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Eosinophilic Esophagitis

Affecting All Ages

ABSTRACT

Eosinophilic esophagitis is a chronic inflammatory disorder in which elevated eosinophils are found in the esophagus, and symptoms related to esophageal dysfunction are experienced. It has been found in both children and adults. Diagnosis is based on 15 or more eosinophils per high power field in one or more esophageal biopsy specimens coupled with a lack of response to acid suppression therapy or a normal pH monitoring study. It is often associated with other allergic conditions such as eczema and asthma. The reported cases of eosinophilic esophagitis have risen in the past decade, but whether this reflects a true increase in incidence or simply an increased recognition of the disorder by providers is not clear. Patients present with a wide range of symptoms from feeding difficulties, food refusal, and vomiting in children, to dysphagia and food impaction in adults. Treatment options for patients include dietary restrictions, topical steroids, and esophageal dilation.

Eosinophilic esophagitis (EoE) is a chronic, relapsing (Assa'ad et al., 2007), inflammatory disorder in which elevated eosinophils are found in the esophagus and symptoms related to esophageal dysfunction are experienced (Chehade & Sampson, 2008; Furuta et al., 2007). Eosinophils play an essential role in allergic responses and parasitic infections and are normally not found in the esophagus (Hurrell, Genta, & Melton, 2011; Straumann & Simon, 2004). In EoE, however, eosinophils infiltrate the esophagus, causing inflammation and tissue damage (Carr & Watson, 2011).

Diagnosis is based on 15 or more eosinophils per high power field in one or more esophageal biopsy specimens coupled with a lack of response to acid suppression therapy or a normal pH monitoring study (Furuta et al., 2007; Liacouras et al., 2011). The disorder occurs in both children and adults and is often associated with other allergic conditions such as eczema, food allergies, and asthma (Straumann, 2012). Because it shares many of the same characteristics as bronchial asthma, EoE is sometimes referred to as "asthma of the esophagus" (Arora & Yamazaki, 2004; Yakoot, 2011).

More than 90% of the literature on the EoE (821 of 892 publications from PubMed, search conducted on September 9, 2012) has been published in the past 10 years, reflecting an increased recognition and possible rising incidence of this disorder. The majority of literature on EoE published in the early 2000s focused on children (n = 65 publications from PubMed conducted on September 9, 2010) with the disorder but a recent study showed that the typical patient was in the 30- to 40 year-old range (Kapel et al., 2008). Patients present with a wide range of symptoms from feeding difficulties, food refusal, and vomiting in children, to dysphagia and food impaction in adults (Allen & Heine, 2011; Straumann, 2012). Treatment options for patients include dietary restrictions (Spergel et al., 2012), topical steroids, and esophageal dilation (Schaefer et al., 2008; Straumann, 2012).

Case Report

Matthew Krell, a 59-year-old man, came into the clinic, complaining of a 2-year history of dysphagia to solid food. He denied odynophagia, history of food impaction, melena, nausea, or vomiting. He also denied history of allergies or a change in appetite or eating habits. An endoscopy was performed, which revealed a ringed esophagus, mild dysmotility, and moderate duodenitis.

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Esophageal biopsies were taken. Given his long-standing dysphagia, a 17-mm Savary dilator was passed over a guide wire into his esophagus with mild resistance. After dilation, an endoscope was passed for evaluation and two mucosal tears were noted in his esophagus. Mr. Krell was sent to radiology for a stat esophagram. Because the esophagram did not show a perforation, he was sent home with swallowed mometasone (a synthetic corticosteroid similar to fluticasone) and a proton pump inhibitor (PPI), omeprazole (Prilosec) 20 mg twice per day. Biopsies showed extensive infiltration of the squamous epithelial fragments by eosinophils.

Historical Perspective

First mentioned in the literature in the late 1970s (Dobbins, Sheahan, & Behar, 1977; Landres, Kuster, & Strum, 1978), EoE was initially thought to be caused by gastroesophageal reflux disease (GERD) (Lee, 1985). But medications given for GERD such as PPIs had little to no effect on eosinophils in the esophagus (Kelly et al., 1995). It was not until the 1990s that EoE came to be regarded as a separate disorder (Borda et al., 1996). Since the 1990s, publications have soared. More than 90% (821 of 892 total publications) of literature on EoE has been published in the past 10 years. An expert panel of allergists, gastroenterologists, and pathologists published guidelines regarding diagnosis and management of the disorder (Furuta et al., 2007). These were updated in 2011 (Liacouras et al., 2011).

Back to the Basics

What Is an Eosinophil?

Eosinophils are a type of white blood cell and part of the immune system (Book & Collins, 2011). Each eosinophil contains granules in its cytoplasm that can be stained red by a dye called eosin (Hurrell et al., 2011). They are produced in the bone marrow and are found in the blood and certain tissues. Elevated eosinophil counts are often found in some diseases such as parasitic diseases, asthma, Crohn disease, and cancer (Medterms, 2012). Excess eosinophils in tissue are associated with inflammation and tissue damage. Eosinophils in the epithelial lining of the esophagus can cause remodeling and fibrosis leading to strictures, dysphagia (Mishra et al., 2008), and dysmotility (Nurko & Rosen, 2008).

The Typical Patient With EoE

Eosinophilic esophagitis affects people of all ages and gender (Liacouras et al., 2005) and is found in persons from a variety of ethnic backgrounds. The typical patient is more likely to be an atopic, Caucasian, male (male-to-female ratio 3:1) (Furuta et al., 2007; Liacouras et al., 2011), and between 30 and 49 years of age (Kapel et al., 2008).

Causes of EoE

Immune Response

The cause of EoE appears to be driven by an aberrant immune response to an allergen. The process is mediated by the T-helper cell (Th-2) type typically seen in other allergic conditions (Straumann, Bauer, Fischer, Blaser, & Simon, 2001). TH-2 produces the cytokines interleukin IL-5, IL-13, and eotaxin 3, which regulate proliferation and activation of mast cells, and eosinophils in the esophagus (Carr & Watson, 2011; Rothenberg, 2009). Eosinophils and mast cells are also the source of transforming growth factor (TGF)-β1, which may induce fibrosis and contribute to dysmotility (Aceves, Newbury, Dohil, Bastian, & Broide, 2007; Mishra, 2009).

Association With Allergies

About 70%–80% (Noel, Putnam, & Rothenberg, 2004; Rizo Pascual et al., 2011) of EoE patients have a history of allergies or family history of allergies. Most patients who follow an allergen-free diet improve (including patients without a history of allergies) (Liacouras et al., 2005). Exposure to airborne allergens such as pollen may also play a part as most patients are diagnosed in the spring, summer, and fall months (Moawad et al., 2010). In one study, adolescents and adults showed greater sensitization to airborne allergens while young children with EoE showed sensitization to food antigens (Sugnanam et al., 2007).

Allergic reactions to food and environmental allergens are classified into immunoglobulin-E (IgE) (immediate hypersensitivity) and non–IgE-mediated reactions (delayed hypersensitivity) (Hong & Vogel, 2010). Eosinophilic esophagitis is believed to be a combined IgE-mediated and non–IgE-mediated reaction disorder (Swoger, Weiler, & Arora, 2007). Skin-prick tests can be used to identify individuals with IgE-mediated reactions. This test is done by placing a drop of a solution containing a possible allergen on the skin, pricking the skin with a needle or lancet allowing the solution to enter the skin, and then watching for a reaction such as a hive or wheal. Atopy patch testing is useful in identifying non-IgE reactions. To test delayed reactions, skin patch testing is done by applying a small quantity of each of several allergens housed in individual square plastic chambers to the upper back. The patches are removed after 48 hours and reactions are interpreted 24 hours after removal. The majority of patients with EoE have been found to have positive skin prick tests and atopy patch tests (Carr & Watson, 2011; Swoger et al., 2007).

Genetics

There may also be a genetic basis for the disorder. There have been studies of families in which more than one member has EoE (Collin et al., 2008; Patel & Falchuk, 2005). As Carr and Watson (2001) state, "… there is evidence suggesting a genetic predisposition for the disease since the gene for eotaxin-3—a chemokine involved in promoting eosinophil accumulation and adhesion-–has been found to be overexpressed in patients with EoE" (p. 2). The level of eotaxin-3 also correlates with disease severity (Blanchard et al., 2006).

Incidence

Twenty years ago, very few people had even heard of EoE. Now there are more and more cases reported every year. There have been several studies attempting to determine the incidence and prevalence of EoE. In one study of children (up to 19 years of age) from Hamilton, Ohio, the annual incidence of EoE was reported as approximately 1 per 10,000 for the years 2000 through 2003 with a prevalence rate of 4.296 cases per 10,000 at the end of 2003 (Noel et al., 2004). In a population-based study of a random sample of 1,000 adults in Sweden undergoing endoscopy with biopsies, approximately 1% had definite or probable EoE (Ronkainen et al., 2007). In an adult outpatient population of symptomatic patients undergoing upper endoscopy for any reason in 2007, the prevalence of EoE was 6.5% (Veerappan et al., 2009).

But Are Cases of EoE Truly Increasing?

Although it is true that more EoE cases are being identified, it is unclear whether this represents a true increase in incidence or simply an increased recognition of the disorder. One study analyzed a group of cases in Iowa from 1990 to 2005 and found that there was no difference in the incidence of EoE during those years (Vanderheyden, Petras, DeYoung, & Mitros, 2007). However, a population-based study in Olten County, Switzerland, revealed that significantly more EoE cases per 100,000 were diagnosed between 2000 and 2009 compared with those diagnosed between 1989 and 1999 (Hruz et al., 2011). There have been similar findings in other studies (Cherian, Smith, & Forbes, 2006; Kapel et al., 2008; Prastad et al., 2009). It seems probable that the increase in cases is a combination of a true increase and heightened awareness by providers. Additional studies will likely resolve this question.

Diagnosis

Eosinophilic esophagitis should be considered in the following cases:

- Infants or children with food refusal or intolerance, emesis, heartburn, regurgitation, abdominal pain, chest pain, or failure to thrive.
- Older children or adults with dysphagia or history of food impactions and GERD unresponsive to PPI therapy. (Furuta et al., 2007; Straumann et al., 2012)

In 2007, the First International Gastrointestinal Eosinophilic Research Symposium (Furuta et al., 2007) made consensus recommendations on guidelines for diagnosis of EoE. These were updated in 2011 (Liacouras et al., 2011). The guidelines note the following considerations:

- Symptoms of esophageal dysfunction
  - lack of response to a 2-month trial of antireflux medications (up to 2 mg/kg/day of PPI) or
  - a normal 24-hour intraesophageal pH monitoring study
- Esophageal biopsy showing 15 or more eosinophils or more per high-powered field in one or more specimens in the absence of other causes (e.g., celiac disease, infections, inflammatory bowel disease, and eosinophilic gastroenteritis)
- Improvement with dietary treatment, topical corticosteroids, or both

Most patients with EoE do not improve or only have partial response to PPI therapy. There is a small subset of patients whose symptoms and eosinophil count improve while on PPIs. Liacouras et al. (2011) suggest that they should be given the diagnosis of PPI-responsive esophageal eosinophilia and recommended future studies on this subgroup of patients.

In addition, esophageal appearance on endoscopy for a patient with suspected EoE will show linear furrows (vertical lines of the esophageal mucosa), white exudates, esophageal lumen narrowing, circular rings, and strictures. The esophageal mucosa may also appear normal (Liacouras et al., 2011).

Treatment

Pharmacology

Corticosteroids. Topical steroids are recommended rather than systemic because of the latter's potential for toxicity with long-term use (Liacouras et al., 2011). Both are successful in resolving symptoms of EoE, but, when stopped, the disease often recurs (Helou, Simonson, & Arora, 2008).

Fluticasone is a topical corticosteroid and also an inhaler used to treat asthma. Suggested doses range from 440 to 880 μg twice daily for adults and from 88 to 440 μg in divided doses daily for children. They should use the metered dose inhaler, without a spacer.

The powder should be swallowed, not inhaled. No rinsing of mouth or eating for 30 minutes after taking Fluticasone. The medication should be continued for 6–8 weeks (Furuta et al., 2007; Liacouras et al., 2011). Budesonide is another topical steroid used as a viscous suspension. In children younger than 10 years, the dose is 1 mg daily. Older children and adults are dosed at 2 mg daily (Liacouras et al., 2011). Upon discontinuation of steroid treatment, patients will often relapse (Liacouras et al., 2005; Schaefer et al., 2008).

Acid Suppression. Acid suppression may be useful in patients with EoE who also have symptoms of GERD (Krarup et al., 2010). It may be useful in a small subset of patients who have PPI-responsive esophageal eosinophilia (Dranove, Horn, Davis, Kernek, & Gupta, 2009).

Dietary Treatment

Amino Acid–Based Formula or Elemental Diet. Designed to be nutritionally complete, the elemental diet is a hypoallergenic formula that eliminates all whole foods. It often needs to be administered via a feeding tube because of its unpalatable taste. In children, it has been extremely effective in helping to relieve their symptoms (Kelly et al., 1995; Markowitz, Spergel, Ruchelli, & Liacouras, 2003). It allows the inflamed esophageal mucosa to rest and heal. Foods are gradually reintroduced every 1–2 weeks starting with the least allergenic to the most allergenic. Periodic endoscopies are performed to ensure that inflammation has not returned (Carr & Watson, 2011).

Specific Food Elimination. Based on allergy testing utilizing skin prick tests and atopy patch testing, food substances that a patient has shown an allergy to are removed from their diet. In one study of patients who followed this type of diet, 75% showed improvement in their symptoms and inflammation (Spergel et al., 2005).

6-Food Elimination. This diet involves removing the six most common allergenic foods (dairy, eggs, wheat, soy, peanuts/tree nuts, and fish/shellfish) without testing for allergies first. Studies show that this diet demonstrates significant improvement in symptoms (Gonsalves et al., 2012; Kagalwalla et al., 2006).

Esophageal Dilation. Useful for patients with dysphagia, esophageal dilation can provide immediate symptomatic relief; however, whether to dilate before or after treatment with topical steroids or food elimination remains controversial. In the 2007 consensus guidelines, it was not recommended until after treatment because of risk of mucosal tears or perforations (Furuta et al., 2007). But recent studies showed that the risk of perforations was actually lower than previously found (Ally et al., 2013; Dellon et al., 2010; Schoepfer et al., 2010). Updated guidelines in 2011 suggest decisions about dilation before treatment be decided on a case-by-case basis and recommended a conservative, careful approach in dilation technique (Liacouras et al., 2011). The underlying tissue inflammation is not significantly affected by dilatation (Schoepfer et al., 2010).

Long-Term Prognosis

Unlike patients with asthma or food allergies, no deaths have been associated with EoE, but it is considered a chronic disease. Long-term prognosis is unknown, but most patients do not experience remission of the disease (Spergel et al., 2009; Straumann et al., 2003). In one study of pediatrics, patients reported a reduced quality of life and persistent symptoms 15 years after diagnosis (DeBrosse et al., 2011).

Untreated EoE may lead to esophageal remodeling that can cause strictures, Schatzki ring, and eventually achalasia (Carr & Watson, 2011). But with treatment, dietary restriction, and/or topical steroids, fibrosis can be reversed in some patients (Lieberman, Morotti, Konstantinou, Yershov, & Chehade, 2012).

Case Study Follow-Up

Mr. Krell returned for a follow-up visit 8 months following his endoscopy. His dysphagia had not returned, he denied GERD symptoms, and his appetite was good. Because his dysphagia improved after his dilatation, he never started the mometasone. He remained on PPI therapy and was doing well without return of dysphagia. Studies have shown that more than 90% of patients treated by esophageal dilation alone had improvement in their dysphagia symptoms for up to 1–2 years (Bohm & Richter, 2011; Straumann et al., 2003). Accordingly, because Mr. Krell never started the topical steroid and because dilation has little effect on underlying tissue inflammation (Schoepfer et al., 2010; Straumann et al., 2003), Mr. Krell will likely experience a recurrence of his dysphagia within the coming year.

Conclusion

Eosinophilic esophagitis is a relatively new disease that has become increasingly recognized and diagnosed. It is a chronic disease that affects both children and adults. Eosinophilic esophagitis has a strong association with allergies and there may be a genetic basis for the disorder. Treatment involves using topical steroids, dietary therapy, and esophageal dilation. Long-term prognosis is unknown, but most patients do not experience remission of the disease. Also unknown is the extent to which esophageal remodeling and fibrosis

is reversible. By working closely with a gastroenterologist, allergist, and dietician, patients with EoE will likely find a treatment plan that works for them. ✪

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