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CASE REPORT

Celiac disease and ulcerative colitis as comorbid diseases – the diagnostic challenge

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ABSTRACT

This study reports the case of a 17-year-old girl with a medical history of abdominal pains, diarrhoea, nausea, vomiting, weight loss, and stools with mucus and blood. The patient was diagnosed with celiac disease (CeD) and ulcerative colitis. No improvement was observed after a gluten-free diet, metronidazole, mesalazine, and systemic steroid treatment. The patient was administered azathioprine, and the systemic steroid therapy was repeated. The clinical condition worsened, and so Infliximab induction treatment was initiated; however, it was discontinued due to lack of response. Cyclosporine treatment was provided with good results. This case is particularly significant because, although the co-occurrence of CeD and inflammatory bowel disease in children is rare, bearing in mind the possible relationship between these disease entities in the diagnosis and treatment of children with gastrointestinal complaints may improve clinical practice and prevent the incorrect diagnosis or worsening the patient's clinical condition and delaying the implementation of appropriate treatment.

KEY WORDS:
celiac disease, Crohn's disease, ulcerative colitis.

INTRODUCTION

The term inflammatory bowel disease (IBD) comprises 2 chronic conditions affecting the digestive tract: ulcerative colitis (UC) and Crohn's disease (CD). The prevalence of CD is estimated at 26–199/100,000 people and UC as 37–246/100,000 people. Inflammatory bowel disease is believed to affect both sexes with similar frequency, usually between the second and the fourth decade of life [1]. Data show that the incidence of UC is increasing worldwide, with a higher prevalence noted in the north of Europe than in the south.

Like IBD, celiac disease (CeD) is a chronic condition that affects the digestive tract. Celiac disease is known to affect about 0.5–1% of the population in Europe [2], with a higher prevalence in women than men, with the ratio ranging from 2 : 1 to 3 : 1 [3]. Although CeD is usually diagnosed in childhood [4], it can be diagnosed at any time in life; however, its incidence peaks once in the first 2 years of life and again in the second to third decade of life [3].

Although the aetiopathogenesis of IBD remains unclear, the pathological process is believed to include various components, including intestinal immune system dysfunction, microbial factors, genetic susceptibility of the individual, and an inadequate response of the immune system to environmental factors [5]. Celiac disease presents with mucosal dysfunction in the small bowel

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caused by intake of gluten, a protein found in wheat, barley, rye, and other grains [6]. Patients who suffer from CeD have been shown to have a genetic susceptibility linked to the human leukocyte antigen (HLA)-DQ2 and HLA-DQ8 haplotypes [7, 8].

Many potential trigger factors for IBD have been pointed out, such as family history of IBD, environmental factors, and smoking [6]. The importance of dietary triggers remains unclear. It is also possible that multiple loci on several chromosomes and HLA subtypes play a role in the development of IBD [9]. Like every autoimmune disease, CeD has a strong link to heredity, and a high familial prevalence has been noted [3]. Data studies in adults have shown that CeD is associated with various autoimmune and idiopathic diseases, including dermatitis herpetiformis, type 1 diabetes mellitus, Hashimoto's thyroiditis, selective immunoglobulin A (IgA) deficiency, Addison's disease, chromosomal diseases, and hepatic autoimmune diseases such as autoimmune hepatitis (primary biliary cholangitis, autoimmune hepatitis, primary sclerosing cholangitis) [3].

The most common clinical presentation of IBD is bloody, mucous diarrhoea. However, other distinctive symptoms have been noted, such as abdominal pain, poor appetite, and weight loss [1]. While any site of the bowel can be affected by CD, UC is limited to the colon and rectum [7].

Unlike UC, CeD can remain asymptomatic; however, symptomatic patients may suffer malabsorption or malnutrition after gluten consumption, with children being either extremely malnourished or barely symptomatic [6]. The most recognizable symptoms of CeD are diarrhoea, abdominal bloating, failure to thrive, and decreased appetite [1, 10]. The typical clinical manifestations of both IBD

TABLE 1. Overlaps and differences between celiac disease and inflammatory bowel disease

Features	Celiac disease	Inflammatory bowel disease	
		Ulcerative colitis	Crohn's disease
Common symptoms	Abdominal pain, diarrhoea, constipation, weight loss, malnutrition, nausea, fatigue, iron deficiency, delayed puberty, osteoporosis		
Blood in stool	–	+	+
Fever	–	+	+
Symptoms outside the digestive system	+ (Duhring's disease, epilepsy, migraine, depression, ataxia, peripheral polyneuropathy, muscle weakness)	+ (Joint pain, inflammation of the eye, liver disease, skin lesions)	+ (Skin lesions, arthropathy associated with Crohn's disease)
Immunological disorders	+	+	+
Genetic disorders and background	+	+	+
Course of disease	Chronic	Chronic	Chronic
Location: small intestine	+	–	+
Location: large intestine	–	+ (Colon or rectum)	+ (The entire length of the digestive tract)
Trigger factors	Gluten intake	Psychological stress, dietary changes, painkillers (especially NSAIDs), intestinal and other organ infections treated with antibiotics	Bacterial infections of the gastrointestinal tract, a fatty diet, smoking, NSAIDs
Onset of the disease	Two peaks of onset – in the first 2 years of life and in the second/third decade of life	The peak incidence is between 20 and 40 years of age	The peak incidence is between 16 and 25 years of age
Asymptomatic type	+	–	–
Diagnosis based on	Activity of specific antibodies + biopsy of small intestine	Clinical presentation, endoscopy, and histological examination of a colonic mucosal tissue	Clinical presentation, endoscopy with biopsy, histopathology, and radiological methods with contrast

and CeD can also be accompanied by various extraintestinal symptoms. These include refractory iron-deficiency anaemia, short stature, uveitis, and primary sclerosing cholangitis in the case of IBD [1], and iron deficiency, osteopaenia or osteoporosis, growth retardation, aphthous stomatitis or tooth enamel defects, and hypertransaminasaemia, as well as neurological manifestations (headache, paraesthesia, anxiety or depression, neuroinflammation) in CeD, with these being visible in both children and adults [3]. The overlaps and differences of CeD and IBD are presented in Table 1.

Because CeD and IBD are both immune-mediated enteropathies with overlapping pathogenic elements, it may be possible for them to co-occur in individuals [3, 11]. Herein we present a case of a 17-year-old girl diagnosed with UC and CeD. This case is particularly significant due to the rarity of such co-occurrence in children, and more importantly, an incorrect diagnosis may delay an appropriate treatment regimen and result in a worse course.

TABLE 2. Results of laboratory testing set

Parameter		Day of stay		
	Normal range	2nd	6th	9th
Hb [g/dl]	11.2–15.7	9.5↓	9.9↓	10.02↓
RDW-C (%)	11.7–14.4	15.9↑	15.7↑	–
PLT [10^3/µl]	132v370	421↑	465↑	520↑
HCT (%)	34.1–44.9	31.8↓	33.2↓	34.4
MCH [pg]	25.6–32.2	22.7↓	22.3↓	22.3↓
MCV [fl]	79.4–94.8	75.9↓	74.9↓	75.3↓
MCHC [g/dl]	32.2–35.5	29.9↓	29.8↓	29.7↓
WBC [10^3/µl]	3.98–10.04	6.75	7.6	8.66
NEUT [10^3/µl]	1.56–6.13	3.97	6.27↑	–
LYMPH [10^3/µl]	1.18–3.74	1.83	1.02↓	–
MONO [10^3/µl]	0.24–0.36	0.74↑	0.28	–
EO [10^3/µl]	0.04–0.36	0.17	0.01↓	–
BASO [10^3/µl]	0.01–0.08	0.04	0.02	–
CRP [mg/l]	$n < 5.00$	11.18↑	4.21	–
ESR [mm/hour]	0–20	27↑	–	–
PCT (%)	0.17–0.38	0.43↑	0.46↑	0.52↑
FC [mcg/kg]	$n < 50$	703↑	–	–
tTG IgA [CU]	$n \leq 19.9$	255↑	–	–
tTG IgG [CU]	$n \leq 19.9$	25.5 CU↑	–	–
IgA EMA	$n < 10 \times$ ULN	1 : 80	–	–
IgG EMA	$n < 10 \times$ ULN	1 : 20	–	–

BASO – basophils, CRP – C-reactive protein, EO – eosinophils, ESR – erythrocyte sedimentation rate, FC – faecal calprotectin, Hb – haemoglobin, HCT – haematocrit, IgA/IgG EMA – anti-endomysial antibodies IgA/IgG, LYMPH – lymphocytes, MCH – mean corpuscular haemoglobin, MCHC – mean corpuscular haemoglobin concentration, MCV – mean corpuscular volume, MONO – monocytes, NEUT – neutrophils, PCT – procalcitonin, PLT – platelet count, RDW – C–red cell distribution width, tTG IgA/IgG – anti-tissue transglutaminase antibodies IgA/IgG, WBC – white blood cells

CASE REPORT

A 17-year-old girl was admitted to hospital due to recurrent abdominal pains, bloody diarrhoea, recurring episodes of nausea, vomiting, and weight loss. The abdominal pains were located in the middle epigastric region. Stools with mucus and blood occurred about 15 times a day. The patient had lost 7 kg over the period of 2 months. According to medical history, the first symptoms had appeared 2 years earlier. The girl complained of abdominal pains, bloating, and nausea. Until 15 years of age, no delay in growth or weight gain were observed, with the patient only suffering from occasional infections. The onset of the child's condition was found to coincide with her school examinations, i.e. a stressful condition. Regarding the family history, the mother was diagnosed with Hashimoto's thyroiditis and insulin resistance, and the father suffered from hypertension; however, the brother (21 years old) was healthy.

In response to the observed symptoms, conservative treatment was provided by a general practitioner, including antispasmodic drugs and proton pump inhibitors. However, non-significant clinical improvement was reported. On admission, the patient was in a moderate condition (PUCAI 55 points). Abnormalities in physical examination included pallor of the skin and mucous membranes. The patient weighed 48.7 kg (10^{th}–25^{th} percentile), her height was 167 cm (50^{th}–70^{th} percentile), and her body mass index (BMI) was 17.46 (N 18.5–24.99). No other abnormalities were revealed by the physical examinations. The laboratory testing indicated anaemia, elevated inflammatory markers, and a high level of faecal calprotectin (Table 2); otherwise, no other abnormalities were observed. Subsequently, the patient underwent gastrointestinal endoscopy, and mucosal biopsies were obtained. Gastroscopy revealed oedema of the duodenal bulb, and grooving and scalloping of the duodenum. No pathologies were observed in the oesophagus, antrum, or stomach. Histological examination of the small intestine revealed villous atrophy and crypt hypertrophy corresponding to grade 3B according to Marsh-Oberhuber. Because the presented clinical symptoms corresponded to celiac disease, anti-tissue transglutaminase antibodies IgA (tTG-IgA) 255 CU (N ≤ 19.9 CU) and tTG-IgG 25.5 CU (N ≤ 19.9 CU) together with IgA anti-endomysial antibodies (EMA) – 1 : 80 and IgG EMA – 1 : 20 were tested. Colonoscopy showed continuous changes, intense oedema of the mucosa, erythema, and mucosal friability. Histological images of the large intestine included intraepithelial lymphocytes in any site long of the bowel, features of cryptitis in the transverse colon, and aphthous ulcers in the descending colon and sigmoid colon. The presented abnormalities suggested UC.

Magnetic resonance enterography was provided to estimate the localization of the affected small intestine bowel; however, no evidence was found of thickening

of the small intestine wall, nor any abnormalities in the terminal ileum. Bowel wall thickening and diffusion restriction were described in the caecum and in the ascending and transverse colon, and loss of haustration was noted around the descending and sigmoid colon. A thickening of Bauhin's valve was noticed, with features of inflammation. The presented outcomes directly correspond to a manifestation of ulcerative colitis. As part of the differential diagnosis, the patient was provided with a psychological consultation, which indicated a link between the stressful situations experienced by the patient and her worsening of gastrointestinal symptoms. Taking into account the endoscopic, histopathological, and immunological outcomes given above, and the clinical presentation, a diagnosis of UC and CeD was established [10].

A gluten-free diet was implemented. The patient was also treated with metronidazole, mesalazine, and systemic steroids, which were gradually tapered off over a period of 3 months. However, a recurrence of bloody diarrhoea and general deterioration were noticed after the termination of the steroid treatment; therefore, additional budesonide was prescribed. Despite this, the symptoms continued to intensify. Subsequently, the patient received 3 doses of induction treatment comprising azathioprine and biological therapy with Infliximab. The therapy was discontinued after the third dose due to the low level of infliximab in serum, the presence of anti-Infliximab antibodies, and a deterioration of the patient's clinical state (recurring bloody diarrhoea, PUCAI 70 points).

The therapy was amended, and systemic steroid treatment was repeated. However, the patient's condition worsened as the dose of steroids was lowered. She was also found to demonstrate *Clostridium difficile* and norovirus infection, which was successfully treated with vancomycin.

The steroid treatment was replaced with cyclosporine treatment, with gratifying results: PUCAI 15 points, remission of gastrointestinal symptoms such as diarrhoea with blood and nausea, and a decreasing number of stools per 24 hours. The patient remained under follow-up cyclosporine treatment, and then, because of her age, she was referred to a gastroenterology clinic for adults. Unfortunately, the patient's condition continued to deteriorate after admission (PUCAI 70 points, weight loss 47–40.9 kg; BMI 14.7). Systemic steroids were administered, and she was qualified for Vedolizumab treatment; she has so far received 2 doses with no clinical improvement.

DISCUSSION

The present case demonstrates the importance of considering that several disease entities may be present in a child with gastrointestinal complaints, because incorrect management may result in mistakes in the applied treatment. Celiac disease and IBD have many common features, one of which being their genetic background.

The genetic similarity of IBD and CeD was first postulated by the identification of 4 shared risk loci: interleukin 18 receptor accessory protein, protein tyrosine phosphatase non-receptor type 2, T-cell activation guanosine triphosphate phase activating protein, and pseudouridylate synthase 10 (PUS10) [7]. These shared genetic pathways may be the reason for their possible comorbidity. Similarly, a clinical presentation described by Cheng *et al*. was found to be in line with a meta-analysis of genome-wide association study datasets comprising case reports of CeD and IBD comorbidity in Caucasian children from Europe [12, 13].

This common genetic background was also discussed by Medrano *et al*. [9], who emphasized that despite the existence of shared susceptibility loci, the observed genetic patterns do not always correspond to the expected results, possibly due to the complexity of gene expression. The authors highlighted the role of genes such as *ZFP36L1*, *ZMIZ1*, *PUS10*, and *BACH2* in autoimmune diseases [9] and reported a considerably higher risk of CeD in adult individuals with IBD, compared with the general population [14].

Although the combination of CeD and IBD has been reported in children, its nature remains unclear. A study of Egyptian children found a significantly higher prevalence of CeD in those with IBD than in the general population [7]. Similar results were presented by Canova *et al*., who found that the prevalence of both UC and CD were significantly higher in CeD patients compared with a reference group; however, the authors noted a possible bias associated with the recruitment algorithm described below, which may be connected with misclassification. When more specific diagnostic criteria were used, the risk of co-occurrence of IBD and CeD was found to be 2-fold greater. In turn, the risk was significantly lower when the authors used patients with a small intestinal biopsy without villous atrophy as a reference, instead of the general population [4].

A systematic review and meta-analysis by Pinto-Sanchez *et al*. assessed the evidence for an association between CeD and IBD. The findings indicated an increased risk of IBD in patients with CeD compared with controls, and conversely an increased risk of CeD in patients with IBD [14]. Inflammatory bowel disease was also found to be significantly more common in patients previously diagnosed with CeD than in the general population [15]. Our present case confirms the possibility of the co-occurrence of IBD and CeD. However, due to the rarity of such co-occurrences, there is a lack of precise data suggesting a higher risk of IBD and CeD in children

A lack of awareness regarding the overlapping clinical presentation of CeD and IBD plays a detrimental role in establishing a proper diagnosis. CeD may remain undiagnosed in cases where previously immunomodulatory treatment was implemented or a gluten-free diet was indicated [7].

The co-occurrence of the 2 disease entities is associated with the possibility of a more severe course of the disease. Oxford *et al.* reported increased usage of immunomodulators among celiac-UC patients, and indicated that patients with IBD and CeD are more likely to suffer from pancolitis [16]. It has also been proposed that the co-occurrence of IBD and CeD may worsen the overall clinical presentation, and in some cases, colectomy was required as an ultimate therapy for UC [15]. The more severe course of the disease observed in our present patient with comorbid CeD-IBD is confirmed by the lack of improvement observed after standard treatment and the need for multiple treatment changes.

As a result of the overlap between the symptoms of IBD and CeD, the process of diagnosis is usually extended in time, and it is likely that one of the conditions would remain undetected. Yang *et al.* [15] found the period between the diagnosis of initial disease and that of concomitant disease in CD-CeD and UC-CeD patients to range from 1 to 12 years in the former, and between a month and 46 years in the latter. In a cohort of paediatric patients, Eskander *et al.* reported that CeD was diagnosed on average 2.4 ±1.8 years after the primary diagnosis of IBD [7]; the authors recommend that comorbidity of CeD should be considered when patients with IBD present excessive abdominal gaseous sensation and bloating. Fortunately, our patient was diagnosed with both IBD and CeD simultaneously; however, a worse outlook can be expected when a correct diagnosis is delayed [15, 16].

Celiac disease is diagnosed by serological markers such as IgA anti-tissue transglutaminase (anti-tTG) antibodies, IgA EMA, and anti-deamidated gliadin peptide antibodies [8]. In addition, anti-*Saccharomyces cerevisiae* antibodies (ASCA) and perinuclear anti-neutrophil cytoplasmic antibodies (pANCA) may be detected in some IBD subtypes [17]. Pinto-Sanchez *et al.* [14] indicated the possibility of elevated anti-tTG antibodies, anti-EMA antibodies, AGA, and anti-DPG in IBD patients compared to controls, and a risk of higher levels of ASCA and pANCA in CeD patients compared to controls. Higher levels of tTG IgA were also reported by Yang *et al.* in both UC and CD patients without CeD, as well as higher ASCA in CeD patients [15].

The outcomes described above may affect clinical management and diagnosis strategies, such as in individuals without villous atrophy, which may occur in cases of CeD; in addition, elevated ASCA or pANCA can be misdiagnosed as CD instead of CeD. A similar situation may be observed in the presence of a higher level of serological markers indicative of CeD and when the duodenum is affected: in such cases, CD might remain undetected. Nevertheless, the authors warn that further research is needed to define the diagnostic value of presented outcomes more precisely [12].

Cheng *et al.* also highlighted the possibility that, due to their similar symptoms, CeD may be overlooked in children already diagnosed with IBD. The authors also note that children with UC and duodenal involvement might be misdiagnosed as CD, rather than a clinical manifestation of UC (large bowel involvement) and CeD (duodenal involvement) [12], and hence treated incorrectly. Such a situation occurred during the diagnosis of our present patient. The correct diagnosis, which excluded the first diagnosis, i.e. Crohn's disease, was made after MRI enterography.

Considering the risk of misdiagnosing these comorbidities, as well as the increasing prevalence of CeD in the general population and the increased concurrency of IBD and CeD, it may be more cost-effective and, more importantly, beneficial to implement screening for CeD in patients with IBD. This approach has been suggested by both Pinto Sanchez *et al.* [14] and Eskander *et al.* [7].

CONCLUSIONS

Inflammatory bowel disease and CeD are both chronic inflammatory disorders whose pathogenesis originates from immune system dysfunction. Both diseases are believed to have a genetic association in the form of shared risk loci. Recent data suggest a higher prevalence of CeD in individuals with IBD. As a result, considering the degree of commonality between IBD and CeD, it may be necessary to review the diagnostic approach taken in children with gastrointestinal symptoms.

Establishing a proper diagnosis requires an awareness of the overlapping symptoms between the diseases and the influence they have on each other's clinical courses. Successful diagnosis can significantly improve the chance of appropriate therapy being applied, thus preventing, or at least decreasing, the risk of acute complications and a fatal course.

DISCLOSURE

The authors declare no conflict of interest.

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