

# Facing Terminal Ileitis: Going Beyond Crohn's Disease

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## Abstract

Terminal ileitis (TI) is an inflammatory condition of the terminal portion of the ileum that may occur acutely with right lower quadrant pain followed or not by diarrhea, or exhibit chronic obstructive symptoms and bleeding and normally it is associated to Crohn's disease (CD) although it may be associated to other different conditions. This review intended to contribute to a better understanding of TI in order to help in the diagnosis, medical approach and patient care. This work was performed on a survey of articles collected in different databases and a retrospective search was carried out to identify relevant studies in the field. Pathological conditions such as ulcerative colitis, the intake of non-steroidal anti-inflammatory drugs, infectious diseases, eosinophilic enteritis, malignant diseases, spondyloarthropathies, vasculitides, ischemia, sarcoidosis, amyloidosis and others may be related to ileitis but it is commonly referred to CD. To a correct therapeutic approach, it is necessary to understand the causes of this inflammation process. The performance of a clinical, laboratory, endoscopic, and histopathological evaluation of the individuals is crucial to the correct diagnosis and treatment once the inflammation of the ileum may occur due to different pathological conditions besides CD, leading to difficulties in the diagnosis. Thus, an individual approach is necessary once the correct diagnosis is crucial for the immediate therapeutic approach and recovering of the patient.

**Keywords:** Terminal ileitis; Inflammatory processes; Crohn's disease; Ulcerative colitis; Behcet's disease; Infectious diseases

## Introduction

Terminal ileitis (TI) is an inflammatory condition of the termi-

nal portion of the ileum described in medical literature since a long time ago. It may occur acutely with right lower quadrant pain followed or not by diarrhea, or exhibit chronic obstructive symptoms and bleeding [1-4].

In 1936, the Epitome of Current Medical Literature [5] described the TI or ileitis terminalis and pointed that this condition recognized by Crohn in 1932 should be described as a new disease. In that Epitome, it is possible to read that "ileitis is a non-specific inflammation of the terminal portion of the ileum which sometimes spreads to the cecum causes ulceration of the intestinal mucosa, thickening and retraction of the intestinal wall... The diagnosis is based on the exclusion of specific infective processes in the ileum such as ileo-cecal tuberculosis and actinomycosis "

In 1937, again in the Epitome of Current Medical Literature [6], it is possible to find two cases of a condition named ileitis terminalis or *Enteritis regionalis* described in a youth aged 17, a traumatic rupture at the ileo-cecal junction, and the ileum, cecum, and appendix, exhibiting a chronic state of inflammation. A resection was reported to this case as well as an end-to-end anastomosis of the small intestine with the ascending colon. The other case described a man aged 44 with a fistula between the ileum and the bladder. Authors related resection of the lowest part of the ileum, cecum, and ascending colon.

Crohn [7] suggested that acute TI is an acute form of the disease in the terminal ileum. Kewenter and Kock [8] postulated that the follow-up of individuals with acute TI is the one way to identify if the acute inflammation is or not due to the Crohn's disease (CD).

As seen above, since many years ago, author's opinions are different as to whether acute TI is a separate condition or an acute form of the classical CD.

Terminal ileum is the most common affected area in CD, although any part of the gastrointestinal tract may be reached. On the other side, it may result from other situations such as infections, and a large variety of diseases may be linked to it. In clinical practice, situations that promote ileum inflammation may mimic CD both histologically and endoscopically, leading to an incorrect diagnosis and to a wrong therapeutic approach, and occasionally an unnecessary surgical procedure may be chosen [3, 4, 9].

The possible misdiagnosis of the TI can bring many physiological and psychological problems to the patients what should make doctors look deeply and carefully to this inflammatory condition. For this reason, this review intends to contribute to a better understanding of TI in order to help in the diagnosis, medical approach and patient care.

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## Literature Retrieval

This work was performed on a survey of articles collected and the following databases: Pubmed, PMC, Medline, and Lilacs. A retrospective search was carried out to identify relevant studies in the field.

## Pathophysiological Aspects

In healthy individuals, the gastrointestinal microbiota interacts with the host in a perfect balance resulting in the maintenance of homeostasis and even in healthy conditions, the gastrointestinal immune system is stimulated by millions of antigens. If this balance is lost for some reason, there is a trigger in the immune system leading to an inflammatory condition that is associated to the pathophysiological processes of several diseases. The imbalance in the gastrointestinal tract is characterized by recurrent inflammation, with relapse and remission phases, and epithelial disturbance [10-14].

When the body is exposed to a pathogenic microorganism, the innate immune system is activated and a response of macrophages, dendritic cells and granulocytes, and activation of pattern recognition receptor which may recognize pathogen-associated molecular patterns normally named as PAMPs are observed. Pattern recognition receptor is capable to respond successfully conducting to the overthrowing of the bacteria and resolution of inflammation process and tissue repair. This acute inflammatory process is important to the homeostasis [15, 16].

In chronic inflammatory processes, epithelial cell necrosis, tissue damage, and liberation of PAMPs which are able to activate Toll-like receptors that are related to the protection of the intracellular cytosolic compartment are observed. When antigens are recognized, there is a recruitment of kinase enzymes that initiate the activation of signaling cascades and activation of nuclear factor-kappaB (NF- $\kappa$ B) and MAPK pathways. These receptors exhibit particular pattern of immunological responses in the gastrointestinal tract [15, 17-19].

The activation of Toll-like receptors may lead to autophagy and disability to distinguish commensal from pathogenic bacteria that triggers the overproduction of tumor necrosis factor  $\alpha$  (TNF- $\alpha$ ) and interleukins (ILs) such as IL-1 $\beta$ , IL-6, IL-12 and IL-23. These inflammatory mediators stimulate the activation of NF- $\kappa$ B resulting in several remarkable symptoms such as pain, bleeding, and changes on the bowel habits. Besides, the inflammatory process may reach different parts of the gastrointestinal tract, including terminal portion of the ileum [1, 13, 18, 20, 21].

Gunther et al [22] performed an interesting study showing the role for caspase-8 in the regulation of necroptosis of intestinal epithelial cells and TI. Authors have used a mice model with a deletion of caspase-8 in the intestinal epithelium and showed that these animals spontaneously developed inflammatory lesions in the terminal ileum and were highly susceptible to colitis. These animals possessed a smaller number of goblet cells and lacked Paneth cells what could lead to the dysregulation in the anti-microbial immune cell functions of the intestinal epithelium. These mice presented increased cell death

in the Paneth cell area of small intestinal crypts induced by TNF- $\alpha$ , and related to increase in the expression of receptor-interacting protein 3 (RIP3). Authors also showed high levels of RIP3 in human Paneth cells and increased necroptosis in the terminal ileum CD individuals and suggested a role of necroptosis in the pathogenesis of this disease. They also postulated a role of caspase-8 in the regulation of the intestinal homeostasis and in protection of intestinal epithelial cells against necroptotic cell death by TNF- $\alpha$ .

Although many studies intended to explain the imbalance and inflammation processes that occur in the gastrointestinal tract, many lacking information are still observed and multidisciplinary teams will be necessary to the comprehension of these conditions.

## Importance of Ileoscopy

Based on the fact that the diagnostic value of ileoscopy is not well documented, Young and Heymann [23] developed a retrospective study with 2,149 patients undergoing colonoscopy. In 16.1% (346 patients), the terminal ileum was intubated and histologic abnormalities were found in 16, resulting in a diagnostic yield of 4.6% of all ileoscopies and authors concluded that this procedure should only be performed when the indication is warranted and that it could interfere in the management. They also suggested that it is not cost-effective to attempt ileum intubation in all patients.

Jeong et al [24] also worried about if the terminal ileum intubation should be used routinely in patients undergoing colonoscopy. With this worry, they investigated the possible diagnostic of terminal ileum intubation during colonoscopy. These authors studied 3,921 individuals undergoing colonoscopy and their results showed that the terminal ileum was intubated in 87.1% of the patients (3,417 individuals) and macroscopic abnormality on terminal ileum was found in almost 4% (125 cases). These abnormalities included ulcers, erosions or aphthous ulcers, nodular or erythematous mucosa, and polypoid lesions. In almost 92%, they found non-specific histological observations not thought to be clinically significant, such as low-grade mucosal damage, non-specific inflammation, and lymphoid hyperplasia. None of these individuals had chronic or recurrent bowel symptoms for a month and the findings related to the TI were not of clinical importance. Histopathology relevance was found in almost 9%. Seven cases were diagnosed as CD, three with intestinal tuberculosis (ITB), and one with Adamantiades-Behcet's disease. Authors have concluded that intubation during colonoscopy is capable to identify significant pathology in almost 2% of patients possessing right lower quadrant abdominal pain, and 0.4% in patients with diarrhea. As the diagnostic yield is very low in other indications for colonoscopy, the performance or not of ileoscopy needs to be based on case-by-case.

## Conditions Related to Ileitis

As pointed before, ileitis is defined as inflammation of the ileum

**Table 1.** Summary of the Conditions Related to the Development of TI (Modified From [3, 4])

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 <i>Clostridium difficile</i> <i>Cryptococcus neoformans</i> <i>Cytomegalovirus</i> <i>Mycobacterium tuberculosis</i> <i>Neutropenic enterocolitis</i> <i>Salmonella spp.</i> <i>Yersinia enterocolitica</i> and <i>Y. pseudotuberculosis</i>
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

and is commonly related to CD. Nevertheless, many diseases can be related to this condition, such as ulcerative colitis (UC), the intake of non-steroidal anti-inflammatory drugs (NSAID), infectious diseases, eosinophilic enteritis, lymphoma, lymphoid hyperplasia, radiation enteritis, spondyloarthropathies, vasculitides, ischemia, neoplasms, sarcoidosis, amyloidosis, and others. These conditions may affect the ileum and could mimic CD, both histologically and endoscopically [4].

Table 1 summarizes some conditions related to TI. As we pointed before the correct diagnosis of the cause of the ileitis

is indispensable for a good therapeutic approach of the patient. Some of the main conditions related to ileitis are described below.

### Inflammatory bowel disease (IBD)

CD and UC are polygenic autoimmune diseases with multifactorial etiology sharing similar peculiarities as risk factors, clinical, endoscopic and histological patterns, and genetic predisposition. The manifestations are systemic and may lead to a serious damage to the gastrointestinal tract, and extra-intestinal manifestations. On the other hand, in UC inflammation pattern is normally restricted to the mucosal surface, starting in the rectum and extending in a uniform pattern throughout the colon and rarely affecting the terminal ileum [25].

### CD

The inflammation of the ileum is often caused by CD that manifests due to an idiopathic transmural inflammation affecting all the wall layers and may occur from mouth to anus but the most common affected site is the distal ileum. Skipped areas of inflammation can be found and this process leads to formation of ulcers that may produce penetrating (fistulizing), fibrostenotic (stricturing), or inflammatory pattern in the perianal region and abdominal wall [26-28].

This disorder was described by Crohn in 1932 after studying 14 cases of TI. CD patterns involve transmural inflammation, thickened submucosa, fissuring ulceration and non-caseating granulomas. It is frequently followed by a number of symptoms such as abdominal pain, diarrhea, gastrointestinal bleeding, malabsorption, and weight loss, and may lead to life-threatening complications [29, 30].

The primary location of CD, in approximately two-thirds of cases, is the small intestine, specifically the terminal ileum, probably due to disruption in the immune response to environmental factors in genetically predisposed individuals and the commonly presence of erosions and ulcers is referred normally to CD. Results of CD biopsies show an inflammatory cellular infiltrate with crypt abscesses, architectural distortion, and occasional granulomas. Nevertheless, the exclusion of other possibilities of TI requires the performance of a clinic, laboratory, endoscopic, and histopathological evaluation of the individuals [3, 31-33].

### UC: backwash ileitis (BWI)

When TI is observed in UC, the name used is BWI that refers to an inflammation process in the distal few centimeters of terminal ileum. This inflammation condition of the ileum occurs due to reduced ileocecal valve function in severe UC (when present, may indicate the differential diagnosis of CD), allowing for retrograde flow of colonic content and inflammation of the ileum. There is stasis that occurs from inflammation-induced colonic hypomotility, or continuous extension of inflammation

from the colon. This ileitis is normally mild and is related to neutrophilic inflammation in the lamina propria, focal cryptitis/crypt abscesses and, rarely, superficial mucosal erosions. Occasionally it may only exhibit mucosal injury, as villous blunting and regenerative epithelial changes. It can be differentiated from CD by the large length of involved small bowel separated by skip regions in the cecum or distal ileum, higher inflammatory process and mucosal injury in the ileum, transmural ileal inflammation and neural hyperplasia, and mucous gland metaplasia of the ileal mucosa. Literature also reports that ileal changes in UC may reach 17%. Normally, the severity of ileum inflammation parallels the severity of the colonic activity, commonly with pancolitis and cecal involvement [3, 34-36].

UC “Crohn-like”, coming from a chronic pancreatic enzyme taking, has been also described in the literature [26, 37, 38].

A conclusive diagnostic criterion for BWI is not available, but we should consider an active enteritis affecting the ileum in a contiguous pattern from cecum with a similar or higher degree of inflammation. The differentiation of Crohn’s ileocolitis and “panulcerative” colitis with BWI is direct when granulomas are found on “histology or aphthous ulcers, cobblestoning, and skip lesions are seen endoscopically, but can be a clinical challenge when these features are absent” [4].

#### *Ileitis and IBD associated with primary sclerosing cholangitis (PSC)*

Background PSC is normally associated with UC and ileocolitis in CD. IBD in PSC is considered to be a quiescent disease, and pancolitis occurs often (but not necessarily), with rates varying from 35% to 95%. Both BWI and rectal sparing are observed infrequently. The reported rates of BWI found for PSC-UC vary from 5.0% to 42.9%. In UC without PSC, the involvement of the ileum is not frequent, ranging from 2.5% to 24% [34, 39-41].

#### **Meckel’s diverticulum**

Meckel’s diverticulum (MD) represents the most common congenital anomalies of the digestive tract that occurs in the gastrointestinal tract, reaching an incidence of 2-4% in the general population, although most patients are asymptomatic. This anomaly refers to the persistence of the embryological connection between the umbilical and bowel. Symptomatic cases usually course with hemorrhage, intestinal obstruction, ulceration, perforation, inflammation, intussusceptions, and malignant transformation [42-45].

Many studies have shown the association among MD and CD, and some authors postulate that ileitis is attributable to acid-secreting gastric heterotopia. Complications of MD are more frequent in male and younger individuals. Bleeding occurs more frequently in adult males and in children, mainly younger than 4 years of age, and it occurs mainly as obstruction [43-45].

In a recent study with 48 adult individuals, Hamilton and Arnason [46] found that some of them presented inflammatory modifications in the small intestine neighboring the diverticu-

lum and concluded that the ileitis reaching short segment of mucosa and submucosa near MD is common, and is not necessarily associated to CD.

#### **Use of NSAIDs**

Aspirin and NSAIDs are related to the reduction of colorectal adenoma and cancer risk but on the other hand, it is also related to injury of the gastrointestinal mucosal. These drugs are mainly involved in the inhibition of cyclooxygenase or prostaglandin-endoperoxide synthase enzymes. The interference that they promote in the intestinal epithelial barrier occurs possibly in the interaction between the gut microbiota and immune cells, thus increasing risk for IBD. Another view of the effects of aspirin and NSAIDs is the effects on the liberation of inflammatory markers and platelet aggregation which may induce the occurrence of IBD pathogenesis [47, 48].

Ashwin et al [49] performed a study with a large number of patients for 20 years and concluded that women who used NSAIDs but not aspirin showed increased risk for IBD in middle age. Authors say that although aspirin and NSAIDs share potential for gastrointestinal toxicity, aspirin was not much associated with IBD in their study probably because of the differences among the action mechanism of aspirin and NSAIDs on the COX isoenzymes. The first class of drugs at analgesic doses inhibits both the COX-1 and COX-2 enzymes while aspirin at low and moderate doses is COX-1-selective. In animal models of colitis, authors showed that inhibition of COX-1 or COX-2 alone does not lead to colitis, but the use of non-selective NSAIDs which are inhibitors of both isoenzymes results in early development of colitis. The deleterious actions of aspirin may also have a counterbalance by the anti-inflammatory or mucosal protective effects. In mice, authors have shown that inhibitors of sphingosine kinase may exhibit therapeutic against colitis [50, 51].

In view of the above, doctors should take into account the use of these medications as being part of the managing protocol of ileitis.

#### **Behcet’s disease (BD)**

BD is a multi-systemic inflammatory condition with unknown etiology and presence of a chronic recurrent clinical course characterized by repeated oral and genital ulcerations, arthritis, vasculitis, ocular lesions, skin manifestations, and gastrointestinal involvement. Intestinal BD may affect 3-60% of patients suffering with BD. The incidence of intestinal BD is more frequent in East Asian countries than in Western or Middle Eastern countries. Any part of the gastrointestinal tract may be affected but the most common location is the ileocecal area. The main endoscopic aspects found are few, large, and deep ulcerations with discrete border. The intestinal BD has many similarities with IBD regarding clinical manifestations, genetics, and therapeutic strategies (biologic agents such as anti-TNF- $\alpha$  antibody), what makes the differentiation of both conditions clinically not easy. Doctors need to require com-

prehensive knowledge regarding the similar characteristics of both diseases in order to make an accurate clinical decision [1, 52]. The main differences compared to CD are the large size of ulcerations on the ileocecal area (round or oval shaped and more discrete and elevated border), fewer number of lesions, non-specific inflammation (lymphocytic or neutrophilic infiltrations), presence of vasculitis (possible) and absence of non-caseating granuloma [1].

On the other side, innumerable ulcerations from small aphthous ulcerations to multiple irregular shaped ulcerations may appear. Lee et al [53] compared colonoscopy findings of 115 intestinal BD and 135 CD individuals and found that round shape, fewer number, focal distribution, and absence of aphthous and cobblestone appearance were independent discriminating factors of intestinal BD. Colonoscopy findings for BD relate five or fewer lesions, oval shape, deep penetrating, discrete border, and ileocecal location as typical ulcerations. Other classification for macroscopic aspects of intestinal BD ulcerations is volcano, geographic, and aphthous types. In CD, the classical aspects found in the colonoscopy may show aphthous ulcerations, discontinuous chronic mucosal inflammation, longitudinal ulcerations, and cobblestone appearance with normal surrounding mucosa. Skipped inflammatory/normal pattern lesions are often found in CD, similar to those of intestinal BD but the distribution of the lesions in CD patients is more diffuse than in intestinal BD patients [1, 54-56].

### Intestinal infections

Intestinal infections may lead to mistakes in diagnosis, and management of symptoms once they can mimic endoscopic and clinical findings of IBD. Some important intestinal infections are described below.

#### *ITB: Mycobacterium tuberculosis*

Extra-pulmonary tuberculosis is becoming common due to HIV infection and treatment and the development is more related (70% of the cases) after ingesting infected sputum in cases of active pulmonary tuberculosis. The gastrointestinal tract involvement produces a similar pattern of CD and the distinction of both is related to clinical and histological evaluations if culture is negative. The most affected areas are ileocecal and jejunum-ileum probably resulting from high densities of lymphoid aggregates, neutral pH environment allowing swallowed mycobacterium to be absorbed and physiologic stasis. Authors have shown that the ileocecal area has been involved in about 90% of ITB patients [4, 57]. Both conditions lead to abdominal pain and mass in the right lower quadrant, presence of ulcerations, and fibrotic lesions resulting in bowel obstructions and fistulae formations. Besides, both conditions may coexist. Due to chronic inflammation, the ileal wall may become fibrotic or stenotic or may form tuberculomas leading to intestinal obstruction or perforation. The differentiation may be based on the presence of anorectal lesions, longitudinal ulcers, aphthous ulcers, and a cobblestone pattern what would indicate CD or

the observation of a patulous ileocecal valve, transverse ulcers, and pseudo-polyps would indicate intestinal tuberculosis. ITB patients may present fever, abdominal pain, a palpable mass, modification of the bowel habits, and/or bleeding. The comparison of clinical and endoscopic aspects, culture and polymerase chain reaction for *Mycobacterium tuberculosis* (positive TB culture is the gold standard diagnosis although it may delay weeks), biopsy, and radiology should drive doctor to a conclusion [3, 53, 58, 59].

#### *Yersinia enterocolitica and Yersinia pseudotuberculosis*

These microorganisms are mainly acquired more commonly by ingestion of contaminated water or food and the most frequent clinical aspect is the presence of enterocolitis with pain, diarrhea, low-grade fever, mucosal ulceration, neutrophil invasion, thickening of the ileal wall (leading to perforation), rectal bleeding, reactive polyarthritis and septicemia. Diagnosis is by stool culture and colonoscopy with biopsy. Endoscopic patterns include aphthoid lesions of the cecum and TI with round or oval elevations with ulcerations that are mostly uniform in size and shape, in contrast to CD. The formation of fistula and fibrotic stenosis appears commonly in CD [4, 60-62].

#### *Salmonella*

*Salmonella enteritidis* (non-typhoidal *Salmonella*) infection may occur in the foodborne leading to the passage of pathogens to the gut epithelial cell and with secondary translocation to the extra-intestinal organs as spleen and liver and the infection is a very common cause of foodborne illness that occurs with the ingestion of contaminated food products. Typhoid fever occurs due to the presence of *Salmonella enterica* serotype Typhi and it is transmitted person to person [63, 64].

Authors have found that hematochezia secondary to typhoid colitis affects mainly terminal ileum followed by the ileocecal valve, ascending and transverse colon. Besides, infection caused by *Salmonella* decreases the antioxidant capacity in the ileal loops due to the reduction of enterocyte glutathione levels. This condition raises the susceptibility of epithelial cells to oxidative damage [63, 64].

The infections promoted by *Salmonella* most often cause self-limited acute gastroenteritis, bacteremia, and vascular infections. The TI leads to circumferential and homogenous thickening of the terminal ileum wall but its differentiation from other causes of ileitis, as in CD, is not easy. Endoscopy procedures with biopsy may help but the definite diagnosis of *Salmonella* is based on culture [4, 65].

#### *Clostridium difficile*

A disrupted microbiota with loss of colonization resistance is the main cause of *Clostridium difficile* infection and it normally causes antibiotic-associated colitis. Enteritis related to *Clostridium difficile* toxin is a nosocomial disease of increas-

ing clinical concern, but inflammation process is unknown. The symptoms normally are related to abdominal or pelvic pain, low-grade fevers, and increased ileostomy output. The diagnosis may be performed by observing pseudomembranes and stool studies showing toxin-producing organisms [66-68].

### Malignant diseases

Small bowel cancer is a relatively rare malignant disease that occurs in only 2% of all gastrointestinal cancers. However, the incidence is increasing, mainly in North America and Europe. Authors' estimate of 5,300 patients, in the United States, and 3,500 in Europe and approximately one-third of cases are related to prior or subsequent other gastrointestinal tract tumors. The most common malignancy lesions are adenocarcinoma, gastrointestinal stromal tumors (GIST), carcinoids or lymphomas. Malignant involvement of the ileum, in almost half of the cases, refers to lymphoma [69-71].

Still in a symptomatic phase more than 50% of patients present metastasis. Due to this malignancy and knowing the specificity of the clinical picture, the professional should perform a deep approach of the disease in order to reach an early diagnosis and consequently possibility of successful in the treatment [71].

The carcinogenesis pathway seems to be associated to the host-bacteria interaction, with changes in the intestinal stem cell function. The chronic inflammation process and secondary and hyper proliferation of the intestinal stem cells initiate malignant modifications, maintenance and metastases. Carcinoids and lymphomas affect mainly the ileum in a proportion of 87% and 60%, respectively. A study from Canada showed that adenocarcinomas occur in the ileum in 16% [72-74].

The small bowel adenocarcinoma presents non-specific clinical manifestation and most lesions occur within 25 cm of the duodeno-jejunal junction. For this reason, individuals presenting pain, vomiting, and anemia should have proximal jejunum as part of the investigation. Most duodenal carcinomas are polypoid and the larger lesions may form ulcerations. The appearance of the mesenteric small bowel carcinomas includes mucosal destruction, irregular luminal narrowing, and rigidity of a short segment, and areas of intestinal obstruction. The distinction from CD is that this pathology normally reaches longer segments, and an appearance of cobblestone is observed. Lymphoma and leiomyosarcoma normally are seen as larger and softer tumors [3, 75, 76].

The small bowel lymphoma originates in the lymphoid follicle of the submucosa and may encircle the bowel, leading to narrowing of the lumen and mimic CD in different ways such as clinically, radiologically and endoscopically. It is possible to find single or multiple segmental thickened areas, circumferential thickening, or ulcerations and consequent development of a fistulous tract to adjacent bowel loops, similar to CD [70, 77].

### Eosinophilic gastroenteritis (EG)

Eosinophilic gastrointestinal disorders may occur in adults and

consist in two types known as EG, that occur due to pathological eosinophile infiltration (without known causes of eosinophilia such as parasitic infection, malignancy, and drug reaction) in the gastrointestinal wall independently of esophageal involvement and eosinophilic esophagitis, characterized by dense infiltration of eosinophile only in esophageal mucosa. EG is considered a non-IgE-dependent T helper 2 type allergic and possibly the food allergens are responsible to the triggering and aggravating factors as the modifications in the mucosal integrity, culmination in the presence of several antigens in the gut wall, resulting in tissue and blood eosinophilia. The main symptoms are abdominal pain and diarrhea [4, 78].

EG may reach the stomach and small intestine, and sometimes the colon. Patients with small-bowel EG may have abdominal pain, diarrhea, or malabsorption and ileal strictures and bowel obstruction may be observed with muscle layer involvement. Endoscopic procedures are limited to identify the presence of EG once the typical endoscopic alterations are not specific (erosion, erythema, nodularity, and edema). On the other hand, a multiple biopsy-based histopathological diagnosis is crucial. Diffuse enteritis with complete loss of villi, submucosal edema, and fibrosis may be present. In EG, there is no typical architectural distortion found in individuals with CD what could help in the differentiation of these two pathologies. Furthermore, the presence of peripheral eosinophilia and/or an eosinophil-rich tissue infiltrate is rare in CD patients [4, 79-81].

### Conclusion

The inflammation of the ileum may occur due to different pathological conditions leading to difficulties in the diagnosis. Normally it is associated to CD but it may also occur, in UC, BD, malignant pathologies, infectious diseases, EG and use of NSAIDs. Although TI occurs in higher percentage in CD, an individual approach is necessary to differentiate from the other conditions once the correct diagnosis is crucial for the immediate therapeutic approach and recovering of the patient.

### Conflict of Interests

Authors declare no conflict of interests.

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