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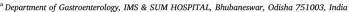
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Abdominal tuberculosis in Indians: Still very pertinent

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Introduction: Tuberculosis is a disease that has been affecting mankind since time immemorial and it still continues to be a global health concern. Objective of the study was to evaluate the burden, clinical profile, diagnosis and diagnostic difficulties and outcome of abdominal tuberculosis (AbT) in non human immunodeficiency virus (HIV) infected adults in the department of gastroenterology at a tertiary care hospital over a period of two years.

Material & methods: It was an observational study and the study period was from January 2016 till January 2018. The patients who were sero positive for HIV virus were excluded from the study.

Results: The number of patients hospitalized during the period of 2016–2018 with abdominal tuberculosis was 58. The burden of tuberculosis of indoor patients was 1.3 cases per every 100 patients admitted. Presenting complaint of most of these patients [61%] was abdominal pain. Constitutional symptoms like fever; weight loss and loss of appetite were present in only 40% of the patients. Ascites was the presenting sign in around 45% of the patients. Peritoneum was the most common site of involvement [27 out of 58]. Almost all of these patients [25 out of 27] presented with abdominal pain and abdominal distension. Intestine was the second most common site. Ileocaecal involvement was present in fourteen patients, while other areas of colon were involved in five patients. All the 58 patients were given anti tubercular therapy. There was complete resolution of tuberculosis in 91% of cases [53 out of 58 patients]. Six patients developed drug induced liver injury. Death occurred in two patients who had disseminated tuberculosis.

Conclusion: Although the burden of the disease remains the same, availability of newer investigations has aided in its early diagnosis and availability of good drugs has reduced the mortality and morbidity.

1. Introduction

Tuberculosis is a disease that has been affecting mankind since time immemorial and it still continues to be a global health concern. Globally around 10 million are affected with tuberculosis and 1.3 million died from the disease in the year 2017 [1]. In developing countries poor living conditions, overcrowding and limited access to health care facilities are the major causes of the disease [2]. On the other hand, the emergence of AIDS epidemic, emigration and ageing population are the causes of rise in tuberculosis cases in developed countries; where it was on the verge of extinction once [3]. India has the maximum number of patients affected with mycobacterium tuberculosis [1]. Despite the availability of good anti tubercular drugs [ATT] and gargantuan efforts from the government in containing this disease, it still continues to be relevant and a major cause of morbidity and mortality in the country. The challenge magnifies in the context of rise of multi drug resistant (MDR) tuberculosis.

Any organ of the body can be affected with tuberculosis and abdomen is the six most common sites [4,5]. The sites of involvement of

abdominal tuberculosis [AbT] are peritoneum; lymph nodes, intestine and solid viscera.

Diagnosis of abdominal tuberculosis [AbT] is an ongoing challenge for most physicians. This difficulty and delay in diagnosis is because of the following reasons: (1) The clinical presentation is subtle with many vague symptoms and non specific signs. The clinical features depend upon the site of involvement. (2) AbT mimics many other pathologies like Crohn's disease [especially those with intestinal involvement]; malignancies [especially those with peritoneum involvement]; lymphomas [those with lymph node involvement] etc. (3) Despite the presence of an armamentarium of diagnostic procedures; yet all these tests are cumbersome, costly and not easily available. (4) Mycobacterium tuberculosis shows very low yield on microscopy or culture.

A high index of suspicion is very important while dealing with a case of abdominal tuberculosis. Many a time a therapeutic trial of ATT based on clinical suspicion can work wonders in these patients.

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1.1. Objective

The objective of the study was to evaluate the burden, clinical profile, diagnosis and diagnostic difficulties and outcome of abdominal tuberculosis in non human deficiency virus (HIV) infected adults in the department of gastroenterology at a tertiary care hospital over a period of two years.

1.2. Methods

All patients who had a provisional diagnosis of AbT and were hospitalized at the department of gastroenterology and biliary sciences at Institute of Medical Sciences and SUM hospital, Bhubaneswar were included in the study. It was an observational study and the study period was from January 2016 till January 2018. The patients who were sero positive for HIV virus were excluded from the study. The patients whose diagnosis changed after complete evaluation were also excluded from the study. Written informed consent was obtained from the patient for publication of this study.

The basic demographic profile of the patients and presenting signs and symptoms of all patients were noted.

All the cases of abdominal tuberculosiswere divided into four categories. They were:

- a Peritoneal. These patients presented with ascites or omental disease. The diagnosis was made on the basis of imaging studies like Ultrasonography (USG) or computerized tomography scan (CT scan) of abdomen and pelvis; ascitic fluid analysis [serum ascitic albumin gradient (SAAG); Adenosine deaminase (ADA); Cytology; Ziehl Neelsen (ZN stain) for acid fast bacilli; tubercular polymerase chain reaction (TB PCR) in selected cases and omental cake biopsies wherever feasible.
- b Intestinal. These patients were diagnosed using imaging studies like CT Scan abdomen and USG abdomen. Diagnosis was done on the basis of gastro duodenoscopies or colonoscopies or enteroscopies [in selected cases] and biopsies and TB PCR from the biopsy samples.
- c Lymph node. These patients were diagnosed using imaging studies like USG abdomen and CT scan abdomen. Diagnosis was confirmed using fine needle aspiration (FNA) and/or biopsies from the lymph nodes. The modalities used to take FNA or biopsy sample was USG or CT guided. Endoscopic Ultrasonography (EUS) was used where the conventional methods were not feasible. Diagnostic laparoscopy was largely avoided.
- d Solid Viscera. Diagnosis of tuberculosis affecting the solid organs like liver, spleen and gall bladder, is done by imaging studies and biopsy from the affected organ.

Routine investigations like complete blood counts, liver function tests; renal function tests; erythrocyte sedimentation rate (ESR) was done in all patients. Chest radiograph (X Ray Chest); sputum analysis and CT thorax [in selected cases] was done in to evaluate pulmonary involvement. Tubercular Quantiferon Gold was done in selected patients.

A case was defined as a confirmed case of abdominal tuberculosis if it fulfilled one of the following criteria: [6]

- 1 Microbiological evidence of the presence of AFB in tissue or fluid or positive culture of the same specimen
- 2 Presence of caseation necrosis in the tissue specimen
- 3 Histology showing characteristic granulomas and/or chronic inflammatory infiltrate, and epitheloid cells.

A case was considered a clinically diagnosed case when, apart from clinical and radiological evidence of abdominal tuberculosis, one of the following features was present:

- 1 Peritoneal fluid shows low SAAG with high ADA values (>32 U/L)
- 2 Exclusion of other differential diagnosis by tissue biopsy and/or cytological analysis of fluid and demonstration of objective response to therapy in the form of mucosal (ulcer) healing or ascites reduction/resolution

All these patients were followed up for at least for 6 months. Follow up in case of peritoneal tuberculosis repeat USG was done at 4 weeks, 8 weeks and 6 months, in Intestinal tuberculosis repeat colonoscopy was done in most cases at 2 months, in solid visceral and in stricture imaging study was used to assess response [7,8]. The clinical outcomes such as complete cure; serious adverse events to anti tubercular drugs such as hepatitis; requirement for surgery; development of drug resistant tuberculosis (MDR) and death was observed in each patient.

2. Results

2.1. Burden

The number of patients hospitalized during the period of 2016–2018 with abdominal tuberculosis was 58. The total number of patients admitted to the department of gastroenterology was 4147 during these two years. The burden of tuberculosis of indoor patients was 1.3 cases per every 100 patients admitted to the department of gastroenterology. The total number of patients admitted during this period with inflammatory bowel disease (IBD), including both Ulcerative colitis and Crohn's Diseasewas 64, which was almost similar.

2.2. Clinical presentation

The male to female ratio was almost similar. Majority [$\sim 80\%$] of the patients belonged to the age group of 20–60 years [Table 1]. The presenting complaint of most of these patients [61%] was abdominal pain. Constitutional symptoms like fever; weight loss and loss of appetite were present in only 40% of the patients. Ascites was the presenting sign in around 45% of the patients [Table 2].

2.3. Site and type of involvement: [Table 3]

a) Peritoneal tuberculosis

Peritoneum was the most common site of involvement [27 out of 58]. Almost all of these patients [25 out of 27] presented with abdominal pain and distension. The diagnosis was made on the basis of ultrasound imaging and CT scan imaging; ascitic fluid analysis; and omental cake biopsies. Tuberculi bacilli were identified on ZN staining microscopy in 4 patients. Histopathology from omental cake biopsies was suggestive of tuberculosis in 11 patients. The rest

Table 1
Age and gender distribution of the patients.

Age distribution	Frequency	Percentage[%]
< 20	3	5
21-40	30	51
41–60	17	29
>60	8	14
Gender distribution	Frequency	Percentage[%]
Female	28	48
Female Male	28 30	48 52
Male		
Male Comorbidity	30	52
Male Comorbidity Diabetes	30 5	52

 Table 2

 Presenting complaints of the patients with abdominal tuberculosis.

Presenting symptoms	No. of Patients	Percentage[%]
Pain abdomen	36	62.1
Fever	25	43.1
vomiting	16	27.6
Wt loss	10	17.2
Cough	6	10.3
Appetite loss	20	34.5
Abdomen distension	25	43.1
Loose motion	9	15.5
Constipation	5	8.6

Table 3Sites of involvement of abdominal tuberculosis.

Site of involvement	Number (n)	Percentage (%)
1. Peritoneal/ascites	27	46.6
2. Lymph nodes	18	31.0
3. GIT		
a. IleoCaecal region	14	24.1
b. Colon	5	8.6
c. Small intestine	2	3.4
d. Gastric	1	1.7
e. Duodenum	1	1.7
f. Esophagus	2	3.4
4. Solid organs	1	1.7
a. GB		
b. Liver	1	1.7
c. Spleen	1	1.7
5. Multiple site		
Peritoneal & intestinal	7	12
Peritoneal, intestinal & lymph node	3	5

patients [12 patients] were given ATT on the basis of their imaging/ascitic fluid analysis [lymphocytic; high protein; high ADA ascites]. All the 27 patients had an excellent response to anti tubercular therapy and were disease free at the end of 6 months.

b) Intestinal tuberculosis:

The intestine was the second most common site. Ileo caecal involvement was present in fourteen patients, while other areas of colon were involved in five patients. All these patients underwent imaging studies like USG abdomen and CT scan. Colonoscopy was done in all these patients. The typical colonoscopic findings are mucosal ulcerations over caecum; deformed ileo caecal valve; mucosal nodules and strictures. Strictures were present in six patients, out of which four patients responded to ATT while two patients needed surgery at a later date. The diagnosis was confirmed on basis of histopathological studies from the tissues obtained by colonoscopy. Oesophageal and small intestinal tuberculosis was present in two patients respectively. Gastric and duodenal tuberculosis was also rare and was seen only in one patient each. All these patients were diagnosed on basis on the histo pathological studies. These tissues were received using upper gastro intestinal endoscopy while enteroscopy was helpful in diagnosing the small intestinal lesions.

c) Tubercular lymphadenopathy:

Abdominal nodal involvement was seen in eighteen patients. All these patients were evaluated using imaging studies like USG abdomen and CT abdomen. USG/CT guided biopsy was feasible and done in 7 cases. EUS guided lymph node biopsies were done in 4 cases where the conventional biopsies were not possible. The EUS guided FNAC/Biopsies showed excellent yield as the tissues in all the four cases were adequate in diagnosing tuberculosis.

Table 4
Diagnosis of tuberculosis.

Total number of patients	Confirmatory diagnosis	Presumptive diagnosis
58	38[66%]	20[34.5%]

d) Visceral tuberculosis:

Solid organs like liver, spleen and gall bladder were very rarely involved [Table 2]. The patient with hepatic tuberculosis had presented with pyrexia of unknown origin (PUO) with deranged liver function tests [bilirubin was elevated and alkaline phosphate (ALP) was very high]. Diagnosis was made on the basis of liver biopsy. Spleen and gall bladder involvement was seen as a part of multi system involvement.

Multiple site involvement was also noted. Combined peritoneal and intestinal involvement seen in seven cases, peritoneal, intestinal and lymphadenopathy were present in three cases.

2.4. Clinical outcome [Table 5]

The number of patients in whom tuberculosis was confirmed on the basis of histology and/or microscopy was 38 [66%]. The rest twenty patients were treated with empirical ATT and all these patients responded [Table 4]. All the 58 patients were given ATT. There was complete resolution of tuberculosis in 91% of cases [53 out of 58 patients]. Six patients developed drug induced liver injury. These patients were started with alternate tubercular regimens [Streptomycin, Levofloxacin and Ethambutol] and switched over to conventional therapy on resolution of DILI. One of the patients had MDR tuberculosis which was diagnosed and followed up by the department of pulmonary medicine. There were two patients who developed small bowel stricture despite being on anti tubercular therapy. These patients were symptomatic and required surgery. Exploratory laparatomy; strictures bowel resection and anastomosis was done in these two patients. These patients did very well post surgery and received anti tubercular therapy for 6 months. Diagnostic laparoscopy was not done any patient. Death occurred in two patients who had disseminated tuberculosis [mortality rate 3%]. These patients had presented very late (> 4 month from initial onset of symptom) and were in a very low condition and multi organ failure was the cause of death.

3. Discussion

The current study of abdominal tuberculosis in non HIV infected patients shows how relevant the disease is. The burden of AbT was around 1.3 patients per every 100 admitted patients in a gastroenterology department at a tertiary care centre. This figure is quite similar to studies done in the early eighties and nineties [9,10]. Kapoor et al. in a review of Indian literature had found that AbT accounted for 0.8% of hospital admissions. The incidence of AbT is quite similar to the incidence of IBD patients, which is the major differential diagnosis. Similar observation was made by an old study from Great Britain in the early eighties [11]. Thus, despite the availability of good and potent

Table 5 Clinical outcomes of the patients.

Clinical outcomes	Number of patients
Complete resolution with ATT	53
Developed drug induced Hepatitis	6
Required surgery	2
Developed MDR TB	1
Death	2

anti tubercular drugs and evolving diagnostic procedures, the burden continues to remain the same. This is probably because of the low socio economic status and delay in diagnosis and initiation of ATT.

Around 60% of the patients with AbT presented with abdominal pain and it is the most common presentation. Studies from India in the last three decades have shown that pain is the most common presenting symptoms and is present in about 80–100% of the patients [11,12,13]. The mode of presentation depends upon the site of involvement. Peritoneal involvement generally presents with abdominal distension and pain. Intestinal variant presents with pain and features of sub acute intestinal obstruction. Hepatic tuberculosis presents with PUO and jaundice with raised ALP levels. However the difficulties arise when presentation is subtle. Pain is absent in around 1/3rd of the patients. Constitutional symptoms suggestive of tuberculosis are present in only 40% of our patients.

Mortality rates have significantly decreased from 20–50% to around 5% – 6% due to prompt diagnosis and use of potent ATT [14,15]. Despite all efforts, unfortunately, patients do die of tuberculosis. In our study two out of 58 patients had died [mortality rate 3%] These were confirmed case of abdominal tuberculosis. One of them had presented very late, had multi organ involvement [pulmonary; brain; abdomen] and there was substantial delay in starting anti tubercular drugs. The other patient was an elderly gentleman with multiple co morbidities like diabetes, hyper tension; chronic kidney disease. Here also diagnosis was delayed as the patient was treated at multiple peripheral centres and developed acute respiratory distress syndrome (ARDS) and shock at time of admission and conventional ATT couldn't be given due to deranged liver function tests and renal function tests. Hence early identification of the disease and quick initiation of anti tubercular drugs will play a major role in reducing the mortality rate.

The vague clinical symptoms and radiographic presentation of the disease mimics many other abdominal diseases, which creates multiple diagnostic dilemmas in the mind of the treating physician. Intestinal tuberculosis is often confused with Crohn's disease [16]. As many as four female patients who presented with exudative ascites and omental cakes were suspected to have ovarian malignancies. CA 125 levels were elevated in these patients. However these patients were ultimately diagnosed to have tuberculosis [on basis of histology] and responded quite dramatically to ATT. Nodal disease were confused with lymphomas. On the other hand, six patients, who were admitted with a provisional diagnosis of tuberculosis, but ultimately were diagnosed to have Crohn's disease; ovarian or colonic malignancy and lymphoma respectively. Previous studies have shown that around 40% patients are given therapeutic trial of ATT [2]. In the present study 38% of the patients received empirical ATT and responded. But we should carefully follow up these patients as diagnosis of diseases like Crohns; lymphoma and malignancies may be delayed.

Any site of the abdomen can be involved in tuberculosis. Peritoneum and intestine are the most common sites [17,18]. In this series, it was found that peritoneum was involved in around 46% while intestine was involved in around 36% of cases. This is different from other recent studies from northern India where intestine was the most common site [25,27]. The response of peritoneal tuberculosis to ATT is very good as there was complete resolution in all the cases. This is probably because the peritoneal variant present early and are well nourished as compared to the intestinal variant. Majority of the intestinal variant are malnourished due to obstructive symptoms.

According to literature, ileocaecal region is the most common site of the gut [19]. The story is no different in our study where ileocaecal region was commonly involved. Colonoscopy is one of quick diagnostic tools to evaluate these lesions. Colonoscopy is also used to distinguish between a Crohn's disease and intestinal tuberculosis [19]. In patients with TB on colonoscopy, ulcers, strictures, nodules, fibrous bands, and deformed ileocaecal valve are seen. Mucosal ulcers in intestinal TB tend to be circumferential and are usually surrounded by inflamed mucosa. The ileocaecal valve is either patulous or destroyed in tuberculosis. On

the other hand colonoscopic features that favour Crohn's disease are apthous ulcers with normal surrounding mucosa; skipped lesions or the presence of cobble stoning [19,20,21]. Despite all these; both intestinal tuberculosis and Crohn's disease always poses a diagnostic challenge. This is mainly because the colonoscopy yield to get typical caesating granulomas is low and this is where the confusion starts. Clinical acumen and evidences [imaging studies; extra intestinal involvement and supportive tests like serology; X ray etc.] helps in differentiating both the conditions. Expert opinion suggests that if dilemma persists; it is always better to give an empirical trial of ATT first in a country like India, rather than giving immune suppressants therapy [21].

Laparoscopy and biopsy is safe and may help in diagnosing peritoneal/nodal TB [22]. However it is invasive and requires anaesthesia. None of our patients underwent a diagnostic laparoscopy. Adequate biopsy sample could be obtained using endoscopies [gastroduodenoscopy/ colonoscopy/ enteroscopy]. EUS is an exciting addition in the armamentarium of diagnostic procedures; which can provide good tissues for study; especially in nodal and peritoneal disease. EUS guided FNA and biopsy was done in four patients in whom USG/CT guided biopsy was not feasible and probably this was the reason why diagnostic laparoscopy was avoided in our series of patients. Puri et al. has demonstrated that EUS guided FNA can show excellent results to diagnose tuberculosis where image guided lymph node biopsy failed [23]. Dhiret at showed that sensitivity and specificity of EUS FNA to diagnose tubercular lymphadenopathy was almost 100% [24].

Almost two thirds of these patients had a confirmatory diagnosis of tuberculosis which is much higher than a study from North India by Mandavdhare et al. [25]. This is probably attributed to the fact that we have taken characteristic histology as confirmed cases whereas the study from Northern India had more stringent case definition criteria. As tuberculosis is more prevalent than Crohn's disease in this part of the country, hence characteristic histology was taken as confirmed cases. EUS also added to the diagnostic yield.

The response to standard ATT is excellent; with more than 90% showing complete resolution. The duration of therapy is 6 months. This is accordance with various studies done in the past [13,25]. The problems with treatment are development of MDR Tb and hepato toxicity. Only two patients had residual symptomatic strictures for which surgery was required. Studies done from surgical departments have shown that around 10-20% of AbT required surgical interventions [26]. However the surgeries are conservative and show very good results. A recent study from AIIMS, Delhi has shown that around 40% of intestinal tuberculosis [ITB] had stricturing disease and only one-fourth of strictures show resolution following ATT [27]. The resolution of strictures is dependent on disease location, duration and severity of stricture. The present series showed strictures in six out of 21 patients with intestinal tuberculosis [28%]. This is probably because of early referral and early initiation of ATT. However, the number of cases with ITB is too less to derive a conclusion.

There are few limitations of the study. The first is that culture and TB PCR was not done in all patients owing to the financial constraints of some of the patients. Further these tests arenot cent percent helpful in diagnosis because of limited sensitivity. In this paper, serial C reactive protein (CRP) measurement was not done to assess the response to ATT. Sharma et al. in a recent paper has shown that CRP is an ideal surrogate marker [6].

4. Conclusions

Abdominal tuberculosis is a common disease with many uncommon presentations. The burden continues to remain significant in a gastroenterology department. AbT can be of various forms like peritoneal tuberculosis, tuberculous lymphadenopathy, intestinal tuberculosis and visceral tuberculosis. The signs and symptoms of AbT can be non-specific. Tuberculosis should always be kept as a differential diagnosis as it can mimic other abdominal pathologies. Availability of newer

investigations has aided in its diagnosis and availability of good drugs has reduced the mortality and morbidity.

Conflict of interest

None.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jctube.2019.100097.

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