Diagnostic challenges of celiac disease in a young child

A case report and a review of the literature

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Abstract

Rationale: Celiac disease is a chronic, immune-mediated, multiorgan disorder that affects susceptible individuals, and it is triggered by gluten and other prolamins.

Patient concerns: We present the case of a 1-year-old male child, with a history of idiopathic pericardial effusion, admitted in our clinic for severe abdominal bloating, irritability, loss of appetite and intermittent diarrheic stools. The clinical findings were: influenced general status, irritability, distended abdomen, and diffuse abdominal tenderness.

Diagnoses: The initial laboratory tests revealed anemia, leukocytosis, increased inflammatory biomarkers, high levels of transaminases, and hypoalbuminemia. The stool culture identified an enterocolitis with enteropathogenic Escherichia coli (E. coli).

Interventions: We initiated antibiotic treatment, substitution therapy with human albumin and probiotics with initial favorable evolution, but after 1 month, the patient was re-admitted for the persistence of intermittent diarrheic stools and abdominal bloating, when we established the diagnosis of cow's milk protein allergy. We initiated diary-free diet.

Outcomes: Unfortunately, the patient was re-admitted after another 8 months, presenting the same clinical and laboratory findings as during the initial admission. We repeated the serology for celiac disease and we performed an upper gastrointestinal endoscopy with duodenal biopsies, which established the diagnosis of celiac disease. After 1 month of gluten-free diet, the patient's evolution improved considerably.

Lessons: Enterocolitis with E. coli could be considered as trigger for CD in our case. The diagnosis of CD in small children can be hindered by an insufficient gluten-exposure, and can lead to a delay in the diagnosis as in the case presented above.

Abbreviations: Alb = albumin, CD = celiac disease, Leu = leukocytes.

Keywords: celiac disease, children, enterocolitis

1. Introduction

Celiac disease (CD) is an immunologic disorder triggered by gluten and other prolamins in individuals that carry susceptible haplotypes, HLA-DQ2 (cis [encoded by HLA-DR3-DQA1*05:01-DQB1*02:01 or trans [encoded by HLA-DR11-

DQA1*05:05 DQB1 03:01/DR7-DQA1*02:01 DQB1 02:02]) or HLA-DQ8 (encoded by DQA1*0301- DQB1*0302), the lack of the association between these genes not being correlated with CD, they being otherwise present in 30% to 40% of the healthy people.[1] This disease carries a chronic pattern with multiorgan impairment, in which the duodenal mucosal damage will lead to a chronic malabsorption syndrome.[2] The etiology of CD is still not fully understood, but the multifactorial determinism is well documented, involving both genetic and environmental factors. Recently, apart from the well-known specific haplotypes, there were identified another 40 genomic loci associated with the development of CD, which also interfere with a great amount of other autoimmune disorders.[3] Environmental factors, also known as triggers, carry a great importance in the development of CD. These factors can involve among others: infectious agents, such as rotavirus,[4] the lack of breastfeeding,[5] the time of gluten-containing food introduction to the infant's diet,[6] or gut microbiota colonization.[5] The prevalence of CD varies greatly worldwide depending on the geographical area, but the incidence tends to increase lately in different geographic areas. This fact might be due partially to progress of diagnostic techniques and the physicians' awareness of the disease. Independently of this variation, the general prevalence of CD worldwide is of approximately 1%.[7,8] In Romania, very few studies assessed the prevalence of CD. Thus, a study published in 2003, on 2436 adult patients, stated a prevalence of 2.22%, while another study

performed on 148 asymptomatic family members of patients with CD, encountered a prevalence of 8.7%.[9,10] Despite its relatively high frequency, CD remains many times underdiagnosed mainly due to the lack of specific symptoms in most of the patients.

The symptoms of CD present a wide variability, and in addition, the disease can remain asymptomatic for an unpredictable amount of time. The patients with CD can present both classic gastrointestinal manifestations, such as chronic diarrhea, weight loss, malabsorption, or iron deficiency anemia, but they can also express only extraintestinal manifestations, like osteoporosis, dermatitis herpetiformis, neurologic disorders, liver impairment, or arthritis.[11–13] The diagnosis of CD must be established based on anamnesis, positive serology for CD (anti-transglutaminase, anti-endomysium, and deaminated gliadin antibodies), and suggestive histologic changes in duodenal biopsies, such as villous atrophy and crypt hyperplasia.[1] A susceptible patient requires at least 6 months of gluten exposure before developing the symptoms. Therefore, in small children who do not acquire tolerance for gluten at all, the diagnosis in uncommonly established within the first year of life. The treatment of CD consists in restrictive free-gluten diet, and, in severe celiac crises, even corticosteroids. The prophylaxis of CD has been thoroughly studied during the last years. Therefore, several preventive strategies have been proposed, such as breast-feeding, the timing of gluten introduction into infants' diet or the amount of gluten that should be introduced in their diet in order to acquire tolerance for gluten.[2] Nevertheless, further studies are required that should focus on assessing the impact of these nutritional strategies in genetically susceptible individuals for CD.

We present the case report of a small child diagnosed with CD after approximately 9 months from the onset of symptoms to underline the difficulties related to the diagnosis of CD in infants and small children.

Informed consent was obtained from the patient's mother (legal guardian) for the publication of this case report.

2. Case report

2.1. Presenting concerns

We present the case of a 1-year-old male child, admitted in our clinic for severe abdominal bloating, irritability, loss of appetite, and intermittent diarrheic stools for approximately 1 month. The personal history revealed a mild pericardial effusion without any obvious etiology, for which the cardiologist recommended a gastroenterology consult.

2.2. Clinical findings

The clinical examination at the time of admission pointed out the following pathologic elements: influenced general status, irritability, distended abdomen, and diffuse abdominal tenderness.

2.3. Diagnostic focus and assessment

The initial laboratory tests revealed anemia (hemoglobin 10.2 g/dL), leukocytosis (Leu 14,550/μL), increased inflammatory biomarkers (erythrocyte sedimentation rate 33 mm/h, C-reactive protein 15 mg/L), high levels of transaminases (aspartate aminotransferase 57.4 U/L, alanine-aminotransferase 42.7 U/L, lactate dehydrogenase 255 U/L), and hypoalbuminemia (albumin [Alb] 2.89 g/dL). The stool culture established the diagnosis of enterocolitis with enteropathogenic *Escherichia coli*. The abdominal ultrasound was hindered by the patient's severe

bloating. Therefore, we also performed an abdominal computed tomography scan, which showed distended bowel loops and mesenteric lymphadenopathy. Based on all the tests mentioned above, we established the diagnosis of enterocolitis with enteropathogenic *E coli*.

2.4. Therapeutic focus and assessment

We initiated antibiotic treatment according to the antibiogram, substitution therapy with human Alb and probiotics. After approximately 1 week, we discharged the patient with the recommendation to continue the treatment with probiotics for approximately 1 month.

2.5. Follow-up and outcome

After approximately 1 month, the patient continued to present abdominal bloating and intermittent diarrheic stools. The laboratory tests revealed the persistence of increased levels of transaminases, without other significant modifications. The stool culture was negative. The cardiologic examination was within normal ranges, and the abdominal ultrasound showed the same changes. Therefore, we raised the suspicion of a food allergy or intolerance. The serology for gluten intolerance was negative, but we identified a cow's milk protein allergy, and we recommended dairy-free diet.

Unfortunately, despite the restrictive diet, after another 8 months, at the age of 1 year and 9 months, the patient was admitted in our clinic with the same symptoms as during the initial admission. The laboratory tests revealed again anemia, hypoalbuminemia, and mildly increased liver transaminases. The cardiologic examination showed the recurrence of the pericardial effusion. We repeated the serology for CD, and we identified increased levels of anti-transglutaminase antibodies, approximately 8 times the normal limit. We decided to perform an upper gastrointestinal endoscopy with duodenal biopsies. The histopathologic examination showed consistent modifications for CD, Marsch 3C stage. Also, the genetic test revealed a high risk for CD (DQ2 homozygous genotype). We initiated the gluten-free diet, and the patient's evolution improved outstandingly after only 1 month. Additionally, after a follow-up time of approximately 3 months, we monitored the progression of the disease by performing the anti-transglutaminase and anti-endomysium antibodies, which were within normal limits.

3. Discussion

The diagnosis of CD in children is burdened by many challenges. One of them is represented by the wide variability of symptoms expressed by these patients. In addition, recent studies support the idea that the clinical spectrum of pediatric CD is shifting more and more toward an atypical symptomatology rather than a classical form with gastrointestinal symptoms, and also state that both the incidence of CD in children and the age of diagnosis are still increasing.[14] Our patient presented with gastrointestinal symptoms, such as severe abdominal bloating, intermittent diarrheic stools, but he also presented recurrent pericardial effusion, most-likely due to the associated hypoalbuminemia. Similarly, a study performed by Elfström et al found a positive association between prior pericarditis and CD.[15] Impairment of liver function expressed by increased levels of transaminases is well-known to be associated in patients with CD.[16] Our patient also presented persistent elevated levels of liver enzymes until the

initiation of gluten-free diet. The increasing incidence of CD is also reported by other studies worldwide, likewise a new epidemiology of CD explained by a spread of this disorder in new areas, such as Asian countries[5]. These new trends in the epidemiology of CD can be a result of multiple factors, such as increased awareness, changes in environmental factors, but also a great progress in diagnosing it. CD, like other autoimmune disorders, tends to be more frequent in females, with a female to male ratio of approximately 2:1.[17] In addition to the well-documented role of susceptible haplotypes for CD, it remains a multifactorial disorder, which is also influenced by the environmental, metabolic, and immunologic factors.[18] The most common tools used for the monitoring of the disease progression are the serologic tests including anti-transglutamin-ase, anti-endomysium, and deaminated gliadin antibodies. Regarding our patient's evolution, we monitored the progression of the disease after approximately 3 months, and we identified the serologic tests within normal limits.

Many studies focused recently on assessing the influence of breastfeeding and timing of gluten introduction to the infant's diet on the development of CD in susceptible children. Therefore, a recent study performed by Vajpayee et al on pediatric patients found that breastfeeding at the time of gluten introduction to an infant's diet and beyond this moment will delay the age of CD diagnosis.[19] Similarly, a meta-analysis conducted by Akobeng et al also stated that infants still breastfed at the moment of gluten introduction to the diet presented a 52% lower risk of developing CD.[20] Nevertheless, prospective studies failed in proving the protective role of breastfeeding against the development of CD in small children.[21] Similarly, we mention that our patient was breastfed at the time of gluten introduction to his diet. Regarding the timing and amount of gluten introduction to the diet, the findings are also contradictory. On the one hand, according to the Polish Society for Paediatric Gastroenterology, Hepatology and Nutrition, gluten-containing food should be introduced in small amounts to the infant's diet independently by the feeding pattern, not before the fifth month of life and not after the sixth month of life.[22] On the other hand, 2 multicentre randomized studies, Prevent CD and CELIPREV, showed that in children with an increased risk for CD, the timing of gluten introduction to the diet and the amount of gluten do not influence the development of CD.[23,24] Regarding our case, the gluten was introduced into his diet in the seventh month of life.

Other recent findings discuss the impact of gut microbiota on the development of CD. Therefore, observational studies found changes in the gut microbiota of patients diagnosed with CD, and also increased virulence-related genes in intestinal patho-bionts.[25] Similarly, another study reported alterations of the gut microbiota which indicate impairment of the normal microbiota maturation process in infants who develop later CD.[26] Also, both intestinal infections and the associated antibiotic therapy can increase the risk of developing CD.[27] Similarly, a study performed by Stene et al showed a positive association between rotavirus infection and CD.[4] In addition, it seems that recurrent gastrointestinal infections during infancy are associated with an increased risk for CD later on in life.[28] Our patient also presented an enterocolitis with enteropathogenic *E coli* prior to the diagnosis of CD, suggesting that this intestinal infection can be considered a trigger for CD. After this infection, our patient was also diagnosed with cow's milk proteins allergy, but this nutritional disorder was most-likely secondary to the intestinal infection. In addition, a large population-based cohort study showed that patients with CD carry an increased risk for *Clostridium difficile* infection than healthy controls.[29]

Even though the role of the genetic factors is well-documented in the etiology of CD, they are not enough for the development of CD. The multifactorial determinism of this disorder is reported by multiple recent studies. These recent data discuss also the role of breastfeeding, the timing of gluten introduction to the infant's diet and the amount of gluten, or the maturation of the gut microbiota. Nevertheless, further prospective studies are needed to elaborate effective preventive strategies for CD.

4. Conclusion

The diagnosis of CD in small children is burdened mainly by the atypical symptomatology and the insufficient exposure to gluten leading to a delay in the diagnosis. Intestinal infections are well-known triggers for CD in high-risk individuals. Pericarditis can be encountered in patients with CD prior to the diagnosis.

Author contributions

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