

Terminal ileal ulcers; Diagnostic dilemma

Abstract

Terminal Ileal (TI) ulcers are occasionally detected in asymptomatic, healthy individuals, regardless of their medication history, including the use of aspirin or Nonsteroidal Anti-Inflammatory Drugs (NSAIDs). In most cases, these ulcers resolve completely on their own without treatment, though some are associated with significant diseases. While Crohn's disease is a common cause of TI ulcers, a variety of other conditions can also lead to their development. These include infectious diseases (such as tuberculosis), spondyloarthropathies, vasculitides, ischemia, neoplasms, medication-induced damage, eosinophilic enteritis, and others.

The clinical presentation of TI ulcers varies widely. Some patients experience an acute, self-limited form of right lower quadrant pain and/or diarrhea. However, conditions like vasculitis or Mycobacterium tuberculosis can lead to a more debilitating, chronic course, often complicated by obstructive symptoms, bleeding, and/or extraintestinal manifestations. When TI ulcers are linked to spondyloarthropathy or NSAID use, they are usually asymptomatic and may go unnoticed. Differentiating between the various types of terminal ileal ulcers remains a matter of clinical judgment. A thorough history, physical examination, laboratory tests, and additional diagnostic methods are necessary to help identify the specific underlying etiology.

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Introduction

As the number of terminal ileal intubations increases, the detection of single or multiple terminal ileal ulcers has become more common [1]. Various mucosal lesions of the terminal ileum can be found in patients undergoing ileocolonoscopy. These lesions may either be part of broader small bowel conditions or occur exclusively in the terminal ileum [2].

The clinical presentation of terminal ileal ulcers varies and may include symptoms such as abdominal pain, small bowel obstruction, perforation, acute or chronic gastrointestinal bleeding, cachexia, fever, or malabsorption syndrome [3]. Among routine ileocolonoscopies, isolated non-specific terminal ileal abnormalities, such as single or multiple ulcers and nodularity, occur in 4–7% of cases [4]. While these abnormalities are frequently detected during ileocolonoscopy,

their clinical significance remains unclear. Terminal ileitis is an incidental finding in only 1.6% of asymptomatic patients, whereas isolated terminal ileal lesions are found in 2–7% of symptomatic patients undergoing colonoscopy [5].

Research has shown that terminal ileal intubation and biopsy can improve the diagnosis of terminal ileum lesions, particularly in patients with abdominal pain [6]. However, no specific guidelines exist for the diagnosis and management of isolated terminal ileal ulcers, as these lesions are often occult, asymptomatic, or present with nonspecific symptoms, and there is limited evidence supporting early diagnosis.

The understanding of nonspecific terminal ileal ulcers remains incomplete, including aspects such as their pathogenesis, clinical characteristics, diagnosis, and treatment, necessitating further study. One study found that patients with nonspecific terminal

ileal ulcers often exhibited no specific gastrointestinal symptoms or signs, leading clinicians to overlook them. Some patients had no noticeable clinical manifestations, and the ulcers were only discovered during routine endoscopic examinations [7].

Causes of terminal ileal ulcers

The exact cause of ulcers in the terminal ileum is not fully understood. It may be linked to bacterial colonization, infections, and the induction of immune responses in the terminal ileum, which results in mucosal damage. Terminal ileal ulcers are often one of the earliest signs of certain diseases, such as Crohn's Disease (CD), and patients with aphthous ulcers may later develop typical CD [8].

While terminal ileal ulcers are commonly associated with CD, they can also be related to various other conditions, including Ulcerative Colitis (UC), Non-Steroidal Anti-Inflammatory Drug (NSAID) use, infectious diseases, eosinophilic enteritis, lymphoma, lymphoid hyperplasia, radiation enteritis, spondyloarthropathies, vasculitis, ischemia, neoplasms, sarcoidosis, amyloidosis, and others. These conditions can affect the ileum and may mimic CD both histologically and endoscopically [9].

The causes of terminal ileal ulcers are summarised in table 1.

The natural history of terminal ileal ulcers

The natural history and clinical significance of terminal ileal ulcers are not well established, and there are no guidelines on whether these patients need further work-up or an interval surveillance colonoscopy.

The diagnostic yield of Terminal Ileal (TI) biopsy varies depending on the indication and endoscopic findings. A retrospective analysis of 414 patients with terminal ileal biopsies revealed that 82% of cases had histologically normal results. The study concluded that biopsies are most valuable in patients undergoing endoscopy for known or strongly suspected Crohn's Disease (CD) or those with abnormal imaging of the terminal ileum. In contrast, biopsies of endoscopically normal mucosa are unlikely to provide diagnostically useful information. However, biopsies can be very helpful when ileitis, ulcers, or erosions are identified [11].

The natural history and clinical course of nonspecific terminal ileitis are not well understood. In a retrospective analysis of 5353 colonoscopies, 92 (1.7%) cases of nonspecific terminal ileitis were identified, suggesting this condition is relatively rare in routine practice. CD was later diagnosed in 20% of patients with nonspecific terminal ileitis and available follow-up, with no significant difference between symptomatic and asymptomatic patients on initial colonoscopy (21% vs. 15%, respectively). The study concluded that asymptomatic patients with isolated nonspecific terminal ileitis have a low risk of developing CD, but persistent symptoms are associated with a higher risk of a subsequent CD diagnosis [12].

In a single-center retrospective analysis of 93 patients, Chang and colleagues assessed the clinical course and significance of isolated terminal ileal ulcers in asymptomatic individuals. Only three patients had specific etiologies, such as intestinal Tuberculosis (TB) or CD, while the remaining 90 had a self-limiting favorable clinical course. The study concluded that most terminal ileal ulcers found incidentally in asymptomatic individuals resolve spontaneously and require no treatment. They also noted that asymptomatic terminal ileal ulcers are

unlikely to progress or cause symptoms if they persist [9].

The results of studies on the fate of terminal ileal ulcers upon follow-up have been variable. A US retrospective study followed 29 patients with isolated terminal ileitis for 2.2 to 12.6 years. About 50% of patients were asymptomatic. Despite chronic features in 11 of 14 asymptomatic patients and focal active ileitis in the remaining three, none developed CD. The study concluded that isolated ileitis found in asymptomatic patients undergoing polyp screening or surveillance does not evolve into CD, despite endoscopic and histologic similarities to CD [13].

A recent study of the clinical course and prognosis of Isolated Terminal Ileal Ulcers (ITIUs) in 120 patients revealed that most nonspecific ITIUs improve naturally without treatment and rarely deteriorate, even if the ulcers persist. The authors suggested that if a definitive diagnosis is not made, observational follow-up, rather than empirical therapy, may be a reasonable approach for patients with ITIUs [14].

In a multi-center study, 134 asymptomatic patients who underwent biopsy of terminal ileal ulcers during colonoscopy were followed up. The median follow-up periods from the first to second colonoscopy and from the second to third colonoscopy were 20 and 24 months, respectively. The study concluded that most TI ulcers observed incidentally showed no unusual findings on biopsy and improved on follow-up colonoscopy without treatment [7].

In contrast, when terminal ileitis is found in symptomatic patients, the likelihood of identifying a specific etiology is much higher. Kedia et al. found that in symptomatic terminal ileitis patients with superficial ulcers and non-specific histology, the absence of fever, diarrhea, gastrointestinal bleeding, or weight loss rules out significant diagnoses like intestinal TB or CD [4]. A prospective observational study of 74 patients undergoing ileocolonoscopy for various gastrointestinal symptoms showed that more than half of ITIUs had specific etiologies, such as CD (25.7%), NSAID-induced ulcers (14.9%), intestinal tuberculosis (12.2%), and eosinophilic enteritis (6.8%). Timely diagnosis and appropriate treatment in these cases can prevent serious complications [15].

Challenges in the diagnosis of terminal ileal ulcers

To date, there are no established societal guidelines for the diagnostic work-up of patients with incidental terminal ileal ulcers found during routine colonoscopy. Clinical practices regarding this issue vary. Some clinicians recommend further evaluation, including an exhaustive clinical assessment, inflammatory biomarker testing, and small bowel imaging to assess risk, while others adopt a follow-up strategy, such as repeating the colonoscopy in one year. Some may even suggest no further work-up at all [16].

In clinical practice, various conditions causing terminal ileal inflammation can mimic Crohn's Disease (CD) both histologically and endoscopically. This can lead to incorrect diagnoses and inappropriate therapeutic approaches, and occasionally, unnecessary surgical procedures may be performed [4].

The relationship between terminal ileitis and CD has been explored in numerous studies, but there is limited evidence suggesting that terminal ileitis progresses to CD. One retrospective study reviewed the clinical, endoscopic, and radiographic records of 108 patients with histologic evidence of isolated acute terminal ileitis. The study found

that isolated acute terminal ileitis detected during diagnostic ileocolonoscopy rarely progresses to CD, with fewer than 5% of cases developing CD. The presence of stricturing or narrowing on cross-sectional imaging was found to be a predictor for the eventual development of CD [17].

A systematic review and meta-analysis of patients undergoing screening or polyp surveillance colonoscopy found that the pooled prevalence of incidentally diagnosed terminal ileitis was 1.6%. The study concluded that the likelihood of terminal ileitis progressing to overt CD is low, suggesting that a “watchful waiting” approach is a reasonable strategy [5].

Given the broad range of diseases that can affect the terminal ileum, it remains challenging to differentiate between CD and other causes of terminal ileitis. A Chinese study evaluating 1099 patients with terminal ileal diseases found that 87.26% had benign etiologies, while 11.56% were diagnosed with CD. The study also found that 24.32% of patients with ileitis and ileal ulcers developed lymphoma or CD during follow-up [18].

A key clinical question is whether patients with asymptomatic terminal ileal ulcers, or certain subgroups of these patients, may have undiagnosed or early-stage CD, or if they are at risk of developing symptomatic CD in the future, thus requiring appropriate follow-up. However, it is equally important not to misdiagnose benign, nonspecific ileitis as CD, which could lead to unnecessary treatments and follow-ups that may affect the patient’s quality of life [16].

For asymptomatic patients with terminal ileal ulcers of undetermined etiology after colonoscopy, ileal intubation, and pathological examination, a key question is whether this diagnosis requires further follow-up with a surveillance colonoscopy, and if so, at what interval [19].

Limited retrospective data suggest that the progression from mild, asymptomatic terminal ileitis to clinically significant CD is low. One notable study on the natural history of isolated terminal ileal ulcers was a retrospective Korean study that followed 93 asymptomatic patients with isolated terminal ileal ulcers found during routine colonoscopy for a mean of 29.9 months. Follow-up colonoscopies showed persistent ileal ulcers in 31 patients, but only one developed CD [9].

Recognizing the predictors of progression from nonspecific terminal ileal ulcers to CD is crucial. Such distinctions would help identify high-risk patients, potentially avoiding unnecessary diagnostic tests and treatments, as well as alleviating patient anxiety. Despite this, formal guidelines for evaluating patients with isolated nonspecific terminal ileitis are still lacking, although some authors have proposed algorithms that emphasize the importance of both intestinal and extraintestinal symptoms, elevated inflammatory markers, and/or abnormalities in small bowel imaging [16].

The endoscopic finding of ileal ulcers in asymptomatic individuals remains controversial and is considered a diagnostic dilemma. Many unanswered questions remain regarding the diagnosis of CD in this group, which may represent a latent form of the disease. Further well-designed studies are necessary to address these questions [20].

Table 1: Causes of terminal ileal ulcers (Modified From [2,10]).

Classification	Condition
Inflammatory disease	Crohn’s disease Ulcerative colitis (backwash ileitis)
Anatomic alteration	Meckel’s diverticulum
Drug intake	Non-steroidal anti-inflammatory Antihypertensives Digoxin Diuretics Ergotamine Oral contraceptives
Vascular conditions	Ischemia Behcet’s disease Giant-cell arteritis Henoch-Schonlein purpura Lymphomatoid granulomatosis Polyarteritis nodosa Systemic lupus erythematosus Wegener granulomatosis
Intestinal infection	Actinomycosis Anisakiasis Clostridium difficile Cryptococcus neoformans Cytomegalovirus Mycobacterium tuberculosis Neutropenic enterocolitis Salmonella spp. Yersinia enterocolitica and Y. pseudotuberculosis
Spondyloarthropathies	Ankylosing spondylitis Arthritis associated with inflammatory bowel disease Psoriasis with arthritis Reactive arthritis Undifferentiated spondylarthropathy
Malignant diseases	Carcinoid tumor Cecal adenocarcinoma Ileal adenocarcinoma Lymphoma Lymphosarcoma Metastatic cancer
Infiltrative	Amyloidosis Eosinophilic enteritis Sarcoidosis

Conclusion

Terminal ileal ulcers are relatively common findings during ileocolonoscopies. The natural course of asymptomatic ulcers is typically self-limiting, requiring no treatment or follow-up. However, in a subgroup of symptomatic cases, further investigation may be necessary to determine the specific etiology. Currently, no guidelines exist for the diagnostic work-up of patients with incidental terminal ileal ulcers found during routine colonoscopy. To resolve this diagnostic dilemma, further studies with large patient cohorts and extended follow-up are needed to better understand terminal ileal ulcers and identify the subgroup of patients who require additional diagnostic work-up, with the goal of achieving early diagnosis and improved management.

Core tip

The terminal ileum is a site of predilection for many infectious or inflammatory processes that almost have similar presentations. The diagnosis of terminal ileal ulcers is still one of the challenges in clinical practice. In asymptomatic individuals, most ileal ulcers recover spontaneously with no specific treatment and do not require follow-up. In symptomatic patients with terminal ileal ulcers, the chances of finding a specific etiology are much higher and usually require further work-up and re-evaluation.

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