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Celiac Crisis: an unusual presentation of gluten-sensitive enteropathy

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ABSTRACT

Celiac disease (CD)—also known as gluten-sensitive enteropathy—is a chronic, genetically predisposing and autoimmune entity with a wide range of clinical manifestations triggered by gluten ingestion, which affects 1% of the general population. Currently, up to 60% of the diagnosis of CD is in adults due to the atypical course of the disease. The severe acute onset of CD—also called celiac crisis—is very uncommon and is still not well documented in adults. We report the case of a 58-year-old man who presented a 45-day history of subtle-onset diarrhea followed by malabsorption syndrome with progressive weight loss, anasarca, and electrolyte disturbances. The diagnostic work-up included an upper digestive endoscopy, which showed scalloping of the duodenal mucosa with pathological features confirmed on biopsies. Specific antibodies were positive, and a satisfactory clinical response was obtained once a gluten-free diet was started. Celiac crisis is a rare initial presentation of CD characterized by severe diarrhea, dehydration, weight loss, hypoproteinemia, and metabolic and electrolyte disturbances. Although rare, it should be considered in patients with apparently unexplained chronic diarrhea.

Keywords
Celiac Disease; Malabsorption Syndrome; Diarrhea, Transglutaminases; Gliadin

INTRODUCTION

Celiac disease (CD)—also called celiac sprue or gluten-sensitive enteropathy—is a permanent dietary disorder caused by an immune response to gluten, which results in abnormal small intestinal mucosa.[1] The prevalence is estimated to be 1:70 to 1:300 in the general population and is highest in the childhood and adulthood of Caucasian Northern Europeans. Typical symptoms include chronic diarrhea, abdominal distention, flatulence, and weight loss. However, clinical manifestations can vary from asymptomatic to life-threatening symptoms requiring hospitalization, such as a celiac crisis (CC).[2] Severe acute onset of CD is very uncommon and is not well documented in adults. Even though it has a bimodal incidence, this type of presentation of CD occurs mainly in children younger than 2 years old.[3] Nevertheless, CC should be

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considered a differential diagnosis in adult patients with profuse diarrhea and severe metabolic disturbances.[4]

CASE REPORT

A 58-year-old male sought medical care complaining of profuse, watery, non-bloody, explosive, "food-scrappy" diarrhea over the last 45 days, accompanied by weakness, progressive weight loss (15 kg) and anasarca. There was no history of fever, nausea, abdominal pain, recent travels, or dietary change—nor the use of any medications. There was no history of similar symptoms; however, the patient did have intermittent pruritic papules on the extensor surface of his elbows, which he'd had for years, and which was associated with sunscreen use. His past medical history included the diagnosis of hypertension and chronic alcohol abuse of approximately 60 g daily.

The physical examination revealed an ill-looking patient, who was emaciated (body mass index: 17.3), dehydrated, afebrile, markedly weak, and barely able to walk on his own. His blood pressure was 90/60 mmHg; his respiratory rate was 23 respiratory movements per minute; and he had marked non-inflammatory edema over his chest wall, abdomen, sacral region, and limbs. His abdomen was distended at the expense of flatulence with increased bowel movement sounds. The remaining examination was unremarkable. The laboratory work-up showed a hemoglobin of 11.6 g/dL (reference range [RR]: 12.3-15.3 g/dL); international normalized ratio 1.6 (RR: 1); albumin 1.8 g/dL (RR: 3.5-5.2 g/dL); ionized calcium 1.15 mmol/L (RR: 1.16-1.32 mmol/L); phosphorus 2.2 mg/dL (RR: 2.5-4.5 mg/dL); amylase 25 U/L (RR: 28-100 U/L); lipase 9 U/L (RR: 13-60 U/L); folic acid 1.1 ng/mL (RR: 4.2-19.8 ng/mL); and vitamin B12 1465 pg/mL (RR: 221-946 pg/mL). Fecal fat testing by Sudam III was markedly positive, and oxaluria was present in the urinalysis. The serology for hepatitis A, B, C, and HIV were all negative. Stool research for ova, parasites, blood, leucocytes, and culture was negative.

The abdominal computed tomography (CT) showed hepatic steatosis, moderate distension of the small intestine, which was predominantly filled with liquid content, and a pancreatic cyst, but there were no signs of pancreatitis. The colonoscopy was normal, but colon biopsies evidenced mild chronic non-specific inflammation, a mild increase in intraepithelial lymphocytes (20 per 100 enterocytes), and focal crypt microabscesses. The upper digestive endoscopy showed severe distal erosive esophagitis Los Angeles C and scalloping of the duodenal mucosa (Figure 1).

The biopsies' histological examination depicted moderate inflammatory duodenitis in activity, with crypt hyperplasia, total/subtotal villous atrophy, increased intraepithelial lymphocytes (over 40 per 100 enterocytes), focal foveolar metaplasia, and neutrophilic infiltration (Figure 2)—type 3c of the Marsh-Oberhuber classification.

The immunoglobulin-A (IgA) anti-transglutaminase (anti-tTG) antibody's determination by ELISA was 142 U (RR: non-reactive < 20 U); the IgA anti-gliadin index

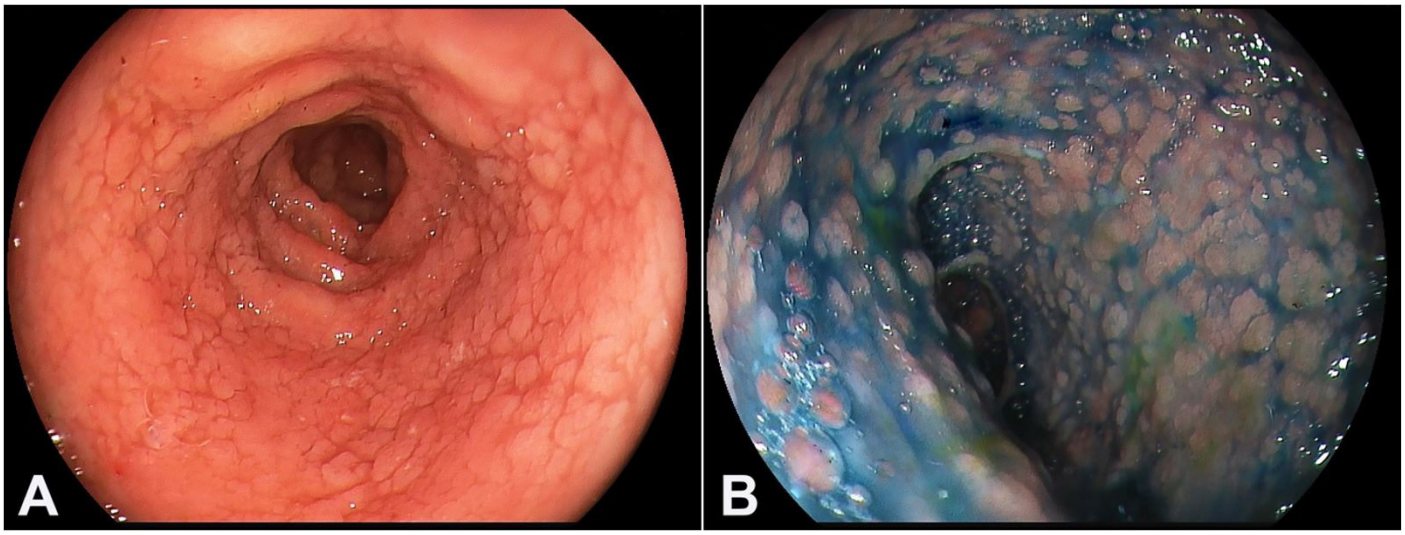

Figure 1. Upper digestive endoscopic view. **A –** Second part of the duodenum showing scalloping of the mucosa; **B –** The same appearance after instillation of indigo carmine dye (chromoendoscopy).

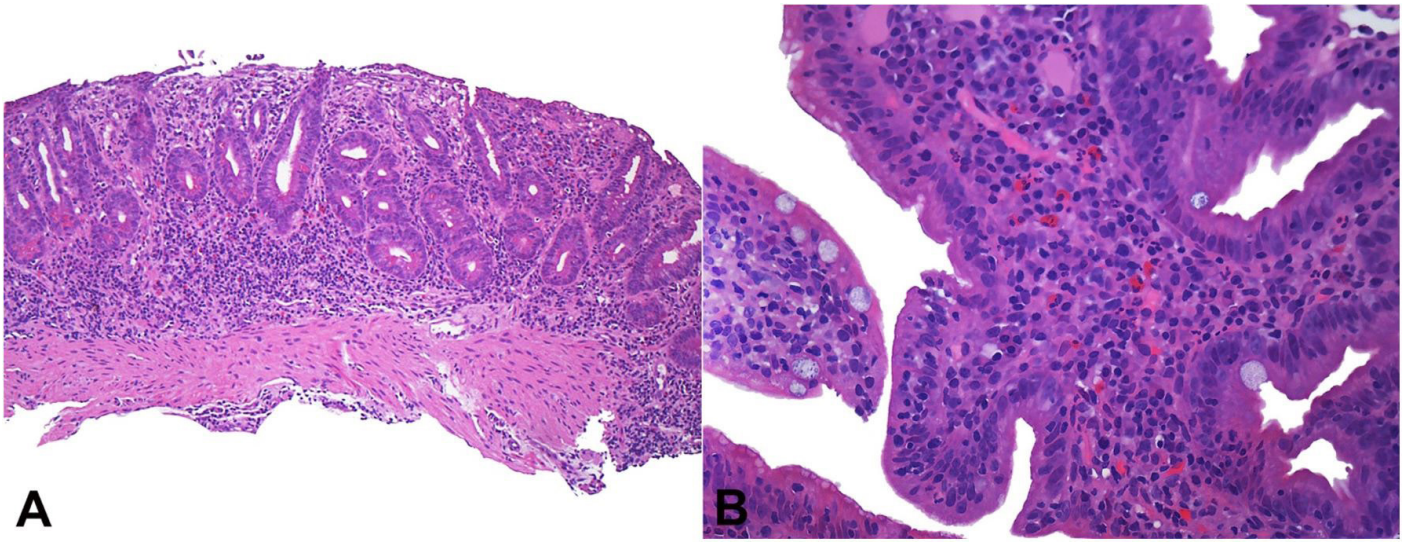

Figure 2. Photomicrography of duodenum. **A –** Total villous atrophy, crypt hyperplasia and inflammation (H&E, 100X); **B –** Detail of duodenal biopsy showing increased intraepithelial lymphocytes (H&E, 400X).

was 6.9 (RR: < 1) by immunoenzymatic assay; and the IgA anti-endomysium was 1:640 (RR: non-reactive) by indirect immunofluorescence. Our patient was diagnosed with CD presenting with CC, considering the clinical features, imaging studies, specific antibody research, and histopathological findings.

Once a gluten-free diet was started, there was a marked clinical improvement followed by complete resolution of diarrhea in 5 days. On day 11 of hospitalization, the patient was discharged on a gluten-free diet with vitamin B, folic acid, and multivitamin supplementation.

DISCUSSION

The term "celiac crisis" was first encountered in the literature in 1953 when Anderson and di Sant'Agnese's (described in Ozaslan et al.[5]) reported a series of 35 cases of children with persistent or recurrent diarrhea, with a fatality rate of 9%. Since then, only a few cases have been described, mainly in children younger than 2 years of age.[6]

PubMed articles published between September 1990 and April 2018, were searched using the uniterm "celiac crisis" in patients older than 18 years; 31 reported cases were gathered (Table 1). The mean age was 52 years ranging from 23 to 83 years and a gender predominance was found among females (1.81:1). Interestingly, amid the 31 cases, only 3 had the diagnosis of CD before the crisis.[4,7,8] Therefore, we dare to assume that, in this age group, CD may first present as CC. The IgA tissue transglutaminase antibody was the most frequent serological marker, with 21 positive cases, while the IgA endomysial antibody was positive in 15 cases, and the IgA delaminated gliadin peptide in 7 cases. Two cases with IgA deficiency were recorded, requiring HLA-DQ2/DQ8 screening for diagnostic confirmation.[4,8] The most common histopathological presentation was Marsh 3, with a predominance of subtype c.[4,6,9,10] A total of 27 cases showed improved clinical status after the introduction of a gluten-free diet,[4,6,9-22] nine patients required corticosteroids for symptom remission,[4,6,12,18] and one death was recorded due to refeeding syndrome.[7]

CC presents with severe diarrhea, dehydration, weight loss, hypoproteinemia, and metabolic and electrolyte disturbances, and may require hospitalization.[1] Hemodynamic instability, metabolic acidosis, and acute kidney injury may occur in a few cases. Gutierrez et al.[6] reported a case with severe hypocalcemia accompanied by tetany and hemorrhagic diathesis, which markedly improved after a gluten-free diet, prednisone, calcium, and vitamin D were started.[6]

CC may be precipitated by a general immune stimulus, such as surgery, infection, or pregnancy. In our case, the patient had no exposure to any previously known triggers, as well as no recent changes in his usual dietary consumption. CC represents a diagnostic challenge, especially in patients without a previous diagnosis of CD. Therefore, it should always

be considered in the differential diagnosis of all patients presenting with subtle-onset severe diarrhea with metabolic disturbances after infectious etiologies have been ruled out. In our case, the history of chronic alcohol abuse initially led us to consider the working diagnosis of chronic pancreatitis, which was deferred due to the absence of abdominal pain and pancreatic structural abnormalities in the CT.

A definition of CC in adults was proposed in 2010 by Jamma et al.[4] (Table 2). According to their diagnostic criteria, the patient herein presented acute onset of gastrointestinal symptoms attributable to CD requiring

Table 1. Description of the published cases retrieved from PubMed between September 1990 and April 2018 with the uniterm "celiac crisis" in adults

Case	Ref.	Sex	Age (ys)	Previous Diagnosis	Histological Report	Positive Antibodies	Use of CS	Outcome
1	10	F	26	N	Marsh 3c*	Anti-tTG	Y	I after a few days
2	6	F	26	Y	Marsh 3c	Anti-tTG IgA & Anti-Gli IgA	Y	HD after 14 days
3	11	M	31	N	Marsh 3b*	NA	N	HD after 6 days
4	12	F	64	N	Marsh 4	Anti-tTG IgA & Anti-EM IgA	N	NA
5	13	F	23	N	Marsh 3b*	Anti-tTG IgA & Anti-Gli IgG	N	I after 3 weeks
6	14	F	82	N	Marsh 3*	Anti-tTG IgG, IgA & Anti-EM	N	HD after 6 days
7	14	M	75	N	Marsh 3c*	Anti-tTG IgG, IgA & Anti-EM	N	HD after 8 days
8	15	M	75	N	Marsh 3a*	Anti-EM	N	HD after 10 days
9	15	F	55	N	Marsh 3b*	Anti-EM & Anti-Gli IgA	N	HD after 8 days
10	7	F	28	Y	Marsh 3*	Anti-tTG, Anti-EM & Anti-Gli	N	Death by RFS
11	8	M	67	N	Marsh 3a	** HLA-DR4-DQ8	N	I after 2 weeks
12	16	M	43	N	Marsh 4	Anti-tTG IgA	N	I after 5 days
13	9	M	46	N	Marsh 3c	Anti-tTG IgA & Anti-Gli	N	I after 2 days
14	17	M	83	N	Marsh 3*	Anti-EM IgA	N	I with diet
15	18	F	30	N	Marsh 3*	Anti-EM IgA	N	I with diet
16	19	F	26	N	Marsh 3b*	Anti-EM & Anti-Gli	N	I with diet
17	21	F	24	N	Marsh 3c	Anti-tTG	N	I after 8 days
18	20	F	50	N	Marsh 3*	Anti-tTG & Anti-EM	Y	I after 3 weeks
19	4	F	34	NA	Marsh 3b	Anti-tTG	Y	HD after 7 days
20	4	M	51	NA	Marsh 3c	Anti-tTG & Anti-EM	Y	HD after 11 days
21	4	F	48	NA	Marsh 3b	**	N	HD after 3-4 days
22	4	M	70	NA	Marsh 3a	Anti-tTG	N	NA
23	4	F	48	NA	Marsh 3a	NA	N	HD after 7 days
24	4	F	68	NA	Marsh 3a	Anti-tTG	Y	HD after 5 days
25	4	F	67	NA	Marsh 3c	Anti-tTG	N	HD after 8 days
26	4	F	74	NA	Marsh 3c	Anti-tTG	Y	HD after 7 days
27	4	M	65	NA	Marsh 3a	Anti-tTG & anti-EM	N	HD after 10 days
28	4	M	68	NA	Marsh 3b	Anti-tTG & anti-EM	N	HD after 11 days
29	4	F	65	NA	Marsh 3c	Anti-tTG	Y	HD after 13 days
30	4	F	49	NA	Marsh 3a	Anti-tTG & anti-EM	Y	HD after 4 days
31	22	F	52	NA	Marsh 3*	Anti-Gli & anti-EM	NA	NA

CS = corticosteroid; EM = endomysium; F = female; Gli = Gliadin; HD = hospital discharge; I = improvement; M = male; NA = not available; N = no; Ref. = reference; RFS = refeeding syndrome; tTG = transglutaminase; Y = yes; ys = years; * = Histological reports were adapted to the Marsh-Oberhuber classification by the authors according to the original article's description; **= IgA deficiency.

Table 2. Criteria for the diagnosis of celiac crisis (Jamma et al.[4]).

Acute onset or rapid progression of gastrointestinal symptoms attributable to celiac disease requiring hospitalization and/or parenteral nutrition along with at least two of the following:
• Signs of severe dehydration, including hemodynamic instability and/or orthostatic changes
• Renal dysfunction, creatinine level, >2.0 g/dL
• Metabolic acidosis, pH <7.35
• Hypoproteinemia (albumin level, <3.0 g/dL)
• Abnormal electrolyte levels including hypernatremia/hyponatremia, hypocalcemia, hypokalemia, or hypomagnesemia
• Weight loss >5 kg

hospitalization, weight loss >10 lbs in 45 days, hypocalcemia, and hypoproteinemia. In addition, determinations of IgA anti-transglutaminase antibody (anti-tTG IgA), IgA anti-gliadin antibody (anti-Gli IgA), and IgA endomysial antibody (anti-EM IgA) were positive in high titers, in accordance with most of the described cases.[4] The endoscopic feature of scalloping of the duodenal mucosa, and the histopathological findings of crypt hyperplasia, villous atrophy, and lymphocytic infiltration, are also characteristic of CD.

The treatment of CC in the patient herein started with a gluten-free diet, parenteral fluid replacement, and nutritional support. With such measures we observed a substantial clinical improvement very quickly, which occurs in about 50% of patients with CC.[4] Ciacci et al.[23] have shown that the use of budesonide improves both the histology and the parameters of absorption in CD, possibly by restoring brush border epithelium enzymes and reducing mucosal inflammation. A brief course of prednisone or budesonide should be considered when standard therapy does not result in rapid improvement.[4] However, the use of corticosteroids may aggravate electrolyte disturbances once it contributes to the depletion of potassium, magnesium, and phosphate.[11]

Over the past decade, the prevalence of CC has increased, which is probably due to the development of diagnostic criteria, suggesting previous underdiagnosed cases.

This case report shows the importance of being aware of the diagnosis of CC for severe, chronic diarrhea in adults. A gluten-free diet is the only evidence-based intervention; nevertheless, the use of additional interventions, such as corticosteroids and parenteral nutrition, has been reported.

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