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.[1,2] 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.[1] 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,[3] 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.[3] 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.[4]

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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.[3] 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.[3] The patient, however, did not have evidence of eosinophilia in the squamous epithelium, which is considered a hallmark of EoE.[1] 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.[5] 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.[6] 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.[7] Studies using endoscopic ultrasonography have demonstrated significant thickening of the submucosa as well as muscularis in both children and adults.[8,9] Finally, case reports of patients undergoing surgical intervention for EoE have demonstrated transmural involvement of eosinophilic inflammation and remodeling.[10]

Interestingly, our group reported a case similar to the one reported by Benias and colleagues.[3] Our patient was an elderly man with dysphagia, esophageal dysmotility, and focal narrowing of the proximal esophagus with normal overlying esophageal mucosa.[11] 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.[12] 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.[3] 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.[13,14] 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.[15] 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^3 in patients with relapse compared with 1100/mm^3 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.[3]

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