Dig Dis Sci (2016) 61:2453–2455
DOI 10.1007/s10620-016-4240-0

EDITORIAL

Established and Emerging Eosinophilic Gastrointestinal Diseases (EGIDs): Seeing Red and Looking Ahead

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Published online: 6 July 2016

In patients with unexplained gastrointestinal (GI) symptoms, eosinophilic GI disease, including eosinophilic gastroenteritis (EG), can be missed unless actively considered [1, 2]. Eosinophils, as part of normal host defence, migrate from the bone marrow to the lamina propria of the GI tract [2]. In health, eosinophils populate the GI tract from the stomach to the colon, but not the esophagus, and are independent of commensal gut bacteria regulated by cytokines (most notably interleukin [IL]-5) and chemokines (particularly eotaxin-1) [2]. GI eosinophils contribute to defence against parasites and bacteria, stimulate cross talk with the enteric nervous system, and modulate T cell function [2].

Eosinophilic gastroenteritis (EG) although rare is a disease with which all gastroenterologists should be familiar as it is treatable and may be misdiagnosed, as pointed out in this issue of *Digestive Diseases and Sciences* by Alhmoud et al. [1]. A landmark Mayo Clinic study defined EG as the presence of GI symptoms and biopsy-proven abnormal eosinophilic infiltration in the absence of parasitic or extraintestinal disease that would otherwise account for the tissue eosinophilia; from 1950 to 1987, 40 cases were diagnosed (two not biopsy confirmed) [3]. Alhmoud et al. undertook a retrospective chart review over 11 years of all cases with GI tract eosinophilia excluding eosinophilic esophagitis (EoE). In a hospital serving a population of 900,000 people over this period, 13 definite EG cases were identified. There are three subtypes of EG defined by the affected zone: mucosa, muscularis, and serosa, that account for the symptomatic presentation, e.g., eosinophilic ascites with serosal disease. Mucosal disease was the most prevalent type in this series; a female predominance was noted in the adults, in contrast to the male predominance observed in EoE and in other EG series [2–4]. Chang et al. reported similar findings in a follow-up study from Mayo Clinic from 1987 to 2007, where of 59 cases with EG, 52 had mucosal disease [4]. Combined, these studies suggest that the number of reported cases of EG, especially mucosal disease, has increased, which may reflect better detection, a rising incidence, or both factors, although EG remains very rare despite its clinical importance.

As eosinophils are normal residents of the stomach and intestine, what defines an abnormal biopsy? Sheets of eosinophils infiltrating the mucosa, muscularis, or serosal layers of the GI tract should be recognized as abnormal by every pathologist [3, 4]. Since in the esophagus any eosinophil is abnormal, no confusion should exist. What then are the normal thresholds that separate normal from pathological for eosinophilic infiltration? In the esophagus, $\geq$15 eosinophils in a single high-power field (HPF) has been arbitrarily used to define EoE, although any esophageal eosinophilia may be abnormal and may not all be attributable to gastroesophageal reflux disease (GERD) [2, 5, 6]. An important population-based endoscopic study reported that esophageal eosinophils were present in nearly 5 % of the population, of which over 50 % did not have troublesome GERD symptoms; the prevalence of EoE, as expected, was much lower at 0.4 % [7]. The clinical relevance of low-grade eosinophilia in the esophagus remains to be determined. A differential diagnosis in EoE is EG, which can be missed if gastric and duodenal biopsies are not taken with the esophageal samples; if a patient with

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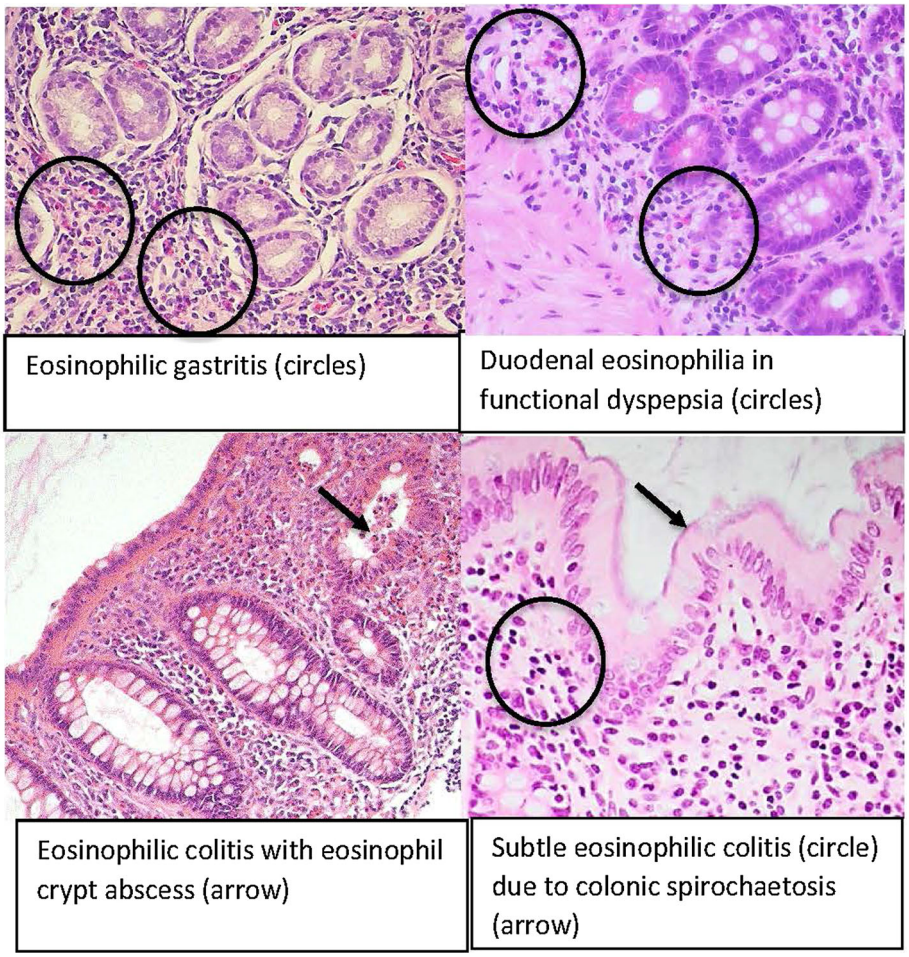

Fig. 1 Examples of histological eosinophilic GI diseases

EoE fails to respond to usual therapy, EG should be considered as a possibility [1].

In the stomach and the intestine, the threshold over which eosinophilic infiltration is considered to be pathological is not defined by compelling evidence. In an autopsy study, low-grade eosinophilic infiltration and degranulation in the gut was observed to occur in normal subjects although eosinophil counting (quantitative histology) was not performed [8]. In the present study by Alhmoud et al. [1], the limit applied was >25 eosinophils/HPF in the proximal GI tract and 50/HPF in the colon. A similar definition was applied in the more recent Mayo Clinic series with a median count of 82 eosinophils/HPF reported in EG but within a remarkably wide range of 4–300/HPF [4]. Hence, a clearly abnormal increase in eosinophils in the intestinal tract may not be detected by even an experienced GI pathologist who is just observing without explicitly counting eosinophils, a practice that may be required to routinely detect abnormality and diagnose some EG cases. If EG is clinically suspected, the data suggest that it is necessary to count a number of HPFs. At our institution, we routinely count 5 HPFs in order to not miss the diagnosis of EG. Another technical issue is that differences in the area of HPFs can be standardized between microscopes by converting the area of a HPF to mm^2. Figure 1 shows subtle differences in histological eosinophilic infiltration in the GI tract.

An endoscopic study of 1000 randomly selected subjects from a Scandinavian community (the Kalixanda study) has provided new insights into the clinical relevance of low-grade GI eosinophilia. The study was conducted in an unselected cohort of subjects with and without GI symptoms in whom other GI diseases were excluded or prospectively identified [9]. Australian investigators reported a case series of patients with functional dyspepsia (FD) in whom EG was established to be the correct diagnosis after further investigation [10]. This observation led the authors to ask if subtle tissue eosinophilia is related to FD pathogenesis, a hypothesis first explored in adults in the Kalixanda study. Compared with data from normal controls from the same population, a mean of ≥22 eosinophils counted in 5 HPF was considered abnormal in the duodenum, even though all of the biopsies would have been routinely read as "normal" (Fig. 1); if there were increased

eosinophils in the first portion of the duodenum, the odds that FD was present were 11-fold increased [9]. Further, the eosinophils displayed increased degranulation, with release of toxic major basic protein (MBP). These results, confirmed in numerous studies globally, have also suggested that a modest increase in duodenal eosinophil density, termed "duodenal eosinophilia" correlates with increased duodenal permeability (as measured by lower transepithelial electrical resistance and abnormal expression of cell-to-cell adhesion proteins) [9] and impaired submucosal neural structure (e.g., gliosis) and function (e.g., decreased neural calcium responses to depolarization) [11], supporting the hypothesis that eosinophils are associated with subtle foregut abnormalities in FD [12]. These striking observations have supported the hypothesis that mildly increased duodenal eosinophilia is related to the pathogenesis of FD, providing a novel testable hypothesis [12]. This work illustrates the added value of looking for links between clinical and subtle pathological observations that can provide clues to disease pathogenesis, helping to drive breakthroughs in fundamental research.

Although Alhmoud et al. [1] report eosinophilic colitis is even less common than proximal gut disease, the eosinophil is also important in the colon. Another new distinct colonic EGID has recently been described linked to chronic bacterial infection and the irritable bowel syndrome (IBS) [13]. In a Swedish population-based colonoscopy study, colonic spirochetes were histologically identified in 2 % of the population; those infected had a threefold increased risk of IBS. A unique pathology was described encompassing increased eosinophils (mean 30 eosinophils/mm^2 versus 9/mm^2 in controls in the sigmoid) and increased subepithelial eosinophil clusters [13]. The data suggest excess eosinophils in the colon should now prompt a search for the subtle "blue fringe" along the apical epithelial border from the bacteria that resembles a false brush border and can be confirmed to be spirochetes by a Warthin–Starry silver stain or by immunostaining.

In conclusion, exciting emerging evidence has identified EGIDs as clinically important. While EG can be missed, it is rare, but the new entity duodenal eosinophilia in FD is common and likely central to the pathogenesis of at least a subset of subjects with the disorder [11]. That more EGIDs are being identified in the twenty-first century likely reflects a true increasing incidence in addition to greater recognition, as has been observed with EoE [5, 6]. The new evidence presented by Alhmoud et al. [1] and elsewhere suggest that increased awareness and recognition of EGIDs in patients with unexplained GI symptoms should encourage pathologists to quantitate eosinophils in the GI tract more frequently, since only a few more than normal may herald disease, and may not actually be "normal."

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