Review Article

Recent advancements in management of gastrointestinal tuberculosis

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ABSTRACT

Abdominal tuberculosis and its protean manifestations still create a worldwide diagnostic challenge for clinicians and remain an important concern in the developing world. Crohn’s disease, which is being increasingly recognized in countries where intestinal tuberculosis is prevalent, needs to be differentiated as the two diseases resemble each other in their clinical presentation, and in their radiological, endoscopic, and histological findings. New diagnostic modalities and scoring systems have facilitated the differentiation of Crohn’s disease from intestinal tuberculosis with good accuracy. Randomized trials have shown 6 months of therapy to be equivalent to longer durations of treatment for patients with abdominal tuberculosis.

Keywords: GI, ATB, Tuberculosis, Diagnosis GI TB, Recent advanced managment, Tuberculosis

INTRODUCTION

Tuberculosis (TB) has ailed humanity for thousands of years and still haunts the human race. TB in developing countries is a major health problem, and causes significant morbidity and mortality. These countries have problems of poverty, immunosuppression (such as HIV or AIDS), overcrowding, and poor sanitation. The population is ignorant and malnutrition is prevalent.1

Abdominal tuberculosis (ATB) includes tuberculosis infection of gastrointestinal tract, mesentery, lymph nodes and omentum, the peritoneum and related solid organs such as liver and spleen.2

TB continues to be the top killer out of all infectious diseases worldwide, particularly in developing countries, according to the World Health Organization (WHO) global TB report in 2016.3 Extra pulmonary TB (EPTB) accounts for 15–20% of all cases and involvement of the abdomen is reported in 3.0–6.7% of EPTB cases.3,4

Due to the insidious course of the disease, the nonspecific and protean manifestations of ATB, and ATB being a great mimicker; it is very difficult to diagnose and to establish the correct diagnosis. A physician needs to have a high index of suspicion to reach to the correct diagnosis.5 Poor socioeconomic status, malnutrition, poor hygiene, use of steroids or biologicals, history of a solid organ transplant (particularly renal transplant), and diabetes, among other factors, increase the risk of dissemination and occurrence of EPTB.6 ATB may be further classified as per the pattern of infection: luminal or intestinal, peritoneal, visceral (involving solid organs like the liver, pancreas, and spleen), or lymph nodal.6 The present review will discuss the recent advances in the field of ATB, and to document the nature of different types of acute presentation in ATB according to involved sites.
ABDOMINAL TUBERCULOSIS

A number of mechanisms have been reported to result in causation of gastrointestinal TB, including spread through the haematogenous route from the primary pulmonary focus that reactivates later or miliary tuberculosis, ingested mycobacteria from the sputum produced from active lung lesions or from infected milk, direct or contiguous spread from adjacent organs, and through the lymphatics of infected lymph nodes.\(^6,7\) Peritoneal involvement is the most common form of ATB, seen in up to 58% of cases, followed by intestinal involvement in 40%.\(^8\) Intestinal tuberculosis exists in one of the three main forms i.e. ulcerative, hypertrophic or ulcero-hypertrophic, and fibrous stricture form.\(^9\) The peritoneal involvement exists in four forms: ascitic, loculated (encysted), plastic (fibrous) and purulent forms.\(^9\) The mesenteric lymph nodes and the retroperitoneum comprise the nodal abdominal tuberculosis. The lymph nodes may caseate and calcify (Khan et al.).\(^10\) In solid viscera like liver and spleen, focal granulomatous lesions are found which are generally multiple. Disseminated abdominal form includes combined involvement of the gastro-intestinal tract, peritoneum, lymph nodes or solid viscera.\(^10\)

Clinical presentation

Peritoneal TB is the most common presentation of ATB and accounts for 1.0–6.1% of all EPTB cases. Usually seen in young adults aged 20–40 years, peritoneal TB is more prevalent in women in developing countries, while in developed countries men are more commonly affected.\(^11\) The usual mode of spread is reactivation of latent foci in the peritoneum, seeding by a haematogenous route, often from distant pulmonary focuses and through ingestion of bacilli and infection of mesenteric lymph nodes. Alternatively, peritoneal TB can occur through contiguous spread from infected nodes, from ileocaecal TB, or directly from the fallopian tubes, stimulating latent foci reactivation.\(^12\)

Clinical presentation is of insidious onset, spanning over weeks to months, and the most common symptom is abdominal pain, seen in (49–100%) of cases, it may present in acute, chronic or acute on top of chronic form. Commonly it runs a chronic course with non-specific symptoms of fever (40–70%), pain (80–95%), diarrhea (11–20%), constipation, alternating constipation and diarrhea, weight loss (40–90%), night sweats, anorexia and malaise.\(^6\) Acute presentation is secondary to complications like complete or partial intestinal obstruction due to mass formation in ileocaecal region or stricture (s) in small intestine, and bowel perforation causing peritonitis especially terminal ileum.\(^14\)

Physical examination reveals ascites in (35–100%) of patients, abdominal tenderness in (47%), and a doughy feel to the abdomen in (≤13%). Tubercular abdominal cocoon presents with intestinal obstruction in (73.3%) and a lump in (60%) of cases, and has previously been treated with surgical intervention, but a recent report describes a successful conservative management with anti-tubercular therapy (ATT) in the majority of the study cases.\(^13\)

Intestinal TB (ITB) is grossly classified as ulcerative, hypertrophic, ulcer hypertrophic, and fibrotic (stricturing). The ileocaecal region is the most common location involved, affecting 44–93% of cases due to the relatively narrow lumen, stasis, and abundant lymphatics.\(^5\)

The second most common location is the colon, while the stomach and oesophagus are rarely involved. Regardless of the site involved, presentation of abdominal pain, weight loss, fever, and features of intestinal obstruction are observed. Diarrhoea is uncommon but may occur with the ulcerative form of ITB.\(^15,16\) In addition to abdominal pain, colonic TB may cause rectal bleeding as one of the dominant symptoms, and occasionally the bleeding may be massive.\(^6\)

Diagnosis

Diagnosis is usually confirmed after the laparotomy or laparoscopy, and histopathology examination. For those cases having been diagnosed with abdominal tuberculosis early in the course of illness and minimal symptoms, treatment is mainly conservative with anti-tuberculosis therapy. Surgical treatment is reserved for complications such as intestinal obstruction and bowel perforation with peritonitis.\(^1)\) The aims of surgery are mainly to remove the focus of the disease and treat the mechanical effects which are causing the presenting morbidity. But even with the advances in medical imaging, early diagnosis of EPTB, especially ATB, is difficult to establish, with the primary reason for this being the low positivity of microbiological tests in this setting and with the clinical features being vague and there being no specific diagnostic test.

Paustian’s criteria suggest that the diagnosis be established if any one of the following four criteria are observed: histology showing tubercles with caseating necrosis, suggestive operative findings and consistent histology from mesenteric lymph nodes, animal inoculation or culture showing growth of Mycobacterium tuberculosis, or histology showing acid-fast bacilli in the lesion.\(^17\) However, Paustian’s criteria is difficult to apply in most cases and Logan’s modification of the Paustian’s criteria, which uses response to ATT, has often been used to establish the diagnosis.\(^18\) On the other hand, the appropriate time and manner of establishing an adequate response to ATT has remained unclear. The investigational modalities for the diagnosis of ATB include radiological, biochemical, histology, and microbiological, including molecular tests and ancillary or supportive tests. Certain tests like Mantoux skin test may have ancillary value but cannot be used as
standalone diagnostic tool as it may be compromised by a false-positive (underlying Bacillus Calmette–Guérin vaccination, cross-reaction with other mycobacteria) and false-negative (disseminated TB, immunosuppression, recent infection, extremes of age).

Chest x-ray may be able to detect active or past evidence of pulmonary TB and thereby provide corroborative evidence of ATB; such changes may be detectable in a quarter of the patients. Interferon gamma release assays (IGRA) may overcome some limitations of Mantoux testing and do not have cross reactivity with Bacillus Calmette–Guérin or other mycobacteria; however, their positivity is consistent with M. tuberculosis infection but cannot be used to diagnose active disease. HIV testing should be performed in all patients suspected to have ATB.

Differential diagnosis

The closest differential diagnosis of tuberculous peritonitis is peritoneal carcinomatosis. These conditions can be differentiated by ascitic fluid analysis, where cytology will be positive for malignant cells with high protein and low gradient ascites. In patients presenting with intestinal obstruction, there is a possibility of extra luminal causes such as adhesions, masses (appendicitis, diverticulitis, peritoneal carcinomatosis, neuroendocrine tumour, and lymphoma), strangulation, hernia, and malrotation. Alternatively, intraluminal causes like inflammatory bowel disease (i.e. Crohn’s disease), intussusception, radiation enteropathy, and malignant masses need to be considered. Peritoneal carcinomatosis has similar imaging features like abdominal cocoon; namely, internal hernia, pseudomyxoma peritonei, peritoneal carcinomatosis, peritoneal mesothelioma, sclerosing malignant lymphoma, and malignant primary mesenteric tumours.

INVESTIGATIONS

Laboratory evaluation

Diagnosis is made through a combination of hematological, microbiologic, histologic, and molecular techniques. Serological investigations have a limited value while PCR is a highly specific test though its use could be restricted because of cost. Microbiological investigation such as BACTEC is a substantially more sensitive, efficient, and fast method than culture techniques in the laboratory diagnosis of Mycobacterial infections.

Histopathological evaluation with positive AFB staining remains the gold standard for diagnosing abdominal TB. However, although the demonstration of AFB in aspirates and tissue sections is a definitive diagnostic method for TB, the positivity for AFB is variable.

Radiological evaluation

Radiological findings in patients with ATB may help in localising the site of involvement and directing further evaluation; however, no radiological finding is diagnostic of TB. Although barium studies were used frequently in the past, computed tomography (CT) provides the ability to identify intraluminal and extramural abnormalities and has replaced the use of barium studies. Findings supportive of a diagnosis include the presence of ascites, peritoneal thickening and enhancement, omental nodularity or thickening, lymphadenopathy, mural enhancement thickening of the bowel wall, and intestinal strictures. The presence of pulmonary lesions, a hypodense centre in an enlarged lymph node suggesting necrosis, and ascites are considered highly suggestive of TB (when discriminating from CD). CT enterography may have value over traditional contrast-enhanced CT, especially for better delineation of strictures.
Figure 3: Pattern of lymph node enhancement on CT; (a): Enlarged homogeneously enhancing mesenteric lymph nodes; (b): Enlarged heterogeneously enhancing retroperitoneal lymph nodes; (c): Peripheral rim enhancing mesenteric lymph nodes; (d): Conglomerate mesenteric lymph node mass; (e): Cluster of normal sized mesenteric lymph nodes; (f): Calcific focus in aortocaval lymph node.

Figure 4: Ileocecal tuberculosis a Cor contrast-enhanced CT: mildly enhancing circumferential symmetrically thickened cecal wall; (a): Thickened cecal wall showing isointense signal, which shows post contrast enhancement in same patient as in. (b): Cor T2 fat suppressed: Cecal wall thickening showing heterogeneous hyperintense signal; (c, d): Cor Pre-contrast T1 weighted and contrast-enhanced T1 fat suppressed: The enhancement on MRI has much better visibility compared to CT.

Figure 5: Lymph node pathology on MRI a Cor T2 fat suppressed: conglomerate mesenteric lymph node mass showing heterogeneous hyperintense T2 signal with hypointense rim and high signal area (arrowhead) (b): Cor contrast-enhanced T1 fat suppressed: Conglomerate lymph node mass same as in (a), Showing peripheral and central enhancement. (c): Ax T2 fat suppressed: Enlarged lymph node showing homogeneous hyperintense signal; (d): Ax contrast-enhanced T1 fat suppressed: Same lymph node as in (a) showing homogeneous enhancement; (e): Ax T2 fat suppressed: Enlarged lymph nodes showing heterogeneous hyperintense signal; (f): Ax contrast-enhanced T1 fat suppressed: Heterogeneous enhancement of the lymph nodes seen in (e).

Tubercular strictures are usually short, smooth, and concentric; however, discrimination from other lesions, including fungal infections and malignant lesions of the peritoneal and intestine, requires histological evidence. A recent paper that compared the use of magnetic resonance enterography with small bowel follow-through suggested that magnetic resonance enterography diagnosed a higher number of strictures except when used in the evaluation of extraintestinal lesions.

Although magnetic resonance imaging (MRI) is routinely done to evaluate tuberculosis of spine, brain, and extremity joints, very few studies have been done to evaluate its role in abdominal tuberculosis. Also, the imaging findings of gastrointestinal tuberculosis using...
Ultrasonography may give the characteristic features of early abdominal tuberculosis which include mesenteric thickness of 15 mm or more and an increase in the mesenteric echogenicity (due to fat deposition), combined with mesenteric lymphadenopathy. Presence of dilated small bowel loops and ascites further substantiate the diagnosis.45

Figure 7: Peritoneal tuberculosis. (a): Ax contrast-enhanced CT; (b): Ax T2 weighted; Smoothly thickened enhancing peritoneum. Thickened peritoneum appears hyperintense on T2 weighted image. (c): Ax contrast-enhanced CT: Loculated ascites in pelvis with enhancing peritoneum. (d): Ax T2 fat suppressed: Loculated ascites with multiple thin septae within ascites.44

**Diagnostic evaluation for peritoneal tuberculosis**

The utility of ascitic adenosine deaminase measurement for the diagnosis of peritoneal TB has been confirmed by systematic reviews.25 Adenosine deaminase is an enzyme secreted by activated lymphocytes and a value of >39 U/L in the ascites is indicative of a diagnosis of peritoneal TB. Since the positivity of microbiological tests, including smear for acid-fast bacilli and culture for TB, is exceedingly low, clinicians have to depend on the adenosine deaminase test to a large extent. However, the test may suffer from high false-negative rates, especially in the setting of underlying cirrhosis.26 Other findings on ascitic fluid analysis, which are consistent with a diagnosis of tubercular peritonitis, show a straw-coloured fluid, lymphocyte predominant cytology, high protein values, and low serum ascites albumin gradient.27 Sensitivity of polymerase chain reaction (PCR)-based tests is expected to be low and has been demonstrated by some studies; however, a positive test on peritoneal fluid is specific for the diagnosis.28 Needless to say, any diagnosis of peritoneal TB on the basis of this test must be established only after exclusion of other differential diagnoses, including peritoneal carcinomatosis by three
cytological evaluations for malignant cells. Peritoneoscopy may need to be used in some cases and can show tubercles, thickened peritoneum, and adhesions.  

**Diagnostic evaluation for intestinal tuberculosis**

Colonoscopy is the most important tool for evaluation of ITB as it helps in the characterisation of lesions, as well as in obtaining samples for microbiological and histological analysis. The colonoscopic findings in ITB include intestinal ulcers (usually transverse), pseudopolyps, strictures (usually short), and involvement of the ileocaecal valve. However, none of these are pathognomonic of TB and may be found in other conditions, including Crohn’s Disease (CD). The histological or cytological diagnosis is often based on fine-needle aspiration or biopsy obtained from radiology-guided sampling of the abdominal lymph nodes, peritoneal or omental thickening, or on endoscopic biopsies from the involved intestinal segments. The features suggestive of TB include the presence of granulomas, giant cells, caseating necrosis, and demonstration of acid-fast bacilli. The presence of granulomas is not unique to TB and may occur in other lesions, especially CD, fungal infections, and sarcoidosis; the presence of caseating necrosis is deemed to provide some degree of specificity to the diagnosis. Discrimination from CD is difficult, but the presence of multiple, large, confluent granulomas may be discriminative for TB. However, granulomas are only detected in a minority of cases (20-50%). Microbiological tools for the diagnosis include smear and culture for acid-fast Bacilli and PCR-based tests; the low yield from the peritoneal fluid and intestinal biopsy samples is the Achilles’ heel of microbiological tests. The use of PCR-based tests has been reported in multiple studies; a report on the use of multiplex PCR (using three probes: 16S rRNA, IS6110, and devR) provided excellent sensitivity for the diagnosis of both peritoneal and ITB but the findings await validation. Although the Xpert® MTB/Rif has emerged as an important tool for the diagnosis of pulmonary TB and some forms of EPTB (lymphadenitis), the reports on the use for ATB have indicated a limited benefit. In a report on the use of Xpert in peritoneal TB, the test was positive in only 4 out of 21 patients who were diagnosed with peritoneal TB. Similarly, in a report on ITB, only 3 out of 37 patients had a positive Xpert MTB/Rif test, suggesting that the sensitivity of the test for ATB would be low. The yield of an in-house PCR (using three genes: hsp-66, esat-6, and IT5 MAC) was also reported to be low. The bulk of evidence therefore suggests that PCR-based tests also provide a low sensitivity for the diagnosis of ATB.

A therapeutic trial of ATT can also be used in the diagnosis and discrimination of ATB from other conditions. A recent study from India has shown that endoscopic healing of ulcers in patients started on empirical ATT may allow differentiation of ITB from CD. While the global symptomatic response with ATT was 38% and 37% in patients with CD at 3 and 6 months, respectively, 94% and 99% of patients with ITB showed a response at 3 and 6 months, respectively. When endoscopic response was observed at the end of ATT, all ITB patients had mucosal healing, while only 5% of CD patients showed mucosal healing; similar findings were also documented in the validation cohort. Therefore, persistent symptoms after 3 months of ATT may indicate a diagnosis of CD; however, the presence of a clinical response to ATT does not exclude the possibility of CD and mucosal healing should be sought. Another concern in the management of ATB is drug resistance and, therefore, the knock-on effect in patients with HIV, those with a previous history of ATT, and those not improving on treatment should be considered and cultures for drug sensitivity must be done.

**TREATMENT OF ABDOMINAL TUBERCULOSIS**

Treatment of ATB, as with other forms of EPTB, is challenging. The challenges a clinician encounters include determining the appropriate duration of treatment, criteria to determine appropriate response to treatment, determining the end points of treatment, and recognition and treatment of sequel of ATB. The systematic review of the three included trials, involving 328 participants, suggests that 6 months of treatment (with isoniazid, rifampicin, pyrazinamide, and ethambutol) is adequate in patients with ATB (primarily intestinal and peritoneal). The included trials did not involve patients with HIV or comorbidities, or those who

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**Figure 8:** (a): Deep, fissuring ulcer in Crohn’s disease - representative picture; (b): patulous ileocecal valve with ulceration in tuberculosis.!
had received ATT previously as well as those with other forms of ATB (e.g., hepatic and pancreatic) and therefore the results may not be applicable to these patients.

The appropriate method of follow-up of patients with ATB is a challenging issue. Even though the disease may heal, persistence of symptoms may be related to sequelae like peritoneal adhesions or intestinal strictures. Continued symptoms may result in an unwarranted prolongation of treatment. Therefore, the follow-up should include both objective and subjective parameters for assessment of response. For ITB, demonstration of endoscopic healing (especially the ulcers) appears to be an excellent method to document response and may be performed at 2–3 months or later. A recent paper demonstrated the use of this approach to discriminate ITB from CD in patients where a therapeutic trial of ATT was administered in indeterminate lesion. In cases of non-healing ulcers, the possibility of drug-resistant TB or an alternative diagnosis must be considered; the frequency of drug-resistant TB varies from one geographic location to another but culture and drug sensitivity should be performed in patients with non-healing mucosal lesions or at the initial evaluation in those with previous history of ATT therapy or patients with HIV. For the follow-up of patients with peritoneal TB, abdominal ultrasonography to look for resolution of ascites could be an appropriate strategy. Other parameters that are often used to assess response include improvement in appetite and general wellbeing, defervesce of fever, and weight gain. A recent paper also suggests that patients with the special form of peritoneal TB, abdominal cocoon, may also benefit from a conservative approach with ATT and the majority of patients can therefore avoid surgery. In a recent multicentre Indian study, the treatment completion rates for ATB were lower than most other forms of EPTB (like pleural, lymph-nodal, genitourinary) although the reasons for this are not clear. Surgery may play an important role in the diagnosis and treatment of abdominal form of tuberculosis. Often surgical intervention is the only therapeutic option for the patients presenting with complications of abdominal tuberculosis. The choice of surgical procedure depends on site and extent of disease, status of the remaining gut, general condition of the patient, surgeon’s expertise and individual preference. In a considerable number of cases complicated with faecal peritonitis and intraabdominal sepsis, a two stage procedure with creation of a stoma (ileostomy) was preferred to primary anastomosis. Creation of a stoma followed by reversal of stoma in a well prepared gut after 10-12 weeks of ATD therapy reduces the risks of anastomotic leaks and septic complications.

**INTESTINAL TUBERCULOSIS VS CROHN’S DISEASE: HOW TO DIFFERENTIATE?**

In countries where ITB is more prevalent, CD is being increasingly recognized. Both these chronic granulomatous disorders have similar clinical, endoscopic, radiologic, and histologic pictures; however, the natural history of both these disorders is strikingly different with serious implications regarding management. Misdiagnosis of one disease as another may be associated with multiple complications, including unnecessary immune suppression, drug toxicity, and delay in appropriate treatment. In one study, the presence of longitudinal or aphthous ulcers, anorectal lesions, and cobblestoning favoured CD, while transverse ulcers, patulous ileocaecal valve, ≤4 segments involved, and scars or pseudopolyps favoured ITB. Addition of CT enterography to colonoscopy increases the diagnostic accuracy and ability to differentiate CD from ITB from 66.7% to 95.2%. Features favouring CD were reported to be male sex, blood in stools, perianal lesions, bowel obstruction, extraintestinal manifestations, longitudinal ulcers on colonoscopy, cobblestone pattern, stricture, mucosal bridging, and rectal involvement. Histology suggesting focally enhanced colitis and CT findings of asymmetrical mural thickening, mural stratification, comb sign, and proliferation of the fibrofatty tissue also indicate the presence of CD. The findings that favoured the diagnosis of ITB were pyrexia, night sweats, pulmonary involvement, ascites, transverse ulcers, patulous ileocaecal valve, and caecal involvement on colonoscopy. Histological findings of submucosal granulomas or confluent granulomas, lymphocyte cuffing, and histiocyte lined ulcers, CT findings of short segmental involvement, and a positive IGRA also favour ITB diagnosis.

**Figure 9: 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.
CONCLUSION

To conclude, ATB remains a diagnostic challenge, having diverse and nonspecific symptomatology, and there being no specific laboratory tests. Early diagnosis is the decisive factor in avoiding systemic and local complications of ITB. The discrimination of ITB from CD is challenging and often necessitates a trial of ATT. ATT therapy for 6 months is usually adequate for mucosal healing and resolution of ascites, but sequelae like intestinal strictures may result in persistent symptoms needing endoscopic dilation or surgical intervention. For those patients presenting in emergency, prompt surgical treatment is necessary to avoid further life threatening complications. A definitive procedure in the form of resection of diseased segment and primary anastomosis is safe and has largely been adopted in place of simple bypass of obstructive lesion with administration of ATT to treat the patients successfully with a complete cure.

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