

Clinicopathologic Study of Nonspecific Ulcers of the Small Intestine

JOHN S. BOYDSTUN, JR., MD, THOMAS A. GAFFEY, MD,
and LLOYD G. BARTHOLOMEW, MD

Fifty-nine cases (31 men and 28 women) of nonspecific small bowel ulceration, representing the Mayo Clinic experience from 1956 to 1979, are reviewed. The average age was 51 years. Presenting symptoms or signs were those of intermittent small bowel obstruction (63%), blood loss (25%), and acute abdomen (12%). Whereas 78% of the ulcers were located in the ileum, 15% in the jejunum, and 7% in the jejunoileum, perforation was by far more common in the jejunum (78%) as compared with the ileum (11%). Diagnosis was rarely made preoperatively, although abnormalities were noted roentgenographically in 66%. Treatment was surgical and was usually curative. Operative mortality was 8.5%. No single cause was implicated.

Ulcers of the small intestine distal to the duodenum are rare, but suggestions concerning their cause are legion. Among the causes listed by Wayte and Helwig (1) and Guest (2) are congenital malformation, inflammation, trauma, vascular abnormality, chemical irritation, neoplasia, and neural involvement. Some ulcers, however, are unexplainable by any specific mechanism and have been termed "nonspecific" or "idiopathic" small bowel ulcers.

Small bowel ulcers were first described by Baillie (3) in 1795, but the true incidence of nonspecific ulceration was obscured (4) until 1932, when regional enteritis was first recognized. By 1963, Watson (5) had found 170 cases in the world literature, and shortly thereafter almost 400 cases were described (6-13).

In 1965, enteric-coated potassium chloride tablets were proved to be one specific cause of ulceration. With the removal of enteric-coated potassium chloride from the market, the incidence of this lesion

declined, and today idiopathic small bowel ulcer remains as it was: a rarely seen, rarely diagnosed, clinical problem.

The Mayo Clinic experience with idiopathic small bowel ulceration was reviewed by Brown and Pemberton (4) in 1936, Evert et al (14) in 1948, and Morlock et al (15) in 1956. We now report findings in 59 cases of small bowel ulceration seen at the Mayo Clinic from 1956 to 1979.

MATERIALS AND METHODS

The surgical and pathologic records of all patients with the diagnosis of small bowel ulceration were reviewed. From this study, we excluded cases associated with radiation therapy, ischemic or inflammatory bowel disease, and Meckel's diverticulum, or those in which surgery could be implicated. Fifty-nine cases remained unexplainable by any known mechanism.

Histories were reviewed for clinicopathologic correlation, and follow-up information was obtained. Tissue specimens preserved in formalin were available for gross and microscopic study. Old sections were reviewed and, when necessary, new slides were prepared.

RESULTS

Of the 59 patients, 31 were men and 28 were women; ages ranged from 17 to 77 years (Table 1), and the average age was 51 years. Three types of

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From the Departments of Internal Medicine and Surgical Pathology, Mayo Clinic and Mayo Foundation, Rochester, Minnesota

Address for reprint requests: Dr. L.G. Bartholomew, Mayo Clinic, Rochester, Minnesota 55905.

TABLE 1. DISTRIBUTION BY AGE OF PATIENTS WITH SMALL BOWEL ULCERATION

Age (yr)	No. of patients	%
11-20	4	7
21-30	4	7
31-40	7	12
41-50	10	17
51-60	14	24
61-70	15	25
71-80	5	8

clinical presentation were apparent. In 37 patients (63%), intermittent crampy abdominal pain, coupled with postprandial distention, emesis, and borborygmi, led to the diagnosis of small bowel obstruction. There were 15 patients (25%) who presented predominantly with evidence of blood loss, eight having anemia and seven having melena or hematochezia. The third group of seven patients (12%) presented with acute pain exacerbating their chronic abdominal distress. The duration of symptoms before hospitalization in the 59 patients varied from 3 days to 20 years. Other than duration, there was essentially no difference in the symptoms in patients presenting acutely or in those with chronic symptoms. One patient with an acute abdomen had had symptoms for 2 years.

Six patients had taken enteric-coated potassium chloride from 5 days to 3 years. In addition, 35 other drugs had been used irregularly by the 59 patients. No medication or class of medication was used often enough to be considered etiologically significant.

Associated Conditions. Cardiovascular disease was present in 11 patients, that is, congestive heart failure (5), hypertension (3), angina pectoris (2), and intermittent claudication (1). Three patients had peptic ulcers previously, two had gallbladder disease previously, two had symptomatic hematologic disorders (myeloproliferative syndrome and acute myelomonocytic leukemia), two patients were currently being treated for Wegener's granulomatosis and histiocytosis X, and five others had a history of sarcoidosis, emphysema, latent syphilis, pituitary adenoma, or Felty's syndrome.

Examination. Abnormalities found consistently at examination were those to be expected in patients with small bowel obstruction: nonspecific abdominal tenderness, distention, borborygmi, and emesis. The patients with a perforated viscus had signs and symptoms characteristic of an acute abdomen. Of the 15 patients presenting with blood loss, nine also

had abdominal pain and signs of intestinal obstruction. In six patients the findings were nonlocalized and nonspecific.

Laboratory Evaluation. Twenty-nine patients were found to be anemic; other blood tests were of no benefit.

Radiographic examinations were performed in all patients. Twelve had abdominal flat and upright films; one of these showed free air and six demonstrated dilated loops of small bowel. Thirty-eight patients had stomach and small bowel barium series. There was evidence of a duodenal deformity with partial obstruction in three patients and an active ulcer crater in two others. In the small bowel films, 18 abnormalities were found, six of which corresponded to the ulcer site at operation. In these six cases, the following diagnoses were suggested by the radiologist: ileal lymphoma, annular lesion with ulcer, carcinoid, terminal ileal ulcer, and, in two instances, a mass or fixed loop of small bowel with partial obstruction. The other abnormalities, which did not correspond to the ulcer site, included spasm in the midileum, an area of altered mucosal pattern in the ileum, and, in 10 instances, small bowel obstruction.

Colon roentgenograms were obtained in 32 patients; 29 of these were reported to be normal. A constricting lesion of the descending colon with sinus tracts secondary to perforation was reported on one examination, and carcinoma of the transverse colon was incorrectly reported on another. One demonstrated an ileal ulcer as a result of reflux of barium into the terminal ileum. No small bowel enemas were performed. There was, however, reflux of barium into the terminal ileum on most of the barium enemas. Only the ileal ulcer mentioned above was noted. It is conceivable that small bowel enteroclysis might provide sufficient mucosal detail for larger ulcers to be demonstrated.

Proctoscopic examinations were done in 29 patients; all gave normal results except one, which demonstrated a rectal carcinoma. Angiographic studies in six patients were of no diagnostic value.

Ten oral cholecystograms were performed; cholelithiasis was demonstrated in two patients. Other tests, including ultrasound, excretory urography, computed tomography, endoscopic retrograde cholangiopancreatography, gastroscopy, and colonoscopy, were unrewarding.

Preoperative diagnoses were small bowel obstruction (25 cases), indeterminate gastrointestinal bleeding (11), ileal carcinoma (2), colon cancer

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TABLE 2. DISTRIBUTION OF ULCERS IN SMALL BOWEL AND INCIDENCE OF PERFORATION

Location	Ulcers		Perforation		
	No. of Patients	%	No. of Patients	%	
Terminal ileum	36	61	5	}	11
Midileum	10	17	0		
Jejunioileum	4	7	1		...
Jejunum	9	15	7		78

(2), possible common bile duct stone (2), chronic cholecystitis (2), and indeterminate abdominal pain (3). Other preoperative diagnoses included intestinal angina, appendicitis, perforated duodenal ulcer, rectal carcinoma, Zollinger-Ellison syndrome, Crohn's disease, anastomotic ulcer (gastrojejunal), lymphoma, carcinoma of the pancreas, and indeterminate steatorrhea. In two patients, the preoperative diagnosis was ileal ulcer or tumor.

Surgery. In 49 patients, surgery was performed without complication. The operation consisted of resection of a segment of small bowel and primary end-to-end anastomosis. More extensive resection was required in three patients because of complications associated with a perforated small bowel ulcer. Six other patients had additional surgery related to an associated disease—partial gastrectomy for active duodenal ulcer (two), Miles' operation for carcinoma of the rectum (one), mesenteric arterial bypass for suspected intestinal angina (one), splenectomy for Felty's syndrome (one), and resection of the transverse colon for suspected carcinoma (one). One patient with an acute perforation died during operation.

A solitary ulcer was found in 41 patients, two ulcers in five patients, and three ulcers in seven patients. In six patients, more than three ulcers occurred. Thirty-six patients had ulcers within 100 cm of the ileocecal valve, 10 in midileum, four in jejunioileum, and nine in jejunum.

In 13 patients, perforation of the small bowel ulcer was found at operation (Table 2). In another instance, perforation had occurred in a sigmoid diverticulum unassociated with the patient's ileal ulcer. Eleven of the perforations occurred in patients with solitary ulcers. Eight patients had evidence of generalized peritonitis, two had no peritonitis, and four had abscesses communicating with the ulcer.

Besides the patient who died during operation, four patients died in the postoperative period—one



Fig 1. Resected specimen of ileal segment showing solitary, nonspecific, annular ulcer with necrotic, fibrinous surface. Fibrous scar formation has produced narrowing of lumen.

of sepsis and gastrointestinal bleeding on the fourth day, one of sepsis secondary to peritonitis on the eighth day, one of a myocardial infarction 2 weeks after operation, and one after a second operation for bleeding gastric ulcer 4 weeks later.

Three additional patients died within 6 months of operation and two of these fatalities can be related to the operation. One patient, in whom small bowel volvulus developed 4 months postoperatively, died of massive gastrointestinal hemorrhage. Another patient underwent a second operation necessitated by adhesive bowel obstruction. A third patient died of sepsis from *Pseudomonas* secondary to a preexisting myeloproliferative syndrome.

Pathologic Features. Ulcers varied from 0.3 cm to 5.0 cm in diameter. In 19 cases, the lesions showed an annular configuration. The ulcers were predominantly antimesenteric, and in some, fibrous scar tissue formation resulted in narrowing of the small intestinal lumen (Figure 1).

Microscopically, the ulcer crater was filled with a layer of necrotic granulation tissue. Adjacent to this was a zone of inflammatory cells, consisting of plasma cells, lymphocytes, and fibroblasts; this inflammatory area was perhaps indicative of chronicity. In one instance an eosinophilic reaction, as described by Morgenstern et al (6), was striking. The edges of the ulcers were sharply demarcated,

and the inflammatory reaction also ended abruptly at the ulcer's edge. No vascular pathologic changes were evident in any of the specimens. The bowel between ulcers was uniformly normal. No etiologic factors could be determined in any of the 59 cases.

Fifteen percent of the lesions affected the jejunum. Reports describing acute, ulcerative jejunitis and steatorrhea as manifestations of malignant lymphoma have been reported previously (16, 17), but we found no clinical or histologic evidence of lymphoproliferative disorders in the intestine. All patients presenting with a small bowel ulcer for which there was any obvious or possible cause were excluded from this study, thus the name "nonspecific" was used for these ulcers of the small intestine. No detectable microscopic differences were noted in any age group or in either sex.

Follow-Up. We received current information on 50 of the 51 patients who survived more than 6 months after operation. Twenty-eight are alive from 2 to 25 years later, and only seven of the 28 patients have continued with gastrointestinal complaints. These include one episode of small bowel obstruction clearing spontaneously, one complaint suggestive of a long-standing irritable bowel, and one case of episodic abdominal pain for which no cause has been demonstrated. The four other patients have suspected recurrence, two who were found to have multiple ileal ulcers at a second operation and two who have recurrent melena but have not had reexploration.

Twenty-two patients died 1–24 years after operation. Twelve patients succumbed to cardiovascular disease: myocardial infarction (six), cerebrovascular accident (two), congestive heart failure (two), and ruptured abdominal aortic aneurysm (two). Other known causes of death included generalized lymphoma (one), metastatic carcinoma of the colon with radiation ileitis (one), and Wegener's granulomatosis (one). The cause of death in the remaining seven patients is not definitely known. Communications with their family or physician suggested that 21 of the 22 patients remained free of gastrointestinal symptoms.

DISCUSSION

In discussing the clinical features of 59 cases of nonspecific small intestinal ulceration, we selected three major subdivisions based on presenting complaints: abdominal pain suggestive of small bowel obstruction in 63%, blood loss in 25%, and surgical

acute abdomen in 12%. Our findings differ from earlier reports in which anemia was rarely present (6–9, 11, 15) and in which perforation and acute abdomen occurred more frequently (5, 14).

Although we found a steady increase in the number of patients in each decade of life from the second to the seventh, most other studies reported no cases (1, 6, 7, 10, 11), one case (8, 18), or at most three (19), in which the patient was less than 30 years old. Analysis of presenting complaint and age shows that patients with obstructive symptoms had an average age of 59 years and those with acute abdomen had an average age of 58 years. Those presenting with bleeding had an average age of only 36 years. Davies and Brightmore (8), reporting 12 cases of small bowel ulceration, had only one patient with anemia, a 16-year-old boy who also was the only person in that series less than 30 years old. Although ulceration is rare in children, Grosfeld et al (19) reported three cases in which ages were 13 months to 15 years, and all three children had presented with gastrointestinal bleeding. Khan and Kennedy (20) and Shah (21) have each added a case—in which ages were 2 and 15 years, respectively—of ileal ulceration presenting as gastrointestinal bleeding. Why younger people might have more difficulty with bleeding is unknown.

Laboratory evaluation showed that 49% of the patients were anemic. In contrast to Brown and Pemberton (4), who reported hematocrits as low as 20% in patients not known to be anemic, we found hemoglobin levels to be only slightly below normal in those patients not briskly bleeding. Our lowest hemoglobin value was 4.4 g/dl in a patient with melena, and the lowest hemoglobin value among those with unexpected anemia was 9.8 g/dl.

Gastrointestinal contrast studies were performed in 108 patients; only five of the studies localized the ulcer. The upper gastrointestinal series gave abnormal results in 13%, and results of the small bowel follow-through were abnormal in 47%. Only 6% of the colon x-ray studies were in any way unusual, but 58% of the abdominal roentgenograms showed evidence of obstruction. In all, 66% of the patients had some radiographically apparent abnormality that suggested the need for surgical intervention.

The operative procedure in all cases was resection of the involved segment of bowel and anastomosis. Although there have been reports of cure by simple closure of the ulcer (14), Guest (2) recounted a case with three recurrences of the same ulcer in 3 years after closure as opposed to resection.

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We documented intestinal perforation in 13 cases (22%), and the five operative deaths occurred in this group. Our total perioperative mortality of 8.5% was lower than that noted by Evert et al (14) in 1948, but it is consistent with more recent studies documenting 0–12% operative deaths (1, 6, 9, 13, 15). Evert et al reported 130 cases; 81% had intestinal perforation, and surgical mortality was 60%. Watson (5) noted a 12% perforation rate and 11% mortality, but Morgenstern et al (6) reported no operative deaths despite a 23% perforation rate. This decreased mortality reflects a change in both the severity of the clinical problem and the use of antibiotics unavailable in earlier series.

Ileal ulcers constitute 78% of this series, jejunal ulcers 15%, and jejunoileal ulceration 7%. Seventy-eight percent of the jejunal ulcers perforated, compared with only 11% of the ileal lesions (Table 2).

Follow-up was possible from 2 to 25 years after operation. The only other prolonged study is that of Morlock et al (15), who reported on 32 patients contacted from 1½ to 25 years after hospitalization. Of their 20 surviving patients, 65% were completely asymptomatic; this rate is less than our 84% cure rate. Two of our patients had surgically proved recurrent ulceration 2 and 10 years after initial resection, but both are currently doing well. Because most patients are completely relieved of their symptoms by surgery, it seems unlikely that an ongoing pathologic process is responsible for recurrence. The disease appears to be self-limited.

The cause of these lesions has always been in question. Baker et al (22), in 1964, and Morgenstern et al (6), in 1965, implicated thiazides and potassium chloride as causal agents. Boley et al (23) were able to induce intestinal ulcers in dogs with the use of enteric-coated potassium chloride but not with thiazides or enteric-coated placebos. Boley et al (24, 25) suggested that the rapid release of potassium within a short segment of bowel causes paralysis of intramural veins, venous stasis, and, finally, infarction.

Even at the peak of the enteric-coated potassium chloride controversy of the 1960s, a survey by Lawrason et al (7) of 440 hospitals in the United States, Canada, South America, Europe, Africa, Australia, and New Zealand involving 395 patients with nonspecific small bowel ulcers revealed that less than half were using enteric-coated potassium or thiazide-potassium preparations. In our series, only six (10%) of the patients were using enteric potassium.

Most series suggest a relationship between car-

diovascular disease and ulceration (1, 2, 8, 21, 22). Congestion of the vessels near the ulcers (8), occlusion of submucosal or mesenteric vessels (10), and narrowing of arterioles have been held as evidence of possible vascular etiologic factors. Eleven of our patients had cardiovascular disease preoperatively, and in 12 others, symptomatic cardiovascular disease developed postoperatively (23 patients, 39%). Review of our pathology specimens showed no indication of a vascular etiology and less than half showed clinical evidence of vascular disease; thus it would seem unlikely to be the significant factor. Cardiovascular disease is one of the leading causes of death today, and a high incidence can be expected in patients aged 50 years or older.

The 59 cases we have reviewed represent approximately four small bowel ulcers per 100,000 new patients registered at the Mayo Clinic. Eleven cases presented from 1956 to 1959 (2.75 cases per year), the incidence was 3.6 cases per year from 1960 to 1969, and the decade 1970–1979 provided only 1.2 cases per year.

For the years 1960–1969, it is likely that the enteric-coated potassium chloride controversy made clinicians more aware of the possibility of small bowel ulceration. We cannot attribute the decreased incidence in the most recent decade to lack of use of enteric potassium, since few of our patients ingested this medication. Rather, this may reflect a decreased awareness of the disease entity.

Unless the question of small bowel ulcer is specifically raised, the diagnosis will not be made preoperatively and, because of the nonspecific nature of the patient's complaints, surgery is unlikely to be performed. Because the majority of patients suffer only recurrent abdominal discomfort, the natural history of this entity is unknown. Spontaneous healing is seldom apparent (14), but the clinical course in many cases suggests that a common terminal event is perforation and death from sepsis.

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