Case Report

Long-standing iron deficiency anemia could be a presentation of non-classical celiac disease: A case report and literature review

Adnan Abdullah Bakarman[1], Samira Awad Banser[2], Rasheed Mohammed Bamekhlah[3]

[1]Assitant Professor of Internal Medicine and Hematology, Hematology Consultant, Department of Medicine, College of Medicine and Health Sciences, Hadramout University, Mukalla, Hadramout, Yemen, [2]Medical Specialist, Department of Medicine, Ibn-Seena Teaching Hospital, Mukalla, Hadramout, Yemen, [3]Professor of Internal Medicine, Senior Medical Consultant, Department of Medicine, College of Medicine and Health Sciences, Hadramout University, Mukalla, Hadramout, Yemen

ABSTRACT

Celiac disease (CeD) is a complex disorder characterized by gastrointestinal (GI) symptoms as well as extraintestinal manifestations, sometimes difficult to diagnose. Commonly referred to as a childhood disease, adult CeD is a well-known entity that should be included in the differential diagnosis of chronic diarrhea or malabsorption syndrome. The pathogenesis involves a genetically mediated autoimmune pathway. In individuals with genetic susceptibility, the mucosa of the small intestine is damaged in response to foods containing gluten. The clinical presentation is variable and ranges from typical GI symptoms to extra-intestinal and systemic manifestations. Clinical improvement and restoration of the intestinal mucosa occur simply by eliminating gluten from the diet. We reported a case of CeD in a young man after 6 years of iron deficiency anemia (IDA), without asserting a clear etiology during this time. In our country, the search for CeD in patients with IDA is usually forgotten and we hereby put it in the spotlight.

Key words: Anemia, Celiac disease, Fatigue, Iron deficiency, Yemen

Iron deficiency anemia (IDA) is the most common cause of anemia worldwide and results from inadequate iron supply for erythropoiesis. It is also the most frequent chronic anemia referral to gastroenterologists. Of all the causes, gastrointestinal (GI) blood loss from colonic or gastric cancer and malabsorption in celiac disease (CeD) is the most important ones that need to be sought. Red cell indices provide a sensitive indicator, and serum ferritin is the most powerful test for iron deficiency. Upper and lower GI investigations should be considered for patients suffering from IDA, unless there is a history of significant overt non-GI blood loss [1]. Chronic refractory IDA is a type of anemia that does not respond to replacement therapy with oral iron preparation [2]. Refractory IDA can be an atypical presentation of non-classical CeD. Pathological diagnosis of CeD is based on a biopsy taken from the second part of the duodenum (D_2) or jejunum and is classified as types [3], or grades [4]. In this report, we describe a young man with refractory IDA as a manifestation of non-classical CeD. The purpose of presenting this case is to raise junior physicians' awareness of this unusual clinical entity.

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CASE REPORT

A 24-year-old male soldier from Shabwah Governorate, Yemen, presented with a history of recurrent attacks of fatigue, dizziness, and exertional dyspnea for approximately 6 years. He visited public, private, and military hospitals and clinics several times where he was investigated. His hemoglobin levels were in the range of 6.4–8.1 g/dL, hematocrit 24.8–32.7%, mean corpuscular volume (MCV) 50–65 fL, and mean corpuscular hemoglobin concentration 26.3–31.1 g/dL, with normal leucocyte and platelet counts. Erythrocyte sedimentation rate was 10–32 mm/h, stool for occult blood was negative 3 times, Coomb's test was negative twice, and serum ferritin level was 1.72 ng/mL (Normal: 21–385). Blood films showed microcytosis hypochromia with increased platelets and normal reticulocyte count (1.1%). Esophagogastroduodenoscopy showed no abnormality except pale duodenal mucosa, and colonoscopy with colonic biopsy was normal. The case was diagnosed many times as IDA and was given oral iron with other supplements without any improvement; 21 pints of blood were transfused during 6 years.

The patient came to our clinic with the same complaints and weight loss, with normal appetite and bowel habits and no history of

Correspondence to: Dr. Adnan Abdullah Bakarman, Department of Medicine, College of Medicine and Health Sciences, Hadramout University, Mukalla, Hadramout, Yemen. E-mail: ab_bakarman@yahoo.com

bleeding tendency. During the clinical examination, he was thin and pale in appearance, with the body mass index of 17.6 kg/m^2. Blood pressure was 110/75 mmHg, and radial pulse rate 95 beats/min, which is regular with average volume. Neither palpable lymph nodes nor hepatosplenomegaly were found. Chest, heart, and abdominal examination were normal. Some investigations were repeated and showed typical IDA. Serum albumin was 2.9 mg/dL and calcium 8.1 mg/dL. Anti-gliadin IgG antibody (AGA-IgG) was 48 U/mL (normal <12), and anti-tissue transglutaminase IgA antibody (AtTG-IgA) was 45 U/mL (normal <25). EGD was repeated and showed pale and granular mucosa of the second part of the duodenum (D_2). Hence, a biopsy was taken, and it revealed normal mucosal surface and villi with an increase in intraepithelial lymphocytes (Fig. 1). The case was diagnosed as CeD with non-classical (formerly atypical) presentation. Gluten-free diet (GFD) was advised with oral iron, folic acid, Vitamin B12, calcium, and Vitamin C. After 2 weeks, the patient started to feel improvement in his life quality. After 6 months on GFD, the patient regained his normal activity with no clinical signs, and all hematological and non-hematological parameters as well as AGA-IgG and AtTG-IgA returned to normal.

DISCUSSION

CeD is an immune-mediated disorder of the small intestine with a variable clinical picture induced by gluten ingestion in genetically predisposed subjects [5]. The immune response in CeD is T-cell–mediated because the majority of the patients express the HLA-DQ2 and DQ8 molecules [6,7]. Gluten is found in cereals, mainly wheat, but may be in rye and barley [8]. This case presented with non-classical CeD. According to Rodrigo-Sáez1 L, although CeD in childhood presents with typical GI symptoms (classic CeD), mainly diarrhea (79% of pediatric cases), in adulthood, atypical presentation including refractory IDA is more common (86% of adult cases) [9].

In this case, the mucosa of D_2 on EGD was pale and granular, which is consistent with the findings of Dicky and Hughes [10].

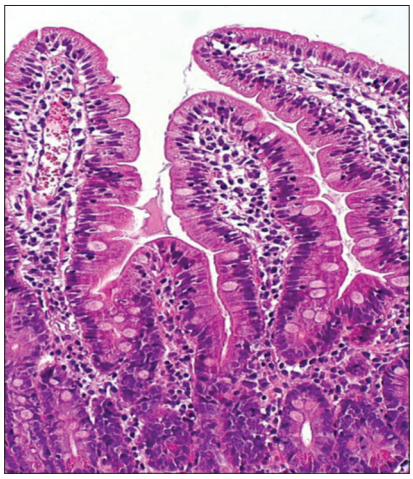

Figure 1: Intraepithelial lymphocytes without villous atrophy in biopsy taken from the second part of the duodenum of a patient with refractory iron deficiency anemia diagnosed as celiac disease (mash Type I, Grade A)

In 1990, Marsh classified the histopathological features of CeD according to the severity, which was modified later, in 1999, by Oberhuber *et al*. into three types called Marsh types: Type I with normal villi and increased intraepithelial lymphocytes, Type II with normal villi and crypt hyperplasia, and Type III with villous atrophy; the latter is subdivided into Type IIIA with partial villous atrophy, Type IIIB with subtotal villous atrophy, and Type IIIC with total atrophy [3]. Our case was Marsh type I. More recently, in 2005, Corazza and Villanacci proposed a new classification: Grade A without and Grade B with villous atrophy [4]; our case was Grade A.

Hopper *et al*. stated that serum AGA levels were previously used for the diagnosis of CeD but are currently considered to not be sensitive nor specific enough. Hence, now, AtTG-IgA is considered the best choice for diagnosing CeD [11]. Our patient had high AGA-IgG and AtTG-IgA levels. Diagnosis of CeD is based on clinical features, pathological findings, and raised serological antibodies. In 2008, Hopper *et al*. and Niewinski found that treatment is directed towards avoiding the offending agent, gluten. Gluten is mainly found in foods such as wheat, pasta, cereals, and breads. However, it can also be found in many other foods, including seasonings and sauces; thus, paying close attention to food labels is essential. Diagnostic studies should be performed before initiating a GFD. Patients must commit to a lifelong GFD. Clinical improvement usually occurs from a few days to weeks of initiation; however, histologic recovery may require more than 24 months [11,12].

Anemia in CeD

In the past, CeD was usually considered only in patients who had frank malabsorption characterized by diarrhea, steatorrhea, weight loss, or failure to thrive or in patients with multiple deficiencies of macronutrients and micronutrients. This could be termed as classic CeD. It has become clear that many, if not most, patients can present with more subtle symptoms, often called non-classical CeD, and often without the classic malabsorption syndrome or even diarrhea. Some, if not many, patients may have silent CeD, wherein they have no symptoms at all [13].

The features of non-classical CeD include a wide range of rheumatologic, neurologic, hematologic, endocrinologic, metabolic, and dermatologic manifestations [14-17]. Among them, hematologic manifestations are one of the most frequent presentations, and, sometimes, they can represent the sole manifestation of the disease [18]. A high index of suspicion for CeD is needed in patients with unexplained, isolated hematological abnormalities, and this depends on better awareness among physicians of general medicine-related specialties [19].

The hematological features of CeD include a variety of conditions anemia, platelet alterations (thrombocytopenia/thrombocytosis), hemorrhagic or thrombotic events, IgA deficiency, hyposplenism, and lymphoma [13,20].

Anemia in patients with CeD is multifactorial in etiology; however, IDA is most commonly reported [21]. The prevalence of anemia, in general, and CeD among patients with IDA have

varied over time and possibly differ according to the geographical area under study [22]. However, in 2022, Roldan *et al*. revealed that IDA occurred among 50.8% of the patients with CeD [23]. On the other hand, silent CeD appeared in 10.4% of the patients with IDA [24].

The main mechanism for IDA in CeD is related to malabsorption, as the site of iron absorption — the proximal duodenum — is almost always involved [20]. Anemia in CeD is not only related to gluten-driven damage of the bowel mucosa, as it was also reported in patients with positive serology before development of atrophy [25]; this supports the need for CeD testing in patients with IDA and early recommendation of a GFD in these potential patients with CeD with extraintestinal manifestations [26]. IDA is one of the most frequent extraintestinal presentations of CeD and, according to current guidelines, is an indication for CeD screening [27]. Therefore, the first step in evaluating the suspicion of CeD in patients with IDA remains serological testing [28], as it is currently recommended in the guidelines [1]. One of the characteristics of IDA in CeD is refractoriness to oral iron supplements [29]. If symptomatic, correction of anemia can be done by intravenous iron. Otherwise, it usually restores in parallel with the histological recovery of atrophic mucosa on a GFD [30]. Lack of anemia correction on follow-up visits should prompt the search for other causes (through colonoscopy and capsule endoscopy) and examination for refractory CeD [31].

Sharing the same site of absorption as iron, folate deficiency can also occur in CeD, leading to macrocytic (or normocytic when deficits are combined) anemia. In addition, we should take into account the fact that normocytic anemia does not rule out IDA, as up to 40% of the patients with IDA have normal MCV [32]. Studies have reported up to one-fifth of patients having low folate levels [33]. Theoretically, Vitamin B12 deficiency was considered to be less common in CeD, as its absorption takes place in the terminal ileum, which is infrequently involved. However, studies have also reported significant proportions for B12 deficiency [13,33].

Anemia of chronic disease, defined by anemia with high ferritin levels and inflammatory syndrome, has also been described in CeD [34,35]. Moreover, associated aplastic anemia has also been reported in isolated cases [36-39].

CONCLUSION

Based on our reported case, non-classical CeD can lead to refractory IDA, but diagnosis is difficult and requires a high index of suspicion. Therefore, for a young man with refractory IDA, examinations of the digestive tract must be started immediately, and non-classical CeD must be considered in the differential diagnosis.

CONSENT FOR PUBLICATION

Written informed consent was obtained from the patient for publication of this case report and all accompanying images.

AUTHORS' CONTRIBUTIONS

All authors contributed to the completion of this work. The final manuscript was read and approved by all authors.

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