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Eosinophils in the GI tract: How many is too many and what do they mean?

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Eosinophils are commonly detected in normal mucosal biopsies from all sites within the gastrointestinal tract where they are dispersed in the lamina propria and, to a lesser extent, in the epithelium. The distinction between the upper limit of normal and abnormally increased tissue eosinophils is not well defined. However, eosinophils that infiltrate the epithelium in more than occasional numbers, coalesce to form aggregates, or show extensive degranulation are always abnormal and raise a broad differential diagnosis. Although the differential diagnosis of purely eosinophilic inflammation is largely limited to hypersensitivity reactions and some infections, they are increased in several gastrointestinal conditions, including gastroesophageal reflux disease, autoimmune gastritis, infections, drug reactions, inflammatory bowel disease, radiation enteritis, and collagen vascular disease. These disorders feature eosinophils as one component of a mixed inflammatory infiltrate that can, in some instances, be prominent enough to cause diagnostic confusion. The purpose of this review is to discuss the normal distribution of eosinophils in the gastrointestinal tract and the differential diagnosis of inflammatory conditions that feature prominent eosinophilia.
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Introduction

Eosinophils are normally detected in many parts of the tubular gut where they may be quite numerous. They can be present in any inflammatory condition that persists for days to weeks, as well as chronic diseases that wax and wane over months to years. Indeed, patients who undergo appendectomy or cholecystectomy days after the onset of symptoms characteristically have large numbers of eosinophils in their appendices or gallbladders; an observation that has led to overuse, and misuse, of terms such as eosinophilic appendicitis and eosinophilic cholecystitis. Eosinophils are also increased, and may be prominent, in gastroesophageal reflux disease, autoimmune gastritis, infections, drug reactions, inflammatory bowel disease, collagen vascular disease, radiation enteritis, neoplasms, and a host of other disorders. Most of these entities show mixed, often neutrophil-rich, inflammation and other features that allow their distinction. However, striking eosinophilia occasionally masks the nature of underlying disease and raises the possibility of another diagnosis, such as eosinophilic gastroenteritis. The purpose of this review is to discuss the normal distribution of gastrointestinal eosinophils as well as the differential diagnosis of inflammatory conditions that feature prominent eosinophilia.

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Eosinophils in normal biopsies of the gastrointestinal tract

Eosinophils are readily detected throughout the tubular gut and can be numerous in some patients, making it difficult to distinguish between variants of normal and inflammatory conditions. One may encounter occasional eosinophils in distal esophageal biopsies obtained from healthy, asymptomatic patients, but this finding does not correlate with the presence of clinical symptoms or their response to acid suppressive therapy. Data regarding the minimal criteria for a histologic diagnosis of esophagitis are not established, although rare eosinophils in the distal esophagus are generally considered insufficient if other evidence of mucosal injury (eg, basal zone hyperplasia, elongated papillae, edema, balloon cells) is lacking. The normal gastric mucosa contains lymphocytes, occasional plasma cells, and scattered eosinophils. Lamina propria eosinophils number fewer than nine per high-power field and generally less than five per high-power field, and intraepithelial eosinophils are absent, or rare.[1] Eosinophils are more numerous in the intestinal lamina propria, where counts frequently range up to

20–30 eosinophils per high-power field and occasionally approach 50 eosinophils per high-power field.[2] Their numbers are greatest in mucosal biopsies of the proximal colon where scattered eosinophils may infiltrate the crypt epithelium. More than half of biopsies from the normal proximal colon show occasional eosinophils in crypt epithelium, whereas fewer than 5% of distal colonic biopsies from asymptomatic patients demonstrate this finding.[3] The number of eosinophils normally present in colonic biopsies also varies as a result of environmental influences. Some data suggest they are more numerous during peak allergy seasons and among individuals living in the southern United States compared to those of northeastern regions.[3,4] As in the small intestine, colonic eosinophils are considered to represent normal constituents of the mucosa when singly dispersed in the lamina propria. Eosinophils that infiltrate the epithelium in more than occasional numbers, coalesce to form aggregates, or show extensive degranulation are always abnormal.

The differential diagnosis of mucosal eosinophilia

Eosinophils as a Component of Mixed Inflammation

Eosinophils can be prominent in virtually any inflammatory condition that persists for days to weeks. Esophageal eosinophilia most frequently reflects chronic mucosal injury due to gastroesophageal reflux disease, in which case the features show considerable overlap with those of eosinophilic esophagitis, as described in subsequent sections. Mucosal eosinophilia is also commonly observed in drug-related and, to a lesser degree, in infectious esophagitis. All of these disorders display variable numbers of eosinophils in combination with intraepithelial lymphocytes and neutrophils, which tend to be present in higher numbers than eosinophils (Figure 1a). These forms of esophageal injury can also cause erosions and ulcers, both of which are uncommon in patients with eosinophilic esophagitis. Detection of pill fragments, fungal forms, or viral inclusions are helpful clues that should, when present, dissuade one from placing too much emphasis on concomitantly increased eosinophils.

Mucosal eosinophilia may be seen in association with acute and chronic forms of gastric injury. Small numbers infiltrate the lamina propria singly or in clusters in cases of chemical gastropathy due to any cause, although they were once considered a specific manifestation of injury due to non-steroidal anti-inflammatory drugs.[5] Eosinophils comprise part of the infiltrate of chronic gastritis and are far more numerous in cases of autoimmune gastritis than *Helicobacter pylori*-related gastritis.[6] Indeed, autoimmune gastritis is always a diagnostic consideration when cases of chronic gastritis show prominent eosinophils, particularly when seen in association with an infiltrate in the deep mucosa (Figure 1b).

Virtually any form of persistent enterocolitis can show increased mucosal eosinophils. Eosinophils are numerous in cases of infectious enterocolitis, medication-related injuries, radiation effect, and inflammatory bowel disease (Figure 1c). Fortunately, many of these disorders show other inflammatory changes that facilitate their diagnosis. Bacterial and drug-induced injuries produce an acute self-limited colitis with neutrophil-rich inflammation in the lamina propria and crypts, but relatively fewer eosinophils (Figure 1d). Biopsies from patients with Crohn disease and ulcerative colitis may show striking mucosal eosinophilia, either in areas of active or quiescent disease. However, eosinophils are accompanied by neutrophilic crypt injury in cases of active colitis, and plasma cell-rich infiltrates and crypt architectural changes serve as helpful clues to the presence of chronic colitis (Figures 1e and f).

Eosinophils are commonly observed in surgical resection specimens from patients with appendicitis and cholecystitis, particularly when there is a slight delay between the onset of symptoms and surgery. Approximately 40% of appendices removed within 12–84 h of symptom onset display mural eosinophils, often in combination with lymphocytes.[7] Similarly, more than 20% of resected gallbladders contain numerous eosinophils as well as other types of inflammatory cells.[8] Most data suggest that these findings reflect the 'subacute' phase of the inflammatory process, rather than a primary eosinophilic disorder, particularly if eosinophils are not the major component of the infiltrate and are evenly dispersed among other inflammatory cells. However, large numbers of eosinophils accounting for most ($>90\%$) of the infiltrate, aggregates of eosinophils, and extensive degranulation should raise the possibility of other disorders, as described below.[9]

Inflammatory Infiltrates Consisting Predominantly, or Exclusively, of Eosinophils

Eosinophilic gastroenteritis. Eosinophilic gastroenteritis is a general term describing disorders characterized by prominent eosinophil-rich inflammatory infiltrates for which other etiologies cannot be identified. Cases of eosinophilic gastroenteritis are classified as mucosal, mural, or serosal forms for historical reasons, although these variants are likely unrelated disorders.[10] The mucosal form of the disease is a manifestation of hypersensitivity similar to eosinophilic (allergic) esophagitis, which may represent a milder or localized form of disease.[11] In contrast, most examples of mural and serosal disease are unrelated to hypersensitivity and can be attributed to other etiologies.[12] The

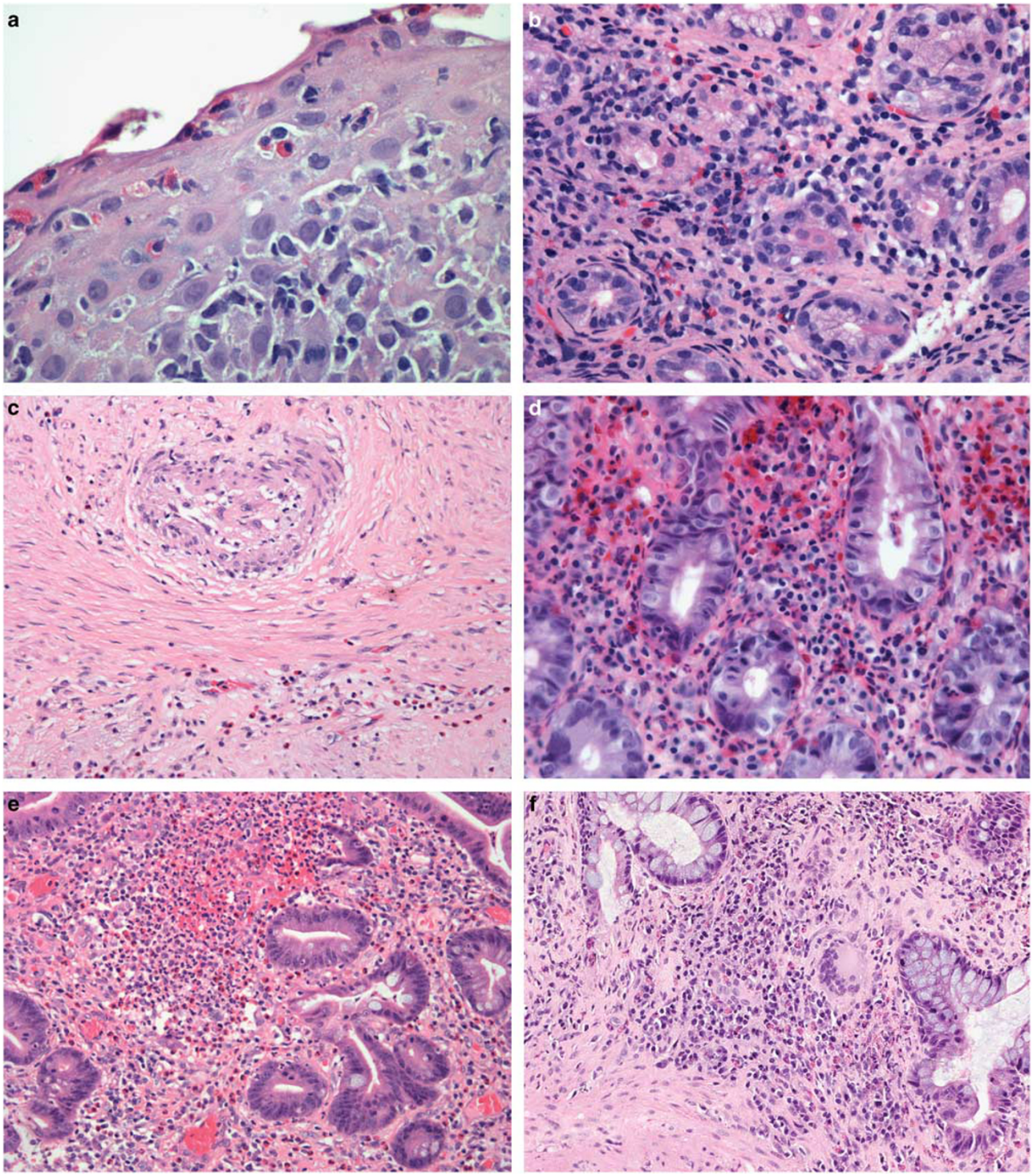

Figure 1 This elderly patient with candidal esophagitis had biopsies from the mid esophagus that display scattered eosinophils in the superficial epithelium, some of which are clustered. Numerous lymphocytes are also present, as are scattered neutrophils (**a**). The inflammatory infiltrate of autoimmune gastritis is associated with deep glands in oxyntic mucosa. Scattered eosinophils are a consistent feature (**b**). Changes of radiation enteritis include intimal hyperplasia with obliteration of arteries and mural fibrosis. This case also features eosinophil-predominant inflammation (**c**). Acute self-limited colitis due to nonsteroidal anti-inflammatory drugs displays numerous eosinophils in the lamina propria as well as neutrophils in injured crypts (**d**). A case of chronic active ulcerative colitis contains numerous eosinophils associated with neutrophilic crypt destruction. Branched, irregular crypts are present in the background mucosa (**e**). Biopsies from this patient with Crohn disease displays multinucleated giant cells in the lamina propria. The background infiltrate is rich in eosinophils and plasma cells. Branched crypts are also present (**f**).

differential diagnosis includes a number of entities that characteristically elicit an eosinophil-rich response, many of which cannot be distinguished from eosinophilic gastroenteritis based on histology alone.

Mucosal eosinophilic gastroenteritis shows a predilection for males and is more common among children. Most patients have one, or more, food allergies and present with multiple lesions affecting any site within the gastrointestinal tract, including the esophagus. Cases that cannot be attributed to identifiable allergic etiologies share many clinical and pathologic features with those with definite allergy associations, including a dramatic response to corticosteroid therapy. Clinical symptoms include malabsorptive diarrhea, failure to thrive, iron deficiency anemia, protein losing enteropathy, vomiting, abdominal pain, and rectal bleeding. Most (>75%) patients have a peripheral eosinophilia as well as elevated serum IgE levels. The diagnosis of mucosal eosinophilic gastroenteritis requires exclusion of other disorders that show a prominent eosinophilic infiltrate, appropriate clinical and laboratory findings, and a therapeutic response to elimination diet or corticosteroid therapy. The disease shows a predilection for the gastric antrum and commonly affects the small bowel, but colorectal involvement is less frequent. Lesions may be patchy and are typically associated with mild endoscopic abnormalities, so extensive sampling, often of normal-appearing areas, may be required to establish a diagnosis. The diagnosis requires exclusion of other disorders that show a prominent eosinophilic infiltrate, appropriate clinical and laboratory findings, and a therapeutic response to elimination diet or corticosteroid therapy.

Mucosal eosinophilic gastroenteritis displays numerous eosinophils that expand the lamina propria and infiltrate the epithelium, producing variable epithelial cell injury. The diagnosis is straightforward in mucosal biopsies of the esophagus and stomach because these sites normally contain minimal numbers of inflammatory cells and, thus, any increase in eosinophils is readily apparent. The features of eosinophilic gastroenteritis involving the esophagus are identical to those of eosinophilic esophagitis. Superficially oriented eosinophils permeate the squamous epithelium and coalesce to form eosinophilic microabscesses (Figure 2a). The background mucosa is edematous and often displays basal zone hyperplasia involving up to 50% of the mucosal thickness (Figure 2b). Distinction from eosinophilic esophagitis requires sampling of the duodenum and stomach, at least one of which is usually involved in cases of eosinophilic gastroenteritis, but show sparing in cases of eosinophilic esophagitis. Gastric samples, particularly those of the antrum, contain aggregates of eosinophils surrounding gastric pits and glands with infiltration of the epithelium in some cases (Figures 2c and d).

Infiltrates in the intestines may be more difficult to recognize, particularly when eosinophils are less abundant, as their numbers may be masked by inflammatory cells normally found in the mucosa. Counting mucosal eosinophils is of little practical value because their distribution is often patchy in eosinophilic gastroenteritis and well-defined criteria for this diagnosis are lacking. More important is their distribution in the mucosa. Eosinophils are normally dispersed singly in the lamina propria and are infrequently observed in the crypts, so any clustering, even of a few cells, in either location is an abnormal finding that should raise suspicion. Eosinophils within the muscularis mucosae are also abnormal and can be a helpful finding when the diagnosis is suspected. Patients with malabsorptive symptoms may have small bowel biopsies that show eosinophilia as well as partial, or complete villous shortening with crypt hyperplasia and variable intraepithelial lymphocytosis that simulate celiac disease.

Mural eosinophilic gastroenteritis is not related to mucosal disease, nor is it associated with a clinical history of hypersensitivity. Most cases were reported prior to the *H. pylori* eradication era and showed a predilection for the antrum, particularly the prepyloric region, where they formed solitary areas of mural thickening that caused obstructive symptoms.[12] The entity is much less commonly described in the current literature, but reportedly responds to *H. pylori* eradication, suggesting that many examples of mural eosinophilic gastroenteritis describe peptic ulcer disease.[13,14] Other entities, including inflammatory fibroid polyp, Crohn disease, infection with parasites or specific fungi, and radiation may show striking eosinophilia in the bowel wall and result in an erroneous diagnosis of mural gastroenteritis (Figure 3). Thus, potential cases of mural eosinophilic gastroenteritis should be carefully evaluated for the presence of underlying gastritis, multifocality, mural lymphoid aggregates, and granulomata suggestive of Crohn disease, worm or egg fragments, fungi, and other clues to suggest a more specific diagnosis.

Serosal eosinophilic gastroenteritis is extremely rare and unrelated to either mucosal or mural types of disease. Patients typically lack a history of hypersensitivity and present with acute onset abdominal pain. Peritoneal washings demonstrate eosinophil-rich ascites due to eosinophilic infiltrates in the serosa and imaging may depict ascites with variable bowel wall thickening. Given the rarity of serosal eosinophilic gastroenteritis, as well as a lack of cohesive clinical and laboratory findings, it is likely that this disorder results from multiple different etiologies and is not a distinct entity (Figure 4). The most common mimic of serosal eosinophilic gastroenteritis is parasitic infestation, particularly anisakiasis, as described in subsequent sections.[15,16] Similar changes can also be seen in patients with metal allergies, such as nickel and/or titanium, who have abdominal surgery requiring use of stapling devices.[17,18]

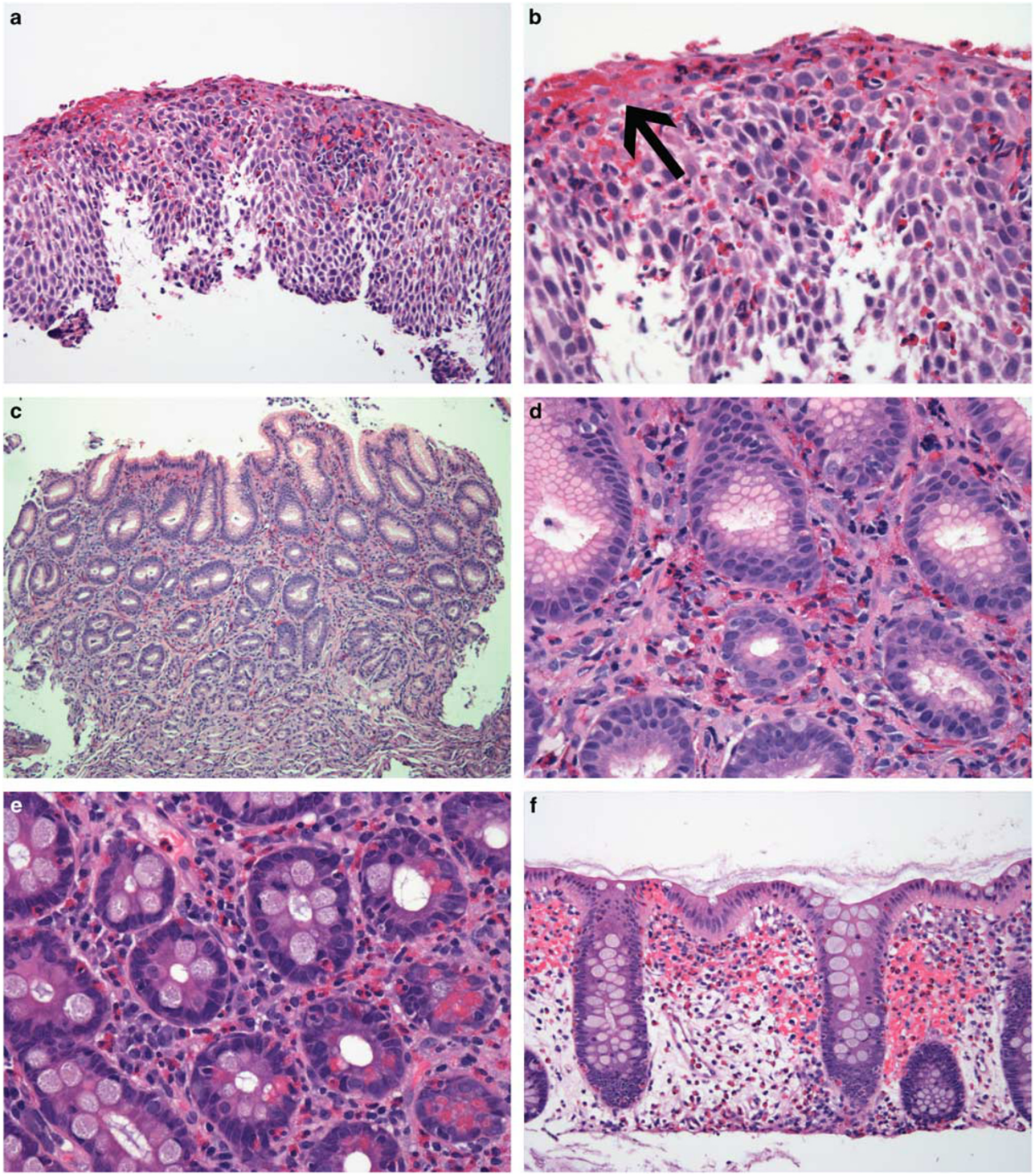

Figure 2 Eosinophilic gastroenteritis involving the esophagus is endoscopically and histologically indistinguishable from allergic (eosinophilic) esophagitis. Biopsies from a young boy with failure to thrive reveal striking intercellular edema with numerous eosinophils (**a**). Clusters of degranulating eosinophils form microabscesses (arrow) near the epithelial surface (**b**). The antral mucosa of the same patient contains increased numbers of eosinophils that expand the lamina propria (**c**). Aggregates of degranulated eosinophils and occasional intraepithelial eosinophils are also present (**d**). Eosinophilic gastroenteritis shows a predilection for the upper gastrointestinal tract, including the duodenum. Eosinophils are increased in the lamina propria and crypt epithelium of this patient (**e**). In contrast, colonic changes of eosinophilic gastroenteritis are often milder than those of the upper gastrointestinal tract. Biopsies from this patient with eosinophilic gastroenteritis show slightly increased eosinophils in the lamina propria and scattered eosinophils in colonic crypts (**f**).

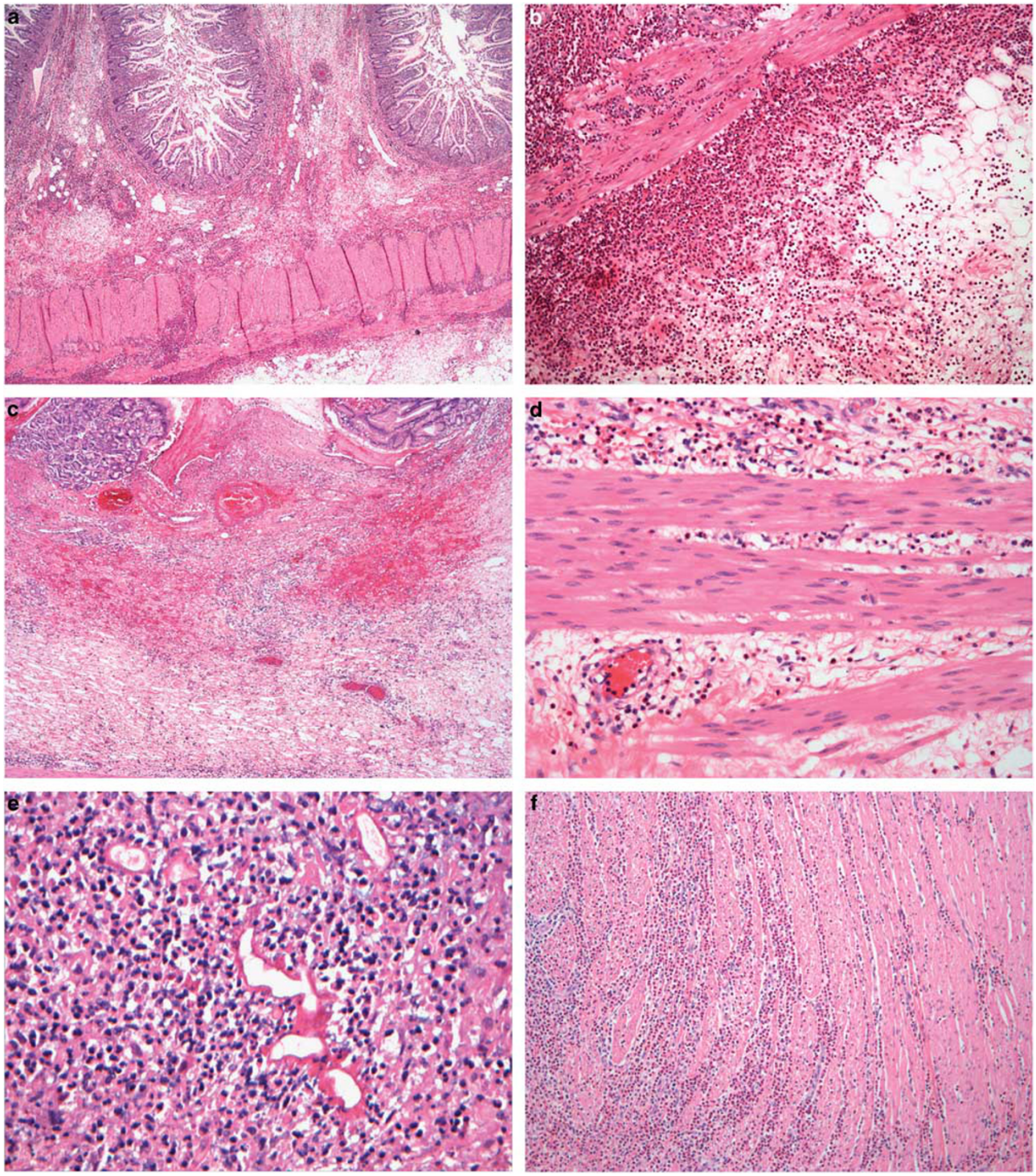

Figure 3 Mural eosinophilic gastroenteritis shows dense eosinophilic infiltrates in the submucosa and muscularis propria (**a**). Sheets of eosinophils are associated with mural edema (**b**). Most cases of mural eosinophilic gastroenteritis are likely secondary to other disorders. This actively inflamed gastric ulcer contains fibrin-rich granulation tissue with mixed inflammation, including numerous eosinophils (**c**). Sheets of eosinophils persist in the muscularis mucosae of a healing ulcer (**d**). Some fungi and parasites cause gastrointestinal disease that mimics mural eosinophilic gastroenteritis. *Basidiobolus ranarum* is a fungus that appears as optically clear pauciseptate branching organisms surrounded by Splendore-Hoeppli phenomenon (**e**). Sheets of eosinophils infiltrate the muscularis propria distant from the site of infection (**f**). Failure to detect organisms may lead to an erroneous diagnosis of eosinophilic gastroenteritis. *Images E and F courtesy of Dr Wade Samowitz, University of Utah, Salt Lake City, UT.*

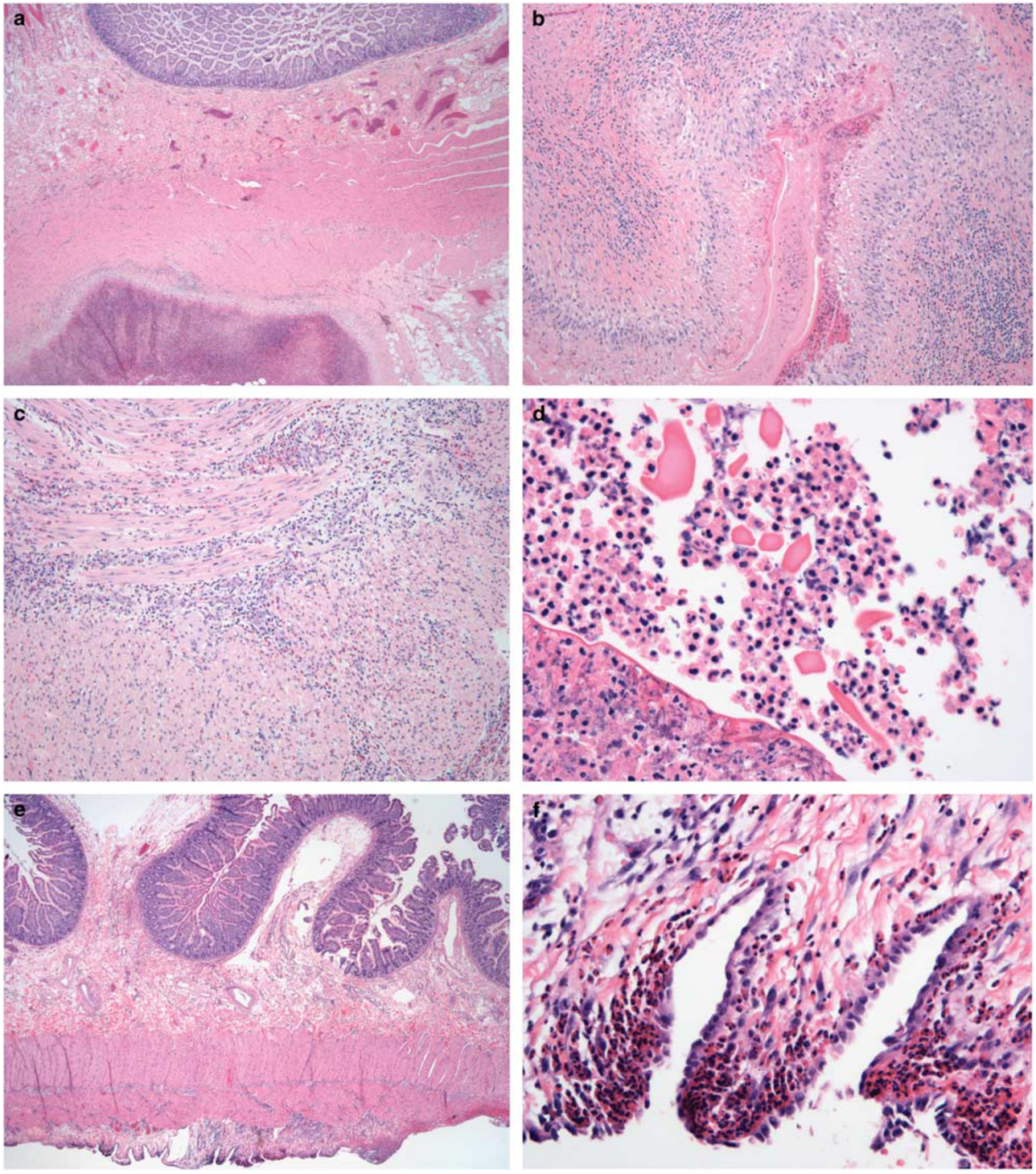

Figure 4 The differential diagnosis of serosal eosinophilic gastroenteritis includes infection, particularly anisakiasis, as well as other forms of hypersensitivity. *Anisakis* is surrounded by an eosinophil-rich abscess subjacent to the peritoneal surface with sparing of the muscularis propria (**a**). High magnification discloses a degenerated parasite surrounded by palisaded granulomatous inflammation and eosinophils (**b**). Intense mural and subserosal eosinophilia are present distant from the parasite (**c**). Necrotic, degranulated eosinophils and Charcot-Leyden crystals on the serosa and in the peritoneum should raise suspicion for this parasite, as the latter are present in far fewer numbers in eosinophilic gastroenteritis (**d**). Another patient underwent surgical resection following acute onset of abdominal pain and obstructive symptoms. The resection specimen displays striking subserosal edema (**e**) with clusters of eosinophils subjacent to the mesothelial lining (**f**). Upon further investigation, the patient was found to have a titanium staple in the abdominal cavity and a long history of metal allergies.

Gastroesophageal reflux disease. Gastroesophageal reflux disease results from retrograde flow of acidic or alkaline fluid into the esophagus and produces symptoms of heartburn, acid regurgitation, dysphagia, chronic cough, and atypical chest pain. Endoscopic features include diffuse or discontinuous inflammatory changes in the distal 5–10 cm of the esophagus, erythema, erosions, ulcers, exudates, or strictures, although 50% of symptomatic patients have normal-appearing mucosae or minimal hyperemia.[19] Intraepithelial inflammation is common: more than half of cases show eosinophils evenly distributed throughout the epithelium or concentrated around papillae (Figures 5a–c). Neutrophils are identified in approximately 30% of patients, in which case their presence usually implies erosive disease. Squamous hyperplasia with elongated papillae, expansion of the basal zone to approximately 10–15% of the mucosal thickness, intercellular edema, and swollen and/or multinucleated squamous cells are often present.[20,21] The differential diagnosis of gastroesophageal reflux disease includes other types of esophagitis, particularly eosinophilic esophagitis. The former typically displays squamous hyperplasia with elongated papillae and eosinophil-rich inflammation that is evenly dispersed throughout all layers of the epithelium, but eosinophils tend to number fewer than 20 per high-power field. Clusters of eosinophils (microabscesses) are rare, even if eosinophils are numerous.

'Eosinophilic' (allergic) esophagitis. Eosinophilic esophagitis is a poorly chosen term used to describe a form of hypersensitivity limited to the esophagus. It is increasingly recognized among pediatric patients and adults, particularly young men. Patients may have symptoms that simulate gastroesophageal reflux disease, although many present with progressive dysphagia and/or recurrent food impaction. The disease likely results from a combination of genetic, immunologic, and environmental factors and is more common among patients with a history of food allergies, atopic dermatitis, peripheral eosinophilia, or bronchial asthma. For these reasons, the entity is most appropriately termed 'allergic esophagitis,' although 'eosinophilic esophagitis' has become popular in the literature and clinical practice. Endoscopic features include plaques of scale crust, linear furrows, and concentric rings that have been described as a feline, or trachealized, esophagus.[22] Mucosal tears and areas of luminal narrowing are common, although the esophagus is endoscopically normal in a minority of cases.[23] The patchy nature of eosinophilic esophagitis necessitates multiple tissue samples from the proximal, distal, and intervening esophageal mucosa, all submitted in separate containers.[24,25] Affected biopsies typically contain numerous (>15/high-power field) eosinophils that are more abundant in the superficial epithelium where they tend to cluster and form microabscesses (Figures 5d–f). Eosinophil aggregates and degranulated eosinophils in adherent keratin are relatively specific findings and helpful diagnostic clues, if present.[26]

The differential diagnosis of eosinophilic esophagitis includes eosinophilic gastroenteritis and gastroesophageal reflux disease. Distinction from eosinophilic gastroenteritis is somewhat arbitrary as the two have overlapping clinical and histologic features and are likely related disorders differing only with respect to disease extent and distribution. Indeed, they are histologically identical when evaluation is limited to esophageal biopsies and can be separated only if biopsies of the remaining gastrointestinal tract are also available. An absence of eosinophilia in duodenal and/or gastric biopsies is a pre-requisite to the diagnosis of eosinophilic esophagitis, whereas eosinophilic gastroenteritis involves the stomach in virtually 100% of cases. From a clinical standpoint, the diagnosis of eosinophilic esophagitis can certainly be suggested based on analysis of esophageal biopsies alone, but cannot be distinguished from eosinophilic gastroenteritis in the absence of biopsies from other sites in the gastrointestinal tract.

Distinction between eosinophilic gastroenteritis/esophagitis and gastroesophageal reflux disease is usually straightforward (Table 1). Acid injury tends to be worse in the distal esophagus, whereas eosinophilic esophagitis can affect any region of the esophagus. The latter characteristically displays superficial eosinophil microabscesses and degranulated eosinophils, as well as striking mucosal edema, all of which are less prominent in gastroesophageal reflux disease. Eosinophilic esophagitis may also cause progressive lamina propria fibrosis that can be a helpful feature in the distinction from gastroesophageal reflux disease.[27] Some cases of eosinophilic esophagitis lack characteristic features to distinguish them from gastroesophageal reflux disease and, conversely, some cases of gastroesophageal reflux disease show striking eosinophilia, thereby mimicking eosinophilic esophagitis.[26,28] Thus, occasional cases of eosinophilic esophagitis and gastroesophageal reflux disease are histologically indistinguishable, particularly when biopsies are limited to the lower esophagus.[29,30]

Eosinophilic gastritis. Some investigators have suggested that detection of more than 30 eosinophils per high-power field in at least five examined fields of the gastric mucosa should be considered to represent 'histologic eosinophilic gastritis,' although available data supporting this designation as a specific clinicopathologic entity are lacking. Indeed, a substantial number of patients with markedly elevated gastric eosinophils also have peripheral eosinophilia or increased eosinophils elsewhere in the gastrointestinal tract, suggesting that a proportion of patients with 'histologic eosinophilic gastritis' are more appropriately diagnosed with

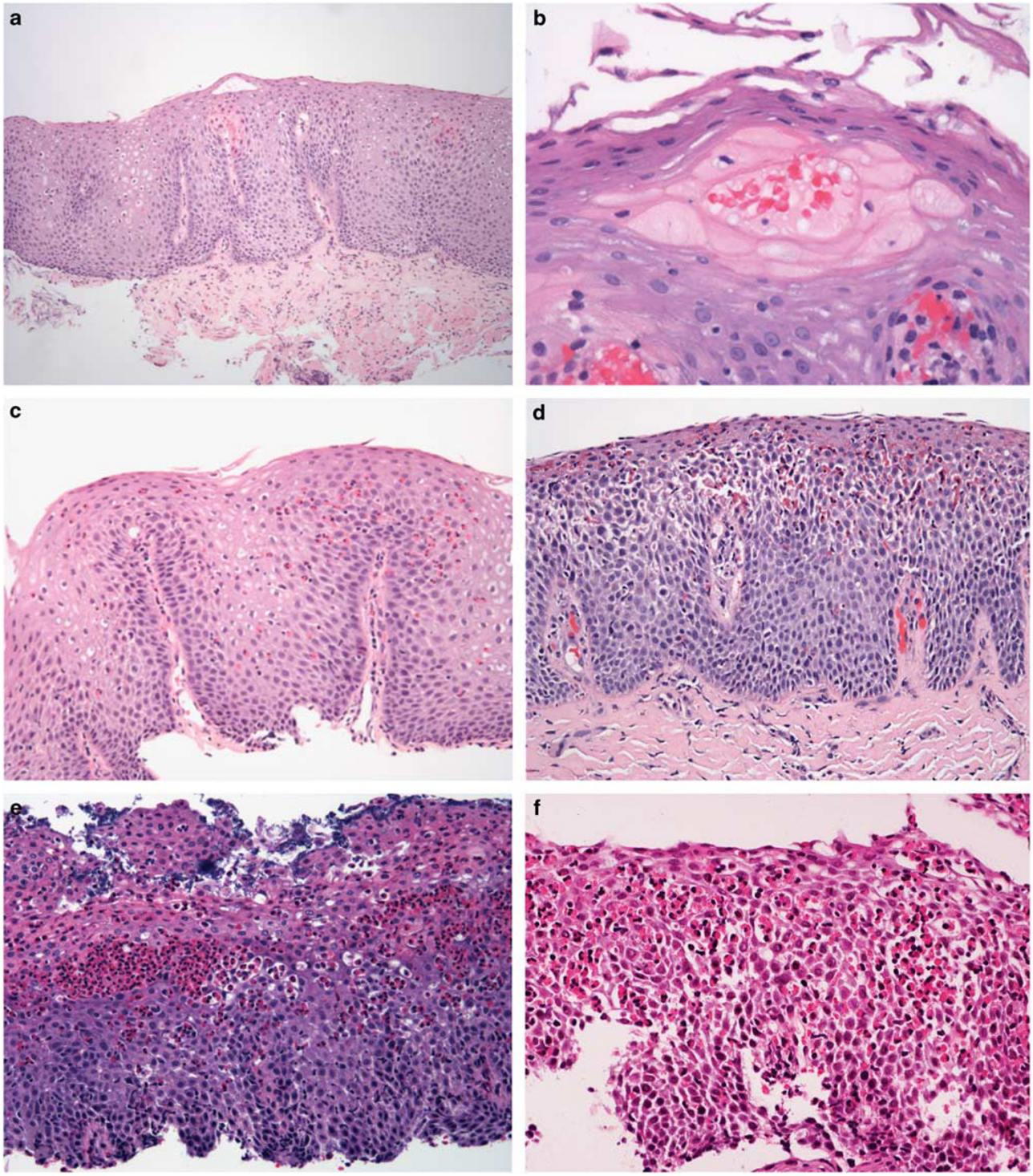

Figure 5 The primary differential diagnosis of eosinophil-rich inflammation in the esophagus includes gastroesophageal reflux disease and eosinophilic esophagitis. Gastroesophageal reflux disease tends to cause more severe changes in the distal esophagus. Characteristic features include elongated papillae and basal cell hyperplasia occupying approximately 10% of the mucosal thickness (**a**). Numerous eosinophils are evenly dispersed in the squamous mucosa or concentrated around papillae (**b**). Ballooned keratinocytes reflect intracellular edema (**c**). Eosinophilic esophagitis shows elongated papillae and increased eosinophils that tend to be superficially oriented (**d**). Some cases display prominent keratin crust containing degranulated eosinophils. Basal zone hyperplasia involves more than 50% of the mucosal thickness (**e**). Striking mucosal edema is a helpful feature of eosinophilic esophagitis. This case also shows extensive infiltration by eosinophils with microabscesses (**f**).

Table 1 Distinguishing features of gastroesophageal reflux disease and eosinophilic esophagitis

	Gastroesophageal reflux disease	*Eosinophilic esophagitis*
Presence of 20 or more eosinophils per high-power field	Uncommon (3–5%)	Frequent (≥90%)
Superficial eosinophil abscesses	Quite uncommon	Helpful, if present
Eosinophils in adherent or detached keratin crust	Quite uncommon	Helpful, if present
Marked (>50%) basal cell hyperplasia	Uncommon (10%)	Frequent (>50%)
Papillary elongation (>50% of mucosal thickness)	Not helpful, commonly present	Not helpful, commonly present
Ballooned keratinocytes	Helpful, if present	Not a characteristic feature

eosinophilic gastroenteritis.[1] Primary eosinophilic gastritis, in the absence of hypersensitivity or generalized involvement of the gastrointestinal tract, is extremely rare. Of note, drug reactions are unlikely to cause intense eosinophilia of gastric mucosa.

Invasive gastric adenocarcinoma. One important entity to consider in the differential diagnosis of gastric eosinophilia is invasive adenocarcinoma. Intestinal-type adenocarcinomas may be infiltrated by neutrophils, whereas signet ring cell and diffuse-type carcinomas frequently recruit eosinophils. The infiltrate is variably prominent and can be limited to the area of the tumor or emanate away from it, thereby simulating the appearance of 'eosinophilic gastritis' in biopsy samples (Figure 6a). More rarely, tumor cells are seen in combination with eosinophils and plump spindle cells that resemble components of inflammatory fibroid polyp.[31] Tumor cells form cohesive clusters or linear arrays enmeshed in collagenous stroma and are enhanced by cytokeratin immunostains (Figures 6b–d).

Parasitic infection. The possibility of parasitic infestation should be considered in any series of biopsies that shows mucosal eosinophilia, particularly if eosinophils form large clusters or are associated with granulomatous inflammation. *Strongyloides* and *Schistosoma* are the most common parasites encountered in mucosal biopsies. Biopsies from patients with heavy *Strongyloides* burdens show larvae and eggs within crypt lumina that tend to be unassociated with a substantial inflammatory response (Figure 7a). Once organisms breach the basement membrane and invade the mucosa, they elicit a brisk, eosinophil-rich inflammatory response (Figures 7b–f). In this situation, *Strongyloides* are found in the deep mucosa surrounded by degranulated eosinophils with Charcot-Leyden crystals.[32] In contrast, schistosomal eggs are observed within the lumina of small vessels in the lamina propria, or in association with granulomatous inflammation in the lamina propria and submucosa.[33] Inflammation is usually absent or mild around eggs confined to vascular lumina, whereas granulomata develop when eggs erode through the vessels into connective tissue. It is important to remember that chronic infestation with any type of parasite induces crypt and villous architectural changes reminiscent of idiopathic inflammatory bowel disease.[34] One should consider the possibility of parasitic infestation when chronic colitis is accompanied by striking mucosal eosinophilia.

Parasites are likely responsible for a substantial number of cases originally diagnosed as mural and serosal eosinophilic gastroenteritis. *Anisakis* is a nematode that infects fish and marine invertebrates and an increasingly recognized cause of eosinophilic ascites. The organism causes gastrointestinal disease in humans when contaminated raw or undercooked fish is ingested. Larval forms penetrate the mucosa and burrow into the bowel wall where they elicit an intense inflammatory reaction that produces symptoms of abdominal pain, hemorrhage, obstruction, and serositis.[12,35] Inflammatory changes in the wall and serosa are characterized by intense eosinophilia and edema that may extend away from the site of infection (Figures 4a–d). Multiple sections are often required to demonstrate the organism.[36,37]

Fungal infection. Most fungal infections elicit a chronic granulomatous inflammatory response with variable numbers of neutrophils, although rare species cause infection that produces intense tissue eosinophilia. One of these, *Basidiobolus ranarum*, has been recently recognized as a human pathogen that shows a predilection for the gastrointestinal tract. Infection may develop in immunocompetent or immunocompromised individuals and most cases in this country occur in patients who reside in the southwest, particularly Arizona. Infected patients present with peripheral eosinophilia and inflammatory masses that simulate malignancy, Crohn disease, or mural eosinophilic gastroenteritis.[38] Symptoms include abdominal pain, fever, weight loss, and an abdominal mass that usually involves the colon. The mucosa may be normal or contain mildly increased eosinophils, whereas inflammatory masses destroy the bowel wall and extend into surrounding soft tissue. Inflammatory changes include prominent eosinophilic infiltrates associated with granulomatous inflammation around fungal forms, many of which are surrounded by a thick eosinophilic cuff (Splendore-Hoeppli phenomenon).[39] Hyphae are irregularly branching, thin-walled, and may show a few

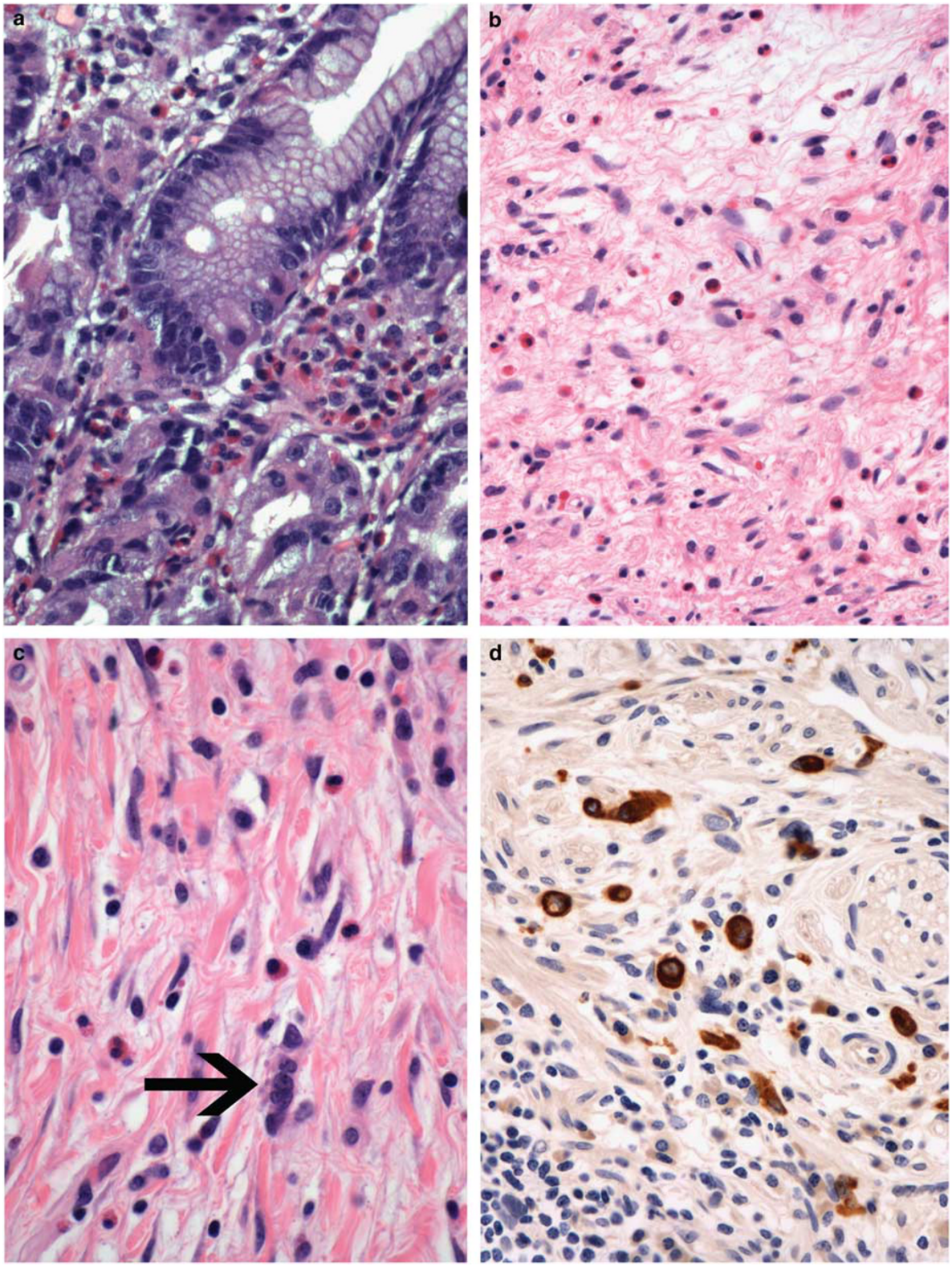

Figure 6 Diffuse-type gastric carcinomas may elicit a striking eosinophil-rich inflammatory infiltrate. This patient with a signet ring cell carcinoma had biopsies containing large clusters of eosinophils in the superficial mucosa, some of which infiltrated gastric glands (**a**). Another case of diffuse-type gastric cancer displays rare, keratin-positive tumor cells (arrow) enmeshed in a mixed inflammatory background with plump spindle cells mimicking inflammatory fibroid polyp (**b**). High magnification of the same case reveals linear arrangements of tumor cells (arrow) associated with scattered eosinophils and plasma cells (**c**). A keratin immunostain confirms plump keratin-positive tumor cells diffusely infiltrating the gastric wall (**d**).

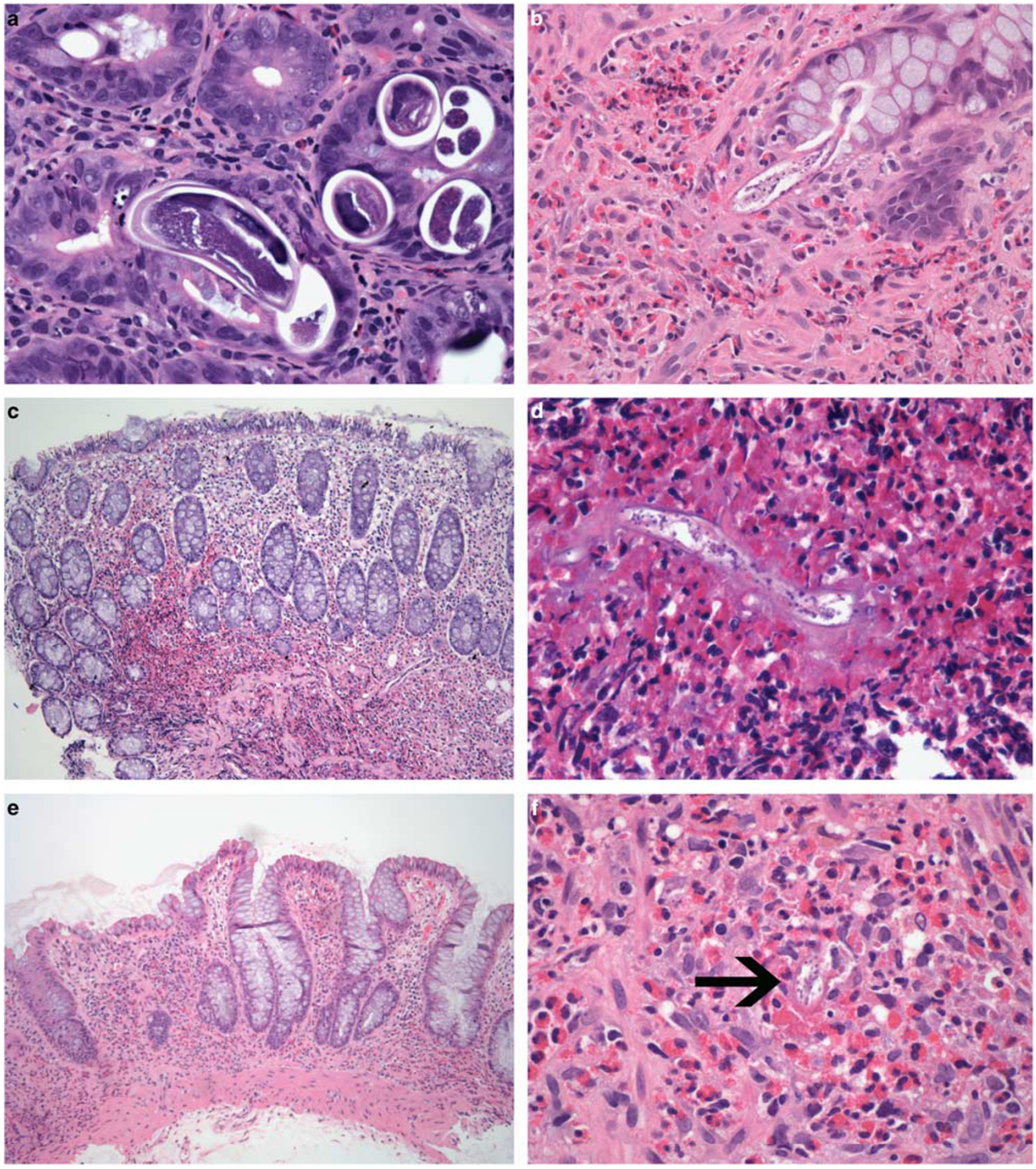

Figure 7 Adult *Strongyloides* reside in the gut lumen and deposit eggs. Both eggs and worms can be visualized in the crypts, where they elicit minimal inflammatory changes (**a**). Rhabditiform larvae in the lumen can become filariform larvae that invade the mucosa, at which point they elicit an eosinophil-rich inflammatory response (**b**). Clues to the presence of a parasitic infection include the localized nature of eosinophil infiltrates, particularly in the deep mucosa (**c**). Deeper tissue levels through these areas reveal larvae in eosinophilic abscesses (**d**). Chronic *Strongyloides* infection elicits crypt architectural changes that simulate features of inflammatory bowel disease. However, the background mucosa lacks dense chronic inflammation and shows sheets and clusters of eosinophils (**e**). Careful examination of eosinophil clusters in the same case reveals worm fragments (arrow) in the mucosa (**f**).

septations (Figures 3e and f). They are usually 8–40 μm in width and are best seen in hematoxylin and eosin-stained sections. Eosinophil-rich inflammation permeates the muscularis propria distant from the site of infection, thereby simulating the appearance of mural eosinophilic gastroenteritis.

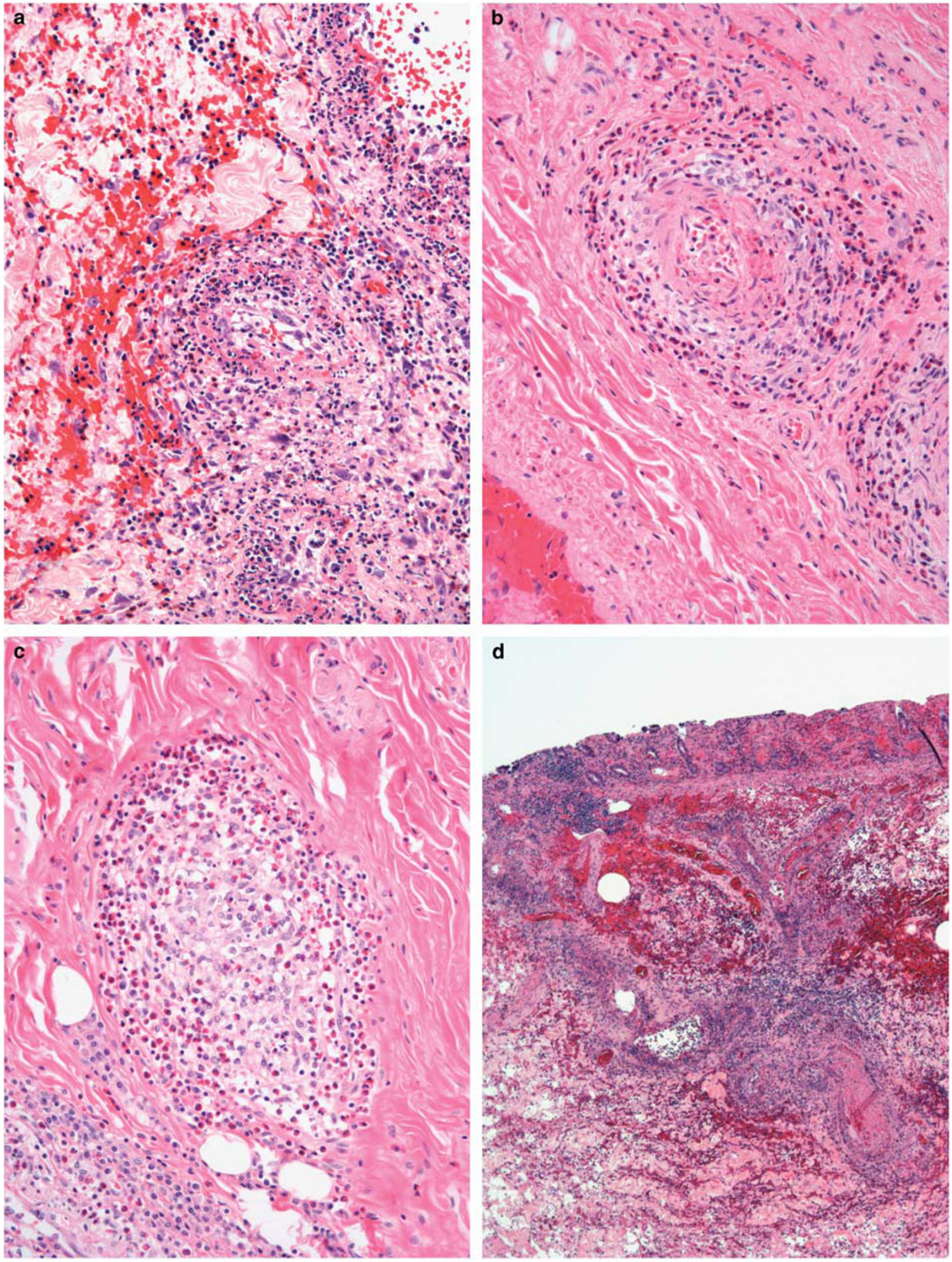

Figure 8 Churg-Strauss vasculitis shows a predilection for small- and medium-sized vessels of the small bowel. Affected blood vessels display mural fibrin deposits in association with necrotic cellular debris (**a**). Eosinophils are concentrically arranged around blood vessels and show degranulation (**b**). Inflammatory infiltrates also contain macrophages that circumferentially involve vascular walls or obliterate blood vessels (**c**). Although eosinophils are numerous in the mucosa, it also shows ischemic-type injury, which should be a clue to the diagnosis (**d**). Ischemic enteritis is not a feature of eosinophilic gastroenteritis or most infections that cause eosinophilia.

Allergic colitis and proctitis. Most patients with allergic proctocolitis are infants and young children under the age of 2 years. Cow's milk protein, either alone or in combination with soy protein, has been implicated as a major etiologic factor. Patients generally respond to elimination of these foods from the diet and lose their sensitivity over several years, such that tolerance improves during adulthood. Most studies describing the features of allergic proctocolitis have limited their analyses to rectal biopsy samples, although it is likely that abnormalities are present throughout the colon. Histologic features are similar to those of eosinophilic gastroenteritis. Biopsies reveal diffusely increased eosinophils in the lamina propria with minimal epithelial cell damage and an absence of crypt architectural distortion or other features of chronic injury. Although it may be difficult to distinguish changes of allergic proctocolitis from normal tissue eosinophilia, the finding of more than 60 eosinophils per 10 high-power fields and extension of eosinophils into the muscularis mucosae are suggestive of allergic proctocolitis.[40]

Churg-strauss syndrome. Eosinophilic granulomatosis with polyangiitis (allergic granulomatosis) is an immune-mediated vasculitis of medium and small vessels in patients with a history of asthma and/or allergic rhinitis. The syndrome is characterized by the development of three clinical stages (allergic stage, eosinophilic stage, and vasculitic stage), although not all patients develop all three stages or progress from one stage to the next. This form of vasculitis shows a predilection for the small intestine and proximal colon and is associated with cANCA autoantibodies, similar to microscopic polyangiitis and Wegener granulomatosis.[41] Resection specimens typically show fibrinoid necrosis of vascular walls in association with intense eosinophil-rich inflammatory cell infiltrates around medium and small vessels in the submucosa and deeper aspects of the bowel wall (Figure 8). Increased numbers of eosinophils may be present in the mucosa, but superficial biopsies generally show striking ischemic changes that dominate the histologic picture. Thus, the primary differential diagnosis includes other causes of ischemic enterocolitis, rather than eosinophilic gastroenteritis in most cases.

Summary and conclusions

Eosinophils are commonly detected in mucosal biopsies from all sites within the gastrointestinal tract. They can be considered to represent a normal finding in most instances, provided they are evenly dispersed in the lamina propria, minimally involve the epithelium, and do not coalesce into aggregates or microabscesses. Increased numbers of eosinophils are encountered in a variety of disorders. When accompanied by abundant neutrophils or granulomatous inflammation, one should consider infectious etiologies or drug-induced injuries. Eosinophils are commonly encountered in cases of idiopathic inflammatory bowel disease, in which case they are accompanied by other features of chronic colitis, including crypt abscesses, lymphoplasmacytic inflammatory infiltrates, and crypt architectural abnormalities. Purely eosinophil-rich infiltrates are increasingly encountered in patients with esophageal symptoms, in which case their presence typically reflects a hypersensitivity reaction (ie, eosinophilic esophagitis or eosinophilic gastroenteritis). However, generalized hypersensitivity of the gastrointestinal tract is infrequent, particularly in the adult population. Thus, a diagnosis of eosinophilic gastroenteritis should only be made after other, more common, etiologies are excluded.

Disclosure/conflict of interest

The author declares no conflict of interest.

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