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**Intestinal Tuberculosis: A Diagnostic Challenge**

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**ABSTRACT**

**Objective:** To describe characteristics, presentation, time to diagnosis and diagnostic findings of patients with intestinal tuberculosis (ITB) in a low-burden country.

**Method:** Retrospective study of 61 consecutive ITB patients diagnosed between 2008-2014 at a large East London hospital.

**Results**: 40 of 61 patients were male. Mean age was 34.6 years. 93% of patients were born abroad, mostly from TB-endemic areas (Indian subcontinent: 88%, Africa: 9%). 25% had concomitant pulmonary TB. Median time from symptom onset to ITB diagnosis was 13 weeks (IQR 3-26 weeks). Ten patients were initially treated for IBD, although patients had ITB. The main sites of ITB involvement were the ileocaecum (44%) or small bowel (34%). Five patients had isolated perianal disease. Colonoscopy confirmed a diagnosis of ITB in 77% of those performed. 42 of 61 patients had a diagnosis of ITB confirmed on positive histology and/or microbiology .

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**Conclusion**: Diagnosis of ITB is often delayed, which may result in significant morbidity. ITB should be excluded in patients with abdominal complaints who come from TB-endemic areas to establish prompt diagnosis and treatment. Diagnosis is challenging but aided by axial imaging, colonoscopy and tissue biopsy for TB culture and histology.

**Keywords:** gastrointestinal, abdominal, TB, London

**INTRODUCTION**

Tuberculosis (TB) may involve any part of the gastrointestinal (GI) tract and intestinal TB (ITB) accounts for 2% of TB cases worldwide[1]. 58% of TB patients in the United Kingdom (UK) present with extra-pulmonary disease, 5.9% have ITB[2]. East London has one of the highest rates of TB in Europe (85.6 cases per 100,000 population in 2015[2]) and serves a large migrant population from the Indian subcontinent and Africa. ITB presents a diagnostic challenge, given its non-specific clinical presentation and tendency to mimic other abdominal pathologies such as IBD[3] and malignancy[4, 5]. Misdiagnosis rates have been as high as 50-70% even in TB-endemic countries[6]. Patients with ITB often suffer from delays in diagnosis and initiation of anti-tuberculous therapy (ATT) leading to significant morbidity and mortality, especially when immunosuppressive therapy is administered for presumed IBD[7, 8].

In this paper we describe characteristics, presentation, time to diagnosis and diagnostic findings of patients with intestinal tuberculosis (ITB) in a low-burden country.

**METHODS**

We conducted a retrospective study of all consecutive patients who were diagnosed with ITB between January 2008 and December 2014 at two large teaching hospitals in East London, UK. Information on patient demographics, site of ITB and clinical, radiological, bacteriological and histological findings were collated from electronic patient records. Details of ATT including duration, complications and treatment outcome were recorded. Statistical analysis was performed using $\chi^2$, Mann-Whitney U, *t*-test and Pearson's Correlation Coefficient. As per UK health research authority guidelines, ethical approval was not required for this study.

**RESULTS**

Of the 147 patients diagnosed with abdominal TB, 61 had TB affecting the GI tract. 40 were male. Mean age was 34.6 (range 13-82) years. 93% of patients were born abroad, with the majority from TB-endemic countries (88% from the Indian subcontinent, 9% from Africa). Patients had been residing in the UK for a median of 5 years prior to diagnosis (IQR 2–11.75 years). Two patients had confirmed human immunodeficiency virus (HIV) infection. 25% had coexisting pulmonary TB. Time from self-reported symptom onset to ITB diagnosis varied, with a median of 13 weeks (IQR 3-26 weeks) (Table 1). The most common presenting complaints were abdominal pain (74%), weight loss (59%), nausea or vomiting (31%), change in bowel habit (25%) and fever (20%)

(Table 2). Three patients presented with weight loss, fevers and night sweats but no abdominal symptoms.

Nineteen patients were initially diagnosed with IBD. Four patients were investigated for colorectal cancer and 4 patients were suspected to have lymphoma. Four patients were diagnosed with appendicitis. Three were diagnosed with gastritis and three with a urinary tract infection (UTI) at first presentation.

Patients with ITB diagnosed at first presentation to our institution (n=23) were less likely to have been investigated previously for IBD or other intestinal diseases (p=0.007 and p=0.001 respectively) than those with ITB diagnosed on subsequent visits (n=38). Characteristics of patients diagnosed with ITB at the initial visit versus those diagnosed subsequently are presented in Table 3. Patients not diagnosed at the initial visit were more likely to develop intestinal obstruction (p=0.04). The patients diagnosed with ITB on their first visit were more likely to be hospitalized when diagnosis was made (p=0.05) and develop more surgical complications (iatrogenic bowel perforation, wound dehiscence, peritonitis, adhesions) (p=0.02). Duration of symptoms did not influence outcomes between the group of patients diagnosed at first visit or subsequent visits (p=0.45). There was no correlation between time since entry to the UK and time to diagnosis between the two groups (p=0.26).

Sites of TB involvement were predominantly the ileocaecal region (44%) and small bowel (34%). The colon was affected in 16 cases, 5 patients had isolated perianal disease and 2 had appendiceal TB. All but 6 of our patients underwent computerised tomography (CT) or magnetic resonance imaging (MRI) of the abdomen, 4 of whom had isolated perianal disease. The most common CT findings were bowel wall thickening (33 patients), intra-abdominal lymphadenopathy (24 patients), intra-abdominal collection (11 patients) or peritoneal thickening (7 patients). MRI of the abdomen showed fistulae (3 patients) or inflammation of the ileum (2 patients). Eight patients had ultrasound examinations, in 4 patients ascites was present and 4 patients had bowel wall thickening. 17 of 42 (40%) had positive histology showing granulomatous changes and necrosis and 28 of 55 (51%) were culture positive for *Mycobacterium tuberculosis*. Three of 61 patients (5%) had isoniazid-resistant TB. All patients with perianal TB were diagnosed from histology and/or microbiology.

Eleven patients had an interferon gamma release-assay (IGRA) performed; 9 of these were positive. Fifteen patients had a tuberculin skin test (TST), which was positive in 13 cases.

Thirty-one patients underwent ileocolonoscopy and 4 underwent gastroscopy. Gastroscopy failed to show any findings associated with ITB. Colonoscopy helped to confirm the diagnosis in 24 out of 31 patients (77%). The most common findings on endoscopy were ileocaecal inflammation (18 patients), ileocaecal ulceration (4 patients) and ileal strictures (4 patients). 20 of 61 patients underwent abdominal surgery (13 underwent laparoscopy, 7 underwent laparotomy). Of the 9 diagnostic laparoscopies performed, 7 laparoscopies yielded positive histology and 4 cultured *M. TB* from pus, ascitic fluid or omental biopsies. Five of 20 patients developed complications from surgery: faecal peritonitis (2 patients), wound dehiscence (2 patients), adhesions (2 patients) and iatrogenic perforation (1 patient) (Table 3).

Twenty of 61 patients did not undergo diagnostic endoscopy or surgery (33%); of those, 4 underwent analysis of ascitic or pleural fluid and 5 had radiologically guided biopsy of intra-abdominal masses, or aspiration of collections. Five patients were diagnosed based on positive TB culture of broncho-alveolar lavage (BAL)

or sputum. Three patients were diagnosed based on radiology and a positive IGRA or TST, two patients were diagnosed on imaging alone in combination with symptoms consistent with TB. One patient had an incidental diagnosis based on histology of tissue removed during an elective hernia repair showing granulomatous change.

Thirty-five of 61 patients received 6 months of treatment, 21 of 61 patients received more than 6 months of ATT, most often due to persistence of symptoms. 58 patients (95%) received standard treatment with rifampicin, isoniazid, pyrazinamide and ethambutol. Isoniazid-resistant *M. TB* was found in 3 patients (5%), and these patients received moxifloxacin instead of isoniazid. One patient was treated with corticosteroids (prednisolone) in addition to ATT. Four patients were lost to follow-up and one died during treatment. Perianal TB was treated for longer (mean 10 months) than ITB without perianal involvement (mean 7.2 months) (p=0.004).

**DISCUSSION**

Our study confirms that ITB is a disease that predominantly affects younger adults[9-12]. Most of our patients were from countries with high TB prevalence presenting with abdominal symptoms[7, 13]. It is recognised in the literature that patients with abdominal TB may present with few or no abdominal symptoms, making diagnosis challenging[14].

Median symptom duration in our patients (13 weeks) was similar to other studies, which reported ranges between 6 weeks and 3 months[7, 8]. In our cohort, there was no correlation between length of stay in the UK and time to diagnosis (p=0.14). There was no correlation between length of time to diagnosis in patients with pulmonary TB (mean 24.2 weeks) and those without pulmonary TB (mean 23 weeks) (p=0.46).

The predominant ileocaecal involvement in ITB is thought to be due to the relative abundance of lymphoid tissue in this area and stasis of faecal matter, increased absorption and close proximity of bacilli to the mucosa[15]. The slow downstream movement of this bacillus-rich faecal matter may explain why the colon is also commonly affected[15, 16].

Five patients in our cohort presented with perianal TB and all had positive histology showing granulomatous changes and cultured *M.TB.* Perianal TB may be confused with a simple fistula-in-ano or isolated perianal Crohn's disease[17] and therefore anal biopsies and/or pus should always be sent for TB culture in patients originating from high-incidence countries.

Abdominal CT findings in ITB patients include bowel wall thickening, abdominal lymphadenopathy with central necrosis, intra-abdominal collections and peritoneal inflammation[9, 16, 18, 19]. MRI of the abdomen is able to delineate peritoneal inflammation through intermediate changes in signal densities[20] and was used in three of our patients. Ultrasound is often limited by the presence of bowel gas and was only used in 8 of our patients. However, ultrasound is low cost, rapid and useful to detect small bowel strictures, omental changes and ascites[21].

IGRA and TST are not routinely recommended as part of the diagnostic strategy for active TB due to their poor sensitivity and specificity [9, 22, 23]. Reported rates of ITB diagnosis from histopathology specimens are 54% and microbiological confirmation has been reported as between 18%-50%[11, 24-26]. Histology had a lower diagnostic yield in our cohort (40%) but our culture confirmation rate was above 50%. Gastroscopy failed to aid di-

agnosis in any of the four patients on which it was performed as TB is unlikely to affect the upper GI tract[15]. Colonoscopy aided diagnosis in 77% of those performed, highlighting the importance of performing endoscopy on suspected ITB patients. If possible, colonoscopy should be performed in all patients with ITB since it provides direct visualisation of mucosal lesions and strictures, as well as allowing tissue biopsy for histology and TB culture[18, 27]. Findings such as terminal ileitis with ulceration, pseudodiverticulae and atrophic mucosal areas should raise suspicions for ITB[14].

Laparoscopy is a rapid, safe and effective technique with a sensitivity of up to 92% for diagnosis of abdominal TB, but there is no evidence as to its utility for diagnosis of ITB without peritoneal involvement[28, 29]. Nine of our patients underwent diagnostic laparoscopy, 7 of which resulted in histological confirmation of disease and 4 cultured *M. TB* from samples obtained from omental or peritoneal biopsy.

ITB typically responds to medical management and early initiation of treatment may help to prevent surgical complications[15]. Tuberculous obstruction is considered the most common complication (24%) and carries a high morbidity, particularly in developing countries[13, 30]. It has been suggested that obstructing lesions <12cm may be managed without the need for surgery[31]. Perforation leads to high levels of mortality and is reported to complicate ITB in up to 11% of adult cases. Our perforation rate was slightly higher (13%), which may be attributable to the late presentation of many of our patients[32].

Of 61 patients, 3 had isoniazid-resistant TB, emphasizing the need for obtaining biopsies for culture whenever possible. As reported in other studies, treatment of abdominal TB was often extended for up to 12 months[15, 33]. However, recent evidence has demonstrated that there is not always benefit in extending therapy beyond 6 months[11]. While other centres have reported using corticosteroids for those with non-resolving obstruction[34, 35], only one of our patients received prednisolone in addition to ATT. Therapeutic drug monitoring (TDM) is indicated in ITB, as GI inflammation may lead to malabsorption and therefore reduced serum drug levels. TDM may guide the clinician on dosing regimes and duration of treatment[36].

Those patients that were not diagnosed with ITB on their initial visit were more likely to have an initial diagnosis of IBD. Differentiating between IBD and ITB is challenging, however both disease entities display different clinical, radiological and endoscopic features. Clinically, patients with ITB present more often with low-grade fever, night sweats and possibly respiratory symptoms than patients with IBD. Crohn's patients are more likely to have haematochezia than those with ITB[37-41]. Radiologically, ITB patients are more likely to have abdominal lymphadenopathy and ascites, whereas those with Crohn's are more likely to display the "comb sign" (vascular engorgement of the mesentery)[42]. Endoscopy often shows circular or transverse ulcers and an increased number of granulomata in patients with ITB, whereas patients with Crohn's disease usually have an increased number of "skip" lesions spread throughout the GI tract with longitudinal ulcers predominating. The presence of cobblestoning is almost pathognomonic for Crohn's[39-41, 43-45].

Although this study was done retrospectively, it presents one of the largest case series of patients with ITB compared to previous studies conducted in low and high incidence countries[7-10, 12, 18, 46-50]. Future large prospective studies are needed in order to develop diagnostic algorithms that would facilitate early diagnosis and thereby help avoid complications of ITB. Close collaboration between gastroenterologists, surgeons, TB

physicians, radiologists, histopathologists and microbiologists in a multidisciplinary setting is essential to identify patients with ITB and initiate early treatment.

**CONCLUSION**

ITB is a rare disease and may be confused with other abdominal diseases including IBD, intestinal infections and colonic malignancies. Clinicians should have a high index of suspicion for ITB in patients from high TB prevalence countries presenting with abdominal symptoms in order to prevent complications resulting from delayed diagnosis. A combination of diagnostic modalities such as cross-sectional imaging, colonoscopy and laparoscopy should be employed, and appropriate tissue obtained for histological confirmation and TB culture.

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**Table 1.** Demographics of patients with intestinal tuberculosis (ITB). (Total number of patients = 61)

| | |
|---|---|
| **Mean age** *(years)* | 34.6 |
| **Gender** | |
| *Male* | 40 (65%) |
| *Female* | 21 (35%) |
| **Place of birth** | |
| *Indian Subcontinent* | 50 (82%) |
| *Africa* | 5 (8%) |
| *UK* | 4 7%) |
| *Other* | 2 (3%) |
| **Median length of stay in the UK before diagnosis** *(years)* | 5 (IQR 2-11.75) |
| **Median duration of symptoms prior to diagnosis** *(weeks)* | 13 (IQR 2-26) |

UK: United Kingdom; IQR: interquartile range

**Table 2.** Presenting symptoms at time of diagnosis in patients with intestinal tuberculosis (ITB)

| **Symptoms at time of diagnosis*** | | **Number of patients (n=61)** |
|---|---|---|
| **Gastrointestinal** | Abdominal pain | 45 (74%) |
| | Nausea/ vomiting | 19 (31%) |
| | Change in bowel habit | 15 (24%) |
| | Rectal bleeding | 3 (5%) |
| | Anal pain | 2 (3%) |
| **Respiratory** | Cough | 5 (8%) |
| | Dyspnoea | 1 (2%) |
| **Constitutional** | Weight Loss | 36 (59%) |
| | Fever | 12 (19%) |
| | Night sweats | 11 (18%) |

*Most patients complained of >1 symptom

**Table 3.** Patients diagnosed at first presentation to our hospitals vs. patients diagnosed at a later date

| | **Patients diagnosed at first visit** (n=23) | **Patients diagnosed after first visit** (n=38) | **Total** (n=61) | **p-value** |
|---|---|---|---|---|
| Treated for alternative diagnosis other than ITB | 2 | 21 | 23 | <0.001 |
| Treated for IBD | 0 | 10 | 10 | 0.007 |
| Mean duration of symptoms before diagnosis of ITB *(weeks)* | 20.7 | 24.8 | n/a | 0.45 |
| Perianal TB | 1 | 4 | 5 | 0.72 |
| Complications of ITB* | 12 | 15 | 27 | 0.33 |

| | | | | |
|---|---|---|---|---|
| *Obstruction* | 0 | 6 | 6 | 0.04 |
| *Perforation* | 4 | 4 | 8 | 0.59 |
| *Stricture* | 2 | 7 | 9 | 0.29 |
| *Abscess/Fistula* | 8 | 7 | 15 | 0.15 |
| Hospitalized at time of diagnosis | 22 | 27 | 49 | 0.05 |
| Mean length of hospital stay *(days)* | 19.8 | 13.1 | n/a | 0.08 |
| Abdominal surgical procedures (total) | 7 | 13 | 20 | 0.76 |
| *Diagnostic laparoscopy* | 2 | 7 | 9 | 0.29 |
| *Laparoscopy for ITB complications* | 0 | 4 | 4 | 0.11 |
| *Laparotomy for ITB complications* | 5 | 2 | 7 | 0.05 |
| Complications of surgery* | 4 | 1 | 5 | 0.02 |
| *Iatrogenic perforation* | 1 | 0 | 1 | 0.18 |
| *Peritonitis* | 1 | 1 | 2 | 0.68 |
| *Wound dehiscence* | 2 | 0 | 2 | 0.05 |
| *Adhesions* | 1 | 1 | 2 | 0.68 |
| Mean treatment duration *(months)* | 7.8 | 6.9 | n/a | 0.09 |
| Deaths during treatment | 0 | 1 | 1 | 0.43 |

ITB: intestinal tuberculosis; IBD: inflammatory bowel disease; TB: tuberculosis.
*Some patients had more than one complication