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Are biopsies from endoscopically normal terminal ileum necessary?

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Abstract

Background The terminal ileum is typically examined during colonoscopies, especially in patients with inflammatory bowel disease (IBD) and diarrhea. The yield from performing biopsies of endoscopically normal appearing terminal ileum is less clear, and may be associated with greater costs, healthcare utilization and risk. We aimed to determine whether the biopsy results from endoscopically normal terminal ileum affect clinical management.

Methods This was a retrospective chart review of patients who underwent an ileocolonoscopy with terminal ileum biopsy at a multisite tertiary healthcare system. Patients with a diagnosis of IBD, prior ileocecal resection, or endoscopically abnormal appearing terminal ileum were excluded. Clinical and laboratory data were obtained from the electronic medical record. Comparison between patients was performed using Pearson's chi-square test.

Results A total of 1018 consecutive patients were identified. Of the 299 who met the inclusion criteria, the majority were female (62.0%) and white (94.7%). Nearly 40% of the patients had a body mass index of 30 kg/m^2 or above (38.1%). Terminal ileum biopsies were abnormal in 13 patients (4.3%): 5 patients had chronic ileitis, 6 had acute ileitis, 1 had acute and chronic ileitis, and 1 had amyloid deposition. All patients with either chronic or acute ileitis had chronic diarrhea listed as an indication for their colonoscopy.

Conclusions In patients with a normal appearing terminal ileum, clinically significant histologic abnormalities on biopsies were found in a very small percentage. Based on our findings, the routine biopsy of endoscopically normal appearing terminal ileum has limited diagnostic and therapeutic utility.

Keywords Terminal ileum, routine biopsy, endoscopy, ileitis, inflammatory bowel disease

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Conflict of Interest: Francis A. Farraye: Consultant for AbbVie, Avalo Therapeutics, BMS, Braintree Labs, Fresenius Kabi, GSK, Iterative Health, Janssen, Pfizer, Pharmacosmos, Sandoz Immunology, Sebela and Viatris. He is an independent contractor for GI Reviewers and IBD Educational Group. He sits on a DSMB for Lilly

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Introduction

The terminal ileum is often intubated and examined during colonoscopy procedures. Endoscopic evidence of inflammation in the terminal ileum can indicate a broad differential diagnosis, including Crohn's disease, use of nonsteroidal anti-inflammatory drugs, infectious enteritis such as tuberculosis, as well as idiopathic ileitis. For evaluation of inflammatory bowel disease (IBD), a terminal ileum examination and biopsy is commonly utilized to establish a diagnosis. The American Society for Gastrointestinal Endoscopy supports biopsy of the terminal ileum for patients with diarrhea in case of suspected IBD, abnormal appearing terminal ileum on imaging, or endoscopically abnormal appearing terminal ileum [1]. Even when the terminal ileum appears endoscopically normal, there is diagnostic value in obtaining terminal ileum biopsies for suspected IBD [2-5].

In the non-IBD population, routine examination and biopsy of the terminal ileum has an inconsistent yield, with abnormal findings reported in 0-5.9% of patients [6-11]. This is particularly controversial if the terminal ileum appears

normal. Biopsies of normal appearing terminal ileum may be associated with greater costs and healthcare utilization, risk, and increased levels of anxiety for patients. One study estimates the cost to be $430 per bottle of terminal ileum biopsies [12]. The benefits of obtaining biopsies from a normal appearing terminal ileum remain unclear. The aim of this study was to determine whether biopsies of normal appearing terminal ileum yielded clinically significant diagnoses that affected the management of patients who were evaluated in our institution.

Patients and methods

Our study was approved by the Institutional Review Board of Mayo Clinic. We completed a retrospective chart review of all adult patients who underwent colonoscopy at a multisite tertiary care health system, with examination and biopsy of the terminal ileum, between July 1, 2020 and June 30, 2021. Patients' clinical and laboratory data, colonoscopy indications, colonoscopy reports, and ileal biopsy pathology results were all collected. Patients were excluded if they had a prior diagnosis of IBD, prior ileocecal resection, or an endoscopically abnormal appearing terminal ileum per the colonoscopy report, or if the pathologist was not able to analyze the biopsy sample.

Histopathology reports were reviewed and classified as normal or abnormal. Abnormal findings included acute ileitis, chronic ileitis, eosinophilic ileitis and amyloidosis. Normal histologic findings included lymphoid hyperplasia. Further chart review was pursued for all patients with abnormal findings to assess whether their management had been affected.

Statistical analysis

Statistical analysis was performed using SPSS version 28 (IBM, Armonk, NY). Comparison between patients were performed using Pearson's chi-square test. A P-value <0.05 was considered statistically significant.

Results

A total of 1018 consecutive adult patients were reviewed. Of those, 572 (56.2%) patients had a history of IBD and were therefore excluded (Fig. 1). A total of 299 patients met the inclusion criteria. The majority were female (185, 62.0%) and white (n=283, 94.7%) with a mean age of 52±17 years (Table 1). Nearly 40% of the patients were obese (n=114, 38.1%), with an overall ean body mass index of 28.9±7.6 kg/m^2. Past medical history included microscopic colitis (n=14, 4.7%), celiac disease (n=5, 1.7%), irritable bowel syndrome (n=35, 11.7%), hypertension (n=98, 32.7%), diabetes (n=35, 11.7%), tobacco use (n=47, 15.7%), and moderate or severe alcohol use (n=72, 24.0%).

The most common indication for colonoscopy was chronic diarrhea (n=176, 58.9%), followed by abdominal pain (n=50, 16.7%), colon cancer screening (n=32, 10.7%), abnormal imaging (n=29, 9.7%), hematochezia (n=28, 9.4%), and surveillance of polyps (n=28, 9.4%). Indications were not mutually exclusive. Nineteen patients (6.4%) also had an indication of suspected IBD. There was no significant diagnostic yield of obtaining terminal ileum biopsies based on indication for colonoscopy (Table 2).

Histology was abnormal in 13 patients (4.3%) (Table 3). Of those, 6 had acute ileitis, 5 had chronic ileitis, 1 had acute and chronic ileitis, and 1 had amyloidosis. There were no cases of eosinophilic ileitis. The finding of acute ileitis affected management in 2 of the 7 patients. These 2 patients had drug-

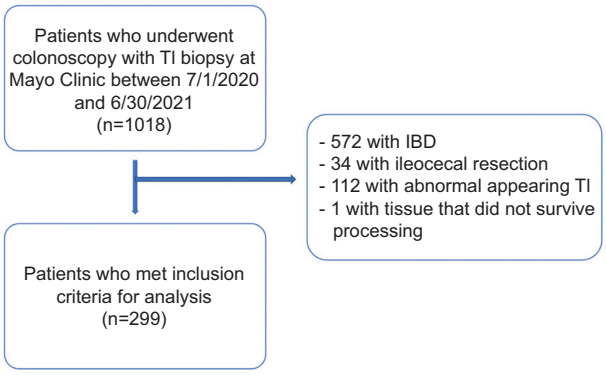

Figure 1 Study design
TI, terminal ileum; IBD, inflammatory bowel disease

Table 1 Patient characteristics

Characteristics	n=299
Female	185 (62.0%)
White	283 (94.7%)
Age (mean years)	52±17
BMI (mean kg/m^2)	28.9±7.6
History	
Microscopic colitis	14 (4.7%)
Celiac disease	5 (1.7%)
IBS	35 (11.7%)
Hypertension	98 (32.7%)
Diabetes	35 (11.7%)
Tobacco use	47 (15.7%)
Moderate or severe alcohol use	72 (24.0%)
Indication for colonoscopy	
Chronic diarrhea	176 (58.9%)
Abdominal pain	50 (16.7%)
Unintentional weight loss	13 (4.4%)
Constipation	2 (0.7%)
Surveillance of polyps	28 (9.4%)
Colon cancer screening	32 (10.7%)
Iron deficiency anemia	9 (3.0%)
Hematochezia	28 (9.4%)
Melena	4 (1.3%)
Abnormal imaging	29 (9.7%)
Common variable immunodeficiency	0 (0%)
Suspected IBD	19 (6.4%)

BMI, body mass index; IBS, irritable bowel syndrome; IBD, inflammatory bowel disease

Table 2 Abnormal terminal ileum histopathology by indication for colonoscopy*

Indication	Total N	Abnormal histopathology N (%)
Chronic diarrhea	176	9 (5.1%)
Abdominal pain	50	3 (6.0%)
Unintentional weight loss	13	1 (7.7%)
Constipation	2	0 (0.0%)
Surveillance of polyps	28	2 (7.1%)
Colon cancer	32	2 (6.3%)
Iron deficiency anemia	9	1 (11.1%)
Hematochezia	28	2 (7.1%)
Melena	4	0 (0.0%)
Abnormal imaging	29	1 (3.4%)
Suspected IBD	19	1 (5.3%)

*Indications are not mutually exclusive

Table 3 Abnormal histopathologic findings

Findings	(n=13)
Acute ileitis	6
Chronic ileitis	5
Acute and chronic ileitis	1
Amyloidosis	1
Eosinophilic ileitis	0

induced injury and the indication for their colonoscopies was chronic diarrhea. The finding of chronic ileitis did not affect the management of any of the patients. The patient with acute and chronic ileitis underwent colonoscopy for suspected Crohn's disease and abnormal imaging, and was diagnosed with Crohn's disease. The patient with amyloidosis underwent colonoscopy for chronic diarrhea and suspected amyloidosis. In total, clinically significant diagnoses were made in 1.3% of all patients (n=4).

Discussion

Very few patients with a normal appearing terminal ileum had abnormal histopathology, and even fewer had clinically significant diagnoses that affected management. Of the 6 patients with acute ileitis, 2 had drug-induced injury (leflunomide and multiple breast cancer chemotherapy agents) which resolved clinically with cessation of the medications. Three patients were not given a specific diagnosis and had resolution of acute ileitis on subsequent examination. One patient was suspected to have prior radiation-induced injury. Of the 5 patients with chronic ileitis, 3 were not given specific diagnoses, but the differential included use of nonsteroidal anti-inflammatory drugs. The other 2 patients had backwash ileitis from lymphocytic colitis, which was present on colon biopsies from the same exam. The patient with acute and chronic ileitis was diagnosed with Crohn's disease, based on enterography findings of multifocal small bowel lesions and terminal ileum biopsy histopathology.

To our knowledge, this is the largest retrospective review of patients who underwent terminal ileum biopsy during colonoscopy and the first to assess the clinical significance of the findings. Sayilir *et al* [9] examined the diagnostic value of performing biopsies of an endoscopically normally appearing terminal ileum for chronic diarrhea. They found abnormal histopathology in 4.4% of all patients and 5.9% of patients with non-bloody diarrhea. For all of these patients, these findings neither resulted in a diagnosis, nor changed their clinical management. Abnormal pathology findings included elevated intraepithelial lymphocytes, shown to be commonly present in asymptomatic patients [13]. Koskal *et al* found a comparable rate of abnormal histopathology with chronic ileitis present in 5.5% of patients with endoscopically normal terminal ileum [3]. However, patients with known IBD were included in this study, whereas we excluded them from our study. A similar study by McHugh *et al* evaluated biopsies taken from endoscopically normal terminal ileum, including patients with known IBD [4]. Abnormal histopathology was found in 5.1% of patients (17 cases). Fourteen of those cases were chronic ileitis, 1 of which was backwash ileitis from ulcerative colitis. The diagnostic yield of performing biopsies of normal appearing terminal ileum was statistically significant for the indication of Crohn's disease only. For indications of diarrhea, abdominal pain, hematochezia and abnormal imaging, there was no statistically significant diagnostic yield. Yusoff *et al* focused on patients undergoing colonoscopy for diarrhea, where 158 of 1131 patients had terminal ileum biopsy with endoscopically normal appearing terminal ileum. None of these biopsies had clinical significance [10].

Our study corroborates previous observations with regard to the yield of abnormal histopathology, but adds value by exclusively evaluating findings in patients with an endoscopically normal appearing terminal ileum. We took further steps by investigating downstream clinical decision-making in all patients with abnormal histopathology, including follow up colonoscopies when available. Four patients (1.3%) had histopathologic findings that impacted management, with 2 diagnoses of drug-induced injury, 1 diagnosis of amyloidosis, and 1 diagnosis of Crohn's disease. Notably, all of these patients had a workup, including history and imaging, that was suspicious for these diagnoses prior to the colonoscopy. The histologic evidence could be considered confirmatory in these cases, rather than a new finding.

One limitation of our study was the retrospective design. Additionally, updated laboratory data were limited and could not be included in the analysis. Large prospective studies are warranted to determine when biopsies should be taken from endoscopically normal terminal ileum.

We conclude that performing biopsies of endoscopically normal appearing terminal ileum lacks clinically significant value, including for indications of chronic non-bloody diarrhea, abdominal pain, hematochezia and abnormal imaging. The risks of increased costs and healthcare utilization, and higher

levels of anxiety for patients may outweigh the benefits of obtaining biopsies.

Summary Box

What is already known:

- The terminal ileum is often intubated and examined during colonoscopy procedures, particularly in the evaluation of inflammatory bowel disease
- Biopsy of the terminal ileum is indicated to diagnose inflammatory bowel disease, even in the case of normal appearing terminal ileum
- Greater costs, risk and healthcare utilization are associated with biopsy of the terminal ileum

What the new findings are:

- Biopsy of normal appearing terminal ileum has limited diagnostic value in patients without inflammatory bowel disease
- Additionally, biopsy of normal terminal ileum does not impact management
- We do not recommend performing a biopsy of normal appearing terminal ileum in patients without inflammatory bowel disease, regardless of indication

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