Concomitant herpetic and eosinophilic esophagitis – a causality dilemma

P. Monsanto[1], N. Almeida[1], M.A. Cipriano[2], H. Gouveia[1], C. Sofia[1]

(1) Gastroenterology Department, (2) Pathology Department, Coimbra University Hospital, Coimbra University Hospital, Coimbra, Portugal.

Abstract

Eosinophilic and herpetic esophagitis are listed as independent causes of dysphagia, especially in young adult males. However, herpetic esophagitis rarely affects immunocompetent individuals. We report the case of a young, not immunocompromised patient, admitted because of severe dysphagia secondary to herpes simplex virus esophagitis. After complete resolution, an endoscopic and histologic reevaluation established the diagnosis of eosinophilic esophagitis. The potential association between the two conditions is discussed. (Acta gastroenterol. belg., **2012**, 75, **361-363**).

Keywords : herpetic esophagitis, eosinophilic esophagitis, immunocompetent.

Introduction

Esophagitis is most often caused by noninfectious conditions, such as gastroesophageal reflux disease. However, it is becoming increasingly evident that similar to the digestive tract mucosa of other digestive organs, the esophagus is immunologically active and able of triggering an immune response to a variety of stimuli. That is reflected in the esophageal infiltration by eosinophils, initially associated to gastroesophageal reflux disease, but subsequently regarded as a hallmark of eosinophilic esophagitis (EE), latter defined as a clinically differentiated entity independent of the rest of eosinophilic diseases of the gastrointestinal tract (1,2). The histological composition of esophageal epithelium is constituted by flat epithelial cells lacking the secretory and absorbent functions of other organs of the digestive tract. The presence of resident immunitary or lymphoids cells is also insignificant. However, the esophageal infiltration by eosinophils reflects its immune response ability and point to the type of effector cell that could be responsible for the inflammatory profile (3). One of the examples is the EE, where the chronic eosinophilic infiltration of the esophagus is part of an allergic response to both food allergens and aeroallergens probably triggered by multiple environment sensitizing antigens. On the other side, infective esophagitis occurs rarely and most often in the presence of immunosuppression. One of those infectious agents is herpes simplex virus (HSV), most frequently affecting solid organ and bone marrow transplant recipients (4). However several cases and reviews of HSV esophagitis in the immunocompetent host have been published (5).

The possible link between herpes esophagitis and EE has been suggested in other case reports. As well as EE may lead to viral infections of the esophagus, HSV esophagitis has also been associated to the development of EE (6,7).

Case report

The authors present the case of a 20 year-old patient admitted to the emergency department with a three-day history of retroesternal pain, accompanied by odynophagia, fever and myalgia. He denied ingestion of drugs or caustics. His medical history included episodic asthma and one episode of food impaction few months before admission where a short course of therapy with proton pump inhibitor was preformed. The electrocardiogram and chest radiograph were normal, but upper gastrointestinal endoscopy showed a very friable mucosa with multiple longitudinal erosions with distinct borders and covered by whitish exudates, involving two thirds of the distal esophagus (Fig. 1). Biopsies and cytology were performed. Laboratory examinations showed normal leukocyte count (eosinophils 40/μL), slightly elevated IgE (151 UI/mL ; N < 100) and negative antibodies to human immunodeficiency virus (HIV) and HSV type I (IgG and IgM). Histological examination of esophageal biopsies showed multinucleated giant cells with ground-glass nuclei indicative of intranuclear inclusions in esophageal epithelial cells compatible with herpetic esophagitis. This diagnosis was later consolidated after seroconversion of antibodies to HSV type I – titer of serum IgG antibody (ELISA) to HSV1 was almost negative at admission (0.14) and increased to 2.500 at six-weeks (cut off value : negative < 0.9 ; positive > 1.1). Intravenous acyclovir therapy was initiated with symptomatic improvement after 48 hours. He was discharged at 6 days under treatment with proton pump inhibitor, remaining symptom-free. However, six-week endoscopic control showed small esophageal linear erosions different from the ones seen during first endoscopy, and esophageal biopsies where repeated from both proximal and distal esophagus. Histological examination showed

Correspondence to : Pedro Monsanto, M.D., Coimbra University Hospital, Department of Gastroenterology, Praceta Mota Pinto, Avenida Bissaya Barreto, 3000-075 Coimbra, Portugal. E-mail : pedromonsanto@gmail.com

Submission date : 01/07/2011
Acceptance date : 09/10/2011

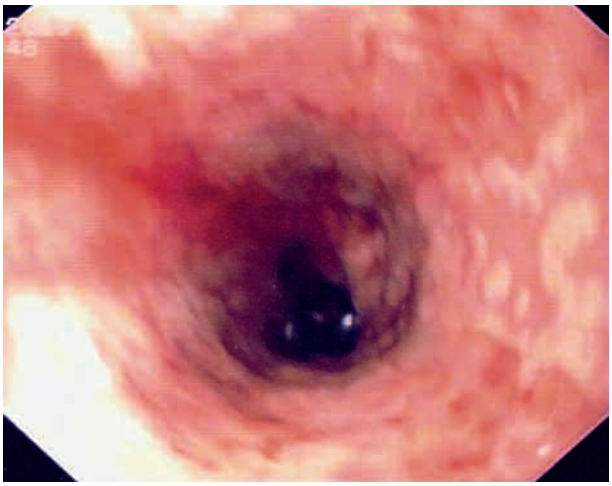

Fig. 1. — Upper gastrointestinal endoscopy showed a very friable mucosa with multiple longitudinal erosions with distinct borders and covered by whitish exudates, involving two thirds of the distal esophagus.

morphology suggestive of EE, with numerous intra-epithelial eosinophils (upper 20 per high-power field), particularly in superficial layers, with small micro-abscesses (Fig. 2). This morphological signs of EE were not present in the first esophageal biopsies. Peripheral eosinophilia (947/μL) was now present in laboratory analysis albeit total IgE levels were normal (94 UI/mL ; N < 100). There was no family history of EE or atopic diseases. Later, the patient initiated new complaints of retrosternal discomfort, and after excluding the recurrence of infectious esophagitis a 6-week course of swallowed fluticasone was initiated (250 μg, two puffs swallowed, twice daily), with relief of symptoms. Reassessment of the esophagus after treatment showed an improved endoscopic appearance, with linear furrowing and no erosions. He was referral to Immuno-allergology consultation were food restriction based on skin prick and patch testing for food allergens was proposed. After 12 month of follow-up he remains symptom-free, with no episodes of impaction or retrosternal pain and without any maintenance treatment.

Discussion

We describe a case of infectious esophagitis with acute HSV infection in a young immunocompetent male, supported by histological typical features and by subsequent seroconversion of antibodies to HSV type I. He was submitted to a short-course treatment with acyclovir with rapid disappearance of symptoms and favorable outcome. Later, after proton pump inhibitor treatment, histological examination of endoscopic small esophageal linear erosions showed morphology features of EE, characterized by dense intraepithelial eosinophilic infiltrate with small micro-abscesses (Fig. 2).

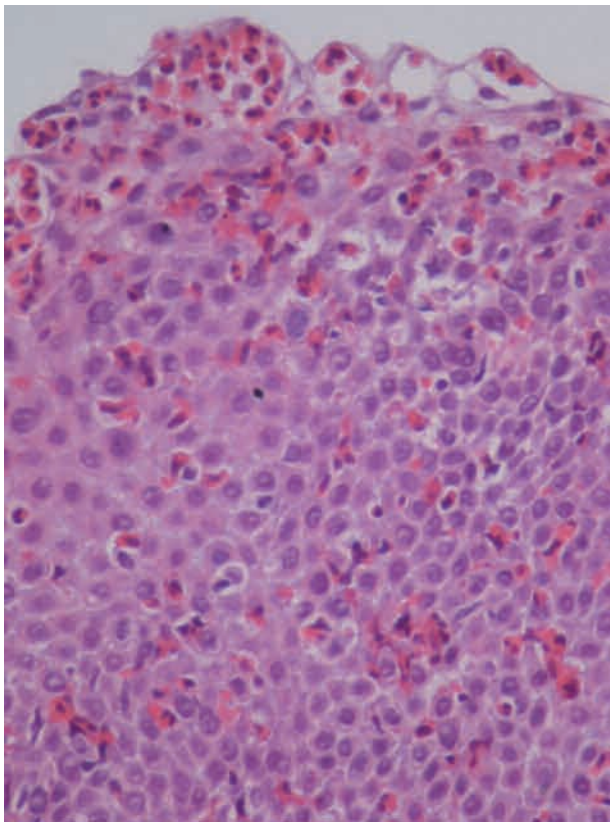

Fig. 2. — Hematoxylin and eosin stain ×400 – Numerous intraepithelial eosinophils, particularly in superficial layers, with small micro-abscesses.

In fact, HSV esophagitis in patients who are immunocompetent it is very rare and affects mainly young males (5,8). It is relatively infrequent and usually only observed in patients with impaired immunity. Clinically, it is characterized by acute onset of retrosternal pain and odynophagia, with or without fever or systemic manifestations. Skin and oral herpetic lesions are uncommon (8). Endoscopic findings depend on the timing of evaluation and affect more frequently the distal or mid-esophagus. Earlier vesicles often join together to form circumscribed ulcers with raised edges, seeming like a “volcano”. For diagnosis, serology is of limited value as in general healthy individuals have a prior exposure to HSV. However, as in this case, the seroconversion has a strong diagnostic value. Ramanathan *et al*. found that histopathology features of HSV were diagnostic of herpetic esophagitis in 68.4% and immunohistochemistry of biopsy specimen in 87.5% of the cases (5). PCR of HSV DNA is the most sensitive, rapid and easiest method if diagnosis, making possible the early initiation of antiviral treatment whenever it is desirable (9). It is normally regarded as a self-limiting condition, rarely complicated with perforation or bleeding, however, the patient we describe, developed, after recovery, esophageal morphologic changes characteristic of EE reflected in dense infiltration by eosinophilic leukocytes in the esophageal mucosa. EE is usually manifested by repeated episodes

of alimentary impaction and dysphagia with a fluctuating course. A cellular hypersensivity reaction, with sensitized T-lymphocytes, mediates a cytokine Th2-type response and eosinophil recruitment (3). Like HSV esophagitis it also affects mainly young men or boys. A history of asthma, atopy or environmental or food allergies are also common. Endoscopy has a limited diagnostic value because eosinophilic inflammation leads to a variety of mucosal endoscopic changes. Therefore, for the diagnosis of EE, typical clinical features and large numbers of eosinophils in the esophagus on pathologic examination must be present. Helpful histological features include eosinophil microabscesses and basal layer hyperplasia (6).

The possible link between herpes esophagitis and EE has been suggested in this case report. Was the HSV infection the sensitizing agent to the development of allergic EE ? Like we said before, in EE the infiltration of the esophagus by eosinophils is part of an allergic response triggered by multiple environment sensitizing antigens. Although the HSV may have not been the sensitizing allergic agent, HSV esophageal tissue injure may have caused a breakdown of immune tolerance and hyperreactivity to other environment antigens. This hypothesis has been postulated in another case report (7). Viral determinants that mimic environmental or food antigens may also have triggered self-reactive T-cell clones to produce an immune cellular type reaction with a Th2-type cytocine secretion profile and the induction of an eosinophilic inflammation. A similar mechanism as also been described in autoimmune herpes stromal keratitis (10).

However, the patient had suffered an episode of food impaction few months before. It is well known that dysphagia or a history of food impaction is the initial manifestation of EE in many patients. So, the other hypothesis is that EE was already present before the HSV esophageal infection. The susceptibility to esophageal infections in EE has been previously described. Esophageal candidiasis and viral infections may occur even in the absence of therapy with topical corticosteroids. This susceptibility can be caused by structural changes in the esophageal mucosa induced by eosinophilic inflammation and an unadjusted immunological response (6). Nonetheless, at the time of the esophageal infection by HSV, the typical histological features of EE (infiltration by eosinophilic leukocytes in the esophageal mucosa) were not present, suggesting that HSV infection precede the development of eosinophilic inflammation.

Other recent reports have highlighted the relationship between HSV infection and EE. Meanwhile, further studies are required to better understand the immune mechanism involved in this association and elucidate this causality dilemma.

References

1. BROWN L.F., GOLDMAN H., ANTONIOLI D.A. Intraepithelial eosinophils in endoscopic biopsies of adults with reflux esophagitis. *Am. J. Surg. Pathol*., 1984 Dec, **8** : 899-905.
2. ATTWOOD S.E.A., SMYRK T.C., DEMEESTER T.R. *et al*. Esophageal eosinophilia with dysphagia. A distinct clinicopathological syndrome. *Dig. Dis. Sci*., 1993, **38** : 109-116.
3. LUCENDO A.J. Immunopathological mechanisms of eosinophilic oesophagitis. *Allergol. Immunopathol*., 2008, **36** : 215-227.
4. MC BANE R.D., GROSS J.B. Jr. Herpes esophagitis : clinical syndrome, endoscopic appearance, and diagnosis in 23 patients. *Gastrointest. Endosc*., 1991, **37** : 600-603.
5. RAMANATHAN J., RAMMOUNI M., BARAN J. JR., KHATIB R. Herpes simplex virus esophagitis in the immunocompetent host : an overview. *Am. J. Gastroenterol*., 2000, **95** : 2171-2176.
6. STRAUMANN A. The Natural History and Complications of Eosinophilic Esophagitis. *Gastrointest. Endoscopy Clin. N. Am*., 2008, **18** : 99-118.
7. SQUIRES K.A., CAMERON D.J., OLIVER M., DA FONSECA JUNQUEIRA J.C. Herpes simplex and eosinophilic oesophagitis : the chicken or the egg ? *J. Pediatr. Gastroenterol. Nutr*., 2009, **49** : 246-250.
8. KATO S., YAMAMOTO R., YOSHIMITSU S. *et al*. Herpes simplex esophagitis in the immunocompetent host. *Dis. Esophagus*, 2005, **18** : 340-344.
9. LEE B., CADDY G. A rare cause of dysphagia : herpes simplex esophagitis. *World J. Gastroenterol*., 2007, **13** : 2756-2757.
10. ZHAO Z.S., GRANUCCI F., YEH L., SCHAFFER P.A., CANTOR H. Molecular mimicry by herpes simplex virus-type 1 : autoimmune disease after viral infection. *Science*, 1998, **279** : 1344-1347.