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Esophageal Eosinophilia with Dysphagia
A Distinct Clinicopathologic Syndrome

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Small numbers of intraepithelial esophageal eosinophils (IEE) may be seen in 50% of patients with gastroesophageal reflux disease and occasionally in normal volunteers. High concentrations of IEE are rarely seen in either setting. During a two-year period we identified 12 adult patients with very dense eosinophil infiltrates in esophageal biopsies (defined as >20 IEE/high-power field). Dysphagia was the presenting complaint in each, but no evidence of anatomical obstruction could be found. Endoscopic esophagitis was absent, but biopsy showed marked squamous hyperplasia and many IEE. Eleven patients had normal esophageal acid exposure on 24-hr pH monitoring. Esophageal manometry showed a nonspecific motility disturbance in 10 patients. For comparison, 90 patients with excess esophageal acid exposure on 24-hr pH monitoring were studied. Thirteen (14%) had motility disturbance, and 21 (23%) had dysphagia. Esophageal biopsies were devoid of IEE in 47 patients; none of the 43 with IEE had infiltrates as dense as those seen in the 12 study patients. The presence of high concentrations of IEE in esophageal biopsies from patients with dysphagia, normal endoscopy, and normal 24-hr esophageal pH monitoring represents a distinctive clinicopathologic syndrome not previously described.

KEY WORDS: dysphagia; eosinophils; esophagitis; motility disorder; allergic gastroenteritis.

High concentrations of intraepithelial eosinophils (IEE) in esophageal biopsies, ie, densities of >20/high-power field (HPF), have rarely been reported. When seen, the finding has been associated with idiopathic (allergic) eosinophilic gastroenteritis (1–3) and gastroesophageal reflux disease (4, 5). This histological abnormality is most apt to occur in children; only eight adult patients have been described (1, 4, 6). A low concentration of IEE is a common finding and is used as a marker of gastroesophageal reflux disease (7, 8). Volunteers with no evidence of esophageal disease may occasionally have one or two eosinophils in a biopsy (9).

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Over the past two years we have been perplexed by a number of patients with marked dysphagia of no apparent cause. These patients consistently showed a dense infiltrate of intraepithelial eosinophils in biopsies from endoscopically unremarkable esophageal mucosa. A retrospective study was undertaken to assess the clinical and pathologic features of these patients, and to compare them to patients with lesser concentrations of IEE.

MATERIALS AND METHODS

Patient Populations. Three patients with a high concentration of IEE were identified from the pathology files of 493 esophageal biopsies performed in 1986–1988. Because of a focused interest in upper gastrointestinal disease at our institution, all of these patients had undergone esophageal motility studies and 24-hr pH monitoring. As the growth of Creighton University's Swallowing Center led to increased patient volume, nine additional individuals were identified prospectively between 1988 and 1990

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TABLE 1. AGE AND SEX OF PATIENTS WITH ESOPHAGEAL EOSINOPHILIA COMPARED TO 90 CONSECUTIVE PATIENTS WITH EXCESS ESOPHAGEAL ACID EXPOSURE

	N	*Median IEE/HPF*	*Mean age*	*Male–female*	*Heartburn*	*Dysphagia*
Esophageal eosinophilia	12	56	32*	10:2	3	12
Acid reflux						
No IEE	47		53	30:17	38	12
Low-grade IEE	43	3.3	55*	23:20	40	9

* = difference statistically significant, $p < .05$

and similarly studied. These 12 patients comprised the study population.

To identify the frequency of IEE in patients with proven gastroesophageal reflux disease, a consecutive series of 90 patients with positive 24-hr pH monitoring was reviewed. This comprised the reference population.

The patients' clinical features were obtained from a questionnaire that is routinely completed by the esophageal nurse at the time of the esophageal function study. Consequently, each patient had prospective grading of foregut symptoms.

Pathology. Endoscopy was performed and biopsies taken from the lower esophagus, more than 2 cm above the lower esophageal sphincter. The mean number of biopsies per patient was 4.2 (range 1–18). The biopsies were fixed in formalin and embedded in paraffin without an orienting substrate. Three slides were prepared from each biopsy with each slide displaying three to six levels of tissue stained with hematoxylin and eosin. The slides were scanned to identify the section with the most dense eosinophilic infiltrate. This area was used to count eosinophils per high-power field (Olympus BHTU microscope, DPlan 40 lens, field of view 0.5 mm diameter). Biopsies with 20 or less IEE per HPF were classified as low grade and those with greater than 20 as high grade.

Hyperplastic changes were evaluated by searching all biopsies for a well-oriented area showing subepithelial papillae visible for their entire length. An eyepiece micrometer was used to measure epithelial thickness, papillary height, and basal zone thickness. Squamous hyperplasia was defined as papillary height greater than 66% of epithelial thickness or a basal zone occupying more than 20% of the epithelium. In selected patients, a Giemsa stain was used to aid in the identification of mast cells.

Clinical Studies. Barium contrast roentgenogram, esophagoscopy, esophageal manometry, and 24-hr ambulatory pH monitoring was performed in all patients. Manometry was done with a five-channel water-perfused catheter (Arndorfer) attached to a Gould eight-channel chart recorder using the stationary pull-back technique of Winans and Harris (10). Data were recorded on the lower esophageal sphincter position, resting pressure, length, and abdominal length and relaxation. The sphincter was defined as mechanically defective if the mean resting pressure was <6 mm Hg, length <2 cm, or abdominal length <1 cm (11). A five-channel study of the esophageal body peristalsis was performed by asking the patient to take 10 swallows of a 5-ml water bolus at 40-sec intervals followed by 10 swallows without a water bolus. Segmental or overall peristaltic weakness was identified if the average wave amplitude was below the 2.5 percentile of the amplitude measured for 50 normal volunteers (12). Specific disorders of motility were diagnosed based on 10 wet swallows according to the following criteria: diffuse esophageal spasm (>20% of simultaneous contractions in two or more esophageal segments), nutcracker esophagus (a mean amplitude >180 mm Hg), and achalasia (complete aperistalsis and incomplete sphincter relaxation) (13).

Twenty-four-hour ambulatory pH monitoring was performed by placing a glass electrode (Ingold, Stockholm, Switzerland) 5 cm above the upper border of the manometrically defined lower esophageal sphincter. pH was sampled every 4 sec and recorded on a portable digitrapper (Synectics, Sweden) (14). Pathologic gastroesophageal reflux was defined by an abnormal composite score as previously published (14). Scores for esophageal acid exposure (pH < 4) above the 95th percentile (>14.8) were considered abnormal.

RESULTS

Characteristics of Patients with High-Grade IEE. Eleven of the 12 patients with high-grade IEE had normal esophageal acid exposure on 24-hr pH monitoring. They differed markedly from the reference population in their young age and their infrequent reflux symptoms (Table 1). All had a normal endoscopy. No patient had Barrett's esophagus. The striking feature of these patients was dysphagia out of proportion to the endoscopic and roentgenographic findings. The dysphagia was characteristically episodic, lasting from two days to several weeks. The duration of the disorder ranged from one to 12 years with a median of three years. Four patients required emergency treatment for bolus impaction and in two this was recurrent. Three of the 12 patients had odynophagia in addition to dysphagia.

Seven patients had some evidence of hypersensitivity: three had a history of asthma, two had chronic sinusitis, and two had allergies to medications. Peripheral eosinophil counts were obtained for seven patients; the range was 0.04–0.792 $\times$ 10^9/liter (normal 0–0.3) and the mean 0.215 $\times$ 10^9/liter. Only one patient had a peripheral blood eosinophil count out-

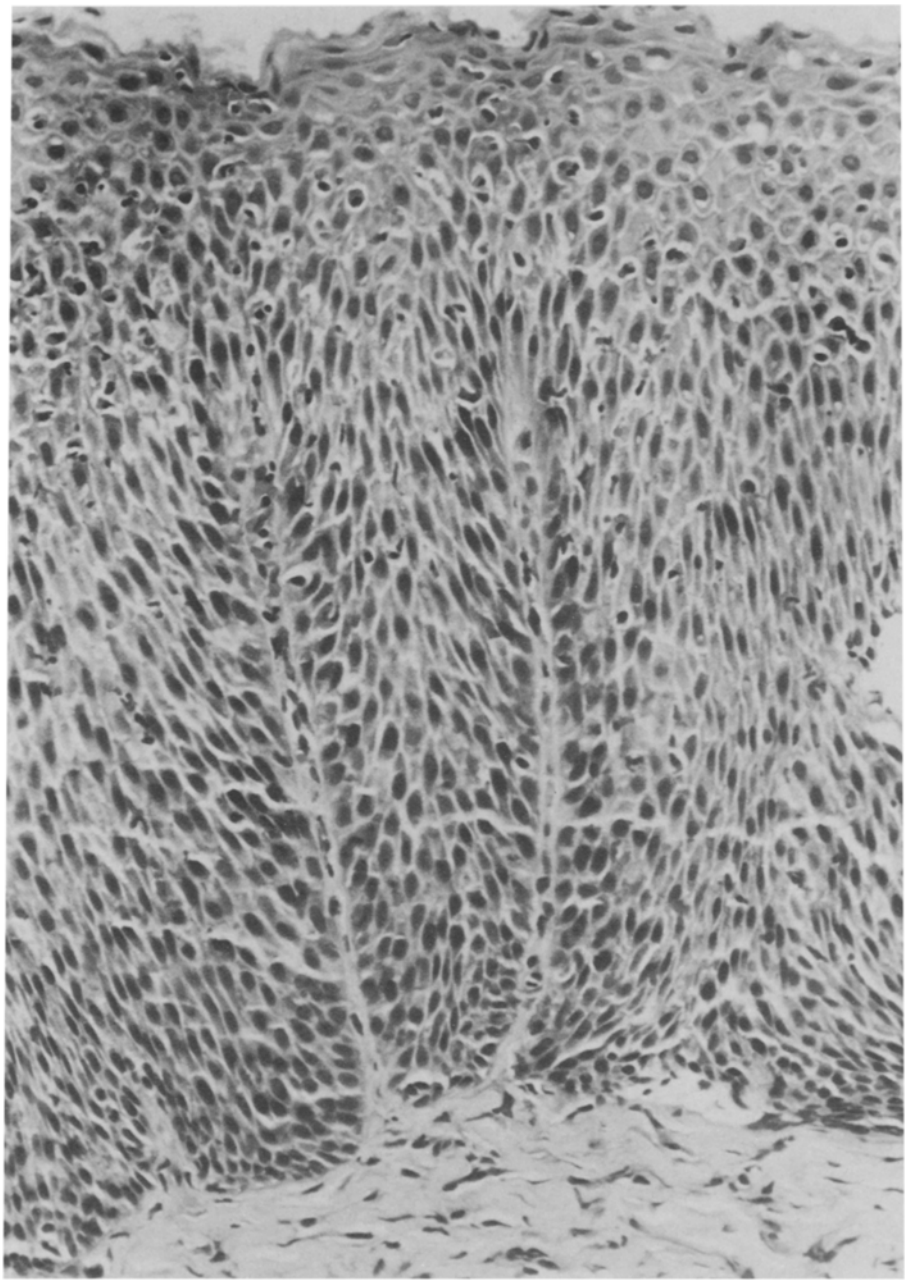

Fig 1. There are more than 50 intraepithelial eosinophils in this high-power field. Most are in the luminal half of the epithelium. The subepithelial papillae occupy 70% of the epithelial thickness and basal zone occupies 50% of the epithelial thickness (×198).

side the normal range. No patient complained of diarrhea, abdominal pain, or vomiting.

Histopathology of High-Grade IEE. Esophageal biopsies with high grade IEE were remarkable for their dense tissue eosinophilia and marked squamous hyperplasia. The mean number of IEE per HPF was 56 (range 21–110). The eosinophils were distributed diffusely in the epithelium, except for a slight tendency to be concentrated near the epithelial surface (Figure 1). In each patient, 10–20% of eosinophils were disrupted, so that eosinophil granules were scattered throughout the tissue. There was minimal eosinophilic infiltration of the basal epithelium and lamina propria. The submucosa was

neither edematous nor inflamed. Marked hyperplastic changes were seen in all well-oriented biopsies (Figure 1). The mean papillary height for the eight evaluable biopsies was 75% of the epithelial thickness, and the mean basal zone thickness was 40%. Only one patient had an occasional neutrophil in the inflammatory infiltrate. Although occasional mast cells were seen, they were scattered and did not form bands in the lamina propria. No fungal, viral, or parasitic organisms were seen; however, special stains were not used to aid in their identification.

Six of the 12 patients had concurrent gastric biopsies (six antrum, three antrum and body). The number of antral biopsies per patient ranged from two to five. Only one individual had a significant antral infiltrate of eosinophils. The same patient also had a small bowel biopsy that contained increased numbers of eosinophils. One other patient had a small bowel biopsy that was normal. No patient had a biopsy of colon.

Five of the 12 patients had repeat biopsy during symptomatic episodes 6–12 months after the initial biopsy. The histologic finding of high grade IEE persisted in all five. No patient was biopsied while asymptomatic.

Motility in Patients with High-Grade IEE. Two patients with high-grade esophageal eosinophilia had diffuse spasm and two had nutcracker esophagus. Three others had a mean amplitude of contraction below the 2.5 percentile of normal, and four had contractions of short duration. Figure 2A and B shows the mean amplitude of contraction at each of five esophageal levels during dry and wet swallows, and Figure 3A and B, the mean duration of contraction in dry and wet swallows. Manometric measurements of lower esophageal sphincter pressure, overall length, abdominal length, and degree of relaxation with swallowing were normal in all 12 patients.

Characteristics of Reference Population: Patients with Proven Acid Reflux. The 90 patients with increased esophageal acid exposure presented with heartburn and regurgitation in 78 (87%) and dysphagia in 21 (23%). The endoscopic appearance of the esophagus was assessed as normal in 29 patients, grade 1–3 esophagitis in 28, Barrett's esophagus in 21, and stricture in 12.

Forty-three of the 90 patients had IEE in esophageal biopsies. In contrast to the study population, there was no dense infiltrate seen and the mean number of IEE per HPF in the area of densest inflammation was 3.3 ± 1 (range 1–19). The mean age of the patients who had eosinophilia and positive 24-hr pH monitoring was 53 years. These patients were similar in age and clinical features to the patients in the reference population who did not have IEE (Table 1). Biopsies containing IEE had additional signs of esophageal injury in the form of neutrophil infiltration (46%), squamous hyperplasia (88%), and Barrett's esophagus (23%). Only rare mast cells were found. Motility studies in the 90 acid refluxers showed that 43 (48%) had a defective lower esophageal sphincter, 10 (11%) had weak amplitude of contractions in the lower esophagus, two had nutcracker esophagus, and one had achalasia.

From this reference group of 90 patients with proven reflux, 12 were randomly selected whose age and sex matched the study population. In this subgroup, the median number of eosinophils in the area of densest inflammation was one per HPF (range 0–5), indicating that age and sex were not responsible for the difference in eosinophil concentration between the 12 patients with high-grade IEE and the reference population.

Therapy of Patients with High-Grade IEE. All 12 patients were treated by dilatation with a mercury bougie. Dysphagia usually recurred in three to six months and responded to a second dilatation. One patient, who received five dilatations at three-month intervals, was given a course of steroids with complete resolution of dysphagia. Intermittent dysphagia returned with withdrawal of steroids, but no dilatation has been required for relief in the eight months following steroid treatment.

DISCUSSION

These 12 patients with high-grade IEE represent a newly recognized clinicopathologic entity consisting of dysphagia in the presence of a normal roentgenographic barium swallow, normal esophagoscopy, and normal esophageal acid exposure on 24-hr pH monitoring. It occurs in young adults, predominantly males, complaining of constant or episodic dysphagia. Other symptoms are conspicuous by their absence.

The 12 patients with high-grade IEE have some similarities to those with the previously reported entity of idiopathic eosinophilic esophagitis. Five case reports have described patients complaining of dysphagia without clinical evidence of gastroesophageal reflux (1, 2, 6, 20, 21). Two of the five had eosinophils in other organs of the alimentary tract, and all five had an elevated peripheral eosinophil count, suggesting a relationship with idiopathic (al-

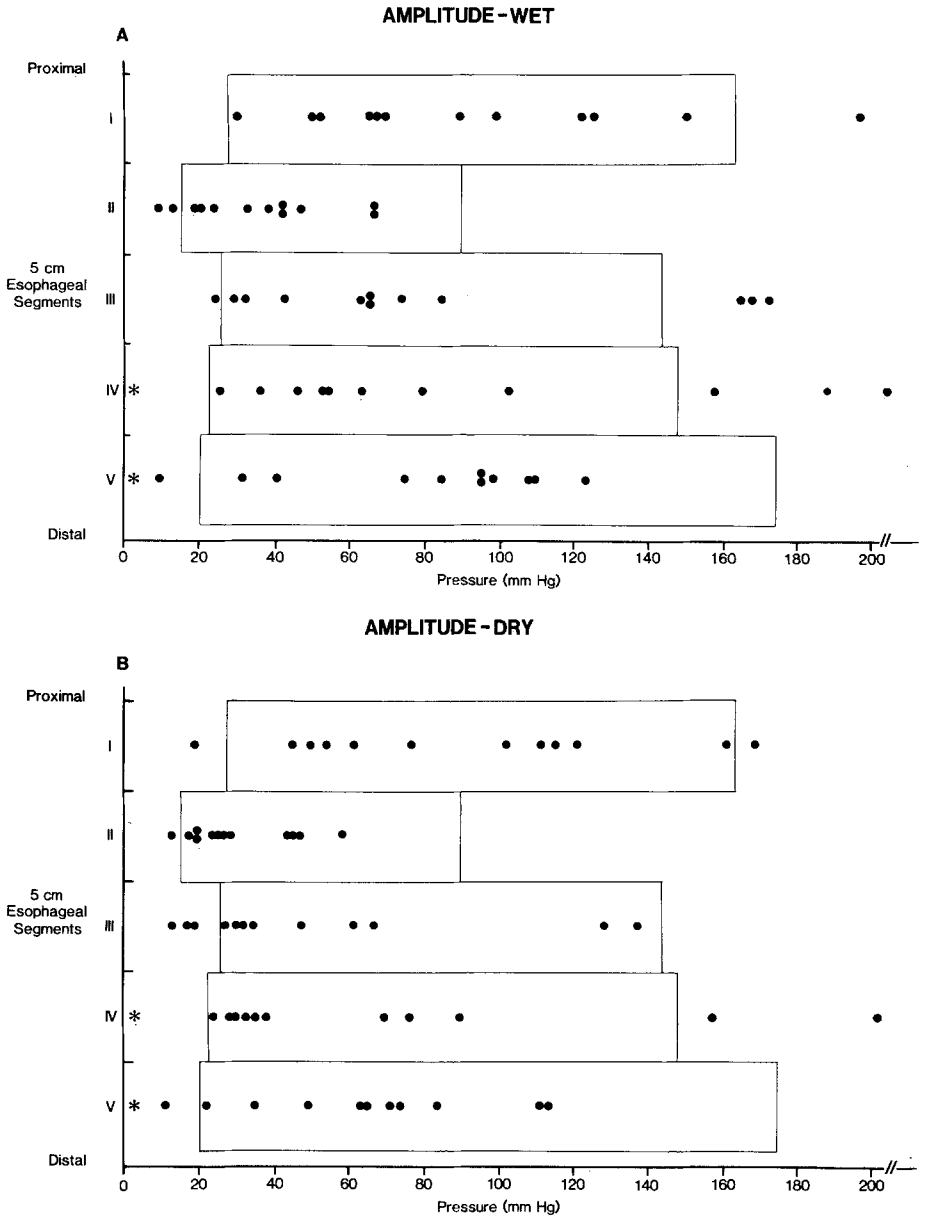

Fig 2. Distribution of amplitude of esophageal contractions in 11 patients with high grade esophageal eosinophilia. The boxes represent the normal range (2.5th to 97.5th percentile) of normal amplitude for each 5-cm segment of the esophageal body. (A) wet swallows; (B) dry swallows. *; No value measured because of a short esophagus.

lergic) eosinophilic gastroenteritis. Conversely, Lee presented 11 patients with high-grade IEE, four adults and seven children, and concluded that most instances of high-grade IEE are associated with gastroesophageal reflux disease and only rarely indicate esophageal involvement by allergic gastroenteritis (4). The diagnosis of reflux in his patients was based on barium esophagram and endoscopic findings and was not documented with 24-hr esophageal pH monitoring. We were able to study the pH environment in patients with IEE and show that low-grade eosinophilia is associated with an increase in the esophageal acid exposure, but high grade eosinophilia is not, at least in this series of adult patients.

At the time of endoscopic exam, generalized gastroenteritis was not suspected and only six of the 12 patients had biopsies taken from elsewhere in the

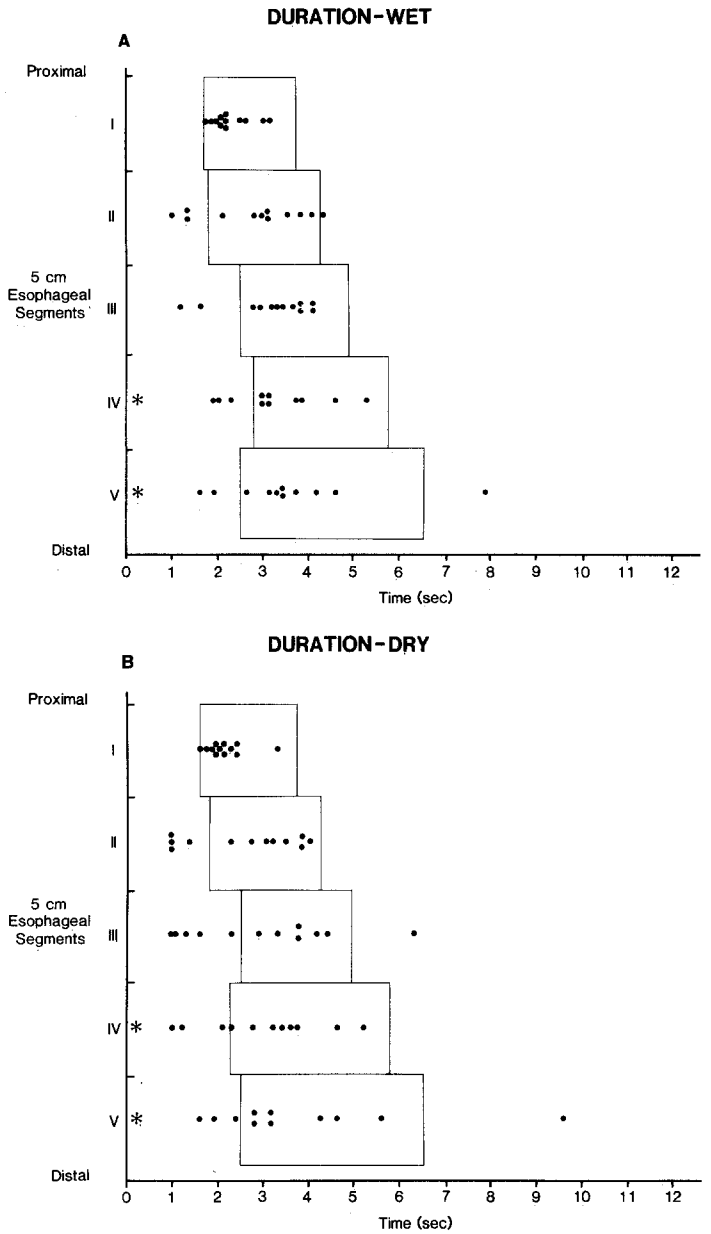

Fig 3. Distribution of duration of esophageal contractions in 11 patients with high grade esophageal eosinophilia. The boxes represent the normal range (2.5th to 97.5th percentile) of normal duration for each 5-cm segment of the esophageal body. (A) wet swallows; (B) dry swallows. *: No value measured because of a short esophagus.

gastrointestinal tract. In one patient, incidental biopsy of the small bowel and antrum showed generalized eosinophilic gastroenteritis; in five others eosinophils were not seen in antral biopsies. Thus, one of our patients may actually have eosinophilic gastroenteritis; one might speculate that the esophageal eosinophilic infiltration seen in our other patients represents a localized variant of generalized eosinophilic gastroenteritis. Indeed, Goldman and Proujansky have shown that esophageal involvement in eosinophilic gastroenteritis may not be rare (3). They found eosinophilic esophagitis in nine of 15 patients who presented with abdominal symptoms and altered bowel habits and were subsequently diagnosed with eosinophilic gastroenteritis. In five of these patients, infiltration of the esopha-

geal mucosa with eosinophils was "the dominant feature at some time in the course of the disease," although dysphagia was apparently not a symptom in any patient.

An allergic history can be obtained in about 50% of patients with eosinophilic gastroenteritis. Three of our 12 patients had a history of bronchial asthma and four others had some history of allergy. In one, the onset of asthma coincided with the onset of dysphagia. Peripheral blood eosinophilia is seen in more than 75% of patients with allergic gastroenteritis; in contrast, only one of the patients tested in our series had an elevated eosinophil count.

Alternative etiologies for IEE include connective tissue disease (eg, scleroderma), drug injury, and carcinoma. There was no systemic evidence of scleroderma in our patients, and they lacked the band-like distribution of eosinophils and prominent mast cell infiltrate described by DeSchryver-Kecskemeti and Clouse in small bowel and stomach biopsies (15).

Our patients used a variety of drugs, including aspirin (10 patients), ascorbic acid (2), and nonsteroidal antiinflammatory drugs (2). We were unable to find any correlation between drug ingestion and the development of IEE.

A specific motility disorder was present in four patients with high-grade IEE. Others had contraction waves with altered amplitude or duration. Abnormalities were seen in the body of the esophagus as opposed to the sphincter. Alterations in peristaltic amplitude ranged from hypercontractility to hypocontractility. An unusual finding was the high prevalence of contractions of short duration rather than long, as is usually seen in patients with a motility disorder. This finding may be a manometric characteristic of the entity.

If esophageal eosinophilia is related to dysphagia, it may be due to the release of neurotransmitters or neurotoxins. Eosinophils contain vasoactive intestinal polypeptide (VIP) and substance P (16). Both of these neuropeptides act as neurotransmitters in the gut, and their release from degranulating eosinophils could result in disruption of motility. Eosinophils also contain eosinophil cationic protein (ECP), a neurotoxin responsible for the development of ataxia and paralysis when injected intracerebrally into experimental animals (the Gordon phenomenon) (17). In a recent report describing achalasia secondary to gastric cancer, Fredens et al demonstrated heavy infiltration of the esophagus by eosinophils, accompanied by a marked decrease in the number of VIP- and substance P-positive nerve fibers (18). Similarly, DeSchryver-Kecskemeti and Clouse found eosinophils in and around nerve fibers in small bowel biopsies from patients with dysmotility in the setting of connective tissue disease (19).

Medical management has been largely unsatisfactory. Some patients appear to gain some benefit from dilatation even though, with no stricture present, there is no rational basis for this therapy. Dysphagia usually recurs in three to six months and is accompanied by recurrence or persistence of the histologic changes. Although the patients complained of dysphagia, none had a significant weight loss and all were in good nutritional status. Consequently, we are reluctant to initiate any treatment associated with potential morbidity. One patient, who was persistently symptomatic and had responded poorly to dilatation, was treated with steroids with good results. A blinded prospective study to evaluate the efficacy of steroid therapy may be indicated.

The combination of dysphagia, normal endoscopy, no acid reflux, and many IEE appears to constitute a unique disease entity. Because the etiology is unclear, affected patients should be followed for the emergence of gastroesophageal reflux disease, a specific motility disorder, or allergic gastroenteritis. Steroid therapy may be indicated for incapacitating dysphagia.

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