

## Eosinophilic Esophagitis in a Pediatric Patient with Herpes Simplex Virus Esophagitis. A Cause or a Consequence?

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### Abstract

**Introduction:** Eosinophilic esophagitis is an inflammatory condition that has a variable presentation, but usually upper gastrointestinal symptoms. This condition can usually lead to long term esophageal sequelae.

**Case:** A previously healthy 12- year old male, presented with a several day history of abdominal pain, vomiting and fever. An esophagogastroduodenoscopy (EGD) was done and herpes simplex esophagitis (HSVE) was diagnosed. He was treated with acyclovir and a proton pump inhibitor and rapidly improved. A HSVE diagnosis prompted an immunology workup, which noted several decreased lymphocyte proliferation responses. He presented again 9 weeks after discharge with worsening abdominal pain and upper gastrointestinal symptoms. A repeat EGD was done and revealed moderate to severe eosinophilic esophagitis (EOE) and no signs of HSVE. Food allergy testing was completed but was negative. Repeat immunologic testing noted minor T and B lymphocyte abnormalities. He was treated for 3 months with high dose omeprazole and repeat EGD continued to show eosinophilic esophagitis. He was then started on swallowed and inhaled steroids with clinical and histological improvement of his EOE.

**Conclusion:** Our patient noted to subsequently developing EOE after HSVE. EOE needs to be considered in patients presenting with upper gastrointestinal symptoms following HSVE.

### Keywords

Herpes simplex virus esophagitis, Eosinophilic esophagitis, Esophagitis

### Abbreviations

EOE: Eosinophilic Esophagitis; HPF: High Power Field; PPI: Proton Pump Inhibitor; HSV: Herpes Simplex Virus; EGD: Esophagogastroduodenoscopy; IHC: Immunohistochemistry; HSVE: Herpes Simplex Esophagitis;

## Introduction

Eosinophilic esophagitis (EOE) is an inflammatory condition of the esophagus more common in males and typically presenting in the pediatric population as food refusal, emesis, abdominal pain, food impaction, and/or dysphasia [1, 2]. Mucosal rings, longitudinal furrows, and/or exudates on endoscopic views are suggestive though not diagnostic of EOE [2]. Though debate exists as to an exact value,  $\geq 15$  eosinophils per high power field (HPF) are considered diagnostic for EOE [3, 4] once other causes of esophageal eosinophilia, including proton pump inhibitor (PPI)- responsive esophageal eosinophilia have been excluded [5]. Peripheral eosinophilia may or may not be present. EOE is thought to be driven by an abnormal immune mediated response, usually associated with food-mediated allergy. Environmental allergens, such as pollen exposure, have also been implicated as EOE triggers [6]. In this report, we present a case of EOE following herpes simplex virus (HSV) esophagitis (HSVE). We propose that HSVE may represent another trigger for EOE. Our literature review yielded sparse case reports on such a presentation, though this phenomenon is being increasingly recognized [7-10], including one case report of simultaneous HSVE and EOE [11]. The clinical course and immunological workup of our patient is presented, as well as a discussion of possible mechanisms relating the two diagnoses.

## Case Report

A previously healthy 12-year-old boy presented with a 4-day history of periumbilical and epigastric pain and a 2-day history of non-bilious, non-bloody emesis and fever to 102°F. Vital signs were stable on admission. Laboratory studies included an elevated white blood cell count of  $23.9 \times 10^3/\text{mm}^3$ , high erythrocyte sedimentation rate (92 mm/hr), and increased C-reactive protein (3.3 mg/dl). Physical exam revealed epigastric tenderness. The patient also had non-bloody, non-mucoid diarrhea, however stool workup was non-diagnostic. Abdominal and pelvic computed tomography was non-diagnostic. Due to non-resolution of symptoms an esophagogastroduodenoscopy (EGD) was performed. Grossly there was significant ulceration and friability of the esophagus with preserved gastric and duodenal mucosa (Figure 1). Histology revealed severe esophagitis with ulceration and intense inflammation including lymphocytic, neutrophilic infiltration in the distal esophagus without eosinophilia. Gastric biopsy revealed scattered lymphocytes, plasma cells and rare eosinophils in the lamina propria, with a normal duodenum. Immunohistochemistry (IHC) and culture were positive for HSV, while tests for cytomegalovirus, fungus, and *H. pylori* were negative. Epstein-Barr virus titers were suggestive of past infection. The patient was treated with acyclovir for 2 weeks and started on a PPI. He improved rapidly and was discharged.

At a 6-week follow-up appointment, the patient remained asymptomatic. However, the diagnosis of HSV esophagitis prompted an immunological workup. No history of immunodeficiency or atopy was noted in the patient or his family. The patient was found to have decreased lymphocyte proliferation responses to phytohemagglutinin, concanavalin A, pokeweed mitogen, and alloantigen, though responses to candida and tetanus were normal. A limited lymphocyte subset analysis performed 10 weeks following discharge was unremarkable (Supplemental Digital Content 1). HIV ELISA was negative and NK cell function and complement panels were normal. Quantitative immunoglobulins were normal. The patient had sufficient amnestic antibody titers to 4 of 7 Prevnar serotypes. Antibodies to tetanus, *Haemophilus influenzae* B, and *Corynebacterium diphtheriae* were normal.

Nine weeks following the initial discharge, the patient developed intermittent abdominal pain. Histology from a repeat EGD revealed moderate to severe EOE in the proximal and distal esophagus, with a normal stomach and duodenum (Figure 1). No ulcerations were noted and sections were negative for herpetic intranuclear inclusions, HSV immunostaining and *H. pylori*. The finding of EOE on EGD prompted extensive food allergy testing including IgE immunocap assay, but none were identified. Repeat lymphocyte subset analysis was remarkable for a high memory T cells (CD4CD45RO+) of 76% and low switched, memory B cells (CD19&CD27+IgD-) of 3% (Supplemental Digital Content 1). In summary, his screening immune deficiency evaluation was mostly normal with only minor T and B lymphocyte abnormalities.

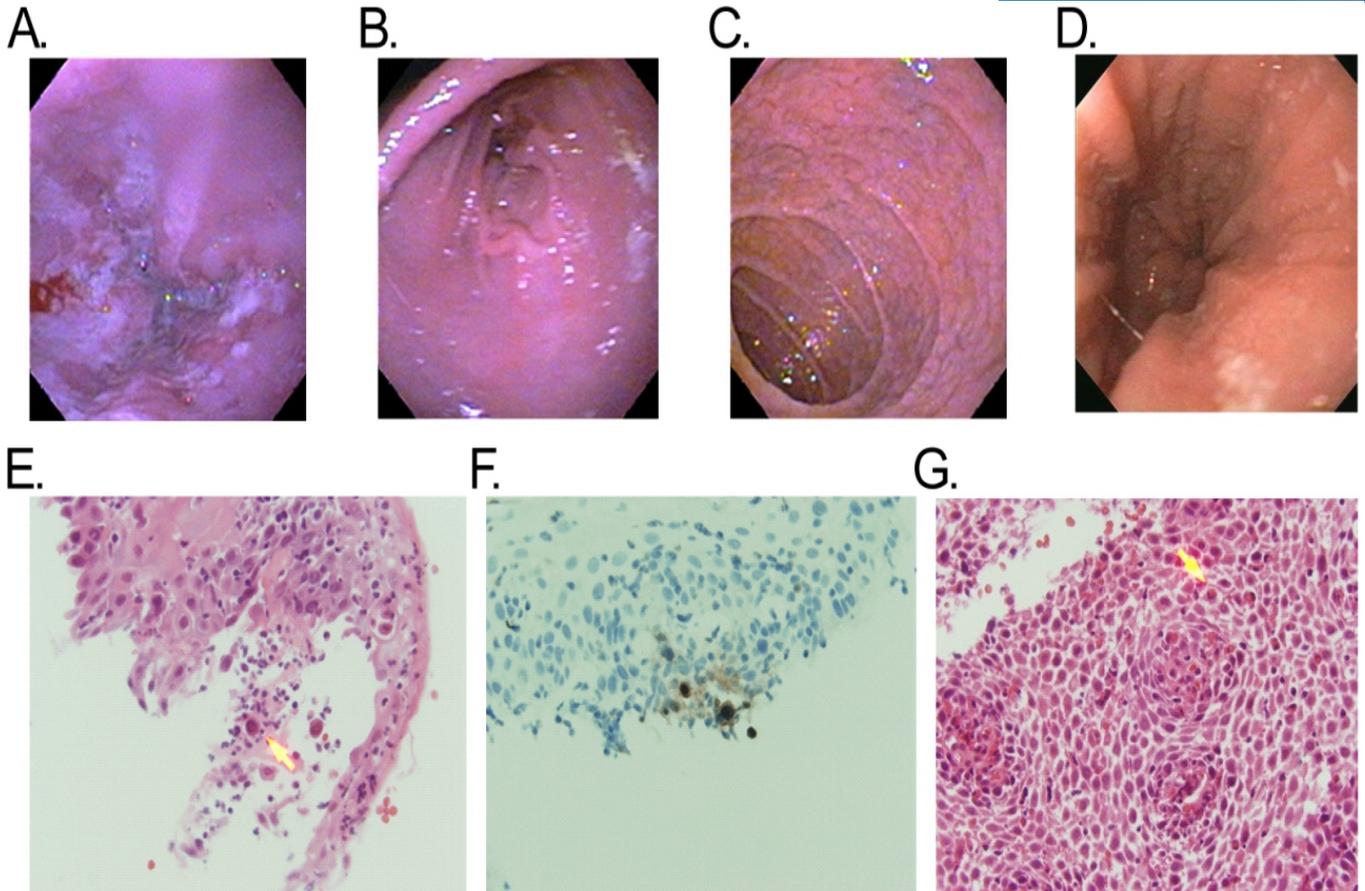
The patient was started on a three-month course of high dose omeprazole. EGD following this treatment continued to show EOE with >25 eosinophils per high power field in both the proximal and distal esophagus. The stomach and duodenum were normal. HSV, fungi, and *H. pylori* tests remained negative. The patient received swallowed and inhaled steroids. Follow-up at six months showed clinical and histological improvement.

## Discussion

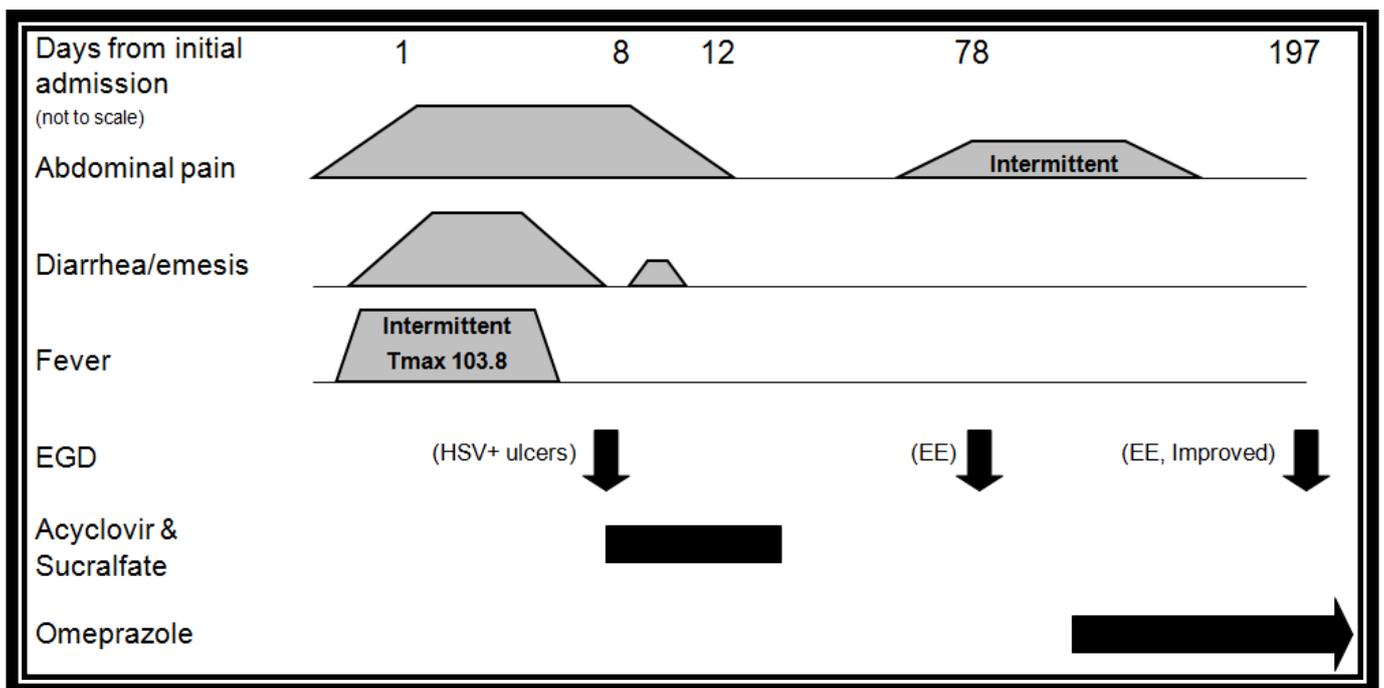
The association of HSVE and EOE is a relatively novel observation. Theories exist as to which condition would predispose to the other. Squires et al. reported a case series of three patients who developed HSVE and then EOE [8]. They proposed that HSVE could predispose these patients to EOE by causing mucosal breakdown, subsequently leading to a break in the immune tolerance and development of hyperreactivity. Alternatively, they proposed that EOE may increase susceptibility to HSVE through a dysregulated Th2 response that allows the virus to establish an infection. Monsanto et al have additionally suggested that viral antigen mimicry may contribute to the development of EOE following HSVE [9]. Our patient was noted to develop EOE after the diagnosis of HSVE, suggesting that the viral infection predisposed to eosinophilic esophagitis. It is unclear whether the very mild T and B cell abnormalities noted may have predisposed to the patient developing HSVE esophagitis. The EOE which was subsequently diagnosed was unusual in that it was not associated with other allergic disorders, or associated with IgE mediated food sensitivity.

## Conclusion

We report a previously healthy patient who developed HSVE and improved on acyclovir. A screening immune deficiency evaluation showed very mild T and B cell abnormalities. The patient subsequently developed EOE, although no IgE mediated food sensitivities were identified. As evidenced by patients such as the one described herein, a diagnosis of EOE should be considered in the differential for patients presenting again with esophageal or upper GI symptoms following HSVE. Further research is needed to elucidate the mechanism behind this phenomenon.



**Figure 1: Esophagogastroduodenoscopy and histopathology findings.** (A-C) Representative gross endoscopy images of (A) esophagus, (B) stomach and (C) duodenum from the first EGD during the initial hospitalization. (D) Representative gross endoscopy image of esophagus from the second (follow-up) EGD. (E-F) Representative histopathology slides from biopsy specimens obtained during the first EGD demonstrating (E) an intranuclear viral inclusion (arrow) and (F) positive staining for HSV (brown). (G) Representative slide from biopsy specimens obtained during the second EGD demonstrating increased eosinophils (arrow) in the esophageal epithelial mucosa.



**Supplemental Digital Content 1. Clinical course.** Shown is the patient's clinical course including pertinent symptoms, assessments, and treatments prior to steroid intervention. Swallowed inhaled steroids were started after omeprazole therapy.

	% of all lymphocytes		
	1/6/10	2/17/10	Normal range
CD3+	53	61	60-76
CD4+	37	33	31-47
CD8+	<i>10</i>	<i>14</i>	18-35
CD4/8 ratio	3.7	2.36	0.7-2.7
CD19+	na	20	13-27
CD27+	na	64	42-90
CD56+	12	17	4-17
CD45RO+ (of CD4+)	na	76	13-30
CD45RA+ (of CD4+)	na	53	46-77
IgD+ (of CD19+CD27+)	na	7	<b>4.6-10.2</b>
IgD- (of CD19+CD27+)	na	3	<b>3.3-9.6</b>

**Supplemental Digital Content 1. Lymphocyte subset analysis.** Values show the percentages of all lymphocytes or of the indicated subsets which stain positive for the indicated markers on flow cytometry. Abnormal values are indicated in bold and italics and normal ranges are given where available. na=not analyzed.

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