Gastrointestinal Tuberculosis

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ABSTRACT Gastrointestinal tuberculosis (TB) is a fascinating disease which can be observed both in the clinical context of active pulmonary disease and as a primary infection with no pulmonary involvement. It represents a significant clinical challenge because of the resurgence of TB as well as the diagnostic challenges it poses. A high clinical suspicion remains the most powerful tool in an era of medicine when reliance on diagnostic technology increases. Antimicrobial therapy is the mainstay of therapy, but surgical and endoscopic interventions are frequently required for intestinal TB. Gastrointestinal TB is truly the "great mimic" and continues to require the astute clinical acumen of skillful clinicians to diagnose and treat.

INTRODUCTION Involvement of the gastrointestinal tract by tuberculosis (TB) remains a prevalent and relevant disease entity in certain areas of the world and in certain at-risk patient populations. Although the more common forms of extrapulmonary TB (EPTB) include lymph node, pleural, disseminated, pericardial, and meningeal TB, gastrointestinal TB is believed to be the next most frequent form (1, 2). Although there is significant variability in the prevalence of intestinal TB by geographic location and by the population’s risk profile, the true prevalence of the disease is difficult to ascertain, as many patients with pulmonary TB may be asymptomatic from their intestinal involvement (3, 4). This requires a very high index of suspicion, as a delay in diagnosis may result in detrimental outcomes. When patients do become symptomatic, their presentation may be nonspecific. Furthermore, as TB can involve any part of the gastrointestinal tract, the manifestations are protean (5).

PATHOGENESIS Mycobacterial infections of the gastrointestinal tract occur in one of several ways: (i) swallowing of infected sputum in a patient with active pulmonary disease, (ii) hematogenous or lymphatic spread from a distant focus, (iii) direct extension from a contiguous site, or (iv) ingestion of milk products infected with Mycobacterium bovis (6). The last mechanism is rare in the United States and other developed nations due to the pasteurization of milk and tuberculin testing of the herd population, although a United Kingdom study demonstrated that M. bovis was responsible for 0.5 to 1.5% of cases of culture-confirmed TB cases (7). Milk products remain a viable means of mycobacterial infection in some countries, particularly in those cultures in which raw milk is consumed as a part of their local tradition (3). Ethiopian cattle owners that consumed the raw milk of their cattle were found to be at a >3-fold-higher risk of TB infection than those who consumed boiled milk (8).

Some authors have described two types of enteric TB: a primary form typically due to the direct ingestion of the bovine bacillus and a secondary form due to the spread of the human bacillus from active pulmonary disease (9). As mentioned above, the primary form is extremely rare in the United States and, when it does occur, likely represents a re-infection from a previous and no longer apparent focus of TB or from an unrecognized pulmonary infection (6). Only 16 to 30% of patients with intestinal TB have evidence of concurrent active pulmonary disease (5, 6, 10–13), but this is highly variable and may reflect the rigidity of the criteria used in...
the studies to make the diagnosis (14, 15). Some studies have suggested that 31 to 50% of patients with smear-positive cavitating pulmonary TB also have tuberculous enteritis, with a statistically significant correlation between the severity of lung disease and the likelihood of intestinal involvement (16–18). As a result, the proportion of patients with concurrent pulmonary and intestinal TB may be underrecognized due to the asymptomatic nature of intestinal TB, proceeding unnoticed and resolving with the treatment of the pulmonary disease (12, 16).

The entire gastrointestinal tract, from the esophagus to the anus, can be involved (19–22). The ileocecal region is the most common location, being involved in 44 to 93% of cases (9, 14, 23). The colon and small bowel alone are the next most frequent sites of infection, while the esophagus and stomach are rarely involved (9, 11). The mycobacteria have a fatty capsule which resists digestion and interferes with release early in the gastrointestinal tract, explaining the rarity of proximal gastrointestinal lesions (5). The narrow lumen and relative stasis of the ileocecal region allow digestion of the capsule and efficient absorption of the organism. Abundant lymphatic tissue for which the organism has an affinity further enhances infections at this site (24). Once in the submucosa, the bacillus colonizes the Peyer’s patches and initiates an inflammatory response, forming granulomas. The tubercles undergo caseous necrosis and release organisms into the lymphatics, allowing migration to regional nodes where further granulomas form. As the tubercles enlarge, the bowel wall becomes markedly thickened and small papillary elevations form in the mucosa. Combined with an associated endarteritis and lymphangitis, the superficial mucosa becomes edematous and circumferentially ulcerated. As the ulcers heal, deposition and contraction of collagen in the submucosa can lead to stricture formation (5, 24, 25). Thus, tuberculous enteritis can be classified grossly as ulcerative, hypertrophic, mixed ulcerohypertrophic, and fibrotic (11, 23). The ulcerative form is more likely to be found in the small intestine and the hypertrophic form in the cecum (5, 26).

**EPIDEMIOLOGY AND RISK FACTORS FOR GASTROINTESTINAL TB**

As TB has been a recognized clinical entity for centuries, the impact of TB on global health was significantly truncated by specific measures targeting improved living conditions, the increased pasteurization of milk, and the widespread distribution of anti-TB medications in the latter part of the 20th century. Although TB was deemed a “rare” disease in United States in the 1960s and 1970s (6), the world witnessed a resurgence of TB with the emergence of human immunodeficiency virus (HIV) (27). The relative risk of developing TB when coinfected with HIV can increase as much as 30-fold (28), increasing the risk of gastrointestinal TB in these patients (29). It has been estimated that TB is the leading cause of death in AIDS patients, at 11% (30); in Africa and parts of Southeast Asia, up to one-third of HIV patient deaths are attributed to disseminated TB (31–33).

Gastrointestinal TB appears to present more frequently and in a more severe form in the HIV-infected population secondary to a deficiency in the host immune response (1). In line with this notion of host factors mitigating a higher risk of developing gastrointestinal TB, one Korean study demonstrated that a higher Charlson comorbidity index was associated with the development of gastrointestinal TB (34). This contrasts with data from a recent Japanese study in which the majority of the cases of intestinal TB were in healthy individuals (35). Altogether, the findings suggest that the risk of developing gastrointestinal TB may increase due to a variety of different risk factors.

The prevalence of gastrointestinal TB appears to vary significantly by geographic location. In North America, gastrointestinal involvement by TB appears to be one of the least prevalent types of extrapulmonary infection (27, 36), whereas it remains a more significant problem in parts of the Middle East, Africa, and Asia. In Saudi Arabia, gastrointestinal TB represented the most common type of EPTB, with 15.8% of cases affecting the alimentary tract (3). In a group of Indian AIDS patients, autopsies demonstrated a 14% prevalence of intestinal TB (37). In more industrialized nations, the prevalence is considerably lower. A retrospective autopsy study in Japan demonstrated a 1.6% prevalence of gastrointestinal TB among patients with a history of active or remote TB infection (38), while in Canada, intestinal TB represented only 4.2% of the cases of extrapulmonary disease (39).

The variability in the prevalence of gastrointestinal TB may, in part, be due to the variable prevalence of TB, lower socioeconomic status, and immunocompromised states in these countries (40, 41). Patients considered immunocompromised include those with HIV/AIDS (42) but also increasingly include patients under treatment with anti-tumor necrosis factor agents (43–45) and solid-organ transplant patients, such as those with renal (46–48), cardiac (49), and liver (50–52) transplants. Because the immunosuppressant agents used in post-
transplant patients target cell-mediated immunity, the response to mycobacterial infections is blunted (50, 52). Studies demonstrate the overall incidence of TB in organ transplant recipients to be 0.35 to 2.3%, with a mortality rate ranging from 0 to 40% (50, 52–55). Several transplant database studies suggest that renal transplant patients appear to be at a particular risk for pulmonary TB and EPTB (56). It is, however, notable that the absolute numbers of intestinal TB cases in these studies are low. A review of 2,333 renal transplantations in southern China revealed 41 cases of TB and only 21 cases of EPTB. Furthermore, only 1 of the 21 cases of EPTB involved the gastrointestinal tract (53). A similar Korean study, over a 22-year period, demonstrated 78 TB cases, of which 24 were EPTB; only 2 of the EPTB cases were intestinal TB cases (57).

Within industrialized nations, an additional risk factor is immigration from a region of high prevalence (16, 23, 25). In the United Kingdom, where there is a low incidence of EPTB, South Asians represented 91% of all the cases of intestinal TB (58). In the United States, 59% of all new cases of TB were in foreign-born patients and 48.8% of those patients were from Mexico, the Philippines, Vietnam, and India (59), areas with high endemicity for TB (27). Despite reports of increased cases of abdominal and intestinal TB in the early 1990s (6), CDC data suggested a peak in TB resurgence in the early 1990s, followed by a downward trend in the incidence of all forms of the disease, both pulmonary and extrapulmonary, over the last 15 years (27).

Several reports indicate that female gender may be an additional risk factor for intestinal TB (60–63). In Nepal, where 45% of the total population is estimated to be infected with TB, being female was identified as an independent risk factor for EPTB in a retrospective analysis of a single, high-volume referral center (64). This finding is consistent with a French study, which also noted a female predominance for EPTB (65). Interestingly, these results contradict the findings of other studies, which demonstrate an equal to slightly greater number of males affected (2, 11, 12, 15, 18, 26, 64, 66–68). A possible explanation for these differences may exist in the cultural differences and varying social norms of certain regions and periods, which may selectively increase the exposure of one gender to possible tuberculous infections (10).

There may be some host-specific genetic factors that yield a greater susceptibility. Although these genetic factors are largely unidentified (69, 70), examining 168 cases of gastrointestinal TB in China revealed that polymorphisms in the LMP2 (Arg60-His) and LMP7 genes, which play a role in the foreign-antigen processing on the major histocompatibility complex I CD8+ cytotoxic T-lymphocyte pathway, resulted in a higher risk of intestinal TB involvement (71). The odds ratios ranged from 1.83 to 3.86, depending on the specific nucleotide polymorphism genotype.

Age is another factor in one’s risk for gastrointestinal TB. In western Nepal, over a 3-year period, more than 40% of the cases of EPTB were found in the population of patients less than 25 years old, while the cohort >50 years old represented only 21.7% of the cases of EPTB (64). A recent study of gastrointestinal TB cases in the large urban hospitals in China revealed a mean age of 34.7 years (72). In these patients, the gastrointestinal tract was noted to be the second most common site of TB involvement, with 14.8% of cases (64). A U.S. study demonstrated that being under the age of 18 alone was associated with a twofold-increased risk for EPTB (73).

CLINICAL MANIFESTATIONS
Diagnosing gastrointestinal TB is a challenge, as it frequently presents with vague, nonspecific symptoms, and there are no pathognomonic signs for enteric TB (24). It has often been described as presenting in “protean” manifestations (2, 5, 74), and it is very difficult to differentiate from other inflammatory conditions that affect the gastrointestinal tract. Compound the nonspecific presentation of the disease with the relative rarity of intestinal TB, and TB is often overlooked in the differential diagnosis (75, 76). The presentation of gastrointestinal TB often resembles that of other disease entities; case reports of intestinal TB presenting as a mimic of esophageal cancer (77), esophageal ulcers (78), submucosal tumors (79, 80), ulcerated gastric masses (81), limitis plastica (82), colorectal cancer (83–85), Crohn’s disease (86–90), sarcomas (6), and appendicitis (23, 91, 92) abound in the literature.

Studies show that physicians entertained the diagnosis in less than 40% of patients on initial presentation, resulting in a delay in diagnosis and treatment (15, 93). The majority of patients present chronically, with symptoms present for several weeks to months (94). The longest reported period of symptoms prior to presentation was 15 years (15). Acute and acute-on-chronic presentations are also observed, and in a large case series by Bhansali (26), these presentations were seen 19 and 28% of the time, respectively. A delay in diagnosis and treatment can result in significant morbidity and mortality (23). The rate of in-hospital mortality alone can be 14%, and overall mortality is 19 to 38% in patients with
ileocecal TB, the most common form of intestinal TB (92, 95).

The complications of intestinal TB are diverse, and there are ample case reports of bleeding (47, 96–99), diarrhea (100), weight loss (101), luminal obstruction (102, 103), intussusception (104), perforation (83, 105–107), gastrointestinal strictureing disease (108–111), and fistulae (112–115). Even a case of chronic inflammatory demyelinating polyneuropathy associated with intestinal TB has been reported (116).

Patients with gastrointestinal TB can also present asymptomatically. One study from Japan reported a case series of 11 consecutive patients over a 15-year period, diagnosed with intestinal TB by colonoscopy; only 1 patient had clinical symptoms of anorexia and weight loss, while the other 10 patients were asymptomatic (117). Similarly, one case report describes a patient with a cavitory lung mass on computed tomography (CT) who underwent a positron emission tomography (PET) scan to rule out lung cancer and had an incidental finding of increased 18F-fluorodeoxyglucose activity in the ileocecal area, which only on subsequent surgical resection was found to be ileocecal TB (118). Up to 53% of enteric TB cases are detected unexpectedly during surgery for an unrelated diagnosis (12).

Because TB can affect any part of the gastrointestinal tract, the presenting symptoms often vary depending on the affected anatomic location of the disease. However, in one Indian study, regardless of the gastrointestinal location of TB involvement, patients most commonly presented with abdominal pain, fever, and weight loss, in order of decreasing frequency (18, 119). These results parallel numerous studies that note abdominal pain as the most common symptom, seen in 70 to 100% patients (9–11, 14, 26, 67, 94, 120). The pain is usually colicky and intermittent in nature and may represent subacute intestinal obstruction. It is frequently located in the right lower quadrant or periumbilical regions, although it may be retrosternal or epigastric in the rare cases of esophageal (119) or gastric (10, 79, 81, 82, 120) involvement. Anorexia and weight loss are seen in a majority of patients (121), while nausea, vomiting, and fevers are seen in about 40% of patients (Table 1). A change in bowel habits is encountered in 42 to 76% of affected patients, with diarrhea more common than constipation (9, 11, 92, 94, 102, 120).

On physical exam, an abdominal mass may be palpable; the frequency of this sign shows a broad range in the literature, varying from 1.8 to 72% (14, 18, 92, 122). The higher range of abdominal mass frequency may in part be related to the heterogeneity of the liter-

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ESOPHAGUS

The first primary case of esophageal TB was described in 1837 from an autopsy by Denonvilliers (125). Primary TB of the esophagus is a rare occurrence, with most cases in the literature being reported as secondary esophageal TB as a result of direct extension of mediastinal or pulmonary TB into the esophagus (23, 126, 127). Endoscopic ultrasound reveals that the subcarinal region is the most common site of involvement (128). The rarity of esophageal TB is believed to be secondary to the peristaltic effects of the esophagus to clear contents through into the stomach, the coating of the esophagus with a layer of saliva and mucus, and the esophagus’ protective squamous epithelium (125, 129). In one case series, esophageal TB constituted only 1 of the cases (0.34%) among the 297 cases of gastrointestinal TB (23).

There are no specific symptoms that suggest esophageal TB. The most commonly reported symptoms are dysphagia, weight loss, anorexia, retrosternal pain, and fever (130–135), while odynophagia was an infrequent complaint (77). Symptoms of a cough, particularly with eating, may signal the presence of a tracheoesophageal fistula. The most common complications associated with esophageal TB include fistulae (aortoesophageal, tracheoesophageal, and esophagomediastinal), strictures, ulcerations, and perforation (131, 136, 137). Half of the patients with esophageal TB reported by Devabhavi et al. were found to have an associated esophagotracheal fistula or an esophagomediastinal sinus (120). Massive hematemesis from erosion into the thoracic aorta or from aortoesophageal fistulae has been reported, with esophageal hemorrhaging occurring both spontaneously and following the initiation of anti-TB therapy (138–145). Cases of isolated esophageal hemorrhage, presenting with hematemesis and melena but without any concomitant symptoms of dysphagia, dyspnea, cough, or abdominal pain, are uncommon but have been reported (142, 143).

The endoscopic appearance of esophageal TB is most commonly a mucosal ulceration, although mucosal infiltration by mycobacteria with or without stricture formation is also seen (77, 133, 135, 145–147). The middle one-third of the esophagus is the most common location for tuberculous involvement (131, 147, 148). Examination of the esophageal wall with endoscopic ultrasound revealed that in 62.5% of cases, it was the middle one-third of the esophagus that was involved with TB (127). In a minority of cases, the focus of TB involvement, presenting as an ulcerative or hypertrophied lesion, is mistakenly identified as a submucosal mass (79, 149) or malignant lesion (77, 131, 150).
Intramural pseudo-diverticulosis has also been reported in association with primary esophageal TB (151).

Endoscopic ultrasound can be a very useful tool in suspected cases of esophageal TB, as both the esophageal wall layers and mediastinum can be examined. Furthermore, the ability to perform FNA may help secure the diagnosis (150). However, a report of mediastinal-esophageal fistulae formation after fine-needle aspiration (FNA) during endoscopic ultrasound (EUS) examination for TB of the mediastinum suggests another possible complication after endoscopy in these patients (152, 153). Additionally, when performing an endoscopy on any patient with a suspected case of TB, it is important to protect endoscopic personnel from possible infection by aerosolized mycobacteria by using appropriate respiratory protection.

Radiographic tests can reveal displacement of the esophagus by mediastinal lymph nodes, sinus tracts, and fistulae into the mediastinum or bronchial tree. The mucosal architecture can be evaluated by barium studies, although these findings can be very subtle. The most common finding on barium swallow is extrinsic compression of the esophagus, but traction diverticula, strictures, sinus/fistulous tracts, and pseudo-tumoral mass lesions have been reported (154, 155). CT provides details of esophageal wall thickening and nodal enlargement as well as mediastinal and pulmonary involvement (156). In a case series of 32 patients, chest CT demonstrated mediastinal lymphadenopathy involving 2 or more groups of lymph nodes in 14 patients (155).

The diagnosis and various medical therapies for esophageal TB are discussed in later sections. Medical therapy is generally considered the mainstay of treatment, and surgical therapy is reserved for those individuals with large or nonhealing fistulae, recurrent or massive hemorrhage, or obstruction (157–159). The first case of successful nonsurgical therapy with anti-TB medications alone as treatment for a tracheoesophageal fistula was in 1976 (160). When fistulae are very large or not responsive to medical therapy, the usual approach is a right thoracotomy with primary resection and closure (159); one series noted a 90% success rate of esophageal fistula closures with medical therapy alone (120). There is limited literature on the use of esophageal or bronchial stents in the setting of esophageal TB (161). Placement of an esophageal endoprosthesis can be used in patients who refuse surgery (162) or are poor surgical candidates, although complications of stent migration and resultant esophageal perforation need to be considered (161).

**STOMACH**

The stomach is a rare site for mycobacterial infections. Earlier literature suggested incidences of 0.004 to 0.1% in resected specimens and 0.03 to 0.5% in autopsy cases (163–165); however, there is a greater incidence in at-risk patients, such as those patients who are immunosuppressed (6, 14, 166). Gastric lesions are usually associated with concomitant pulmonary or disseminated disease (16), although reports of sporadic or isolated gastric TB exist (82, 167–169). The relative resistance of the stomach to tuberculous involvement has been attributed to multiple factors, including the low pH, the absence of lymphatic follicles, the integrity of the gastric mucosa, and the relative rapid emptying process of the stomach (16, 82, 163).

The symptoms of patients are often nonspecific, and patients can present with bleeding (163), epigastric pain (170), fever of unknown origin (171), abscess formation (172), gastric mass (82, 168, 173), symptoms of peptic ulcer disease (82, 174), perforation (175, 176), and gastric outlet obstruction (167, 177, 178). Rarely, a palpable mass can be observed (174). On CT imaging, the appearance is nonspecific, demonstrating a thickened gastric wall with surrounding lymphadenopathy (179). Consequently, the gastric TB can mimic inflammatory conditions or malignancy, such as lymphoma, gastrointestinal stromal tumor, or intestinal-type gastric adenocarcinoma (174, 180). In South Korea, where the prevalence of gastric cancer is high, a case of “coexisting histopathologically and bacteriologically confirmed gastric cancer and tuberculosis” was reported (181). Gastric outlet obstruction is believed to be secondary to mycobacterial infiltration, secondary fibrosis, and localized edema in the region of the pyloric outlet (163, 165). As a result, obstruction tends to occur most frequently in the hypertrophic form of gastric TB (82, 182, 183). In India, 61% of all patients with gastric TB presented with gastric outlet obstruction and another 26% presented with gastrointestinal bleeding (183).

The lesser curvature of the antrum and the pylorus (particularly the posterior wall) are the most frequent locations of tuberculous infection, with fundic involvement being very rare (82, 175). Gastric manifestations of TB include most commonly the ulcerative and hypertrophic subtypes of gastric TB (2). Ulcerations can be single or multiple (81) and are usually superficial, rarely extending beyond the submucosa or muscle layer (82); consequently, perforation is a rare, but reported, sequela of gastric TB (163, 173).

The diagnosis is either suspected or confirmed by histopathologic examination of endoscopic mucosal biopsy.
specimens, brush cytology, and culture of biopsy specimens (123, 169, 184), although submucosal foci of TB can be difficult to reach with endoscopic biopsy forceps (171). A patient who had a 5-mm prepyloric nodule (negative Ziehl-Neelsen staining and cultures of the biopsy specimens) was ultimately diagnosed on the basis of a PCR for Mycobacterium tuberculosis complex DNA (185). PCR analysis of gastric aspirates has been used to confirm the diagnosis, with an overall specificity of approximately 85% (186).

Antimicrobial treatment is discussed in a later section, but in the past, surgery played an important, if not vital, role in the treatment of patients with gastric TB involvement (178). Surgery was typically either a gastrojejunostomy or antrectomy with Billroth II reconstruction (164, 182). However, successful treatment of outlet obstruction with a combination of medical and endoscopic therapy (serial balloon dilations) without surgical intervention (163, 187) is emerging as an alternative strategy. The rate of successful endoscopic therapy for gastric outlet obstruction from gastric TB may be as high as 92%, and these reports suggest that endoscopic management with anti-TB agents may be a reasonable first choice in the treatment of these patients (188). Additionally, a few reports of medical therapy alone with several months of anti-TB medications have also yielded promising results (169, 189). As a result, an attempt at treating with medical therapy with adjunctive endoscopic treatment, in the appropriate patient, is a reasonable consideration prior to surgery.

SMALL INTESTINE
The small bowel is a frequent site of involvement with gastrointestinal TB. The likelihood of infection increases as one moves distally, with the likelihood of TB involvement in the ileum being three times higher than in the jejunum (16, 26). In India, among 173 cases of confirmed gastrointestinal TB, only 2% of cases involved the duodenum, whereas the ileocecal region was involved 49% of the time (102). A study from New York City in the early 1990s demonstrated duodenal involvement by TB to be at 0.3%, whereas the rates of jejunoileal and ileocecal involvement were 35 and 42%, respectively (6). A rare case of isolated TB of the ampulla of Vater masquerading as a periampullary carcinoma was also reported (190). Although the ileum is usually involved in conjunction with the cecum, isolated ileal involvement is observed in up to one-third of cases of small intestinal TB (11, 102, 120).

The presentation of tuberculous enteritis is usually insidious, and when apparent, the clinical symptoms are most likely due to a specific complication (102). Obstruction is the most frequent complication and is seen in up to 44% of cases (191). The obstructive process is gradual, and the bowel may adapt to the progressive luminal narrowing (120). When obstruction occurs, it is most frequently at the ileocecal valve (Fig. 1), and on endoscopic view, the ileocecal valve has a patulous appearance with a classic, fish mouth deformity (Fig. 2) (109). Pathologically, tuberculous enteritis typically presents as either an ulcerative (in the jejunum or ileum) or a hypertrophic (ileocecal) phenotype. Both pathologic morphologies can result in obstructive symptoms. This is attributed to multiple factors, including circumferential strictureing from secondary fibrotic changes, focal nodular mucosal inflammation, and extrinsic compression from adenopathy (1, 123, 192–194). Strictures can be multiple, with three or more strictures present in up to 28% of reported cases (26, 195, 196). Enterolith formation is rare, occurring proximal to a stricture due to intestinal stasis, suggesting a chronic process. The symptoms of obstruction from TB are similar to those of other causes of intestinal obstruction and include nausea, vomiting, and abdominal pain (103, 192). Gastric outlet obstruction has been reported from tuberculous duodenal involvement (194, 197, 198). On physical examination, abdominal distension and signs of hyperperistalsis are universally present, although
Perforation from small intestinal TB is the second most common complication. The clinical presentation may be surprisingly nonspecific and variable; however, most reports suggest abdominal pain as the primary symptom in 85 to 100% of cases (26, 199). Although one report of 300 patients demonstrated an incidence of perforation of 7.6% (26), other reports have noted the rate of intestinal perforation secondary to TB involvement to be as high as 25 to 32.7% (18, 200), with mortality after perforation approaching 30% (25). Multiple sites of perforation are not uncommon, occurring in 25 to 40% of the cases; the mortality in this setting appears to be higher, attributable to either an increased burden of intraperitoneal contamination or a more aggressive infection due to a higher degree of host immunodeficiency (201–204). There are multiple reports of perforation in the context of ongoing anti-TB therapy, and the likely mechanism is a dramatic reduction in the intestinal wall inflammation before a sufficient fibrous response, resulting in a compromise in intestinal wall integrity (5).

The clinical scenario of a patient with pulmonary TB presenting with an acute abdomen or signs of peritonitis should raise strong concern for a perforated tuberculous ulcer (205). The absence of radiographic evidence of pulmonary disease or pneumoperitoneum does not rule out the diagnosis and should not deter the clinician from further investigation. In fact, in one series of eight patients with documented perforation from intestinal TB, only two patients presented with the classic finding of subdiaphragmatic free air (200). The lack of reliability in this radiographic finding in assessing for perforation in intestinal TB may be due to the fibrotic and adhesive changes associated with the chronic inflammation of intestinal TB, which limits the spread of intraluminal contents and intraperitoneal air (203). Accordingly, in a series of 28 patients with enteric TB and perforation, it was noted that 23 of the perforations were contained, with only five demonstrating free leakage into the peritoneum (115).

Life-threatening upper and lower gastrointestinal bleeding from ulceration of the small intestine has been reported but remains an uncommon complication (47, 151, 206). Mucosal ulcers resulting from inflammatory changes from tuberculous involvement are accompanied by an obliterator endarteritis, which makes hemorrhaging a less likely outcome. However, in areas where TB is endemic, such as India, it appears that despite the rarity of overt gastrointestinal hemorrhaging in developed countries, intestinal TB can be a common etiology for either obscure or overt gastrointestinal bleeding. In eastern India, among 40 patients presenting for evaluation for obscure gastrointestinal bleeding, 10% of patients had intestinal TB (207). In another case series from India, involving 91 patients with massive gastrointestinal hemorrhaging, eight patients were found to have ileal TB (208). Fistulae from the small intestine to vascular structures, such as the aorta and mesenteric arteries, are the etiological source of massive gastrointestinal hemorrhage, associated with a high mortality (209–211). Although a case of hemorrhaging from isolated gastric varices secondary to jejunal TB-related splenic vein thrombosis has been documented, it is a rare presentation (212).

In general, fistulae are rare occurrences. In two Indian studies, involving 173 and 110 cases of confirmed intestinal TB, only one subject was reported to develop a fistula (18, 102). Enterocutaneous fistulae are the most common, followed by enterenteric and enterocolonic fistulae (115). Fistulae from the duodenum to the biliary tree (114, 213, 214) and from the duodenum to the kidneys (215, 216) have been described. Since fistulae are also seen as a complication of Crohn’s disease, their presence in tuberculous enteritis further adds to the complexity in differentiating these two diseases.

Malabsorption is suspected to occur in approximately 20% of cases (40, 93), but it is more difficult to diagnose...
than the aforementioned complications due to a lack of definitive radiologic or surgical findings. Intestinal TB is the second most common cause for malabsorption in South Africa and India (105), and the pathogenesis most likely involves a combination of bacterial overgrowth from stricturing, decreased absorptive surface area secondary to diffuse mucosal ulceration and inflammation, lymphatic congestion, and bypassing of intestinal segments via fistulous tracts (26, 217). Tandon et al. demonstrated that greater rates of malabsorption in intestinal TB occurred in those patients with high-grade intestinal obstruction than in patients with low-grade or no obstruction (218). Furthermore, when these patients underwent surgical correction of their obstruction, the malabsorption was also corrected. The authors suggest that the concurrence of intestinal obstruction, malabsorption, and bacterial overgrowth point to a “stagnant loop syndrome” in which the luminal obstruction leads to stagnation of luminal contents, causing bacterial overgrowth and subsequently malabsorption. Besides causing diarrhea, malabsorption leads to a hypoproteinemetic state with a consequently higher rate of post-surgical mortality and subtherapeutic serum levels of anti-TB drugs. There has been the suggestion of using the absence of the expected urine color change with rifampin therapy as a screen for malabsorption in patients with intestinal TB (93).

ILEAL TB VERSUS CROHN’S DISEASE

The clinical dilemma of differentiating ileal TB from Crohn’s disease remains extremely difficult (219, 220). Both disease processes can involve a chronic process of bowel wall inflammation, intermittent luminal obstruction, and fibrostenotic disease. Furthermore, the radiographic, clinical, and pathologic presentations may be identical. The importance in distinguishing these two disease processes is further highlighted because the treatments are vastly different (221–223). In fact, the immunosuppressant medications used in Crohn’s disease are potentially toxic and may exacerbate intestinal TB (43, 44). Although an empiric trial of anti-TB medications may be initiated before a definitive diagnosis of ileal Crohn’s disease is made (224, 225), this strategy inherently results in a delay in treatment in patients who are ultimately diagnosed with Crohn’s disease. Although intestinal TB was uncommon in industrialized countries in the past while Crohn’s disease was infrequent in developing nations, this has dramatically changed due to the emergence of HIV and AIDS as well as the rapid globalization trends of population shifts from immigration (27). These evolving factors have resulted in a significant overlap in the epidemiology of these two disease entities, which was not previously observed, resulting in the increased importance of the ability of physicians to differentiate between ileal Crohn’s disease and TB.

A number of studies have investigated whether the colonoscopic appearance of the intestinal mucosa could differentiate between the two disease processes. On colonoscopy and ileoscopy, intestinal TB and Crohn’s colitis can both present with mucosal ulcerations, nodularity, mucosal edema, ileocecal valve and cecal deformity, fibrous bands, strictures, and pseudopolyps in the ileocecal area (88, 110, 226, 227). Studies have investigated whether the disease processes demonstrated any features typical or characteristic of these usual endoscopic findings, which would allow adequate differentiation (228). It is suggested that ulcerations in intestinal TB are more likely to extend in a transverse or circumferential manner, while Crohn’s ulcerations are longitudinal in appearance (87, 225, 229–231).

One prospective study with patients with endoscopic ileocecal findings found that the only endoscopic feature with statistical significance in patients differentiating Crohn’s disease from intestinal TB was aphthous-appearing ulcers, which more likely represented Crohn’s disease than intestinal TB in 66.7% versus 22.2% of patients, respectively (224). A Korean study of 88 patients, who were diagnosed with either Crohn’s or intestinal TB, demonstrated that having fewer than four segments involved and having transversely positioned ulcerations were most suggestive of intestinal TB, while demonstration of anorectal lesions, aphthous ulcers, and longitudinally aligned ulcers were the most statistically significant findings in predicting the diagnosis of Crohn’s disease (87).

COLON

Colonic TB can involve any portion of the large intestine; however, the ileocecal region is the most common site of intestinal involvement, followed by the ascending colon. The sigmoid colon and rectum are the least commonly involved (6, 85). Various studies have noted overall colonic involvement to occur in 20 to 33% of cases of intestinal TB (6, 102), and about two-thirds of cases are seen in patients with pulmonary disease (117, 232).

Colonic TB can be asymptomatic or present with nonspecific symptoms of acute or chronic abdominal pain, fever, weight loss, diarrhea, nausea, vomiting, and, rarely, hematochezia (117). Endoscopy can assist in the
diagnosis by providing pathologic specimen acquisition and assessing for characteristic images consistent with colonic TB. Classically on colonoscopy, the appearance of colonic TB is circumferential, white- to yellowish-based ulcers with surrounding inflammation, nodules, and edema (231, 232, 233). Tuberculous colitis has also been described as involving multiple small pink nodules with moderate erythema, friability of the surrounding mucosa, pseudopolyposis, and stenoses (Fig. 3) (225, 234, 235). Segmental colitis has been reported for 19 to 26% of patients with colonic TB (229, 232), involving every location throughout the colon, including the appendix (91, 108). When colonic TB involves the appendix, the presentation can be similar to classical appendicitis (233, 236). In the majority of patients with segmental tuberculous colitis, the affected colonic segment was usually solitary and measured 4 to 8 cm (229, 232). A marked hypertrophy of the mucosa along with stenosis due to chronic colonic TB can be easily misdiagnosed as malignancy (83, 85, 97, 98, 106, 115, 242, 243). Obstruction is the most common complication, reported in 15 to 60% of series, and has a predilection to occur in short segmental areas with tight stenoses (16, 66, 110, 225, 235). Hemorrhage is unusual and massive bleeding even rarer (208, 244–246); the low rate of bleeding is believed to be secondary to the obliterative endarteritis caused by the chronic mycobacterial infection. Colonic TB often requires surgical intervention for its complications. In a large surgical series, 58% of colonic TB subjects required either a hemicolectomy or a segmental resection. A fistulotomy was required in 10%, and in an additional 12% of subjects, the surgical procedure played a critical diagnostic role (232).

**DIAGNOSIS**

The diagnosis of intestinal TB should be considered in anyone with abdominal symptoms from an area where TB is endemic. Patients with a prior exposure or known infection should increase one’s clinical suspicion of extrapulmonary disease and be further evaluated if clinical clues point to mucosal disease. With the increased use of immunosuppressant medications and diseases of immunodeficiency, reactivation of latent TB infection is always a concern and real possibility. Endoscopic evaluation is best facilitated by multiple biopsies, the specimens of which should be sent for histology, acid-fast bacillus (AFB) stain/culture, and PCR (125, 205, 229, 230, 247, 248). Under ideal circumstances, the mucosal biopsy specimens taken during endoscopy would demonstrate AFB or caseous necrosis to enable the diagnosis of intestinal TB; however, the prevalence of these findings is very low (87). Among 225 patients who were ultimately diagnosed with intestinal TB, only 23.1% had either of the findings (caseous necrosis or AFB positivity) to enable the diagnosis of intestinal TB; however, the prevalence of these findings is very low (17, 249). The classic histology of caseating granulomas may not be seen if the endoscopic biopsies are superficial, as the granulomas of intestinal TB may be located in the submucosa, which highlights the importance of multiple deep biopsies to increase diagnostic yield. The concurrent use of AFB staining and histologic findings of caseous necrosis from endoscopic biopsies for diagnosis only marginally increases the sensitivity for intestinal TB. In one retrospective series from Korea, the sensitivities of the findings of caseous necrosis and AFB positivity were only 11.1% and 17.3%, respectively (87). Among 225 patients who were ultimately diagnosed with intestinal TB, only 23.1% had either of the findings (caseous necrosis or AFB positivity) to enable the diagnosis of intestinal TB, and the addition of *Mycobacterium* culture increased the sensitivity only to 38.7%. Despite the low sensitivity of AFB staining, it remains a useful adjunct in clinical practice because of its high specificity, and it should remain an important component of testing with endoscopic biopsy specimens (3).
PCR analyses of mucosal biopsy specimens from endoscopy have been shown to be a valuable tool in improving diagnostic yield, with a high specificity, 95% (250). PCR has also been found to be more sensitive than acid-fast stains and culture in diagnosing intestinal TB (185, 251, 252). Some studies have proposed the use of a serologic enzyme-linked immunospot assay, which detects the interferon gamma made in response to exposure to specific mycobacterial TB antigens with a specificity of >90%, increasing the diagnostic yield in cases when the diagnosis of intestinal TB versus Crohn’s disease is uncertain (86, 253, 254). A recent study highlights the use of an immunohistochemical test for an antibody to Mycobacterium tuberculosis as an adjunct in equivocal cases (255).

The new group of tests that assay interferon gamma release have been valuable for the diagnosis of TB. A recent study demonstrated the efficacy of an interferon gamma release assay along with radiographic, endoscopic, and clinical parameters for differentiating intestinal TB from Crohn’s disease. The assay was valuable in excluding the diagnosis of TB (256). The use of these newer serum tests is more common, and the clinical utility in establishing or excluding a diagnosis of intestinal TB is evolving (256–259).

Radiographic imaging studies usually provide correlative information to prompt further investigation but rarely establish the diagnosis because of the nonspecific signs of intestinal TB. Radiologic findings are rarely pathognomonic for TB but can be suggestive of intestinal TB in the appropriate clinic context and when the clinical suspicion is high. For example, multiple radiographic tests, including barium enema, CT, and magnetic resonance imaging of the abdomen, have been shown to be helpful in aiding in the diagnosis of colonic TB (217–260). Although many of the findings observed in these tests are nonspecific for intestinal TB, there are some frequently encountered signs which may suggest intestinal TB, such as ulcerations, nodularity, tumor-like lesions, deformity to the ileocecal region, strictures, and fistulae (3, 102, 261). Barium studies can demonstrate findings of spasm and hypermobility with ileocecal valve deformity and edema, while double-contrast studies frequently reveal ulcerations with elevated margins and linear ulcers arranged perpendicularly to the longitudinal axis of the colon (261, 262). Multiple areas of luminal narrowing often can be appreciated with proximal dilation.

CT scans are now being used more commonly than barium studies (Fig. 4). One study suggested that CT improves differentiation of intestinal TB from ileal Crohn’s disease. The authors reported that CT provided the correct diagnosis in 81% of cases with a previous indeterminate finding on barium study (263). The most common CT finding was abdominal lymphadenopathy, and several studies noted the finding of abdominal lymphadenopathy in 60 to 88% of patients with documented intestinal TB, most frequently in the pararenal, mesenteric, and paracaval lymph nodes (234, 264–266). The enlarged lymph nodes also frequently presented with findings consistent with caseous necrosis, which on CT manifested as central hypodensity. Intestinal TB can also manifest with an asymmetric thickening pattern to the bowel wall on CT scan, which has been suggested as a sign of more severe tuberculous involvement (60, 113). In 2009, one group reported the first case of ileocecal and proximal colonic tuberculosis as examined by CT colonography (virtual colonoscopy) and described circumferential bowel wall thickening with mild enhancement of the intestinal wall, mucosal nodularity, edema, and incompetence of the ileocecal valve, as well as an area of circumferential superficial ulceration (267). CT enteroclysis is a particularly useful tool given the propensity of TB to localize in the small intestine. One large study of 265 cases of proven small intestinal TB demonstrated that the most common findings on CT enteroclysis were strictures, adhesions, and ulcers, at 62.7, 21.8, and 9.1%, respectively (268). These findings were better defined by CT enteroclysis than by barium studies, as enteroclysis was found to have the ability to test the distensibility of the small bowel in areas of prestenotic dilatation, where

FIGURE 4 CT scan demonstrating segmental and circumferential wall thickening of the proximal colon due to TB involvement. (Courtesy of Si Young Song, Yonsei University School of Medicine, Seoul, South Korea.)
minimal strictures can often be present—a finding not as easily demonstrated by conventional barium follow-through examinations (268, 269). Algorithms have been proposed using CT enterography to diagnose tuberculous involvement of the luminal gastrointestinal tract (270).

Magnetic resonance images can also demonstrate caseating granulomas, which on T2-weighted images appear as a hyperdense center surrounded by a hypodense rim (1, 60). PET scans can be useful in localizing EPTB (271), particularly when there is no pulmonary disease and the clinical suspicion of intestinal TB is low (272). In a case report of an elderly woman, a PET scan was performed for a lung mass and incidentally uncovered an abnormal accumulation of 18F-fluorodeoxyglucose within the ileocecal region, which facilitated the decision to pursue colonoscopic biopsies to confirm the diagnosis of intestinal TB (118). Magnetic resonance enterography offers an axial imaging method that is radiation free to aid in the diagnosis of intestinal TB with well-described findings (273).

Endoscopic ultrasound is a modality that has been in practice for more than 30 years and continues to witness an increase in its application. The addition of an ultrasound probe at the distal tip of the endoscope provides it the ability to observe anatomical structures outside the confines of the gastrointestinal tract. Although EUS has been found to be useful in the diagnosis of granulomatous diseases, such as histoplasmosis (274, 275), less is known about its role in intestinal TB. EUS is limited to the upper gastrointestinal tract and the distal colon because the endoscope is a side-viewing device and, thus, the passage of the endoscope is not under direct visualization. Upper gastrointestinal tract TB and rectal TB are significantly rarer than small intestinal TB, and the rarity of these conditions has limited the description of EUS characteristics and the diagnostic capability of EUS in intestinal TB. One Turkish group described two cases of esophageal TB in which they noted the EUS features of esophageal wall thickening with the concomitant presence of multiple large mediastinal lymph nodes (276). Another key feature was the loss of an ultrasonographic border between the lymph nodes and the adjacent esophageal wall (274, 277). However, these findings are very nonspecific and not unique to TB involvement of the gastrointestinal tract. The mediastinal lymph nodes can be round or oval shaped and heterogeneously or homogenously hypoechoic but typically have regular borders with some fine central calcifications (276).

EUS also allows for the acquisition of cytology specimens by FNA, a proven modality for the diagnosis of intestinal TB (278). EUS-FNA holds the theoretical advantage of a higher diagnostic yield than endoscopic brush biopsies because it can access the submucosa and extraintestinal locations of TB, although no studies directly comparing the two modalities have been performed. Other studies have demonstrated the utility of percutaneous FNA, and although this represents a valuable diagnostic tool, EUS-FNA is a less invasive alternative (279–282).

**TREATMENT**

Anti-TB medical therapy is extensively covered elsewhere. Most experts recommend therapy similar to that used for active pulmonary TB; however, the data on duration of therapy remain controversial. Although some retrospective data have suggested that short-course chemotherapy (6 months of anti-TB medications) is sufficient (283), much of the data are gathered from other sites of extrapulmonary involvement and not directly from studies involving cases of intestinal TB (284–286). As a result, there remains a disinclination among some clinicians to treat gastrointestinal TB with short-course chemotherapy because the clinical response to therapy is often ill-defined (287). One recent prospective trial randomized 90 patients with intestinal TB to either 6 or 9 months of therapy with isoniazid, rifampin, and ethambutol with pyrazinamide during the first 2 months (288). The intention-to-treat analysis revealed that the 6-month therapy was as effective as 9-month therapy in patients with intestinal TB, with the additional benefits of reduced treatment cost and increased compliance. A recent case report from Brazil demonstrated the efficacy of injectable anti-TB medications when there was severe gastrointestinal involvement and oral therapy was precluded (289).

Surgery is used as an adjunct for significant bleeding, obstruction, abscess formation, and fistulae that are large or refractory to antimicrobial drugs. Although endoscopic balloon dilatation therapy, applied specifically to strictures of the ileocecal valve and the colon from TB involvement, has been reported, there remains a paucity of long-term safety and feasibility data on prospective endoscopic therapy (109, 290). Both surgery and endoscopic interventions need to be tailored to the specific site of infection and the type of lesion involved.

**CONCLUSION**

Gastrointestinal TB is a fascinating disease which can be observed both in the clinical context of active pulmonary...
disease and as a primary infection with no pulmonary involvement. It represents a significant clinical challenge because of the resurgence of TB, as well as the diagnostic challenges it poses. A high clinical suspicion remains the most powerful tool in an era of medicine when reliance on diagnostic technology increases. Antimicrobial therapy is the mainstay of therapy, but surgical and endoscopic interventions are frequently required for intestinal TB. Gastrointestinal TB is truly the "great mimic" and continues to require the astute clinical acumen of skillful clinicians to diagnose and treat.

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