

Case Report

Cow's Milk Protein–induced Eosinophilic Esophagitis in a Child With Gluten-sensitive Enteropathy

*Amir F. Kagalwalla, *Ameesh Shah, ‡Sally Ritz, †Hector Melin-Aldana, and *B.U.K. Li

**Department of Pediatrics, Division of Gastroenterology, Hepatology, and Nutrition, †Department of Pathology, Northwestern University Feinberg School of Medicine, and ‡Children's Memorial Hospital, Chicago, IL*

INTRODUCTION

Eosinophilic esophagitis (EE) was first described in 1978 in an adult with dysphagia (1). However, it only became recognized as a distinct clinical entity in children in 1995 after a report of a cohort of children with gastroesophageal reflux symptoms resistant to aggressive acid suppression therapy whose condition promptly improved with elimination of all intact protein with an elemental amino acid–based formula (2). Not unlike in gluten-sensitive enteropathy (GSE), increased awareness has led to dramatic increase in the frequency with which EE is being diagnosed worldwide (2–8). We recently evaluated a child with characteristic findings of EE and GSE, an association that, to our knowledge, has not been previously reported and is the basis for this case report.

CASE REPORT

A 7-year-old black male with reactive airway disease, eczema, and type 1 diabetes mellitus was referred to the gastroenterology clinic for positive celiac serologic findings. He had had recurrent abdominal pain for several years that was not associated with nausea, vomiting, solid food dysphagia, food impaction, diarrhea, or weight loss. Diabetes, asthma, and eczema were poorly controlled and he required insulin for diabetes, daily albuterol inhaler treatment for wheezing, and topical corticosteroids for eczema. However, he was not receiving inhaled steroids for the treatment of asthma. Weight and height were both at the 75th percentile and the physical examination findings were within normal limits. The initial laboratory investigations are summarized in Table 1. Upper

endoscopy revealed white plaques in the esophagus. Four-quadrant esophageal biopsies from the midportion of the esophagus (10 cm above the gastroesophageal junction) and distal esophagus (3 cm above the gastroesophageal junction) revealed 90 and 120 eosinophils per high-power field (HPF), respectively. Eosinophilic microabscesses, basal-cell hyperplasia, and increased papillary height were noted in all of the esophageal biopsies. Esophageal biopsy specimens treated with periodic acid–Schiff stain did not reveal fungal elements. Findings of gastric biopsies were normal. Duodenal biopsies demonstrated marked villous blunting, crypt hyperplasia, increased intraepithelial lymphocytes, and epithelial damage. Eosinophils admixed with a large number of plasma cells and lymphocytes were present in the duodenal lamina propria. Eosinophilic microabscesses and eosinophilic cryptitis were not seen.

In addition to excluding gluten, his family was offered and accepted the option of also excluding milk protein, egg, soy, and peanuts from his diet to treat EE; his diet already excluded seafood. The 6-food exclusion diet approach, including diet counseling for appropriate calories during temporary exclusion of 6 major proteins from the diet, was previously described (9). One of the 6 excluded foods was reintroduced, and 6 weeks later upper endoscopy and esophageal biopsies were performed before proceeding with the next food reintroduction. Within a few weeks of instituting the 6-food elimination diet, the abdominal pain, eczema, and reactive airway disease resolved and he no longer required albuterol and corticosteroid ointment. His insulin requirement also decreased. He had gained weight at the time of his repeat endoscopy in 6 months. Visually, the esophagus appeared normal and multiple 4-quadrant middle and distal esophageal regions revealed 8 and 0 eosinophils per HPF, respectively. Basal-cell hyperplasia resolved and eosinophilic microabscesses were not seen. Duodenal biopsies revealed normal villous architecture, and the

Received June 9, 2006; accepted August 27, 2006.

Address correspondence and reprint requests to Amir F. Kagalwalla, MD, University of Illinois-Chicago, 840 S Wood St (MC 858), Chicago, IL 60612 (e-mail: akagalwa@uic.edu).

TABLE 1. Findings of laboratory investigations

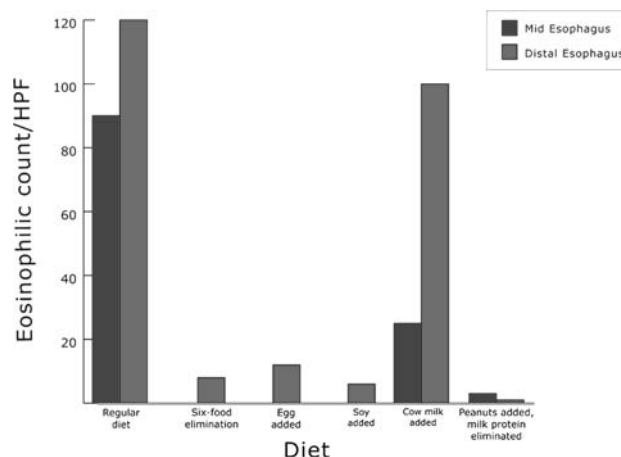
Measurement	Value
Hemoglobin, g/dL	12.2
Hematocrit, %	35.8
White blood count	4.73/mm ³
Neutrophils, %	50.2
Lymphocytes, %	35.3
Monocytes, %	5.7
Eosinophils, %	7
Basophils, %	1.8
Albumin, g/dL	4.2
Normal range	3.5–4.5
IgA, mg/dL	185
Normal range	45–234
Anti-gliadin antibodies	
IgA (U)	90 (normal <25)
IgG (U)	55 (normal <25)
Tissue transglutaminase (ie, IgA)	97 (normal <20)
Endomysial antibody (ie, IgG)	1:160 (normal negative)
HLA	DQ2
IgE, kU/L	1162 (normal <176)
IgG, mg/dL	1050 (normal 584–1509)
IgM, mg/dL	65.5 (normal 49–230)
C3, mg/dL	86.2 (normal 93–203)
C4, mg/dL	18.1 (normal 13–52)
CD3 ⁺ CD4 ⁺ absolute count	585/mm ² (normal 548–1720/mm ²)
Antitetanus titer, IU/mL	4.64 (normal <0.15)

Ig indicates immunoglobulin.

lamina propria was free of plasma cells, eosinophils, and intraepithelial lymphocytes. Thereafter, repeat endoscopic esophageal biopsies performed every 6 weeks after sequential reintroduction of 1 of the excluded foods including egg, soy, and peanuts were normal. However, reintroduction of cow's milk protein in his diet led to recurrence of abdominal pain, eczema, and edema with white plaques in the esophagus. Esophageal biopsies from middle and distal esophageal regions revealed 25 and 100 eosinophils per HPF, respectively. The initial histological findings and subsequent eosinophilic response to different food allergens is shown in Fig. 1. The gastric and duodenal biopsies remained normal following all 4 food challenges. Because seafood had not been part of his diet, he was not challenged with seafood. He is currently asymptomatic on a diet excluding cow's milk and gluten. He was not prescribed inhaled steroids during dietary treatment of EE and GSE.

DISCUSSION

In 1937, Kaijser originally described eosinophilic gastroenteritis (EGE) as a disorder characterized pathologically by infiltration of eosinophils into the mucosa of any part of the gastrointestinal tract (10). A disorder characterized by dense isolated infiltration of the esophageal mucosa, EE gained recognition as a distinct clinical entity in 1995 (2). Our patient had more than

**FIG. 1.** EE response to exposure to various food allergens.

20 eosinophils per HPF in esophageal biopsies and, although gastroesophageal reflux disease was not excluded with 24-hour pH monitoring or an adequate trial of proton pump inhibitors for acid suppression, his response to an elimination diet with normalization of esophageal histology and subsequent recurrence with reintroduction of cow's-milk protein substantiated a diagnosis of EE (6,11). The additional involvement of the duodenum in our patient raised the diagnostic possibility of EGE, but the mixed cellular infiltrate of lymphocytes, plasma cells, and eosinophils is typically seen in GSE, whereas the inflammatory infiltrate in EGE is predominantly eosinophilic (12). The absence of gastric eosinophilic inflammation suggests that the patient does not have EGE (13). In addition, other nonspecific findings such as anemia and hypoalbuminemia that are frequently associated with EGE were absent in our patient. Villous atrophy is rarely seen in EGE, but when it is present it fails to return to normal with elimination of gluten from the diet (14,15).

Common variable immunodeficiency can present with autoimmune disorders and various forms of gastrointestinal inflammation. Our patient did not have a history of recurrent infections and exhibited normal quantitative immunoglobulins, humoral immunological response to tetanus toxoid, and lymphocyte subpopulations, ruling out immune dysfunction.

The diagnosis of GSE was strongly suggested by presence of serological markers, confirmed by the duodenal biopsy and normalization of duodenal histology after elimination of dietary gluten. The presence of the genetic marker HLA DQ 2 is additional evidence in support of a diagnosis of GSE in our patient.

Eosinophilic esophagitis is characterized as immune-mediated food hypersensitivity disorder, and GSE results from intolerance to dietary gluten. Two different food allergens, gluten and cow's milk protein, were

responsible for the inflammation in the duodenum and esophagus, respectively. Upon reintroduction of cow's milk protein in this patient's diet, which still excluded gluten, EE relapsed, whereas GSE remained in remission. This further supports the presence of 2 distinct clinical disorders: EE and GSE in the same patient.

Both GSE and EE are distinct and different clinical entities except for a few minor similarities. Affliction of 8% of first-degree relatives of patients with GSE is similar to that reported in 10% of first-degree relatives of patients with EE (16). The genetic basis for GSE (ie, HLA DQ 2) is well established and differs from that of EE, in which overexpression of eotaxin-3 was recently described (17). Immune-mediated mucosal inflammatory damage occurs in both of these disorders; it is limited to the esophagus in EE and is associated with T_H2-type cytokine inflammatory response with overexpression of cytokines interleukin-5 and eotaxin-3 (18,19). In GSE the damage is predominantly limited to the proximal small intestine and is T_H-1 mediated with overexpression of cytokines interferon- γ and interleukin-1 β (20). Although inflammation is triggered by foods in both conditions, 2 different foods caused 2 different types of inflammatory responses in 2 separate intestinal locations. Gluten was not responsible for inducing the esophageal eosinophilia typical of EE and was not the trigger of the EE. Therefore, within the limits of the known pathogenesis of EE and GSE, this patient had 2 separate diseases that were not linked by a single pathogenic mechanism, and we are reporting this as a unique association.

Eosinophilic gastroenteritis and celiac disease have previously been described in the same patient in 2 separate case reports, but to our knowledge this is the first reported case of a patient with EE associated with GSE (21,22). After cow's milk protein-induced EE was treated, abdominal pain resolved and atopic symptoms including eczema and reactive airway symptoms improved to the point that the patient no longer required medications for these conditions. This novel case demonstrates that EE and GSE can coexist in the same patient and underscores the importance of close visual examination of the esophagus and performance of esophageal biopsies when evaluating children for GSE.

REFERENCES

- Landres RT, Kuster GG, Strum WB. Eosinophilic esophagitis in a patient with vigorous achalasia. *Gastroenterology* 1978;74:1298-301.
- Kelly KJ, Lazenby AJ, Rowe PC, et al. Eosinophilic esophagitis attributed to gastroesophageal reflux: improvement with amino acid-based formula. *Gastroenterology* 1995;109:1503-12.
- Tietelbaum JE, Fox VL, Twarog FJ, et al. Eosinophilic esophagitis in children: immunopathological analysis and response to fluticasone propionate. *Gastroenterology* 2002;122:1216-25.
- Noel RJ, Putnam PE, Collins MH, et al. Clinical and immunopathologic effects of swallowed fluticasone for eosinophilic esophagitis. *Clin Gastroenterol Hepatol* 2004;2:568-75.
- Fox VL, Nurko S, Furuta GT. Eosinophilic esophagitis: it's not just kid's stuff. *Gastrointest Endosc* 2002;56:260-70.
- Orenstein SR, Shalaby TM, Di Lorenzo C, et al. The spectrum of pediatric eosinophilic esophagitis beyond infancy: a clinical series of 30 children. *Am J Gastroenterol* 2000;95:1422-30.
- Walsh SV, Antonioli DA, Goldman H, et al. Allergic esophagitis in children: a clinicopathological study. *Am J Surg Pathol* 1999;23:390-6.
- Kumar R, Sentongo T, Nelson SP, et al. Eosinophilic esophagitis in children: a review. *Clin Applied Immunol Rev* 2003;4:173-88.
- Kagalwalla AF, Sentongo TA, Ritz S, et al. Effect of six-food elimination diet on clinical and histological outcomes in eosinophilic esophagitis. *Clin Gastroenterol Hepatol* 2006;4:1097-102.
- Kajiser R. Zur Kenntnis der allergischen Affektionen des Verdauungskanalns vom Standpunkt des Chirurgen aus. *Arch Klin Chir* 1937;188:36.
- Liacouras CA, Wenner WJ, Brown K, et al. Primary eosinophilic esophagitis in children: successful treatment with oral corticosteroids. *J Pediatr Gastroenterol Nutr* 1998;26:380-5.
- Talley NJ, Kephart GM, McGovern TW, et al. Deposition of eosinophil granule major basic protein in eosinophilic gastroenteritis and celiac disease. *Gastroenterology* 1992;103:137.
- Goldman H, Proujansky R. Allergic proctitis and gastroenteritis in children: clinical and mucosal biopsy features in 53 cases. *Am J Surg Pathol* 1986;10:75-86.
- Waldmann TA, Wochner RD, Laster I. Allergic gastroenteropathy: a cause of excessive gastrointestinal protein loss. *N Engl J Med* 1967;276:761-9.
- Greenberger NJ, Tenenbaum JJ, Ruppert RD. Protein losing enteropathy associated with gastrointestinal allergy. *Am J Med* 1967;43:777-84.
- Rothenberg ME. Eosinophilic gastrointestinal disorders (EGID). *J Allergy Clin Immunol* 2004;113:11-28.
- Blanchard C, Wang N, Stringer KF, et al. Eotaxin-3 and a uniquely conserved gene-expression profile in eosinophilic esophagitis. *J Clin Invest* 2006;116:536-47.
- Straumann A, Bauer M, Fischer B, et al. Idiopathic eosinophilic esophagitis is associated with a T_H2-type allergic inflammatory response. *J Allergy Clin Immunol* 2001;108:954-61.
- Schmid-Grendelmeier P, Altnauer F, Fischer B, et al. Eosinophils express functional IL-13 in eosinophilic inflammatory diseases. *J Immunol* 2002;169:1021-7.
- Farrell RJ, Kelly CP. Celiac sprue. *N Engl J Med* 2002;346:180-8.
- Butterfield BH, Murray JA. Eosinophilic gastroenteritis and gluten-sensitive enteropathy in the same patient. *J Clin Gastroenterol* 2002;34:552-3.
- Amirav I, Rosenthal E, Bentur L, et al. Coexistence of celiac disease and eosinophilic gastroenteropathy. *J Pediatr Gastroenterol Nutr* 2001;33:200-1.