

CASE REPORT

Celiac Disease and Cystic Fibrosis: Challenges to Differential Diagnosis

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Cystic fibrosis and celiac disease were considered a single clinical entity for many years. Differentiation between the diseases occurred some time in the 1930s of the 20th Century. Both diseases may present the intestinal malabsorption syndrome and similar clinical manifestations that contribute to difficulties with clinical distinction. We describe a report of two patients with initial diagnosis of cystic fibrosis, who were subsequently diagnosed with celiac disease.

These case reports emphasize the possibility of false positivity being shown in the sweat test in CD, which may result in delayed diagnosis and inadequate management of this disease.

INTRODUCTION

Cystic fibrosis (CF) is a chronic and progressive autosomal recessive genetic disease that affects various organs and systems of the body¹. According to the Cystic Fibrosis Foundation, approximately 70 thousand persons in the world have CF.² In Brazil, the most recent data of the Brazilian Register of Cystic Fibrosis (REBRAFC), accounted for approximately 4 thousand patients.³ Celiac disease (CD) is a systemic disease mediated by permanent susceptibility to gluten, triggered by autoimmune mechanisms in genetically predisposed individuals.¹ The prevalence of CD is estimated at around 1% of the population worldwide.⁴ CF and CD were recognized as a single clinical entity for many

years, since the intestinal malabsorption syndrome occurs in both⁵, and the clinical manifestations of the diseases may be similar, which contributed to the difficulty in distinguishing between the two illnesses in the past⁶.

At present there are specific diagnostic methods for each disease. According to the Guidelines of the European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN, 2012), in patients with gluten-dependent symptoms, the diagnosis of CD may be confirmed by elevation in the levels of antibodies specific for CD and the presence of alleles HLA-DQ2/DQ8, which may eliminate the need to perform intestinal biopsy in these cases. Histopathological exam must be

performed when the above mentioned studies are not available.⁷ As criteria for the diagnosis of CF, the Cystic Fibrosis Foundation Consensus Panel established the presence of a phenotypical clinical condition or family history of CF, or positive newborn screening associated with the elevation of chloride concentration in sweat or identification of two mutations of CFTR; or *in vivo* demonstration of nasal epithelial ion transport abnormalities.⁸

As reported by Genkova (2013), the sweat test may be false positive in the presence of the malabsorption syndrome⁹ which may raise doubts as regards diagnosis between the two diseases. This emphasizes the importance of careful clinical observation in medical practice. The possibility of diagnostic confusion between these diseases may delay the adequate treatment of each disease. This report describes two patients with initial diagnosis of cystic fibrosis who received diagnostic confirmation of CD during follow-up, therefore the diagnosis of CF was excluded. The free and informed consent

of the persons responsible for the patients was obtained in the preparation for this study.

CASE REPORT 1

The patient, an eleven-month-old girl, was transferred to the University Hospital Professor Edgard Santos of the Federal University of Bahia (HUPES/UFBA) in Salvador, Brazil, for investigation of severe protein-energy malnutrition (PEM) and treatment for pneumonia. At the time, she presented a positive sweat test (chlorine = 69/66 mEq/L), that had been performed for diagnostic investigation of the severe PEM at the above mentioned hospital. On admission, productive coughing with a duration of 15 days was reported, and the patient presented with apathy, abdominal distension, and important delay in neuro-psychomotor development. She had been exclusively breastfed up to the 15th day of life, and was then put onto a first milk formula that she used until she was six months old. From this age onward, the first milk formula was replaced with whole cow's milk associated with cereals. On

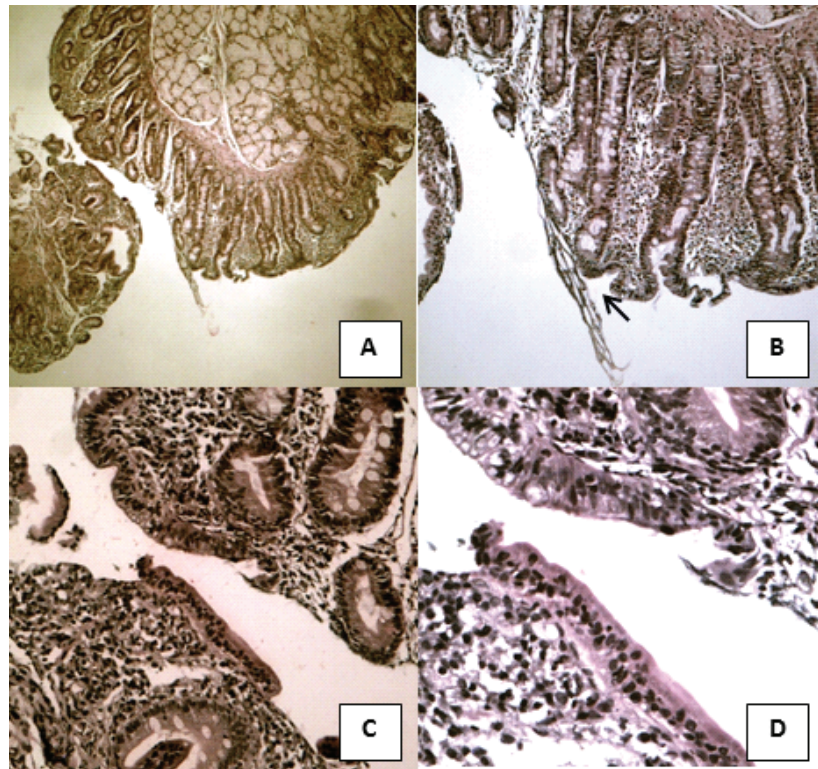
Table 1. Main Complementary Exams in Case 1

Exam	Result
High digestive endoscopy	Duodenum with ample and distensible bulb, mucosa with normal aspect, in addition to mucosa with whitened aspect, with pavement-like pattern, with apparent reduction of the folds and villi in the second portion of the duodenum, with the aspect being suggestive of celiac disease.
IgA anti-endomisium antibodies (RV: negative – Titer < 1/5)	Reagent 1:160
IgG anti-endomisium antibodies (RV: negative)	Reagent 1:20
IgA anti human tissue transglutaminase (RV: negative < 7 U/ML) Enzymatic Immunoassay method	28 UI/ml.
IgG anti human tissue transglutaminase (RV: negative < 10 U/ML) Enzymatic Immunoassay method	11 UI/ml.
Total IgA (RV: 25-141 mg/dl)	76 mg/dl
IgA anti-gliadine antibodies (RV: < 23 UI/ml.)	213.0
IgG anti-gliadine antibodies (RV: < 28 UI/ml.)	133.0
Fecal Elastase (RV: > 200 mcg/gram feces)	500 mcg/gram feces
Fecal Steatocrit (RV: 2%)	3.72%

RV: Reference value.

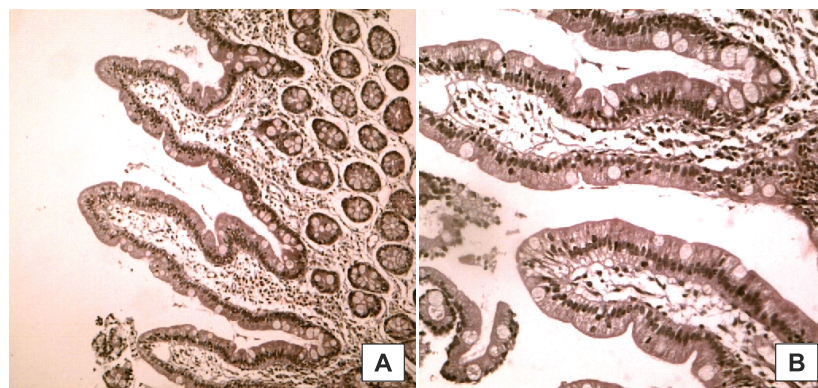
physical exam, she weighed 4.750 kg, presented with a weight/age ratio (W/A) $Z = -4.84$; mean 61.1 cm, height/age ratio (H/A) $Z = -4.68$ and weight/height ratio (W/H) $Z = -2.98$ (WHO, 2006).¹⁰ She showed good oxygen saturation in ambient air, and lung auscultation revealed fine crackle and wheezing, particularly on the right side. Radiography of the thorax was performed, which showed opacity

in the right superior lobe. Antibiotic therapy was administered for pneumonia, for 10 days. Nutritional recovery therapy was initiated with a hypercaloric diet, consisting of an initial rate of 78.5 Kcal/kg/day and Total Energy Value (TEV) of 373 Kcal/day. The child developed with clinical improvement, but maintained an unsatisfactory weight gain. A new positive sweat test was performed (chlorine = 70



A. General View of Duodenum (Objective at 4x magnification). Alteration observed in crypt:villous ratio, with prevalence of crypts. **B.** Objective at 10x magnification. Arrow indicates villous remainder. **C.** Objective at 20x magnification. Flattening of mucosa is observed. **D.** Objective at 40x magnification. Loss of villi, lymphoplasmocyte infiltrate in lamina propria.

Figure 1. Histopathological Findings of Case 1.



A. Objective at 10x magnification. Observe normal villa in healthy duodenum. **B.** Objective at 20x magnification. Absence of intra-epithelial lymphocytes in lamina propria of normal duodenum.

Figure 2. Histopathological images of normal duodenum.

and 73 mEq/L). Diagnosis of CF was established, and pancreatic enzyme replacement therapy (PERT) was initiated, at the dose of 1000 UI lipase per gram of dietary fat offered. She was discharged after 14 days of hospitalization on ERT and prescription of polyvitamins, folic acid, and diet with high calorie rates of 230% for her age. She was referred to the Multidisciplinary Outpatient Clinic for CF ("Ambulatório Multidisciplinar para FC - AMFC") for follow-up. During follow-up, low weight gain was observed in spite of ERT, and the nutritional input higher than that recommended for fibrocystic patients.

After 18 months, she was again hospitalized for nutritional therapy and diagnostic reassessment, and was investigated for CD. She was submitted to high digestive endoscopy with biopsy and specific antibody dosage, which confirmed the diagnosis of CD. A new sweat test was performed showing a dubious result (chlorine = 45 and 44 mEq/L). The study of mutation Phe508del was negative. She was discharged weighing 6.640 kg (W/A) $Z = -3.72$, measuring 68.4 cm (H/A) $Z = -4.24$ and (W/H) $Z = -1.7498$ (WHO, 2006).¹⁰ A gluten-free diet and calorie rate of 200% for her age was indicated. She developed with significant progress in neuro-psychomotor development, good weight gain, and nutritional recovery, but maintained a low stature. At 26 months of age, she presented with a weight of 9.975 kg, (W/A) $Z = -1.52$, height of 76 cm (H/A) $Z = -3.73$ and (BMI/A) $Z = +1.36$ (WHO, 2006).¹⁰ Complementary exams are listed in **Table 1**.

The histopathological findings are shown in **Fig. 1**. Under microscopy, intense chronic duodenitis with accentuated villus atrophy (villus to crypt ratio 1/1) was observed. Images of the normal duodenum for purpose of comparison are shown in **Fig. 2**.

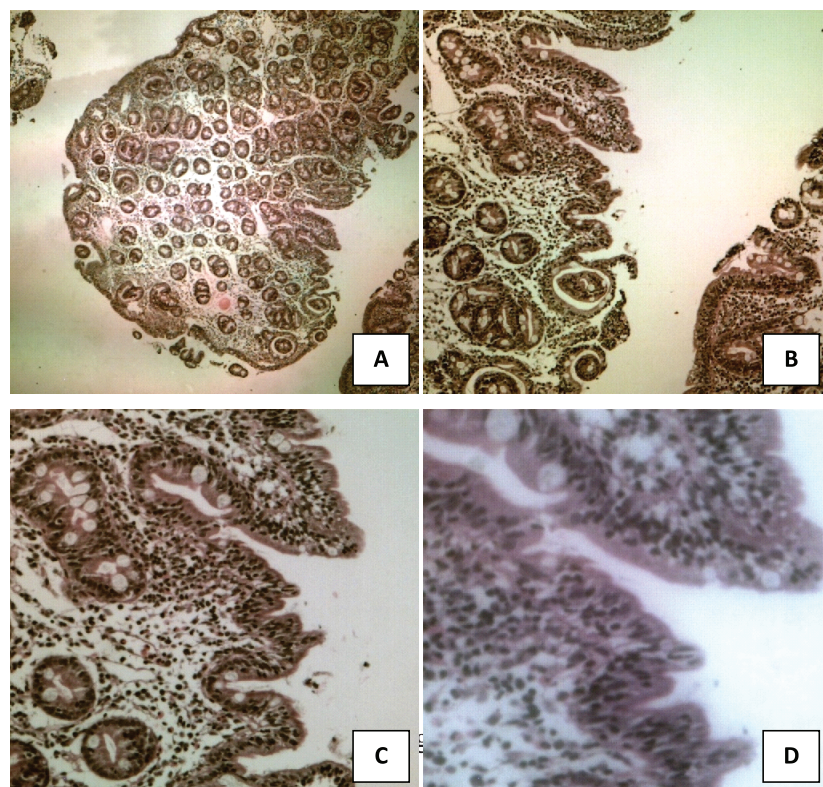
CASE REPORT 2

The patient, a 22-month-old girl, was referred for follow-up to the AMFC of the HUPES/UFBA, because she was diagnosed with CF. She had a history of repeated respiratory infections, wheezing, recurrent diarrhea, vomiting, abdominal distension and insufficient weight gain since 5 months of age. She was exclusively breastfed up to 3 months of life, and was then put onto whole milk associated with cereals. At 6 months of age, she began to receive mashed vegetables and fruits. Her history showed a report of increased abdominal volume after eating foods containing wheat. At 20 months of age, she was hospitalized in the pediatric hospital for pneumonia associated with diarrhea, abdominal distension and anemia. She received antibiotic therapy for 10 days. At that time, the diagnosis of suspected CF was made, and sweat tests were performed and showed positivity in two samples (1st test: chlorine = 77 and 74 mEq/L; 2nd test: chlorine = 62 and 68 mEq/L). On physical exam during the first consultation at AMFC, she weighed 9.920 kg (W/A) $Z = -1.35$, measuring 81.5 cm; (H/A) $Z = -1.55$ and (W/H) $Z = 0.71$ (WHO, 2006).¹⁰ Accentuated abdominal distension was noted. The remaining physical examination data were unaltered. The clinical data lead to the suspicion of CD. She

Table 2. Main Complementary Exams in Case 2

Exam	Result
High digestive endoscopy	Non erosive duodenitis and nodular lymphoid hyperplasia of the duodenum
IgA anti-human tissue transglutaminase (RV: < 20 U) Method: ELISA	234 U
IgA anti-human tissue transglutaminase (RV: < 20 U) Method: ELISA	21.3 U
IgA anti-endomisium antibodies (RV: negative – Titer < 1/5)	1/320
Total IgA (RV: 25-141 mg/dl)	165.3 mg/dl
Fecal Steatocrit (RV: 2%)	2.1%

RV: Reference value



A. General view of duodenum (magnification 4x). Note the flattening of villi. **B.** Objective at 10x magnification. Atrophic villi. Observe presence of crypts only. **C.** Objective at 20x magnification. **D.** Objective at 40x magnification. In images C and D, presence of large quantity of intra-epithelial lymphocytes may be observed in lamina propria, demonstrating activity of the disease.

Figure 3. Histopathological findings in Case 2.

was hospitalized for diagnostic investigation by means of high digestive endoscopy, with biopsy and specific antibody dosage, which confirmed the disease. She was discharged after 15 days of hospitalization with restriction on gluten in the diet, and with clinical follow-up by the pediatric nutritional team at the outpatient clinic. At 32 months of age, she remained eutrophic, weighing 11.6 kg (W/A) $Z = -0.99$, measuring 89.5 cm; (H/A) $Z = -0.96$ and (W/H) $Z = 0.71$, according to the Z score (WHO, 2006).¹⁰ The last sweat test performed was negative (chlorine = 27 and 24 mEq/L).

The main exams the patient underwent are shown in **Table 2**.

In **Fig. 3**, the findings of the pathological anatomy are presented, showing chronic duodenitis with intense villus atrophy and intra-epithelial lymphocytosis.

DISCUSSION

CF was initially described in 1938, when pancreatic fibrosis was noted in the necropsies of patients clinically diagnosed with celiac syndrome.⁵ CF is a

disease with characteristics similar to those of CD. In fact, the intestinal malabsorption syndrome occurs in both,¹¹ and the sweat test may be falsely positive in the presence of the malabsorption syndrome.⁹ This may lead to doubtful diagnoses between the two diseases and should alert the doctor to make a judicious diagnosis of the two conditions.

Both patients described initially presented two positive sweat tests. The first report concerning a patient in a severe state of malnutrition, which could elevate chlorine levels in sweat, was made by Mace et al (1971).¹² However, in spite of the description of chlorine level elevation in the sweat of undernourished patient, in comparison with eutrophic children, these are not expected to attain values compatible with those in CF.¹² The development of Case 1 suggested that in addition to CD, malnutrition may have contributed to elevation of chlorine in the sweat, since the exam showed normality after the improvement in nutrition and exclusion of gluten from the diet.

In the report on Case 2, the history of abdominal distension associated with the ingestion

of gluten-containing foods drew attention, and led to the suspicion of CD and the possibility of the sweat test being falsely positive. Normalization of the exam after excluding gluten from the diet corroborated the initial clinical impression and highlighted CD among the different clinical conditions that may accompany elevations of electrolytes in the sweat.¹³ The two patients herein reported were submitted to intestinal biopsy for diagnostic confirmation, because research of the HLA-DQ2/DQ8 alleles is not available at the center where they were treated. As execution of allele exams is restricted to more developed centers, this justified the use of a more invasive exam to confirm the diagnosis of CD.

On the other hand, association between these two diseases has been reported; however, their coexistence in one and the same individual has been described as a casual finding.¹¹ Some authors have discussed the hypothesis of a non-casual link between them, making diagnosis of the two diseases more challenging.¹¹

The frequency of being simultaneously affected by the two pathologies is unknown, but it has been estimated that the incidence of CD among patients with CF varies between 1:87 to 1:373.⁶ In 2009, Fluge et al. conducted a multicentric study, performing screening for CD in patients with CF, and found a prevalence of 1.2%.¹¹

Diagnosis of CF in patients with CD has also been described. In 1999, Venuta et al. described a 14-month-old patient with chronic diarrhea, recurrent respiratory infections and growth deficit, who had a confirmed diagnosis of CD. The child developed with poor clinical response to the restriction of gluten in the diet. Later diagnostic investigation confirmed CF, revealing an association between the two diseases.¹⁴

There is no consensus in the literature about when to investigate CD in patients with CF. Genkova et al. (2013) suggested investigation in all patients with CF that present the following clinical manifestations: intestinal malabsorption without improvement with standard treatment, delay in neuro-psychomotor development, co-morbidity that predisposes to autoimmune phenomena (diabetes mellitus type 1, juvenile idiopathic arthritis, autoimmune thyroiditis, Down syndrome), persistent anemia ferropriva, first episode of hypoprothrombinemia or any other sign of hepatic involvement.⁹ In the cases herein related, research for CD was performed due to poor response to treatment in the first case, and

due to the clinical history suggestive of CD in the second case.

These case reports emphasize the possibility of the sweat test being falsely positive in CD, which may confound the medical conduct of the case, delaying diagnosis and adequate treatment of this disease. However, the possibility of coexistence between the two diseases must also be borne in mind. Pediatricians must consider the investigation of CD in patients with CF, who do not present with good weight-height development, or have poor control of symptoms of malabsorption in spite of receiving adequate therapy.

CONCLUSIONS

These case reports emphasize the possibility of the sweat test being falsely positive in CD, which may confound the medical conduct of the case thus delaying diagnosis and adequate treatment of this disease. However, the possibility of coexistence between the two diseases must also be borne in mind. Pediatricians must consider the investigation of CD in patients with CF that do not present with good weight-height development, or have poor control of symptoms of malabsorption in spite of receiving adequate therapy.

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Целиакия и кистозный фиброз: возможности, стоящие перед дифференциальным диагнозом

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Кистозный фиброз и заболевание целиакия считаются клиническим проявлением в течение многих лет. Дифференциация заболеваний возникла ориентировочно в 30-х г.г. 20 века. Оба заболевания могут сопровождаться синдромом кишечной мальабсорбции и схожими клиническими проявлениями, которые способствуют возникновению затруднений при клиническом разграничении. Описывается доклад о состоянии двух пациентов с первоначальным диагнозом "кистозный фиброз", у которых впоследствии была диагностирована целиакия. В данных докладах о клинических случаях обращается внимание на возможность получения ложноположительного результата при взятии пробы пота на целиакию, что может привести к задержке с установлением диагноза и неподходящему лечению этого заболевания.