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Case Report

Don't jump into the Marsh: Awareness of Celiac Disease overdiagnosis in adult community practices: A Case Series of Misdiagnosed Celiac Disease in adult patients

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Abstract

Celiac Disease (CeD) is an immune mediated systemic disorder caused by ingestion of gluten resulting in small intestinal damage. The gold standard of diagnosis continues to be with small intestinal biopsies, but the interpretation of histology requires the proper context. The diagnosis of CeD is made by histology, but only in the right context, which includes symptoms, serologies and exclusion of other disorders. We describe a case series of 6 adults who were "un-diagnosed" with CeD upon review of all the components of the diagnosis.

Introduction

Celiac Disease (CeD) is a systemic autoimmune disorder with a genetic predisposition. It can develop at any age, presenting with myriad of symptoms that range from typical symptoms to atypical symptoms to asymptomatic individuals. Typical symptoms include abdominal pain, bloating and constipation, while atypical symptoms can include brain fog, rashes, arthralgias, and hepatitis. Until the 1950s, CeD was a clinical diagnosis based on observations focused on malabsorptive features [1]. Now, the first step in determining if a patient has CeD is to obtain serologies, as this disorder results in duodenal damage caused by the ingestion of gluten, found in wheat, barley, and rye. The most sensitive serologies include tissue transglutaminase IgA (tTG IgA) and Endomysial Antibody (EMA). The gold standard of diagnosis continues to be with small intestinal biopsies. Villous atrophy is not pathognomonic when diagnosing CeD, as it can also be found with the use Olemsartan, Giardiasis, Crohn's Disease, autoimmune enteropathy, food allergies, Common Variable Immunodeficiency, and collagenous sprue, to name a few. However, villous atrophy of the small intestine with positive celiac antibodies does confirm the diagnosis of CeD [2].

Characteristic biopsy findings are based on Marsh classification (Marsh 0-4) and include villous blunting with crypt hyperplasia and greater than 25 intraepithelial lymphocytes (IEL) per 100 epithelial cells [3]. However, a histologic finding of IEL's without villous atrophy is common and presents in a wide spectrum of other disorders, including H pylori, and peptic duodenitis. Kakar et al, identified 43 patients with increased IEL's and normal villous architecture and only 10% of those patients had a true diagnosis of CeD [4]. The confirmation of a diagnosis of CeD should be based upon a combination of findings from the medical history, physical examination, antibody testing, HLA testing and histology. In our case series, we describe six adult patients given a misdiagnosis of CeD based only on infiltrative histology, without villous atrophy. We identified 97 patients through a retrospective chart review of adult patients who presented between 2017 and 2019 to the University of Maryland Center for Celiac Disease and Gluten Related Disorders as a second opinion for a presumed diagnosis of CeD. The study received Institutional Review Board (IRB) approval. Clinical and demographic data were collected, including age, sex, presenting symptoms, endoscopic findings and histological features. Of those, six cases (6%), all presenting with IEL's (Marsh 1), were determined not to have CeD.

Case Series

Case 1

A 36-year-old female presented with anxiety, nausea, epigastric pain and a 4.5kg weight loss and underwent an upper endoscopy with biopsies. The patient was informed that the histology from the duodenal biopsies was suspicious for CeD and biopsies from

the stomach were suspicious for gastritis. The pathology report was described as increased inflammation in the duodenum, as there was an increase in IEL's. Celiac serologies were found to be negative. She was advised to start a Gluten Free Diet (GFD) and was prescribed a 4-week course of esomeprazole. She initially had resolution of her symptoms after implementing a gluten free diet. Pathology slides from her endoscopy were obtained and reviewed by our Gastrointestinal (GI) pathologist who determined there was no evidence of CeD, as the slides only presented evidence of acid injury secondary to peptic duodenitis, as no villous atrophy was appreciated. There are 5-16% of cases where biopsy findings will be consistent with CeD, despite having normal serologies [5,6]. To resolve the confusion of her diagnosis, celiac genetic testing was performed, and the patient carried neither of the HLA genes.

Case 2

A 72-year-old female presented for evaluation of CeD after presenting with a 20-year history of intermittent abdominal pain and pruritis, followed by diarrhea and nonbloody/nonbilious emesis. She had an upper endoscopy and colonoscopy with biopsies. Pathology was consistent with >25 IEL's per HPF in the duodenum and antral gastritis, but no abnormalities were seen in the villous architecture. Blood work was negative for endomysial antibody. The deaminated gliadins (IgA & IgG) were normal, but neither tTG IgA nor tTG IgG were drawn at time of initial diagnosis. Genetic testing revealed a positive HLA DQ8. Slides were obtained and reviewed by our pathologist. Findings were consistent with peptic injury, not CeD.

Case 3

A 47-year-old female with a history of diverticulosis presented with reflux and underwent an upper endoscopy. A hiatal hernia was identified and she was started on pantoprazole. Her biopsies identified increased IEL's (> 25 per HPF), without any abnormalities in the villous architecture. Celiac serologies and HLA genetic testing were negative. However, the patient was diagnosed with CeD based on the pathology findings. She started a GFD, which seemed to help her symptoms. Slides were obtained and reviewed by our pathologist and revealed no evidence of CeD.

Case 4

A 59-year-old female presented with an acute weight loss. She was evaluated by her primary care physician (PCP) where work up included an ultrasound, abdominal CT and labs, which were negative for malignancy. She was referred to a gastroenterologist for the continued weight loss and for development of intermittent bouts of bloating and diarrhea. An upper endoscopy with small intestinal biopsies was performed and was reported to be consistent with CeD. A GFD was initiated. Her slides were reviewed with our pathologist, who concluded the biopsies were consistent with peptic injury, as there was an increase in IEL's (>25 per HPF) without villous atrophy. Genetic testing was positive, as the patient was positive for both HLA DQ2 and DQ8, placing her at an increased risk of developing CeD [7]. She performed a gluten challenge for 8 weeks followed by a repeat upper endoscopy with biopsies, which showed no evidence of CeD.

Case 5

A 61-year-old female presented with increased transaminases. She had an abdominal ultrasound performed, which was negative. She did not present with any typical symptoms, but her work up proceeded. She was found to have a tTG IgG of 10 U/mL (normal <4 U/mL) with a negative tTG IgA. Because of this lab finding, she had an upper endoscopy with biopsies, and was told she had scalloping in the duodenum, which was consistent with CeD. Based upon these gross findings, she was told to start a GFD. Pathology from the duodenal biopsies showed no changes consistent with CeD and HLA gene testing was negative.

Case 6

A 38-year-old female was evaluated for left upper quadrant pain not related to specific foods. Work up included a negative abdominal CT. Because of the persistent pain, she underwent an upper endoscopy with biopsies, which revealed increased IEL's (>25 per HPF) with preserved villous architecture. No celiac serologies were drawn. She was diagnosed with CeD and advised to start a GFD. Review of her original histology revealed preserved villous architecture without any evidence of IEL's.

Discussion

Our case series describes six adult patients with varied symptoms, who were given a diagnosis of CeD, based solely on the presence of IELs in the absence of villous atrophy [1]. A 1993 case series study by Jeffers, et al, concluded that infiltration of intraepithelial lymphocytes in the duodenal mucosa can also occur in peptic duodenitis and should not be the sole modality of diagnosing CeD [8]. Five out of 6 patients, after review of their original biopsies, were, in fact, found to have peptic duodenitis. One patient was found to have no inflammatory changes on biopsies. IEL's can be found in a spectrum of different conditions, including the H pylori, and peptic duodenitis [4]. Our case series reiterates the finding that a diagnosis based only on increased IELs on histology is inadequate to diagnose CeD. Though this finding has been classified as Marsh 1, it is not pathognomonic for CeD. A proper diagnosis of CeD should only be considered in the setting of villous atrophy with positive antibody testing and/or positive HLA genetic testing.

Conclusion

Celiac Disease (CD) is an autoimmune enteropathy that results in damage to the small intestinal mucosa when gluten, found in wheat, barley, and rye, is ingested, which only occurs

in genetically susceptible individuals. The broad range of clinical presentations may lead to diagnostic difficulties and, at times, incorrect diagnoses. Our case series highlighted 6 adult patients who were incorrectly diagnosed with Celiac Disease, based solely on presence of IEL's in the small intestine. When diagnosing one with Celiac Disease, celiac serologies should be drawn, followed by a small bowel biopsy. If there is still a question of a proper diagnosis, HLA gene testing should be drawn. With the incorrect diagnosis, patients unnecessarily adhere to a GFD, which is expensive and affects one's quality of life. A proper diagnosis of CeD should only be considered in the setting of villous atrophy with positive antibody testing and/or positive HLA genetic testing.

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Informed patient consent was obtained for publication of the case details.

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