

Eosinophilic Enteritis with Systemic Lupus Erythematosus

Prashanth R. Sunkureddi, MD, Nguyen Luu, MD, Shu-Yuan Xiao, MD, Wendell W. Tang, MD, and Bruce A. Baethge, MD

Abstract: Gastrointestinal manifestations are common in systemic lupus erythematosus (SLE). Eosinophilic enteritis is a rare disorder of uncertain cause that was recently reported for the first time in association with SLE. This report presents a second case of eosinophilic enteritis in a 47-year-old female patient with SLE. The patient presented with recurrent episodes of abdominal pain, nausea, vomiting, and diarrhea. Complete blood counts on occasion showed elevated eosinophil counts. The patient underwent a comprehensive workup over several weeks, culminating in a small bowel biopsy that showed eosinophil infiltration in the muscularis propria, establishing the diagnosis. The patient was treated with a prolonged taper of prednisone with successful resolution of symptoms.

Key Words: eosinophilic enteritis, systemic lupus erythematosus, peripheral eosinophilia

Primary eosinophilic gastroenteritis (PEG) is an uncommon disorder of unknown cause, characterized by abdominal symptoms of pain, vomiting, and diarrhea as the result of eosinophilic infiltration of the gastrointestinal tract. For a diagnosis of PEG, secondary causes such as parasitic infections and other diseases must be excluded (Table). Gastrointestinal symptoms in systemic lupus erythematosus (SLE) are common, and gastrointestinal manifestations directly attributable to lupus have been reported in 1 to 28% of patients.¹ Disease findings involving the small intestine in SLE include primary vasculitis, bowel infarction, protein-losing enteropathy, intestinal pseudo-obstruction,² fat malabsorption, and infectious diarrhea. The association of PEG with SLE has been reported only once.³ We describe the case of a patient having both conditions, which, to our knowledge, is only the second reported incidence of this unusual finding.

From the Division of Rheumatology, the Department of Internal Medicine, and the Department of Pathology, University of Texas Medical Branch, Galveston, TX. Email: prsunkur@utmb.edu

Reprint requests to Dr. Bruce A. Baethge, UTMB, 301 University Boulevard, Galveston, TX 77551-1165.

Accepted May 10, 2005.

Copyright © 2005 by The Southern Medical Association

0038-4348/0-2000/9800-1049

Case Report

The patient is a 47-year-old female with SLE initially diagnosed in 1993 with manifestations of arthritis, malar rash, lymphopenia, antinuclear and antismooth muscle antibodies. Her SLE had been well controlled with 200 mg hydroxychloroquine twice each day and 5 to 10 mg prednisone taken daily for years. She initially presented to our hospital in August 2004 with complaints of abdominal pain, nausea, vomiting, and diarrhea. She described intermittent episodes of similar symptoms occurring sporadically and resolving in 3 to 4 days for a few weeks before admission. She had no history of exposure to diarrheal illness or parasites and no history of foreign travel. The intensity and duration of symptoms worsened with each episode until she was hospitalized for further workup and treatment. On initial examination by the rheumatology service, the patient was a mildly obese woman in some distress due to abdominal discomfort. The vital signs were unremarkable. She had no evidence of active SLE with normal findings on cardiopulmonary, joint, and skin examination. The initial

(continued next page)

Key Points

- Eosinophilic enteritis is a rare disorder of unknown cause characterized by general abdominal symptoms of pain, nausea, vomiting, and diarrhea.
- This report describes a case of eosinophilic enteritis in association with systemic lupus erythematosus.
- Peripheral eosinophilia is often present but is not necessary for the diagnosis.
- The diagnosis is made by intestinal biopsy and the demonstration of eosinophils in the intestinal layers.
- Gastrointestinal complications are common in systemic lupus erythematosus, and workup should include consideration of eosinophilic enteritis.

(Case Report continued from previous page)

abdominal examination revealed a diffusely tender abdomen with no involuntary guarding or rebound tenderness. Rectal examination was unremarkable, with a negative test for occult blood in stool.

Laboratory tests showed an erythrocyte sedimentation rate (Westergren method) of 16 mm/h (normal, 0 to 20), and a C-reactive protein level of 0.4 mg/dL (normal, 0 to 0.8). Serum complete blood count showed an absolute lymphocyte count of 1,100/mm³ (normal, 1,300 to 4,400). C3 complement was 50 mg/dL (normal, 86 to 154) and C4 complement was 5.2 mg/dL (normal, 20 to 59). Basic metabolic profile was significant for a serum potassium level of 2.5 mmol/L. Liver enzyme tests and urinalyses were within normal limits. Anti-dsDNA antibodies were not detected. She was given an increased dose of prednisone, and her symptoms seemed to improve. Despite improvement with steroids, there was disagreement among consultants as to the cause of her symptoms.

Gastrointestinal symptoms recurred and waxed and waned in severity over many months. She had a weight loss of 20 pounds during this time. She ultimately had an extensive inpatient and outpatient evaluation. Multiple stool tests for fecal leukocytes, ova and parasites, occult blood, *Clostridium difficile* toxin, and stool cultures were negative. Complete blood counts revealed elevated eosinophil counts of 500 to 700/cmm (normal, 0 to 400). Abdominal radiographs were normal. CT imaging of the abdomen was performed more than once with inconsistent findings. The initial CT of the abdomen revealed

diffusely thickened and edematous loops of small bowel involving most of the ileum. A subsequent CT of the abdomen showed resolution of the small bowel thickening but showed circumferential thickening of the colon wall from the mid transverse colon through the rectum. A third CT of the abdomen showed thickening of both the small and large bowels. During one admission, the patient underwent an esophagogastroduodenoscopy and colonoscopy with biopsy specimens that showed no pathologic findings. A gastric emptying study showed delayed gastric emptying. A magnetic resonance angiogram of the abdominal vessels showed normal large vessels, but the small vessels could not be properly evaluated with this technique. The patient eventually underwent an exploratory laparoscopy with an excisional biopsy of the small bowel that showed significant infiltration of the muscularis propria by eosinophils accompanied by degenerative changes of the smooth muscle. Neither thrombosis nor vasculitis were identified. (Figure) The diagnosis of primary eosinophilic gastroenteritis (muscularis subtype) was made on the basis of clinical, laboratory, and histopathologic findings. The patient was started on 40 mg prednisone daily, and the dose was tapered over a few weeks. Eight weeks later, the patient reported no symptoms and was stable, taking 5 mg prednisone daily. The serum eosinophil count at follow-up was 200/cmm. Hydroxychloroquine was continued because of its benefit as a long-term maintenance drug for systemic lupus erythematosus.⁴

Discussion

Primary eosinophilic enteritis is a rare disorder of unknown cause that affects the gastrointestinal tract. Diagnosis must be made in the absence of known causes of eosinophilia such as malignancy, drug reactions, and other secondary causes (Table).⁵ It is considered to be part of the spectrum of eosinophilic gastrointestinal inflammatory disorders that include eosinophilic esophagitis, gastroenteritis, and colitis.

Primary eosinophilic gastroenteritis is subdivided into the atopic, nonatopic, and familial variants. Histologically, three subtypes have been classified on the basis of tissue involvement and include mucosal, muscularis, and serosal forms.⁵ The typical symptoms include abdominal pain, nausea, vomiting, and diarrhea. Peripheral eosinophilia is seen less than 50% of the time.⁵ The mucosal form is the most common variant and is characterized by severe abdominal symptoms that may be associated with iron-deficiency anemia, malabsorption, protein-losing enteropathy, and failure to thrive. The muscularis form usually shows infiltration of the muscularis layer, which can lead to thickening of the bowel

wall. The serosal form is the least common variant and may be associated with eosinophilic ascites and peripheral eosinophilia.⁶ Eosinophilic gastroenteritis has also been associated with hypereosinophilic syndrome, which is characterized by peripheral eosinophilia of at least 1,500 cells/mm² and infiltration of organs such as lung, liver, skin, and gastrointestinal tract that occur in the absence of known causes of eosinophilia such as parasites.

The first case of eosinophilic gastroenteritis associated with systemic lupus erythematosus was recently reported in a patient with idiopathic thrombocytopenic purpura, who was simultaneously diagnosed with eosinophilic gastroenteritis and SLE.³ An association with other connective diseases including scleroderma and idiopathic inflammatory myopathy has been reported.^{7,8} The incidence of primary eosinophilic gastroenteritis is unknown, but eosinophilic gastrointestinal disorders have been reported with increasing frequency, especially in children.⁹ The cause of these disorders is not well understood, but allergic mechanisms have been implicated in some patients, although supporting evidence is not present in all.

Eosinophils are normal constituents of the gastrointestinal tract. They are mainly found in the lamina propria and have a primary role in host defense against helminthic parasites. However, eosinophilic infiltration of the deeper layers is only seen in the eosinophilic gastrointestinal disorders, both primary and secondary.¹⁰ The expansion and tissue distribution of eosinophils is primarily regulated by IL-5 and eotaxin 1, among other cytokines. Eosinophils also contain granules that are composed of toxic cationic proteins such as major basic protein and eosinophil cationic protein. These cytokines, along with extracellular deposition of eosinophil granule constituents, have been demonstrated in patients with eosinophilic gastroenteritis.^{6,11} However, the triggering events for this inflammatory cascade are not fully understood.

The diagnosis of eosinophilic gastroenteritis is often difficult. Symptoms are nonspecific, and peripheral eosinophilia is often not present. Endoscopic appearance of the gastrointestinal tract is often normal. As a result, the diagnosis is often delayed, as in our patient. One study reported a mean of 4 years of symptoms before the diagnosis was established.¹² Findings that support the diagnosis of PEG include (1) the presence of increased numbers of eosinophils in biopsy specimens with infiltration of the eosinophils into abnormal regions such as the intraepithelial, superficial mucosal, and intestinal crypt regions; (2) the presence of extracellular eosinophilic staining constituents; (3) the lack of involvement of other organs; and (4) the exclusion of other causes of eosinophilia. Food allergy and peripheral eosinophilia are not required for the diagnosis.⁵

Treatment of primary eosinophilic gastroenteritis depends on the subtype. In the allergic subtype, dietary modification, including elimination of foods implicated by skin prick testing or RAST, and institution of amino acid-based elemental diets might be beneficial in some patients.¹³ Cor-

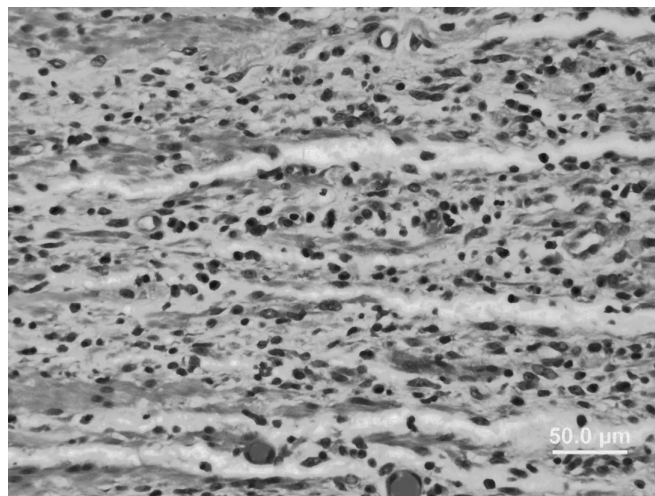


Fig. Infiltration of muscularis propria by eosinophils accompanied by degenerative changes. Hematoxylin and eosin stain.

ticosteroids are often effective in patients refractory to dietary changes. Although there are no clear guidelines regarding dosage, prednisone (20 to 40 mg/d), followed by a 2- to 3-month taper, has been reported to have rapid symptom resolution in 90% of patients.¹⁴ Mast cells have been found in increased levels in patients with eosinophilic gastroenteritis. As a result, mast cell stabilizers such as cromolyn and ketotifen have been used with mixed results. Montelukast has also been used with mixed results. New drugs such as anti-IL-5 mepolizumab and the tyrosine kinase inhibitor imatinib have shown promise for use in eosinophilic gastrointestinal disorders.⁵

This is the second known case of eosinophilic gastroenteritis associated with SLE reported in the literature. It is impossible to tell if there is a pathologic relation between PEG and SLE, based on these two cases. This case also illustrates the point that gastrointestinal symptoms in patients with SLE should not be attributed to lupus-related pathology without a workup that excludes other unrelated gastrointestinal disease.

References

- Hallegua D, Wallace D. Gastrointestinal manifestations of systemic lupus erythematosus. *Curr Opin Rheumatol* 2000;12:379–385.
- Nguyen H, Khanna N. Intestinal pseudo-obstruction as a presenting manifestation of systemic lupus erythematosus: case report and review of the literature. *South Med J* 2004;97:186–189.
- Barbie DA, Mangi AA, Lauwers GY. Eosinophilic gastroenteritis associated with systemic lupus erythematosus. *J Clin Gastroenterol* 2004;38:883–886.
- Petri MA. Systemic lupus erythematosus: New management strategies. *J Musculoskel Med* 2005;22:108–116.
- Rothenberg ME. Eosinophilic gastrointestinal disorders. *J Allergy Clin Immunol* 2004;113:11–28.
- Talley NJ, Shorter RG, Phillips SF, et al. Eosinophilic gastroenteritis: A

Table. Classification of eosinophil-associated gastroenteritis⁵

Primary (mucosa, muscularis, serosal forms)

Atopic

Nonatopic

Familial

Secondary

Eosinophilic disorders

Hypereosinophilic syndrome

Noneosinophilic disorders

Celiac disease

Connective tissue disease

Iatrogenic

Infection

Inflammatory bowel disease

Vasculitis (Churg-Strauss)

- clinicopathological study of patients with disease of the mucosa, muscle layer and subserosal tissues. *Gut* 1990;31:54–58.
7. DeSchryver-Kecskemeti K, Clouse RE. A previously unrecognized subgroup of 'eosinophilic gastroenteritis': Association with connective tissue diseases. *Am J Surg Pathol* 1984;8:171–180.
 8. Buchman AL, Wolf D, Gramlich T. Eosinophilic gastrojejunitis associated with connective tissue disease. *South Med J* 1996;89:327–330.
 9. Bates B. 'Explosion' of eosinophilic esophagitis in children. *Pediatr News* 2000;34:4
 10. Rothenberg ME, Mishra A, Brandt EB, et al. Gastrointestinal eosinophils. *Immunol Rev* 2001;179:139–155.
 11. Talley NJ, Kephart GM, McGovern TW, et al. Deposition of eosinophil granule major basic protein in eosinophilic gastroenteritis and celiac disease. *Gastroenterology* 1992;103:137–145.
 12. Guajardo JR, Plotnick LM, Fende JM, et al. Eosinophil-associated gastrointestinal disorders: a world-wide-web based registry. *J Pediatr* 2002; 141:576–581.
 13. Justinich C, Katz A, Gurbindo C, et al. Elemental diet improves steroid-dependent eosinophilic gastroenteritis and reverses growth failure. *J Pediatr Gastroenterol Nutr* 1996;23:81–85.
 14. Fenoglio LM, Benedetti V, Rossi CM, et al. Eosinophilic gastroenteritis with ascites: A case report and review of the literature. *Dig Dis Sci* 2003;48:1013–1020.

When we remember we are all mad, the mysteries disappear and life stands explained.

—Mark Twain