



Perspective

Eosinophilic gastrointestinal disorders

The journey to diagnosis remains arduous

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ARTICLE INFO

Article history:

Received for publication July 30, 2019.

Received in revised form September 5, 2019.

Accepted for publication September 10, 2019.

Although great strides have been made in diagnosing eosinophilic esophagitis (EoE) over the past decade, the journey to diagnosis of eosinophilic gastrointestinal disorders (EGIDs) below the esophagus remains arduous. Eosinophilic gastrointestinal disorders are named after the location of the gastrointestinal tract that is infiltrated by eosinophils. These include eosinophilic gastritis, enteritis, gastroenteritis, and colitis. Although the prevalence of EGIDs is currently reported to be approximately 2 to 5/100,000, possibly it is underestimated given the difficulties many EGID patients face before establishing their diagnosis. We clinicians need to be aware of potential obstacles to the diagnosis of EGIDs, so that we can reduce the current delay in diagnosis and improve patients' lives.

The first obstacle to diagnosis lies in the nonspecificity of the disease demographic characteristics. Eosinophilic gastrointestinal disorders seem to occur at any age. In contrast to the male predilection seen in EoE, no sex-linked predilection has been identified in EGIDs.^{1,2} However, similar to EoE, atopic co-morbidities seem to be prevalent in EGIDs, although this still needs to be confirmed in larger, case-control studies.^{1,2} As a result, just like the possibility of EoE comes to mind when the clinician encounters an atopic patient with solid food dysphagia, the possibility of EGID needs to be considered when chronic gastrointestinal symptoms are reported by an atopic patient, to prevent diagnostic delay.

A second obstacle to diagnosing EGIDs is the heterogeneity and nonspecificity of symptoms. Depending on the depth of eosinophilic infiltration through the gastric or intestinal tissue, patients can present with different symptoms. In the mucosal variant, patients can have abdominal pain, emesis, diarrhea, anorexia, weight loss, and even failure to thrive in the case of children.^{1,2} In the muscular variant, symptoms are rather consistent with a gastric

outlet or intestinal obstructive picture, depending on the location infiltrated by eosinophils.² With the serosal variant, patients present with ascites.² Even with the mucosal disease, the most common of the 3 variants, the differential diagnosis of the gastrointestinal symptoms is quite large given the nonspecificity of symptoms. Patients are often erroneously given the diagnosis of irritable bowel syndrome or inflammatory bowel disease. A subset of EGID patients also have protein-losing enteropathy (PLE),³ which can be particularly confusing to the practitioner, because these patients have concurrent anemia, hypoproteinemia, and hypoalbuminemia, also potentially leading to the erroneous suspicion of inflammatory bowel disease. In addition, when PLE is severe, serum immunoglobulin G level is decreased because of its loss secondary to increased gut permeability.³ This finding in a young child may erroneously lead the practicing physician down the path of an immunodeficiency, hence overlooking an EGID diagnosis.

A simple test that can increase the index of suspicion for EGIDs is the peripheral eosinophil count, which is elevated in a large subset of patients with active disease.^{1,2} Unfortunately, requesting a differential white blood cell count is not common practice, and it needs to be considered. Furthermore, elevated stool alpha-1-antitrypsin levels can diagnose a PLE as the cause of hypoproteinemia and move the clinical workup in the right direction.

A third obstacle to diagnosing EGIDs resides in the heterogeneity of endoscopic findings and the patchy nature of the disease. In the absence of diagnostic guidelines that would cover the gamut of features to look for, the diagnosis can be missed, because the endoscopic features are highly variable. The subtle finding of erythema without other features such as erosions, ulcers, or nodularity, and the presence of a normal mucosa are not uncommonly encountered in children with EGIDs,¹ which may lead the gastroenterologist to omit obtaining biopsies from these areas, hence missing the disease. In addition, the patchy nature of the disease can also lead to a false-negative diagnosis if multiple sites of the gastrointestinal tract do not undergo biopsies.¹

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Disclosures: none.

Funding Sources: Mirna Chehade received research funding from the NIH, PCORI and APFED/AAAAI, consulting fees from Regeneron, Shire, Allakos, Adare, clinical trial funding from Regeneron, Allakos and Shire, and lecture fees from Nutricia.

<https://doi.org/10.1016/j.anai.2019.09.011>

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In addition, histological diagnostic criteria are not yet established for EGIDs. In contrast to the esophageal mucosa, which is normally devoid of eosinophils, the gastrointestinal mucosa below the esophagus contains small numbers of eosinophils in healthy individuals, which vary in number in different locations of the gastrointestinal tract. Therefore, to diagnose EGID, we would need to look for a relative increase of gut eosinophil numbers. Guidelines to establish threshold numbers of eosinophils considered pathologic for each part of the gastrointestinal tract do not yet exist. Efforts are currently underway by the Consortium for Eosinophilic Gastrointestinal Disease Researchers to study EGIDs in depth through large multicenter prospective observational studies focusing on examination of EGID clinical, endoscopic, histological, molecular, and patient-related outcomes.⁴ When faced with a patient with gut eosinophilia, we still need to keep in mind other causes besides EGIDs, including parasitic infection, inflammatory bowel disease, and hypereosinophilic syndrome among others, and rule them out in the proper clinical setting.

The arduous journey to getting diagnosed with EGIDs has tremendous negative impact on the health-related quality of life of those patients, affecting the psychological, physical, social, and financial domains.⁵ Instead of fear, patients with EGIDs reported relief when their diagnosis was made, and reported improvement of health-related quality of life with effective treatment.⁵ To relieve their arduous journey, we eagerly await results of ongoing efforts to establish adequate patient-reported outcome measures and endoscopic and histological diagnostic criteria for EGIDs. We also need to better understand the pathophysiology of EGIDs, particularly

confirming preliminary data that point to an allergic cause, based on the high prevalence of atopic co-morbidities, increased levels of allergic cytokines in the tissue, and evidence of disease remission in response to avoidance of common food allergens.^{1–3} Confirming concurrent atopy and food responsiveness in larger studies will help establish therapy options for these patients. In the interim, we need to consider EGIDs in our differential diagnosis of patients with nonspecific chronic gastrointestinal symptoms, especially those with atopy, consider obtaining a peripheral eosinophil count, and in the case of anemia and hypoproteinemia, examine for evidence of PLE among other causes. Establishing the diagnosis in a timely manner will lead to proper follow-up and management of patients suffering from EGIDs, with resultant improvement in their well-being and that of their families.

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