

Intestinal tuberculosis

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Purpose of review

Intestinal tuberculosis (TB) is increasing due partly to the HIV pandemic. Its clinical presentation mimics inflammatory conditions such as Crohn's Disease and malignancies, which are becoming more prevalent, so its diagnosis is problematic.

Recent findings

Greater awareness of intestinal TB is needed, both in countries where TB is endemic and developed countries with immigrant populations. Some strains of *Mycobacterium tuberculosis* are associated with more extrapulmonary disease and greater dissemination, thereby exacerbating the rise in HIV-associated extrathoracic TB. Recent retrospective and prospective studies are leading to the development of diagnostic algorithms. A wide range of imaging techniques is available for sampling and diagnosis. New biochemical, immunological and molecular diagnostic methods are being developed but must be standardized and validated. Developments in drug delivery will facilitate oral therapy even in patients suffering from malabsorption.

Summary

There is increasing consensus on the risk factors and clinical presentations of intestinal TB . Imaging techniques, coupled with fine needle biopsies, are useful aids to diagnosis, but most important is a greater awareness of the condition by clinicians.

Keywords

abdomen, clinical presentation, diagnosis, *Mycobacterium tuberculosis*, treatment

Introduction

More than two billion people are infected with tuberculosis (TB), and in 2006, 1.7 million people died from TB, including 231,000 people coinfecting with HIV [1]. Extrapulmonary tuberculosis (EPTB) is increasing and accounts for one in five registered TB patients [2]. The commonest forms are lymph node, pleural, disseminated, pericardial and meningeal TB.

Abdominal (ATB) or intestinal tuberculosis (ITB) is the sixth most prevalent presentation of EPTB. The symptoms of ITB mimic those of many other conditions, especially inflammatory bowel diseases, such as Crohn's Disease. These are increasing in incidence in TB-endemic countries such as India and southeast Asia [3**,4]. Most patients are managed without laboratory confirmation, so simplified standardized guidelines are required based primarily on clinical observations. Standardized diagnostic algorithms are available for the more common forms of EPTB [2] but not for ITB.

Epidemiology

Poverty, malnutrition, overcrowding and HIV co-infection aid the spread of TB. In HIV co-infected patients, there is more EPTB and more rapid progression, due to a deficient host cellular immune response. The incidence and severity of ATB is increased in HIV-positive patients, by reactivation of latent TB and new infections [5*,6].

The profile of patients with ATB differs around the globe. In Pakistan, ATB is the most common extrapulmonary site, and is increasing [7*]. Studies from Pakistan [7*,8,9*] West Africa [10,11] and Turkey [12*] found ATB to be a disease of young adults, especially women. A Zambian study [13**] of 31 HIV-positive patients with clinical signs of ATB found 22 (71%) cases with an age-range of 18-46 years and a predominance of women.

However, studies from China [14], Singapore [15*], India [16] and the UK [17*] found a lower incidence but equal or greater numbers of male patients. The UK is a low incidence country, but the proportion of EPTB is rising and varies according to place of birth: 29% of UK-born cases had EPTB but 51% of non-UK born cases [18]. Ramesh et al [17*] found that 91% of UK patients with ATB were of South Asian origin. In addition to the effect of age, sex and immune status, the host-pathogen interaction may differ between ethnic groups due to host susceptibility/resistance factors [19**].

Pathogenesis

The principal cause of ITB is *Mycobacterium tuberculosis*. ITB may be a primary infection, or secondary following reactivation, usually from a primary pulmonary focus. Assumed routes of infection of the gastrointestinal tract are ingestion, for example, of bacilli in sputum from an active focus in the lung, haematogenous spread from the lung, from infected lymph nodes and direct spread from adjacent organs. Unpasteurized milk and milk products are regarded as the main route of transmission of zoonotic TB caused by *Mycobacterium bovis* in countries where there are no effective eradication programmes. However, in the UK, *M. bovis* accounts only for 0.5 -1.5% of all culture-confirmed TB cases [20]. A rare case of ITB in a 90-day infant was due to postnatal transmission from the mother [21].

The genotype of *M. tuberculosis* has important clinical consequences, as it influences the presenting features of pulmonary and EPTB. The East Asian/Beijing lineage, predominantly found in Asia, is associated with greater dissemination and a higher incidence of drug-resistance. It alters disease presentation by influencing the intracerebral inflammatory response, resulting in more meningeal disease [22**]. The outcome of exposure to *M.*

tuberculosis depends on both human and bacterial genotypes. For example, a the single nucleotide polymorphism, T597C in the Toll-like receptor-2 (TLR2) gene, is more commonly found in patients infected with East-Asian/Beijing strains of MTB [23**]. It is highly likely that more examples of such interactions will come to light.

M-cells, found in the follicle-associated epithelium of intestinal Peyer's patches of gut-associated lymphoid tissue, provide a route of entry for pathogens into the mucosa and can phagocytose tubercle bacilli. Therefore, the higher number of lymphoid Peyer's patches in young adults may be one reason why ITB is often associated with this age group.

Pathology

The ileocaecal region is the most common site of involvement, although ATB can have a focus at any site in the gastrointestinal tract, associated lymph nodes and/or the peritoneum. ITB usually has one of three forms: ulcerative, hypertrophic or ulcerohypertrophic or fibrous [24]. Tuberculous granulomas initially form in the mucosa or Peyer's patches, whilst ulcers are relatively superficial, with a different appearance from those in Crohn's disease. ITB progresses slowly and presents late with complications, especially acute or sub-acute obstruction due to mass (tuberculoma), stricture formation in the ileocaecal region or perforation leading to peritonitis. Peritoneal TB (PTB) is rare in the absence of any other debilitating disease. In PTB the peritoneum is studded with multiple yellow-white tubercles.

Site of involvement and clinical presentation

ATB is difficult to diagnose because of its lack of specific symptoms and variable manifestations depending upon anatomical localization of the disease. About 40% of cases originate from the gastrointestinal tract. The major diagnostic dilemma of ITB is to differentiate it from Crohn's disease [25*], although ITB mimics other conditions and may present as an acute abdomen, carcinoma, malabsorption or perforation. ITB patients often

have fever, night sweats and weight loss, altered bowel habits, and abdominal pain. If the abdominal cavity is involved there may be ascites. In some patient groups cirrhosis of the liver is associated with PTB [26*].

In ITB, all regions from the oesophagus to the rectum may be involved. Oesophageal TB is very uncommon and mimics oesophageal carcinoma. Gastroduodenal TB may mimic peptic ulcer disease or present with symptoms of pyloric obstruction, thus being confused with adenocarcinoma. Ileocaecal TB presents with abdominal pain, a right iliac fossa mass and/or altered bowel habits and bleeding, which mimics Crohn's disease, carcinoma, amoebiasis, enteric fever or *Yersinia enterocolitica*. Colonic TB occurs in about 10% of cases, mimicking carcinoma or, more rarely, ulcerative colitis. In rectal TB the predominant symptom is bleeding, and in anal TB, fistulae are common, both mimicking carcinoma or Crohn's disease. The main presenting symptoms are shown in Table 1 although the frequency differs slightly in different studies [3**,8,9*,12*,25*,27, 28,29*]. The diagnostic criteria for HIV-positive patients differ from those who are HIV-negative. The common features of HIV-positive patients with abdominal TB from Zambia were ascites, enlarged para-aortic nodes, hepatosplenomegaly and a mesenteric mass, none of which were identified in HIV-positive TB-negative controls [13**].

In children the presenting features of PTB are similar with abdominal pain, fevers and ascites [30*,31]. Malnutrition is a common feature of ATB in children.

Table 1

Principal clinical presentations in abdominal tuberculosis and Crohn's Disease

Oesophageal	Intestinal	Peritoneal	Crohn's Disease
Dysphagia	Abdominal pain	Abdominal pain	Diarrhoea
Fever	Fever	Ascites	Abdominal pain
Night sweats	Night sweats	Fever	Weight loss
Weight loss	Weight loss	Weight loss	Bleeding
	Diarrhoea		Fistula
	Mass		
	Bleeding		

Data from [3**,8,9*,12*,25*,27,28,29*]

Diagnosis

The criteria for diagnosing ATB are histological evidence of caseating granuloma with acid-fast bacilli stained by Ziehl-Neelsen and culture/PCR positivity. When patients present with acute abdominal obstruction, diagnosis is normally made during surgery, or by examination of the removed tissue. The main diagnostic utilities are imaging, biopsy for histology and culture. Clinical chemistry, immunology and nucleic acid amplification techniques are not used routinely but have potential.

Imaging

An abdominal radiograph yields no specific information identifying ATB but may reveal obstruction or perforation and calcified mesenteric lymph nodes. Barium studies are particularly useful in demonstrating mucosal lesions. The main imaging techniques are ultrasonography, computerized axial tomography (CT), positron emission tomography (PET)

and magnetic resonance imaging (MRI). The common imaging features that may be seen in ATB are as follows:

- (1) enlarged para-aortic nodes,
- (2) asymmetric bowel wall thickening,
- (3) ascites,
- (4) inflammatory mass of bowel wall lymph nodes and omentum,
- (5) narrowing of the terminal ileum with thickening and gaping of the ileocaecal valve,
- (6) 'white bowel' sign due to lymphatic infiltration and
- (7) 'sliced bread sign' due to fluid surrounding bowel caused by inflammation of the bowel wall.

Ultrasonography is a non-invasive technique, especially useful for detecting fluid and imaging ascites in PTB. The asymmetric thickening of the bowel wall is typical of ITB [32**]. CT shows the major features of ITB, and contrast-enhanced CT can visualize non-calcified, low-density lesions [33]. Some authors believe CT to be the imaging method of choice for ATB, but on balance, MRI is preferable to CT because of the lack of radiation, particularly for chronic conditions where repeated images may be necessary and in children. MRI scans give a variable appearance of lymphadenopathy depending on the weighting and the stage of the granuloma. Typically, there is a hyperdense centre and hypodense rim in caseating granuloma (T2-weighted). Abnormal bowel wall shows a decreased intensity on T1-weighting and an increased density on T2-weighting. These MRI findings are not specific to TB but can also occur in Crohn's disease, malignancy or other infections. Distension of the bowel with iso-osmotic saline enables better visualization of gastrointestinal transmural

abnormalities by CT or MRI, and this is being used increasingly to identify lesions in Crohn's disease or TB [34,35*].

F18-fluorodeoxyglucose (FDG) accumulates in gastrointestinal and peritoneal TB making F18-FDG PET a useful imaging technique. Although non-specific, it is used for the detection of EPTB and monitoring of treatment [36] in studies of ascites of undetermined origin [37,38*]. Radiopharmaceuticals with greater specificity may enable F18-FDG PET to become a more valuable diagnostic technique for ITB.

Sampling techniques

Diagnosis of ATB is limited by the invasiveness and expense of the procedures needed to obtain appropriate samples for histology or culture, or both. Inflammatory bowel disease and amoebic colitis can mimic TB on endoscopy and biopsy, so diagnosis is difficult [39].

Laparoscopy, laparotomy, colonoscopy, percutaneous biopsy, or all may be required, and although ascitic fluid is more accessible, its culture has low sensitivity [13**]. Early laparoscopy coupled with histology of frozen biopsy sections is particularly useful in diagnosing ATB in patients with no evidence of extra-abdominal disease [40*]. Laparoscopy is also useful in the management of acute pain in children, enabling recognition of presumptive ATB for confirmatory tests [41*]. Similarly, laparoscopy can establish the diagnosis in atypical PTB [42]. Terminal ileoscopy is useful in colonoscopy patients suspected of having ileocolonic TB [43]. Colonoscopy greatly improves the diagnosis of ileocaecal ulcer [44]. The ITB/Crohn's disease differential diagnosis [25*] is assisted by colonoscopic evaluation of the effect of short-term anti-TB treatment to monitor any improvement [45].

Fine needle aspirates (FNAs) are less invasive, so are more feasible in resource-poor settings.

FNAs, combined with a Ziehl–Neelsen stain and PCR, ensured a speedy and reliable diagnosis in HIV-positive children in South Africa [46]. In this study, TB was the second commonest diagnosis in children who presented with mass lesions. Similarly, an Indian study [47] found that from 1999-2006, 92 cases of ATB were diagnosed by FNA cytology, and it was a simple, fast, accurate and inexpensive diagnostic procedure.

Laboratory investigations

Microscopy is the most rapid diagnostic tool. In ideal settings it can produce same day results, but it is very insensitive, yielding only 10-30% of culture-positive samples, especially in severely immunocompromised individuals [13**]. Culture is sensitive, but may take four weeks to obtain conclusive results even with enhanced culture systems. Therefore, other potential diagnostic markers are needed.

Microscopy can be improved significantly by using immunohistochemistry to visualize tubercle bacilli. In a study of 33 histologically diagnosed cases of ATB [48], immunostaining of the *M. tuberculosis*-specific antigen MPT64 in archival formalin-fixed tissues was positive in 25 (75.7%), whereas two non-TB controls were positive (11.1%). None of the ATB biopsies were positive by Ziehl-Neelsen stain. Immunohistochemistry based on the *M. tuberculosis* 38-kDa antigen in FNAs from TB lymphadenitis [49] found more than 96% of cases positive compared with 36-44% that were positive by Ziehl-Neelsen stain.

In cases of PTB, a meta-analysis [50] of 12 prospective studies concluded that adenosine deaminase (ADA) levels in ascitic fluid provide a fast and discriminating test . When ADA is compared with ascitic fluid interferon-gamma (IFN- γ), both have similar accuracy, but

ADA is more accessible in resource-poor settings. ADA levels are proportional to the degree of T-cell activation, so are increased in PTB due to the stimulation of cells by mycobacterial antigens. Other markers used for malignancy diagnosis, such as serum cancer antigen 125 (CA-125), may be raised in PTB, so this possibility should be considered, especially in patients from TB-endemic countries [51]. In female patients with ascites, abdominal pain and elevated CA-125 levels, PTB mimics malignancies such as ovarian cancer.

Serological tests for EPTB are inconsistent and perform no better than microscopy. However, IFN- γ assays provide a sensitive and specific test for TB pleuritis [52*]. Very few studies have examined material from ITB patients. An IFN- γ release assay, QuantiFeron-*TB* Gold (Cellestis Inc, Carnegie, Victoria, Australia), was used in two IBD cases [53] and showed promise. A modified antigen-specific IFN- γ -based assay for cavity fluid specimens performed better than assays for cavity fluid ADA or whole blood IFN- γ assays [54].

Amplification methods for the direct detection of *M. tuberculosis* DNA in clinical samples have been developed but for pulmonary TB. Most are based on a specific region of the insertion element IS6110, which is normally present at 8-10 copies/cell of *M. tuberculosis*. However, it is entirely absent in some strains and is only present as a single copy in *M. bovis*. No commercial kit has been validated for ATB, although the BDProbeTec ET Direct Detection assay (Becton Dickinson, Sparks, Maryland, USA) found *M. tuberculosis* in 24 of 35 (68.5%) formalin-fixed, paraffin-embedded tissue specimens from sites with necrotizing granulomatous inflammation, including the gastrointestinal tract and peritoneum [55]. In-house PCRs have been described but are not readily transferred to other centres and will

require rigorous assessment and validation [52*]. PCR can differentiate ITB from Crohn's disease, and in-situ PCR can directly visualise *M. tuberculosis* DNA in tissue sections, but with low sensitivity [56]. PCR detected *M. tuberculosis* DNA in 84 (85%) of dried aspirate smears from tuberculous lymphadenitis patients [57**], compared with 15 (15.3%) positive by Ziehl-Neelsen stain and 24 (24.4%) by culture. The combination of broth culture and PCR gives culture results after only 8-15 days instead of 26-30 days, which enables presumptive antituberculous treatment to be maintained or discontinued [58].

A PCR method based on *IS1081* [59] has more potential as there are 6 copies/cell of *IS1081* in all members of the *M. tuberculosis* complex. PCR inhibition, a common problem when clinical samples are used directly, must be controlled, and PCRs should be optimized to maximum efficiency of reaction. This is best carried out using newer methodologies, including real-time PCR, which may not be economically feasible in resource-poor countries.

Management and treatment

Surgical management is conservative, with perforation being managed by resection and end-end anastomosis and obstruction managed by strictureplasty, or in severe cases by resection. Obstruction and fistulae may respond to purely medical management. Because of the difficult diagnostic challenge of ATB, a high index of suspicion is needed, particularly in nonendemic areas, as medical treatment can be curative and save unnecessary surgery [60*].

Standard treatment for ITB is conventional chemotherapy (Rifampicin+Isoniazid+Pyrazinamide+Ethambutol, RIPE) for 2 months, with Rifampicin+Isoniazid (RI) continuing for a further 4 -7 months. Most countries adopt the WHO guidelines of directly observed treatment short course (DOTS) given on a daily or

thrice weekly basis. A study [61] comparing daily RIPE for 2 months followed by RI for 7 months, with DOTS receiving RIPE thrice weekly for 2 months followed by RI thrice weekly for 4 months, showed comparable cure rates .

The role of corticosteroids in ITB is not clear, and further studies are required. Management of patients who are co-infected with TB and HIV presents problems related to compliance, drug interactions and immune reconstitution inflammatory syndrome [62]. Avoidance of drug interactions can be improved if rifampicin is replaced by rifabutin [62], or nucleos(t)ide-only anti-HIV regimens are used [63*]. Current preliminary UK recommendations for treatment of co-infection are: if the CD4 cell count is less than $100 \times 10^6/\mu\text{l}$ to commence highly active antiretroviral treatment (HAART) immediately, if the CD4 cell count is $100\text{--}200 \times 10^6$ cells/ μl , one can defer HAART until completion of the initial 2-month phase of anti-TB treatment; and if the CD4 cell count is above 200×10^6 cells/ μl , the complete course of anti-TB treatment can be finished before starting HAART [64].

Patients who receive antitumour necrosis factor (anti-TNF) therapy for Crohn's disease are susceptible to TB reactivation or acquisition [65,66]. To reduce latent TB reactivation patients should receive RI for 3 months prior to commencement of anti-TNF therapy, or if they develop TB during treatment, be given standard anti-tuberculous therapy.

Future developments will be in novel drug delivery systems such as the slow release of antituberculous drugs from polyDL-lactide-coglycolide (PGL) and gelatin, although their effects on clinical cure rates are not yet reported [67]. Other developments for the treatment of ITB could involve the use of targeted gold nanoparticles to block uptake of iron to the

microbe or targeted gold/iron nanoparticles combined with radiofrequency-induced heating, which could kill the microbe. Both techniques are independent of microbial antibiotic sensitivity and would be active against multi-drug resistant TB.

Conclusions

ITB has been somewhat neglected by researchers, although it is increasing due to HIVcoinfection. It is a particular problem in some localities, possibly due to the genetic characteristics of host and pathogen, plus socioeconomic factors. In resource-poor countries diagnosis will continue to be mainly by clinical presentation, so a high index of suspicion is required. Several sophisticated imaging and detection techniques are available, but molecular methods require validation for ITB. Innovative work is in progress formulating oral drug delivery systems.

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