

Histopathology Associated with Eosinophilic Gastrointestinal Diseases

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KEYWORDS

- Pathology • Eosinophilic gastrointestinal disease
- Eosinophilic esophagitis • Eosinophilic gastritis
- Eosinophilic enteritis • Eosinophilic colitis

Eosinophils normally reside in the mucosa of most segments of the gastrointestinal tract (GIT) and normally perform protective functions.^{1,2} Eosinophilic gastrointestinal disorders (EGIDs) are broadly defined as diseases that characteristically exhibit excessive numbers of eosinophils, in normal and abnormal locations, in one or more GIT segment. Eosinophilic esophagitis (EE), eosinophilic gastritis, eosinophilic enteritis, and eosinophilic colitis refer to eosinophilic inflammation in the esophagus, stomach, small bowel, and colon, respectively, and are all forms of localized EGIDs. If the inflammation involves more than one GIT segment, the specific segments affected should be designated in pathology reports. The term *eosinophilic gastroenteritis* (EG) signifies inflammation specifically involving the stomach and small intestine but has also been used more broadly as a synonym for EGIDs.^{3,4}

In addition to involving one or more segments of the GIT, the eosinophilic inflammation in EGIDs may affect one or more layers of the wall of the affected segment.³ The inflammation in EGIDs may occur in the mucosa, submucosa, muscularis propria, serosa, or in any combination of these layers. Although the mucosa is commonly involved, in approximately 10% of EGIDs cases, the mucosa does not exhibit changes diagnostic of EGIDs, possibly because of sampling error in a disease that may be patchy.⁵ Because bowel biopsy samples obtained by endoscopy generally consist of mucosa only, endoscopy may not yield diagnostic tissue. The absence of mucosal eosinophilic inflammation, however, does not exclude the possibility that other layers

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of the underlying bowel wall are inflamed with eosinophils. In such cases, the diagnosis can be made by examination of a transmural biopsy or resected specimen.

NORMAL DISTRIBUTION OF EOSINOPHILS IN THE GASTROINTESTINAL TRACT

Few studies report the number of eosinophils present in normal GIT mucosa. Two reports of normal pediatric GIT mucosa have documented that eosinophils are normally found in mucosa in the stomach, small intestine, and colon^{6,7} but are rarely present in esophageal epithelium.⁷ One report of eosinophils in mucosal biopsy specimens of the descending and sigmoid colon of adults demonstrated that the mean number of eosinophils is greatest in samples obtained in the southern part of the United States compared with those from the northern United States.⁸ A similar study has not been performed in children. In addition to varying according to geographic site in the United States, GIT mucosal eosinophil density may also show seasonal variation.⁹

Knowledge about the density of eosinophils in various parts of the GIT, in the various layers of the GIT wall, and at various ages is essential to accurately diagnose EGIDs. Some studies of EGIDs have based the diagnosis on finding greater than 20 eosinophils per high-power field (HPF) in mucosal biopsy specimens.¹⁰⁻¹³ Although one study of normal biopsy specimens from adults reported a peak mucosal eosinophil count of 21/HPF in samples from descending and sigmoid colon,⁸ another study of normal biopsy specimens from adults reported a peak eosinophil count of 68/HPF in the ascending colon and 50/HPF in the descending colon.⁹ Studies of normal biopsy specimens from children have identified peak eosinophil counts exceeding 21/HPF in small intestine and colon,^{6,7} including a peak eosinophil count in the right colon of 50 to 52/HPF. Quantitative eosinophil evaluations of normal biopsy tissue from infants are rarely reported. In one study, rectal biopsy tissue from infants to evaluate for Hirschsprung's disease contained an average of 1.3 eosinophils per HPF; a peak count was not provided.¹⁴ In a different study of rectal biopsy tissue obtained to evaluate for Hirschsprung's disease in patients aged 3 days to 5 years, a mean number of 2 eosinophils per HPF was reported in samples lacking ganglion cells, and a mean of 5.3/HPF was reported in samples containing ganglion cells; a peak count of 18/HPF was reported in the ganglionated biopsy samples. In that study, mucosal eosinophil density did not differ significantly with patient age.⁶ A somewhat higher peak count, 32/HPF, was found in normal rectal biopsy tissue from patients beyond infancy.⁷

Asymptomatic children do not undergo endoscopy; therefore, analyzing normal tissue remains difficult and problematic in pediatrics. Nonetheless, it is extremely important for pathologists and gastroenterologists to be aware that based on current evidence, normal mucosal eosinophil density varies among segments of the GIT, and for that reason, a single peak value cannot be applied to all segments of the GIT in children or in adults. Pathologists must avoid overdiagnosis of EGIDs by applying site-specific criteria for eosinophil density to mucosal biopsy specimens. Gastroenterologists must avoid contributing to overdiagnosis by submitting biopsy samples from each segment of the GIT separately, especially from the colon where the maximum mucosal eosinophil density in the right side normally exceeds that of the more distal colon.

RECOMMENDED HISTOPATHOLOGIC TERMINOLOGY

Studies of large numbers of normal biopsy specimens from multiple sites in the GIT, from multiple areas of the United States and the world, at multiple times of the year, and in multiple age groups are lacking, but pathologists are nonetheless required to render diagnoses based on mucosal biopsy. Some studies report mean mucosal

eosinophil numbers with standard deviations and do not provide a peak, or maximum, number. Counting eosinophils in multiple or in every HPF of a biopsy sample yields more complete information and may be preferable for research, but a peak count of eosinophils in the most densely inflamed HPF is informative and more practical for daily surgical pathology sign-out.

Using the results of published studies or of unpublished intradepartmental studies to establish norms for peak eosinophil numbers in endoscopic biopsy samples, pathologists should consider the diagnosis of mucosal eosinophilia to signify mildly increased numbers of eosinophils without other pathologic changes (**Fig. 1**). Biopsy samples showing only mildly increased numbers of eosinophils may indicate diseases other than EGIDs. For example, small numbers of intraepithelial eosinophils in esophageal biopsy specimens are consistent with gastroesophageal reflux disease (GERD) but not with EE. Genome-wide analysis of esophageal biopsy tissue shows different transcriptomes for samples containing no or few eosinophils compared with those containing numerous eosinophils, consistent with EE;¹⁵ these data may serve as a molecular basis to distinguish EE from GERD and from normal tissue. Similarly, mildly increased numbers of eosinophils without other histologic changes in other parts of the GIT may represent potentially normal variations including those associated with geographic region of the United States, season of the year, or an early nonspecific sign of inflammatory bowel disease.⁵ Until more studies of normal GIT biopsy tissue in children and adults are reported, pathologists should acknowledge that eosinophil density that appears to be mildly increased but does not include other alterations may or may not indicate EGIDs. This approach avoids potential overdiagnosis that could lead to inappropriate or unnecessary therapy, including the use of steroids, which has more potential adverse effects in children than in adults. Because EGIDs may be patchy, when initial mucosal biopsy specimens are normal or only mildly inflamed and when clinical suspicion for EGIDs remains strong, repeat biopsies may be indicated and may provide more definitive results.



Fig.1. Mucosal eosinophilia. In this section of ileum, numerous eosinophils are present in the lamina propria, but the architecture remains intact and intraepithelial eosinophils are not increased.

Terms such as EGIDs, eosinophilic gastritis, eosinophilic enteritis, and so forth should be reserved for biopsy specimens that show changes in addition to increased eosinophils, such as eosinophilic glandulitis/cryptitis, eosinophilic crypt abscesses, chronic architectural changes, and others (**Box 1**) (**Figs. 2–5**). Caution must be exercised when rendering these diagnoses as well, because normal biopsy tissue from children and adults may contain scattered small numbers of intraepithelial eosinophils.^{7,9,14}

In general, markedly increased numbers of mucosal eosinophils are seen in biopsy specimens that also display other changes. Some specimens, however, exhibit indisputably increased numbers of eosinophils in the lamina propria with remarkably few, if any, other histologic alterations. In such cases, a diagnosis of marked mucosal eosinophilia versus eosinophilic gastritis, for example, might be used. Conversely, in general, mildly increased numbers of mucosal eosinophils are found in biopsy specimens that show few, if any, other remarkable changes. Eosinophil density, however, is not the only indicator of eosinophilic inflammation, and on occasion, although only mildly increased numbers of eosinophils are present, eosinophilic cryptitis/glandulitis or eosinophilic crypt or gland abscesses are found. The term *eosinophilic gastritis* or *eosinophilic enteritis*, therefore, is preferred as the diagnosis, even though the overall amount of eosinophilic inflammation is not remarkable. A relatively small amount of eosinophilic inflammation can be damaging because of the potent cytotoxins released by eosinophils.^{1,2} Assessing eosinophil activation may not be as

Box 1
Histologic features of eosinophilic gastrointestinal disease
<i>Mucosal eosinophilia</i>
At all sites: increased numbers of eosinophils without any other pathology
<i>Eosinophilic esophagitis</i>
Increased numbers of intraepithelial eosinophils (peak count >15/HPF)
Degranulated eosinophils
Eosinophil microabscesses
Eosinophil surface layering
Marked basal layer hyperplasia
Elongated papillae
Lamina propria eosinophilia and fibrosis
<i>Eosinophilic gastroenteritis/colitis</i>
Increased number of mucosal eosinophils
Degranulated eosinophils
Intraepithelial eosinophils (surface and gland/crypt epithelium)
Eosinophil gland/crypt abscesses
Epithelial degenerative and regenerative changes
Foveolar/crypt hyperplasia
Villous atrophy in the small bowel
Minimal acute and chronic inflammation
Eosinophils in muscularis mucosa, submucosa, or both

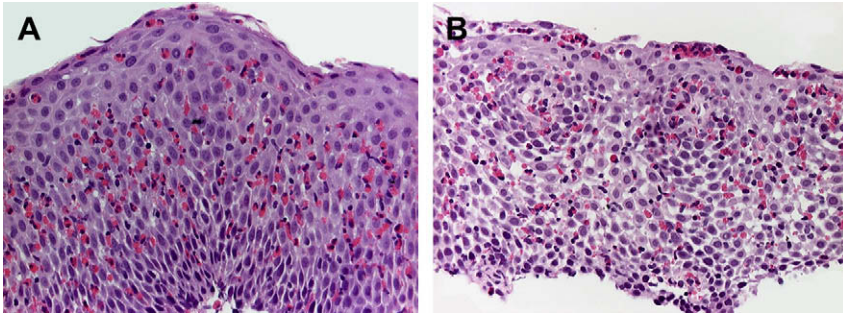


Fig. 2. Eosinophilic esophagitis. (A) Numerous intraepithelial eosinophils (peak count 123/HPF) and marked basal layer hyperplasia are seen. (B) Surface layering of eosinophils and spongiosis are present.

simple as finding extracellular granules, because trauma during tissue handling may cause eosinophil disruption.^{7,16}

This approach should assist the pathologist in distinguishing for the clinician biopsy samples showing histopathology that may be at the upper range of normal from those showing more definitive and conclusive evidence of tissue damage associated with eosinophilic inflammation. It is hoped that this distinction will avoid overdiagnosis and underdiagnosis of EGIDs. The optimum communication occurs not in a pathology report but when pathologist and clinician review biopsy specimens together and jointly form a clinicopathologic diagnosis.

DIFFERENTIAL DIAGNOSIS

Diseases associated with GIT eosinophilic inflammation include infection, food allergies, medication reaction, connective tissue disease and vasculitis, inflammatory fibroid polyps, hypereosinophilic syndrome, inflammatory bowel disease, organ transplantation, allergic granulomatosis, chronic granulomatous disease, neoplasms such as Langerhans cell histiocytosis, lymphoma, and others.^{4,5,17} When a specific cause for the eosinophilic inflammation cannot be identified, the disease is considered primary EGIDs. Examination of mucosal biopsy specimens may reveal infectious

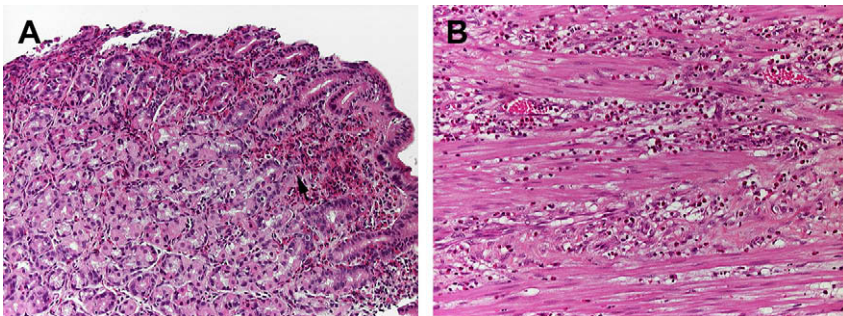


Fig. 3. Eosinophilic gastritis. (A) Extremely large numbers of eosinophils are seen mostly near the surface, with gland infiltration and destruction by eosinophils (eosinophilic glandulitis) (arrow). (B) Marked eosinophilic inflammation in the muscularis propria.

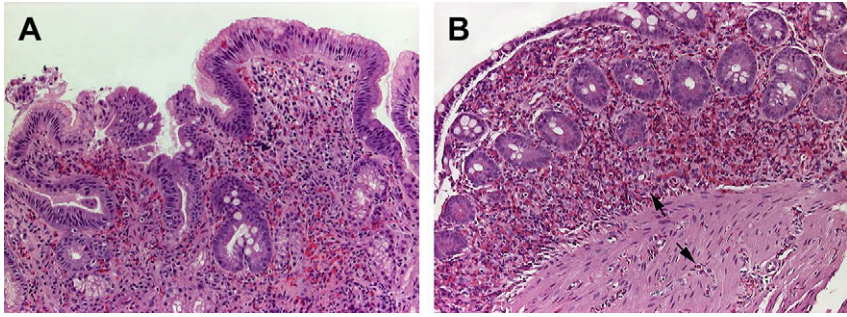


Fig. 4. Eosinophilic enteritis. (A) Duodenal bulb shows predominantly eosinophilic inflammation with marked architectural changes and reactive epithelial changes. This patient also had eosinophilic esophagitis. (B) Ileum intensely inflamed with eosinophils shows villous atrophy, crypt destruction (*upper arrow*), and numerous eosinophils in the muscularis mucosa (*lower arrow*).

organisms or vasculitis when the submucosa is included, but in most cases, the histopathology is nonspecific.

EOSINOPHILIC ESOPHAGITIS

The pathology of EE is the best characterized of the EGIDs, probably because there is universal agreement that, in contrast to other sites in the GI tract in which mucosal eosinophils are normally present, eosinophils are absent from or rarely found in normal esophageal epithelium (see [Fig. 2](#)). A recent consensus statement based on review of the EE literature¹⁸ recommended that at least 15 intraepithelial eosinophils per HPF are required to diagnose EE, and a higher peak number is appropriate for research. In most cases of EE, in addition to numerous intraepithelial eosinophils, esophageal epithelium is altered and the changes include basal layer hyperplasia, elongated papillae, eosinophil microabscesses, and eosinophil surface layering.¹⁹ Characteristically, the epithelial inflammation in EE involves the proximal and distal esophagus. The major differential diagnosis for EE is GERD. The histologic changes in GERD are usually confined to the distal esophagus, and the eosinophilic

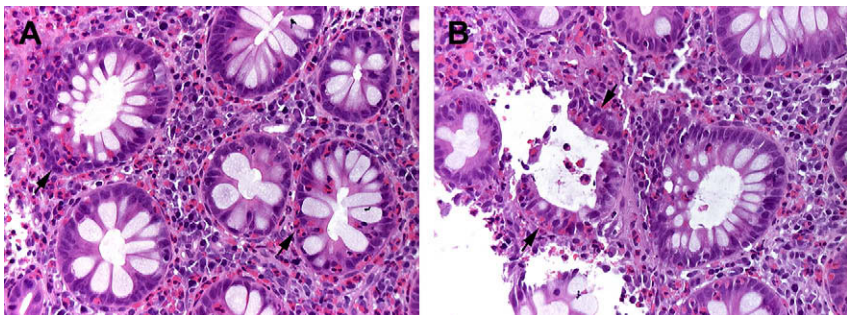


Fig. 5. Eosinophilic colitis. (A) Marked eosinophilic inflammation with numerous intraepithelial eosinophils creating eosinophilic cryptitis (*arrows*). (B) Eosinophilic cryptitis/crypt abscess (*arrows*). Pinworms were found in the biopsy samples in [Figs. 1](#) and [5](#) taken during colonoscopy.

inflammation, if present, is generally much less than in EE. Several studies, however, document that the histology of GERD may be indistinguishable from EE.^{20,21} Primary EE is a clinicopathologic diagnosis that requires characteristic histology in addition to the proper clinical setting; histopathology or clinical data alone are not sufficient for diagnosis. Infection with parasites such as *Gnathostoma spinigerum*²² and *Anisakis simplex*²³ has been implicated as a cause of EE.

EOSINOPHILIC GASTRITIS

A peak count of 8 eosinophils per HPF in antral gastric mucosa and 11/HPF in fundic gastric mucosa is normal in pediatric gastric biopsy specimens.⁷ Increased numbers of eosinophils in the lamina propria; numerous eosinophils in the surface epithelium, gland epithelium, or both; in the lumen of glands, muscularis mucosa, and submucosa; and reactive and regenerative epithelial and gland architectural changes including gland distortion and dropout are all features of eosinophilic gastritis^{5,24} (see **Fig. 3**). The pathologic changes may be patchy, and numerous biopsies may be necessary to identify the changes. In cases in which the mucosa is not inflamed, the diagnosis must be made by transmural biopsies or resections. Numerous eosinophils may be found in the muscularis propria or subserosa in those cases. Strictures and gastric outlet obstruction may occur with muscularis propria inflammation. Infection with the parasite *Eustoma rotundatum*²⁵ or with cytomegalovirus^{12,26} has been associated with eosinophilic gastritis/EG. Few reports associate infection with *Helicobacter pylori* with gastric mucosal eosinophilia.²⁷

EOSINOPHILIC ENTERITIS (EOSINOPHILIC DUODENITIS, EOSINOPHILIC JEJUNITIS, EOSINOPHILIC ILEITIS)

The peak number of eosinophils per HPF in normal pediatric mucosal biopsy specimens was reported as 26/HPF for duodenum and 28/HPF for ileum in one study⁷ and 52/HPF for duodenum and 68/HPF for ileum in another study.⁶ Changes characteristic of eosinophilic enteritis include (in addition to numerous eosinophils) crypt hyperplastic villous atrophy and epithelial cell necrosis (see **Fig. 4**). When submucosa is present, edema is commonly seen. Eosinophilic inflammation may be seen in muscularis mucosa, muscularis propria, and subserosa.^{5,24}

EOSINOPHILIC COLITIS

Pathologists and clinicians must realize that although studies of normal biopsy tissue are scant, several studies of normal tissue from adults and children have documented that eosinophil density is greater in the right colon compared with the left colon^{6,7,9} and that intraepithelial eosinophils may be more common in tissue from the right colon compared with the left colon in adults.⁹ Therefore, biopsy samples from more than one site in the colon should be submitted separately and clearly marked according to site of origin. Increased numbers of mucosal eosinophils may be an early nonspecific finding of inflammatory bowel disease.⁵ Eosinophilic colitis is characterized by increased numbers of eosinophils and other abnormalities, including crypt architectural changes, Paneth cell metaplasia in the distal colon, basal lymphoid aggregates and diffuse plasmacytosis, and eosinophils in the muscularis mucosa (see **Fig. 5**). Allergic proctocolitis is characterized by increased numbers of eosinophils in the lamina propria, surface and crypt epithelium, and muscularis mucosa, without significant architectural changes.²⁸ The lack of chronic changes may be a function of patient age because most affected patients are young.

SUMMARY

EGIDs have multiple possible etiologies. The histopathology in mucosal biopsy tissue is often characteristic but does not usually identify a specific etiology. More studies of normal biopsy tissue and tissue from patients who are known or suspected to have EGIDs, with clinicopathologic correlations, are required to more fully define the spectrum of histopathology in EGIDs.

REFERENCES

1. Rothenberg ME, Mishra A, Brandt EB, et al. Gastrointestinal eosinophils in health and disease. *Adv Immunol* 2001;78:291–328.
2. Zuo L, Rothenberg ME. Gastrointestinal eosinophilia. *Immunol Allergy Clin North Am* 2007;27:443–55.
3. Klein NC, Hargrove RL, Sleisenger MH, et al. Eosinophilic gastroenteritis. *Medicine* 1970;49:299–319.
4. Khan S, Orenstein SR. Eosinophilic gastroenteritis. *Gastroenterol Clin North Am* 2008;37:333–48.
5. Noffsinger A, Fenoglio-Preiser CM, Maru D, et al. Gastrintestinal diseases. An atlas of nontumor pathology. Washington, DC: American Registry of Pathology; 2007. Fascicle 5.
6. Lowichik A, Weinberg AG. A quantitative evaluation of mucosal eosinophils in the pediatric gastrointestinal tract. *Mod Pathol* 1996;9(2):110–4.
7. DeBrosse CW, Case JW, Putnam PE, et al. Quantity and distribution of eosinophils in the gastrointestinal tract of children. *Pediatr Dev Pathol* 2006;9(3):210–8.
8. Pacal RR, Gramlich TL, Parker KM, et al. Geographic variations in eosinophil concentration in normal colonic mucosa. *Mod Pathol* 1997;10(4):363–5.
9. Polydorides AD, Banner BF, Hannaway PJ, et al. Evaluation of site-specific and seasonal variation in colonic mucosal eosinophils. *Hum Pathol* 2008;39:832–6.
10. Lee CM, Changchien CS, Chen PC, et al. Eosinophilic gastroenteritis: 10 years experience. *Am J Gastroenterol* 1993;88:70–4.
11. Talley NJ, Shorter RG, Phillips SF, et al. Eosinophilic gastroenteritis: a clinicopathological study of patients with disease of the mucosa, muscle layer, and subserosal tissue. *Gut* 1990;31:54–8.
12. Whittington PF, Whittington GL. Eosinophilic gastroenteropathy in children. *J Pediatr Gastroenterol Nutr* 1988;7:379–85.
13. Chen M-J, Cheng-Hsin C, Shee-Chan L, et al. Eosinophilic gastroenteritis: clinical experience with 15 patients. *World J Gastroenterol* 2003;9(12):2813–6.
14. Winter HS, Antonioli DA, Fukagawa N, et al. Allergy-related proctocolitis in infants: diagnostic usefulness of rectal biopsy. *Mod Pathol* 1990;3:5–10.
15. 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.
16. Kato M, Kephart GM, Talley NJ, et al. Eosinophil infiltration and degranulation in normal human tissue. *Anat Rec* 1998;252:418–25.
17. Talley NJ. Gut eosinophilia in food allergy and systemic and autoimmune diseases. *Gastroenterol Clin North Am* 2008;37:307–32.
18. Furuta GT, Liacouris CA, Collins MH, et al. Eosinophilic esophagitis in children and adults: a systematic review and consensus recommendations for diagnosis and treatment. *Gastroenterology* 2007;133:1342–63.
19. Walsh SV, Antonioli DA, Goldman H, et al. Allergic esophagitis in children. *Am J Surg Pathol* 1999;23:390–6.

20. Ngo P, Furuta GT, Antonioli DA, et al. Eosinophils in the esophagus—peptic or allergic eosinophilic esophagitis? Case series of three patients with esophageal eosinophilia. *Am J Gastroenterol* 2006;101:1666–70.
21. Rodrigo S, Abboud G, Oh D, et al. High intraepithelial eosinophil counts in esophageal squamous epithelium are not specific for eosinophilic esophagitis in adults. *Am J Gastroenterol* 2008;103:435–42.
22. Muller-Stover I, Richter J, Haussinger D. Infection with *Gnathostoma spinigerum* as a cause of eosinophilic oesophagitis. *Deutsche Medizinische Wochenschrift* 2004;129:1973–5 [in German with English abstract].
23. Bircher AJ, Gysi B, Zenklusen HR, et al. Eosinophilic esophagitis associated with recurrent urticaria: is the worm *Anisakis simplex* involved? *Schweizerische Medizinische Wochenschrift. Journal Suisse de Medecine* 2000;130:1814–9 [in German with English abstract].
24. Fenoglio-Preiser CM, Noffsinger AE, Stemmermann GN, et al. *Gastrointestinal pathology. An atlas and text*. 3rd edition. Philadelphia: Lippincott Williams & Wilkins; 2008.
25. Johnstone JM, Morson BC. Eosinophilic gastroenteritis. *Histopathology* 1978;2:335–48.
26. Takeyama J, Abukawa D, Miura K. Eosinophilic gastroenteritis with cytomegalovirus infection in an immunocompetent child. *World J Gastroenterol* 2007;14:4653–4.
27. Papadopoulos AA, Tzathas C, Polymeros D, et al. Symptomatic eosinophilic gastritis cured with *Helicobacter pylori* eradication. *Gut* 2005;54:1822 [Letter].
28. Odze RD, Bines J, Leichtner AM, et al. Allergic proctocolitis in infants: a prospective clinicopathology biopsy study. *Hum Pathol* 1993;24:668–74.