SMALL BOWEL ULCERATIONS

Shu-Yuan Xiao
Professor of Pathology
University of Chicago

CS05
DISCLOSURES

In the past 12 months, I have not had a significant financial interest or other relationship with the manufacturer(s) of the product(s) or provider(s) of the service(s) that will be discussed in my presentation.
Index Case

- 49 yo female: generalized abd pain and wt loss; abnormal CT
- Colonoscopy: tubular adenoma
- Upper device-assisted enteroscopy without fluoroscopy: localized nodular mucosa in the duodenal bulb; many superficial ulcers in the distal jejunum at 260 cm; remainder of exam normal
Pathologic Findings

- Ulcerated distal jejunum: active chronic enteritis with ulcerations, extensive surface and glandular metaplasia of gastric pyloric type; no granulomas
- Differential considerations:
  - CD
  - Drug-induced
  - Chronic ischemia
Techniques for small bowel examinations

- Small bowel follow through (SBFT)
- Computed tomography enterography (CTE)
- Magnetic resonance imaging enterography (MRE)
- Capsule endoscopy (CE)
- Device-assisted enteroscopy (with or without fluoroscopy)
  - Double Balloon Enteroscopy (DBE)
  - Single Balloon Enteroscopy (SBE)
- Mesenteric angiogram (CTA, MRA) and mesenteric Doppler study for vascular causes of disease
Small bowel ulcers: differential considerations

- Inflammatory disorders
  - Peptic ulcer (duodenum)
  - Isolated terminal ileal ulcers
  - Treatment-related: drugs (NSAIDs; 中药灌肠); radiation
  - Crohn disease
  - ITB
  - Other

- Vascular disorders
  - Vasculitis (systematic)
  - Behcet’s disease
  - Other inflammatory venoocclusive diseases
    - SLE
    - Enterocolic lymphocytic phlebitis
  - Vascular “dysplasia”
  - Microangiopathic ischemic ulcers (MAIU)

- Enteropathy-associated ulcers

- Neoplastic

- CMUSE
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# Isolated Ileitis

## TABLE 3. Morphologic Findings and Clinical Presentation as Predictors of Progression to CD in Patients With an Isolated Ileitis

<table>
<thead>
<tr>
<th></th>
<th>Outcome = CD</th>
<th>Outcome = No CD</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Blinded Morphological Categorization</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CAI—favor CD (n = 15)*</td>
<td>7 (47%)</td>
<td>8 (53%)</td>
</tr>
<tr>
<td>FAI—not diagnostic of Crohn disease (n = 14)</td>
<td>3 (21%)</td>
<td>11 (79%)</td>
</tr>
<tr>
<td><strong>Clinical Presentation</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asymptomatic (n = 14)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CAI present (n = 11, 79%)</td>
<td>0</td>
<td>11 (100%)</td>
</tr>
<tr>
<td>CAI absent (n = 3, 21%)</td>
<td>0</td>
<td>3 (100%)</td>
</tr>
<tr>
<td>Symptomatic (n = 15)†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CAI present (n = 10, 67%)</td>
<td>8 (80%)</td>
<td>2 (20%)</td>
</tr>
<tr>
<td>CAI absent (n = 5, 33%)</td>
<td>2 (40%)</td>
<td>3 (60%)</td>
</tr>
</tbody>
</table>

* Morphologic categorization into CAI or FAI was not a statistically significant predictor of progression to CD ($P = 0.24$; 2-tailed Fisher exact test).
† The presence of symptoms at the time of index colonoscopy was a significant predictor of progression to CD in patients with an isolated ileitis ($P < 0.001$). None of the asymptomatic group patients progressed to CD.
CAI indicates chronic active ileitis, favor CD; CD, Crohn disease; FAI, focal active ileitis, not diagnostic of CD.

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NSAIDs-induced injury

- Clinical:
  - GI bleeding
  - Ulcerations
  - Small bowel obstruction (usually subacute)

- Pathogenesis:
  - Topical irritation
  - Increased permeability due to damage to epithelial cells and tight junctions
  - Changes to microcirculation
  - All leading to infiltration by luminal antigens, inflammatory agents, which cause erosions or ulcers
NSAIDs-induced injury

- **Pathology**
  - Mucosal erosion or ulceration
  - Toxic-ischemic pattern
  - Focal chronic changes in small bowel similar to CD
  - Diaphragm disease: submucosal edema, fibrosis involving submucosa and muscularis propria), leading to stricture, usually multiple

TI  Jejunal stricture
NSAIDs-induced injury

Pathology

- Mucosal erosion or ulceration
- Toxic-ischemic pattern
- Focal chronic changes in small bowel similar to CD
- Diaphragm disease: submucosal edema, fibrosis involving submucosa and muscularis propria), leading to stricture, usually multiple

Plicae circulares

Diaphragm
### NSAID (LIST OF NON STEROIDAL ANTI-INFLAMMATORY)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Trade Names</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Aspirin</strong></td>
<td>Anacin, Ascriptin, Bayer, Bufferin, Ecotrin, Excedrin</td>
</tr>
<tr>
<td>Choline and magnesium salicylates (CMT, Tricosal, Trilisate)</td>
<td></td>
</tr>
<tr>
<td>Choline salicylate (Arthropan)</td>
<td></td>
</tr>
<tr>
<td>Celecoxib (Celebrex)</td>
<td></td>
</tr>
<tr>
<td>Diclofenac potassium (Cataflam)</td>
<td></td>
</tr>
<tr>
<td>Diclofenac sodium (Voltaren, Voltaren XR)</td>
<td></td>
</tr>
<tr>
<td>Diclofenac sodium with misoprostol (Arthrotec)</td>
<td></td>
</tr>
<tr>
<td>Diflunisal (Dolobid)</td>
<td></td>
</tr>
<tr>
<td>Etodolac (Lodine, Lodine XL)</td>
<td></td>
</tr>
<tr>
<td>Fenoprofen calcium (Nalfon)</td>
<td></td>
</tr>
<tr>
<td>Flurbiprofen (Ansaid)</td>
<td></td>
</tr>
<tr>
<td><strong>Ibuprofen</strong></td>
<td>Advil, Motrin, Motrin IB, Nuprin</td>
</tr>
<tr>
<td>Indomethacin (Indocin, Indocin SR)</td>
<td></td>
</tr>
<tr>
<td>Ketoprofen (Actron, Orudis, Orudis KT, Oruvail)</td>
<td></td>
</tr>
<tr>
<td>Magnesium salicylate (Arthritab, Bayer Select, Doan's Pills, Magan, Mobidin, Mobogesic)</td>
<td></td>
</tr>
<tr>
<td>Meclofenamate sodium (Meclomen)</td>
<td></td>
</tr>
<tr>
<td>Mefenamic acid (Ponstel)</td>
<td></td>
</tr>
<tr>
<td>Meloxicam (Mobic)</td>
<td></td>
</tr>
<tr>
<td>Nabumetone (Relafen)</td>
<td></td>
</tr>
<tr>
<td>Naproxen (Naprosyn, Naprelan*)</td>
<td></td>
</tr>
<tr>
<td><strong>Naproxen sodium</strong></td>
<td>Aleve, Anaprox</td>
</tr>
<tr>
<td>Oxaprozin (Daypro)</td>
<td></td>
</tr>
<tr>
<td>Piroxicam (Feldene)</td>
<td></td>
</tr>
<tr>
<td>Rofecoxib (Vioxx)</td>
<td></td>
</tr>
<tr>
<td>Salsalate (Amigesic, Anaflax 750, Disalcid, Marthritic, Mono-Gesic, Salflex, Salsitab)</td>
<td></td>
</tr>
</tbody>
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Small bowel ulcers: differential considerations

- **Inflammatory disorders**
  - Peptic ulcer (duodenum)
  - Isolated terminal ileal ulcers
  - Treatment-related: drugs (NSAIDs; 中药灌肠); radiation
  - Crohn disease
  - ITB
  - Other

- **Vascular disorders**
  - Vasculitis (systematic)
  - Behcet’s disease
  - Other inflammatory venoocclusive diseases
    - SLE
    - Enterocolic lymphocytic phlebitis
  - Vascular "dysplasia"
  - Microangiopathic ischemic ulcers (MAIU)

- **Enteropathy-associated ulcers**

- **Neoplastic**

- **CMUSE**
Crohn Disease

- Involves any segment of the GI tract
  - Small bowel only (40%), colon only (30%), other (30%)
- Multifocal or segmental disease
  - Sharply demarcated lesions with intervening normal mucosa (skip lesions)
- Disease beyond the mucosa, often transmural, leading to stricture, fissure, sinus tract, fistula
- Granulomatous
- Deep ulceration
- Relatively unique clinical and endoscopic features when present
Crohn disease involving gastric mucosa
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Intestinal TB
Features that help distinguish between Crohn disease and intestinal tuberculosis

<table>
<thead>
<tr>
<th>Clinical manifestations</th>
<th>Crohn disease</th>
<th>Intestinal tuberculosis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Perianal disease</td>
<td>High-swinging fever (&gt;38.5°C) in absence of intraabdominal abscess</td>
</tr>
<tr>
<td></td>
<td>Evidence of pulmonary TB on chest radiograph</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Radiographic findings (CT/MRI)</th>
<th>Crohn disease</th>
<th>Intestinal tuberculosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symmetrical bowel wall thickening</td>
<td>Mesenteric fibrofatty proliferation (creeping fat)</td>
<td>Asymmetrical bowel wall thickening</td>
</tr>
<tr>
<td>Mesenteric vascular engorgement (comb sign)</td>
<td>Small homogenous pericecal lymph nodes</td>
<td>Inflammatory mass centered around the cecum and enveloping the terminal ileum</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Large mesenteric nodes with necrotic centers</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ascites</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Endoscopic findings</th>
<th>Crohn disease</th>
<th>Intestinal tuberculosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Longitudinal ulcers</td>
<td>Aphthous ulcers</td>
<td>Transverse ulcers</td>
</tr>
<tr>
<td>Cobblestoned mucosa</td>
<td>Preservation of ileocecal valve</td>
<td>Hypertrrophic mucosa</td>
</tr>
<tr>
<td>Multiple skip lesions</td>
<td>Anorectal lesions</td>
<td>Scars/fibrous bands/inflammatory polyps</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Gaping/destruction of ileocecal valve</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hyperemic nodules</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Histopathologic findings</th>
<th>Crohn disease</th>
<th>Intestinal tuberculosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single granulomas</td>
<td>Architectural distortion distant from granulomatous inflammation</td>
<td>Caseating granulomas or positive acid-fast bacilli staining*</td>
</tr>
<tr>
<td>Confluent (≥5/biopsy) and large (diameter &gt;200 micrometers) granulomas; submucosal granulomas</td>
<td>Ulcers lined by epithelioid histiocytes</td>
<td>Disproportionate submucosal inflammation</td>
</tr>
</tbody>
</table>

TB: tuberculosis; CT: computed tomography; MRI: magnetic resonance imaging.

* Features pathognomonic for intestinal TB but present in <30 percent of cases; no single variable described above is absolutely specific for either condition otherwise.
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Vascular disorders

- Large arterial vasculitis or thromboemboli lead to diffuse mucosal necrosis or transmural infarct, and usually not part of the differential diagnosis of discrete ulcers
- Small to medium-sized vessel disorders
Ischemic pattern of injury
Small bowel ulcers: differential considerations

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Behçet’s Disease (BD)

- First described by Hulusi Behçet, a Turkish dermatologist, in 1937
- Recurrent systemic inflammatory disorder of unknown origin
- Clinical: remission and exacerbation of mucocutaneous (oral, genital), ocular, articular, vascular, or GI lesions
- Most common in populations along the ancient Silk Road
  - Turkey has the highest prevalence: 80-370 cases/100,000
  - East Asia: 13.5-20 cases/100,000
  - North America: 0.12-0.33 cases/100,000
- Age of onset: 20 – 40 y

Lee et al. Inflamm Bowel Dis 2013;19:1833–1838
Davatchi et al. Clin Rheumatol 2010; 29: 823-833
BD: clinical

- Oral to anus: **TI and cecum** main sites for ulceration in GI tract
- Ulcers: punched-out; round or oval shaped; deep; volcano-type; single (~70%) or multiple
  - Tend to cause perforation
- **Fistula, hemorrhage, perforations** may occur

Behcet’s disease: diagnosis

- No pathognomonic lab tests or histopathologic findings
- Clinical criteria
  - Mason & Barnes
  - Japanese
  - Hamza
  - O’Duffy
  - Cheng & Zhang
  - Dilsen
  - International Study Group (ISG)

Dervis & Geyik J Dermatol 2005:32:266
# Diagnostic criteria for Behçet's syndrome

<table>
<thead>
<tr>
<th>Criterion</th>
<th>Required features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrent oral ulceration</td>
<td>Aphthous (idiopathic) ulceration, observed by physician or patient, with at least three episodes in any 12-month period</td>
</tr>
<tr>
<td>Plus any two of the following:</td>
<td></td>
</tr>
<tr>
<td>Recurrent genital ulceration</td>
<td>Aphthous ulceration or scarring, observed by physician or patient</td>
</tr>
<tr>
<td>Eye lesions</td>
<td>Anterior or posterior uveitis cells in vitreous in slit-lamp examination; or retinal vasculitis documented by ophthalmologist</td>
</tr>
<tr>
<td>Skin lesions</td>
<td>Erythema nodosum-like lesions observed by physician or patient; papulopustular skin lesions or pseudofolliculitis with characteristic acneiform nodules observed by physician</td>
</tr>
<tr>
<td>Pathergy test</td>
<td>a papule 2 mm or more in size developing 24 to 48 hours after oblique insertion of a 20-gauge needle 5 mm into the skin, generally performed on the forearm</td>
</tr>
</tbody>
</table>

Disease Activity Index for Intestinal BD

Table 1. Disease activity index for intestinal Behçet’s disease [14]

<table>
<thead>
<tr>
<th>Item</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>General well being for 1 week</td>
<td>None</td>
</tr>
<tr>
<td>Well</td>
<td>0</td>
</tr>
<tr>
<td>Fair</td>
<td>10</td>
</tr>
<tr>
<td>Poor</td>
<td>20</td>
</tr>
<tr>
<td>Very poor</td>
<td>30</td>
</tr>
<tr>
<td>Terrible</td>
<td>40</td>
</tr>
<tr>
<td>Intestinal complications</td>
<td>10 per item</td>
</tr>
<tr>
<td>Fever</td>
<td>0</td>
</tr>
<tr>
<td>&lt;38 °C</td>
<td>0</td>
</tr>
<tr>
<td>≥38 °C</td>
<td>10</td>
</tr>
<tr>
<td>Number of liquid stool in 1 week</td>
<td>0</td>
</tr>
<tr>
<td>Extraintestinal manifestations</td>
<td>5 per item</td>
</tr>
<tr>
<td>Oral ulcer, genital ulcer, eye lesion, skin lesion, arthralgia, vascular involvement, or central nervous system involvement.</td>
<td></td>
</tr>
</tbody>
</table>

Table 2. Cutoff scores of the disease activity index for intestinal Behçet’s disease

<table>
<thead>
<tr>
<th>Disease activity</th>
<th>DAIBD score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Remission</td>
<td>≤19</td>
</tr>
<tr>
<td>Mild</td>
<td>20–39</td>
</tr>
<tr>
<td>Moderate</td>
<td>40–74</td>
</tr>
<tr>
<td>Severe</td>
<td>≥75</td>
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DAIBD, disease activity index for intestinal Behçet’s disease. Adapted from Cheon et al. Inflamm Bowel Dis 2011; 17:605–613
BD: pathological

- Mucosal lesions more likely ischemic type
  - Vasculitis (particularly venules)
- Neutrophilic infiltration more prominent
  - Secondary to ischemic mucosal damage
- In contrast to CD:
  - Usually lack of epithelioid granulomas
  - Lack of prominent mucosal architectural distortion
  - Lack of nerve fiber hypertrophy
Small bowel ulcers: differential considerations

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- Enteropathy-associated ulcers

- Neoplastic

- CMUSE
Enterocolic lymphocytic phlebitis (ELP)

- A rare form of vasculitis localized to the veins of the gastrointestinal tract without evidence of systemic vasculitis
- Term was coined by Saraga and Costa in 1989
- Other names:
  - Necrotizing and giant cell granulomatous phlebitis (Stevens, 1976)
  - Mesenteric venous thrombosis (1971)
  - Enterocolic lymphocytic phlebitis (Haber, 1993)
  - Mesenteric inflammatory veno-occlusive disease (Flaherty, 1994): (MIVOD)
- Some cases may be related to drugs (Flutamide)
- Mucosal ulcerations of small bowel and/or colon, of ischemic pattern
  - Vasculitis of venules with lymphocytic infiltration, with thrombi (bowel wall, mesentery)
  - Fibrointimal proliferation, thrombosis, venous occlusion

Haber et al. J Clin Gastroenterol 1993; 17: 327
Flaherty et al. AJSP 1994; 18:779
Ngo et al. Arch Pathol Lab Med 2007; 131:1130
Ischemic mucosal ulcerations

Ngo & Chang. Arch Pathol Lab Med 2007; 131:1130
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Idiopathic myointimal hyperplasia of mesenteric veins (IMHMV)

- Usually segmental (rectosigmoid), young, otherwise healthy
- But rarely in older patients, ileal
- Protected abdominal pain, wt loss, bloody diarrhea
- Clinically mimic IBD: unresponsive to meds -> resection
- Biopsy: usually non-specific or ischemic pattern
- Resected specimen: nonthrombotic, noninflammatory occlusion of the mesenteric veins secondary to intimal smooth muscle hyperplasia
- Also called idiopathic mesenteric phlebosclerosis (IMP)

Platz et al. Gastroenterol Hepatol 2012; 8:700
Lanitis et al. Gastroenterol 2012; 142:e5-7
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Thrombotic microangiopathy (TMA)

- Thrombocytopenia and microangiopathic hemolytic anemia in association with diffuse microthrombi of the arterial capillaries
- Spectrum of microangiopathic anemias:
  - Hemolysis elevated liver enzymes and low platelet count syndrome (HELLP)
  - Hemolytic uremic syndrome (HUS)
  - Thrombotic thrombocytopenic purpura (TTP)
- Rare cases associated with transplantation (stem cell or solid organ) with immunosuppressive drug exposure (cyclosporine, tacrolimus, mitomycin or quinine), present with systemic thrombi with relative sparing of the kidneys

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Classical Musicians Everywhere

What does everyone have planned for today? If you have a few minutes (or 18 hours) to spare, you could watch 40 pianists in a live performance of the longest piano piece in music history.

Calgary to host performance of longest piano piece in history
CMUSE
(Cryptogenic multifocal ulcerous stenosing enteritis)

- First described in 1964

- Chronic nonspecific multiple ulcers (CNSU) of the small intestine by Japanese
  - Neuromuscular and vascular hamartoma (NMVH): oblitative vascular changes

- Believed to be a special form of polyarteritis nodosa
Pathology

- Multiple short stenosis involving jejunum and ileum; some with ulceration
- Ulcers superficial; mucosa normal in between the ulcers;
- Obliterative vascular changes in some cases

Setaffy et al. Endoscopy 2015; 47:345
CMUSE/CNSU: Diagnosis

1. Persistent and occult blood loss from the GI tract except during bowel rest or postoperative period
2. Intermittent bouts of intestinal obstruction
3. Confirmation of characteristic small intestinal lesions by gross examination, radiography, enteroscopy.
   1. Circular or oblique in alignment
   2. Sharply demarcated from surrounding normal mucosa
   3. Geographic or linear in shape
   4. Multiple ulcers with <4 cm distance from each other
   5. Shallow ulcers
   6. Scarred ulcers (healing stage)
4. Exclusion of Crohn, NSAIDs and chronic infections

Perlemuster et al. Gut 2001; 48:333
Kohoutova et al. Gastroent Res Pract 2013: ID918031
Index Case - continue
Mesenteric ischemia due to fibromuscular dysplasia (FMD)

- Non-inflammatory, non-atherosclerotic angiopathy
- More common in young to middle-aged women
- Usually involves the renal and internal carotid arteries, but also mesenteric or intramural blood vessels of the bowel in some patients

Pathology:
- Medium-sized arteries
- Fibromuscular proliferation of intimal or medial layers
- Narrowing and gradual occlusion of the vascular lumen
Ischemia due to mesenteric or enteric blood vessels

Idiopathic myointimal hyperplasia of mesenteric veins (IMHMV)

Fibromuscular dysplasia (FMD) of arteries

Mesenteric Arteriovenous Dysplasia/Vasculopathy Is Distinct From Fibromuscular Dysplasia

Patil et al. AJSP 2016
# Vascular “dysplasia”

<table>
<thead>
<tr>
<th></th>
<th>FMD</th>
<th>IMHMV</th>
<th>MAVD/V</th>
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</thead>
<tbody>
<tr>
<td>Arteries</td>
<td>Arteries</td>
<td>Veins</td>
<td>Arteries &amp; veins</td>
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<tr>
<td>Strictures, ulcers, multifocal</td>
<td>Ulcers, perforation</td>
<td>Nodularity, multifocal ulcers</td>
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<tr>
<td>Ischemic or CD-like</td>
<td>Ischemic or non-specific</td>
<td>Ischemic, CD-like, mass, obstruction</td>
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<tr>
<td>Partial thickening of intima or media</td>
<td>Intimal thickening causing venous occlusion</td>
<td>Intimal and medial hyperplasia; adventitial fibrosis</td>
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<td>No</td>
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Dolak et al. J Crohn’s and colitis 2012; 6:354
Lanitis et al. Gastroenterol 2012; 142:e5-7
Patil et al. AJSP 2016;
Small bowel ulcers: differential considerations

- Inflammatory disorders
  - Peptic ulcer (duodenum)
  - Isolated terminal ileal ulcers
  - Treatment-related: drugs (NSAIDs; 中药灌肠); radiation
  - Crohn disease
  - ITB
  - Other

- Vascular disorders
  - Vasculitis (systematic)
  - Behcet’s disease
  - Other inflammatory venoocclusive diseases
    - SLE
    - Enterocolic lymphocytic phlebitis
  - Vascular “dysplasia”
  - Microangiopathic ischemic ulcers (MAIU)

- Enteropathy-associated ulcers

- Neoplastic

- CMUSE
Thank you