ORIGINAL ARTICLE

Eosinophilic esophagitis in adults: clinical, endoscopic, histologic findings, and response to treatment with fluticasone propionate

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Background: Eosinophilic esophagitis is an increasingly recognized disorder characterized by intense eosinophilic infiltration of the esophageal mucosa. The aim of this study was to define the clinical syndrome, the endoscopic features, and the distribution of the eosinophil infiltrate in adults with eosinophilic esophagitis. We undertook a prospective evaluation of the symptomatic and histologic response to treatment with fluticasone propionate.

Methods: Twenty-six patients (18 men; mean age 36 years) had symptom assessment and barium studies, esophageal motility recordings, and 24-hour esophageal pH studies. Upper-GI endoscopy was performed with quantitative eosinophil counts of biopsy specimens from the proximal and distal esophagus, the gastric antrum, and the duodenum. Nineteen subjects received 4 weeks of swallowed fluticasone propionate. After treatment, symptom assessment and endoscopic biopsies were repeated.

Results: All 26 patients had a history of dysphagia, and 11 presented acutely with food-bolus obstruction. Esophageal peristalsis was normal in most and gastroesophageal reflux coexisted in 10 patients. Characteristic endoscopic findings of furrows (20) and rings (18) were observed. All 19 treated patients had symptom improvement and a significant decrease in esophageal eosinophil counts.

Conclusions: Eosinophilic esophagitis is a distinct entity that may coexist with gastroesophageal reflux. Swallowed fluticasone propionate is an effective treatment. (Gastrointest Endosc 2006;63:3-12.)

Eosinophilic esophagitis (EE) is an increasingly recognized condition in adults presenting with dysphagia and chest pain.[1] EE is characterized by eosinophilic infiltration of the esophageal mucosa; its pathogenesis is unknown.[2,3] There is a debate as to the association between EE, GERD, and eosinophilic gastroenteritis.[4-8] The condition has been well described in the pediatric literature but has been underrecognized in adults. In the majority of studies to date, individuals affected by EE have been predominantly male children and adolescents.[1] Associations have included atopy, allergy, peripheral eosinophilia, and recurrent food-bolus obstructions.[9] A number of endoscopic features have been described, including strictures (frequently proximal), mucosal rings (often multiple), mucosal ulceration, linear furrows, small-caliber esophagus, and multiple white papules (eosinophilic microabscesses).[10-17]

EE can be suspected on clinical history but requires histologic confirmation by finding large numbers of intraepithelial eosinophils. This is in contrast to GERD, where small numbers of eosinophils may be present, primarily in the distal esophagus.[18]

Optimal treatment for EE has not been defined. Approaches include esophageal dilation; elimination and elemental diets; use of antihistamines, sodium cromoglycate, and systemic and topical corticosteroids; and leukotriene receptor antagonists.[15,19-24] Mepolizumab, an anti-interleukin-5 monoclonal antibody, recently has been reported to have histologic and clinical benefit in an adult case of EE.[25] Problems with many of these treatment modalities include poor patient compliance, limited tolerance, and troublesome systemic side effects. Esophageal dilation has been associated with deep mucosal tears, severe pain, and perforation[14,15,17] Experience with fluticasone propionate (FP), an inhaled corticosteroid routinely used in the management of asthma, has shown benefit in a pediatric population with EE[3] and, more recently, in adults.[23,24] FP has not always been efficacious, particularly in the allergic EE subgroup.[24]

The aims of this study were to further define the clinical syndrome in adults, the endoscopic characteristics, and the distribution of the eosinophilic infiltrate, and to

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clarify the association of EE with allergy, GERD, and esophageal dysmotility. In addition, we assessed the symptomatic and histologic response of EE in adults to treatment with swallowed FP.

Capsule Summary

What is already known on this topic

- Increasingly recognized, EE is characterized by intense eosinophilic infiltration of the esophageal mucosa.
- The relationship of EE to GERD and eosinophilic gastroenteritis is debatable.
- FP may benefit pediatric and adult EE patients.

What this study adds to our knowledge

- EE is an underrecognized cause of dysphagia, food-bolus obstruction, and chest pain in adults.
- EE is distinct from eosinophilic gastroenteritis and may coexist with GERD.
- FP treatment results in symptom improvement and a significant decrease in esophageal eosinophil counts.

PATIENTS AND METHODS

Patients

Twenty-six adult patients (aged $\geq$ 17 years) with a histologic diagnosis of EE were enrolled in this prospective study. Patients were excluded if systemic or inhaled corticosteroids had been used in the preceding 3 months. Histologic diagnosis required a mean intraepithelial eosinophil density $>$15 eosinophils/high power field (HPF) in the absence of gastric or duodenal eosinophil infiltrates. Esophageal biopsy specimens were taken in patients with a history of dysphagia or food-bolus obstruction, or when indicative endoscopic findings were recognized. The study was approved by the ethics committee of the Princess Alexandra Hospital.

Study protocol

After obtaining written informed consent, the 26 patients were enrolled by using a standardized protocol. A symptom score assessed the presence and the frequency of symptoms, including dysphagia, chest pain, heartburn, regurgitation, vomiting, and abdominal pain.[26] Each symptom was scored from 0 to 3 (0, absent; 1, 3 times per week; 2, often; 3, daily), with a total score of 18. Atopic status was based on history. Specific food allergies were recorded if previously confirmed on immunoglobulin E (IgE)–radioallergosorbent (RAST) or skin prick/patch testing.

Each patient had baseline investigations of a barium swallow with liquid barium and marshmallow and esophageal manometry to assess the presence of associated dysmotility. Esophageal manometry was performed with a pneumohydraulic capillary infusion system (flow rate, 0.5 mL/mm) that used an 8-lumen tube that incorporated a perfused sleeve device to straddle the lower esophageal sphincter (LES). The amplitude of the peristaltic wave in the distal esophagus was the mean of pressures recorded from 6 wet swallows. The mean LES pressure was calculated from the sleeve recordings of 6 swallows. The 24-hour ambulatory esophageal pH studies assessed and quantified gastroesophageal reflux by using a Medtronic Digitrapper pH data logger (Medtronic Inc, Minneapolis, Minn) and Zinetics dual channel pH catheter (Medtronic Inc). Acid suppression medication was withdrawn for 5 days before testing. Recording sites were placed 5 and 20 cm above the LES. Acid exposure and the DeMeester score were calculated on Polygram 98 software (Medtronic Inc). Serum IgE levels and the full blood count (FBC) with differential were performed to further define associated atopy. Peripheral eosinophilia was defined as the following: normal, $<$350 cells/mm^3; slightly elevated, 350 to 1500 cells/mm^3; moderately elevated, $>$1500 to 5000 cells/mm^3; and severely elevated, $>$5000 cells/mm^3.[27]

Upper-GI endoscopy was performed in the sedated patients with a standard video gastroscope (Pentax EG2901; Pentax Corp, Tokyo, Japan). Biopsy specimens (outside forceps diameter, 2.2 mm) were taken from the proximal third and the distal third (approximately 2 cm above the gastroesophageal junction) of the esophagus. Gastric antral and duodenal (3rd part) biopsies were performed to exclude eosinophilic gastroenteritis. Two biopsy specimens were taken from each site. Symptom score, FBC, serum IgE, and endoscopy with biopsies were all performed before commencing therapy and within 72 hours of completing treatment.

Treatment

Participants received active treatment with 4 weeks of swallowed FP, 250-mcg metered aerosol, 2 puffs twice daily. Swallowing (instead of inhaling) allows maximal topical esophageal effect and minimizes systemic absorption because of high first-pass hepatic metabolism.[28,29] Patients were advised to avoid food and liquids for 30 minutes after administration and then to perform a mouth rinse to minimize the risk of developing oral candidiasis. The efficacy of treatment was assessed on the symptom score and the histologic response.

Histological analysis

Mucosal biopsy specimens were fixed in formalin, embedded in paraffin, serially sectioned, and stained with H&E. A single pathologist (C.C.) assessed the sections in a blinded fashion. All 3 levels on each specimen were reviewed. The number of eosinophils in 5 consecutive HPFs was counted in the areas with the densest infiltrate, and values were expressed as the mean number of eosinophils per HPF. One HPF was calculated to have an area of 0.24 mm^2 (Olympus BX41 microscope, WH $\times$10 eyepiece