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OBSERVATION

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Multifocal stenosing ulceration of the small intestine

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Abstract

Several reports have described an apparently uncommon clinicopathological disorder that is characterized by multifocal stenosing small-intestinal ulceration. Compared to Crohn's disease, the ulcers are not transmural and typically remain shallow, and involve only the mucosa and submucosa. The disorder seems to be localized in the jejunum and proximal ileum only, and not the distal ileum or colon. Only nonspecific inflammatory changes are present without giant cells or other typical features of granulomatous inflammation. Most patients present clinically with recurrent obstructive events that usually respond to steroids, surgical resection, or both. With the development of newer imaging modalities to visualize the small-intestinal mucosa, such as double-balloon enteroscopy, improved understanding of the long-term natural history of this apparently distinctive disorder should emerge.

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Key words: Ulcer; Stenosis; Intestinal diseases; Small intestine; Crohn's disease

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INTRODUCTION

A syndrome that is characterized by intermittent episodes of small-intestinal obstruction caused by benign multifocal ulcerated stenosis has been described, largely, but not entirely, in the French literature[1-10]. This disorder has also been termed "cryptogenic multifocal ulcerous stenosing enteritis" (CMUSE) and has been reported to localize largely within the jejunum or proximal ileum. CMUSE typically is associated with shallow, rather than deep transmural ulceration, and has also been noted to be usually responsive to steroids, although occasionally, surgical resection is required. The location of ulceration and strictures in the more proximal small intestine, along with the absence of any associated granulomatous inflammatory changes in resected material are believed to differentiate this entity from Crohn's disease, which usually is localized in the distal ileum and the colon[11]. CMUSE appears to be an entirely distinct disorder from other small-bowel disorders, which is characterized by multifocal ulceration with stricture formation. With new imaging modalities increasingly becoming available, particularly double-balloon enteroscopy, further appreciation of this entity and its natural history should result.

DIFFERENTIAL DIAGNOSIS

A number of other entities may cause multifocal small-bowel ulcers (Table 1). Idiopathic ulcerative jejunoileitis, described elsewhere in detail[12], is a small-intestinal ulcerative disorder, often associated with celiac disease, or at least, with concomitant flattening of the villous architecture of the small bowel. Some believe that the disorder may represent a specific complication of celiac disease, but ulceration of the small intestine in this setting may also be caused by a difficult-to-diagnose focal lymphoma with lymphomatous cells localized at the ulcer edges[13].

A variety of infectious agents, some common, may also cause small bowel ulceration[7], but most of these (e.g. *Campylobacter*, *Shigella*, *Yersinia* and *Salmonella*) seem to resolve completely without stricture formation. Of course, the natural history of many infections in the small intestine are not particularly well defined (e.g. tuberculosis and cytomegalovirus infection), especially if immune

Table 1 Other causes of multifocal small-bowel ulceration and stenosis

Ulcerative jejunoileitis with celiac disease or sprue-like intestinal disease
Lymphoma (especially mucosa only), including T-cell enteropathy and α-chain disease (Mediterranean type)
Crohn's disease involving the small intestine
Infections (e.g. *Campylobacter* and *Shigella*)
Drug-induced type (especially with NSAIDs)
Zollinger–Ellison syndrome (gastrinoma) or other hypersecretory disorders
Traumatic injury (e.g. endoscopic or surgical treatment, seat-belt injury)
Ischemia related to vasculopathy (e.g. collagen vascular disease, coagulopathy, or inflammatory vasculitis)

NSAIDs: Nonsteroidal anti-inflammatory drugs.

Table 2 Differentiation of CMUSE from Crohn's disease

Absence of clinical or laboratory features of an inflammatory syndrome
Absence of small-intestinal transmural inflammatory process or ulceration
Absence of small-intestinal giant-cell granulomatous inflammatory process
Absence of small-intestinal fistula formation despite recurrent chronic disease
Absence of disease in other parts of gastrointestinal tract (i.e. stomach or colon)
Absence of most extraintestinal features of Crohn's disease (e.g. skin manifestations)

CMUSE: Cryptogenic multifocal ulcerous stenosing enteritis.

suppression from a concomitant disease or drug treatment is present. Other infectious agents appear to cause a completely different pathological reaction, although ulceration may conceivably occur (e.g. *Tropheryma whipplei* or *Mycobacterium avium intracellulare*).

Drug-induced causes of small-bowel ulceration are numerous and include potassium, gold and chemotherapeutic agents. Currently, the most common causes of drug-induced mucosal injury are nonsteroidal anti-inflammatory drugs (NSAIDs) that may cause frank ulcers, erosions, broad strictures and so-called diaphragm disease[8]. Alternatively, NSAIDs also have been associated with the small-bowel-mucosal lesion that is characteristic of untreated celiac disease in the absence of ulcer formation[14].

Peptic ulceration may occur but this is unusual in the jejunum and proximal ileum[7]. In this location, a peptic ulcer could hypothetically be a clue to an occult Zollinger-Ellison syndrome from a gastrinoma, or heterotopic functioning gastric mucosa. Meckel's diverticulum may be associated with small-bowel ulceration caused by heterotopic functioning gastric mucosa, but usually, the ulceration occurs in the more distal ileum.

Crohn's disease may occur in the jejunum without disease elsewhere, but this seems to be uncommon[15], and as noted earlier, usually is associated with other clinical and pathological features of Crohn's disease (Table 2).

Traumatic injury may also occur. Surgical injury (including peri-anastomotic ulceration) and external trauma from seat belts in motor vehicle accidents are being increasingly recognized. Endoscopic biopsies for diagnostic purposes, therapeutic interventions (e.g. cautery for polypectomy) or foreign bodies (e.g. ingested suture materials) may induce or be associated with small-intestinal ulcerations.

Finally, ischemic pathogenesis that results from a variety of causes may occur. For example, some systemic diseases have been associated with multifocal ulcers and stricture formation including: thrombotic diseases, Dego's disease, pseudoxanthoma elasticum, myeloproliferative disorders, anti-thrombin Ⅲ deficiency and vasculitis associated with an occult collagen vascular disease (e.g. systemic lupus erythematosus or polyarteritis nodosa).

CLINICAL FEATURES

A previous retrospective evaluation[7] of reported cases of CMUSE has revealed that virtually all patients complained of abdominal symptoms and about 70% had extraintestinal symptoms that included weight loss, fever, malaise and joint symptoms. The lesions in the small intestine were considered characteristic of stenosis (1-25, mean 8) found in the jejunum or the proximal ileum. The remainder of the small intestine appeared to be completely normal. Ulceration was superficial, involved the mucosa, sometimes the submucosa, but did not extend deeper into underlying tissues. All of these stenosis were associated with a nonspecific inflammatory infiltrate only. About 40% had persistent pain. Abdominal pain appeared to resolve with steroids but ongoing treatment was reported to be required in 50% of patients. Surgical resection resulted in complete recovery in about 40% but a second resection for recurrent stenosis was needed in 25% of patients. Occasionally, some required multiple resection. Vascular changes and complement component deficiency also have been associated with CMUSE[7].

FUTURE DIRECTIONS

CMUSE needs to be defined carefully and more precisely. Its etiology and pathogenesis are unknown. Diagnosis of CMUSE should be considered only after exclusion of each entity listed in the differential diagnosis above, especially Crohn's disease and drug-induced ulceration with stenosis. Nonspecific small-intestinal ulceration without stricture formation should be considered a separate entity. With the development of better imaging methods for the small intestine, especially double-balloon enteroscopy, the opportunity now may be present to further explore this intriguing entity.

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