Herpetic Esophagitis and Eosinophilic Esophagitis: A Potential Association

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Patient: Male, 26-year-old

Final Diagnosis: Herpetic esophagitis • eosinophilic esophagitis

Symptoms: Fever • adynamia • retrosternal pain • dysphagia

Medication: —

Clinical Procedure: Endoscopy • pathological examination

Specialty: Gastroenterology • Pathology

Objective: Rare coexistence of disease or pathology

Background: Gastroesophageal reflux disease, infectious esophagitis, and eosinophilic esophagitis are the most frequent causes of esophagitis, the latter 2 etiologies being generally considered independently. However, the association between both entities has been suggested through case reports in immunocompetent patients.

Case Report: We present the case of an immunocompetent 26-year-old man presenting with fever, adynamia, retrosternal pain, and dysphagia. Endoscopy was performed, showing whitish lesions in circular plates with erosions, and in some depressed areas in the middle and distal esophagus. Biopsies showed the presence of ulcerated foci covered by fibrinoleukocyte exudate in granulation tissue and nuclear inclusions with a viral appearance. The immunohistochemical study for herpes simplex virus (HSV) was positive. The patient was treated symptomatically and progressed favorably. The endoscopic control carried out at 3 months showed longitudinal grooves and trachealization, findings compatible with the diagnosis of eosinophilic esophagitis and with biopsies that confirmed the etiology by showing an increase in eosinophil count >20 per field, without isolating HSV.

Conclusions: This clinical case confirms the possible relationship between esophagitis caused by HSV and eosinophilic esophagitis. Alterations at the immune level and damage to the esophageal mucosa barrier may explain this relationship. In this scenario, an endoscopic follow-up should be considered.

Keywords: Eosinophilic Esophagitis • Esophagitis • Immunocompetence • Keratitis, Herpetic

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**Background**

Infectious esophagitis is the third leading cause of esophagitis after gastroesophageal reflux disease and eosinophilic esophagitis (EoE), and can be caused by bacteria, viruses, fungi, and parasites [1]. In relation to herpes simplex virus (HSV), a large part of the adult population is seropositive and the virus often remains latent and non-pathogenic. However, primary infection or reactivation of the latent virus can cause clinically significant disease, with HSV-1 infection being more common in the adult population [2].

Herpetic esophagitis occurs mainly in immunocompromised patients, as in the case of patients with acquired immunodeficiency syndrome (HIV/AIDS), hematological neoplasms, solid tumors, transplant patients, or patients undergoing treatment with immunosuppressive drugs, among others [2]. However, it is important that the healthcare teams also suspect this condition in immunocompetent patients and look for risk factors, given the potential morbidity this disease entails [3]. In this group of patients, the presence of predisposing factors and associated comorbidities, such as malnutrition, alcohol consumption, or the use of corticosteroids, have been associated with the development of viral esophagitis (including HSV) [1]. An association between EoE and herpetic esophagitis has also been suggested in some studies, but it is still controversial. Several pediatric and adult report cases [4-10] have mentioned this association in an attempt to explain the diagnosis of infectious esophagitis due to HSV in immunocompetent patients without other predisposing factors to this infection.

In summary, the objective of this clinical case report is to describe the association between HSV esophagitis and EoE. In relation to this report and other cases collected in the literature [4-10], in immunocompetent patients with HSV infectious esophagitis, an endoscopic follow-up should be considered in order to search for a previously predisposing EoE or one triggered by esophageal infection.

**Case Report**

A 26-year-old man with no history of characteristic symptoms of EoE (eg, dysphagia, odynophagia, chest pain, a feeling of food impaction). There was no personal or family history of allergic diseases (eg, atopic dermatitis, asthma, environmental or food allergies, and vaccine desensitization). The patient presented on 12 December 2020 with fever (temperature 37.8°C), adynamia, odynophagia, and cough, and was examined in the Emergency Service. The following tests were performed: normal blood count, C-reactive protein (CRP) 46 mg/L (normal <5), normal biochemical profile, normal chest X-ray, and negative COVID-19 PCR Test. After 3 days his condition evolved with retrosternal pain and heartburn, with decreased food intake and consequent weight loss of 5 kg. The general and segmental physical examination was normal. An upper gastrointestinal endoscopy was performed and showed presence of whitish lesions in circular plaques with erosions in some depressed areas in the middle and lower esophagus (Figure 1A). Biopsies showed the presence of ulcerated foci covered by fibrinoleukocyte exudate in granulation tissue, with no evidence of eosinophilic infiltrate. The squamous epithelium neighboring the area of ulceration revealed viral-like nuclear inclusions. No fungal elements were observed in PAS staining and the immunohistochemical study was positive for the presence of Herpes virus I and II, and was negative for cytomegalovirus (Figure 2A, 2B). The HIV blood study was negative. IgM and IgG serology for HSV was 1.5 and 1.6 UE, respectively (normal value 0.0-0.9). Treatment with esomeprazole 40 mg twice a day, sucralfate 10 ml 4 times a day, and Gaviscon® (sodium bicarbonate and calcium carbonate) 3 times a day was indicated. The patient’s condition evolved favorably, and he was...

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**Figure 1.** (A) Corresponding to the lower third of the esophagus, showing multiple superficial ulcerations with exudate and geographic borders ascending longitudinally from the distal esophagus. (B) Lower third esophagus showing some unstructured circumferential grooves. (C) Corresponding to the middle esophageal mucosa, evidencing trachealization of the mucosa.
asymptomatic 5 days later. Given this evolution, the treatment was suspended after 10 days. In the context of a possible relationship between HSV esophagitis and EoE, an endoscopic control was performed 3 months later. Macroscopic findings were compatible with EoE (longitudinal grooves and esophageal trachealization) (Figure 1B, 1C), with esophageal biopsies that showed an increase in eosinophils >20 per field and without HSV isolation (Figure 2C). Gastric and duodenal mucosa biopsies were normal. In the context of the diagnosis of EoE, the patient was prescribed esomeprazole 40 mg per day.

Discussion

The clinical manifestation of herpetic esophagitis, both in immunosuppressed and in immunocompetent patients, includes prodromes of fever, myalgia, anorexia, dysphagia, and respiratory symptoms, subsequently evolving with nausea, vomiting, chest pain, dysphagia, and heartburn [3,11]. Our patient presented many of these symptoms during the evolution of esophagitis.

The diagnosis of herpetic esophagitis is based on endoscopic and histological findings, highlighting the presence of multiple small ulcers with or without raised margins and fibrin exudate, which mainly involves the distal esophagus [3]. Biopsies show multinucleated giant cells with nuclear patterning giving the appearance of ground glass [3]. In our patient, endoscopic alterations and histological findings confirmed the diagnosis of HSV esophagitis type 1-2.

Although immunosuppressed patients with HSV esophagitis should be treated with acyclovir or valacyclovir [2,3], there is less evidence whether this strategy should be followed in immunocompetent patients. In this group of patients, infection is usually self-limited, with resolution of symptoms within the first 2 weeks [2]. However, case series have suggested that in immunocompetent patients, the use of acyclovir can lead to a faster symptomatic response [12]. In our patient, although antiviral therapy was not indicated, the response was early, being asymptomatic 5 days later. Studies should define in which patients this therapeutic strategy would be more cost-effective.

EoE is a chronic immune-mediated inflammatory disease characterized by esophageal dysfunction and transmural infiltration of the esophagus by eosinophils, and is a particular form of food allergy [13]. Although our patient did not present esophageal symptoms after the diagnosis of herpetic esophagitis, the esophageal alterations found in the endoscopy added to the findings in the biopsies support the diagnosis of EoE or at least of esophageal eosinophilia [14].

In numerous publications, the possible association between infectious esophagitis due to HSV and EoE is described [4-10]. All of these case reports involved immunocompetent patients, of which the majority had atopic diseases. However, these are isolated clinical cases that do not allow definitive conclusions to be drawn [4,5,7]. For this reason, it can be argued that the diagnosis of infectious esophagitis due to HSV in an immunocompetent patient requires ruling out another series of predisposing local inflammatory processes not necessarily related to immunodeficiency states, such as EoE. Since biopsies of the non-ulcerated proximal and distal esophageal mucosa were not taken at the time of herpetic esophagitis diagnosis, we cannot rule out or confirm whether EoE was a cause or consequence of the HSV infection. A second evaluation by the pathologist ruled out eosinophilic or other characteristic findings of EoE in the first biopsy. Although the association between these 2 diseases is not yet established, 2 physiopathogenic mechanisms have been suggested. First, HSV infection can cause damage to the esophageal mucosal barrier,
resulting in the development of hypersensitivity to food and environmental antigens and thus an altered response of TH2 lymphocytes [4,5]. On the other hand, EoE through inflammation of the esophageal mucosa predisposes to infection by Candida and viruses such as HSV [15]. As suggested by some authors, if herpetic esophagitis is confirmed, endoscopic follow-up should be performed at 8-12 weeks to establish if EoE is present [10], as was done for our patient.

Conclusions

In immunocompetent patients with suspected herpetic esophagitis, it seems important to do the following: collect symptoms related to EoE (eg, stoppage or food impactions, typical symptoms for esophageal reflux); gather personal or family history of atopic diseases (eg, atopic dermatitis, asthma, environmental or food allergies); and take biopsies during diagnostic gastroscopy of the proximal and distal esophagus to assess the presence of eosinophilic infiltrate (in the most common locations of herpetic esophagitis).

Declaration of Figure Authenticity

All figures submitted have been created by the authors, who confirm that the images are original with no duplication and have not been previously published elsewhere in whole or in part.

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