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Intestinal tuberculosis versus crohn's disease: Clinical and radiological recommendations

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Abstract

Intestinal tuberculosis is a common clinical problem in India. The clinical features of this disease are nonspecific and can be very similar to Crohn's disease. Radiological evaluation of the small bowel has undergone a paradigm shift in the last decade. This long tubular organ that has traditionally been difficult to evaluate can now be well-visualized by some innovative imaging and endoscopic techniques. This article highlights the state-of-the-art evaluation of ulceroconstrictive diseases of the bowel and provides recommendations for the differentiation of intestinal tuberculosis from Crohn's disease.

Key words: Barium studies; Crohn's disease; enterography; ileocecal tuberculosis; intestinal tuberculosis

Introduction

Extrapulmonary tuberculosis (EPTB) accounts for 10–12% of the total tuberculosis cases, and amongst EPTB, 11–16% of cases involve the abdomen. Abdominal tuberculosis can involve the intestine, peritoneum, lymph nodes, or solid abdominal organs.[1] Commonly considered as a disease of the developing world, there is a resurgence of interest in Western countries because EPTB represents up to 50% of tuberculosis cases in patients with human immunodeficiency virus positivity.[2] Intestinal TB (ITB) may be localized to the bowel or may be a part of disseminated disease. Terminal ileum and ileocecal junction are the most common sites of involvement followed by the colon and jejunum.[3] Associated features such as necrotic nodes and ascites, if present, help in making a diagnosis. However, in recent years, there has been an increase in the incidence of Crohn's disease (CD) in the Indian subcontinent, which could be because of a genuine increase in incidence coupled with greater awareness and better imaging modalities.[4,5] ITB and CD are chronic granulomatous disorders with phenotypic similarities that make the differentiation between them a challenging task. There is a close resemblance in the clinical, radiological, endoscopic, surgical, and histological features of CD and ITB; thus, differential diagnosis of these two conditions is challenging. Imaging features of CD closely mimic ITB and diagnosis is often difficult in the absence of ancillary radiologic findings.[6] In the context of intestinal TB and Crohn's disease, this review describes various imaging modalities used, the imaging characteristics of both ITB and CD, and the clinical, histopathological, and imaging features that differentiate ITB from CD.

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Imaging Modalities

Various imaging and endoscopic modalities are available for the evaluation of ITB and CD [Table 1]. Each modality has its merits and demerits and they often complement each other in making a diagnosis.

Conventional techniques

Plain abdominal radiographs have little role in making a diagnosis of ITB or CD. The only benefit they provide is in acute abdomen to look for acute intestinal obstruction or pneumoperitoneum.[7] Chest radiograph may show features of active or healed tuberculosis in up to 15% of patients.[2] Barium meal follow through (BMFT), a single contrast study, may show thickening of mucosal folds, ulcerations, strictures, dilatation, and clumping of bowel loops in both these diseases and provides information on bowel motility.[8,9] However, the study takes a long time, is associated with radiation (although less than CT enterography), and provides no extraluminal information. At present, the main role of BMFT is in the evaluation of bowel motility, differentiation of true obstruction from pseudo-obstruction, and demonstration of complex fistula.[10] Barium enema (BE), single or double contrast, is helpful in the evaluation of colonic involvement.[11] Barium enteroclysis is a double contrast study, which has higher sensitivity for detecting mucosal abnormalities and mild strictures.[12] It can also show bowel loop clumping, fistulas, and motility disorders. The advantages are that it achieves good distension of the small bowel loops to enable the detection of early abnormalities, is a more controlled procedure, and is less time consuming. The disadvantages include discomfort to the patient due to the tube and active bowel distension, radiation, absence of duodenal evaluation, and that it gives no information regarding the bowel wall and extraintestinal manifestations.

Ultrasonography

Ultrasonography (USG) is a simple and widely available modality without the effects of ionizing radiation, however, it is not very useful in the differentiation of ITB from CD. Its main role is in the evaluation of disease activity based on color flow in the wall, which helps in assessing the response to treatment.[13] The limitations of USG include operator dependence, bowel gas, obesity, and long scan times required for complete evaluation.

Table 1: Imaging and endoscopic modalities for bowel evaluation

Imaging modalities	Endoscopic modalities
Plain radiographs	Ileocolonoscopy
Ultrasonography	Enteroscopy
Barium studies	Capsule endoscopy
CT scan	Upper GI endoscopy
MRI	
PET-CT	

MRI: Magnetic resonance imaging, PET-CT: Positron emission tomography-Computed tomography

Computed tomography

Computed tomography (CT) is often the initial investigation performed for the evaluation of suspected bowel pathology. Oral contrast and intravenous water soluble nonionic iodinated contrast is mandatory. CT scan can be either conventional CT or CT enterography. Conventional CT, although useful as an initial investigation in patients with nonspecific symptoms, does not provide adequate distension of the bowel. The positive contrast only depicts bowel wall thickening, stricture, and dilatation, but not mucosal abnormality. CT enteroclysis is performed after inserting a nasojejunal tube and injecting neutral contrast agent to provide adequate distension of the small bowel.[14] This procedure requires additional fluoroscopy time for the placement of the tube.[15] The tube and active bowel distension often causes discomfort to the patient. Recent studies have shown that tubeless CT enterography is equally effective in achieving bowel distension and has nearly replaced CT enteroclysis in most centers.[16]

CT enterography (CTE), performed by passively distending the bowel loops without inserting nasojejunal tube, is the most valuable and often the initial investigation performed for suspected bowel disease.[17,18] Neutral oral contrast agents, which include water, polyethylene glycol solution, or Volumen (low density barium in sorbitol) are administered for distending the bowel. Adding osmotic agents such as mannitol, sorbitol, or polyethylene glycol improves bowel distension.[19] We prefer using mannitol (20%) which is prepared by diluting 300 mL of mannitol in 1500 mL of water. This solution is ingested in 4 aliquots over 1 h and the patient is scanned subsequently. The solution intake protocol is 450 mL at 60 min and 40 min prior to scanning and 225 mL at 20 and 10 min prior to scanning. The last 250–300 mL is ingested on table, just prior to scanning. The last aliquot is for gastric distension and can be water instead of the mannitol solution. Intravenous iodinated contrast agent is given at a rate of 4 mL/s. Scanning is done in either single phase (venous, at 70 s) routinely or dual phase (late arterial at 30 s, venous at 70 s) in cases of gastrointestinal bleed. The venous phase shows mural features, wall thickening, and extraluminal abnormalities. An enteral phase has also been described that is typically acquired at 45 s and bowel wall shows maximal enhancement in this phase.[17] Images are best viewed on a workstation so that thin slices can be evaluated along with multiplanar reconstructions.

Multiple CT enterography studies are associated with the risks of cumulative radiation exposure.[20] The estimated effective radiation dose of a single phase CTE is 12–20 mSv.[21] Low dose CTE, which reduces the dose by 53–69% to 5–7 mSv, can be performed by limiting scan coverage, reducing kilovoltage and milliampere-second, and by using tube current modulation, automatic

exposure control techniques, and iterative reconstruction algorithms.[20]

Magnetic resonance imaging

Magnetic resonance imaging (MRI), due to the lack of ionizing radiation, is often the imaging modality of choice for the follow-up of patients with inflammatory bowel disease.[22] Adequate bowel distension is necessary for optimal imaging which is achieved by MR enterography (MRE).[23] MRE, similar to CTE, is performed after the administration of neutral oral (similar to CTE) and gadolinium-based intravenous contrast agent. After ingestion of oral contrast, plain T1- and T2-weighted and balanced steady-state free precession sequences are acquired in axial and coronal planes, either in breath hold or respiratory triggered modes. Cine imaging, which provides functional information, involves continuous acquisition of 15–25 frames for each slice position, which can be reviewed in the cine mode. This technique helps in the detection of fixed stenosis, adhesions, and dilatation.[24] Diffusion weighted imaging (DWI), acquired with b-values of 0, 400, and 800, is useful for detecting the sites of active inflammation, which shows restriction of diffusion.[25] This is followed by administration of intravenous gadolinium-based contrast (0.1 mmol/kg at 1–2 mL/s) and acquisition of breath hold 3D gradient T1-weighted axial or coronal sequences in arterial and venous phases. Administration of glucagon or hyoscine butyl bromide is helpful in relaxing the small bowel and avoid peristalsis-related artifacts. It is important that motility imaging is performed before the administration of paralytic agents. The MRI protocol for enterography is shown in Table 2. In addition, MRI is accurate for the assessment of perianal fistula and abscesses in patients of IBD.[26]

Positron emission tomography–Computed tomography

PET-CT is performed after the intravenous administration of ^{18}fluorodeoxyglucose (FDG).[27] Administration of iodinated contrast agent is optional. Typically, this is also done as an enterography technique after administering neutral oral contrast agent to distend small bowel loops.

Table 2: Protocol for magnetic resonance enterography

Sequence	Plane of acquisition	Slice thickness	Fat saturation
Balanced SSFP	Axial and coronal	4-5 mm	Yes
T2W FSE	Axial and coronal	4-5 mm	Yes
T1W GRE	Axial	4-5 mm	No
DWI	Axial	5 mm	Yes
T2W single shot thick slab	Coronal	30-60 mm	Yes
Motility imaging-balanced SSFP	Coronal	4-5 mm, continuous acquisition 1fr/s	No
Dynamic post contrast T1W GRE	Axial and coronal	3D: 0.6-1 mm; 50% overlap	Yes

SSFP: Steady state free-precession, FSE: Fast spin echo, GRE: Gradient recalled echo, DWI: Diffusion weighted imaging

The main advantages of PET-CT enterography are in the demonstration of disease activity, detection of multiple sites of involvement and assessment of response to treatment. However, in view of high radiation dose and cost, its use in routine practice is limited.[27]

Intestinal tuberculosis

ITB occurs in three forms, namely, ulcerative, hypertrophic, and ulcerohypertrophic, with the ulcerative type being the most common.[28] Ulcerative disease usually shows transverse ulcers, which are often superficial and heal by fibrosis.[29] Hypertrophic form shows thickening and mass-like appearance of bowel associated with scarring and fibrosis.[30,31] Although ileum is the most common bowel segment involved in ITB, it can involve any part of the bowel from duodenum to rectum. Imaging in the form of barium studies were the initial investigation for intestinal TB, but in the past decade, CT scan, and recently, CTE has almost replaced barium studies due to a better depiction of mural and extraintestinal involvement.

BMFT appearance of ITB may be broadly classified into two stages, namely, active and healed, even though overlapping features are often seen. Active ITB typically shows irregular and nodular narrowing of ileocecal junction with the involvement of adjacent terminal ileum and cecum. Often, deep ulcers are seen. The ulcers in ITB are linear, transverse, or stellate and often oval. The extent of involvement of cecum is often more than that of ileum [Figure 1]. The cecum is contracted and pulled-up due to associated fibrosis. Narrowed rigid segment results in the dilatation of the bowel segment proximal to it. Uncommonly, there may be thickening of intestinal mucosal folds or flocculation of barium caused by malabsorption. Multiple segments may be involved infrequently. Separation of bowel loops may be seen due to mesenteric adenopathy. Fistula and sinuses are uncommon. Healing often occurs by fibrosis which leads to strictures. This is seen as relatively smooth luminal narrowing of a short bowel segment with proximal dilatation. Enteroliths may also be seen in the dilated proximal segment in long standing cases. Various signs are used to describe the changes of ITB on BMFT.[32] Stierlin's sign is defined as the rapid emptying of cecum with passage of barium from terminal ileum to ascending colon, which occurs due to irritable mucosa of cecum. Fleischner's sign, also called inverted umbrella sign, refers to a wide patulous and gaping ileocecal valve with narrowing of adjacent terminal ileum. Goose neck deformity occurs due to contracted, cicatrized, and pulled-up cecum as well as straightening of terminal ileum. String sign describes persistently narrowed segment of intestine due to inflammation or stricture. Other signs include conical cecum (contracted and pulled-up cecum) and purse-string stenosis (focal stenosis opposite ileocecal valve with dilated terminal ileum and smooth cecum). It is important to note that these signs,

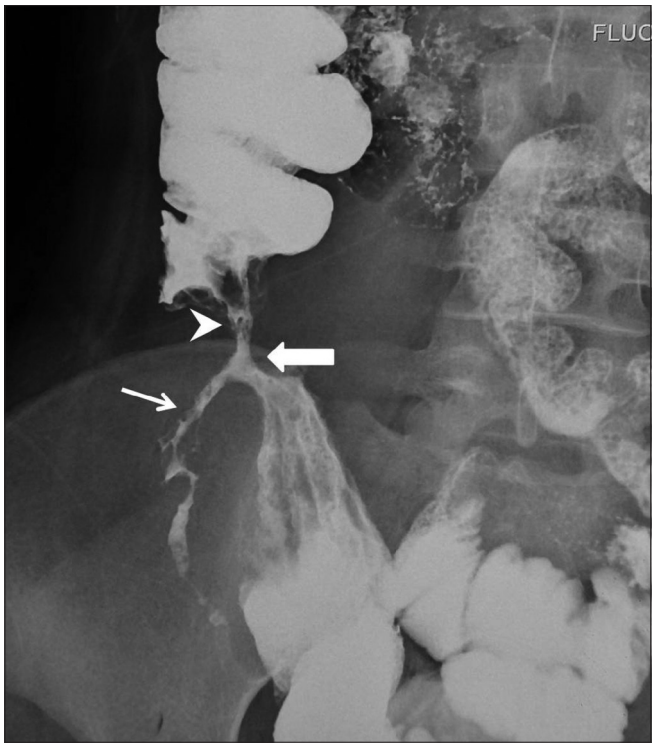

Figure 1: Ileocecal tuberculosis. Barium meal follow through showing severe narrowing of ileocecal junction (block arrow), contracted cecum (arrow), and adjacent ascending colon (arrow head)

although are suggestive of ITB, are not pathognomonic and may also be seen in CD. Enteroclysis shows findings similar to BMFT, however, it is sensitive in detecting early mucosal lesions, mucosal thickening, subtle strictures, and obstructions.[33]

Conventional CT scan or CTE and MRE findings can be divided into two groups; intestinal and extraintestinal abnormalities.[34,35]

Intestinal changes

Active ileocecal disease typically shows circumferential wall thickening of terminal ileum, ileocecal junction and cecum with narrowed lumen [Figures 2 and 3]. Dilatation of the proximal bowel segment may be seen with air-fluid levels. Enhancement of mucosa or the entire wall suggests active inflammation.[35] The intestinal wall thickening is usually homogeneous without stratification. Stratification or layering of the wall occurs due to the contrast enhancement of mucosa and muscularis with hypodense edema of submucosa. Similar wall thickening may be seen in any other segment of bowel involved by the disease. Healed disease presents as strictures that are seen as short segments of wall thickening without wall enhancement or stratification with proximal bowel dilatation.[35] Enteroliths may be seen in the dilated segment. Less often, small bowel feces sign (air-bubbles trapped in intestinal contents giving the appearance of feces) may also be seen in subacute or chronic disease. Ileocecal valve may also become scarred with stricture and

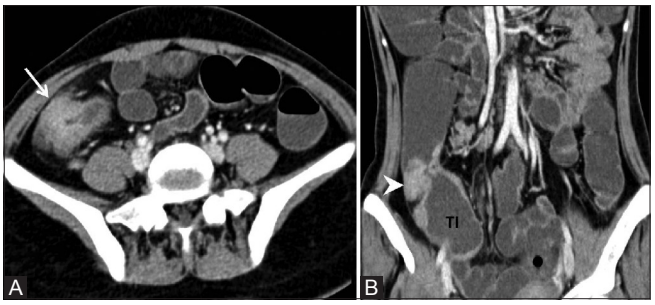

Figure 2 (A and B): Axial (A) and coronal (B) computed tomography enterography images of ileocecal tuberculosis showing gross thickening of ileocecal valve (arrow) and thickening and contraction of cecum (arrow head) with pericecal fat stranding. Terminal ileum (TI) is dilated

terminal ileal dilatation. Less frequently, the valve may become patulous with loss of valve function. Usually, the site of involvement is single. Multiple sites of involvement may also be seen infrequently, and then differentiation from Crohn's disease is difficult [Figure 4]. Isolated segmental colonic involvement may be seen in 10% of abdominal tuberculosis, with sigmoid, ascending, and transverse colon being common sites.[36] Anal tuberculosis is rare and may present with multiple fistula formation.[37] Complications developing with ITB include intestinal obstruction due to presence of strictures, intestinal perforation usually proximal to the site of stricture, intussusception in hypertrophic type, and fistula or abscess formation.[38] Intestinal obstruction and perforation are relatively common with ITB whereas fistula or abscess formation is uncommon.[32]

Extra-intestinal changes

These changes occur in the mesentery.[35] Mesenteric nodal enlargement is seen that may occur as discrete nodes or conglomerate nodal masses. The enlarged nodes are often necrotic, which helps in making an accurate diagnosis. On healing, the nodes may disappear or may show calcification. Soft tissue stranding of perienteric and mesenteric fat is uncommon. Omental or peritoneal thickening may be seen with omentum showing nodularity or caking in severe cases. There may be associated abdominal cocoon, developing due to thin film of fibrosis encasing the bowel loops that appears clumped. This is seen on CT scan or MRE as an area of clumped, often dilated, small bowel loops with thin hypodense or hypointense capsule around it. In long standing cases, there may be proliferation of surrounding fat, although infrequently. Associated involvement of other organs such as the liver, spleen, or peritoneum also helps in making a diagnosis.

Crohn's disease

CD, similar to ITB, shows changes in the small bowel on barium studies, CT scan, and MRI. The imaging appearance in CD has been classified into four stages that help in planning therapy.[39] These include (a) active inflammatory, (b) fibrostenotic, (c) penetrating, and (d) reparative or regenerative subtypes. Active inflammation shows various

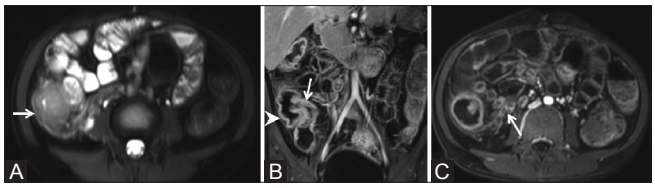

Figure 3 (A-C): Magnetic resonance enterography of intestinal tuberculosis. (A) Axial T2-weighted image showing thickening of ileocecal junction and cecum (arrow). (B) Coronal contrast enhanced T1-weighted image showing thickening and enhancement of ileocecal junction (arrow) with thickened wall of cecum (arrow head). (C) Axial contrast enhanced T1-weighted image showing multiple necrotic mesenteric nodes (arrow)

features on imaging, as described below, including ulceration and mucosal enhancement. Fibrostenotic disease suggests a healing phase that occurs due to collagen deposition and stricture formation. Penetrating disease occurs due to the extension of deep ulcers resulting in extraintestinal inflammation, abscesses, sinuses, and fistulas. Often, multiple stages coexist in the same patient or bowel segment.

Barium studies typically show aphthous ulcers, longitudinal, and transverse ulcers, deep ulcers, fissures, cobble-stone appearance, and fistula [Figure 5].[40] Aphthous ulcers are seen as foci of barium accumulation with surrounding lucency. Longitudinal ulcers can be superficial or deep, and are seen as irregular mucosal outline. Fissures are viewed as deep thin irregular extension of barium from the lumen. Cobble-stone appearance, often characteristic of CD, occurs because of submucosal edema between longitudinal and transverse ulcerations. Fistula are seen as irregular extensions of contrast from one loop to the other. During healing of longitudinal ulcers, there is shortening of mesenteric border of the bowel with resultant sacculations on the antemesenteric border. Strictures are seen as segments of narrowing with proximal dilatation. Similar to ITB, ileocecal region is the most common site of involvement. Involvement of multiple segments with normal intervening bowel segment is typically seen, but this alone may not be specific. Barium studies have a sensitivity of 67–72% in the detection of terminal ileitis and 32–37% for extraintestinal complications of CD.[41]

The imaging appearance of CD on CTE and MRE is similar. In a typical case, it shows circumferential symmetric wall thickening of terminal ileum and ileocecal junction, with the involvement of terminal ileum more than that of cecum [Figure 6]. The wall may show homogeneous enhancement or stratification, both of which indicate active disease.[42,43] Strictures are seen as hypodense short segment wall thickenings with narrowing of lumen and proximal bowel dilatation. These have to be differentiated from the segments of active inflammation, which also show narrowed lumen, because management is different. Typically, segments of active disease show mural contrast enhancement and stratification whereas strictures are seen as homogeneous

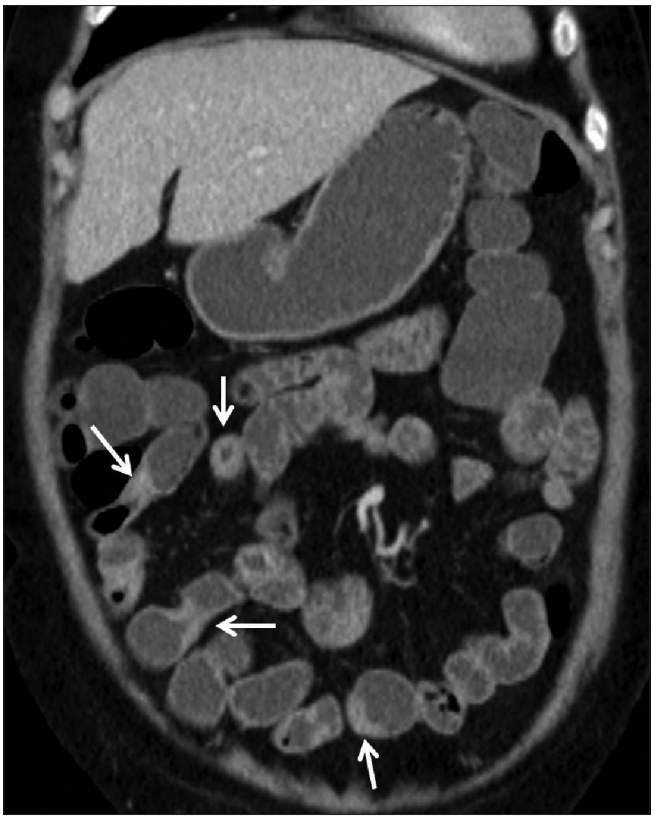

Figure 4: Computed tomography enterography image showing multiple short segment strictures (arrows) in proximal and midileal loops with mild proximal dilatation. The findings are nonspecific and may be seen in both intestinal tuberculosis and Crohn's disease

nonenhancing or hypoenhancing walls. Long standing cases show increase in submucosal and perienteric fat, especially along the mesenteric border.[18] Deep ulcers may lead to the formation of abscesses or fistulas. Abscesses form either in the mesentery or may extend into adjacent retroperitoneum. Fistula formation increases with increasing the duration of the disease.[44] Types of fistula include enteroenteric, enterocolic, colocolic, and perianal fistulas. Although CTE is usually performed with neutral oral contrast, positive contrast may be useful whenever fistulizing disease is clinically suspected.[45] Adjacent mesenteric changes are seen in both the active and chronic disease. Mesenteric changes of active disease include (a) prominent mesenteric vasculature giving rise to "comb sign;" (b) soft tissue stranding of mesenteric fat; and (c) small homogeneous mesenteric nodes. Fibrofatty proliferation suggests long standing disease. One of the problems with the interpretation of CTE is differentiating affected bowel segment from collapsed segment of bowel. Points suggesting its pathological involvement are abnormal enhancement compared to the adjacent bowel segment, proximal bowel dilatation, and changes in the adjacent mesentery.[46] Extraenteric findings include cholelithiasis, urolithiasis, and sacroilitis.[47]

MRE shows similar findings in CD as in CTE. The findings of mural enhancement, thickening and stratification,

strictures, proximal bowel dilatation, and extraintestinal features such as fat stranding, fat proliferation, prominent vasa recta, fistula, and abscesses are also viewed on MRE [Figure 7]. In addition, some findings are seen only on MRE. Actively inflamed segment shows hyperintense signal on T2W images.[48] DWI shows the restriction of diffusion in the same segments. DWI is useful in the detection of active inflammation in segments and can be used in the follow-up of these patients to assess treatment response without the need of intravenous contrast agents.[25] Fibrotic strictures show hypointense signal on T2W images because of the deposition of collagen in addition to the loss of stratification, homogeneous mild contrast enhancement, and no restriction of diffusion.[49] The accuracy of MRE in detecting active inflammation is higher than detection of fibrosis. Motility imaging can be performed using fast balanced steady-state free precession sequences and is useful in distinguishing inflamed from noninflamed bowel segments and increasing lesion detection.[50] In addition, it helps in detecting motility changes, which are known to occur in early inflammatory changes in the bowel wall.[51] Magnetization transfer (MT) imaging is a new technique of MRI that has the potential of detecting fibrosis in the bowel wall.[52] Fibrotic segments show increased MT and appear hyperintense on the sequence. The role of MRI in the evaluation of perianal fistulas has been discussed above.

The sensitivity and specificity of CTE and MRE in the detection of active inflammation in CD are 85.8% and 83.6% and 87.9% and 81.2%, respectively.[53] The benefits and limitations of CTE and MRE are compared in Table 3.

Differentiation of intestinal tuberculosis from Crohn's disease

This diagnostic dilemma is a greater problem in India where ITB is endemic; moreover, the incidence of CD is also increasing in India.[54] The avenues for diagnostic differentiation include clinical, endoscopic, imaging, and histological features. In addition, a variety of serological tests, immunological tests, and response to trial of antituberculous therapy have been employed to differentiate between both these entities. Challenge arises because there is no single gold standard test to make a diagnosis of CD, and the tests used for making a diagnosis of TB at any site have a poor sensitivity in the case of ITB.

Clinical, radiological, endoscopic, and histological features are helpful in differentiating ITB from CD.[55-57] These differences are presented in Table 4.

Clinical

There is no specific symptom complex that can differentiate between ITB and CD.[6,58,59] The common presenting symptoms of a patient with CD include chronic diarrhoea, pain in abdomen, bleeding per rectum, recurrent episodes of partial bowel obstruction, fever, anorexia, weight loss, and perianal fistula. ITB is characterized by fever, anorexia, loss of weight, abdominal pain, altered bowel habits, recurrent partial bowel obstruction, or the presence of an abdominal

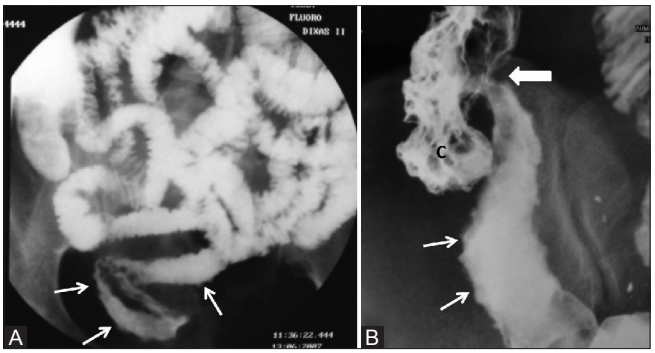

Figure 5 (A and B): Barium enteroclysis of a patient of Crohn's disease showing a long segment narrowing of ileum (arrows in A) with small ulcerations and narrowing of ileocecal junction (block arrow in B) with ulcers in terminal ileum (arrows in B). Cecum (C) is underdistended

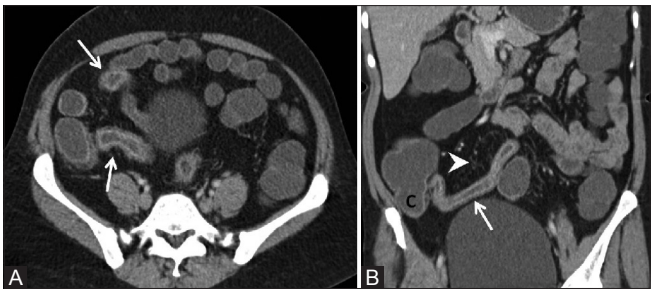

Figure 6 (A and B): Axial (A) and coronal (B) computed tomography enterography images of Crohn's disease showing wall thickening, stratification, and abnormal mucosal enhancement in two segments of distal ileum (arrows in A). There is long segment of involvement of distal ileum (arrow in B) with prominent mesenteric vasculature (arrow head). Presence of stratification, abnormal mucosal enhancement, and increased mesenteric vascularity suggest active disease. (C – Cecum)

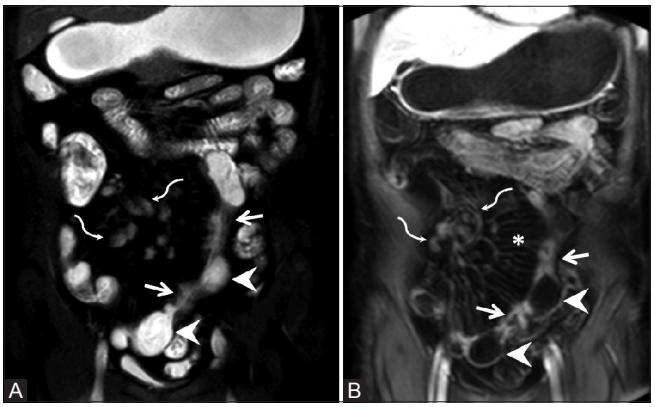

Figure 7 (A and B): Magnetic resonance enterography of classical Crohn's disease. T2-weighted fat saturated coronal MR image (A) and postcontrast coronal T1-weighted fat saturated image (B) showing asymmetric wall thickening of two segments of an ileal loop (straight arrows) with sacculations along antemesenteric border in-between (arrow heads), prominent mesenteric vascularity (asterisk in B), and multiple small mesenteric nodes (curved arrows)

mass. Extraintestinal manifestations such as polyarthritis, uveitis, and erythema nodosum are seen in both ITB and CD, but more so in the latter.[60]

Radiological

Site of involvement: Terminal ileum is more commonly involved in CD (97%) when compared with ITB, which involves terminal ileum with ileocecal valve (81–87%) more commonly.[57] Right colon including cecum is more commonly involved in ITB (83%) compared to CD (33%). Left colon involvement in ITB is rare (4% vs. 27% in CD).

Skip lesions: This is a characteristic finding of CD and is seen in 99% of the patients when compared with ITB (15%).

Bowel wall thickening: This is usually more than 6 mm in CD and less than 6 mm in ITB.[6] Asymmetric wall thickening is observed more commonly in CD.

Wall enhancement: Differentiation of ITB and CD based on wall enhancement is difficult, although stratification is more commonly seen with CD and homogeneous enhancement with ITB.[6] A recent study has shown that there is no significant difference in the pattern of wall enhancement between ITB and CD.[57]

Strictures: Asymmetric strictures with pseudosacculation along antimesenteric border is characteristically seen in

Table 3: Comparison of techniques of computed tomography enterography and magnetic resonance enterography

Feature	CTE	MRE
Examination time	Short	Long
Spatial resolution	High	Lower
Contrast resolution	Low	High
Radiation exposure	Present	Absent
Functional imaging (DWI, cine imaging)	Not possible	Possible
Artifacts (peristaltic, bowel gas)	Less	More
Cost	Cheaper	Expensive

CTE: CT enterography, MRE: MR enterography, DWI: Diffusion weighted imaging

Table 4: Differentiating features of intestinal tuberculosis and Crohn's disease

Features	ITB	CD
Duration of symptoms	Relatively shorter duration	Long standing symptoms
Symptoms	Fever more common	Diarrhea, hematochezia more common
Perianal fistulae	Less common	More common
Extraintestinal manifestations	Less common	More common
Radiological		
Site of involvement	Cecum more than ileum	Ileum more than cecum
Length of involvement	Shorter segment	Long segment
Multiple site involvement	Uncommon (<4 segments)	Common
Skip lesions	Rare	Common
Type of enhancement	Homogeneous	Stratified
Mural stratification	Rarely seen	Commonly seen
Perianal fistula	Uncommon	Common
Mesenteric abscess	Very rare	May be seen
Inter-bowel fistula	Rare	Common
Strictures	Concentric	Eccentric with sacculations
Enteroliths	More common	Less common
Increased mesenteric vascularity	Uncommon	Common
Fibrofatty proliferation	Uncommon	Common
Mesenteric nodes	Larger, necrotic	Small, homogeneous
Omental involvement	Often associated	Rare
Ascites	Frequent	Uncommon
Solid organ involvement	May be seen	Very rare
Endoscopic		
Mucosal changes	Transverse ulcers, pseudopolyps	Deep longitudinal ulcers, aphthous ulcers, cobblestoning
Skip lesions	Uncommon	More common
Fistulae	Uncommon	Common
Patulous ileocecal valve	Common	Rare
Anorectal disease	Uncommon	Common
Histology		
Granulomas	Multiple, confluent, large, caseating, submucosal	Microgranulomas, single, nonconfluent, noncaseating
Disproportionate submucosal inflammation	Common	Rare

ITB: Intestinal TB, CD: Crohn's disease

CD, which is very unusual in ITB. Stenotic and patulous ileocecal valve is typically seen in ITB (26–36%) and is rare in CD (1–5%).

Sinus/Fistula: Clumping of bowel loops in stellate pattern suggesting enteroenteric fistula is seen in CD. Enterocutaneous fistula are also more commonly seen with CD. The clumping pattern seen in ITB is typically floccus because of "cocoon" formation.

Extraintestinal: Peritoneal thickening, enhancement, nodularity, caking, and ascites are characteristic of ITB and usually not seen with CD. Mesenteric lymph nodes are small and homogeneous in CD and large and necrotic in ITB. Comb sign is seen in 95% and fibrofatty proliferation on 48% of patients with CD compared to ITB (30% and 19%, respectively). Mesenteric phlegmon and abscesses are seen in 30% of the patients of CD (vs. 6% in ITB).[6,57]

In summary, asymmetric involvement, left colon disease, abscess, and comb sign for CD and contracted and patulous ileocecal valve, right paracolic nodes, and necrotic nodes for ITB have high accuracy (95.7%), positive predictive value (97.8%), and negative predictive value (89.8%).[57]

In our experience, a short segment single stricture in the terminal ileum with the involvement of the ileocecal junction and associated necrotic lymph nodes, measuring greater than 1 cm, strongly suggest a tubercular etiology. On the other hand, long segment ileal involvement with more than three segments involved and skip areas with engorged vasa recta favor the diagnosis of Crohn's disease. Marked fibro-fatty proliferation and pseudosacculation are features that suggest Crohn's disease of long duration.

Endoscopy

The most common site of involvement for both ITB and CD diseases is the ileocolonic region, and hence ileocolonoscopy is crucial for the diagnostic workup of both diseases. Common colonoscopic appearances in CD include the discontinuous involvement of colon, longitudinal ulcers, cobblestoning, aphthous ulcers, and perianal lesions [Figure 8A].[61] Majority of ITB cases involve the ileocecum with varying degrees of contiguous colon and small bowel involvement [Figure 8B]. Isolated colonic involvement is seen in 20% cases and skip lesions in 44% of patients. ITB usually shows involvement of less than four segments, a patulous ileocecal valve, transverse ulcers, and greater amount of scarring.[61] Enteroscopy, antegrade as well as retrograde, has been used for lesions that are limited to the small intestine. Video capsule endoscopy as a diagnostic tool should be used with caution in these patients as there is a high risk of capsule getting retained because of the inherent ulceroconstrictive nature of these diseases, and a prior CT enterography may be required to exclude a stricture. Using features such as anorectal lesions, aphthous and longitudinal ulcers, and cobblestone appearance for CD and transverse ulcers, patulous ileocecal valve, and less than four segment involvement for ITB have positive predictive values of 95% and 89%, respectively.[61]

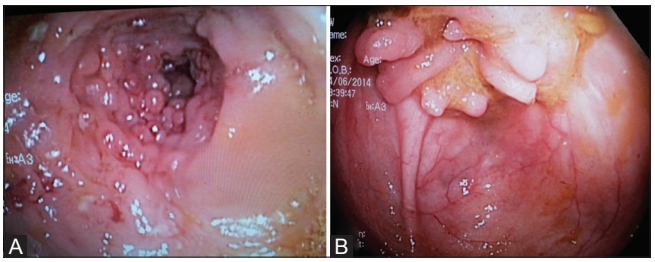

Figure 8 (A and B): Colonoscopic image: (A) Crohn's Disease—Deep longitudinal ulcers and nodules in ascending colon. (B) Intestinal tuberculosis—ulceroproliferative lesion at the ileocecal valve

Laboratory diagnosis

Tuberculin skin test (Mantoux test) is considered positive when the induration is ≥10 mm in diameter and may suggest active or latent infection. However, false positives are known to occur due to BCG vaccination and nontuberculous mycobacteria. An induration of ≥20 mm strongly suggests tubercular infection. Quantiferon TB gold test is a type of interferon gamma release assay (IGRA) for the detection of latent tuberculous infection.[55] In two recent meta-analysis on the role of IGRA in the differential diagnosis of ITB and CD, the pooled sensitivity was up to 81% and pooled specificity was up to 87%.[62,63]

The available microbiological tests for biopsies from patients with suspected ITB include staining for acid-fast bacilli (AFB) (Ziehl–Neelsen stain staining), culture for Mycobacterium tuberculosis culture (MTB), crush smear (AFB in crush/brush smears, MTB-PCR and GeneXpert). Although the sensitivity of AFB staining is very low (<20%) in ITB, a positive stain is 100% specific for ITB. A positive TB culture has a poor yield and is present in 10–20% of the cases. The sensitivity of mucosal biospy TB-PCR has varied across various studies ranging from as low as 21% to as high as 87.5%. Positive PCR in intestinal tissue sample must be interpreted in light of other clinical, endoscopic, and histologic findings because concerns have been raised about false positivity in luminal tissue samples. The literature on the role of GeneXpert in the diagnosis of abdominal TB is sparse and majority of the studies are on peritoneal TB.

Histopathology

ITB and CD are both chronic granulomatous diseases with subtle histological differences between them [Figure 9]. Although caseation and necrosis in granulomas or positive stain for AFB is virtually diagnostic for ITB, the problem is the poor yield of endoscopic sampling, which is diagnostic in less than 30% of cases.[64] Histological features suggesting ITB include confluent granulomas, multiple granulomas, large granuloma size, bands of epithelioid histiocytes lining

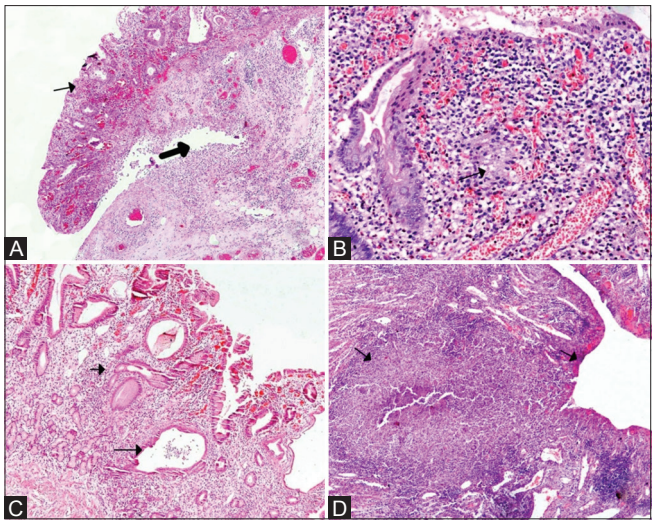

Figure 9 (A-D): Crohn's disease. Photomicrograph shows colonic mucosa with distorted crypt architecture (thin arrow), with a deep rail track-like ulcer (thick arrow), extending up to the deeper part of the submucosa [A: H and E ×40]. A pericryptal microgranuloma (arrow) is also noted [B: H and E ×20]. Tuberculosis. Ileal mucosa showing distorted crypt architecture with crypt branching (arrow) and flattened and broadened villi [C: H and E ×40]. Focally wide mucosal ulceration and a large necrotizing epithelioid cell granuloma is identified in submucosa, reaching up to the muscle layer (arrow) [D: H and E ×100]

ulcers, submucosal granulomas, and disproportionate submucosal inflammation, that is, submucosal inflammation that significantly exceeds mucosal inflammation. Features seen more frequently in CD include microgranulomas, nonconfluent granulomas, single granulomas as the only foci of granulomatous inflammation, and architectural distortion distant from granulomatous inflammation.[55]

Trial of antitubercular therapy in diagnostic dilemma

In a substantial proportion of patients (30–40%), ITB and CD cannot be differentiated and a therapeutic trial of antitubercular therapy (ATT) is initiated to classify the patients as having ITB or CD based on the response to ATT.[65] The ATT trial is given for 8–12 weeks and patients are assessed for clinical and colonoscopic response at the end of the trial. There is a higher rate of complete symptomatic response at 3 months in intestinal TB patients (94%) compared to patients with CD (38%). If there is symptomatic improvement and healing on colonoscopy at the end of 6 months of antitubercular therapy, it confirms the diagnosis of ITB. If there is persistence of inflammatory mucosal lesions on colonoscopy, irrespective of symptomatic improvement, and if a repeat biopsy does not suggest multidrug resistant–TB, a diagnosis of CD is made and treatment started for the same.

Future Directions

Computed tomography scoring system

A CT-based predictive model would be an ideal and more objective tool for resolving this conundrum. One such system devised by our group uses a simple score based on three findings on imaging,[66] namely, long segment involvement, terminal ileal disease with or without spill over to cecum, and abdominal lymph node >1 cm. All the three variables are given a score of 1. Based upon the model, a risk score (with values ranging from 0–3) is generated, with scores 0 and 1 having specificity of 100% and 87%, respectively, and positive predictive value (PPV) of 100% and 76%, respectively, for ITB; scores 2 and 3 having specificity of 68% and 90%, respectively, and PPV of 63% and 80%, respectively, for CD.[66] However, in clinical practice, there are outliers to the abovementioned criteria and in a given case the distinction may be very challenging.

Fat estimation

Mesenteric fat is thought to have a role in the inflammatory process observed in CD. Visceral fat quantification is a new paradigm which is being evaluated in the differentiation of CD from ITB.[67] A study by Ko *et al*. has shown that ratios of visceral fat to total fat and visceral fat to subcutaneous fat are significantly higher in patients with CD than ITB. They found that a cutoff value of visceral fat to total fat ratio of 0.46 has a specificity of 93% and PPV of 89%.

Recommendations

Any patient coming with clinical suspicion of ITB or CD should be evaluated thoroughly, that is, both clinically and radiologically.

Initial clinical evaluation

Clinical symptoms and detailed history should be noted along with physical examination. Routine blood investigations such as hematology, erythrocyte sedimentation rate (ESR), and routine liver and renal function tests should be done. Chest radiograph and Mantoux testing should be done. Any patient presenting with clinical features of ulceroconstrictive disease of the bowel should undergo endoscopic procedure (upper GI endoscopy, enteroscopy, or ileocolonoscopy depending on the site of involvement), endoscopic mucosal biopsy and CTE or MRE. CTE is needed in most of the cases for evaluation of the small bowel.

Radiological evaluation

First presentation

CTE should be performed as an initial investigation in patients presenting with symptoms of ulceroconstrictive disease of the bowel.[68] This helps in making a diagnosis, defining the extent of the disease, presence of complications, and ancillary findings. It also helps in identifying active inflammation that is seen as abnormal mucosal enhancement, stratification, and thickening of the bowel wall, increased adjacent mesenteric vascularity, adjacent mesenteric fat stranding, and small adjacent mesenteric nodes. Healed disease is seen as a short segment of homogeneous wall thickening with luminal narrowing and without any mesenteric changes or mucosal enhancement.

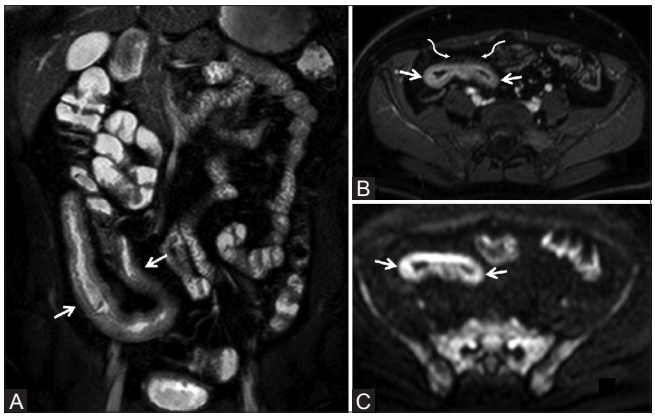

Figure 10 (A-C): Magnetic resonance enterography showing features of active inflammation in Crohn's disease. Hyperintense signal of thickened bowel wall on T2-weighted images (arrows in A); bowel wall stratification and mucosal enhancement (straight arrows in B) and prominent mesenteric vascularity (curved arrows in B) on post contrast T1-weighted images; restriction of diffusion on diffusion weighted images (arrows in C)

MRE should be preferred in pediatric patients even at the time of initial presentation due to the risk of radiation with CTE. On MRE, active inflammation is seen as thickened stratified bowel wall, hyperintense signal of thickened wall on T2W, restriction of diffusion on DWI, abnormal mucosal enhancement, and mesenteric changes [Figure 10]. Fibrotic stricture is seen as thickened hypointense bowel wall on T2W, homogeneous enhancement, absence of motility, no restriction of diffusion, and normal mesentery.

Markers of response

1. Clinical—resolution of symptoms
2. Lab investigations—reduction in the levels of CRP and ESR, if previously elevated
3. Endoscopic—healing of ulcers
4. Radiological
   a. Disappearance of abnormal mucosal or intramural contrast enhancement
   b. Normalization of wall thickening
   c. Disappearance of bowel wall stratification
   d. Disappearance of abnormal mesenteric vasculature and mesenteric fat stranding
   e. Resolution of mesenteric nodes
   f. Disappearance of diffusion restriction.

Follow-up

Once a diagnosis has been made, the patient is put on ATT for ITB or immune-modulators for CD. If the patient is responding well clinically, follow-up imaging is usually not necessary. In cases where there is no response to therapy, clinical progression of disease or development of new symptoms imaging is required.

For this purpose, MRE is the modality of choice because it is free of radiation risk. This will provide information on the status of previously affected segment and any new lesions. MRE is also helpful in regular follow up of patients with CD.

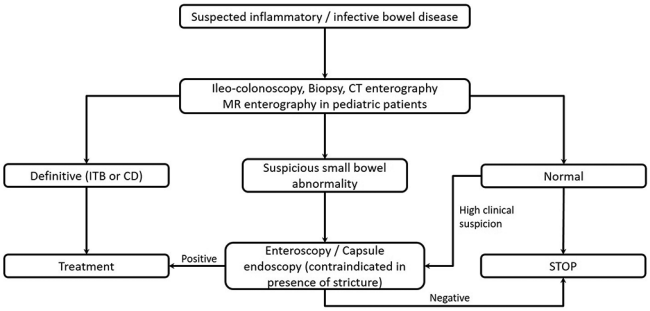

Figure 11: Flow chart showing the recommended protocol to be followed in a suspected case of ulceroconstrictive bowel disease

DWI provides an additional paradigm for assessing response to treatment in these patients and can substitute contrast-enhanced sequence in patients where gadolinium contrast agents cannot be used (such as pregnancy and renal failure). The imaging recommendations are shown in Figure 11.

Conclusion

ITB and CD are common intestinal disorders requiring early diagnosis and treatment to prevent the development of complications. Appropriate clinical and imaging evaluation is required for making a diagnosis of ITB or CD. Clinical and imaging distinguishing features of these two diseases presented here help in diagnosis. However, such differentiation may be difficult and in endemic regions empirical ATT may need to be started and response will help in making a diagnosis. We have also presented recommendations for detecting disease activity in CD and imaging protocol for diagnosis and follow-up of these patients.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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