COVER PAGE

Title of the Manuscript: Coexistence of Eosinophilic Esophagitis and Ulcerative Colitis in a Patient: Case Report and Review of Literature

Authors and Affiliations: Sameen Khalid MD[1], Aamer Abbass MD[1], Jie Ouyang MD[2], Luis Guarda MD[2], Irteza Inayat MD[3]
[1]Internal Medicine Department, Florida Hospital Orlando
[2]Pathology Department, Florida Hospital Orlando
[3]Gastroenterology Department, Florida Hospital Orlando

Corresponding Authors Contact Data:
Sameen Khalid
2501 N. Orange Avenue, Ste 235, Orlando, FL 32804
sameen.khalid.md@flhosp.org
407-747-3850

Irteza Inayat
2501 N. Orange Avenue, Ste 235, Orlando, FL 32804
irteza.inayat.md@flhosp.org
203-809-9667

Financial Disclosure and Conflict of Interest:
The authors have no financial disclosures to declare and no conflicts of interest to report.

Prior Publication:
This work has not been previously published and is not under consideration elsewhere.

Ethics and consent:
Consent was obtained from the patient.
Institutional Review Board (IRB) approval was received for this work.

Propriety Statement:
None of the authors have any financial, commercial or proprietary interest in any drug, device, or equipment mentioned in the submitted article.

ABSTRACT

Eosinophilic esophagitis (EoE) is a chronic inflammatory condition of the esophagus characterized by hypersensitivity reaction mediated by T-helper lymphocyte (Th) type 2 immune response. Ulcerative colitis (UC) is an autoimmune chronic inflammatory bowel disease associated with Th type 2 immune response. Both EoE and UC have been reported to occur with other autoimmune diseases; however, limited literature exists regarding coexistence of EoE and UC. We describe the first reported case of a patient who presented with symptoms related to both EoE and UC. Endoscopy revealed findings of EoE as well as UC and after being started on treatment, the patient showed clinical and endoscopic improvement.

INTRODUCTION

Eosinophilic esophagitis (EoE) is an inflammatory condition involving the esophagus that is thought to be associated with T-helper lymphocyte (Th) type 2 response [1,2]. Ulcerative colitis (UC) is an autoimmune chronic inflammatory bowel disease mediated by Th type 2 immune response. Both EoE and UC have been reported to occur with other atopic conditions such as asthma and also with other autoimmune diseases such as celiac disease [1-4]; however, limited literature exists regarding coexistence of EoE and UC. We report a case of a patient with symptoms related to both EoE and UC and discuss the diagnostic and management challenges on the basis of literature review. To the best of our knowledge, this is the first reported case of EoE and UC coexisting in the same patient.

CASE PRESENTATION

A 40-year-old male was referred to a gastroenterologist due to complains of progressively worsening solid food dysphagia for 10 months and bloody diarrhea of fluctuating severity for 8 years. His past medical history was significant for hypertension and hemorrhoids. His family history was negative for inflammatory bowel disease or gastrointestinal malignancy. He was not on any medications. Esophagogastroduodenoscopy revealed esophageal edema (E), rings (R) and multiple luminal strictures (S) (Figure 1). EoE endoscopic reference score (EREFS) was E1R3E0F0S1.The presence of >15 eosinophils per high-power field (hpf) involving proximal and distal esophagus confirmed the diagnosis of EoE (Figure 3). Biopsies from stomach and duodenum revealed no eosinophils. He underwent balloon dilation of the strictures and treatment with oral fluticasone and pantoprazole was initiated. Colonoscopy revealed mucosal erythema, ulcerations and exudates in cecum, ascending colon and rectum (Figure 2). Biopsy showed acute and chronic inflammation in cecum, ascending colon and rectum characterized by acute cryptitis, crypt abscesses, increased lamina propria inflammatory infiltrates and crypt distortion (Figure 3). He was started on oral and per-rectal mesalamine. At a follow-up visit at three months, the patient had significant improvement in his symptoms. Repeat endoscopy at four months showed improvement in EREFS (E1R1E0F0S0) (Figure 1) and normal mucosa from rectum to cecum (Figure 2) with no evidence of active inflammation on biopsy (Figure 3).

DISCUSSION

EoE is a chronic inflammatory condition of the esophagus, described as a pathologic finding of increased eosinophilic infiltration of esophageal epithelium. It is characterized by Th2 immune-mediated hypersensitivity reaction [1,2]. Recent population estimates in the United States show prevalence of EoE to be 57 cases per 100,000 [5]. Most patients were reported to be white males between the ages of 20 and 50 years [5,6]. Increasing prevalence is likely to be due to increased recognition of the disease. EoE is now recognized as the second leading cause of dysphagia in adults [5]. Clinical presentation of EoE includes dysphagia, food impaction, occasional heartburn, atypical chest pain and abdominal pain [4-6]. About 70% of the patients with EoE have co-existing atopic conditions such as asthma, allergic rhinitis and atopic dermatitis [5-7].

DIAGNOSIS

It is a clinicohistopathologic diagnosis, with both clinical and histopathologic criteria taken into consideration rather than in isolation. It is defined by symptoms of esophageal dysfunction, endoscopic appearance and marked eosinophilic infiltration (≥ 15 eosinophils/hpf) of esophageal mucosa [4,6-9]. Secondary causes of esophageal eosinophilia must be excluded. These include hypereosinophilic syndrome, Celiac disease, Crohn's disease, achalasia, infections, vasculitis, drug hypersensitivity, connective tissue diseases, graft versus host disease, pemphigus, eosinophilic gastrointestinal diseases and proton-pump inhibitor-responsive esophageal eosinophilia [6,7].

Endoscopic appearance of EoE includes esophageal narrowing, edema, multiple concentric rings giving esophagus an appearance of trachea (trachealization of esophagus), white plaques, linear furrows and mucosal friability [4,5,7,8]. EoE endoscopic reference score (EREFS) has been developed to classify and grade endoscopically detected esophageal features in EoE. This score takes into account the presence of five major endoscopically identified esophageal features in eosinophilic esophagitis: esophageal edema, described as loss of vascular markings and mucosal pallor (E), rings (R), exudates, also described as white plaques or spots (E), longitudinal furrows or vertical lines (F) and strictures (S) [5]. Endoscopic severity of EoE as measured by the EREFS correlates with symptom severity and clinical outcomes. Histologic severity as measured by the eosinophil density has limited correlation with symptom severity and clinical outcomes [2]. The number of eosinophils required for the diagnosis of EoE is 15 eosinophils in at least one high-power field [4,6-9]. Sensitivity and specificity of this cut-off value have been reported as 100% and 96%, respectively, for establishing the diagnosis of EoE [6]. 2 to 4 biopsies from at least two different locations in the esophagus should be taken in order to maximize diagnostic yield, as mucosal inflammation in EoE is patchy [5,7-9]. Increased eosinophils are usually seen in both proximal and distal biopsies as compared to GERD where eosinophils are more profound in distal biopsies. Biopsies from the stomach and duodenum should also be obtained to rule out eosinophilic gastroenteritis [8].

MANAGEMENT

Management of EoE involves dietary, pharmacologic and endoscopic treatments. Dietary elimination is usually recommended as the initial treatment in the management of EoE in both adults and children [7]. Elemental, allergy-testing-directed elimination and empiric six food elimination diets have been proposed for the management of EoE. Selection of a specific dietary approach should be based on individual patient's needs and available resources. Six food elimination diet (SFED) involves elimination of six most common food allergens - milk, soy, nuts, eggs, wheat and shellfish from diet for six weeks [5-7]. This diet has resulted in significant improvement in the symptoms, endoscopic and histologic features, making it the most popular diet in the treatment of EoE [5]. There are three phases of the SFED protocol: (1) induction phase, during which the six foods are eliminated from the diet, (2) reintroduction phase, during which the foods are reintroduced in the diet sequentially, followed by repeat endoscopies and biopsies to monitor disease recurrence, (3) maintenance phase, during which the identified food triggers are avoided [5]. Assessment of response to dietary treatment can be done either by monitoring improvement in clinical symptoms or by performing endoscopy with esophageal biopsies [7]. Pharmacologic treatment involves the use of topical (swallowed) corticosteroids such as fluticasone or budesonide. Topical corticosteroids are the mainstays of pharmacologic therapy for EoE. Efficacy of topical steroids in causing symptomatic and histologic improvement after 2 to 12 weeks of therapy

ranges from 53 to 95% [6]. Fluticasone is given as 880-1760 mcg/day in a divided dose. Budesonide is given as 2 mg/day in a divided dose [6,7]. Topical corticosteroids are anti-inflammatory and also decrease expression of interleukin-5 (IL-5) and eotaxins, both of which are involved in recruiting eosinophils [9]. Side effects of topical steroids include oropharyngeal and esophageal Candidiasis and secondary adrenal insufficiency [5,6,9]. Even though compared to inhaled steroids, swallowed steroids maximize first pass hepatic metabolism but the dose used for EoE is more than the dose used for asthma and other atopic conditions [5]. Esophageal dilations can be performed in symptomatic patients with esophageal strictures. Complications of esophageal dilation include post-dilation chest pain, bleeding and esophageal perforation [6,7].

A significant proportion of patients also respond to acid suppression therapy. This subset of patients has proton pump inhibitor (PPI)-responsive esophageal eosinophilia [4,8,9]. PPI-responsive esophageal eosinophilia is diagnosed when patients have symptoms related to esophageal dysfunction and presence of eosinophils on esophageal biopsy but these patients respond to PPI by demonstrating symptomatic and histologic improvement after being started on PPI [7,9]. American College of Gastroenterology guidelines recommend initiating a 2-month course of PPI in patients with EoE followed by endoscopy and biopsies [7]. Recent studies and current views recommend against excluding EoE based on responsiveness to PPI and recommend starting PPI as initial step in patients with esophageal eosinophilia [5]. In a prospective cohort conducted by Dellon et al, about one-third of the patients with > 15 eosinophils/hpf had clinical and histological improvement following initiation of PPI therapy [10].

COMPLICATIONS

Complications of EoE occur due to esophageal remodeling as a consequence of chronic inflammation and fibrosis. These complications include food impaction, esophageal strictures, esophageal perforation and malnutrition [5,6]. The strongest predictor of the risk of developing esophageal strictures is the duration of disease. Action of mediators such as transforming growth factor β produced by eosinophils leads to smooth muscle contraction fibrotic strictures [2,6]. There is a high likelihood of symptom recurrence if treatment is discontinued due to chronic nature of the condition [6].

ASSOCIATION OF EOSINOPHILIC ESOPHAGITIS WITH ULCERATIVE COLITIS

Ulcerative colitis is an inflammatory bowel disease characterized by inflammation limited to the mucosal layer of the colon. It commonly involves the rectum and may extend in a continuous fashion to involve other parts of the colon. Symptoms of ulcerative colitis include diarrhea, which is usually bloody, urgency, tenesmus, fecal incontinence and colicky abdominal pain. Ulcerative colitis is diagnosed based on the presence of chronic diarrhea for more than four weeks and evidence of active inflammation on endoscopy and chronic changes on biopsy. The endoscopic findings in patients with ulcerative colitis include mucosal erythema, petechiae, exudates, edema, erosions, friability and loss of vascular markings due to engorgement of the mucosa. The biopsy features suggestive of ulcerative colitis include crypt abscesses, crypt atrophy, increased lamina propria cellularity and basal lymphoid aggregates. The presence of two or more of these histologic features is highly suggestive of ulcerative colitis.

Both EoE and UC are idiopathic Th2 mediated conditions in which inflammation is caused by dysregulated mucosal immune response. Coexistence of these two Th2 mediated conditions probably originates from overlapping immunopathogenetic mechanisms and emphasizes a rare association between them. Interleukin-13 (IL-13) is a cytokine that plays an integral role in allergic and inflammatory conditions. It is a Th2 family cytokine and is produced by CD4 T cells. Overexpression of IL-13 has been cited to play an important role in mucosal inflammation and fibrosis in patients with UC and EoE [6,8,11]. IL-13 has been shown to down-regulate proteins associated with barrier function (filaggrin) and adhesion molecules (desmoglein-1) [6]. Altered esophageal epithelial barrier function may be an inciting factor leading to a permissive environment for antigen penetration through the barrier which in turn leads to recruitement of eosinophils [6]. Involvement of IL-13 in pathogenesis of UC and EoE is based on data from animal models and from subsequent confirmation of excess IL-13 production in human diseases [6,8]. Many drugs that target IL-13 are currently being tested for new therapies to treat these conditions [8].

Fifi et al [1] and Suttor et al [2] described coincidental occurrence of EoE and Crohn's disease in pediatric and adult patients, respectively. In a large population-based cohort study, Peterson [3] observed genetic associations between EoE and UC. EoE probands were found to be 3.79 times more likely than controls to be diagnosed with UC. Increased association was also observed in first-degree family members and second-degree relatives [3]. McIntire et al [12] conducted a retrospective cohort study on patients who had simultaneous upper and lower endoscopy performed to determine if IBD is more common in patients with EoE and found that UC was more frequent with increasing number of esophageal eosinophils per high power field. They concluded that patients with increased esophageal eosinophils were more likely to have concurrent inflammatory bowel disease, especially UC [12].

CONCLUSION

This case emphasizes the value of awareness among physicians regarding the possibility of coexistence of multiple autoimmune diseases. This will help in timely evaluation of symptoms suggestive of other autoimmune conditions in a patient with an existing autoimmune disease. The coexistence of EoE and UC may also provide better understanding of the complex interactions of the immune system in the pathogenesis of both diseases. Further large scale retrospective and prospective studies are required to confirm this association.

REFERENCES

1. Fifi A, Langshaw A, Miller T. Coincidental eosinophilic esophagitis and Crohn's disease in 3 pediatric patients. Clinical Vignette Abstarcts – NASPGHAN. Accessed online on November 5, 2016. http://www.naspghan.org/files/documents/pdfs/annual-meeting/2015
2. Suttor VP, Chow C, Turner I. Eosinophilic esophagitis with Crohn's disease: A new association or overlapping immune-mediated enteropathy? Am J Gastroenterol. 2009; 104(3):794-5. doi: 10.1038/ajg.2008.114.
3. Peterson K, Firszt R, Fang J, et al. Risk of autoimmunity in EoE and families: A population-based cohort study. Am J Gastroenterol. 2016; 111(7):926-32. doi: 10.1038/ajg.2016.185.

4. Dellon ES, Gonsalves N, Hirano I et al. ACG clinical guideline: Evidenced based approach to the diagnosis and management of esophageal eosinophilia and eosinophilic esophagitis. Am J Gastroenterol. 2013; 108:679-692. doi: 10.1038/ajg.2013.71.
5. Hirano I. 2015 David Y. Graham lecture: The first two decades of eosinophilic esophagitis – from acid reflux to food allergy. Am J Gastroenterol. 2016; 111:770-776. doi: 10.1038/ajg.2016.136.
6. Dougherty T, Stephen S, Borum ML, et al. Emerging therapeutic options for eosinophilic esophagitis. J Gastroenterol Hepatol. 2014; 10(2): 106-116.
7. Furuta GT, Katzka DA. Eosinophilic esophagitis. N Engl J Med. 2015; 373:1640-1648. doi: 10.1056/NEJMra1502863.
8. Mannon P, Reinisch W. Interleukin 13 and its role in gut defence and inflammation. Gut. 2012; 61:1765-1773. doi: 10.1136/gutjnl-2012-303461.
9. Almashat SJ, Duan L, Goldsmith JD. Non-reflux esophagitis: A review of inflammatory diseases of the esophagus exclusive of reflux esophagitis. Semin Diagn Pathol. 2014; 31:89-99.
10. Dellon ES, Speck O, Woodward K, et al. Clinical and endoscopic characteristics do not reliably differentiate PPI-responsive esophageal eosinophilia and eosinophilic esophagitis in patients undergoing upper endoscopy: A prospective cohort study. Am J Gastroenterol. 2013; 108:1854-1860.
11. Grin A, Streutker CJ. Esophagitis. Old histologic concepts and new thoughts. Arch Pathol Lab Med. 2015; 139:723-729.
12. McIntire M, Saboorian MH, Genta RM. Eosinophilic esophagitis is associated with an increased prevalence of inflammatory bowel disease. Accessed online on November 5, 2016. http://www.miracalifesciences.com/wordpress/wp-content/uploads/2013/10/ACG_2013_EoE_IBD.pdf

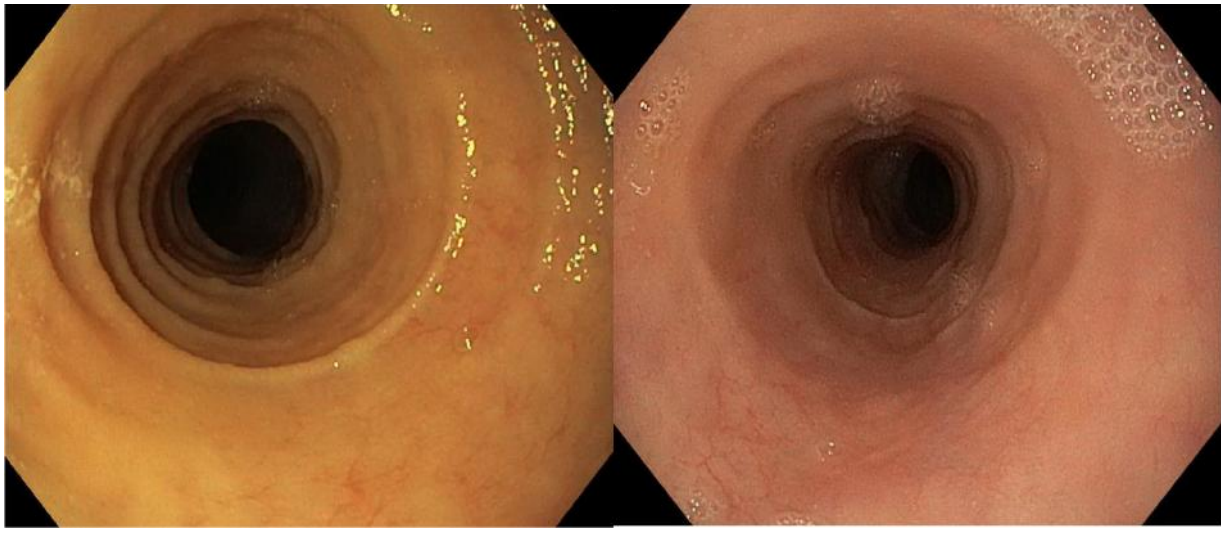

Figure 1:
Esophagogastroduodenoscopy before treatment (left) shows esophageal edema and multiple concentric rings giving esophagus an appearance of trachea.
Esophagogastroduodenoscopy after treatment (right) shows normal appearance of esophagus.

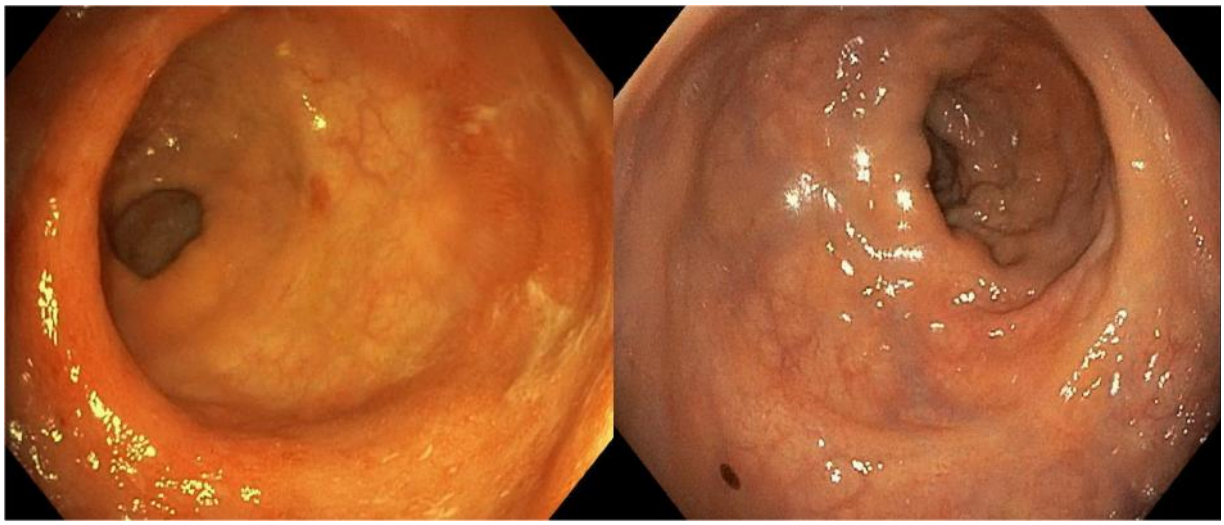

Figure 2:

Colonoscopy before treatment (left) shows mucosal erythema, ulcerations and exudates.
Colonoscopy after treatment (right) shows normal colonic mucosa.

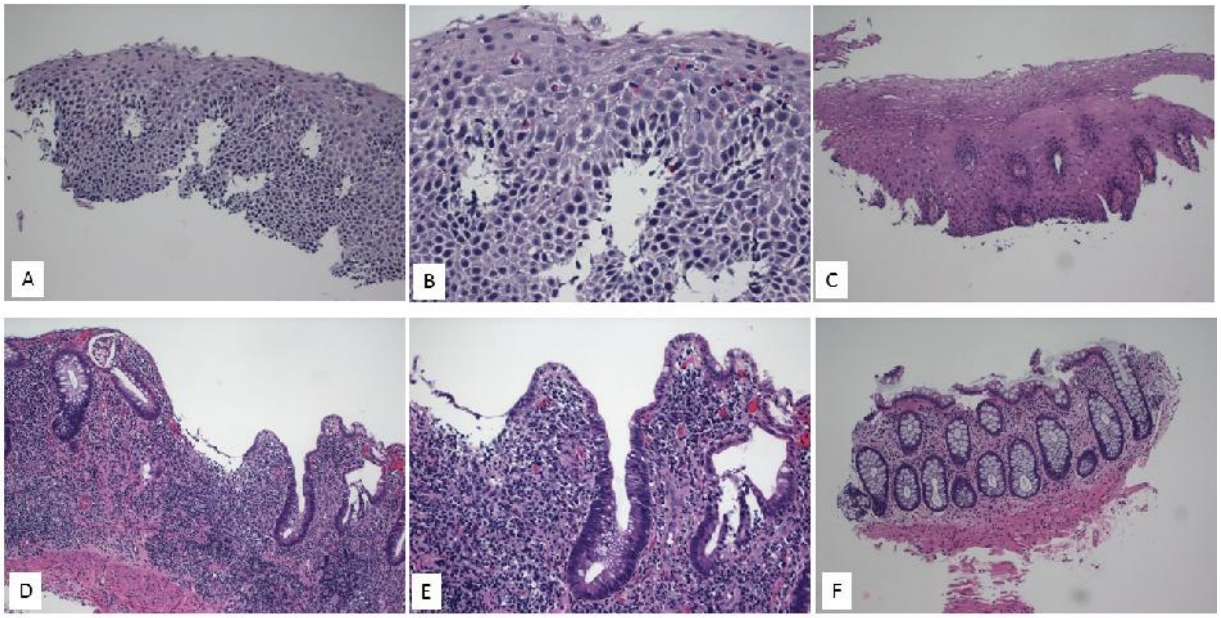

Figure 3:
Biopsies of distal esophagus before treatment show marked intraepithelial eosinophils (up to 30 eosinophils/hpf) in association with a thick basal cell layer and intercellular edema on pictures A (low power, x 20) and B (high power, x 40).
After treatment biopsy shows normal squamous esophagus on picture C (low power, x 20).
Biopsies of cecum and rectum before treatment show moderately active chronic colitis and proctitis characterized by acute cryptitis, crypt abscess, full thickness lamina propria lymphoplasmacytic infiltrates and crypt distortion on pictures D (low power, x 20) and E (high power, x 40).
After treatment biopsy shows normal colon and rectum on picture F (low power, x 20).