Endoscopic Features and Clinical Characteristics of Ulcerations With Isolated Involvement of the Small Bowel

Feng-fei Wu[1], Qian Xie[1], Xiao-shan Huang[1], Wei-dong Wang[1], Yan Liao[1], Jie Shi[1], Shi-bo Sun[2], Lan Bai[1,*], Fang Xie[1,*]

[1]Guangdong Provincial Key Laboratory of Gastroenterology, Department of Gastroenterology, Institute of Gastroenterology of Guangdong Province, Nanfang Hospital, Southern Medical University, Guangzhou, China
[2]Department of Hepatobiliary Surgery, Nanfang Hospital, Southern Medical University, Guangzhou, China

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ABSTRACT

Background: *Double-balloon enteroscopy (DBE) enables the detection of ulcerations in the small bowel. However, determining an etiological diagnosis remains challenging. This study was conducted to investigate the clinical and endoscopic features of ulcerations with isolated involvement of the small bowel (UIISB) to improve diagnostic ability.*

Methods: *Patients (n = 565) who underwent DBE and presented with ulcerations in the small bowel at Nanfang Hospital from January 2005 to January 2018 were eligible. Medical records were retrospectively examined. Predictors to determine ulceration etiology were identified by logistic regression analysis.*

Results: *After excluding patients with extra-ulcerations in other sites (n = 306) and those without follow-up records (n = 50), 209 patients with UIISB were enrolled. Among them, 59.3% of the ulcers were in the ileum, 26.8% in the jejunum, and 13.4% in the jejunoileum. Initial symptoms included abdominal pain (54.1%) and obscure gastrointestinal bleeding (30.0%). The multiplicity of ulceration was categorized as a single (22.0%) or multiple (78.0%). Cases were diagnosed with Crohn's disease (50.7%), chronic nonspecific inflammation (21.5%), diverticulum (9.1%), lymphoma (6.2%), gastrointestinal stromal tumor (4.3%), intestinal tuberculosis (1.9%), adenocarcinoma (1.4%), infective enteritis (1.4%), hemangioma (1.0%), cryptogenic multifocal ulcerous stenosing enteritis (1.0%), anastomotic ulcer (0.5%), intestinal duplication (0.5%), or neuroendocrine tumor (0.5%). Etiology identification indicated the if patients were aged 40 years or more, or had overt bleeding, single ulceration, and ulcer at jejunum, it as more prone to be neoplastic ($P < .05$).*

Conclusion: *When we manage patients with UIISB, Crohn's disease should be first under consideration. Age≥40, overt bleeding, single ulceration, and ulcer at jejunum were reasonable indications for etiology of neoplasm or non-neoplasm.*

Keywords: *Small bowel, ulceration, etiology, double-balloon enteroscopy (DBE)*

INTRODUCTION

The small intestine is a 6-7 meter-long hollow tube that begins at the pylorus and ends at the ileocecal valve, where most chemical digestion occurs.[1] Viewed as a "black box" in the gastrointestinal tract, small bowel diseases are regarded as relatively rare disorders.[2,3] Hence, this area remained unexplored, and reaching an etiological diagnosis in patients with ulcerations with isolated involvement of the small bowel (UIISB) remained challenging and resulted in substantial morbidity, mortality, health-care costs, and unnecessary surgery.[4-6] The introduction of capsule endoscopy (CE)[3] in 2001 and double-balloon enteroscopy (DBE)[7,8] in 2003 enabled endoscopists to examine the entire small bowel in addition to the stomach and colon. Diagnosing and treating small bowel disorders has since improved markedly.[9,10] DBE is the most practical procedure for detecting UIISB, because DBE permits direct visualization of the small bowel mucosa, retrieval of biopsies and enables therapeutic interventions.[4,6,7] However, etiological diagnoses remain challenging in patients with UIISB.

Because DBEs enable a relatively high detectability of small bowel lesions, positive DBE findings can partially reflect the small bowel disease pattern.[11] However, several diseases can account for small bowel ulcers, and their clinical manifestations are extremely similar.[12,13] Therapeutic regimens for different causes are difficult to distinguish from one another and could accelerate disease development if the small bowel ulcers are inaccurately diagnosed.

*These authors contributed equally to this work.

Corresponding author: **Lan Bai**, e-mail: **bailan99@hotmail.com** and **Fang Xie**, e-mail: **stellaff@126.com**
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This study was conducted to retrospectively analyze the clinical manifestations, endoscopic features, and further etiology of DBE-detected UIISB.

MATERIALS AND METHODS

Patients

The DBE database of Nanfang Hospital, Southern Medical University University, was screened to identify patients with ulcerations in the alimentary canal, between January 2005 and January 2018. Five hundred sixty-five patients had gastrointestinal ulcerations on endoscopy during the study period. The upper gastrointestinal and colorectal mucosa of all patients were successfully evaluated via esophagogastroduodenoscopy (EGD) or ileocolonoscopy. Of these, patients who had extra-ulcerations in the esophagus, stomach, proximal duodenum, ileocecal valve, or large intestine (n = 306), and those without follow-up records (n = 50) were excluded (Figure 1). This retrospective study was conducted in accordance with the Helsinki Declaration and approved by the Medical Ethics Committee of Nanfang hospital. All patients provided written informed consent to undergo endoscopies, including endoscopic therapy.

Diagnosis

The following diagnoses were made: Crohn's disease (CD)[14], chronic nonspecific inflammation (CNI), intestinal tuberculosis (ITB)[15], infective enteritis (IE), and anastomotic ulcer (AU), which were diagnosed using a defined combination of clinical presentation, endoscopic appearance, and pathological examinations, also partially according to the patients' response to treatment during the long-term follow-up after routine diagnosis and treatment. The cryptogenic multifocal ulcerous stenosing enteritis (CMUSE)[16] cases were identified mainly by postoperative pathology, combined with clinical information and endoscopic findings. The AU case had a primary disease of benign lipoma, with ulceration presenting 3 months after surgical resection, which ruled out the possibility of lipoma recurrence. Patients with lymphoma, gastrointestinal stromal tumor (GIST), adenocarcinoma, hemangioma, intestinal duplication (ID), and neuroendocrine tumor (NET) were determined based on clinical information, endoscopic findings, and postoperative pathological examinations, while a few were diagnosed via endoscopic biopsy. According to National Comprehensive Cancer Network (NCCN) guidelines[17], the accurate diagnosis of GIST should be based on tumor morphology and immunohistochemistry. Additionally, 16 out of all the 19 cases with diverticulum presented a diverticular cavity under DBE, and 10 were determined by postoperative pathology, including the remaining 3 cases. In our study, patients with CNI who showed UIISB had histopathological evidence of chronic and nonspecific inflammation and mostly met the qualifications of clinical remission without recurrence. Few had persistent symptoms during follow-up after a series of medical treatments, including medications for intestinal mucosal protection, flora regulation, and surgery. During follow-up, all patients in our study presented no history of specialized drug use, including nonsteroidal anti-inflammatory or chemotherapeutic drugs.

Main Points

- *The diagnosis of small bowel ulcers remains challenging, and the etiology is varied. We reported 209 patients with ulcerations with isolated involvement of the small bowel.*
- *Crohn's disease is the main cause, followed by chronic nonspecific inflammation, diverticulum, lymphoma, gastrointestinal stromal tumor, intestinal tuberculosis, adenocarcinoma, and others.*
- *When we manage patients with ulcerations with isolated involvement of the small bowel, Crohn's disease should be first under consideration. Age≥40, overt bleeding, single ulceration, and ulcer at jejunum are reasonable indications for etiology of neoplasm or non-neoplasm.*

Multiplicity of Lesions

The multiplicity of UIISB was categorized as single or multiple ulcers. Single ulcers (n = 46) were identified via the following 5 methods: (1) DBE communication through the anus and mouth (n = 2), (2) CE observation of the whole small intestine (n = 20), (3) surgical exploration if necessary, combined with DBE, and postoperative pathology (n = 30), (4) computed tomography enterography (CTE) showed that the lesion was limited to a specific small intestinal segment (n = 4), and (5) surgical exploration and CE confirmed simultaneously (n = 6).

Statistical Analysis

Predictors to identify the etiology of ulcerative lesions were evaluated in patients with non-neoplasm/neoplasm-associated ulcers by univariate analysis with Pearson's chi-squared test or Fisher's exact test, as appropriate. Individual odds ratios and 95% CIs were computed for each variable by logistic regression analysis.

RESULTS

General Characteristics of UIISB

Two hundred 9 patients underwent 275 DBEs (49 antegrade, 94 retrograde, 66 both antegrade and retrograde).

Table 1. Baseline Characteristics of the Patients with Ulcers With Isolated Involvement of the Small Bowel

Characteristics, *n* (%)	Total (*n* = 209)
Age ≥ 40 years	101 (48.3)
Sex, male	159 (76.1)
Overt bleeding	100 (47.8)
Blood transfusion before diagnosis	10 (4.6)
NSAIDs	4 (1.8)
Duodenum/Jejunum/Ileum/Jejunoileum	1/56/124/28 (0.5/26.8/59.3/13.4)
Single ulceration	46 (22.0)
Duodenum/Jejunum/Ileum	1/19/26 (2.2/41.3/56.5)
Multiple ulceration	163 (78.0)
Jejunum/Ileum/Jejunoileum	37/98/28 (22.7/60.1/17.2)
Intestinal stenosis	87 (41.6)

M, male; NSAID, non-steroidal anti-inflammatory drug.

Three patients completed the entire small intestinal examination via oral and anal approaches. All procedures were successfully performed. No perforation, hemorrhage, or other serious adverse events occurred in any of the endoscopic procedures.

Of the 209 patients, 159 were male and 50 were female; the ages at initial diagnosis ranged from 11-75 years (Table 1), and the average age was 40 years. The ulcers were in the duodenum (0.5%), jejunum (26.8%), ileum (59.3%), and jejunoileum (13.4%). Ulcerations in patients with GIST and adenocarcinoma were mainly located in the jejunum, while CD, CNI, diverticulum, lymphoma, ITB, and IE were mainly located in the ileum.

Initial Symptom and First Impression of the Endoscopists Relative to the Etiological Classification of Patients With UIISB

Table 2 summarizes that the most frequent initial clinical symptom of small intestinal ulcers was abdominal pain (54.1%), followed by obscure gastrointestinal bleeding (OGIB, 30.0%), and less frequently, abdominal distension (3.3%) and chronic diarrhea (1.9%). Patients with GIST, adenocarcinoma, and hemangioma presented with OGIB as the initial symptom. Chronic diarrhea (1.9%) and other initial symptoms (3.3%, including fever, perianal fistula or abscess, abdominal mass, dental ulcer, and purpura) only occurred in patients with CD. The most common initial symptom of CD patients was abdominal pain (63.2%), which was consistent with lymphoma (61.5%) and ITB (50%).

Considering the clinical manifestations, endoscopic findings and pathological examinations, 106 cases (50.7%) were diagnosed as CD, 45 (21.5%) as CNI, 19 (9.1%) as diverticulum, 13 (6.2%) as lymphoma, 9 (4.3%) as GIST, 4 (1.9%) as ITB, 3 (1.4%) as adenocarcinoma, 3 (1.4%) as IE, 2 (1.0%) as hemangioma, 2 (1.0%) as CMUSE, and 1 (0.5%) each as AU, ID, and NET. The endoscopists' first impressions relative to the etiological classification of UIISB were analyzed (Table 2). The highest coincidence rates for the diagnoses were diverticulum (84.2%), followed by CD (73.6%), CNI (60.0%), GIST (44.4%), adenocarcinoma (33.3%), IE (33.3%), ITB (25.0%), and lymphoma (15.4%) (Table 2 and Table S1). In 18 cases with diverticulum, a double lumen sign or diverticular orifice was seen directly in 15 cases under DBE; no diverticulum was found in 3 cases because of the intestinal stenosis, where diverticulum could be seen during surgery.

Endoscopic Diagnosis of UIISB

UIISB multiplicity was categorized as single (*n* = 46, 22.0%) or multiple ulcers (*n* = 163, 78.0%). As for patients with a single ulcer, 19 cases (41.3%) had neoplastic ulceration and 27 cases (58.7%) had non-neoplastic ulceration. Endoscopic findings in patients with neoplasm-associated single ulcerations displayed substantial circular ulcers with necrotic debris occupying most of the circumferential lumen, local ulcerations in the middle of the mass, occasional narrowing of the intestinal lumen, or bleeding easily on contact during endoscopy. In the 19 cases of neoplasm-associated single ulcerations, 8 were GIST, 6 were lymphoma, 3 were adenocarcinoma, 1 was hemangioma and 1 was NET. The non-neoplastic ulcerations included diverticulum (*n* = 14), CNI (*n* = 10), ITB (*n* = 1), IE (*n* = 1), and AU (*n* = 1).

Of the 163 cases of multiple ulcerations, 154 (94.5%) were non-neoplastic ulcerations and 9 (5.5%) were neoplastic ulcerations. The ulcers in patients with non-neoplasm-associated multiple ulcerations were superficial, approximately 3-8 mm in diameter with a central depression, affected the mucosa and the submucosa, and were occasionally covered with white moss, fibrin, or inflammatory infiltrate. The mucosa on both sides of the ulcers was normal. In the 154 cases of non-neoplasm-associated multiple ulcerations, 106 were CD, 35 were CNI, 5 were diverticulum, 3 were ITB, 2 were IE, 2 were CMUSE and 1 was ID. The neoplastic ulceration incidence was lymphoma (*n* = 7), GIST (*n* = 1), and hemangioma (*n* = 1).

Table 2. Initial Symptom and First Impression of the Endoscopists Relative to the Etiological Classification of Patients With Ulcers with Isolated Involvement of the Small Bowel

		Initial symptom, *n* (%)								
	Number of Patients	Abdominal Pain	OGIB	Abdominal Distension	Chronic Diarrhea	Constipation	Vomiting	Weight Loss	Others[a]	Accurate first impression,[b] *n* (%)
CD	106 (50.7)	67 (63.2)	22 (20.8)	4 (3.8)	4 (3.8)	0	1 (0.9)	1 (0.9)	7 (6.6)	78 (73.6)
CNI	45 (21.5)	23(51.1)	17 (37.8)	2 (4.4)	0	2 (4.4)	0	1 (2.2)	0	27 (60.0)
Diverticulum	19 (9.1)	6 (31.6)	12 (63.1)	0	0	1 (5.5)	0	0	0	16 (84.2)
Lymphoma	13 (6.2)	8 (61.5)	4 (30.8)	0	0	0	1 (7.7)	0	0	2 (15.4)
GIST	9 (4.3)	0	9 (100.0)	0	0	0	0	0	0	4 (44.4)
ITB	4 (1.9)	2 (50.0)	1 (25.0)	1 (25.0)	0	0	0	0	0	1 (25.0)
Adenocarcinoma	3 (1.4)	0	3 (100.0)	0	0	0	0	0	0	1 (33.3)
IE	3 (1.4)	2 (66.7)	1 (33.3)	0	0	0	0	0	0	1 (33.3)
Hemangioma	2 (1.0)	0	2 (100.0)	0	0	0	0	0	0	0
CMUSE	2 (1.0)	2 (100.0)	0	0	0	0	0	0	0	0
AU	1 (0.5)	1 (100.0)	0	0	0	0	0	0	0	0
ID	1 (0.5)	1 (100.0)	0	0	0	0	0	0	0	0
NET	1 (0.5)	1 (100.0)	0	0	0	0	0	0	0	0
Total	209	113 (54.1)	71 (34.0)	7 (3.3)	4 (1.9)	3 (1.4)	2 (1.0)	2 (1.0)	7 (3.3)	129 (61.7)

OGIB, obscure gastrointestinal bleeding.

[a] Other symptoms include fever, perianal fistulas or abscess, abdominal mass, dental ulcer, and purpura.

[b] Accurate first impression represents the coincidence rate between the first impression of the endoscopists and the final etiologic diagnosis.

Table 3. Predictors to Identify Ulceration Etiology of the Patients with Ulcers With Isolated Involvement of the Small Bowel

	Neoplasm†	Non-neoplasm‡	Crude OR	
Characteristics, n (%)	(*n* = 28)	(*n* = 181)	(95% CI)	*P*
Age ≥ 40	24 (85.7)	64 (35.4)	10.2 (3.4-10.7)	<.001
Sex, M	16 (57.1)	143 (79.0)	0.4 (0.2-0.8)	.017
Overt bleeding	21 (75.0)	78 (43.1)	4.8 (1.9-12.5)	<.001
Blood transfusion before diagnosis	1 (3.6)	9 (5.0)	0.7 (0.1-5.8)	1.000 §
NSAIDs	0 (0)	4 (2.2)	NA	1.000 §
Single ulceration	19 (67.9)	27 (14.9)	12.0 (4.9-29.39)	<.001
Jejunum	15 (26.8)	41 (73.2)	3.9 (1.7-8.9)	.001
Intestinal stenosis	14 (50.0)	71 (41.3)	2.1 (0.9-4.6)	.099

Bold values indicate statistical significance.
Etiologies that were classified as neoplasm were lymphoma, gastrointestinal stromal tumor, adenocarcinoma, hemangioma, and neuroendocrine tumor.
Etiologies that were classified as non-neoplasm were Crohn's disease, chronic nonspecific inflammation, diverticulum, intestinal tuberculosis, infective enteritis, cryptogenic multifocal ulcerous stenosing enteritis, anastomotic ulcer, and intestinal duplication.
They were analyzed by Fisher's exact test.
M, male; NSAID, non-steroidal anti-inflammatory drug; OR, odds ratio.

Eighty-seven patients (41.6%) had small intestinal strictures, of which the patients with CD, lymphoma, ITB, adenocarcinoma, CMUSE, and NET were more likely to develop intestinal stenosis; CNI and diverticulum cases were less prone to stenosis. Moreover, the causes of stenosis of the lymphoma were stenosis of the intestinal segment, peripheral ulcers, and blockage of the intestinal cavity by the tumor. Six cases of diverticular stenosis included diverticular orifice stenosis (33.3%), intestinal stenosis due to peridiverticular ulcer (50.0%), and stenosis ring in the middle of the diverticular cavity (16.7%). Although NET was a G1 phase lesion, endoscopy showed an ulcerative mass, local swelling with circumferential infiltration, and stenosis, accounting for approximately 80% of the intestinal lumen. No intestinal stenosis occurred in patients with GIST, IE, hemangioma, AU, or ID.

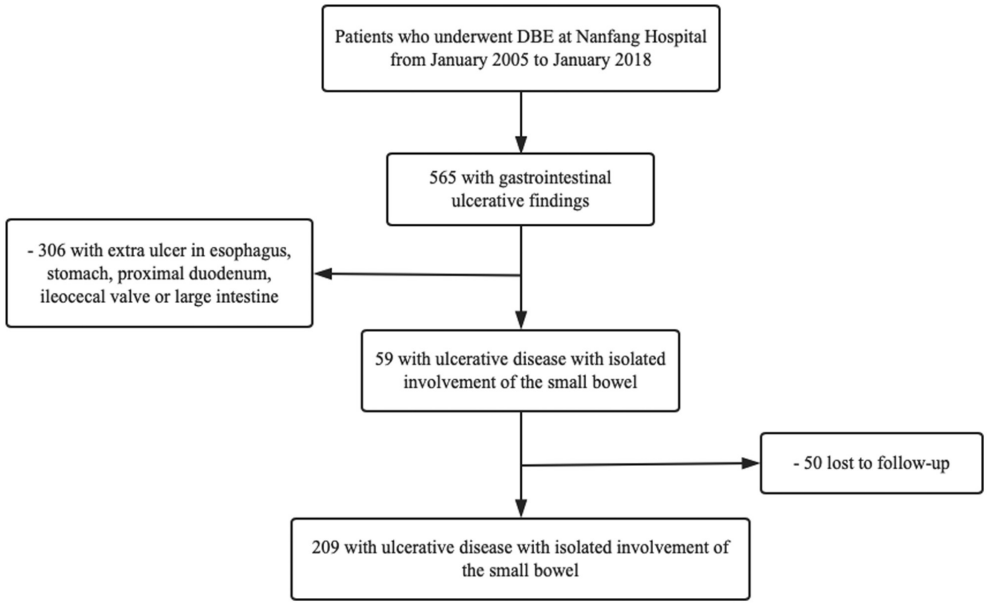

Figure 1. Flow chart of the patient selection process.

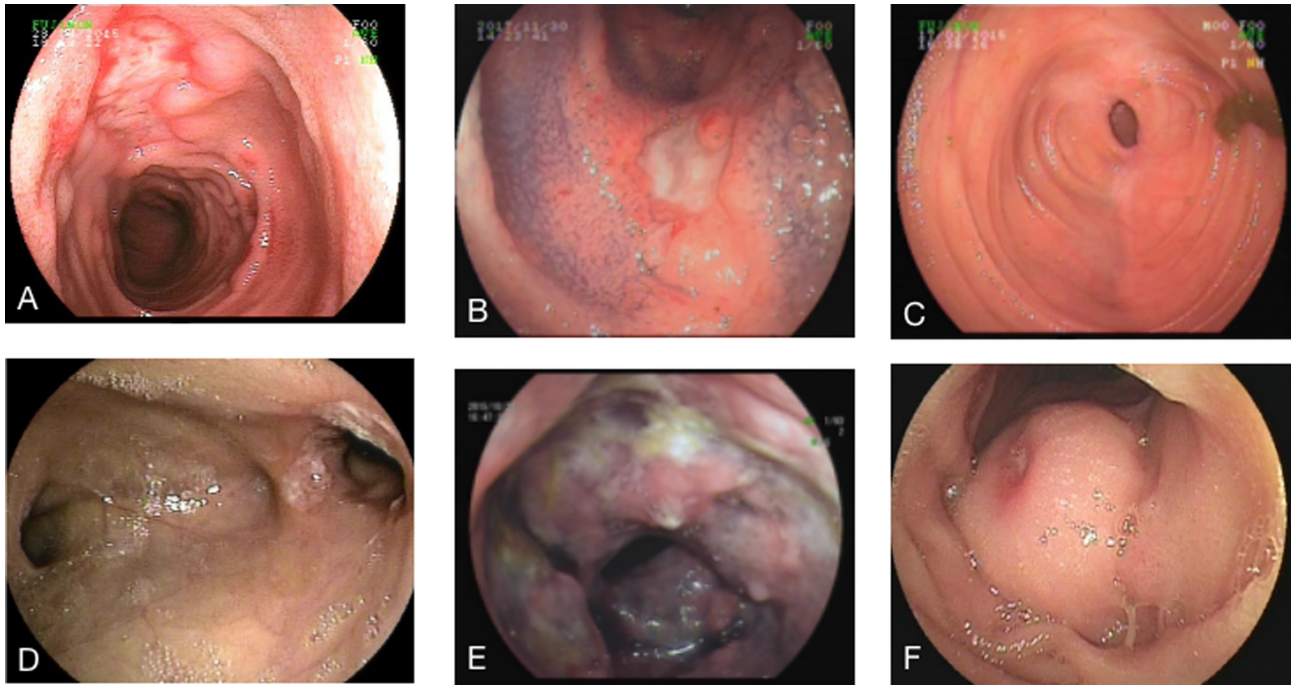

Figure 2. (A) Crohn's disease. Longitudinal linear ulcer and cobblestone in the jejunum. (B) Crohn's disease. Inflammatory changes in the small bowel with extensive ulcer. (C)Superficial ulcers of CNI in small bowel. (D) Diverticulum. Ulcerations at the mouth of the diverticulum. (E) Lymphoma. Large circular ulcers with filthy fur occupying most of the circumferential lumen. (F) GIST. Mucosal ulceration of tumors.

Predictors of Etiologies

Of the 209 patients with UIISB, the neoplastic etiology was diagnosed in 28 (13.4%) cases (Table 3). In the etiology determination, age ≥40 ($P < .001$), male sex ($P < .05$), overt bleeding ($P < .001$), single ulceration ($P < .001$), and ulcer at jejunum ($P = .001$) were more common in patients with neoplasm-associated ulceration than in those with non-neoplasm-associated ulceration. After excluding insignificant factors, age≥40, overt bleeding, single ulceration, and ulcer at jejunum ($P < .05$) remained as predictors for neoplastic or non-neoplastic etiologies (Table S2).

Etiological Classification of Patients With UIISB CD

CD was the most common cause of UIISB, with an average patient age of 36 years and a male ratio of 84%. The most common site was the ileum (57.5%) and all the ulcerations were multiple. Endoscopic findings showed a skipped involvement of the small bowel (59.8%), longitudinal linear ulcers (49.1%), aphthous ulcers (29.5%), irregularly shaped shallow ulcers (22.3%), cobblestone appearance (6.3%), and luminal stricture (49.1%) (Figure 2A and B). Patients with stenosis underwent computed tomography (CT), magnetic resonance imaging, or CTE to determine the expansion and activity of the disease.

CNI

Of the 45 patients with CNI, most presented with differently shaped superficial ulcers (Figure 2C), and a few showed multiple segmental longitudinal ulcers (14.2%). Intestinal stenosis occurred in 10 cases, and nonadjacent segmental and asymptomatic diverticulum occurred in 6 cases in the whole small bowel. Among all patients with CNI, only 6 required surgery, of which 3 underwent surgery because of ulcer-induced intestinal stenosis and obstruction. In the other 3 cases, DBE revealed both ulcerations and multiple asymptomatic diverticula, resulting in simultaneous resection of the 2 nonadjacent intestinal segments. Endoscopic biopsies were performed in all 45 patients, of which 40 had chronic mucosal inflammation, and 6 had chronic mucosal inflammation with acute inflammatory reaction. Most patients achieved clinical remission after nonspecific treatment, with no recurrence during the follow-up period except in 6 patients with CNI (Figure 3) who were followed-up for an average of 4.16 years.

Diverticulum Complicated With Ulceration

Ulcerations (Figure 2D) were localized primarily at the mouth of the diverticulum (57.9%), partly in the

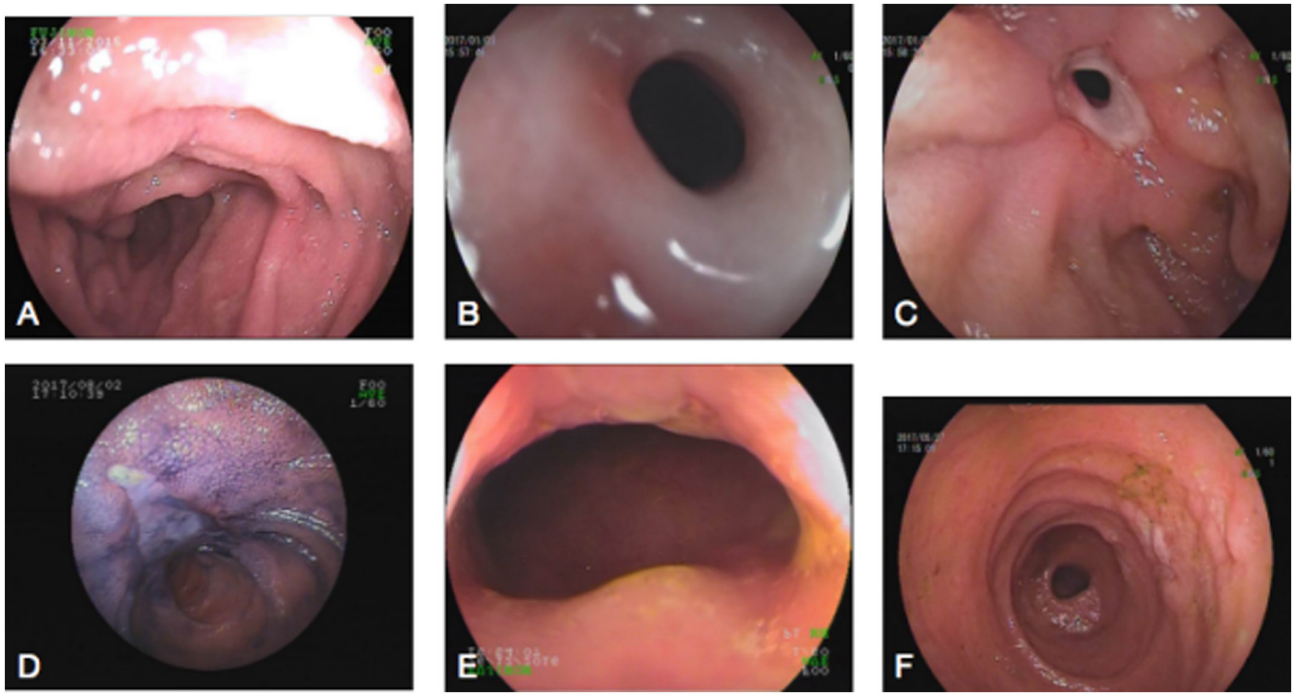

Figure 3. Six cases with CNI respectively. (A) Multiple shallow ulcers in multiple sites of the small bowel. (B) Circumferential ulcer in the jejunum. (C) Circumferential ulcer in the ileum. (D) Multiple ulcers in the ileum. (E) Ulcer in the terminal ileum. (F) Multiple superficial ulcers in multiple sites of the small bowel.

diverticular cavity (26.3%), and a few at the tissue bridge between the lumen and diverticulum (15.8%). Among them, 5 cases were multiple diverticula with multiple ulcers. All presented with variable degrees of gastrointestinal bleeding (12 cases of melena and 7 of hematochezia) throughout the disease course, including 6 patients with the initial symptom of abdominal pain whose first occult bleeding test was positive. Patients with diverticulum in the jejunum (15.8%) exhibited much less abdominal pain than did those with diverticulum in the ileum (73.7%) and jejunoileum (10.5%). Of 10 cases of Meckel's diverticulum, a large area of ectopic gastric mucosa was detected histologically in 4 cases.

Lymphoma

The endoscopic characteristics of lymphoma (Figure 2E) were deep circular ulcers with a mass occupying most of the circumferential lumen. Six cases had circular ulcers, 5 had longitudinal ulcers, and 2 had ulcerative masses and a narrowed intestinal lumen. The ulcer diameters exceeded 12 mm (length of the 2 biopsy forceps) in 11 cases; the maximum diameter was 30 mm. The ulcers bled easily on contact during endoscopy. Forceps biopsies histologically diagnosed lymphoma in 2 of 13 cases (15.4%), whereas the others were all diagnosed using surgical specimens, including 11 cases of ulcerative diffuse large B-cell lymphoma (84.6%), and 2 enteropathy-associated T-cell lymphomas (15.4%). In addition to the main symptoms at presentation, such as abdominal discomfort/pain, and OGIB, several systemic symptoms were also present in 4 patients. One patient had bone marrow involvement.

Others

Five patients presented with GIST lesions (Figure 2F) detected as mucosal tumoral ulcerations; 2 had extraductal growth with large mucosal ulcerations, 1 had large ulcerations with surrounding edema, and 1 exhibited linear ulceration. The average maximum tumor diameter was 6 cm (range, 3-10 cm). Figure 4 shows the endoscopic findings for ITB, adenocarcinoma, IE, hemangioma, CMUSE, AU, ID and NET.

DISCUSSION

The various etiologies of ulceration make UIISB challenging to diagnose. One key strength of our study was that only patients with UIISB were enrolled, with more than 200 patients who were well-characterized regarding

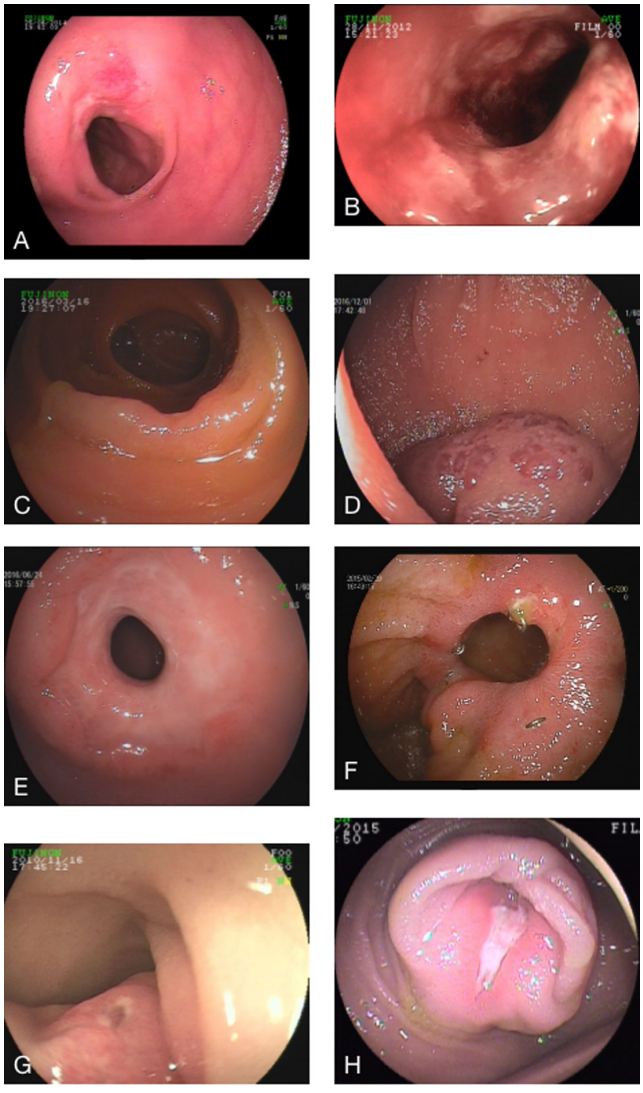

Figure 4. (A) ITB. Coexistence of active lesions and atrophic scar bands, stenosis formation. (B) Adenocarcinoma. Multiple irregular huge ulcers with surrounding hyperemia leading to stenosis of the lumen. (C) IE. Superficial ulcer with central depression. (D) Hemangioma. Multiple granular villi, multiple punctate hyperemia and ulcers on the surface of the mass. (E) CMUSE. Shallow circular mucosal ulcerations and stenosis in the small bowel. (F) Anastomotic ulcer. A superficial ulcer at the anastomotic site 3 months after lipoma surgical resection. (G) Ileum duplication. Superficial ulcer covered with white fur and blood scab, and surrounding hyperemia, edema of small bowel. (H) NET. Ulcerative masses in the ileum.

clinical, endoscopic, histopathologic, and hematological data, as small bowel ulcers are already rare, compared to other diseases of the digestive tract.

The patients' age and etiological classifications showed that those with IE, CD, diverticulum, CMUSE, CNI, ITB, and lymphoma were on average aged 27-48 years at initial diagnosis ranked by average age, and those with GIST, NET, ID, adenocarcinoma, hemangioma, and AU ranged in age from 51-58 years. In our study, male patients predominated, except for those with GIST, IE, AU, ID, and NET. The male : female ratio was 166 : 51. Chen et al.[18] reported that 400 patients with small bowel disease had a mean age of 47 years (range, 14-86 years), and the male : female ratio was 250 : 150. Conversely, Hatzaras et al.[19] reported that among 1260 small bowel tumor patients, 628 were men (49.8%), and 632 were women (50.16%), with a mean age at presentation of 65.2 years. In our study, 28 patients had small bowel tumors: 16 men (57.1%) and 12 women (42.9%), with a mean age at presentation of 45 years. We documented 113 patients (54.1%) with abdominal pain and 71 patients (34.0%) with OGIB as the initial symptom. Gong et al.[20] reported 67 patients referred mainly for OGIB (40.3%) and abdominal pain (29.8%).

Among 209 patients with UIISB, CD was the main cause (50.7%), followed by CNI (21.5%), diverticulum (9.1%), lymphoma (6.2%), GIST (4.3%), ITB (1.9%), adenocarcinoma (1.4%), IE (1.4%), hemangioma (1.0%), CMUSE (1.0%), AU (0.5%), ID (0.5%), and NET (0.5%). Recent epidemiological studies have indicated an increased incidence of small bowel neoplasms, particularly for malignant tumors.[19] It is worth noting that age≥40, overt bleeding, single ulceration, and ulcer at jejunum were indications for diagnosis. Nineteen (67.9%) out of all 46 patients with single ulcers had small bowel neoplasm, of which GIST (42.1%) was the major cause, followed by lymphoma (31.6%), adenocarcinoma (15.8%), hemangioma (5.3%), and NET (5.3%). Nine (5.5%) out of all 163 patients with multiple ulcers had non-neoplasm-associated diseases, including lymphoma (77.8%), GIST (11.1%), and hemangioma (11.1%). Moreover, single ulcerations indicated localized disease, and their etiologies were more likely to be tumors. In a previous report,[21] 5 of 68 patients with small bowel ulcerations had single lesions and were all diagnosed with small bowel tumor. To improve the diagnostic rate, selecting between the antegrade or retrograde DBE route is important for accessing the lesions.[22] Predicting the location of the ulcerations on imaging examinations can be difficult because the small bowel can fold up in the abdominal cavity. Prediction by CE is also difficult because the passing speed of the capsule differs between the jejunum and ileum. Combining the analysis of ulcer location and imaging examination demonstrates that the ulcer located in jejunum is more likely to develop into tumor. Of the ulcers in our study, ileal ulcers constituted 59.3%, jejunal ulcers 26.8%, jejunoileal ulcers

13.4%, and duodenal ulcers 0.5%. Site stratification by etiological classification showed that ulcerative lesions in patients with GIST (77.8%), adenocarcinoma (100.0%), and NET (100.0%) were more common in the jejunum than in other sites; whereas the ulcers with CD (57.5%), CNI (71.1%), diverticulum (73.7%), lymphoma (46.2%), tuberculosis (75.0%), and IE (66.7%) were more common in the ileum. A 2014 survey by Wada et al.[23] revealed that small bowel ulcers in 4 patients were all located in the ileum. Most cases occurring in the proximal jejunum included less than 50 cm of the Treitz ligament, while in the ileum, the distal ileum within 50 cm of the ileocecal valve was more frequent.

In our study, multiple ulcerations indicated non-neoplasm-associated diseases despite 9 cases of (5.5%) identifying tumor, and their etiologies were more likely to be CD (65.0%), CNI (21.5%), ITB, IE, CMUSE, or ID, which is consistent with the report of Aoki T et al.[21] After excluding patients with diverticulum, ulcers in patients with CD (57.5%) and CNI (71.4%) tend to be more in the ileum than in other sites. Besides, in patients with multiple ulcerations, clinical information, such as non-steroidal anti-inflammatory drug use, blood transfusion histories, symptoms, medical histories, and laboratory data could lead to the presumption of ulceration etiology. To sum up, combined with the results of univariate and multivariate analysis, it is shown that age≥40, overt bleeding, single ulceration, and ulcer at jejunum were reasonable indications for etiology of neoplasm or non-neoplasm.

Prior studies of the small bowel were limited and insufficient, making the diagnosis difficult.[6] Our recent analysis greatly contributes to understanding the etiological diagnosis of UIISB. Initially, CD should be ruled out, because in our study, it was the most frequent cause of UIISB, accounting for 52.1%. The 72.6% of final diagnoses with CD were consistent with the first impressions of the experienced enteroscopists in our study. However, microscopic features were minimally assessed on mucosal biopsy but completely assessed on operative specimens. Even when granulomas were found on biopsy, their presence had to be interpreted in the appropriate clinical context, as they might also be seen in association with ITB and sarcoidosis, Yersinia infection, and even disrupted crypts in severe crypt abscesses in ulcerative colitis. These granulomas, in association with entities other than CD, frequently have a different appearance, and their specificity should be addressed by a gastrointestinal pathologist in cases in which the diagnosis of CD is in doubt.

The results of our study indicated that CD is easily confused with CNI, lymphoma, and ITB. CNI can achieve short-term remission clinically using medications for intestinal mucosal protection and flora regulation. Multiple biopsies taken from multiple sites adjacent to the ulcerative lesions can increase the diagnostic rate of lymphoma.[24,25] Lymphoma margins are relatively mild and discrete, and the correct diagnostic rate could be increased by visualizing the auricular-like levee. Strong positive TB-spot and tuberculin tests enable a more accurate determination of the etiology of patients thought to have ITB. Furthermore, 84.2% of patients with diverticulum were diagnosed via DBE findings with direct visualization of the diverticular cavities. About 50 % of symptomatic Meckel's diverticula have been found to contain ectopic tissue, especially gastric mucosa (35-45 %), which can cause ulceration and hemorrhage; 75% of hemorrhagic Meckel's diverticula contain gastric ectopic mucosa.[26]

In addition to lymphoma (46.4%), GIST (32.1%), and adenocarcinoma (10.7%) were the most common small bowel tumors, followed by hemangioma (7.1%) and NET (3.6%). Nine patients with GIST presented with melena as the initial symptom; all were diagnosed via postoperative histopathological examinations. Duodenal or jejunal ulcerative masses are usually initially considered to be GIST; ileal masses present less certainty. Deep jejunal ulcers are difficult to distinguish from adenocarcinoma, however, for endoscopic findings combined with biopsies, the diagnostic rate increases. Endoscopic findings of small bowel tumors include irregular hemorrhagic masses or ulcers leading to lumenal stenosis, and localized ulcers are the most common. Clinical symptoms may include abdominal pain, nausea, vomiting, and other symptoms of intestinal obstruction, anemia, and melena (or hematochezia). Early diagnosis is difficult because the tumors are usually in an advanced course when patients present with symptoms. Radiology and endoscopy show slippable submucosal masses, sometimes with bleeding due to ulcers or from the tumor surface, and sometimes within the tumor in addition to the lumen. Cases with only slight changes in the mucosal surface can be difficult to diagnose. Some examinations are valuable for diagnosis, such as DBE with direct visualization, plier palpation, EUS, biopsies, and CT/CTE. The ulcers can also be tattooed with a pigmented dye to assist with subsequent site localization at surgery. Long-term follow-up and regular endoscopic evaluations were extremely important in 6 cases of CNI without remission in our study.

Choi et al.[27] evaluated the Korean Association for the Multicenter Study of Intestinal Disease. Aoki et al.[21,28] reported managing small bowel ulcerative lesions with obscure gastrointestinal bleeding. Kunihara et al.[29] discussed managing occult obscure gastrointestinal bleeding in patients based on long-term outcomes. However, no studies have focused on UIISB etiologies. Our study enrolled 209 patients and evaluated the endoscopic findings and initial symptoms of diverse etiologies.

Our study had some limitations beyond those inherent to retrospective research. Because of the retrospective design, decisions to perform DBE via an antegrade or retrograde approach were at the discretion of the attending physicians, which may have resulted in selection bias.

When we manage patients with UIISB, CD should be first under consideration. Age≥40, overt bleeding, single ulceration, and ulcer at jejunum are reasonable indications for etiology of neoplasm or non-neoplasm.

Ethics Committee Approval: This retrospective study was approved by the Medical Ethics Committee of Nanfang Hospital.

Informed Consent: All patients provided written informed consent to undergo endoscopies, including endoscopic therapy.

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