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The Metamorphosis of a Horse into a Zebra: A Case of Primary Eosinophilic Gastroenteritis

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Chronic diarrhea is a common diagnostic entity faced by many primary care physicians. Primary eosinophilic gastroenteritis (PEG), a relatively rare but not uncommon cause of chronic nonbloody diarrhea, presents with nonspecific symptoms, making clinical consideration and diagnosis extremely challenging. In PEG, eosinophils selectively target the gastrointestinal tract, where they degranulate, causing inflammation and irritation. We report the case of a 46-year-old female with recurrent hospitalizations for nausea, vomiting, and diarrhea over a nine-month period. After an extensive workup ruling out secondary causes of eosinophilia, she was diagnosed with PEG.

INTRODUCTION

Chronic diarrhea is a common diagnostic dilemma faced by many internists. First reported by R. Kaijser in 1937, primary eosinophilic gastroenteritis (PEG) is associated with eosinophilic infiltration and degranulation in the digestive tract (DT). Presentation is often nonspecific but commonly depends on the depth of eosinophilic infiltration in the DT. While diagnosis is based on clinical symptoms and a biopsy specimen, peripheral eosinophilia is commonly absent. Herein, we describe a patient with multiple hospital admissions for diarrhea, who was ultimately diagnosed with PEG.

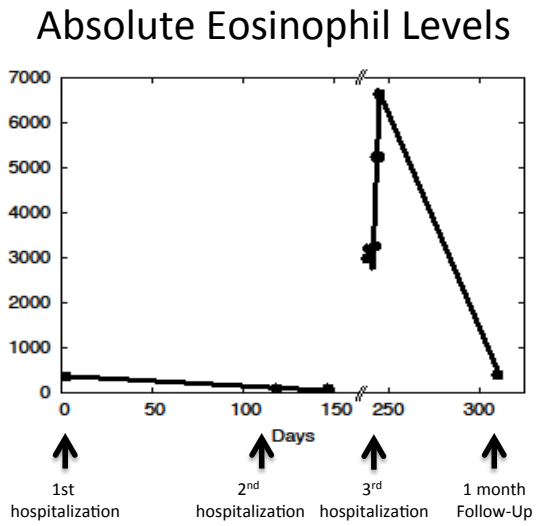
CASE PRESENTATION

We report the case of a 46-year-old female with no past medical history who presented with recurrent hospitalizations for relapsing remitting abdominal pain and diarrhea over nine months. On two prior hospitalizations, no fever or eosinophilia was reported, and she received metronidazole with a working diagnosis of bacterial gastroenteritis (Figure 1A). Five days prior to admission, she had developed cramping epigastric pains and five to 10 episodes of foul-smelling, yellow, nonbloody, watery, mucousy diarrhea. Upon her arrival in the emergency room, her vital signs were within normal limits. A physical exam revealed hyperactive bowel sounds and mild tenderness throughout the abdomen. A rectal examination revealed light-brown guaiac-negative stool. She had an elevated white blood cell count (14,200) with a differential showing elevated eosinophils (25%, 2,820; Figure 1A). IgE levels were elevated (2130/ul; n = < 180/ul). An abdominal computed tomography scan was unremarkable. Infectious labs, including *Clostridium difficile* toxin and stool for ova and parasites x3, were negative. Further evaluation revealed a normal ANA panel, thyroid function tests, folate and vitamin B_{12} levels, and fecal fat and electrolytes. A duodenal biopsy specimen demonstrated chronic enteritis with villous shortening, crypt hyperplasia, regeneration, and increased stromal mononuclear (eosinophil) inflammation and infiltration (Figure 1B). She was diagnosed with PEG. While hospitalized, the patient was advised to adhere to an elemental diet. Her symptoms improved within one week without medication and she was followed up closely as an outpatient. At her one-month follow-up, she reported decreased pruritus, drowsiness, and frequency of diarrhea. She was able slowly to advance her diet. Her IgE and eosinophil levels began to trend down (983 and 600/ul respectively; Figure 1A) without therapeutic intervention. Continuous monitoring was initiated in the clinic to screen for a relapse of symptoms.

DISCUSSION

Pathogenesis

Eosinophils are created in the bone marrow and, following exposure to growth factors, mature and relocate throughout the body. They can be found at different levels throughout the gastrointestinal system (e.g., 0/high power field [hpf] in the esophagus and up to 68/hpf in the appendix) and play a protective role, especially in fighting parasitic infections (DeBrosse, Case, Putnam, Collins, & Rothenberg, 2006; Khan & Orenstein, 2008). Eosinophils are activated by the TH2 cellular pathway through proinflammatory stimulant cytokines such as IL-4, IL-5, and TGF-ß (Khan & Orenstein, 2008). Studies have shown an increased production of TH2-associated cytokines (IL-41 and IL-5) in PEG (Jaffe et al., 1994). The precise trigger for increased tissue eosinophilia in PEG remains elusive. Recent evidence points to an interplay between genetic and environmental factors. For example, a positive family history is present in up to 10% of patients with PEG (Guajardo et al., 2002). Alternatively, the observation of a high correlation between PEG and atopy and food allergies may indicate an environmental trigger. This is further supported by multiple observations that PEG can be ameliorated or even reversed with a change to an elimination or elemental diet (Khan & Orenstein, 2008; Méndez-Sánchez, Chávez-Tapia, Vazquez-Elizondo, & Uribe, 2007; Zuo & Rothenberg, 2007).



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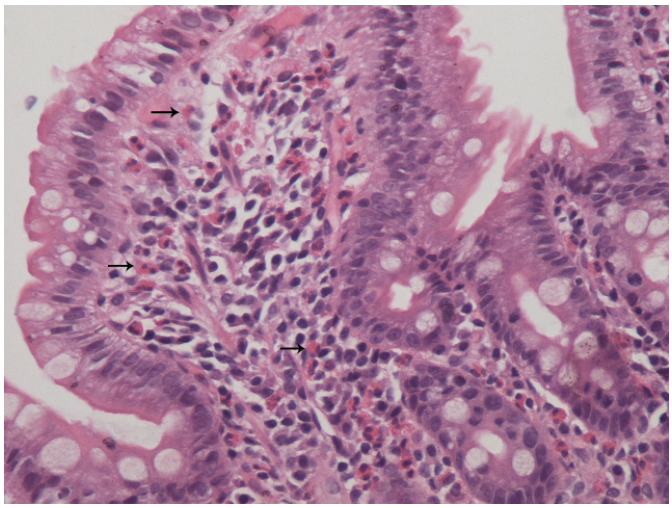

B

Figure 1 | Eosinophil Levels and Intestinal Biopsy. (A) Absolute eosinophil levels on two previous hospitalizations and current admission (third hospitalization), as well as at one month post current admission. (B) Photomicrograph of small intestine biopsy showing increased eosinophils (arrows) and chronic inflammatory cells in the lamina propria with villous architecture preservation and no intraepithelial inflammation (making celiac disease, autoimmune mediated injury, or infections unlikely).

Presentation

PEG has been dubbed a "great imitator" due to its variable and nonspecific symptoms, making clinical consideration and diagnosis extremely challenging. Common symptoms include abdominal pain (most common, in up to 75% of patients), nausea, vomiting, diarrhea, and anorexia (Méndez-Sánchez et al., 2007; Talley, Shorter, Phillips, & Zinsmeister, 1990). Some have reported PEG presenting similar to intussusceptions (Huang, Ko, Huang, & Lee, 2001), pyloric stenosis (Khan & Orenstein, 2000), appendicitis (Tran, Salloum, Tshibaka, & Moser, 2000), pancreatitis (Le Connie & Nguyen, 2004), and ascites (Khalil & Granieri, 2003).

Level of eosinophilic infiltration is strongly associated with presenting symptoms. Mucosal predominant pathology commonly presents with a protein-losing enteropathy, malabsorption, nausea, vomiting, and diarrhea (Mason & Andablo, 2003). Alternatively, muscularis-predominant infiltration presents with intestinal obstruction (Khan and Orenstein, 2008), while serosal-predominant infiltration presents with ascites (Khalil & Granieri, 2003). Mucosal involvement is most common (up to 100%), with serosal involvement least common (up to 40%); however, these findings may be due to the ease of obtaining mucosal tissue on routine endoscopic biopsy as compared to serosal tissue, which necessitates a full thickness biopsy (Khan & Orenstein, 2008; Talley et al., 1990).

Diagnosis

Diagnosis of PEG is based on gastrointestinal symptoms, exclusion of any known causes of eosinophilia in the DT (e.g., neoplasm, drug interactions, parasitic infection), and a positive biopsy sample. Peripheral eosinophilia is commonly absent (>50% of the time [Sleisenger & Fordtran, 1993]), and not necessary in the diagnosis of PEG. Furthermore, degree of peripheral eosinophilia, if present, has not been correlated with severity of eosinophilic infiltration in the intestinal system (Huang et al., 2001). The sensitivity of endoscopic biopsies may be low due to the variety of permeating patterns (patchy vs. continuous) and layers of infiltration (Simon, Wardlaw, & Rothenberg, 2010). Endoscopically, macroscopic signs of mucosal inflammation are uncommon, but may include ulcerations and friability. Microscopically, histopathologic evidence consists of analysis of eosinophil density, degranulation, and absence of other disease features. Diagnosis of muscular or serosal involvement requires an open biopsy via laparotomy or laparoscopy.

Treatment

To date, there are no random controlled trials or definitive treatments for PEG. Diet modification to an allergen-free or gluten-free diet has been reported as helpful in ameliorating or even reversing symptoms as well as reducing the need for medical therapy (Méndez-Sánchez et al., 2007). Glucocorticoids have been the standard medication for management of those who fail diet alteration. Acceptable responses have been reported using prednisone (20–40 mg) for four to eight weeks (Khan & Orenstein, 2008; Vara-Thorbeck, Toscano-Mendez, & Osorio, 1997). Overall, experience has demonstrated varying responses from complete remission to a chronically relapsing pattern (Khan &

Orenstein, 2008; Lee et al., 1993). Therefore, due to the side effects of long-term steroid therapy, many attempts have been made to find more-targeted immunotherapy. For example, small trials have demonstrated successful outcomes using immunomodulators such as Montelukast, Suplatast, and Omalizumab (Foroughi et al., 2007; Quack et al., 2005; Shirai et al., 2001; Stein et al., 2006).

CONCLUSION

PEG is a rare but not uncommon disease that should be considered in the differential diagnosis for chronic relapsing nonenterohemorrhagic diarrhea. This case highlights the need for a heightened degree of clinical suspicion to diagnose PEG due to its varied presentations, and often normal laboratory values without peripheral eosinophilia. While our patient improved without medical therapy, a definitive diagnosis explained her chronic debilitating symptoms. This led to relief for both the patient and the physician, and allowed for close follow-up with a known focus. Increasing physicians' awareness of PEG may help those suffering from its debilitating symptoms.

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Conflict of Interest Disclosure
The authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. No conflicts were noted.

Author Contributions
All authors had access to the data and an equal role in writing the article.

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