

Endoscopic features of gastrointestinal tuberculosis and crohn's disease

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Abstract

Endoscopic examination of the gastrointestinal (GI) tract plays a very important role in the diagnosis and follow-up of patients with Crohn's disease (CD) and intestinal tuberculosis (TB). The clinical, morphological, and histological features of GI TB and CD are so similar that it becomes difficult to differentiate between these two entities. In geographical regions such as India where both GI TB and CD are prevalent, differential diagnosis between the two is challenging. While there is a lot of similarities between these two disorders, these two can be differentiated from each other with a combination of clinical, endoscopic, histological, radiological, and endoscopic features. The observation of the characteristic lesions at endoscopic examination and the extent of involvement in CD and intestinal TB is an important step in differentiation between these two disorders. While the most important endoscopic characteristics such as involvement of left side of the colon and presence of longitudinal ulcerations and cobblestoning support a diagnosis of CD, predominant involvement of ileocecal region and transverse ulcers support the diagnosis of intestinal TB. In this review, we have described the usefulness and limitations of endoscopic modalities in the diagnosis and differentiation of intestinal TB and CD.

Key words

Cobblestoning, Crohn's disease, gastrointestinal tuberculosis

Introduction

Extrapulmonary tuberculosis (TB) accounts for approximately 20% of patients having TB and 7%–10% of them have abdominal TB.^[1-3] While abdominal TB continues to be a common problem in developing countries including India, increasing population migration and epidemic of acquired immunodeficiency syndrome have led to resurgence of this disease in regions where TB had previously been largely controlled.^[1-3] Abdominal TB remains an important disease in


countries where TB is still endemic.^[1-7] While TB is endemic in India, there has been a rise in number of patients with Crohn's disease (CD) from every part of India.^[8,9] In a study by the Indian Society of Gastroenterology Task Force on inflammatory bowel disease (IBD) including 1159 patients with IBD from secondary and tertiary care centers in India, 35.3% of them had CD.^[10]

The clinical, morphological, and histological features of gastrointestinal (GI) TB and CD are so similar that it becomes difficult to differentiate between these two entities.^[11-14] In geographical regions such as India where both GI TB and CD are prevalent, differential diagnosis between the two is challenging.^[11-14] The natural history of CD is quite different from that of GI TB. While GI TB gets cured with appropriate

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anti-TB treatment, CD has a remitting/relapsing or persistent course and stays life-long usually. Although treatment with an immunosuppressant with a mistaken diagnosis of CD may worsen TB, an empiric treatment with anti-TB therapy on the other hand may delay the diagnosis of CD in such patients. Furthermore, use of biologics, which have become one of the important treatment modalities for CD, can lead to flare of TB if the mistaken diagnosis of CD is made in a patient having GI TB.^[15-17] Because of similarity in the clinical presentation, endoscopic appearance, and histological characteristics between these two diseases, many of them are treated empirically with anti-TB drugs at times.^[9,18]

Diagnostic Criteria

Diagnostic criteria for gastrointestinal tuberculosis

A definitive diagnosis of GI TB can be made based on the presence of any of the following three criteria:

- Culture of tissue (colonic biopsy, lymph nodes) resulting in growth of *Mycobacterium tuberculosis*
- Histological demonstration of typical acid-fast bacilli (AFB)
- Histological evidence of necrotizing granuloma.

While a positive culture, demonstration of AFB on smear, and histological evidence of a caseating granuloma are gold standard tests for the definitive diagnosis of TB, the sensitivity of the combination of the three or any one test is approximately 30%–50%.^[19] In rest of the patients, the diagnosis is considered presumptive based on clinical, endoscopic, radiological, and histological evidence. The unequivocal response to anti-TB therapy for 6 months confirms the diagnosis of TB in these patients. It should be emphasized that adherence to treatment is extremely important in those with presumptive diagnosis of TB who are receiving anti-TB therapy empirically.

Diagnostic criteria for Crohn's disease

There is no single gold standard test, and the diagnosis of CD is based on a combination of clinical features, endoscopic characteristics, and histological characteristics. Both the

Asian Pacific Associations of Gastroenterology and the Indian Society of Gastroenterology guidelines on CD suggest exclusion of infective causes, especially TB before making a diagnosis of CD.^[20,21]

Sites of Involvement in Gastrointestinal Tuberculosis and Crohn's Disease

TB may involve any part of GI tract (GIT), from the esophagus to the anal canal. There is a striking tendency for intestinal TB to affect the ileum and ileocecal (IC) area preferentially.^[22] Other common sites of involvement in TB are colon, appendix, and jejunum [Table 1]. In the colon, the frequency of involvement decreases segmentally from the ascending colon to the rectum. The involvement of rectum and anal canal is uncommon in patients with GI TB. Patients with TB may have involvement of lymph nodes, peritoneum, and solid viscera either alone or in combination with GIT.

Types of Morphological Lesions

The changes caused by acute inflammation of the colonic mucosa, namely, edematous mucosal folds, mucosal ulcerations and nodularity, luminal narrowing, strictures, and pseudopolyps, can occur in both intestinal TB and CD. The morphological features of intestinal TB (ITB) and CD depend on the stage of the disease. The lesions may vary from mild lesions such as loss of vascular pattern, erythema, and superficial ulcerations to more advanced lesions including deep ulcerations, nodularity, and strictures. One should realize that the evolution of disease takes from months to years both for GI TB and CD. The classical morphological features, as described in most textbooks, are seen in advanced stages of the disease. Some of the patients may present in early stages of evolution of the disease, thereby one may not find classical lesions and instead finds minute lesions. The wisdom lies in identifying these minute lesions so that the progression of the disease can be prevented with timely institution of appropriate treatment. Table 2 shows the types of lesions and their characteristics for universal reporting.

Table 1: Sites of involvement in patients with intestinal tuberculosis and Crohn's disease

Site	Amarapurkar et al. ^[8]		Makharia et al. ^[23]		Li et al. ^[24]	
	CD (n=26) (%)	ITB (n=26) (%)	CD (n=53) (%)	ITB (n=53) (%)	CD (n=130) (%)	ITB (n=122) (%)
Stomach	0	2 (7.7)	3 (5.6)	1 (1.8)		
Duodenum	1 (3.8)	2 (7.7)	3 (5.6)	2 (3.7)		
Jejunum	2 (7.7)	1 (3.8)	9 (16.9)	0		
Ileum	16 (61.5)	20 (76.9)	13 (24.5)	8 (15)	86 (66.2)	73 (59.8)
Ileocecal region	20 (76.9)	21 (80.7)	47 (88.6)	49 (92.4)	72 (55.4)	92 (75.4)
Ascending colon	18 (69.2)	21 (80.7)	34 (64.1)	23 (43.4)	60 (46.2)	76 (62.3)
Descending colon	10 (38.4)	5 (19.2)	32 (60.3)	7 (13.2)	44 (33.8)	30 (24.6)
Sigmoid colon			35 (66.3)	6 (11.3)	58 (44.6)	28 (23)
Rectum	8 (30.7)	5 (19.2)	33 (62.2)	10 (18.8)	50 (38.5)	20 (16.4)
Anal canal	2 (7.7)	1 (3.8)	8 (15)	2 (3.7)		

CD=Crohn's disease, ITB=Intestinal tuberculosis

Table 2: Terminology of endoscopic lesions in Intestinal tuberculosis and Crohn's disease

Mucosal damage	Description	Grading
Loss of vascular pattern	Loss of normal mucosal appearance without well-demarcated, arborizing capillaries	From patchy or blurred to complete loss
Erythema	Unnaturally reddened mucosa	From discrete or punctiform to diffuse erythema
Granularity	Mucosal pattern produced by a reticular network of radiolucent foci of 0.5-1 mm of diameter with a sharp light reflex	From fine to coarse or nodular due to abnormal light reflection
Friability/bleeding	Bleeding or intramucosal hemorrhage before or after the passage of the endoscope	From contact bleeding (bleeding with light touch) to spontaneous bleeding
Erosion	A definite discontinuation of mucosa <3 mm in size. Also described as pinpoint ulceration	Isolated, diffuse
Aphthous ulcer	White depressed center surrounded by a halo of erythema	Isolated, multiple
Ulcer	Any lesion of the mucosa of unequivocal depth with or without reddish halo	Isolated or multiple based on morphology: Circular, linear, stellar, serpiginous, irregular shape, superficial or deep
Ulcer size	Defined in mm or classified as: ≤ 5 mm; 5-20 mm; >20 mm	
Stenosis	Narrowing of the lumen	Single, multiple, passable (by standard adult endoscope), un-passable, passable after dilation, ulcerated, nonulcerated
Postinflammatory polyps	Polypoid lesion, usually small, glistening, isolated or multiple, scattered throughout the colon Sometimes cylindrical or giant (>2 cm) in size	Isolated, diffuse, occluding ("giant")
Cobblestone	Mucosal pattern with raised nodules, resembling the paving of a "roman" road	With or without ulceration

Pathological and Clinical Correlation

The diameter of a normal intestine decreases from the duodenum to jejunum and then to the ileum. The diameter of the jejunum is 3 cm and that of the ileum is 2.5 cm.^[25,26] The content, which flows through the intestine, is mostly chyme (liquid). The diameter of the intestinal lumen, at which the obstruction to the flow of chyme occurs, is not well established. In a rat model, it was observed that the pressure in the intestine started rising and the flow of the contents started decreasing when the luminal diameter decreased to 60% of the original diameter.^[27] Therefore, in the early stage of diseases, when there is no cicatrization of the lumen, the flow of chyme is not affected and thus patients may not have any intestinal symptoms. With progression of the disease, the effective diameter of the intestinal lumen decreases, resulting in obstruction to the flow of the intestinal contents. Therefore, the severity of symptoms increases progressively as the intestinal luminal diameter decreases. The initial symptoms of intestinal colic are usually episodic and are precipitated by the episodes of GI infection resulting in transient mild intestinal wall edema which further compromise the diameter of the already compromised intestinal lumen because of the disease process. While inflammation caused by acute GI infection in the normal intestine is not critical and does not lead to critical decrease in the effective diameter of the intestine, even a mild decrease in the diameter of the intestine can lead to a critically low diameter in already compromised lumen due to the primary disease process. Such episodic symptoms may also be precipitated by a high fiber diet or the ingestion of seeds. As disease progresses, the interval between the episodes of symptoms also decreases. Ultimately, the symptoms of intestinal colic become more frequent and patients develop

partial intestinal obstruction. The ulcerations and nodularity caused by the tissue destruction can lead to oozing of blood from the ulcers, resulting in anemia.

After effective treatment of the disease, there is resolution of active inflammation and healing of ulcers, which results in the improvement in symptoms. As it is well known that chronic inflammatory process heals with fibrosis, the healing of ulcers and inflammation of the intestine leads to scarring of the intestinal lumen and thus compromise the normal intestinal diameter.^[28] There is a fundamental difference in the diseases affecting solid/spongy organs and luminal organs. In spite of residual changes in a part of the solid/spongy organ, there still may be sufficient organ volume to maintain the functions of the organ. On the contrary, healing of the intestinal lesions may result in the fibrotic stricture and patients may continue to be symptomatic. Most of the times, however, despite the residual intestinal stricture/narrowing, the luminal diameter may remain sufficient to allow uninterrupted the passage of intestinal contents. On occasions, healing of lesions can result in a critical stricture resulting in frequent symptoms and such strictures may require resection or stricturoplasty.

Endoscopy in Intestinal Tuberculosis and Crohn's Disease

Endoscopic examination of the GIT is essential not only for the diagnosis but also for evaluation the extent of the disease, assessment of the activity of the disease, and monitoring the response of the therapy in most patients with GI TB and CD.

Ileocolonoscopy is the first recommended test for the diagnosis of both ITB and CD.^[20,21,29]

Endoscopic features in patients with gastrointestinal tuberculosis

IC region is most often involved area in patients having GI TB, possibly because of the increased physiological stasis, increased rate of fluid and electrolyte absorption, minimal digestive activity, and an abundance of lymphoid tissue at this site.^[30-32] Retrograde ileoscopy should be done in all patients suspected to have ITB and biopsies should be obtained even if the mucosa in the terminal ileum appears normal. The biopsies of normal appearing terminal ileum may reveal granulomas in additional 4% of patients with clinical suspicion of ITB.^[33,34] Terminal ileal involvement alone with relative cecal sparing is uncommon in ITB.^[35] In 10%–20% of patients, segmental colonic involvement may occur in the absence of IC involvement.^[36,37] Approximately 5% of patients may present with pancolitis, which may mimic ulcerative colitis.^[38]

The endoscopic findings in ITB may vary from mild lesion(s), such as loss of vascular pattern, erythema, small ulcerations, and superficial ulcerations, to more advanced lesions including deep ulcerations, nodularity, and strictures [Figure 1]. The endoscopic lesions in ITB are classified as ulcerative (60%), ulcerohypertrophic (30%) characterized by inflammatory mass around IC valve with ulcerated thick wall, and hypertrophic (10%) characterized by fibrosis and pseudotumor lesions.^[39] The ulcers in ITB are typically transverse, often circumferential with ill-defined, sloping or overhanging edges, and are usually surrounded by inflamed mucosa.^[19,40-42] The strictures in patients with TB are generally shorter in length. IC valve is often patulous in them [Figure 1]. A stricture in the intestine has also been described due to extraluminal cause such as lymph nodes causing compression even without apparent mucosal lesion.^[6]

In tuberculous colitis, the colonic mucosa surrounding an ulcer exhibits features of inflammation, such as erythema, nodularity, or edema. The rectum is rarely involved.^[43] Traction diverticula and sinus tracts due to adjacent lymphadenitis may be seen in tubercular colitis.^[39]

In gastroduodenal TB, comprising 1% of abdominal TB, the most common endoscopic findings observed are ulceration and nodularity in the pyloroduodenal area along with strictures, and the disease could be multifocal, involving pyloroduodenal area and the second part of the duodenum (15%) or even present as antral hypertrophic nodular mass.^[40]

Endoscopic features in Crohn's disease

CD can affect any part of the GIT, from the oropharynx to the anorectum. Once CD has settled in, the location of the disease remains stable generally, although exceptions do occur, especially following surgical resections^[41] [Table 1]. Similar to TB, CD also affects IC area commonly.^[42] In a multicenter study conducted by the Indian Society of Gastroenterology, of 397 patients with CD, 39.2% had involvement of both small and large intestine (ileocolonic), 31.2% had isolated

colonic, and 22.9% had involvement of only small intestine. The involvement of upper GI (UGI) was reported in 5.8% of patients. While 18.8% had stricturing disease, 4.4% had fistulizing disease. Nearly 6.9% patients had perianal disease as a disease modifier.^[10]

Isolated perianal disease is rare (2%–3%) although perianal abnormalities, in conjunction with other sites of intestinal involvement, are common.^[43-45] UGI involvement, when occurs in patients with CD, it almost always occurs in association with small intestinal and/or colonic involvement.

The earliest and most characteristic endoscopic finding in CD is the aphthous ulcer.^[46,47] It can be found throughout the GIT. An aphthous ulcer represents a small (≤ 5 mm) superficial ulcer surrounded by a characteristic tiny rim of erythema [Figure 2]. They have clear margins and are often surrounded by normal colonic mucosa with very little reactive change. Aphthous ulcers can be localized or multifocal.^[48] They are often seen in groups and lie in longitudinal fashion in the GIT, tend to enlarge concentrically, become nodular, and give rise to larger and deeper ulcerations.^[46] The best model to study the earliest lesions in CD is the postoperative recurrence condition, where these early lesions recur within weeks to months after surgery.^[46]

The ulcers in CD can be of various sizes and shapes. The mucosa lying between long linear ulcerations can be normal or very edematous, reddish, and hyperplastic, giving an appearance of cobblestone [Figure 2].^[49] The involvement of the colon and small intestine in patients with CD is characteristically patchy. The lesions may involve only one side of the colonic mucosa in the same segment [Figure 3]. Rectum is involved in approximately 50% [Figure 2].

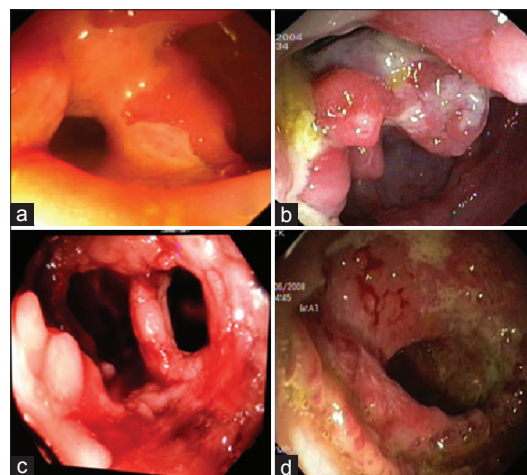


Figure 1: Endoscopic lesions in a patient with intestinal tuberculosis. (a) Ulcers over the ileocecal valve in a patient with intestinal tuberculosis. (b) Multiple nodules and deep ulcers (with neoplasm-like appearance) in cecum with patulous ileocecal valve. (c) Fixed patulous ileocecal valve with nodules in cecum and ascending colon in a patient with intestinal tuberculosis. (d) Circumferential ulcerative lesion in a patient with tuberculosis

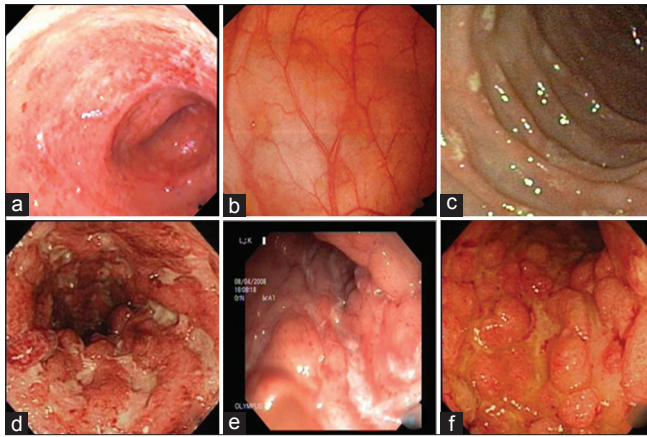


Figure 2: Endoscopic features in a patient with Crohn's disease. (a) Erythema and loss of vascular pattern in a patient with Crohn's disease. (b) A few aphthous ulcers in the colon in a patient with Crohn's disease. (c) Discrete ulcers in the colon in a patient with Crohn's disease. (d) Multiple deep longitudinal ulcers in colon in a patient with Crohn's disease. (e) Longitudinal ulcers with cobblestone appearance in the colon. (f) Cobblestone appearance in a patient with Crohn's disease

Where the inflammation is deep and extensive, luminal narrowing or strictures can occur.^[48,49] Strictures virtually always arise in areas having severe ulceration. Both length and width of the strictures can vary considerably, 3–10 cm in length.^[42] The strictures in patients with CD may be longer than that seen in patients with TB. Strictures with surrounding nodularity and eccentric lumen may also be due to malignant transformation.^[50] The inflammation and ulcerations in CD are often deep, transmural, and can lead to perforation, inflammatory mass, and/or fistula formation. Fistulas are most often seen proximal to strictures or within the strictures and are frequently surrounded by extensive inflammatory changes.^[51]

When CD becomes quiescent, vascular pattern may remain diminished. In patients with more extensive CD, irregular healing may lead to hypertrophic zones alternating with areas of atrophy (pseudopolyps) and mucosal bridging.

Upper gastrointestinal involvement in Crohn's disease

UGI endoscopy is routinely performed in the assessment of children with suspected IBD to accurately classify IBD.^[52] While UGI endoscopy and biopsies may be useful in all patients for evaluation of the extent/location of the disease at the time of diagnosis, whether it should be performed routinely in all adult patients remains unclear.^[52] The UGI endoscopy, however, should be done in at least in those who have UGI symptoms.

Isolated involvement of UGI tract is rare in patients with CD, and whenever there is an involvement of UGI tract, it occurs concomitantly with the involvement of either small intestine or the colon or both.^[53] Gastrointestinal involvement often presents with additional symptoms such as epigastric pain and features of high-gut obstruction. The ulcers in the gastrointestinal CD may be linear or serpiginous, unlike

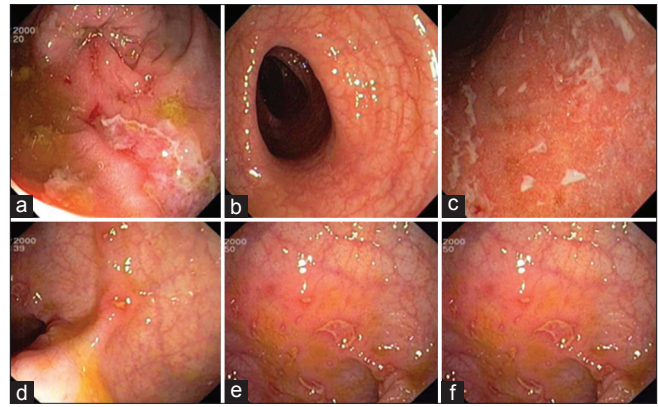


Figure 3: Skip lesions in a patient with Crohn's disease. (a) Discrete ulcerated lesion in the rectosigmoid region. (b) Normal looking mucosa in the descending colon. (c) Multiple ulcers with loss of vascular pattern in transverse colon. (d) Discrete ulcers in the ascending colon. (e and f) Discrete ulcers in the cecum

circular or transverse ulcers seen in peptic ulcer disease, which involves gastroduodenal area far more often than CD.^[54] In isolated duodenal disease, any part of the duodenum can be involved, but the second part is most frequently affected. Deep ulceration and inflammation can lead to stricture in gastroduodenal area and high-gut obstruction.

Diaz *et al.* in a review of 20 articles reporting 2511 patients with CD (CD group) reported involvement of UGI tract in 815 (34%) patients (UGI group).^[55] The endoscopic features in the CD group were gastric erythema in 5.9%, gastric erosions in 3.7%, duodenal ulcers in 5.3%, and erythema in the duodenum in 3% of patients.^[55] The most common histopathological features in the CD group was nonspecific gastric inflammation in 32%, gastric granuloma in 7.9%, and focal gastritis in 30.9% of patients.^[55] In the UGI CD group, gastric inflammation was present in 84% of patients, followed by duodenal inflammation in 28.2% and gastric granuloma in 23.2%. The detection of UGI tract involvement is higher (17%–75% for upper endoscopy) when biopsies of gastric mucosa are done routinely in patients with CD compared to the practice when UGI endoscopy and biopsies are done only if one observes any abnormality in symptomatic patients (0.5%–13%).^[53,55]

Endoscopy during Follow-up of Patients

In patients treated for intestinal TB, it is expected that there will be complete resolution of the lesions, detectable by endoscopy or by imaging, following completion of therapy. In a study of 49 patients with IC or colonic TB treated with anti-TB treatment, complete healing of mucosal lesions was observed in 73.5% of the participants at the end of 2 months and in 100% of participants at the end of 6 months.^[56,57] It is therefore appropriate to re-endoscope patients who were treated empirically for ITB and to establish complete mucosal healing at the end of 6 months. The Indian Society of Gastroenterology Task Force on IBD was in agreement that

this should be done, in view of the possibility that recurrent symptoms would make it difficult to judge whether the patient was in fact having ITB or CD during the first episode.

There is now emerging evidence that mucosal healing should be one of the goals of the treatment of CD. Therefore, it appears appropriate that the status of healing process is assessed during the treatment period. While many agree to do that, the protocol and timing of assessment is yet to be defined.

When diagnosis remains in doubt, both endoscopic and histologic assessments are appropriate as demonstrated by a large proportion of patients initially classified as indeterminate colitis or possible IBD were diagnosed as non-IBD after 5 years (22.5% vs. 50%) in the IBSEN study.^[58] In patients of definite ileocolonic CD, routine endoscopic evaluation for patients in clinical remission may not always be necessary, unless clinicians suspect that re-evaluation may have influence on the optimization of the management strategy. Fecal calprotectin or lactoferrin may be used as surrogate markers of mucosal healing and may reduce the need of repeated endoscopies.^[59]

Ileocolonoscopy is the gold standard in the diagnosis of postoperative recurrence. It is recommended to be done at 6–12 months after surgery. After resection of the IC region in patients with CD, the postoperative recurrence rate is around 65%–90% within 12 months and 80%–100% within 3 years of surgery in the absence of postoperative prophylaxis.^[60,61]

Mucosal biopsies

With increasing use of endoscopic procedures to visualize the intestinal lumen and obtaining targeted biopsies from the diseased segments of the intestine, endoscopic mucosal biopsies have mostly replaced the surgical biopsies for microscopic examination. For a reliable diagnosis of CD, multiple biopsies from different segments of the colon (including the rectum) and the ileum should be obtained.^[62] Multiple biopsies imply a minimum of two samples from each site.^[62] Biopsies should be representative from areas of minor and major inflammation to mirror correctly the intensity and spectrum of inflammation. In addition, biopsies must also be taken from “normal appearing” mucosa.^[62] Targeted biopsies from areas of stenosis, any unusual polypoid lesions, or any other lesion that may attract endoscopists attention should be obtained in separate bottles. Biopsies should also be obtained for microbiological tests including molecular diagnosis of TB (polymerase chain reaction [PCR], GenExpert), acid-fast stain, and culture.

Isolation of *M. tuberculosis*, using culture or by staining of the smear, is the most specific method for the diagnosis of active TB. The sensitivity of both these techniques, however, remains low.^[63-66] While culture can detect 10–100 bacilli/mL of the sample, *M. tuberculosis* bacilli can be cultured from 10% to 30% of mucosal biopsies in patients with colonic TB.^[63-66] A presumptive diagnosis of TB may be considered by detection

of AFB on intestinal biopsies which have been reported with a variable frequency (25%–36%) in patients with intestinal TB.^[19,67]

PCR using *M. tuberculosis*-specific primer shows a positivity varying from 20% to 64%. Detection of *M. tuberculosis* by PCR has a fair sensitivity, but the results of a positive PCR should be interpreted cautiously.^[19,68-70] PCR may be reported positive because of contamination in the laboratories. Passage of saprophytic mycobacteria may also test positive in colonic biopsies. In one study, *in situ* PCR for TB in mucosal biopsies was positive in 6 of 20 intestinal TB patients.^[63]

Small Bowel Endoscopy

In patients suspected of having intestinal TB or CD, especially when ileocolonoscopy does not show definite evidence of the disease and contrast-enhanced computed tomography (CT) or CT-enterography (CTE) or magnetic resonance-enterography (MRE) shows small bowel wall thickening or stricture (with or without proximal bowel dilation), small bowel endoscopy may be needed to look for mucosal abnormalities suggestive of the disease and to obtain biopsies for histological assessment. Balloon-assisted and spiral enteroscopy are preferred modalities for evaluating the small bowel today because of biopsy and therapeutic capabilities. Histological assessment of the small intestinal lesion(s) is essential as the etiological diagnosis of the ulcerating lesions cannot be made based on endoscopic appearances alone.^[71] In patients with suspected CD and negative ileocolonoscopy, small bowel capsule endoscopy (SBCE) may be the diagnostic modality for the evaluation of the small bowel, in the absence of obstructive symptoms or known stenosis. The sensitivity and specificity for the diagnosis of CD have been reported to be 100% and 91% by SBCE, 81% and 86% by MRE, and 76% and 85% by CTE, respectively.^[72]

In patients having intestinal obstructive features or known to have small intestinal stricture, a cross-sectional imaging modality such as MR-enterography or CTE is a preferable initial investigation.^[52]

The data regarding capsule endoscopy in ITB are limited. Reddy *et al.* have described multiple scattered short, oblique, or transverse mucosal ulcers with a necrotic base in the jejunum and ileum in patients with ITB.^[73] Cello described the characteristics of small intestinal tubercular ulcers to be shallow with irregular geographic borders, and transverse in their lie, rather than longitudinal.^[74]

SBCE is a safe noninvasive modality for the diagnosis of CD. As per the results of a meta-analysis, SBCE is superior to all other modalities for diagnosing nonstricturing small bowel CD, with a number needed to test (NNT) of 3 to yield one additional diagnosis of CD over small bowel barium radiography and NNT of 7 over colonoscopy with ileoscopy.^[75]

Fidder *et al.* defined a positive SBCE result for CD as the presence of four or more ulcers, erosions, or a region with clear exudate and mucosal hyperemia and edema.^[76] They reported that the greatest yield of SBCE in diagnosing CD is achieved in young patients who present with symptoms of abdominal pain plus diarrhea.^[76] SBCE has a high negative predictive value for small bowel CD.^[52]

Endoscopic differentiation of small bowel CD from drug-induced lesions or other diseases is unreliable. Nonsteroidal anti-inflammatory drugs should be withdrawn at least 4 weeks before SBCE if there is a diagnostic possibility of CD.^[52] The small lesions detected by SBCE may not be specific for CD and may be found in healthy people and patients with drug-induced enteropathy and vasculitis. In a study, among 102 patients with suspected CD, 37% were initially found to have small bowel ulcerations on SBCE, but CD was diagnosed definitively in 13% only at 1-year follow-up.^[77]

The Capsule Endoscopy Crohn's Disease Activity Index (CECDAI) or Niv score has been recently validated in a multicenter prospective trial.^[78,79] This scoring index evaluates three parameters: inflammation (A), extent of disease (B), and presence of strictures (C), both for the proximal and distal segments of the small bowel [Table 3]. The final score is calculated by adding the two segmental scores: CECDAI = proximal $([A1 \times B1] + C1)$ + distal $([A2 \times B2] + C2)$.

CE may play an important role in the monitoring of patients with CD and may have a unique role in assessing mucosal healing after medical therapy, for assessing early postoperative recurrence. The role of SBCE in patients with established CD should focus on patients with unexplained iron deficiency or obscure GI bleeding or in those with unexplained symptoms, when other investigations are inconclusive.^[52,80]

After a negative ileocolonoscopy and negative CTE or small bowel follow through, SBCE has not been found to be a

Table 3: Capsule endoscopy Crohn's disease activity index^[78]

Score	Point	Features
Inflammation score	0	None
	1	Mild to moderate edema/hyperemia/denudation
	2	Severe edema/hyperemia/denudation
	3	Bleeding, exudate, aphthae, erosion, small ulcer (<0.5 cm)
	4	Moderate ulcer (0.5-2 cm), pseudopolyps
Extent of disease score	5	Large ulcer (>2 cm)
	0	No disease
	1	Focal disease (single segment)
	2	Patchy disease (2-3 segments)
	3	Diffuse disease (>3 segments)
Stricture score	0	None
	1	Single-passed
	2	Multiple-passed
	3	Obstruction (nonpassage)

cost-effective third test, even in patients with high pretest probability of CD.^[81] The International Conference on Capsule Endoscopy recommended that patients with suspected CD should be selected to undergo SBCE if they present with typical symptoms (chronic abdominal pain, chronic diarrhea, weight loss, or growth failure) plus either extraintestinal manifestations (fever, arthritis or arthralgia, pyoderma gangrenosum, perianal disease, or primary sclerosing cholangitis), inflammatory markers (iron deficiency, erythrocyte sedimentation rate, C-reactive protein, leukocytosis, or serology), or abnormal small bowel imaging (small bowel series or CT scan).^[82]

The ability of CE in distinguishing between ITB and CD is not clearly established.

Endoscopic Dilatation of the Strictures

Endoscopic dilatation of strictures in CD is a safe and effective alternative to surgery in experienced hands and should be considered before surgery in selected patients.^[52] Endoscopic balloon dilatation has been used to treat uncomplicated strictures, with a maximal length of 4 cm, in patients with CD.^[83] It has often been combined with local injection of steroids at the site of the stricture. Endoscopic dilatation should be done only after control of the disease activity. A systematic review of 13 studies including 347 patients with CD showed that endoscopic dilatation was mainly used in postsurgical strictures, with 86% technical success, 2% complication rate, and 58% long-term efficacy.^[84] A stricture length equal to or less than 4 cm was associated with a surgery-free outcome. Another study including 776 dilatations in 178 patients with CD further confirmed that the endoscopic dilatations had been done mostly for anastomotic strictures (80%).^[85] Technical success rate was 89%. In a subset of patients who were followed up, 80%, 57%, and 52% required no further intervention or one additional dilation only at the end of 1, 3, and 5 years, respectively. Cumulative proportions of patients undergoing surgery at 1, 3, and 5 years were 13%, 28%, and 36%, respectively. Complication rate per procedure was 5.3%, and included bowel perforation (1.4%), major bleeding requiring blood transfusion (1%), minor bleeding (1.3%), and abdominal pain or fever (1.5%).

Endoscopic Differences between Intestinal Tuberculosis and Crohn's Disease

Zhou and Luo^[86] compared the records of 30 patients of CD and 30 patients with ITB. The comparison of endoscopic findings among various studies between ITB and CD is presented in Table 4.

Lee *et al.*^[87] evaluated the diagnostic value of colonoscopy in differentiating ITB ($n = 44$) from CD ($n = 44$) and observed that four parameters (anorectal lesions, longitudinal

Table 4: Endoscopic differences between gastrointestinal tuberculosis and Crohn's disease

	Zhou and Luo ^[86]		Lee et al. ^[87]		Amarapurkar ^[8]		Makharia ^[23]		Li et al. ^[24]		Dutta et al. ^[88]		Zhang et al. ^[89]	
	CD (n=30) (%)	ITB (n=30) (%)	CD (n=44) (%)	ITB (n=44) (%)	CD (n=26) (%)	ITB (n=26) (%)	CD (n=53) (%)	ITB (n=53) (%)	CD (n=130) (%)	ITB (n=122) (%)	CD (n=30) (%)	ITB (n=24) (%)	CD (n=92) (%)	ITB (n=31) (%)
Skip lesions					23.1	7.7	66	16.9	53.8	44.3	36.7	8.3	44.6	29
Aphthous ulcers			81.8	20	34.6	19.2	54.7	13.2	53.8	44.3	36.7	16.7	44.6	29
Linear ulcers			40.9	2.3	57.7	23.1	30.1	7.5	54.7	8.2	33.3	4.2	80.4	58.1
Transverse ulcers			25	65.9				4.6	4.6	4.1	6.7	25	18.5	64.5
Nodularity							24.5	49	48.5	32.8				
Cobblestoning	20	0	34.1	6.8	57.7	23.1	16.9	0	27.7	1.6	10	0	33.7	32.3
Strictures			9	8	30.7	19.2					26.7	16.7	18.5	12.9
Pseudopolyps	46.7	40	27.3	52.3	34.6	19.2					30	8.3	7.6	38.7
Patulous IC valve			9.3	40							6.7	8.3		
IC lesions			90.7	100							20	4.2	17.4	6.5
Anorectal lesions			84.1	9.1										
<4 segments involved			18.2	81.8										

CD=Crohn's disease, ITB=Intestinal tuberculosis, IC=Ileocecal

ulcers, aphthous ulcers, and cobblestone appearance) were significantly more common in patients with CD than in patients with ITB. Four other parameters (involvement of fewer than four segments, a patulous IC valve, transverse ulcers, and scars or pseudopolyps) were observed more frequently in patients with ITB than in patients with CD.^[87] A patulous valve with surrounding heaped-up folds or a destroyed valve with a fish mouth opening was more likely to be caused by TB than that by CD. In their study, if CD was diagnosed based on the presence of higher number of parameters characteristic of CD than those characteristic of ITB, and vice versa, the diagnosis was correct in 87.5% and incorrect in 8%.^[87]

Amarapurkar *et al.* studied 26 patients with ITB and 26 patients with CD and found that the accuracy of endoscopic features (deep linear/serpiginous ulcers and cobblestone appearance) was 67.3% compared to the 84.6% for clinical score and 82.6% for positive TB-PCR.^[8]

We, in a study of 53 patients with intestinal TB and 53 patients with CD, observed that while skip lesions, aphthous ulcers, linear ulcers, and cobblestoning were more common in patients of CD than that in intestinal TB; nodularity was however more common in those with intestinal TB.^[23] We also observed that the involvement of rectum (62.2% vs. 18.8%, $P < 0.001$), sigmoid colon (66% vs. 11.3%, $P < 0.001$), descending colon (60.3% vs. 13.2%, $P < 0.001$), ascending colon (64.1% vs. 43.4%, $P = 0.03$), and jejunum (16.9% vs. 0%, $P < 0.001$) was significantly more common in patients with CD than in patients with ITB.^[23] There was no significant difference in the involvement of the IC region (88.6% vs. 92.4%, $P = 0.5$), ileum (24.5% vs. 15%, $P = 0.2$), stomach, and duodenum in patients with CD and intestinal TB.^[23]

Li *et al.*^[24] in their study including 122 patients with ITB and 130 patients with CD observed that that rectum and sigmoid colon involved lesions were more common in patients with CD. On the other hand, cecum and IC valve involved lesions and fixed-open IC valve were more often seen in patients with ITB. Ring-like ulcers and rodent-like ulcers were more common in ITB, while longitudinal ulcers, grid-like ulcers, cobblestone appearance, and nodular hyperplasia were more commonly found in CD [Table 4].

Dutta *et al.* followed up 30 patients of ITB and 30 patients of CD and reported that patients with CD had longer duration of symptoms ($P < 0.001$), blood mixed stool ($P = 0.006$), longitudinal ulcers ($P = 0.005$), skip lesions ($P = 0.008$), and involvement of higher number of colonic segments ($P = 0.004$).^[88] Yu *et al.*^[90] studied 43 patients with ITB and 53 patients with CD and observed that transverse ulcers and patulous IC valve were more common in ITB. Longitudinal ulcer was a significant predictor in differentiating CD from ITB (odds ratio 35.5, confidence interval 1.8–683.2).

Zhang *et al.*^[89] also reported that transverse ulcers, rodent-like ulcers, and patulous IC valve were more common in those with ITB and longitudinal ulcers in patients with CD.

The reasons for a greater frequency of involvement of left side of the colon in patients with CD and occurrence of aphthous ulcers, linear ulcers, cobblestoning of mucosa in higher frequency in CD and nodularity, patulous IC valve in higher number in those with ITB, are not well known and need more research.

Approach in a Patient Where a Differentiation between Intestinal Tuberculosis and Crohn's disease Cannot Be Made

The clinical, endoscopic, and histological features that help in differentiation between ITB and CD are summarized in Table 5. From the Table 5, it is obvious that almost all the features are often present in these two conditions and none of the features is pathognomonic of either of the diseases. However, with the use of a combination of these features, one may be able to make a diagnosis of either TB or CD in almost half of the patients.

Table 5: Clinical, endoscopic and histological differentiation between intestinal tuberculosis and Crohn's disease

Variables	Intestinal Tuberculosis (%)	Crohn's Disease (%)
Chronic diarrhea	20-40	60-80
Blood in the stools	10-20	50-70
Abdominal pain	90	60-80
Constipation	50	10-30
Symptoms		
Partial intestinal obstruction	50-60	20-30
Peri-anal disease	5	30-80
Fever	40-70	30
Loss of appetite	40-80	40-60
Weight loss	60-90	50-60
Extra-intestinal manifestations	10	20-50
Anal canal	<5	15-50
Rectum	10-20	40-60
Sigmoid colon	5-10	10-50
Involvement of Intestine		
Descending colon	5-10	10-50
Ascending colon	40-60	50-70
Ileocaecal area	70-90	60
Ileum	10-20	20-40
Aphthous ulcers	5-10	30-50
Endoscopic features		
Linear ulcers	5	20-30
Deep ulcers	50-70	30-40
Nodularity	50	20
Cobblestoning	None	15-20
Histological features		
Granuloma	30-60	30
Necrosis in the granuloma	10-30	None

There are situations where differentiation between ITB and CD is not possible despite extensive investigation. Under these circumstances, both the Asia Pacific Association of Gastroenterology and the Indian Society of Gastroenterology consensus on CD suggest a trial of anti-TB treatment.^[20,21] This is based on the rationale that the treatment of TB is finite, whereas treatment for CD continues indefinitely.^[20,21] Furthermore, there is a risk in treating patients with corticosteroids if the diagnosis actually is TB. Obviously the decision to treat for one disease or the other would take into account other clinical considerations including the nature of presentation of the patient, whether acutely ill and requiring immediate definitive therapy or not. It would also be accompanied by a complete discussion with the patient of the possibilities and therapeutic alternatives. Compounding the problem of differentiation between intestinal TB and CD and a therapeutic trial of anti-TB drugs to resolve the issue, a proportion of patients with CD also respond to anti-TB therapy at least symptomatically.^[91]

In patients treated for intestinal TB, it is expected that there will be a complete resolution of the lesions, detectable by endoscopy or by imaging, following therapy. It is, therefore, appropriate to re-endoscope the patients who were treated empirically for ITB and to establish complete mucosal healing at the end of 6 months.^[20,21]

In summary, while many of endoscopic features overlap in patients with ITB and CD, certain endoscopic features have been identified by most of the investigators as suggestive of CD. These features include involvement of left side of the colon, involvement of multiple segments of the intestine, and presence of longitudinal ulcers and cobblestoning of the mucosa. Healing of the lesions should be demonstrated in patients suspected to have ITB and being treated empirically with anti-TB therapy.

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Conflicts of interest

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