In extremis diagnosis of celiac disease and concomitant wheat allergy

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ABSTRACT

Celiac disease (CD) and concomitant wheat allergy are not commonly described in the literature. Both can have almost the same treatment consisting of a gluten-free or wheat-free diet. On the other hand, they are based on totally different pathogenetic mechanisms and can be easily underdiagnosed, particularly CD.

We describe a peculiar case of a young female patient affected by wheat allergy whose serological and histological data were not diagnostic for CD. Organ culture system successfully detected specific antibodies for CD in duodenal biopsy supernatant, supporting the diagnosis of CD.

Keywords: *Celiac disease, wheat allergy, organ culture, histology, gluten-free diet*

INTRODUCTION

Celiac disease (CD) and concomitant immunoglobulin E (IgE)-mediated wheat allergy are not commonly described in the literature, and even the possible coexistence of T helper 1 (Th1)- and Th2-type diseases is still under debate (1-3).

Wheat allergy has a prevalence rate of 0.2%-0.9%, and since it is an IgE-mediated reaction, Th2-type lymphocytes are mostly involved in. It may also present with irritable bowel syndrome-like gastrointestinal symptoms, making differential diagnosis difficult. Its diagnosis is based on skin tests and in vitro tests for specific IgE (4).

On the other hand, CD is a chronic inflammatory bowel disease considered to arise from an inappropriate T cell-mediated immune response against ingested gluten (5). It arises in genetically susceptible individuals presenting with HLA DQ2 and/or DQ8 and has a prevalence rate of approximately 1%. The only treatment currently available is a lifelong gluten-free diet (GFD). Its diagnosis is supported by the histological finding of intestinal atrophy as well as sensitive and specific serological anti-endomysial antibody (EMA) and anti-transglutaminase (anti-tTG) antibodies (6). Moreover, duodenal biopsy organ culture has proven to be helpful in solving diagnostic dilemmas when gluten-related disorders are suspected and in particular when histology and serology are inconclusive, a GFD is started before adequate diagnostic work-up or even in antibody deficiency syndromes. Organ culture system consists in finding EMA and anti-tTG antibodies (IgA and/or IgG) in supernatants of cultured duodenal biopsies (7).

Here, we present a singular case of wheat allergy in which diagnosis of CD was also performed, taking advantage of the refined diagnostic capabilities of the organ culture system.

CASE PRESENTATION

A 25-year-old female Caucasian patient referred to our Gastroenterology Unit complaining the recent onset of swelling, abdominal pain, diarrhea and weight loss. Atopic dermatitis and erythematous skin lesions mainly localized on the face were also present since adolescence.

She reported a significant improvement of all symptoms after a self-administered diet low in cereals and gluten. Moreover, laboratory tests showed mild iron deficiency anemia (red blood cells, 4.28×10^{12}/L; hemoglobin (Hb),

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11.8 g/dL; mean corpuscular volume, 88 fL; hematocrit, 36.9%; and ferritin, 20 µg/L), hypocholesterolemia (143 mg/dL), and vitamin D deficiency (26.8 ng/mL). Osteoporosis was confirmed using Computerized Bone Mineralometry (lumbar spine T-score, -2.3; femoral neck T-score, -2.6). Therefore, a disorder related to wheat or gluten was presumed.

Written informed consent was obtained from the patient. All tests and diagnostic procedures were in agreement with the guidelines and current literature. The local ethics committee approved this case study.

Given the recent intake reduction, a 6-week gluten challenge was started, suggesting at least 50 g of gluten per day (8), although the patient poorly tolerated it because of a new exacerbation of symptoms. Moreover, symptoms appeared immediately or within the first 2 hours after ingestion of gluten-containing foods. Skin prick test for wheat showed a positive result. Thereafter, total serum IgE and specific IgE against wheat, barley, oats, rye, gluten, and cow's milk proteins (β-lactoglobulin, lactalbumin, and casein) were measured by fluorometric sandwich immunoassay using Immuno-CAP system (Phadia, Uppsala, Sweden) with a detection range of 2-5000 kU/L and 0.1-100 kU_A/L, respectively, where A represents the allergen-specific antibodies. Total serum IgE>100 kU/L and specific IgE≥0.35 kU_A/L were considered as positive results. Total serum IgE concentrations resulted in 271 kU/L, and specific IgE against wheat was 1.23 kU_A/L. The other specific IgE tested were negative. A flow cytometry-assisted basophil activation test (BAT) for wheat was performed to confirm the diagnosis of wheat allergy. It is an in vitro functional test for the diagnosis of immediate-type allergy, which is a good alternative for those patients at risk of severe anaphylactic reactions or with contradictory test results. BAT for wheat was performed using two flow cytometric procedures based, respectively, on the expression of CD63 (Becton Dickinson-BD Biosciences, San Jose, CA) and CD203c (Beckman Coulter, Fullerton, CA) on the cell surface of basophils activated in vitro by exposure to wheat in double dilution. In both procedures, at least 500 basophils were tested for each whole blood sample, and the activated cells/total counted cells ratio was >15% (used as the cut-off value to identify positive results for BAT).

In addition, specific serology for CD has been performed, showing borderline results: IgA anti-tTG antibodies resulted in 9.5 UA/mL (n.v.<9), whereas IgA EMA showed negative results. Haplotype HLA DQ8 (DQA1*03 e DQB1*03:02) was also found by genetic testing to confirm a suspected case of CD. Upper endoscopy was performed, and no macroscopic alterations were documented. Histology of six duodenal biopsies (from bulb and second portion) mainly revealed type I-II alterations according to the Marsh-Oberhuber classification (infiltrative-hyperplastic type: normal villous architecture and crypt hyperplasia with >25 intraepithelial lymphocytes per 100 enterocytes). Not clear and only focal villous sub-atrophy compatible with type IIIA was described in only one out of six biopsy specimens (9). Organ culture system has been also performed to successfully detect IgA EMA and anti-tTG antibodies in duodenal biopsy supernatant after 48 h of incubation (anti-tTG 1.069, n.v.<0.300).

Wheat allergy and CD were concurrently diagnosed in these conditions. Both gastrointestinal symptoms and dermatological manifestations receded after 12 months of strict GFD. An improvement was also observed in Hb levels (12.5 g/dL), cholesterolaemia (176 mg/dL), ferritin (53 µg/L), and vitamin D (48 ng/mL). IgA EMA and anti-tTG (4.72 UA/mL, n.v.<9) revealed negative results. Upper endoscopy had been performed again, and histology of duodenal biopsies revealed type 0 and focal type I alterations according to the Marsh-Oberhuber classification, further confirming the correctness of diagnosis of CD.

DISCUSSION

Gluten-related gastrointestinal disorders, such as CD, should be always considered when investigating allergy to gluten, wheat, or other cereals. In fact, clinical manifestations may be overlapping, and these different pathological entities may even be present simultaneously. On the other hand, a proper diagnostic investigation in this field may be affected by an already started GFD as well as an insufficient or not tolerated gluten challenge. Moreover, villous atrophy in CD may be patchy (pathologists usually take the most severely abnormal biopsy specimen to make a diagnosis), and this condition can make the diagnosis of CD even more difficult. In our case, all these circumstances resulted in a not diagnostic histology with mild and non-specific alterations described (9). In addition, serologic tests for CD revealed borderline or negative results, possibly due to an inadequate or non-continuous intake of gluten. Conversely, organ culture system was confirmed to be a useful tool to assist histology and serology in difficult diagnosis of CD (10). An improvement in clinical, serological, and histological data after a GFD was achieved. It further supported the reliability of this technique and the correctness of concomitant diagnoses of CD and wheat allergy.

In conclusion, both CD and wheat allergy can share clinical manifestations and can eventually coexist. Their differential diagnosis may be difficult; therefore, proper diagnostic tools and timing are fundamental. Avoiding CD underdiagnosis is crucial to prevent and treat possible complications of this multisystem inflammatory disease (5). Furthermore, it has considerable economic implications, because patients with CD in Italy receive financial support to buy gluten-free foods, unlike those affected by wheat allergy.

Informed Consent: Written informed consent was obtained from the patient who participated in this study.

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