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Case Report

Celiac crisis with thrombocytopenia and coagulopathy in a child

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ABSTRACT

Background. Celiac disease rarely presents with edema, hypoalbuminemia, acute metabolic deterioration, and electrolyte imbalances. This life-threatening condition is defined as a celiac crisis and may mimic disorders with metabolic derangement and sepsis. The crisis may present at onset or develop in celiac disease patients with poor compliance to a gluten-free diet. The fluid resuscitation and replacement of electrolyte deficits are life-saving modalities.

Case. A 14-month-old girl was admitted with fever, lethargy, severe dehydration, edema, hypotension, and commenced sepsis therapy. However, the patient had a growth delay and loss of weight with diarrhea and delayed motor skills. On admission, laboratory evaluation showed anemia, coagulopathy, hypoalbuminemia, electrolyte disturbances, and metabolic acidosis and developed thrombocytopenia during follow-up. The celiac serological tests and upper gastrointestinal endoscopic duodenal mucosa appearance, and duodenum histopathology findings suggested celiac disease.

Conclusions. This case highlights that a celiac patient may present with a severe illness like sepsis and may be associated with cytopenia and coagulopathy in the celiac crisis.

Key words: celiac crisis, thrombocytopenia, coagulopathy.

Celiac disease is an autoimmune and inflammatory disease that develops in genetically susceptible individuals against the gluten protein in wheat, barley, and rye.[1] The prevalence is 0.7-1.4 %, and is common in Europe.[1] The estimated prevalence of celiac disease is 0.47% in Turkish school children.[2] The most severe and rare complication is the celiac crisis.[3] The crisis may present at onset or develop in celiac disease patients with poor compliance to a gluten-free diet. The mortality rate has been reported as 9% in the crisis.[4] A celiac crisis is presented with edema, hypoalbuminemia, fluid and electrolyte imbalances, and metabolic acidosis following diarrhea requiring hospitalization and parenteral nutrition (Table I).[3] The diagnostic criteria are not clarified in children.

To the best of knowledge, the celiac crisis was accompanied by thrombocytopenia in one child reported in the literature, while the celiac crisis accompanied by coagulopathy was not reported in children.[5] We present a 14-month-old girl admitted with fever, lethargy, severe dehydration, edema, hypotension, metabolic acidosis mimicking sepsis, accompanying anemia, thrombocytopenia, and coagulopathy who was diagnosed with the celiac crisis.

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Table I. Celiac crisis criteria.[3]

1. 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:
2. Signs of severe dehydration including hemodynamic instability and/or orthostatic changes
3. Neurologic dysfunction
4. Renal dysfunction, creatinine level, >2.0 g/dL
5. Metabolic acidosis, pH <7.35
6. Hypoproteinemia (albumin level, <3.0 g/dL)
7. Abnormal electrolyte levels including hypernatremia/hyponatremia, hypocalcemia, hypokalemia, or hypomagnesemia
8. Weight loss, >4.5 kg

Case Report

A 14-month-old girl was admitted with irritability, poor feeding, diarrhea for the last two days, and a 38.6 °C fever. She had lethargy, and moderate to severe dehydration findings. Blood pressure (BP) was 58/38 mmHg (systolic BP below 5th percentile, diastolic BP at 75th percentile), and the heart rate was 136/minute, the respiratory rate was 42/minute and capillary refill time was 3 seconds. She had reduced skin turgor and pretibial edema. Her weight was 6.5 kg (z score -3.46), and her height was 69 cm (z score -3.03). She had no cough, dyspnea, and rhinorrhea. COVID-19 was excluded in the patient by nasal swab polymerase chain reaction and chest radiography. She had severe metabolic acidosis in her blood gas analysis. The laboratory values are shown in Table II. The blood smear test showed hypochromia, microcytosis except for schistocytes and helmet cells, which were not compatible with hemolysis.

Fluid replacement containing potassium phosphate and bicarbonate therapy commenced. The fever did not recur again. C-reactive protein was 0.005 g/L (N: <0.005). The patient had a growth delay and weight loss in the preceding two months with diarrhea, steatorrhea, and delayed motor skills. The parents are consanguineous, and there was no celiac disease in her family. The stool microbiological and microscopic examinations and the rotavirus and adenovirus antigen tests were negative. The platelet level decreased to 83.000 $x10^9$/L, which was confirmed by peripheral smear, and recovered to >150.000 $x10^9$/L in a week. The Coombs test was negative. No bleeding was observed. The international normalized ratio (INR) was not corrected with vitamin K treatment, possibly due to disseminated intravascular coagulation (DIC). The DIC score (including platelet count, d-dimer, PT, fibrinogen level) was three. A score lower than five is not suggestive of overt DIC. The blood, urine, and fecal bacterial cultures were negative. The metabolic screening tests, including tandem mass spectrometry, urine, and blood amino acid levels, were normal. The tissue transglutaminase immunoglobulin (Ig) A and endomysium IgA were positive, >200 RU/mL (N: ≤20), 1/100 titers, respectively. The upper gastrointestinal endoscopy revealed a cracked-mud appearance in duodenum mucosa, accompanied by Marsh 3C duodenal histopathological changes (severe villous flattening, crypt hyperplasia, increased intraepithelial lymphocytes, and lymphoplasmacytic inflammation in lamina propria) suggesting celiac disease (Fig. 1). After that, a gluten-free diet and enteral feeding formulas were initiated. Vitamin A, vitamin E, folic acid and vitamin B_{12} serum levels were normal. The serum 25-OH-vitamin D level was 16 ng/mL (<20: deficiency), and the serum zinc level was 67 mg/dL (N: 70-120), so vitamin D 600 IU/day and zinc 5 mg/day were supplemented. The serum glucose levels and thyroid function tests were normal. Genetic testing for HLA-DQ2 was positive. She gained

Table II. Laboratory results of the patient.

Laboratory Test; Normal range	Day 1	Day 4
Hemoglobin, 11-13 g/dL	8.7	9.8
MCV; 70-85 fL	74	86.5
RDW; 11-16 %	19	20
WBC; 5.4-13.6 x10^9/L	11.36 x10^9	6.49 x10^9
Platelets; 160-385 x10^9/L	373 x10^9	90 x10^9
pH; 7.37-7.45	6.8	7.3
HCO_3; 18-26 mmol/L	6	24.4
Base Excess; ±2 mmol/L	-26	0.8
Creatinine; 0.3-0.6 mg/dL	1.11	0.05
Albumin; 32-48 g/L	27	29
Sodium; 132-149 mEq/L	139	141
Potassium; 3.5-5.5 mEq/L	1.7	5.0
Chloride; 99-109 mEq/L	121	118
Calcium; 9.1-10.3 mg/dL	8.2	8.9
Phosphorus; 2.9-4.8 mg/dL	2.6	4.1
Magnesium; 1.3-2.7 mg/dL	2.2	1.6
Fibrinogen; 1.7-4.2 g/L	1.2	1.5
PT; 9.8-14 seconds	17.6	17.7
aPTT; 21-32 seconds	28.9	27
INR	1.52	1.54

MCV: mean corpuscular volume, RDW: red cell distribution width, WBC: white blood cell, PT: prothrombin time; aPTT: activated partial thromboplastin time, INR: International normalized ratio

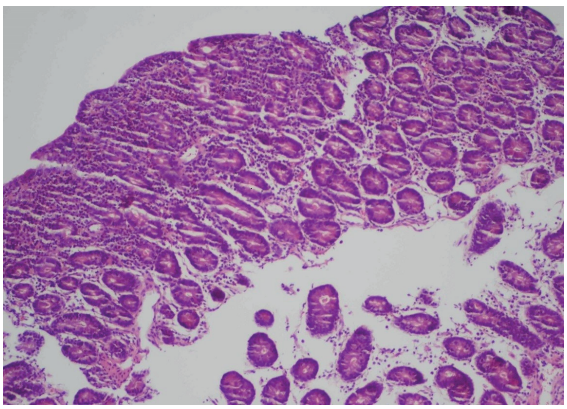

Fig. 1. Severe villous flattening, crypt hyperplasia, increased intraepithelial lymphocytes, and lymphoplasmacytic inflammation in lamina propria (HE, x100).

weight at an outpatient clinic visit after 30 days of beginning the gluten-free diet and vitamin and zinc supplements. The patient caught up on developmental milestones.

Informed consent was received from the parents for the publication of this case report.

Discussion

Celiac disease's pathophysiology involves autoimmune and innate immune responses affected by environmental, chemical, and infectious factors based on genetic susceptibility, including HLA DQ2 and DQ8. It is characterized by a loss of gluten tolerance. Patients may present with intestinal and/or extraintestinal findings such as arthritis, cardiomyopathy, ataxia, peripheral neuropathy, encephalopathy, dermatitis, and hematological involvement or celiac crisis.[6] The crisis findings, including dehydration, electrolyte imbalances, hypoalbuminemia, metabolic acidosis, lethargy, and increase of creatinine, occurred in our case. The fluid resuscitation and replacement of electrolyte deficits are life-saving modalities for the crisis. Corticosteroids may be used in refractory cases, but their efficiency is controversial.[4] The crisis should be considered in patients with acute metabolic deterioration accompanied by chronic fatty diarrhea, growth, and developmental delay. Switching to a gluten-free diet as soon as the patient is diagnosed is the first step to avoiding this fatal crisis.

Anemias in celiac disease are common due to the malabsorption of iron, vitamin B_{12}, folate, and micronutrients such as zinc and copper.[7] A meta-analysis revealed that 3.2% of the patients with iron deficiency anemia had celiac disease.[8] Also, elevated cytokines due to intestinal mucosa inflammation may stimulate hepcidin production, which eventually decreases iron absorption and leads to iron accumulation in the reticuloendothelial system contributing to chronic disease anemia.[9] The more severe mucosal histopathological findings correlate with more severe anemia.[9] Our patient had anemia and coagulopathy attributed to iron, zinc, and vitamin K deficiency due to malabsorption. The literature suggests that vitamin B_{12} deficiency anemia is more common than iron deficiency anemia.[10] However, our

patient had iron deficiency anemia, while serum vitamin B_{12} was normal. Although the patient's histopathology was severe, she had moderate anemia. Thrombocytopenia, leukopenia, and aplastic anemia are rarely associated with celiac disease.[11,12] It has been suggested that the intestinal mucosa and hematopoietic stem cells in the bone marrow are damaged by autoreactive T cells.[13] Thrombocytopenia is rare compared to other hematological manifestations, such as anemia, thrombocytosis, and hypersplenism.[14] As in our case, thrombocytopenia that occurs with the crisis may also result from auto-inflammatory processes. Celiac disease may also be accompanied by autoimmune disorders, including Evans syndrome and immune thrombocytopenic purpura (ITP).[15,16] Karunakaran et al.[17] reported that celiac disease in adult patients with ITP was significantly higher than in the healthy population. Although this study did not report an increase in platelets with a gluten-free diet, other studies report an increase in platelet count with introducing a gluten-free diet.[17,18] They speculated that gluten-related inflammatory mechanisms of celiac disease might lead to autoimmune hematologic manifestations.[17] In our case, chronic disease anemia was associated with celiac disease, nevertheless mild thrombocytopenia was associated with the celiac crisis. The absence of ongoing fever, lack of viral symptoms, and examination findings did not support the infection. A 14-year-old girl diagnosed with a celiac crisis accompanied by severe thrombocytopenia showed gastrointestinal bleeding and died of pulmonary hemorrhage.[5] Another hematologic manifestation that causes bleeding diathesis in celiac disease is coagulopathy, often caused by vitamin K deficiency due to malabsorption. Also, DIC may lead to anemia and thrombocytopenia. However, the DIC score and peripheral smear findings did not suggest overt DIC in the presented case. On the other hand, the coagulopathy or thrombotic condition that can be seen in celiac disease is attributed to causes such as chronic inflammation, endothelial damage, the presence of phospholipid Ig A autoantibodies, and hyperhomocysteinemia due to protein loss in the intestinal wall or related to folate deficiency.[19-21]

In children, while thrombocytopenia and coagulopathy are rarely seen in the course of celiac disease, this association has been described for the first time in the celiac crisis. This case highlights that a celiac patient may present with a severe illness like sepsis and may be associated with thrombocytopenia and coagulopathy in the crisis. Early diagnosis and commencing a gluten-free diet as soon as possible can be life-saving.

Ethical approval

Written informed consent was obtained from the parents for the publication of this case report.

Author contribution

The authors confirm contribution to the paper as follows: study conception and design: ŞH, SD, AÜA; data collection: GH, BBA; analysis and interpretation of results: HTD, AMD; draft manuscript preparation: AÜA, DİM. All authors reviewed the results and approved the final version of the manuscript.

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Conflict of interest

The authors declare that there is no conflict of interest.

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