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Co-occurrence of Type 1 Diabetes, Celiac Disease, and Genetically Confirmed Cystic Fibrosis in an Adolescent: A Case Report

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ABSTRACT

The coexistence of type 1 diabetes mellitus (T1DM), celiac disease (CD), and cystic fibrosis (CF) is exceptionally rare in pediatric patients. We report the case of a 16-year-old girl diagnosed with T1DM at the age of 2 years and CD at 6 years through routine screening. Despite regular multidisciplinary follow-up and appropriate management, persistent gastrointestinal symptoms continued for several years. At the age of 13 years, borderline sweat chloride levels together with severe pancreatic exocrine insufficiency prompted genetic testing, which confirmed cystic fibrosis. The overlapping gastrointestinal manifestations of celiac disease and cystic fibrosis may have contributed to a prolonged interval between the diagnosis of celiac disease and the eventual recognition of genetically confirmed cystic fibrosis. Pancreatic enzyme replacement therapy resulted in partial clinical improvement. This case illustrates the diagnostic challenges created by overlapping gastrointestinal manifestations in children with multiple chronic disorders. Although the coexistence of type 1 diabetes mellitus, celiac disease, and cystic fibrosis has been previously reported, detailed pediatric case reports emphasizing delayed recognition of genetically confirmed cystic fibrosis remain scarce in the literature.

KEYWORDS. Adolescent; Celiac Disease; Cystic Fibrosis; Diagnostic Challenge; Pancreatic Exocrine Insufficiency; Type 1 Diabetes Mellitus.

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INTRODUCTION

Type 1 diabetes mellitus (T1D) is one of the most common chronic autoimmune diseases of childhood and is strongly associated with other autoimmune disorders, particularly celiac disease (CD). Because of their shared genetic susceptibility, routine screening for CD is recommended in children with T1D. [1] Celiac disease is a chronic immune-mediated enteropathy affecting approximately 1% of the general population worldwide. It is characterized by gluten-induced inflammation of the small intestine, resulting in malabsorption and a broad spectrum of gastrointestinal and extraintestinal manifestations. [2]

Cystic fibrosis (CF), in contrast, is an autosomal recessive disorder caused by pathogenic variants in the CFTR gene. Defective chloride transport leads to abnormal mucus production, chronic pulmonary disease, and pancreatic exocrine insufficiency. [3,4] Clinical presentation is variable, and some individuals may present later in childhood or adolescence and may have sweat chloride concentrations in the intermediate range. [3]

Although the coexistence of T1D and CD is well recognized, the coexistence of T1D, CD, and CF is exceptionally rare. It presents a considerable diagnostic challenge because CF and CD share several gastrointestinal manifestations, including malabsorption, abdominal discomfort, and poor nutritional status. Persistent symptoms may therefore be mistakenly attributed to the known autoimmune disease, delaying the diagnosis of CF.

According to the International Diabetes Federation Diabetes Atlas (11th edition), type 1 diabetes remains one of the most common chronic diseases of childhood worldwide. [5] We report the case of an adolescent girl with type 1 diabetes mellitus (T1DM) and celiac disease (CD) in whom genetically confirmed cystic fibrosis (CF) remained unrecognized for several years despite regular multidisciplinary follow-up. To place this case in the context of the existing literature, we performed a structured literature search in PubMed/MEDLINE using combinations of the terms "cystic fibrosis," "celiac disease," "coeliac disease," "type 1 diabetes," "type 1 diabetes mellitus," "insulin-dependent diabetes," and "autoimmune diabetes." Although previous publications have documented the coexistence of these disorders, detailed pediatric case reports that emphasize the diagnostic challenges

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posed by overlapping gastrointestinal manifestations remain scarce in the literature. This report highlights the importance of maintaining a broad differential diagnosis when persistent symptoms cannot be fully explained by pre-existing autoimmune disease.

CASE

A female patient was born after an uncomplicated full-term pregnancy and vaginal delivery. There was no known family history of cystic fibrosis, celiac disease, type 1 diabetes mellitus, or other autoimmune disorders. The patient had no history of consanguinity. Growth and psychomotor development during early childhood were reported as appropriate for age until the onset of diabetes mellitus.

At 2 years and 4 months of age, she presented with vomiting, abdominal pain, tachypnea, and a one-month history of progressive polyuria, polydipsia, and poor weight gain. Laboratory investigations demonstrated hyperglycemia, HbA1c of 8.3%, partially compensated metabolic acidosis, and ketonuria, consistent with the diagnosis of type 1 diabetes mellitus. Insulin therapy was initiated immediately, together with structured diabetes education and dietary counseling. Because this is a retrospective case report, complete historical laboratory documentation, including diabetes-associated autoantibodies, C-peptide, plasma glucose concentration, acid–base parameters, and electrolyte values, was not available for retrieval during manuscript revision.

Following treatment initiation, the patient's clinical condition improved rapidly. Appetite normalized, weight gain resumed, and glycemic control remained stable during regular follow-up. However, intermittent mild abdominal pain persisted despite otherwise satisfactory metabolic control.

At the age of 6 years, routine screening for celiac disease (CD) was performed because of the known association between type 1 diabetes mellitus and CD. Total serum IgA was 146 mg/dL, confirming IgA sufficiency, and tissue transglutaminase IgA (tTG-IgA) was 128 U/mL (laboratory upper limit of normal: <7–10 U/mL), representing a markedly elevated value. HLA typing identified HLA-DQA101:02, HLA-DQA103:01, HLA-DQB103:02, and HLA-DQB106:04. Based on the available serologic findings and specialist evaluation by a pediatric gastroenterologist, a diagnosis of celiac disease was established, and a strict gluten-free diet was initiated. Endomysial antibody (EMA-IgA) testing and upper gastrointestinal endoscopy with duodenal biopsy were not performed as part of the diagnostic work-up.

Because of the persistence of gastrointestinal symptoms despite a gluten-free diet, the patient remained under regular gastroenterology follow-up. However, retrospective review of the available medical records did not identify sufficient documentation regarding serial serologic measurements, formal dietary reassessment, or additional investigations for alternative gastrointestinal disorders.

At the age of 13 years, she developed an occasional dry cough without an obvious precipitating factor. Initially, the family considered the symptom insignificant. However, after discussing similar experiences with parents of children affected by comparable conditions, they reported the symptom during a routine follow-up visit. Given the persistent gastrointestinal symptoms and evolving respiratory complaints, further investigations for cystic fibrosis (CF) were undertaken.

The diagnostic evaluation demonstrated:

- Sweat chloride concentration: 42 mmol/L (intermediate range)/
- Fecal elastase: 3 µg/g/

Because of the intermediate sweat chloride concentration and profound pancreatic exocrine insufficiency (fecal elastase 3 µg/g), CFTR genetic analysis was performed, which identified the pathogenic CFTR variant c.1545_1546delTA (1677delTA) in the homozygous state, confirming the diagnosis of cystic fibrosis. Pancreatic enzyme replacement therapy (Creon® 10,000 units, two capsules four times daily) was initiated, resulting in partial improvement of gastrointestinal symptoms. Two years after the diagnosis of cystic fibrosis, at the age of 15 years, the patient was hospitalized with her first episode of pneumonia. She received intravenous ampicillin/sulbactam (1.5 g three times daily) for five days, followed by oral amoxicillin/clavulanic acid (1 g twice daily) for an additional five days, with complete

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clinical resolution of productive cough, pleuritic chest pain, and low-grade fever.

At the most recent follow-up, the patient was 16 years old, with a height of 161 cm, weight of 64 kg, and body mass index (BMI) of 24.7 kg/m². She continues insulin therapy, pancreatic enzyme replacement therapy, and adherence to a gluten-free, carbohydrate-controlled diet under multidisciplinary follow-up. Pulmonary function testing, chest computed tomography, and respiratory microbiological cultures had not been performed as part of routine follow-up. No treatment-related adverse events were documented during follow-up. (**TAB.1**).

TABLE 1. Chronological timeline of clinical events

Age	Clinical findings	Investigations	Working diagnosis	Treatment	Outcome
2 y	Polyuria, polydipsia, weight loss	Hyperglycemia, HbA1c 8.3%, ketonuria	T1DM	Insulin	Stable glycemic control
6 y	Persistent abdominal pain	Elevated tTG-IgA, HLA typing	Celiac disease	Gluten-free diet	Persistent GI symptoms
6–13 y	Abdominal discomfort, bloating	Repeated follow-up	CD	Continued GFD	Symptoms persisted
13 y	Dry cough + persistent GI symptoms	Sweat chloride (42 mmol/L), fecal elastase (3 µg/g), homozygous CFTR c.1545_1546delTA (1677delTA)	Cystic fibrosis	Pancreatic enzymes	Partial improvement
15 y	Pneumonia	Chest X-ray	Pulmonary infection	Antibiotics	Clinical recovery
16 y	Stable follow-up	Clinical assessment	T1DM + CD + CF	Ongoing multidisciplinary care	Stable

Abbreviations: CD, celiac disease; CF, cystic fibrosis; CFTR, cystic fibrosis transmembrane conductance regulator; GFD, gluten-free diet; GI, gastrointestinal; HbA1c, glycated hemoglobin; HLA, human leukocyte antigens; T1DM, type 1 diabetes mellitus;tTG-IgA, tissue transglutaminase-immunoglobulin A.

DISCUSSION

Type 1 diabetes mellitus (T1DM) and celiac disease (CD) are autoimmune disorders that frequently coexist because of their shared genetic susceptibility, particularly HLA class II haplotypes such as DR3-DQ2 and DR4-DQ8. More than 90% of patients with CD carry the HLA-DQ2 haplotype, supporting the rationale for routine CD screening in children with T1DM. [6] In our patient, CD was detected through routine screening, consistent with current recommendations.

To evaluate the novelty of this case, we conducted a structured literature search using PubMed/MEDLINE with combinations of the terms "cystic fibrosis," "celiac disease," "coeliac disease," "type 1 diabetes," "type 1 diabetes mellitus," "insulin-dependent diabetes," and "autoimmune diabetes." The search identified reports describing the coexistence of cystic fibrosis and celiac disease, including a Scandinavian cohort study in which one patient also had type 1 diabetes mellitus. [7] However, detailed pediatric case reports focusing on the diagnostic process and the impact of overlapping gastrointestinal manifestations remain exceptionally uncommon. Therefore, rather than representing the first documented coexistence of these three disorders, our case contributes additional educational value by illustrating how diagnostic anchoring may delay recognition of genetically confirmed cystic fibrosis in a child with established autoimmune disease.

The diagnosis of type 1 diabetes mellitus was established based on the patient's characteristic

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clinical presentation together with hyperglycemia, ketonuria, metabolic acidosis, and elevated HbA1c. Because this report is retrospective, complete historical documentation regarding diabetes-associated autoantibodies, C-peptide concentration, and additional biochemical parameters was unavailable. We acknowledge that inclusion of these data would have provided more comprehensive documentation of autoimmune diabetes and recognize this as a limitation of the present report.

The diagnosis of celiac disease was based on markedly elevated tTG-IgA levels in an IgA-sufficient child together with HLA susceptibility and evaluation by a pediatric gastroenterologist. Because this case was diagnosed before the current ESPGHAN recommendations were widely implemented in routine clinical practice at our institution, neither endomysial antibody (EMA-IgA) testing nor duodenal biopsy was performed. [8] We acknowledge that, according to current pediatric diagnostic guidelines, these data would further strengthen the diagnostic documentation and recognize their absence as a limitation of this retrospective case report.

Both diseases are characterized by dysregulated $CD4^+$ T-cell–mediated immune responses directed against distinct target antigens. In genetically predisposed individuals, this immune dysregulation contributes to the development of multiple autoimmune disorders. The institution of a gluten-free diet is generally associated with improvements in intestinal inflammation and nutrient absorption. However, mucosal recovery and normalization of celiac serology vary considerably among individuals, and the effect on glycemic control in children with concomitant T1DM and CD is not uniform. Persistent elevation of tTG-IgA in patients receiving a gluten-free diet requires careful clinical reassessment. Potential explanations include ongoing gluten exposure, persistent active celiac disease, pancreatic exocrine insufficiency, gastrointestinal manifestations of cystic fibrosis, and other gastrointestinal disorders. In the present case, the coexistence of severe pancreatic exocrine insufficiency and subsequently confirmed cystic fibrosis likely contributed to the persistence of gastrointestinal symptoms. Because this is a retrospective case report, complete historical documentation regarding serial celiac serology, dietary reassessment, and evaluation of competing gastrointestinal diagnoses was unavailable. Consequently, the relative contribution of each potential mechanism cannot be determined with certainty.

Despite adherence to a gluten-free diet, our patient continued to experience persistent gastrointestinal symptoms, which were initially attributed to celiac disease. In retrospect, persistent gastrointestinal symptoms together with severe pancreatic exocrine insufficiency raised the possibility that cystic fibrosis had been present for several years before the diagnosis was established. Although the interval between the diagnoses of celiac disease and cystic fibrosis was approximately seven years, the retrospective nature of this report does not allow for a precise determination of when cystic fibrosis first became clinically recognizable. Nevertheless, overlapping gastrointestinal manifestations may have contributed to the delayed consideration of cystic fibrosis in the differential diagnosis. Several clinical factors may have contributed to the delayed recognition of cystic fibrosis. The patient did not experience recurrent severe respiratory infections during early childhood, and the sweat chloride concentration was within the intermediate range (42 mmol/L), necessitating CFTR genetic analysis to establish the diagnosis.

The overlap between CD and CF further complicated the diagnostic process in this patient. Both disorders may present with malabsorption, abdominal pain, bloating, nutritional deficiencies, and impaired growth. Consequently, persistent gastrointestinal complaints were initially attributed to CD rather than prompting evaluation for an additional disorder. Furthermore, pancreatic exocrine insufficiency secondary to CF likely aggravated intestinal malabsorption despite appropriate dietary treatment, thereby contributing to persistent gastrointestinal symptoms.

The coexistence of CD and CF has been recognized since the first published report in 1969. [9] Although the exact pathogenic relationship remains uncertain, several mechanisms have been proposed. Pancreatic enzyme deficiency may increase exposure of the

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intestinal mucosa to incompletely digested gluten peptides. In contrast, chronic intestinal inflammation in CF may increase intestinal permeability and facilitate autoimmune responses. [10] The patient demonstrated severe pancreatic exocrine insufficiency, reflected by a fecal elastase concentration of 3 µg/g, and experienced partial clinical improvement after initiation of pancreatic enzyme replacement therapy (Creon®). At the most recent follow-up, she remained clinically stable with ongoing multidisciplinary management. Because this is a retrospective case report, detailed longitudinal nutritional assessments, pulmonary function testing, chest computed tomography, and respiratory microbiological surveillance were not available. We acknowledge that these investigations would have provided a more comprehensive characterization of the patient's cystic fibrosis phenotype and recognize their absence as a limitation of the present report.

The patient's first episode of pneumonia occurred two years after the diagnosis of cystic fibrosis. Although this respiratory event is compatible with pulmonary involvement in cystic fibrosis, no pulmonary function testing, chest computed tomography, or microbiological evaluation was available to further characterize the respiratory disease. Therefore, the extent of pulmonary involvement cannot be determined from this retrospective report.

This case also emphasizes the importance of genetic counseling for families of patients with cystic fibrosis. Family counseling should include discussion of the hereditary nature of the disease, recurrence risk, and the potential role of genetic evaluation for biological relatives, where clinically appropriate. Early recognition of affected family members may facilitate timely diagnosis, multidisciplinary follow-up, and initiation of appropriate disease-specific management.

This report has several limitations inherent to its retrospective design. Complete historical documentation of the original diagnostic work-up for type 1 diabetes mellitus, celiac disease, and cystic fibrosis was unavailable, and several investigations requested by current diagnostic guidelines—including diabetes-associated autoantibodies, endomysial antibodies, pulmonary function testing, chest computed tomography, and comprehensive nutritional assessments—were not available for review. The principal diagnostic challenge in this case was the overlap of gastrointestinal manifestations between celiac disease and cystic fibrosis, which complicated clinical interpretation and delayed consideration of an additional underlying disorder. Despite these limitations, the present case provides educational value by illustrating the diagnostic complexity associated with overlapping gastrointestinal manifestations in children with multiple chronic disorders.

CONCLUSIONS

This case highlights the importance of thorough clinical reassessment when symptoms persist despite seemingly adequate treatment. Persistent gastrointestinal manifestations in children with well-controlled autoimmune disease should not automatically be attributed to the existing diagnosis. Instead, clinicians should maintain a high index of suspicion for alternative or additional disorders, particularly when gastrointestinal phenotypes overlap, as earlier recognition of cystic fibrosis with an atypical clinical presentation may facilitate timely treatment and improve long-term pulmonary and nutritional outcomes.

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INFORMED CONSENT

Written informed consent for publication of this case report and accompanying clinical information was obtained from the patient's mother, who acted as the patient's legal guardian. All potentially identifying information has been removed or anonymized to protect patient privacy.

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