CASE REPORT

Eosinophilic oesophagitis and coeliac disease: is there an association?

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SUMMARY

A 25-year-old man was seen in outpatient clinic for progressive solid food dysphagia. He was already medicated with a proton pump inhibitor with no improvement. His blood tests showed a slight microcytic anaemia and peripheral eosinophilia. The oesophago-gastro-duodenoscopy showed longitudinal furrows in the distal two-thirds of the oesophagus and a concentric distal stenosis. The biopsies taken showed eosinophilic infiltrates consistent with eosinophilic oesophagitis. There was no improvement with topical fluticasone, so the patient was started on a systemic corticosteroid with resolution of dysphagia and of the oesophageal stenosis. He was kept on topical steroids for symptomatic control. On repeat endoscopy, the duodenal mucosa showed multiple papules that were biopsied. Histology showed features consistent with coeliac disease. The patient was asymptomatic but there was evidence of iron deficiency anaemia, and so a gluten-free diet was started. Despite only a partial adherence to the diet, the iron deficiency anaemia resolved.

BACKGROUND

Eosinophilic oesophagitis (EoE) and coeliac disease (CD) are two distinct gastrointestinal disorders whose described prevalence has been increasing in the last decades.^{1,2} Since 2007, when both entities were first described in the same patient, the association between EoE and CD has been investigated by multiple studies with heterogeneous results.³

This case report describes the co-occurrence of two relatively rare diseases that might appear in the same patient with a frequency higher than expected and constitutes a reminder that we should have a low threshold for investigating the presence of CD in patients with EoE and vice-versa. The description of this case constitutes the starting point for a review of what has been written so far about a possible association between EoE and CD.

CASE PRESENTATION

A 25-year-old Caucasian man was sent to the gastroenterology outpatient clinic for progressive solid food dysphagia since the age of 17 years. He denied heartburn, regurgitation, anorexia or weight loss. At the time, he was under a proton pump inhibitor twice daily, but with no symptomatic relief. His medical history included Klinefelter syndrome and allergic rhinitis.

His blood tests showed only a slight microcytic anaemia with a haemoglobin of 12.4 g/dL (N

13–17 g/dL), a mean corpuscular volume (MCV) of 82.6 fL (N 83–101 fL) and peripheral eosinophilia with 1.6×10^9 cells/L (N < 0.4 cells/L).

INVESTIGATIONS

In the oesophago-gastro-duodenoscopy (OGD), there were longitudinal furrows in the distal two-thirds of the oesophagus and a concentric stenosis with whitish mucosa in the distal third of the organ (figure 1). The stomach and duodenum were normal. The biopsies taken from the oesophagus showed eosinophilic infiltrates with >15 eosinophils per high-power field, fulfilling criteria for EoE (figure 2). Both the oesophageal and gastro-duodenal transit studies were normal.

The patient was then referred to an immunoallergologist: the skin prick allergy tests made were negative and the total and specific IgE values were within normal range.

TREATMENT

The patient was started on swallowed fluticasone 500 µg two times per day without improvement in symptoms or endoscopic aspects after several months of treatment. For this reason, a systemic corticosteroid (prednisolone 20 mg/day) was prescribed with significant improvement of dysphagia after just a few weeks. The follow-up endoscopy showed resolution of the distal oesophageal stenosis but also a papular duodenal mucosa (particularly in the second part of the duodenum); biopsies were taken from the oesophagus, stomach and duodenum. Oesophageal histology continued to show some eosinophilic infiltration and the duodenal histology showed non-specific chronic inflammation; gastric histology from random biopsies was normal. Faced with this symptomatic and endoscopic resolution (although with no histological improvement), it was decided to wean off the systemic corticosteroid; however, it was necessary to restart fluticasone for symptomatic control of dysphagia.

OUTCOME AND FOLLOW-UP

About a year and a half later, with the patient still asymptomatic, a repeat endoscopy was performed: once again there was no evidence of oesophageal stenosis despite the presence of a 'crêpe-paper' mucosal appearance in the distal two-third of the organ; in the duodenum, multiple papules were observed (figure 3). Duodenal biopsies showed villous atrophy, crypt hyperplasia and an increased

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Figure 1 OGD showing longitudinal furrows and a stenosis in the distal oesophagus. OGD, oesophago-gastro-duodenoscopy.

number of intraepithelial lymphocytes and very few eosinophils, primarily suggesting CD, corresponding to type 3c in the Marsh-Oberhuber classification (figure 4). An analytic evaluation showed iron deficiency anaemia with haemoglobin of 12.7 g/L, MCV of 81.6 fL, serum iron of 37 µg/dL (N 60–160 µg/dL) and ferritin of 17 ng/mL (23–336 ng/mL). The diagnosis of CD was confirmed by the presence of increased IgA antitransglutaminase antibodies (119 UA/mL; N < 15).

Although the patient presented no diarrhoea or other symptoms that could be attributed to CD, we assumed we were before an atypical form of CD and gluten-free diet was prescribed. There was only a partial adherence to the diet, but on follow-up analysis the iron deficiency anaemia had resolved and the IgA antitransglutaminase antibodies had decreased.

DISCUSSION

EoE can be defined as a chronic oesophageal disease clinically characterised by symptoms of oesophageal dysfunction and histologically by an eosinophil-predominant inflammation (≥ 15 eosinophils per high-power field (eos/hpf)).⁴ The estimated prevalence is 45–55/100 000.^{4,5} The main symptoms in adults include dysphagia, food impaction, heartburn and chest pain.^{5,6} Endoscopy with oesophageal biopsies is required to establish the diagnosis. Topical steroids such as fluticasone and budesonide constitute the most consensual first-line therapy for EoE. Different forms of dietary elimination also constitute therapeutic options with positive results.^{4,7} Our patient's symptoms

Figure 2 Biopsies of oesophageal mucosa showing multiple eosinophils (black arrows).

Figure 3 OGD showing papular duodenal mucosa. OGD, oesophago-gastro-duodenoscopy.

and endoscopic features did not improve initially with topical steroids alone; for this reason, we decided to start him on systemic steroids. This approach was based on the clinical guidelines available at the time of diagnosis⁴; however, more recent guidelines do not seem to endorse this practice.⁷

CD affects between 1% and 3% of the world's population. It can be defined as chronic condition characterised by an immune response triggered by dietary gluten in genetically susceptible individuals. Clinical manifestations include gastrointestinal symptoms (diarrhoea and abdominal pain) and extraintestinal manifestations such as anaemia, neurological or dermatological symptoms. The diagnosis can be established based on the presence of IgA tissue transglutaminase antibodies or endomysium antibodies together with duodenal biopsies with typical histological findings (increased intraepithelial lymphocytes, crypt hyperplasia and villous atrophy)—both aspects were present in our patient. Removal of gluten from the diet is essential for the treatment of CD. This implies avoiding all foods containing wheat, rye and barley and other potential sources of hidden gluten like processed foods. Although very demanding, this gluten-free diet results, in most cases, in significant symptomatic and histological improvement.⁸ In our case report, iron-deficiency anaemia was the only manifestation of an atypical CD, and it did, in fact, improve after the implementation of a gluten-free diet.

Since the first description in 2007 of EoE and CD occurring simultaneously in the same patient, much has been published about a possible association between these two diseases, although no consensus has yet been reached.³ Despite of being regarded as two clinically and histologically distinct gastrointestinal entities, EoE and CD share some common features, with genetic and environmental factors playing a role in both conditions. Some genetic polymorphisms were identified that seem to be responsible for an increased susceptibility to EoE; one of those is located on the gene encoding eotaxin-3.⁹ In CD, genetic predisposition is related to the presence of HLA-DQ2 and, to a lesser

Figure 4 Biopsies of duodenal mucosa showing villous atrophy (A) and crypt hyperplasia with increased intraepithelial lymphocytes (B).

extent, to HLA-DQ8. However, the prevalence of those alleles in patients with EoE does not seem to be higher than in the general population, and no polymorphism suggesting a common genetic basis between EoE and CD was identified yet.¹⁰ As for environmental factors, both diseases appear to share a component of aberrant immune response to ingested antigens and a response to dietary restrictions. In the case of CD, this immune response is predominantly mediated by type 1 T helper (Th1) cells after gluten ingestion while in EoE the type 2 T helper (Th2) cells are responsible for the initial inflammatory response, with eosinophilic predominance and production of eotaxin-3 and interleukin 5 after the exposure to dietetic allergens.¹¹ An association between EoE and multiple allergic conditions such as asthma, rhinitis and atopic dermatitis has long been recognised, since 50%–80% of EoE patients are atopic. The patient from our case report is included within this group since he suffered from allergic rhinitis.⁶ In CD, the risk of developing atopic conditions remains to be elucidated.¹²

Wheat has been described as one of the most common food triggers for EoE.⁷ However, data are still contradictory regarding the hypothesis of gluten being the main antigen responsible for oesophageal eosinophilia present in patients with CD and EoE.^{13–18} In the most recently published study on this topic, authors conclude that children with CD and oesophageal eosinophilia suffer from two coexisting conditions, rather than oesophageal eosinophilia being one of CD-associated findings. Furthermore, the majority of their patients later developed EoE-associated symptoms, in a stage where they were already under a gluten-free diet and with normal CD-associated serology.¹⁹

Throughout the years, there have been some theories trying to explain the possible association between these two entities. One of such theories suggests that the increased intestinal permeability originated by CD could allow a greater exposure of the gastrointestinal immune system to a larger variety of antigens. In genetically predisposed individuals, this could lead to hypersensitivity reactions, manifesting in the oesophagus as eosinophilic infiltrates.²⁰ Another theory suggests the presence of a dysfunctional T regulatory cell population in these patients, which would enable the simultaneous development of both Th1-mediated and Th2-mediated disorders.¹⁷

There have been somewhat heterogeneous results in the studies performed in order to verify the existence of an association between the two diseases.

Earlier papers from 2007 described an increased prevalence of CD ranging from 9% to 35% in paediatric patients with EoE.^{13 21} In one of those studies, all six children with both diagnoses experienced a complete symptomatic remission after the institution of a gluten-free diet (and histological remission in half).¹³ However, in other two studies in paediatric patients describing increased prevalence of EoE (3%–4%) among CD patients, there was resolution of duodenal changes after a gluten-free diet but the persistence of oesophageal eosinophilia.^{14 15} In a study involving children and adults, there was an increased incidence of EoE in patients with CD from both age groups: in adults, there was a standardised incidence ratio (SIR) of 13.1; in the paediatric population, an SIR of 35.6 was obtained. In most adults, the diagnosis of EoE was made after the establishment of a gluten-free diet for CD.²² Other studies that followed showed an increased prevalence of EoE in patients with CD or vice versa.^{17 20 23–25}

However, not every study favours the existence of an association between EoE and CD. In a study by Ludvigsson *et al*, there was no increased risk of CD in patients with EoE, and Ahmed *et al* concluded that the association between CD and EoE might not be causal but incidental.^{22 26} A systematic review

concluded that although the lack of valid studies prevented the complete exclusion of an association between EoE and CD, the available evidence did not favour this hypothesis.¹⁸ The reasons presented for the apparently contradictory results on this topic might include major differences in the design among studies, different inclusion criteria and relatively small and potentially biased samples. Finally, an observational study and meta-analysis of five studies conducted in the Mayo Clinic did not find an increased risk of developing EoE in children with CD. However, the fact that 30% of patients who had both CD and EoE in this paper had a normal appearing oesophagus prompted the authors to recommend the performance of biopsies in patients with CD, even in those with no oesophageal changes.²⁷

In conclusion, there is still much to be elucidated concerning the existence and nature of an association between EoE and CD. For now, it seems sensible to bear in mind in our daily practice that the two entities may coexist in the same patient, perhaps with a frequency higher than expected. Some studies suggest the acquisition of oesophageal biopsies in patients with suspicion of CD or duodenal biopsies in patients with EoE. Despite the absence of specific studies evaluating the cost-effectiveness of these measures, they should be considered as an option, particularly in patients with suggestive symptoms.^{12 14 15 17 23}

Learning points

- ▶ Eosinophilic oesophagitis (EoE) and coeliac disease (CD) are two diseases with increasing prevalence.
- ▶ Despite being two distinct gastrointestinal entities, they both share some common features such as the influence of genetic factors and the main role of the immune system on their pathogenesis.
- ▶ Many studies have been conducted regarding the existence of an association between EoE and CD, but the results are heterogeneous.
- ▶ Until more definitive evidence arises, it could be sensible to have a low threshold for investigating the coexistence of both diseases in the same patient.

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