

Chronic urticaria: A cutaneous manifestation of celiac disease

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Celiac disease, or gluten-sensitive enteropathy, is an immune-mediated disease of the small bowel that results in malabsorption. It classically presents with gastrointestinal symptoms including chronic diarrhea, weight loss, abdominal bloating and anorexia. It is becoming more frequently identified in asymptomatic patients with a diagnosis of deficiencies related to malabsorption of iron, folic acid, vitamin B₁₂ and vitamin D. It is increasingly identified as a cause for early or refractory osteoporosis. Occasionally, celiac disease presents with cutaneous manifestations alone. Dermatitis herpetiformis is a well-recognized cutaneous manifestation of celiac disease. Other cutaneous manifestations include alopecia, angular stomatitis and aphthous ulcerations. Described here is a case of a 24-year-old woman who presented with intermittent urticaria and gastrointestinal complaints. She was found to have celiac disease on small-bowel biopsy. Both her gastrointestinal symptoms and urticaria resolved when she was put on a gluten-free diet, suggesting that her urticaria was a cutaneous manifestation of celiac disease.

Key Words: *Celiac disease; Chronic urticaria*

CASE PRESENTATION

A 24-year-old woman was referred to a gastroenterologist for assessment of a possible food allergy. She had a six-month history of episodic abdominal cramping, diarrhea and vomiting. The patient would awaken at night with severe abdominal cramping, followed by vomiting and watery diarrhea. The abdominal cramping was relieved by vomiting. She did not have hematemesis or bloody diarrhea. These symptoms occurred at night and resolved, for the most part, by the following morning. She was unable to associate any particular foods with her symptoms. In between episodes, she felt well and her bowel movements were normal. Her weight was stable. She had not travelled or been exposed to well water. She had never experienced similar symptoms, and had no history of gastrointestinal disease. There was no family history of gastrointestinal disease.

She also described a four month history of intermittent hives. Initially, she would notice a raised itchy eruption around her wrists. This would last approximately 24 h and subside. As time went on, the eruption would last longer and spread to her torso and her knees (Figure 1). On two occasions, she experienced swelling of the lips and tongue. She had no

L'urticaire chronique : Une manifestation cutanée de la maladie coéliquaque

La maladie coéliquaque, ou entéropathie sensible au gluten, est une maladie à médiation immunitaire de l'intestin grêle responsable d'une malabsorption. D'ordinaire, elle s'accompagne de symptômes gastro-intestinaux, y compris une diarrhée chronique, une perte de poids, des gonflements abdominaux et une anorexie. Elle est de plus en plus dépistée chez des patients asymptomatiques ayant reçu un diagnostic de carences reliées à la malabsorption du fer, de l'acide folique, de la vitamine B₁₂ et de la vitamine D. En outre, elle est de plus en plus tenue responsable d'une ostéoporose précoce ou réfractaire. Il arrive toutefois que la maladie coéliquaque ne s'accompagne que de manifestations cutanées. La dermatite herpétiforme en est une manifestation bien connue. L'alopecie, la perlèche et les ulcères aphteux en sont d'autres. Est décrit aux présentes le cas d'une femme de 24 ans qui a consulté en raison d'une urticaire intermittente et de troubles gastro-intestinaux. La biopsie du grêle a révélé une maladie coéliquaque. Ses symptômes gastro-intestinaux et son urticaire ont tous deux disparu grâce à un régime sans gluten, ce qui indique que l'urticaire constituait une manifestation cutanée de la maladie coéliquaque.

personal or family history of urticaria. She was referred to an allergist who confirmed that this was chronic urticaria. She was found to be allergic to dust mites, pollens and moulds by skin prick testing. The allergist did not offer any recommendations on how to treat the urticaria.

The patient was otherwise healthy, and her only medication was an oral contraceptive pill. She was a nonsmoker and rarely drank alcohol.

At the time of her assessment in the gastrointestinal clinic, her physical examination was unremarkable. She did not have any urticarial lesions.

Initial laboratory work revealed a normal complete blood count, with a normal differential and normal blood smear. Her thyroid hormone concentrations were normal and her stool was negative for parasites.

The working differential diagnosis included irritable bowel syndrome, celiac disease (CD) and eosinophilic enteritis. Further laboratory work showed positive tissue transglutaminase immunoglobulin A serology. She also had a low ferritin concentration, normal immunoglobulin concentrations, normal transaminases, normal folate and normal eosinophil counts. An esophagogastroduodenoscopy

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Figure 1) Chronic urticarial eruption associated with celiac disease

revealed normal appearing esophageal, gastric and duodenal mucosa. Histology of biopsies taken from the second part of the duodenum showed marked blunting of the villi and intraepithelial lymphocytosis, consistent with CD.

The patient was referred to a dietician and advised to adhere to a gluten-free diet. She had no recurrence of chronic urticaria between the time of the diagnosis and beginning the gluten-free diet. In the last year, since beginning the diet, her gastrointestinal symptoms have resolved, and she has not experienced any further episodes of urticaria.

DISCUSSION

The association between CD and chronic urticaria has been previously reported. In 1987, Hautekeete et al (1) first reported the case of a 47-year-old man who presented with chronic urticaria, followed by gastrointestinal complaints suggestive of CD. The patient's gastrointestinal complaints and urticaria resolved on a gluten-free diet. More recently Scala et al (2) described a case of a 24-year-old woman with chronic urticaria who did not have gastrointestinal symptomatology suggestive of CD. This patient was positive for serum anti gliadin, antireticulin and antiendomysial antibodies, and subsequent small-bowel biopsy confirmed CD. Her urticaria also resolved on a gluten-free diet. Gallo et al (3) investigated 43 patients with chronic urticaria for CD. They found that three of 43 (7%) patients had histology consistent with CD on small-bowel biopsy (3). This rate is higher than the prevalence in the general population, which is estimated to be one in 250 (4). Levine et al (5) reported a case in the pediatric literature of an 11-year-old girl with chronic urticaria and CD (5). This young patient was treated with a gluten-free diet and she improved clinically; however, her urticaria persisted. The persistence of urticaria in the pediatric patient argues against the hypothesis that chronic urticaria is a cutaneous manifestation of CD. It is unclear why this patient responded differently from the others. Perhaps compliance with the gluten-free diet was not complete, although her clinical improvement argues against this. Perhaps the patient had another cause for her

chronic urticaria. The cases do suggest an association between CD and chronic urticaria.

The cutaneous manifestations of CD have been well described in a review by Poon and Nixon (6). They classify the cutaneous manifestations into two etiological groups: immunologically mediated conditions; and conditions resulting from the complications of CD.

Dermatitis herpetiformis is the best known immunologically mediated cutaneous manifestation of CD. It presents as a pruritic bullous rash classically found on the elbows, knees and buttocks (7).

Alopecia areata is another immunologically mediated phenomenon that has been associated with CD. Two Italian studies have shown an increased prevalence of biopsy-proven CD in patients with alopecia areata. The first study reported a prevalence of one in 89, and the second study reported a prevalence of one in 116, both of which are significantly more frequent than the background prevalence of CD in the Italian population, which is one in 305 (8,9).

Chronic urticaria is defined as urticarial lesions that are present, intermittently, for six weeks or longer. The urticarial lesions usually last between 4 h and 36 h. The pathogenesis of chronic urticaria has not yet been fully determined. It has been shown that patients with chronic urticaria have an autoantibody that inappropriately activates mast cells. Functional assays have indicated that the autoantibody is an immunoglobulin G molecule directed against the alpha-subunit of the immunoglobulin E receptor on mast cells. The immunoglobulin G autoantibody binds to the immunoglobulin E receptor and causes mast cell degranulation resulting in urticaria. Complement activation causes the recruitment of many immune cells resulting in the perivascular infiltrate seen on histology (10).

In 1983, Leznoff et al (11) first identified that patients with chronic urticaria have a higher incidence of antithyroid antibodies than the background population. This discovery provided the first evidence that patients with chronic urticaria might have an autoimmune disorder. The additional discovery that patients with chronic urticaria have a higher incidence of CD, another autoimmune disorder, further strengthens this hypothesis.

The pathogenesis of CD remains incompletely understood. We know that gliadins, glutenins, hordeins and secalins, all proteins from cereal grains, can cause CD in susceptible people. These proteins are degraded into negatively charged peptides that cross the mucosa of the small intestine by some unclear mechanism. In genetically susceptible people, these peptides are then taken up by DQ2 or DQ8 antigen presenting cells and presented to CD4+ T cells. The activation of these DQ2 and DQ8 restricted CD4+ T cells results in a Th1 inflammatory response that leads to tissue damage (12).

We propose that chronic urticaria is another immunological manifestation of CD. How it causes chronic urticaria is unclear. Perhaps the inflammatory response generated in CD is responsible for activating cells that produce the immunoglobulin G autoantibody in chronic urticaria.

On the basis of our case presentation, we suggest that clinicians consider the diagnosis of CD in patients with chronic urticaria of unclear etiology.

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