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Single Case

Hypoalbuminemia and Generalized Edema as the Presenting Symptoms of Celiac Disease in a Two-Year-Old Girl: A Case Report

Michael R. Weaver William C. Schultz Ahmed Rafay Afzal Kara L. Oliver
Osama F. Almadhoun

Department of Pediatrics, Jacobs School of Medicine and Biomedical Sciences, Buffalo, NY, USA

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Abstract
Introduction: Celiac disease (CD) is a systemic, immune-mediated enteropathy that occurs following dietary consumption of gluten in genetically susceptible individuals. The global prevalence of celiac disease is estimated to be approximately 1.4%, with variation based on age, sex, and geographic location. CD typically presents early in life with diarrhea, abdominal pain, abdominal distention, weight loss, and impaired growth. In severe cases, patients with CD can present in a state of celiac crisis (CC), classically characterized with profuse diarrhea and life-threatening metabolic derangements. ***Case Presentation:*** In this report, we discuss a 23-month-old girl in a state of CC who presented atypically with hypoalbuminemia, generalized edema, and constipation. ***Conclusion:*** Even in the presence of atypical symptoms, such as edema or constipation, CD should be considered as a differential diagnosis in pediatric patients with severe gastrointestinal disturbances. Additionally, we propose a revised definition of CC that is specific to the pediatric population.

Introduction

Celiac disease (CD, also known as celiac sprue or gluten sensitive enteropathy) is a systemic, immune-mediated enteropathy that occurs following dietary consumption of gliadins in genetically susceptible individuals, such as those with the HLA-DQB1*02 gene variant

Correspondence to:
Michael R. Weaver, mweaver2@buffalo.edu

[1, 2]. Gliadins are a poorly digestible group of prolamines (proline-rich plant proteins) that form a major component of gluten and are found in various cereal grains such as wheat, barley, and rye [3]. In the small intestine, gliadins cross into the submucosa, are enzymatically deaminated, and then interact with specific cell surface proteins to trigger an inflammatory response. The incidence of CD is on the rise, in part due to enhanced recognition and testing [4]. The current worldwide prevalence of CD is estimated to be 1.4% based on seropositivity, resulting in significant economic costs and impact to psychosocial well-being [5, 6]. Patients are additionally impacted by a number of autoimmune comorbidities associated with CD, such as irritable bowel syndrome, inflammatory bowel disease, and eosinophilic esophagitis.

CD is a heterogeneous disorder with multiple classifications, including subclinical, classical, and nonclassical forms [3]. The classical form of CD generally presents early in life with diarrhea, abdominal pain, abdominal distention, weight loss, and impaired growth. Rarely, severe cases of CD can present in a state of celiac crisis (CC), which includes life-threatening metabolic derangements requiring hospitalization and is associated with significant mortality [7, 8]. Several case-based reviews discuss the heterogeneity even within CC [8–10]. Early recognition of CC is important to ensure adequate management and to mitigate adverse outcomes.

Diarrhea is a particularly common presenting symptom of CD that is found in 88–90% of new cases, while constipation is much rarer, occurring in 2.7% of all cases [9, 10]. Another rare presenting symptom of CD is edema, which is found in 3.5% of all new cases of CD and has previously been reported to occur in combination with severe diarrhea in CC [9, 11–13]. Constipation and edema each have broad differential diagnoses that can result in a delay in disease recognition and initiation of proper treatment. In this report, we discuss the unusual case of a 23-month-old girl in CC who presented with hypoalbuminemia, generalized edema, and constipation.

Case Report

Our patient was a 23-month-old female who was admitted to the hospital due to constipation, abdominal distension, and generalized edema. She had a viral illness with vomiting, cough, and congestion 3 weeks prior to presentation. She was noted to have abdominal distension following this illness which progressively worsened and was associated with loose, foul-smelling stools.

Family history includes maternal irritable bowel syndrome, type I diabetes mellitus in the maternal grandfather, and multiple instances of paternal family members with asthma and gluten intolerance. The patient was born after a normal prenatal course by uncomplicated caesarean section at 38w3d. Birth measurements included a weight of 3,450 g (74th percentile), length of 49.5 cm (58th percentile), head circumference of 35 cm (80th percentile), and body mass index of 14.08 kg/m^2. The patient passed meconium on her first day of life and tolerated a diet of Enfamil Gentlease with encouraging growth through infancy. Gluten was introduced to the diet between 4 and 6 months of age. During the first 15 months of life, the patient's weight trended along the 25th percentile, while her length and head circumference trended along the 50th percentile. At approximately 18 months of age, her weight and length dropped to the 8th and 10th percentiles, respectively, while her head circumference remained stable. She was seen regularly by her pediatrician for routine well child care. No additional sick visits, hospitalizations, or reported symptoms occurred prior to the presentation described in this article.

In the emergency department (ED), the patient was noted to be ill-appearing, pale, and lethargic. Her abdomen was markedly distended and tense with non-pitting edema of the

bilateral lower extremities. Vitals were stable with a temperature of 37.5°C, respiratory rate of 22 breaths per minute, pulse of 125 beats per minute, blood pressure of 90/58 mm Hg, and SpO_2 of 98%. Her height was 78 cm (1st percentile), weight was 10.35 kg (22nd percentile), and body mass index was 17.01 kg/m^2 (86th percentile). Laboratory analyses in the ED revealed borderline anemia, hypoalbuminemia, hypocalcemia, normal transaminases, and normal brain natriuretic peptide. Urinalysis was negative for proteinuria, hematuria, and glycosuria. Abdominal X-ray demonstrated a large rectosigmoid stool burden with air-fluid levels in the small bowel, ascending colon, and transverse colon, with absence of volvulus. Ultrasound studies noted biliary sludge and a 2.5 cm diameter segment of small-to-small bowel intussusception. A repeat ultrasound several hours later showed resolution of the intussusception, consistent with normal peristalsis. The patient was treated with two soap suds enemas for constipation (with only mild effect), administered intravenous isotonic fluids for hydration. She was admitted with gastroenterology consultation on hospital day 2. At the time of admission, the main differential diagnoses for abdominal distension with bilateral lower extremity edema included liver dysfunction with poor protein synthesis, malnutrition from CD or dietary deficiency, and protein losing enteropathy. Other differential diagnoses for edema, such as nephrotic syndrome and cardiac failure, were unlikely given the normal urinalysis, normal brain natriuretic peptide, and lack of tachypnea and rales on physical exam.

Initial laboratory testing following admission was significant for hypoproteinemia, hypoalbuminemia, hypocalcemia, and elevated PT and INR (shown in Table 1). An abdominal computed tomography scan demonstrated normal size and enhancement of the liver and spleen. It also showed a large stool burden with distended small and large bowel and bladder. A nasogastric tube was placed for bowel decompression. Polyethylene glycol 3350 was added for a bowel clean out and the patient was given two additional soap suds enemas (with moderate effect). The patient's abdominal distension continued to worsen and a repeat abdominal X-ray was concerning for a paucity of air in the right lower quadrant. Therefore, the patient underwent a contrast enema, which ruled out volvulus, but showed a continued concern for chronic constipation with a dilated colon.

A celiac panel was ordered on admission to investigate CD as a possible etiology of the patient's symptoms. Celiac panel testing results returned on hospital day 2 and revealed extremely elevated titers of all CD markers tested (shown in Table 1). Therefore, CD with an unusual presentation of CC became the leading differential diagnosis. The patient remained on nil per os status with an NG tube for bowel decompression.

Given the concern for CC, a peripherally inserted central venous catheter was placed to maintain adequate nutrition with total parenteral nutrition (TPN) and to facilitate bowel rest due to a suspected high degree of bowel wall edema. Steroids were considered but were deferred due to clinical improvement and the potential for adverse effects, such as hypokalemia in a patient with multiple preexisting metabolic derangements.

The patient then underwent examination under anesthesia, flexible sigmoidoscopy, and esophagogastroduodenoscopy. The EUD and flexible sigmoidoscopy demonstrated no perianal or anorectal lesions and an absence of strictures or masses. Ganglion cells were present with a normal pattern of calretinin staining in full-thickness rectal biopsies at 1 cm and 3 cm above the dentate line. Together, these results ruled out anatomical obstructions and Hirschsprung's disease. Esophagogastroduodenoscopy, obtained as per NASPGHAN guidelines, showed mucosal edema with flattening and loss of mucosal folds in the duodenum. Histopathological examination of duodenal biopsy specimens revealed active and chronic inflammation, villous atrophy, gland hyperplasia, and increased intraepithelial lymphocytes, consistent with the Marsh type 3C classification of CD (shown in Fig. 1) [3]. The combined clinical, serological, and histopathological findings led the clinical team to conclude CD with

Table 1. Patient's laboratory values

	General laboratory values			
	admission	hospital day 7	1 month post discharge	reference values
Erythrocytes, $\times 10^{12}$/L	4.27	–	4.45	4.0–5.5
Hemoglobin, g/dL	12.6	–	12.4	10.5–14.0
Hematocrit, %	37.5	–	37.3	32–42
Leukocytes, $\times 10^{9}$/L	10.8	–	14.2	6.0–17.0
Platelets, $\times 10^{9}$/L	**543** ↑	–	**541** ↑	150–450
Sodium, mmol/L	136	139	140	130–147
Potassium, mmol/L	3.9	4.6	5.1	3.5–5.1
Chloride, mmol/L	**112** ↑	106	107	95–108
Bicarbonate, mmol/L	**18** ↓	**25** ↑	23	20–28
Calcium, mg/dL	**7.6** ↓	**8.6** ↓	10.1	8.8–10.8
BUN, mg/dL	11	**4** ↓	7	2–20
Creatinine, mg/dL	0.3	**0.24** ↓	0.44	0.3–0.7
Bilirubin, mg/dL	0.1	**<0.1** ↓	0.2	0.1–1.2
AST, U/L	44	62	35	20–60
ALT, U/L	28	50	19	5–55
Protein, g/dL	**3.9** ↓	4.4	6.8	6.0–8.0
Albumin, g/dL	**2.5** ↓	**2.7** ↓	4.6	3.4–5.2
PT, s	**15.8** ↑	–	–	12.2–15.5
INR	**1.27** ↑	–	–	0.8–1.2
PTT, s	27.6	–	–	26.5–35.5
Celiac disease markers				
Anti-tTg antibody, IgA, U/mL	**>4,965.5** ↑	–	17.9	<20
Anti-gliadin antibody, IgG, U/mL	**621.4** ↑	–	7.0	<20
Anti-gliadin antibody, IgA, U/mL	**2,214.2** ↑	–	<5.2	<20
Anti-endomysial antibody, IgA	**1:2,560** ↑	–	<1:5	<1:10

BUN, blood urea nitrogen; AST, aspartate aminotransferase; ALT, alanine aminotransferase; PT, prothrombin time; INR, international normalized ratio; PTT, partial thromboplastin time; tTg, tissue transglutaminase; ↑, elevated; ↓, decreased; –, value not measured.

possible CC was the most likely primary diagnosis. The patient's parents were promptly provided education on adherence to a strict gluten-free diet.

While on TPN and total bowel rest, the patient's clinical condition steadily improved and she had resolution of her abdominal distention, edema, and a progressive return to normal bowel function by hospital day seven. Laboratory analysis noted improvement in several values, such as serum chloride, calcium, protein, and albumin (shown in Table 1). During this time, the patient experienced hypophosphatemia secondary to refeeding syndrome, for which the phosphate level within the TPN was adjusted. After 4 days of TPN, the patient's NG tube was removed and she was gradually advanced to a gluten-free liquid and then solid diet as tolerated, with continued improvement in her mood and energy and daily bowel movements. After initiation of an oral diet, there was a recurrence of abdominal distention. Abdominal X-ray revealed a moderate colonic stool burden. Polyethylene glycol 3350 was continued,

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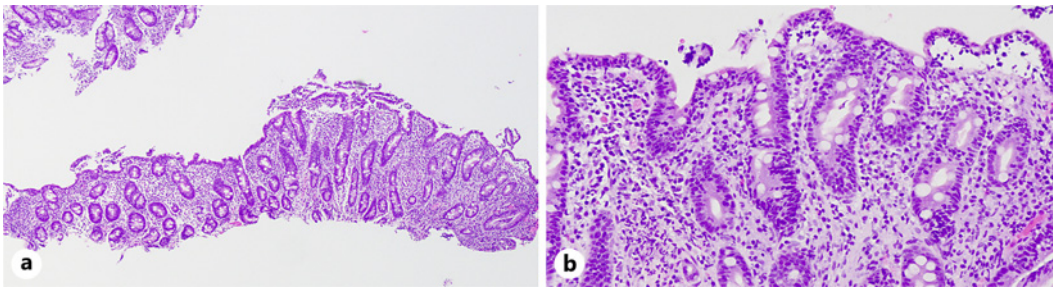

Fig. 1. Duodenal biopsy showing villous atrophy, gland hyperplasia, inflammation, and increased intraepithelial lymphocytes. H&E stain at ×5 (**a**) and ×20 (**b**).

senna was added to the bowel regimen, and dairy products were restricted, leading to swift resolution of the recurrent abdominal distention. The patient continued to advance her diet and regain vigor. She was subsequently discharged home 11 days after initially presenting to the ED. She was followed up in the gastroenterology clinic 1 month after discharge, at which time she was reported to be symptom free and gaining weight, with normalization of all laboratory values (Table 1). As of this writing, the patient has been stable on a gluten-free diet for 22 months. Her weight and height have increased to the 33rd and 11th percentiles, respectively.

Discussion

In this report, we describe a previously healthy, 23-month-old girl who presented with hypoalbuminemia, generalized edema, and constipation. These symptoms are rare in the initial presentation of CD, with hypoalbuminemia occurring in 14.2%, edema occurring in 3.5%, and constipation occurring in 2.7% of cases [9, 10]. The differential diagnoses of these symptoms in the pediatric population are broad, with causes of edema previously discussed by Ahel et al. [12]. In this patient, edema was likely due to a hypoalbuminemia-induced reduction in capillary oncotic pressure with subsequent extravasation of fluid into the interstitium. This appeared to be confirmed with resolution of her edema following bowel rest and parenteral nutrition, which also correlated with improved albumin levels.

Major categories of pediatric etiologies of constipation include physiologic, neurogenic, endocrine, metabolic, anatomic, and iatrogenic [14]. Gastrointestinal dysmotility in CD, which may result in diarrhea or constipation, is multifactorial [15]. For example, esophageal motor abnormalities and delayed gastric emptying may be partially mediated by hormonal derangements, such as increased neurotensin and plasma peptide Y. Inflammation of the small intestine and colon can lead to additional hormonal dysfunction and abnormalities of enteric nervous system signaling that disrupt normal peristalsis. This inflammation can also alter the normal luminal absorptive surface, which can potentially lead to harder, bulkier stools and constipation via mechanisms such as increased permeability to water. This may be exacerbated by dehydration from poor intake and hypoalbuminemia-induced third spacing of fluid. To the best of our knowledge, we present the first case of severe constipation as a major presenting symptom of CC in a pediatric patient.

While the term “celiac crisis” was first described in 1953 by Anderson and Di Sant’Agnese [7], it was not until 2010 that Jamma et al. [8] suggested a formal definition of CC . This definition requires severe, acute-onset gastrointestinal symptoms due to CD in addition to at

Table 2. Diagnostic criteria of pediatric CC

Acute onset or rapid progression of gastrointestinal symptoms attributable to celiac disease requiring hospitalization and/or parenteral nutrition along with at least 2 of the following
Signs of severe dehydration, including hemodynamic instability and/or orthostatic changes
Neurologic dysfunction
Renal dysfunction (creatinine level >2.0 g/dL)
Metabolic acidosis (pH <7.35)
Hypoproteinemia (albumin level < 3.0 g/dL)
Electrolyte abnormalities, including:
Hyponatremia/hypernatremia
Hypocalcemia
Hypokalemia
Hypomagnesemia
Weight loss (>10% prior bodyweight)

Table reproduced and modified with permission from Jamma et al. [8].

least two other inclusion criteria. Inclusion criteria met by our patient at admission included hypocalcemia, hypoproteinemia, and marked hypoalbuminemia, with additional hypomagnesemia (1.5 mg/dL) identified on later testing, prior to the onset of refeeding syndrome. Some inclusion criteria, such as blood pH, were not assessed. However, the inclusion criteria described by Jamma et al. [8] were designed to identify CC in adult patients. While the metabolic abnormalities in Jamma et al.'s [8] definition are translatable to pediatric patients, the absolute weight loss of >10 pounds is not applicable to small children, such as our patient. To the best of our knowledge, inclusion criteria specific to the pediatric population have not been formally described. Therefore, we suggest a formal definition of CC in the pediatric population based on a modified version of Jamma et al. [8], wherein absolute weight loss is substituted for a relative weight loss of 10% (Table 2). With this pediatric definition, clinicians may be able to recognize CC more readily and confidently in the pediatric population, leading to more rapid institution of appropriate care. Additionally, formal guidelines for diagnosing pediatric CC would help standardize clinical research on the topic.

In summary, the initial presentation of CD in pediatric patients is diverse and includes typical and atypical symptoms. Even in the presence of atypical symptoms, such as edema or constipation, CD should be considered as a differential diagnosis. Additionally, we propose a revised definition of CC that is specific to the pediatric population.

The CARE Checklist has been completed by the authors for this case report, attached as online supplementary material (for all online suppl. material, see https://doi.org/10.1159/000545732).

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Statement of Ethics

Ethics committee approval was not required for this study in accordance with local or national guidelines. Written, informed consent was obtained by the patient's parent for publication of the details of their medical case and any accompanying images.

Conflict of Interest Statement

O.F.A. is a speaker for Dupixent (dupilumab) and its use in the treatment of eosinophilic esophagitis. The authors are not aware of any studies considering Dupixent as a therapeutic in celiac disease or celiac crisis. The authors have no additional conflicts of interest to declare.

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Author Contributions

M.R.W. wrote the majority of the manuscript. M.R.W., W.C.S., A.R.A., K.L.O., and O.F.A. revised the manuscript. M.R.W., W.C.S., A.R.A., K.L.O., and O.F.A. provided clinical care for the patient.

Data Availability Statement

All data pertaining to the results described here are available as part of the article, and no additional source of data is required. Further inquiries can be directed to the corresponding author.

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