

## 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.<sup>1</sup> EE is characterized by eosinophilic infiltration of the esophageal mucosa; its pathogenesis is unknown.<sup>2,3</sup> There is a debate as to the association between EE, GERD, and eosinophilic gastroenteritis.<sup>4-8</sup> 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.<sup>1</sup> Associations have included atopy, allergy, peripheral eosinophilia, and recurrent food-bolus obstructions.<sup>9</sup> 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).<sup>10-17</sup>

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.<sup>18</sup>

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.<sup>15,19-24</sup> Mepolizumab, an anti-interleukin-5 monoclonal antibody, recently has been reported to have histologic and clinical benefit in an adult case of EE.<sup>25</sup> 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.<sup>14,15,17</sup> Experience with fluticasone propionate (FP), an inhaled corticosteroid routinely used in the management of asthma, has shown benefit in a pediatric population with EE<sup>3</sup> and, more recently, in adults.<sup>23,24</sup> FP has not always been efficacious, particularly in the allergic EE subgroup.<sup>24</sup>

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

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.

## 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.<sup>26</sup> 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<sup>3</sup>; slightly elevated, 350 to 1500 cells/mm<sup>3</sup>;

### 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.

moderately elevated,  $>1500$  to  $5000$  cells/mm<sup>3</sup>; and severely elevated,  $>5000$  cells/mm<sup>3</sup>.<sup>27</sup>

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.<sup>28,29</sup> 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<sup>2</sup> (Olympus BX41 microscope, WH  $\times 10$  eyepiece

**TABLE 1. Clinical features of 26 adult patients with eosinophilic esophagitis**

| Patient no.        | Age, y | Gender | Symptom duration before diagnosis, y | Presenting symptoms | No. history of food-bolus obstructions | Atopic history     |
|--------------------|--------|--------|--------------------------------------|---------------------|----------------------------------------|--------------------|
| Treated patients   |        |        |                                      |                     |                                        |                    |
| 1                  | 29     | M      | 11                                   | D                   | 1                                      | As, Hf, Rh, Ad, FA |
| 2                  | 33     | M      | 6                                    | FB, D               | 2                                      | As, FA             |
| 3                  | 29     | M      | 19                                   | D                   | 1                                      | Hf, Rh             |
| 4                  | 40     | M      | 17                                   | CP, D               | 0                                      | Nil                |
| 5                  | 60     | M      | 20                                   | D                   | 0                                      | As, Rh             |
| 6                  | 34     | M      | 12                                   | FB, D               | 2                                      | AS                 |
| 7                  | 35     | M      | 3                                    | FB, D               | 1                                      | As, Hf             |
| 8                  | 27     | M      | 17                                   | FB, D               | 3                                      | Hf, Rh             |
| 9                  | 30     | M      | 4                                    | D                   | 0                                      | Nil                |
| 10                 | 20     | M      | 1                                    | FB, D               | 1                                      | As                 |
| 11                 | 21     | M      | 5                                    | FB, D               | 1                                      | Hf, Rh             |
| 12                 | 31     | M      | 6                                    | FB, D               | 1                                      | As, Hf, Rh, FA     |
| 13                 | 61     | M      | 2                                    | FB, D               | 4                                      | Hf, Rh, Ad         |
| 14                 | 39     | F      | 2                                    | D                   | 0                                      | Nil                |
| 15                 | 42     | F      | 4                                    | CP, D               | 0                                      | As, Hf             |
| 16                 | 49     | F      | 1                                    | D                   | 0                                      | As                 |
| 17                 | 45     | F      | 32                                   | D                   | 0                                      | As, Hf, Rh, FA     |
| 18                 | 25     | F      | 13                                   | D                   | 2                                      | Hf, FA             |
| 19                 | 28     | F      | 6                                    | D                   | 0                                      | Rh, FA             |
| Untreated patients |        |        |                                      |                     |                                        |                    |
| 20                 | 41     | M      | 2                                    | D                   | 6                                      | Nil                |
| 21                 | 18     | M      | 1                                    | D                   | 3                                      | As                 |
| 22                 | 38     | M      | 4                                    | FB, D               | 3                                      | Hf, Ad             |
| 23                 | 17     | M      | 6                                    | FB, D               | 2                                      | As                 |
| 24                 | 20     | M      | 3                                    | FB, D               | 2                                      | Nil                |
| 25                 | 52     | F      | 45                                   | D                   | 3                                      | As, Hf, Rh, FA     |
| 26                 | 65     | F      | 20                                   | D, CP               | 0                                      | Nil                |

D, Dysphagia; As, asthma; Hf, hayfever; Rh, rhinitis; Ad, atopic dermatitis; FA, food allergy; FB, food bolus; CP, chest pain.

with UPlan  $\times 40$  objective; Olympus Optical Co Ltd, Tokyo, Japan).

### Statistical analysis

Data were expressed as means  $\pm$  standard error of the mean. Statistical significance of the differences between groups was assessed by the Wilcoxon matched-pairs

signed rank test. A two-tailed  $p$  value  $<0.05$  was considered to be significant.

### Long-term follow-up

Patients were followed in consultation at 3 months, and, if unable to attend, contact was made via telephone.

**TABLE 2. Endoscopic features of 26 adult patients with eosinophilic esophagitis**

| Patient no.        | Endoscopic findings  | No. previous endoscopies | No. previous dilations |
|--------------------|----------------------|--------------------------|------------------------|
| Treated patients   |                      |                          |                        |
| 1                  | LF, R, ErE, WP       | 2                        | 1                      |
| 2                  | NB                   | 6                        | 3                      |
| 3                  | LF, R, NB, ErE, PS   | 1                        | 0                      |
| 4                  | LF, R, WP            | 2                        | 1                      |
| 5                  | LF                   | 2                        | 0                      |
| 6                  | LF, R, ErE           | 1                        | 1                      |
| 7                  | NB, PS, R            | 3                        | 0                      |
| 8                  | LF, PS, R            | 0                        | 0                      |
| 9                  | LF, R                | 0                        | 0                      |
| 10                 | LF, R (fine)         | 0                        | 0                      |
| 11                 | Nodular mucosa       | 0                        | 0                      |
| 12                 | LF                   | 0                        | 0                      |
| 13                 | LF, R (fine)         | 0                        | 0                      |
| 14                 | LF                   | 4                        | 0                      |
| 15                 | LF, R (fine), PS, NB | 0                        | 0                      |
| 16                 | NB, R, LF, ErE       | 2                        | 0                      |
| 17                 | LF, R, ErE, WP       | 1                        | 1                      |
| 18                 | LF, R                | 4                        | 2                      |
| 19                 | LF, R, ErE, WP       | 3                        | 2                      |
| Untreated patients |                      |                          |                        |
| 20                 | LF, R, ErE           | 6                        | 0                      |
| 21                 | LF, PS               | 1                        | 1                      |
| 22                 | R, NB, PS            | 3                        | 1                      |
| 23                 | PS                   | 1                        | 1                      |
| 24                 | normal               | 1                        | 0                      |
| 25                 | R, LF, NB            | 4                        | 1                      |
| 26                 | LF, R                | 2                        | 0                      |

LF, Linear furrows; R, rings; ErE, erosive esophagitis; WP, white papules/plaques; NB, narrow bore; PS, proximal stricture.

mean age of the pretreatment cohort was 36 years (range 17-65 years).

### Clinical features

Baseline clinical characteristics of the pretreatment group are shown in Table 1. All 26 patients had a history of dysphagia for solid food. Seventeen had prior episodes of food-bolus obstructions, often multiple, and 11 presented to the emergency department with an impacted food bolus during the period of the study. Two patients had chest pain as their dominant symptom at presentation. Eleven patients had previous dilations for dysphagia, with symptomatic improvement. However, each described severe chest pain after dilation, lasting up to 7 days. In one case, a postdilation endoscopy was performed and revealed a long, deep, linear mucosal tear. Dysphagia was present for 1 to 45 years (mean, 10 years) before confirming a diagnosis of EE. Three patients had distinct childhood memories of recurrent choking episodes with a meat bolus.

Twenty patients had a history of atopy: asthma, hay fever, rhinitis, atopic dermatitis, or food allergy. Asthma was present in 13 patients and dated from early childhood in 10. Food allergies (7 patients) were varied and included reactions to shellfish, avocado, peanuts, and honey. Two patients had symptom correlation with occupational allergen exposure. One, a baker by trade (RAST testing strongly positive for wheat), noticed that both his dysphagia and asthma were worse on workdays and improved when on vacation. A horse trainer had a similar correlation with hay exposure.

GERD had been the presumed diagnosis in 17 patients. All had previously been managed with escalating doses of proton pump inhibitors. At the time of enrollment, 13 patients were on acid suppression medication. Ten of the 26 patients reported symptoms of heartburn. One patient had a previous laparoscopic fundoplication.

### Endoscopic findings

In 25 patients, there were distinct endoscopic findings (Table 2). These findings included linear furrows in 20 (Fig. 1A), multiple mucosal rings (distinct from Schatzki's and peptic rings) in 16 (Fig. 1B), narrow bore esophagus in 7, white papules/plaques in 4 (Fig. 1C), and proximal strictures in 3. When specifically biopsied, the plaques/papules were found to be eosinophilic microabscesses (Fig. 1D). Three patients had longitudinal furrows only, most pronounced in the proximal esophagus. Nineteen of the 25 patients had undergone a previous gastroscopy. In 7 (37%), the esophagus was reported as normal, and in only one was the diagnosis queried.

### Histology

All patients demonstrated a marked increase in the number of intraepithelial eosinophils in the esophageal biopsy specimens. The density and the distribution of the esophageal infiltrate in the pretreatment biopsy

## RESULTS

### Patients

Between November 2002 and December 2003, 26 patients (18 men, 8 women) were recruited. Nineteen patients (13 men, 6 women) completed baseline investigation, treatment, and follow-up. Seven patients dropped out of the study before commencing treatment. The

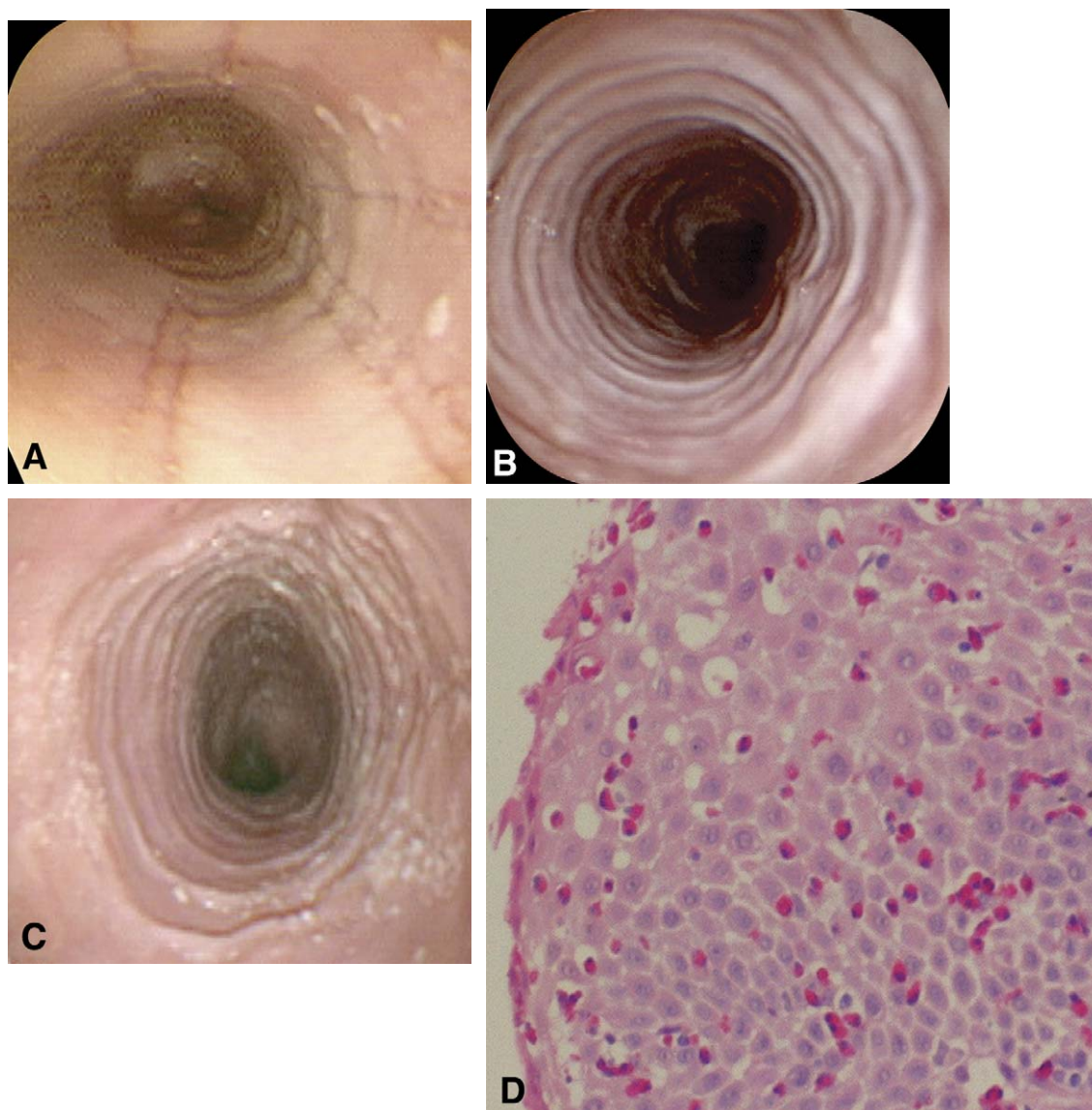


**Figure 1.** **A**, Linear furrows in esophageal lumen. **B**, Mucosal rings. **C**, Multiple white papules/plaques in esophagus. **D**, Histologic appearance of esophageal biopsy specimens, demonstrating markedly increased intraepithelial eosinophils. (H&E, orig. mag.  $\times 100$ ).

specimens varied between the proximal and distal sites within individual patients. The mean eosinophil count was 25.6 eosinophils/HPF (0.2–69.6 eosinophils/HPF) in biopsy specimens from the proximal esophagus and 37.6 eosinophils/HPF (3.8–109 eosinophils/HPF) in biopsy specimens from the distal esophagus. If only distal biopsy specimens had been obtained, the diagnosis would have been missed in one patient with 3.8 eosinophils/HPF in the distal biopsy specimens but 25.8 eosinophils/HPF at the proximal site. In 6 patients, the proximal (but not the distal) eosinophil count was  $< 15$  eosinophils/HPF. Eosinophil counts in the antral and duodenal biopsy specimens in all patients were insignificant.

### Baseline investigations

Twenty-four patients underwent 24-hour ambulatory pH studies, and 23 had esophageal motility studies (Table 3). The pH study was normal in 14 (58%). Ten patients had GERD, as defined by excessive acid exposure at the distal recording site and increased DeMeester score. There was a good correlation between increased acid exposure and a reduced LES pressure at esophageal motility studies. Eight of the 10 patients with acid reflux had reduced LES pressure. Good quality peristalsis was present in all but one patient (patient no. 3) who had aperistalsis and a low-pressure LES. Unfortunately, he declined repeat motility studies after treatment with FP.

TABLE 3. Baseline investigations

| No.                | 24-H pH study               |         |                    | Interpretation | Manometry                         |              | Barium study                     |
|--------------------|-----------------------------|---------|--------------------|----------------|-----------------------------------|--------------|----------------------------------|
|                    | Acid exposure,<br>% of time |         | DeMeester<br>score |                | Peristalsis<br>amplitude (distal) | LES pressure |                                  |
|                    | Proximal                    | Distal  | Distal             |                | N > 10,<br><180 mm Hg             | N =          |                                  |
|                    | N < 1                       | N < 3.4 | N < 14.72          |                |                                   | 10-25 mm Hg  |                                  |
| Treated patients   |                             |         |                    |                |                                   |              |                                  |
| 1                  | 1.2                         | 5.6     | 25.6               | GER            | 79                                | 8            | HH, GER, mild dysmotility        |
| 2                  | 0.1                         | 2.1     | 8                  | Normal         | 84                                | 12.7         | Normal                           |
| 3                  | 2.1                         | 4.2     | 24                 | GER            | Nil                               | 0            | Normal                           |
| 4                  | 0.1                         | 5       | 21.8               | GER            | 97                                | 8            | Delayed MM swallow               |
| 5                  | 0.2                         | 0.0     | 1.9                | Normal         | 155                               | 25           | Delayed MM swallow               |
| 6                  | 0.5                         | 7.6     | 40.6               | GER            | 94                                | 0            | HH, GER                          |
| 7                  | 0.9                         | 3.1     | 14                 | Normal         | 203                               | 9            | Normal                           |
| 8                  | 0.3                         | 0.1     | 2.7                | Normal         | 224                               | 27           | Normal                           |
| 9                  | 0.1                         | 3.2     | 10.5               | Normal         | 133                               | 19           | Normal                           |
| 10                 | 1.9                         | 7.5     | 20.6               | GER            | 103                               | 13           | HH                               |
| 11                 | 0.6                         | 2.4     | 14.1               | Normal         | 136                               | 3            | HH, Delayed MM swallow           |
| 12                 | 3.7                         | 4.8     | 24                 | GER            | 89                                | 3            | Delayed Ba and<br>MM swallow     |
| 13                 | 2.2                         | 9       | 29.5               | GER            | 181                               | 13           | Normal                           |
| 14                 | 0.0                         | 0.5     | 3.8                | Normal         | 94.5                              | 12           | Normal                           |
| 15                 | 1.6                         | 7.2     | 25.5               | GER            | 59                                | 0            | Delayed Ba and<br>MM swallow     |
| 16                 | 1.6                         | 8.5     | 46                 | GER            | 99                                | 0            | Normal                           |
| 17                 | 0.5                         | 2.7     | 13.3               | Normal         | 90                                | 18           | Delayed MM swallow               |
| 18                 | 1.2                         | 2.8     | 12                 | Normal         | 192                               | 14           | Normal                           |
| 19                 | 0.7                         | 5.6     | 17.1               | GER            | 90                                | 0            | Normal                           |
| Untreated patients |                             |         |                    |                |                                   |              |                                  |
| 20                 | 0.5                         | 2.3     | 13.2               | Normal         | 103                               | 14           | Reproduced dysphagia<br>MM phase |
| 21                 | 1.2                         | 3.2     | 13                 | Normal         | 138                               | 23           | Normal                           |
| 22                 | 0.7                         | 2.3     | 14.1               | Normal         | 120                               | 27           | Normal                           |
| 23                 | n/a                         | n/a     | n/a                | –              | n/a                               | n/a          | Normal                           |
| 24                 | n/a                         | n/a     | n/a                | –              | n/a                               | n/a          | n/a                              |
| 25                 | 0.2                         | 2.0     | 8                  | Normal         | n/a                               | n/a          | n/a                              |
| 26                 | 0.0                         | 0.0     | 0.3                | Normal         | 80                                | 10           | n/a                              |

LES, Lower esophageal sphincter; GER, gastroesophageal reflux; HH, hiatus hernia; MM, marshmallow; Ba, barium HH; n/a, not available.

Barium swallow with a marshmallow phase was undertaken in 23 patients. This study was normal in 13. In 7 patients, there was delayed passage of the marshmallow. In one patient, there was reproduction of the symptom of dysphagia with the solid phase at the mid esophagus.

“Felinization,” a mucosal ridging pattern, which has been reported in the literature as a barium contrast radiologic finding associated with EE, was demonstrated in only one case.<sup>14</sup>

Serum IgE levels were measured in all patients as a surrogate marker of atopy. In Australia, 3% of healthy blood

donors have serum IgE > 2400 µg/L (95% are atopic), and 20% have an IgE level between 240 µg/L and 2400 µg/L (40% are atopic) (Reference Laboratory, Queensland Health Department, Brisbane, Australia). In our cohort, one patient had a serum IgE > 2400 µg/L, and 7 had levels IgE between 240 µg/L and 2400 µg/L.

Peripheral eosinophilia was noted in 8 patients (5 slightly elevated, 3 moderately elevated) with 5 in the treated group.

## TREATMENT

### Follow-up

All 19 treated patients (including 10 with significant reflux) had a dramatic improvement in symptoms with 4 weeks of treatment. Eleven became asymptomatic. The mean symptom score decreased from 5.42 to 0.68 ( $p < 0.0001$ ) (Fig. 2). All patients had histologic improvement. Eighteen subjects had a significant decrease in the eosinophils/HPF count in both the proximal and the distal esophageal biopsy specimens, with complete resolution in 4. One patient had a rise in his proximal count (38.4-61 eosinophils/HPF) but a decrease in his distal count with clinical improvement. The mean proximal eosinophil count fell from 24.98 eosinophils/HPF to 4.46 eosinophils/HPF ( $p < 0.0004$ ). The mean distal eosinophil count fell from 39.34 eosinophils/HPF to 3.81 eosinophils/HPF ( $p < 0.0001$ ) (Fig. 3). The fluctuation in the serum IgE and peripheral eosinophil count before and after FP treatment failed to reach significance.

All patients completed treatment and found the treatment easy to use. Three patients had developed mild asymptomatic esophageal candidiasis at the posttreatment endoscopy. Of the 19 treated patients, 16 have continued with long-term assessment. Of these, 14 had begun to develop recurrent symptoms at the 3-month review. Consequently, they were offered a number of treatment options and elected to restart FP and to maintain it for a further few weeks. Patients with GERD (on pH study) and EE have been managed with a combination of acid suppression and FP.

## DISCUSSION

EE is a distinct clinicopathologic entity that extends beyond childhood. There appears to be a lack of awareness of EE, its defining features (which can be subtle), and treatment options among adult gastroenterologists. Most series have been published within the last 5 years and raise the question: Is EE increasing in incidence or increasing in recognition? Recent pediatric population based and adult observational studies<sup>30,31</sup> support the concept of increasing incidence. Our local experience suggests that recent awareness of the condition by adult gastroenterologists has been responsible for the increased

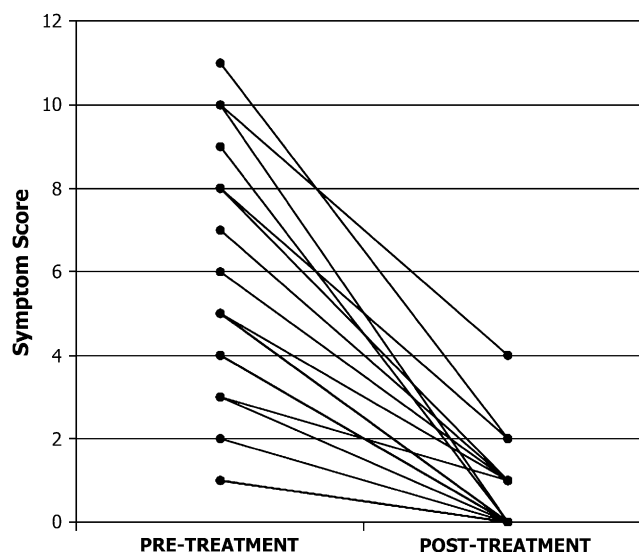


**Figure 2.** Symptom score before and after treatment with swallowed fluticasone propionate. Cumulative symptom score based on presence and frequency of dysphagia, chest pain, heartburn, regurgitation, vomiting, and abdominal pain (each scored 0 to 3).

frequency of adult EE diagnosed at our institution. The typical presentation of an atopic young man with dysphagia, recurrent food-bolus impaction, and peripheral eosinophilia is supported by our results. However, the clinical spectrum of presentation is much wider and includes women and a broad age range. Noncardiac chest pain also may be a presenting feature. There was an important correlation between EE and atopy and asthma. Other investigators have noted similarities between asthma and EE.<sup>32</sup> These reports include the presence of atopy, peripheral eosinophilia, the beneficial role of topical corticosteroids and leukotriene receptor antagonists, and the possible role of eotaxin and Th2 mediation.<sup>21,33-36</sup> Allergy-related diseases appear to be increasing in incidence in developed countries, with debate on the role of the hygiene hypothesis.<sup>37</sup> There is evidence that EE may be precipitated by food and aeroallergens that stimulate a Th2 response.<sup>38</sup> Work by others highlights the potential role of interleukin (IL) 5 and eotaxin.<sup>25,39</sup> The Th2 cytokine, IL-5 is important in eosinophil regulation. IL-5 may be elevated in EE.<sup>34,40</sup> Monoclonal antibodies, e.g., mepolizumab, have shown early promise in hypereosinophilic syndromes, including EE.<sup>32</sup>

The pathophysiology of EE is poorly understood. The amplitude of the esophageal peristaltic sequences was well maintained in most of our patients. Esophageal dysmotility, therefore, is unlikely to contribute to the dysphagia. It is postulated that the eosinophilic infiltrate leads to edema and inflammation, perhaps evolving over time to fibrosis. Straumann et al<sup>32</sup> have demonstrated architectural alteration and increased fibrous tissue in some patients with long-standing EE. EUS studies have demonstrated the full-thickness nature of the condition.<sup>41</sup> This supports

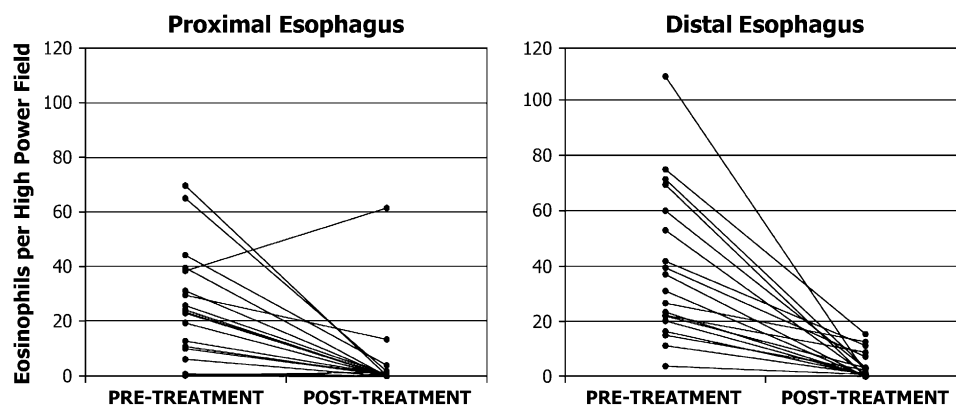


**Figure 3.** Mean eosinophils/HPF in proximal and distal esophageal biopsy specimens before and after treatment with swallowed fluticasone propionate.

the concept of a narrow-bore esophagus as the cause of dysphagia. Interestingly, 3 of the 4 patients with complete resolution of the esophageal eosinophilia also had resolution of the mucosal rings and furrows. One patient with a proximal stricture had resolution with FP treatment. Ten patients had gastroesophageal reflux as defined by 24-hour pH recording. The majority of these patients also had a reduced LES pressure. Our patients with coexistent GERD and EE all had prior minimal response to medical treatment for GERD and, in one case, surgical fundoplication. They all responded to the addition of FP. Our study clearly demonstrates that GERD and EE may coexist. This finding likely reflects the high prevalence of GERD in the general population. However, it is possible that the underlying esophageal changes induced by EE may induce LES dysfunction. It would have been useful to clarify this with pH studies before and after FP treatment.

All but one of our evaluated patients had abnormal endoscopic findings. Linear furrows, often proximal, and mucosal rings, which may be multiple and subtle, are the hallmark features. Proximal esophageal strictures, a narrow lumen, and the white plaques of the eosinophilic microabscess also may be present. Methylene blue dye spraying can be useful to highlight the furrows and thus could be evaluated in the routine assessment of patients with dysphagia.<sup>15</sup> The delay in the diagnosis of patients in our series highlights that the endoscopic features often are overlooked. There appears to have been a general lack of desire among adult gastroenterologists to take biopsy specimens from the “normal” esophagus. EE is a diagnosis dependent on histology and, therefore, esophageal biopsy. Distal esophageal biopsy alone may miss the diagnosis of EE as the eosinophil infiltration is not uniform. We would advocate a more aggressive approach. On the basis of our findings and the evolving literature, it has become our practice to perform proximal and distal esophageal biopsies in patients with dysphagia, noncardiac chest pain, food-bolus obstruction, and resistant GERD symptoms.

In our experience, the radiologic identification of the disorder lacked sensitivity.

There has been considerable debate about the relationship of EE to eosinophilic gastroenteritis and GERD.<sup>7,8,42</sup> Our data demonstrate that EE is distinct from eosinophilic gastroenteritis. In eosinophilic gastroenteritis, peripheral eosinophilia is associated with extensive full-thickness eosinophilic infiltration throughout the GI tract. None of our 26 patients had histologic evidence of an eosinophilic infiltrate in their pre- or posttreatment gastric or duodenal biopsy specimens. Eosinophil infiltration of the esophageal epithelium has been described in GERD, but the number of eosinophils seen usually is  $<4$  eosinophils/HPF and is limited to the distal esophagus.<sup>1,9,22,43</sup> In contrast, in EE, there are at least 15 eosinophils/HPF and usually many more.<sup>3,9,14,15,17,22,23</sup> The infiltrate may be associated with basal-cell hyperplasia, intercellular edema, and eosinophilic microabscesses. Importantly, the histologic features are seen in both proximal and distal specimens, and may be present even when the esophagus appears endoscopically normal.

The interpretation of finding patients with 3 to 15 eosinophils/HPF is unresolved. The pediatric literature suggests that these patients share the same pathophysiology and treatment response.<sup>44</sup> The symptoms of EE fluctuate as also noted in patients with asthma. It is likely that the eosinophil count also will fluctuate. Seasonal fluctuation, symptomatic and histologic, in EE has been clearly documented in a case report.<sup>33</sup> If there is a strong clinical suspicion of EE, repeated esophageal biopsies at times of significant symptoms may be warranted.

FP is an appealing treatment for EE. Simple administration allows maximal topical effect and minimal side effects, thus enhancing compliance. Our prospective study confirms the utility of FP in adults. FP previously has been used successfully in pediatric patients and recently in adults.<sup>3,23,24</sup> A recent study found that not all adult patients respond to EE.<sup>24</sup> All patients in our study had some degree of histologic and symptomatic improvement on FP, even

those with the allergic variant. Importantly, 4 patients had complete resolution of esophageal eosinophilia. However, 74% of patients had experienced some symptom recurrence after completing treatment with FP. A possible explanation for our universal response to FP is that our cohort had a significant component of esophageal inflammation and less established fibrosis. Only 3 patients developed mild esophageal candidiasis (all asymptomatic). The tolerability of FP was emphasized by the desire of the majority of patients to continue with FP treatment (alone if appropriate or in combination with proton pump inhibitor if coexistent with GERD) at follow-up. A recent pediatric study,<sup>45</sup> published in abstract form, that compared FP to oral prednisone showed a slightly greater benefit for prednisone. We would continue to favor swallowed FP as the initial corticosteroid of choice given its more favorable side-effect profile.

In summary, EE is an underrecognized cause of dysphagia, food-bolus obstruction, and chest pain in adults that may coexist with GERD. EE has characteristic endoscopic findings and defining histologic features. With greater awareness, the at-times subtle endoscopic changes of EE will be appreciated. Swallowed FP is a successful treatment, with minimal morbidity, that perhaps will minimize the risk of stricture formation and the need for subsequent dilation. Presumably, as with asthma, long-term preventative medication may be required to maintain remission.

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