



# REVISTA DE GASTROENTEROLOGÍA DE MÉXICO

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## EDITORIAL

### Diagnosing eosinophilic esophagitis: cytokine sizzle and fizzle - Mexican style<sup>☆,☆☆</sup>



### Diagnosticando la esofagitis eosinofílica: chisporroteo y siseo de citocinas a la mexicana

It can be challenging to distinguish eosinophilic esophagitis (EoE) from gastroesophageal reflux disease (GERD) in some patients. At face value, this might seem surprising, considering how different the etiologies of the two disorders are. EoE is an immune-mediated, allergic disease, whereas GERD is a condition that develops when the reflux of gastric contents causes troublesome symptoms and/or complications. The problem is that some of the troublesome symptoms and complications of GERD are the same as those of EoE, including dysphagia, heartburn, chest pain, and strictures. The two disorders also share a number of common histologic features, including eosinophilic infiltration, basal cell hyperplasia, and dilated intercellular spaces in the esophageal squamous epithelium.<sup>1</sup> Initially, we gastroenterologists thought we could distinguish these diseases by the patient's response to a trial of proton pump inhibitors (PPIs). Since the inhibition of gastric acid secretion was the only widely recognized effect of PPIs, we reasoned that only an acid-peptic disorder like GERD could respond to those medications. And this line of reasoning seemed fine, until we recognized a condition called "PPI-responsive esophageal eosinophilia" (PPI-REE).<sup>2</sup> PPI-REE patients have esophageal eosinophilia with typical EoE symptoms and histology, they

have no evidence of GERD by endoscopy or pH monitoring, and yet they show a clinical and histologic response to PPIs.<sup>3</sup> This condition is not rare, as approximately 30 to 50% of patients with symptomatic esophageal eosinophilia respond to PPIs.<sup>4</sup> Recent molecular studies on gene expression using an RNA microarray for 59 allergic-type EoE genes in esophageal biopsies have shown similar expression patterns in EoE and PPI-REE patients, suggesting that PPI-REE is a condition within the same disease spectrum as EoE.<sup>5</sup>

Some investigators have proposed a predictive modeling strategy based on 9 factors (clinical, endoscopic, and histopathologic) that can distinguish EoE from GERD with high reliability.<sup>6</sup> However, clinicians are likely to find such a model too cumbersome for regular use in clinical practice. Other investigators have developed an EoE Endoscopic Reference Score, known as EREFS, which shows good inter and intra-observer agreement in the reporting of endoscopic findings.<sup>7,8</sup> The EREFS has recently been recommended for use by clinicians to standardize reporting of endoscopic findings in EoE.<sup>9</sup>

In this issue of the *Revista de Gastroenterología de México*, Soto-Solis et al. report clinical and endoscopic findings from the largest Mexican case series of patients with EoE. Patients diagnosed with EoE at a private medical unit in Mexico City and at a university hospital in Veracruz were entered into a registry recording their clinical history and symptoms, endoscopic findings, histopathology abnormalities, and response to treatments (PPIs, steroids, diet). Using a subset of these well-characterized EoE registry patients (9 total), the investigators conducted a case-control study in which the EoE patients (cases) were matched with GERD patients (controls) by age and sex. Cases and controls were compared in regard to history of asthma, symptoms of

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<sup>☆☆</sup> See related content at DOI: 10.1016/j.rgmxen.2016.11.002, Soto-Solis R, Santana-de Anda K, González-Uribe N, Gallegos C, Romo-Aguirre C, Remes-Troche JM, et al. How to improve the diagnosis of eosinophilic esophagitis: Experience from a case series in Mexico. *Revista de Gastroenterología de México*. 2017;82:5-12.

food impaction, dysphagia, and chest pain according to the Straumann scale<sup>10</sup>, the Carlsson-Dent GERD questionnaire, and endoscopic findings. The goal was to identify predictive elements that might be used to differentiate EoE from GERD.

The investigators found that histories of asthma and food impaction were significantly more common in patients with EoE than in those with GERD. There was no significant difference between EoE and GERD patients in the response score to the Carlsson-Dent GERD questionnaire. Skilled endoscopists (4 total) evaluated endoscopic photographs from cases and controls in a blinded fashion. The endoscopists correctly identified 53% of the images from EoE patients, and incorrectly identified 8% of the images from GERD patients as EoE findings. After reviewing reference endoscopy images of EoE findings, the endoscopists then re-evaluated the same images in a blinded fashion. After this review, the rate of identification of EoE patients based on endoscopic findings increased (to 100%), but so did the rate of false-positive identifications (28%) of EoE in GERD patients. Kappa (K) values for inter-observer agreement among endoscopists ranged from 0.16-0.32 in the initial review, and increased to 0.6-0.82 in the second review. Two study pathologists that were blinded to the diagnosis evaluated esophageal biopsy specimens taken from the middle and distal esophagus. Agreement for the histologic diagnosis of EoE was 88% with a K value of 0.6. The authors concluded that the clinical data analyzed were insufficient to distinguish EoE from GERD. However, they propose that a directed patient interview focused on a history of asthma and food impaction might raise the endoscopist's suspicion in relation to EoE diagnosis. With this suspicion in mind, subtle endoscopic findings of EoE that might otherwise be dismissed could be recognized, resulting in the performance of biopsy of the middle third of the esophagus to aid in the diagnosis of EoE.

This report on the Mexican experience of difficulty in distinguishing EoE from GERD based on symptoms is right in line with reports from the US, which raises the following question: "Why is it so hard to differentiate 2 esophageal conditions that seem to arise from 2 such disparate causes?" I propose that this distinction can be difficult because both conditions arise from cytokine-mediated processes, and it is the cytokines and their resulting inflammation that are responsible for the clinical symptoms and complications.

EoE is an allergic disorder in which a food allergen activates the immune system to cause naïve CD4-positive T cells to differentiate into T-helper 2 (Th2) cells that produce Th2 cytokines, such as interleukin (IL)-5, IL-4, and IL-13. IL-5 activates eosinophils that reside in the bone marrow. Meanwhile, the surrounding Th2 cells, mast cells, and eosinophils themselves release other pro-inflammatory cytokines, such as IL-13 and IL-4, which stimulate the production of the cytokine eotaxin-3 by the esophageal epithelial cells. Eotaxin-3 is a potent chemoattractant for activated eosinophils, causing them to home to the esophagus. Finally, degranulation products released by eosinophils contribute to the epithelial injury. Thus EoE results from an immune-induced, cytokine-mediated injury. Indeed, my group has shown that PPIs

can block esophageal production of eotaxin-3 stimulated by Th2 cytokines, which might explain the PPI response of patients with PPI-REE.<sup>11</sup> Moreover, recent data suggest that reflux esophagitis is primarily a cytokine-mediated disease, as well.

Traditionally, reflux esophagitis was assumed to develop when cells in the surface layer of the esophageal squamous epithelium succumb to the caustic chemical effects of refluxed gastric acid and pepsin.<sup>12</sup> This caustic death of surface cells was thought to attract granulocytes (neutrophils and eosinophils), and to stimulate the proliferation of basal cells in order to replace the lost surface cells.<sup>13,14</sup> However, our studies in a rat model showed that reflux esophagitis started with T lymphocytes (not granulocytes) infiltrating the esophageal submucosa (not the surface epithelium), and with basal cell hyperplasia that preceded the loss of surface cells. Moreover, we showed that a solution of acidic bile salts caused human esophageal epithelial cells in culture to secrete pro-inflammatory and pro-proliferative cytokines.<sup>15</sup> Based on those findings, we proposed a new concept for reflux esophagitis pathogenesis, in which refluxed gastric juice does not kill esophageal epithelial cells directly, but rather stimulates them to secrete cytokines that induce proliferative changes and attract the T lymphocytes and other inflammatory cells that ultimately damage the mucosa. Recently, we reported the results of a clinical study on GERD patients that tested our new hypothesis regarding reflux esophagitis pathogenesis. In patients with reflux esophagitis healed by PPIs, we induced acute esophagitis by interrupting PPI therapy.<sup>16</sup> As in our rat model, we found that "acute" reflux esophagitis in humans began with T lymphocyte-predominant inflammation, and with the development of basal cell hyperplasia before any loss of surface cells.<sup>16</sup> Similar to the pathogenesis of EoE, reflux esophagitis also appears to result from a cytokine-mediated injury, an alternative concept for its pathogenesis.

So the question becomes, "Can symptoms related to esophageal dysfunction (dysphagia, heartburn, and chest pain) result from a cytokine-mediated injury?" The esophagus is innervated by vagal and spinal pathways, and sensory afferents in both pathways innervate the longitudinal and circular muscles, as well as the mucosa.<sup>17</sup> Some of these esophageal sensory neurons express acid-sensing ion channel 3 (ASIC3), transient receptor potential vanilloid receptor 1 (TRPV1), and transient receptor potential A1 (TRPA1). These neurons are nociceptors that can be triggered by acid and inflammatory mediators involved in the generation of heartburn symptoms.<sup>18-22</sup> In a guinea pig model of EoE, infiltration of the esophagus with eosinophils and mast cells increased the sensitivities of TRPA1- and TRPV1-expressing esophageal vagal sensory afferents to various triggers including acid exposure.<sup>22</sup> Moreover, IL-13 has been shown to upregulate the expression of TRPV1 in bronchial cells in certain mouse models of asthma.<sup>23</sup> In addition, Reider *et al.* demonstrated that cytokines released by esophageal mucosal biopsies from patients with reflux esophagitis caused a significant reduction in contractility of cat esophageal circular muscle in response to electrical (i.e. neural) stimulation.<sup>24</sup> Moreover, this same group found a significant reduction in cat esophageal circular muscle contractility induced by EoE-related cytokines and eosinophil degranulation products.<sup>25</sup>

Regarding the study by Soto-Solis et al., it is intriguing to speculate that clinical symptoms did not distinguish between EoE and GERD, because those symptoms resulted from a common mechanism of cytokine-mediated injury that rendered the esophagus hypersensitive to acid and inflammatory mediators. Both in EoE and in GERD, the epithelium might “sizzle” with the inflammatory cells beckoned by pro-inflammatory cytokines, while the esophageal muscle “fizzles” in response to those same molecules.

The study by Soto-Solis et al.<sup>26</sup> provides more evidence confirming the fact that symptom-reporting in the clinical setting is inadequate to distinguish EoE from GERD. However, if the diagnosis of EoE is considered by the endoscopist, he or she might recognize the subtle endoscopic findings delineated in the EREFS, and in turn, biopsy the esophagus to improve diagnostic accuracy for EoE. Elucidation of the fundamental mechanisms underlying cytokine-mediated esophageal diseases is needed to develop pathogenesis-based diagnostic criteria, rather than today’s flawed “if it responds to a PPI, then it must be GERD” approach to distinguish EoE from GERD. Focusing on the underlying pathogenesis of these two cytokine-mediated esophageal conditions could improve diagnostic accuracy, preventing clinicians from being burned by the cytokine sizzle and fatigued by the cytokine fizzle.

## Conflict of interest

The author declares that there is no conflict of interest.

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