

# Esophageal Obstruction as a Result of Isolated Eosinophilic Gastroenteritis

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**E**osinophilic gastrointestinal disorders (EGIDs) are being recognized with an increasing frequency. They are characterized by prominent eosinophilic infiltration in the absence of parasitic infection, vasculitis, neoplasm, or other known causes of eosinophilia.<sup>1,2</sup> They are routinely classified according to anatomic location or depth of inflammation and can have a variety of presentations and symptoms.<sup>3,4</sup> We report an unusual case of eosinophilic gastroenteritis (EG) in a middle-aged woman who presented with severe dysphagia and associated weight loss.

## Case Report

A previously healthy Haitian woman, age 50 years, was referred for symptoms of severe dysphagia to solids and liquids and a 15-lb weight loss over 4 weeks. Her medical history was significant for childhood asthma. She had no other relevant personal or medication history. Findings of an initial endoscopy performed by a community physician suggested extrinsic esophageal obstruction but were ultimately nondiagnostic. At our hospital, we repeated the endoscopic examination (Figure 1) and found a distensible lumen without any specific segmental stricture, although there was an impression that the overall caliber of the esophagus was narrowed. This finding was supported by results of a barium esophagram (Figure 2). Biopsies of the midesophagus revealed only occasional eosinophils (1 to 2 eosinophils per high-power field [eos/HPF]).

We also performed an endoscopic ultrasound (EUS), which revealed a diffuse thickening of the mucosal and submucosal layers throughout the entire esophagus without evidence of extraluminal compression or lymphadenopathy



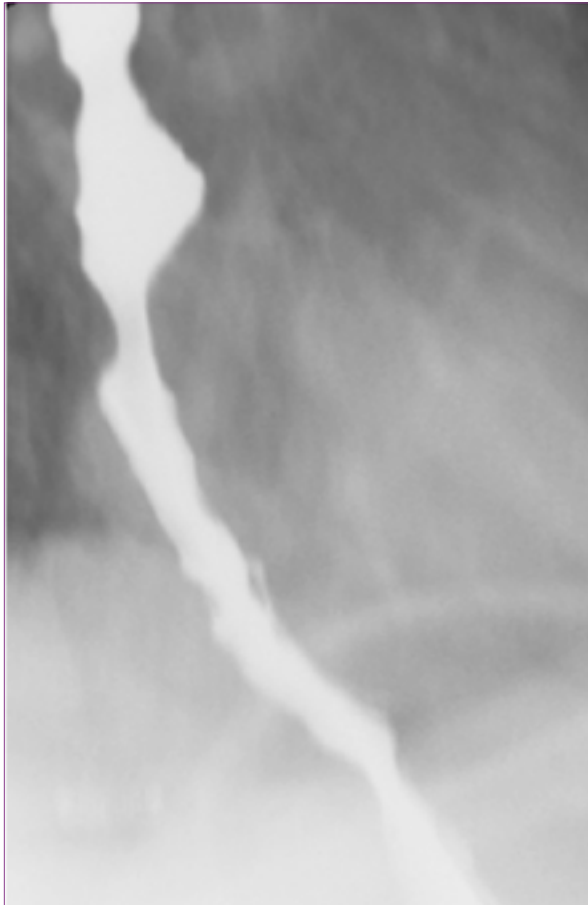
**Figure 1.** A long endoscopic view of the esophagus during the index endoscopy.

(Figure 3). To exclude a diffusely infiltrating process, we performed an endoscopic mucosal resection (EMR) using a band ligation and snare technique. Histologic analysis revealed greater than 60 eos/HPF limited to the deep mucosa, muscularis mucosa, and parts of the submucosal layer (Figure 4). Significant edema and some eosinophils dissecting the muscle layers were found. The epithelial layer, however, was devoid of any significant eosinophilia. No other types of inflammatory cells were present, and there was no evidence of malignancy. The pattern of inflammation was consistent with what has been described in EG when it extends to the esophagus.

Subsequently, we performed an EMR of the patient's stomach and obtained deep biopsies of the duodenum, which did not identify eosinophilia. Tests for parasites,

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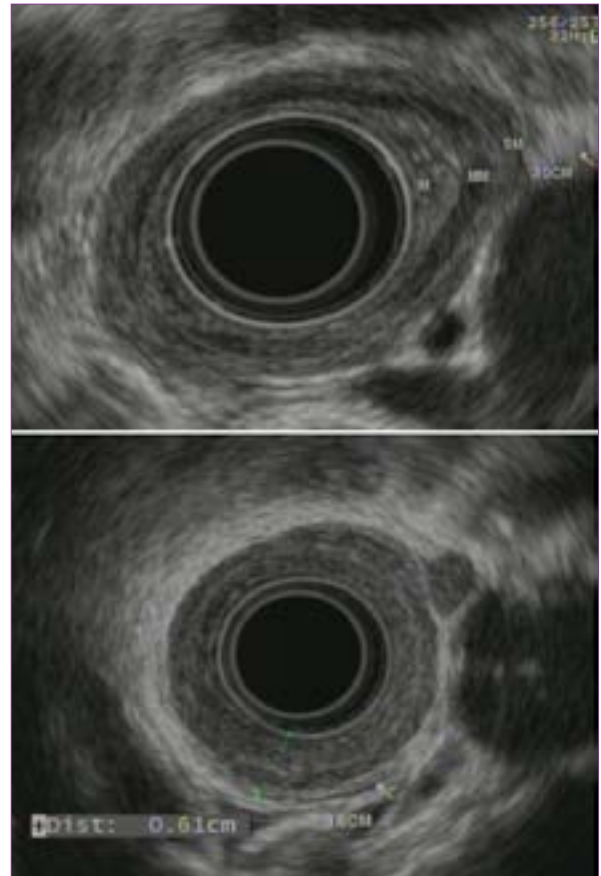


**Figure 2.** Long circumferential tapering of the mid- and distal esophagus on a barium esophagram.

autoimmune disorders, and HIV infection were all negative. Given the severity of the patient's symptoms, a course of twice-daily prednisone was initiated. In addition, serum allergy testing was performed for food and environmental allergens, which did not identify any specific allergic trigger. The patient's oral intake of solids and liquids improved within 48 hours, and follow-up at 2, 4, and 6 weeks suggested that the patient's symptoms had completely resolved with an associated return to baseline weight. A repeat EUS performed at 8 weeks showed a marked improvement in the thickness of the mucosal and submucosal layers (Figure 5). Given the patient's symptomatic resolution and evidence of improvement via EUS, therapy was discontinued at 8 weeks, and the patient has continued to do well.

## Discussion

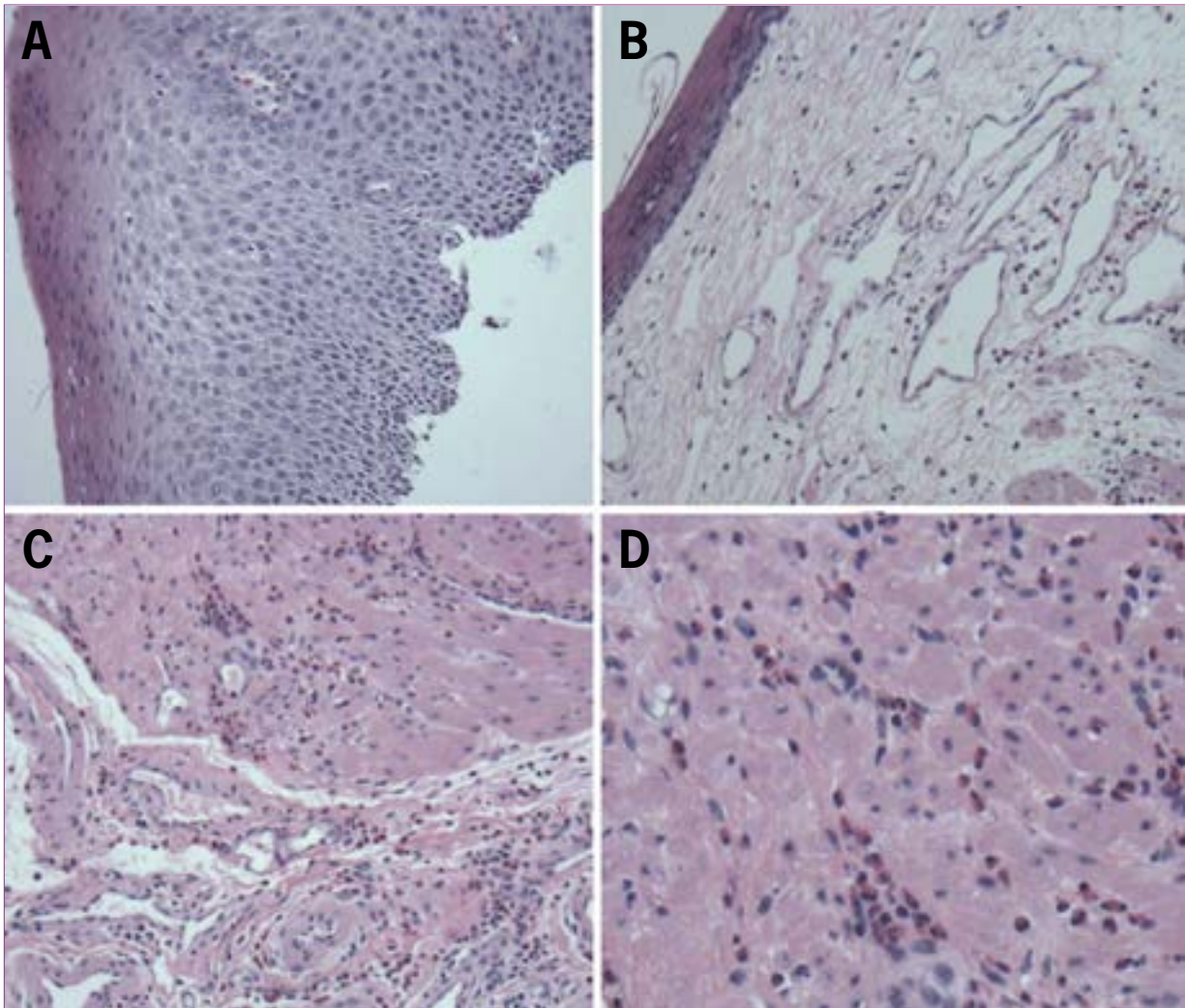
Eosinophilic esophagitis (EoE) is the most commonly recognized form of EGIDs, with a prevalence of 5 per 10,000 persons.<sup>5,6</sup> Other EGIDs, such as EG and eosinophilic colitis, are far less common, with an unknown prevalence.<sup>7</sup>



**Figure 3.** Endoscopic ultrasound views of the midesophagus showing diffuse concentric thickening of the deep mucosa, muscularis mucosa, and submucosal layers.

As opposed to EoE, these disorders vary significantly in the extent and depth of gastrointestinal involvement, resulting in a wide range of symptoms.<sup>3</sup> Despite this spectrum in presentation, all EGIDs share eosinophilic infiltration as a common feature, perhaps implicating an allergic mechanism. A strong personal or family history of allergy can be found in more than 50% of patients.<sup>4</sup> In addition, genetic factors have been implicated, with case reports of similar disease processes in monozygotic twins,<sup>8</sup> but, overall, there is a lack of firm evidence to support a hereditary component.

EG, specifically, can involve 1 or more segments from the esophagus to the rectum. In 1970, Klein and colleagues arbitrarily classified patients according to the depth of involvement (ie, those with predominantly mucosal, muscular, or serosal disease).<sup>1-4,9</sup> Since its first description in 1937, less than 300 cases of EG have been reported, most of which have been single case reports or small case series.<sup>7,8,10,11</sup> EG is most commonly reported in the small bowel, particularly the second portion of the duodenum. Rarely, it has been described in the esophagus as part of a larger systemic disorder.<sup>3,4</sup> Patients typically



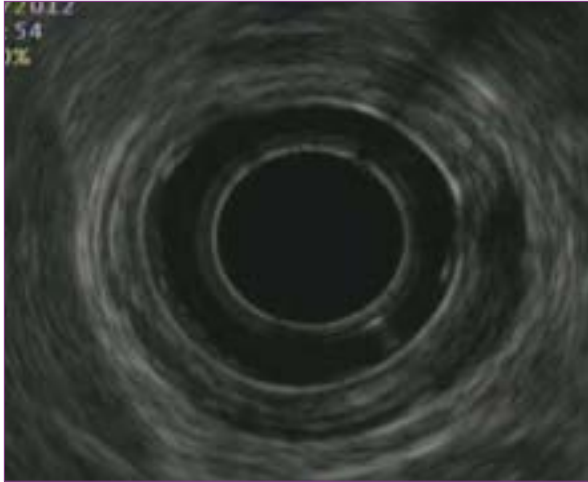
**Figure 4.** Hematoxylin and eosin stains showing (A) no eosinophilic infiltration of the mucosal layer (10× magnification); (B) eosinophilic infiltration of the lamina propria, deep mucosa, and some submucosa with reactive edema (10× magnification); (C) eosinophilic infiltration of the muscularis mucosa (10× magnification); and (D) muscularis mucosa showing interweaving eosinophils (40× magnification).

present in the third through fifth decades of life, but the disease can affect any age group and probably has an equal gender distribution.<sup>4</sup> Symptoms are directly related to the extent of the gastrointestinal involvement. Patients with predominantly mucosal disease have symptoms of diarrhea, malabsorption, and abdominal pain, whereas those with muscular involvement present more commonly with bowel thickening and symptoms of pyloric or intestinal obstruction. When the disease extends to the serosal layer, ascitic fluid accumulation can occur.<sup>4,10</sup>

Our patient presented with symptoms of esophageal obstruction secondary to severe eosinophilic infiltration with reactive edema. Although manometry was not performed in our case, dysmotility is a common finding,<sup>6</sup> which was evident in the narrow caliber and spasmodic

appearance of the patient's esophagus during the esophagram (Figure 2). Although the patient's symptoms were directly related to esophageal eosinophilia, her disease is distinct from the more commonly encountered EoE, particularly because there was preferential infiltration of eosinophils in the deep mucosal and submucosal layers of the esophagus. In adults, EoE is entirely mucosal, resulting in an epithelial surface layering of eosinophils. Occasionally, deeper layers can be affected but to a lesser extent than the epithelium, setting it apart from mucosal EG, which involves multiple layers equally. In this case, the epithelium showed no eosinophilia (Figure 4A), supporting our diagnosis of EG rather than EoE. It is also notable that the 2 disorders can occur in the same individual as distinct processes, albeit not concurrently.<sup>11</sup>





**Figure 5.** An endoscopic ultrasound view of the midesophagus showing decreased thickening of the deep mucosal and submucosal layers after treatment.

For EGIDs, the main therapeutic options include oral or topical corticosteroids, montelukast, sodium cromoglycate, and restrictive diets. For EG, the results of each of these therapies are variable; however, it is clear that corticosteroids are associated with faster resolution of symptoms.<sup>3</sup> Our patient had complete symptomatic resolution within 8 weeks on a tapered corticosteroid regimen. Serum allergy testing did not identify a particular food trigger that could be avoided, and for most patients, long-term avoidance of foods can be impractical. A repeat EUS confirmed an improvement in the mucosal and submucosal edema associated with symptom resolution. Our diagnostic approach to this patient, overall, has been unique, incorporating a combination of EUS and EMR for diagnosis and follow-up. This highlights the diagnostic challenge for this disease and the limitation of traditional biopsies, which only sample small sections of the superficial mucosa.

To our knowledge, isolated eosinophilic infiltration of the esophagus, in a pattern consistent with EG, has never been described in the literature. Previously, a handful of reports have described esophageal involvement in extensive EG of the upper gastrointestinal tract.<sup>4</sup> In these cases, esophageal involvement occurs later in the disease process and can be a marker of severity. Our case is unique in that there was no evidence of involvement apart from the esophagus. This case may represent a variant in the spectrum of EGIDs or an early form of esophageal EG with the potential to progress to involvement at other sites. In most cases, the diagnosis can be quite difficult

to establish, and treatment often must be empiric. The ability to use multiple imaging modalities, as well as techniques for tissue sampling, helped identify the patient's condition early, and prompt treatment resulted in complete resolution of symptoms.

## Summary

EG is an uncommon entity characterized by heavy eosinophilic infiltration of the gastrointestinal tract wall. Its symptoms can range from nonspecific abdominal pain to luminal obstruction. It can affect a single segment, but it more commonly affects multiple segments and causes an array of symptoms. Esophageal involvement rarely occurs, and isolated esophageal EG, as with our patient, has never been reported in the literature. EG is histologically distinct from the more common EoE, and, perhaps, the triggers and mechanisms of inflammation also may differ. Our approach to this case highlights the current diagnostic- and treatment-related obstacles regarding this disorder and emphasizes the importance of multimodality imaging and sampling techniques that are not routinely employed.

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## Review

### Eosinophilic Esophagitis: Are We Just Scratching the Surface?

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Over the past 20 years, eosinophilic esophagitis (EoE) has emerged as a leading cause for esophageal symptoms in both children and adults.<sup>1,2</sup> Prevalence estimates for EoE now approximate those for inflammatory bowel disease and continue to rise. The clinical presentation of EoE in adults is dominated by dysphagia and food impaction, although additional symptoms of chest pain and heartburn are recognized.<sup>1</sup> Eosinophilic gastroenteritis (EoG), on the other hand, is a more heterogeneous and less common disorder that has been recognized in every segment of the gastrointestinal tract. EoG preferentially affects distinct compartments of the intestinal wall, specifically the mucosa, muscularis propria, and serosa. The specific segment and layer of the intestinal wall determine the symptom presentation. Peripheral eosinophilia is a clinical clue to the diagnosis of EoG and is present in most cases. Although the peripheral eosinophil level was not reported in the case study by Benias and colleagues,<sup>3</sup> the sensitivity of this test for isolated esophageal disease is unknown.

In the aforementioned case study, a woman, age 50 years, presented with dysphagia and weight loss and had a narrow-caliber esophagus without apparent mucosal abnormalities on endoscopy.<sup>3</sup> The differential diagnosis of the narrow-caliber esophagus includes EoE, prolonged nasogastric intubation, radiation esophagitis, caustic injury, lichen planus, long-segment Barrett esophagus, bullous cutaneous disorders, congenital esophageal stenosis, and esophageal intramural pseudodiverticulosis. Neoplastic processes, including stromal cell tumors, can infiltrate the esophagus in a submucosal manner but typically present with more focal strictures. Over the past 20 years, EoE has emerged as one of the leading causes of the narrow-caliber esophagus.<sup>4</sup>

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A conceptual question regarding this case report is whether the patient has a variant of EoE or an esophageal manifestation of EoG.<sup>3</sup> In support of the diagnosis of EoE, the eosinophilic inflammation was confined to the esophagus without endoscopic or histologic involvement of the stomach or duodenum.<sup>3</sup> The patient, however, did not have evidence of eosinophilia in the squamous epithelium, which is considered a hallmark of EoE.<sup>1</sup> Although it is possible that the presence of esophageal mucosal eosinophils could have been suppressed by use of proton pump inhibitors or intermittent use of medications for the patient's remote history of asthma, these are unlikely explanations. As the esophageal eosinophilia in EoE can be patchy, multiple (>5) biopsies from different areas of the esophagus have been recommended to maximize detection.<sup>5</sup> In this case, an unspecified number of biopsies were obtained only at the level of the midesophagus.

Specific aspects of this case argue against the diagnosis of EoE, but the distinction between EoE and EoG is not well delineated. The patient's clinical presentation with a relatively short duration (4 weeks) of dysphagia and associated weight loss is atypical for EoE. In adults with EoE, progressive dysphagia typically manifests over several years prior to diagnosis. Weight loss is uncommon in adults, although it is sometimes a feature in children. Endoscopically demonstrable esophageal features, including edema, rings, exudates, and furrows, are present in the majority of patients but were not noted in this patient.<sup>6</sup> The authors suggest that the deeper infiltration of the esophageal submucosa and muscularis supported the diagnosis of EoG rather than EoE. It should be noted, however, that deeper infiltration of the inflammatory and remodeling processes has been reported in both pediatric and adult presentations of EoE. Deep tissue biopsies have demonstrated eosinophil infiltration of the lamina propria and subepithelial fibrosis in up to 90% of patients with EoE.<sup>7</sup> Studies using endoscopic ultrasonography have demonstrated significant thickening of the submucosa as well as muscularis in both children and adults.<sup>8,9</sup> Finally, case reports of patients undergoing surgical intervention for EoE have demonstrated transmural involvement of eosinophilic inflammation and remodeling.<sup>10</sup>

Interestingly, our group reported a case similar to the one reported by Benias and colleagues.<sup>3</sup> Our patient was an elderly man with dysphagia, esophageal dysmotility, and focal narrowing of the proximal esophagus with normal overlying esophageal mucosa.<sup>11</sup> Both computed tomography imaging and endoscopic ultrasonography demonstrated marked thickening of the esophageal wall. A fine-needle aspiration of the esophagus demonstrated cellular atypia that resulted in esophageal resection. The pathology of the esophagus demonstrated eosinophilic inflammation of the muscularis propria in the absence

of significant mucosal eosinophilia. Similarly, one of the earliest case reports of EoE described a man, age 44 years, with achalasia.<sup>12</sup> The patient was managed with a surgical myotomy of the distal esophagus. Operative biopsies demonstrated muscle hypertrophy with extensive eosinophil infiltration. Similar to the other 2 cases, eosinophilic inflammation was not detected in the esophageal, gastric, or duodenal mucosa. Benias and colleagues are to be applauded for the nonoperative diagnosis of submucosal EoE (or EoG) by means of band ligation and endoscopic mucosal resection that was able to identify eosinophilic infiltration of both the submucosa and muscularis mucosa.<sup>3</sup> Their novel diagnostic intervention led to initiation of systemic corticosteroids, with rapid symptom resolution.

In this case report, the distinction between EoE and EoG has both pathophysiologic and therapeutic implications. Current evidence suggests that the pathogenesis of EoE involves antigen activation of a TH2-type immune response, most commonly in response to ingested foods.<sup>13,14</sup> Increased expression of allergic cytokine mediators and inflammatory cells combined with demonstration of disease remission by means of elimination of dietary proteins have led to the hypothesis that EoE is a food allergy or hypersensitivity response. Epithelial permeability may be an important predisposing factor in genetically susceptible individuals that allows for local antigen presentation to resident immune cells in the deeper epithelial space and lamina propria. The pathogenesis of EoG is unknown, but response to systemic corticosteroids is almost universal. Use of frontline therapies for EoE, including swallowed topical corticosteroids or dietary elimination of potential food stimuli, has less conceptual appeal for a more systemic disease process such as EoG.

The natural history of EoG is variable. In a prospective cohort study, 43 patients with EoG were followed for 13 years, revealing 3 distinct patterns of disease.<sup>15</sup> Some patients followed a pattern of disease relapse and remission (37%), whereas others demonstrated persistent, chronic activity (21%). However, there was a subset of patients who presented with a single flare lasting less than 6 months with absence of any relapse after the initial presentation (42%). The authors of this study observed that peripheral eosinophilia at diagnosis was associated with an increased risk of clinical relapse in patients who

had achieved remission; the median blood eosinophil count was 3035/mm<sup>3</sup> in patients with relapse compared with 1100/mm<sup>3</sup> in patients without relapse. The authors also observed that 40% of their patients had spontaneous remission and that absence of spontaneous remission was another factor associated with relapse. Although the patient in the case study by Benias and colleagues quickly went into remission with corticosteroid therapy and did well after treatment cessation, long-term follow-up of the patient would be of interest.<sup>3</sup>

*The authors have no conflicts of interest to disclose.*

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