

Eosinophilic Esophagitis in Children: Clinical Manifestations

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During the past decade, the increasing number of recognized cases of eosinophilic esophagitis in children and adults has resulted in a dramatic expansion of the medical literature surrounding it. Clinical and basic research has contributed to a better, but still incomplete, body of knowledge regarding its clinical and histologic manifestations, as well as its immunologic and genetic pathogenesis.

This article provides a broad framework for recognizing the remarkable variety of clinical manifestations of eosinophilic esophagitis in children. There is not a convenient “one size fits all” description of the presentation of eosinophilic esophagitis, and therefore physicians must consider it as part of the differential diagnosis in many different clinical situations. Prompt, accurate diagnosis is required for timely management, symptom control, and prevention of untoward sequelae from the disorder.

Much of the medical literature related to eosinophilic esophagitis exists as case reports, case series, and reviews from centers in North America. The larger case series form the basis for the current understanding of the clinical manifestations of eosinophilic esophagitis in children and come from the tertiary referral centers that focus on diagnosis and management of pediatric eosinophilic esophagitis [1–6]. In addition, the recent publication of diagnostic guidelines will allow standardization for clinical care and future research studies [7].

Although most of these works were not designed primarily as epidemiologic studies, the demographics of the identified patients support several common findings. For reasons that remain unclear, approximately 70% of children who have eosinophilic esophagitis are males. A series in the United States also has confirmed the clinical impression that the majority (94.4%) of patients are white [2].

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In southwest Ohio, the incidence of eosinophilic esophagitis in children has been estimated at 1.25 cases per 10,000 children per year [6]. Formal epidemiologic studies encompassing the broader population are needed to understand more precisely the risk for developing eosinophilic esophagitis in North America and abroad.

SYMPTOMS OF EOSINOPHILIC ESOPHAGITIS

The most frequent symptoms of eosinophilic esophagitis are nonspecific and include dysphagia, pain, and vomiting. The age at which the symptoms develop varies considerably [6]. Feeding difficulty was the predominant reason for referral and evaluation of infants and toddlers ultimately diagnosed as having eosinophilic esophagitis. Preschool and school-aged children commonly complained of abdominal pain or vomiting, whereas dysphagia generally appeared as a primary complaint in the preadolescent years. In that analysis the chief complaint was recorded, but most patients had more than one symptom attributable to the disorder.

Dysphagia

Dysphagia caused by eosinophilic esophagitis is described variously by affected individuals and is notoriously intermittent. Age and ability to communicate effectively influence how a child describes his or her own difficulty swallowing. Some note that food “goes down slowly,” whereas others say that food gets stuck temporarily somewhere in the throat or chest before proceeding down. Some report difficulty initiating the swallow while the bolus is still in the mouth or recognize anxiety promoted by prior episodes of food impaction. Retrospective analyses note that dysphagia was present for more than 2 years before diagnosis in some patients [8,9]. As detailed in the article by Katzka, elsewhere in this issue, dysphagia has been the predominant presenting symptom in adults.

A careful history in patients who complain of dysphagia reveals that they have learned to compensate by eating slowly, drinking after each bite, taking small bites, chewing excessively, or avoiding specific food consistencies that are problematic such as meat or bread. This phenomenon may help to explain the intermittent experience of dysphagia, because the failure to compensate at a particular meal or even for a single bite may allow the symptom to manifest and “reset” the compensatory mechanisms.

Food impaction requiring endoscopic removal as the initial contact between an adolescent and the medical community is a fairly common presentation for eosinophilic esophagitis. Often the dysphagia has been long standing but mild and intermittent. Many individuals report years of symptoms that were ignored, compensated for, attributed to “taking too big a bite”, or that were blamed on “not chewing food well enough.”

The author and colleagues also have diagnosed eosinophilic esophagitis when called to remove from the esophagus impacted but nonobstructing foreign bodies that normally would have passed, such as coins. It is good practice to obtain mucosal biopsies from the esophagus, remote from the site of the

impaction, after endoscopic removal of a foreign body, especially food impactions. Endoscopic evidence for eosinophilic esophagitis (thickening, furrowing, or pinpoint or diffuse white exudate) (Figs. 1 and 2) is frequently present in affected individuals at the time of the impaction, but because the endoscopic appearance may be influenced by the foreign body on the one hand, and because up to one third of patients who have eosinophilic esophagitis may have a normal-appearing esophagus at endoscopy on the other hand [4], mucosal biopsy is warranted after extracting a foreign body in children.

Less common but clearly problematic, gastroenterologic consultation has been requested for some individuals after long periods of psychiatric evaluation and treatment of chronic dysphagia without radiographic evidence for dysmotility or stricture. The authors have seen children ultimately proved to have eosinophilic esophagitis whose dysphagia has been attributed to underlying anxiety, obsessive-compulsive disorder, eating disorder, or pervasive developmental disorder. One boy was diagnosed with bulimia at age 10 years because he vomited after eating, although he had symptoms since infancy.

Dysphagia in patients who have eosinophilic esophagitis can be caused by mechanical obstruction of the esophagus and can manifest endoscopically and/or radiographically as a ring (Fig. 3) focal stricture, Schatzki ring, or long-segment narrowing (so-called “small-caliber esophagus”) [10]. It is more common, however, for children to complain of dysphagia in the absence of radiographic narrowing of the esophagus [9]. Nurko and colleagues [8] examined the esophageal histology proximal to radiographically diagnosed Schatzki rings in 18 children and discovered that eosinophilic esophagitis was present in 8 of them. Notably, endoscopic evidence for Schatzki ring was not present in the children who had histologic eosinophilic esophagitis, suggesting that focal transient spasm accounted for the radiographic finding.



Fig. 1. Endoscopic appearance of furrowing.



Fig. 2. Endoscopic appearance of exudate.

It is tempting to attribute dysphagia to the degree of inflammation, duration of disease, degree of lamina propria fibrosis, or the impact of chronic inflammation on deeper layers of the esophagus. The deep layers of the esophagus are affected, as evidenced by the thickening of the entire wall of the esophagus demonstrated by endoscopic ultrasound [11]. Nonspecific manometric abnormalities were observed in 60% of studied adult patients who had eosinophilic esophagitis [12]. In that study, parallel improvement in manometric and histologic findings was observed.

It is tempting to speculate that adolescents and adults who have had longstanding untreated disease develop dysphagia as a consequence of persistent inflammation-induced damage including lamina propria fibrosis or remodeling, but because the age of disease onset often is unknown in that group, it has not been possible to associate dysphagia directly with the duration of inflammation in many individuals [13,14].

Stricture is a feared complication of eosinophilic esophagitis and has been described as early as 7 months of age [9]. Although the strictures are amenable to dilatation, esophageal mucosa with eosinophilic inflammation is more prone to tear during dilatation than the mucosa overlying a peptic stricture, and perforation of the esophagus has been described as a complication of attempted dilatation in adults [10,15,16]. Many clinicians managing adults who have eosinophilic esophagitis-associated dysphagia now recommend aggressive medical management of the inflammation before attempting dilatation unless clinical circumstances dictate more immediate relief of the obstruction [17]. Prospective study has not confirmed that this approach reduces the number of dilatations or the risk of perforation, but this approach is reasonable until refuted. Similarly, dogmatic historical concepts generated by experience in dilating peptic strictures should be abandoned and replaced by recommendations for gentle, gradual dilatation only when necessitated by failure of medical therapy for eosinophilic esophagitis.

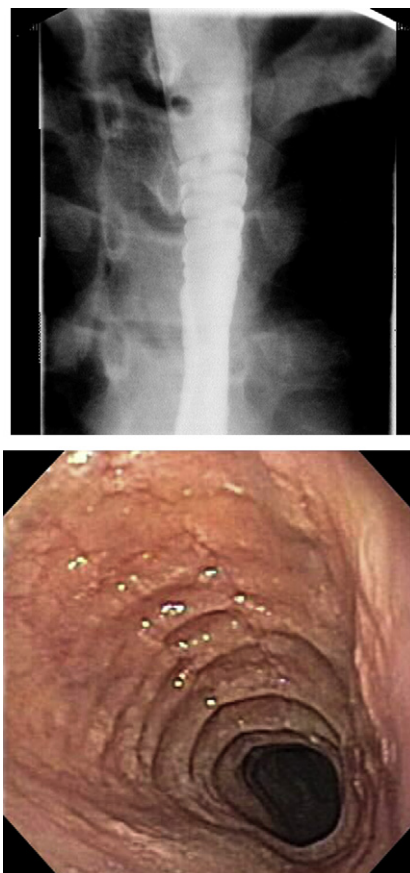


Fig. 3. (Top) Radiographic appearance and (bottom) endoscopic and radiographic appearance of the ringed proximal esophagus.

Infants and preverbal toddlers who have eosinophilic esophagitis may present with feeding difficulties that manifest as gagging, choking, food refusal/aversion, or vomiting [18]. It is not well understood whether these problems are consequences of dysphagia, nausea, anorexia, pain, fear or anxiety after untoward experiences with eating, or a combination of these factors. Clinicians participating in the evaluation of young children who have feeding disorders must be knowledgeable in the evaluation and treatment options for eosinophilic esophagitis and have a low threshold for early evaluation and intervention. Because there are overlapping issues, concurrent therapy to account for all of the child's conditions (gastroesophageal reflux disease [GERD], behavioral feeding aversion, and eosinophilic esophagitis) may be necessary.

Vomiting

Vomiting as a primary complaint among pediatric patients who have eosinophilic esophagitis occurs most often in young children. It can mimic reflux, manifest as effortless regurgitation, but eosinophilic esophagitis is seldom diagnosed in the first 6 months of life when GERD is common. Accurate diagnosis of eosinophilic esophagitis in very young children who vomit is often delayed by months to years, during which time treatment for symptoms attributed to GERD is attempted. In the author's experience, parents describe vomiting more often than effortless regurgitation.

Circumstances surrounding episodes of vomiting vary. Vomiting can be part of an overt and immediate allergic response to a recently ingested food. In that case, the family generally recognizes that there is a consistent reaction to that food and chooses to avoid it. Immediate vomiting may be associated with other manifestations of an adverse immune response such as hives, diarrhea, pain, or even anaphylaxis. Some children who have eosinophilic esophagitis and multiple food allergies have a history of developing different constellations of symptoms in response to various foods, up to and including food protein-induced enterocolitis syndrome.

Chronic, episodic, unpredictable vomiting of variable severity also occurs in patients who have eosinophilic esophagitis, and it is not clinically distinguishable from other causes of emesis. This vomiting does not occur proximate to exposure to a particular food, which precludes devising an appropriate diet based solely on history.

In the first year of life, clues that eosinophilic esophagitis, rather than reflux, is the underlying culprit include early onset of vomiting (within days to weeks of birth) associated with eczema, vomiting associated with irritability that does not respond to acid suppression, and onset of vomiting in the second half of the first year of life during the introduction of solid foods.

After infancy, vomiting is more chronic, intermittent, and not readily associated with particular foods, although it is usually meal related. Vomiting to the point of excess calorie loss resulting in failure to gain weight or weight loss is possible but uncommon.

Rarely, nausea without vomiting is the sole presenting manifestation of eosinophilic esophagitis. Although usually present with other symptoms, it has been an isolated complaint in a few individuals. Nausea has been responsive to standard treatment of the esophagitis in most individuals, but the author and colleagues have seen other children who have remarkably recalcitrant nausea as a persistent complaint after resolution of active eosinophilic inflammation.

Retching to remove a piece of food that is stuck may be called "vomiting" by some patients and needs to be distinguished from emesis of gastric contents. Retching can be recognized as such by careful history. The patient will report that something got stuck and he or she retched to remove or otherwise dislodge it.

Pain

Pain is a frequent but not universal complaint among individuals who have untreated eosinophilic esophagitis. Children who have pain associated with

eosinophilic esophagitis report chest, epigastric, and/or abdominal pain. Overt odynophagia is not typical. Some individuals have been evaluated the emergency department for episodic crushing substernal pain concerning for heart disease. Those individuals have been remarkably free of symptoms between pain attacks, which have been unpredictable in frequency and which lack an obvious inciting event.

The pain may be described as heartburn and may respond to acid suppression. When histologic eosinophilic inflammation persists despite effective therapy for GERD, a clinical diagnosis of eosinophilic esophagitis is established.

A remarkable number of children indicate that their pain is in the epigastrium or the periumbilical area. They often have difficulty describing the pain in more sophisticated terms. It is imperative that these complaints promote appropriate investigation, particularly when the broader clinical picture is concerning, such as a boy who has asthma or eczema or a history of food allergy. The absence of complaints referable to the chest should not preclude consideration of esophageal disease.

Associated Conditions

Communicative children who have eosinophilic esophagitis may present with a single symptom, but careful questioning often elicits additional symptoms that are attributable to the inflammation. In addition, many children who have eosinophilic esophagitis have other medical conditions with symptoms that may overlap, contribute to, or serve to confuse the issue at presentation. For example, chest pain may accompany episodes of bronchospasm in a child who has asthma, and that phenomenon may divert attention away from other potential causes of chest pain, such as esophagitis (reflux or otherwise).

The profile of individuals who have eosinophilic esophagitis is quite varied, but there are notable associations. Because definitions and rigor in establishing a formal diagnosis vary, the precise frequency of associated conditions is subject to interpretation. Nevertheless, eosinophilic esophagitis coexists or is a parallel phenomenon associated with asthma, eczema, and environmental and food allergies in up to 75% of children [2,19].

The association of eosinophilic esophagitis with other conditions is becoming more apparent from experience. The epidemiology and immunobiology are as yet unexplored. For example, esophageal eosinophilia has been seen in the Cincinnati Center for Eosinophilic Disorders in a handful of children who have other gastrointestinal conditions such as *Helicobacter pylori* gastritis, Crohn's disease, or celiac disease.

Esophageal involvement can be seen in patients who have eosinophilic gastroenteritis. It is inappropriate to make a clinical diagnosis of eosinophilic esophagitis when substantial eosinophilic inflammation of stomach, small intestinal, or colon is present concurrently or sporadically in a patient who has had eosinophilic infiltration of the esophagus. Studies have examined the number of eosinophils in normal gastrointestinal mucosa, but formal histologic and clinical definitions of eosinophilic gastroenteritis are yet to be developed [20,21]. As

such, separating patients who have eosinophilic esophagitis who happen to have mild and clinically irrelevant mucosal eosinophilia distal to the esophagus from cases of eosinophilic gastroenteritis with esophageal involvement can be challenging. Diarrhea, anemia, hypoalbuminemia, failure to thrive, and gastrointestinal bleeding are not typical features of isolated eosinophilic esophagitis, and individuals who display them should be evaluated appropriately, even if a provisional diagnosis of eosinophilic esophagitis has been made.

A number of children who have underlying neurologic or neurodevelopmental conditions have been diagnosed as having eosinophilic esophagitis. Eosinophilic esophagitis has been seen in children who also have intractable seizures, cerebral palsy, Chiari malformation, pervasive developmental disorder, sensory integration disorder, or migraine. Hypersensitivity to antiepileptic drugs has been implicated in the development of eosinophilic esophagitis, so it is important to account for medication use in this group [22]. Otherwise, no obvious, direct, cause-and-effect relationship between these neurologic conditions and eosinophilic esophagitis has been discerned to date.

The epidemiology of eosinophilic esophagitis in children who have concurrent neurodevelopmental conditions has not been explored formally. It is not clear whether the prevalence of eosinophilic esophagitis is indeed higher in that population of children or whether clinicians have become more thorough in evaluating them. GERD is said to occur frequently in this population as well, but it is no longer safe to assume that GERD is responsible for nonspecific upper gastrointestinal symptoms.

Similarly, eosinophilic esophagitis has been discovered in children who have other syndromes, without comment on the epidemiology. A case report notes the association of eosinophilic esophagitis in Rubenstein-Taybi syndrome [23]. The author and colleagues have seen eosinophilic esophagitis in children who have coloboma, heart anomalies, choanal atresia, retardation of growth and development, and genital and ear anomalies (CHARGE syndrome), vertebral, anal, tracheo-esophageal, and radial limb or renal anomalies (VATER syndrome), Pierre-Robin syndrome, Klinefelter's syndrome, Moebius syndrome, and Pfeiffer syndrome.

EOSINOPHILIC ESOPHAGITIS AND DISEASE OF THE RESPIRATORY TRACT

Eosinophilic esophagitis has been discovered in children presenting with airway and respiratory complaints, who may or may not have concomitant gastrointestinal symptoms [24,25]. Although the prevalence of eosinophilic esophagitis in children presenting with primary airway disease is unknown, it must be considered in children who present with stridor, adenoidal hypertrophy, recurrent croup, recurrent pneumonia, or aspiration. The diagnosis has been made in children who have airway anomalies such as subglottic stenosis or laryngeal cleft [26].

No criteria yet exist on which to base recommendations for formal diagnostic evaluation for eosinophilic esophagitis in patients who have these presenting

symptoms. At the Cincinnati Center for Eosinophilic Disorders, more than 50 children who have eosinophilic esophagitis have been seen in the tertiary, multidisciplinary clinic dedicated to the evaluation and treatment of significant airway problems resulting in tracheostomy tube dependence. Most have had subglottic stenosis caused by prolonged intubation after premature birth, and none were suspected of having or diagnosed as having eosinophilic esophagitis before evaluation in this institution. Many had failed prior attempts at surgical laryngotracheoplasty. Because the mechanisms involved are not established, it is not clear whether there is any direct relationship between the esophagitis and the recurrent stenosis, but the association and concern has been sufficient for the author and colleagues to consider evaluation for and treatment of eosinophilic esophagitis in this population warranted before committing to elective airway surgery until prospective studies further examine the pathogenesis.

DO DIFFERENT PHENOTYPES OF EOSINOPHILIC ESOPHAGITIS EXIST?

Studies that describe the symptom complex in children who have eosinophilic esophagitis have generally lumped all individuals with defined histology together, and the disorder is considered as a single entity. Those who have followed a large number of children with eosinophilic esophagitis, however, suspect that clinically distinct patterns occur. Whether these presentations are simply at opposite ends of a continuum or deserve a separate diagnosis or classification scheme is not established. A particular single nucleotide polymorphism in the eotaxin-3 gene is present in some individuals with eosinophilic esophagitis, but it is not clear how that information can or should be used in clinical practice at this time [27].

In clinical practice, it is possible to categorize children loosely into clinical subtypes or phenotypes. For example, there is a group of children in which the individuals are extraordinarily atopic and exhibit a constellation of eosinophilic esophagitis, eczema, chronic rhinitis, asthma, repeated respiratory infections, and multiple food allergies. These children often present in early infancy with vomiting and irritability. Eczema, chronic nasal congestion, recurrent bronchospasm, and repeated upper respiratory infection become apparent in the first 2 years of life. In some, the eczema has been severe. Although the gastrointestinal symptoms respond to dietary restriction (most often requiring an elemental diet with an amino acid-based formula), the asthma is generally an independent phenomenon requiring standard therapy and does not resolve as a result of diet change alone. In this group, a clinical diagnosis of GERD has been made almost universally, but the children do not respond completely to antireflux therapy. Some of these children have been extraordinarily sensitive to food and exhibit recurrent eosinophilic esophagitis with virtually any food added to the diet.

At the other end of the spectrum is group of children who have eosinophilic esophagitis in the absence of atopy, eczema, or asthma. Evidence for food allergies is lacking by formal allergy testing, and the children do not respond to

dietary therapy even with an elemental diet. This group of patients generally responds well to topical (swallowed) steroids (usually fluticasone or budesonide) as mainstay of chronic therapy. Recurrence after discontinuation of steroids is nearly universal, although follow-up of these patients is still relatively brief (<10 years for children).

If these presentations are considered as a spectrum, the middle of the spectrum is populated by children who have eosinophilic esophagitis and food allergies, often with asthma, and/or mild eczema. They develop eosinophilic esophagitis with several foods but can be maintained on an elimination diet, avoiding those foods that trigger the inflammation. This group seems to be large and to incorporate the majority of children who have eosinophilic esophagitis who have been evaluated in the Cincinnati Center for Eosinophilic Disorders.

FAMILIAL EOSINOPHILIC ESOPHAGITIS

Eosinophilic esophagitis has been demonstrated in more than one individual within many families [28]. The occurrence across generations suggests a genetic rather than environmental pathogenesis, but only now are the details being explored. Careful assessment of the family history may identify other individuals who already have been diagnosed, but the author and colleagues frequently hear about adults with longstanding dysphagia, perhaps requiring dilatation, attributed to reflux or Schatzki ring. Siblings who exhibit symptoms deserve early endoscopic evaluation to establish a diagnosis.

RESPONSE TO THERAPY

Much of what has been learned about children who have eosinophilic esophagitis has come directly from studies designed to observe the response of the inflammatory process to therapy, be it dietary antigen elimination or steroids [4,19,29–33]. By convention, eosinophilic esophagitis is distinguished from reflux by the failure to respond to aggressive antireflux therapy. In the landmark description of eosinophilic esophagitis in children, the complete response of otherwise recalcitrant eosinophilic esophagitis to an elemental diet was a defining feature [34]. Now, the same parameters are used to make a formal diagnosis (ie, failure to respond to antireflux therapy) and to distinguish the food allergic variant (ie, response to diet). Specifically, complete clinical and histologic resolution of active eosinophilic esophagitis in response to diet therapy either with specific antigen avoidance or total antigen elimination (eg, diet replaced by an elemental formula) supports a diagnosis of the allergic variant of eosinophilic esophagitis. In theory, patients who do not respond to an elemental diet still may have an allergic variant, although the assumed nonfood environmental antigens involved remain unclear. Because up to 98% of children who have eosinophilic esophagitis respond to an elemental diet, the vast majority of affected children would seem to have the disease as a manifestation of adverse response to dietary antigens [32].

CONTROVERSIES IN EOSINOPHILIC ESOPHAGITIS

One of the great difficulties in managing children who have eosinophilic esophagitis has been the absence of symptoms in treated individuals who nevertheless have active esophageal eosinophilia. Symptoms typically abate with therapy (diet or medication), but some patients still have unaltered or only minimally improved esophageal histology.

Another common scenario is for the esophagitis to return without overt symptoms during attempts at reintroducing food to the diet or upon withdrawal of steroid therapy [2,4]. This phenomenon has generated considerable debate as to whether the symptom(s) or the histology should be treated. Because only endoscopy with biopsy has been an adequate method for reassessment in the absence of symptoms, one of the concerns has been the risk and cost of the number of endoscopies that need to be performed during the lifetime of an individual undergoing food elimination/reintroduction. Early work that examined genetic, biochemical, and/or immunologic markers for the disease failed to discover factors with sufficient predictive value to be used routinely in place of endoscopy and histology [27,35,36]. The debate has not been resolved officially, although expert consensus now supports treating the histology irrespective of the absence of symptoms, because of the known longer-term risks of esophageal remodeling, fibrosis, and potential stricture formation [17].

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