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Eosinophilic Esophagitis in Children and Adults

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ABSTRACT
Children with eosinophilic esophagitis, an isolated, severe esophageal eosinophilia, present with symptoms similar to gastroesophageal reflux but do not experience response to aggressive antireflux therapy. Increasingly, eosinophilic esophagitis is considered to be a separate entity from reflux disease. Current theory suggests that the former may be caused by cell-mediated food hypersensitivity or may be a subset of eosinophilic gastroenteritis. Reports support the efficacy of dietary restriction or corticosteroid therapy. Additional research is needed to determine etiology, allow earlier clinical recognition, and improve treatment. ***JPGN 37(Suppl):S23–S28, 2003.*** **Key Words:** Eosinophilic esophagitis—Eosinophilic gastroenteritis—Food allergy—Food hypersensitivity—Pediatric gastroesophageal reflux. © 2003 Lippincott Williams & Wilkins, Inc.

It's not what you don't know that will hurt you, it's what you know that just ain't so. –Satchel Paige

Before 1995, esophageal eosinophilia was routinely associated with reflux esophagitis. However, recent studies suggest that a large number of isolated eosinophils in the esophagus may represent a separate diagnosis. The current article reviews the possible etiology, clinical presentation, diagnosis, and treatment of this disorder, which has been called not only allergic esophagitis (which may be the most likely cause), but also eosinophilic esophagitis, primary eosinophilic esophagitis, and idiopathic eosinophilic esophagitis.

Eosinophilic granules are thought to release proinflammatory mediators, such as cationic proteins, leukotrienes, and prostaglandins. They also exert cytotoxic effects by producing oxygen free radicals and peroxidase. In healthy subjects, a small number of eosinophils are commonly visualized in almost all parts of the gastrointestinal tract except the esophagus. Their pervasiveness often makes it difficult for the pathologist to diagnose a pathologic process secondary to the eosinophilia. Eosinophils in the gastrointestinal tract have long been associated with intestinal inflammatory disorders, such as inflammatory bowel disease and parasitic disorders.

Eosinophilic esophagitis is a disorder in children and adults characterized by an isolated, severe eosinophilic infiltration of the esophagus. Pediatric patients with eosinophilic esophagitis typically manifest vomiting, regurgitation, epigastric and chest pain, and water brash. Older children and adults may also experience heartburn and dysphagia. Although the symptoms are similar to those seen in gastroesophageal reflux disease (GERD), patients experience mild or no response to acid suppression and other forms of antireflux therapy.

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CLINICAL TRIALS OF EOSINOPHILIC ESOPHAGITIS

In 1982, Winter et al. (1) correlated the presence of esophageal eosinophils with markers of reflux esophagitis. They performed pH studies, manometry, and endoscopy with biopsy in 46 children (aged 3 months to 19 years) with reflux esophagitis and compared the results with those in 9 control subjects. A finding of intraepithelial eosinophils in the esophagus correlated with prolonged esophageal acid clearance and histologic features of esophagitis (basal cell hyperplasia and papillary lengthening).

Of the 46 patients with reflux esophagitis, 18 had intraepithelial eosinophils. Twelve of those 18 had, on average, less than 1 eosinophil per high-power microscopic field (HPF). Eosinophils were found in both the distal and the proximal or midesophagus, with a slightly higher number in the distal esophagus. Subsequent studies in adults confirmed the presence of intraepithelial eosinophils in adults with reflux esophagitis (2,3). Tummala et al. (3) pointed out that some control subjects also had eosinophils–maybe as few as one eosinophil in the entire biopsy specimen–located, in particular, within 5 cm of the lower esophageal sphincter.

Because of these and other articles, children presenting with reflux-like symptoms who had evidence of eosinophils in the esophagus often were characterized as having reflux esophagitis and treated aggressively for GERD. Approximately 90% to 95% of these patients experienced improvement with acid blockers, prokinetic agents, or occasionally antireflux surgery, and presumably they had GERD. However, there continued to be a subset of children with increased esophageal eosinophils who did not experience response to antireflux therapy.

The article that provoked a tremendous interest in eosinophilic esophagitis, from a pediatric perspective, was published in 1995 (4) and described the effects of an amino acid-based formula in children with this condition. Kelly et al. (4) identified 10 patients with GERD symptoms who also had a severe esophageal eosinophilia (median, 41/HPF) and experienced no response to antireflux therapy. On the theory that a food allergy or intestinal allergy might be the cause, they placed the patients on a strict elemental diet (an amino acid-based formula) for a median of 17 weeks. The patients were allowed clear liquids and only solid foods made from apples or corn. After an average of 3 weeks on the diet, 8 of the 10 children experienced symptom resolution, with improvement in the other 2. On second biopsy, all 10 demonstrated resolution of eosinophilia (<1 eosinophil/HPF). Open food challenges led to recurrence of symptoms. This study indicated that not all cases of esophageal eosinophilia represent reflux disease.

On review of the adult literature, isolated eosinophilic esophagitis probably was first recognized in 1985 by Lee (5). A pathologist, Lee described a series of 11 adults with eosinophilic esophagitis (>10 eosinophils/HPF) who presented with dysphagia, other reflux symptoms, and in 3 patients, esophageal stricture. Before 1985, there were several reports of significant eosinophilia in the esophagus, but always in association with eosinophilia elsewhere in the gastrointestinal tract (e.g., antrum, duodenum, or colon) (6,7). Between 1978 and 1990, there were other reports of adults with esophageal eosinophilia who had GERD symptoms and esophageal strictures that appeared to respond to esophageal dilatation. However, esophageal biopsies typically were not performed in these studies, and the underlying disorder was not identified. Apparently, gastroenterologists treating adult patients often make a presumptive diagnosis of reflux based on visual findings and treat patients with antireflux therapy.

In 1993, Attwood et al. (8) were among the first to compare patients with isolated eosinophilic esophagitis with those with reflux esophagitis. They found a significant difference between the two groups with regard to the presence and number of esophageal eosinophils. The 12 patients with a severe esophageal eosinophilia had a mean of 56 eosinophils/HPF, compared with a mean of 3.3/HPF in 43 of 90 patients with reflux. In addition, the 12 with esophageal eosinophilia also had dysphagia, allergic symptoms, normal pH studies, and a visually normal mucosa in the esophagus. In 1995, Vitellas, a radiologist, and colleagues (9), reported a series of 13 men with isolated eosinophilic esophagitis. Most of these patients had dysphagia, allergic symptoms, peripheral eosinophilia, and proximal esophageal strictures. Almost all experienced response to systemic corticosteroids and did not require esophageal dilatation.

ETIOLOGY OF EOSINOPHILIC ESOPHAGITIS

The etiology of eosinophilic esophagitis is not known. Increasing emphasis has been placed on the role of food allergy (10,11), but eosinophilic esophagitis may also be a subset of eosinophilic gastroenteritis, an autoimmune disorder.

Food Allergy

Food allergies are vague, ill-defined, and difficult to diagnose. It often is difficult to identify food allergens. Most allergists consider food allergy to be an "adverse reaction," which denotes any clinically abnormal response attributable to ingestion of a food or food additive.

There are two main types of reactions: food "intolerance" and food hypersensitivity. Food intolerance can refer to toxicity or poisoning, e.g., ptomaine poisoning. It can also refer to pharmacologic reactions, such as caffeine-causing diarrhea, and metabolic responses, such as diarrhea in people with lactose intolerance. Food intolerance can also consist of idiosyncratic reactions.

More often, eosinophilic esophagitis is a form of food hypersensitivity, i.e., an immunologically mediated reaction to a food unrelated to any physiologic effect. In eosinophilic esophagitis, a type IV (cell-mediated) reaction, rather than a type I reaction (mediated by immunoglobulin E, or IgE), is most likely involved. It has been the author's experience that patients with eosinophilic esophagitis have negative results on skin or radioallergosorbent (RAST) testing for IgE antibodies. In patients with type IV food hypersensitivity, symptoms often occur hours to days after ingestion of the causative food. Mast cell activation probably is related.

In one series (12) of 53 children with allergic proctitis or gastroenteritis, when a corresponding upper endoscopy was performed, eosinophilia was found in 100% of antral biopsy specimens, 79% of small-intestinal biopsy specimens, and 60% of esophageal biopsy specimens, which suggests that some allergic disorder may involve the entire gastrointestinal tract.

Eosinophilic Gastroenteritis

The presence of an isolated, severe eosinophilic esophagitis might also be a subset of eosinophilic gas-

troenteritis. This disorder, originally described by Kaijser (13) in 1937, remains poorly understood. It is characterized by intense tissue eosinophilia and often affects different layers of the bowel wall (14,15). Klein (16) described three categories of eosinophilic gastroenteritis: the mucosal, muscular, and subserosal forms. The stomach and small bowel are almost always affected. In children, eosinophils are found principally in the gastric antrum. Patients with this disorder often present with colicky abdominal pain, diarrhea, and weight loss. They also may have iron-deficiency anemia, protein-losing enteropathy, and growth failure. Approximately 50% have a personal or family history of allergy (asthma, nasal polyps, or rhinitis); approximately 50% also manifest food allergies. In 80% of patients, there is evidence of elevated blood eosinophils.

CLINICAL PRESENTATION OF EOSINOPHILIC ESOPHAGITIS

Eosinophilic esophagitis occurs in children and adults but rarely in infants. Food allergy in infancy often presents with diarrhea, abdominal pain, and a bloody colitis; however, eosinophilic esophagitis more often occurs in toddlers, older children, and adults.

Boys appear to be affected more often than girls. Typical symptoms include vomiting, regurgitation, epigastric abdominal pain, and poor eating. Peripheral eosinophilia and increased immunoglobulin E levels have been reported in 20% to 60% of patients. There is often a personal or family history of allergy, such as asthma, rhinitis, and eczema. In one study (17), 80% of patients with eosinophilic esophagitis had a history of another allergic disorder, compared with only 29% of patients with GERD. Approximately 62% of patients may have bronchospasm (18).

DIAGNOSIS

Currently, a definitive diagnosis of eosinophilic esophagitis is made by identification of an isolated eosinophilic infiltration in the esophagus of patients who have reflux-like symptoms and who have normal (or borderline normal) pH studies and are refractory to acid inhibition. Some patients may experience a slight symptomatic response to acid blockade, but findings on biopsy do not change. Esophageal pH monitoring often reveals frequent, brief reflux episodes but normal esophageal acid clearance and reflux index. The diagnosis is also dependent on patients demonstrating a clinical and histologic improvement to a food elimination trial or corticosteroid therapy. It has been suggested that patients with eosinophilic esophagitis have an endoscopic appearance characterized by granularity, subtle furrowing, and an esophageal ring formation (18). Currently, biopsy remains the most important diagnostic test.

Whether the number or location of eosinophils can distinguish eosinophilic esophagitis from other diagnoses remains unknown. A review of studies from the past 5 years suggests that most patients with eosinophilic esophagitis have 20 or more eosinophils/HPF. In general, there appears to be no difference in the number of eosinophils identified in the midesophagus when compared to the distal esophagus, and in some studies the distal esophagus was found to have a greater number of eosinophils per HPF. In one cohort study (17), children with eosinophilic esophagitis had $\geq$30 esophageal eosinophils/HPF, whereas children with GERD had <5/HPF.

Most adults with eosinophilic esophagitis reportedly have a significant number of eosinophils in the midesophagus. However, many of these patients did not have biopsy of their distal esophagus. Recently, our group showed that the absence of eosinophils in the midesophagus does not exclude a diagnosis of eosinophilic esophagitis (unpublished data). Indeed, the diagnosis is related more to the number of eosinophils found in the esophageal mucosa regardless of location. In a comparison of 64 patients with isolated eosinophilic esophagitis and 45 with GERD, the latter all exhibited eosinophilia in the distal esophagus, whereas only approximately 10% had midesophageal involvement. In addition, in children with GERD, the degree of eosinophilia was mild, with a mean of 2.3 eosinophils/HPF in the distal esophagus and 1.8 eosinophils/HPF in the proximal esophagus. In contrast, children with eosinophilic esophagitis all had eosinophilia in the distal esophagus (mean, 38.6/HPF), whereas 20% had midesophageal involvement (mean, 25/HPF).

It would be clinically useful if a cutoff value for the number of eosinophils could establish the diagnosis of eosinophilic esophagitis. Our group evaluated 102 patients with reflux symptoms who did not experience response to combination therapy with a histamine-2 (H_2) receptor antagonist plus prokinetic drug (19). Subsequently, patients with persistent symptoms after 3 months of the combination regimen were switched to a proton pump inhibitor (PPI). Patients who then experienced improvement and eventually discontinued acid blockade had, on average, 1.1 eosinophils/ HPF before therapy and received diagnoses of GERD. Another group of patients also appeared to have a response to PPI therapy. However, in contrast to the patients with GERD, when the PPI therapy was discontinued, their symptoms recurred. This group demonstrated an average of 6.4 eosinophils/HPF. Finally, patients ultimately receiving diagnoses of eosinophilic esophagitis did not experience response to PPI therapy and had an average of 24.5 eosinophils/HPF.

TREATMENT APPROACHES

As has been noted, patients with symptomatic eosinophilic esophagitis may show some clinical improve-

ment with acid-suppressive therapy, but there is no histologic improvement. In a case report (20) of two patients with severe esophagitis (eosinophilic infiltration) unresponsive to aggressive medical therapy, Nissen fundoplication resulted in neither resolution of reflux symptoms nor improvement in esophageal eosinophilia.

In recent years, a number of management approaches have been evaluated. Kelly et al. (4) demonstrated prompt clinical and histologic improvement with an amino acid-based formula and strict elemental diet. In that study, 8 of 10 patients became symptom free, and the median number of eosinophils decreased from 41/HPF to <1/HPF. The efficacy of this approach has subsequently been confirmed.

Oral corticosteroid therapy was evaluated by our group in 20 patients with persistent GERD symptoms, esophageal eosinophilia (>15/HPF), and normal or borderline pH studies (reflux index, 5.1%) (21). These patients were refractory to aggressive antireflux therapy (PPI plus prokinetic). By the eighth day of treatment with an oral corticosteroid, 19 of 20 patients reported symptom resolution. Repeat biopsy at 4 weeks demonstrated almost complete resolution of esophageal eosinophils (from 34/HPF to 1.5/HPF). However, on discontinuation of the corticosteroid, 90% experienced a symptom relapse within 1 year.

Results with inhaled corticosteroid were reported in 4 patients with symptomatic GERD (dysphagia or pain) and severe esophageal eosinophilia refractory to acid inhibition (22). A regimen of fluticasone, 4 puffs twice a day, produced clinical improvement, but two patients experienced relapse and required repeat inhalation therapy. Long-term follow-up data beyond 8 months were unavailable, but it is possible that chronic use of inhaled corticosteroids will be necessary.

FUTURE RESEARCH QUESTIONS

More studies are needed to effectively differentiate patients with eosinophilic esophagitis from those with reflux esophagitis. It would appear that significant esophageal eosinophilia (>20/HPF) suggests a diagnosis of eosinophilic esophagitis, whereas <5/HPF and an improvement with acid blockade suggest GERD. The diagnosis is equivocal when an esophageal biopsy reveals 5 to 20 eosinophils/HPF, thus leading to the question, what is the best way to diagnose eosinophilic esophagitis and treat patients with the disorder?

Future research should focus on clarifying the prevalence and natural history (e.g., the potential development of strictures) and optimizing the diagnostic approach and treatment options. Many unanswered questions remain. Why has eosinophilic esophagitis been reported in some parts of the United States and not at all in others? Can the diagnosis be made using less invasive techniques than endoscopy with biopsy? How can we better identify offending food antigens and allergens other than with elemental formulas with a strict protein elimination diet? Are there medications that can cure the disease?

In addition, biochemical studies should be performed to determine the cause of eosinophilic esophagitis. Is the eosinophil dysregulation caused by an immunologic defect or an allergy? These and other research questions reinforce the limitations of our current understanding of isolated esophageal eosinophilia.

QUESTIONS AND ANSWERS

Q: Are you saying that 80% of your patients had essentially no eosinophils when the midesophagus was biopsied?

A: In the majority of patients whom we have diagnosed with eosinophilic esophagitis (EE), those with esophageal strictures or dysphagia usually have a significant number of eosinophils in the midesophagus. However, we have found that these patients have just as many or more eosinophils in the distal esophagus. On the other hand, there are also many patients who present with symptoms of reflux unresponsive to antireflux medication and who have no strictures. These patients are typically younger than those who present with esophageal strictures. We have found that this group of patients often has a significant distal esophageal eosinophilia, while their proximal esophagus may have little or no evidence of eosinophilia. Thus, you may miss the diagnosis of EE by biopsying the proximal esophagus alone. At present, we don't know why some patients have no midesophageal involvement, but the main points are that people should not think that eosinophilia in the midesophagus is necessary to make a diagnosis of eosinophilic esophagitis and that both the mid- and distal esophagus should be biopsied when attempting to diagnose EE.

Q: It appears that the symptoms of allergy may be indistinguishable from the symptoms of GERD. Are these children a unique subgroup of symptomatic reflux patients who do not respond to acid and whom, therefore, we need to exclude from clinical trials of antireflux medications? Because one could hypothesize that eosinophils in the stomach may be part of the mechanism for inducing acid reflux via an effect on gastric emptying.

A: I believe that children with EE have an allergy-based mechanism of disease that causes a secondary acid reflux condition, and these patients should be excluded from clinical studies that are designed to evaluate children with gastroesophageal reflux (GER). Classically, children with GER do not respond to changing formula but do respond to acid suppression. Conversely, children with EE do not respond histologically to acid suppression, but do respond to either a strict dietary elimination or corticosteroid use. It is very important to be rigorous in the definition and diagnosis of GERD and EE.

In past studies, an isolated esophageal eosinophilia was almost always thought to represent GER. Over the past 5 years, we have learned that patients with a severe, isolated esophageal eosinophilia most likely have an allergic disorder with secondary acid reflux. Thus, the small number of infants who in the past may have responded to a hypoallergenic diet may have had EE and not simple GER.

Comment: From what people have said, if we are going to design clinical trials to evaluate the efficacy of acid suppression therapy in children, we need to exclude children with EE. Currently this population is not excluded from adult studies because in adult trials, either biopsies are not done or the condition doesn't exist in adults. I think that allergy probably plays an important role in the conduct of clinical studies in children compared with adult studies.

Q: Are the eosinophils in the esophagus a response to acid or to allergy? Is this a manifestation of GERD or a totally separate disease?

A: It is a separate entity. Some patients may have secondary reflux, but there are studies that have found differences in immunoregulatory cells–differences in esophageal dendritic cells and lymphocyte populations.

Q: Do patients who have eosinophilic esophagitis also have GERD?

A: A subset probably does. Some likely have an element of lower esophageal sphincter dysfunction as a result of mucosal inflammation, but the predominant problem is not acid reflux. As part of our diagnostic procedure, patients have biopsies performed after 2 months of acid blockade. I think the key is whether there is marked eosinophilia after they've been on some form of acid blockade. In addition, esophageal pH monitoring may be used to rule out GERD as a cause of eosinophilia.

Tissue sections demonstrate three features within the squamous epithelium: large numbers of eosinophils, eosinophilic microabscesses, and layering of eosinophils along the luminal surface. The abscesses rise up to the luminal surface and appear almost like the "volcano" lesions in *Clostridium difficile*, one that is composed primarily of eosinophils. This histologic appearance, which is present in up to 50% of patients, may help to differentiate eosinophilic esophagitis from GERD. Interestingly, some adult series reported a normal gross appearance of the esophagus, whereas most pediatric studies noted that it appears grossly abnormal, with descriptions of esophageal rings, furrows, white papules, and exudates. The reasons for this difference are not certain but may explain the lack of appreciation of eosinophilic esophagitis by our adult colleagues. Some animal models are being developed that look at eosinophilic esophagitis and eosinophilic diseases of the gut. It is hoped these models will be useful in understanding the pathophysiology of these conditions. The eosinophil is clearly the effector cell. I think we are beginning to understand that a large contributor to the pathogenesis of these diseases is T-cell dysregulation with overproduction of eosinophilic chemokines.

Q: Is this a new disease, or are we just recognizing it now? It may be like allergic colitis: nobody ever saw it and then all of a sudden we saw it. Why is there such regional variability, with some people seeing it a lot while others do not?

A: While this may not be a new disease, it certainly seems to have become more prevalent. In general, it seems as though many allergic disorders are on the rise. Eosinophilic esophagitis was initially described in adults in papers published years ago. Currently, I believe that pediatric gastroenterologists have made progress in diagnosing many GI conditions because of the availability and ease of endoscopy. Why it appears that EE is more prevalent in some geographic localities and not in others is difficult to explain.

Q: Children with eosinophilic esophagitis seem to be older. Yet we see many infants with reflux-like symptoms who respond to a hypoallergenic diet. Since we don't biopsy all patients, could they also have eosinophilic esophagitis?

A: This is a difficult question. Certainly, many infants with uncomplicated reflux symptoms do not undergo endoscopy and are treated with antireflux medications, with some improvement in symptoms. In addition, some infants are given a hypoallergenic diet and seem to improve. It is difficult to assess the outcome of these patients without histologic specimens. While food allergy in infants typically presents with bloody stools and a histologic colitis, I have not seen that many infants with food allergy have significant EE. Even in infants with GER, it is uncommon to find a large number of eosinophils. Obviously, patients with EE have to begin to accumulate eosinophils in their esophagus at some point. Thus, I believe there must be a subset of infants with food allergy who respond to a hypoallergenic diet but who do not have a significant esophageal eosinophilia. I suspect that if these patients were left untreated and were closely followed, they would eventually develop EE.

Comment: I believe that dietary modification is the mainstay of treatment for patients with EE. While there have been studies demonstrating both clinical and histologic improvement with corticosteroids (systemic and inhaled), in almost every case the disease recurs on discontinuation of the medication. On the other hand, dietary restriction appears to not only produce clinical and histologic improvement but also prevent the underlying problem when the offending antigens are discovered and totally removed from the diet. These patients are symptom free and do not require medication. I have great concerns about giving patients long-term corticosteroids (or other medications) when most patients can be treated with dietary exclusion. Unfortunately, at the present time, allergy testing is limited, and in only a small percentage of patients is the food allergen(s) identified without a strict elimination diet. In addition, patients with

ongoing symptoms and a histologic esophageal eosinophilia are often given what the gastroenterologist thinks is a restricted diet and continue to have a significant esophageal eosinophilia. While it is true that most patients with EE have allergies to the typical food allergens (milk, soy, wheat, eggs, nuts), many have multiple food allergies, and their allergies do not appear to be IgE mediated but rather are a delayed cellular response. Many times, the only way to accurately assess these patients is by upper endoscopy with biopsy. Thus, I strongly believe that patients suspected of having EE who have seen an allergist and either have not had food allergens identified or had foods identified but continue to have EE, should be placed on an elemental diet. The strict elemental diet will promote healing of the esophagus and will then allow the allergist to add foods slowly, one at a time, to better attempt to identify potential food allergens.

Comment: In all the series that have been published thus far, a significant number of children have undergone fundoplication for their symptoms. This is the wrong treatment for what is a disease of immunologic dysregulation. It really reinforces the importance of establishing the correct diagnosis and initiating appropriate treatment.

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