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CASE REPORT

What does not look like celiac disease and instead it is

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ABSTRACT

The celiac disease (CD) diagnosis sometimes is challenging and diagnostic process cannot always follow a simple algorithm but it requires a close collaboration between histo-pathologists, clinicians, laboratory and genetic experts. The genetic predisposition for CD is related to HLA-DQ2 and/or DQ8 but other HLA haplotypes and non-HLA genes may be involved in genetic predisposition. In particular DQ7 may represent an additive and independent CD risk associated haplotype. We describe an unusual case of a female 42 year old with a previous diagnosis of Hodgkin lymphoma, who has a clinical presentation suggestive for CD with negativity for anti-transglutaminase and anti-endomysium antibodies and HLA-DQ7 positivity.

Keywords: Celiac disease, HLA-DQ7, Gluten free diet.

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Introduction

Celiac disease (CD) is a chronic immune-mediated inflammatory disorder of small intestine triggered by gluten proteins of wheat, rye and barley in genetically predisposed individuals who carry human leukocyte antigen (HLA) haplotypes almost always either HLA DQ2 or HLA DQ8. The diagnosis of CD arises from combination of histological mucosal changes and positivity of serological tests, antitransglutaminase antibodies (tTG) or anti-endomysium antibodies (EMAs). Demonstration of the carriage of the HLA DQ2 and/or HLA DQ8 may also be required since the absence of these haplotypes effectively excludes the diagnosis of CD. Sometimes the diagnosis of CD can be very challenging and the diagnostic process cannot always follow a simple algorithm. We describe an unusual case of a female 42 year old, affected by possible seronegative CD, HLA DQ7 positive.

Case report

The patient had three regular pregnancies, no miscarriages and has regular life's condition (no drinking, no smoking). She had an important family oncology history (father with gastric cancer, mother with breast cancer and further relapse, a first-degree cousin with Hodgkin lymphoma, an uncle with lung cancer).

The patient remembers common infectious childhood diseases, tonsillectomy and adenoidectomy in younger age. In 2009, a diagnosis of Hodgkin lymphoma, localized in the mediastinal region was performed and resolved after 12 sessions of chemotherapy (February-August 2009 according to ABVD-Dacarbazine 566 mg, Doxorubicin 37.9 mg, Bleomycine 15.1 mg, Vinblastin 9.06 mg scheme) and radiotherapy (September 2009-January 2010- 30.6 Gy in 17 sessions with photones x of 15 MV).

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Because of persistent dyspepsia and bloating, in December 2021 an endoscopic examination of upper digestive system (EUDS) was performed, with evidence of microrelevated lesion in cardial region and mild hyperemia of gastric mucosa with gastric histology negative for the presence of Helicobacter Pylori. Duodenal histology was suggestive for CD (as detailed above) and a gluten free diet (GFD) was prescribed, despite negativity for tTG and EMAs. Autoimmune diseases, drug use and parasitic infections were ruled out.

In March 2022, a screening thyroid ultrasound evaluation notes a reduced size of thyroid lobes with diffuse altered echo pattern with fibrous scars suggestive for autoimmune inflammatory process. A bone densitometry in May 2022 evidenced a femur osteopenia with a T Score of -1.6 and a normality of lumbar vertebres. A genetic study showed the presence of HLA-DQ7. The serology for Transglutaminase and anti-Endomisium was completely negative.

At blood examination in November 2022, a low level of red blood cells (3.69 mil/mmc with median globular volume 101), low blood level of D Vitamin (11 ng/ml) and of vitamin B12 (576 pg/ml) were detected. Because of the positivity of fecal occult blood, a complete colonscopy was performed in February 2022, with the endoscopic removal of a 4 mm colonic polyp in transverse colon, with a histology suggestive for tubular adenoma with low grade dysplasia.

A further EUDS, performed in August 2022 after 8 months of strictly adherence to GFD, revealed a single mucosal erosion in distal esophagus, a cardial incompetence, edema and hyperemia of antral gastric mucosa with focal microerosions and a complete histologically recovery of duodenal mucosa alterations. At present the patient is asymptomatic and still following a GFD.

Histopathology

In the first series of biopsies (December 2021) the histology revealed villi with low-moderate atrophy with a pathological increase of T lymphocytes in the superficial epithelium (> 25 /100 epithelial cells range 35/58) confirmed by immunohistochemistry with CD3 monoclonal antibody and CD8 antibody (type 2+3 according to Marsh classification, type 2+3A according to Marsh classification modified by Oberhuber, type A+B1 according to Corazza-Villanacci classification) (Figure 1)

In the second series of biopsies (august 2022), after 8 months of GFD, the biopsies evidenced normal villi without a pathological increase of T lymphocytes (<25 /100 epithelial cells) confirmed by immunohistochemistry with CD3 monoclonal antibody and CD8 antibody (Figure 2).

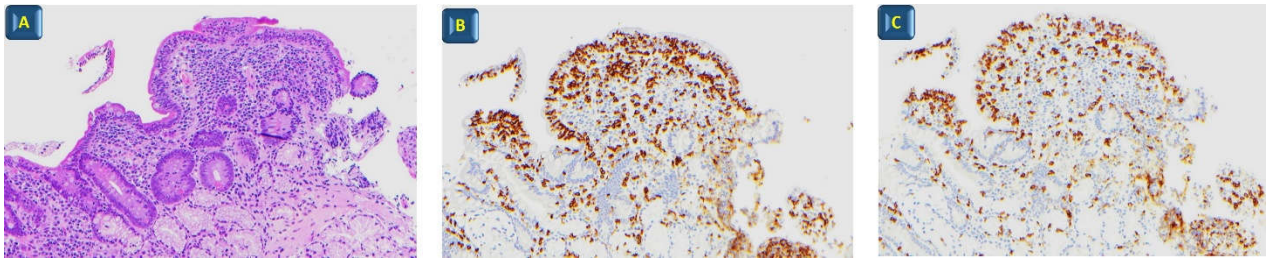

Figure 1. Low atrophy of villi with pathological increase of T lymphocytes. A) H&E x 10, B) immunohistochemistry for CD3 x 10, C) CD8 x 10.

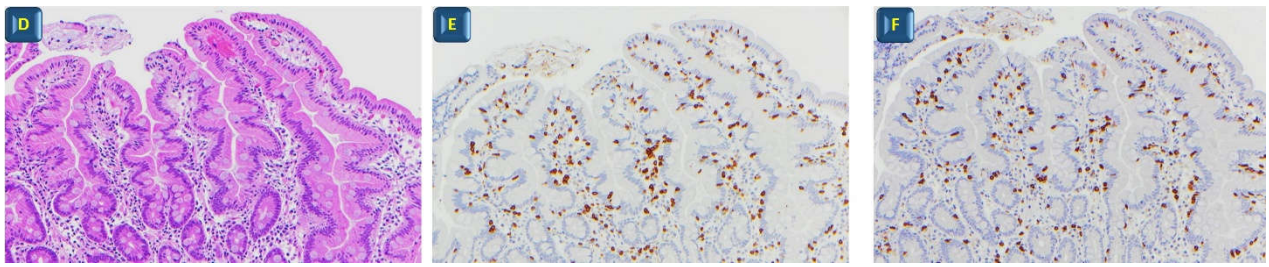

Figure 2. Normal villi without pathological increase of T lymphocytes. D) H&E x 10, E) immunohistochemistry for CD3 x 10, F) CD8 x 10.

Discussion

The genetic predisposition for CD is related to HLA class II genes that encode the DQ2 and DQ8 molecules. HLA-DQ molecules on the surface of antigen presenting cells are involved in CD pathogenesis and, because of their high affinity for deamidated gluten peptides, bind and present them to CD4+T cells in the intestinal mucosa, triggering the immunological reaction that evolves into CD. About 87–93, 7% of individuals with CD carry the HLA-DQ2 and 5-8% HLA-DQ8 (1). Genetic predisposition is necessary but not sufficient to develop CD and many other factors play a role in the development of CD (2). In fact approximately 20–30% of the general population of Europe, America, Australia and some areas of Asia also carry HLA-DQ2 or DQ8 haplotype and only 3% of these compatible individuals will go on to develop CD (3).

DQ2 exists in two homologous variants: DQ2.5 and DQ2.2. The DQ2.5 has a strongest association, with a fort risk for CD compared to DQ2.2 and DQ8 (4). Since 2003, there is evidence in medical literature, that the few patients, who are not DQ2.5, DQ2.2, or DQ8, are almost all DQ7.5 (1), and several authors consider that DQ7 may represent an additive and independent CD risk associated haplotype (5). Patients with CD, DQ2 and DQ8 negative, are widely described and their frequency in different geographical areas is variable ranging from 0% to 12,5% (1, 5, 6, 7). The frequency of CD patients with DQ7 positive and other DQ risk haplotype negative varies from 0,4% to 3,6% (5, 7, 8, 9).

DQ2.5, DQ2.2 and DQ7.5 differ in specificity requirements for peptide binding and in amounts of gluten peptides being presented to CD4+ T cells. This could explain why the three DQ variants have distinct risks for CD (10) and are associated with different damage of intestinal mucosa.

Our case opens an important challenge about the importance to routinely perform intestinal biopsies in dyspeptic patients (11) and, actually, there isn't a complete accordance between Gastroenterologists and intestinal biopsies are not always performed in patients with these symptoms. Freeman et al (12) studied a total of 9665 patients, including 4008 (41.5%) males and 5657 (68.5%) females, underwent elective endoscopies and duodenal biopsies. Of these, 234 (2.4%) exhibited changes of CD including 73 males (1.8%) and 161 females (2.8%). The authors concluded that endoscopic duodenal biopsy is an important method of identifying underlying CD and should be routinely considered in all patients undergoing an elective endoscopic evaluation.

Another controversial aspect of our diagnosis, that is worth to be discussed, is the complete negativity of both tTG and EMAs. When evaluating a suspicion of CD, we have to keep in mind the importance in performing serological and histological evaluations, during a gluten containing diet, but in clinical practice, often patients start decreasing gluten ingestion before the completion of the diagnostic algorithm (because of a subjective relief of symptoms). In such patients both complete villous atrophy and positive CD serology may lack (13). We believe that negative CD serology in our patient was linked to the absence of villous atrophy; the great pathological increase of T lymphocytes in the surface covering epithelium, an element to always keep in mind in the initial forms of celiac disease, was the main factor that prompted us to test gluten free diet as a further diagnostic tool. Moreover, as described by Ieradi and colleagues, in a small rate of CD patients, other two possible mechanisms may explain negative CD serology: the incomplete maturation of plasma cells, with consequent lack of antibodies production, or the mucosal deposition of tTG/anti-tTG immune-complexes without antibodies passage in the systemic circulation (14).

Moreover, when a CD diagnosis is highly suspected, the clinicians must keep in mind that absence of HLA DQ2 and HLA DQ8 does not always exclude this condition. In the clinical case described it is important to consider that the increase in T lymphocytes was firstly considered as connected to the lymphoma of which the subject had been a carrier and treated in the sense of an activation of the T lymphocytes, data confirmed by the substantial negativity of the data laboratory such as transglutaminase but especially HLA. The gluten-free diet with the subsequent endoscopic and histological control, made it possible to reconsider the case as CD. Moreover, the low serum levels of vitamins D and B12, the osteopenia condition and the suspected thyroid autoimmune disorders are further suggestive clinical data for a CD condition.

Conclusion

In conclusion, as it often happens in clinical practice, the diagnostic process in every single patient does not always follows a simple algorithm. This case report underlines the importance and the need of a close collaboration between histo-pathologists, clinicians, laboratory and genetic experts in evaluating case by case the complex picture of CD, always facing new paths and challenges from clinical, genetic, laboratory and histologic points of view.

Conflict of interests

The authors declare that they have no conflict of interest.

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