal complications are common and diagnosis can be challenging. We describe a case report of a young female adolescent with severe lung disease, diabetes and biliary cirrhosis that presented with a pulmonary exacerbation and developed gastrointestinal symptoms dominated by abdominal pain. Diagnosis was challenging, mainly because of associated comorbidities and atypical presentation of gastrointestinal symptoms. Team approach and careful monitoring resulted in successful management of the case.*

Key words: *cystic fibrosis, appendicitis, diagnosis*

1. Introduction

Cystic fibrosis (CF) is a multisystemic, autosomal recessive disorder [3]. The prevalence in Caucasians is approximately 3 to 3000 live birth [12].

The CFTR (cystic fibrosis transmembrane conductance regulator) gene mutations cause changes in the protein that controls chloride and bicarbonate transport through cell membrane [15]. This dysfunction produces dehydration in the cells and accumulation of viscous secretions with impairment in mucociliary clearance [8] in many organs such as: lungs, pancreas, liver, intestine [7].

Due to progress in genetics that facilitates diagnosis even in atypical forms of the disease and multidisciplinary care in specialized centers, life expectancy

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significantly increased, in many western centers the number of adult patients surpassing pediatric patients. Access to complex therapies and care, including gene modulators, became easier, making the progress of the disease more benign compared to 50 years ago [12].

The chronic obstructive lung disease is the main cause of morbidity and mortality. Gene dysfunction leads to bronchial bacterial colonization that sets a vicious circle of inflammation-infection, that will determine chronic infection with specific, multidrug-resistant germs and destruction of the lungs [2], [12]. This irreversible process leads to need for lung transplant, usually already in young adults, depending on the speed of disease progression. It has been demonstrated that by the age of 3 years there already exists mucus obstruction, bronchiectasis and colonization with *Pseudomonas aeruginosa* or *Staphylococcus aureus,* by the age of 5 years, the lungs structure being already altered [12].

Cystic fibrosis is also characterized by extrapulmonary manifestations: pancreatic insufficiency (90% of patients), diabetes, meconium ileus, liver disease with biliary cirrhosis and portal hypertension, [8] male infertility [2]. CF is the most frequent cause of exocrine pancreatic insufficiency. The ion channel dysfunctions lead to thickening of the pancreatic secretion, that determines obstruction of the lumen, acinar cell atrophy, fibrosis and cysts formation. [4] Pancreatic insufficiency can determine distal intestinal obstruction syndrome, an entity more common in adolescents and adults [15]. Liver disease is described even before the prepubertal period and is caused by the viscous bile secretion that leads to accumulation of toxic bile acids, inflammation, infection and, finally fibrosis with biliary cirrhosis.

Because of local mechanisms related to the genetic defect in the gastrointestinal tract, some complications may appear in adults, but even pediatric patients. Gastroesophageal reflux [11], distal intestinal obstruction syndrome [3], gallstones [1], pancreatitis in pancreatic sufficient patients [14] celiac disease, [18] appendicitis [5] and fibrosing colonopathy. [9] may complicate the outcome of CF patients.

Usually, they are accompanied by abdominal pain and tenderness, which may be difficult to interpret in many cases.

2. Case Report

We are presenting a case report of a 17 years old female adolescent admitted to the Clinical Emergency Children's Hospital of Brasov for cough, respiratory distress and fever. She was diagnosed with cystic fibrosis, homozygous for del F508, as she was 7 months old and has been monitored since then. Her medical history includes frequent pulmonary exacerbations, chronic colonization with *Pseudomonas aeruginosa,* poor nutritional status and, recently diagnosed cystic fibrosis associated diabetes. She is treated with pancreatic enzymes replacement therapy, inhaled Pulmozyme and Tobramycin, Ursofalk, Azithromycin, fat soluble vitamins and LANTUS insulin. To date, because of being from a poor community with inadequate living conditions, with poor compliance to treatment, this led to a rapid deterioration of her health status, due to severe lung disease, diabetes and liver disease.

During the current hospitalization, she presented with a pulmonary exacerbation with mild respiratory failure. The clinical examination showed a poor nutritional status, weight=38kg, height=160cm, BMI=14.8, pale skin, bronchial obstruction, respiratory distress, subcostal retractions, 90% oxygen saturation in room air and bilateral crackles. The examination of the abdomen was normal, without pain on palpation, normal bowel movements and no micturition disorders. Neurological examination was also normal.

Laboratory findings at admission showed a mild inflammatory syndrome, elevated total and direct bilirubin, respiratory acidosis and metabolic alkalosis.

Table 1

Laboratory findings at admission

	At admission	**Normal range**
Leucocytes	10.090/ µl	4500-13500/ µl
CRP	4.13 mg/dl	0-1 mg/dl
Total bilirubin	1.27 mg/dl	0-1.2 mg/dl
Conjugated bilirubin	0.34 mg/dl	0-0.52 mg/dl
Unconjugated bilirubin	0.92 mg/dl	0-0.5 mg/dl

	At admission	**Normal range**
pH	7.33	7.35-7.45
pCO2	57.4 mmHg	35-45 mmHg
PO2	36 mmHg	83-108 mmHg
HCO3	30.5 mmol/l	22-26 mmol/l

Sputum culture revealed *Pseudomonas aeruginosa* and *Methicillin-Susceptible Staphylococcus Aureus.*

The chest x-ray showed multiple bronchiectasis and a consolidation in the right upper lobe.

Based on the patient's history, the clinical examination and the laboratory findings the diagnosis of pulmonary exacerbation was confirmed, and treatment was started with intravenous antibiotics (Ceftazidime and Meropenem), systemic corticosteroids, inhaled bronchodilator (salbutamol), inhaled Colistin and continuation of chronic medication. The abdominal ultrasound showed a large liver, with irregular contour and micronodular structure with increased reflexivity, the spleen with a long axis of 12.5 cm and average amount of peritoneal fluid. The bowel loops were relaxed with dense, hyperechogenic content and the appendix was not visualized.

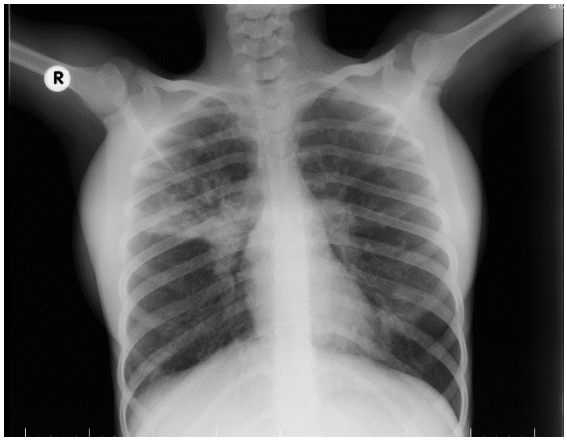

Fig. 1. *Chest x-ray at admission*

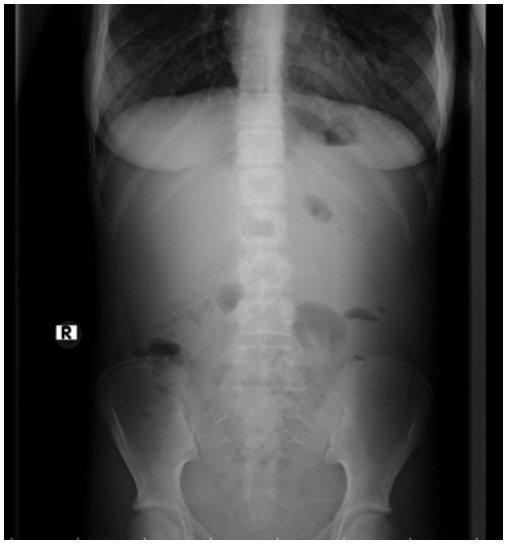

Fig.2. *Abdominal plain radiography at admission*

During the first days of admission the respiratory status improved, as well bronchial obstruction and blood sugar levels were normal with insulin treatment.

After 6 days, during the night, she started vomiting and having diffuse abdominal pain with no bowel movements for 24 hours. The next day pain was localized in the upper abdomen and right iliac fossa. Repeated laboratory tests showed an increased level of leukocytes and transaminases, metabolic alkalosis, but normal inflammatory markers.

Table 2

Laboratory findings 7 days after the admission

	7 days after the admission	**Normal range**
Leucocytes	24.000/ µl	4500-13500/ µl
CRP	0.21 mg/dl	0-1 mg/dl
Bilirubin	1.88 mg/dl	0-1.2 mg/dl
Conjugated bilirubin	0.51 mg/dl	0-0.52 mg/dl
Unconjugated bilirubin	1.37 mg/dl	0-0.5 mg/dl
AST	46 U/l	0-34 U/l
ALT	116 U/l	0-31 U/l
Amylase	44 U/l	0-100 U/l

	7 days after the admission	**Normal range**
pH	7.47	7.35-7.45
PCO2	40.8 mmHg	35-45 mmHg
PO2	53 mmHg	83-108 mmHg
HCO3	29.7 mmol/l	22-26 mmol/l

In this situation, with sudden onset of the symptoms, the following diagnoses were considered:

- distal intestinal obstruction syndrome
- acute pancreatitis
- acute gastritis
- acute appendicitis
- decompensated liver damage (at initial presentation, ascites fluid was present, transaminases increased, serum protein electrophoresis was modified)

Treatment with Pantoprazole, Metoclopramide and hydroelectrolytic rebalancing infusion was added.

After the surgical examination the diagnosis of appendicitis was suspected, and appendectomy was performed. Open appendectomy was performed, with removal of the appendix using the antegrade technique.

The intraoperative appearance of the appendix was large, turgid, with false membranes (phlegmonous appearance) with multiple coprolites in the lumen.

Postoperative outcome was improving slowly with persistent peritoneal fluid for 5 more days. After postoperative day 4, her general status improved, the bowel movements were normal and oral food intake was permitted. She was discharged after 14 days of hospitalization with the recommendation of continuing her chronic treatment for CF, at home.

3. Discussions

Taking into account that the presented CF patient evolved by having acute abdominal pain during the hospitalization for a pulmonary exacerbation, we will discuss causes of abdominal pain in such patients. The most frequent cause of abdominal pain in cystic fibrosis is the distal intestinal obstruction syndrome [7]. The entity appears when bowel content becomes viscous and leads to intestinal obstruction, due to the poor chloride secretion that determines poor water secretion. It is described in 10-15% of the patients with cystic fibrosis. Usually, after the first episode, the risk of recurrence is 10 times higher [13].

The distal intestine obstruction syndrome (DIOS) can be complete or incomplete and can be differentiated from a simple constipation by the rapid onset of the symptoms. [10] Patients present to the hospital with recurrent abdominal pain, vomiting, abdominal distension, palpable mass in the right lower abdomen and absence of the bowel movements [13]. The bowel movements can be present in the first days in incomplete DIOS [17]. The abdominal x-ray may reveal air-fluid levels and dilated intestinal loops. First line therapy is orally administered polyethylene glycol 2g/kg/day [16]. Orally or by nasogastric tube, Gastrografin, (50 ml in 200ml water for children under 6 years or 100 ml in 400 ml water for children greater than 6 years) may be used. For more severe cases, orally lactulose and enemas with Gastrografin are recommended [10]. Surgical treatment is indicated only when medical treatment is not effective or in case of complications such as intussusception or volvulus [10].

Fibrotic colonopathy is a complication described in cystic fibrosis patients caused by excessive intake of pancreatic enzymes that determine strictures mostly in the right side of the colon.

Gastroesophageal reflux appears frequently and is caused by increased intraabdominal pressure because of chronic couch, esophageal dysmotility or

therapies that decrease the pressure of the esophageal sphincter (aminophylline).

Acute appendicitis is a rare complication in patients with cystic fibrosis with a prevalence of 3% compared with 7% in general population. This low prevalence is due to repeated antibiotic therapies that decreases local inflammation and the protective effect of the mucus of the appendix lumen [5]. The appendix content, abnormal thickened in CF patients, can lead to a large appendix without evolving to appendicitis. A normal appendix in these patients may have a diameter longer than 6 mm, while in a patient without cystic fibrosis 6 mm is the highest limit [6]. Diagnosis of appendicitis is difficult and often late. Antibiotic therapy for pulmonary exacerbations may mask gastrointestinal pathology until complications as abscesses or perforation can occur [1]. A retrospective study on 1224 patients demonstrated that there is a delay between the onset of the symptoms and the diagnosis even of 12 days, so the perforation can occur in approximative 80% cases.

In the presented case, diagnosis of appendicitis was made relatively quickly after the starting symptoms, even this being not the first option in our medical judging.

The medical condition of the patient was taken into account, with epigastric and right quadrant abdominal pain, constipation, and known liver disease. The initial suspicion was of DIOS and possibly, of aggravation of liver disease with ascites. Laboratory finding were also in favor of that and excluded acute urinary tract infection.

Ultrasound examination in this case was not very helpful, because of intestinal content that masked the appendix.

Abdominal pain in the described patient was initially in the upper abdomen and suggested an acute gastritis.

Appendicitis was suspected by the surgeon after repeated examinations and, at the time of confirmation, was considered atypical.

4. Conclusions

Appendicitis may be considered a difficult diagnosis even in patients that have no other gastrointestinal conditions. Often, abdominal pain has an atypical localization and may disappear after a first attach.

More so, appendicitis is rare in cystic fibrosis.

Abdominal pain in CF patients may have several causes, usually related to malabsorption, constipation or poor intake of pancreatic enzymes.

The presented case, being initially treated for a pulmonary exacerbation, the reason of hospital admission, could have had a masked inflammation of the appendix, fact thar has been mentioned in medical literature.

When diagnosis of appendicitis was made, and surgery performed with no complications, recovery followed soon and the patient could continue chronic treatment for cystic fibrosis and related comorbidities, being discharged in a relatively good shape.

We consider that presentation of appendicitis was atypical and that team approach, frequent and close examination and follow up of this patient with severe cystic fibrosis and comorbidities, were the

key of a successful diagnosis and treatment.

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