Tuberculosis of the Gastrointestinal system

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My family has stood like a rock behind me during the preparation of this book. My parents (Mr Yograj Sharma and Mrs Sunita Devi, both retired teachers) have always had belief in me. My wife (Dr Alka Sharma, a physician) has taken more than her share of responsibility in homely affairs to allow time for this book. I dedicate this book to my beautiful and loving daughters, Shravya and Anvisha.

Preface

Tuberculosis is a global problem but an issue of immense concern in the less developed world. While pulmonary tuberculosis has received appropriate attention, the nuances in the diagnosis and management of extrapulmonary tuberculosis have largely remained unaddressed. In this regard, 'Tuberculosis of Gastrointestinal Tuberculosis' will fill a vacuum, there is hardly any book which deals with this important clinical condition. The diagnosis, even for the most experienced, is difficult because abdominal tuberculosis is largely a paucibacillary disease. Also, it closely mimics many conditions (Crohn's disease, peritoneal carcinomatosis). The book in your hands has been created for the clinicians, providing detailed information on the clinical presentation, diagnostic evaluation and therapeutic aspects. Discrimination from close mimics is dealt with in separate chapters. In addition, the book also elucidates the approach to follow-up patients while they are being treated for gastrointestinal tuberculosis.

We have attempted to organize the book systematically: with topics of general interest dealt with first, individual sites (luminal, peritoneal and visceral) in the further sections. This is followed by various evaluation techniques followed by management issues which one may encounter. There are separate chapters on imaging in intestinal and peritoneal tuberculosis. There are some chapters which are unique and there are virtually no prior reviews on these topics: differentiating peritoneal TB and carcinomatosis; role of endoscopic ultrasound and advanced nuclear medicine technology in such patients. These unique facets would make this a helpful book for clinicians, residents and students of medicine, gastroenterology, gastrointestinal surgery as also researchers interested in the field. For a clinician, the information would be priceless. The authors of various chapters have also taken care to make the information forward looking and therefore, we know what to expect in coming years in this field. I hope that you would enjoy reading the book as much as I enjoyed putting it together.

Chandigarh, India — Vishal Sharma

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This project has had many supporters and well-wishers. Prof Deepak Bhasin, retired chief of gastroenterology at Postgraduate Institute of Medical Education and Research, Chandigarh and Prof Vineet Ahuja, Professor at AIIMS, New Delhi, introduced me to the field of gastrointestinal tuberculosis. Prof Vineet Ahuja also agreed to pen the most important chapter in the book on intestinal TB. One person responsible for this book coming out is Prof Aman Sharma, a renowned rheumatologist at PGIMER, Chandigarh. He was instrumental in removing all cobwebs in my mind regarding the feasibility of bringing this book out and also my sounding board for ideas and doubts. There are colleagues and friends who have contributed to the peer review of the chapters (Prof Kaushal K Prasad, Professor of GI Histopathology, PGIMER; Dr Gaurav Muktesh, Consultant at NMC Healthcare in Dubai; Dr Anupam K Singh, Assistant Professor at PGIMER, Chandigarh; Dr. Manoj Gupta, Consultant, Nuclear Medicine Department, Rajiv Gandhi Cancer Institute and Research Centre, Delhi) to whom I am grateful. I received total support from Prof Rakesh Kochhar, ex-HoD of Gastroenterology at PGIMER, Chandigarh at all times and he also advised in choice of topics for the book. The support provided by the Springer team has been wonderful and I must thank Kumar Athiappan, the project coordinator for the efforts taken in making this work see light.

Contents

Part VII Miscellaneous

Part I

General

Abdominal Tuberculosis: A Brief History

1

Antriksh Kumar and Harshal S. Mandavdhare

The saying "a person is always followed by its shadow" truly applies to Mycobacterium tuberculosis that has followed human beings like a shadow since ages. Tuberculosis can remain latent in the human body for years and, whenever a person has some disturbance in his disease controlling equilibrium, resurrect and take one form or the other like a "masquerader."

1.1 Ancient and Archeological Evidence

Although the exact time since when human beings and TB share this bond is uncertain, however, genetic data of tubercle bacilli that infect humans postulates that our homonid ancestor nearly three million years from now might have been infected by this organism [1]. From the early dynasty period of 3400 BC, there are descriptions in the Egyptian papyri of deformities highly resembling vertebral TB, although a clear description that these are of tuberculosis cannot be found [2]. The first written documentary evidence of TB can be found in the Chinese and Indian Literature (Riga Veda Hymns) between 2000 and 3500 years ago [3]. In ancient Greece, Hippocrates (460–370 B.C)- "The Father of Medicine" recognized TB as a distinct entity the evidence of which is clear from the description of symptoms of nocturnal fever and drenching sweats as we know today in his Aphorisms [4]. However, he never considered it to be a disease that could be contagious. Aristotle for the first time described that it could be a contagious disease. Galen (130–210 A.D), whose work became the basis of medical literature for centuries in Europe and who practiced medicine in the Roman empire during his last 3–4 decades, described

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symptoms of TB as coughing of blood, yellow putrid sputum, fever considered it contagious and advised isolation of such patients [5, 6].

1.2 The Medieval Age

During this period an extrapulmonary form of TB affecting the cervical lymph nodes what was known as Scrofula had a unique place and had gained popularity with an unusual ritual especially in erstwhile England and France where it was believed that it could be both diagnosed and cured by the monarchs. It was believed that the kings and Queens have the divine power bestowed upon them of curing the scrofula by giving a royal touch to the affected and this gave rise to the popular term of "King's Evil" given to scrofula and its treatment by "Royal Touch" by the liege. In the early modern era between the sixteenth and eighteenth centuries as the scientific temper grew this ritual was more and more questioned and ridiculed [3].

1.3 The Pre-modern Era

From sixteenth century onward more scientific approach toward TB started to appear. Girolamo Fracastoro an Italian scientist was the first person to propose the contagious nature of TB and that it could be caused by a living inviable organism [7]. Francisus Sylvius, a Dutch physician and scientist, in 1679 gave a detailed description of the pathological lesions of TB in his book that was published after his demise [3]. In Venice reporting of tuberculosis became obligatory in 1772. The same year, the regulation was published on the method to be used to purge the stuff. These laws were observed until 1797 when the French Health Committee, suppressed these public health provisions. In the same years (1773–1774) the measures taken in Venice were adopted in Bologna, Ferrara, and Rome. In the late eighteenth century, the Italian health board started issuing public instruction regarding the contagious nature of the disease and began isolating the patients from others and planned to create a hospital exclusively for TB patients. However, this isolation fell into disrepute due to social stigma and judgment of the community and heated debate between contagionists and anti-contagionist. While this debate was going on the eighteenth century also saw the dawn of scientific progress in TB. Benjamin Marten, an English physician in 1720 gave the first clear theory of infectious origin of TB in his work "A New Theory of Consumptions more Especially of Phthisis or Consumption of the Lungs" in which he theorized that TB may be caused by minute life forms that caused the lesions of TB that lead to the symptoms of the disease. He stated that close proximity with the TB patients (consumptive/Phthisis as it was called in those days), eating and drinking with them, frequently conversing with them close enough to inhale the breath he/she exhales could lead to catching of the disease [8]. Robert Whytt, a Scottish physician and a neurophysiologist, in 1768 gave the first clinical description of what we today know as tubercular meningitis

[9]. Tubercular spondylitis or popularly known as Pott's disease was described by Percivall Pott an English surgeon in 1779 [10]. Willian Stark (1741–1770) is credited for studying in detail the pathological presentation of TB in the form of round firm structures which later on were termed as "tubercles" by Matthew Ballie in 1793 [11]. He described the variation stages of evolution of these structures from small to large cavities and proposed these are the common denominators of all the various presentations of TB throughout the body [12]. The industrial revolution of the eighteenth century led to the crowding of cities and this along with poor sanitation, malnutrition, and ill-ventilated working environs made a conducive media for TB to thrive and during this period TB became widespread with epidemic proportion. TB epidemic became popularly known as "Captain of All These Men of Death" [13].

1.4 The Landmark Century of Scientific Advances in TB- The Nineteenth Century

Gaspard Laurent Bayle in 1810 in his seminal work of "Research of pulmonary tuberculosis" recognized that TB not just affected the lung but could affect any part of the body and described various presentations of TB in the body [14]. René-Théophile-Hyacinthe Laennec, one of the greatest inventors and physicians invented the stethoscope in 1816, and his exhaustive work of corroborating his auscultatory findings with those of autopsy lead him to describe the various macro pathologic changes of TB and other lung diseases, viz, pneumonia, bronchiectasis, pleurisy, emphysema, pneumothorax so on and so forth [15]. The current name of the disease as "Tuberculosis" owes to Johann Lukas Schönlein, a German professor of medicine who gave the name in 1839 [16]. Hermann Klencke, a physician from Germany successfully reproduced TB in rabbits by inoculating them with tuberculous material [3]. The concept of sanatoria proved to be the first effective method to show that TB is a curable disease and is credited to Hermann Brehmer, a German physician who himself had developed TB and on return from the Himalayas he found himself cured and wrote a thesis on TB as a curable disease and went on in 1854 to start the first sanatorium. These were places where patients were exposed to fresh air, healthy diet, exercise and rest. In the subsequent decades, this model of sanatoria was replicated throughout Europe and the USA [17]. However, it proved beneficial for only those with a milder form of disease, while those with a more severe and advanced disease would ultimately succumb to the illness [18]. Jean Antoine Villemin, a French physician in 1865 objectively demonstrated TB as an infectious disease by inoculating rabbits with tuberculous material from human cadavers [19]. He was also fascinated with the epidemiology of TB and observed that it occurs through human-to-human transmission in crowded conditions [19]. The work of Villemin only became relevant with the discovery of tuberculosis bacillus by Robert Koch in 1882 for which he received Nobel Prize in Medicine in 1905 [20]. 24th March 1882 was the day on which he presented his discovery of tuberculosis bacillus in the monthly evening meeting of the Berlin Physiological Society. Commemorating this, 24th March is now celebrated as "World TB Day."

1.5 Abdominal Tuberculosis

That gastrointestinal system could be affected by tuberculosis was perhaps known to Hippocrates who described that the patients of phthisis die when diarrhea sets it. The autopsy of King Louis XIII in 1643 had shown pulmonary cavity along with intestinal ulceration suggesting tuberculosis as a cause of his death. This could be an early reference of abdominal tuberculosis in the literature. However, extrapulmonary disease has never received the attention which often is received by the pulmonary counterpart for obvious reasons. Louis Robert Koch and Friedrich Loeffler in 1884 proposed the famous "Koch's postulates" that describe the causality of a microbe for a disease. This set of postulates was described to propose the etiology of diseases such as cholera and tuberculosis. In cases of EPTB, as there is a paucity of microorganisms, the routine microscopic techniques often failed to establish the diagnosis. Paustian in his work published in 1964 proposed that the diagnosis of abdominal tuberculosis could be considered if one of the following is present: histology showing tubercles with caseating necrosis, suggestive operative findings and consistent histology from mesenteric lymph nodes, animal inoculation or culture showing growth of Mycobacterium tuberculosis, or histology showing acid-fast bacilli in the lesion (Fig. 1.1) [21]. The Paustian criteria are difficult to establish in every patient with abdominal tuberculosis. Five years later, Logan VS proposed his modification of the Paustian's criteria by adding another criterion to the list: disease response to anti-tubercular therapy (ATT) [22]. Interestingly, the original Logan modification talks of healing of lesions and this is now the standard definition of response to therapy in intestinal tuberculosis. Of course, what we have further learned is that the response is detected as early as two months into the ATT (early mucosal response).

The first attempt to classify intestinal tuberculosis based on morphology was made by Crohn BB et al. as early as 1932 [23]. The usefulness of streptomycin as a combination drug to successfully treat abdominal tuberculosis was first described by H C Sweany [24]. One of the earliest case series describing abdominal tuberculosis from India dates back to 1972. Tandon HD et al., reported findings of 212 patients who had presented with intestinal obstruction. The surgical specimen of 159 and 10 patients on evaluation was suggestive of tuberculosis and Crohn's

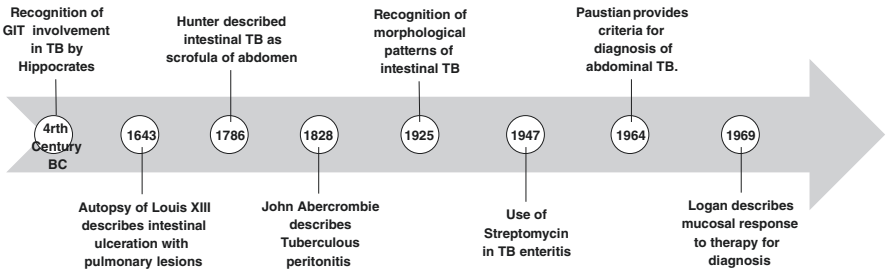

Fig. 1.1 Evolution in understanding of abdominal tuberculosis

disease respectively [25]. In 1976, Mandal BK et al., from London found tuberculous peritonitis, gastrointestinal tuberculosis, and tuberculous hepatitis were the three major forms of abdominal tuberculosis in their series of 15 patients. In approximately 50% of the patients, chest X-ray was unremarkable [26]. Bhansali SK described 300 surgically verified cases of abdominal tuberculosis [27]. Intestinal involvement was seen in 196 cases while the rest of the cases showed either lymph node and/or peritoneal involvement. Histological confirmation could be done in 229 cases.

The challenge to diagnose abdominal tuberculosis was recognized in the twentieth century when an etiologically different disease, Crohn's disease, was recognized which mirrors tuberculosis. With increasing awareness, these diseases were getting increasingly recognized from developing countries as well and one diagnosis (i.e. Tuberculosis) fits all now did not hold true.

Acknowledgment Dr. Vishal Sharma for creating the Figure.

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Epidemiology of Gastrointestinal Tuberculosis

2

Preetam Nath

Key Points

1. Abdominal tuberculosis is a common form of extra-pulmonary tuberculosis with increased incidence in patients with HIV co-infection and cirrhosis of the liver.
2. Exact prevalence is not known due to the absence of mandatory reporting of organs involved in extra-pulmonary tuberculosis.
3. Peritoneal and intestinal TB are the most common type of abdominal TB and may contribute around 10% of the overall EPTB cases.
4. Most cases recover with standard ATT with mortality in a minority of cases due to association with severe malnutrition.
5. Drug resistance in gastrointestinal tuberculosis is well recognized but depends on the underlying rates of drug resistance in various geographic locations.

2.1 Introduction

Tuberculosis (TB), one of the most common communicable diseases, continues to be a major health problem despite recent advances in its diagnosis and management. It is one of the top 10 causes of death worldwide and most importantly the leading

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cause of death from a single infectious agent (*Mycobacterium tuberculosis*) [1]. Almost a third of the world's population is infected with TB. India is the global capital for tuberculosis with around 26% cases of the world TB cases, followed by China and South Africa [1]. The emergence of the human immunodeficiency virus (HIV) and acquired immunodeficiency syndrome (AIDS) epidemic, globalization with frequent emigration, and aging population had led to a resurgence in the rate of tuberculosis (TB) in developed as well as developing countries [2–4]. Likewise, in a study conducted in western India, HIV seroprevalence has been observed in 16.6% of patients with abdominal TB as compared to 1.4% in voluntary blood donors [5]. Hence, once considered a controllable entity after the discovery of anti-tubercular drugs, TB has now re-emerged as a major killer in both developed and developing nations. The infected individuals are at risk of developing TB disease in virtually all sites/organs of the body which may occur concurrently with active lung infection (pulmonary TB) and following the healing of the latter. Although pulmonary TB is the most common manifestation, disseminated and extra-pulmonary diseases have recently increased in frequency [6]. Around 10–30% of patients with HIV infection develop extra-pulmonary tuberculosis [7, 8]. The diagnosis of abdominal TB requires a high degree of suspicion as it presents with wide nonspecific clinical and radiological features. Further, as it mimics other non-tubercular abdominal pathologies, the diagnosis can be challenging in most cases.

Abdominal tuberculosis accounted for 11% of extra-pulmonary tuberculosis before the era of acquired immune deficiency syndrome (AIDS) [9]. However, there is a scarcity of data on the incidence and proportion of abdominal TB as routine data collection by most national TB programs does not report extra-pulmonary TB cases by the organs and/or systems affected. The estimates of the prevalence of abdominal TB vary from 3% to 10% of cases with extra-pulmonary TB [7, 10–13] (Table 2.1). Moreover, abdominal TB is a frequent site of extra-pulmonary TB after lymphatic, genitourinary, bone, miliary and CNS tuberculosis [15, 16]. Early diagnosis and prompt initiation of anti-tubercular therapy (ATT) are essential to prevent morbidity and mortality. Though most of the patients respond dramatically to standard ATT, surgery may be required in a minority of cases. Despite being a benign disease, a delayed diagnosis can lead to irreversible physical impairment and in some cases

Table 2.1 Relative proportion of abdominal tuberculosis in extra-pulmonary tuberculosis cases

Study	Region	Total cases of extra-pulmonary tuberculosis	Proportion of abdominal tuberculosis
Kang et al. 2020 [10]	China	202,998	7.0%
Sandgren et al. 2013 [11]	European Union	108,345	2.7%
Peto et al. 2009 [7]	United States	47,293	4.9%
García-Rodríguez et al. 2011 [12]	Spain	705	4.6%
Prakasha et al. 2013 [13]	India	528	9.7%
Cherian JJ et al. 2017 [14]	India	2219	12.8%

death (1.4%) [17]. That is why a thorough knowledge of the global as well as regional epidemiological patterns of all kinds of abdominal TB are essential for devising better national policies.

2.2 Peritoneal Tuberculosis

It is one of the most common manifestations of extra-pulmonary TB. The incidence of peritoneal TB among all forms of TB varies between 0.1% and 0.7% globally [18]. Besides, it is usually found to occur in 3.5% of cases of active pulmonary TB, whereas concomitant pulmonary disease may be observed in 14% of patients with peritoneal TB [19]. It is often reported as the most common form of abdominal tuberculosis and comprises 31–58% of cases of abdominal TB [20–22]. It usually affects individuals who belong to the age group between 35 and 45 years with equal sex distribution [19]. The risk factors for developing peritoneal TB are cirrhosis of liver, immunosuppressive states (especially HIV/AIDS), chronic kidney disease requiring dialysis, and malnutrition [23]. Association with cirrhosis of liver, frequently leads to delayed diagnosis [24]. The reported incidence of chronic liver disease in patients with peritoneal TB could be as high as 62% in studies from the west [19]. In contrast studies in developing countries report the presence of underlying liver diseases in less than 13% of patients with tubercular peritonitis [25, 26]. The overall mortality was 13% in all cases of peritoneal TB three decades ago, with deaths occurring exclusively among cirrhotic patients [19]. However, with recent advances in diagnostic tools the case fatality rate has been brought down close to zero. Complications of peritoneal TB include intestinal obstruction secondary to fibrous adhesions, which may require surgery [20].

2.3 Gastrointestinal Tuberculosis

Gastrointestinal TB is the second most commonly encountered abdominal TB following peritoneal TB. However, studies from tertiary centers often report intestinal tuberculosis as the most frequent pattern which may be due to a referral bias. The commonest site of involvement is ileocecal area (also known as ileocecal TB), followed by jejunum and colon. In contrast, tuberculosis of esophagus, stomach, and duodenum are uncommon with individual cases reports and small case series.

2.3.1 Esophageal Tuberculosis

Esophageal involvement in tuberculosis is a very rare manifestation of abdominal tuberculosis, which can be attributed to the rapid clearance of esophageal contents to stomach during swallowing. The overall prevalence of esophagus TB is not more than 3.3% of all forms of gastrointestinal TB [27]. The mean age of affected patients varies from 20 to 60 years with a male predominance. Most patients respond to

anti-tubercular therapy and a few may require surgery [28–30]. Mortality is rare and is mostly observed in cases of disseminated TB rather than isolated esophageal TB.

2.3.2 Gastro-Duodenal Tuberculosis

The stomach and duodenum are rarely involved sites for extra-pulmonary TB. The reported incidence of gastro-duodenal TB was 0.5% in old autopsy series during the pre-HIV era [31], whereas isolated gastric TB is even rarer and varies from 0.03% to 0.21% in routine autopsies [32]. Gastric TB is often found concomitantly in pulmonary tuberculosis with a direct relation with severity (ranging from 1% in mild cases TB to 25% cases with severe pulmonary TB) [33]. In a recent review of 22 cases of gastric TB, the mean age was 38.6 years with female predominance (54.5%). Almost all affected patients respond to standard ATT [34]. A subset of these patients may require surgery due to various complications, such as gastric outlet obstruction (GOO), upper gastrointestinal (UGI) bleed, and pseudo-tumor-like lesion resembling malignancy [34, 35]. Mortality is infrequent and could result from persistent bleeding from extensive lesions [35].

Isolated duodenal involvement is also unusual with a reported proportion of 1% of surgically verified cases [36]. In a case series of 28 cases, the mean age was 32.1 years with equal sex distribution [37]. Most patients presented with GOO (82.1%) followed by dyspeptic symptoms. Surgery was required in two-third of cases with GOO. However, for those who were diagnosed after 1997, surgery could be avoided with conservative ATT due to advances in radio diagnosis which enabled confirmation of diagnosis without laparotomy.

2.3.3 Intestinal Tuberculosis

The small intestine is one of the most common types of abdominal TB following peritoneal TB and accounts for 1–3% of all cases of TB [38]. The ileocecal region is the most commonly involved area of the luminal gastrointestinal tract due to various factors such as stasis, abundant lymphoid tissue, and an increased rate of absorption at this site. However, a definitive diagnosis of intestinal TB before ATT is challenging at times due to the lack of a highly sensitive and specific method to confirm diagnosis and to differentiate from Crohn's disease. As a result, a final diagnosis is often resolved by response to a therapeutic ATT trial, which usually delays diagnosis [39].

The most common acute presentations of intestinal TB are bowel obstruction, perforation peritonitis, and rarely gastrointestinal bleeding. Tubercular involvement of intestine can lead to acute abdomen, which accounts for 10% of all cases of acute abdomen in a series [40]. Intestinal tuberculosis accounts for 14–22% of all cases of intestinal obstruction [41, 42]. Though the most common complication of intestinal TB is subacute intestinal obstruction (41.8%), acute intestinal obstruction is not uncommon (5.4%) [43]. The mortality in patients with acute intestinal obstruction

due to TB could be very high (57.1%) because of the frequent association of severe malnutrition in these subgroups of patients [41]. Tuberculosis accounts for 5–9% of all small intestinal perforations in India, which happens to be the second most common cause following typhoid fever [44]. Further, the incidence of perforation in gastrointestinal TB has been reported from 7.5% to 13.3% [41, 45]. Tubercular bowel perforation is associated with high mortality (around 30%) irrespective of the timing and type of surgical procedures adopted [46]. Rectal bleeding has also been reported in 5.5% of cases of GI TB [39]. Massive lower intestinal bleeding has also been reported. Ileal TB had contributed 8.8% cases of massive lower GI bleeding in an old case series [47]. Most cases of small intestinal TB with strictures usually respond with ATT with resolution of symptoms. However, surgery may be required in a minority of cases (8%) [48]. Predictors of need for surgery were long strictures (>12 cm) and multiple areas of involvement.

Colonic involvement in TB is seen in up to 10% of cases and is mostly seen in patients with ileocecal TB. However, isolated colonic TB is rare [49, 50]. The most common site of isolated colon involvement varies among different studies. Nevertheless, the commonest sites of involvement are transverse colon [51] and in some studies ascending colon, whereas multifocal involvement is seen in 54% of cases. Diagnosis in cases with isolated colonic TB is difficult due to its close resemblance with inflammatory bowel disease and colon cancer and is usually confirmed by colonoscopic mucosal healing assessment after a period of 8–12 weeks of starting ATT. Mortality is very low and 6% of patients may require surgery due to the development of colonic stricture [52].

2.3.4 Hepatobiliary Tuberculosis

Tubercular involvement of the liver is generally seen as a part of disseminated disease. On the other hand, isolated hepatic tuberculosis is very infrequent with only isolated case reports and short series available in the literature [53, 54]. The exact incidence of hepatic TB remains unknown, because of the unfamiliarity of the disease. However, in old retrospective studies where hepatic TB was diagnosed upon surgery or autopsy, the estimated incidence is approximately 1% of all active TB cases [55, 56]. Hepatobiliary tuberculosis usually affects individuals in the second to fifth decade of life with peak incidence in the second decade with a male preponderance [57]. In contrast, isolated hepatic tuberculosis is more commonly seen in the age group of 40–60 years [58]. The nonspecific clinical features usually lead to a delayed diagnosis attributing high mortality in these cases. The case fatality rate varies between 12% and 42% without HIV infection [49, 51]. In patients with HIV-co-infected hepatic TB, the mortality (40%) is comparable to those without HIV despite prompt initiation of ATT [53]. Factors associated with poor prognosis are age less than 20 years, co-existent miliary TB, presence of other immunosuppressive states such as patients on corticosteroids, chronic kidney disease, diabetes mellitus, systemic lupus erythematosus, and alcohol use disorder [59].

Table 2.2 Relative proportions of type of abdominal tuberculosis

Study	Region	*n*	Luminal	Peritoneal	Visceral	Nodal	Mixed
Cho et al. 2018 [67]	South Korea	139	49.6	20.1	16.5	5.0	8.6
Tan et al. 2008 [68]	Singapore	57	57.9	22.8	19.3	42.1	
Ramesh et al. 2008 [69]	UK	86	44.2	47.7	9.3	5.8	
Singh et al. 2019 [70]	Bhubaneswar, India	58	24.1	46.6	1.7	31	17
Mandavdhare et al. 2019 [71]	Chandigarh, India	93	45.2	25.8	–	5.4	23.7

TB of biliary tract is very rare and usually presents with obstructive jaundice [60]. Differentiation from malignant neoplasia especially cholangiocarcinoma is extremely difficult and may require a diagnostic laparotomy to exclude malignancy. In view of frequent presentation with cholangitis, most patients require biliary drainage (ERCP: Endoscopic retrograde cholangiopancreatography or PTBD: Percutaneous transhepatic biliary drainage or hepaticojejunostomy) before initiation of ATT.

2.3.5 Pancreatic Tuberculosis

Recently there has been a rise in the number of reports on pancreatic tuberculosis due to the availability of better imaging modalities as well as the endoscopic advances which enable to obtain specimens from the pancreatic parenchyma [61–64]. In a recent review by Sharma et al. [65], on 8 case series comprising of a total of 174 patients with pancreatic TB, mean age varied from 36 to 56 years with slight male preponderance (55.7%) Similarly in a systematic review by Panic et al. [66], mean age was 41 years with male preponderance (62%). 22.3% of these patients were found to have concurrent HIV infection. Apart from HIV, other risk factors were intravenous drug abuse, alcohol use, and smoking. One-fourth of patients required surgery and mortality was seen in 8.7% of cases.

The relative proportion of all types of abdominal tuberculosis is depicted in Table 2.2 [67–71].

2.4 Drug-Resistant Abdominal Tuberculosis

As the bacteriological diagnosis in most cases of abdominal tuberculosis is difficult due to low culture-positive rate in the intra-abdominal specimens [72], the exact incidence of drug-resistant cases in abdominal tuberculosis is unknown. Further, the sensitivity of molecular methods such as Xpert MTB/RIF varies from 23% to 30% depending upon the type of specimen [73–76]. The reported incidence of resistance to a single anti-tubercular drug varies from 1.7% to 17.6% of all cases of abdominal

Table 2.3 Incidence of drug resistance abdominal tuberculosis

Study	Region	*n*	Mono-resistance	Multi-drug resistance (MDR)	Extreme-Drug resistance (XDR)
Udgirkar et al. 2019 [74]	India	176	3	8	0
Samant et al. 2014 [75]	India	61	5	3	0
Sonambekar et al. 2017 [76]	India	43	4	6	0
Ye et al. 2012 [77]	South Korea	74	13	2	0
Bellam BL 2019 [78]	India	25	NA	1	0

tuberculosis [74–77]. Likewise, the incidence of multi-drug resistant cases is described in 2.7–13.9% (Table 2.3). Hence, in the patients with minimal or absent response to category I, anti-tubercular therapy, mycobacterial culture with sensitivity and/or molecular tests like PCR and line probe assays should be done wherever feasible. The anti-tubercular regime should be modified according to drug sensitivities. In case of negative results of mycobacterial culture or molecular methods, second line (category II) treatment can be initiated if there is strong suspicion for tuberculosis.

2.5 Conclusion

High degree of suspicion should be observed for diagnosis of each and every sort of abdominal tuberculosis cases, in view of vague clinical manifestations and close resemblance with other diseases. In the absence of clear epidemiological knowledge including local pattern of prevalence of abdominal tuberculosis, an ideal algorithmic approach in all cases is lacking. Therefore, reporting of the organs and/or systems affected in extra-pulmonary TB should be mandatory for routine data collection by all national TB programs. Further, all cases with a suspicion of abdominal TB who are on empirical ATT should be followed up closely to reach a final diagnosis. A better understanding of global and regional epidemiology of abdominal TB will not only help in early diagnosis but also enable the policymakers to refine the national TB control programs.

Conflict of Interest None.

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Classification and Case Definitions in Gastrointestinal Tuberculosis

3

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Key Points

1. A proper classification of abdominal tuberculosis is required for a better understanding of the disease and to guide management.
2. Various classifications have been proposed for ATB. There is a lot of overlap and confusion about the classification of ATB in literature.
3. ATB can be classified based on the organ involved as luminal (esophageal, gastric, jejunal, ileal, ileocecal, colonic, or anal), peritoneal, lymph nodal, and visceral (hepatobiliary, pancreatic, splenic).
4. Based on the pathology, intestinal TB has been traditionally classified into three types—ulcerative, hypertrophic, and ulcerohypertrophic.
5. Tuberculosis could also be labeled as primary (if only at the particular site) or secondary (if arising from other sites).
6. On the basis of diagnosis, tuberculosis may be labeled as confirmed, if microbiological positivity or caseating granuloma is present, and clinically diagnosed, if the diagnosis is based on clinical, radiological, histological, and biochemical parameters.

3.1 Introduction

The abdomen is a common site for extrapulmonary tuberculosis (TB). TB can affect most of the organs in the abdominal cavity, either individually or in combination. Abdomen, being a localized compartment, the symptoms of various organ

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involvement can be overlapping. As such, there is a need for a proper classification system for a better understanding of the disease, and to guide management of abdominal TB (ATB). In this chapter, we will focus on the classification of ATB and its importance in guiding management.

3.2 Abdomen and TB

The abdominal cavity contains many vital organs associated with gastrointestinal, hepatobiliary, pancreatic, and genitourinary functions. The abdominal cavity is lined by a serous membrane, called the peritoneum, which covers vital organs of the abdominal cavity. The peritoneum supports the viscera and acts as a conduit for blood supply to and lymphatic drainage from the viscera. The omentum and the mesentery formed by the peritoneum enclose the small bowel. Tubercular bacilli spread from lungs to abdomen, where it remains dormant and can reactivate later. The other routes of spread to the abdomen can be contiguous involvement from adjacent lymph nodes or the primary involvement of intestine [1, 2].

As such, TB can involve any of the abdominal organs, including the peritoneum. It can either involve a single organ or multiple organs, with or without the involvement of the peritoneum. ATB can thus be classified based on the organ involved. **According to organ involvement**, ATB can be gastrointestinal (or luminal), i.e., esophageal, gastric, duodenal, jejunal, ileal, ileocecal, colonic, or anal), peritoneal, lymph nodal or visceral (hepatobiliary, pancreatic, splenic, etc.). Traditionally, genitourinary TB has not been included in the classification of ATB because of its different pathophysiology and management. Esophagus, although an extra-abdominal organ, is usually considered as a part of luminal (gastrointestinal) tuberculosis. Intestine is the most common abdominal organ involved in adults; whereas, in children, peritoneal and lymph nodal involvement is common [3].

3.3 Case Definition of Tuberculosis

Traditionally TB has been defined using the **Paustian's criteria**. This criterion requires at least one of these four features: caseating granuloma on histology, acid-fast bacilli (AFB) positivity in tissue, suggestive operative findings, and consistent histology from mesenteric lymph nodes, and lastly growth of Mycobacterium tuberculosis on animal inoculation or culture [4]. As microbiological and histological evidence has low sensitivity for the diagnosis of TB, diagnosing TB using this criterion could be a daunting task. Logan later modified this criterion and suggested that response to treatment should be added as one of the criteria for the diagnosis (**Logan's criteria**) [5]. Indian extrapulmonary tuberculosis (INDEX-TB) guidelines have come up with a suggestion to classify a case of TB as either "bacteriologically confirmed case" (microbiological tests positive for tuberculosis) or a "clinically diagnosed case" (negative

microbiological cases but the clinical, radiological, and histological evidence are suggestive of tuberculosis with the exclusion of other conditions) **(INDEX-TB criteria)** [6]. A drawback of this definition is that it is not specifically made for ATB, and the presence of caseating granulomas, a pathognomic feature of TB has not been included in the definition of a confirmed case. Hence, one suggested approach from PGI Chandigarh is to establish a diagnosis of "confirmed abdominal tuberculosis" in the presence of conclusive histological (caseating granulomas) or microbiological evidence (positive AFB smear, culture, or polymerase chain reaction); whereas, in cases where the evidence is suggestive (granulomas or chronic inflammation, elevated ascitic adenosine deaminase) the diagnosis of a "clinically diagnosed abdominal tuberculosis" should be made [7].

3.4 Classification of ATB

Since the historic description of gastrointestinal lesions associated with tuberculosis, including ulcerations in intestine and lesions in the liver, spleen, uterus, intestines, and peritoneum, many attempts have been made to understand the perplexity of this complex disease [8, 9]. The classical presentation of intestinal tuberculosis (ITB) was described in 1891 by Hartmann and Pilliet [1]. The broad classification of abdominal TB into **intestinal and peritoneal** can be dated back to 1914, when Dailey et al. presented an etiopathological classification of ATB (Table 3.1). Broadly, they classified ATB into two categories; **lesions beginning within intestinal mucosa and lesions beginning in the serosa** (peritoneal TB). The former category was classified etiologically as primary or secondary; and morphologically as ulcerative, stenotic, and hypertrophic. The peritoneal TB (PTB) was classified as miliary; ulcero-caseous acute, chronic or pseudo-suppurative; fibroid or plastic type, and ascitic type [15].

Meanwhile, there were many other reports of tuberculosis involving other parts of gastrointestinal lumen (esophagus, stomach, appendix, colon, rectum) and viscera of abdomen including liver, spleen etc. (Table 3.1) [11, 12]. Blair et al. tried to classify ATB based on presentation (Table 3.1). They classified ATB as **typical and atypical types**. The typical form included PTB and ITB. The atypical form included fulminant tubercular septicemia and unusual forms of TB like visceral TB (spleen, liver, abdominal lymph nodes, and bile ducts) [12]. Another classification of ATB was proposed by Dutta et al. in 1948, wherein they classified ATB into intestinal, peritoneal, general miliary tuberculosis (acute), tabes mesenterica, and complications of intestinal tuberculosis (stricture of intestine, fecal fistula, hemorrhage and perforation) [13]. Based on clinical presentation ATB was also classified as **acute, chronic or acute on chronic** [10, 14] (Table 3.1). All said, to date, there is no unified system to classify ATB. We summarize the various historical classifications of ATB in Table 3.1. After review of all literature, we propose a practical way of classifying ATB which is outlined in Table 3.2.

Table 3.1 Historical classifications of abdominal TB and its subtypes

Abdominal TB	I. Swain et al., 1904 [10]	II. Dailey et al., 1914 [15]	III. Morley, 1922 [11]
	(A). Acute tuberculous peritonitis resembling intestinal obstruction and appendicitis. (B). Chronic tuberculous peritonitis resembling ovarian cyst or appendicitis. (C). Tuberculosis of Mesenteric glands resembling retro-peritoneal abscess.	(A). Lesions beginning within the Mucosa (a). Based on mode of acquisition. (i). Primary. (ii). Secondary. (b). Pathologic types: (i). Ulcerative. (ii). Stenotic. (iii). Hypertrophic. (B). Lesions beginning in the intestinal serosa (i). Miliary intestinal tuberculosis. (ii). Ulcero-caseous acute, chronic or pseudo-suppurative type. (iii). Fibroid (sometimes known as adhesive)or plastic type. (iv). Ascitic type.	(A). Tuberculosis of the Intestine. (B). Tuberculosis of the appendix. (C). Tuberculosis of the Liver. (D). Tuberculosis of the Mesenteric glands. (E). Peritoneal tuberculosis. (i). Ascitic type. (ii). Plastic type.

	IV. Blair et al., 1947 [12] (A). Typical Abdominal tuberculosis. (i). Abdominal primary complex(milk-borne bovine TB). (ii). TB of peritoneum or abdominal due to dissemination from pulmonary primary complex. (iii). Intestinal tuberculosis due to sputum-borne tuberculous bacilli. (B). Atypical Abdominal tuberculosis (i). Fulminant tuberculous septicemia. (ii). TB restricted to abdominal organs like liver, spleen, abdominal lymph glands, or bile ducts. (iii). TB of abdominal lymphatic system. (iv). Hematogenous spread in liver and/or spleen with cavitation.	V. Dutta et al. 1948 [13] (A). Intestinal tuberculosis. (i). Ulcerative type. (ii). Hypertrophic or hyperplastic type. (B). Tuberculous peritonitis (i). Ascitic type. (ii). Adhesive type. (C). General miliary tuberculosis (acute) (D). Tabes mesenterica (E). Complications of intestinal tuberculosis (ulcerative) (i). Stricture of intestine. (ii). Fecal fistula. (iii). Hemorrhage. (iv). Perforation.	VI. Kapoor et al. 1998 [14] (A). Acute (intestinal obstruction, peritonitis, acute mesenteric lymphadenitis, acute tubercular appendicitis). (B). Acute-on-chronic (C). Chronic
	VII. Sharma et al. 2004 (A). Luminal or intestinal (B). Peritoneal (C). Visceral (involving solid organs like the liver, pancreas, and spleen) (D). Lymph nodal		

(continued)

Table 3.1 continued

Intestinal TB	I. Dailey et al., 1914 [15] (A). Lesions beginning within the Mucosa (a). Based on mode of acquisition (i). Primary (ii). Secondary (b). Pathologic types: (i). Ulcerative (ii). Stenotic. (iii). Hypertrophic. (B). Lesions beginning in the intestinal serosa (i). Miliary intestinal tuberculosis. (ii). Ulcero-caseous acute, chronic or pseudo suppurative type. (iii). Fibroid (sometimes known as adhesive)or plastic type. (iv). Ascitic type.	II. Hoon et al. 1950 [2] 1. Ulcerative. 2. Ulcerohyperplastic. 3. Hyperplastic. III. Paustian et al. 1959 [1] (A). Ulcerative. (B). Hypertrophic/hyperplastic/nodular/schirrous. (C). Ulcerohypertrophic. IV. Tandon et al., 1972 [16] (A). Ulcerative. (B). Ulcerohypertrophic. (C). Healed tuberculosis.	

Gastroduodenal TB	I. Rao et al., 2004 [17] (A). Gastric outlet obstruction. (B). Upper GI bleed. (C). Gastric/periampullary mass.	II. Shah et al., 2020 (DIPS Classification) [18] (A). Diagnostic category. D1: Microbiologically confirmed: Positive by mycobacterial culture, acid-fast bacilli staining, or polymerase chain reaction (Xpert Mtb/Rif) D2: Clinically diagnosed: Based on presence of granulomas or caseation, with exclusion of other differential diagnosis (B). Involvement category. I1: Primary GDTB: When the bulk of disease is in the gastroduodenal part with or without locoregional lymph nodes I2: Secondary GDTB: When GDTB is part of multisystem involvement or due to local invasion by lymph nodes (C). Presentation category. P1: Gastric outlet obstruction P2: Others: Presentations with pain, fever, hematemesis (D). Site of involvement. S1: Gastric: Isolated gastric involvement S2: Duodenal: Isolated duodenal involvement S3: Gastroduodenal: Both gastric and duodenal involvement	
Anal TB	I. Logan et al. 1960 [5] (A). Simple (anal ulcers and perianal abscess). (B). Complex (extensive perianal sinus, horseshoe high-level fistula, supra-levator fistula and rectal stricture and supra-levator abscess discharging into rectum).	I. Findaly et al., 1980 [19] (A). Ulcerative. (B). Verrucous. (C). Lupoid. (D). Miliary. (E). Fissure.	

(continued)

Table 3.1 continued

Peritoneal TB	I. Bhargava et al., 1992 [20] (A). Peritoneal thickening with miliary yellowish-white tubercles with or without adhesions. (B). Peritoneal thickening without tubercles, with or without adhesions. (C). Fibroadhesive pattern with grossly thickened peritoneum and thick adhesions with abdominal viscera.	II. Ahamed et al. PGI Classification 2019 [21] (A). Distension-dominant. (B). Pain-obstruction dominant.	
Hepatobiliary TB	I. Hepatic TB (Alvarez et al., 1998) [22] (A). Miliary form. (B). Granulomatous form. (C). Localized hepatic TB (granulomatous hepatitis, liver abscess/pseudotumor/ tuberculoma and calcified granuloma).	II. Hepatobiliary TB (Amrapurkar et al., 2008) [23] (A). Isolated hepatic. 1. Granulomatous hepatitis. 2. Liver abscess/pseudotumor/ tuberculoma. 3. Calcified granuloma. (B). Isolated biliary 1. Biliary strictures. 2. Gall bladder involvement. 3. Biliary obstruction due to portal lymph nodes. 4. Mixed (Hepatobiliary).	
Other sites	Esophageal TB (Fahmy et al., 1969) [24] (A). Based on mode of acquisition. (i). Primary. (ii). Secondary. (B). Based on naked-eye appearance (i). Ulcerative. (ii). Hypertrophic. (iii). Granular.	Splenic TB [25] 1. Miliary. 2. Nodular. 3. Tuberculous. 4. Splenic abscess. 5. Calcified. 6 Mixed	Colonic TB Nagi et al. 2003 [26] (A). Strictures. (B). Colitis/ulcers. (C). Polypoidal mass.

Table 3.2 Proposed Approach Classification of Abdominal TB

Diagnostic Category	Microbiologically confirmed (Mention the test AFB Stain/Culture/Xpert or any other PCR) Confirmed (Microbiological or Histological- caseating granuloma) Probable/Clinically diagnosed: Mention criteria, e.g., Necrotic LN, Granuloma, Response to therapy
Involvement	Primary or Secondary (Mention pulmonary involvement or other sites, e.g., CNS, disseminated, etc.)
Presentation	Asymptomatic/Pain/Constitutional symptoms only/Abdominal distension
Site	Lumen (Ileocecal, ileal, colonic, esophageal, etc.) Peritoneal Visceral Lymph nodal
Morphology	Luminal: Ulcerative, hypertrophic, Ulcerohypertrophic Peritoneal: Ascitic, Sclerosing encapsulating peritonitis
Complications	Obstruction, bleeding, perforation

3.5 Gastrointestinal TB/Luminal TB

3.5.1 Intestinal TB (ITB)

Intestine is the most common site of involvement by tubercular bacilli in the abdominal cavity. In the intestine, terminal ileum and the ileocecal area are the commonest sites of involvement [1, 16, 27]. Intestines can also be affected secondarily by hematogenous spread from distant tubercular focus, with reactivation occurring later on, or contagious spread (directly or via lymphatics) from adjacent foci of TB [1]. Based on the pathology, intestinal TB has been traditionally classified into three types—ulcerative, hypertrophic, and stenotic (Table 3.1) [1, 2, 14–16].

The **ulcero-caseous lesion** begins as a millet seed-sized focus, i.e., tubercle, and then spread along the course of lymphatics. The ulcers are usually placed transversely along the long axis of the gut. The ulcers may be single or multiple, sometimes with skip areas. Draining mesenteric lymph nodes may be enlarged [15, 16]. Ileum is the commonest site. The lesions usually also involve the ileocecal valve, making it incompetent, and then involving the cecum and ascending colon.

The **hypertrophic variety** is characterized by marked enlargement of cecum and nearby mesenteric lymph nodes, often involving the ileum and ascending colon. This typically forms a tumor-like lesion composed of the ileocecal area, surrounding lymphatics, lymph nodes, and mesenteric fat, which may be palpable as a lump in the right iliac fossa [9, 15, 16]. The lumen of bowel may also be compromised, leading to symptoms of intestinal obstruction [9].

Tubercular ulcers, which are usually transversely placed, may become circumferential as the disease progresses. Cicatricial healing of these circumferential ulcerative lesions results in formation of stricture [11, 16]. Ischemia due to

occlusive arterial changes also contributes to the development of tubercular strictures. This entity has been described in literature as the **stenotic variety** of ITB [11].

Although, classically these three forms exist, in practice there is considerable overlap between these entities. As such, many overlapping types like **ulcero-constrictive** and **ulcerohypertrophic** lesions have been described [1, 2, 16, 28, 29]. Tandon et al. in 1972, classified ITB into two broad categories- ulcerative and ulcerohypertrophic types [16]. They also described another entity called **healed TB**, wherein specific morphological changes were not seen. The mucosa in such cases showed nodules of 2–3 mm size representing hypertrophic payer's patches [16]. Paustian et al. classified ITB into three major categories- ulcerative type, hypertrophic (also called hyperplastic, nodular, and scirrhous) type and ulcerohypertrophic type. The ulcerohypertrophic variety has features of both ulcerative and hypertrophic types and is usually classified under the hypertrophic category [1] (Table 3.1).

Small bowel lesions are generally ulcerative or stenotic, whereas, in colon ulcerohypertrophic lesions can predominate. There is also a clinical correlation of these pathological entities. The ulcerative forms usually present with symptoms of enteritis, malabsorption, and diarrhea, sometimes with blood in stool. With impending perforation, they tend to form localized masses. Whereas, the stenotic and hypertrophic variety usually presented with obstructive symptoms. The ulcerative type of disease is common in undernourished patients, while the hypertrophic type predominates in patients with preserved nutritional status [30]. Also, in the ulcerative type, surgery has a doubtful role; whereas, in the hypertrophic type there is a role of surgery [14].

3.5.2 Colorectal TB

Although ileocecal area is the most common site involved, colonic involvement in absence of ileocecal can also be present. This entity is called segmental or isolated colonic TB and is seen in around 3–10% of cases of ATB [26]. Ascending colon is usually involved in continuity with ileocecal area. Transverse colon, rectum, and sigmoid colon are other sites involved in cases of isolated colorectal TB [26]. Involvement of multiple segments has been reported in 15–50% of cases [26, 31, 32]. Clinically, it may present with pain abdomen, bleeding per rectum. Rectal involvement commonly presents with hematochezia. Based on radiological findings, three types of presentation are seen—strictures, ulcers/colitis, and polypoidal mass [26] (Table 3.1).

3.5.3 Gastroduodenal TB (GDTB)

The gastroduodenal region is rarely involved by TB. Gastroduodenal TB accounts for only 0.5–2.5% of all ATB [27, 33]. Low pH due to gastric acid act as an inhibitory factor for proliferation of tubercular bacilli, resulting in rarity of this entity. Symptoms of GDTB can vary from vague non-specific symptoms like dyspepsia to

symptoms of gastric outlet obstruction. Loss of weight, anorexia, fever, or hematemesis may be present at times. Involvement of other parts of gastrointestinal tract as well as pulmonary involvement is common [17, 18, 33–35].

Based on clinical presentation Rao et al. classified GDTB into three forms- gastric outlet obstruction, upper gastrointestinal bleed, and pseudotumor (periampullary mass, stomach mass) [17] (Table 3.1). Shah et al. have recently proposed a very comprehensive classification of GDTB, the DIPS classification [18] (Table 3.1). Cases are classified on the basis of diagnostic category, involvement category, presentation category, and site of involvement. Although proposed for GDTB, it seems to be a logical classification system for other forms of ATB as well.

3.5.4 Esophageal TB (ETB)

The first report of esophageal TB in literature can be traced way back to 1837 in the post-mortem study by Denonviller. But, it was Schrotter who first diagnosed ETB ante-mortem in 1907 [24]. ETB is rare and accounts for only 0.2% of all cases of ATB [27, 36]. Esophageal tuberculosis can be classified as **primary or secondary** [24] (Table 3.1). In primary ETB the patients have no evidence of TB elsewhere in the body. It is rare because of the esophageal protective mechanisms which include stratified squamous epithelium, peristaltic cleaning, saliva, and rapid transit. Esophagus is usually secondarily involved by swallowed sputum from active pulmonary focus, or by contagious spread from adjacent structures like spine (Pott's spine) lungs (tuberculous cavity) and mediastinum (tuberculous lymph nodes) or from retrograde lymphatic spread [24, 37]. Dysphagia is the most common symptom, and middle third of esophagus is the most commonly affected site. Complications include the formation of fistulae with nearby organs (trachea, bronchus, mediastinum, aorta, etc.) [37].

Endoscopically, ETB is classified into three forms: **ulcerative, hypertrophic, and granular** (Table 3.1). Ulcerative type is the most common. The ulcers are usually shallow with smooth border, a gray purulent base, and an irregularly infiltrated edge. Formation of strictures is common. The hypertrophic type resembles the hypertrophic form of the intestinal TB. The granular type is the rarest of all, presenting as grayish velvety lesions in the esophagus [24].

3.5.5 Anal TB

Anal TB is a very rare form of TB, anal involvement being seen in <1% cases of intestinal TB [38]. Clinically, they present with symptoms of rectal discomfort, burning, itching, and sometimes pain on defecation. Nonhealing ulcers, anal fistula, sinus, perianal swelling are the common presentation [39].

Logan in 1969 classified anorectal TB into **simple and complex types** [5] (Table 3.1). The simple variety includes anal ulcers and perianal abscesses. The involvement in these patients is superficial with minimal undermining, and anal

communication, if present is at a lower level. The complex variety includes extensive perianal sinus, horseshoe high-level fistula, supra-levator fistula, and rectal stricture and supra-levator abscess discharging into rectum. These patients have deep extensions and complex ramifications [5].

J N Findaly in 1980 described five types of anal and perianal TB—**ulcerative, verrucous, lupoid, miliary, and fissure forms** [19] (Table 3.1). The most common type is the ulcerated form which typically presents as a superficial ulceration, having well-defined boundaries with a hemorrhagic necrotic base covered with thick pus. The verrucous type presents as a wart like involving the anal canal and the perianal region. It can also manifest as a haemorrhoidal nodule, perianal abscess, or anal fistula. The lupoid type presents with a small, round reddish nodule which later ulcerates in the center. Miliary lesions occur as a part of disseminated TB [19].

3.6 Peritoneal TB (PTB)

Peritoneal involvement is common in ATB. Peritoneum can be involved either in isolation or along with other abdominal viscera. PTB can occur without intestinal involvement in about one-third of cases [2]. In various studies, peritoneal involvement has been seen in 31–58% of cases of ATB. Concomitant involvement of peritoneum and intestine has been reported in 10–33% of cases [20, 40].

Various classifications of PTB exist in literature. Way back in 1914, Dailey et al. classified it into four varieties: military, ulcero-caseous, fibroid or plastic, and ascitic type [15]. Based on post-mortem studies Morley et al. classified it into two major types: the ascitic type and the plastic type [11]. Based on the laparoscopic appearances, Bhargava et al. classified PTB into three types: peritoneal thickening with miliary yellowish-white tubercles with or without adhesions, peritoneal thickening without tubercles, with or without adhesions, and fibroadhesive pattern with grossly thickened peritoneum and thick adhesions with abdominal viscera [20] (Table 3.1).

However, the most commonly used classification classifies PTB into three types-**the wet ascitic type, dry plastic type, and fibrotic fixed type** (Table 3.1). The wet ascitic type is characterized by the accumulation of ascitic fluid in the peritoneal cavity without any peritoneal or omental thickening. The dry plastic type is characterized by omental thickening and infiltration, caseous masses, and involvement of intestinal wall, but without ascites. The fibrotic fixed type is characterized by a hypervascular peritoneum, omental thickening, matted bowel loops, omental masses, mesenteric involvement, and loculated ascites. The wet ascitic type is the most common type of PTB, found in 70–90% of cases. The dry plastic type is found in 4–22% of cases, and fixed fibrotic type in 10–20% of cases. However, one study showed that the mixed type characterized by ascites along with peritoneal, mesenteric, and omental thickening is the most common type seen in 75% of cases.

As pointed out by Ahamed et al., there is substantial confusion in this classification of PTB as it fails to classify some patterns of peritoneal tuberculosis like abdominal cocoon and there exists substantial overlap in various types [21, 41]. Abdominal cocoon (also known as sclerosing encapsulating peritonitis), an

uncommon type of peritoneal tuberculosis, is characterized by formation of a fibrous membrane encasing a part or whole of the small bowel loops. It frequently presents as abdominal pain and intestinal obstruction. Cocoon is usually diagnosed based on imaging or surgical findings. As cocoon can be caused by other etiology. As such, diagnosis of TB should be established using clinical, radiologic, histologic, biochemical, and microbiologic findings. At times these are inconclusive, and we need to treat it empirically and rely on response to treatment criteria (Logan's criteria) for diagnosis [42].

Ahamed et al. suggested a PGI clinico-radiological classification, which classified PTB into two categories: **distension-dominant and pain-obstruction dominant** (Table 3.1) [21]. The patients with distension-dominant are characterized by slowly progressive development of ascites without significant abdominal pain or features of intestinal obstruction. This group can usually be managed non-surgically. The pain-obstruction dominant category is characterized by abdominal pain interspersed with features of intestinal obstruction. The pathophysiology behind this category could be due to the formation of adhesions between the peritoneum and the bowel loops or adhesive clumping of the bowel loops. This group of patients may require surgical treatment.

3.7 Lymph Nodal TB

Abdominal lymphadenopathy is common in ATB. Lymph nodes are usually involved along with other viscera, but they can also be enlarged in isolation [14]. Mesenteric lymph nodes are most commonly involved. Mesenteric lymph nodal involvement usually presents as lump in the central abdomen. Sometimes lymph nodes at the root of mesentery can cause obstruction at the third part of the duodenum. Omental, peri-portal, celiac, peri-pancreatic nodes are the other common abdominal lymph nodes involved. Portal vein compression leading to portal venous thrombosis and common bile duct compression causing obstructive jaundice have been reported [43, 44]. Tubercular lymph nodes are usually matted and can form conglomerated mass. Caseation necrosis and granulomas are commonly seen [2, 9].

3.8 Visceral Tuberculosis

3.8.1 Hepatobiliary Tuberculosis

It is common for liver to be involved as a part of disseminated TB, but localized hepatobiliary tuberculosis (HBTB) is sparingly seen (<1% cases) [45].

Alvarez classified HBTB into three types- **miliary form, granulomatous form, and localized hepatic TB** (with or without bile duct involvement) [22]. The miliary form is a part of generalized miliary TB and usually has no hepatobiliary symptoms. The granulomatous hepatitis form usually presents with pyrexia of unknown origin with mild jaundice, with or without liver enlargement. On liver biopsy, caseating

granuloma is seen and has a good response to antitubercular therapy. The localized form without bile duct involvement usually presented with solitary or multiple nodules, tuberculoma and tubercular liver abscess [46]. The localized form with bile duct involvement presented with obstructive jaundice, which can be either due to compression of bile duct with enlarged nodes or inflammatory benign biliary stricture as a result of the involvement of bile ductal epithelium by the infection [22].

Another classification proposed by Amrapurkar D et al. classifies HBTB based on the site of involvement as **hepatic, biliary, and mixed** (Table 3.1) [23]. Further localized/isolated hepatic TB was classified in three different forms—granulomatous hepatitis, liver abscess/pseudotumour/tuberculoma, and calcified granuloma. They classified biliary TB into three forms—biliary strictures, gall bladder involvement, and biliary obstruction due to portal lymph nodes [23].

3.8.2 Splenic Tuberculosis

Splenic tuberculosis is rare and restricted largely to immunocompromised populations. Splenic tuberculosis was first described in the literature in 1846 by Coley [47]. Although commonly seen in immunocompromised patients, it has also been reported in immunocompetent patients in some case reports. The differential diagnosis includes malignant lymphoma, metastatic cancer, echinococcal cysts, hemangioma, etc. [25] Winternitz in 1912 classified splenic TB as **primary and secondary types** [48]. However, there exist differences in opinion regarding this, as many researchers believe that all patients of splenic TB are secondary to the previous infection. Spleen is commonly involved as a part of disseminated TB. Occasionally, the contiguous spread of infection is the cause [49]. Morphologically, splenic TB is classified into five types—**miliary, nodular, tuberculous splenic abscess, calcific, and mixed type** [25].

3.9 Conclusion

Abdomen is the common extrapulmonary site for tuberculosis, and diagnosis may at times be difficult. Almost all organs within the abdomen can be involved, and certain entities may require additional therapies other than antitubercular drugs. As such a proper classification of the disease is of paramount importance to understand the disease and guide therapy.

Conflict of Interest The authors have no conflict of interest to declare.

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Part II

Luminal Tuberculosis

Esophageal Tuberculosis

4

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Key Points

1. Esophageal tuberculosis is an uncommon form of tuberculosis that usually results from secondary involvement of esophagus by tuberculosis of the mediastinal lymph nodes.
2. Dysphagia is the most common presentation followed by pain, odynophagia, and hematemesis.
3. Endoscopy with biopsy establishes the diagnosis in the majority of cases.
4. Endoscopic ultrasound-guided tissue acquisition can be used if endoscopic biopsies are negative or in cases with submucosal lesions.
5. Antitubercular treatment has excellent outcomes but occasional patients may need endoscopic or surgical intervention to treat complications like fistula.

4.1 Introduction

Tuberculosis (TB) can involve any organ of the human body however due to its inherent nature of some organs being less affected than others. The gastrointestinal tract is a common site of extra-pulmonary TB (EPTB) however esophagus is affected less frequently [1, 2]. Though esophageal TB (Eso-TB) is uncommon, it is

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an important cause of dysphagia in TB endemic areas. The earliest record of esophageal TB (Eso-TB) available is of post mortem recognition by Denovilliers in 1837 [3]. The first antemortem record of a documented case of Eso-TB was back in 1907 by von Shrotter [4]. Since then, to date, more than 300 cases of Eso-TB have been documented in the literature. The prognosis of Eso-TB has improved remarkably due to early diagnosis with the advent of endoscopy and highly effective treatment with antitubercular (ATT) therapy [3, 5].

4.2 Epidemiology

One of the earliest available autopsy studies found that esophagus was involved in 25 patients out of 16,489 tuberculosis cadavers studied; the overall rate of Eso-TB thus was only 0.15% [3]. Another study by Carr et al. showed only one of 1400 tubercular cadavers (0.07%,) had Eso-TB [6]. Similarly in study from India carried out on 11,746 TB cadavers, esophagus involvement was noted in 0.07% cases and Eso-TB constituted 0.2% of abdominal TB [2]. In a study by Marshall et al., Eso-TB constituted 0.3% of diagnosed abdominal TB cases [1]. A recent study from Korea had 2.15% of Eso-TB cases among all abdominal TB cases [7]. The higher number of cases in recent studies and case series can be attributed to improvised detection techniques along with a rise in EPTB cases [8].

Both genders are affected almost equally in Eso-TB. In 300 cases of Eso-TB reviewed, 145 (48.3%) were males and 155 (51.7%) were females. The Eso-TB has been documented throughout the globe but like PTB, it is more common in areas where TB is prevalent like South-east Asia and Africa. Even in the West, majority of cases are the patients who have migrated from TB endemic areas [9–11].

4.3 Classification of Esophageal Tuberculosis

Esophageal tuberculosis is divided into two types for description, i.e., primary and secondary according to pathophysiology [12]. Primary Eso-TB is defined as involvement of the esophagus without the involvement of any other organ in body. Secondary Eso-TB is the involvement of esophagus secondary to the other organs and most often due to spread from the adjacent mediastinal lymph nodes (MLN). Miliary TB, when involves the esophagus, is also considered secondary Eso-TB. Secondary Eso-TB is more commonly observed type and contributes 88.7% of all Eso-TB cases, while the primary form is uncommon and only 33 such cases have been reported in the literature.

4.4 Pathophysiology and Risk Factors

The pathogenesis of Primary Eso-TB is still not clear and multiple plausible ways of involvement of esophagus have been proposed [3, 13]. Primary esophageal involvement may occur due to direct inoculation by swallowing the infected air droplets or one's own infected sputum from a silent pulmonary focus, as a part of miliary spread when esophagus may be the first and sole organ showing manifestations or as a focus of reactivation after silent bacteremia.

Despite common primary TB infections and chest infections, primary esophageal involvement is quite rare. The resistance of esophagus for primary infection may be related to multiple factors like rapid clearance of ingested food or sputum from the esophagus, tubular structure without any mucosal folds, stratified squamous epithelial lining which may be less permeable, sparse lymphatics, and possible protective effect of saliva and salivary enzymes [3, 14]. For secondary Eso-TB, multiple modes of involvement have been described which include an extension from mediastinal lymph nodes, lungs, vertebrae, aortic tuberculosis, or larynx. Secondary Eso-TB may also be due to ingestion of infected sputum from primary pulmonary TB or hematogenous spread (Table 4.1) [3, 12].

Esophageal involvement from the mediastinal lymph nodes is the most common type of involvement. The stages of tubercular lymphadenitis are proliferative lymphadenitis (Stage I), necrosis and fusion of lymph nodes (LN) to each other (Stage II and III), and cavitation due to caseous necrosis (Stage IV) [15]. Esophagus can be involved directly or from retrograde infection from LN via lymphatics. Sometimes LN ruptures into esophagus forming mediastinal sinus leading to drainage of pus. We suggest modified staging to account for fibrosis and calcification which can be easily detected on endoscopic ultrasound (EUS). Apart from this, extension from pulmonary lesions either as direct extension or due to ingested sputum can infect esophagus. Rare reports describes direct extension of the laryngeal tuberculosis into the proximal esophagus [5, 16]. Spine lies in close proximity to the esophagus and Pott's spine can cause simultaneous esophageal involvement [17–19]. Occasional reports have described the esophageal involvement from tubercular pseudo-aneurysm of aorta [20].

Table 4.1 Modes of esophageal involvement in secondary esophageal Tuberculosis

Mode of Involvement	Number (Out of 260 cases studied)	%
Mediastinal LN	247	95.36%
Cervical LN	1	<1%
Abdominal LN	1	<1%
Laryngeal extension	2	<1%
Miliary TB	3	1.15%
Direct extension from lung	3	1.15%
Potts spine/paraspinal abscess	2	<1%
Aortic pseudo-aneurysm	1	<1%

Reported risk factors for Eso-TB include conditions like immunosuppression, malnutrition, overcrowding, and family history of TB which are also applicable to TB infection elsewhere. HIV infection, post-transplant immunosuppressive therapy, and hemodialysis are also risk factors for Eso-TB as noted in the literature [21–23]. Tuberculosis may also afflict diseased esophagus occasionally in the setting of corrosive injury, esophagitis, and carcinoma esophagus.

Pathologically, on gross inspection, three different types of lesions—ulcerative, granular, hypertrophic have been described in esophagus like tubercular lesions elsewhere in gastrointestinal tract [12, 24, 25]. Ulcerative type is usually associated with solitary ulcers but, sometimes multiple ulcers can be seen. By description, ulcers are variable in size and could be large, deep with an irregular border, grayish base, and may be surrounded by small gray nodules. Granular type is uncommon and is associated with miliary type involvement. It may appear as velvety, grayish translucent tubercles which later may enlarge become yellowish, caseate, and can break down to form a proper ulcer. Hypertrophic form is also uncommon and resembles the hypertrophic variety at other places in gastrointestinal tract like at ileocecal region. Esophageal stricture can develop as a sequelae of hypertrophy which may involve a long segment of the esophagus.

4.5 Clinical Presentation

Tuberculosis is the great masquerader and the Eso-TB is no exception. It could present with a myriad of symptoms depending on the site and morphology of involvement as also any underlying complication. The most common symptom is dysphagia followed by retrosternal pain. Pain sometimes may be felt in the epigastrium and can be perceived as discomfort only. Odynophagia is another common symptom and possibly due to the ulcerative nature of the disease. Hematemesis also is seen in a significant number of patients (Table 4.2). Hematemesis in these patients either indicates spontaneous rupture of bulge with ulcer formation or aorto-esophageal fistula. Bleeding from ulceration is usually small in amount and self-limited, while that from aorto-esophageal fistula is a massive and fulminant type [5, 26]. Those

Table 4.2 Symptoms and their frequency (From pooled data of 300 patients)

Symptom	No of patients (Out of 300 cases studied)	%
Dysphagia	249	83
Odynophagia	50	16.66
Pain-mostly retrosternal	92	30.66
Pain-epigastrium	3	1
Hematemesis	14	4.6
Cough on swallow	14	4.6
Anorexia	39	13
Weight loss	72	24
Fever	50	16.66

patients who have broncho/tracheoesophageal fistula can have cough on swallow which can be more common with liquids. Those with esophagocutaneous fistula, swallowed food can be seen coming through percutaneous sinus tract. Twenty-five percent of patients have constitutional symptoms, weight loss being most common followed by fever and anorexia. Clinical examination can reveal peripheral, especially neck lymphadenopathy and lung lesions in a few patients.

4.6 Differential Diagnosis

1. **Esophageal Carcinoma:** Most common differential diagnosis for Eso-TB is esophageal carcinoma. The endoscopic appearance with histopathology is helpful in differentiating them.
2. **Esophageal Crohn's disease:** Common endoscopic findings include aphthous ulcers, serpiginous ulcers, nodules, pseudo polyps, and skip lesions. Ultimate differentiation may require additional clinical features, other organ involvement and histopathology [27].
3. **Syphilis:** Involvement depends upon stage of syphilis. Generally, punched-out ulcers with regular borders are seen in syphilis. In late stages stricture formation or fistula formations is also common. Overall, syphilis is rare nowadays and serological tests confirm the diagnosis.
4. **Sarcoidosis:** In sarcoidosis, **the** most common site of involvement is the lower esophagus. Involvement is likely due to infiltration of mucosa and submucosa, or muscle layer or enteric nervous plexus, and very rarely due to extrinsic compression by lymph nodes. Ulcer and LN bulge are very rare [28]. Additionally, in presence of LN, endoscopic ultrasound (EUS) can help further along with fine-needle aspiration cytology (FNAC) to differentiate it from TB [29].
5. **Viral ulcers:** Viral esophagitis is a common cause of esophageal ulcers and should be recognizable as the underlying cause on histology.

4.7 Evaluation and Investigations

4.7.1 Endoscopy

The standard investigation in the patient presenting with esophageal symptoms is upper gastrointestinal endoscopy (UGIE). The first endoscopic description of Eso-TB in 1907 by von Shrotter described two types of lesion—ulcerative and hypertrophic [30]. Another description is from 1940 which described a bulge as a manifestation [31]. The UGIE findings in Eso-TB can vary from mucosal bulge, bulge with ulcer to rarely proliferative growth-like appearance [32]. The bulge with summit ulcer (extrinsic impression on endoscopy with ulcer on its top) is the hallmark of Eso-TB (Fig. 4.1). The ulcer in Eso-TB is usually solitary with slight irregular hanging edges and a grayish base. Also, ulcers are usually deep, shape is usually linear /longitudinal, and are eccentric but rarely may occupy the entire

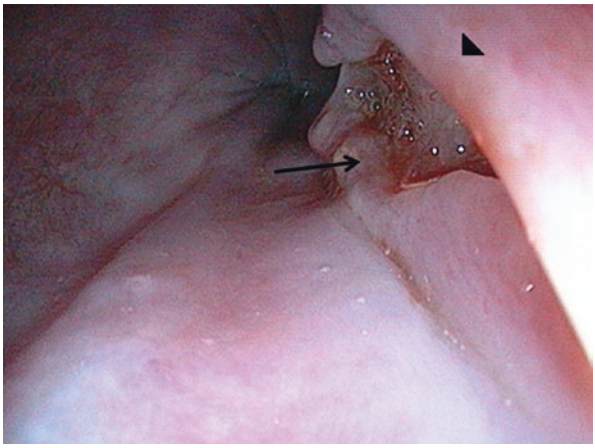

Fig. 4.1 Endoscopic picture showing with bulge (arrowhead) with overlying ulcer (arrow) in mid-esophagus [26]

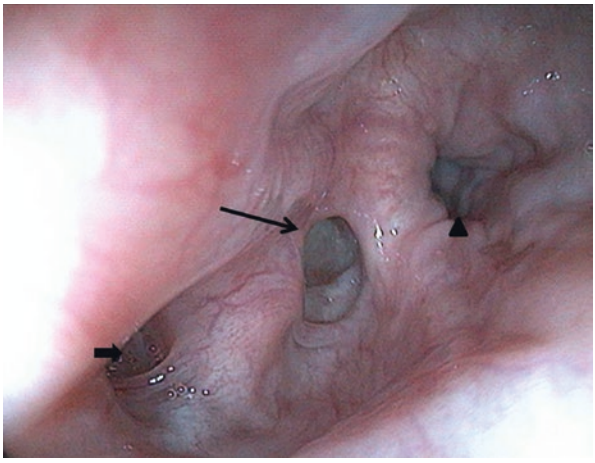

Fig. 4.2 Esophagopulmonary fistula (long arrow—fistula, arrowhead—Esophageal opening, short arrow—diverticulum') [26]

circumference. Occasionally, Eso-TB ulcers are multiple and superficial. The pus discharge may be visible at the center of ulcer in a few cases. In UGIE fistula is usually seen as opening either in ulcer or as a separate opening with smooth margins (Fig. 4.2). The presence of blood clot over the large deep ulcer is alarming as it may indicate aorto-esophageal fistula. The diverticula can occur after healing of active Eso-TB. The stricture as sole finding also has been described. An analysis of 244 cases showed ulcer as the most common finding (29%) followed by bulge with ulcer (22%) and bulge only (19%). More than one descriptive lesion was found in 6% of patients.

Table 4.3 Classification of endoscopic lesions in esophageal tuberculosis

Type of Endoscopic lesion	Endoscopic appearance	Underlying Pathophysiology	Mimic	Incidence (244 patients)
Type I	Smooth extrinsic impression/bulge in lumen. Subtle redness and few nodules occasionally can be seen	Mostly secondary ETB causing extrinsic pressure effect. Rare variety of primary presenting as esophageal mesenchymal tumor.	Esophageal submucosal tumor	50 (19.37%)
Type II	Bulge with summit ulcer: Extrinsic impression with ulcer at top of it. Sometimes pus exuding from it can be seen.	Rupture of mucosa and may be of underlying LN. Pus may discharge from caseating LN	Malignancy	59 (22.86%)
Type III	Linear/longitudinally oriented ulcer Usually deep Shaggy/irregular edges Hanging/rolled down edges Grayish base Usually occupy 1/4 to 1/3 of circumference	Pressure relieved by rupture; pus may be drained out. Ulcer is in fully developed stage.	Malignancy/ infective ulcer	75 (29.06%)
Type IV Rare can present alone but mostly accompany first three types	a. Fistula	Mediastinal or bronchial communication		17 (6.5%)
	b. Diverticulum	Indicate healed lesion		5 (1.9%)
	c. Polyp			4 (1.5%)
	d. Stricture			9 (3.5%)
	e. Mass or ulcero-proliferative growth or polypoidal growth	Mostly indicate hypertrophic variety		6 (2.3%)
	f. Nodularity			3 (1.1%)

The most common part of esophagus involved is the mid-esophagus. In 255 reviewed patients of Eso-TB, mid-esophagus was involved in 80% of cases followed by lower esophagus in 10% and upper esophagus was involved only in 5.5% of patients with rest having multiple sites of involvement. We propose a classification for endoscopic appearance of esophageal TB secondary to MLN (Table 4.3).

Enhanced Imaging Role of narrow-band imaging (NBI) during endoscopy has been described in one case with a small tubercle-like structure detected on intact mucosa. Intrapapillary capillary loops were partly preserved but extended by the

granule while the arborescent vessels that run deeper part of mucosa were obscured by the presence of the granule. Further characterization in future might help to better target biopsies to increase the yield [33].

Endoscopic Biopsy The reported yield of endoscopic biopsy is variable possibly due to differences in the nature of the underlying lesion, variable techniques used, and number of biopsies obtained. One study describes that a single session of biopsy yield was only 50%, which was enhanced to 100% by repeated biopsies with requirement of up to 3 sessions [34]. One study also described the role of endoscopic cytology with yield more than biopsy [35]. This series predominantly constitute primary Eso-TB and also, in our experience base of ulcer can give good yield considering bacterial nature of disease with dominant activity at the center. So, to maximize yield biopsy should be obtained both from the base of ulcer and edges. An old series also depicted the use of FNAC under endoscopic vision with good yield but with the availability of endosonography (EUS), it appears to be obsolete. The endoscopic biopsies in 124 patients on histopathology showed 74% biopsies had some findings (caseating granuloma in 41.12%, non-caseating granulomas in 33%) which helped in diagnosing Eso-TB. On subset analysis of 59 patients, if additional bacteriological studies are applied to biopsies like Polymerase Chain Reaction (PCR), AFB stain and TB culture yield can go up to 96%. So, it is recommended to do a biopsy in all patients in which some mucosal abnormality is detected. As per our opinion, one should do a biopsy both from edges and base with minimum of 4–6 biopsies [19]. Also, AFB staining in histopathological examination (HPE) should be done along with bacteriological investigations like PCR/culture if available to maximize yield as it complements HPE.

4.7.2 Endoscopic Ultrasound (EUS)

Endoscopic ultrasound is a boon for mediastinal pathologies and so for esophageal TB diagnosis. Safety and efficacy of EUS for mediastinal LN evaluation and tissue acquisition are well established [29]. Primary Eso-TB can manifest as esophageal thickening or pure submucosal lesion mimicking gastrointestinal stromal tumor/Leiomyoma/neuroendocrine tumor [36–38]. One case report describes diffuse thickening of esophagus with loss of wall layer mimicking carcinoma. Eso-TB may also involve vessels with loss of fat plane further adding confusion. Henceforth, FNAC or fine-needle aspiration biopsy (FNAB) is an important tool and tissue sampling can resolve the dilemma. This also can avoid unnecessary surgery. EUS may also show a pure intramural lesion arising from second/third/fourth layer and is generally hypoechoic, heterogenous with or without hyperechoic strands [39]. There is no characteristic visual finding on EUS and given the rarity of disease, it is important to perform EUS guided FNAC/FNAB to avoid unnecessary surgery [40, 41]. EUS is of special importance in submucosal lesions (endoscopy shows bulge only) and becomes investigation of choice for evaluation.

It is the mediastinal LN tuberculosis that manifests as secondary esophageal involvement mostly. By far, subcarinal, right tracheobronchial and left hilar groups are commonly involved [42–44]. Radial EUS can describe lymph nodal enlargement and esophageal wall involvement but tissue cannot be obtained with it; that is why it is the linear EUS that is used for evaluation and sampling [45, 46]. Three good-quality series have demonstrated and established the role of EUS with FNAC/FNAB in ETB [47–49]. Various visual features have also been described for the same. We have modified and categorized them according to stages of LN involvement and given in Table 4.4 [15, 50]. Most common finding is mediastinal LN with encroaching esophageal wall layer (Fig. 4.3). Disruption of adventitia with thickening of wall leading to disruption of wall layer structure is usually seen [15, 49]. Overall, EUS has an excellent correlation with LN stages of TB. Esophageal wall disruption was seen in almost 43–50% of cases [47, 48]. Calcification is rarely seen but hyperechoic strands and foci (spots and straps) are common and highly suggestive of tuberculosis [47]. We suggest a description system devised by Fujiwara et al. for future descriptions of LN to provide uniform reporting [51]. Diagnostic yield of

Table 4.4 Classification categories of EUS Findings of mediastinal LN in TB with esophageal involvement

Category	EUS Description				Classification correlate [50] (Jones and Campbell)	Pathology correlate [15] (Liu FG)
	Lymph Node		Border	Esophageal wall		
Type I	Hypoechoic	Homogenous	Distinct	May compress but adventitia intact	Stage I. firm discrete	Stage I. lymphocyte infiltration and capillary proliferation
Type II	Hypoechoic	Heterogenous	Fused with each other, matted, Indistinct	Adventitia breached Five-layer structure may be lost Incrassated wall	Stage II. Rubbery fixed to surrounding tissue	Stage II/ III. LN with necrosis ongoing with membrane disruption
Type III	Hypoechoic	Anechoic areas within	Fused with each other, matted, Indistinct	Adventitia breached, Five-layer structure may be lost, Incrassated wall	Stage III. Abscess	Stage IV. Necrosis abscess formation
Type IV	Hypoechoic	Hyperechoic strands and foci (spots and straps) with or without shadowing	Peripheral calcification may be present	Adventitia breached, Five-layer structure may be lost, Incrassated wall	–	Fibrosis and calcification

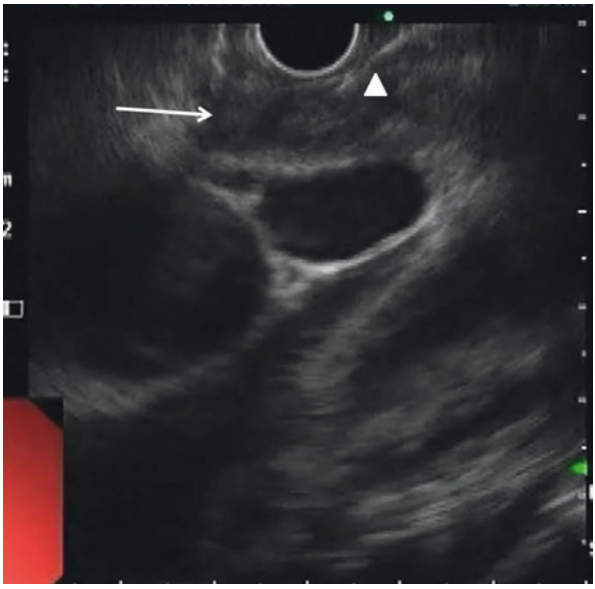

Fig. 4.3 Endoscopic ultrasound showing subcarinal lymph node (arrow—lymph node, arrowhead—FNAC needle) [26]

EUS FNAC is 72–100%. The study reported 72% yield had used sclerotherapy needle in one-third cases which might have resulted in the lower yield. One study which has used FNAB has shown a yield of 94.3%. The average yield in EUS FNAC/FNAB in 81 patients studied was 88%.

Secondary Eso-TB must always be distinguished from esophageal cancer and submucosal tumors. Esophageal cancer originates from the first (mucosal) layer and the findings include disruption of mucosal layer integrity, homogeneous or heterogeneous hypoechoic lesions are noted without hyperechoic spots and strands and no thickening of the esophageal adventitia. The metastatic lymph nodes generally do not adhere to or fuse with the esophageal adventitia which is common in TB. Esophageal mesenchymal tumors originate from the esophageal muscular layer. These benign tumors show a smooth and glossy surface of the mucosal membrane at endoscopy and a mucosal bridge and blood capillary network are frequently seen. At EUS, homogeneous hypoechoic lesions of fusiform or almost round shape are detected; the borders are clear, and the esophageal adventitia is intact, without thickening; and no swelling can be detected in the mediastinal lymph nodes. Rare submucosal tumors of the esophagus, such as neuro-fibrosarcoma and leiomyosarcoma are difficult to distinguish from Eso-TB especially of primary variety [15]. Therefore, EUS guided tissue acquisition plays an important role in establishing a definitive diagnosis of Eso-TB [36, 39, 47–49]. Another differential diagnosis is sarcoidosis in which LN is usually larger, uniform size, homogenous hypoechoic with slight vascularity. Classical hyperechoic strands and foci of TB are absent. Also, sarcoid LN rarely invades esophageal wall [29].

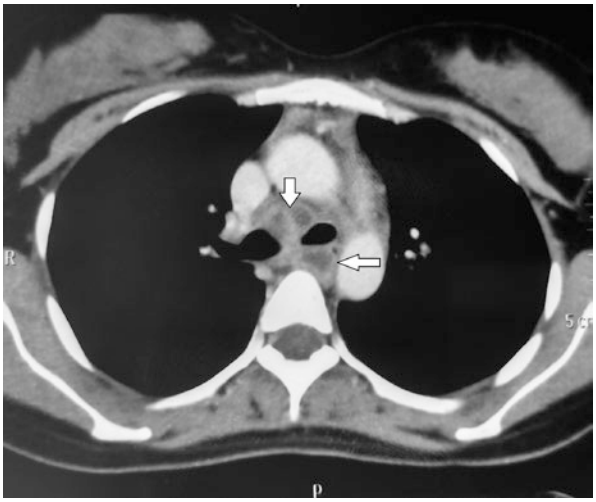

Fig. 4.4 Computed tomography scan showing subcarinal lymph node mostly necrotic compressing esophagus to the extent it cannot be identified separately (down arrow—subcarinal lymph node, right arrow—lymph node compressing esophagus)

4.7.3 Routine Investigations

Routine blood investigations can reveal elevated ESR. Chest roentgenogram can reveal abnormality in 44% (46 out of 104) patients like wide mediastinum, parenchymal abnormalities and should be routinely done. Mantoux test (Tuberculin skin sensitivity) though not diagnostic can be positive in 72% of patients (44 out of 61) [11, 26, 52, 53]. Computed tomography (CT) of chest and abdomen is important to rule out secondary nature of TB and simultaneous involvement of other organs. CT findings can be enhanced with oral contrast addition especially in presence of fistulous complications. CT may demonstrate mediastinal lymphadenopathy, lung parenchymal abnormality, and esophageal thickening (Fig. 4.4). Additionally, complications like mediastino-esophageal fistula/tracheoesophageal fistula/aorto-esophageal fistula can be easily delineated as mentioned above.

Barium swallow, rarely used nowadays, may show extrinsic compression/bulge/mucosal irregularity correlating to endoscopic findings (Fig. 4.5) [54]. Also, fistulas can be very well delineated by barium swallow along with stricture.

4.7.4 Diagnosis

The case of Eso-TB can be defined as a confirmed (microbiologically positive) case if bacteriological proof [Acid Fast Bacilli (AFB) in tissue, positive culture or PCR for Mycobacterium TB (MTB)] is present. In absence of

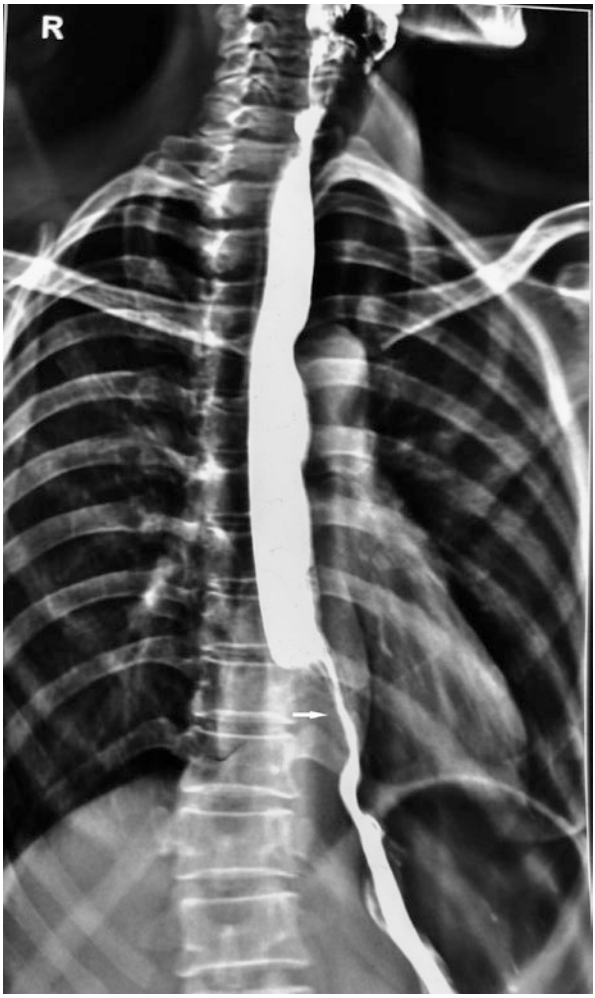

Fig. 4.5 Barium swallow depicting extrinsic compression in lower esophagus (arrow) with mucosal irregularities in lower part (arrowhead)

microbiological positivity but in presence of caseating granulomas or non-caseating granulomas on histopathology the cases are labeled as probable (or clinically diagnosed) cases which must be followed up closely to demonstrate a response to ATT. The easiest and most commonly used techniques for obtaining tissue are endoscopy and endoscopic ultrasound. Alternatively, bronchoscopy, CT guided FNAC of mediastinal LN or vertebral column lesion can be done as per clinical presentation.

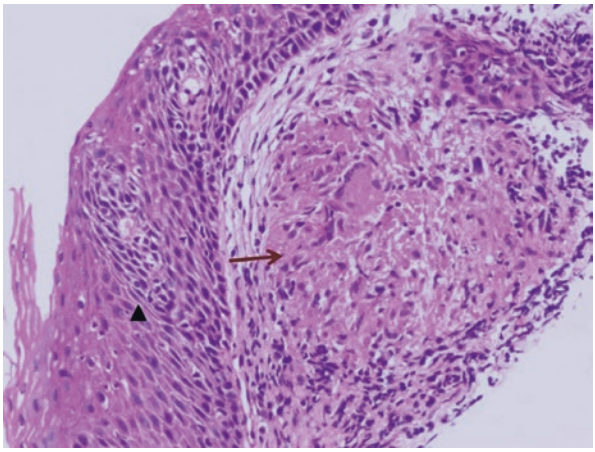

Fig. 4.6 H& E stain at 20× magnification showing stratified squamous epithelium with caseating well-defined epitheloid granuloma [26]

4.7.5 Pathological and Microbiology

Overall histopathology yield (from endoscopic biopsies/autopsy/surgical specimens) is high and is around 83% (142 out of 171 patients, caseating granuloma—86, non-caseating—56) (Fig. 4.6). Overall, tissue AFB positivity rate is 46% (analyzed in 71 patients of whom 35 were positive). Tissue culture for mycobacterium tuberculosis is proven method with excellent results but sparingly used in practice due to availability and delayed results and also lack of suspicion of underlying TB on initial endoscopy. Limited data of 14 patients show high positivity rate of 92% [55]. There are few reports which used PCR for *Mycobacterium tuberculosis* as an additional modality. Overall, PCR test positivity rate is 64% (data available for 17 patients, 11 are positive) [18, 37, 45, 46, 56–66]. Recently, nested PCR with automatic amplification which is a cartridge-based technique called as Gene Xpert has been increasingly used for tuberculosis. To date only five cases are available which used this technique with excellent results with 80% sensitivity [26, 67].

4.8 Complications

Eso-TB can result in complications if not diagnosed and treated timely. Overall, complications were seen in 17% of Eso-TB patients (53/300). The complications are as described below:

1. *Mediastinoesophageal fistula*: Mediastinal LN turns into abscess and then ruptures into esophagus. This is the most common complication occurring in 6% of patients. CT can show air in mediastinum with or without air fluid level. No specific treatment is generally required [5, 26, 68–70].

2. *Tracheoesophageal fistula (TEF)*: Mediastinal LN erodes into trachea/bronchus on one side and esophagus on another, thus leading to fistula formation. Most common involved area is right main bronchus but left-sided involvement is well documented [9, 71, 72]. Earlier, it was thought to be only can be treated with surgery as shown in a review of 26 cases, 22 of which required surgery [73]. In our review of 300 cases, 12 (4%) had TEF. Most TEF patients were treated with ATT and improved [9, 26, 54, 74–77]. Surgery and endoscopic interventions are helpful in cases for whom ATT fails.
3. *Aorto-esophageal fistula*: In presence of TB aorta can be involved in four ways by either erosion of esophageal (or mediastinal lymph node) into the aorta or vice versa. [78–80]
4. *Pleuroesophageal fistula:* Fistula can be formed between esophagus and pleura if LN rupture into pleura on one side and esophagus on the other. Similarly, primary pleural involvement with secondary esophageal involvement can also lead to pleuroesophageal fistula formation [81].
5. *Esophagoesophageal fistula*: Esophageal involvement can lead to tunneling with rupture at two different points leading to esophagoesophageal fistula [70].
6. *Stricture*: Esophageal stricture is relatively uncommon in esophageal tuberculosis. Eccentric rather than concentric involvement, secondary nature of involvement, and rapid healing on treatment may contribute to less amount of periesophageal fibrosis and hence low stricture rate in Eso-TB. Nonetheless, if it formed dilatation with ATT or surgical reconstruction can be tried if not resolved with ATT [12].
7. *Perforation:* Esophagus can perforate as a result of Eso-TB leading to catastrophe events. It can rupture either into the mediastinum or into the abdomen [24].
8. *Esophagocutaneous fistula*: This is an extremely rare complication and only two cases have been reported. The classical feature in this is swallowed food comes out through cutaneous opening. In both documented cases, the fistula healed with ATT [82–84].

4.9 Treatment

Treatment of tuberculosis has evolved from the nineteenth century approach of observation and sanatorium approach to multidrug therapy as of now [25, 85, 86]. Most of the cases treated surgically are either undiagnosed initially or have complications that mandate surgery. ATT is the standard of care with a cure rate of almost 100%. Multidrug-resistant tubercular cases are being reported lately in Eso-TB as well but can be treated with available treatment options. Symptoms improve rapidly with ATT at around 1–6 weeks. Alternate provision for enteral feed like feeding jejunostomy/gastrotomy may be occasionally needed in patients who are already malnourished and/or have a fistulous complication which may preclude oral feeding [77].

4.9.1 Specific Treatment

Presently, only a few cases might require specialized surgical/endoscopic care as per underlying complications. Aorto-esophageal fistula requires urgent surgical intervention and if not treated could be fatal. The endoscopic dilatations might be required for strictures not improving on ATT. In selective cases, surgery is required for stricture and gastric pull up/ colonic interposition has been used [78, 87, 88]. In non-healing symptomatic fistulas, endoscopic management with over the scope clip (OTSC)/self-expanding metallic stent (SEMS) can also be tried prior to surgery [72].

4.9.2 Outcomes

The cure rate of ATT in the latest series has been 100% [5, 26, 48, 89]. Of 300 reviewed patients of Eso-TB, 276 received some sort of treatment. Rest either refused or were lost to follow up or died [70, 90]. Of these 15 received some surgical treatment [81, 91]. Overall, in 286 patients in whom follow-up is available, 265 were cured with a cure rate of 92.60%, 21 died with a mortality rate of 7.40%.

Eso-TB is an uncommon but not a rare entity. With advances in diagnostic modalities (especially cross-sectional imaging, endoscopy, and endoscopic ultrasound) and effective chemotherapy (ATT), the outcome in patients with Eso-TB is usually good.

Conflict of Interest None

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Gastroduodenal Tuberculosis

5

Parmeshwar Ramesh Junare and Pravin Rathi

Abbreviations

AFB	Acid-fast bacilli
CBD	Common bile duct
CT	Computed tomography
EUS	Endoscopic ultrasound
EMR	Endoscopic mucosal resection
GDTB	Gastroduodenal tuberculosis
GI	Gastrointestinal
GIST	Gastrointestinal stromal tumor
HIV	Human immune deficiency virus
MDR	Multi-drug resistance
NAAT	Nucleic Acid Amplification Test
PUD	Peptic ulcer disease
QFT-G	Quantiferon- TB Gold
TB	Tuberculosis
USG	Ultrasonography

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Key Points

- Gastroduodenal tuberculosis is an uncommon form of abdominal tuberculosis.
- Clinical presentations are non-specific and misdiagnosis is not uncommon even in tuberculosis endemic regions, requiring a high index of suspicion.
- It is desirable to look for evidence of tuberculosis elsewhere in the body.
- Combination of radiologic imaging, endoscopy, histology, and microbial studies (acid-fast bacilli staining/microbial culture/PCR-based tests) are required for definitive diagnosis and evaluation of disease extent.
- Antitubercular drugs with or without endoscopic balloon dilation are the mainstay of therapies in management.
- Role of surgery has declined in the modern era; however, it may be required in a minority of patients.

5.1 Introduction

Evidence for gastric involvement by tuberculosis dates back to 1824 when Barkhausen described the first case report of possible gastric tuberculosis well before the discovery of tubercle bacilli by Koch in 1882 [1]. Ileocecal region is most commonly affected site in gastrointestinal (GI) tract [2]. Tubercular involvement of gastroduodenal region, i.e., Gastroduodenal tuberculosis (GDTB), is infrequently seen [3]. Presentation of GDTB is variable and there are no specific clinical, radiologic, or endoscopic features. Misdiagnosis/delay in diagnosis of GDTB may occur requiring a high index of suspicion. Multiple diagnostic modalities are often required for evaluation. Antitubercular therapy remains a mainstay in treatment. Endoscopic and surgical management may be needed in selected cases.

5.2 Incidence

Abdominal TB constitutes 1–3% cases of all cases of TB and 11% cases of extrapulmonary tuberculosis [4]. An autopsy study conducted at K.E.M. Hospital, Mumbai found incidence of 3.72% for abdominal tuberculosis [5]. Rathi et al. noted 16.6% HIV seroprevalence among the abdominal tuberculosis patients, which was significantly higher compared to pulmonary tuberculosis [6]. Involvement of stomach and duodenum is rare in abdominal tuberculosis. An autopsy series have reported an incidence around 0.5% and in about 60–70% of patients with gastroduodenal involvement, there is evidence of TB elsewhere [7, 8].

5.3 Aetiopathogenesis

Isolated gastroduodenal tuberculosis is rare. Four possible routes of infection include direct inoculation in gastroduodenal area via oral route, swallowed sputum, hematogenous route, and spread from contiguous organ source [1]. Most patients have primary pulmonary tuberculosis or tuberculosis elsewhere in the body. Rarity of primary GDTB is due to gastric acidity, fewer lymphoid follicles in stomach, gastroduodenal motor activity, and intactness of mucosa [9, 10]. Breach in these defense mechanisms may predispose to GDTB. Predisposing factors could include long-term acid suppression by H2-Blocker and/or proton pump inhibitor therapy and various immune-compromised states including HIV as seen in endemic areas [11–13].

5.4 Pathology

Various pathologic types of GDTB have been described in literature similar to tuberculosis elsewhere in the GI tract. These include ulcerative, hypertrophic, ulcero-hypertrophic lesions, and tubercles/tuberculomas [14, 15]. Among all these, ulcerative lesions are most common in various studies. Antrum is the most frequently involved part of the stomach while in duodenum, third part is most commonly affected [9]. In duodenal area, the majority of cases are due to extrinsic compression by enlarged periduodenal lymph nodes rather than intrinsic lesions [16–18]. Extension of the primary lesion may result in sinus tract formation, gastrocolonic, choledocho-duodenal, duodeno-pancreatic, hepato-gastric fistulae, perforation of gastroduodenal area, and compression of common bile duct resulting in obstructive jaundice [13, 19–26].

5.5 Clinical Features

Clinical features are variable and non-specific. Delay in diagnosis can occur because the diagnosis is often not considered even in the endemic regions. In recent systemic review, common clinical features of GDTB include recurrent vomiting (64.4%), evidence of gastric outlet obstruction (47.1%), abdominal pain (43.5%), loss of appetite (32.4%), loss of weight (24.0%), fever (16.4%), abdominal lump (7.6%), and features mimicking malignancy in 5.3% cases [27]. Some cases may present with superior mesenteric artery syndrome. Case reports of massive gastrointestinal bleed secondary to gastroduodenal lesions, obstructive jaundice due to common bile duct compression and cholangitis have been described [13, 28]. Patients may have evidence of past or active tuberculosis elsewhere in the body including pulmonary tuberculosis and tuberculosis in other parts of the GI tract [29]. Physical

examination may reveal peripheral lymphadenopathy and signs of malnutrition and nutritional deficiencies. On per abdominal examination, abdominal lump may be palpable and usually represents associated lymphadenopathy. Also, clinical features of gastric outlet obstruction like succussion splash may be demonstrated.

5.6 Diagnostic Work-Up

1. *Ancillary tests:* Erythrocyte segmentation rate is usually elevated. Mantoux positivity is common in endemic countries like India pointing to past or present infection. Chest X-ray may reveal findings of past or present infection when concomitant pulmonary lesion is present. In cases of active pulmonary lesions sputum examination with acid-fast staining for tubercle bacilli provides important microbiologic evidence for making a positive diagnosis when suspicion for GDTB is high. Fine-needle aspiration examination of tubercular lymphadenitis can provide similar evidence [30]. Quantiferon- TB Gold (QFT-G) is FDA approved blood test for diagnosis of latent which is based on the release of interferon-gamma in response to M. tuberculosis antigens. Latest WHO guidelines do not support the use of QFT-G in the setting of active TB [31].
2. *Endoscopy:* As patients with isolated GDTB present with various gastrointestinal symptoms, upper GI endoscopy is often ordered during the initial evaluation. Various endoscopic findings include stricturous narrowing of antro-pyloric and or gastroduodenal regions (70.4%), ulceration mimicking peptic ulcer disease (9.9%), or ulcero-proliferative mass (8%) masquerading malignancy [27]. Extrinsic compression by enlarged periduodenal lymph nodes with smooth overlying mucosa is common in duodenal area. Fistulous opening may be noted in gastric and duodenal areas with gastro-colonic, choledocho-duodenal and pancreatico-duodenal fistula formation. All suspected lesions need to be biopsied and sent for histopathologic and microbiologic evaluation. Sometimes, only submucosal lesion is seen in which cases bite and bite (well) biopsy technique and endoscopic ultrasound-guided sampling are useful for obtaining representative tissues. Recently, endoscopic mucosal resection has been described for obtaining greater quantum of tissue. Recent endoscopic modalities have the potential to avoid surgery for sole diagnostic purpose [32, 33]. When lesions in suspected in lower GI tract, colonoscopy is performed for evaluating disease extent.
3. *Radiology:* Radiology is useful for determining extent of disease and any extraluminal findings. Common findings on barium study are deformed pyloric region of stomach, duodenal strictures, mucosal lesions like ulcers, polyps, mass lesions in stomach, extrinsic compressions by enlarged periduodenal lymph nodes, and various fistulae as mentioned previously [13, 27, 29].

   Ultrasonography (USG) of the abdomen is useful for the demonstration of dilation of intrahepatic biliary radicles when common bile duct compression is

present. Enlarged lymph nodes may be seen on USG abdomen at periduodenal area, porta hepatitis as well as bulky enlarged pancreas and/or retroperitoneal mass. Free or loculated intra-abdominal fluid collection and interloop ascites may be seen on ultrasonographic imaging [13, 34]. Ultrasound may also be used to target the lymph nodes for sampling of tissue.

Computed tomography (CT) abdomen is the most helpful imaging modality to assess disease extent and demonstrates both intraluminal as well as extraluminal lesions. Common CT findings in GDTB are asymmetrical mucosal thickening, polyps, and mass lesions involving stomach and duodenum as well as deformed antro-pyloric region [13, 27, 29]. Enlarged multiple conglomerated peri-gastric, retroperitoneal, and porta hepatis lymph nodes are commonly seen. Other findings may include fistulous communication with proximal transverse colon, jejunum, pancreas, and common bile duct along with clumping of bowel loops. CT thorax is useful for demonstration active and old tuberculous pulmonary lesions which provides important supportive evidence in making a positive diagnosis.

4. *Histopathology:* Histopathologic examination of endoscopic biopsy specimen may show granulomatous inflammation with or without caseation while acid-fast bacilli are rarely recovered from endoscopic biopsy specimens. In a review of 27 patients with GDTB, granulomatous inflammation was observed in only 7 cases while 20 cases showed non-specific duodenitis [35]. This is because of submucosal location of lesions and paucibacillary nature of GDTB. In these difficult-to-diagnose cases with strong suspicion of GDTB, recent endoscopic modalities are very useful. Studies have demonstrated granulomatous inflammation in 90–100% cases using multiple endoscopic biopsies and endoscopic mucosal resection [32, 35, 36]. Typical tuberculous granulomas contain predominantly epithelioid macrophages, Langhans giant cells, and lymphocytes with characteristic cheese-like material in the center suggestive of caseation necrosis [37].
5. *Gene X-pert/MTB RIF and mycobacterial culture:*

Gene X-pert (GXP)/MTB RIF is polymerase chain reaction (PCR) based Nucleic Acid Amplification Test (NAAT) which amplifies M. tuberculosis DNA from biopsy specimen as well as simultaneously detect rifampicin resistance. This is of particular utility for making an early diagnosis of GDTB given the paucibacillary nature where organisms present in small amounts. The use of GXP/MTB RIF has been advocated by WHO for the diagnosis of extrapulmonary tuberculosis also [38–40]. Recent reports have shown the usefulness of Gene X-pert/MTB in the diagnosis of GDTB although systematic studies are still lacking. Mycobacterial culture has infrequently been reported to be positive in GDTB but it can provide Drug Sensitivity Testing (DST) and thereby help in the diagnosis of Multi-drug Resistance (MDR)-TB [41] (Figs. 5.1, 5.2 and 5.3).

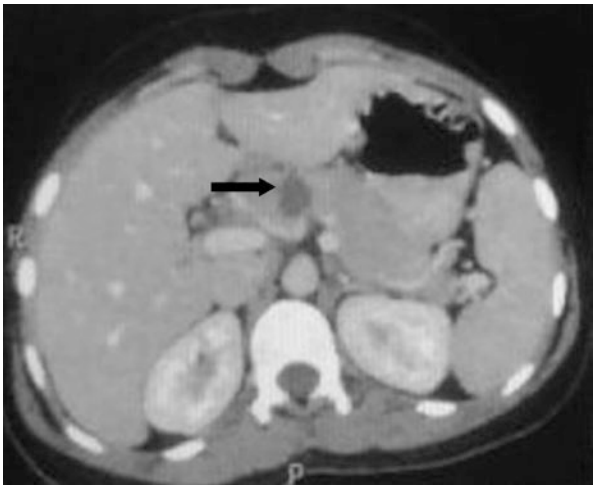

Fig. 5.1 Showing antro-pyloric region thickening along with large conglomerated lymph nodal mass at porta hepatis

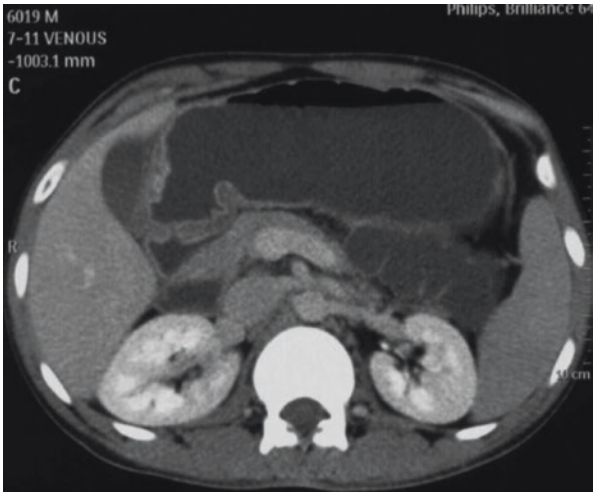

Fig. 5.2 Showing thickening of D1 and D2 junction

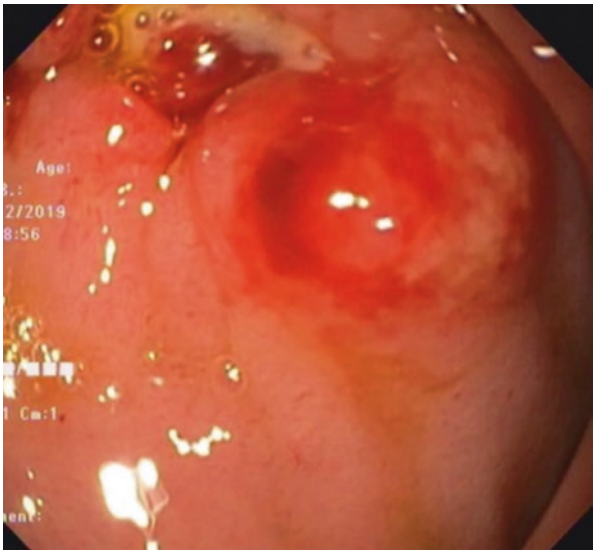

Fig. 5.3 Upper Gastrointestinal Endoscopic image showing ulcero-nodular lesion in second part of the duodenum along with pus discharge suggestive of fistulous communication

5.7 Differential Diagnosis

1. *Peptic Ulcer Disease (PUD):* Clinical, endoscopic, and radiologic features of PUD disease resemble GDTB. Because of rarity of isolated GDTB, it is often initially misdiagnosed as peptic ulcer disease. Histology is useful for making a positive diagnosis of Helicobacter Pylori-related PUD and as the response to anti-Helicobacter Pylori therapy. However refractory PUD disease may possess a particular diagnostic challenge when GDTB is not considered and maybe mistreated, thereby delaying effective treatment.
2. *Crohn's Disease:* Involvement of Gastroduodenal region in Crohn's disease is uncommon and usually associated with concomitant involvement of small intestines and/or colon. Although rarely isolated gastroduodenal Crohn's disease may occur, diagnosis should be done with caution and close follow-up is indicated for subsequent development of Crohn's disease elsewhere in the GI tract or other granulomatous diseases such as TB or sarcoidosis. Symptoms are non-specific such as epigastric pain, nausea, vomiting, loss of appetite, and weight loss [42–45]. Endoscopic findings include reddened mucosa, irregularly shaped serpiginous ulcers, nodular lesions with erosions on top of the lesions, and cobblestone pattern. Antrum and pre-pyloric region are the most commonly affected parts in stomach [46, 47]. Histology shows granulomatous gastritis and or focally advanced gastritis. Granulomas may be seen in endoscopically normal mucosa. Granulomas in cases of Crohn's disease are non-caseating and negative for acid-fast bacilli [48, 49]. Other features differentiating from Crohn's disease and

intestinal tuberculosis can be read elsewhere in this book. In difficult-to-diagnose cases, long-term follow-up with clinical and endoscopic response to antitubercular therapy has been suggested.

3. *Sarcoidosis:* Isolated gastroduodenal sarcoidosis is uncommon and rarely encountered in our country. Gastroduodenal involvement usually occurs as part of disseminated sarcoidosis. Antrum is most common part affected in GI tract. Epigastric pain, nausea, vomiting, and weight loss are common presenting symptoms. Massive GI bleed and gastric outlet obstruction may occur. Radiologically gastric sarcoidosis may mimic diffuse form of gastric carcinoma (linitis plastica) [50, 51]. Pulmonary involvement and presence of granuloma in GI tissue occur in both tuberculosis and sarcoidosis which may create a diagnostic dilemma. Negative tuberculin test and acid-fast staining along with raised serum calcium and ACE level point toward the diagnosis of sarcoidosis.
4. *Malignancy:* Gastric and duodenal adenocarcinoma may resemble GDTB clinically and endoscopically [13, 27]. Endoscopy demonstrates various mucosal lesions ranging from mucosal erosions, ulcers, polys, strictures, fungating mass, fistulae, and/or sinus tract. Pancreatic carcinoma may present with extrinsic compression or infiltration of gastroduodenal region and enlarged periduodenal lymph nodes. Imaging studies and histology are useful for these suspected cases of adenocarcinoma.
5. *Idiopathic granulomatous gastritis*: An isolated idiopathic granulomatous gastritis is rare entity. It may resemble GDTB both endoscopically and clinically. It is a diagnosis of exclusion. Other causes of granulomatous gastritis including Helicobacter pylori gastritis, GDTB, Crohn's disease, sarcoidosis, mycosis, and foreign body reaction need to be ruled out. Some of the cases of idiopathic granulomatous gastritis may eventually evolve into these diagnoses [52, 53].
6. *Other differential diagnoses* Hypertrophic gastropathy is a rare condition that presents with giant gastric folds with epithelial cell hyperplasia, resembling GDTB. There are numerous causes of hypertrophic gastropathy ranging from Ménétrier disease, gastric adenocarcinoma, lymphoma, gastric varices, gastric tuberculosis, eosinophilic gastritis, and ZE syndrome [54]. Mucosal-associated lymphoid tissue (MALT) lymphoma is a low-grade B-cell neoplasm with a strong association with Helicobacter pylori gastritis. Clinical presentations are non-specific ranging from vague dyspepsia to gastrointestinal bleed and gastric outlet obstruction. Although classic B symptoms such as fever, night sweats, and weight loss are extremely rare in MALT lymphoma presentation resemble GDTB [55]. Gastrointestinal stromal tumor (GIST) usually remains silent till they reach a large size. Fundus of stomach is the most commonly affected part in GI tract. Submucosal bulge with punch-out ulcer is a classical appearance on endoscopy. EUS demonstrates origin of lesions from the second or fourth layer. Immune-histochemical analysis of biopsy specimens is required for diagnosis [56].

5.8 Diagnosis and Classification

Definitive diagnosis of tuberculosis is established when microbiologic evidences in the form of positive AFB staining/microbial culture/Gene-Xpert have been demonstrated. Although non-specific, histologic evidence of granuloma with caseation likely suggest diagnosis of tuberculosis. Recently the DIPS classification of GDTB has been suggested based on more comprehensive characterization lesions including diagnostic category, involvement category, presentation category, and site of involvement. This classification may have possible implications for treatment and follow-up [27].

5.9 Management

Once diagnosis of GDTB is established, most of the patients improve clinically and endoscopically with medical therapy with standard antitubercular drugs. Some of the patients with gastroduodenal strictures and features of gastric outlet obstruction require endoscopic therapy with balloon dilatation. Surgical treatment is usually reserved for complicated diseases including fistula formation, perforation, refractory strictures, and ulcerations. Rarely surgery may be required when diagnostic dilemmas persist.

5.10 Medical Therapy

Therapy with standard antitubercular drugs is highly effective and remains the cornerstone of management. Efficacy of antitubercular therapy is well proven in intestinal TB [57, 58]. Studies have shown good response to treatment with antitubercular drugs in cases of GDTB with improvement in obstructive symptoms, weight gain, and fever [13, 27, 32]. According to standard practice guidelines, four drugs (rifampicin, isoniazid, ethambutol, and pyrazinamide) need to be given for initial 2 months followed by three drugs (rifampicin, isoniazid, and ethambutol) for the next 4 months. Some authors have suggested the use of syrup preparations of rifampicin and isoniazid during initial treatment phase as they less likely vomited out completely than tablets or capsules in patients with gastric outlet obstruction. Once patients tolerate normal diet, tablet/capsule formulations can replace syrup preparations [32]. It is of utmost importance to perform follow-up evaluation both endoscopy and or imaging and also to ensure compliance to treatment. Some of the case reports had mentioned co-existent gastric tuberculosis and gastric malignancy which need to be looked for when initial diagnosis is not based on microbiological evidence (Acid-fast bacilli staining/microbial culture/Gene-Xpert test). Exact timing for repeat endoscopy is uncertain. Case reports have shown mucosal response on endoscopic examination at 2 months of antitubercular therapy [27, 29, 59].

Another means to assess response are barium imaging studies with a demonstration of free passage of barium across gastroduodenal stricture, resolution of gastric thickening and lymph nodes on ultrasonography and or CT scan of abdomen. Prevalence of drug resistance tuberculosis is increasingly seen in practice and may be responsible for recurrent or persistent symptoms in patients correctly diagnosed as having TB and treated with first-line antitubercular drugs [60–62].

5.11 Role of Endoscopic Therapy

Endoscopy plays a vital role in both diagnosis and treatment. Making a positive diagnosis of tuberculosis tissue always remains a major issue. Routine upper gastrointestinal endoscopy provides tissue for histopathological examination, microbial culture, and PCR-based tests, although the diagnostic yield is variable in different studies ranging from 3% in initial studies to 92% in more recent studies [63]. Recent advances in endoscopic techniques such as multiple pinch biopsies, endoscopic ultrasound-guided fine-needle aspiration, and endoscopic mucosal resection of hypertrophic nodules have significantly improved the diagnostic yield [64]. Their advantages lie in providing a greater quantum of tissue for histological examination and microbial culture [27, 32]. These endoscopic techniques potentially avoid surgery for sole diagnostic purposes. However, more data on utility and safety are still lacking for routine use of endoscopic mucosal resection in these diagnostically challenging cases. Also, endoscopic ultrasound (EUS) safely allows fine-needle aspiration of periduodenal lymph nodes in cases of suspected tubercular lymphadenitis [27, 64, 65]. Another important role of endoscopy lies in treatment of gastroduodenal stricture. Endoscopic balloon dilatation can be safely performed in cases tubercular gastroduodenal strictures. Usually, multiple sessions of endoscopic balloon dilation required are for improvement in symptoms of gastric outlet obstruction and number of sessions required is variable in different studies. This is because of the recoiling effect of extensive circumferential fibrosis observed in GDTB. Most of the published literature suggests four sessions of endoscopic balloon dilations to alleviate vomiting and able to resume normal diet with resultant weight gain over a period of time. Reports of successful placement of self-expanding metal stent (SEMS) across tubercular gastroduodenal strictures have been reported, which avoids the need for multiple sessions of endoscopic balloon dilation and possibly provides greater final luminal diameter [32, 33]. Endoscopy is also required to document the healing of mucosal abnormalities when a patient is treated with antitubercular therapy alone as mentioned previously.

5.12 Role of Surgery

In the modern era role of surgery has declined. However, surgery may be required when endoscopy and radiologic studies fail to reach the definitive diagnosis and also when antitubercular and endoscopic therapy fails or is not possible due to long

or too tight strictures. Elective surgery is also needed for management of complications such as fistula formation, obstruction, and refractory ulceration, and strictures. Gastrojejunostomy is the preferred surgery in patients with gastric outlet obstruction. Pyloroplasty may be difficult in these scenarios due to extensive fibrosis around pyloroduodenal area and recurrence of symptoms may occur due to stenosis associated with healing of tubercular lesions [13]. In some patients, obstruction may persist even after adequate gastrojejunostomy due to involvement of neural plexus and gastric atony due to prolonged gastric stasis. To overcome this, some authors have suggested feeding jejunostomy in addition to gastrojejunostomy [66, 67]. In some patients, tubercular ulcers may persistent. These patients require vagotomy and antrectomy. Reports of massive upper GI bleed due to tubercular gastric ulcer and arterioduodenal fistula requiring emergency surgery have been described [13, 68]. Sometimes endoscopic, radiologic, and laparoscopic findings mimic malignancy in which cases resection with curative intent along with antitubercular therapy is required.

5.13 Conclusion

GDTB is a rare form of extra-pulmonary tuberculosis even in tuberculosis endemic regions. Presentations are variable and endoscopic and radiologic findings are nonspecific, requiring a high index of suspicion. GDTB should be considered in cases of unexplained gastroduodenal lesions such ulcers, strictures, polys, and masses. Obtaining adequate representative tissue remains an important issue in the diagnosis. AFB staining, microbial culture, and PCR tests confirm the diagnosis but are infrequently reported to be positive. Recent advances in endoscopic modalities have shown promising results with an increase in diagnostic yields. Histology is nonspecific and patients treated with a presumptive diagnosis of GDTB need to be monitored clinically and endoscopically to document complete response to antitubercular therapy. Some patients with gastroduodenal strictures may require multiple sessions of endoscopic balloon dilations. In the modern era, the role of surgery is limited and reserved mainly for the management of complications.

Conflict of Interest Nil

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Intestinal Tuberculosis: An Overview

6

Saurabh Kedia and Vineet Ahuja

Key Points

1. Intestinal tuberculosis is the commonest form of abdominal tuberculosis which has a non-specific clinical presentation and mimics other infectious and non-infectious disorders affecting the intestine.
2. The diagnosis requires a high degree of clinical suspicion, algorithmic approach, every possible attempt at tissue acquisition for microbiological and histopathological analysis, and in equivocal cases a therapeutic anti-tubercular therapy (ATT) trial.
3. The definite diagnostic criteria have a very poor sensitivity because of paucibacillary nature of disease, and a presumptive diagnosis is made in a significant proportion of patients.
4. Intestinal TB, in cases of presumptive diagnosis, needs to be differentiated from Crohn's disease, especially in TB endemic areas where the disease burden of CD is also on the rise.
5. The treatment approach is similar to pulmonary TB and consists of 6 months of ATT, although duration may be extended in patients with partial response, as per the discretion of the physician.
6. In non-responders to ATT, one needs to exclude multi-drug resistant TB, fibrotic stricture, and Crohn's disease.

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6.1 Introduction

With the changing diet and lifestyle, the developing world is witnessing the rising burden of non-communicable diseases, reflecting the epidemiologic transition from infectious to non-infectious disorders [1]. However, despite this transition, India and similar countries continue to persist at the cross-roads with the stable incidence of infectious disorders such as tuberculosis and rising burden of non-infectious disorders [2]. As per the Global TB report, in 2019, the 30 high TB burden countries accounted for 87% of new TB cases globally [3]. Further, of all TB cases, extrapulmonary tuberculosis (EPTB) represented 16% of the 7.1 million incident cases that were notified in 2019, ranging from 8% in the WHO Western Pacific Region, 19% in the South-East Asian region to 24% in the Eastern Mediterranean Region, and this proportion has gradually increased over the years [3]. As per the Centers for Disease Control and Prevention, the proportion of EPTB cases has remained high, and the overall decline in TB cases has been almost due to the reduction in pulmonary TB cases [4]. The persistent burden of TB and the rising burden of EPTB in these countries present a challenge to the physicians across all specialties, both with respect to diagnosis and management of these paucibacillary forms of TB. For the gastroenterologists, intestinal TB constitutes an important component of their patient population and continues to be an important diagnostic as well as management dilemma for them. Intestinal TB remains one of the greatest mimickers despite many advances in diagnostics and continues to confound clinicians with its myriad presentations [5].

6.2 Epidemiology

There are no population-based studies on the incidence or prevalence of ITB, and most of the data can be extrapolated from the studies assessing the proportion of ITB patients among overall population of patients with EPTB. Abdominal TB has been considered the sixth most common form of EPTB, accounting for approximately 6% cases of EPTB, and intestinal TB is the commonest, accounting for 30–50% cases of abdominal TB and may co-exist with peritoneal TB in one-third of cases [6]. However, there is considerable heterogeneity in these estimates and as per the recent reports these percentages vary from as low as 2.25% to as high as 31% of all EPTB cases; depending upon location, means of diagnosis, and underlying setting (Table 6.1) [7–21]. In a recent large-scale multi-center study from China, of a total of 202,998 cases of EPTB hospitalized between January 2011 and Dec 2017, ITB accounted for 2.25% of all EPTB cases [21]. In another recent study from Pakistan, of 15,790 EPTB cases, abdominal TB accounted for 21% cases [20]. In relatively older study from the USA, from 1993 to 2006, there were 18.7% EPTB cases of a total of 2,53,299 cases of TB [9]. Of these peritoneal TB accounted for

Table 6.1 Proportion of patients with intestinal/abdominal tuberculosis among patients with extra-pulmonary TB

Author year	Country	Number EPTB	Number Abdominal	Percentage Abdominal	Type	Order of frequency
Lin 2008	Taiwan	102	19	18.6	Abdominal	3
Sreerama-reddy 2008	Nepal	230	34	14.8	Abdominal	2
Peto 2009	USA	47,293	2296	4.9	Peritoneal	6
Otaibi-Al 2010	Saudi Arabia	248	33	13.3	Abdominal	3
Gunal 2011	Turkey	103	10	9.7	Peritoneal	7
Ducomble 2013	Germany	14,087	750	5.3	Abdominal	6
Sevgi 2013	Turkey	141	15	11	Intestinal	5
Karstaedt 2014	South Africa	2963	30	2.9	Peritoneal	5
Sunnetcioglu 2015	Turkey	203	20	9.9	Peritoneal	3
Guler 2015	Turkey	168	10	2.7	Abdominal	6
Sama 2016	USA	46	4	8.7	Intestinal	5
Tatar 2016	Turkey	397	11	4.9	Intestinal	4
Gaifer 2017	Oman	96	30	31	Abdominal	2
Tahseen 2020	Pakistan	15,790	3313	21	Abdominal	3
Kang 2020	China	202,998	4571	2.25	Intestinal	11

4.9% of all TB cases (Table 6.1). In a recent case series from India, 1.3/100 of all admitted patients in gastroenterology ward had abdominal TB, and of these ($n = 58$), 43% ($n = 25$) patients had intestinal TB [22]. In a relatively old retrospective epidemiological study, among 20,732 Bangladeshis residing in UK, the incidence of abdominal TB was 7.7 cases per 100,000 population per year [23].

6.2.1 Have the Rates of Intestinal TB Gone Down?

Though the burden of inflammatory bowel disease is on the rise in India and other developing countries, the disease burden of intestinal TB continues to persist, as evidenced by a recent report from Mumbai, in which there was no inverse correlation between incidence of intestinal TB and CD over 15 years [2]. However, in another study conducted among Bangladeshi patients in East London, it was observed that the incidence of inflammatory bowel disease had increased and that of abdominal TB had fallen over the past decade. The standardized incidence of abdominal TB was 2.5/100,000/year (95% confidence interval (CI) 0.2–4.8) in 1997–2001, and 7.4 (95% CI 2.1–12.7) in 1985–1989 ($p < 0.05$). The standardized ratio for the incidence of TB in the two periods was 0.22 (95% CI 0.07–0.53) [24].

6.3 Pathogenesis and Risk Factors

6.3.1 Pathogenesis

The gastro-intestinal tract can get infected with MTB in the following ways: (a) Swallowing of infected sputum in a patient with active pulmonary disease, (b) hematogenous spread from a distant pulmonary focus, (c) contiguous spread from an adjacent site, (d) lymphatic spread [25, 26]. Up to 25% cases of ITB may have concomitant pulmonary disease, the frequency of which may increase with better diagnostic modalities such as CECT chest. The reverse association has also been studied, with earlier studies demonstrating a very high frequency of asymptomatic intestinal TB in patients with pulmonary TB [27]. Recent studies have also demonstrated this association, along with a correlation between severity of lung disease and the frequency of intestinal TB [28]. Tuberculosis can involve the entire GI tract from esophagus to anus, although the ileocecal area is the most commonly involved site due to the reasons mentioned in Box 6.1. Once the organism reaches the submucosa, it initiates granuloma formation followed by necrosis, endarteritis, and lymphagitis (Fig. 6.1). The associated endarteritis and lymphagitis are responsible for transverse ulcer formation, and the subsequent fibrotic reaction leads to stricture formation.

6.3.2 Risk Factors

Although ITB has been most commonly seen in immunocompetent adults without any co-morbidities in the TB endemic regions, possibly due to high disease burden, the risk increases with conditions which reduce the immunological competence [29]. Intestinal TB has been reported more frequently in HIV infected individuals [30], those with co-morbidities as reflected by high Charlson co-morbidity index [31], patients on treatment with immunosuppressant medications such as anti-tumor necrosis factor therapy and solid organ transplant patients [32–35]. Other factors such as gender and age have been heterogeneously reported without any consistent association. Although genes associated with autophagy such as IRGM have been associated with TB, a Chinese study reported specific association of LMP2/LMP7 genes with increased susceptibility for ITB [36].

Box 6.1 Factors responsbile for ileocaecal area being the commonest site of involvement in intestinal tuberculosis

1. Resistant fatty capsule of MTB, which hinders the release of bacteria in the proximal GI tract.
2. Physiological fluid stasis at ileocecal region, which creates a milieu for capsule digestion and mucosal uptake of the organism.
3. Abundance of submucosal lymphoid tissue which creates a niche for the organism.

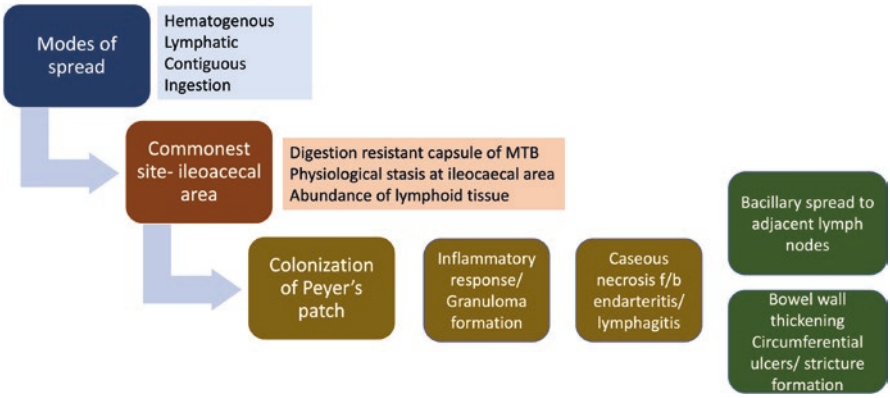

Fig. 6.1 Pathogenesis of intestinal tuberculosis

6.4 Site of Involvement and Morphology

Hoon et al. had originally classified gross morphological appearance of involved bowel into ulcerative, ulcerohypertrophic, and hyperplastic varieties [37]. Tandon and Prakash described the bowel lesions as ulcerative and ulcerohypertrophic types [38]. The ulcerative form has classically been described in more malnourished adults, while hypertrophic from in relatively well nourished adults. Ulcerative and stricturous forms are usually seen in small intestine while colonic and ileocecal lesions are usually ulcerohypertrophic.

The most common site of involvement is ileocecal area ranging from 25 to 90% across various series followed by small intestine (6–67%), colon (2–32%), and gastroduodenal area (0.5–5%) (Table 6.2a and b) [38–52]. The frequency of bowel involvement declines as one proceeds both proximally and distally from the ileocecal region.

6.5 Clinical Manifestations

The clinical features of intestinal TB depend upon the site of involvement, duration of presentation, and whether the presentation has been acute or chronic. The older series demonstrated higher frequency of complications such as obstruction and perforation with greater proportion of patients undergoing surgical procedures. However, the recent series (over the last 2 decades) have demonstrated more of a chronic presentation with a disease duration of 6 months to 1 year in maximum patients (Table 6.2a and b). The average age of presentation varies in third to fifth decade of life in maximum series with almost similar representation of males and females. Abdominal pain has been the most common symptom, seen in >70%

Table 6.2 Demographic and clinical features in patients of intestinal tuberculosis in different series

(a)

Author/year	Tanoglu 2020	Udgirkar 2019	Patel 2018	Jung et al. 2016	Gan et al. 2016	Tripathi 2009	Wang 2007	Sircar 1996	Singh 1995
Area	Multi-center	India	India	S. Korea	S. Korea	Indian	China	India	India
Age at presentation (years)	39.5	21–40	33.7	42.6	32.4	21–40	46.8		
Symptom duration (months)	–	–	8.4 m	–	8 m	–	–	–	–
Number of patients	104	176	69	109	81	110	134	298	145
Site of involvement									
Terminal ileum	44.2%	50%	–	–	67.3%	39.1%	–	–	–
Ileocecal area/ cecum		28.9%	84.1%	–	83.6%	50.9%	25.4%	–	40%
Small intestine	34.6%	–	36.2%	–	–	6.4%	10.4%	–	54%
Colon	27.8%	23.1	31.9%	–	61.8%	1.8%	12%	–	5.5%
Gastroduodenal	5.7%	–	–	–	–	–	–	–	5.5%
Perianal	1%	–	–	–	–	–	–	–	0.7%
Clinical feature									
Abdominal pain	76.9%	83.5%	76%	40.4%	87.7%	82.7%	67.2%	30%	88%
Loss of appetite	90.2%	86.4%	–	–	–	–	–	–	30.1%
Weight loss	50%	80.1%	60.9%	11%	80.2%	53.6%	29.1%	8%	21%
Fever	66.3%	59.1%	72.5%	6.4%	43.2%	58.2%	44.8%	21%	66%
Diarrhea	24%	5.7%	28.9%	22%	46.9%	29.1%	–	–	21%
Constipation	21.2%		7.3%		16%		–	–	24%
Hematochezia	10.6%	7.4%	14.5%	12.8%	9.9%	5.4%	–	5%	6%
Sub-acute obstruction	–	2.8%	10.2%	–	18.5%	36.4%	–	28%	–
Concomitant PTB	27.8%	7.4%	–	–	25.9%	12.7%	29.1%	16%	27.9%

(b)

Author/year	Tandon 1986	Palmer 1985	Vaidya 1978	Das et al. 1976	Bhansali 1977	Prakash 1975
Area	India	UK	India	India	India	India
Age at presentation (years)	20–30	34.9	29.7	21–30	–	20–40
Symptom duration (months)	–	–	>6 m	1–6 months	–	>12 m
Number of patients	186	42	102	93	196	92
Site of involvement						
Terminal ileum	–	–	28%	–	–	–
Ileocecal area/cecum	60.6%	93%	54%	40.8%	54%	–

Table 6.2 (continued)

(b)						
Author/year	Tandon 1986	Palmer 1985	Vaidya 1978	Das et al. 1976	Bhansali 1977	Prakash 1975
Area	India	UK	India	India	India	India
Small intestine	22.9%		4%	53.7%	44%	–
Colon	18.9%	5%	26%	5.4%	3.6%	–
Gastroduodenal	0.8%		3%	–	0.5%	–
Perianal	–	2.5%	–	–		–
Clinical feature						
Abdominal pain	88.6%	100%	81%	94%	100%	96.7%
Loss of appetite	30.1%	–	–	44%	–	–
Weight loss	30.8%	42%	–	35%	–	–
Fever	28.9%	60%	–	42%	49%	–
Diarrhea	25.3%	–	–	11%	15%	28.3%
Constipation	26.4%	–	–	47%	41%	–
Hematochezia	5.5%	–	–	–	–	–
Sub-acute obstruction	–	–	–	50%	–	44%
Concomitant PTB	27.9%	27.9%	28%	27.9%		13%

Table 6.3 Complications associated with intestinal TB in various series

	Gan et al	Palmer et al.	Wang et al
Partial intestinal obstruction	17.3%	10%	17.4%
Intestinal perforation	7.4%		7.3%
Complete intestinal obstruction	3.7%		
Gastro-intestinal bleeding	2.5%		
Fistula	1.2%		9.2%

patients. Pain is usually dull aching, colicky, periumbilical in location, and may be associated with borborygmi. Patients with associated lump may have localized pain in the right iliac fossa. Other manifestations include constipation, weight loss, and loss of appetite. Fever and other constitutional symptoms may be seen in 30–70% patients. Diarrhea (~15–20%) and bleeding per-rectum (<10%) are seen less frequently in patients with ITB as compared to Crohn's disease (CD). Patients with ITB can also present acutely with complications such as acute intestinal obstruction, perforation, massive gastro-intestinal bleeding, and fistula formation, which have been reported at a frequency of 17.3%, 7.4%, 2.5%, and 1.2–9%, respectively (Table 6.3) [42, 46, 48]. Of all patients presenting with these complications to the emergency, ITB accounts for approximately 3–15% cases [53–55].

6.5.1 Malabsorption as a Symptom of TB

Malabsorption is also one of the complications of ITB, and presence of abdominal pain in a patient with malabsorption suggests the diagnosis of ITB [56]. In a study of 40 patients with intestinal TB, the presence of malabsorption as detected by glucose/lactose tolerance tests, D-xylose test, fecal fat, and Schilling's test (for vitamin B12 malabsorption) was significantly higher in those with bowel stricture as compared to those without. These tests were abnormal in 28%, 22%, 57%, 60%, and 63%, respectively, in patients with stricture compared with 0%, 0%, 8%, 25%, and 30%, respectively, in those without strictures [57]. Tandon et al. also reported biochemical evidence of malabsorption in 75% of patients with intestinal obstruction and in 40% of those without it. The cause of malabsorption in intestinal TB is postulated to be bacterial overgrowth in a stagnant loop, bile salt deconjugation, diminished absorptive surface due to ulceration, and involvement of lymphatics and lymph nodes [58].

6.5.2 Segmental Colonic Tuberculosis

Segmental or isolated colonic tuberculosis refers to the involvement of colon without the ileocecal region and constitutes 9.2% cases of all intestinal TB [59]. It commonly involves ascending, transverse, and sigmoid colon, and multifocal involvement can be seen in one-third cases with colonic TB [60, 61]. Abdominal pain can be seen in 78–90% patients, hematochezia is seen in less than one-third of patients, and other manifestations could be fever, anorexia, and altered bowel habits [61]. Rare cases presenting like ulcerative colitis, aphthous ulcers, and tumor like perforation have also been reported [62–65].

6.5.3 Rectal and Anal Tuberculosis

Rectal TB most commonly presents as hematochezia, and constipation followed by constitutional symptoms [66, 67]. Hematochezia could occur because of rectal ulcer or due to trauma by hard stool passing through the rectal stricture. The annular stricture can be felt through per-anal examination. Stricture is usually tight, of variable length, within 10 cm of anal verge and with focal areas of deep ulceration. Though rare, rectal TB can present with isolated involvement of the rectum without involvement of any other intestinal site. Patients may have associated pulmonary TB and a chest TB can help in such a setting. Rectal TB may also present as rectal submucosal growth [68].

Anal tuberculosis may be associated with intestinal TB either as an extension of the original lesion or due to its spread via the lymphatics. It may present as pilonidal sinus, anal ulceration with inguinal adenopathy, recurrent perianal growth, anal

fissure, anal fistulae, or anal stricture [69–71]. Tubercular fistulae are usually multiple, and in a series, 12 out of 15 multiple fistulae were of tuberculous origin, as compared with only four out of 61 solitary perianal fistulae [72]. Shukla et al. reported that, in India, TB accounted for up to 14% of cases of fistula in ano, presenting as anal discharge and perianal swelling. No patient had constitutional symptoms [73]. Tubercular anal lesions should be differentiated from Crohn's disease, herpes simplex, syphilis, sarcoidosis, amoebiasis, deep mycosis, and lymphogranuloma venereum.

6.5.4 Gastroduodenal Involvement

Patients with gastroduodenal involvement can present with abdominal pain, early satiety, post prandial fullness, nausea, and vomiting. In a recent systematic review of 11 studies (225 patients), recurrent vomiting, symptoms of gastric outlet obstruction, abdominal pain, loss of appetite, loss of weight, and fever were present in 64.4%, 47.1%, 43.5%, 32.4%, 24.0, and 16.4% patients, respectively. Approximately 43.5% patients had active TB at other sites, of which 29 had associated ileocecal involvement and 17 had pulmonary TB [74].

6.6 Endoscopic and Histologic Features

6.6.1 Endoscopy

- *Ileocolonoscopy:* Ileocecal area, including the IC valve is the most commonly involved site in patients with ITB, being reported in 42–82% patients, followed by ileal, right colonic, transverse colonic, and left colonic involvement (Table 6.4) [48–52, 75–80]. The colonoscopic findings that have classically been associated with ITB include patulous ileocecal valve, transverse ulcer, contiguous involvement or involvement of lesser than 4 segments, strictures and pseudopolyps or nodularity [80] (Fig. 6.2). Less commonly reported findings include longitudinal ulcers, cobblestoning, aphthous ulcers, and anorectal lesions, which are more commonly seen in patients with CD. However, none of these features are specific for ITB, and can be seen in other inflammatory disorders also. Hence, endoscopy alone cannot diagnose ITB, and a constellation of clinical, histologic, radiologic, and serological features is required for diagnosis of ITB.
- *Capsule endoscopy:* In patients with suspected small intestinal involvement, which is out of reach for endoscopy or colonoscopy, capsule endoscopy can be done, if stricture is ruled out on cross-sectional imaging [81]. However, the data on capsule endoscopy in ITB is scarce, limited to case series, and there is no

Table 6.4 Endoscopic features of patients with intestinal tuberculosis

	Udgirkar 2019	Patel 2018	Tanoglu 2020	Jung 2016	Gan 2016	Lee 2005	Makharia 2010	Li 2011	Yu 2012	Yunho Jung 2016	Bae 2017	Kedia 2015
	India	India	Multi-center	S. Korea	S.Korea	S. Korea	India	China	China	S. Korea	S. Korea	India
Number of patients	162	69	96	109	81	44	53	122	43	98	40	50
Site of involvement												
Terminal ileum	45.5%	36.2%	32.3%	–	67.3%	–	15%	60%	88%	64%	–	22.4%
Ileocecal valve	41.6%	84.1%	–	32.1%	83.6%	–	–	75%	82%	–	–	42.8%
Right colon	35.2%	31.9%	21.9%	–	61.8%	–	92%	62%	63%	61%	–	49%
Transverse colon	5.6%	5.8%		–	29.1%	–	–	33%	51%	28%	–	14.3%
Left colon	3.1%	2.9%		–	21.8%	–	19%	25%	37%	9%	–	8.2%
Type of involvement												
Transverse ulcer	–	57.9%	30.2%	–	52.7%	66%	–	41%	70%	73%	63%	28.6%
Patulous IC valve	–	28.9%	–	–	65.5%	40%	–	51%	26%	21%	43%	
Stricture	17.9%	8.7%	15.6%	–	29.1%	18%		23%	–	9%	–	40.8%
Nodularity	–	21.7%	4.2%	–	45.5%		49%	33%	–	–	–	26.5%
Skip lesions	–	7.3%	–	42.2%	36.3%	18%	17%	–	58%	–	–	

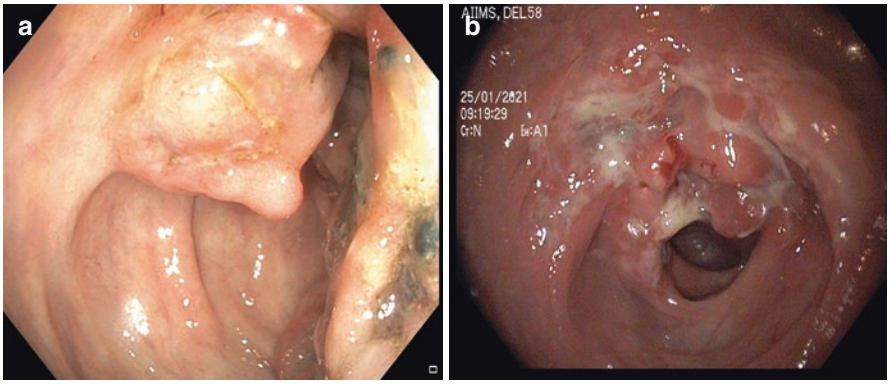

Fig. 6.2 Colonoscopic image of a patient with intestinal tuberculosis demonstrating: (**a**) ulcers over ileocecal valve and (**b**) transverse ulcer in cecum and ulcerated ileocecal valve

specific finding. In a study on patients with active pulmonary TB without any pulmonary symptoms, small bowel annular ulcers on capsule endoscopy were seen in 4 patients [82].

- *Double balloon enteroscopy:* Patients with small bowel involvement distant from the reach of gastroduodenoscopy or ileocolonoscopy might be taken up for enteroscopy which may aid in obtaining biopsies and endoscopic therapy in patients with symptomatic strictures.

6.7 Histology

Obtaining biopsies from normal as well as abnormal areas is essential in establishing the diagnosis. Minimum of 4 biopsies each should be taken in both formalin (for histopathology) and saline (for culture), although in a recent study, the culture positivity for MTB increased by 14% by increasing the number of biopsies from 4 to 8 [83].

6.7.1 Histopathology

The histological features associated with ITB can be non-specific such as architectural abnormalities (crypt distortion, shortening, branching, irregular mucosal surface), chronic inflammation of lamina propria, focal cryptitis, basal plasmacytosis, increased intra-epithelial lymphocytes, and granulomas. Granuloma, a collection of epithelioid histiocytes (macrophages) with vaguely defined outlines, is often seen in ITB, and the granuloma characteristics can differentiate ITB from CD. Tubercular granulomas are usually large (> 200 μm), confluent, dense (> 5–10/hpf), located in submucosa, and are often characterized by central caseation, which is diagnostic

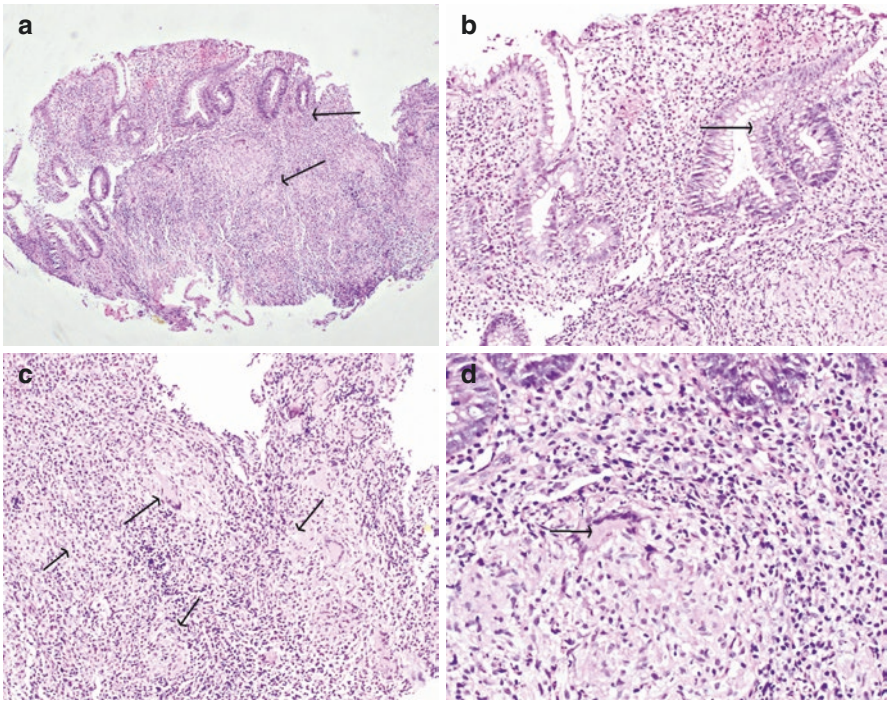

Fig. 6.3 Photomicrograph shows features of chronic active ileitis (arrow) with submucosal large, confluent epithelioid cell granulomas (arrow) [A × 40]. Ileal mucosa shows blunting of ileal villi, with crypt branching (arrow) and moderate inflammation in lamina propria including polymorphs [B × 100]. High power image shows submucosal large confluent epithelioid cell granulomas (arrows) with surrounding lymphoid cuffing [C × 100]. High power image shows one of the epithelioid cell granuloma with Langhan's type of giant cell (arrow). Necrosis is not seen [D × 200]

and exclusive for ITB [84–86] (Fig. 6.3). The frequency of granuloma positivity in patients with ITB varies from 40 to 81% [48–51, 60, 61, 76, 79, 87–93], while that of caseation necrosis varies from 5.5 to 39% (Table 6.5) [48, 49, 76, 79, 88–93]. Other histological features commonly associated with ITB include submucosal granulomas, ulcers lined by a band of epithelioid histiocytes, and disproportionate submucosal inflammation. In a recent meta-analysis of 10 studies (316 patients with ITB), the three most specific features associated with ITB were caseating necrosis, confluent granulomas, and ulcers lined by epithelioid histiocytes [94]. These features had >95% specificity for diagnosis of ITB, although their sensitivity was quite low (<40%). The significance of biopsies from normal appearing area on endoscopy was highlighted in a study, where, in 50 patients with suspected colonic tuberculosis, biopsies from terminal ileum in 4 patients revealed presence of granuloma or loosely arranged epithelioid cells, suggesting the diagnosis of ITB [95]. Another study highlighted the significance of obtaining biopsies proximal to the stricture after stricture dilatation. Of 130 patients with colonic TB, strictures were dilated in

Table 6.5 Histologic and microbiologic features of patients with intestinal tuberculosis

Author	*N*	Granulomas	Caseating granuloma	TB-PCR	MGIT/LJ medium	Gene-Xpert	AFB positive
Bhargava 1985	28		–	–	41%*	–	–
Bhargava 1992	29	41%	–	–	40%*	–	–
Vij 1992	37	67.5%	–	–	43%*	–	–
Shah 1992	50	74%	18%		6%*		
Singh 1996	62	43.5%	–	–	–	–	0
Wang 1998	134	–	–	–		–	42.7%
Lee 2004	225	72.4%	11.1%	–	29.3%*	–	17.3%
Khan 2006	103	–	–	–	7%*	–	–
Leung 2006	22	100%	36.3%	–	40%**	–	69.5%
Kirsch 2006	18	78%	22%		11%**		
Amarapurkar 2008	26	57.7%	34.60%	65.4%	23%**	–	–
Shah 2010	28	–	–	–	48%*	–	–
Shah 2010					76%**		
Makharia 2010	53	62.2%	13.2%	–		–	–
Ye 2012	400	–	–	–	44%*	–	–
Samant 2014	61	–	–	–	51%**	–	–
Sekine 2015	50	51%	8.2%	25%	50%**	–	38%
Jung 2016	109	40.3%	5.5%	–	14.7%**	–	3.7%
Jung 2016	98	67.4%	38.8%	29.9%	17.1%**	–	15.9%
Gan 2016	81	58.2%	25.5%			–	–
Kumar 2017	29					8%	
Patel 2018	69	71.1%	–	71.1%	20.3%**	–	–
Udgirkar 2019	176	80.8%	–	35.8%	25.7%**	4.5%	–
Bellam 2019	–		–	–	–	32%	–
Lowbridge 2020	52	–	–	50%	35%**	95.7%	31%
Tanoglu 2020	104	–	–	–	78.8%**	–	–

*LJ medium, **MGIT
LJ Lowenstein–Jensen, *MGIT* Mycobacterial growth indicator tube

22 patients, of which 11 had proximal lesions, and histological examination from these lesions established diagnosis in 5 additional patients [96].

6.7.2 Microbiology

Biopsies are also sent for acid fast bacillus staining (AFB), culture of MTB, and Gene-Xpert, as positivity for either of these tests has 100% specificity for

ITB. Though associated with 100% specificity, the definite microbiological tests for diagnosis of ITB are associated with poor sensitivity because of paucibacillary nature of disease. The diagnostic accuracies of various microbiological tests have been mentioned in Table 6.5.

1. *TB-PCR*: The role of polymerase chain reaction (PCR) for MTB remains controversial, as it has also been demonstrated in patients with CD and irritable bowel syndrome. The sensitivity and specificity of TB-PCR for diagnosis of ITB ranges from 22 to 66% and 95 to 100%, respectively. Thus, PCR as a standalone test cannot be diagnostic for ITB [50, 51, 76, 92, 93, 97, 98].
2. *Culture for MTB:* Mycobacterial culture was traditionally done on egg based Lowenstein–Jensen medium, which had a long turn-over time, but has now been replaced by MGIT (Mycobacterial growth indicator tube) BACTEC 960 system, which has shorter turn-around time of less than 2 weeks, and higher sensitivity than LJ medium. The culture positivity rates on LJ medium vary from 7 to 48% [61, 87–89, 99–102], and that on MGIT from 15 to 79% [49–52, 76, 90–93, 98, 101, 103]. It has also been reported that combination of granuloma with culture yielded higher sensitivity for diagnosis of ITB than either alone (77% vs 51% and 50%) [93].
3. *Stain for acid fast bacillus (AFB):* The yield for AFB positivity is the lowest, ranging from 3.7% to 38% [49, 76, 89, 90, 93, 98].
4. *Gene-Xpert:* The positivity rate for Gene-Xpert-MTB-RIF in patients with ITB ranges from 8 to 95.7% [51, 98, 104, 105]. In a recent systematic review and meta-analysis on Gene-Xpert assay for abdominal tuberculosis, the pooled sensitivity and specificity was 23% and 100%, respectively [106].

6.8 Radiology

6.8.1 Chest Radiology

Evidence of TB in a chest radiograph supports the diagnosis and is recommended in all patients with suspected ITB. Evidence of active/healed TB on chest-X ray has been demonstrated in up to 29% patients with ITB (Table 6.2a and b). However, detection of associated PTB with more sensitive technique such as CECT chest can increase the sensitivity of detecting PTB, and aid in definite diagnosis of ITB. In a recent study, addition of CT chest to diagnostic algorithm increased the diagnostic sensitivity of definite ITB diagnosis from 26% to 57% [107]. Hence, for patients with suspected ITB, when chest-X ray is non-contributory, a CT chest is suggested in the diagnostic algorithm.

6.8.2 Ultrasound Abdomen

Ultrasonographic features of patients with ITB include bowel thickening in the involved areas, which can be diffuse, focal, or concentric along with

lymphadenopathy, ascites, omental caking, and cecal spasm [108]. A recent study on contrast enhanced ultrasound revealed ileocecal or hepatic flexure thickening with two types of bowel wall enhancement pattern—serosal followed by mucosal or diffuse, and the enhancement was either diffuse or heterogenous [109].

6.8.3 Barium Examination

Small bowel follow-through: Features which can be seen on small bowel barium meal include accelerated intestinal transit; hypersegmentation of the barium column ("chicken intestine"), precipitation, flocculation, and dilution of the barium; stiffened and thickened folds; luminal stenosis with smooth but stiff contours ("hour glass stenosis"); possibly multiple strictures with segmental dilatation of bowel loops; and fixity and matting of bowel loops [110–112].

Barium enema: Barium enema can demonstrate early involvement of the ileocecal region manifesting as spasm and edema of the ileocecal valve, thickening of the lips of the ileocecal valve and/or wide gaping of the valve with narrowing of the terminal ileum ("Fleischner" or "inverted umbrella sign"). Other features include "conical caecum" shrunken in size and pulled out of the iliac fossa due to contraction and fibrosis of the mesocolon; goose neck deformity (loss of normal ileocecal angle and dilated terminal ileum appearing suspended from a retracted, fibrosed cecum); purse string stenosis (localized stenosis opposite to the ileocecal valve with a rounded-off smooth cecum and a dilated terminal ileum); Stierlin's sign (manifestation of acute inflammation superimposed on a chronically involved segment and characterized by lack of barium retention in the inflamed segments of the ileum, cecum, and variable lengths of the ascending colon, with a normal configured column of barium on either side); and string sign (persistent narrow stream of barium indicating stenosis) [113–115].

6.8.4 Cross-Sectional Imaging (CT/MR Enterography)

There are three important roles for cross-sectional imaging in the diagnostic evaluation of a patient with suspected ITB—establishing diagnosis, differentiating from CD, and demonstrating response to therapy. Enterography (CT/MR) requires adequate distension of bowel loops with administration of adequate amount of negative oral contrast (diluted Mannitol or polyethylene glycol—enables evaluation of bowel wall characteristics). An initial evaluation of CT findings in 11 patients of ileocecal TB revealed characteristic thickening in ileocecal area, IC valve, and medial cecal wall along with large surrounding lymph nodes with central hypodensity suggestive of central necrosis [116]. Subsequently reported findings on CTE in patients with small bowel tuberculosis include short segment strictures with symmetric concentric mural thickening and homogenous mural enhancement [117–119]. Other less common findings include lymphadenopathy, enteroliths, peritoneal thickening and enhancement, and ascites. Findings on MRE in 19 patients with

ITB included ileocecal involvement, small bowel concentric mural thickening, lymphadenopathy, ascites, and peritoneal enhancement [120]. Among studies which compared CT findings of CD and ITB, involvement of ileocecal area, shorter length of involvement, and presence of lymph nodes larger than 1 cm have been more common in ITB [121]. In a recent meta-analysis on this aspect, presence of necrotic lymph node had 100% specificity for ITB (although very poor sensitivity of 23%), while skip lesions, comb sign, left colonic involvement, asymmetric bowel wall thickening, and fibrofatty proliferation were more common in CD [122]. To summarize, short segment symmetric bowel wall thickening, contiguous ileocecal involvement with involvement of ileocecal valve, and large lymph nodes are suggestive of ITB, while presence of necrotic lymph nodes in the background of these findings is exclusive for ITB (Fig. 6.4). However, necrotic lymph nodes can also be seen in other conditions, and their presence should be interpreted in the context of other clinical and radiological findings. Other findings such as mural stratification can be seen in both the conditions. Quantification of visceral fat on

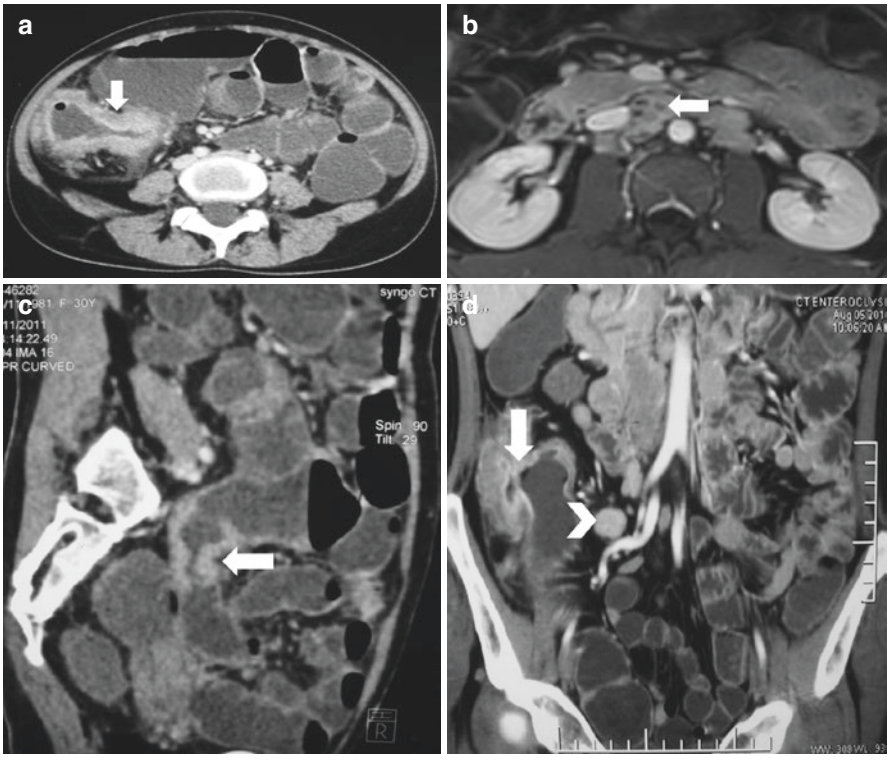

Fig. 6.4 CT enterographic images of patients with intestinal TB demonstrating: (**a**) Axial image of a patient with contiguous short-term thickening of ileocecal area (white arrow); (**b**) Axial image of a patient with necrotic abdominal lymph nodes (white arrow); (**c**) Coronal image of a patient with short segment ileal stricture; (**d**) coronal image of a patient with ileocecal valve thickening and stricture with proximal terminal ileal dilatation

CT abdomen has been recently developed as a modality to differentiate CD from ITB, and visceral to subcutaneous fat (VF/SC) ratio > 0.63 predicts the diagnosis of CD with more than 80% diagnostic accuracy [123]. In a separate study, the presence of long segment bowel wall thickening and VF/SC ratio > 0.63 had >95% specificity for diagnosis of CD [124].

6.9 Serology

The positivity for tuberculin skin test (TST) or Mantoux should be interpreted in the context of previous BCG vaccination, and higher cutoff values are suggested for patients with positive history. The positivity rates for TST in patients with ITB have varied from 42.7% to 88% (Table 6.6) [38, 48, 49, 51, 52, 75–78, 125, 126].

Interferon gamma release assays (IGRA) are independent of prior BCG vaccination and detect the INF-gamma release by the peripheral blood mononuclear cells in response to tubercular antigen. In a meta-analysis of 8 studies that assessed role of IGRA in differentiating ITB from CD, the pooled sensitivity and specificity of IGRA for diagnosis of ITB were 81% and 85%, respectively [127]. However, both TST and IGRA are markers of latent TB, and can neither rule in or rule out active TB as stand-alone tests. However, they can be supportive for diagnosis of ITB in combination with other investigations.

Though IGRA as a stand-alone test is not diagnostic for active TB and is not recommended in the diagnostic algorithm for EPTB, in a recent study, levels of IGRA were associated with the severity of disease, and IGRA >100 ng/ml was highly suggestive of TB. However, this test requires validation before being recommended for clinical use [128].

Table 6.6 Mantoux or IGRA (interferon gamma release assay) positivity in patients with intestinal tuberculosis

Author year	Number of patients	Mx	IGRA
Udrikar 2020	176	64.2%	–
Cheng 2019	85	88.2%	85.7%
Tanoglu 2019	104	88%	86%
Bae 2017	40	–	75%
Jung 2016	109	–	75.2%
Gan 2016	81	51.9%	86.4%
Jung 2016	98		75.8%
Yu 2012	43	48.3%	–
Li 2010	122	42.7%	–
Singh 1990	95	77%	–
Prakash 1975	92	84.7%	–

A recently developed immunological marker (enumeration of FOXP3 T-regulatory cells in peripheral blood with a cutoff >32.5% cells favoring ITB) showed good specificity of >90% in differentiating ITB from CD and demonstrated

similar diagnostic accuracy in another prospective validation study [129, 130]. Hence, this test would support the diagnosis of ITB in suspected cases but requires validation at other centers and its use would be limited to tertiary care centers.

6.10 Diagnosis of Intestinal Tuberculosis

Defined in 1884, the Koch's postulates laid down for diagnosis of tuberculosis and other infections were replaced by Paustian's criteria for diagnosis of abdominal TB [131]. According to Paustian's criteria, abdominal TB would be diagnosed in the presence of one of following: (a) positive culture/animal inoculation of MTB from suspected tissue, (b) histology of specimen demonstrating MTB, (c) histological evidence of caseation necrosis, (d) typical findings on gross examination of operative specimen and positive findings on mesenteric lymph node histology [25, 26]. Because of its paucibacillary nature, these criteria are not fulfilled in all cases of ITB and were modified by Logan who added positive response to anti-tubercular therapy (without development of CD on follow-up) and/or presence of clinical/radiological evidence of TB elsewhere (most commonly pulmonary TB) as additional diagnostic criteria [132]. Recently, the presence of necrotic abdominal lymph nodes on cross-sectional imaging in a patient with suspected ITB has demonstrated 100% specificity for ITB diagnosis and can also be considered as a definite criterion [122]. Hence, in line with these findings we suggest the following diagnostic algorithm for a patient with suspected ITB (Fig. 6.5).

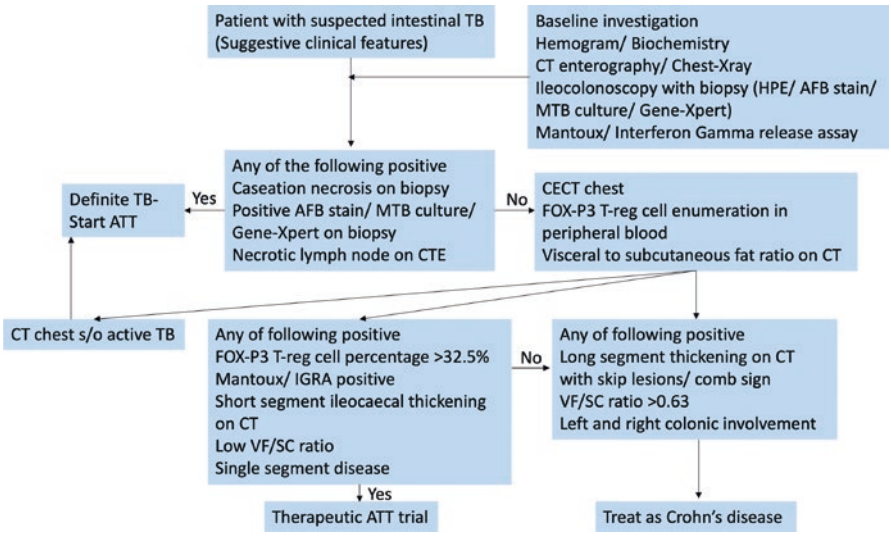

Fig. 6.5 Diagnostic algorithm for a patient with intestinal tuberculosis

Diagnostic laparoscopy can be considered in patients with suspected intestinal TB and presence of tubercules over peritoneum and mesentery, thickened peritoneum, and suggestive biopsy findings may point toward the diagnosis of ITB. Moreover, laparoscopy may also aid in obtaining biopsies from endoscopically inaccessible areas, the need for which, although, has reduced after double balloon enteroscopy.

6.10.1 Therapeutic ATT Trial

Therapeutic ATT trial is considered in patients with suspected ITB who do not meet the definite diagnostic criteria for ITB, but have clinical, radiologic, endoscopic, histologic, or serologic features suggestive for ITB. The diagnosis of ITB is confirmed in patients who document clinical and endoscopic/radiologic response to ATT and remain stable on FU without developing relapse of clinical symptoms. A study of 131 patients with CD (who received ATT trial before diagnosis of CD) and 157 patients with ITB showed 100% endoscopic response in patients with ITB as compared with <5% endoscopic response in CD patients (even though ~40% patients had clinical response on ATT), and forms the basis for diagnostic role of therapeutic ATT trial in this setting [133]. Such patients require clinical assessment after 2–3 months of ATT, and patients who worsen or show no response to ATT should be re-evaluated for alternate diagnoses. However, because of recent demonstration of worse outcomes (higher stricture formation and rates of surgery) in patients with CD who received ATT trial before confirmation of CD diagnosis [134], more emphasis should be put on efforts to differentiate CD from ITB before ATT trial is begun, and in patients who are started on ATT, early objective assessment of response to ATT should be done so as to reduce the duration of ATT in patients with presumptive CD. Hence, in addition to clinical assessment at 2–3 months, endoscopy should be done to document mucosal healing, and in patients with persistent inflammation, diagnosis of CD should be actively pursued. Recent studies have shown the utility of biomarkers such as CRP and fecal calprotectin for early assessment after ATT trial, but will require validation in larger cohorts from other centers [135, 136].

6.11 Treatment

6.11.1 Medical

Regimen The treatment for ITB consists of an intensive phase with 2 months of rifampicin (10 mg/kg), isoniazid (5 mg/kg, with pyridoxine—20 mg/day), ethambutol (15–20 mg/kg), and pyrazinamide (20–25 mg/kg) and continuation phase with same doses of rifampicin, isoniazid, and ethambutol for 4–7 months.

Duration As per the INDEX-TB guidelines the usual treatment duration for intestinal TB is 6 months of ATT (2 months intensive and 4 months continuation) [137]. A recent RCT of 191 participants (75% ITB) observed similar cure rates between 6 and 9 months ATT (91.5% vs 90.8% on per-protocol, 75% vs 75.8% on intention to treat analysis) with only 1 patient in the 6 month and no patient in the 9 month group having recurrence [138]. Further, in a Cochrane review of 3 RCTs with 328 participants, 6 months treatment regimens were similar to 9 months treatment for both intestinal and peritoneal TB in terms of clinical cure rate at end of therapy and relapse at end of follow-up [139]. Two trials (in this meta-analysis) also reported similar healing of active lesions between two treatment arms, and the rates varied from 91 to 100% [140, 141] (Table 6.7).

Response Both clinical and endoscopic response rates are more than 90% with 6 months of ATT in most patients as evidenced by controlled trials as well as real world studies. Hundred percent endoscopic healing was demonstrated in 157 patients with ITB after ATT [133], while in a recent study of 93 patients with abdominal TB, most of the patients had objective clinical response [142]. With respect to intestinal strictures, though the data is heterogeneous, most studies report stricture healing rate of <50% after ATT. Initial studies which used only streptomycin (> 60 years back) showed poor stricture response in patients with ITB [143–145], while a prospective study done 20 years back revealed a 70% stricture healing rate after streptomycin based combination ATT [146]. Another study of 30 patients with colonic TB revealed only 53% stricture resolution in their cohort [147]. In the latest and largest study on this aspect, only 23.6% of 106 patients with ITB had stricture resolution after ATT [148]. Recent demonstration of increased stricture formation in patients with CD who received ATT trial and poor healing of strictures in ITB patients would point toward pro-fibrotic effect of ATT, which however needs further mechanistic and clinical inputs. Moreover, efforts are also required to explore other mechanism of poor stricture resolution and also toward therapies which can improve the stricture healing rates. Regarding the radiologic response after ATT, in a recent study of 19 patients, 15 patients had complete or partial response to ATT, as assessed by diffusion weighted MR enterography, and the responders had significant rise in ADC value, indicating the utility of ADC in objective monitoring of response to ATT [149].

6.11.2 Endoscopic/Surgical

6.11.2.1 Endoscopic Balloon Dilatation

Patients with symptomatic strictures which do not resolve with ATT may require surgical therapy or endoscopic dilatation. Endoscopic dilatation can be attempted in patients with short segment strictures (<4 cm) within reach of endoscopy, and the evidence suggests good response to endoscopic therapy. In 37 patients with gastroduodenal TB, endoscopic dilatation was effective in 94% patients without any

Table 6.7 Summary of trials reporting comparison of 6 months vs 9 months treatment in patients with intestinal tuberculosis

	Makharia 2015		Park 2009		Tony 2008	
Country	India		South Korea		India	
Number randomized	191		90		47	
Site	Gastro-intestinal tract (77% versus 73%), peritoneum (23% versus 19.8%), or both (2% versus 1%)		Intestinal TB		Intestinal TB: ileocecal region, colon, or both.	
Duration of ATT	6 months	9 months	6 months	9 months	6 months	9 months
Number of participants	100	91	45	45	23	24
Regimen	2(HRZE)3/4(HR)3	2(HRZE)3/7(HR)3	2HRZE/4HRE	2HRZE/7HRE	2(HRZE)3/4(HR)3	2HRZE/7HR
Median FU duration of completing ATT	12 months	12 months	39 months	32 months	27 months	26 months
Relapse	1.3%	0%	2.4%	0%	0%	0%
Clinical cure	95.1%	93.4%	95.6%	91.1%	100%	100%
Complete healing of active lesions			93.3%	91.1%	100%	100%
Treatment failure	2.4%	1.3%	0%	0%	0%	0%

symptom recurrence at 2 years of follow-up [150]. Though limited to small case series, endoscopic dilatation has also shown effectiveness in patients with colonic, ileocecal valve, and ileal strictures [151–154]. Extrapolating evidence from CD stricture dilatation, 4–5 sessions of dilatation should be attempted with a maximum balloon size of 15–18 mm. The end point is passage of colonoscope through the stricture, and patients not reaching this endpoint are classified as failures. Few patients may require repeat dilatation at 1–2 years after initial session.

6.11.2.2 Surgery

With the improvement in medical and endoscopic therapy, surgery for intestinal TB has reduced in frequency and is mostly limited to complications such as perforation, obstruction, and refractory bleeding [155]. Surgery may also be considered in patients with strictures refractory to medical/endoscopic therapy [156]. Commonly performed surgeries are bowel resection with primary anastomosis or diversion ileostomy. In patients with multiple strictures, stricturoplasties can be performed to avoid extensive bowel resection [157].

6.12 Multi-Drug Resistant Intestinal Tuberculosis

Unlike pulmonary TB, intestinal TB is a paucibacillary disease, which makes multi-drug resistant (MDR) TB rare among patients with ITB. The prevalence of MDR in ITB across various series has been summarized in Table 6.8, which varies from 0 to 13.9%, and depends upon patient population, concomitant pulmonary TB, and method of detection [51, 102–104, 158–160]. MDR TB should be suspected in patients with definite TB showing absence of clinical and objective response to ATT. In patients not responding to therapeutic ATT trial, CD is the first possibility, although multiple biopsies should be obtained to rule out rare possibility of MDR TB before switching the diagnosis to CD.

Table 6.8 Prevalence of multi-drug resistance in patients with intestinal TB

Author/ year	Number of patients	Technique	Single drug resistance	Multi-drug resistance
Lin 2009	30	LJ medium		13%
Ye, 2012	74	LJ medium	17.6%	2.7%
Samant, 2014	43	MGIT	14.3%	5.4%
Malik 2015	38	MGIT		8%
Sonambekar 2017		MGIT	9.3%	13.9%
Kumar 2017	29	Gene-Xpert	0	0
Udgirkar 2020	176	MGIT		4.5%

LJ Lowenstein–Jensen, *MGIT* Mycobacterial growth indicator tube

6.13 Conclusion

Despite the rising disease burden of non-infectious disorders in developing countries, the incidence of infections such as intestinal TB has remained stable. Intestinal TB, because of its paucibacillary nature, poses significant diagnostic challenge to the clinicians at the initial evaluation. Though there has been improvement in the sensitivity of upfront ITB diagnosis, a proportion of patients still require a therapeutic ATT trial for confirmation. The algorithm for following patients on therapeutic ATT trial is also being reformed with an emphasis on early objective recognition of non-response to ATT. The important differentials in patients who do not respond to ATT include Crohn's disease (in patients on ATT trial) and MDR-TB (in patients with definite TB); however, MDR-TB should be excluded in all non-responders with adequate tissue acquisition. Newer diagnostic modalities such as MR enterography with diffusion weighted imaging have the potential to improve the monitoring and follow-up of these patients. However, more thrust needs to be put on improving the diagnostic accuracy of definite ITB diagnosis, thereby reducing the frequency of ATT trial and its adverse consequences.

Conflict of Interest None.

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Differentiating Intestinal Tuberculosis from Crohn's Disease

7

Julajak Limsrivilai

Key Points

1. Differentiating Crohn's disease from intestinal tuberculosis is a difficult clinical problem in countries where tuberculosis is endemic.
2. Certain features like shorter duration, presence of fever or pulmonary complaints, ileocecal involvement, transverse ulcers, short segment involvement, necrotic lymph nodes may favor the diagnosis of intestinal tuberculosis but other than necrotic lymphadenopathy none is specific.
3. Models integrating potential features have been proposed. However, external validation of them is required.
4. Anti-tuberculous therapy helps in differentiating these two diseases because the ulcers of intestinal tuberculosis heal with ATT as early as 2 months of treatment (early mucosal response).

Crohn's disease (CD) has become an important differential diagnosis of intestinal tuberculosis (ITB) in Asia because its incidence and prevalence is increasing in this region [1]. Both diseases share many similar presentations. A definite diagnosis of ITB depends on methods that have unsatisfactorily low sensitivities including 5.3–37.5% for acid-fast bacilli (AFB) tissue staining [2–4], 23–46% for mycobacterial culture [5, 6], and 36.4–67.9% for polymerase chain reaction (PCR) [4, 5, 7–9]. As a result, ITB cannot be confidently excluded—even when all of the above results are negative. A misdiagnosis of intestinal tuberculosis and treating it as Crohn's disease can cause life-threatening complications [10]. On the other hand, delayed CD diagnosis due to misdiagnosis with ITB can lead to exacerbation of disease and

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disease-related complications [11]. There have been multiple reports on the demographic, clinical, endoscopic, pathologic, radiologic, and serologic features and in differentiating CD and ITB, and several predictive models have been developed. This chapter summarizes the data from the studies reporting on differentiating CD and ITB. These features are summarized in Table 7.1.

7.1 Demographic Features

Meta-analysis by Limsrivilai et al. including all studies aiming to differentiate CD from ITB from inception till September 2015 found that ITB and CD patients tend to afflict similar age groups [12]. The mean age of CD patients has been reported from 26.8 to 37.4 years whereas it was 29.3–49.3 years in ITB patients [2–4, 7, 9, 13–22]. Male gender has been reported to be more predominant in CD in the meta-analysis but may not have much discriminative value alone [12]. Living in urban domicile, graduation at high school level or higher, and higher income have been reported to have a trend to be favored CD [23] while immunocompromised status, particularly HIV infection is an important risk factor for ITB [24].

7.2 Clinical Features

Clinical presentations are categorized into 3 groups which include intestinal symptoms, extra-intestinal involvement, and systemic symptoms.

For intestinal symptoms, duration of presentation was reportedly longer in CD. The median and range of presenting duration was 6–53.3 months and 0.3–300 months in CD, and 3–23.4 months and 0–120 months in ITB, respectively [2, 7, 16, 20, 23, 25, 26]. Diarrhea and hematochezia have been reported more in CD patients with the reported prevalence of 33–80% and 20–68%, respectively. The corresponding prevalence in ITB patients was 18–65% and 3–31%, respectively [2–4, 7, 9, 13, 15, 16, 18, 20, 23, 25, 27–36]. Abdominal pain has been reported at high prevalence, 60–90% in both diseases [2–4, 7, 9, 13, 15, 16, 18, 20, 23, 25, 27–31, 34]. For disease complications, intestinal fistula has been reported in 5.6–15% of CD and 0–6.7% of ITB patients while intestinal obstruction has been reported in 21–31% of CD and 10–55% of ITB patients [2, 12, 16, 31].

For extra-intestinal involvement, presence of extra-intestinal immunologic manifestations and perianal involvement are more frequent in CD (7–61% in CD and 0–23% in ITB) [2, 4, 12, 13, 15, 18, 27, 36, 37]. The prevalence of perianal disease was 10–34.7% in CD and 0–14.8% in ITB [2, 7, 9, 15, 16, 18, 25, 27, 28, 31–36]. In contrast, pulmonary involvement was significantly higher in ITB patients with the reported prevalence of 12.7–55.6% while in it was 0–8.8% in CD [4, 13, 15, 16, 18, 27, 33, 34, 36].

For systemic symptoms, fever and night sweat were found predominantly in ITB [12]. Fever was reported at the prevalence of 30–90% in ITB and 0–57% in CD, and night sweat was reported at 31–55% in ITB [2–4, 7, 9, 13, 15, 16, 18, 20, 23, 25,

Table 7.1 Features differentiating Crohn's disease from intestinal tuberculosis

Features	Crohn's disease	Intestinal tuberculosis
Demographic	• Uncommon in extremely old age • High socioeconomic	• Any age • Immunocompromised status
Clinical features		
• Duration of presentation	Longer (median 6–53.3 months)	Shorter (median 3–23.4 months)
• Intestinal symptoms	More common for • Diarrhea (33–80%) • Hematochezia (20–68%)	Less common • Diarrhea (18–65%) • Hematochezia (3–31%)
• Systemic symptoms	Less common for • Fever (0–57%) • Night sweat (2–22%)	More common for • Fever (30–90%) • Night sweat (31–55%)
• Fistula	Not uncommon (5.6–15%)	Rare (0–6.7%)
• Perianal disease	Not uncommon (10–34.7%)	Rare (0–14.8%)
• Extra-intestinal manifestations	Not uncommon (7–61%)	Rare (0–23%)
• Lung involvement	Rare (0–8.8%)	Not uncommon (12.7–55.6%)
Endoscopic features		
• Longitudinal ulcer	More common (10–63%)	Less common (0–33%)
• Transverse ulcer	Less common (4–36%)	More common (25–83%)
• Aphthous ulcer	More common (9–82%)	Less common (0–38%)
• Cobblestone appearance	More common (10–58%)	Less common (0–37%)
• Patulous ileocecal valve	Less common (2–20%)	More common (10–51%)
• Rectal involvement	More common (17–62%)	Less common (2–28%)
• Sigmoid/left-side involvement	More common (31–66%)	Less common (11–37%)
Pathological features		
• Granuloma	Present in 0–63% (small and vague)	Present in 25–100% (confluent, large, multiple, submucosal)
• Focally enhanced colitis	More common (22.5–67.9%)	Less common (20–35.8%)
Imaging features (CTE/MRE)		
• Lymph node >1 cm in size with central necrosis	Not reported found	Very suspicious if present
• Skipped lesions (>3)	Strongly favor	Strongly against

(continued)

Table 7.1 (continued)

Features	Crohn's disease	Intestinal tuberculosis
• Long segment involvement (>3 cm)	Favor	Against
• Comb sign.	Strongly favor	Strongly against
• Fibrofatty proliferation	Favor	Against
• Asymmetrical wall thickening	Favor	Against
• Visceral/subcutaneous fat	Favor	Against
Serological tests		
• Interferon-gamma release assay	Strongly against (0–24.6%)	Strongly favor (66.7–100%)

27–31, 33, 34] and 2–22% in CD [3, 9, 15, 16, 18, 25, 27, 29], respectively. Weight loss was reported nonsignificantly different in the meta-analysis [12]; the reported prevalence was 32.5–92.6% in CD and 51–93.3% in ITB [2, 4, 7, 13, 15, 16, 18, 20, 23, 25, 27, 29–31, 33].

As above, there is overlapping of the reported prevalence in almost clinical presentations. Therefore, clinical presentation along cannot distinguish between these two diseases.

7.3 Endoscopic Features

Endoscopic findings have been reported to differentiate ITB from CD by Lee et al in 2006 [38]. They reported four findings favoring ITB (transverse ulcers, scars or pseudopolyps, a patulous ileocecal (IC) valve, and involvement of less than 4 of 6 segments of the colon, including the ileocecum, ascending colon, transverse colon, descending colon, sigmoid colon, and anorectum), and 4 findings favoring CD (longitudinal ulcers, aphthous ulcers, cobblestone appearance, and anorectal involvement). After this study, many studies relating to differentiation of CD from ITB reported endoscopic findings in these two diseases. Meta-analysis found that aphthous ulcers, longitudinal ulcers, and cobblestone appearance significantly favored CD [12]. The reported prevalence of these findings was 9–82%, 10–63%, and 10–58% in CD, and 0–38, 0–33, and 0–37% in ITB, respectively. On the other hand, transverse ulcers and patulous IC valve were found significantly higher in ITB. The reported prevalence of these findings was 4–36% and 2–20% in CD, and 25–83% and 10–51% in ITB, respectively [2, 3, 7, 9, 13, 15, 16, 20, 23, 25–30, 38]. Figures 7.1 and 7.2 showed longitudinal ulcer in CD and transverse ulcer in ITB, respectively. Difference in location of involvement has also been reported between ITB and CD [12]. The reported prevalence of sigmoid involvement was 31–66% in CD and 11–37% in ITB, and the prevalence of rectum involvement was 17–62% in CD and 2–28% in ITB [7, 13, 15, 16, 20, 25, 27].

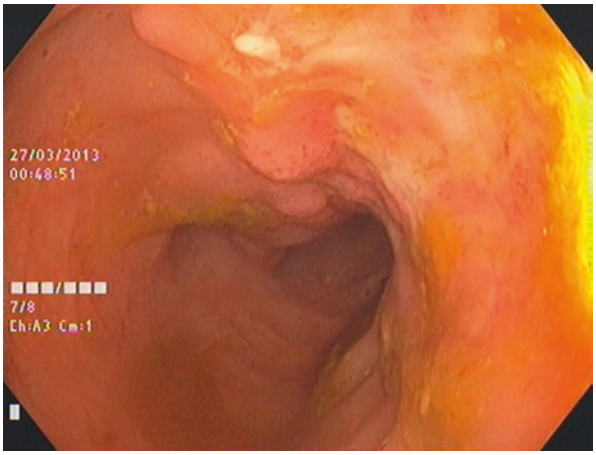

Fig. 7.1 Longitudinal ulcer in Crohn's disease

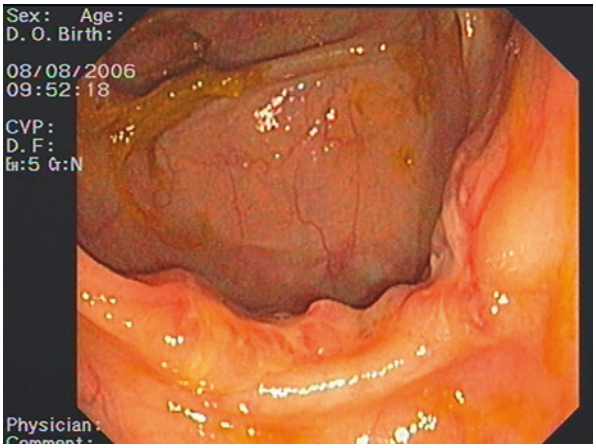

Fig. 7.2 Transverse ulcer in intestinal tuberculosis

As in clinical presentation, overlapping of the prevalence of both endoscopic findings and location of involvement between the two diseases. Endoscopic findings alone, therefore, cannot completely differentiate ITB from CD.

7.4 Pathological Features

In 1972, Tandon and Prakash reported the pathology of intestinal tuberculosis and its distinction from Crohn's disease based on 169 cases (10 CD and 159 ITB) who presented with intestinal obstruction and who underwent intestinal resection. They described that granuloma was present in all ITB, but absent in at least 25% of

CD. The granulomas in TB were often large, usually had caseation, and are often confluent. Furthermore, submucosal widening and fissures were generally present in CD while absent in ITB. Lymph node involvement was found in ITB although no intestinal lesions, but not in CD [39].

Nowadays, most pathological specimens are obtained from colonoscopy. Therefore, some features cannot be evaluated such as fissuring ulcers, transmural inflammation, and granuloma in lymph node. Studies describing microscopic features have been published. Pulimood et al divided the findings into 4 groups including characteristics of granulomatous inflammation, focal crypt-related inflammatory changes such as focally enhanced colitis, other features of mucosal damage such as architectural alteration, deep ulceration, aphthous ulceration, and acute/chronic inflammation, and segmental distribution of changes [40]. These definitions were used by subsequent studies. The meta-analysis found that features more common in ITB included confluent granuloma, large granuloma, multiple granulomas per section, submucosal granuloma, granuloma with surrounding cuffing lymphocytes, and ulcer lined by histiocytes, whereas focally enhanced colitis was found more in CD [12].

Patterns of macrophage polarization may be helpful in differentiating ITB from CD. Proinflammatory M1ϕ polarization was more common in colonic mucosa of CD patients, especially in the presence of mucosal granulomas [41].

There are some limitations of using pathological findings. First, most features are required to characterize granuloma features; however, granuloma was reportedly present in 0–63% in CD and 25–100% in ITB [7–9, 13, 16, 19, 23, 28, 30, 31, 36, 38, 40, 42]. Furthermore, the definition of each finding may not be well known. Many pathologists may not be able to accurately describe these findings.

7.5 Imaging Features

Cross-sectional imaging such as computed tomography enterography (CTE) and magnetic resonance imaging enterography (MRE) have been increasingly used at present. Many studies using CTE in differentiating ITB from CD including two meta-analyses by Kedia et al and Limsrivilai et al have been published recently [12, 18, 20, 26, 43, 44]. Useful features can be grouped into 3 groups including bowel wall changes, mesenteric changes, and pattern of involvement.

The findings at bowel wall include bowel wall thickness and mural stratification. Asymmetrical bowel wall thickening was reported in both meta-analyses that it was significantly associated with CD. However, the performance in differentiating CD from ITB was fair; the area under the curve for summary receiver operating characteristic curve (AUCSROC) was 0.68, sensitivity was 41%, and specificity was 90% [44]. Mural stratification, which is defined as visualization of a two- or three-layer appearance within the small bowel wall, was not a significant finding in one meta-analysis [44]. The other meta-analysis found that it was significant finding favoring CD with an odds ratio of 2.3, but with the lower bound of 95% confident interval close to 1 (1.04–5.17) [12].

Mesenteric changes included comb sign, fibrofatty proliferation, and necrotic lymph node. Fibrofatty proliferation and comb sign were significant findings associated with CD in both meta-analyses [12, 44]. Comb sign had a good performance in differentiating ITB from CD. Its AUCSROC was 0.89 with the sensitivity and specificity of 82% and 81% in one meta-analysis [44], while the other meta-analysis reported its odds ratio favoring CD of 19.8 [12]. Fibrofatty proliferation had an AUCSROC of 0.69, and its sensitivity and specificity were 41% and 89%, respectively, in one meta-analysis [44], and its odds ratio favoring CD was 4.05 in the other [12]. Lymph node necrosis was found only in ITB, not in CD in one meta-analysis [44], and because of this, the other meta-analysis did not do analysis for this finding [12].

The pattern of involvement includes long- or short segmental involvement (> or < 3 cm) and skip involvement (>3 areas). Short segmental involvement was found to be significantly associated with ITB with an odds ratio favoring CD of 0.11 [12], whereas it was not significant in the other meta-analysis [44]. Skip involvement favored CD and had a good performance in one meta-analysis with an AUCSROC of 0.87, sensitivity of 86, and specificity of 74 [44].

More recently, visceral fat/subcutaneous fat ratio of more than 0.63 was reported to be favored the diagnosis of CD with a sensitivity and specificity of 81% and 78%, respectively [45]. Then this parameter had been integrated in a model together with long segmental involvement and lymph node necrosis. The model had been shown to have a specificity of 100% in diagnosis of CD [46].

Based on the above findings, the Indian Society of Gastroenterology and Indian Radiological and Imaging Association recommends that CTE/MRE complements other modalities in differentiation between ITB and CD. The presence of lymph nodes greater than 1 cm in size with central necrosis favors a diagnosis of ITB over CD. On the other hand, the presence of skip lesions (>3), long segment involvement (>3 cm), comb sign, fibrofatty proliferation, left colonic involvement, and asymmetric thickening favor the diagnosis of CD over ITB [47].

7.6 Serological and Other Blood Tests

Interferon-gamma release assays (IGRA) is a marker for latent tuberculosis. Several studies including 3 meta-analyses have been published [12, 48, 49]. Meta-analysis by Ng et al found that the pooled sensitivity, specificity, positive likelihood ratio, and negative likelihood ratio of IGRA for the diagnosis of ITB were 81% (95% CI, 75–86%), 85% (95% CI, 81–89%), 6.02 (95% CI: 4.62–7.83), and 0.19 (95% CI: 0.10–0.36), respectively. The AUC was 0.92 [49]. The results went in the same direction in the more recent meta-analysis, which showed that the odds ratio of diagnosis of CD was only 0.02 (0.01–0.04) of IGRA was positive [12].

The anti-*Saccharomyces cerevisiae* antibody (ASCA) has been recognized as a specific serologic marker of CD. ASCA was reported to be positive in about 50% of CD patients [50]. However, the results of studies using ASCA for differentiating

ITB from CD are conflicting [35, 51, 52]. In meta-analysis by Limsrivilai et al., ASCA had a trend to favor the diagnosis of CD, but not statistically significant [12].

Serum proteomic profiles have been shown in a study by Zhang et al. (30 CD, 21 ITB) that a differential diagnostic model comprising three potential biomarkers protein peaks (M/Z 4267, 4223, 1541) can well distinguish CD patients and ITB patients, with a specificity and sensitivity of 76.2% and 80.0%, respectively [53].

Frequency of CD4 + CD25 + FOXP3+ Treg cells in peripheral blood was significantly increased in ITB as compared to CD in a prospective study of 124 patients (32 CD, 16 ITB, 38 ulcerative colitis, and 33 controls). FOXP3+ cells in peripheral blood showed an AUROC curve of 0.908 in differentiating ITB from CD. At a cut-off value of>32.5%, a sensitivity of 75% and a specificity of 90.6% had been demonstrated [54].

7.7 Models Differentiating Intestinal Tuberculosis from Crohn's Disease

Many clinical, endoscopic, pathologic, imaging, and serological features have been shown to be significantly different between ITB and CD, but none of those features are exclusive to either ITB or CD. Many models integrating significant features have been proposed to differentiate ITB from CD to help decrease the rate of incorrect empirical therapy [55]. The early models included diagnostic parameters routinely available and used in clinical practice, such as clinical features, endoscopic findings, and pathologic findings [7, 15, 16, 21, 38]. The diagnostic models developed later included more advanced diagnostic parameters, such as high-resolution imaging [18, 20, 26, 46] and serological testing [12, 19, 22, 56, 57]. The published models are summarized in Tables 7.2, 7.3, and 7.4. These models are required to be validated by external populations. For the models using clinical, endoscopic, and pathological features, the model with more significant parameters seems to be more accurate [58].

7.8 Anti-Tuberculous Therapeutic (ATT) Trial

In 2008, Park et al prospectively analyzed the colonoscopic findings before and after short-term antituberculosis treatment in 18 patients with nonspecific ulcers on the ileocecal area and compared them with 7 patients of confirmed tuberculous colitis by acid-fast bacilli or caseating granuloma on colonic biopsy [59]. This study found that endoscopic mucosal healing after short-term ATT could differentiate ITB from CD.

In 2016, Pratap Mouli et al studied in 131 patients who received anti-tubercular therapy before being diagnosed as CD and in 157 ITB patients. In ITB patients, 94% showed global symptomatic response by 3 months, and all had endoscopic mucosal healing at 6 months. In CD patients, global symptomatic response with ATT was seen in 38% at 3 months and in 37% who completed 6 months of ATT, but

Table 7.2 Models integrating clinical, endoscopic, and pathological findings

Authors	Country	Study Design	Model type	Parameters	Model detail		Performance	
Lee YJ et al. Endoscopy 2006	Korea	Prospective CD 44, ITB 44	Scoring system	8 endoscopic findings	Favor CD (+1/each): Longitudinal ulcer, aphthous ulcer, cobblestone appearance, anorectal involvement Favor ITB (−1/each): Transverse ulcer, scars or pseudopolyps, a patulous ileocecal valve, involvement <4 segments Final score: 1–4: Crohn's disease 0: Indeterminate (−1) – (−4): ITB		Correct diagnosis: 87.5% Incorrect diagnosis: 8% Indeterminate: 4.5%	
Makharia et al. Am J Gastroenterol 2010	India	Prospective CD 53, ITB 53 (training) CD 20, ITB 20 (validation)	LR model	4 (2 clinical, 1 endoscopic, 1 pathological findings)	+ 2.3 × weight loss – 2.1 × blood in stool – 2.5 × involvement of sigmoid colon – 2.1 × focally enhanced colitis + 7		AUROC Training 0.906 Validation 0.893	
Li X et al. Dig Dis Sci 2011	China	Retrospective CD 130, ITB 122	LR model	6 clinical, 6 endoscopic findings	*Clinical score* Hematochezia Surgery history Perianal disease Pulmonary TB Ascites PPD skin test	*Endosc. Score* Rectum Long. Ulcers Cobblestone IC valve Tran. Ulcers Rodent-like ulcer	*Clinical* Se 90% Sp 77% Acc 84%	*Endoscopy* Se 83% Sp 82% Acc 83%
Yu H et al. Digestion 2012	China	Retrospective CD 53, ITB 43	LR model	3 (1 clinical, 1 endoscopic, 1 pathological findings)	– 2.0 × night sweat + 3.6 × longitudinal ulcer – 3.8 × granuloma		AUROC 0.864	

(continued)

Table 7.2 (continued)

Authors	Country	Study Design	Model type	Parameters	Model detail	Performance
Jung Y et al. Am J Gastroenterol 2016	Korea	Retrospective CD 79, ITB 49 for training CD 79, ITB 49 for validation	LR model	7 (4 clinical, 3 endoscopic findings)	Diarrhea Longitudinal ulcers Involvement of sigmoid colon Age Female gender Ring shape ulcers Suspicious of pulmonary TB	AUROC Training 0.979 Validation 0.978

AUROC area under receiver operating characteristic curve, *LR* logistic regression
(Adapted from Limsrivilai J, Pausawasdi N. Intestinal tuberculosis or Crohn's disease: a review of the diagnostic models designed to differentiate between these two gastrointestinal diseases. Intest Res 2020 with permission)

Table 7.3 Model integrating computed tomography enterography

Authors	Country	Study Design	Model type	Parameters	Model detail		Performance
Zhao HS et al. Inflamm Bowel Dis 2014	China	Retrospective CD 141, ITB 47	LR model	6 clinical 8 CTE findings	*Clinical model* Hematochezia Perianal disease PPD test Ascites Pulmonary TB Night sweat	*CTE model* Left colon Asymmetrical wall Abscess Comb sign LN along rt. colic artery. Contracted IC Fixed patulous IC LN with necrosis	*AUROC* Clinical model 0.916 CTE model 0.986
Kedia S et al. Indian J Gastroenterol 2015	India	Retrospective CD 54, ITB 50	Scoring system	3 CT/CTE findings	Long segment involvement+ (1–ileocecal region involvement)+ (1–LN ≥1 cm)		Risk score for CD 3: Se 37, Sp 90 Risk score for ITB 0: Se 14, Sp 100
Mao R et al. Endoscopy 2015	China	Prospective, consecutive 67 CD, 38 ITB for training 40 CD, 20 ITB for validation	Algorithm (combining Lee's endoscopic score)	2 CTE findings 8 endoscopic findings	Presence of comb sign or/and Segmental small bowel lesion		Increase accuracy of endoscopic score alone 71.6% − > 88.3%
Kedia S et al. J Gastroenterol Hepatol 2018	India	Retrospective 32 CD, 27 ITB for training 38 CD, 31 ITB for validation	Scoring system	2 CT/CTE findings	VF/SC ratio > 0.63 + long segment involvement		Validation set Risk score for CD 2: Se 50, Sp 97 Risk score for ITB 0: Se 61, Sp 84

AUROC area under receiver operating characteristic curve, *CD* Crohn's disease, *CTE* computed tomography enterography, *IC* ileocecal valve, *LN* lymph node, *LR* logistic regression, *Se* sensitivity, *Sp* specificity, *TB* tuberculosis

(Adapted from Limsrivilai J, Pausawasdi N. Intestinal tuberculosis or Crohn's disease: a review of the diagnostic models designed to differentiate between these two gastrointestinal diseases. Intest Res 2020 with permission)

Table 7.4 Models integrating clinical, endoscopy, pathology, imaging study, and laboratory tests

Authors	Country	Study Design	Model type	Parameters	Model detail		Performance
Huang X et al. World J Gastroenterol 2015	China	Prospective CD 25, ITB 40	Scoring system	12 findings (2 clinical, 5 endoscopic, 4 CTE, 1 IGRA)	*Favor CD (+1)* Longitudinal ulcers Nodular hyperplasia Cobblestone Intestinal diseases Intestinal fistulas Target signs Comb signs	*Favor ITB (−1)* Night sweats Positive PPD tests Positive T-SPOT.TB Ring ulcers Ulcer scars	AUROC 0.997
Bae JH et al. Inflamm Bowel Dis 2017	Korea	Prospective CD 40, ITB 40 for training CD 14, ITB 23 for validation	Scoring system	8 endoscopic findings 2 images (CXR, SBFT) 2 laboratory tests (ASCA, IGRA)	*Endosc. Score* (8 findings)	*Lab-radio score* *Favor CD (+1)* - proximal SB (SBFT) - ASCA *Favor ITB (−1)* - pulmonary TB (CXR) - IGRA	AUROC Training 0.990 Validation 0.981
					(+)➔1, 0➔0, (−)➔(−1)	(+)➔1, 0➔0, (−)➔(−1)	
					Summation (−2, −1) = > ITB, (0,1,2) = > CD		

Wu X et al. Inflamm Bowel Dis 2018	China	Prospective CD 107, ITB 60 for training CD 46, ITB 26 for validation	LR model	5 (2 clinical, 2 endoscopic, 1 IGRA)	Perianal disease Longitudinal ulcer Left colon Pulmonary TB-specific Ag to phytohemagglutinin	AUROC Training 0.975 Validation 0.950
He Y et al. Am J Gastroenterol 2019	China	Prospective CD 143, ITB 69 for training CD 76, ITB 22 for validation	Step1: Select variable from a random forest regression model Step2: LR model	2 models 8 (1 clinical, 2 endoscopic, 3 CTE, 2 IGRA/PPD)	*Model 1* Age Rectum involvement Transverse ulcer Skipped involvement of small bowel Comb sign IGRAs	AUROC Training 0.977 Validation (cut-off $p = 0.5$) Se 86.8% Sp 90.9% Accuracy 87.8%
					Model 2 Age Rectum involvement Transverse ulcer Skipped involvement of small bowel Target sign PPD	AUROC Training 0.930 Validation (cut-off p = 0.5) Se 84.2% Sp 100% Accuracy 87.8%

(continued)

Table 7.4 (continued)

Limsrivilai et al. Am J Gastroenterol 2017		Meta-analysis Validation cohort 29 CD, 22 ITB	Step 1: Select significant variables with low heterogeneity based on meta-analytic results Step 2: Integrate the variables to Bayesian model	9 clinical, 8 endoscopic, 5 pathological, 5 CTE, and 1 IGRA (can select only available parameters)	bit.ly/ITBvsCD	AUROC Clinical + endoscopy 0.920 Clinical + endoscopy + pathological findings 0.943

ASCA Anti-*Saccharomyces cerevisiae* antibody, *AUROC* area under receiver operating characteristic curve, *CD* Crohn's disease, *CTE* computed tomography enterography, *CXR* chest X-ray, *IC* ileocecal valve, *IGRA* interferon-gamma release assay, *LN* lymph node, *LR* logistic regression, *SBFT* small bowel follow through, *Se* sensitivity, *Sp* specificity, *TB* tuberculosis

(Adapted from Limsrivilai J, Pausawasdi N. Intestinal tuberculosis or Crohn's disease: a review of the diagnostic models designed to differentiate between these two gastrointestinal diseases. Intest Res 2020 with permission)

only 5% had endoscopic mucosal healing at 6 months. The same response pattern was observed in a validation cohort of 55 patients who were prospectively recruited. This study suggested that symptom persistence after a therapeutic trial of 3 months of ATT may indicate the diagnosis of Crohn's disease, and emphasizing a need for repeat colonoscopy for diagnosing CD [60]. Healing of ulcers has been reported as early as 2 months after initiation of ATT and this early mucosal response may discriminate ITB and CD [61].

Sharma et al did a retrospective study in 112 patients suspected abdominal tuberculosis (105 TB, 3 CD, 7 other diagnoses). This study found that lack of decline in CRP may suggest alternative diagnosis or drug-resistant TB [62].

In summary, response to ATT trial is reliable for differentiating ITB from CD, and the Asia-Pacific guidelines recommend 8–12 weeks of empirical antituberculosis treatment (ATT) for patients with diagnostic uncertainty due to the possible onset of potentially fatal complications if immunosuppressive agents are inappropriately prescribed to ITB patients [63].

7.9 Conclusion

Crohn's disease is very difficult to be distinguished from intestinal tuberculosis. The tools we have in hand currently help us to improve diagnostic capability. However, the problem has not been solved. ATT is still required in some situations. Future research is warranted.

Conflict of Interest None.

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Imaging of Intestinal Tuberculosis

8

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Key Points

- Radiology has an important role in diagnosis, determining the extent and site of involvement and in assessing response to treatment in intestinal tuberculosis.
- Characteristic imaging features of gastrointestinal tuberculosis include ileocaecal involvement, skip lesions in bowel, and necrotic abdominal lymphadenopathy.
- Differential diagnoses of ileocaecal tuberculosis on imaging include lymphoma, carcinoma, Crohn's disease, and amoebiasis.
- CT enteroclysis/enterography are sensitive modalities for determining the extent of the disease in small bowel tuberculosis.
- MR enteroclysis/enterography along with diffusion-weighted imaging can be used as a tool for diagnosing as well as assessing the treatment response of tuberculosis.

8.1 Introduction

Radiology plays a pivotal role in the diagnosis and evaluation of gastrointestinal tuberculosis. It not only helps in the diagnosis but also determines the extent of involvement, the treatment response, and the complications caused by the disease.

To decide the best imaging modality to be used in a patient of intestinal tuberculosis, clinical history is important. If history points towards mucosal and

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intraluminal disease abnormalities, then endoscopy and barium studies could be better. If mural and extramural abnormalities are suspected, cross-sectional imaging modalities like CT and MRI are better. Advances in CT and MRI (enterography and enteroclysis) provide both intraluminal and extraluminal information. Ileocaecal region is the most common gastrointestinal part to be involved followed by the colon, appendix, anorectum, oesophagus, stomach, and duodenum. Complications include obstruction, perforation, enterolithiasis, perianal fistulae, and haemorrhage [1, 2].

8.2 Barium Studies

Conventional radiographic techniques include abdominal X-ray and barium studies. X-ray is used for the initial evaluation in patients who are suspected cases of obstruction and perforation, both of which are known complications of gastrointestinal tuberculosis. Barium meal follow through (BMFT) study is done for the evaluation of small bowel. The sensitivity of BMFT for diagnosing small bowel tuberculosis is about 70–100%. BMFT study can provide physiologic information about the flow of food in the intestine. It can provide information about intestinal transit time. It evaluates the motility disorders as well as organic lesions. The disadvantage of this procedure is that it is a lengthy examination. It can be false-negative due to overlapping of bowel loops and poor distensibility of segments. Miller, in 1979, introduced the technique of barium enteroclysis for the small bowel [3]. It involves the distension of the small intestine by intubating the jejunum with the help of a nasogastric tube. Barium enteroclysis is better as compared to BMFT because it is faster and allows better visualization of small lesions, mucosal surface pattern and relationship between adjacent loops. It is useful in patients of subacute obstruction as it detects the early and incomplete strictures.

8.3 Cross-Sectional Imaging

Computed Tomography (CT) and Magnetic Resonance Imaging (MRI) techniques are cross-sectional modalities, which not only provide information about the bowel wall but also the extra-intestinal abnormalities in cases of tuberculosis. They can evaluate concurrent abnormalities like lymph nodes, peritoneal thickening, vascular changes, and ascites. They can visualize the whole bowel at once, the extent of disease, and the associated complications. They are also more reliable, better tolerated, and more accurate.

8.4 Computed Tomography

CT is the imaging modality of choice for suspected intestinal obstruction and perforation. Multiplanar reformations (MPR) help in visualizing intestinal abnormalities in multiple planes. The disadvantage of CT is that it is not able to provide information about the mucosal and intraluminal abnormalities, which are better visualized on barium studies or endoscopy studies. It also cannot detect the motility changes and changes in secretion of the intestine. Recent advances in radiology techniques include CT enteroclysis, CT enterography, and CT colonography. These procedures help in the better evaluation of mucosal and intraluminal abnormalities as compared to basic CT technique. CT enterography involves the ingestion of hyperosmolar fluid causing adequate distension of small bowel, leading to increased clarity of intraluminal abnormalities as well as incomplete strictures [4]. CT enteroclysis has similar utility. However, it involves intubation of small bowel with fluid through a nasogastric tube inserted till the level of jejunum. CT enterography is often preferred to CT enteroclysis due to the patient discomfort associated with nasogastric tube insertion [5]. Both of these techniques are useful in patients of tuberculosis having pain or obstruction due to strictures. They combine the advantages of barium enteroclysis with that of CT. Another recent CT technique for the evaluation of small bowel pathologies is virtual CT enteroscopy, which involves the distension of the small bowel using carbon dioxide. This allows the virtual endoscopic evaluation of small bowel and may be comparable with capsule endoscopy [6]. CT colonography is also called virtual colonoscopy. It is used for the evaluation of the large bowel, which is distended by insufflating air or carbon dioxide per-rectally. It can visualize the intraluminal and mucosal abnormalities of the colon like colonoscopy, as well as provide information about wall thickness and extraluminal abnormalities [7]. The disadvantages of all these CT based techniques are the usage of ionizing radiation and intravenous contrast.

8.5 Magnetic Resonance Imaging

Tuberculosis patients may need to undergo recurrent imaging examination because of the chronicity of the disease and the association of long-term complications like strictures. Many researchers are nowadays focusing on MRI based examination, the advantage being no radiation, better soft-tissue evaluation, and the assessment of bowel wall abnormalities. Like CT, MR advances in radiology techniques include MR enterography, MR enteroclysis, and MR colonography. These procedures help in better evaluation of mucosal and intraluminal abnormalities as compared to basic MRI [8]. Recent advances in MRI techniques like diffusion-weighted imaging (DWI) help in assessing disease activity [9].

8.6 Ultrasound

Abdominal ultrasound (US) has a limited role in the evaluation of intestinal tuberculosis. It cannot evaluate the complete extent of bowel and has low sensitivity for mucosal and intraluminal abnormalities. However, it can evaluate concomitant extra bowel abnormalities like lymphadenopathy, ascites, and peritoneal thickening. It can also diagnose intestinal obstruction or perforation, which are complications of tuberculosis. Its advantages are that there is no radiation involved, it is faster to perform, and can be done at the bedside. The disadvantages include that findings are subjective, depend on the expertise of the observer leading to interobserver differences. Nowadays, US is used along with endoscopy procedures known as endoluminal ultrasound, which can detect the intraluminal and bowel wall abnormalities better. This has been elaborated in another chapter in this book. Recent advances in US like contrast-enhanced ultrasound have been reported to provide useful information for the diagnosis of suspected patients of tuberculosis [10]. Sonoenteroclysis is another useful technique, which involves doing abdominal ultrasound after infusion of an isotonic nonabsorbable electrolyte solution containing polyethylene glycol through naso-jejunal tube. It helps in better assessment of the small bowel lesions and has been found to be comparable to barium enteroclysis [11].

8.7 Ileocaecal and Small Intestinal Tuberculosis

The most common site of involvement in the small bowel is the ileocaecal region. Two thirds of gastrointestinal tuberculosis is ileocaecal in nature [12]. Concomitant jejunal involvement may be there. However, isolated involvement of jejunum or ileum is rare. Abdominal X-ray is the primary investigation done in suspected cases of obstruction or perforation. Obstruction is the most common complication of gastrointestinal tuberculosis. X-ray will show dilated bowel loops with air-fluid levels indicative of obstruction. Free air under the diaphragm is seen in patients of perforation. Enteroliths may be seen proximal to a long-standing stricture in patients of chronic tuberculosis [13]. In addition, the involvement of lymph nodes may be seen in the form of calcified lymph nodes. There may be evidence of other concomitant findings like ascites and intussusception on X-ray.

Barium studies show features which depict the underlying pathological changes [14].

The lesions that have been described on conventional barium studies are ulcerative, hypertrophic, or fibrosing types [9, 11]. The initial stage of intestinal tuberculosis is caused due to superficial invasion of the mucosa. Spasm or hypermotility is seen in the early phase. The first stage shows accelerated intestinal transit time. There will also be disturbance in the peristaltic constrictions resulting in hypersegmentation of the barium column (called ‘chicken intestine’). There are disturbances, which will result in precipitation, dilution, or flocculation of the barium. The contour of the intestine may be altered. It may be irregular, crenated, or spiculated. The mucosal folds may become soft and thick. Terminal ileum may be

narrowed due to irritability causing rapid emptying. In the second stage of tuberculosis, there is the presence of ulcers, which may be stellate or linear in shape. Linear ulcers are perpendicular to the long axis, which results in spasm in early stages and circumferential ulcers also develop later. Stellate ulcer shows central barium fleck with converging folds. In the third stage, there are sclerosis, hypertrophy, and stenosis. Tuberculosis leads to penetrating ulcers, which leads to short stenotic segments. They have a smooth and stiff wall. Multiple strictures may be seen on barium study with intermittent areas of dilatation. Other features, which may be seen, are matting of loops and spiculation. The ileocaecal valve may become fixed, gaping, irregular, and incompetent. Terminal ileum may be narrowed due to stricture formation. The caecum classically becomes shrunken, conical, and retracted out of the iliac fossa, due to contraction of the mesocolon (Figs. 8.1 and 8.2). The hepatic flexure may be pulled down.

There are several signs of ileocaecal tuberculosis, described on barium studies [13]. 'Fleischner or inverted umbrella' sign is said to be present when the thickening of ileocaecal valve lips is seen with their wide gaping and narrowing of the terminal ileum [15]. 'Goose neck deformity' is seen when there is the loss of normal ileocaecal angle and dilated terminal ileum appears suspended and hanging from a retracted, shortened caecum. 'Purse string stenosis' is said to be present when smooth, rounded caecum is seen with partial stenosis of the ileocaecal valve and dilated terminal ileum. 'Stierlin's sign' is seen due to repeated acute inflammation superimposed on a chronically involved segment of ileum, caecum, and ascending colon. This sign shows shrunken, rigid caecum with gaping ileocaecal valve and narrow terminal ileum due to rapid emptying. 'String sign' is caused due to a narrowed

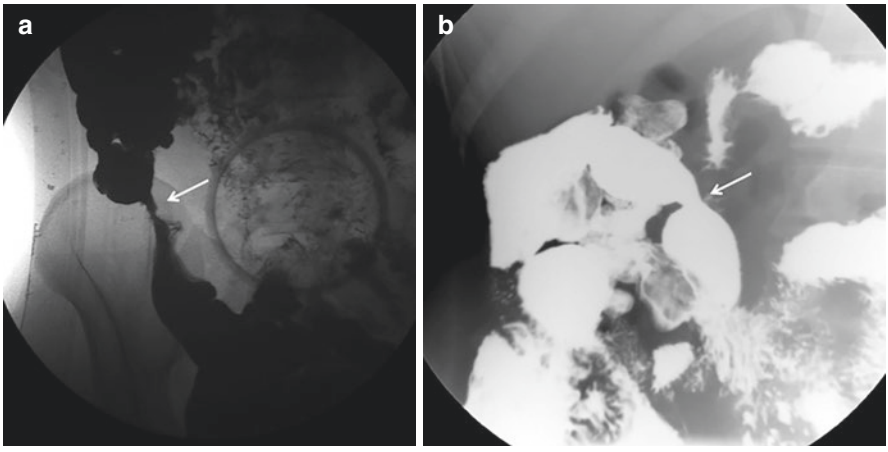

Fig. 8.1 BMFT study of a 50-year-old female who complained of intermittent abdominal pain with episodes of subacute obstruction. (**a**) AP view of ileocaecal region shows narrowed terminal ileum (arrow) with contracted caecum. There is mild dilatation of the proximal ileum. (**b**) Oblique view showing one of the proximal ileum loops with short segment stricture (arrow)

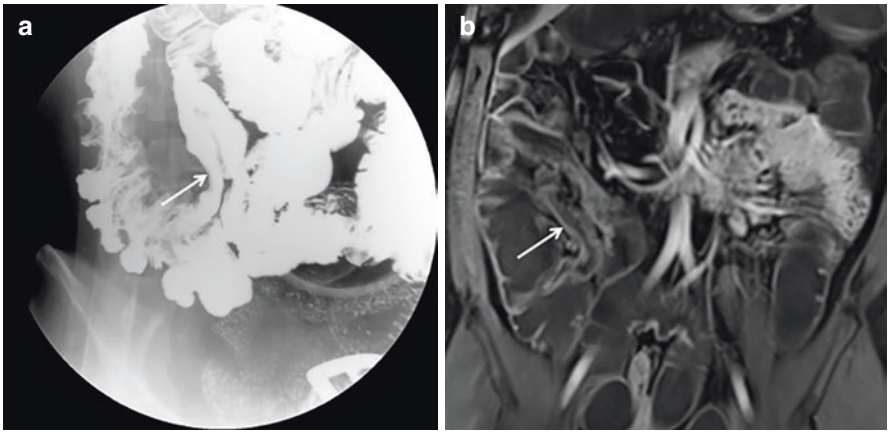

Fig. 8.2 A 40-year-old male who complained of abdominal pain. (**a**) Barium enteroclysis study shows a long segment stricture (arrow) in terminal ileum. There was slow passage of contrast through it. (**b**) MR enterography of the same patient shows the stricture with the bowel wall showing mild thickening and enhancement (arrow)

stenotic segment of bowel. Barium enteroclysis is more sensitive as compared to BMFT and shows a better demonstration of the small bowel and ileocaecal findings.

US is less sensitive and specific as compared to barium studies and CT. Early mucosal details are not visible on US. However, a deep ulcer may be seen as echogenic intraluminal contents extending into the wall. Circumferential wall thickening of the bowel, described as measuring more than 5 mm in undistended and more than 3 mm in distended stage, may be seen. The medial caecal wall and asymmetrical wall thickening of the ileocaecal valve can be seen. 'Pseudokidney' sign may be seen when bowel thickening is seen in a subhepatic location. 'Pseudokidney' sign is said to be present when kidney like appearance is formed due to the thickened bowel wall; where the opposing mucosal surfaces of the bowel wall lead to the echogenic stripe at the centre and the hypoechoic periphery is caused by the thick bowel wall. Ileocaecal tuberculosis is often hyperplastic and gross morphology can be evaluated on US. However, it is difficult to locate jejunal and proximal ileum lesions, because of the difficulty in visualizing the entire bowel length and overlapping bowel gases. Advanced tuberculosis causes gross thickening of wall, adherent bowel loops, and enlarged regional lymph nodes [13]. Lymph nodes showing hypoechoic centre indicate necrosis, which is highly suggestive of tuberculosis. Mesenteric thickening may lead to the mass formation. Intestinal obstruction is diagnosed by detecting dilatation of bowel and hyperperistaltic movements proximal to the site of obstruction. Enteroliths may be visualized in patients of chronic obstruction. Perforation is diagnosed if ascites and free air are seen in the peritoneal cavity. Intussusception caused by bowel wall lesions in children can also be seen on US [12]. US can also be used for the follow-up of intestinal tuberculosis patients. A recent study reports that a reduction in the size of lesion of bowel wall by 50% and a decrease in 'Limberg score' of vascularity by 2 grades are recognized as good treatment response.

Limberg score is a score used to define bowel wall thickness and vascularity. Grade 0 means bowel wall thickness of 3–4 mm without increased vascularity. Grade 1 is increased bowel wall thickness of >4 mm, grade 2 is bowel wall thickening with short segments of vascularity, grade 3 is bowel wall thickening with long segments of vascularity, and grade 4 is bowel wall thickening with increased vascularity of mesentery [16]. The characteristics of contrast-enhanced ultrasound have also been described in patients of intestinal tuberculosis. Two types of bowel wall enhancement are seen in intestinal tuberculosis patients; Type 1 in which serosa enhances first and mucosa enhances gradually; Type 2 in which the whole bowel wall shows diffuse quick enhancement [10].

CT may show skip lesions of concentric mural thickening and enhancement, with associated luminal narrowing in the small bowel, with or without proximal dilatation. Mild circumferential bowel thickening in early stages and severe and asymmetrical wall thickening in late stages may be seen in the ileocaecal region. Small bowel lesions along with ileocaecal involvement strongly suggest the diagnosis of tuberculosis on CT (Figs. 8.3 and 8.4) [17]. CT can also show contracted caecum with irregular contours and superior displacement of caecum in patients of chronic tuberculosis. CT can show matting of bowel loops and 'cocoon' formation (Figs. 8.5 and 8.6). Cocoon formation also called 'encapsulating peritoneal sclerosis' is the encapsulation of bowel within fibro collagenous thick peritoneal membrane, resulting in recurrent episodes of intestinal obstruction [18]. Chronic cases may also show calcification of the intestinal wall. The most important advantage of CT is that it can show extra-enteric findings in patients of tuberculosis, especially when there is a diagnostic dilemma. 'Extra-bowel' findings include regional necrotic lymphadenopathy with lymph nodes showing central hypodense areas suggestive of necrosis. Pericaecal or mesenteric fat stranding may be seen. CT can show concomitant involvement of other organs like the liver, spleen, and genitourinary system [19]. When extra-enteric findings like ascites, peritonitis, hypodense lesions in liver and spleen, and lymphadenopathy are seen along with bowel changes, tuberculosis is a strong possibility [17, 20]. There may be associated findings of pulmonary tuberculosis seen on chest CT sections (Fig. 8.7).

Complications of gastrointestinal tuberculosis like obstruction and perforation are well visualized on CT scan. Perforation of bowel will lead to ascites and air in the peritoneal cavity. If intraluminal contrast is given, CT can show the extravasation of contrast from the bowel into the peritoneum. Many times, it can detect the exact site of bowel perforation. Sometimes tuberculosis may lead to fistula formation with the other bowel loops or with the skin, which can be better visualized on CT scan with the help of multiplanar reconstructions. CT can diagnose obstruction. In these patients, bowel loops are dilated proximal to the site of obstruction. CT enteroclysis or enterography shows greater sensitivity and specificity for small bowel findings. Subacute obstruction is common in patients of tuberculosis. Partial strictures, which may be missed on basic CT technique, are better visualized on CT enterography/enteroclysis. Mild wall thickening and enhancement are also better visualized with well-distended bowel loops, obtained on CT enterography or enteroclysis techniques. CT enteroclysis and enterography are better than barium

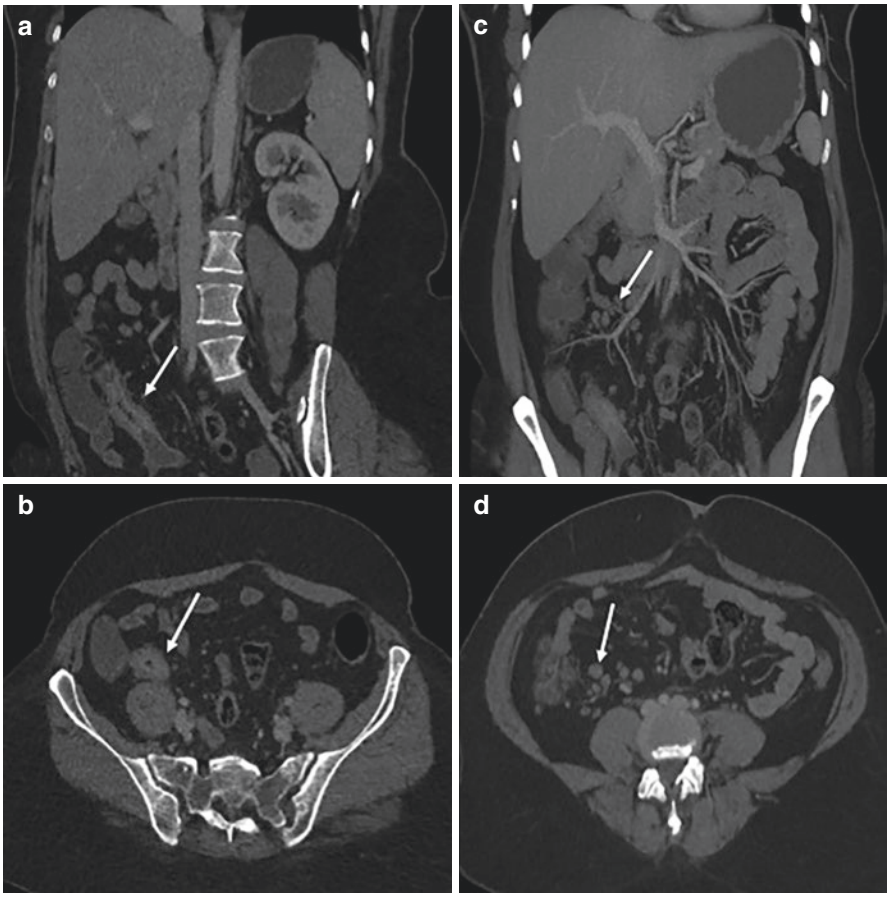

Fig. 8.3 A 60-year-old female, who complained of constipation. (**a** and **b**) Coronal and axial CT images showing wall thickening and luminal narrowing of terminal ileum (arrows). (**c** and **d**) Coronal and axial CT images showing multiple mesentery lymph nodes predominantly in the ileocaecal region (arrows)

enteroclysis in detecting multiple strictures as barium enteroclysis is a 2D representation that may lead to underdiagnosis of ileal strictures in the pelvic area due to overlapping loops [6].

MRI shows the same findings as CT but with better soft-tissue resolution. Mucosal abnormalities are also better demonstrated. Exophytic soft-tissue mass around a narrowed segment or minimal symmetric or asymmetric wall thickening with spiking/tethering of mucosal outline is seen. The bowel wall is T1 hypointense, T2 hyperintense with heterogeneous enhancement. MRI can differentiate between acute ulcerative and subacute scarring stages of the disease. Recent studies have shown MR enterography intestinal findings to correlate well with barium studies. Also, MR enterography provides information about extra-intestinal findings. MR

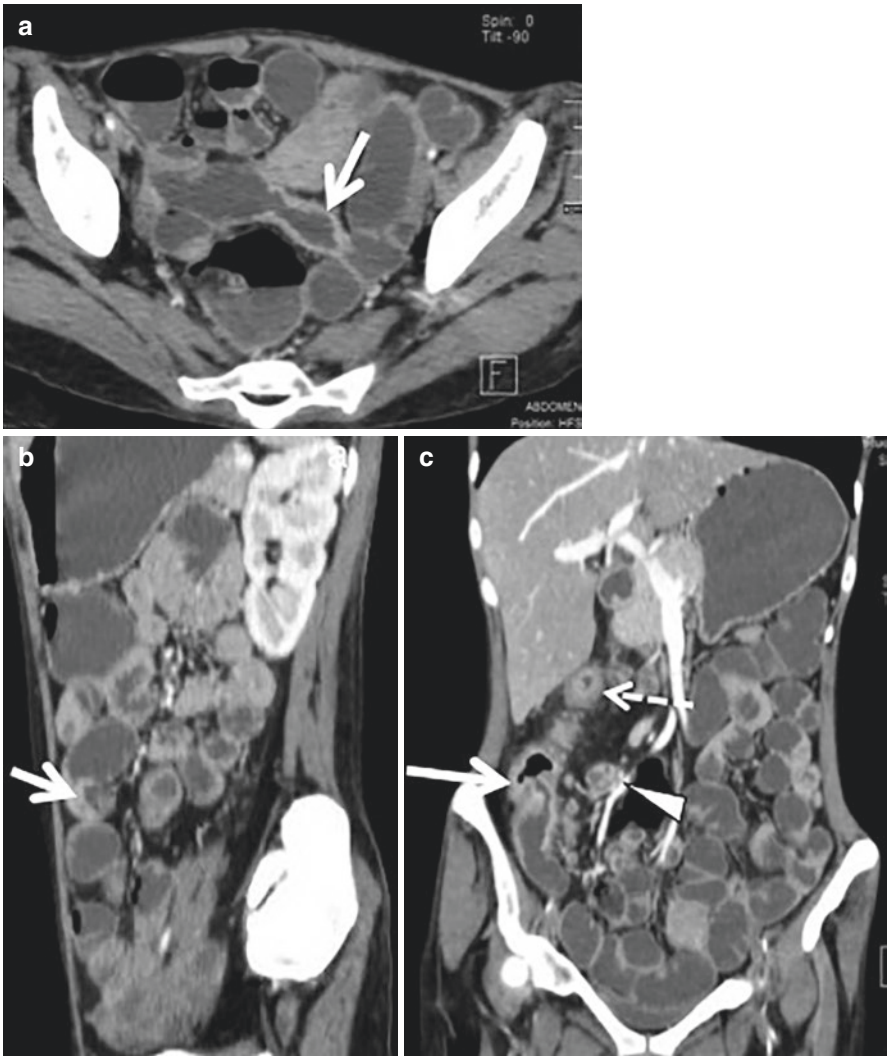

Fig. 8.4 CT enterography showing multiple small bowel strictures with ileocaecal involvement in a 30-year-old male patient of tuberculosis. (**a**) Axial CT image shows stricture in the ileum (arrow) with pre-stenotic dilatation. (**b**) Oblique sagittal CT image shows stricture in the jejunum (arrow) with pre-stenotic dilatation. (**c**) Coronal CT image shows ileocaecal involvement (arrow), regional necrotic lymphadenopathy (arrowhead), and colonic thickening (dashed arrow)

enterography can become the one-stop radiation-free tool in the evaluation of small bowel TB (Fig. 8.8) [8]. Advanced MRI techniques like diffusion-weighted imaging have been shown to be helpful in quantifying the treatment response in intestinal tuberculosis. Mathur et al have found that apparent diffusion co-efficient (ADC) values show good correlation with treatment response in intestinal tuberculosis and

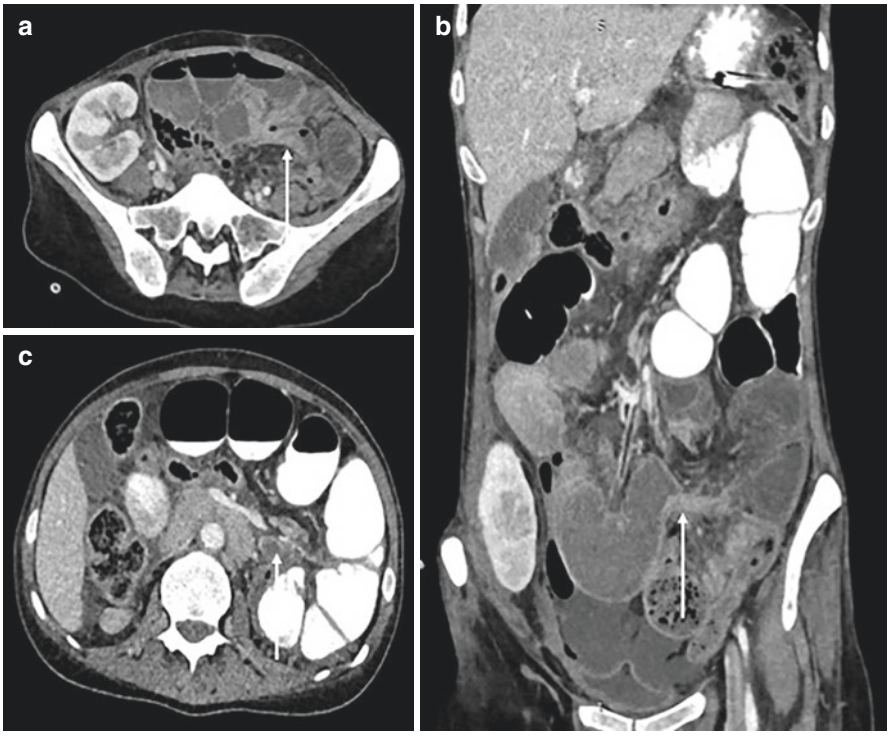

Fig. 8.5 A 38-year-old male, post renal transplant who complained of diffuse abdominal pain, with constipation. (**a**) Axial CT image showing adherent small bowel loops with bowel wall thickening and luminal narrowing in left iliac fossa (arrow). (**b**) Coronal CT image showing similar finding (arrow) with associated dilatation of proximal ileal loops. (**c**) Axial CT image showing retroperitoneal and regional necrotic lymphadenopathy (arrow)

an increase in ADC values is a reliable and objective marker of good response to treatment [9].

Differential diagnoses of ileocaecal tuberculosis on imaging include lymphoma, carcinoma, Crohn's disease, and amoebiasis. Early-stage tuberculosis is difficult to differentiate from Crohn's disease and lymphoma. However, advanced tuberculosis is easier to differentiate from these disease entities. In lymphoma, bowel wall thickness is more and obstruction is less common; enlarged homogenous abdominal lymphadenopathy and hepatosplenomegaly are seen. Crohn's disease shows stratification with asymmetrical thickening of the bowel wall, skip lesions (>3), long segment involvement, abscesses and fistulae, mesenteric fat proliferation, increased mesentery vascularity, absence of ascites, and absence of necrotic lymph nodes on CT [20–23]. Amoebiasis may show shrunken caecum. However, the terminal ileum is not involved. Caecal cancer thickening is also limited by the ileocaecal valve [21].

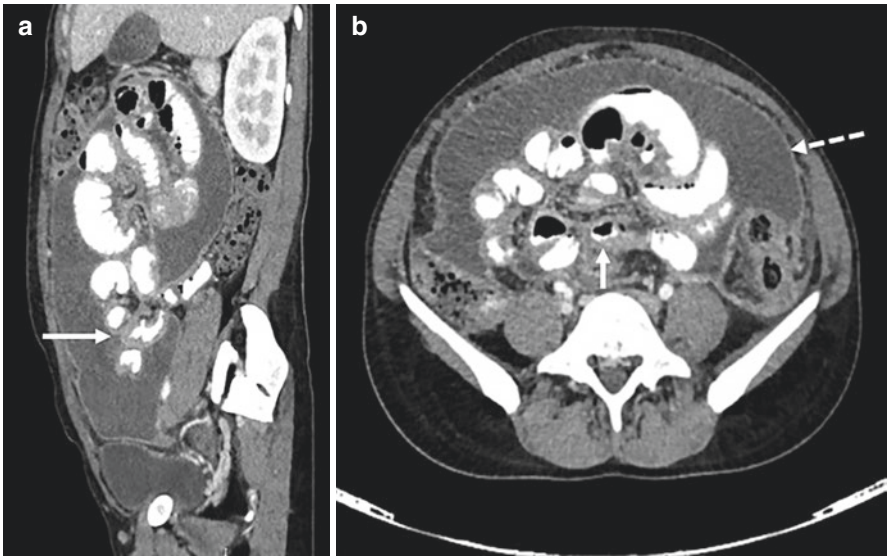

Fig. 8.6 A 36-year-old male, who complained of abdominal pain. (**a** and **b**) Sagittal and axial CT images showing wall thickening and luminal narrowing in multiple areas of small bowel (arrow). Small bowel loops show clumping in mid abdomen. There are associated gross ascites and diffuse peritoneal thickening (dashed arrow)

8.8 Large Intestine Tuberculosis

Colonic tuberculosis is usually contiguous involvement of ascending colon with ileocaecal involvement. Isolated colonic tuberculosis is rare and seen in only 10.8% of cases [1]. Barium enema was the traditional method for evaluating colonic tuberculosis. Segmental involvement is seen on barium enema. Depending on the pathological form of tuberculosis whether ulcerative, hypertrophic, or combined form: ulcers, strictures, or polyps maybe seen. However, abdominal CT is essential for the complete evaluation of intestinal and extra-intestinal abnormalities. The combination of asymmetrical mural thickening with enlarged necrotic lymph nodes suggests the diagnosis of tuberculosis colitis. Colonoscopy with colonoscopic biopsy/FNAC provides the final diagnosis. The commonest site of isolated involvement is transverse colon, followed by descending colon, sigmoid colon, and rectum. Complications include perforation, fistulae, and pericolic abscesses. Differential diagnoses on imaging are ulcerative colitis, Crohn's disease, and malignancy. It is difficult to differentiate tuberculosis colitis from ulcerative colitis and Crohn's disease on the basis of radiology. Necrotic lymph nodes will help in suggesting the diagnosis of tuberculosis colitis [1]. While anal and internal fistulae are more common in Crohn's disease, perforation is more common in patients of tuberculosis [24].

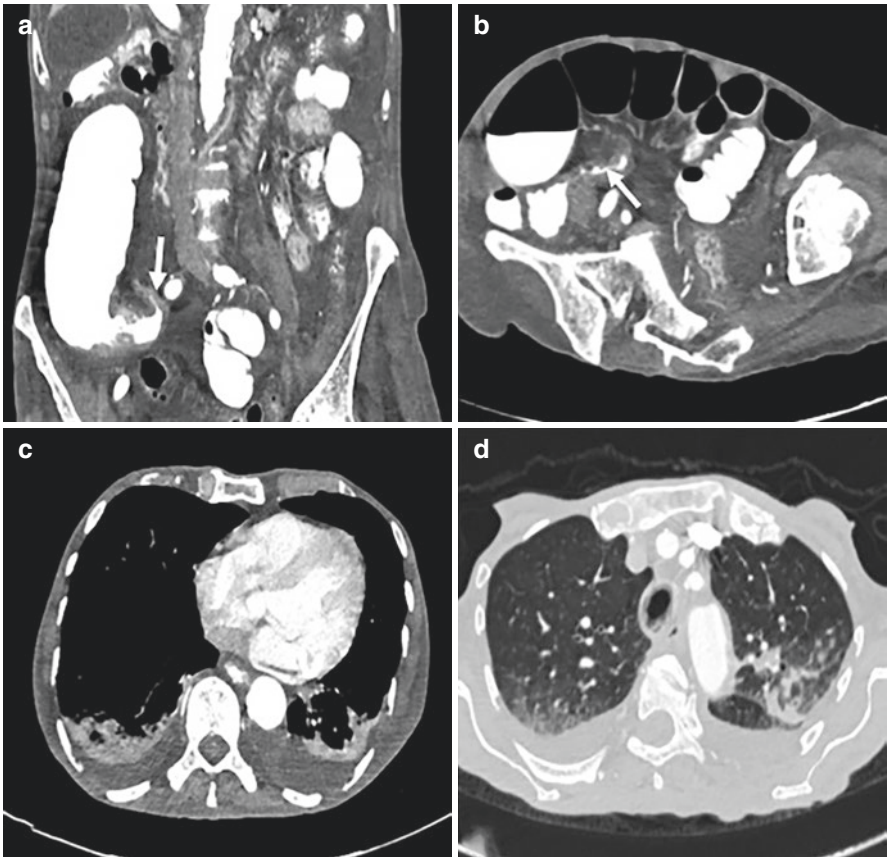

Fig. 8.7 A 44-year-old male, who complained of fever, cough, and abdominal pain. (**a** and **b**) Coronal and axial CT abdominal images showing asymmetric concentric wall thickening of distal ileum (arrows) with luminal narrowing and proximal dilatation of bowel loops. (**c** and **d**) Axial CT chest images showing bilateral pleural effusions with air space nodules in left upper lobe

8.9 Anorectal Tuberculosis

Rectal tuberculosis is rarer than small and large intestine tuberculosis. It leads to significant luminal narrowing with areas of deep ulcers, which are located approximately 10 cm from the anal verge (Fig. 8.9). Anorectal tuberculosis can also present as fistulae, strictures, and chronic ischiorectal abscesses. Pre-sacral space may be increased due to inflammation or fibrosis [21]. The differential diagnoses for this entity include lymphogranuloma venereum, amoebiasis, actinomycosis, and schistosomiasis.

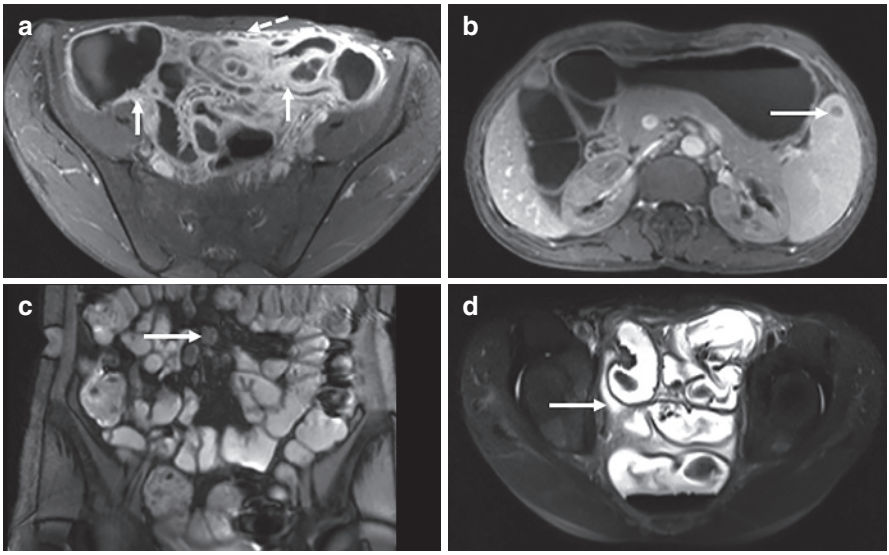

Fig. 8.8 MR enterography study of a 50-year-old male who presented with subacute obstruction and diagnosed with abdominal tuberculosis. (**a**) Axial post contrast T1 FS image showing multiple areas of bowel wall thickening with luminal narrowing (arrow). There is associated omental thickening (dashed arrow). (**b**) Axial post contrast T1 FS image showing small hypoenhancing lesion in spleen (arrow). (**c**) Coronal T2 True FISP study showing necrotic lymph nodes in mesentery (arrow). (**d**) Axial T2 FS images showing dilated pelvic ileal loops with mild ascites (arrow)

8.10 Appendiceal Tuberculosis

Isolated appendiceal tuberculosis is a very rare presentation [25]. It may present as chronic appendicitis due to intrinsic disease [26]. It may also be involved due to surrounding lymph nodes or due to a caecal mass leading to obstruction and appendicitis.

8.11 Duodenal Tuberculosis

2 to 2.5% of intestinal tuberculosis is duodenal [27]. The third part of the duodenum is most commonly involved. The involvement can be extrinsic or intrinsic. Extrinsic involvement is most commonly due to adhesions or surrounding lymph nodes. The barium study will show the widening of the C-loop or impressions on the medial aspect of the C-loop. Intrinsic involvement is less common and can be ulcerative or ulcerohyperplastic. The intrinsic disease can show ulcers or polypoidal growth and can lead to short segment narrowing [24]. It can sometimes simulate superior

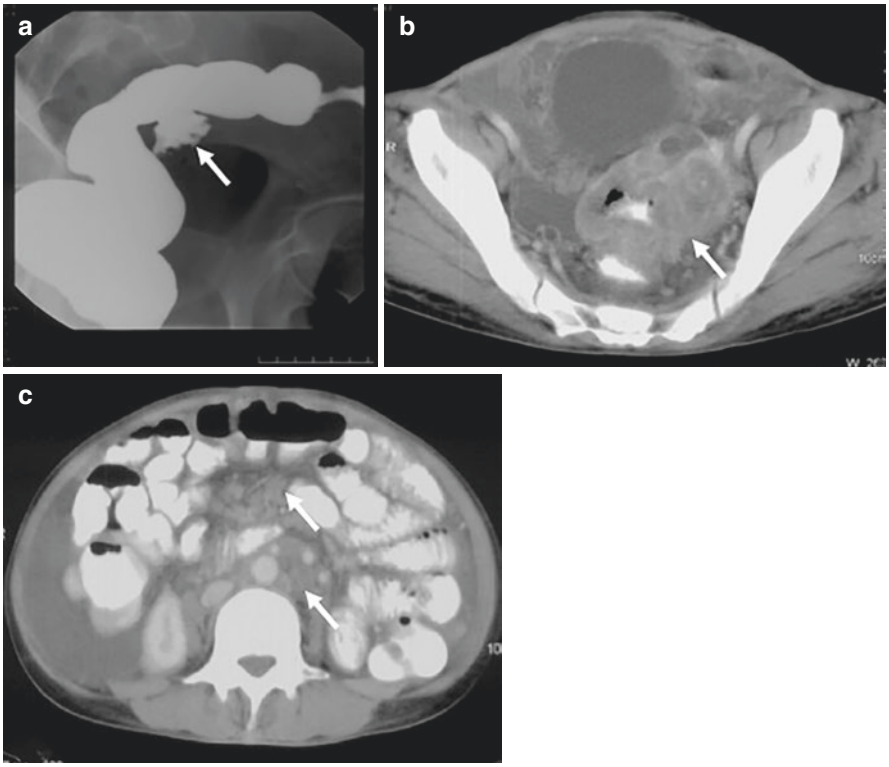

Fig. 8.9 A 40-year-old retropositive female with lower gastrointestinal bleed. (**a**) Barium enema study shows a deep ulcer on the left lateral aspect of rectum (arrow). (**b**) Axial CECT pelvis shows asymmetrical wall thickening of rectum (arrow), with areas of necrosis within the wall. (**c**) Axial CECT abdomen shows enlarged mesenteric and retroperitoneal lymph nodes (arrows) with ascites. Patient was diagnosed to have tuberculosis on colonoscopic biopsy

mesentery artery (SMA) syndrome [20]. The incompetence of sphincter of Oddi can lead to air in the biliary tree, which can be seen on an imaging study. CT will show thickened wall of the duodenum and necrotic lymph nodes. Complications of duodenal tuberculosis are stricture leading to obstruction, fistula formation, and perforation. Differential diagnosis includes lymphoma, malignancy, pancreatic cancer, and peptic ulcer disease.

8.12 Conclusion

Radiology is an important tool for the diagnosis, characterization, and management of gastrointestinal tuberculosis. Gastrointestinal tuberculosis has a varied spectrum of appearances. Knowledge of these will help the radiologist to consider the diagnosis of gastrointestinal tuberculosis, especially in patients who are living in endemic

areas. The confirmatory diagnosis of tuberculosis requires positive bacteriological culture or histopathological examination. However, certain characteristic imaging features like ileocaecal involvement, skip lesions, and necrotic lymphadenopathy can allow the radiologist to arrive at the correct diagnosis in an appropriate clinical setting. Though gastrointestinal tuberculosis usually involves the ileocaecal region, it can affect any part of the gastrointestinal tract. Diagnosis of tuberculosis is difficult in areas, which are not commonly involved and a high degree of suspicion is required to make a diagnosis in these areas. There has been an exponential increase in imaging technology in the last few decades. CT enteroclysis/enterography is being widely used for making the diagnosis and determining the extent of the disease. With newer image acquisition techniques like DWI and ADC, MR enteroclysis/enterography needs to be evaluated as a tool for diagnosing as well as assessing the treatment response of tuberculosis. The radiologist needs to know the wide spectrum of gastrointestinal tuberculosis features on conventional and newer imaging modalities, which can help him to suggest the diagnosis, advise appropriate strategy to confirm the diagnosis and assess treatment response.

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Conflict of Interest None.

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Perianal Tuberculosis

9

Pankaj Garg, Vipul D. Yagnik, and Sushil Dawka

Key Points

- The most frequent presentation of perianal tuberculosis (TB) is abscess and/or fistula.
- TB fistulas are significantly more complex than non-TB fistulas.
- Polymerase chain reaction (PCR) has a higher detection rate than histopathology.
- Pus has a higher microbiological positivity than tissue (fistula tract lining/wall) to detect TB.
- A single negative sample does not exclude the presence of TB and repeated samples should be considered in suspicious cases.
- The cure rate is excellent when TB is detected, and ATT is started before surgery or within 6 weeks of surgery.

9.1 Introduction

Every year, ten million new cases are diagnosed with tuberculosis (TB) and it is the world's top infectious killer [1]. Extrapulmonary TB accounts for 3–46% of all types of tuberculosis patients across the world [2]. It can involve any part of the

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gastrointestinal tract from mouth to anus. Gastrointestinal involvement accounts for 1% of all TB cases and, amongst these, TB of the perianal region accounts for only 0.7% of cases [3]. Though perianal TB is a miniscule proportion of the huge overall TB burden, yet the proportion of anal fistulas associated with TB is much higher [3]. This is especially true of TB endemic areas. Various studies have reported that TB can be detected in 2.3–16% cases of anal fistulas in developing countries (endemic regions) and 0.3–1.2% in developed countries [3–9].

9.2 Etiopathogenesis

There are two hypotheses regarding the involvement of the perianal region with TB. The first is ingestion of pulmonary secretions heavily laden with TB bacilli, and the second is reactivation of a latent focus [10]. Other mechanisms like hematogenous spread from pulmonary TB, lymphatic spread from regional lymph nodes, or direct extension from neighboring affected organs seem exceedingly rare [11]. However, most researchers believe the first hypotheses (ingestion of pulmonary secretions) is the most common mechanism [10]. Though the association of TB with anal fistulas and abscesses is undisputed, there is no evidence or clinical data available which can indicate as to whether TB has the potential to cause a new disease process (formation of anal fistula/abscess) or TB bacilli can only infect an already existing fistula-in-ano and complicate it [10, 12]. But it is likely that once a fistula is infected by TB, then this infection needs to be treated for the fistula to heal [12]. In the absence of anti-TB therapy, the fistula would either not heal after surgery or would recur a few weeks to months after clinical healing [12]. This is so because TB bacilli are very slow growing. Therefore, at times, they may not be able to prevent the fistula from healing temporarily but once they have slowly multiplied in sufficient numbers over a few weeks, they can cause recurrence of fistula/abscess [12].

There have been reports recently that non-tuberculous mycobacteria (NTM) can also be associated with perianal fistulas [13]. Though this is rare, it needs to be kept in mind because it can cause confusion in the diagnosis. Moreover, the treatment of most NTM is quite different from usual anti-TB treatment [13–15].

9.3 Clinical Manifestations

Perianal TB is commonly seen in males with a male: female ratio of 7:1 [12]. The age groups most frequently afflicted are the third and fourth decades of life [12]. The most common presentations of perianal TB are anal fistula and anorectal abscess [16]. Occasionally, it may present as a pilonidal sinus [17] or as an anal ulceration with inguinal lymphadenopathy [18]. Rarely, perianal TB may also present as a recurrent perianal mass [18], anal fissure, [19] anal stricture [20], hemorrhoids [21], or as a rectal submucosal tumor [22].

Anal fistulas associated with TB are much more complex than cryptoglandular non-TB fistulas [3] (Figs. 9.1, 9.2 and 9.3). In a recently published large study, the proportion of complex fistulas was significantly higher in TB fistula (69%-78/113) than in non-TB fistula cohort (44.3%-278/727) ($p < 0.00001$, significant, Fisher's exact test) [12]. As per St James's University Hospital (SJUH) classification [23] and the newly described Garg classification [24–27], the presence of fistulas of higher grade (III, IV & V) were significantly higher in the TB fistula group as compared to the non-TB fistula groups [12]. Garg classification has been shown to grade fistulas as per their severity much more accurately and also guides in the management of the disease [24, 25].

There are several possible reasons for higher proportion of complex fistulas in setting of TB [12]. First, due to low prevalence or incidence of TB in anal fistulas, it is usually not suspected. Second, good diagnostic tests which can detect TB with reasonably high sensitivity and specificity are not available. Third, most first-line antibiotics commonly prescribed for pyogenic infections are not effective in TB. Therefore, underlying tubercular disease process continues to spread. Fourth, anti-TB therapy is quite long and cumbersome. Therefore, poor compliance of patients for completing treatment could lead to MDR-TB (multi-drug resistant TB) which further makes treatment difficult and fistulas become more complex [3]. Fifth, contrary to an acute pyogenic abscess, TB usually presents with a cold abscess with minimal symptoms, and it has a slow, indolent progressive course [3]. Therefore, patients tend to ignore the disease until it is well advanced. Sixth, due to above factors, TB fistulas have a higher recurrence rate requiring multiple operations [3]. Repeated surgery can lead to sphincter damage which makes the fistula more complex and treatment difficult [12].

9.3.1 Clinical Features Which Raise Suspicion of a Possible TB Infection [3]

Though there are no pathognomonic or specific clinical features of anal fistula or abscess due to TB [10], certain features raise the level of suspicion of a possible TB infection [3]. These features include the presence of a very complex fistula, non-healing fistula, development of new abscesses or tracts while the fistula is being treated and a relapse of fistula within 6 months after complete healing [12].

The samples (tissue or pus) should be tested for TB, especially in these scenarios. It is recommended that in endemic regions, routine TB testing of all pus and tissue samples from anal fistulas should be considered [3]. In countries where TB is not endemic, selective sample testing may be done (fistula associated with HIV/AIDS, fistula refractory to treatment, etc.) [5].

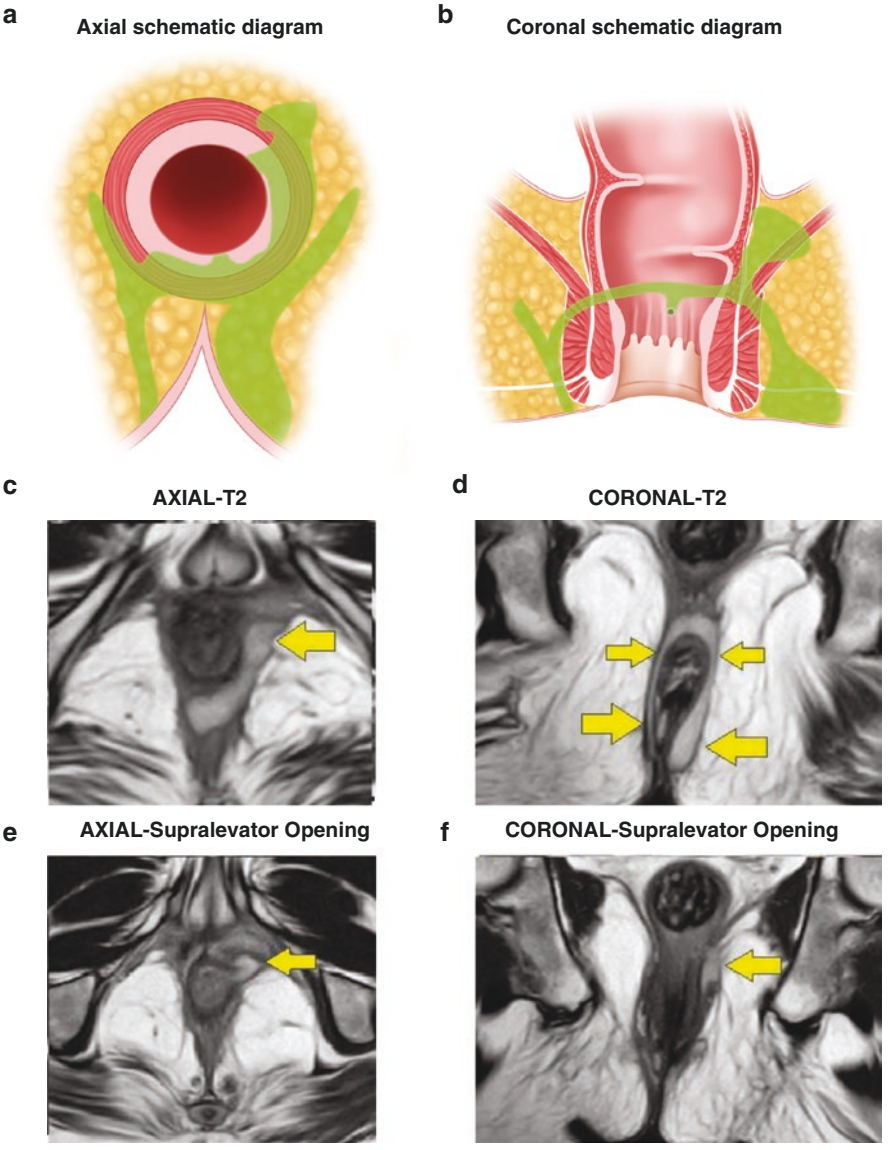

Fig. 9.1 A 55-year-old male patient with TB infected high recurrent transsphincteric horseshoe complex anal fistula with multiple tracts and supralevator extension with supralevator rectal opening at 2 o'clock (SJUH grade V). (yellow arrows show fistula tracts). (**a**) Schematic diagram—Axial section (**b**) Schematic diagram—Coronal section. (**c**) MRI—Axial Section-T2 sequence. (**d**) MRI—Coronal Section-T2 sequence. (**e**) MRI—Axial Section-T2 sequence: high level showing supralevator rectal opening at 2 o'clock. (**f**) MRI—Coronal Section-T2 sequence: showing supralevator rectal opening

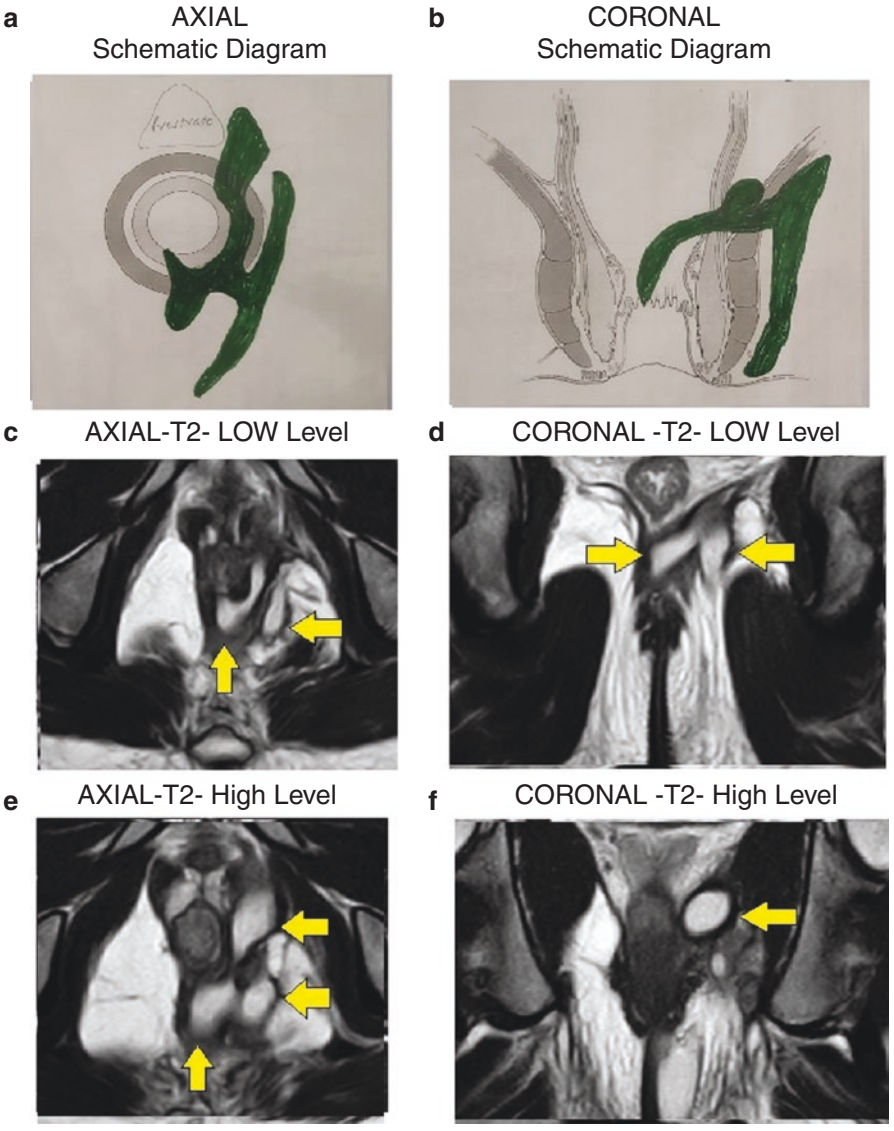

Fig. 9.2 A 17-year-old male patient with TB infected high recurrent transsphincteric horseshoe complex anal fistula with multiple tracts and supralevator extension (SJUH grade V). The fistula is extending up to the left lateral aspect of the prostrate (yellow arrows show fistula tracts). (**a**) Schematic diagram—Axial section (**b**) Schematic diagram—Coronal section (**c**) MRI—Axial Section-T2 sequence (**d**) MRI—Coronal Section-T2 sequence (**e**) MRI—Axial Section-T2 sequence: high level showing supralevator extension (**f**) MRI- Coronal Section-T2 sequence: showing supralevator extension

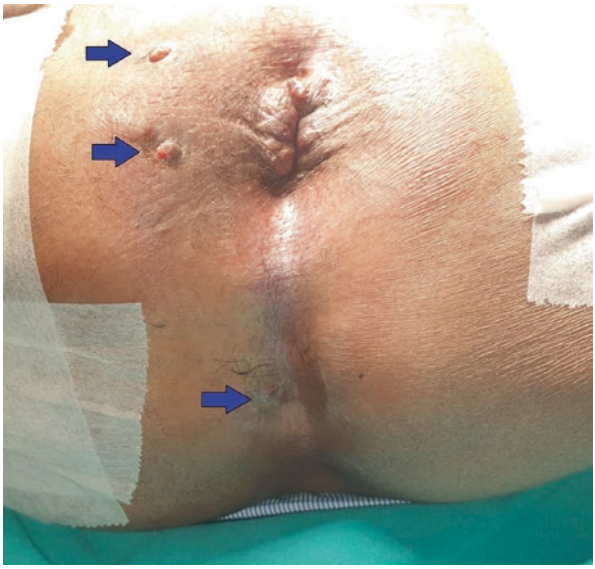

Fig. 9.3 A 52-year-old male patient with TB infected highly complex anal fistula associated with an abscess and multiple tracts. The three external openings can be seen (marked by dark blue arrows)

9.4 Diagnosis

The diagnosis of perineal tuberculosis is difficult due to lack of a satisfactory test that has reasonably high sensitivity and specificity [10]. TB bacilli are slow-growing and ubiquitous, leading to difficulty in culture and the problem of contamination [28]. Several tests have been utilized to detect TB, which include culture, histopathology (HPE), Acid-fast bacilli (AFB) stain, tuberculin test, ELISA, polymerase chain reaction (PCR), GeneXpert or CBNAAT (cartridge-based nucleic acid amplification test), rapid immunochromatographic assay, etc. [10, 29] However, the commonly used tests amongst these are AFB stain, culture, HPE, PCR, and GeneXpert [28]. These tests can be done on either pus (from anorectal abscess or discharge oozing out from fistula tracts) or tissue (fistula tract lining epithelium or fistula tract wall) or both [29].

AFB staining is done by Ziehl–Neelsen stain. This method has a low detection rate [30]. Therefore, the clinical utility of this test is low [28]. TB culture with Lowenstein–Jensen medium has a high specificity, and the drug sensitivity profile can also be assessed at the same time [31]. However, the sensitivity of culture is quite low and culture takes a long time (6 weeks to 6 months) due to which the clinical utility of culture especially in perianal TB becomes very limited [31]. Moreover, culture cannot differentiate between infection and contamination [30]. BACTEC 460 TB system is a new technique for culture-based diagnosis that works on the principle of early specific detection of mycobacterial growth [32]. It provides results

within 3 weeks [32]. It has been reported that 76% of patients with abdominal TB showed positive BACTEC 460 TB cultures [33]. But this test has not been studied in perianal TB.

HPE is one of the commonest tests done around the globe [3, 28, 29]. HPE utilizes HE (hematoxylin and eosin) stain [29]. The features which suggest mycobacterial disease on HPE are confluent granulomas, a lymphoid cuff around granulomas, granulomas larger than 400 μm in diameter, five or more granulomas in biopsies from 1 segment, granulomas located in the submucosa, granulation tissue (often as palisaded epithelioid histiocytes), excessive submucosal inflammation and/or Langerhans giant cells [13, 34]. Amongst these, the caseation of granulomas is one of the most specific features of TB [35, 36]. However, these features can also be present in Crohn's disease or other chronic granulomatous diseases [34, 36]. As the specificity as well as the sensitivity of HPE is not very high, therefore, HPE is not a reliable method to detect TB [3, 12, 28].

Real time-*Polymerase Chain Reaction (PCR)* has a high sensitivity to diagnose TB [15]. TB PCR is rapid (can detect bacterial DNA within 48 h) as well as an accurate diagnostic method [37, 38]. Apart from tissue, PCR can also be done on pus from the abscess or fistula tracts [3, 12, 28]. Specific PCR can also differentiate between TB and NTM (non-tuberculous mycobacteria) [3, 12, 28]. Several studies had recommended that PCR should be employed routinely to detect TB [6, 15, 39, 40]. However, most of the studies utilized HPE [4, 5, 7–9, 41, 42], and very few studies in the literature have used PCR for testing [3, 6, 28]. A recent study analyzed 1336 samples in 776 patients of anal fistula and highlighted that PCR of tissue was significantly more sensitive than HPE to detect TB (7.4% vs 1.5%) [12]. The same study also demonstrated that PCR of pus was significantly better to detect TB than PCR of tissue (23.2% vs 7.4%) [12]. In this study, the rpobF and rpobF primers targeting the gene, rpobB were used [43, 44]. The limitation of PCR is that it can lead to false-positives as PCR cannot distinguish between dead and viable mycobacteria [3, 28]. Therefore, it is recommended that a positive PCR test should always be correlated with clinical features [3, 12, 28].

GeneXpert MTB/RIF assay (CBNAAT) uses a disposable cartridge. The advantage of this test is that it simultaneously detects TB as well as resistance to rifampin (RIF) and can be done in less than 2 h [12]. In 2010, the WHO recommended the use of the GeneXpert as a preliminary test for TB detection and improve diagnosis of rifampicin (RIF) resistance in pulmonary and extrapulmonary TB (EPTB) specimens [45]. However, this test has low sensitivity in EPTB cases and false-positives in strains that contain synonymous mutations [46, 47]. The only study which utilized GeneXpert in perianal TB found the sensitivity of GeneXpert to be quite low as compared to PCR (0.9% vs. 7.4%) [12].

Considering the high sensitivity of PCR, it has been recommended that PCR should be done in every fistula patient especially in endemic regions [3, 12, 28]. In cases where a pus sample is available, it should also be tested as the detection rate in pus is quite high [3, 12]. It has also been highlighted that TB may not be always detected in the first sample tested [3, 12, 28]. Therefore, repeated samples should be sent for testing in patients with high level of clinical suspicion of having TB as

mentioned above (a very complex fistula, a fistula in which the healing is not occurring in the usual expected course, development of new abscesses or tracts while the fistula is being treated or relapse of fistula within 6 months after complete healing) [3, 12]. In a large study of 740 operated fistula patients with a long-term follow-up, it was noted that TB was detected by repeat samples (sent in the postoperative period) in 15.9% (18/113) patients [12]. This diagnosis would have been missed if repeat samples had not been sent. Therefore, the importance of maintaining a high index of suspicion for TB before and after surgery and promptly sending samples (pus or tissue) as per the clinical picture plays a pivotal role in increasing the detection rate of TB [3, 28].

9.4.1 Tubercular vs. Crohn Disease-Related Perianal Disease

It is important to discuss the ways to differentiate TB from Crohn's disease (CD) since both these diseases can cause or present as anal fistulas or an anorectal abscesses. While the CD is more common in the developed world, TB is more common in low-income countries, though this differentiation is getting diluted in the last few years [48]. CD fistulas tend to occur in younger age group [median-23 years] as compared to TB fistulas [median-37 years] [49]. The type of fistulas (intersphincteric, transsphincteric, or suprasphincteric), presence of multiple tracts or number of recurrences seem to be comparable in both types of fistulas [49]. In comparing histopathological findings, TB fistulas are associated with much higher proportion of caseating granulomas (62% in TB vs. 0 in CD), while CD fistulas have significantly higher number of non-caseating granulomas (34% in TB vs. 58% in CD) [49]. On colonoscopy, the mucosal inflammation is much more common in CD (97%, along with aphthous ulcers, longitudinal ulcers and cobblestone appearance) than in TB patients (33%, along with transverse ulcers and aphthous ulcers) [49]. However, the site of involvement was similar in both the diseases (the most common sites being ileocecal region, ascending colon, transverse colon and other areas in decreasing order) [49]. The differentiating features between TB and CD are tabulated (Table 9.1)

Table 9.1 Features differentiating between Tuberculosis and Crohn's disease

	Tuberculosis	Crohn's Disease
Clinical features	Fever/night sweats	Diarrhea/hematochezia/perianal disease
Endoscopic features	Transverse ulcers/patulous ileocecal valve	Longitudinal/aphthous ulcers
Histologic features	Caseating/confluent/large granuloma	Micrograniuloma
Microbiologic features	Positive stain/culture for acid fast-bacillus	
Radiological features	Necrotic lymph node/contiguous ileocecal involvement	Long segment involvement/comb sign/skip lesions
Anti-TB therapy (ATT) trial	Improvement	No improvement

[48]. However, it is important to realize that these features have more suggestive value as the specificity of these features is not very high [48]. The only features with very high specificity are the presence of caseation granulomas and positive AFB smear and culture for TB [48].

9.5 Radiology

The commonly used modalities employed to assess anal fistulas are fistulography, transrectal ultrasound (TRUS) and MRI. With the advent of advanced modalities (MRI and TRUS), the utility of fistulography has markedly diminished as it does not show any relevant soft tissue structures (anorectum, anal sphincters, etc.). MRI is considered the gold-standard to evaluate anal fistulas as it has a slight edge over TRUS. There are no specific features on MRI or TRUS that can help in the diagnosis of TB in anal fistulas.

As discussed above, TB fistulas are more often complex and are more commonly associated with multiple tracts [4, 5, 7, 9, 41]. MRI and TRUS can help in accurately identifying multiple tracts and other features which make the fistula complex like horseshoe tract, supralevator extension, associated high abscess, etc. (Figs. 9.1 and 9.2) [50]. Secondly, MRI and TRUS are highly sensitive to detect non-healing of fistulas in postoperative period [51]. Thus, these advanced radiological modalities are extremely helpful in identifying features that raise suspicion of a possible TB infection. Thus, these modalities are an integral part of armamentarium available with physicians to combat TB fistulas.

9.6 Treatment

The treatment of anal fistulas especially complex ones is an uphill task [3], and when TB is associated with such fistulas, the management becomes even more challenging [10]. The management of such fistulas is in two steps [3]. First, the internal opening is the culprit which needs to heal properly for the fistula to be cured completely [12]. If the internal opening does not heal within few weeks after surgery, it gets epithelialized, and the chance of fistula healing becomes remote [12]. Second, the main challenge in TB fistulas is accurate detection of associated TB infection and timely initiation of anti-TB therapy [3, 12]. This step, in itself, is also not straightforward as the timely detection of TB is not easy. An algorithm has been suggested to diagnose and manage TB associated with anal fistulas [3].

Recent studies conducted in large samples have demonstrated that anti-TB therapy should be started within 6 weeks (preferably 3 weeks) of surgery for anal fistula [3, 12]. If anti-TB therapy is initiated after 6 weeks, then the chances of non-healing and recurrence of fistula are quite high [3, 12]. In most surgical procedures, the fistula tracts and the internal opening are thoroughly debrided and cleaned due to which the microorganism load is reduced drastically. Therefore, in the postoperative period, the TB bacilli do not hinder the healing process during the first 6 weeks as

these bacilli are quite slow growing. So, if the TB is detected and anti-TB therapy is started within that time, then the infection can be eradicated and chances of fistula healing are quite high [3, 12]. On the other hand, if the detection of TB is missed, then bacilli would keep on multiplying to a considerable number and would lead to

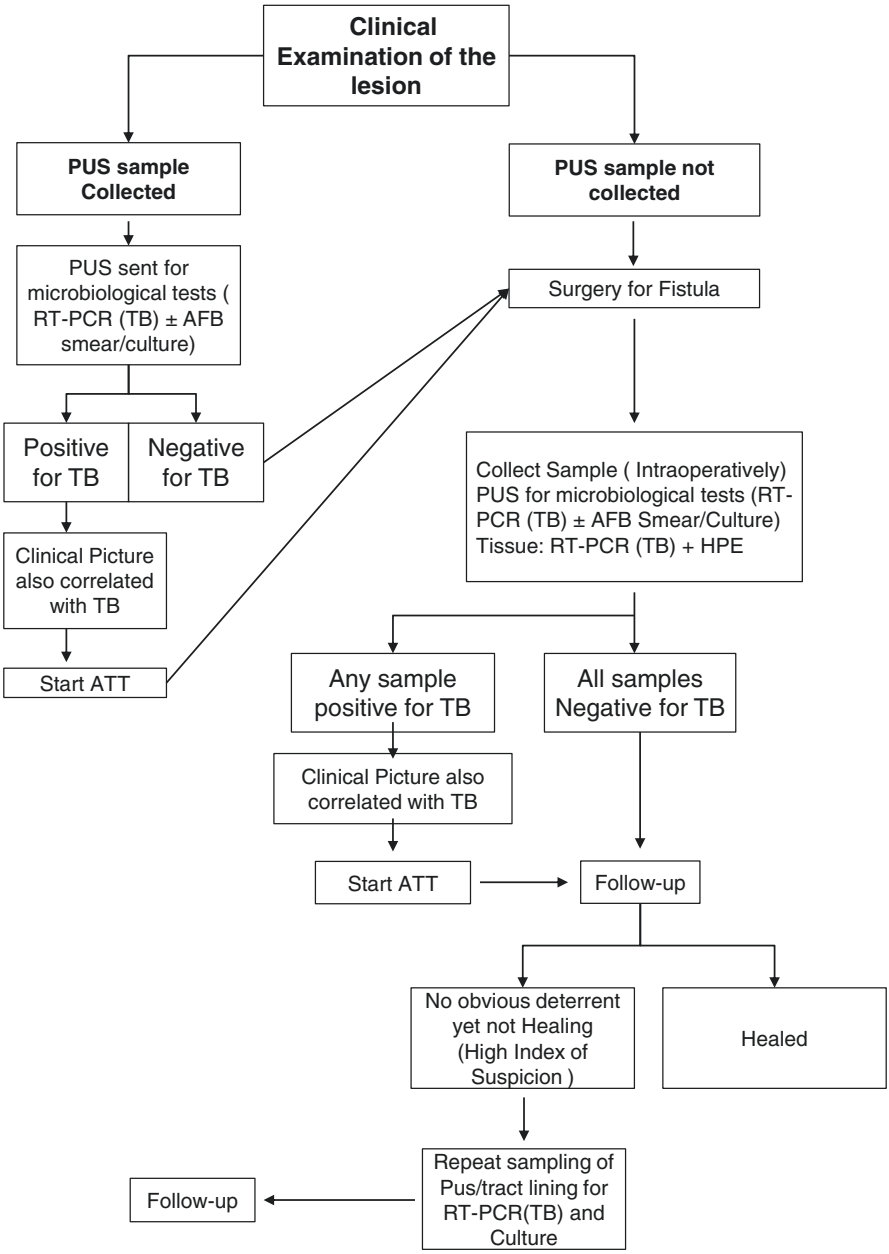

Fig. 9.4 Algorithm recommended to diagnose and manage tuberculosis in anal fistulas [3]

non-healing of internal opening or an abscess formation [12]. Thus, the importance of timely detection of TB infection present in anal fistulas/abscesses cannot be understated [3, 12].

In pursuance of the same goal, it is recommended that in the patients with high suspicion levels for having TB but with initial (first) negative report, repeat samples (pus or tissue) should be tested to detect missed TB infection (Fig. 9.4). In studies (cited above), the TB infection in up to 16% TB patients was detected on repeat samples [12].

As mentioned above, PCR tests cannot differentiate between viable and dead mycobacteria [3]. Therefore, it is recommended that a positive PCR test should always be correlated with clinical features [3]. A patient with a low simple fistula can be given the option of not starting anti-TB therapy, whereas therapy should be started in patients with complex fistulas or with high level of suspicion of TB clinically [3, 12].

9.7 Anti-TB Therapy

The patients scheduled to get anti-TB treatment are recommended the standard four-drug anti-TB regimen for first 2 months (intensive phase). This should be followed by the three-drug regimen (Isoniazid-5 mg/kg, Rifampicin and Ethambutol) for the next 4 months (maintenance phase) [3, 10]. It has been recommended that in patients who test positive for TB and have complex fistulas, injection Streptomycin (15 mg/kg, maximum of 750 mg/day, intramuscular) may also be administered during the first 2 months of the intensive four-drug regimen. The reason behind this is that Streptomycin penetrates well into most body tissues [3]. Conventionally, there has been a ceiling on the standard TB drugs (Isoniazid-300 mg, Rifampicin-600 mg, Pyrazinamide-1500 mg and Ethambutol-1000 mg). There have been recommendations that higher dosage of anti-TB drugs may be given as per body weight, unrestricted by the ceiling [1]. But there is no experience or data as to whether the recommended higher dosage of anti-TB drugs is better than conventional dosage (with the ceiling). However, existing data highlights high cure rates with conventional dosage (with the ceiling) [3, 12].

It has been also been recommended that anti-TB therapy may be extended for 9–18 months in complicated cases [41] but there is no consensus on that. The treatment in multi drug-resistant TB (MDR-TB) patients can be quite challenging. In MDR-TB patients, second-line drugs are recommended. In these patients, the intensive phase involves 6–9 months of second-line drugs like Kanamycin, Levofloxacin, Ethambutol, Pyrazinamide, Ethionamide and Cycloserine and 18 months of maintenance phase with Levofloxacin, Ethambutol, Ethionamide, and Cycloserine [45].

To conclude, TB associated with anal fistulas and anorectal abscesses poses a plethora of diagnostic and management challenges. Though TB is associated with more complex fistulas, a high level of suspicion especially in endemic regions, timely detection, and meticulous treatment lead to reasonably high cure rates that are similar to non-TB fistulas.

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Part III

Peritoneal Tuberculosis

Peritoneal Tuberculosis

10

Mohammed Kareem. Shariff, Adnan Alzanbagi, and Faisal M. Sanai

Abbreviations

ADA	adenosine deaminase
AFB	acid fast bacilli
ATT	anti-tuberculous treatment
CRP	C-reactive protein
CT	computed tomography
EPTB	extrapulmonary tuberculosis
ESR	erythrocyte sedimentation rate
IG	interferon gamma
LTB	latent tuberculosis
MBT	*Mycobacterium tuberculosis*
MRI	magnetic resonance imaging
NAAT	nucleic acid amplification tests
NPV	negative predictive value
PCR	polymerase chain reaction
PPV	positive predictive value
PTB	peritoneal tuberculosis
SAAG	serum-ascites albumin gradient
TB	tuberculosis
TNF	tumor necrosis factor
WHO	World Health Organization

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Key Points

1. Female gender, extremes of age, ethnic origin, end-stage renal or liver disease, and impairment in immune defense mechanisms increase the risk of peritoneal tuberculosis (PTB).
2. Presentation of PTB is nonspecific demanding a high index of clinical suspicion. Slowly progressive symptoms with limited discerning features may delay its diagnosis.
3. A low serum-ascites albumin gradient, lymphocyte predominance with high protein and adenosine deaminase level in ascitic fluid, may lead to a diagnosis of PTB.
4. The paucibacillary nature of PTB warrants early testing with a combination of advanced diagnostic tools of microscopy, imaging and culture with molecular tests.
5. Timely initiation of therapy is key to reducing mortality. Six months of therapy with standard anti-tuberculous medications is sufficient to achieve response.

10.1 Introduction

Abdominal tuberculosis (TB) may involve the gastrointestinal tract, peritoneum, or the mesenteric lymph nodes. Peritoneal Tuberculosis (PTB) is the primary infection of the visceral and parietal peritoneum that forms the mesentery, omentum and the peritoneal ligaments. The peritoneum is one of the common extrapulmonary sites of tuberculous infection. The disease remains a significant problem in parts of the world where tuberculosis is prevalent. Increasing population migration, availability and usage of more potent immunosuppressive therapy, and the acquired immunodeficiency syndrome epidemic has contributed to a resurgence of this disease in regions where it had previously been largely controlled.

Given the anatomy of the peritoneum, it is not surprising that PTB is associated with the tuberculous infection of other organs that the peritoneum covers, like the gastrointestinal tract, lymph nodes and the solid organs like liver and spleen. Occasional overlaps between these forms have also been described. Nonetheless, the remarkable similarity between this illness and ovarian carcinoma, peritoneal carcinomatosis and complicated portal hypertensive ascites continues to pose significant challenges to the diagnosis of this disease. This is partly a consequence of the lack of specific identifying features that would otherwise help in pursuing the diagnosis when suspected and also to the limited yield of the commonly used diagnostic tests. In this chapter, we will discuss the associated risk factors, disease presentation, and review the current knowledge of the diagnostic measures available and the treatment options.

10.2 Epidemiology

Despite a steady decline in tuberculosis (TB) worldwide, around ten million people were affected in 2018, of which more than a million died [1]. TB can affect any organ of the body and when it affects regions other than the lungs it is termed extrapulmonary TB (EPTB). It is estimated that globally 8% to 24% of TB cases were extrapulmonary, making up an average of 15% of the total TB cases notified to the World Health Organization (WHO) [1]. This variation is reflected in the population and region where the study was carried out. In India, the country with the highest burden, 20% of TB cases were EPTB; of this, 34% were lymphatic TB, 25% pleural, followed by abdominal at nearly 13% [2, 3]. China is another high burden country where EPTB constituted about 31% of all TB cases, of which the commonest site was, unexpectedly, the skeletal system (41%), followed by pleura (26%). The abdominal site was not specifically looked at, and the unclassified "other" site formed 14% of all EPTB cases [4]. A study from Pakistan, which carries the fifth-largest burden of TB, showed that the proportion of EPTB was nearly 30% of all the notified TB cases; 21% of EPTB cases were abdominal in origin, following pleural (29.6%) and lymphatic (21.5%) locations [5]. In countries with medium-sized TB burden, EPTB constituted 13% of all TB cases, with 9% of these being abdominal TB, making it the sixth commonest site [6]. A low TB incidence country like the United States had EPTB make up 20% of all TB cases, with the most common site being the lymphatics (40%), and the abdomen being the fourth commonest site at 6% [7]. In another North American country, Canada, EPTB was seen in 25% of TB cases, with abdominal TB being the second most common site of infection (10%) [8]. Similarly, in Europe, extrapulmonary location accounted for 17% of all TB cases, with the abdomen (3%) being the sixth commonest site [9]. In South Africa, a sub-Saharan country that has high TB and HIV burdens, nearly 43% of all TB cases presented as EPTB, and of this, 26% involved the abdomen, the third commonest site after pleura and lymphatics [10]. In a co-infected population of HIV and TB from a multicenter cohort, EPTB accounted for 28% of all TB cases, with abdominal TB ranking third (11%) among the affected sites [11].

The incidence of TB in general is dropping across the globe; however, the proportion of EPTB is on the rise. Europe has seen this increase from 16.4% to 22.4% within a decade [12], and in the USA, the proportion has risen from 15.7% in 1993 to 20.4% in 2018. In contrast, the overall rates of abdominal TB have remained the same over the years, suggesting that it is following the trends of EPTB [7, 13]. Similarly, a rising trend of EPTB has also been reported from a high-incidence country like India [14], and this may in part be due to increasing awareness and better diagnostic tools, and additionally may reflect an increase in associated risks such as HIV infection, over the years.

Hence, abdominal TB constitutes around 6% to 26% of all EPTB cases. This wide variation in disease occurrence reflects the country where the study was done, the burden of TB and the rates of coexisting HIV infection. Of all the abdominal TB

infections, gastrointestinal tract infections account for 43% to 65% of cases, followed by PTB infections (20% to 47% of cases) and tuberculous infection of abdominal lymph nodes (4% to 42%), and less commonly solid organs like liver, gall bladder, spleen and pancreas (1% to 23%). Again, the proportion of PTB was more than double between studies. Apart from these studies originating in different countries, the criteria used to define PTB also differed. Some used a strict definition of culture and AFB positivity, whereas other relied on a combination of clinical suspicion and biochemical, radiological and histological parameters to diagnose PTB. In up to 33% of cases, PTB was associated with TB infections of other sites within the abdomen and between 15% to 54% had coexistent pulmonary TB (Table 10.1) [15–28].

10.3 Risk Factors

In general, the risk factors associated with PTB tend to be similar to those for EPTB [9, 29, 30]. Younger age, female gender, Asian ethnicity and Black race have been found to be risk factors for PTB in studies from the USA [29, 30]. In Europe, having origins from the Indian subcontinent or Africa, extremes of age (<15 and > 64 years) and female gender were strongly associated with PTB. In contrast, prior history of treatment for TB was less likely to be associated with the occurrence of PTB [9]. Another European study from the Netherlands national tuberculous registry showed a significant association of PTB with young age (<14 years), female gender and regional ethnicity of Somali, Moroccan, or Asian region [31]. A nationwide study from Pakistan reported similar risk patterns, i.e., female gender, age < 15 years and coming from a specific region (like a tribal area within Pakistan) for PTB [5]. Hence, female gender, extremes of age, ethnic origin and end-stage renal disease seem to increase the risk of PTB. In addition, impairment in immune defense mechanism mainly due to vitamin D deficiency, genetic polymorphism and social set up including diet have also been postulated as possible causes for PTB in susceptible ethnic populations [31].

Around 30% of the world's population is estimated to have latent TB (LTB), of which 10–15% may reactivate to an active infection [32]. Latent TB is more of a concern in low-incidence areas of TB, such as the USA, where 80% of active TB cases are due to reactivation of LTB [33]. Reactivation of LTB tends to present more in the EPTB sites, including PTB. England saw a 50% increase in EPTB, with an 80% rise in PTB over a five-year period that was mainly attributed to reactivation of TB [34]. Hence, factors that increase reactivation of LTB like immunosuppression directly influence the risk of PTB. Two such important risk factors are solid organ transplantation and the use of anti-tumor necrosis factor (TNF) alpha medications.

Table 10.1 Proportion of abdominal tuberculosis affecting different infected sites

Study	Cho JK et al. [15]	Chalya PL et al. [16]	Ramesh J et al. [17]	Mamo JP et al. [18]	Singhal A et al. [19]	Chien K et al. [20]	Singh A et al. [21]	Tan KK et al. [22]	Mandavdhare HS et al. [23]	Uygur-Bayramicli O et al. [24]	Muneef MA et al. [25]	Urabinahatti KA et al. [26]	Nayagam JS et al. [27]	Khan R et al. [28]	
n	139	256	86	17	59	24	58	57	93	31	46	40	65	209	1180
Country	S. Korea	Tanzania	UK	UK	UK	Canada	India	Singapore	India	Turkey	KSA	India	UK	Pakistan	
Gastrointestinal	69 (50)	127 (50)	38 (44)	11 (65)	26 (52)		25 (43)	33 (58)	51 (51)	15 (48)		(60)		103 (49)	43%–65%
Peritoneal	28 (20)	106 (41)	41 (47)	5 (29)	16 (32)	10 (41)	27 (47)	13 (23)	33 (33)	11 (35)		(40)	23 (35)	87 (42)	20%–47%
Lymph nodal	7 (5)	10 (4)				14 (58)	18 (31)	24 (42)	41 (41)	5 (17)				9 (4)	4%–58%
Solid Organs	23 (17)	7 (3)	7 (8)	1 (6)	8 (16)	3 (12)	2 (8)	11 (20)					2 (3)	10 (5)	1%–20%
Mixed	12 (9)		28 (33)				10 (17)						22 (33)		9%–33%
Coexistent Pulmonary TB		58 (23)	22 (26)		(54)	10 (41)		27 (47)	27 (29)	11 (35)	7 (15)		20 (31)	134 (64)	3%–64%

10.3.1 Immunosuppression

It was noted that patients with solid organ transplant have a high prevalence of LTB, and prophylaxis prior to transplantation reduces the incidence significantly [35, 36]. In a meta-analysis of TB in liver transplanted patients, PTB was the commonest site accounting for 35% of all EPTB cases; similarly, in a multicenter study on TB in renal transplant recipients, PTB was the third leading location, comprising 22% of all EPTB sites [37, 38]. Holty et al. noted that the incidence of TB post-transplantation had two peaks—early (< 2 years post-transplant) and late (>5 years post-transplant)—and postulated that early TB could be due to high immunosuppression and the late form probably arising from a new TB infection due to exposure [38]. The presence of an opportunistic infection, chronic liver disease and diabetes mellitus increase the chances of PTB in transplanted patients [39, 40].

Another risk factor is the use of anti-TNF alpha medications, which is recognized to reactivate LTB. For this reason, screening for TB prior to starting these medications is a standard recommendation. From surveillance data of the US FDA, the incidence of TB in patients on anti-TNF alpha was fourfold higher than the background rate, and EPTB accounted for 56% of these cases. PTB was the third commonest form of EPTB, a higher than usual proportion, implying an increased association with anti-TNF alpha use [41]. This was further confirmed in a French registry study that reported a similar proportion of 61% of EPTB, with PTB being the third commonest [42]. Given the high burden of TB in developing countries, the risk associated with anti-TNF usage is estimated to be substantially higher and thus EPTB and PTB are estimated to have higher incidence too [43]. The incidence of TB is high in the first year after initiating anti-TNF therapy suggesting a role of reactivation of LTB [42].

In addition, end-stage liver disease increases the risk of PTB. Cirrhosis is an immunodeficient state that is multifactorial and increases the risk of infections [44]. A population-based study from Denmark noted that the incidence of TB in cirrhotic patients was 14 times higher than the general population, with a significantly high mortality in patients who had EPTB (odds ratio 1.38 CI 0.44–4.30), wherein the etiology of the underlying cirrhosis made no impact [45]. This was further confirmed from a study from India, where the incidence of TB was almost 15-fold higher, with EPTB being more common, accounting for 60% of all TB cases. PTB was noted as the second commonest site of EPTB infection [46]. In addition, other studies have also shown that EPTB is more common than pulmonary TB in cirrhosis, seen in 60% to 65% of cases, with PTB being the most commonly affected site constituting up to 45% of all EXTB cases [47–49].

10.3.2 Co-Infection with HIV

There are more than a quarter of a million deaths due to TB in HIV-positive patients worldwide [1]. HIV-positive patients carry a very high risk of developing TB, estimated to be around 26-fold higher than average, and this risk increases with falling

CD4 T-cell count. EPTB, including PTB, is more common in HIV-infected TB patients with low CD4 count [50, 51]. Systemic reviews and meta-analysis have suggested that HIV is more commonly seen in EPTB than pulmonary TB, with the difference being more pronounced in patients with a CD4 count of <100 [52, 53]. Reduced antibody and T-cell response against TB, including interferon gamma have been implicated as possible reasons for reactivation of TB leading to EPTB in people with low CD count in HIV infection [51].

10.3.3 Diabetes Mellitus

Diabetes and TB in general influence each other. The risk of TB in diabetes is high and the presence of TB affects the glycemic control in diabetes [54]. Similarly, the prevalence of diabetes is high in EPTB, although this does not translate into diabetes being an independent risk factor for pulmonary or extrapulmonary TB [55, 56].

10.4 Pathogenesis

The mechanism behind EPTB development is not fully understood. Various factors involved in the manner of pathogen interaction with the host may play a role, however the dynamics of this is not well understood [50]. It is now increasingly recognized that the prime route of transmission of TB is through inhalation that causes the pulmonary infection, followed by the infection of the other organs by spread from this primary focus (Fig. 10.1). This happens predominantly through the

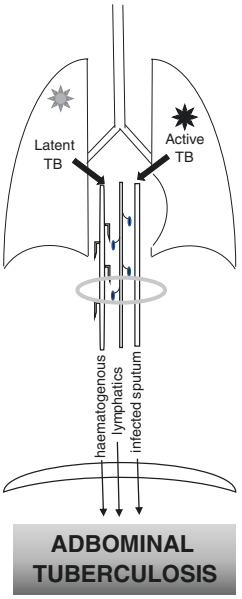

Fig. 10.1 Schema of pulmonary tuberculosis transmission to intra-abdominal sites

lymphatic systems and the bloodstream. The initial breach from the pulmonary epithelium to get to the extrapulmonary sites is proposed to occur by one of the four following mechanisms—(1) by the help of macrophages, (2) direct infection of the epithelial cells, (3) through microfold cells (M cells), a kind of specialized epithelial cells or (4) by assistance of dendritic cells [57]. Genetic lineage of TB may determine the EPTB site and its clinical presentation, with Indian lineage closely associated with EPTB [58]. Specific lineages of TB may have predilection to cause EPTB due to their ability to replicate more and invade the macrophages [59].

Another route of infection postulated is through ingestion of infected sputum from the lungs (Fig. 10.1); the ingested mycobacterium gains entry into the gut through the intestinal mucosa with the help of M cells and dendritic cells as explained above. Macrophages, mainly present in the lymphoid tissue in the intestinal mucosa, ingest these mycobacteria leading to an immune response and this can be translocated to the peritoneum. In addition, ingestion of milk or food infected with bovine mycobacterium was previously a well-recognized route, with bacilli initially infecting the lymphoid follicles of intestine and translocating through the intestinal wall into the peritoneum. However, the pasteurization of milk and prevention of bovine mycobacterial infection in livestock has made this rare. Whether PTB occurs as a primary infection or as a secondary spread from a pulmonary focus is not well defined; coexisting pulmonary TB and PTB is reported in 15% to 71% cases of TB [60–62]. Contiguous spread from an adjacent organ such as the reproductive tract is a possible mechanism.

10.5 Clinical Features

Tuberculous infection of the peritoneum has classically been divided into three types—wet, fibrotic, and dry plastic types. However, these different types have not been very well defined, and a considerable overlap exists. A systematic review looking at these different definitions concluded that these distinctions were neither helpful for establishing the diagnosis or institution of therapy, and at best were confusing. The authors proposed a new classification of PTB into two distinct types—"distension dominant" and "pain obstruction dominant" types, arguing that this facilitated both in diagnostic and therapeutic approaches. This classification is yet to be validated and is presently not in clinical use [63].

10.5.1 Clinical Presentation of Peritoneal Tuberculosis

PTB presentation in the twenty-first century is usually chronic or acute-on-chronic with nonspecific symptoms. The duration of illness before diagnosis varies from weeks to months, with some reporting a lag time of up to 2 years, with an average of around 12 weeks (mean reported durations of 7 to 24 weeks) [60–62, 64–71]. It is a disease of the young with a mean age at diagnosis usually in the 30s or 40s with a male preponderance (40% to 67%) [60–62, 67, 70, 71].

The symptoms are insidious in onset and can be broadly classified into systemic and localized. Constitutional or systemic symptoms include fever of low grade that is present in over a half of the patients and up to two-thirds in some studies [60–62, 65–70]. This can be associated with night sweats in about 17% to 57% of cases [60, 62, 64, 65, 67, 68, 71]. Weight loss is commonly encountered and can be seen in nearly 84% of patients, with a similar number having anorexia [60, 62, 64, 65, 67, 69, 71]. Abdominal pain is the most common localized symptom reported in the vast majority of patients (50% to 100% of cases) and is usually chronic, although it could be acute and severe enough to present as an emergency in a small proportion of cases (12% to 21%) [22, 60–62, 64–71]. Nausea, vomiting and diarrhea can manifest independently of gastrointestinal involvement in 6% to 35% [60, 62, 66–68, 71].

On physical examination, most have abdominal distension seen in 56% to 100% of cases vastly due to ascites that can be detected clinically or radiologically in 78% to 96% of cases [60–62, 64–68, 70, 71]. Abdominal tenderness is another sign that can be often elicited (up to 72% of cases) [65, 67, 71]. A palpable abdominal mass is not a characteristic feature and is reported in only 6% to 19% of patients [15–18, 23–26, 65, 71]. As previously mentioned, a small fraction of patients can present with an acute abdomen and signs of peritonitis. When the adjoining viscera are concurrently involved with PTB, lymphadenopathy and abdominal organomegaly may be present infrequently [60, 68, 71]. Serious complications like intestinal obstruction rarely leading to perforation can happen as a result of dense adhesions and bands formation from the fibrinous peritoneum in about 10% [17, 19, 22]. When there is a concurrent pulmonary TB, cough and dyspnea may be present and complicate the clinical picture.

History of contact with TB or a family member with TB is reported in only a third of cases [60, 62, 64, 70]. Similarly, the previous history of TB is also infrequently reported (in 36%) [62, 64, 66, 70].

Although a number of comorbidities serve as risk factors for PTB, they are not frequently present. The commonest documented comorbidity is cirrhosis in about 38% of cases and comes from a study from East Asia [61]. In other regions, this varies from 1% to 18% [60, 62, 65]. End-stage renal disease is reported in 2% to 33%, diabetes in 6% to 27%, and excess alcohol consumption in 1% to 13% [60–62, 65, 66]. Immunosuppressive states like the presence of underlying malignancy, HIV infection, and use of immunosuppressive medications are present in about 18%, 2%, and 10% of cases, respectively [61, 62, 65, 66].

10.6 Diagnosis

10.6.1 Biochemistry

Generally, a raised erythrocyte sedimentation rate (ESR) should raise suspicion of the disease, as it is observed in 64% to 100% of PTB cases [17, 19, 24, 25, 67–69, 71]. The mean increase in ESR varies from 48 to 68 mm/hr. and more than half have

an ESR well above 50 mm/hr. [60, 64, 68, 69]. There is a corresponding rise in C-reactive protein (CRP) (mean values range from 71 to 98 mg/L) in 72% to 100% of cases [66, 68, 69]. Anemia is also common, seen in 22% to 100%, and is usually mild to moderate, normochromic and normocytic [17, 19, 20, 24, 25, 64, 67, 69, 71]. Other abnormalities are hypoalbuminemia, reported in around 28% to 73% of PTB patients [17, 19, 24, 25, 68, 71]. A purified protein derivative skin test may be positive in 24% to 71%, and an interferon gamma release assay test like QuantiFERON can be positive in 73% of PTB patients [60, 62, 65, 67–69]. While these tests aid in diagnosis, a negative result does not exclude PTB.

Ascites is a valuable source for diagnosis, and the detailed evaluation is discussed in another chapter. Ascitic fluid is typically described as straw colored with white cell counts of 500 to 1500/mm^3 (predominantly lymphocytic) [72–74]. The protein in the fluid is typically elevated, with levels >2.5 g/dL and a serum-ascites albumin gradient (SAAG) of <11 g/L [17, 25, 61, 64, 70–74]. A high index of clinical suspicion, in addition to other parameters like lymphocyte predominance with high protein and adenosine deaminase level in ascitic fluid, may lead to a diagnosis of PTB [75, 76].

A meta-analysis revealed that ADA levels between 36 to 40 IU/L have a sensitivity and specificity of 100% and 97% and suggested an ADA level of ≥39 IU/L to be most diagnostic [77], and a later meta-analysis including 17 studies estimated the sensitivity and specificity of 93% and 94%, respectively, however the range of ADA cut-off was wider and less discriminatory, ranging between 21 to 40 IU/L [78–80]. The levels used for diagnosis varied from 0.35 U/L to 9 U/L, or 20 pg/mL to 112 pg/mL [79]. However, when compared with ADA levels, the diagnostic accuracy of IG was no better [79]. A novel idea of measuring cell-free *Mycobacterium tuberculosis* DNA in ascitic fluid has recently been explored and shown to have a sensitivity of 70.9% (95% CI, 51.9–85.8) and a specificity of 97.1% (95% CI, 84.7–99.9) [81].

10.6.2 Radiology

Radiological imaging is a cornerstone of PTB diagnosis. The use of ultrasonography to look for specific features of PTB did not fare well as a diagnostic tool. In a Cochrane review of 11 studies, the overall sensitivity and specificity was 63% and 68%, respectively [82]. However, it is a handy and easy tool for the detection and aspiration of ascites for diagnostic studies. Computed tomography (CT) is the preferred modality of imaging. Features suggestive of PTB include ascites and the pattern of involvement of the peritoneum, mesentery and omentum. Peritoneal involvement, as manifested by its thickening, is the commonest finding. The pattern of involvement has been variously described as smooth, irregular, or nodular. Similarly, omental thickening could be in the form of either smudge pattern or caking or nodular. Lastly, the thickening of mesentery may be seen as soft tissue stranded, nodular or diffuse infiltrative [83–86]. Ascites can be seen either as loculated or free with fibrin strands and has high attenuation [83–85]. It is seen on CT in 91% to 100% of cases [60, 62, 65, 68, 69, 86]. Peritoneal thickening can be

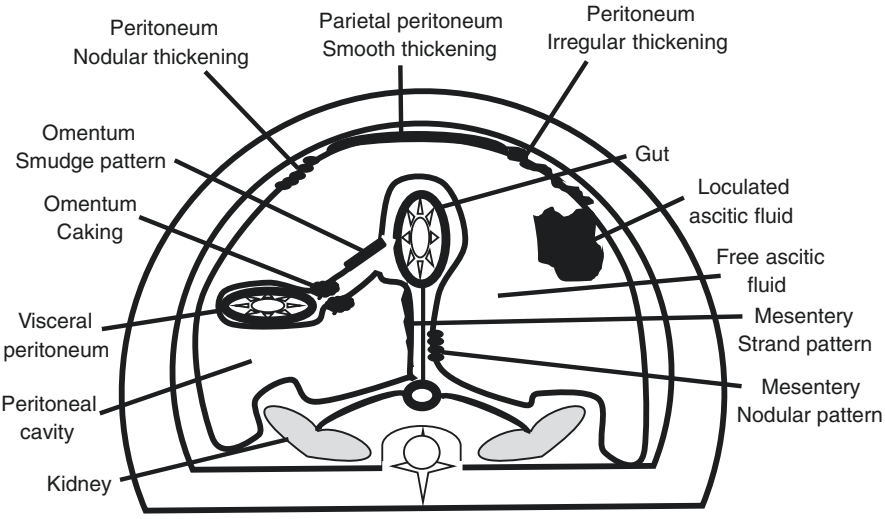

Fig. 10.2 Illustration of abdominal CT scan findings of peritoneal tuberculosis

recognized in nearly 93% with the smooth pattern in 76% to 87%, irregular in 12% and nodular in 13% [60, 62, 65, 68, 69, 85, 86]. Thickening of omentum is observed in 27% to 88%, with smudge pattern in 50% to 82%, caking in 6% to 9%, and rarely nodular [85, 86]. Involvement of the mesentery was seen in all cases in one study with soft tissue strand pattern in 65%, nodular in 29%, and diffuse in 6% of cases (Fig. 10.2) [86]. A combination of these CT findings helps in reaching a diagnosis and in excluding other potential pathological states that may mimic PTB. In addition, this modality provides a safe mean to obtain tissue for further confirmatory tests. The details of radiological findings and characteristics are provided elsewhere in a separate chapter.

10.6.3 Diagnostic Laparoscopy

The use of laparoscopy in patients presenting with peritoneal disease has been useful in establishing a diagnosis of PTB. Typical appearances on laparoscopy of thickened peritoneum with erythema, whitish nodules and adhesions are shown to be accurate in diagnosing PTB with a sensitivity and specificity ranging between 84% to 100% and 96% to 100% (Fig. 10.3) [87]. In more recent series, the sensitivity of the typical appearance is higher and ranges from 89% to 96% [17, 25, 60, 64, 71, 88–90]. However, laparoscopy requires expertise and hospitalization and may not be successful in up to 16% of cases, mainly limited by adhesions [87]. In addition, it is an invasive procedure and carries its own risks. Major complications in the form of bleeding can occur in 2%–4% and perforation in 2%, with an overall rate of 6% to 9%. Furthermore, some cases of diagnostic laparoscopy may result in laparotomy (in up to 9%) due to technical issues or dense bands of fibrosis and adhesions [88–90].

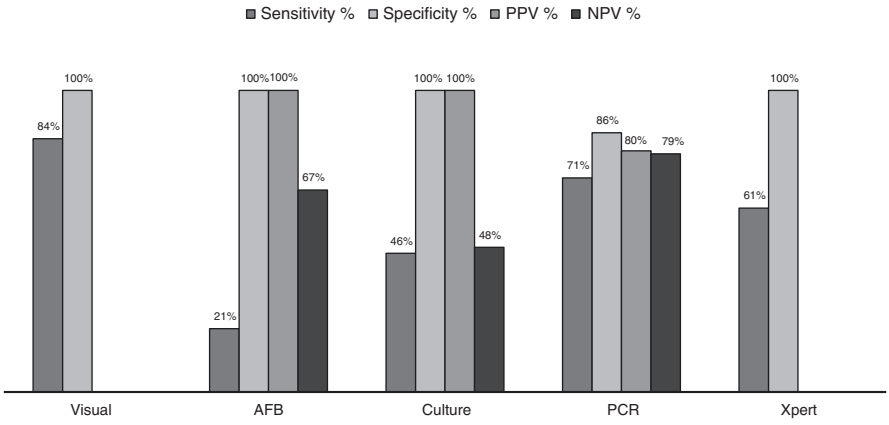

Fig. 10.3 Laparoscopic diagnostic yield in peritoneal tuberculosis

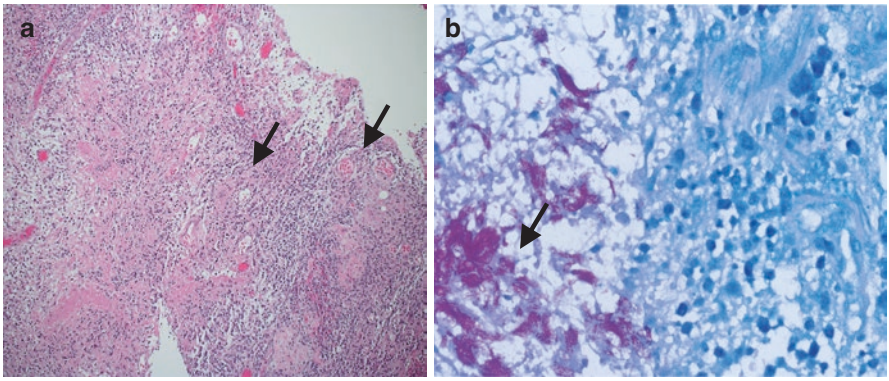

Fig. 10.4 (**a**) Mesenteric biopsy in a patient with peritoneal tuberculosis demonstrating granuloma formation (black arrows) and chronic inflammation (hematoxylin & Eosin stain) and (**b**) Ziehl–Neelsen stain demonstrating epithelioid granuloma

10.6.4 Histopathology

Histopathological analysis of the biopsy specimens usually reveals chronic nonspecific inflammation associated with granulomas (Fig. 10.4). Granulomas are found in around 64% to 100% of specimens analyzed and are typically well-defined, large, mean number per section of 2.5 to 4.8 [25, 60–62, 64, 65, 67–71, 87–89]. The characteristic central caseation necrosis within the granulomas is considered typical of TB and is reported in 32% to 100% of cases [25, 60, 62, 64, 65, 67–71, 87–89]. These necrotic granulomas, when found on biopsy specimens taken at laparoscopy, give an estimated sensitivity and specificity of 71% to 100% and 100%, respectively [87]. However, the presence of a granuloma without caseation gives a sensitivity of 10% to 48% [64, 65, 68, 69, 71, 88, 89].

10.6.5 Microbiology

Microbiological analysis of ascitic fluid or biopsy specimen can be carried out for acid-fast bacilli (AFB) on smear, polymerase chain reaction (PCR) and mycobacterial culture. The number of mycobacterial organisms present in the specimens determines the accuracy of the test. *Mycobacterium tuberculosis* (MBT) needs to be in the thousands for detection on smear, in hundreds to grow on culture and in tens for PCR. Body fluids are generally paucibacillary for MBT with consequent low detection. The yield on ascitic fluid of stain for acid-fast bacilli is low with reported sensitivities of 2% to 52% [25, 28, 60, 61, 64, 65, 68, 71, 73]. The diagnostic yield in terms of sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) for detection of AFB on peritoneal fluid are 5% to 29%, 100%, 100% and 41% to 63%, respectively (Table 10.2) [91–93]. On the other hand, the smear positivity for AFB on laparoscopic biopsy specimens is relatively higher, ranging from 24% to 59% (Fig. 10.3) [25, 60, 65, 73, 94].

Traditional cultures usually take weeks, with reported positivity on peritoneal fluid ranging from 7% to 58%, and for cultures on laparoscopic biopsies from 20% to 98% [25, 28, 60–62, 64, 65, 67–69, 71, 87, 89]. The diagnostic accuracy reported in literature in terms of sensitivity, specificity, PPV, and NPV for traditional peritoneal fluid culture are 17% to 43%, 100%, 100%, and 44% to 48%, respectively (Table 10.2) [92, 93].

Improvements on traditional culture techniques include nucleic acid amplification tests (NAAT) that can detect a small amount of MBT. These are quick to perform, with the results potentially available within hours. Simple PCR is one such platform used in PTB diagnosis. A number of studies demonstrated that PCR for MBT culture on ascitic fluid was better than traditional methods with sensitivity, specificity, PPV and NPV ranging from 62% to 79%, 68% to 100%, 79% to 100%, and 78% to 87%, respectively (Table 10.2) [91, 95, 96]. Performance of PCR on laparoscopic biopsies did not improve the sensitivity in studies that reported it and varied from 25% to 60% (Fig. 10.3) [62, 65, 89].

Further improvement in NAAT has come with the development of Xpert MTB/RIF assay, an automated test with a quicker turnaround time requiring much lesser hands on time. Three meta-analyses have reported on the use of Xpert MTB/RIF assay on ascitic fluid for PTB diagnosis with sensitivity and specificity varying from 59% to 86% and 97% to 98%, respectively (Table 10.2) [97–99]. In addition, the studies that examined this test on peritoneal biopsies showed that the sensitivity and specificity varied between 50% to 61% and 92% to 100%, respectively (Fig. 10.3) [100, 101]. The main limitation of utilizing this test in high disease burden areas (generally in low-income economies) is the cost.

Some authors have also made comparative evaluations of different tests towards the diagnosis of PTB. A study in 191 (115 PTB and 76 non-PTB cases) Chinese patients compared AFB, traditional culture, Xpert and ADA levels on ascitic fluid and showed that traditional culture detected 12% (14/115) more (sensitivity 17.2%) and Xpert 13% (15/115) (sensitivity 18.3%) more cases than AFB that detected only 6 cases of PTB (6/115, sensitivity 5.2%). On the other hand, ADA confirmed 65%

Table 10.2 Ascitic fluid diagnostic yield in peritoneal tuberculosis

Test	AFB			Traditional Culture		PCR Culture			Xpert Culture		
Study	Bandyopadhyay et al (89)	Liu R et al (90)	Flores et al (91)	Liu R et al (90)	Flores et al (91)	Hallur V et al (92)	Bandyopadhyay et al (89)	Kulkarni S et al (93)	Kholi M et al (94)	Penz E et al (95)	Sharma V et al (96)
N	49	191	44	191	44	23	49	50	16 studies	5 studies	18 studies
Sen.	5%	5%	29%	17%	43%	62%	79%	77%	59%	86%	64%
Spec.	100%	100%	100%	100%	100%	100%	87%	68%	98%	98%	97%
PPV	100%	100%	100%	100%	100%	100%	79%	80%	–	–	–
NPV	63%	41%	52%	44%	48%	78%	87%	73%	–	–	–

N number, *Sen* sensitivity, *Spec.* specificity, *PPV* positive predictive value, *NPV* negative predictive value

Table 10.3 Comparison of the performance of different diagnostic tests for peritoneal tuberculosis; each additional arrow represents better performance, *includes histopathology

Study	Ascitic AFB	Ascitic Culture	Ascitic PCR	Ascitic Xpert	Ascitic ADA level	CT Scan	Lap. Visual
Liu et al [90]	↔	↑	↑↑	↑↑↑	↑↑↑↑	Not done	Not done
Hong et al [92]	↔	↑	↑↑	Not done	↑↑↑↑	↑↑↑	↑↑↑↑
Bandyopadhya et al [89]	↔	Not done	↑	Not done	↑↑	Not done	Not done
Flores et al [91]	↔	↑	↑↑	Not done	Not done	↑↑↑	↑↑↑↑
Hallur et al [93]	↔	↑	↑↑	Not done	↑↑↑	Not done	Not done

(75/115) more cases (sensitivity 89.6%) in addition to the cultures [92]. In the absence of a validated gold standard, the authors used clinical diagnosis as the standard for comparison, potentially explaining the low sensitivities of the tests used. In a separate study from Korea, the authors concluded that laparoscopy was better at diagnosing PTB in comparison to ascitic fluid analysis and CT scan [94]. Another study from India compared ascitic AFB with ADA activity and PCR culture and showed that PCR was significantly better than the former two [91]. In a Mexican study, laparoscopy with histopathology was deemed to the best diagnostic tool in relation to ascitic fluid analysis, culture and CT scan [93]. Finally, in another study, ADA activity performed better than ascitic AFB and culture both by traditional method and by PCR (Table 10.3) [96].

These studies highlight the variability in data and difficulties encountered in approaching patients with suspected PTB. Clearly, no single investigation consistently performed as the diagnostic test of choice in the above studies. Although the studies differed in their criteria used to confirm PTB and the methodology used to compare tests, this merely serves to demonstrate the lack of a standardized approach and the inherent difficulties in diagnosing PTB, and the inability to reach a diagnosis based on a single test. Hence, it remains that a combination of investigations and a high index of clinical suspicion are essential to establish a diagnosis of PTB.

10.7 Differential Diagnosis

Ascites is a common presentation in PTB, however other diseases can cause ascites. The commonest cause of ascites is related to end-stage liver failure (found to be the cause is nearly 85% of cases) [102]. Other less common causes include heart failure, nephrotic syndrome, pancreatitis, lymphatic leak and peritoneal carcinomatosis [102]. Good history and physical examination are important to differentiate cirrhosis from PTB. The presence of spider naevi, palmer erythema and bruises help in making a diagnosis of cirrhosis. Ascitic fluid analysis serves as the key, cell count

with differential, albumin level with SAAG and amylase level may establish the right diagnosis. However, considering that cirrhosis and PTB can co-exist, particularly in the context of alcoholism, and that such patients may manifest a high SAAG ascites, more incursive and specialized tests such as ADA, PCR, fluid culture and laparoscopic biopsy may eventually be required.

Peritoneal carcinomatosis including ovarian cancer can present with abdominal mass, ascites, and peritoneal involvement similar to abdominal TB [103–105]. Advanced imaging using PET/CT is emerging as an attractive tool to confirm peritoneal carcinomatosis [106, 107]. Another chapter discusses in detail the discrimination of PTB and peritoneal carcinomatosis. Other rare conditions like granulomatous chronic infections, including histoplasmosis and Cryptococcus and chronic inflammations with granulomas without central caseation like sarcoidosis need to be considered in the differential diagnosis.

In situations where the clinical suspicion remains highly in favor of TB, an empirical course of anti-tubercular treatment is a valid diagnostic and therapeutic tool and remains an established tool in clinical practice.

10.8 Treatment

The mainstay of therapeutic approach is medical and is similar to treatment of pulmonary TB. In addition, surgery may be indicated in patients who do not respond to medical therapy or in cases of complications like obstruction, perforation, abscess collection or peritonitis. International guidelines recommend 6 months therapy with standard regimens similar to pulmonary TB [108, 109]. Despite such recommendations, 9 months therapy is used at times with a view that the therapeutic benefit is difficult to document and to ensure complete eradication of the bacilli. However, a Cochrane systemic review of three randomized controlled trails concluded that 6 months therapy is sufficient to achieve response and any further prolongation did not provide additional benefit [110]. Delay in treatment initiation can lead to significant mortality. Chow et al. reported a considerable deterioration in clinical condition of more than 80% of patients during the diagnostic work-up [61]. The overall mortality in this study was 35%, while in the subset of patients with underlying cirrhosis, it was substantially higher at 73%. Average mortality from the cumulative data of 18 series comprising of more than 800 patients was 19% [87].

There are currently five drugs that are considered first-line medications: isoniazid (INH), rifampicin (RIF), pyrazinamide (PZA), ethambutol (EMB) and streptomycin (SM). In most circumstances, the treatment regimen for adult patients with previously untreated TB should consist of a 2-month initial phase of INH, RIF, PZA and EMB given on a daily basis. This is followed by a continuation phase where INH, RIF and EMB are continued for another 4 months. There are various second-line drugs such as fluoroquinolones, bedaquiline, and linezolid, which along with either clofazimine or cycloserine form the second-line option in multi-drug resistant TB. Drugs such as ethionamide, aminosalicylic acid, amikacin, PZA, EMB or

meropenem can be utilized when above second-line medications cannot be used [111].

Response to therapy is usually difficult to assess objectively. Symptomatic improvement either in form of global or generalized well-being, resolution of fever and/or biomarkers like ESR and CRP are considered as surrogates for therapeutic efficacy. The amelioration of symptoms due to anti-tuberculous treatment (ATT) is usually seen within weeks and majority show full recovery by 2 months. In serial evaluation, 45% showed improvement of global symptoms at 1 month, 66% at two, 94% at 3 and 99% at 6 months [112]. Similarly, 52% normalized CRP at 2 months following therapy and more than 93% at 6 months [113]. In addition, resolution of ascites is an objective assessment for response to therapy. However, a small proportion of patients may need surgery despite ATT. Overall, 86% to 91% of surgeries in PTB were done in an emergency, and only 9% to 14% were electively performed [16, 19]. The reasons for surgery included adhesions (27% to 59%), strictures (31% to 51%), perforation (18% to 72%), peritonitis (23% to 36%), and failed ATT (9% to 14%) [16, 19, 26, 28]. The types of surgery included adhesiolysis (27% to 56%), followed by segmental resection (26%), and right hemicolectomy (7% to 18%) [19, 26, 114, 115].

The role of corticosteroids in abdominal TB is not well defined and is used mainly for its anti-inflammatory properties with moderate benefit. A recent systemic review and meta-analysis of three studies did confirm this limited efficacy restricted to peritoneal TB [116]. Nonetheless, international guidelines do not recommend it. Based on these aspects, we propose an algorithm that simplifies treatment strategy for PTB (Fig. 10.5), wherein treatment regimens comprising the standard ATT could be potentially extended beyond the usual 6 months when clinical symptoms and signs do not resolve, or corticosteroids and/or surgery considered in the face of persisting clinical abnormalities despite 6 months of ATT.

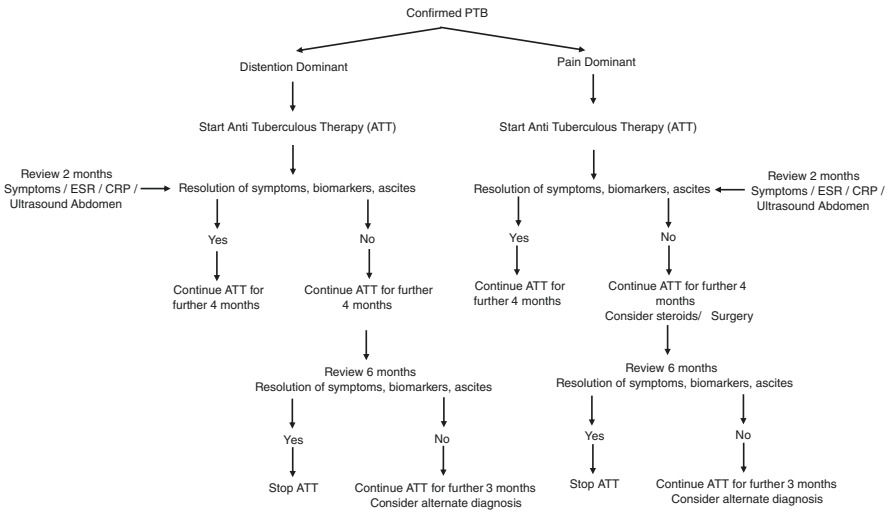

Fig. 10.5 Proposed algorithm for treating peritoneal tuberculosis

10.9 Conclusion

PTB remains a pertinent disease both in the developing and developed world. Old classical teaching of "doughy abdomen" and classifications like "wet-type, fibrotic-type and dry-type" are not relevant in current literature of PTB. Despite improvements in diagnostics, PTB continues to be an elusive diagnosis to establish. However, good historical information, combination of appropriate investigations on a background of high index of suspicion will mostly clinch the diagnosis. Early institution of therapy is the key as response to ATT is excellent. Although PTB is a distinctive disease, the prevalent literature usually reports it consolidated with other TB infected organs as EPTB or abdominal TB. Given the importance of PTB in clinical practice, particularly in areas where it is commonly encountered, development of clear clinical guidance is paramount. Current guidance, however, is inadequate and a focused appraisal with explicit clinical recommendations is needed.

Conflict of Interest None.

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Discriminating Tuberculous Peritonitis and Peritoneal Carcinomatosis

11

Anuraag Jena, Daya Krishna Jha, and Vishal Sharma

Key Points

1. Peritoneal tuberculosis and peritoneal carcinomatosis are close mimics with respect to their clinical and radiological findings.
2. The discrimination between the two is based on positive malignant cytology in peritoneal carcinomatosis and a positive microbiological test in tuberculous peritonitis.
3. CA-125 levels may be elevated in both conditions in serum and ascites, however, elevations of CEA and CA19-9 may be discriminative for peritoneal carcinomatosis.
4. Adenosine deaminase levels may be elevated in ascitic fluid in tuberculous peritonitis but may also be occasionally elevated in lymphomatous causes of ascites.
5. Peritoneoscopy / Diagnostic laparoscopy may be needed in occasional patients where other evaluation is non-contributory.

11.1 Introduction

Tuberculosis (TB) is a significant problem in developing countries and identified as one of the deadliest diseases (Global tuberculosis report 2019, WHO). While majority of TB cases are pulmonary, the frequency of abdominal TB appears to be rising. Abdominal TB is a common extrapulmonary (EP) site for TB infection, after lymphatic, genitourinary, osteo-articular, miliary, and meningeal [1]. Abdominal

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tuberculosis (TB) comprises up to 5–15% of all EPTB cases and may involve the gastrointestinal tract, solid organs, lymph node, pancreatobiliary system, peritoneum, or combination of these systems [2]. Abdominal TB is frequently mistaken for other abdominal diseases such as inflammatory bowel disease, advanced ovarian cancer, peritoneal carcinomatosis and other infectious etiology. Peritoneal TB can mimic peritoneal carcinomatosis: it can be challenging to distinguish the two clinically as both the conditions have nonspecific symptoms and signs, as well as overlapping features on laboratory evaluation and imaging [3].

Peritoneal tuberculosis (PTB) constitutes 25–50% of abdominal TB cases and 0.1–0.7% of all TB cases. It is the most common type of abdominal TB [4]. This condition is diagnosed through a combination of microbiologic, laparoscopic, radiologic, histological, and molecular techniques. PTB has previously been defined to be having one of the three patterns: wet type with ascites, dry type with adhesions and fibrotic type with loculated ascites and omental thickening. The definitive diagnosis is based on the detection of organism in ascitic fluid or peritoneum tissue. Lymphocytic predominant, low serum to ascites albumin gradient (<1.1 g/dl) and high protein [> 3 g/dl] ascites is suspicious of PTB. Despite all investigations, the diagnosis may be delayed as these investigations employed may not always be precise. Purified protein-derived tuberculin skin test may be negative even in PTB patients who have histologically confirmed diagnosis. Cultures are positive in only 30–40% of cases making bacteriological diagnosis difficult in all cases. Molecular diagnostic techniques have a variable sensitivity, with Xpert having a sensitivity of around 30% when compared to composite reference standard [5].

Peritoneal carcinomatosis (PC) results from invasion of the serous membrane lining of abdomen by malignant cells. The term was first used by Sampson in 1931 for ovarian metastatic cancer cells in peritoneal stromal surface [6]. Several gastrointestinal, lung, breast, and gynecological malignancies have the potential to spread in the peritoneal cavity. Peritoneal carcinomatosis until recently was associated with disease progression and poor prognosis. Occasionally, patients with pseudomyxoma peritonei, a low-grade malignancy, survive for several years. Nonspecific clinical presentation often leads to delay in diagnosis and reduction in survival. Encouraging results in highly selected patients from cytoreductive surgery and intraperitoneal chemotherapy have provided some hope to patients with colorectal, appendiceal, ovarian, and gastric carcinoma [7].

Investigations to differentiate PTB from PC like ascitic fluid protein, lactate dehydrogenase (LDH), CA-125 and the serum/ascites glucose ratio are usually inadequate [8]. Low sensitivity of conventional polymerase chain reaction [PCR] on ascitic fluid and need for further validation of modified PCR techniques increases morbidity. Laparoscopy with peritoneal biopsy has been considered as an ideal investigation for prompt diagnosis in patients with doubtful PTB and PC, but these are invasive and not routinely available [9]. Thus, it is important to differentiate the above two conditions as the advent of effective anti-tubercular therapy for PTB has led to significant reduction in morbidity and mortality. Patients with PC, if selected early for specialized therapy have improved prognosis.

11.2 Basic Anatomy

The peritoneum consists of a single layer of mesothelial cells with a thin layer of fibrous tissue. It is made up of two layers—superficial parietal and deep visceral layer. The visceral peritoneum covers the pelvic organs. The space between the parietal and visceral layer of the peritoneum is known as the peritoneal cavity. This space contains approximately 50–100 ml of serous fluid that prevents friction between the two layers. Peritoneal cavity is closed in males and communicates to the environment through the fallopian tube in females. Omentum is basically a layer of visceral peritoneum extending from greater and lesser curvature of the stomach to adjacent organs. Greater omentum hangs down from greater curvature like an apron containing fat and macrophages in the form of milky spots. It acts as an insulating layer. The mesentery consists of a double layer of visceral peritoneum and is an important support organ of the body. It originates from the superior mesenteric root region and spreads out to cover the bowel loops from duodenum to rectum. It is compactly folded in a spiral conformation within the peritoneal cavity. The small intestinal mesentery is highly mobile, while the right and left mesocolic regions along with the medial mesosigmoid region are attached to the posterior abdominal wall. Intervening regions of transverse mesocolon and remaining mesosigmoid are mobile. Mesentery suspends the small intestine and prevents it from collapsing. The spreading of different peritoneal diseases is decided by not only on the gravity, the gut peristalsis and negative pressure, but also on the various peritoneal folds and recesses.

11.3 Pathogenesis

PTB is often associated with a primary lesion of tuberculosis being distant. Lung is often the primary focus; however nearly one-third of the patients have clinical or imaging evidence of pulmonary TB. The paucity of bacilli required for extrapulmonary disease combined with relative inaccessibility makes laboratory confirmation even more difficult. Peritoneal spread of the bacteria can take place transmurally through the intestine via mesenteric lymph node or directly through fallopian tubes and psoas abscess, through lymphatic channel or hematogenously from primary focus (Table 11.1).

Table 11.1 Routes of dissemination in tuberculous peritonitis and peritoneal carcinomatosis

Routes of spread in PC	Routes of spread in PTB
Hematogenous: Melanoma, Breast cancer, Lung cancer	Hematogenous spread from pulmonary focus
Direct Contiguous: Ovarian Cancer	Direct contiguous spread: genitourinary tract
Lymphatic: Greater omentum, Sub-phrenic system	Rupture from mesenteric lymph nodes
Peritoneal Surface Spread: Gravity and peristaltic redistribution	Spread from intestinal lesions

Pathogenesis of PC can be explained by a dynamic process comprising multiple steps. There are three basic pathogenetic mechanisms of PC. The first way is the spread from a primary tumor as a result of exfoliation of malignant cells (stomach cancer, colonic cancer and pseudomyxoma peritonei). Second mechanism is by seeding from primary tumor (peritoneal mesothelioma), and third mechanism is from primary tumor and implants in peritoneum originating independently (ovarian malignancies) [10]. These mechanisms may act in combination for pathogenesis. The spread of tumor cells in the peritoneum may be due to spontaneous/iatrogenic perforation of the primary tumor or from blood vessels and lymphatics. Thereafter three basic routes decide the spread: gravity, peristalsis of gut, and negative pressure exerted by movements of diaphragm. There are areas with arrested flow which may be more likely to harbor timour deposits like pouch of Douglas, retro-vesical space, termination of mesentery of small intestine at ileo-cecal junction, superior portion of sigmoid mesocolon, right paracolic gutter and right subdiaphragmatic space.

11.4 Overlapping Clinical Manifestations

PTB and PC can present with mutually shared clinical features which are nonspecific, although PTB is more likely to predominate in the younger age group, however it can be difficult to differentiate the two entities due to minimal constitutional symptoms in the elderly (Table 11.2).

PTB is usually has a subacute presentation and its symptoms develop over weeks to months which can mimic PC, where patients become symptomatic during the advanced stage of the disease. The presence of co-morbid conditions in PTB, such as renal insufficiency and liver disease, result in atypical presentations that may lead to delayed diagnosis. The presentation of PC is often dependent upon the location as well as the extent of the disease [12]. In PTB, patients clinically present with acute or chronic symptoms including abdominal pain, fever, weight loss, diarrhea, and constipation, which can be very similar to PC except for fever which is significantly more common in patients with PTB [11]. Intestinal obstruction is one of the most troublesome consequences of PC. It is associated with symptoms such as abdominal pain, nausea, vomiting, distention, and the inability to tolerate any feed. Symptomatology of PC can also vary depending on whether the origin is of gynecological or non-gynecological. Gynecological malignancy can have pelvic pain, menopausal symptoms or abnormal vaginal bleeding. For some disease processes, peritoneal carcinomatosis may be incidentally detected at the time of evaluation. While diseases such as pancreatic and ovarian malignancies are often more subtle, and the clinical presentation of PC may be the only clues for the diagnosis.

Both PTB and PC often manifest as increased abdominal girth from ascites. On physical examination in PTB, patients may show abdominal tenderness, hepatomegaly, and ascites. In PTB, there is considerable overlap between dry plastic and fixed fibrotic type. In PC, the signs and symptoms of underlying malignancy may also present like jaundice, upper abdomen pain, lump abdomen, anorexia, and weight loss. Nearly two-thirds of pancreatic malignancies will occur in the head of

Table 11.2 Clinical parameters to discriminate tuberculous peritonitis and peritoneal carcinomatosis

Clinical parameter	PTB	PC
Age	Younger	Elderly
Presentation	Acute- Subacute-Chronic	Subacute-Chronic
Clinical features	Constitutional symptoms Fever- More common Wet- Ascites Dry- Adhesions/Fibrosis/Caseous nodules Fixed fibrotic- Loculated ascites and omental thickening Pain/obstruction dominant or distention dominant	Constitutional symptoms Fever- Less common Ascites Obstruction
Laboratory parameter		
Ascitic fluid	Lymphocyte predominant Low SAAG Raised ADA	Abnormal Cells Low SAAG
Mantoux, IGRA	Positive	Negative
Tumor markers [11]	Serum CA125- elevated Serum CEA- not elevated Serum CA 19.9- not elevated	Serum CA-125, CEA, and CA19.9 are usually elevated
Liquid biopsy		miRNAs (like miRNA21 for GI cancers)

pancreas. They cause symptoms of obstructive jaundice very early in the disease course. The symptoms of PC may be present by the time jaundice is noticed. For those tumors in the body or tail region of the pancreas, the presenting symptomatology may be generalized like pain abdomen, significant weight loss and the signs and symptoms of PC [13]. The presence of abdominal lump may indicate the primary lesions but more often may represent peritoneal or omental deposits in patients with malignancy. Occasionally, patients with peritoneal tuberculosis may also have lump due to clumped bowel loops or cocoon formation.

11.5 Diagnostic Evaluation

Insidious nature of illness and nonspecific symptoms related to both PTB and PC makes the diagnosis entirely dependent on high degree of clinical suspicion. Routine laboratory markers and radiology are rarely diagnostic. Anemia can be variably found in both disorders and raised ESR has poor sensitivity to diagnose PTB. Positive tuberculin test and abnormal CXR have poor sensitivity in detecting active tuberculosis. Interferon gamma release assays like Quanti-FERON gold and T-spot TB tests, done on peripheral blood, are unable to differentiate between latent or active TB. Positive acid-fast bacilli staining of clinical samples are less than 3% and

culture positivity of fluid sample is around 35% by regular method in confirmed cases of PTB, making them diagnostic tests with poor sensitivity.

11.5.1 Ascitic Fluid

Ascitic fluid analysis is frequently performed to differentiate PTB and PC. Both the conditions have low SAAG. PTB has lymphocytic ascites, although PTB complicating renal failure can have neutrophilic ascites [14]. Ascitic fluid cytology aids in diagnosis in almost 50%–60% of cases of malignant ascites. However, cytology has been demonstrated to be positive in 97% of patients with peritoneal carcinomatosis if tested thrice. It makes ascitic fluid evaluation the gold standard for diagnosing PC [15] [16]. Other biochemical properties have not been found to be definitive in distinguishing between benign and malignant ascites. Adenosine deaminase (ADA) is an aminohydrolase that has role in purine metabolism. It is also a potent modulator of T cell differentiation. Ascitic fluid ADA has very high sensitivity and specificity in the diagnosis of PTB. At predetermined levels of ADA value >39 IU/L has a reported sensitivity of 100% and a specificity of 97.2% [17]. However, ADA has its limitations. Ascitic fluid ADA is falsely positive in spontaneous bacterial peritonitis, lymphomatous ascites, and pyo-peritoneum. It can be falsely negative in patients with HIV, mixed ascites and loculated collections [18]. Increased levels of gamma-IFN in ascitic fluid may be as valuable as the ADA levels in the diagnosis of PTB. In fact, the combination of both tests has shown good sensitivity [19]. New molecular diagnostic Xpert® MTB/RIF assay has good sensitivity with sputum samples, however, it has performed poorly on ascitic fluid samples [20]. Xpert® MTB/RIF assay, when performed on peritoneal tissue samples, provides a rapid diagnosis of tuberculosis and information on rifampin resistance. A meta-analysis of 19 studies on Xpert® MTB/RIF assay showed a pooled sensitivity of 64% and specificity of 97% when compared to culture but a sensitivity of only 30% when composite reference standard was used [5]. Thus, no single test is comprehensive in diagnosing either PTB or PC but combination of cytology, ADA, IGRA, and Gene Xpert on peritoneal tissue can help differentiate both the disease entities.

11.5.2 Tumor Markers

Tumor markers can be increased in both PTB and PC. Carbohydrate Antigen-125 (CA-125), the common tumor marker of ovarian malignancy, is also increased in patients with pulmonary as well as extrapulmonary TB. CA-125 antigen is a large transmembrane glycoprotein and arises from pleura, pericardium, peritoneum, endometrium and fallopian tube epithelium. CA19-9 and CEA have been found to be elevated in PC as compared to PTB [11]. Normal serum CA 19-9, CEA, and raised CA-125 can provide discriminative roles in establishing PTB as compared to

PC. Raised CEA and composite index (calculated by multiplying CA-125 and CEA) have been advocated as markers of non-ovarian carcinoma-associated PC [21].

11.5.3 Imaging

Imaging findings are not characteristic for either PC or PTB. But imaging may aid in diagnosis when considered together with clinical presentation, immunological features and the demographic origin (Table 11.3). Ultrasonography, although useful, has poor sensitivity in differentiating TBP from PC. It can be utilized for localizing adnexal mass in cases of PC and show matted pattern with central necrosis in

Table 11.3 Radiological parameters to discriminate tuberculous peritonitis and peritoneal carcinomatosis

Parameter	PTB	PC
CT Abdomen		
Ascites	90% Loculated Fibrinous High density (>20 Hounsfield units)	70%
Peritoneum [22, 23]	Presence of a smooth/uniform peritoneum with no/minimal thickening and increased enhancement post-contrast	Multinodular/Nodular implants and irregular peritoneal thickening
Mesentery [24]	Densification of the mesenteric root fat planes, which may occur in up 70% of cases Macro-nodules, Calcification	Micronodules
Omentum abnormalities [25]	Smudge type Omental Rim sign	Nodular and cake types
Lymph node [25]	Lymph nodes (size <1 cm) and lymph nodes in peripancreatic region more frequently seen in PTB, Lymphadenopathy with areas of central necrosis or calcification	Lymph nodes (size ≥1 cm), homogeneous retroperitoneal lymph nodes enlargement and contour abnormality of liver/spleen more frequently seen in PC
PET CT		
Parietal peritoneum [26]	≥4 involved regions, string of beads F-FDG uptake, susceptible area for peritoneal implantation (SAPI) less common	SAPI distribution more common, LSAPI distribution (Less-susceptible area for peritoneal implantation exclusively in PC), clustered F-FDG uptake, focal F-FDG uptake
Laparoscopy		
Appearance	Peritoneal thickening with or without military whitish nodules, fibro-adhesions, micronodules (< 1 cm)	Macro-nodules (>1 cm)

tubercular lymphadenopathy of abdomen. Necrotic lymph nodes can also be seen in disseminated malignancy. Ultrasound can detect ascites, peritoneal thickening and nodules, omental masses, lymphadenopathy, and mesenteric thickening. Ultrasound also serves as a good modality for guided FNAC/biopsy.

A better modality for differentiation between PTB and PC is CT with contrast. CT can show a combination of mesenteric, omental, peritoneal, and lymph nodal involvement in both the condition. However, the most common CT findings noted with PTB are ascites, smooth peritoneal thickening, densification of root of mesenteric fat planes and lymph node enlargement with central necrosis or calcification. In contrast most frequent findings in PC are irregular and multinodular peritoneal thickening, retroperitoneal lymphadenopathy and omental caking [27]. Although most of the findings analyzed on CT overlap in both the disease, useful tomographic signs to differentiate are smooth and regular peritoneal thickening in PTB, nodular and irregular peritoneal thickening in PC, mesenteric macronodule in PTB, omental line and splenic abnormality including splenomegaly or calcification in PTB [28, 29]. Visceral scalloping, although more common in peritoneal carcinomatosis and pseudomyxoma peritonei, can also be seen in PTB [24]. Omental rim signs on CT scan could help identify 85% patients of peritoneal TB [29]. When the site of primary malignancy is also demonstrable on CT, the diagnosis of PC can be made with more certainty. MRI can be utilized in pregnant and children to avoid ionizing radiation of CT scan.

FDG PET has a role in differentiating PTB from PC apart from the assessment of disease burden and response to treatment in PTB [26]. Combination of FDG PET and CT has higher sensitivity and positive predictive value than of CT alone for the diagnosis of peritoneal lesions [30]. Due to interplay of the physiological forces directing the movement of peritoneal fluid peritoneal implantation of malignant cells can be divided into susceptible areas for peritoneal implantation (SAPI) and less-susceptible areas for peritoneal implantation (LSAPI). In SAPI distribution, the lesions are primarily localized in pelvic and right subdiaphragmatic regions of the parietal peritoneum, and when lesions are localized in remaining regions, they are called as the LSAPI distribution. SAPI distribution occurred more frequently with PC compared to PTB and LSAPI distribution, although infrequent, occurred exclusively with PC. However, uniform distribution occurred more frequently with PTB compared to PC. With regards to the morphological pattern of FDG uptake string of beads uptake (string of beads sign) occurred more frequently with PTB, clustered FDG uptake and focal uptake are seen more frequently with PC. However, SUV_{max} did not show a meaningful difference between TBP and PC [26].

11.5.4 Laparoscopy

Laparoscopy is the diagnostic modality of choice in patients with doubtful PTB and PC. It not only allows direct visualization of the peritoneum but also allows obtaining of specimens for histopathology and microbiological confirmation. They are not

commonly performed due to the invasive nature of the procedure, complications (bleeding and bowel perforation) and lack of availability at peripheral healthcare setup. In PTB, laparoscopic examination has high diagnostic yield with a sensitivity of the macroscopic appearances as high as 93%. When analyzed with histopathological findings (epithelioid granulomas with caseation or mycobacterial identification), it has shown impressive sensitivity and specificity [31]. Findings of tubercular disease on laparoscopy are nonspecific and similar appearance may be seen with non-tubercular peritonitis, peritoneal carcinomatosis, and mesothelioma. Laparoscopic appearance of PTB can be grouped into three types: most commonly, they present as peritoneal thickening with miliary whitish nodules, only peritoneal thickening with or without adhesions and thirdly, it can present as fibro-adhesive pattern [32]. PTB may have omental thickening and bowel strictures, which are consequences of cicatricial healing of circumferential ulcers. Mesenteric lymph nodes may be enlarged and matted. Classical granulomas may be found only in the mesenteric lymph nodes. This is usually seen in patients who have taken anti-tubercular therapy for short duration. The reverse, i.e., the presence of granulomas in the intestinal epithelium and not in the draining lymph nodes are rare [33]. Peritoneal involvement and adhesions in PC can mimic PTB, however, PC is more likely to have macro-nodules (>1 cm) as compared to micronodules (<1 cm) when compared to PTB [34].

Diagnostic laparoscopy has higher sensitivity and specificity for the diagnosis of PC than helical CT scan [35] The use of laparoscopy in the assessment of PC extent is now accepted universally. This procedure aids in defining the origin of the neoplasm. It also helps in calculating the peritoneal cancer index (PCI) as well as the extent of involvement of the small intestine and its mesentery. It assesses the feasibility of resection and the index of attainable cytoreduction. This procedure can be taken up safely as it generally results in very low morbidity.

11.6 Conclusion

Differentiation between PC and PTB is an integral part of management. A multimodality approach which includes ascitic fluid analysis, tumor markers, imaging, diagnostic laparoscopy and image-guided biopsy is crucial for true distinction (Fig. 11.1). The advent of effective anti-tubercular therapy for peritoneal tuberculosis and specialized therapy for peritoneal carcinomatosis has improved prognosis and survival. Further prospective studies would show a better picture of the horizon for true differentiation.

Conflict of Interest Nil.

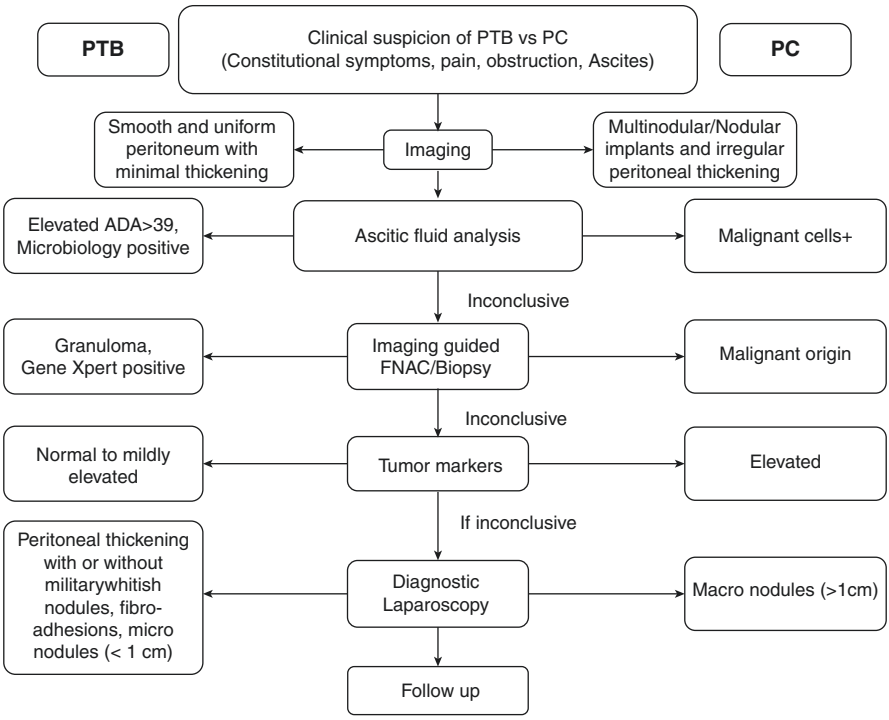

Fig. 11.1 Algorithm for distinguishing Peritoneal Tuberculosis (PTB) and Peritoneal carcinomatosis (PC)

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Imaging for Peritoneal Tuberculosis

12

Pratyaksha Rana and Pankaj Gupta

Key Points

1. Peritoneal tuberculosis is a common presentation of abdominal tuberculosis.
2. Imaging plays a crucial role in the diagnosis, classification, and management of peritoneal tuberculosis.
3. Computed tomography is the most widely utilized imaging test for patients with suspected peritoneal tuberculosis.
4. Imaging features may allow differentiation of peritoneal tuberculosis from other diseases involving the peritoneum but none of the findings are specific.
5. Image-guided sampling is a safe and feasible strategy for minimally invasive diagnosis of peritoneal tuberculosis.

12.1 Introduction

Abdominal tuberculosis accounts for 11–12% of cases of extrapulmonary tuberculosis [1]. Abdominal tuberculosis comprises the involvement of gastrointestinal tract, abdominal lymphatic system, peritoneum, and its reflections and solid visceral organs [1, 2]. Peritoneal tuberculosis is the most common presentation of abdominal tuberculosis accounting for 31–58% of abdominal tuberculosis cases. It includes the involvement of the peritoneal cavity, omentum, and mesentery [2–4]. Risk factors include human immunodeficiency virus infection, immunosuppression, diabetes mellitus, cirrhosis, peritoneal dialysis, among other conditions [3–5] Possible

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routes of spread to peritoneum include reactivation of silent tubercular focus in the peritoneal cavity, rupture of involved abdominal lymph nodes, hematogenous spread, contiguous spread from adjacent hollow viscera and solid abdominal organs [6–8].

Accurate and timely diagnosis of peritoneal tuberculosis is crucial [3, 7]. However, early diagnosis is challenging [9]. The clinical features are often nonspecific and variable, overlapping with other common diseases. The hematological and biochemical tests for diagnosis have poor sensitivity and low discriminatory values [10]. The gold standard for diagnosis of peritoneal tuberculosis is laparoscopy and peritoneal biopsy. Laparoscopy, however, is an invasive procedure with associated morbidity [10–12].

Imaging plays a crucial role in the diagnosis, classification, and management of peritoneal tuberculosis. Apart from the diagnosis of peritoneal tuberculosis, it allows detection of involvement of other sites, which is essential in management. Image-guided sampling is a less invasive procedure, with lower complication rates [3, 10].

12.2 Classification of Peritoneal Tuberculosis

Peritoneal tuberculosis is commonly classified into three types based on imaging features and clinical manifestations–wet type, fixed fibrotic type, and dry plastic type (Table 12.1) [13]. The frequency of various patterns is unclear, although the wet type is considered the most common type, ascites being the most common manifestation [13]. The wet and fibrotic types commonly present with abdominal distension and dry type with doughy abdomen [4].

Table 12.1 Types of peritoneal tuberculosis[b]

	Type	Salient features	Overlapping features
Old Classification[a]	Wet	Free ascites	Loculated ascites, peritoneal thickening and enhancement, tiny peritoneal nodules
	Fibrotic fixed	Mesenteric, omental, peritoneal thickening, nodules, and masses	Loculated ascites, adhesions, clumped bowel loops
	Dry plastic	Fibrosed peritoneum, caseous nodules	Clumped bowel loops, dense adhesions
PGI Clinico-radiological classification	Distension-dominant	Ascites	Mesenteric, omental involvement, peritoneal nodules
	Pain - Obstruction Dominant	Bowel involvement as cocoon, peritoneal fibrosis or adhesions	

[a]Lack of uniformity is a concern with this system of classification

[b]Abdominal cocoon can be considered distinct forms of peritoneal tuberculosis or continuous spectrum with the above types

The wet type is characterized by ascites, peritoneal thickening, and enhancement. Fibrotic fixed type is characterized by omental and mesenteric masses and thickening, fixed, and matted bowel loops with hypervascular peritoneum. Dry plastic type is defined by fibrous thickening of the peritoneum and mesentery with caseous nodules and dense adhesions. Despite the characteristic features described above, overlapping features exist. Loculated or encysted ascites can be found both in the wet and fibrotic types. Adhesions and clumping of bowel loops can occur in both dry and fibrotic types [4]. This classification system, although commonly used, lacks consistency due to overlapping features. Further, this system is not helpful in making a treatment plan and prognostication [4].

A new clinical-radiological classification system (PGI classification of peritoneal tuberculosis) has been proposed by Ahamed et al. This clinically oriented classification takes radiological and surgical features into account [4]. Two broad categories have been described: Distension dominant and pain obstruction dominant peritoneal tuberculosis. This classification system was proposed as the management and prognosis of both the types differed. Local complications like obstruction were more frequent in pain-obstruction type. In distension-dominant type, the main challenge is to differentiate it from other causes of ascites and peritoneal diseases. This type is effectively managed with the current antitubercular treatment (ATT) regimen. In pain-obstruction dominant type, multidisciplinary management is needed. This involves diet modifications, ATT, and surgery in refractory cases.

12.3 Other Manifestation of Peritoneal Tuberculosis

Abdominal Cocoon: Abdominal cocoon, also known as sclerosing encapsulating peritonitis or encapsulating peritoneal sclerosis, is characterized by encapsulation of bowel loop in a fibrous membranous sac. Earlier described in patients with chronic ambulatory peritoneal dialysis, it is now becoming a common entity and has various benign and malignant causes [14]. Tuberculosis is an important cause of tubercular abdominal cocoon, especially in endemic regions. Various case series and reports describe imaging features of abdominal cocoon [15–25]. The etiopathogenesis of tubercular abdominal cocoon remains unclear. Few researchers believe it to be a part of fibrosis and adhesions in peritoneal tuberculosis, while some consider it a distinct entity [2, 15, 16].

It is classified into three types depending on the structure encased within the membrane [17, 26]. Type 1 is characterized by encasement of only a part of the small bowel, type 2, entire small bowel, and type 3 large bowel and adjacent solid organ along with small bowel. Another classification categorizes tubercular abdominal cocoon as partial (only small bowel) and complete (small bowel, large bowel, or other organs) [27].

Preoperative diagnosis of tubercular abdominal cocoon allows proper planning of surgery with good clinical outcomes [28].

Intraperitoneal Tubercular Abscess: Intraperitoneal tubercular abscess is rare, but a serious manifestation of peritoneal tuberculosis encountered in immunocompromised individuals [7, 29]. Dong et al. described two types of intraperitoneal abscesses based on etiopathogenesis with certain distinct imaging features: Lymph node fusion and encapsulation type [7]. Early diagnosis is crucial as delayed detection is associated with increased mortality.

12.4 Role of Imaging Modalities in Peritoneal Tuberculosis

12.4.1 X-Ray Chest and Abdomen

Radiographs have poor accuracy for the diagnosis of peritoneal tuberculosis and have been replaced by cross-sectional imaging. Findings of pulmonary tuberculosis can be co-existent with abdominal tuberculosis in 15–20% of patients [30, 31]. Nonspecific features of peritoneal tuberculosis include elevation of the diaphragm, medial deviation of the lateral edge of the liver, cecum, and ascending colon, diffuse abdominal haziness, indistinct psoas margin and bowel loop displacement. These signs suggest ascites only when it is moderate to gross [32–34]. Dilated bowel loops with or without air–fluid levels may be seen in intestinal obstruction. There is a higher propensity of acute intestinal obstruction in tubercular abdominal cocoon as compared to other forms of peritoneal tuberculosis [14]. Peritoneal calcification and calcification of membranous sac in cocoon have also been described [2, 35].

12.4.2 Barium Studies

Findings of gastrointestinal barium studies are not specific for the diagnosis of peritoneal tuberculosis. There can be displacement of bowel loops due to ascites, dilated bowel loops due to adhesion and fibrosis, or there may be dysmotility of the intestine. The rigid and fixed cluster of bowel loops, kinking, and tethering of bowel loops due to adhesions can also be present. In cases of abdominal cocoon, the characteristic features are conglomerated appearance of small bowel loops in a concertina-like fashion. Serpentine arrangement of dilated small bowel loops in a fixed U-shaped configuration is considered characteristic [14].

12.4.3 Ultrasound

Ultrasound is a non-invasive, radiation free, cost-effective modality, which is the first method of investigation in patients with nonspecific abdominal symptoms commonly encountered in peritoneal tuberculosis. Apart from the advantage of real-time imaging, positional imaging is also possible to see for loculations or encapsulation of fluid. The role of ultrasound for the evaluation of peritoneum, specifically, has been described. A systematic peritoneal survey is vital to scan the

entire abdominal cavity [36]. Low frequency curvilinear (3.5–5 MHz) transducer is first used to scan the full depth of the peritoneal cavity with appropriate gain and focus settings, followed by scanning with a high-frequency linear transducer (5–12 MHz) for superficial structures. Graded compression can be applied to displace the bowel loops and study their motility in real time. Color Doppler can be used to study increased vascularity of inflamed peritoneal structures. Harmonic imaging allows improved resolution and detection of echoes and septation in ascites. The presence of ascites, free or loculated with location, amount, echogenicity, septations should be assessed. Peritoneal, mesenteric, omental thickening, and pattern of thickening and omental nodules should be reported. Also, the arrangement of bowel loops, lymphadenopathy, solid visceral organ involvement needs evaluation [14, 37–39].

The minimal amount of ascites can be diagnosed with ultrasound. Ultrasound is better than CT in detecting septations and echoes in ascites. Peritoneal, omental, and mesenteric findings are better visualized in the presence of ascites [30].

Despite this, there are certain limitations of ultrasound, which include operator dependence, subjective nature of assessment, and many nonspecific imaging features. Its diagnostic capability is also dependent on the subjects' body habitus. Ultrasound is less efficient than CT in the detection of peritoneal abnormalities other than ascites [3].

12.4.4 Computed Tomography

Computed tomography (CT) is a widely available modality that offers wide coverage with good spatial and temporal resolution. Due to its multidetector capabilities, thin isotropic voxel, multiplanar, and three-dimensional reconstruction, its diagnostic potential has significantly improved and is the modality of choice for imaging of abdominal tuberculosis [4, 40, 41]. Proper image acquisition with good breath hold is of paramount importance for diagnostic image quality. Contrast-enhanced CT of the abdomen and pelvis is performed. Positive oral contrast or neutral oral contrast (water/polyethylene glycol) can be administered to rule out concomitant GI tract involvement. Single porto-venous phase is sufficient for the diagnosis of peritoneal tuberculosis. Non-contrast CT can be acquired to see calcifications in selected cases. Apart from findings evaluated on ultrasound, attenuation of ascitic fluid, presence and pattern of thickening and enhancement of peritoneum, omental thickening, pattern of omental and mesenteric involvement, nodules and masses along with their size and characterization should be assessed [4, 14, 40–42].

CT is considered a better imaging modality to evaluate peritoneal, mesenteric, and omental changes as compared to ultrasound [30]. The sensitivity to detect peritoneal tuberculosis by CT is 69–88% [43, 44]. The imaging features are however nonspecific with considerable overlap between malignant and other benign peritoneal diseases [43, 45]. Also, the diagnostic capability of CT is also partially dependent on the presence of ascites and the location of lesion [43, 46]. The most important peritoneal disease that needs differentiation from peritoneal tuberculosis is peritoneal carcinomatosis, which would be discussed later.

12.4.5 Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) is currently used primarily for the evaluation of solid abdominal organs due to its superior soft tissue contrast resolution. Artifacts due to intestinal peristalsis, breathing, and long acquisition time are problematic in the evaluation of intestinal pathologies. These limitations have been dealt to certain extent with advances like respiratory compensation, breath hold acquisition and fast imaging technique [47, 48]. There is a limited literature on role of MRI for the evaluation of peritoneal tuberculosis [48–50]. The presence of ascites with diffusion restriction as well as peritoneal thickening with enhancement and diffusion restriction can be seen in peritoneal tuberculosis. Normal peritoneal enhancement is less than or equal to the liver. Abnormal enhancement of the peritoneal is better depicted with MRI as compared to CT [14]. Distinction of malignant and benign ascites using MRI has been described [51]. Better detection of septa in ascites has been reported with MRI as compared to CT [48].

12.4.6 F-18-FDG-Positron Emission Tomography (PET)-CT

PET-CT combines the functional and anatomical information. The role of PET-CT in the evaluation of ascites of undetermined origin has been studied with promising results. Higher sensitivity and accuracy have been reported in depicting the primary cause of ascites as compared to CT alone [52]. Based on standardized uptake values, FDG uptake and pattern of uptake in peritoneum, differentiation of peritoneal tuberculosis and peritoneal carcinomatosis is possible [53, 54].

12.5 Imaging Features of Peritoneal Tuberculosis

The characteristic imaging features of peritoneal tuberculosis include ascites and changes in peritoneum, omentum, and mesentery. Secondary changes in bowel loops and visceral organs occur due to fibrosis and adhesions. The less common manifestations include abdominal cocoon and intraperitoneal abscess. Often the features of different forms of peritoneal tuberculosis are overlapping, and thus it is important to describe each radiological finding separately. Often other manifestations of abdominal tuberculosis can also co-exist [2, 9, 31, 55].

12.5.1 Ascites

Ascites is the most common manifestation of peritoneal tuberculosis and is variably reported in 30–100% of cases [30, 42, 56]. It can be free (found in wet type) or encapsulated (wet and fibrotic fixed types). Dependent positions in the peritoneal cavity (pelvis, morrison pouch) are frequent sites of mild ascites, when non-loculated. Atypical fluid distributions can suggest loculations. Ascites can be

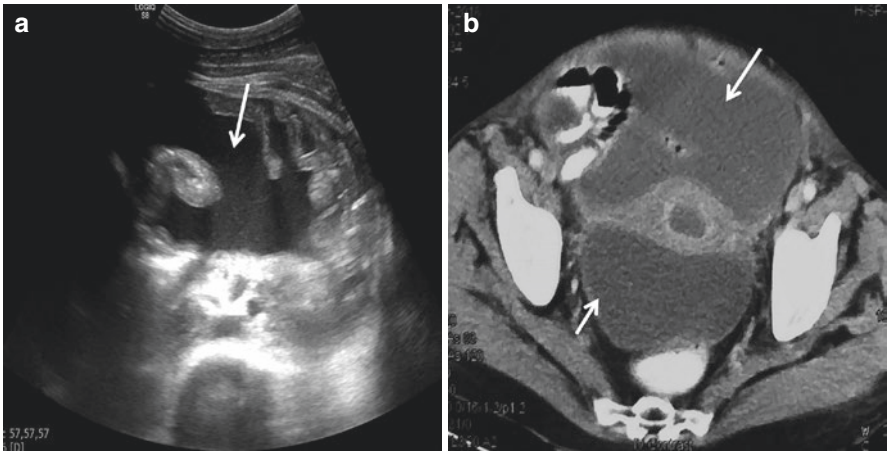

Fig. 12.1 Loculated ascites in Peritoneal tuberculosis. (**a**) Axial transabdominal ultrasound image of the central abdomen shows loculated ascites with fine internal echoes (arrow). (**b**) Axial contrast-enhanced CT of the lower abdomen shows loculated ascites in the pelvis, displacing the small bowel loops (arrow) with smooth thin regular peritoneal thickening (small arrow). Note the air foci in ascites are likely post-intervention

anechoic in the early stages of disease, however, is frequently hypoechoic with multiple, complete, or incomplete septations and fine internal echoes (Fig. 12.1a) [37–39]. There is thickening of interface between fluid and adjacent structures. Adhesions appear as linear septa between bowel wall and anterior abdominal wall. Fine septations in ascites are suggestive of tuberculosis in appropriate clinical settings [57, 58].

Attenuation of ascites is generally high (25–40 HU) due to high protein and cellular contents. Along with high attenuation, fine septa and debris are reported as characteristic finding on CT [42, 50, 59]. Loculated ascites, not depicted on ultrasound can be better evaluated with CT. Delayed post-contrast enhancement can be present due to exudates (Fig. 12.1b).

Signal intensity on MRI also varies depending on the composition of ascites. Additionally, there can be diffusion restriction and post-contrast enhancement depending on the nature of ascites [50]. Visceral scalloping by tubercular ascites has been reported and thus is not pathognomonic of pseudomyxoma peritonei and peritoneal carcinomatosis, particularly in endemic areas [60].

12.5.2 Peritoneal Changes

Peritoneal changes are encountered in all types of peritoneal tuberculosis to various extent [38–42, 61–64]. Both parietal and visceral peritoneum can be involved. There is peritoneal thickening which is hypoechoic on ultrasound and shows pronounced enhancement on CT. Enhancement is depicted in 80% of cases on CT [42, 63]. It is important not to misinterpret normal peritoneal enhancement, which is thin, smooth,

discontinuous, and barely perceptible as pathological. Regular, smooth, uniform thickening is the most common pattern, with irregular thickening and nodularity being less frequently observed [40–42]. Peritoneal nodules without thickening as an isolated finding is rare. The thickening varies between 2–5 mm with nodules usually <5 mm in size [50]. There can be diffusion restriction of peritoneal thickening on MRI. The peritoneal changes are better depicted in the presence of ascites. Smooth peritoneal thickening with high attenuation ascites is considered the most reliable imaging feature for diagnosing peritoneal tuberculosis (Fig. 12.1b) [44]. Large peritoneal masses and nodules are atypical findings. PET-CT can demonstrate increased metabolic activity in thickened inflamed peritoneum, which is nonspecific [3].

12.5.3 Omental Changes

Omental changes are depicted in 80% of cases of peritoneal tuberculosis on CT [30, 38–43, 63]. Omental thickening (> 1 cm) is very suggestive of tuberculosis [38]. Three patterns of involvement have been described on ultrasound. Trilaminar thickening (thick hyperechoic central layer surrounded by two thin hypoechoic peripheral layers, is the most common pattern (Fig. 12.2a). Heterogenous hyperechoic thickening with hypoechoic nodules and thickened hyperechoic monolayer pattern are less frequent (Fig. 12.2b, c) [38].

On CT, the most common appearance is that of smudged omentum (Fig. 12.2d, e). Nodular and caked appearance are less frequently seen in tuberculosis as compared to peritoneal carcinomatosis [40, 42]. An "omental rim sign" has been described and reported to be characteristic of peritoneal tuberculosis. It is a thin or thick rim of uniform thickness, enhancing either moderately or significantly, outlining the entire or part of omentum on venous phase of CT [41, 43]. The reported sensitivity and specificity were 85% and 96%, respectively, to differentiate peritoneal tuberculosis from peritoneal carcinomatosis by Ramanan et al., but validation studies are lacking [41]. Ha et al. reported a sensitivity of 50% and 5%, respectively, in peritoneal tuberculosis and peritoneal carcinomatosis [43].

12.5.4 Mesenteric Changes

Mesenteric changes are seen in 98% of cases on CT and less frequently on ultrasound [30, 38–43]. Hypoechoic thickening of mesenteric leaflet (> 2.5 mm) with clumping of small bowel loop can be seen on ultrasound [38]. In the early phases of disease, there is thickening of mesenteric leaves with loss of normal mesenteric configuration. Patterns of involvement include thickened soft tissue strands along mesenteric vasculature (most common pattern), mesenteric nodules and diffuse infiltration with soft tissue masses (Fig. 12.3) [40, 42]. Thickening of mesentery is due to edema, lymph nodes or fat deposition [64]. Both micronodules (< 5 mm) and macronodules (> 5 mm) can be seen, although macronodules are more specific for

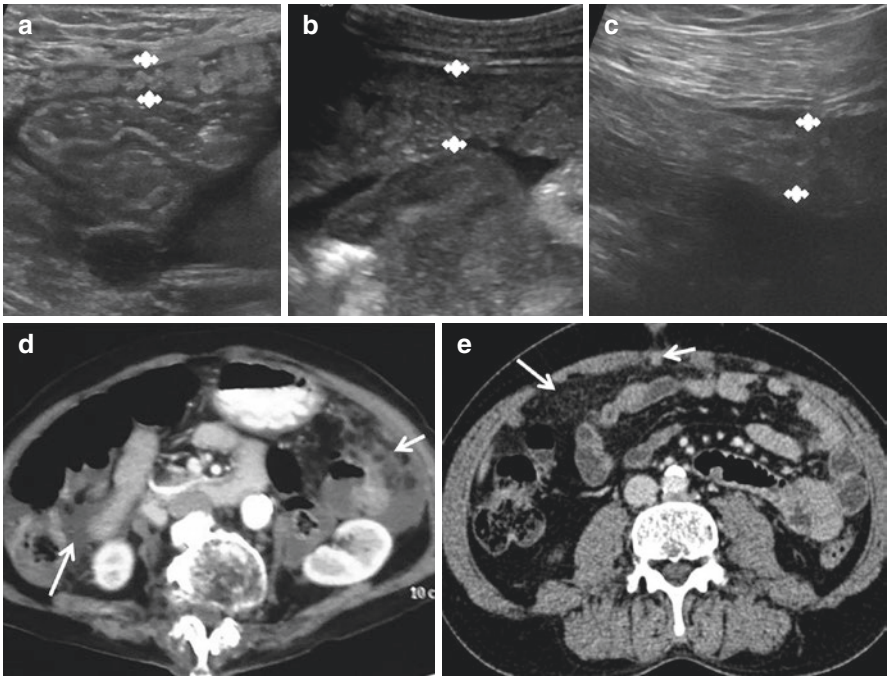

Fig. 12.2 Omental changes in peritoneal tuberculosis on ultrasound (**a–c**) and CT (**d–e**). (**a**) Trilaminar pattern (thick Central hyperechoic layer surrounded by peripheral thin hypoechoic layers, cursors) of omental thickening (most common pattern). (**b**) Heterogenous pattern of omental thickening (cursors). (**c**) Monolayer hyperechoic pattern of omental thickening (cursors). (**d**) Axial contrast-enhanced CT shows smudged pattern of omental thickening (short arrow) with ascites (arrow). (**e**) axial contrast-enhanced CT scan shows smudged pattern of omental thickening (arrow) with omental micronodules (short arrow). Smudged pattern of omental thickening on CT is the most common pattern observed in peritoneal tuberculosis

tuberculosis especially with low-density center and calcification [43]. Stellate sign on ultrasound refers to fixed loops of bowel and mesentery appearing as spokes radiating from mesenteric root [62]. Another sign "club sandwich sign" depicting the appearance of loculated ascites between inflamed bowel loops and mesentery has also been described [62].

12.5.5 Other Features of Abdominal Tuberculosis

It is important to look for concomitant involvement of lymph nodes with their distribution, necrosis, or calcification, changes in bowel loops like bowel wall thickening, stricture, angulations, ulcers, lesions in solid visceral organs and genitourinary tract. A combination of findings is needed for accurate diagnosis. Pleural effusion and lung changes of tuberculosis may be present.

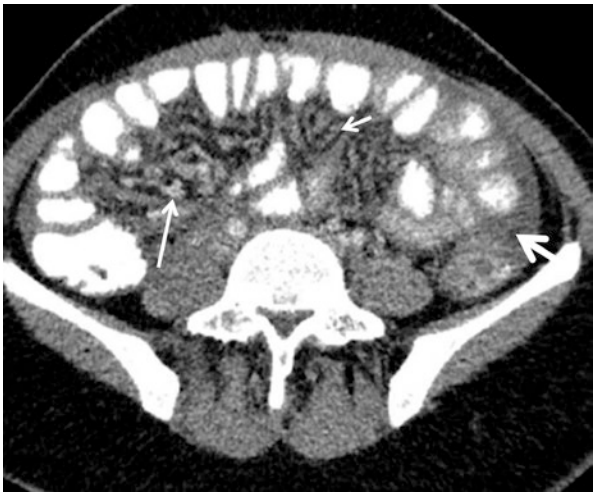

Fig. 12.3 Mesenteric changes in peritoneal tuberculosis. Axial CT scan of lower abdomen shows diffuse thickening of mesenteric leaves (short arrow), mesenteric micronodules (arrow) with ascites and smooth thin peritoneal thickening (thick arrow). A combination of findings is often present in a single patient which aids in diagnosis

12.5.6 Abdominal Cocoon

Abdominal cocoon is characterized by clumping of small bowel loops with or without large bowel loop or adjacent viscera in a fibrous membranous sac [14–17]. Concertina or cauliflower pattern of clumping of bowel loops with surrounding "trilaminar membrane" has been described [14]. The membrane appears as a hypoechoic structure over the surface of bowel. On CT, the bowel loops are displaced towards the center, appearing congregated in the center of abdominal cavity and are enclosed by a soft tissue mantle depicting the membranous sac (Fig. 12.4) [14–17]. There can be calcification of the sac. Various signs like cauliflower sign(broad "head" formed by bowel loops with narrow mesenteric apex), bottle gourd sign(dilatation of 2nd and 3rd part of the duodenum with encasement of distal duodenum and jejunal loops) and concertina pattern sign (concertina-like bowel loop arrangement) have been described [26, 65, 66]. There is associated bowel wall thickening, abnormal enhancement and peristalsis, angulation, tethering, kinking, interbowel adhesions, strictures and interbowel fluid [14, 17].

12.5.7 Intraperitoneal Tubercular Abscess

Tubercular abscess is a rare manifestation. It frequently occurs in right perihepatic and subphrenic space [29]. On imaging, it appears as a regular, multiseptated, hypoechoic, or hypodense mass with peripheral enhancement. High attenuation of internal contents with absence of air/air–fluid level is seen (Fig. 12.5a, b). Multiple

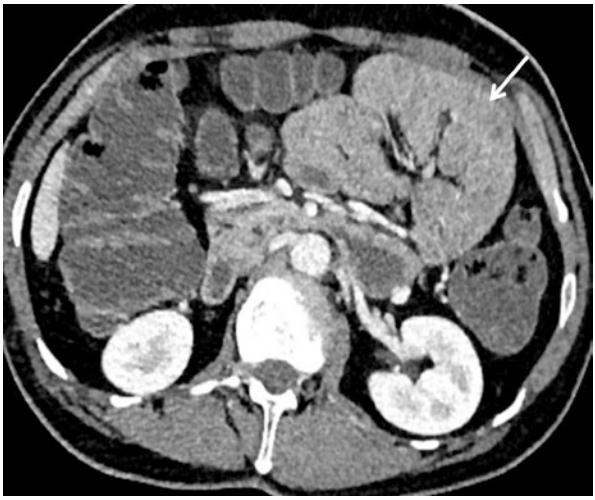

Fig. 12.4 Tubercular abdominal cocoon. Axial contrast-enhanced CT section of abdomen shows clumped small bowel loops below the anterior abdominal wall with "cauliflower" pattern of arrangement typical of abdominal cocoon formation (arrow). The typical membranous sac enclosing the small bowel loops is sometimes difficult to appreciate on imaging and fixed, clumped, and concentric pattern of arrangement should point towards the diagnosis

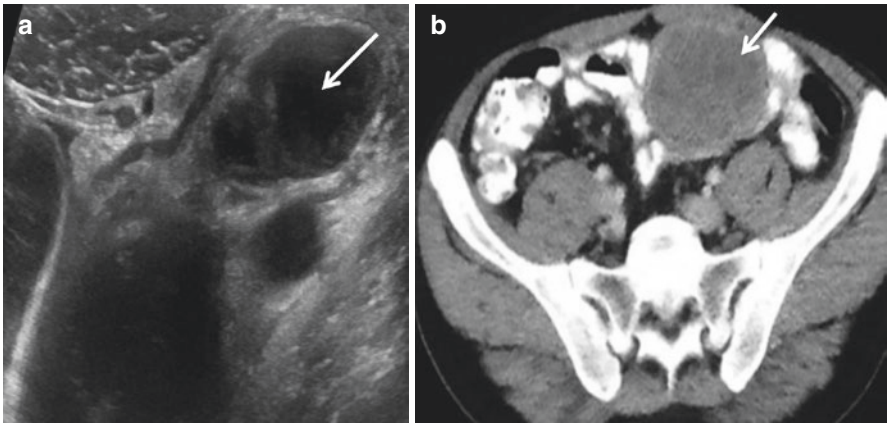

Fig. 12.5 Intraperitoneal tubercular abscess. (**a**) transabdominal ultrasound of right lumbar region shows a well-circumscribed heteroechoic lesion with thick echogenic wall below the anterior abdominal wall and anterior to aorta suggestive of abscess (arrow). (**b**) axial contrast-enhanced CT section shows a well-circumscribed heterogenous multiseptated hypodense lesion with enhancing peripheral wall in left infracolic compartment of peritoneum (arrow)

enlarged homogenous and rim enhancing lymph nodes are seen. Lymphadenopathy can, however, be absent. Other features of the peritoneal disease are frequently present [7, 29, 62].

12.6 Complications of Peritoneal Tuberculosis

These include acute intestinal obstruction due to adhesions, fibrosis, or cocoon formation. There can be bowel gangrene, although rare. Rupture of tubercular abscess with frank peritonitis is also rare [67].

Table 12.2 summarizes the important imaging manifestations of peritoneal tuberculosis.

12.7 Differential Diagnosis

A wide spectrum of pathologies can affect the peritoneum and can have common clinical, biochemical, and imaging features that can mimic peritoneal tuberculosis. Differential diagnoses include peritoneal carcinomatosis, pseudomyxoma peritonei, lymphomatosis, sarcomatosis. Other uncommon diseases include peritoneal mesothelioma, desmoid tumor and papillary carcinoma [50, 68].

12.7.1 Peritoneal Carcinomatosis

Peritoneal carcinomatosis is the intraperitoneal dissemination of any tumor not originating from the peritoneum itself [69]. The distinction between peritoneal tuberculosis and carcinomatosis is often difficult. This is especially true when there is no suggestion of primary tumor on CT [70]. Preoperative misdiagnosis is common (Fig. 12.6a) [71, 72].

Sometimes, there is concomitant occurrence of both the entities and a high index of clinical suspicion is needed to diagnose malignancy in patients with tubercular peritonitis [73]. Clinical features are nonspecific. Tumor markers like CA-125, CEA can also be elevated in both conditions [74]. Imaging plays an important role. A combination of findings reliably differentiates two in an appropriate clinical

Table 12.2 Salient imaging features of peritoneal tuberculosis

Findings	Characteristic of tuberculosis
Ascites (free or encapsulated)	Fine internal echoes with septations and debris
Peritoneal changes	Smooth regular diffuse peritoneal thickening with enhancement
Mesenteric changes	Thick soft tissue strands with crowding of vascular bundles Nodules with necrosis or calcification. Macronodules
Omental changes	Smudged appearance of omentum. Uniform omental thickness Omental rim sign Micronodules
Others	Necrotic lymph nodes Bowel wall thickening with predilection for IC junction Hepatosplenomegaly with hypodense and calcified splenic and liver lesions Tubo-ovarian abscess

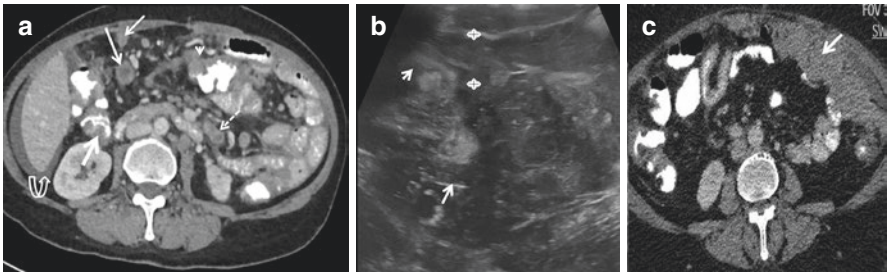

Fig. 12.6 Differential diagnosis of peritoneal tuberculosis. (**a**) axial contrast-enhanced CT section shows an FNAC proven case of peritoneal carcinomatosis with overlapping features with peritoneal tuberculosis in form of ascites (curved arrow), omental macronodule (arrow) and micronodules (short arrow), mesenteric lymph node (dashed arrow), small bowel wall (arrow head), and colonic thickening (thick arrow) possessing a diagnostic dilemma. (**b**) transabdominal ultrasound image of central abdomen depicting heterogenous omental thickening (cursors) with echogenic omental nodules (short arrow) and ascites with coarse internal echoes (arrow) in case of peritoneal carcinomatosis. The omental thickening of >19.5 mm is highly predictive of malignant etiology. (**c**) axial CT scan depicts omental caking (arrow), which is typical pattern of omental thickening in peritoneal carcinomatosis

background and risk population. CT is the most common imaging modality used to differentiate these conditions on imaging [75, 76]. A recent meta-analysis found certain features of high specificity(> 90%) in peritoneal tuberculosis- omental rim sign, mesenteric macronodules and lymph node necrosis and calcification. The smooth peritoneal thickening is of high diagnostic accuracy in tuberculosis [77]. Differentiation of two can also be made on ultrasound with hypoechoic and irregular omental thickening more suggestive of peritoneal carcinomatosis. Also, omental thickness of >19.5 mm predicted malignancy with high diagnostic accuracy on ultrasound [39]. (Fig. 12.6b, c).

In females with diagnostic dilemma between the peritoneal tuberculosis and carcinomatosis, attenuation of ovary, ovarian capsular changes, and size of ovary along with pattern of peritoneal involvement helped in differentiation [71, 78]. In study by Shim et al., ovarian capsular changes were observed more in normal sized ovarian cancer with peritoneal carcinomatosis as compared to female with tuberculosis. Also, the attenuation of normal sized ovary in tuberculosis was significantly lower than in peritoneal carcinomatosis [78].

Wang et al. used FDG- PET to differentiate peritoneal tuberculosis from peritoneal carcinomatosis based on features in parietal peritoneum. In tuberculosis, there is uniform distribution of lesions in parietal peritoneum involving >4 regions showing string of bead and smooth uniform peritoneal thickening. This contrasts with peritoneal carcinomatosis, which shows clustered focal uptake in peritoneal implants in pelvis and subdiaphragmatic location showing irregular thickening and nodularity [54].

12.7.2 Peritoneal Mesothelioma

Mesothelioma is a rare neoplasm of the peritoneum mostly occurring in the setting of asbestos exposure. It is characterized by multifocal nodular or sheet-like peritoneal thickening with small amount of ascites. The imaging features are remarkably like peritoneal carcinomatosis. Certain features that point towards mesothelioma include asbestos exposure, pleural lesions, calcified pleural plaques and absence of liver or lymph node lesions [69, 79].

Peritoneal lymphomatosis and sarcomatosis have bulky and large peritoneal and omental masses with lymphadenopathy which is not typically seen in tuberculosis [69].

12.7.3 Differentiation of Intraperitoneal Tubercular Abscess from Other

1. Crohn's Disease—The intraperitoneal abscess due to Crohn disease is more often situated on left side of colon, with homogenous and subcentimetric lymph nodes. On the other hand, tubercular abscess is often located in right subphrenic space with enlarged necrotic lymph nodes [7].
2. Pyogenic Abscess—The internal air and air–fluid level typical of pyogenic abscess (although not seen in all) is absent in tubercular abscess [29].

12.8 Image-Guided Sampling and Diagnosis

The clinical features of peritoneal tuberculosis are nonspecific and overlapping with other diseases, making clinical diagnosis difficult. No specific biomarker is available for diagnosis. Peritoneal tuberculosis is usually suspected in diagnosed cases of pulmonary tuberculosis or extrapulmonary tuberculosis with unexplained ascites or bowel obstruction. However, it can be incidentally diagnosed as well [80]. In the presence of ascites, ascitic fluid analysis for protein, serum-ascites albumin gradient, adenosine deaminase (ADA) level analysis is useful. Gene amplification assay is often run in case of exudative ascites and suspicion of tuberculosis. Elevated lymphocyte count, lactate dehydrogenase, total protein, ADA levels>35 IU/L and SAAG <1.1 have been used to suggest peritoneal tuberculosis. Cases where ascitic fluid analysis is non-suggestive, tissue sampling is needed. In cases without ascites, tissue sampling is often needed [81]. *Mycobacterium tuberculosis* smears and cultures of peritoneal fluid are often insufficient for diagnosis, cumbersome and take 4–6 weeks (in case of cultures) [82–84]. However these are considered gold standard for diagnosis [11–13, 83].

Earlier laparoscopy was frequently employed for sampling peritoneal and omental lesions. Laparoscopy permits the observation of the entire peritoneal space and samples can be taken from pathological area for histological and microbiological diagnosis. The gross laparoscopic findings suggesting tuberculosis include ascites,

thickened hyperemic peritoneum, whitish granular nodules, adhesions, and caseous nodules. Laparoscopic examination with histopathological analysis is sensitive and specific [4, 85].

However, Laparoscopy results are considered operator dependent, with risk of complications including infection, bleeding, and perforation specially in fibrotic type of peritoneal tuberculosis [85]. These drawbacks make laparoscopy less preferred method for obtaining tissue samples in current scenarios [3, 10, 85].

Peritoneoscopy is a less invasive procedure than laparoscopy. It has also been utilized to obtain samples from peritoneal lesions with promising results [86, 87]. Laparoscopic and peritoneoscopy are both invasive procedures. However, these are used as the last resort for diagnosis [3, 4]. Although it is the reference method to obtain samples, still due to risk associated ultrasound/CT-guided sampling is preferred [3].

There is growing role of image-guided peritoneal sampling from various compartments due to complex manipulation and certain complications of laparoscopy. Image guidance is preferred over blind sampling. Both ultrasound and CT guidance can be used. Ultrasound-guided sampling is real time and radiation free. CT is helpful in sampling lesions, not well visualized on ultrasound. Ultrasound-guided FNAC is safe, minimally invasive, and effective method for sampling of both palpable and non-palpable lesions. A 22 G needle is sufficient to obtain samples. Real-time and accurate manipulation of needle can be done to obtain adequate samples. Ascitic sampling as well as therapeutic drainage are effectively performed under ultrasound guidance.

As compared to FNAC, biopsy yields tissue specimens on which histological confirmation can be carried out. Ascites should be significantly reduced before performing the biopsies. A specific histopathological diagnosis is reached in >90% of cases [37, 88–90]. Ultrasound-guided procedures have been found to have high diagnostic accuracy in distinguishing between benign and malignant causes of ascites [37, 91]. CT-guided omental biopsies have also yielded promising results [37, 92].

The role of endoscopic FNAC/Biopsy of peritoneal lesions has also been evaluated with promising results [82, 93]. However, data from a limited number of patients is available.

12.9 Conclusion

Peritoneal tuberculosis is the most common manifestation of abdominal tuberculosis. Timely diagnosis is important. Imaging plays a crucial role in diagnosis and decision-making. Image-guided sampling may avoid more invasive methods of tissue sampling in a large proportion of patients. It is important to differentiate peritoneal tuberculosis from other peritoneal diseases using a comprehensive clinical, biochemical, microbiological, radiological, and histological assessment.

Conflict of Interest None.

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Ascitic Fluid Testing for Peritoneal Tuberculosis

13

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Key Points

- Peritoneal Tuberculosis / Tuberculous peritonitis should be suspected in high SAAG lymphocytic ascites, especially in endemic countries.
- Immunological tests like ascitic adenosine deaminase level, Interferon γ levels and ascitic fluid Interferon gamma assay aid in management.
- Ascitic adenosine deaminase is a rapid, inexpensive, and reproducible test with high accuracy, so due weightage should be given if positive (usually levels >39 U/L).
- Diagnosis of tuberculous peritonitis is confirmed by AFB staining, culture, and NAAT.
- Gene Xpert testing should be done to have an opportunity for early confirmatory diagnosis and to know about rifampicin resistance.

13.1 Introduction

Peritoneal tuberculosis or tuberculous peritonitis (TBP) is a common form of abdominal tuberculosis and comprises 30–60% of abdominal tuberculosis [1]. If not diagnosed early, it can lead to morbidity in the form of disseminated disease, bowel obstruction, cocoon formation and female infertility. The diagnosis of TBP is made by clinical suspicion, imaging studies, ascitic fluid analysis, evidence of extraperitoneal tuberculosis (EPTB) and laparoscopy. Ascitic fluid is the most easily accessible sample for confirmatory diagnosis of TBP [2]. Ascitic fluid testing comprises

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of cytology, biochemical evaluation, immunological, and microbiological tests to confirm or to add on the diagnosis of TBP. Isolation of mycobacteria by ascitic fluid culture is the gold standard but has a low sensitivity. This chapter is a review of ascitic fluid analytical techniques and their utility in a case of suspected peritoneal tuberculosis.

13.2 Sample Collection and Assessment

A diagnostic paracentesis should be done aseptically either blindly or ultrasonography guided. The ultrasonography guided approach should be preferred in case of loculated ascites, obesity and when amount of fluid is small. Ascitic fluid removed should be divided taken both in EDTA (or Heparinised) vial and a plain vial for various cytological, biochemical, and microbiological analysis. On macroscopic appearance, the ascitic fluid in TBP is usually yellow or straw-colored in 77–91% of cases, but it can also be cloudy, chylous, or hemorrhagic [1, 2]. The cytological evaluation of ascitic fluid in TBP usually shows leucocytosis. The total cell count in ascitic fluid may range from 100–5000 cells/mm [3] however most of the patients have a cell count between 500–1500 cells/mm^3 [4–6]. However, ascitic fluid leucocytosis is not a rule in all patients of TBP [7]. On differential leucocyte count, the ascitic fluid is lymphocytic predominant [6].

In a meta-analysis of 13 studies (477 patients) of TBP, a lymphocytic ascites was found in 68.3% of patients [8]. Exceptionally, ascites is neutrophilic predominant especially in the early phase of TBP, concomitant renal failure, ascitic fluid infection and in patients on peritoneal dialysis [9, 10].

13.3 Biochemistry

13.3.1 Ascitic Fluid SAAG and Ascitic Fluid Total Protein

The most common cause of ascites is cirrhosis, so this should be ruled out first. This is done by the biochemical analysis of ascitic fluid. Using this ascites is classified based on the serum ascites albumin gradient (SAAG). Ascites with high SAAG (>1.1 g/L) property is highly specific for underlying portal hypertension [11].

In case of mixed ascites (cirrhosis with concomitant other disease), SAAG is >1.1 g/L and ascitic fluid total protein is more than 2.5 g/L. TBP should be ruled out in such cases, especially in the West, where most patients with TBP may have underlying cirrhosis. Hence SAAG should always be taken in consideration along with the ascitic fluid total protein [12]. The protein content in the peritoneal fluid of TBP is usually >2.5 g/dl with low SAAG (<1.1 g/L). Low SAAG ascitic fluid is highly sensitive for TBP without cirrhosis, but its specificity is low [6, 13].

13.3.2 Ascitic Fluid Lactate Dehydrogenase (LDH)

Ascitic fluid lactate dehydrogenase (LDH) has been reported to be high in TBP. In uncomplicated cirrhotic ascites patients, the ascitic fluid concentration of LDH is usually less than half of the serum level. In infections, including TBP, the ascitic fluid LDH level rises because of the release of LDH from neutrophils. Shakil et al. showed that LDH above 90 U/L carries a sensitivity of 90% and a specificity of 14% for TBP, but the same was not reproduced in later studies [5, 14]. The major limitation of LDH testing is its low specificity for TBP, as raised ascitic LDH also occurs in patients with peritoneal carcinomatosis, pancreatic ascites and few patients of cirrhosis and congestive cardiac failure [15]. Hence this test is not of much discriminatory value and should not be routinely used.

13.3.3 Ascitic Fluid Glucose Concentration

Ascitic fluid glucose concentration in cirrhosis is similar to serum glucose as it is freely permeable in the peritoneum. In diseases affecting peritoneum, ascitic fluid glucose may be decreased due to increased consumption. This phenomenon is not specific to TBP as low ascitic fluid glucose is seen in peritoneal carcinomatosis, primary and secondary bacterial peritonitis [16, 17].In some studies, ascitic /blood glucose ratio was evaluated to differentiate among causes of ascites, but this was not found to be of much help [18]. Therefore, due to its low diagnostic sensitivity and specificity, the routine application of ascitic glucose analysis is not recommended.

13.4 Immunological Tests

These tests detect the indirect evidence of tubercular infection in ascites. They depend on the measurement of cell-mediated immune activation. They include adenosine deaminase (ADA) levels, interferon γ level and ascitic fluid interferon gamma release assay (IGRA).

13.4.1 Adenosine Deaminase (ADA)

ADA is an amino-hydrolase enzyme that converts adenosine to inosine and is thus involved in the catabolism of purine bases. The enzyme activity is more in T-lymphocytes than in B-lymphocytes and is proportional to the degree of T-cell differentiation. ADA is increased in the tuberculous ascitic fluid due to the stimulation of T-cells by mycobacterial antigens, so ADA is an indirect marker of T-cell activity. Ascitic fluid ADA level has been widely used for the diagnosis of TBP due to its simplicity, low cost and rapid turnaround time that makes it a desirable test.

ADA is measured by two methods a) conventional, most commonly being the modified Giusti method and b) automatic methods. These two methods have a very good concordance [19].

ADA elevation is not specific to TBP as it can be increased in other conditions with lymphocyte activation such as peritoneal carcinomatosis, lymphoma, multiple myeloma, connective tissue disorders, secondary bacterial peritonitis and in infections like infectious mononucleosis [20–22].ADA levels can be false low in cases with concomitant HIV, cirrhosis and in patients on immunosuppression [23, 24].

Ascitic fluid ADA has been extensively studied in TBP and its level between 30–40 IU/ml has sensitivity ranging from 92–100% and specificity between 94–100%. This difference between cut-off value could be due to variable testing method, hypoproteinaemia, immunosuppression and stage of disease [25, 26, 28, 29]. Levels of ADA in TBP have a positive correlation with ascitic fluid protein level but not with lymphocytes counts [25–27].

In a meta-analysis that included 17 studies and 1797 patients, it was shown that sensitivity and specificity of ascitic fluid ADA were 0.93 and 0.94, respectively. And on meta-regression analysis, there was no effect of study quality, ADA cut-off value, TB prevalence, and method of study [30]. Few studies measured ascitic fluid ADA and Interferon γ level in patients of TBP and found a positive correlation between them and if used in combination leads to increased sensitivity and specificity [23, 31, 32].

Cirrhosis is a predisposing condition for TBP and may be present in around 50% of cases of TBP in Western countries [33]. TBP with concomitant cirrhosis needs a special mention as few studies found lower sensitivity of ADA to diagnose TBP in such a scenario [23, 24]. This lower diagnostic yield could be due to immunocompromised status, dilutional phenomena and hypoproteinemia [24]. However, some other studies specifically aimed to study the effect of concomitant cirrhosis on the diagnostic value of ascitic fluid ADA and found that performance of ascitic ADA is good even in the presence of underlying cirrhosis [34, 35].

Hence, ascitic fluid ADA is a rapid inexpensive and widely available marker with good diagnostic power to diagnose TBP and ADA measurement is recommended, and elevated levels (usually >39 U/L) can be used as a basis of empirical treatment when other causes like peritoneal malignancy have been excluded [36].

13.4.2 Interferon γ Level

Interferon γ is a key lymphokine produced by T-lymphocytes and it activates macrophage bactericidal activity [37]. Interferon gamma is raised in the early phase of the disease, so its measurement can be helpful in the diagnosis of TBP [8].

Many authors have studied the role of ascitic fluid interferon gamma level in the diagnosis of TBP and found that sensitivity and specificity of its measurement (threshold-0.35 U/L to 9 U/L) were 93–100% and 94–100%, respectively [31, 37]. In a meta-analysis involving six studies and 440 patients showed that sensitivity,

specificity, PLR, NLR, and DOR was 0.93, 0.99, 41.49, 0.11and 678.02, respectively, and AUC was 0.98 [38].

Although interferon γ measurement is rapid, useful, and recommended, it is not cost-effective and has limited availability, these factors limit its applicability, especially in resourced constraint settings [31, 36]. Also, its benefit in addition to ADA testing is uncertain.

13.4.3 Ascitic Fluid IGRA

The most widely used immunological tests are tuberculin skin test and blood IGRA, however, these tests have a poor specificity to active tuberculosis, especially in high endemic areas and they, are less sensitive in the case of TBP [39, 40]. IGRA can be done by two methods a)T-SPOT/ELISPOT and B) QuantiFERON gold. It was hypothesized that there is a compartmentalization of mononuclear cells at active tuberculosis site, hence if we do IGRA on affected fluid, it will be more diagnostic than blood IGRA and this approach showed good results in pleural TB [41–44].

In various studies, ascitic fluid IGRA assay was used in the diagnosis of TBP and found to have sensitivity between 90–100% and a good specificity [45–47].In these studies, mainly the ELISPOT test was used and there was good inter-laboratory reproducibility and the best results were obtained by ESAT-6 antigen. Few studies compared ascitic fluid IGRA and ADA and found no added advantage of ascitic fluid IGRA over ADA [44, 48].

In a meta-analysis that studied the role of body fluid IGRA in extrapulmonary TB, sub-analysis of the role of ELISPOT in TBP found a pooled sensitivity of 94% and specificity of 97%. Body fluid IGRA was shown to perform significantly better than peripheral blood IGRA. It was also noted that there was no effect of TB endemicity on the performance of this test signifying that they are less affected by latent TB [49]. This test can be falsely negative in individuals who have diminished cell-mediated immunity, which includes the elderly, immunosuppressed patients, and malnutrition [50]. Ascitic fluid IGRA is rapid, as a result is obtained within 24 hours. This test also has a good diagnostic power & can be used as a surrogate marker in the diagnosis of TBP and guide for empirical treatment. The limitation, however, is its cost, availability, and problem of indeterminate results.

13.5 Microbiological Tests

13.5.1 Acid Fast Bacilli (AFB) Microscopy

AFB microscopy is a rapid, inexpensive, and technically simple test to perform and it provides an early opportunity to diagnose TBP with a sensitivity and specificity of <5% and > 90%, respectively [36]. A positive AFB smear needs>5000 bacilli/ml of

specimen, and TBP is a paucibacillary condition [36, 51, 52]. In a review involving 615 patients of TBP diagnostic yield of ascitic fluid AFB microscopy was 2.93% [8].

Various efforts have been done to increase the sensitivity of AFB microscopy like concentration methods and Auramine staining [53]. Auramine staining is a good advancement in AFB microscopy. Auramine staining increased the sensitivity of microscopy by 10% in sputum samples, it is cost-effective and needs less expertise. This method was recommended by WHO since 2011 as a replacement to conventional Z-N staining [54, 55]. Some studies using auramine staining on ascitic fluid did not find it helpful in increasing the sensitivity [56].

13.5.2 Mycobacterial Culture

Mycobacterial culture is the gold standard for the diagnosis of TBP [8]. Culture is the most sensitive method available as it can detect bacilli as less as ten organisms/ml of the specimen and it also allows drug sensitivity testing (DST). Mycobacterial culture is 35–69% sensitive and > 97% specific in EPTB**.**

There are two types of culture medium: solid culture medium (egg-based, e.g., Lowenstein–Jensen or agar-based, e.g., Middlebrook 7H10/11) and liquid culture methods (broth based). Although solid media is cheap, stable, and a widely used culture technique, it requires a long time (4–8 weeks, average 45 days) for mycobacterial growth [8, 52, 57]. Solid culture methods can detect as low as 100 bacilli/ml of specimen and have sensitivity of around 35% in TBP [8, 58]. The diagnostic yield may be improved to 83% by use of larger volumes after centrifugation but this has practical limitations [8, 59]. Liquid culture methods can detect as low as ten bacilli/ml of specimen hence are more sensitive than solid culture technique [60]. These cultural methods are rapid as they can detect mycobacteria in 14–27 days (average 15 days), and they provide a rapid platform for drug sensitivity. Liquid culture methods are however, expensive and they are more prone to contamination [8, 52, 61, 62]. Semiautomatic BACTEC 460 medium uses detects radioactive carbon dioxide produced by mycobacteria metabolism [63].BACTEC Mycobacteria Growth Indicator Tube (MGIT) system utilizes nonradioactive fluorochromes for the detection of growth and drug screening and provides an early detection (7–12 days) of mycobacterial [64].MGIT culture can be manual or automatic (MGIT 960 system). Various studies compared MGIT with other liquid medium and Lowenstein Jensen (LJ) medium and found the highest and rapid yield in MGIT 960 system [65].MGIT is approved by WHO for both culture and drug sensitivity. Microscopic Observation Drug Susceptibility (MODS) is a novel non-commercial liquid broth assay, in which mycobacteria are cultured in liquid media on a multiwell plate and then examined microscopically for characteristic serpentine cording. The addition of antimicrobial agents to the media allows drug susceptibility testing to be performed simultaneously. MODS assay yields result in 7 to 10 days with a diagnostic yield similar to commercially available liquid broth systems [66]. It has been approved by WHO in 2009 for respiratory samples [58].

Although both solid and liquid culture media are approved by WHO, liquid media specially MGIT is preferred due to rapid results and better diagnostic yield. To increase the diagnostic yield of culture large volume of ascitic fluid should be sent to the laboratory, and pre inoculation concentration methods should be used [53, 59].After the growth of mycobacteria further testing should be done to correctly identify mycobacterial tuberculosis complex (MTC). For species identification, genotypic methods or immunochromatographic assays are preferred [36, 52].

13.5.3 Nucleic Acid Amplification Test (NAAT)

NAATs emerged as a diagnostic tool in the 1990s and require as few as ten Bacilli in a sample [63, 67]. NAATs are based on the principle of Polymerase Chain Reaction (PCR), and they have revolutionized the diagnosis of tuberculosis especially pulmonary tuberculosis, because of their speed and accuracy [68]. Although less sensitive than culture they are far more sensitive than AFB microscopy. Their acceptable sensitivity and rapid results make them practical to use in the diagnosis of TBP as a complimentary test [63, 69, 70]. In EPTB NAAT sensitivity is compromised due to paucibacillary nature and presence of PCR inhibitors in specimens [63]. NAAT technique can target Deoxyribonucleic acid (DNA) or Ribonucleic acid (RNA) of MTC and amplify that for detection. If DNA targets are used, there are more chances of false-positive results because they cannot differentiate live and dead bacilli but they can detect genes responsible for some drug resistance mutation. If NAAT targets RNA, they are less susceptible to false-positive results as RNA has a short half-life. So NAAT cannot be used to monitor disease response due to false-positive results by dead bacilli.

Gene Xpert analyzer/CB (Cartridge Based) NAAT is an automated real-time PCR cartridge test to detect MTC. Xpert MTB/RIF also detects rpoB mutation responsible for rifampicin resistance [71]. It is rapid as results are obtained within 2 hours. The limit of detection (LOD) is 116 CFU/ml of specimen [72]. There is a concern about false-positive rifampicin resistance; hence it should be confirmed by second Xpert MTB/RIF or by other drug sensitivity testing [58]. Gene Xpert fulfills the criteria of point of care (POC) diagnostics as it is simple, needs little training, requires fewer biosafety facilities, not prone to contamination, and may be used on-demand- rather than batched [73].

Although the manufacture has not claimed Xpert use in non-sputum samples, this test has been endorsed by WHO and Food and drug administration (FDA) for the diagnosis of pulmonary TB and multiple forms of EPTB [70, 71]. Many authors have studied the role Xpert Mtb/Rif in the diagnosis of TBP and found that it has a variable sensitivity between 9–100% with high specificity approaching 100% [74–79]. In a subgroup analysis of Cochrane review on gene Xpert in EPTB, the sensitivity of Xpert Mtb/Rif in comparison to culture was 59.2% sensitive and the specificity was 97.9% [71]. In a more recent systematic review by Sharma V et al. the sensitivity and specificity were 64% and 97% when compared to culture but the sensitivity

dropped to 30% (with 100% specificity) when compared to the comprehensive reference standard [80].

Xpert MTB/RIF Ultra is next-generation Xpert MTB/RIF that was developed by adding two more gene amplification targets (IS6110 and IS1081) and 25 targets for rifampicin mutation [81].Xpert MTB/RIF ultra has LOD of 15 CFU/ml and it is more sensitive as compared to Xpert MTB/RIF [72, 73]. In 2017 WHO recommended gene X pert MTB/RIF ultra as an alternative to Xpert MTB/RIF and advised to replace it in all indications [82]. GENE XPERT OMNI is a miniature form of current gene Xpert and is less expensive and runs on 4 hours inbuilt battery [83].

13.5.4 Other Polymerase Chain Reaction Based Tests (PCR)

PCR is a conventional method of NAAT used for the detection of Mycobacterial tuberculosis directly in the specimen. Its sensitivity will depend on the type of nucleic acid gene, number of genes target and presence of PCR inhibitors [63]. Most commonly used target in PCR is IS6110 gene because there are multiple copies of it in the MTB genome, but few studies showed that it can be absent in some cases [84, 85]. Hence studies have used the multiplex PCR method, including multiple gene target primers to enhance its sensitivity. These genes targets are 16SrRNA, IS6110 and devR, rpoB, gyrB, hsp65, recAand sod A [86, 87].Ascitic fluid PCR has variable sensitivity ranging from 7%–100% in the diagnosis of TBP, and multiplex PCR is superior to conventional single-target PCR [7, 21, 88–93].

PCR for *Mycobacterium tuberculosis* can be done with a commercially available PCR. COBAS TaqMan MTB is the only commercially available FDA-approved qualitative real-time PCR assay (TaqMan MTB; Roche Diagnostics, Tokyo, Japan). This is based on the amplification of 16 S rRNA by reverse transcription technique. It is rapid, with a turnaround time of 2.5 hours [81]. Although it was approved only for respiratory samples, it was also used in extrapulmonary samples. When it was used in EPTB it was less sensitive than in pulmonary TB (63% vs. 88%) [94].

13.6 Proteomics

Proteomics is the characterization of an entire protein complement of a cell, tissue, or organism. There are two general technologies for TB proteomic studies, including 1) two-dimensional electrophoresis (2DE) combined with mass spectrometry (2DE-MS), 2) isotope labeling followed with multiple-dimensional liquid chromatography separation combined with mass spectrometry analysis [95–97].In various proteomic study antigens were detected and found useful for diagnosis of TBP examples of these markers are- 65-kDa HSP, 71-kDa HSP, 14-kDa HSP, and Ag 85 complex proteins [98].

The major limitation of proteomics is its cost, technical expertise and its availability.

13.7 Conclusion

Diagnosis of TBP is based on combination of clinical suspicion, imaging studies, ascitic fluid analysis, laparoscopy, and response to treatment. Ascitic fluid tests pertinent to TBP are summarized in Table 13.1 and a proposed algorithm is shown in Fig. 13.1. TBP should be suspected in all cases of high SAAG, lymphocytic ascites, especially in endemic countries. Ascitic fluid ADA level, Interferon γ level, ascitic fluid IGRA are complementary tests and can help to decide for invasive tests like laparoscopy and empirical therapy. Diagnosis is confirmed by isolation of Mycobacteria by AFB microscopy, culture, or by NAAT. For Mycobacterial culture MGIT culture medium is preferred and maximum possible volume of ascitic fluid should be used. Rapid confirmatory tests like gene Xpert and PCR should be done if available.

Table 13.1 Various ascitic fluid tests pertinent to peritoneal tuberculosis

Test	Sensitivity	Specificity	Advantages	Disadvantage
ADA level	93%	94%	Rapid, inexpensive, widely available, high diagnostic power Most commonly used biomarker for empirical treatment	Can be false negative with concomitant cirrhosis, immunosuppression, and HIV
Interferon γ level	93%	99%	Rapid test Recommended by CDC Diagnostic synergism with ADA	Expensive, poor availability
Ascitic fluid IGRA	94%	97%	Rapid, high specificity for active disease, less affected by latent TB	Expensive, limited availability, problems of indeterminate results
AFB microscopy	3%	90%	Rapid, widely available Recommended by CDC	Very poor sensitivity, cannot differentiate from NTM
Culture	35–69%	97%	Acceptable sensitivity, gold standard for diagnosis, can give information about drug sensitivity	Time consuming (solid medium- 6 weeks, liquid medium 2 weeks) Less sensitivity hence cannot rule out
NAAT (Xpert Mtb/Rif)	30%	100%	Rapid, high specificity, can be used as point of care test, gene Xpert can detect rifampicin resistance	Expensive, availability, Not specifically recommended for PT

Abbreviations: *AFB* acid fast bacilli, *NAAT* Nucleic acid amplification test, *ADA* adenosine deaminase, *IGRA* interferon gamma release assay, *HIV* Human Immunodeficiency virus, *NTM* nontubercular mycobacteria

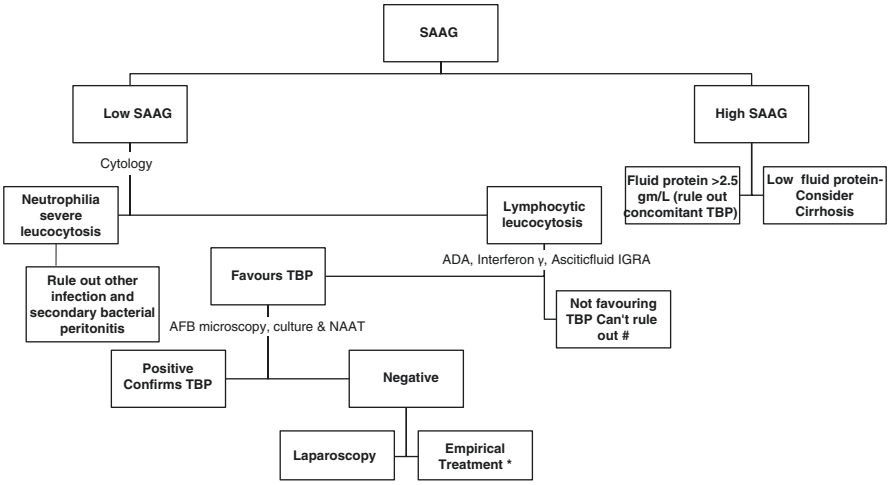

Fig. 13.1 Approach for ascitic fluid analysis in a suspected case of Peritoneal tuberculosis. # Can be false negative in concomitant cirrhosis, Human Immunodeficiency virus infection, immunosuppression. *Empirical treatment can be considered if clinical suspicion and imaging are suggestive and laparoscopy is not available or feasible. Abbreviations: *SAAG* serum ascitic albumin gradient, *TBP* tubercular peritonitis, *AFB* acid fast bacilli, *NAAT* Nucleic acid amplification test, *ADA* adenosine deaminase, *AF IGRA* ascitic fluid interferon gamma release assay

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Conflict of Interest None.

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Part IV

Visceral TB

Hepatic Tuberculosis

14

Manas Kumar Panigrahi and Chandan Kumar

Key Points

1. Miliary form of hepatic tuberculosis is thought to be the major pattern of hepatic tuberculosis.
2. Localized forms of hepatic tuberculosis may be mass forming or an abscess.
3. Computed tomography scan may show a hypo-enhancing central region with peripheral rim enhancement mimicking malignancy.
4. Well-formed granuloma is the most common histological findings. Differentials of other causes of granuloma should always be considered.
5. Treatment options include medical therapy with anti-tubercular therapy, surgery, minimal invasive approach like percutaneous aspiration, endoscopic retrograde cholangiopancreatography (ERCP) with stenting/percutaneous transhepatic biliary drainage (PTBD).

14.1 Introduction

Two centuries ago, the statement by Charles Dickens (1812–1870) that tuberculosis (TB) is "a dread disease in which struggle between soul and body is gradual quiet and solemn, that day by day, and grain by grain, the mortal part wastes, and withers away" still holds in the present context. With changing times, the effect of HIV on TB and improvement in diagnostic modalities, the recognized patterns of clinical

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resentation are changing. Even western gastroenterologists may encounter abdominal tuberculosis because of the rising incidence of HIV/AIDS and immigration.

Hepatic tuberculosis is an infrequent manifestation of tuberculosis. Hepatic involvement by the mycobacterial infection may occur as a part of disseminated tuberculosis or in isolated forms. A myriad of terms have been used in the literature to describe the hepatic involvement including nodular tuberculosis, hepatic tuberculomas, tuberculous hepatitis, hepatobiliary tuberculosis, tuberculous pseudotumor, tubercular liver abscess, etc. [1–5]

As we know it is challenging to treat tuberculosis in the background of liver disease, similarly, it is equally challenging to diagnose hepatic tuberculosis. This is because it is uncommon, has a nonspecific presentation, and therefore less frequently considered as a differential in the evaluation of hepatic lesions.

14.2 Classification

Table 14.1 depicts the various classifications suggested for hepatic TB [6–8]. Alvarez suggested the classification of hepatic tuberculosis into miliary form (part of miliary TB without specific signs and symptoms of liver involvement) and localized hepatic TB. Further, the hepatic involvement was divided into two forms with or without concomitant biliary tract involvement. Localized hepatic TB without bile duct involvement could be in the form of tuberculoma, tuberculous hepatic abscess, solitary or multiple nodules. Localized hepatic TB with bile duct involvement leads to obstructive jaundice because of enlarged periportal lymph nodes compressing bile duct or ductal involvement by tuberculosis causing strictures [7].

14.3 Epidemiology

Hepatic involvement in tuberculosis may be asymptomatic with slight derangement of hepatic function, which is usually unnoticed hence unreported. The pattern of presentation with a frequency of distribution in hepatobiliary tuberculosis in a series of 38 patients from Western India included hepatic TB (52.6%) and biliary TB

Table 14.1 Classification systems for Hepatic tuberculosis

Leader classification (1952) [6]	Alvarez (2006) [7]	Suggested
(i) Miliary TB	(i) Miliary form	Part of systemic disease • Miliary (0.5–2 mm) • Other (concomitant to other locations)
(ii) Local TB (a) Focal/nodular (b) Tubular	(ii) Localized Hepatic TB (a) Without bile duct involvement (b) With bile duct involvement	Localized Hepatic tuberculosis • Mass forming (macronodular: single or multiple) • Infiltrative (TB hepatitis) • Abscess like
	(iii) Granulomatous disease	

(39.4%). The hepatic TB could be granulomatous hepatitis (26.3%), liver abscesses or pseudotumor (26.3%), and calcified hepatic granuloma (0%). The biliary TB could be in form of biliary strictures (5.2%), gall bladder involvement (2.6%), or biliary obstruction due to lymph node masses (31.5).

Hepatic involvement may occur as a part of miliary tuberculosis or isolated hepatic tuberculosis and can involve both immunocompetent and immunodeficient hosts. About 50–80% of patients who succumb to pulmonary tuberculosis have hepatic involvement and on autopsy, rates as high as 91% have been reported [9]. Hepatobiliary tuberculosis may be more frequent in males (2:1) with age ranging from 17 to 66 years, with 75% cases in the age group of 20–40 years [10]. The exact incidence of hepatic TB is unknown, possibly because most cases are diagnosed post-surgery or autopsy. Essop et al. and Tai et al. have found a 1% prevalence of hepatic tuberculosis in active TB cases [10, 11]. Considering the world's TB incidence of 8.7 million per year, the incidence of hepatic TB in the world can be presumed as 87,000 cases per year [12].

14.4 Pathogenesis

Miliary form of hepatic tuberculosis is a most common form that accounts for 79% of all hepatic tuberculosis and the rest of 21% is accounted for by local hepatic TB [12]. Tubercular bacilli reach the hepatic nidus by the hematogenous route. Hepatic spread in miliary tuberculosis occurs via the hepatic artery and later on forms characteristic tubercles of size 0.6 to 2 mm, usually in both lobules of the liver. In local/isolated hepatic TB, bacilli reach via portal vein from gastrointestinal tract focus. However, the size of granuloma in an isolated form is greater than 2 mm in diameter, usually located near the portal triad region [13]. Occasionally, large mass (often termed tuberculoma) may form from multiple granulomas, and liquefaction of these may result in tubercular abscess [14].

Granuloma formation is a T cell response (cell-mediated response) to tubercular bacilli antigen and characterized by aggregation of macrophages (including Kupffer cells) surrounded by lymphocytes and fibroblasts. Macrophages may coalesce to form larger Langerhans giant cells. Dysfunction in cell-mediated immune response in HIV/AIDS explains the absence of poorly formed hepatic granuloma.

14.5 Clinical Features

The clinical manifestations of hepatic TB are usually nonspecific without any characteristic sign and usually cannot be differentiated from other causes of liver lesions, causing a diagnostic delay. Based on a review, Hersch C et al. noted that the most frequent clinical features are right-sided upper abdominal pain (65–87%) and constitutional symptoms like fever, anorexia, and weight loss (55–90%) [13].

Hepatomegaly is the most common sign (median range 80%) followed by splenomegaly (30%), ascites (23%), and jaundice (20%). The presence of jaundice usually indicates biliary involvement. Jaundice may result from biliary compression by

porta hepatis node, tubercular granuloma rupture in the bile duct, pericholangitis, tuberculous stricture, compression from tuberculous pseudotumor, or less commonly granulomatous involvement [15]. Hepatic TB may present with fever of unknown origin and portal hypertension and may mimic cirrhosis rarely. Case with fulminant liver failure due to tubercular hepatic involvement have been described [16].

14.6 Diagnosis

The diagnosis of hepatic tuberculosis is often delayed, in part because tubercular involvement of the liver is rarely considered as a differential diagnosis.

(a) *Laboratory features*: Like clinical features, laboratory features are also nonspecific. Abnormalities in liver function tests are usually nonspecific and less helpful for making the diagnosis [13, 17–21]. The most consistent laboratory abnormalities include raised alkaline phosphatase and gamma-glutamyl transferase. The elevation of AST and ALT is not a frequent occurrence. However, the elevation of transaminases is found in 90% of icteric patients as compared to 10% in non-icteric patients [1] The reversal of albumin globulin ratio has often been reported [22–24].

(b) *Imaging*: Imaging modalities are most useful in identifying parenchymal abnormalities. Ultrasonography of the abdomen is considered the first imaging test, but it lacks specificity as no characteristic abnormalities specific to hepatic TB have been described. It may show round and hypoechoic lesions (complex mass) in the liver and sometimes mimics malignancy where it is very difficult to characterize the lesion [2, 25]. Such lesions on CT abdomen usually show low attenuation (central area of hypo enhancing or non-enhancing region) that represent area of caseous necrosis with peripheral enhancement corresponding to the outer rim of granulation tissue [2, 26, 27]. The larger (macronodular) lesions may show target sign"/bull's eye appearance that represents the central nidus of calcification (Fig. 14.1). Endoscopic retrograde cholangiopancreatography and percutaneous transhepatic cholangiography are not routinely

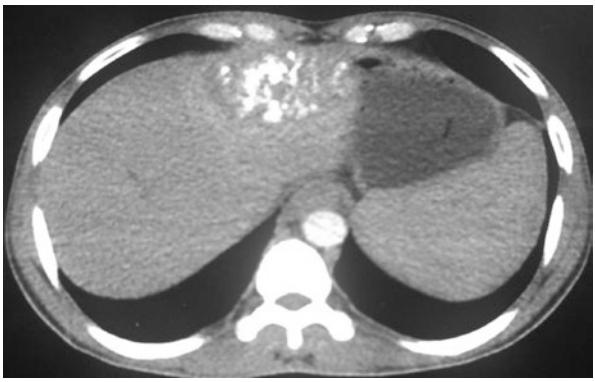

Fig. 14.1 CECT abdomen: heterogenous lesion with internal calcification at left lobe of liver

required. They may be needed in presence of biliary stricture or compression resulting in jaundice or cholangitis [7, 28]. Alvarez S et al. described cholangiographic features in 26 patients. They described the beaded appearance of CBD with areas of dilatation and constriction. The most common finding was hilar stricture (61.5%). The presence of scattered hepatic calcifications favors the diagnosis of tuberculosis [7].

(c) *Histopathology*: Histopathology is the cornerstone of establishing the diagnosis when samples are obtained by liver biopsy or infrequently laparoscopy. Laparoscopic description for hepatic TB includes irregular cheesy white nodules of variable size [1]. The pathological changes on macroscopy may be nodular appearance (tuberculoma), abscess, and enlarged porta hepatis nodes. Microscopy may demonstrate granulomatous hepatitis, conglomerate tubercles, miliary tubercles. Nonspecific findings like inflammatory cell infiltrate, portal inflammation, Kupffer cell hyperplasia, portal inflammation, etc. The histological findings in patients with hepatic tuberculosis reported are well-formed granuloma (95.8%), caseation (83.3%), fatty change (42%), portal fibrosis (20%), AFB positivity (9%) [10].

Histological evidence of epithelioid cell granuloma is not specific to tuberculosis and may occur in sarcoidosis, vasculitis like granulomatous polyangiitis, Q fever, Hodgkin's lymphoma, brucellosis, toxoplasmosis, etc. [28, 29]. Needless to mention, the causes of hepatic granuloma includes a long list viz. systemic diseases (sarcoidosis, Wegner's granulomatosis, Crohn's disease), infections (atypical mycobacteria, syphilis, brucellosis, Q fever, listeriosis, toxoplasmosis, and fungal), and chemicals (beryllosis, drug reactions) and primary liver disease (primary biliary cholangitis) [30]. HIV-infected patients have poorly formed granuloma or absent granuloma because of a defect in cell-mediated immunity [31, 32]. The differentiation of sarcoid granuloma from tuberculosis is important as both the entities are close mimics. Sarcoid granuloma is typically discrete, numerous, non-caseating, peripheral in location with Schaumann bodies or Asteroid bodies with a thin rim of lymphocytes and a hyalinised scar in old granuloma. Tubercular granuloma is characterized by caseation and tendency to coalesce as epithelioid granuloma, irregular contour with a dense cuff of lymphocytes [33]. Caseation, considered as a classical hallmark of tubercular granuloma varies with frequency 30–83% in different series. Korn et.al [34]. reported caseation necrosis in 30%, Alvarez et.al [1]. in 67% and Essop et al. reported caseation in 83% cases [10].

(d) *Microbiology*: Alcantara-payawal et al. used PCR (polymerase chain reaction) assay for diagnosis of hepatic tuberculosis in liver biopsy specimen. They found a success rate of 100% in patients with caseating granuloma and in patients with presumptive diagnosis of hepatobiliary TB success rate is 78%. The overall TB PCR assay positivity is 88% [35]. Positive culture for Mycobacterium tuberculosis is considered as traditional gold standard for diagnosis of tuberculosis however positive rate is only 0–10% in hepatic TB cases with the maximum culture-positive rate from granuloma within caseating necrosis [36]. Xpert Mtb/Rif has been reported to be useful in diagnosis of hepatic tubercular abscess in a series of four patients [37].

Table 14.2 Showing Yield of various microbiological and histological findings in Hepatic tuberculosis

	AFB Positivity	Culture Positivity	PCR Positivity	Non caseating Granuloma	Caseating Granuloma
Amarapurkar DN et al. [8]	10/20 (50%)		12/12 (100%)	4/10 (40%)	6/10 (60%)
Alvarez SZ et al. [1]	2/30				48/71
Essop AR et al. [16]	8/96 (9%)			96%	83%
Maharaj B et al. [23]	59%				52%
Schinina V et al. [38]		6/12	6/12		
Gounder L et al. [12]	14/20	5/14		07/20	13/20

Table 14.2 shows the yield of various histological and microbiological findings and tests in hepatic TB.

14.7 Case Definition

In line with the Indian Extra-pulmonary tuberculosis (INDEX-TB) guidelines we suggest the case to be described as microbiologically positive (AFB culture or PCR positivity from tissue or fluid) or clinically diagnosis (based on clinical and radiological picture with consistent histology in form of caseating or non-caseating granuloma) [39] The patients who are clinically diagnosed must be kept on close follow-up while on ATT to document the radiologic resolution of lesions.

14.8 Treatment

Standard anti-tubercular therapy-based four drugs anti-tubercular therapy is the mainstay of treatment. The reported duration of therapy is generally 1 year and it is unclear if shorter (6 months) of therapy are efficacious in hepatic tuberculosis [1, 40–42].

Percutaneous aspiration-Percutaneous aspiration/drainage of tubercular abscess beside standard anti-tubercular therapy has been described in literature with good clinical responses [3, 43]. Drainage is helpful in diagnosis (by provision of fluid for analysis and microbiological testing) and treatment. Hepatectomy is not usually needed but has been reported for solitary tuberculous pseudotumor [44]. ERCP with stenting/percutaneous transhepatic biliary drainage (PTBD) /surgical decompression may be required in patients who present with obstructive jaundice or cholangitis. Biliary decompression should be done in addition to use of anti-tubercular therapy [1].

14.9 Sequelae and Complications

Parenchymal calcifications may be noted as sequelae. Tuberculous cholangitis and bile duct stricture have been reported and may result in jaundice or cholangitis [45]. Occasionally, portal hypertension due to compression of portal vein by tubercular lymph nodes or massive liver involvement by tuberculosis may occur.

14.10 Outcomes

The overall mortality varies in different series ranging from 12to 75% [1, 13]. In a series of Alavrez S et.al, one-third of patients died because of massive oesophageal variceal hemorrhage from portal hypertension. The cumulative mortality rate was 42%. Factors associated with increased mortality include acute presentation, presence of comorbidities, and coagulopathy [22]. With early diagnosis and treatment, in the absence of comorbidities, the outcome should be good.

Hepatic tuberculosis is a rare manifestation of tuberculosis with very nonspecific clinical presentation and sometimes even mimics malignancy. The advent of newer modalities to diagnose the condition holds promise in near future. High index of clinical suspicion and early detection and treatment of this entity may prevent the occurrence of irreversible complications.

Conflict of Interest None.

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Gall Bladder and Biliary Tuberculosis

15

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Abbreviation

AFB	Acid fast bacilli
ATT	Antitubercular therapy
CECT	Contrast enhanced computerized tomogram
DNA	Deoxyribonucleic acid
EBD	Extrahepatic bile ducts
ESR	Erythrocyte sedimentation rate
EUS	Endoscopic ultrasound
GB	Gallbladder
GBC	Gallbladder cancer
HIV	Human immunodeficiency virus
PET	Positron emission tomogram
RNA	Ribonucleic acid
TB	Tuberculosis
USG	Ultrasonogram
WHO	World Health Organization

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Key Points

1. Gallbladder and biliary tuberculosis though rare can be encountered in endemic zones.
2. Radiology and tumor markers cannot usually discriminate between benign and malignant GB pathology.
3. Diagnostic laparoscopy can assist in diagnosing these cases and it can aid for biopsy of the suspected nodules.
4. Fine needle aspiration of the GB mass is suggested only in surgically non-resectable cases.
5. All the resected specimens should be examined pathologically to prevent clinical mismanagement.

15.1 Introduction

Tuberculosis (TB) is a common disease in the developing economies of the world [1]. Pulmonary TB accounts for the bulk of the disease. Abdominal TB can involve lymph nodes, peritoneum, viscera, and gastrointestinal system [2]. 15–25% of the patients can have concomitant abdominal and pulmonary involvement [3, 4]. There may be an increase in TB in developed countries due to immunocompromised states and HIV coinfection [5]. Hepatobiliary system forms only 1% of the total abdominal TB cases [6, 7]. These cases pose a difficult therapeutic and diagnostic challenge more so in areas with a high prevalence of hepatobiliary malignancies. Varied presentations of these patients still add to the challenge and definitive diagnosis is often established after a morbid hepatobiliary surgical procedure. Upfront antitubercular drugs (ATT) can help alleviate symptoms provided these patients are diagnosed preoperatively [8].

15.2 Epidemiology

Gallbladder (GB) malignancy is a more common and important cause of gallbladder mass and mural thickening seen in general surgery practice. The GBTB, though rare, is occasionally encountered in high endemic zones. These patients are often mistreated as malignancy and undergo a morbid procedure only to be diagnosed as a histologic surprise [9]. Tuberculosis generally involves males more commonly than females and same is true regarding hepatobiliary TB [10]. This is in contrast to malignancy patients where females are more commonly affected [11]. Most of the patients are between 11 and 50 years of age [12]. Gallbladder is usually not involved primarily by tuberculosis. Alkaline nature of bile and resilience of the biliary epithelium to the bacilli seem to provide an effective barrier to the primary tubercular infection. However, large stones in the gallbladder may cause ulceration of the biliary epithelium predisposing to acquisition of infection. Chronic impaction of the

stone in the cystic duct also leads to resorption of the bile salts, predisposing GB mucosa to infection [13, 14]. Gallbladder TB has been seen as four varieties. It can be 1) a component of miliary tuberculosis in children and adults, 2) a component of disseminated abdominal tuberculosis, 3) isolated gall bladder tuberculosis without any focus of infection anywhere else in the body, or 4) involvement of the gallbladder in immunodeficiency states [6].

15.3 Pathogenesis

Tubercular bacilli infect the abdomen through ingested sputum or ingested milk [2]. The tubercular bacilli infect the lymphoid tissue leading onto granuloma formation and ulcerations. Gallbladder is involved through peritoneal, hematogenous, and biliary routes. Bacilli reach the gallbladder through hepatic artery and cystic artery in disseminated form of the disease [10]. It can directly involve the biliary system retrogradely through ampulla of Vater and duodenum. Peritoneal involvement of the abdomen may directly involve the surface of the gallbladder. Occasionally, lymphnodal enlargement may secondarily obstruct the biliary system resulting in biliary involvement.

15.4 Clinical Features

Gallbladder pathologies are varied and usually have a wide spectrum of presentation. The Indian subcontinent is endemic to both cholelithiasis as well as gallbladder malignancy [11]. The endemicity of tuberculosis in this region still adds to the therapeutic as well as diagnostic challenges. Biliary tuberculosis though rare usually presents with the symptoms of benign gallstone disease. As cholelithiasis is often associated with the tubercular involvement of the GB the patients may complain of right hypochondrial pain which increases after taking fatty meals. These patients can present with generalized features of TB like fever and malaise with unintentional weight loss [15]. There are multiple clinical presentations that are reported in the English literature, but the commonest is it being a histopathological surprise.

All the conditions mentioned in Table 15.1 can have multiple differential diagnoses. GBTB is not usually considered upfront as it is a rare pathology. Malignancy is endemic in India along the Indo-Gangetic plain [23]. Subjecting these patients to fine needle aspiration upfront could upstaging the disease, especially because of needle seeding of the tract [11]. There have been reports of patients presenting with biliary colic and they were found to have peritoneal nodules on laparoscopy raising the suspicion of malignancy in them. Biopsy of these nodules proved them to be tuberculosis and these patients underwent completion surgery after a course of antitubercular chemotherapy [24]. So, the nonspecific nature of clinical presentation makes it difficult for the clinician to suspect a diagnosis of GB tuberculosis. This is a diagnosis essentially made after exclusion. However, the diagnosis should be

Table 15.1 Various clinical presentations of gallbladder tuberculosis [8, 10, 16–22]

Gallbladder mass with wall thickening
Gallbladder polyp
Gallbladder perforation and biloma
Obstructive jaundice with cholangitis
Acute cholecystitis
Acalculous cholecystitis
Tubercular Hepatic abscess secondary to biliary obstruction
Hemobilia
Umbilical sinus
Multiloculated cystic mass
Persistent port site sinus

considered in patients with multisystem involvement (including pulmonary lesions) who have associated gallbladder lesions, especially in endemic regions.

15.5 Investigations and Diagnosis

The patients with suspected GBTB can have nonspecific findings including anemia of chronic disease and elevated ESR on their hematological workup [5]. The biochemical profiles may be deranged if there is associated biliary obstruction or liver involvement. The liver enzymes especially the alkaline phosphatase can be raised. The coagulation profile of these patients is deranged depending on the extent of the biliary obstruction and underlying liver dysfunction. The tuberculin test may help in highly suspicious cases but these may not be helpful in endemic countries of tuberculosis where false positives may be encountered. The chest X-rays in these patients may show signs of previously healed lesions provided a history of ATT ingestion could be elicited [10]. However, in case of suspected malignancy pulmonary nodules may be pointers toward a disseminated malignancy. Contrast enhanced tomogram of the chest along with the endobronchial lavage with biopsy of the lesions can help to establish TB.

As with any gallbladder pathology, ultrasonogram (USG) forms the first line of radiological investigation. USG is routinely available and has a low cost. Jain et al. [25] reported the sonological features of GBTB demonstrating the replacement of gallbladder by a mass with stones embedded in it. These features are nonspecific and can be seen in a case of malignancy. Presence of mesenteric lymphadenopathy and omental thickening seem to favor TB whereas the liver infiltration with metastatic nodules is commonly seen in malignancy. None of these features is, however, specific. The presence of ascites and portal lymphadenopathy can be seen in both scenarios. Radiological regression of the visceral disease after a course of antitubercular therapy has been described.

Contrast enhanced computerized tomogram (CECT) has been established as an important cross-sectional radiological modality. It can demonstrate other signs of

abdominal tuberculosis like ascites, visceral involvement, and gut involvement [2]. However, these signs are not exclusive to TB as these can be seen in disseminated malignancy as well. Xiu-Fang Xu et al. [7] classified gallbladder TB into three different types based on CECT: a)micronodular type, b) mass forming type, and c) thickened wall type. Micronodular type is a small polypoidal lesion in the GB wall. A benign GB polyp and early GB malignancy can be the differential diagnoses in these cases. The mass forming type typically has the features of GB malignancy but the presence of flecked calcifications with a huge GB mass can be a pointer toward tuberculosis. Actinomycosis of the GB is a differential diagnosis for the mass forming type of TB. The thickened wall TB can show uniform thickness or an irregular thickness. The irregularly thickened wall again had malignancy as it is differential. However, xanthogranulomatous cholecystitis can be a mimicker of the regularly thickened GB wall [9]. The authors further opined that the homogenous enhancement of the tubercular GB showed less caseation as compared to the heterogenous ones. The overlap of radiological findings among patients with TB and malignancy makes it really tough for treating physicians.

Positron emission tomography (PET) is used both for staging the disease as well as to assess the therapeutic response to neoadjuvant treatment [26, 27]. The thick-walled gallbladder is a common finding in patients with gallstone disease. PET scan can help differentiate between benign and malignant GB thickening [28]. However, there are reports of false-positive PET scan in patients with tuberculosis. Ramia et al. [29] and Deo et al. [8] have reported a false positive FDG PET scan in a patient with GBTB. These patients were treated on the lines of malignant GB mass and they responded well to antitubercular treatment. 11 choline scan along with FDG can be used to differentiate TB from malignancy. SUV values of both FDG and 11 choline scan are raised in malignancy whereas the SUV of 11 choline decreases and FDG increases in patients with TB. The study was reported in cases of lung cancer and pulmonary TB and the utilization of these investigations in cases of GBTB is debatable [30].

Isolation of acid-fast bacilli from the bile in patients with suspected biliary cancer could help in guiding the therapy. The yield of AFB in endoscopically aspirated bile is low and it cannot be used as a reliable method of tubercular detection [18]. Endoscopic ultrasound (EUS) can be used to determine the extent of lymphnodal enlargement and can guide the endoscopist for fine needle aspiration and this might help in increasing the diagnostic yield. Immunological evaluation using serologies or antigens is not usually recommended [31, 32]. Various tumor markers like carbohydrate antigen 19.9 and carcinoembryogenic antigen (CEA) have been mentioned in literature which are not specific to malignancy, however, when raised, malignancy should be the working diagnosis [33].

Histopathological evaluation may show areas of caseation and necrosis with epithelioid cells and Langhans type giant cells [5]. Acid-fast bacilli may not be detected. Absence of acid-fast bacilli on histopathological examination makes it difficult for the pathologist to differentiate it from other granulomatous disorders affecting gallbladder. Schistosomiasis, Crohn's disease, and xanthogranulomatous cholecystitis can also show granulomas but these are usually noncaseating in nature [34–36].

Subjecting the tissue to real-time polymerase chain reaction can help detect mycobacterium where the yield of microscopy is low [37]. Every resected specimen should be subjected to examination as gallbladder is notorious for pathological surprises [23].

15.6 Extrahepatic Biliary Tuberculosis

Extrahepatic bile ducts (EBD) are rare sites to be involved by tubercular infection [10]. Direct EBD involvement is a rare phenomenon. The pericholedochal lymph nodes are usually involved as a part of the lymphnodal or the miliary process [38]. EBD are involved as part of direct infiltration from these nodes, as pericholedochal inflammatory process or the rupture of the tubercular granuloma into these ducts. These ducts when involved usually produce the symptoms of extrahepatic biliary obstruction, with or without Charcot's triad. The symptoms once produced put the clinician toward the suspicion of cholangiocarcinoma and these patients could land up in morbid surgical procedure [18]. In advanced stages, tubercular liver abscesses may occur. The granulomas heal with calcifications leading to tubercular pseudocirrhosis. The compression of portal vein by lymphnodes and granulomas can manifest as signs of portal hypertension with splenomegaly and esophageal varices. Prolonged TB in the ducts causes multiple strictures with amyloid deposition in the liver causing hepatic insufficiency [39–41]. Diagnosis of TB in EBD is a tedious process as with GB. Similar investigations are performed with dismal results with regard to the definitive preoperative diagnosis. The management in this form of tuberculosis may require frequent stenting of the EBD to alleviate the symptoms of biliary obstruction. These patients may require excision of the stricture bearing segment of the EBD with hepaticojejunostomy and access loop if the cicatrix persists even after ATT. Anatomical resection of the liver is required in case of atrophy/hypertrophy complex and intractable cholangitis. Liver transplant may be required in rare cases though the reports on this management are lacking, especially due to the rarity of the disease itself.

15.7 Conclusion

TB of the biliary and EBD is a rare disease. Though rare, these cases are encountered in the clinical practice. These patients are a nightmare to the surgeons as the morbid surgery is performed for a medically treatable disease. The complications of the surgery though less in modern era, are the bitter truth of the treatment plan. Preoperative definitive diagnosis can prevent surgical complications and medical management can be instituted early. Further trials on cancer biomarkers with high sensitivity and specificity can prevent dilemma and benign nature of negative cases can be ascertained definitively.

Conflict of Interest None.

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Pancreatic Tuberculosis

16

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Key Points

1. Pancreatic TB is a rare entity and misdiagnosis/late diagnosis is common.
2. The most common site of pancreatic TB is head, followed by body of the pancreas, and tail is least commonly affected by TB.
3. CT features are nonspecific and often resemble other inflammatory or neoplastic masses or cystic lesions of the pancreas.
4. Image-guided core needle biopsy has a high diagnostic yield in pancreatic pathologies. It is considered as a superior diagnostic modality to FNAC in characterizing pancreatic lesions as it can differentiate granulomatous lesions and other radiographically comparable lesions.
5. Once a correct diagnosis has been made, pancreatic TB is curable with standard antituberculous treatment.
6. Surgical intervention is indicated for complications, and failed medical therapy and occasionally when the discrimination from malignancy is uncertain.

16.1 Introduction

Pancreatic tuberculosis is an uncommon entity that is often confused with space-occupying pancreatic solid and/or cystic lesions. Even in miliary tuberculosis, hepatic and splenic involvement is more common than pancreatic involvement. Pancreatic tuberculosis has a nonspecific clinical presentation, unique patient

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population, epidemiological features and specific treatment. Since the most common cause of mass lesion in pancreas is pancreatic carcinoma, misdiagnosis of pancreatic tuberculosis as malignancy was very common. Fortunately, earlier clinical recognition, improvement in diagnostic and therapeutic imaging and endoscopic ultrasound and improvements in treatment regimens have improved patient diagnosis and outcomes.

16.2 Predisposing Factors

Patients who develop pancreatic tuberculosis (TB) have been reported to have some risk factors or comorbid conditions [1]. Patients with pathologies resulting in abnormal host-defense mechanisms such as acquired immunodeficiency syndrome (AIDS), complement deficiency, leukemia are at increased risk of developing pancreatic TB [2]. The human immunodeficiency virus (HIV), diabetes mellitus, use of steroids, chemotherapeutic agents, and other immunosuppressive medications have been associated with an increased incidence of pancreatic tuberculosis in adult patients. For all types of pancreatic abscesses including tuberculous abscess, immunosuppressed states are the predisposing factors in two-thirds of patients. Other predisposing factors are alcoholism, nutritional deficiencies, and prolonged illness associated with bacterial infections [2]. Alcoholics also have a high risk of pancreatic abscess formation. Pancreatic trauma resulting from blunt or stab or unrecognized iatrogenic injury, history of endoscopic retrograde cholangiopancreatography (ERCP), and foreign body retention in pancreatic duct also have been associated with pancreatic tuberculosis [3].

16.3 Etiopathogenesis

In the pancreas, pancreatic enzymes function as a primary barrier and also a filter for the clearance of pathogens from biliary, vascular, and local sources. The two important factors responsible for relative resistance of pancreas to tuberculosis are pancreatic enzymes and antimycobacterial effect of pancreatic tissue itself. The highly resistant qualities of the tubercle bacillus are believed to be due to its envelope, which contains a high percentage of fats and waxes. It has been reported that pancreatic lipase causes lipolysis of mycolic acid in the envelope of tubercular bacilli [4]. Once this envelope is gone, tubercular bacilli become very susceptible. Human pancreatic gland extract contains glycerine esterases, lecithinase, and a very high concentration of esterases [4]. These enzymes result in complete bacteriolysis of tubercular bacillus. In addition to lipases, the antimycobacterial effect of deoxyribonucleases has also been suggested [4–6]. Therefore, loss of exocrine function and other immune abnormalities like vitamin D deficiency has also been implicated to play a role in the reactivation of tuberculosis [7, 8].

Pancreatic tuberculosis can be primary or secondary. In primary cases, there is no evidence of TB elsewhere. Primary and isolated pancreatic tuberculosis is a rare occurrence. Pancreatic tuberculosis is usually secondary to pulmonary infection or as a part of multifocal gastrointestinal tuberculosis or miliary tuberculosis. The most common site of pancreatic TB is head, followed by body of the pancreas, and tail is least commonly affected by TB. Pancreatic TB has also been reported in association with pancreatic carcinoma [9]. The possible routes of tuberculous infection of pancreas are:

1. Hematogenous spread is considered to be the most common route of spread as tuberculous lesions are most commonly located in the head of pancreas.
2. Lymphatic dissemination from peripancreatic lymph nodes also explains the involvement of head of pancreas as peripancreatic lymph nodes are present in close vicinity to the head region.
3. Direct contiguous spread through tuberculous lesions in the biliary tree.
4. Reactivation of a dormant bacillus in an immunosuppressed patient.
5. Toxic allergic reaction of the pancreatic tissue in response to generalized TB.

Based on the mode of involvement, pancreatic tuberculosis can be classified into the following:

1. Local, with isolated involvement of pancreas in the form of a primary complex with caseation of the associated peripancreatic lymph nodes. Dissemination of infection from draining lymph nodes is the most common mode of involvement in patients with AIDS.
2. Pancreatic TB develops secondary to pulmonary TB.
3. As a part of multifocal involvement of gastrointestinal tract.
4. Miliary TB, as a part of generalized TB resulting in the involvement of pancreas as well. This is associated with immunosuppressed states.

16.4 Epidemiology

The prevalence of abdominal TB in developing countries has been estimated to be as high as 12% [10]. Active pulmonary TB has been reported to occur in 6–38% of cases of abdominal TB [11]. Pancreatic involvement with TB is rare even in the setting of miliary TB, ranging from 2.1 to 4.7% [12]. Paraf et al. reported an incidence of 2% (11/526 cases) in an autopsy series in 1966 [13]. A recent study from India reported that the incidence of pancreatic involvement is 8.3% among patients with abdominal TB [1]. The incidence of isolated pancreatic TB has been reported to be less than 5% [14, 15]. Pancreas is affected by TB in 7% of cases with disseminated intra-abdominal TB [16]. Majority of the reported cases of pancreatic TB are of Asian and African origin. Only 16 cases of pancreatic TB were reported during the

period 1950 and 2000, while the number of cases reported during twenty-first century 72. The reasons for this rise could be related to a global increase in TB, increased extrapulmonary TB, especially in immunocompromised patients, and better diagnosis and imaging.

16.5 Pathology

As described earlier, the mode of involvement is the best predictor of number, site, and size of pancreatic tuberculous involvement. Generally, pancreatic tuberculous lesions are solitary. Nodular lesions are small while abscesses may be large and multiple. Miliary lesions are usually multiple. The affected part of the pancreas is mild-to-moderately enlarged in most cases. Diffuse massive enlargement of pancreas is rare. The most common gross pathological finding is presence of multiple white caseating nodules in the head of pancreas, coalescing to form a large yellowish mass of solid consistency (Fig. 16.1). Pathologically, pancreatic TB may have focal enlargement, multiple intrapancreatic hard nodules, multiple intrapancreatic cystic lesion, or nonspecific diffuse enlargement. The hallmark of tuberculosis caused by *Mycobacterium tuberculous* bacillus is epithelioid granulomas composed of aggregates of macrophages, epithelioid cells, and langhans giant cells with variable degrees of central caseous necrosis. Macrophages are circumscribed by a cuff of both T- and B-lymphocytes contained within the rim of fibroblasts. The lesions vary in size from 1 mm to >2 cm. Fibrosis may develop in relation to granulomas. Peripancreatic lymph nodes may also show caseating granulomas. In granuloma, mycobacterial DNA can be found with numbers ranging from 0 to 9% [17].

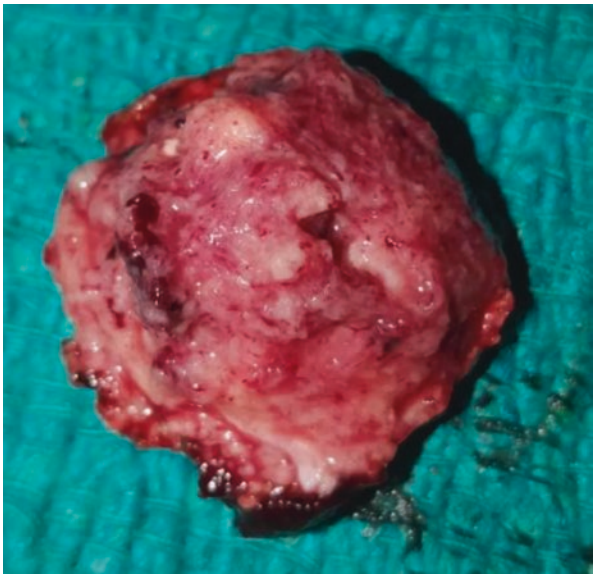

Fig. 16.1 Resected specimen from pancreatic head mass showing white cheesy material

16.6 Clinical Features

There are no specific clinical features of pancreatic TB. Clinical features of pancreatic tuberculosis depend on its manifestation. The various manifestations of pancreatic TB are given in Table 16.1. The clinical symptoms evolve insidiously. The average age at diagnosis is 38 years (14–74 years). Majority of the patients present in 4th decade of life. Males are affected more frequently, with a male to female ratio of 3.6:1. The patients may remain asymptomatic initially. Most patients manifest symptoms ranging from 2 to 6 weeks. A more indolent course has been reported in approximately one-fourth of patients. Patients with such chronic course usually have a mass or nodule formation in the pancreas. Upper abdominal pain is the most common symptom present in more than 85% of patients, followed by fever present in more than 60% of patients. Up to 30% of patients with pancreatic abscess present with classic spiking fever patterns associated with other types of abdominal abscesses. Approximately 10% of patients present with fever of unknown origin. The triad of symptoms encountered most frequently is upper abdominal pain, fever, and weight loss seen in more than 25% of patients. The vague and nonspecific symptoms such as nausea, vomiting, malaise, anorexia, jaundice, and pruritus occur in more than 30% of patients. Other less common symptoms are diarrhea, dyspepsia, malena, hematemesis, night sweats, and backache. Less than 50% of patients have a family history of TB.

Epigastric and right hypochondrial tenderness are the only consistent physical findings. Less common findings are epigastric mass and jaundice (Table 16.2). Rare presentations of pancreatic tuberculosis are given in Table 16.3.

16.7 Diagnosis

A delay in diagnosis is common because the disease is rare, clinical presentation is vague and nonspecific. Up to 80% of patients suffer delayed evaluation and management. In 46% of cases, diagnosis is made after major surgical resection on histopathological examination. Clinical presentation, laboratory, and imaging studies support the diagnosis of pancreatic TB but the definitive diagnosis requires demonstration of MTB on histologic examination. Isolated pancreatic TB is even rarer and diagnosis is challenging. Criteria/definition for isolated pancreatic TB is given in Table 16.4. In clinical scenarios with a high index of suspicion for the disease, treatment should not be withheld until the diagnosis is confirmed. The diagnosis should be considered in patients from areas having high incidence of active TB, those with

Table 16.1 Various manifestations of pancreatic tuberculosis

Manifestations	% cases
Pancreatic mass	54.7
Peripancreatic lymph nodal mass	16
Intrapancreatic collection/abscess	16
Peripancreatic collection/abscess	14.6

Table 16.2 Clinical presentations of pancreatic tuberculosis (from published literature since 1951)

Clinical presentations	% cases
Symptoms	
Pain upper abdomen	89
Fever	82
Weight loss	76
Nausea and vomiting	74
Malaise	62
Constitutional symptoms	60
Signs	
Jaundice	22.6
Epigastric tenderness	21.2
Epigastric mass	8.3
Ascites	2
Hepatomegaly	2

Table 16.3 Rare presentations of pancreatic tuberculosis (from published literature since 1951)

Rare presentations	Number of cases
Pancreatic abscess	23
Obstructive jaundice	17
Acute pancreatitis	4
Chronic pancreatitis	2
Portal hypertension	1
Iron deficiency anemia	1
Massive gastrointestinal bleeding	1
Diabetes mellitus	1
Pancreatobiliary fistula	1
Dyspepsia	1
Progressive dysphagia	1
Focal pancreatitis and segmental portal hypertension	1

past history or exposure TB, involvement of other sites like lungs, underlying immunodeficiency, and having pancreatic lesion(s).

16.8 Laboratory Evaluation

A number of nonspecific laboratory abnormalities may be seen in a pancreatic TB patient. Decreased hemoglobin and serum albumin level, elevated ESR, and positive tuberculin test support the diagnosis of TB. Approximately two-thirds of patients may show positive tuberculin test. C-reactive protein may also be raised. Serum amylase and lipase could be elevated in acute cases. In patients with a pancreatic

Table 16.4 Criteria for isolated pancreatic tuberculosis

A young patient presenting with pain upper abdomen, fever, and weight loss
No past history of pulmonary TB or EPTB
A clear chest X-ray
No clinical features suggestive of gastrointestinal obstruction or any other gastrointestinal pathologies
Disease localized to pancreas and no other detectable foci of TB on imaging studies
Biopsy from pancreatic lesion suggestive of TB
Improvement in symptoms on initiation of ATT

head mass obstructing ampulla and common bile duct, serum bilirubin and alkaline phosphatase levels are elevated. HIV antibody testing should also be done as should evaluation for underlying diabetes.

16.9 Microbiological Tests

Specimen for AFB staining, culture, and PCR may be obtained from bile through ERCP, or by aspiration of pus/tissue using imaging or endoscopic ultrasound. The success rate of identifying acid-fast bacilli is maximum with the biopsy specimen; in the range of 20–40% [18, 19]. Cultures were found to be positive in about 77% of cases [18]. Bile obtained on ERCP may also occasionally identify the bacilli. In case of an abscess, pus aspiration under image guidance may also show bacilli. Bacilli may also be isolated from other sources such as sputum, bronchus, and urine.

PCR helps in supporting diagnosis of TB occurring at an uncommon site such as pancreas and in conjunction with other noninvasive modalities, it is helpful in diagnosing pancreatic TB and laparotomy can be avoided. PCR is able to pick up more extrapulmonary TB patients as compared to conventional methods and it has been found to be superior to smear and culture in detecting *Mycobacterium tuberculosis* [5]. The sensitivity of PCR is similar to culture and the results can be obtained within a day. Drug susceptibility cannot be reliably determined with PCR.

16.9.1 Radiology

The diagnosis in most patients is supported by noninvasive imaging studies. A detailed review study in the year 2014 concluded that pancreatic TB should be considered in cases with a space occupying lesion of pancreas with associated necrotic peripancreatic lymph nodes. Necrotic peripancreatic lymph nodes were noted in 27% of cases. X-ray chest should always be done in suspected cases of pancreatic TB as up to 19% of patients have a past history of pulmonary or extrapulmonary TB and a coexisting pulmonary TB was present in 6–38% of cases [11]. The radiological features could vary from mass lesion, cystic lesion, or peripancreatic lymphadenopathy. Ultrasonography is an excellent imaging modality for the initial evaluation

and preliminary screening to confirm the presence of a suspected space occupying pancreatic lesion. Because of resolution limitations, computed tomography scan is often required to confirm the nature of the lesion. Conventional USG may show diffuse enlargement of the pancreas, isolated lesion appears as a focal hypoechoic lesion at or adjacent to the pancreas that may sometimes show central liquefaction or heterogeneously hypo-isoechoic lesions, enlarged multiple peripancreatic and para-aortic and other abdominal lymph nodes (seen in up to 75% of patients), common bile duct and pancreatic duct dilatation are rarely seen even if the mass is located centrally in the head of the pancreas. Diffuse form of pancreatic TB is characterized by pancreatic enlargement with narrowing of the main pancreatic duct and heterogenous enhancement [20].

On endoscopic ultrasound (EUS), pancreatic TB lesions appear as hypoechoic lesions with or without calcification. Associated peripancreatic lymph nodes or ductal dilatation can be found. On EUS using elastography, in TB, the affected pancreatic tissue is stiffer compared to the surrounding healthy pancreatic parenchyma and the focal pancreatic lesions are less sharply demarcated in contrast to ductal adenocarcinoma [20]. Contrast-enhanced US (CEUS) shows heterogenous enhancement pattern; non-enhancement in the necrotic zones and hyperenhancement in the most active zones. CEUS is important in differentiating pancreatic TB from pancreatic ductal adenocarcinoma; in the arterial phase, pancreatic TB shows iso- or hyperenhancement compared to the surrounding tissues [20].

CT is probably the most effective study in diagnosing pancreatic TB; it typically detects lesions greater than 0.5 cm in diameter, even smaller lesions may be visualized with newer contrast-enhanced spiral techniques. CT features are nonspecific and often resemble other inflammatory or neoplastic cystic lesions of the pancreas. CT scan findings are in the form of focal mass lesions, or bulky and heterogenous pancreas (Fig. 16.2). It may also show complex masses and presence of intrapancreatic collections. CECT shows hypodense, hypovascular well-defined mass with irregular borders and peripheral enhancement; areas of central enhancement may result in a multiloculated appearance with adjacent necrotic or nonnecrotic lymphadenopathy [21]. The presence of a thick solid rim of pancreas around the cystic/solid lesion is consistent with tuberculosis. The presence of hypodense enlarged lymph nodes with rim enhancement in the peripancreatic region, and ascites may suggest the possibility of pancreatic TB [22]. Presence of calcifications in pancreatic lesions was reported as a characteristic feature of pancreatic TB [5, 23–25]. In a study, calcifications were present in 56% of pancreatic tuberculous lesions [23].

MRI can identify pancreatic lesions as small as 0.3 cm in diameter and it is also superior to other imaging techniques in defining vascular anatomy. MRI features of focal pancreatic TB are sharply delineated mass showing heterogenous enhancement. The lesions are hypointense on fat-suppressed T1-weighted images and show a mixture of hypo- and hyper-intensity on T2-weighted images. In TB, diffuse involvement of pancreas is characterized by enlargement with narrowing of the main pancreatic duct and heterogenous enhancement; signal intensity abnormalities include hypointensity on fat-suppressed T1-weighted images and hyperintensity on T2-weighted images [2].

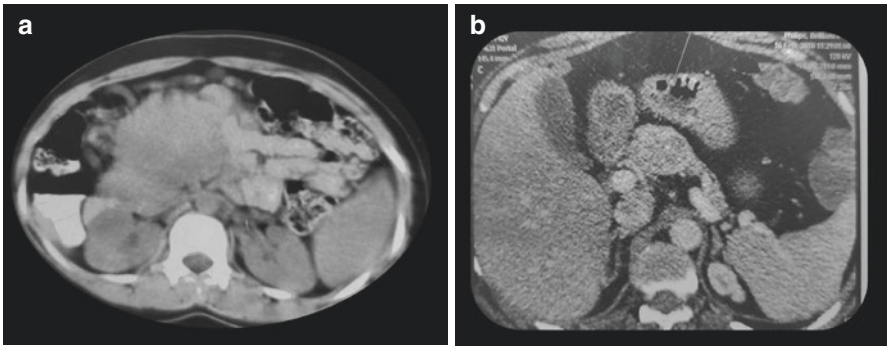

Fig. 16.2 CT (**a** and **b**) showing pancreatic head mass with hypodense collection

Table 16.5 Biopsy techniques for diagnosis

Biopsy technique	% cases
Surgery (Whipple procedure)	45.4
EUS-FNA	25.3
Core needle biopsy during surgery	12
US-FNA	10.7
CT-FNA	9.3
FNA during surgery	1.5
US-core biopsy	1.3
CT-core biopsy	1.3
Excisional biopsy during surgery	1.4

16.9.2 Image-Guided Biopsy

The best way to diagnose TB is a direct histopathological and microbiological examination by taking excisional biopsy. This helps exclude malignancy which is the most common differential diagnoses. Direct histopathological examination by laparotomy is indicated only when imaging studies and guided biopsy fail to confirm diagnosis; though, in majority of reported studies diagnosis was made on laparotomy (Table 16.5). Imaging studies not only help in lesion characterization but also in obtaining a sample for culture, biopsy, and PCR. Image-guided biopsy is mandatory to differentiate between benign and malignant mass lesions. Results of image-guided biopsy studies vary from endoscopists' experience to pathologists' skills.

Under US/CT guidance transcutaneous cytology/core biopsy can be taken but they are associated with a risk of injury to the intestine as well as vessels and there is chance of needle tract dissemination in presence of malignancy. Most of the studies have concluded that EUS-FNA is better than other image-guided modalities [24, 26, 27] but Mallory et al. suggested that there is no difference in accuracy between EUS/US/CT-guided techniques of pancreatic biopsy [28]. Core needle biopsy (CNB) has a high diagnostic yield in pancreatic pathologies. It is considered as a

superior diagnostic modality to FNAC in characterizing pancreatic lesions as it can differentiate granulomatous lesions and other radiographically comparable lesions. CNB is associated with high rates of complications such as bleeding and a high risk of injury to the intestine.

EUS-guided biopsy is the safest and best method to diagnose pancreatic TB. Image-guided transcutaneous biopsy was successful in accurate diagnosis of pancreatic TB in less than 50% of cases [29]; while EUS-biopsy was able to confirm the diagnosis in 76.2% of cases [24]. FNAC/core biopsy can be taken from pancreatic lesions and/or peripancreatic lymph nodes. In a study by Song et al., EUS-guide FNAC showed granulomatous inflammation on histopathological examination in 61.9% of cases, 66.7% were positive on TB PCR assay, 37.5% patients had positive cultures for *M. tuberculosis* and ZN staining was positive in 26.7% of patients [24]. The sensitivity of EUS-FNA ranges from 85 to 90% and specificity is 100% [30]. Small lesions, less than 1 cm are easily missed on USG. EUS-FNA is the preferred diagnostic modality for diagnosing small lesions located in body and tail regions of the pancreas.

16.9.3 Differential Diagnosis

The differential diagnosis for pancreatic TB includes pancreatic carcinoma, focal chronic pancreatitis, retroperitoneal tumors, lymphoma, and cystic neoplasms of the pancreas. The differential diagnosis for granulomatous inflammation in the pancreas includes fungal infections, sarcoidosis, Wegner's disease, inflammatory bowel disorder, and foreign body retention [3, 31].

It has been reported that in 52% of cases, first working diagnosis was wrong as pancreatic adenocarcinoma or peripancreatic malignancy [32]; and 2–7% patients were considered for palliative chemotherapy because of misdiagnosis [33] and up to 45% of patients underwent unnecessary major surgical procedures [5]. There is no radiological difference between cystic neoplasm of the pancreas and tuberculous pancreatic abscess.

16.9.4 Treatment

There are no specific guidelines for management of pancreatic TB because of the rarity of disease. The management of pancreatic TB depends on the clinical presentation, its pathological stage, the stage at which diagnosis is made, immunological status, type of disease—whether reactive or occurring as a new pathology, and its occurrence in isolation or as a part of disseminated disease. The principles of treatment are timely diagnosis with noninvasive diagnostic modalities, treatment in combination with optimum doses and duration of antituberculous drugs (ATT), timely surgical intervention whenever indicated with pre- and postoperative ATT, prevention of complications, management of complication; if they develop and regular assessment of disease burden and follow up.

Once a correct diagnosis has been made, pancreatic TB is curable with standard antituberculous treatment (ATT) [5]. According to WHO guidelines, isolated

pancreatic TB with no past history of TB should be considered as a new case of EPTB and ATT should be given for 6 months [34]. The best results of ATT are seen in patients with isolated pancreatic tuberculosis without abscess formation [5]. Isolated EPTB is associated with a lower bacillary burden than pulmonary disease. Therefore, isolated EPTB such as pancreatic tuberculosis can be treated with standard short-course regimens that are effective for pulmonary disease. However, disseminated disease with tuberculous pancreatic involvement may need longer treatment [5, 20]. Imaging may be performed to assess response to therapy.

As hepatic involvement has been reported in some cases of pancreatic TB [33], ATT should be initiated cautiously and careful monitoring for drug-induced hepatitis with weekly assessment of liver enzymes and serum bilirubin is recommended. USG is the investigation of choice for follow-up and also in guiding the duration of therapy. CT imaging is preferred over USG for confirmation of complete resolution of the pathology and also in patients requiring any form of surgical intervention during or after the course of ATT [5, 20].

Indications of surgical intervention may include presence of tuberculous abscess, failure to diagnose pancreatic TB or exclude malignancies, failure to show complete clinical response with ATT or lack of radiological improvement even after standard ATT and the mass needs to be resected for histopathological confirmation. The cornerstone for management of tuberculous pancreatic abscess is prompt drainage of purulent collection and initiation of appropriate ATT. Drainage of an abscess cavity may be done by percutaneous, endoscopic, or surgical techniques [34–37]. In case of pancreatic head mass causing biliary obstruction (especially cholangitis), endoscopic retrograde cholangiopancreatography (ERCP) with stenting is a preferred technique to relieve obstruction. Since ATT is curative, major surgical intervention may not be required. Bile for culture and tissue for histology, staining and PCR can also be obtained simultaneously. In a clinical scenario, when diagnosis is not confirmed, exploratory laparotomy may be done, frozen section confirms the diagnosis and bilioenteric anastomosis relieves the obstruction to the biliary tree (Fig. 16.3).

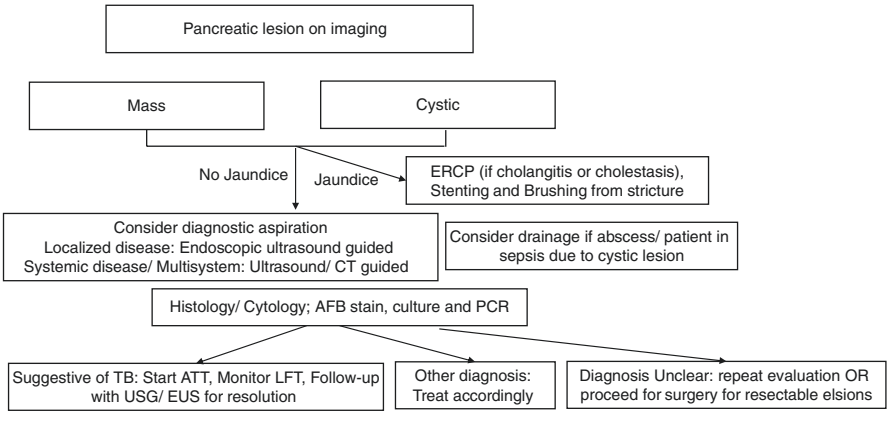

Fig. 16.3 Flow chart showing management of suspected pancreatic tuberculosis

16.10 Complications, Prognosis, and Follow-Up

Complications in pancreatic TB cases develop because of delayed diagnosis. Immunocompromised patients with tuberculous abscess or diffuse involvement of pancreas develop complications more frequently as compared to immunocompetent patients; and complications in such patients are often catastrophic. Because of delay in initiation of treatment ARDS can develop. Six such cases are reported in the literature [36]. The known complications are rupture of tuberculous abscess into hollow viscera or into the peritoneal cavity. Other rare complications that increase both morbidity and mortality rates are intestinal perforation, massive gastrointestinal bleeding, pancreatobiliary fistula, and portal hypertension.

Response to therapy can be assessed by improvement in symptoms, normalization of laboratory parameters, radiological regression of disease. For follow-up, during each monthly visit, along with detailed clinical assessment, hemogram, serum albumin, and liver function test should be done. USG should also be done monthly for first six months and first CT scan needs to be done after completion of therapy. CT scan can be done early if there is no clinical improvement or clinical deterioration. If untreated, nearly all cases of pancreatic TB prove fatal. The disease has a mortality rate of 9.1% in immunocompetent patients and 10.8% in immunocompromised patients [20, 37].

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Conflict of Interest None.

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Part V

Investigations and Evaluation

Histopathology for the Diagnosis of Abdominal Tuberculosis

17

Arvind Ahuja and Ravi Hari Phulware

Key Points

- Biopsy and histopathological examinations supplemented with microbiological tests (culture, GeneXpert/RIF assay, PCR) play an important role to reach a diagnosis of abdominal tuberculosis.
- Ulceration of the mucosa, infiltrative or hypertrophic mass, stricture, fistula, or sinus formation is the common gross findings.
- Well-formed epithelioid cell granulomas, usually confluent with caseous necrosis and Langhans giant cells are the classical microscopic findings.
- The differential diagnosis includes other granulomatous infections, Crohn's disease, and sarcoidosis.
- Clinical, endoscopic, imaging, microbiological, and histological correlation is mandatory to reach a definitive diagnosis.

17.1 Introduction

Abdominal tuberculosis (TB) may present as intestinal, peritoneal, lymph node, or visceral tuberculosis either alone or in any combination [1, 2]. Intestinal TB may account for 50–80% of abdominal TB. Ileo-cecum is the most common site followed by a decline in involvement as one proceeds orally or anally [3]. Multiple sites of the bowel are often affected. Ileocecal region is affected in up to 75% of cases [3]. Clinically, abdominal TB often mimics inflammatory bowel disease,

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especially Crohn's disease, intestinal malignancy, and other infectious diseases. Endoscopic examination and imaging may aid in the diagnostic workup. However, biopsy and histopathological examination supplemented with microbiological tests (culture, GeneXpert/RIF assay, PCR) is the gold standard to reach a definite diagnosis. In modern era, EUS-guided FNAC/B is playing a very important role in the diagnosis, especially in the organs where biopsy was difficult or not possible. Clinical, endoscopic, imaging, microbiological, and histological correlation is mandatory in most of the cases to reach a definitive diagnosis.

17.1.1 Etiopathogenesis

Mycobacterium tuberculosis is the organism responsible for causing tuberculosis. The pathogenic bacteria spreads to the gastrointestinal lumen by one of these routes: swallowed sputum, hematogenous spread from the pulmonary lesions, contiguous involvement from the infected lymph nodes, and occasionally *M. bovis* infection from unpasteurized milk [4–6].

The mycobacterial invasion and the resulting inflammation can eventually cause gastrointestinal ulceration, bleeding, and perforation. Extrapulmonary disease, including gastrointestinal tuberculosis, is recognized to occur more frequently in individuals who are HIV seropositive or immunocompromised [2, 5–8].

Mesenteric vascular involvement is well recognized in intestinal tuberculosis and contributes to the various morphological changes. On microscopic examination, granulomatous inflammation has been noted in mesenteric vessels and this could be associated with luminal thrombosis of the vessels. Ischemia may contribute to exacerbation of gastrointestinal injury and promote development of ulcers, perforation, fibrosis, and strictures [2, 5, 6, 9].

17.2 Esophagus

Esophageal tuberculosis (ETB) is uncommon site in GIT [10]. ETB is usually secondary to respiratory tract infection or mediastinal involvement. Direct extension from adjacent mediastinal structures is believed to be the main pathogenesis [10–12]. Most often ETB is misdiagnosed as malignancy due to overlapping signs and symptoms between the two pathologies.

Gross On gross examination most common site of involvement is thoracic esophagus [13]. Most of the specimens show ulceration of the mucosa. Infiltrative mass, fistula, or sinus formation can be seen in few cases. Rarely ETB can cause stricture. In the modern era, most of the samples received in the pathology lab are either endoscopic biopsies or EUS-guided FNAC samples.

Microscopy On histopathological examination, the mucosa is usually hyperplastic and often accompanied by surface ulceration. Subepithelium shows ill-defined to well-formed epithelioid cell granulomas with or without caseation necrosis or

Langhans type of giant cells. Ziehl-Neelsen (ZN) stain has low sensitivity and therefore it is usually negative. Often, the granulomas are located deeper part of the mucosa or in the submucosal layer, therefore, multiple and deep endoscopic esophageal biopsies are warranted [11, 13, 14]. In one study from India, esophageal biopsy could clinch the diagnosis in 11 of the 18 patients in whom it was performed. Five biopsies showed caseating granulomas, six showed noncaseating epithelioid cell granuloma, whereas ZN stain was positive in 2 cases only [13].

Most common differential diagnosis of granulomatous inflammation in esophagus is usually histoplasmosis or other fungal infections, especially in an immunocompromised patient with HIV/AIDS [12, 15, 16]. Therefore, in addition to ZN stain, fungal stains should be applied.

17.3 Gastroduodenal TB

Stomach and duodenum are rare sites of tuberculosis due to a combination of factors such as an acidic milieu, paucity of lymphoid tissue, and the rapid passage of swallowed bacilli of mycobacterium. Primary involvement of the stomach and duodenum is rare (0.4%–2%) [11].

Gross Gastric antrum and pylorus along the lesser curvature are usually the most common site of tuberculous lesions; while the gastroesophageal junction is uncommonly involved [17]. In the duodenum, D2-D3 was most commonly involved, however in our experience D1-D2 are more commonly involved [11]. Gastrectomy specimens mostly show large non-healing ulcerative lesions. However, most patients may show gastric outlet obstruction and rarely nondescript hypertrophic submucosal mass or pseudotumor formation [11, 17, 18]. In case of disseminated tuberculosis, miliary tubercles can be seen. Most of the specimens show associated regional lymphadenopathy.

In duodenal TB lesions are ulcerative, hypertrophic, or ulcero-hypertrophic. It frequently shows mucosal fold thickening, deep irregular ulcers, and later obstruction, which can be either due to stricture or due to external compression by lymph node [17–19]. In one of the large studies, 82% of 28 cases had obstructive symptoms due to narrowed lumen and 72% of these had an external compression [19]. Less common manifestation includes fistula formation, and choledocho-duodenal, pyelo-duodenal, and aorto-duodenal fistulas have been reported in the few case reports.

Microscopy The histopathological diagnosis of gastro-duodenal TB mainly rests on the identification of epithelioid cell granulomas with caseous necrosis and Langhans giant cells with prominent lymphoid aggregate in lamina propria or submucosa. In advanced disease, inflammatory reaction spreads deep into the muscularis propria causing fibrosis and thickening of the gastric wall and frequently pyloric stenosis, presenting sometimes as gastric outlet obstruction [2]. However, in the absence of caseating granulomas, it becomes difficult for the pathologist to differentiate it from other inflammatory and granulomatous lesions.

The most common differential diagnosis of gastric TB includes Crohn's disease, fungal infections, especially histoplasmosis and candidiasis, sarcoidosis, malignancy, parasites usually *Anisakis* sp., *Yersinia* infection and rarely *H. pylori* infection [17, 18]. The morphological pattern of the granulomas does not usually help in determining the cause except when on microscopy one could demonstrate foreign material, AFB, fungal spores or hyphae by doing special stains [20].

In sarcoidosis, granulomas are usually several, discrete, and may show Langhans type giant cells. However, Schaumann and asteroid bodies are not generally seen in gastric sarcoidosis. Gastric granulomas can be seen in 10–15% cases of Crohn's disease [21, 22]. About 30% to 70% of patients with Crohn's disease show focally enhanced gastritis with localized and intense lymphoplasmacytic, histiocytic and neutrophilic infiltrate with or without granulomas, and intervening uninvolved mucosa [23]. Focally enhanced gastritis is more frequently found in antral region than the body of the stomach. Concomitant involvement of ileum or colon helps to reach the diagnosis of Crohn's disease [22, 23].

Biopsies from the duodenal lesions usually show erosive mucosa along with mixed inflammation, lymphoid aggregate with multiple caseating or non-caseating epithelioid cell granulomas and langhans type of giant cells in the mucosa or submucosa of duodenal wall. ZN stain may show presence of acid-fast bacilli in the granulomas or necrotic material. Granulomas are in many instances located in the submucosa, therefore may be missed if the endoscopic biopsies are superficial. The regional lymph nodes usually show multiple granulomas with caseation necrosis and Langhans type giant cells [17, 24].

17.4 Ileo-cecal TB

Ileo-cecal region is the most common site for abdominal tuberculosis. Ileo-cecal region is affected in up to 75% of cases. The possible reasons for high ileocecal involvement predilection may be related to abundant lymphoid tissue (Payer's patches), a region with physiological stasis of intestinal contents, a neutral pH of the luminal surface, and transport mechanisms that could allow absorption of swallowed bacilli [25].

Gross Involved bowel wall in ileocecal TB on gross examination shows three morphological forms: ulcerative, ulcerohypertrophic, and hypertrophic [25, 26]. Resected specimens frequently reveal thickened bowel walls and the serosal surface may be studded with military nodules. The size of these nodules could be variable. Small bowel (ileum and jejunum) can show ulcers or strictures (due to fibrosis) and occasionally formation of entero-enteric fistulae. Colonic and ileocaecal lesions are usually ulcero-hypertrophic. The ulcers in ITB are superficial and the depth of ulcers does not extend usually beyond the muscularis propria [26]. The ulcers may be single or multiple, the later cases show presence of variable length of intervening

uninvolved mucosa [26]. These ulcers are often circumferential and oriented transversely, in contrast to the longitudinal or serpiginous ulcers of Crohn's disease [25, 26]. The mesenteric lymph nodes may be enlarged and can demonstrate caseation necrosis.

Microscopy Tuberculous granulomas, usually present just below the ulcer bed, initially in the lamina propria (Fig. 17.1) or the Peyer's patches. Granulomas, however, may be present in any of the layers of the gastrointestinal lumen. While the size of the granulomas is variable, these tend to be confluent and this serves as an important point of discrimination from Crohn's disease [25, 26]. The periphery of the granulomas may have infiltration by lymphocytes, plasma cells, and Langhans giant cells. Older lesions are commonly hyalinized; and show variable degrees of fibrosis and calcification. Granulomas can be observed in the wall of adjoining bowel.

The mass in the hypertrophic lesion is formed by the exuberant granulomatous tissue response extending from mucosa to the serosa. It is also contributed by the mesenteric fat, matted lymph nodes, fibrotic tissue, and hypertrophied muscularis propria [26]. Cicatricial healing of the circumferential ulcers often results in fibrotic stricture formation. Ischemia due to occlusive mesenteric arterial changes could also contribute to fibrosis and strictures. The endarteritis possibly explains the low frequency of massive gastrointestinal bleeding in tuberculosis [25, 26].

Often, the granulomas are demonstrable only in the lymph nodes while the serial section of the intestinal wall shows only nonspecific features [26]. Furthermore, in some cases granulomas may be noted only in some of the lymph nodes (Figs. 17.2 a and b). Healed granulomas may be noted in the lymph nodes which are characterized by granulomas being circumscribed by hyalinized tissue and subsequently completely replaced by it [25, 26].

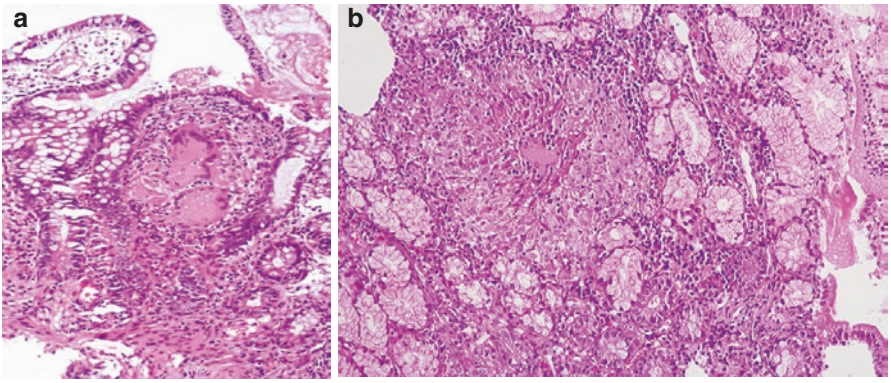

Fig. 17.1 Mucosal granulomas (**a**) Granuloma with Langhans giant cells in the superficial lamina propria (**b**) Granuloma with cental necrosis in deeper part of lamina propria with Brunner glands

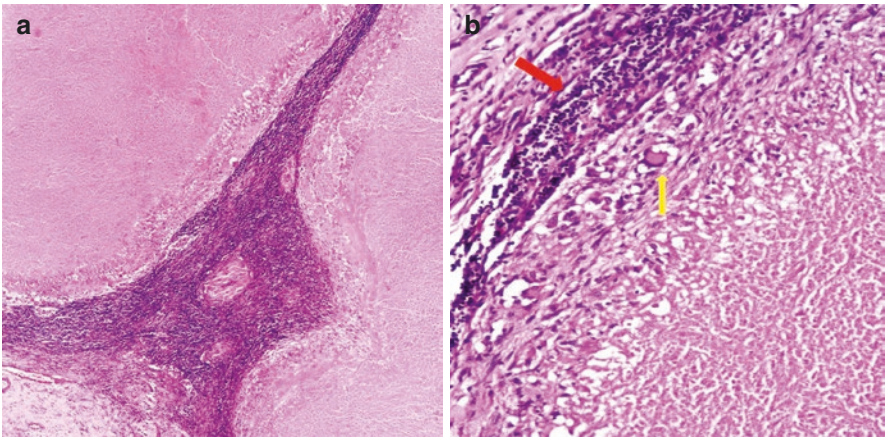

Fig. 17.2 Lymph nodal granuloma with extensive caseation necrosis (**a**) low power; (**b**) high power showing Langhans giant cell (yellow arrow) and residual lymphoid cells (orange arrow) at the periphery (hematoxylin and eosin)

The most common differential diagnosis of intestinal TB includes Crohn's disease, fungal infection, especially histoplasmosis, *Yersinia* infection, and rarely sarcoidosis [25, 26].

17.4.1 Differentiating Intestinal Tuberculosis from Crohn's Disease

Differentiating intestinal TB from Crohn's disease (CD) is both clinically and histologically challenging. On gross examination, the presence of left colonic disease, longitudinal ulcers, skip lesions, aphthous ulcers, cobblestoning favor CD, whereas the presence of patulous or incompetent ileocecal valve and cecal (right colonic) involvement, transverse or circumferential ulcers favor TB [6, 26, 27]. Presence of deep transmural cracks and fissures extending beyond submucosa favor CD while such lesions are uncommon (and superficial, if present) in TB [26–28].

On microscopic examination, ITB-related granulomas are large (> 200 μ), multiple, confluent and submucosal. They can also occur in any region of the gut wall and the presence of central caseation is considered diagnostic for intestinal TB (Figs. 17.3 and 17.4). Granulomas in CD are smaller (microgranuloma), discrete, ill-defined, scant, mucosal, and usually lack peripheral collar of lymphomononuclear cells [6]. Adjoining lymph nodes show granulomas with caseous necrosis in intestinal TB, whereas they are rare in CD and if present, they are small, discrete, and non-caseating [27]. Other features favoring CD include transmural inflammation with multiple lymphoid aggregations, basal lymphoplasmacytosis, fissures, widened submucosa with fibrosis, and neural hyperplasia [26, 28].

Some researchers consider that the presence of lymphocytic and granulomatous lymphangitis in small intestine biopsies is the fundamental alteration of CD and has a better specificity and sensitivity for the diagnosis [29, 30].In a meta-analysis, the

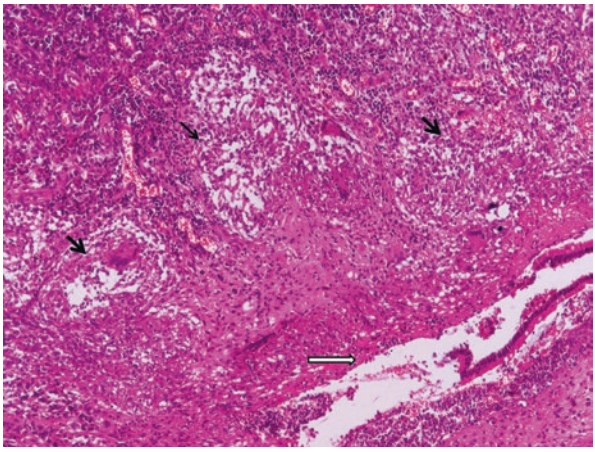

Fig. 17.3 Multiple confluent granulomas and Langhans giant cells (black arrows) with ulceration of the overlying mucosal lining epithelium (white arrow) (hematoxylin and eosin)

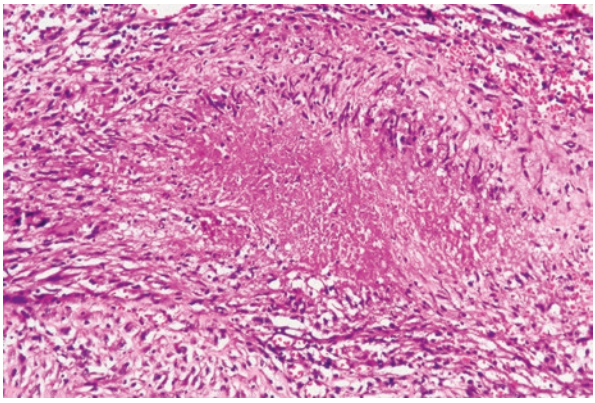

Fig. 17.4 Granuloma with central caseous necrosis (hematoxylin and eosin)

findings of caseating necrosis, confluent granuloma, and ulcer where the base is lined by histocytes had high specificity for the diagnosis of intestinal TB over CD although the sensitivity was low [30].

17.5 Abdominal Visceral TB

Isolated visceral involvement of abdominal organs by TB is uncommon, with 15 to 20% of all patients with abdominal tuberculosis experiencing it. The liver is the most commonly affected abdominal organ, followed by the spleen, pancreas, and gallbladder. Hematogenous or local spreads are the commonest modes of transmission. Concomitant pulmonary tuberculosis affects a small percentage of people [11, 31, 32].

17.5.1 Liver

Hepatobiliary TB is infrequent, accounting for just around 1% of all tuberculosis infections [6]. The most specific diagnostic test for hepatic TB is mycobacteria culture done on tissue obtained by liver biopsy. Hepatic tuberculosis patients may present with pyrexia of undetermined origin (PUO) and abnormal liver function tests (LFT); diagnosis is usually made on the histology and microbiological examination of the liver biopsy [32]. Manifestations of hepatic TB include pseudotumor-like lesions, tuberculous liver abscess, granulomatous hepatitis, and fulminant liver failure have all been documented, but fulminant liver failure is extremely unusual manifestation of hepatic TB [6, 33, 34].

Tuberculosis of the liver and biliary tract can occur alone or in combination with intestinal involvement, and it can also occur in the context of miliary tuberculosis. The liver could be engaged in two different ways. (a) In a subgroup of disseminated tuberculosis, the military type is distinguished by the involvement of the liver, with tubercules mostly affecting the hepatic lobules. (b) The localized type, on the other hand, is usually acquired from gastrointestinal infection and has larger hepatic lesions. Localized hepatic TB has been variably labelled as tuberculoma or pseudotumoral pattern. Hepatic abscess could potentially be a sign of hepatic tuberculosis with a confined form [6, 33, 34]. Miliary TB is responsible for majority of cases (approx. 80%), while local hepatic TB is responsible for the rest [35].

Microscopy Histopathological examination is used to provide a definitive diagnosis. Miliary hepatic TB causes widespread involvement of the hepatic lobules, with tubercles ranging in diameter from 0.6 to 2.0 mm. Tubercles larger than 2 mm in diameter, found near the portal tract, are typical of local hepatic tuberculosis [35]. Microscopically, there are epithelioid cell granulomas, Langhan's giant cells, reticulin framework disintegration, with a lymphocytic cuff. Large calcified tuberculomas can occur when these caseating granulomas consolidate. Large calcified tuberculomas are more common in the liver than in other TB-affected parts of the gastrointestinal system. Caseation and liquefaction necrosis of a tuberculoma can result in the formation of a tubercular abscess [36]. In portal tracts, lymphomononuclear cell infiltrates are frequent, as are portal fibrosis and hemosiderin pigmentation. Nonspecific fatty changes are often found adjacent to granulomas. Fatty liver in tuberculosis might be the result of malnutrition caused by the disease or tubercular toxemia, or it can be an innocent bystander. Hepatocytes in the surrounding areas may exhibit nonspecific alterations such as enlargement with sinusoidal compression, feathery or vacuolar degeneration, and vacuolated nuclei. Hepatocellular necrosis, hyperplasia of Kupffer cell, lymphocytic and histiocytic aggregates, periportal fibrosis, or portal inflammation are all unusual and nonspecific features. Patients with tuberculous abscess and liquified caseous material are more likely to test positive for AFB. Rarely, amyloid deposition can be observed [6, 33–37].

Differential diagnosis granulomatous hepatitis includes sarcoidosis, primary biliary cholengitis, drug-induced liver injury (DILI), and other infectious causes.

Differentiating between tuberculosis and sarcoidosis can be challenging at times, especially when only non-caseating epithelioid granuloma is present. Numerous, distinct, non-necrotizing, periportally distributed granulomas with a small rim of lymphocytes, and concentric hyalinized scars in old granulomas indicate sarcoid granuloma histopathologically. Tuberculous granulomas, on the other hand, exhibit caseation and a tendency to coalesce. There is no zonal preference for the localization of granulomas in hepatic TB [35–37]. The presence of TB elsewhere in the patient and regional lymph nodes can support a diagnosis of hepatic TB based on non-caseating granulomas on a liver biopsy.

Primary biliary cholengitis is an autoimmune disorder in which the small intrahepatic bile ducts are destroyed. Granulomas, which are found in the portal tracts, are often components of the florid duct lesion [35, 38]. Numerous drugs can elicit a granulomatous response, which can occur alone or in conjunction with hepatitis and/or cholestasis. Quinidine, hydralazine, and phenytoin are the most common drugs which cause granulomatous response. Granulomas are noncaseating and can be of variable sizes. They can be found in the liver parenchyma or the portal tracts. Langerhans giant cells are not often seen while eosinophils are commonly found [35, 38].

Other than tuberculosis, the most prevalent infectious causes are brucellosis, chlamydia, fungal infections, schistosomiasis, and leishmaniasis [38]. When a pathologist encounters granuloma in a liver biopsy, he or she should look at the morphology as well as the location of the granuloma, the presence or absence of necrosis, the type of any associated infiltration, and any other morphological clues in the rest of the liver biopsy. Special stains should be done for any organism or foreign material inside the granuloma [38].

17.5.2 Gall Bladder and Biliary TB

Gall bladder tuberculosis is a rare form of tuberculosis that can be isolated, accompanied by further intestinal involvement, or present as a complication of disseminated tuberculosis. Because the gallbladder is particularly resistant to tuberculosis, presumably due to the inhibitory role of bile, it is a less common location of abdominal TB. Gall bladder TB is frequently discovered histologically in individuals undergoing surgery for suspected cholecystitis or gallbladder malignancy. Symptoms of biliary colic or cholecystitis are the most typical signs of gallbladder TB. Biliary tuberculosis is also exceedingly uncommon and could result in biliary stricture or compression by enlarged tuberculous lymph nodes [6, 33].

Gross Cholecystectomy specimen may show gall stone, thickened wall, or rarely mass or sinus formation [39].

Microscopy Epithelioid cell granulomas (with or without necrosis) are seen in the subepithelium or serosal surface. There may be accompanied fibrosis or calcification.

17.5.3 Pancreatic TB

Pancreatic TB is a rare condition that can arise from primary pancreatic or peripancreatic lymph node involvement, be coupled with further intestinal involvement, or develop in the setting of disseminated tuberculosis. Clinically and radiologically, it could be mistaken for malignancy. In endemic tuberculous regions, the most prevalent cause of pancreatic mass is also a pancreatic malignancy; thus, pancreatic tuberculosis is usually identified after a Whipple's procedure for suspected pancreatic cancer. Ultrasound, EUS, or CT-guided FNAC may provide the diagnosis preoperatively in good number of cases. FNAC material may be used for making smears, ZN staining, culture, GeneXpert/RIF assay or PCR. Pancreatic TB manifests itself in 80 percent of patients as pancreatic masses [40]. Abdominal pain, fever, loss of weight or appetite, jaundice, biliary obstruction, abdominal lump, and other symptoms of pancreatic TB can occur [6, 33, 41].

Smears or sections may show epithelioid cell granulomas, Langerhans giant cells, and lymphocytic infiltrate with or without caseation necrosis under the microscope. A positive ZN stain for AFB is uncommon. Granulomas have been found in between 57 and 100% of patients [41]. Sarcoidosis, autoimmune pancreatitis, Crohn's disease, and other infectious disorders are some of the differentials for granulomatous pancreatitis.

17.6 Conclusion

Histopathology remains one of the most suitable methods for diagnosing abdominal TB. EUS guided FNA or biopsy has expanded the role of tissue diagnosis vastly, especially in the organs where biopsy was difficult or not possible. In tuberculosis endemic countries with financial constraints, endoscopy, and histopathological examination of the biopsy is the reliable mode of investigation and gold standard. TB should be considered in the differential diagnosis whenever the biopsy reveals granulomatous pathology.

Conflict of Interest None.

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Microbiological Diagnosis of Gastrointestinal Tuberculosis

18

Megha Sharma and Kusum Sharma

Key Points

1. For microbiological diagnosis, tissue samples achieved through multiple-site biopsies or fine-needle aspirations are most suitable.
2. ZN staining has poor sensitivity and culture takes too long to give a result.
3. Nucleic acid amplification tests offer higher sensitivity and rapid results:
   (a) Incorporating more than one gene target improves detection yield.
   (b) Commercial systems like GeneXpert allow simultaneous detection of rifampicin resistance.
   (c) LAMP can be used as an alternative method for resource-limited settings.

18.1 Introduction

Tuberculosis is a perilous disease with a potential to involve any organ of the human body [1]. The risk factors range over a wide spectrum, from malnourished poverty-struck overcrowded populations to immunocompromised people living with HIV/AIDS (PLHA) to other vulnerable populations rendered immunosuppressed secondary to advanced critical care and transplant facilities; thereby increasing the incidence of TB in both immunocompetent and immunosuppressed populations [2, 3]. The primary site of infection is mostly pulmonary from where the tubercular bacilli spread to other organs causing extrapulmonary tuberculosis (EPTB). Nearly 20% of all cases of TB, that is one in every five patients, has EPTB [4]. Abdominal

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tuberculosis (ATB) constitutes approximately 10% of all EPTB cases [3]. However, with a mortality ranging from 8% to as high as 50% in untreated patients, [3] it is pertinent that timely and accurate diagnosis is made so that the antitubercular therapy (ATT) is initiated on time. Further, ATB is the second most common cause of small intestine perforation in India [5]. Hence, prompt diagnosis of ATB is crucial for preventing the associated morbidity and mortality.

The tubercular bacilli reach the abdomen via several routes: hematogenous spread, ingestion of sputum containing bacilli, direct spread from draining lymph nodes, and contiguous organs like fallopian tubes [5]. The clinical presentations of ATB are varied and often protean, mimicking with several other infectious and non-infectious diseases of the digestive system [6]. Broadly, ATB can be anatomically divided into four types: gastrointestinal, solid visceral organ, peritoneal, and lymphadenopathy [7]. The clinical signs, endoscopic features, radiological findings, and laboratory investigations overlap with other disease conditions and hence inadequate in forming a reliable diagnosis of ATB [8]. World Health Organization (WHO) advises against the use of interferon-gamma release assays and tuberculin skin test for the diagnosis of active TB in low- and middle-income countries [9]. Histopathological findings of caseous necrosis with acid-fast bacilli are hallmark for ATB but they are seen only in 13–30% of cases [10]. The differentiation becomes very important in conditions like Crohn's disease, ulcerative colitis, and carcinoma of the abdomen as the treatment differs remarkably and can prove counterproductive [11]. Hence, microbiological diagnostic algorithm is essential for diagnosis of ATB.

18.2 Samples to Be Sent for Microbiological Investigations

The diagnostic yield depends upon the quality of sample collected for microbiological investigations, which in cases of ATB, is often limited by the invasiveness of the procedure and the risk involved. A tissue biopsy, obtained through endoscopy, colonoscopy, laparoscopy, laparotomy, and even percutaneously, forms the most important sample type for detecting *Mycobacterium tuberculosis* [12]. Ascitic fluid, though easiest to obtain, does not contribute much as it has poor sensitivity to culture. Early laparoscopy along with suggestive histological features on biopsy can help form a diagnosis of ATB in absence of lung involvement. Though nearly any site from the anatomical classification can get involved in ATB, it is the ileocecal region that has the maximum predilection [7].

Fine needle aspirates (FNA) are also useful for microbiological investigations. They are less invasive and can be carried out in resource-limited settings also. FNA cytology was found to be a rapid, reliable, and inexpensive method for diagnosis of ATB in a large series of 92 cases from India [13]. FNA along with acid-fast stain and polymerase chain reaction served as important tools in diagnosing ATB among HIV-positive children of South Africa [14]. An increase in the yield of detection is obtained when multiple biopsy/FNA samples are obtained from different sites of the lesion [15].

18.3 Microbiological Investigations

18.3.1 Conventional Techniques

18.3.1.1 Microscopy for Visualizing *M. tuberculosis*

Microscopy is the most rapid diagnostic tool, but has poor sensitivity. In ideal settings, a Ziehl-Neelsen stain showing the acid-fast bacilli can give the diagnosis of ATB within a single day. Analytical sensitivity for a smear to be positive is 10,000 bacilli/ml of sample. Being paucibacillary condition, only a fraction of samples are positive on smear microscopy The sensitivity of AFB smear varies between 10 and 30% of culture-positive samples, that too in severely immunocompromised patients where the bacterial load is expected to be high [12]. Auramine staining can facilitate the detection of tubercular bacilli against a black background, but it requires a fluorescent microscope and an experienced observer. Microscopy can be improved significantly by incorporating immunohistochemical stains for visualizing tubercle bacilli. MPT64 is a common antigen used for immunostaining as it is specific for *M. tuberculosis* complex. In a study evaluating histological specimens suspected of ATB, immunostaining based on MPT64 could identify 75% of the samples while ZN staining was positive in none [16]. In another study evaluating tubercular lymphadenitis from FNA samples, 96% of cases were positive by 38-kDa tubercular antigen while only 40% were positive by ZN staining [17]. Caution is advised as 11% of cases from non-TB control were positive by MPT64 immunostaining, [16] the false-positivity arising due to various technical factors.

18.3.1.2 Culture for *M. tuberculosis* Isolation

Culture remains the ultimate gold standard for diagnosing any form of tuberculosis, including ATB. Analytical sensitivity for culture to be positive is 10–100 live bacilli/ml of sample. Isolation of the organism in culture from an otherwise sterile site proves the disease causation and also provides an opportunity for phenotypic drug susceptibility testing, thus being crucial for patient management [18]. Three types of culture media are available for *M. tuberculosis*: the traditional egg-based Lowenstein-Jensen (LJ) medium, agar-based Middlebrook 7H10 or 7H11, and liquid-based (Middlebrook 7H12 and commercially-available broths). The colonies of *M. tuberculosis* on LJ medium are classically described as rough, buff, and tough owing to their rugged surface, light brownish pale color, and hard consistency causing difficulty in picking. The yield of culture on LJ medium is poor, ranging from 6% to 48% [18]. It takes anywhere between 2 and 8 weeks for colonies to show on culture, an inevitable delay that makes the test unsuitable for clinical decision-making. An evaluation of different culture methods on extrapulmonary samples showed that agar-based Middlebrook 7H10 had the least yield of detection (39%), LJ culture had 44% while liquid-based commercial broth had the highest yield of detection 51% [19]. Further, the time to detection was 26 days in first two, while it was half (13 days) for commercial broth [19]. Important examples of commercial broth-based culture techniques include radiometric BACTEC 460 system and MGIT BACTEC 960 systems, both developed by Becton Dickinson, NY, USA. The

BACTEC system is based on the detection of radioactive carbon dioxide generated by the growing microorganisms from palmitic acid substrate. The Mycobacterial Growth Indicator Tube (MGIT), on the other hand, is based on the fluorometric observation of the growth of *M. tuberculosis* and its susceptibility to select drugs like rifampicin, isoniazid, streptomycin, and ethambutol. The MGIT system has several advantages: radiation-free, eliminates loading and unloading of tubes; automated continuous monitoring of tubes thereby preventing cross-contamination; non-dependency on carbon dioxide tanks. The MGIT has become the most favored method of mycobacterial culture for ATB [20].

18.3.2 Proteomics for Diagnosing ATB

Proteomics has been used in two different ways for the diagnosis of ATB–detection of the organism (*M. tuberculosis*) and differentiation of ATB from Crohn's disease. Colonies obtained on solid or liquid culture can be processed and plated onto the target plate for evaluation using matrix-assisted laser desorption ionization time-of-flight mass spectrometry (MALDI-TOF MS). The MALDI TOF MS works on the principle of ionizing proteins from the given sample/organism and then allowing their movement across a vacuum tube on the basis of their mass-to-charge ratio. These molecule signals are collected on the other end of the vacuum where they are converted into peaks of different intensities depending upon their mass and charge. A summation of such peaks forms a spectrum from the sample/organism which is then matched with the in-built or in-house database, thus allowing rapid detection. MALDI-TOF MS has been used not only for the detection of *M. tuberculosis* but also for differentiating *M. tuberculosis* from other non-tubercular mycobacteria from cultures [21]. Also, protein profiling from serum proteins has been successfully used to differentiate ATB from Crohn's disease [22]. MALDI TOF MS, however, is a costly equipment and limited to tertiary care settings.

18.3.3 Molecular Diagnosis of ATB

Advances in molecular biology have revolutionized the diagnosis of tuberculosis, including ATB [23]. Molecular methods offer the advantages of rapid detection of nucleic acid of *M. tuberculosis* with a much higher sensitivity than conventional methods, reaching theoretically to a single cell of *M. tuberculosis*. Unlike conventional culture techniques, nucleic acid amplification tests (NAAT) provide result within hours. Further, few of them also offer the extra advantage of detection of resistance to first-line ATT drugs like rifampicin and isoniazid. NAATs, however, suffer from the disadvantage of amplifying DNA from even the dead bacilli. They can be useful in forming a diagnosis of ATB in presence of other circumstantial evidence based on clinical, endoscopic, and radiological features. mRNA-based

NAAT can, however, differentiate between live and dead bacilli and can be used to diagnose active disease and response to therapy.

18.3.3.1 Conventional Polymerase Chain Reaction

Several polymerase chain reaction (PCR) methods have been developed for amplifying and detecting the nucleic acid of *M. tuberculosis* from abdominal samples. A particular gene from the genome of the *M. tuberculosis* complex is identified and primers consisting of ATCG codons are designed against that gene. Then, in the presence of specific temperature and buffer conditions, the double-stranded DNA of *M. tuberculosis* is first denatured to separate out the two strands, followed by amplification with the help of Taq polymerase leading to an exponential increase in the copies of that particular DNA fragment. The reaction is finally stopped by changing the temperature conditions. The amplified product is added onto specific wells and visualized as bands on 2% agarose gel electrophoresis. The molecular marker serves as an indicator of the base pair size of the band, thus aiding in identification and differentiation from nonspecific bands if any. The yield of detection depends on several factors, adequacy of sample, bacterial load, gene targets used, population studied, chemistry used, etc. IS6110, the insertion sequence present in 1–25 copies in the genome of *M. tuberculosis* is the favored gene target used in PCR, however, 10–40% of Indian isolates of *M. tuberculosis* may have only a few or no copies of IS6110 at all [24]. Another multicopy gene is IS1081, which is present in all *M. tuberculosis* isolates. MPB64 is another commonly used gene target that is highly specific to *M. tuberculosis* complex. The reported sensitivity of PCR for diagnosing ATB by IS6110 was 70% and that by MPB64 was 75% [25].

18.3.3.2 Multiplex PCR

Combining more than one gene targets, in a multiplexed format increase the sensitivity of detection. In this technique, primer pairs for more than one gene of interest are put into the same reaction tube and get amplified simultaneously. They are visualized as two bands of different base pair sizes arising from the same well. Several multiplex combinations have been evaluated for EPTB but data regarding ATB is limited. A multiplex involving IS6110 and MPB64 had a sensitivity of 77.5% in diagnosing ATB [25]. Multiplex involving IS6110, MPB64, and protein B had a sensitivity, specificity, positive predictive value, and negative predictive value of 87.5%, 100%, 100%, and 86.2%, respectively [10]. Another multiplex PCR involving IS6110, 16SrRNA, and devR had a sensitivity, specificity, positive predictive value, and negative predictive value of 87.5%, 96.4%, 94.6%, and 91.5%, respectively, for intestinal TB and 75.7%, 100%, 100%, and 85.7%, respectively, for peritoneal TB [26].

18.3.3.3 Nested PCR

Nested PCR aims to increase the sensitivity and specificity of detection by performing two sets of PCR reactions wherein the amplified product from the first reaction

serves as the template for the second. Nested PCR using IS6110 gene has been used to detect four cases of tubercular fistula-in-ano, which had granulomatous inflammation but no acid-fast bacilli [27].

18.3.3.4 Real-time PCR

Real-time PCR, as the name suggests, allows assessment of the ongoing amplification in real time. Unlike conventional PCR where the result whether amplification has taken place or not can only be seen after the completion of entire reaction and running the amplified product on gel, in real-time PCR the amplification can be visualized from the beginning to the end in the form of a graphical representation. There is no need for end point processing of amplified product thereby decreasing the chances of contamination and second step of gel electrophoresis. The result is presented as cycle threshold (Ct value), which can be extrapolated to calculate the quantitative bacterial load in the sample. However, it requires more sophisticated equipment and costly reagents than conventional PCR. Real-time assay using fluorescent resonance energy transfer hybridization has been used in ATB wherein 36% cases with clinical and radiological suspicion of TB were detected which were missed on culture and acid-fast staining [28].

18.3.3.5 Loop-mediated Isothermal Amplification

First described in 2009, loop-mediated isothermal amplification (LAMP) is a relatively new amplification technique [29]. As the name suggests, the major difference in this NAAT is that the amplification is achieved at a single uniform temperature without the need of changing temperature for each amplification cycle. Since amplification occurs isothermally, there is no requirement for sophisticated thermocycler equipment and battery operated water bath can also be used for amplification. This makes it highly suitable for resource-limited settings wherein continuous electricity supply is not available. There are specifically designed primers for LAMP, used either as two or three pairs, with one pair of sets working as loop primers. This amplification reaction requires Bst Taq polymerase. The amplified product can be easily visualized by turbidity in the tube and by apple-green fluorescence obtained by adding SYBRgreen fluorescent dye. The strategically placed primers also increase the sensitivity of detection when used in LAMP format as compared to simple PCR despite using the same gene target. The result is obtained in 60–90 min, unlike PCR where 3–4 h are required. The LAMP assay is also much less technically demanding and inexpensive. More than one gene targets, used in a separate reaction mix, can be also be used and a combination of IS6110 and MPB64 had a sensitivity and specificity of 100% and 100%, respectively, for diagnosing confirmed (culture positive) ATB and 95.7% and 100%, respectively, in diagnosing clinically suspected (culture/smear negative) cases of ATB [30].

18.3.3.6 GeneXpert MTB/Rif Assay

The Xpert MTB/rif assay was endorsed by WHO in 2010 as a rapid test for diagnosing tuberculosis. It has a turn-around time of 2 h and simultaneously detects not only the presence of *M. tuberculosis* but also resistance to rifampicin. Its limit of

detection is reported to be 131 CFU/ml (in spiked sputum sample). The semiautomated system enables working by minimally trained staff and the closed cartridge-based system prevents cross-contamination. Xpert MTB/rif assay uses real-time chemistry to amplify rpoB gene for detection of *M. tuberculosis* and five unique overlapping probes to detect the commonly reported mutations in rpoB gene that confer rifampicin resistance. Positive results by Xpert assay can rapidly identify tuberculosis but a negative result does not rule out tuberculosis. The disadvantages of Xpert MTB/rif assay are that it requires a continuous electricity supply and it does not detect resistance arising due to mutations other than the 81 bp region of rpoB gene it screens. Another important disadvantage is the reporting of false rifampicin resistance [31]. It is an expensive test (~$10/test) although it is being provided free of cost by health authorities at certain places. Xpert MTB/rif assay has shown a sensitivity of 70% in comparison to MGIT culture when evaluated on ascitic fluid samples for diagnosing ATB [32]. In a recent meta-analysis, the sensitivity of Xpert Mtb/Rif (in ascites) for diagnosis of peritoneal TB was 30% and for intestinal tuberculosis (on intestinal tissue) was 23% when compared to composite reference [33].

Table 18.1 summarizes the pros and cons of various tests for diagnosis of abdominal tuberculosis.

18.3.3.7 GeneXpert Ultra MTB/Rif Assay

The Xpert Ultra is the next generation of Xpert assay [34]. It has an increased sensitivity of detection with a limit of detection of 16 CFU/ml, thus reaching very near to culture itself. It incorporates two multicopy genes IS6110 and IS1081 for the detection of *M. tuberculosis* and rpoB gene for rifampicin resistance. The greater cartridge volume enables a larger volume of sample, thus increasing yield of detection. The amplification chemistry has also been changed from real-time in Xpert to high-resolution melt curve analysis in Xpert ultra. The real-time chemistry used in Xpert detected rifampicin resistance by absence of binding of specific DNA probes targeting the 81-bp region of rpoB gene; and was hence prone to error due to non-binding of probe in low bacterial load setting. The change of chemistry allows to detect even small fractions of rpoB gene. WHO has released guidelines for the use of Xpert Ultra as the first-line test in TB diagnosis as a replacement for Xpert [35]. The present literature lacks any study in which Xpert ultra has been evaluated for specific diagnosis of ATB and future studies are needed to evaluate its actual performance in these patients.

18.3.3.8 MTBDRplus Assay or Line Probe Assay

MTBDRplus is another commercially available diagnostic platform for tuberculosis. It makes the amplified product run on a strip on which probes for detecting *M. tuberculosis* DNA as well as common sites of mutations for rifampicin on rpoB gene and isoniazid on inhA gene are already incorporated. If the sample contains tubercle bacilli and/or resistance to the two drugs, the respective probes hybridize with the amplified DNA and appear as specific bands on the strip. The line patterns so obtained help to decipher whether *M. tuberculosis* is present or not and whether resistance to rifampicin and/or isoniazid is present or not. The advantage is that

Table 18.1 Summary of benefit and limitations of various techniques for diagnosis of abdominal tuberculosis

	Benefits	Limitations	Sensitivity	Specificity	Any other comments
Staining techniques					
ZN Stain	High specificity, available at microscopic centers	Low sensitivity, technical and observer subjectivity	10–30%	High ~95%	Better yield in homogenized tissue sample rather than ascitic fluid
Auramine	Easier visualization against dark background, relatively rapid than ZN	Needs fluorescent microscope, special staining, trained personnel	15–40%	Moderate 70–90%	Artifacts also take up the fluorescent dye and need to be differentiated
Antigen detection					
MPT 64 immunostaining	Differentiates Mtb from NTM	Costly, technically demanding	75%	89%	Artifacts need to be carefully differentiated
Culture methods					
LJ method	Pure colony, can be subjected to further tests	Lengthy procedure	6–48%	High >95%	Need infrastructure and biosafety measures
MGIT	Relatively rapid culture method	Cannot achieve pure colony	15–50%	High >95%	Can be used for automated phenotypic DST
PCR based					
IS6110	Multicopy gene	10–40% north Indian population may lack or have single copy	70%	100%	Most common gene target used for Mtb
MPB64	Specific for MTB complex	Cannot differentiate species within the complex	75%	100%	Single copy gene
Multiplex	Increased yield of detection	Needs standardization	75–87%	96–100%	Simultaneous targeting more than one gene increases chances of detection

(continued)

Table 18.1 (continued)

	Benefits	Limitations	Sensitivity	Specificity	Any other comments
Xpert Mtb/Rif	Commercially available automated system, simultaneous detection of rifampicin resistance	Need continuous power supply, expensive cartridge	8–70%	100%	Sensitivity varies greatly depending upon the sample type
LAMP	Useful for resource-limited centers, minimal cost involved	No detection of rifampicin resistance	97% (for multi-targeted)	100%	Isothermal amplification can be done on battery operated water bath

simultaneous detection of both the organism and resistance to two drugs can be made, thus improving the management in endemic areas with substantial rates of drug resistance. The disadvantages are that stringent conditions are required for each step of extraction of nucleic acid, amplification, and hybridization with well-demarcated physically separated working areas to prevent cross-contamination. It is costlier than Xpert assay as well with an estimated $22/test. The turn-around time of MTBDRplus is around 24 h. False rifampicin resistance has been reported with MTBDRplus assay also [31]. Currently, no study has yet evaluated MTBDRplus assay on samples from cases of suspected ATB. It is recommended either from cDNA extracted from positive MTB culture or from samples that are positive for AFB.

18.3.3.9 Gene Sequencing

Sequencing is the molecular gold standard for diagnosing any microorganism. The amplified nucleic acid is subjected to another set of PCR and the product is matched with the in-built freely available global databases. Sequencing deciphers each and every codon sequence of the amplified product and matches long lengths of such sequences with online databases, giving a score of >99% for perfect matching. Gene sequencing is the final confirmation of resistance arising due to gene mutations as sequencing can specify the codon at which mutation took place and also the kind of mutation. It is advocated that samples reported rifampicin-resistant by Xpert assay or MTBDRplus assay should be confirmed by rpoB gene sequencing as false-rifampicin resistance has been reported with these techniques. Multiplex PCR can also be combined with rpoB gene sequencing as a relatively cheap and foolproof method of detecting *M. tuberculosis* with high sensitivity and detecting rifampicin resistance also [31]. Gene sequencing, however, is a technically demanding process requiring highly sophisticated equipment.

18.3.4 Typing of *M. tuberculosis*

Whole genome sequencing is the latest technology by which the entire genome of *M. tuberculosis* can be decoded to obtain relevant information about the strain, its virulence factors, pathogenesis determinants, resistance profile, and lineage. 24-loci Mycobacterial Interspersed Repetitive Units-Variable Number of Tandem Repeats (MIRU-VNTR) analysis is also a recommended method for detecting the lineage of *M. tuberculosis*. The common lineages of *M. tuberculosis* are Central Asian family (CAS-type), East African India (EAI), Beijing, Haarlem, and T-type. The knowledge of these lineages is important because they are geographically variable and have different susceptibility profiles, with Beijing genotype being the most resistant and CAS being the most predominant [36].

18.3.5 Drug Susceptibility Testing (DST) for ATB

Drug susceptibility for *M. tuberculosis* for first and second-line ATT can be carried out either by phenotypic or genotypic methods. The phenotypic method remains the gold standard for DST. DST on solid culture medium can be performed by the proportion method, the absolute concentration method, or the resistant ratio method. The proportion method is the most preferred one among conventional methods, but the absolute concentration method is also commonly used as it is simpler in terms of preparation of inoculation and reading of results [37].

In order to shorten the turnaround time, DST can be performed in liquid broth using commercially available MGIT SIRE tubes. Precoated 96-well microtiter plates are also commercially available for carrying out susceptibility of first- and second-line ATT drugs. Molecular DST can be carried out by detecting specific gene mutations using different molecular platforms like gene sequencing, GeneXpert MTB/Rif assay, or MTBDRplus assay.

Conflict of Interest None.

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Endoscopic Ultrasound for Gastrointestinal Tuberculosis

19

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Abbreviations

AFB	Acid-fast bacilli
AT	Abdominal tuberculosis
ATT	Anti-tubercular treatment
CE-EUS	Contrast-enhanced EUS
CH-EUS	Contrast-enhanced harmonic EUS
ET	Esophageal tuberculosis
EUS	Endoscopic ultrasound
EUS-E	EUS elastography
EUS-FNA	Endoscopic Ultrasound-guided Fine needle aspiration
EUS-FNB	Endoscopic Ultrasound-guided Fine needle biopsy
LN	Lymph node
PUO	Pyrexia of unknown origin
SMTs	Submucosal tumours
SOL	Space occupying lesion
ZN	Ziehl-Neelsen

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Key Points

1. Endoscopic ultrasound is a tried and tested tool in the diagnosis of most abdominal structures involved by tuberculosis (TB) like lymph nodes and solid viscera (pancreas, liver, spleen).
2. EUS is also documented as case reports for diagnosis of TB of peritoneum and gastrointestinal tract.
3. EUS can serve as follow-up modality for defining response rather than CT as it avoids radiation and the need for contrast.
4. Endoscopic Ultrasound Fine needle aspiration (EUS-FNA) is a safe as well as feasible in difficult situations also like sub-centemetric lymph nodes, lymph nodes at difficult locations, in the presence of liver cirrhosis and collaterals.
5. Role of elastography and contrast harmonics during EUS need to be studied in abdominal TB.

Abdominal tuberculosis (AT) can involve each and every structure in the abdomen, i.e. peritoneum, ascitic fluid, solid viscera, intestine and lymph nodes. There is a fair degree of challenge in making of diagnosis of AT and the diagnosis is often delayed. Role of anti-tubercular treatment (ATT) therapeutic trial based on clinical suspicion alone can have adverse consequences including hepatitis and acute liver failure, should be avoided. There are many reasons for significant delay in diagnosis: (a) there are no characteristic signs or symptoms specific to AT (b) need to do a battery of tests, few of which are costly as well as not available widely, (c) low yield of cytopathology/histopathology and microbiology and (d) also location of target tissue remains a challenge to get adequate tissue for proper diagnosis.

Endoscopic ultrasound (EUS) is a very important tool in the diagnosis of AT, as most of the abdominal structures are accessible for tissue acquisition except for a limited role in luminal tuberculosis. There are some typical diagnostic features on EUS suggestive of tuberculosis, however, it is always advisable to get tissue if feasible. TB is diagnosed on basis of presence of caseating granuloma on microscopy with either acid-fast bacilli (AFB) positivity on Ziehl-Neelsen (ZN) stain or positive geneXpert or TB-PCR or a positive culture for mycobacteria. EUS can also be used as a good modality for treatment response on follow-up.

We shall discuss the role of EUS in diagnosis of abdominal TB in the following locations:

1. Lymph nodes
2. Solid organs
3. Gastrointestinal lumen and sub-epithelial lesion
4. Peritoneum

19.1 Lymph Nodes

Lymphadenopathy can occur due to benign as well as malignant causes. Benign aetiologies include tuberculosis, histoplasmosis and reactive enlargement, while malignant causes are lymphoma and metastatic carcinoma. Intraabdominal lymph nodes are invariably involved in tuberculosis; either with primary organs or even without.

There are three ways to examine abdominal lymph nodes. Examination below gastro-oesophageal junction is useful to study porta/peri-pancreatic nodes, and celiac/para-aortic nodes while the examination from antrum of the stomach and first part of duodenum are useful in peri-pancreatic and porta lymph nodes. Examination from the second part of duodenum helps to evaluate portocaval and aorto-caval/para-aortic lymph nodes [1].

There is some checklist of finding we should document during EUS, these include location of lymph nodes, size, shape, echogenicity, margin, discrete or matted appearance and presence or absence of necrosis and calcification should be noted during EUS examination. EUS-FNA should be performed from the largest and hypoechoic node and it should be most accessible, via either trans-gastric or trans-duodenal route (Fig. 19.1a, b). In a patient with lymph nodes enlargement or lymphadenopathy; the first step is to differentiate between benign and malignant disease in absence of primary. Then we need to identify tuberculosis among benign causes. Morphology alone is suggestive but not confirmatory, and cytopathology or histopathology should be obtained. In a study by Catalano et al., lymph node size of more than 1 cm, round or oval shape with well-defined margins and hypoechoic in nature were suggestive for the presence of malignancy [2]. Sometimes, however, these criteria can be manifested by benign lymph nodes whereas malignant nodes may not fulfil all these criteria. Therefore, it is better to take tissue for diagnosis.

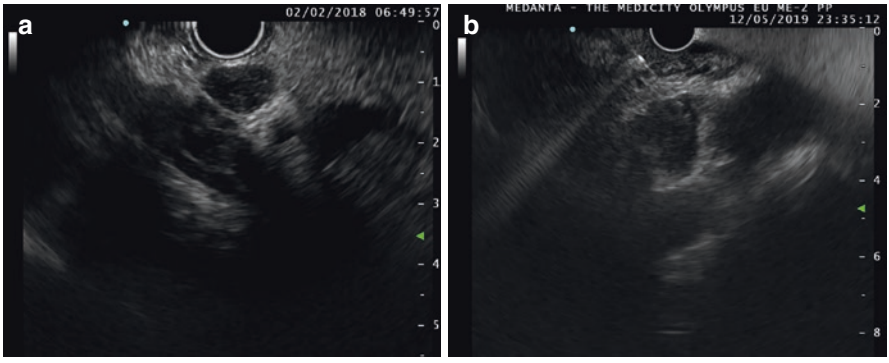

Fig. 19.1 (**a**) Linear EUS image of enlarged, well-demarcated, hypoechoic porta lymph node in a patient with TB. (**b**) Linear EUS image showing hypoechoic enlarged tubercular aorto-caval lymph nodes with areas of necrosis and FNA needle in situ

Role of elastography and contrast EUS is mainly for malignant disease, role in TB is not studied.

As discussed earlier, TB is diagnosed on the basis of presence of caseating granuloma on microscopy with either AFB positivity on ZN stain or positive culture for mycobacteria or positive geneXpert or TB-PCR. In the absence of AFB/geneXpert or negative culture, a positive case can be diagnosed in presence of necrosis and granuloma on microscopy, and a good clinical response to ATT. Granulomas are present in histoplasmosis also, along with presence of caseating necrosis, however, small intracellular budding yeast cells present in macrophages on Gomori methenamine silver stain can differentiate it from tuberculosis [3].

EUS FNA from lymph node is quite sensitive and specific diagnostic modalities. In a recent systemic review and meta-analysis involving 774 patients with abdominal lymphadenopathy, Li et al. showed a pooled sensitivity and specificity of 94% (95% CI: 91% to 96%) and 98% (95% CI: 96% to 99%), respectively [4]. Generally, one or more groups of lymph nodes are involved but sometimes a single lymph node is enlarged alone. We need to target more pathological lymph nodes for EUS-FNA. In a study of 477 patients with abdominal nodes where EUS-FNA was performed, the distribution was taken peri-portal nodes in 184 cases followed by retroperitoneal nodes in 166 patients followed by celiac axis nodes in 106 cases and peri-pancreatic nodes in 21 cases [3]**.** Bodh et al. showed features to differentiate between TB and reactive lymph nodes. They showed that EUS morphological features including larger size, hypoechoic nodes with calcification, well-defined borders, conglomerated nodes and purulent aspiration as well as cytopathological features of presence of necrosis and or granulomas are suggestive of TB [5]. We should also target sub-centimetric lymph nodes (defined as <10 mm in size along short axis), which are though presumed benign, but maybe pathologic as shown by Choudhary et al. [6]. In patients with liver cirrhosis also, EUSFNA can be done safely and it also modified management significantly [7]**.** EUS FNA also proved its worth in patients with hepatocellular carcinoma and lymphadenopathy, as it detected metastatic disease hence avoided liver transplantation in thirty-three percent of the patients in that study [8], at the same time, some of the lymph nodes were proven to be tubercular and liver transplantation could be done after treatment of tuberculosis.

EUS image enhancement techniques (EUS-elastography and contrast-enhanced/harmonic EUS) have also been studied to differentiate between malignant and benign lymph nodes, however, role in tubercular lymphadenopathy is unclear. EUS elastography (EUS-E) displays tissue stiffness or hardness with a specific colour scale in which blue represents stiffer and more suggestive of malignant in comparison to green colour. So, EUS-E could be used as a targeting method for EUS-FNA to increase the accuracy and reduce the number of needle passes. Xu W et al. published a meta-analysis which reported sensitivity and specificity of EUS-E for the differentiation of benign and malignant lymph nodes was 88% (95% CI, 0.83–0.92) and was 85% (95% CI, 0.79–0.89), respectively [9].

In a meta-analysis by Lisotti A et al., four studies (336 patients) were included with a sensitivity of 82.1% (75.1–87.7%) and specificity of 90.7% (85.9–94.3%). On sub-group analysis, CH-EUS (two studies, 177 LNs) showed a pooled

sensitivity of 87.7% (77.0–93.9%) and specificity of 91.8% (84.5–96.4%). So, CH-EUS should have a role in the diagnostic algorithm [10]. Thus, EUS FNA along with EUS-elastography and contrast-enhanced/harmonic EUS is a promising tool to improve the overall diagnostic accuracy, however, role needs to be studied in TB.

19.2 Solid Organs

19.2.1 Pancreas

The pancreas is less commonly affected by abdominal TB. Possible reasons for rarity of this infection are: pancreas is a retroperitoneal structure, which is minimally affected by direct environmental exposure. Pancreatic enzymes like lipases, DNAses and others have anti-mycobacterial properties [11–13]. Recently, there are few evidence in terms of case reports as well as case series of tuberculosis of pancreas in both immunocompromised as well as immunocompetent patients. Pancreatic tuberculosis is increasingly diagnosed nowadays because of the availability of effective imaging methods, especially CT. EUS FNA also has good sensitivity to get adequate specimens [14]. Generally, it is a part of abdominal TB but isolated pancreatic/peri-pancreatic TB is also reported in literature. Previously, Auerbach et al. [15] and Bhansali et al. [16] reported pancreatic involvements in only 4.7% and in 0% of patients, respectively, in autopsy series. However, Panic et al. recently published a systemic review that includes 116 studies reporting data on 166 patients [14].

Pancreatic TB sometimes present as a pancreatic space-occupying lesion and is often misdiagnosed. So, it is essential to diagnose pancreatic TB infection well before time as well as to start treatment, so that risk involved with surgical procedures can be minimized [17]. In the systematic review by Panic et al. [14] more than 50% of the patients were males and Asian. Mean age of diagnosis was 41.61+/−13.95 years. Around one-fourth of cases had Human Immunodeficiency Virus (HIV) infection. Peripancreatic lymph nodes were the most frequent site of extra-pancreatic TB involvement and involved around half of the cases. Laparotomy was done in more than half of patients (55.2%) while EUS-FNA/B was done in 21.08%. Though this was a comprehensive analysis, but lots of studies were excluded [18–23]. Verma et al. [24], highlighted a dilemma about the unavailability of guidelines regarding monitoring for the ATT response. Monitoring using imaging like USG or CT has been described in literature, however, EUS can be a good and safe tool for follow-up.

Pancreatic TB can mimic as a pancreatic tumour on clinical and radiographic images, hence most of the time diagnosis of pancreatic/peri-pancreatic tuberculosis is a clinical dilemma and required surgical exploration. Even on EUS, pancreatic TB is not distinguishable from pancreatic malignancy. In an Indian study of 6 patients with isolated pancreatic head tuberculosis, were compared with 25 patients with pancreatic head malignancy in terms of EUS finding and found that both diseases had similar EUS characteristics. However, a significant finding in terms of pancreatic duct was noted as it was dilated in 80% with pancreatic adenocarcinoma

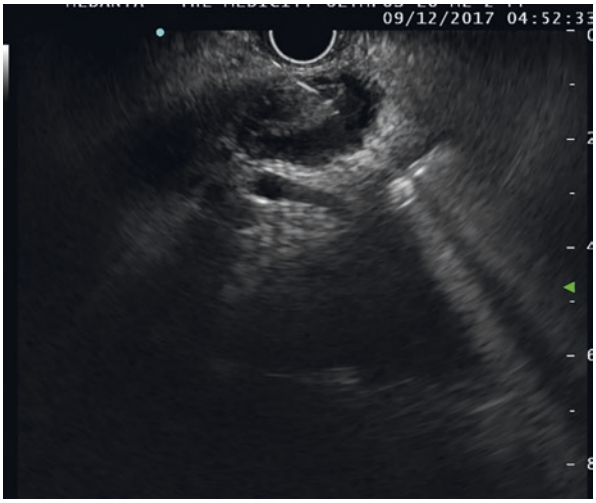

Fig. 19.2 EUS image of hypoechoic, well-defined, pancreatic mass with evidence of FNA needle in patient with TB

while it was dilated in 16% of patients with pancreatic tuberculosis ($P < 0.05$). Complete resolutions of cholestatic symptoms were documented in all 6 patients within one month of initiating ATT [25].

EUS with FNA has proven as an impressive modality to characterize as well as to get a sample from pancreatic lesions as it is quite sensitive and specific (Fig. 19.2). EUS-FNA is the preferred diagnostic modality for pancreatic masses as recommended by the American Joint Commission on Cancer [26]. EUS features of pancreatic tuberculosis are variable but may include peripancreatic lymph nodes, pancreatic masses or cystic lesions [17]. EUS-FNA sampling of pancreatic tissue for ZN staining, cytology, culture and sensitivity are required to establishing the diagnosis of pancreatic TB [25–27]. Caseation necrosis, granuloma and presence of AFB documented on microscopy are characteristic features for TB, however, bacteriological confirmation is quite rare [28]. EUS is also can be used a follow-up imaging for treatment response.

19.2.2 Adrenal

Enlargement of adrenal can occur due to benign as well as malignant aetiology. Benign aetiologies are tuberculosis and histoplasmosis and require timely treatment [29]. The left adrenal is identified by tracing the descending aorta to the celiac trunk and then rotating EUS in a clockwise direction and appears as a "seagull". Right adrenal is identified in the long loop position and seen between upper pole of the right kidney and inferior vena cava. Size of the adrenal along with echo features (echogenicity, presence or absence of necrosis) should be noted in all cases. All specimens with presence of necrosis and or granulomas should be also stained with

fungal stains as well as ZN stain. Diagnostic criteria for identification of TB and histoplasmosis are same as for lymph nodes.

A retrospective study of EUS-FNA from enlarged adrenals was done in patients with pyrexia of unknown origin (PUO), in whom a definitive diagnosis could not be confirmed. Approximately 90% of patients had bilateral adrenal enlargement in this series. In 50 patients, EUS-FNA was done from the left adrenal. Technical successes and diagnostic adequacy of the specimens were achieved in 100% cases. Nineteen-gauge needle was used in ¾th of the patients while 22-G needle was used in rest 1/4th of the patients [30]**.** In around 75% (*n* – 38) cases, it appeared as heteroechoic while in the rest it was hypoechoic (Fig. 19.3). In half of the patients, there was necrosis. Adrenal TB was diagnosed in thirty-six patients (69.23%); all had caseating granulomas while almost half of them had AFB positive (Fig. 19.4). Positive tubercular culture was seen in 2 patients while geneXpert was positive in 15 patients. One-fourth of patients (n-13) were diagnosed with adrenal histoplasmosis. Rest 3 had malignancy [lymphoma (n = 2), and metastasis from undiagnosed neuroendocrine tumour of lung (n = 1)]. No procedure-related complications were reported in any patients, establishing EUS as a safe tool to get tissue from adrenals.

19.2.3 Splenic

Splenic tuberculosis is invariably associated with primary TB lesion and is seen as space occupying lesion (SOL) on routine imaging. Tissue diagnosis in splenic SOL is required to differentiate other causes like splenic abscess, lymphoma or metastasis and EUS-FNA has been reported to be a useful modality for cytopathological

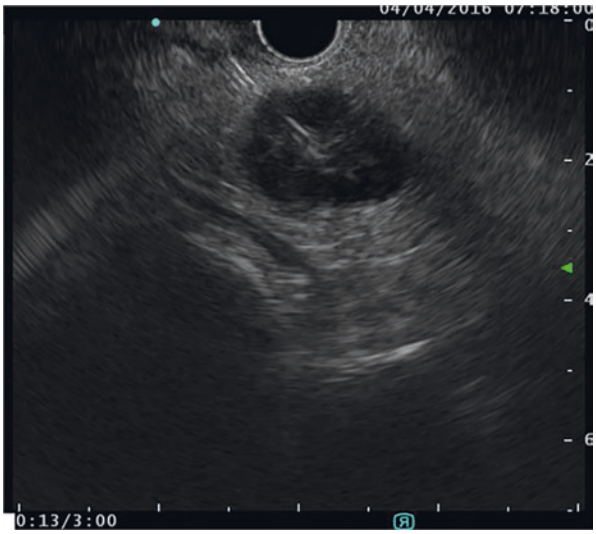

Fig. 19.3 EUS image of enlarged left adrenal gland in patient with TB

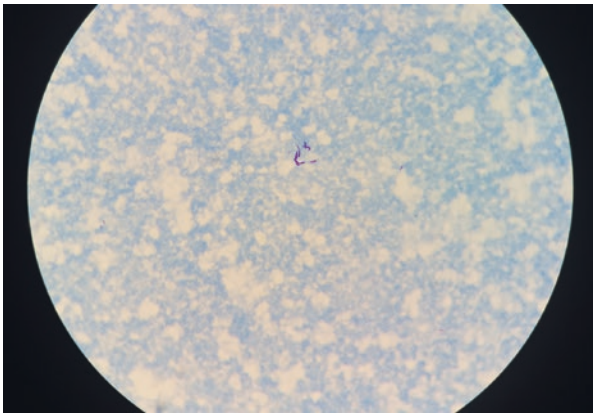

Fig. 19.4 Acid-fast bacilli seen on adrenal FNAC on ZN stain (x100X)

diagnosis of splenic lesions [31–33]**.** There is very limited published data in literature regarding EUS-FNA in splenic TB in which EUS examination showed multiple hypoechoic lesions in the spleen along with mediastinal lymphadenopathy. In a report of 16 patients with splenic lesions, six had splenic tuberculosis and all these had multiple hypoechoic lesions on EUS with cytological examination AFB positivity in three cases [34]**.**

We can assess the spleen through the gastric wall. There is lack of data on aspiration of splenic lesions, as generally it is not needed in presence of other sites to take tissue. However, EUS-FNA is an accurate, safe and minimally invasive approach for differential diagnoses of splenic lesions.

19.2.4 Hepato-biliary

Hepato-biliary tuberculosis is reported in literature. Extrahepatic bile duct obstruction secondary to extrinsic compression by tubercular porta lymphadenopathy or pancreatic head mass or peri-pancreatic lymphadenopathy, can present with jaundice. TB can also directly involve intrahepatic or extrahepatic biliary epithelium and resulting in a biliary stricture. Though there are not much data about the role of EUS-FNA in hepato-biliary TB, however, it can be a good and safe modality to target these focuses (Fig. 19.5). There is a recent interest in EUS guided liver biopsy and this modality can be utilized in evaluation of mass forming hepatic lesions, which could be a manifestation of hepatic tuberculosis.

19.3 Gastrointestinal Lumen and Sub-epithelial Lesion

19.3.1 Oesophageal TB

Primary ET is very rare [35, 36], mostly ET occurs secondary to oesophageal wall involvement by surrounding mediastinal lymph nodes, that is why mid-oesophagus

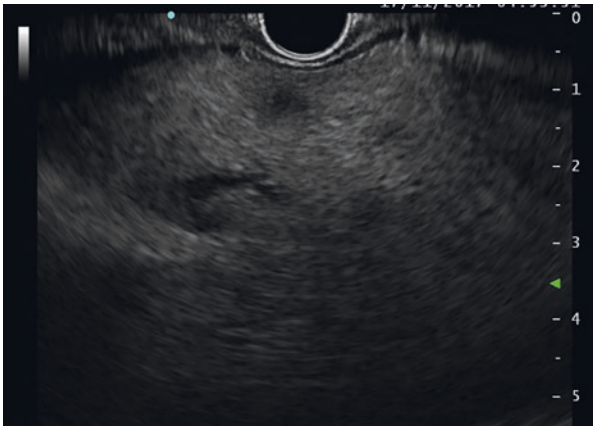

Fig. 19.5 A hypoechoic tubercular lesion in liver seen on EUS

is the commonest site [37]. Endoscopic ultrasound (EUS) is a very much promising tool as it can identify the exact layer of the involved oesophageal wall and lymph nodes beyond the wall. We also get tissue specimens for TB bacilli in the same sitting with much higher sensitivity.

There is very limited data regarding the utility of EUS in ET diagnosis [38–41]**.** Tang et al. [42] reported the largest study of 35 patients with ET in which EUS was performed. They did mini-probe and linear EUS examination and performed tissue acquisition. The most common morphological feature on EUS was oesophageal wall thickening or mass formation with adventitia disruption. Most of the patients (n-30) had full oesophageal wall thickness involvement. EUS showed multiple hypoechogenic, diffuse or matted mediastinal lymphadenopathy with indistinct margins. The hyperechogenic foci were not accompanied by acoustic shadowing [42]**.** Heterogeneous and iso-hypoechoic lymph nodes on EUS correlate with caseous necrosis with matted, observed in mid-stage of TB. In the later stage of fibrosis and calcification, hyperechogenic strands and foci are seen distributed unevenly [42]**.**

On cytopathology, the most common finding was presence of epithelioid granuloma (n-33). In 13 patients, caseous necrosis was seen while in 14 patients had AFB stain positivity. EUS-guided deep excavation biopsy (a derivative of EUS-FNA) had a high diagnostic yield (93.9%) [42]. In a study by Rana et al. 100% yield was obtained in 14 patients with ET [41]**.** We can do either FNA or biopsy on case-to-case basis. We should also do polymerase chain reaction (TB-PCR) or TB culture in addition.

Two entities, i.e. oesophageal carcinoma and submucosal tumours (SMTs), have similar presentations like ET and should be distinguished. There are two findings which differentiates. First, malignant lymph nodes do not fuse with the oesophageal wall. Second, absence of hyperechogenic foci or strips. Hence, EUS-guided tissue acquisition has essential role in establishing a diagnosis [42]**.**

So, EUS morphology along with EUS-guided tissue acquisition is a safe as well as a reliable tool in ET diagnostic evaluation and we should add this tool during ET work up.

19.3.2 Gastric

Gastric tuberculosis is very rare, generally mimics as peptic ulcer disease or malignancy; presenting with either dyspepsia or gastric outlet obstruction related symptoms [43–45]. There are multiple causes of gastric sub-epithelial bulge with normal overlying mucosa, rarely reported with tuberculosis also [46–47]. Isolated gastric tuberculosis is very rare with antrum being the most common site of involvement, and its endoscopic appearances are variable with both ulcers and polypoidal lesions being described [47–50]. The confirmatory diagnosis of gastric TB is based on positive histopathology or cytopathology. There is a very limited role of endoscopic biopsy in gastric TB as most of the time lesions are submucosal. So, EUS is a very helpful tool for diagnosis.

A case report of EUS finding of gastric TB by Sharma V et al. showed gastric wall thickening with loss of wall stratification along with well-defined predominantly hypoechoic adjacent lymphadenopathy. EUS-guided FNA from both the sites revealed caseating granulomas with positive AFB stain [51]. In a recent case series of 3 cases, author concluded some typical features on EUS for the diagnosis of gastric tuberculosis. These features are as follows: (1) a thickened and deformed ill-defined wall; (2) hypoechoic lesions with irregular boundaries and non-homogeneous inner echo; (3) presence of para-gastric or abdominal lymphadenopathy and (4) connection between the gastric wall lesion and lymphadenopathy. The fourth finding shows importantly that TB in lymph nodes has spread directly to the stomach [52]. EUS-guided fine needle aspiration or EUS-guided fine needle biopsy (EUS-FNA or EUSFNB) should be performed to define TB [51].

Therefore, EUS is an excellent modality for evaluation of gastric TB, especially those mimicking submucosal lesions. EUS can determine the nature and the origin of the lesion and also provide tissue material for diagnosis. It is also used for follow-up as a treatment response.

19.4 Peritoneal

Peritoneal tuberculosis (TB) contributes 1–2% of tuberculosis [53]. Ascitic fluid culture is around 35% sensitive and takes four to six weeks while a similar sensitivity is provided by Xpert Mtb/Rif [54]. Laparoscopic examination and histopathology are highly sensitive and specific, however, it has its own limitation in term of being invasive in nature and possibility of complications. Peritoneal tissue can be assessed by EUS-FNA, especially in patients with decompensated liver cirrhosis. There are few case reports favouring EUS-FNA, a recent report of 5 patients revealed granuloma in all patients while AFB stain was positive in 40% of them [55]. They localized stomach, examined the surrounding omentum and identified thickened omentum. They performed trans gastric FNA with a 22 G needle. Four passes with multiple to and fro movements during each pass were used to get the tissue. So, EUS FNA of the peritoneum appears to be a good and safe tool for establishing diagnosis of tuberculosis, however, it should be noted that data is limited to

a few reports only, and not all parts of peritoneum are accessible by EUS. Further additional yield over transabdominal approach is uncertain.

19.5 Conclusions

EUS is an important tool for diagnosis of various morphological forms of abdominal tuberculosis, by providing characteristic morphology and tissue sampling with high sensitivity.

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Conflict of Interest None.

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Positron Emission Tomography/ Computed Tomography Imaging in Abdominal Tuberculosis

20

Rajender Kumar, Apurva Sood, Harmandeep Singh, and Bhagwant Rai Mittal

Abbreviations

ATT	anti-tubercular therapy
CT	computed tomography
FDG PET/CT	^{18}F-fluoro-2-deoxy-D-glucose (FDG) positron emission tomography/computed tomography
GI	Gastrointestinal
LN	lymph nodes
MDR	Multidrug resistance
MIP	Maximum intensity projection
PC	Peritoneal carcinomatosis
SUV	standardized uptake value
TB	tuberculosis
TBP	tuberculous peritonitis

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Key Points

1. Diagnosis of abdominal TB is challenging and relies on combined clinical, laboratory, endoscopic, and radiological findings with identification of bacteria in culture/microscopy or demonstration of caseating granulomas in histopathology
2. ^{18}F-FDG PET/CT plays an essential role in early diagnosis, guiding the site of biopsy from the metabolically active site, disease mapping, response to anti-tubercular therapy, prognostication, and identification of non-responders, i.e., multidrug resistance TB.
3. PET/CT has the potential to determine treatment duration and individualize therapy instead of empirical treatment to all the cases.
4. The development of newer radiotracer for PET imaging will be a boon for these patients, which may help in determining the adequacy of anti-tubercular accumulation at infected sites and help in bioimaging of the in vivo drug kinetics.

20.1 Introduction

Tuberculosis (TB), caused by an acid-fast bacillus, *Mycobacterium tuberculosis*, continues to be a menace to humans with a growing incidence of multidrug resistance (MDR) and HIV co-infection despite various efforts to curb the disease [1, 2]. Extrapulmonary TB accounts for 20% of all TB cases and the commonly involved sites are lymph nodes (LNs), gastrointestinal tract, pleura, genitourinary system, and central nervous system [3, 4]. Abdominal TB comprises 5–20% of all the cases of EPTB worldwide [5]. It presents with involvement of LNs, peritoneum, gastrointestinal (GI) tract, pancreas, and hepatobiliary tree. It is classified into four forms: tubercular lymphadenopathy, peritoneal TB, GI TB, and visceral TB involving the solid organs. The diagnosis of abdominal TB is challenging and relies on combined clinical, laboratory, endoscopic, and radiological findings with the identification of bacteria in culture/microscopy or demonstration of caseating granulomas in histopathology. The various radiological studies used for diagnosis are ultrasonography, computed tomography (CT), barium studies, and magnetic resonance imaging (MRI) [6].

^{18}F-fluoro-2-deoxy-D-glucose (FDG) positron emission tomography combined with CT (PET/CT) has been successfully used in tumor imaging due to high metabolism in cancer cells. With routine use of FDG PET/CT, it was found that FDG, a glucose analog, showed increased concentration in infection and inflammatory conditions leading to its increased use in non-oncological indications [7]. Activated macrophages, lymphocyte, and granulocytes in the granuloma of an active tuberculous lesion have high glucose utilization and hence show increased FDG uptake [8]. Therefore, FDG PET/CT provides us with functional in addition to anatomical information. This added value of PET/CT makes this modality a viable option for

the evaluation of TB in clinical settings and can contribute to its correct diagnosis, staging, and assess treatment response.

20.2 PET/CT in Diagnosis

Diagnosis of abdominal TB remains a challenge as it has a wide range of clinical and radiological presentations, which can mimic a variety of diseases like intestinal lymphoma, carcinomatosis, Crohn's disease, bacterial peritonitis and chronic liver disease. Early and correct diagnosis of abdominal TB is crucial as delay and injudicious treatment is associated with high morbidity and mortality [9–11].

CT is the mainstay for investigating possible abdominal TB because firstly, it allows evaluation of the abdominal organs, lymph nodes, ascites, and peritoneal involvement. Secondly, it is readily available, and physicians are well familiar with the modality. CT findings of abdominal TB include abdominal lymphadenopathy, free or loculated ascites, smooth peritoneal thickening and enhancement, mesenteric stranding, and mural thickening of the intestine predominantly the ileo-caecum region [12, 13].

In routine practice, PET/CT is not used for establishing the diagnosis of abdominal TB. However, PET/CT might help in clinching the diagnosis in certain conditions. Patients with known malignancy are immunocompromised and are known to have a higher risk of reactivation of latent TB or to acquire TB [14, 15]. Various reports of false-positive findings caused by TB in patients being evaluated for malignancy are present in the literature [16–20]. When undergoing PET/CT for staging, restaging, and response assessment, these patients might show increased FDG uptake or radiological changes in sites that are inconsistent with known malignancy and might point towards TB presence. A limitation of FDG PET is that neither semiquantitative analysis nor dual time point imaging technique can help in differentiating TB from the malignant lesion. Therefore, the definite diagnosis and exclusion of active TB by a histopathological/ microbiological study is required (Fig. 20.1).

A considerable increase in referrals for PET/CT is also seen in patients with fever of unknown origin (FUO) (Fig. 20.2). The aim is to rule out infection, inflammation, or malignancy. Infection is the most common cause of FUO, and in developing countries like India, TB is the most frequent infection. Due to its high sensitivity, PET/CT plays an essential role in detecting these lesions [21, 22]. Tek Chand K et al., in a study of 20 cases with FUO, found—50% of the cases had TB diagnosed on FDG PET/CT [23]. FDG uptake in abdominal lymphadenopathy, peritoneal thickening, hepatic lesions, and ileo-caecum may be signs of TB requiring further histopathological/ microbiological confirmation.

Another utility of PET/CT for diagnosis of TB is PET-guided biopsy. PET demonstrates increased glucose concentration (suggesting infection/inflammation) even before anatomical changes are evident on CT. Therefore, an image-guided biopsy will help in early and accurate histologic diagnosis. Besides, PET/CT helps to improve diagnostic accuracy by indicating active areas in lesions with necrosis and fibrosis [24, 25].

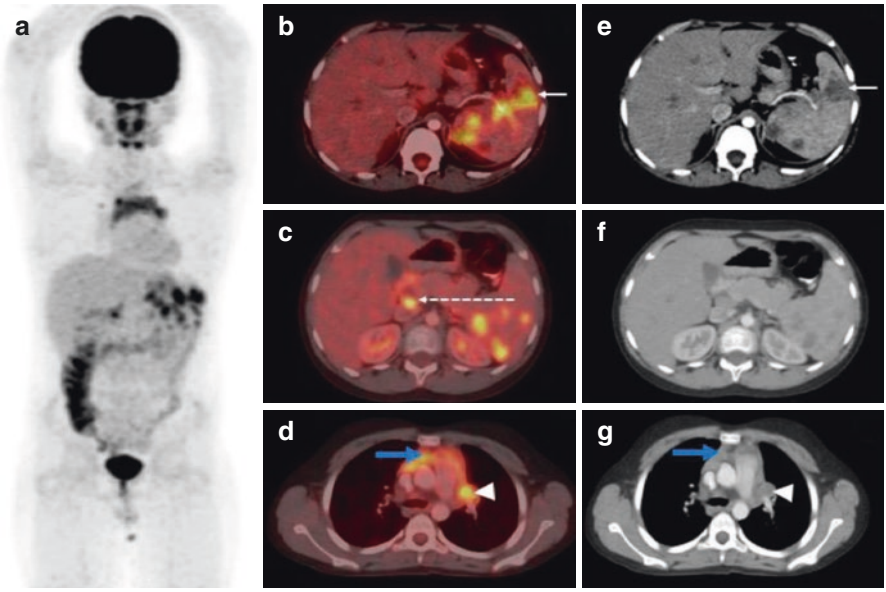

Fig. 20.1 A 12 years old male child presented with loss of weight and fever. CT scan of thorax showed mediastinal lymphadenopathy. Multiple hypoechoic lesions were seen in spleen. Patient underwent ^{18}F-FDG PET/CT to look for the activity and pattern of disease. MIP (**a**), PET/CT fused (**b, c, d**) and CT only (**e, f, g**) images showed FDG avid multiple hypodense lesions in spleen (arrow, **b, e**); enlarged portocaval (dashed arrow **c, d**) and mediastinal (arrowhead, **d, g**) lymph nodes. Physiological FDG uptake was also seen in thymus (blue arrow, **d, g**). The image findings were suggestive of either lymphoma or tuberculosis. The biopsy of the mediastinal lymph node was suggestive of tuberculosis

20.3 PET/CT for Staging

Whole-body PET/CT consists of imaging the body from the head to mid-thigh. Hence, in one study, disease activity at multiple sites can be detected. It is known that approximately 15–25% of cases of abdominal TB have concurrent pulmonary TB [26–28] (Fig. 20.3). Various studies have shown that FDG PET/CT is more sensitive than CT alone in identifying lesions, especially the LNs, which are not enlarged on CT and marrow lesions [29–31]. A study done in 87 patients showed that FDG PET/CT detected additional lesions in 72% of the cases than clinically suspected [29]. Identification of additional sites like CNS and skeleton warrants a longer duration of anti-tubercular treatment (ATT) intake [32].

20.4 Findings of Abdominal Tuberculosis on PET/CT

20.4.1 Abdominal Lymphadenopathy

Lymph node enlargement is the most common manifestation of abdominal TB and is seen in 55–60% of the patient [33]. Mesenteric, paraaortic, omental, and peripancreatic LNs are mostly affected. On CT, the nodes are enlarged, discrete, or matted

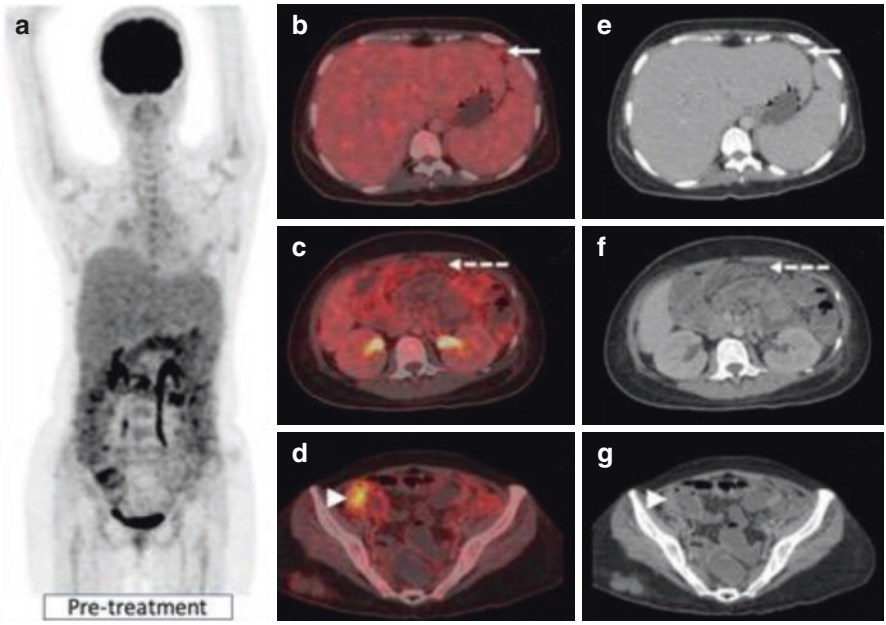

Fig. 20.2 An 18 years old female with fever of unknown origin underwent ^{18}F-FDG PET/CT. MIP (**a**), PET/CT fused (**b, c, d**) and CT only (**e, f, g**) images show low-grade FDG avid subcentimetric anterior diaphragmatic lymph node (Arrow, **b, e**), FDG avid omental and mesenteric nodules and stranding (Dashed arrow, **c, f**) and increased FDG uptake in mural thickening in the ileum and caecum (arrowhead, **d, g**). An endoscopic biopsy of the ileum showed granulomatous lesion and culture positive for tuberculosis. She was started on ATT and a ^{18}F-FDG PET/CT was done 4 months after initiation of ATT. MIP (**h**), PET/CT fused (**i, j, k**) and CT only (**l, m, n**) images show resolution of previously seen omental and mesenteric lesions, persistence of mural thickening in the ileum and caecum (arrowhead, **k, n**) and appearance of new lesions in form of increased FDG uptake in subcapsular liver deposits (Arrow **i, j**) and FDG avid subcentimetric paraaortic lymph nodes (Dashed arrow, **j**) suggestive of disease progression and second-line ATT was started. Physiological FDG uptake was also seen in the thymus (Black arrow, **h**)

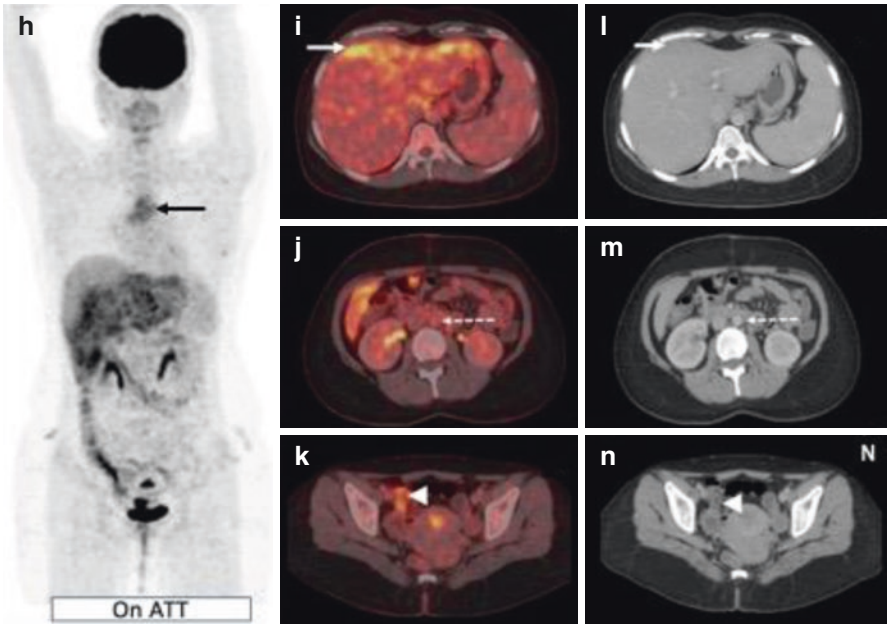

Fig. 20.2 (continued)

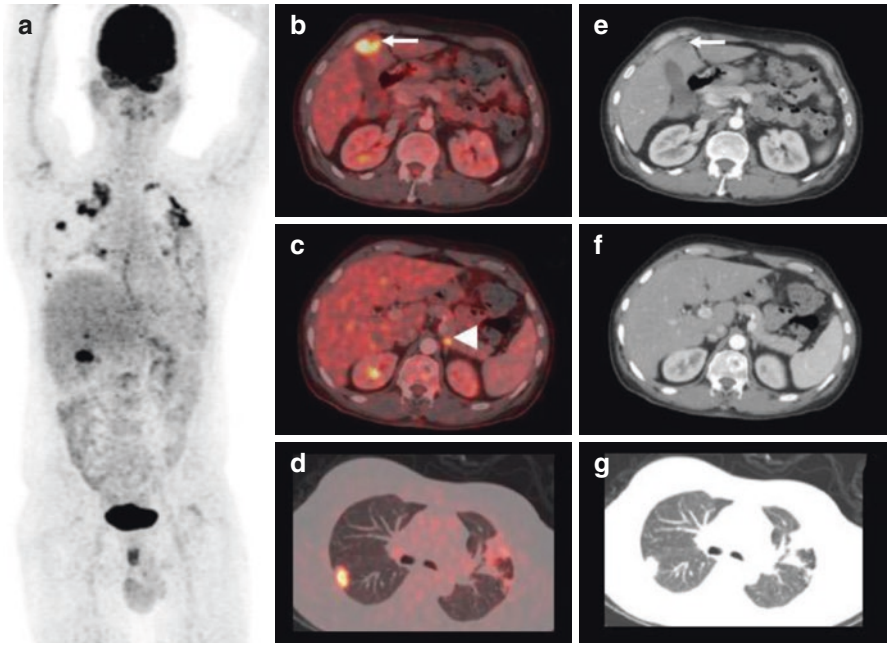

Fig. 20.3 A 32 years old male presented with fever and loss of weight. USG abdomen revealed a lesion in segment IVB of liver. FNAC of the liver lesion revealed TB. ^{18}F-FDG PET/CT MIP (**a**), PET/CT fused (**b, c, d**) and CT only (**e, f, g**) images revealed FDG avid hypodense lesion in segment IVB of liver (arrow, **b**); subcentimetric ill-defined lesion in body of left adrenal gland (arrow head, **c**) and FDG avid consolidation and nodules in both lung fields (**d, g**)

and may show peripheral enhancement and central necrosis. Involved LNs demonstrate increase concentration of FDG on PET even if they are not yet enlarged to be detected on CT [34].

20.4.2 Peritoneal TB

The involvement of peritoneum, also known as tuberculous peritonitis (TBP), is a rare form of extrapulmonary tuberculosis, accounting for 0.1 to 0.7% of all TB types [35]. Peritoneal TB is primarily caused via hematogenous spread but can occur secondary to fallopian tube involvement, tuberculous LNs, or GI lesion. Peritoneal involvement conventionally has been divided into wet, dry, and fibrotic types. The wet type presents as free or loculated ascites. Mesenteric thickening, fibrous adhesions, and cake-like omentum are seen in the dry type. The fibrotic type manifests as omental or mesenteric masses, matted bowel loops, or cocoon formation [6] (Fig. 20.4). These findings are nonspecific and can also be seen in peritoneal carcinomatosis, mesotheliomas, and rarely lymphoma. FDG accumulates in the inflammation and granulomatous disease involving the peritoneum, mesentery, and omentum. However, the intensity of FDG uptake cannot differentiate between TBP

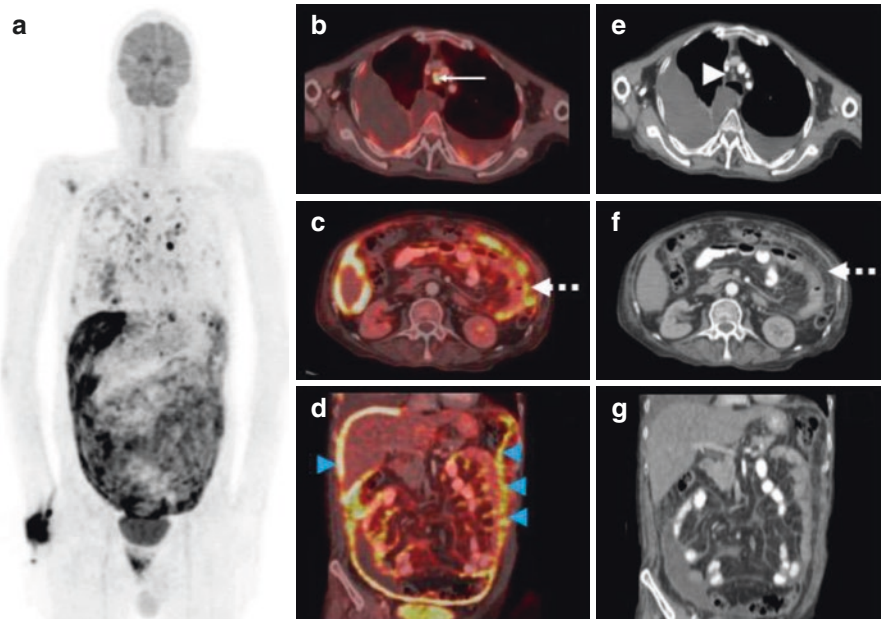

Fig. 20.4 A 48 years old male presented with pain abdomen, loss of weight and appetite diagnosed with peritoneal TB. ^{18}F-FDG PET/CT Maximum intensity projection (MIP) (**a**), PET/CT fused (**b, c, d**) and CT only (**e, f, g**) images show FDG avid mediastinal lymph nodes (arrow **b**), which are subcentimetric in size on CT (arrowhead, **e**)) and low-grade FDG avid moderate bilateral pleural effusion. Increased FDG uptake is also seen in omental stranding and nodularity (dashed arrow, **c, f**), peritoneal and serosal thickening throughout the abdomen and pelvis (blue arrow heads, **d**). Thickening in the abdomen is encasing small bowel loops with cocoon-like formation

and peritoneal carcinomatosis (PC). Wang et al. conducted a retrospective study in 76 patients with peritoneal involvement (TBP = 25 and PC = 51) to see if the pattern of FDG uptake and CT changes can help in differentiating between TBP and PC. They found that involvement of more than four regions of the peritoneum, string bead appearance of FDG uptake, and smooth uniform thickening of the peritoneum was seen in cases of TBP. While cases of PC showed irregular peritoneal thickening with nodules, focal, or clustered FDG uptake and predominantly involved the pelvis and right subdiaphragmatic area [36]. Chen R et al. studied 103 patients with peritoneal lesions and established that FDG avid irregular peritoneal thickening was seen more often in PC [37]. Therefore, CT findings with FDG uptake might help in the diagnosis of TBP, but this requires further validation.

20.4.3 Gastrointestinal TB

TB can involve any part of the GI tract from mouth to anus. Terminal ileum and the ileocecal region is the most common site of GI involvement because of range of contributing factors like presence of abundant lymphoid tissue, physiological stasis, closer contact of the bacilli with the mucosa and minimal digestive activity [38, 39]. FDG uptake is noted in the bowel segment with mural thickening, which can be either concentric or eccentric. FDG avid localized lymphadenopathy with surrounding fat stranding is also seen. The involvement of the esophagus, stomach, duodenum, and small bowel is still uncommon [6]. Singh et al. in a prospective study performed FDG PET/CT enterography in 34 patients with ileocecal thickening and found that FDG uptake was higher in cases with ileocecal TB and Crohn's disease in comparison to patients with clinically insignificant diagnosis like nonspecific ileitis. However, FDG uptake was unable to differentiate TB from Crohn's disease and a clinicopathological evidence is required to reach a diagnosis [40].

20.4.4 Visceral TB

Isolated involvement of solid abdominal organs is relatively uncommon and seen in—15–20% of all cases of abdominal TB [41]. FDG accumulates in the TB lesions involving the liver, adrenal, pancreas, spleen, and kidney [42–44] (Figs. 20.1 and 20.3). FDG uptake in the liver can be solitary, multiple, or diffuse and is indistinguishable from other pathologies like metastases [45, 46]. Few studies have shown the involvement of the liver on FDG PET with no focal lesion or changes on CT images. The kidney shows high physiological tracer activity on FDG PET/CT imaging; this may mask the lesions. Delayed imaging in such cases may be useful in defining the TB lesions [44].

20.5 PET/CT for Evaluation of Treatment Response

Response assessment using ^{18}F-FDG PET/CT is potentially the most promising and important clinical application of this modality. Currently, the response is assessed on the basis of clinical and radiographic findings with no objective biomarker.

^{18}F-FDG PET/CT can be of clinical use as metabolic change often occurs before the morphological variation is evident. Numerous studies have confirmed the role of ^{18}F-FDG PET/CT in follow-up, evaluation of response to treatment, and when drug resistance is suspected. While there is heterogeneity in the time interval of PET/CT done after ATT initiation in these studies like at 2, 3, and 6 months; findings indicate that a significant decrease in SUV max (pooled decrease SUVmax −54.38% (95% CI – 57.81, − 50.96) imply a favorable outcome with lesser chances of disease recurrence [29, 31, 46–49]. In a series, scan findings of the appearance of new lesions (Fig. 20.2) or an increase in SUVmax in interim scan showed that these patients had a higher risk of mortality, drug resistance, and longer duration of ATT intake [29]. In a study cohort of 28 patients with multidrug-resistant (MDR)—TB Chen et al. demonstrated that ^{18}F-FDG PET/CT done at 2 months had 96% sensitivity for predicting treatment success and 79% specificity for predicting treatment failure. Similar findings were achieved by CT scans but at a duration of 6 months [47]. Sathekga et al. reported that a cut-off of 5 or more LN basins separated tuberculostatic responsive from non-responsive TB infected HIV patients with 88% sensitivity, 81% specificity, and 93% negative predictive value [50]. Another possible use of ^{18}F-FDG PET/CT is to individualize therapy depending on the lesion activity. WHO currently recommends ATT for 6 months duration for both pulmonary and extrapulmonary TB and 18–24 months of treatment after negative sputum in MDR and extended resistant TB [32]. Assuming that FDG avid lesion is suggestive of residual disease and warrants continuation of ATT, individualization of treatment duration can be done. Stelzmueller et al. reported a longer mean duration of ATT with no additional side effects when findings of FDG PET/CT were considered [31]. This strategy, however, requires further validation with large prospective studies.

20.6 Other PET Tracers for TB

Various PET tracers, besides ^{18}F-FDG PET/CT, have been investigated for imaging TB (Table 20.1) to increase the understanding of pathogenesis and differentiate it with malignancy. Hypoxia within the tubercular lesions can be imaged using 18F-Fluromisonidazole. It has been demonstrated that within the same patient, TB lesions have heterogeneous levels of hypoxia. This might help in the development of therapeutic drugs by better understanding the disease process [51]. Lesion hypoxia stimulates neovascularization in the periphery of the lesion and can be imaged using 68Ga-alfatide II. Neovascularization is higher in malignant lesions and hence tends to show higher avidity [52]. Non-specificity of the available tracers has led to an interest in the development of bacterial specific tracers for PET imaging. Radioisotope labeled anti mycobacterial chemotherapeutic agents act by binding to a component of bacteria. Rifampicin, isoniazid, and pyrazinamide, the first line anti-tubercular drugs, are labeled with ^{11}C and can determine whether there is an adequate accumulation of drugs in infected sites. The radiopharmaceuticals, apart from imaging the TB lesions, help in bioimaging of the in vivo drug kinetics. Dynamic PET imaging has the potential to real-time monitor the distribution of drugs in the whole body [53, 54].

Table 20.1 Non-FDG PET tracers for evaluation of tuberculosis

Tracer	Mechanism of uptake	Use
^{18}F-Fluroethylcholine/^{11}C-Choline [55]	Choline is a precursor for biosynthesis of cell membrane	Used along with ^{18}F-FDG PET/CT can help in differentiating malignancy from TB lesions. Low uptake of choline seen in TB lesions.
^{18}F-Fluoro-L-Thymidine [56]	Incorporated into nucleic acid, hence, reflects cell proliferation	Helps distinguish TB from malignant lesions when combined with ^{18}F-FDG
^{18}F-Fluromisonidazole [51]	Accumulates in hypoxic cell	Demonstrates hypoxia levels within the tubercular lesions.
^{18}F-sodium fluoride [57]	Binds to microcalcification	Shows uptake in chronic TB lesions with calcification
^{68}Ga-alfatide [52]	Images neoangiogenesis. Binds to integrin $\alpha_v\beta_3$ receptors in endothelium of neovessels	Show higher uptake in malignant lesions in comparison to tubercular lesions
^{68}Ga-citrate [58]	Accumulates in bacterial siderophores	Better sensitivity than CT to detect extrapulmonary lesions and may provide a way to distinguish active from inactive lesions
^{11}C-Rifampicin [53, 54] ^{11}C-Isoniazid ^{11}C-Pyrazinamide	Radioisotope labeled anti-tubercular drugs	Can determine whether there is adequate accumulation of drug in infected sites and help in bioimaging of the in vivo drug kinetics

20.7 Conclusion and Future Prospective

^{18}F-FDG PET/CT is a non-invasive biomarker that can potentially help in the clinical management of TB. PET/CT is useful in diagnosing TB, especially in immunocompromised cases and patients with FUO. PET/CT can also help in identifying the site of biopsy in cases with suspected TB. Pre therapeutic PET/CT can provide information about the pattern and extent of the disease with sensitivity higher than CT alone. Post ATT initiation, PET/CT has the potential to assess the treatment response, prognosticate, and help identify cases resistant to ATT. Finally, PET/CT can determine treatment duration and individualize therapy instead of empirical treatment in all cases.

Utilizing ^{18}F--FDG PET/CT for deciding the duration of ATT requires further validation in large prospective studies. PET/CT imaging of TB has the potential to impact areas of research in vivo assessment of disease. Development of new tracers to understand the disease process and anti-tubercular drug kinetics may play a significant role in managing TB and amounts for further research.

Conflict of Interest None.

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Part VI

Management Issues

Response to Therapy in Abdominal Tuberculosis

21

Chhagan Lal Birda and Vishal Sharma

Abbreviation

ATB	Abdominal tuberculosis
ATT	Antitubercular therapy
ITB	Intestinal tuberculosis
TB	Tuberculosis

Key Points

1. Assessment of response should be considered in each patient with abdominal tuberculosis but is mandatory in those who are clinically diagnosed.
2. Objective response criteria (ulcer healing, ascites resolution, disappearance of radiologic lesions) should be preferred over subjective features like weight gain or sense of well-being.
3. Lack of response could be due to misdiagnosis, drug resistance, or sequelae of tuberculosis.
4. Two months is a reasonable time to assess response in intestinal tuberculosis by looking for healing of ulcers (early mucosal response).
5. Role of biomarkers in response assessment is upcoming with a potential role for serum CRP and fecal calprotectin in intestinal TB.

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21.1 Introduction

Abdominal tuberculosis (ATB) is a heterogeneous entity encompassing the involvement of various luminal (intestine, esophagus, stomach) and extraluminal (peritoneum, visceral organs, and lymph nodes) structures [1]. Across the various subtypes of abdominal tuberculosis, the major problem in making a diagnosis is the low positivity of microbiological tests [2–4]. The yield of various microbiological tests is low and even with a combination of microbiological and histological/cytological tests, the yield remains below 50% in clinical practice. Similar to many other sites of extrapulmonary tuberculosis, clinicians are forced to embark on antitubercular therapy (ATT) on empirical grounds [5]. In such situations, certain precautions need to be ensured: all efforts should be exhausted to make a confirmed diagnosis prior to embarking on the adventure of "empirical therapy" and a close follow-up of such patients be done so as to identify "non-responders" and to look for underlying causes of "non-response." Response can be assessed by clinical, radiological, microbiological, endoscopic, and immunological or biochemical basis [6]. Clinical response is assessed by improvement in performance status, weight gain, and resolution of systemic and organ-based symptoms. Radiological response can be assessed by a decrease in mesenteric thickening, mural thickening of the bowel wall, resolution of stricture, healing of ulcers, disappearance of lymphadenopathy, and ascites. Microbiological response is difficult to assess in view of paucibacillary nature and low yield by Zeihl–Neelsen (ZN) staining and PCR-based tests but should be considered in non-responding patients to rule out multidrug-resistant tuberculosis. Immune response can be assessed by declining acute phase proteins or modification of cytokines or T-lymphocyte subset [7, 8]. Although it may seem fairly simple, the definitions of "response" and "non-response" are not entirely clear and there are many issues regarding these definitions. There is a need to have clear definitions and guidance for clinicians treating abdominal tuberculosis on basis of the published evidence. The chapter will deal with various armamentariums which have been used to define response, clinical symptoms and monitoring, biomarkers, imaging and endoscopic methods, and address the yin and yang of each of these methods.

21.1.1 Traditional Definition of Response

In 1969, Logan first suggested the use of "response to therapy" as an important method for the diagnosis of anorectal tuberculosis. This modification of the diagnostic criteria has since been used frequently in clinical practice and also for defining abdominal tuberculosis in research. The definition used by Logan included probable cases with a consistent clinical and radiological profile where the "'*sarcoid' reaction indistinguishable between Crohn's disease and tuberculosis*" was present and "*satisfactory response to chemotherapy*" was documented [9]. In the present chapter, we will focus on the definitions of "satisfactory response" for the many subtypes of abdominal tuberculosis.

21.2 Luminal Tuberculosis

21.2.1 Intestinal Tuberculosis (ITB)

Intestinal tuberculosis (ITB) is one of the common patterns of involvement in abdominal tuberculosis [10]. The clinical presentation is variable with patients presenting with a mix of constitutional symptoms and localizing features. Abdominal pain and episodes of intestinal obstruction dominate the clinical presentation. The condition closely simulates inflammatory bowel disease, especially Crohn's disease (CD) [5, 11]. CD has a similar clinical presentation (with abdominal pain, diarrhea), endoscopic findings (ulcers, pseudopolyps), imaging findings (mural thickening), and histological findings (changes of chronicity and granulomatous inflammation). In regions where both these diseases are common, clinicians often find it difficult to conclusively distinguish the two [11]. If even after appropriate evaluation the diagnosis is uncertain, clinicians often embark on "empirical ATT" to sort out the diagnostic confusion [11, 12]. The reasons for preferring "empirical ATT" over empirical therapy for Crohn's disease are manifold. The therapeutic endpoints for ITB are clear and the treatment usually involves 6 months of therapy. While ATT carries the risk of adverse effects, prescription of steroids/immunosuppressants for presumed CD could be dangerous as it can result in the dissemination of tuberculosis. Also, as we will discuss, the resolution of mucosal ulcers with ATT is a definite method to exclude CD.

21.2.1.1 Symptomatic Response

The clinical symptomatology of intestinal tuberculosis is dominated by abdominal pain. The underlying causes for abdominal pain may include the presence of strictures or hypertrophic forms of intestinal tuberculosis causing intestinal obstruction. Additional causes could include the formation of adhesions due to concomitant peritoneal involvement. Other symptoms could include diarrhea (especially in cases with extensive ulceration) and constitutional symptoms like fever and weight loss. Some of the studies have evaluated the clinical response to antitubercular therapy in patients with intestinal tuberculosis. In the study by Mouli et al., clinical response was noted in 66% of patients with ITB at 2 months and 99% of them by 6 months. In contrast, 28% of patients with Crohn's disease (CD) had a symptomatic response at 2 months while 37% of them had a response at 6 months (Tables 21.1) [13]. The study clearly demonstrated that while resolution of symptoms occurred more frequently with ITB, some of the patients with CD also had a symptomatic response with ATT and therefore resolution of symptoms alone may not have adequate discriminative ability. Also, it is not clear if symptoms like fever, abdominal pain, and weight loss differ vis-à-vis the response rates between these patients. Sharma V et al. reported that 83.8% of patients with abdominal tuberculosis responded to 6 months of ATT. Subjective response to treatment was measured by improvement in clinical features like weight gain, increased appetite, defervescence, and improvement of pain abdomen [14]. A study by Anand BS et al. in patients with tubercular ileal stricture reported 91% clinical response at the end of 1 year of ATT. Clinical

Table 21.1 Response to ATT in intestinal tuberculosis

Study	Clinical Response	Definition of Clinical Response
Mouli et al. [13]	66% at 2 months and 99% at 6 months[a]	>50% improvement in global symptom response reported by patients on visual analog scale of 0–100.
Sharma V et al.[14]	83.8% response at 6 months of ATT	Improvement in constitutional symptoms, pain, and distension
Anand B S [15]	91% at 1 year of ATT	Complete response or vague pain abdomen not requiring analgesics

[a]Unclear if additional strategies like endoscopic dilatation or surgery were used

response was defined as resolution of pain abdomen or vague pain abdomen not requiring analgesics [15].

21.2.1.2 Mucosal Response

Terminal ileum and right side colon are the most common site of involvement of intestinal tuberculosis [16]. Common endoscopic features are ulcers, nodularity, and luminal narrowing. Mucosal healing is the most well-studied objective response to ATT in patients with ITB. Mouli et al. reported mucosal healing in 100% of ITB patients compared to only 5% of patients with Crohn's disease at the end of 6 months of ATT [13]. Mucosal healing is a very important tool in differentiation of ITB with CD especially if ATT was started empirically as clinical improvement with ATT can be seen in a significant percentage of patients with CD. Persistence of ulcers on ATT points toward alternate diagnosis like CD. We reported healing of ulcers on colonoscopy as early as 2 months of starting ATT in patients with ITB [17]. In this study, 89% of patients showed complete or partial "early mucosal response." Causes of non-response were infection by multidrug-resistant (MDR) mycobacteria in one patient and CD in another three patients [17]. This is an important observation, as an early initiation of immunosuppression in case of CD could prevent strictures and provide better long-term outcomes. Also, it is likely to be more cost-effective and can prevent adverse events and costs of continuing ATT [17]. A similar observation was reported by Park et al. in patients with nonspecific ileocecal ulcers. In this study, nine patients of suspected tubercular colitis on median follow-up of 107 days showed mucosal healing. Equal number of patients showed no response to ATT and were later confirmed as IBD or nonspecific colitis [18]. Although the mucosal response is an established tool of response assessment but is limited by invasive nature, patient discomfort, intolerable bowel preparation, and incomplete evaluation in presence of strictures or proximal ileal/jejunal involvement.

21.2.1.3 Biomarkers

Acute-phase proteins like C-reactive protein (CRP) are frequently elevated in patients with tuberculosis. Studies in patients with pulmonary tuberculosis reported that CRP rapidly declines within the first week after starting ATT [19]. Persistently elevated CRP >20 mg/l is associated with adverse treatment outcomes [20]. We studied the role of serial CRP measurement in patients with suspected abdominal

tuberculosis. In this study, 101 of 112 patients with suspected abdominal tuberculosis patients had elevated CRP at baseline. After starting ATT, CRP at 2 and 6 months showed a declining trend in 94 patients, all of them were confirmed as ATB. Out of 7 patients with persistently elevated CRP, 5 were confirmed as alternative diagnosis (3 CD, 1 lymphoma, 1 carcinoma gallbladder with peritoneal carcinomatosis), 1 had ATB with intercurrent infection (Urinary tract infection), and 1 had disseminated tuberculosis with nonhealing ulceration and narrowing at 6 months. This study concluded that a lack of decline in CRP suggests alternate diagnosis or drug-resistant tuberculosis [21]. Studies in patients with pulmonary tuberculosis suggest modification of cytokine and T-lymphocytes subsets after successful ATT [22]. Level of TNF-α decreases and shift of MTB specific TNF-α expressing CD4 T-cells to polyfunctional CD4 (expressing INF-γ, TNF-α, and IL-2) with ATT [23]. Tuberculosis causes elevated levels of certain matrix metalloproteinases leads to enzymatic destruction of extracellular matrix and cavity formation. Levels of MMP-1, MMP-3, and MMP-8 elevate in pulmonary tuberculosis and MMP-9 in tubercular meningitis and successful treatment with ATT causes normalization of these MMPs [24]. However, studies regarding change of cytokine profile and MMPs are lacking in patients with abdominal tuberculosis.

Fecal calprotectin could also be used for the assessment of response to therapy. We have reported that fecal calprotectin measured at baseline and at 2 months of ATT provides a better discriminative value than serum CRP to differentiate ITB and CD. Most patients with ITB have an elevated fecal calprotectin but an occasional patient may have a normal level at the baseline. The use of fecal calprotectin and serum CRP could obviate the need for a repeat colonoscopy to assess mucosal response [25].

21.2.1.4 Imaging

In a small report of 20 patients, 18 patients were followed using CT Enterography and seven by using gastrointestinal ultrasound (GIUS). The definition of complete response was reduction in lesion by 50% or significant decrease in bowel thickness, lymph node size, and bowel enhancement. Similar definitions and a decline in Limberg score by two grades was considered as a definition of response on GIUS. Limberg score, utilized frequently in Crohn's disease, grades bowel involvement from 0–4 using parameters like bowel wall thickness, and vascularity in bowel wall and perienteric fat and mesentery. With ATT, the thickness of the bowel wall reduced, and mural stratification was better visualized. However, changes in vascularity did not seem to be pronounced. Although limited by the small numbers, the study showed the feasibility of the use of GIUS for response assessment in these patients [26].

Jain R et al. studied sonographic findings in 56 patients with early abdominal tuberculosis and also assessed the response of ATT on sonographic findings. Early tuberculosis was defined as no history of intestinal obstruction and normal barium study. Compared to healthy control (n = 30), presence of thickened (≥15 mm) and echogenic mesentery and mesenteric lymphadenopathy suggest abdominal tuberculosis. Other findings included dilated small bowel loops (n = 38), minimal ascites (n = 17), matted small bowel loops (n = 5), and omental thickening (n = 3). After

starting ATT, regression of all of these lesions was noted on serial follow-up USG at 1, 3, 6, and 12 months of ATT [27].

Kedar RP et al. studied US findings in 90 patients with abdominal tuberculosis. Common findings include concentric bowel wall thickening ($n = 51$), ulcers ($n = 8$), ascites ($n = 36$), abdominal lymphadenopathy ($n = 23$), adhesions ($n = 14$), peritoneal thickening ($n = 13$), cold abscess ($n = 10$), club sandwich sign ($n = 5$) and peritoneal nodules ($n = 3$). The presence of fibrinous strands in ascites, loculated ascites, presence of caseation (central echo poor areas in lymph nodes) & calcification of lymph nodes, bowel thickening at ileocecal junction and subhepatic location were highly suggestive for diagnosis of tuberculosis. Follow-up of 38 patients with US at 3 months was available and regression of bowel wall thickening, ascites, lymph node size, and cold abscess was noted in these patients [28].

In a study that used magnetic resonance enterography and diffusion-weighted imaging, the apparent diffusion coefficient (ADC) values were calculated pretreatment and posttreatment. Of 31 diseased segments, 29 segments showed diffusion restriction. On posttreatment imaging, eight patients had complete resolution on conventional MR imaging and the hyperintense signal on T2W as well as the enhancement on posttreatment also resolved. The ADC values showed an increase in those having response to therapy. In other patients who were eventually diagnosed with Crohn's disease, there was no increase in the ADC values suggesting that ADC values could be an objective non-invasive parameter for evaluation of response to therapy. Unfortunately, no data is yet available at 2 months, and therefore it is unclear if this change in ADC values could occur early or if the response is detectable only at the end of therapy (6 months) [29].

Response to ATT can also be assessed by change in abnormal metabolic activity by using 18 FDG PET CT. Chen et al. reported that PET CT was better than sputum or CT alone at 2 months of ATT for response assessment in 35 south Korean patients with MDR pulmonary TB. FDG PET can identify the presence of cavity, nodule, and consolidation as well as metabolic activity [30]. V. Martinez et al. reported the role of FDG PET as an early non-invasive marker for therapeutic response to ATT. Out of 21 patients, 10 had extrapulmonary tuberculosis {Ovarian TB ($n = 3$), Bone ($n = 1$), and lymphadenitis ($n = 6$)}, 10 had disseminated TB (pulmonary and lymph nodes) and 1 had pulmonary tuberculosis. Median SUV max at baseline was 8.6 and 1 month after ATT was 5.3, with a median fall of 31%. 19/21 patients showed a fall in SUV max as well as clinical improvement 1 month after ATT. One of the two patients with no response on FDG PET was later diagnosed as NHL, while other patients had drug-sensitive tuberculosis [31]. The role of FDG-PET in patients with abdominal tuberculosis is reported in case reports. Park et al. reported a case of disseminated TB (right pleural effusion and right psoas abscess) where FDG-PET CT at baseline showed metabolic activity and on repeat scan at 9 months of ATT showed that regional hyperactivity previously revealed disappeared completely [32].

Anand et al. reported the role of barium series in the assessment of response to ATT in 39 patients with tubercular strictures. Trial was completed by 34 (87%) of

the patients, clinical response was reported in 31 (91%) of patients, rest of the 3 required surgery. Barium series after 1 year of ATT (Streptomycin 1 gm/day for 3 months, Rifampicin 450 mg/day for 1 year & Isoniazid 300 mg/day for 1 year) was available in 23 patients, 16 (70%) patients showed complete response to ATT. Of 7 (30%) patients with no response at 1 year, two patients showed response to another 1 year of ATT [15]. Another study by Appasani S et al. in 41 patients with abdominal tuberculosis reported most common site of stricture was at ileocecal region (n = 16, 36%), followed by ileum (n = 9, 21%), jejunum (n = 9, 21%), gastroduodenal (n = 6, 14%) and both jejunum and ileum in 4(9%) of patients. After 6–12 months of ATT barium series showed complete response in 11 (27%) patients, partial response in 11 (27%) patients, no response in 9 (22%) patients and worsening in 10 (24%) of the patients. Clinical improvement was reported in 80% of the patients while the radiological response was noted only in 54% of the patients [33]. Barium studies are not routinely used nowadays as cross-sectional techniques are being preferred.

21.2.2 Gastroduodenal Tuberculosis

Gastroduodenal tuberculosis is an uncommon form of intestinal tuberculosis. Common clinical features include recurrent vomiting, gastric outlet obstruction (GOO), pain abdomen and constitutional symptoms like fever, anorexia and weight loss. Involvement of other sites reported to be present in close to 40% of patients with the commonest sites being ileocecal, pulmonary and lymph nodal tuberculosis. Common endoscopic findings are presence of duodenal or prepyloric strictures, ulcers, growth, and extrinsic compression. Diagnostic yield of endoscopic and lymph node biopsy is low. We did a systematic review on gastroduodenal tuberculosis and found that only one-third of patients had granulomatous inflammation and only 3.6% of patients had AFB positivity, reasons being uncommon disease, paucibacillary nature, and submucosal involvement. Response to standard antitubercular therapy for 6 months and endoscopic dilatation of strictures is good. Response can be assessed clinically, symptoms like vomiting and GOO usually improve by 4–6 weeks and constitutional symptoms subside after the first month of ATT [34]. A study by Puri AS et al. reported 12 patients with gastroduodenal tuberculosis who presented with gastric outlet obstruction and managed with ATT for 6 months and endoscopic balloon dilatation. Patients were followed up clinically, endoscopically and serial upper GI barium series. Resolution of strictures was documented by passing of standard gastroscope and free passage of contrast on barium series [35]. Studies by Dalal A and Amarapurkar DN reported resolution of dyspeptic symptoms & vomiting and there was weight gain after starting ATT. Upper GI endoscopy was repeated which showed ulcer healing and resolution of strictures [36–38]. Study by Upadhyaya VD reported free passage of contrast on barium series after starting ATT [39]. These patients also can be followed by a trans-abdominal ultrasound to document normalization of wall thickness and resolution of lymphadenopathy. Endoscopic ultrasound may

be useful to document resolution especially if the predominant disease is submucosal [40].

21.2.3 Esophageal Tuberculosis

Esophageal tuberculosis is an uncommon form of extrapulmonary tuberculosis and usually involves secondary to mediastinal lymphadenopathy. Common presentation includes dysphagia, odynophagia, cough, hematemesis, and constitutional symptoms. Esophagoscopy and endosonography guided histopathology/cytology are the common modes of diagnosis while chest radiograph, barium swallow, and CT scan have a supportive role in diagnosis. On endoscopy, mid esophagus is the most common site of involvement with the presence of ulcer, stricture, submucosal bulge, fistula and pseudotumor are common findings. On EUS, presence of hypoechoic mediastinal lymphadenopathy with hyperechoic strands, matted lymph nodes, esophageal wall thickening and adventitial disruption are common findings [41–43]. Response to treatment can be assessed on clinical ground as the resolution of local and systemic symptoms. A study by Devarbhavi et al. reported 10 cases of esophageal tuberculosis, presenting as dysphagia, cough, and hemoptysis. After being treated with ATT for 6 months, all except one improved clinically and there was the healing of esophageal ulcers and sinuses/fistulas on follow-up endoscopy [44]. Similarly, Jain SK et al. reported clinical and endoscopic profile in twelve cases of esophageal tuberculosis. Dysphagia, retrosternal pain, cough, fever, and weight loss were reported common symptoms. Esophagoscopy revealed mid and lower esophagus ulcer, strictures, and pseudotumor. After 9 months of ATT, complete clinical and endoscopic recovery was reported in 9 patients, while 3 patients had concomitant carcinoma esophagus and later underwent surgery & radiotherapy [45]. Study by Tang Y et al. reported 35 cases of esophageal tuberculosis and followed up by endoscopy and EUS after 6 months of ATT. Follow-up EUS showed resolution of esophageal mass, esophageal wall thickness normalized and decrease in size of mediastinal lymph nodes with remnant hyperechoic patches was noted [46].

21.3 Peritoneal Tuberculosis

21.3.1 Biomarkers

CA 125 Serum CA-125 level can be elevated in patients with pulmonary and extrapulmonary (pleural, peritoneal, pelvic, miliary) tuberculosis. CA-125 is expressed by cells of coelomic epithelium and activation by inflammation and tumor can lead to an increased level in serum as well as in body fluids including pleural fluid and ascites [47, 48] Very high levels of CA-125 are reported in pelvic-peritoneal tuberculosis and it frequently masquerades as malignancy and reduction of serum CA-125 level with treatment is a valuable criterion for differentiation of tuberculosis from malignancy [49, 50]. A study by Yilmaz A et al. reported significantly

higher serum CA-125 levels at baseline in patients with active pulmonary tuberculosis compared to healed pulmonary tuberculosis patients and healthy control. Serial serum CA-125 levels at 2, 4, and 6 months of ATT and at 3 years of follow-up showed decreasing trend signifies role in the assessment of response to therapy [51]. Various case reports showed a reduction of CA-125 level after starting ATT in patients with pelvic-peritoneal tuberculosis. High level of CA-125 in ascites is reported by O'Riordian DK et al. and it is one of the markers of activity of tuberculosis [52]. Gurgan T et al. reported that after treatment level of CA-125 declines both in serum and body fluids and thus helps in differentiation from malignancy [53].

21.3.2 Ultrasonography of Abdomen

Study by Jain R et al. in 56 patients with early abdominal tuberculosis reported the presence of minimal ascites, mesenteric lymphadenopathy, bowel wall, and mesenteric thickening were the most common ultrasonographic (USG) findings. Ascites and omental thickening were reported in 30% (n = 17) and 5% (n = 3) patients respectively. Follow-up ultrasound at 1, 2, 6, and 12 months of ATT showed regression of both ascites and abdominal thickening [27].

Study by Kedar RP et al. reported peritoneal involvement is common in patients with abdominal tuberculosis. Common findings were ascites in 40% (n = 36), adhesions in 15.3% (n = 14), and peritoneal thickening in 14.4% (n = 13) of the patients. Other less common findings were club sandwich sign in 5.5% (n = 5) and peritoneal nodules in 3.3% (n = 3) of the patients. Follow-up of 38 patients with USG at 3 months was available and regression of ascites, bowel thickening and lymphadenopathy was noted [28].

21.4 Visceral Tuberculosis

21.4.1 Pancreatic Tuberculosis

Pancreatic tuberculosis is an uncommon form of abdominal tuberculosis and a great mimicker of pancreatic malignancy. Common presentations reported in literature are pain abdomen, anorexia, weight loss, jaundice, fever, and night sweats. Imaging features include solitary or multiple hypoechoic or mixed iso-hypoechoic solid or cystic lesions in pancreas with peripancreatic lymphadenopathy. Dilated pancreatic and common bile ducts, calcification and invasion of surrounding vascular structures are also reported. Other organ system involvement such as lungs, ileocecal junction, peritoneum, spleen and liver, and HIV positivity is reported in up to 50% of patients. EUS guided FNAC of pancreatic lesions or lymph nodes is a common mode of diagnosis and the presence of granuloma is the most common finding. Duration of ATT in available literature varies between 6 and 12 months and the cure rate is ~90% [54–56]. Response of therapy can be assessed by resolution of symptoms such as pain abdomen, fever, jaundice, and weight gain. Liver function tests

(LFTs) should be monitored more frequently as these patients may have cholestatic jaundice at presentation. Usually, cholestatic symptoms resolves after 2–4 weeks but complete normalization of LFTs might require 10–16 weeks [56]. Worsening of LFTs suggests ATT hepatitis or paradoxical reaction. Resolution of pancreatic mass, decrease in size of lymphadenopathy, and resolution of lesions at distant sites on follow-up USG and CT can be used for assessment of response to therapy. Kim JB et al. in their study of 42 patients reported that at 6 months of ATT only 30% of patients showed complete radiological response while two-third patients had a partial radiological response. In this study, 30 of the 42 patients received ATT for at least 9 months or more [57]. Follow-up EUS for the pancreaticobiliary system also can be used for assessment of response to treatment. A case series of six patients reported resolution of pancreatic mass 16–20 weeks after starting ATT [58]. One case report reported the utility of FDG-PET in the evaluation of response assessment in a patient with pancreatic tuberculosis [59].

21.4.2 Hepatobiliary Tuberculosis

Hepatobiliary tuberculosis is a rare form of extrapulmonary tuberculosis and usually associated with miliary, pulmonary, or intestinal tuberculosis. Hepatobiliary tuberculosis is classified as miliary tuberculosis and local/focal tuberculosis which is further divided into nodular TB (including tuberculous hepatic abscess, tuberculomas) and into the tubular form (involving intrahepatic ducts). Most common presentations of hepatic tuberculosis reported are pain abdomen, fever, anorexia, and jaundice. Jaundice could be due to granulomatous hepatitis or due to biliary tract involvement secondary to hepatic tuberculoma, biliary stricture, or extrinsic compression due to lymph nodal enlargement [60–62]. Alvarez et al. reported that abnormalities on chest X-ray and hepatic calcification on abdominal X-ray are common findings in these patients [62]. Common radiological findings include the presence of hypodense nodular lesions, abscess, features of extrahepatic biliary obstruction, and lymphadenopathy [63, 64]. Treatment is the same as abdominal tuberculosis and duration of ATT in literature varies between 6 and 12 months [61, 62]. Biliary obstruction may require biliary drainage along with ATT [65]. Biliary drainage can be done either by endoscopic retrograde cholangiopancreatography (ERCP) or percutaneous transhepatic biliary drainage (PTBD). Response to therapy is assessed by clinical response, improvement of liver function test (in granulomatous hepatits), and radiological resolution of hepatic lesions (focal or nodular hepatic TB). Alvarez et al. reported good clinical response to standard ATT in two-third of the patients [62]. Clinical response can be assessed by the disappearance of pain abdomen and fever, increase in appetite and weight. Biochemical response can be assessed by improvement of LFT and radiological response can be assessed by a decrease in size of liver, disappearance of hepatic nodules, abscess and

Table 21.2 Assessment of response to ATT in abdominal organs

Site of ATB	Clinical response	Lab parameter	Biomarker	Radiological response	Endoscopic healing
Intestinal TB	Improvement in pain abdomen, intestinal obstruction, diarrhea	Decrease in CRP, Decrease in fecal calprotectin Decrease in serum CA-125		Decreased bowel wall thickness, vascularity, and lymphadenopathy on GIUS, CTE, MRE. Decreased metabolic activity on FDG PET	Resolution of ulcers, pseudopolyps & narrowing
Gastroduodenal TB	Improvement in vomiting, GOO, pain abdomen	Decrease in CRP		Decreased bowel wall thickness, vascularity, and lymphadenopathy	Gastroscopy—resolution of ulcers & strictures. EUS—resolution of submucosal lesion.
Esophageal TB	Improvement of dysphagia, odynophagia, chest pain, and UGI bleed	Decrease in CRP		Decrease thickness of esophageal wall, resolution of mediastinal & paraesophageal lymphadenopathy	Esophagoscopy—resolution of ulcer, stricture, fistula. EUS—resolution of LAP, normalization of esophageal wall thickness
Peritoneal TB	Improvement in abdominal distension and pain	Decrease in CRP Decrease serum and ascitic fluid CA-125		Disappearance of ascites, peritoneal thickening & nodularity	
Pancreatic TB	Improvement in pain abdomen and jaundice	Normalization of LFTs Decrease in CRP		Decrease in pancreatic and distant lesions, improvement of peripancreatic and mediastinal LAP	EUS—decrease in pancreatic lesion, improvement of peripancreatic and mediastinal LAP
Hepatobiliary TB	Improvement in pain abdomen and jaundice	Normalization of LFTs Decrease in CRP		Decrease size of liver, improvement in liver abscess and nodular lesions of liver, resolution of abdominal LAP	

lymphadenopathy. Alvarez and Chen et al. reported that strictures due to hepatobiliary tuberculosis may be multifocal and difficult to treat and might require multiple percutaneous or endoscopic intervention [66, 67]. Adverse drug reaction to ATT is common in these patients due to malnutrition, underlying liver disease including cirrhosis and portal hypertension secondary to hepatobiliary tuberculosis. Close monitoring of LFTs is recommended during treatment in these patients. Despite ATT, these patients have high mortality because of concomitant respiratory failure due to miliary tuberculosis, esophageal variceal bleed due to associated cirrhosis and underlying HIV infection.

21.5 Conclusion

In a study of abdominal TB from South Korea, it was noted that intestinal, peritoneal, and visceral forms had a good response to therapy while those with nodal tuberculosis were less likely to achieve complete response [68].

To conclude, assessment of response to therapy is important in most forms of EPTB including abdominal tuberculosis. The response assessment should be mandatory in patients where the diagnosis is not microbiologically confirmed. While for visceral forms radiological assessment may be appropriate, endoscopic assessment for ulcer healing should be used in luminal forms (Table 21.2).

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Conflicts of Interest None.

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Surgery for Gastrointestinal Tuberculosis

22

Gautham Krishnamurthy and Harjeet Singh

Key Points

1. Abdominal tuberculosis is a significant problem in endemic country, which may require surgical intervention in a subset of patients.
2. Intestinal obstruction, perforation, and persistent symptoms despite medical management are indications for surgery.
3. The type of surgery, extent of resection, and creation of stoma or anastomosis depends upon patient's general condition, comorbidities, and disease process in the abdomen.
4. Antitubercular therapy should be the first line of therapy in stricturing disease but continuous symptoms may require endoscopic dilatation or surgical intervention.
5. Abdominal tuberculosis is curable with appropriate medical treatment and surgical intervention.

22.1 Epidemiology

Incidence of abdominal tuberculosis varies based on geographic distribution with incidence higher in endemic regions of tuberculosis. Abdominal tuberculosis accounts for 12% of all extra-pulmonary tuberculosis [1]. In India, 5–9% of small intestine perforations are secondary to tuberculosis [1]. The overall response rate

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with multidrug antitubercular regimens is around 90% [2]. This is associated with good mucosal healing and clinical improvement in terms of symptoms. However, a subset of patients do not exhibit adequate clinical response despite appropriate medical management. This could be due to poor response due to multidrug resistance, good responders but with dominant fibrotic healing, complications like intestinal obstruction or perforation, and co-existing diseases such as malignancy.

The advent of effective antitubercular therapy has reduced the requirement for surgery in abdominal tuberculosis. While ATT remains the first choice for chronic and subacute presentations, 20–40% of abdominal TB have acute abdomen and require emergency surgery [1]. It is imperative for surgeons, in endemic and non-endemic regions of tuberculosis, to have comprehensive knowledge of this pathology since delayed diagnosis and inappropriate treatment are responsible for poor outcomes in 4–12% of patients [3]. In addition, incidence of postoperative complications including intra-abdominal infection, recurrent obstruction, and wound related complications is higher. Mortality in acute setting can be as high as 25% [4].

22.2 General Considerations in Surgery for Abdominal Tuberculosis

22.2.1 Patient Related

The prevalence of risk factors for tuberculosis such as poor nourishment, endemic region, underlying immunosuppressive status among patients with abdominal tuberculosis diminish their physiological reserve [5]. Two additional factors may co-exist to play a counterproductive role. One is the compromise of the intestinal lumen, either intrinsic due to stricture or extrinsic as sclerosing peritonitis or adhesions. This results in reduced oral intake due to attendant abdominal pain thereby worsening the nutritional condition of the patient. Acute physiological derangement due to intestinal perforation can be the additional insult. Sepsis accompanying these individuals can be fatal given the underlying chronic debilitation due to the pathological process.

22.2.2 Disease Related

Abdominal tuberculosis is accompanied by history or active pulmonary tuberculosis in 50% of patients [2]. Respiratory reserve and infectivity of the pulmonary tuberculosis has to be considered when surgery is contemplated. Anesthesiologists are at risk in these scenarios and measures such as appropriate scheduling, possible negative pressure theater, increased frequency of air exchange, and wearing N95 masks might reduce the infectivity [6]. Similarly, preoperative chest physiotherapy cannot be overemphasized for reduced lung volume. Awareness of drug interactions of anesthetic agents with antitubercular drugs must be noted. The notable

interactions arise from induction or inhibition of cytochrome P450 enzyme by rifampicin and isoniazid, respectively [6]. Intraoperatively these patients are prone for hypothermia given the likely sarcopenia [6].

The chronic nature of the disease also mandates attention to nutrition. High carbohydrate and protein diet is necessary to improve outcomes of surgery. If not orally tolerated, nasogastric tube feeding or even perioperative parenteral nutrition may be required. Attention must be paid towards correcting fluid and electrolyte disturbances. Possibility of refeeding syndrome in chronically malnourished patients should be considered.

22.3 Indications for Surgery

Surgery for abdominal tuberculosis is indicated in the following clinical scenarios:

1. Symptomatic abdominal tuberculosis
   (a) Emergent indications—obstruction, perforation, and bleeding
   (b) Persistent symptoms—ileocecal mass, stricture, cocoon abdomen
   (c) Fistulizing intestinal tuberculosis
2. Diagnostic dilemmas
   (a) Diagnostic laparoscopy
   (b) Resection of bowel

Gastrointestinal involvement including peritoneal tuberculosis could be incidentally detected during surgery performed for other indications.

22.4 Surgery for Symptomatic GITB

22.4.1 Intestinal Obstruction

Obstruction is most commonly caused by intestinal stricture. Intestinal strictures occur in nearly half of patients with intestinal tuberculosis [7]. Patients with tuberculous stricture usually present with recurrent subacute intestinal obstruction (SAIO) leading to malnourishment and poor quality of life. However, it is not rare for delayed presentation with acute intestinal obstruction. Despite good response of tubercular pathologies with antitubercular therapy, only one-fourth of tubercular strictures shows complete resolution with medical therapy and nearly one-fifth of them requires surgery [2, 8]. They can also be associated with perforation in acute setting [9]. Multiple strictures can occur in nearly one-third of patients with tubercular strictures [9].

Stricturoplasty offers the advantage of preserving gut length especially in multiple strictures [10]. In patients who had previously proven and treated tuberculosis, strictures are highly cicatrized and inactive. In this group of patients, stricturoplasty is preferred. The safety of stricturoplasty has been well established [10, 11]. It is

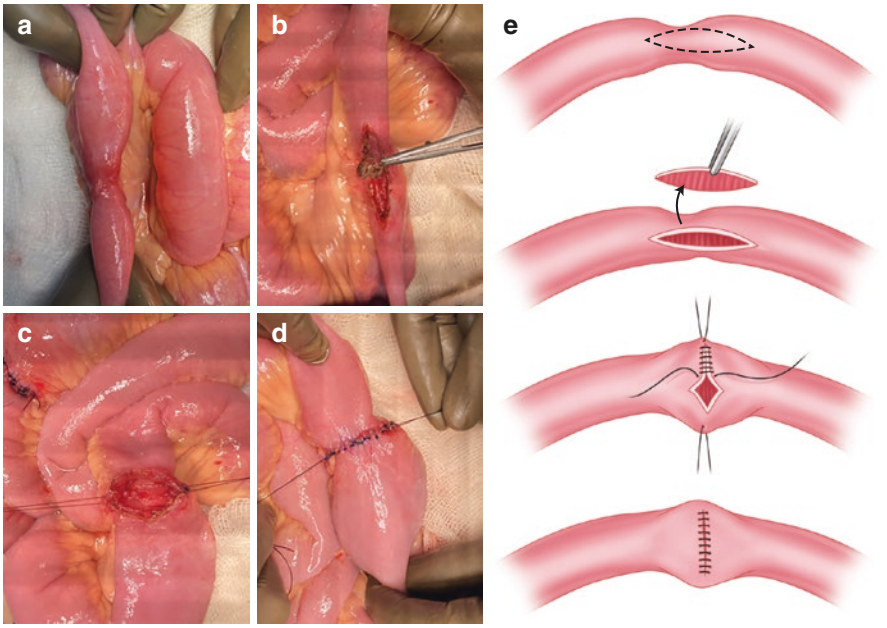

Fig. 22.1 Intraoperative picture and illustration showing stricturoplasty technique. (**a**) showing tubercular stricture involving terminal ileum. (**b**) Small elliptical disc of tissue is removed in longitudinal axis for biopsy. (**c** & **d**) defect is closed transversely with interrupted sutures. (**e**) Depiction of the technique

performed for isolated tubercular strictures with no associated mass forming lesions or perforation. Both small bowel and large bowel strictures are amenable for stricturoplasty (Fig. 22.1). Resection for tubercular strictures is preferred during emergency surgeries, absence of definitive preoperative diagnosis (especially diagnostic dilemma with Crohn's disease), and when associated with perforation. The choice of primary anastomosis or stoma formation is based on the general condition of the patients and surgeon's preference based on the clinical circumstances [9]. Resection can be combined with stricturoplasty in case of multiple strictures. Multiple strictures which are placed closely to each other can be resected. Otherwise, the dominant stricture believed to be responsible for the symptoms could be resected and stricturoplasty performed for the rest of the strictures to conserve remnant bowel length.

22.4.2 Perforation

Incidence of tubercular perforation ranges from 1–11% of intestinal tuberculosis (Fig. 22.2) [12]. Among the patients undergoing surgery, the proportion of this subgroup of patients can be as high as one third [9, 12]. The mechanism of perforation includes proximal blow-out secondary to distal distention (stricture or adhesion),

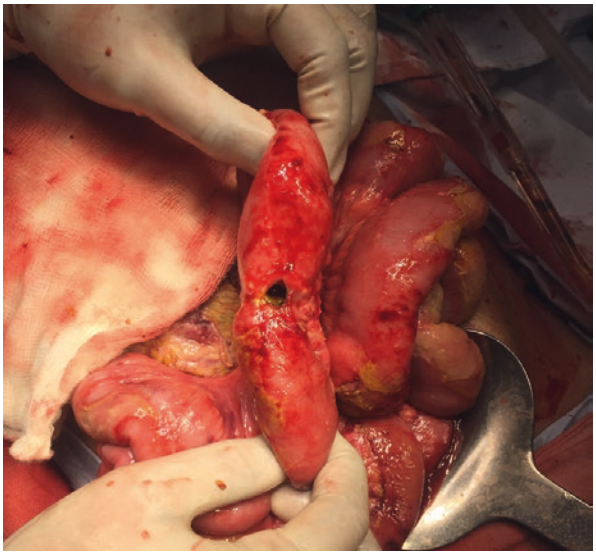

Fig. 22.2 Intraoperative picture showing tubercular perforation in terminal ileum

perforation of tubercular ulcer, and possible vasculitis [13]. Multiple perforations and associated stricture are common [14]. Spectrum of clinical presentation ranges from free perforation with peritonitis, contained perforation, chronic perforation in cocoon abdomen, and chronic fistula [12, 14]. For example, pneumoperitoneum can be absent in over 60% of cases of tubercular perforation due to the multiple adhesions localizing the peritoneal contamination [14]. The varied clinical presentation often results in significant diagnostic dilemma and requires tailoring of the surgical approach. Tubercular perforations have poor outcome with mortality as high as 30% [15].

Free perforation of tuberculous ulcer requires management like intestinal perforations of other etiologies. Care must be exercised in obtaining appropriate samples for histological and microbiological analysis to confirm tuberculosis since 10% of patients may not have antecedent history of tuberculosis. After resuscitation, formal laparotomy and peritoneal lavage are performed. In the presence of associated stricture and/or multiple perforations, segmental resection is recommended [16]. Given the poor general condition of these patients, stoma formation is preferred over primary anastomosis but is not mandatory [9, 12]. Primary closure has limited role in the management of acute free perforation given the high incidence of associated stricture and poor general condition of these patients. Perforations can also be multiple in around half of patients with tubercular perforation mandating resection [17]. In the absence of the above features simple perforation closure can be attempted.

Contained perforation within an adhesion or cocoon abdomen is sometimes difficult to diagnose preoperatively [15, 18]. They may be explored for persistent SAIO despite maximal medical management. On exploration, the intestines might be densely adherent to each other and multiple perforations opening within the cavity

may be detected. Aggressiveness of dissection should be customized based on the hostility of the abdomen. In most scenarios, it may be possible to perform adhesiolysis and perform resection of perforated bowel segments. However, sometimes the friable nature of bowel and dense adhesions poses high risk for iatrogenic bowel injury. Postoperative proximal enterocutaneous fistula in these compromised individuals could endanger life. Therefore, it might be prudent to place multiple drains to lateralize the enteric contents and be aggressive in the postoperative period with regard to management of enterocutaneous fistula, antitubercular therapy, and nutrition.

22.4.3 Gastrointestinal Bleeding

Intestinal tuberculosis causing gastrointestinal bleed is rare [19]. Though the common source of bleed is an ileocecal pathology, rest of the small and large intestine can also be sites of bleeding tubercular pathology. While occult bleed is usually managed medically, massive bleed requires emergency laparotomy [20, 21]. In case if localization is not possible prior to laparotomy, site of tubercular bleed might be indicated by morphological changes such as stricture or adjacent lymphadenopathy. In the absence of such features or when multiple lesions identified intraoperatively, it is ideal to perform intraoperative enteroscopy for localization. After localization, segmental resection of the involved bowel segment can be performed.

22.4.4 Ileocecal Mass

Apart from presenting along with stricture or perforation, surgery for ileocecal tubercular mass may be performed for resistant tubercular disease or persistent symptoms (Fig. 22.3) [9]. They account for 10% of indications for surgery in

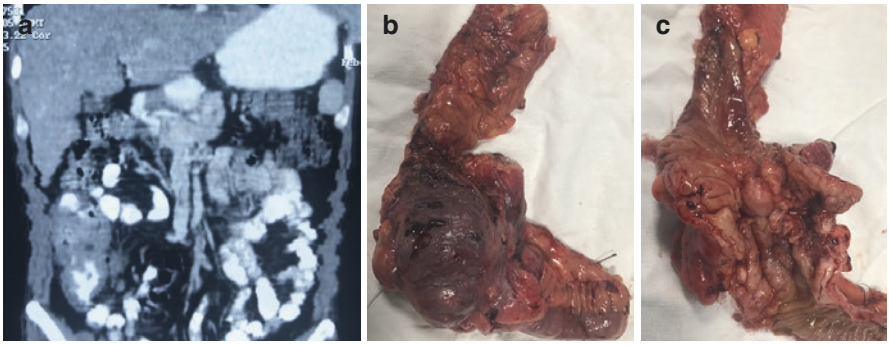

Fig. 22.3 (**a**) Contrast enhanced CT showing mass lesion involving ileocecal and ascending colon. (**b**) Resected ileocecal specimen. (**c**) Cut section showing hypertrophic lesion with formation of pseudopolyps

abdominal tuberculosis. Rarely, they have been found to harbor secondary pathology such as malignancy [22]. Conservative surgery is usually sufficient given the benign nature of the disease [1]. Hence ileocecal resection is preferred to right hemicolectomy. The dense adhesions with retroperitoneum, associated peritoneal disease, and shortened right colon may make identification of ureter problematic and could result in difficult ileocecal resection as compared to other indications. Laparoscopic approach is feasible but is associated with need for extra port, longer operative time, and lateral to medial approach when compared to laparoscopic right colonic resection for malignancy [23]. Postoperative outcomes are however similar.

22.4.5 Abdominal Cocoon

Abdominal cocoon is characterized by small bowel encasement by fibrocollagenous sac (Fig. 22.4). Tuberculosis is one of the important causes for abdominal cocoon. The patients might present with intestinal obstruction or peritonitis [24, 25]. Surgery for tubercular abdominal cocoon has additional morbidity when compared to non-tubercular etiologies. Apart from the covering membrane, the dense inter-bowel adhesions pose high risk for iatrogenic complication [24].

Principles of surgery include complete excision of membrane by sharp dissection, minimal manipulation of bowel, and beginning dissection from inter-mesentery to inter-bowel during adhesiolysis [25]. In case of perforation, resection of perforated bowel segment is preferred. In few patients, proximal enterostomy can be performed to overcome obstruction and avoid iatrogenic injuries. Definitive management, if required, can be performed after optimization of the patient (antitubercular therapy and nutrition). Surgery for tubercular cocoon is associated with significant morbidity (enterocutaneous fistula, early postoperative small bowel obstruction, burst abdomen, etc.) and mortality of 13.3% [24, 25]. Technical

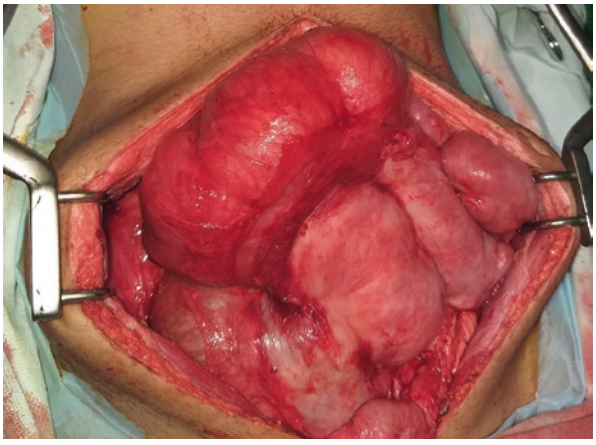

Fig. 22.4 Intraoperative picture showing tubercular cocoon

demanding nature of the pathology makes outcomes likely to be better in high volume center and is thus preferable to be performed by experienced surgeons.

22.5 Diagnostic Laparoscopy

22.5.1 Peritoneal Involvement

After extensive evaluation with imaging and peritoneal fluid analysis, it might not be possible to diagnose tuberculosis unequivocally [26]. This situation is further compounded by differential diagnosis like peritoneal carcinomatosis wherein the further management differs. Diagnostic laparoscopy in such scenarios is of immense help. In fact, few studies have advocated early laparoscopy to overcome the diagnostic dilemma [26, 27]. Visual characterization of the peritoneal disease can accurately predict as high as 95% [28]. These include distribution and size of nodules (tubercles or yellow-white miliary nodules) over the parietal or visceral peritoneum. Bigger targeted sample of these and biopsy of lymph node if present improves accuracy.

22.5.2 Technical Considerations

Peritoneal tuberculosis is compounded by dense inter-bowel adhesion and adhesion of bowel with parietal wall. The placement of the first port hence remains a challenge. Preoperative imaging might indicate an area of relatively safe abdominal wall for entry in case of segmental sclerosing peritonitis. However, open technique should be preferred. The consequences of inadvertent bowel injury in the cocoon abdomen during entry, especially when performed for diagnostic purposes, can be devastating. The peritoneal tuberculosis might also limit the expansion of the abdominal cavity given the decreased compliance of the abdominal wall. Distended bowel, ascites, and dense adhesions further limit visualization. Peritoneal biopsies when performed should ensure adequate tissue for analysis. Performing lymph node biopsy in a conglomerate of lymph nodes will require energy devices to secure hemostasis and hence appropriate planning with additional ports may be required. Given the relatively small size of these tissues, energy sources should be avoided during biopsy to avoid cautery artifacts. The tissue samples must be sent in appropriate solutions such as formalin for histological evaluation and normal saline for GeneXpert or AFB culture (MGIT).

22.5.3 Resection for Diagnosing Intestinal Tuberculosis

Another important dilemma is limited ileocecal disease but lack of clarity regarding underlying diagnosis. This is especially common when the concern is regarding differentiating intestinal tuberculosis and Crohn's disease. The improved efficacy and

newer adjuncts in endoscopy have reduced the requirement for performing surgery for diagnostic purposes. However, the diagnosis may remain unclear even after repeated endoscopic biopsies and assessment. In such situations, empiric ATT is often resorted to in endemic countries with assessment of endoscopic healing at two months (early mucosal response). However, in patients who have symptoms consistent with obstruction, upfront surgery may provide an immediate symptomatic relief with a conclusive diagnosis.

22.5.4 Technical Considerations

The diminished abdominal fat and possible underlying adhesions require abdominal exploration to be meticulous. The initial step will be assessment of the disease process. It is better to perform resection methodically following a specific sequence. Apart from ascertaining the disease burden, additional information altering management may be encountered. These include distal stricture in case CT enterography limited by failure of contrast to pass distally precluding evaluation of distal intestinal segment. Similarly, intestinal stricture diagnosed with endoscopy might be associated with extraneous early cocoon formation missed during preoperative imaging. After assessment, multiple biopsies must be taken in case of lack of definitive preoperative histological diagnosis.

22.6 Incidentally Detected Abdominal Tuberculosis

In endemic regions of tuberculosis, it is not uncommon to detect tuberculosis during surgery performed for other indications [29]. It can be either in elective or emergency settings. Sometimes surgery is performed with preoperative suspicion of malignancy or inflammatory pathologies but histology of resected specimen shows concomitant tuberculosis [22]. Managing these patients with histological surprise is generally straightforward which includes administration of antitubercular therapy. The more challenging situation is to manage patients who are diagnosed with incidental peritoneal tuberculosis during exploration for other conditions. Problems posed with incidentally detected peritoneal tuberculosis are two-fold. The diagnostic dilemma of differentiating it from peritoneal carcinomatosis and the safety of proceeding with the proposed procedure. Based on our experience, we suggest frozen section for diagnosis and proceeding with proposed surgery with postoperative antitubercular therapy [29].

22.7 Fistulizing Intestinal Tuberculosis

Intestinal tuberculosis may manifest with entero-enteric, enterocutaneous, and enterovesical fistula [30]. They may be either spontaneous or post-surgical. Ruling out causes of spontaneous fistula such as diverticulitis, malignancy, Crohn's

disease, and radiation is essential. Pathological and microbiological examination is sufficient in majority to establish diagnosis of tubercular fistula. In the absence of emergent indications, antitubercular therapy remains first line of treatment [31]. Persistent fistula after antitubercular therapy requires fistula excision along with the underlying diseased bowel segment to avoid recurrence [32]. In endemic regions, undiagnosed tuberculosis can be cause of recurrence or refractoriness of perianal fistula [33, 34]. Hence, in these situations, it is prudent for the surgeon to rule out tubercular infection by additional investigation such as PCR [33].

It is not uncommon for patients operated for proven or suspected abdominal tuberculosis to develop enterocutaneous in the postoperative period [17]. Iatrogenic injury to intestine during extensive adhesiolysis or anastomotic leak are the usual etiologies. It is also possible for secondary tubercular perforation in the postoperative period to present in such a manner. Apart from the routine management in enterocutaneous fistula (control of sepsis, fluid and electrolyte correction, nutrition and wound care) immediate initiation of antitubercular therapy should be considered. It can be initiated even based on clinical suspicion since the microbiological results such as cultures might be delayed. Intravenous antibiotics and nutrition should be administered in case a patient is not tolerating orally [35]. Once the acute management of enterocutaneous fistula is completed, definitive management of fistula can be delayed until completion of 6-month regimen in the absence of emergent indications.

22.8 Antitubercular therapy for surgeons

Figure 22.5 shows the algorithm we follow in surgical patients requiring antitubercular therapy.

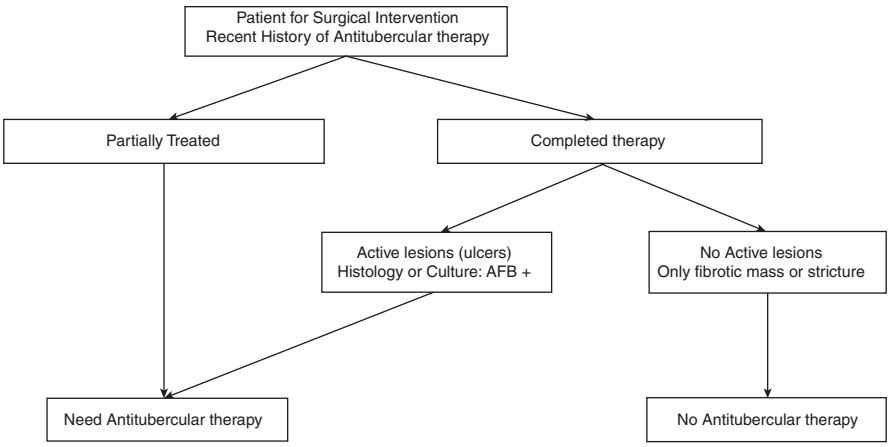

Fig. 22.5 Algorithm for surgical patients with prior history of antitubercular therapy

22.9 Conclusion

The role of surgery in abdominal tuberculosis is largely limited to emergent indications. These include intestinal obstruction, perforation, and bleeding. Intestinal obstruction may be secondary to intestinal or peritoneal tuberculosis. Surgeons should be aware that abdominal tuberculosis is basically a medical condition and the surgery is directed at tackling the emergency rather than the removing macroscopic disease which are asymptomatic. In case of absent preoperative histological evidence of tuberculosis, it is prudent to take multiple biopsies to improve diagnostic yield.

Conflict of Interest None**.**

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Antitubercular Therapy-Related Hepatitis

23

Sandeep Satsangi, Shivani Randev, and Sunil Taneja

Abbreviations

ACLF	acute-on-chronic liver failure
ALF	acute liver failure
ALT	alanine aminotransferases
ATP	adenosine triphosphate
ATS	American Thoracic Society
ATT	anti-tuberculous therapy
BTS	British Thoracic Society
CHB	chronic hepatitis B
CHC	chronic hepatitis C
CLD	chronic liver disease
CTP	Child–Turcotte–Pugh
DILI	drug-induced liver injury
ETH	ethambutol
FQL	fluoroquinolones
GST	glutathione S-transferase
HAART	highly active antiretroviral therapy
HEV	hepatitis E virus

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HIV	human immunodeficiency virus
INH	isoniazid
NAC	N-acetylcysteine
NAT	N-acetyltransferase
NICE	National Institute for Clinical Excellence
PT	prothrombin time
PZA	pyrazinamide
RMP	rifampicin
RNTCP	Revised National Tuberculosis Control Programme
ROS	reactive oxygen species
TB	tuberculosis
ULN	upper limit of normal
WHO	World Health Organization

Key Points

1. ATT constitutes one of the most prevalent drugs which lead to drug-induced liver injury.
2. Among the first-line antitubercular therapy drugs, pyrazinamide is believed to be most hepatotoxic, followed by isoniazid and rifampicin.
3. There are several risk factors like age, gender, nutritional status, concomitant chronic viral hepatitis, and presence of underlying chronic liver disease, which are reported to influence the predilection of a patient with TB to develop ATT-related hepatotoxicity.
4. Prompt withdrawal of hepatotoxic ATT medications remains the cornerstone for the immediate management of ATT-related DILI.
5. With the current data, it would be acceptable to suggest that a sequential regimen of starting ATT with or without pyrazinamide rather than a concomitant regimen would be suitable as a re-introductory regimen especially in patients having a higher risk of developing ATT-related hepatotoxicity.

23.1 Introduction

Although the majority of tuberculosis (TB) cases (85%) are treated successfully with anti-tuberculous therapy (ATT) drugs, treatment-related adverse effects remain a prime reason for treatment discontinuation. Skin reactions, gastrointestinal upset, and hepatotoxicity are among the most common adverse effects of ATT drugs. Drug-induced liver injury (DILI) leads to discontinuation of the drug in about 11% of patients receiving a combination of rifampicin (RMP), isoniazid (INH), and pyrazinamide (PZA) [1]. DILI is primarily of three types: (a) direct, (b), idiosyncratic, and (c) indirect [2]. (Table 23.1) ATT drugs constitute one of the most prevalent groups which lead to idiosyncratic DILI [3, 4]. Overall, DILI due to ATT drug therapy has been reported in around 5% to 28% of patients [3]. The reported

Table 23.1 Types of drug-induced liver injury

	Types of drug-induced liver injury		
	Direct	Idiosyncratic	Indirect
Dose dependency	Yes	No	No
Frequency	Common	Rare	Rare
Latency period	Usually short	Very variable	Typically delayed
Mechanism	Due to agents that have inherent toxicity to liver. Predictable	Due to agents with no inherent toxicity to liver Unpredictable	Due to action of the drug rather than its hepatotoxic potential Partially predictable
Example	High-dose acetaminophen, aspirin, niacin	Amoxicillin–clavulanate, minocycline, nitrofurantoin, isoniazid	Glucocorticoids (leading to fatty liver), Rituximab (hepatitis B flare)

mortality after the onset of jaundice due to ATT DILI is about 4% to 12%. Patients with ATT-related ALF are also reported to have higher mortality (67%) [4]. Among the first line of ATT drugs that are used (INH, PZA, RMP, and ethambutol), the first three are associated with hepatotoxicity. Among the three, PZA is the most hepatotoxic, followed by INH and RMP [5]. The following section describes in detail about these hepatotoxic ATT drugs.

23.2 Isoniazid (INH)

INH has bactericidal properties and is effective both against the extra- and intracellular organisms. It acts by inhibiting the mycolic acid synthesis. INH-induced liver toxicity is primarily hepatocellular, causing necrosis and steatosis. The toxic metabolites of INH bind to cellular macromolecules and lead to DILI [6]. Around 0.5% of the patients being treated with INH monotherapy develop raised aminotransferase levels [7]. In patients wherein combination therapies of INH are used (without RMP), the usual incidence of liver toxicity is around 1.6%, whereas in patients with regimens including both INH and RMP, the incidence of hepatotoxicity is around 2.5% [8]. INH is primarily cleared by the liver and is metabolized by two pathways, cytochrome P4502E1 (CYP2E1) and N-acetyltransferase 2 (NAT2) pathways [9]. (Fig. 23.1) The NAT2 pathway leads to the formation of diacetyl hydrazine which is a nontoxic compound. The other pathway involving the hydrolysis and cytochrome P4502E1 pathway leads to the formation of toxic metabolites like acetyl diazine and other reactive acetyl onium ions and acetyl radicals, which have the capacity to covalently bind to cellular macromolecules and cause DILI. Hydrolysis constitutes the minor pathway for INH metabolism; however, in the presence of RMP and in slow acetylators, this minor pathway could dominate, leading to increased incidence of DILI [10]. Genotypes of NAT2 which have been associated with slow acetylation have about a fourfold higher risk of having INH-related DILI [11]. In a

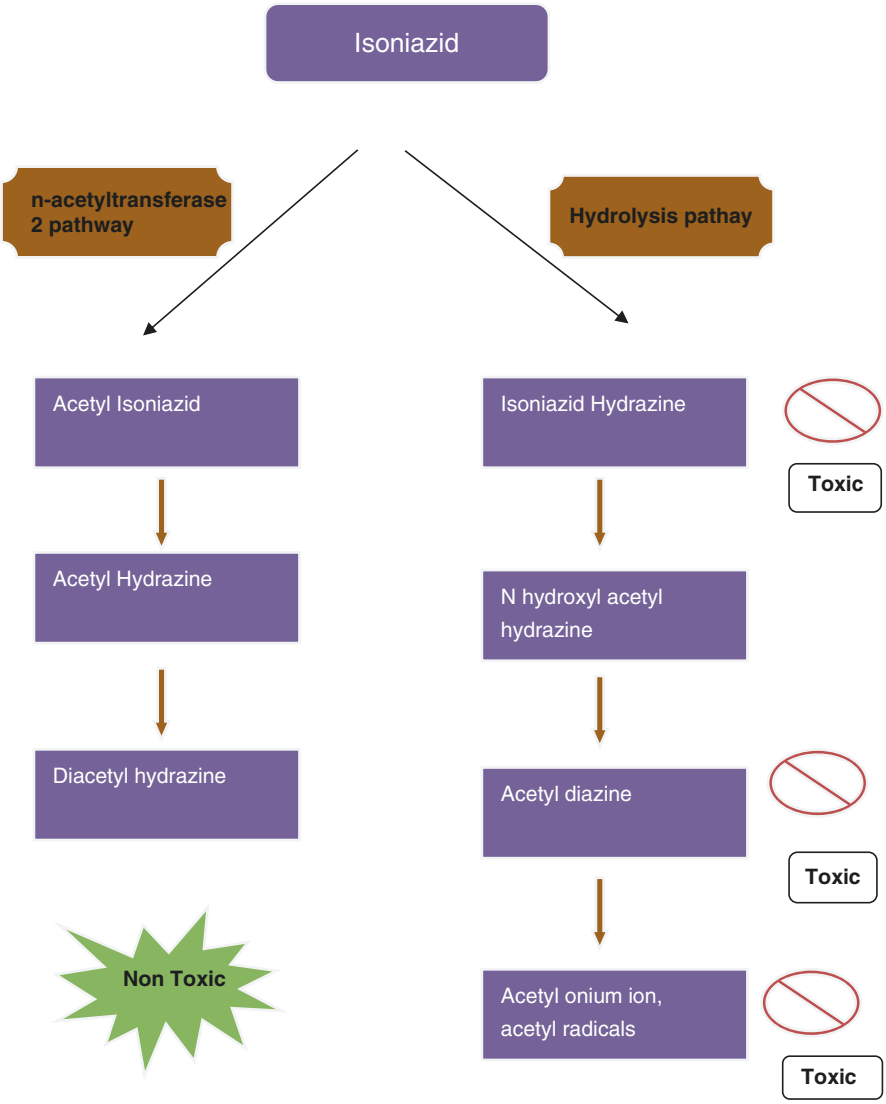

Fig. 23.1 Pathway of isoniazid (INH) metabolism

meta-analysis that included 474 cases and 1446 controls, the odds ratio to develop INH-related hepatotoxicity was 4.6 in slow acetylators [12]. Glutathione is known for its free radical scavenging properties and removal of toxic metabolites of drugs, and it was hypothesized that individuals having polymorphisms at the glutathione S-transferase (GST) loci would have a higher incidence of ATT DILI. In a pivotal study by Roy et al. [13], it was shown that null mutations of GSTM1 were two times more common in cases with anti-TB DILI when compared to controls. INH-related

hepatotoxicity thus appears to be an immune-related idiosyncratic phenomenon due to the toxic metabolites [14].

23.3 Rifampicin (RMP)

RMP possesses bactericidal properties and leads to inhibition of mycobacterial DNA-dependent RNA polymerase. RMP is metabolized by deacetylation to deacetyl rifampicin and hydrolysis to 3 formyl rifampicin. These metabolites are usually excreted in the bile. RMP-medicated hepatotoxicity is idiosyncratic in nature [15]. RMP-related DILI is usually hepatocellular, and it potentiates the hepatotoxicity of other ATT drugs. RMP may also cause dose-dependent interference in the bilirubin uptake as it competes with it for clearance at the sinusoidal membrane. This can lead to mild unconjugated hyperbilirubinemia without hepatocellular injury. However, RMP can also inhibit the major bile salt exporter pump, which impedes the secretion of conjugated bilirubin. This can transiently lead to conjugated hyperbilirubinemia [16]. Idiosyncratic type of RMP-induced DILI is known to occur in the first month of therapy [17].

23.4 Pyrazinamide (PZA)

PZA is a derivative of nicotinic acid and undergoes deamidation to form pyrazinoic acid, which is the active form of PZA. The half-life of PZA is longer than RMP and INH. When given at a high dose of 40–50 mg/kg, hepatotoxicity appears in about 15% of patients [18]. Doses of 25–30 mg/kg, which are currently employed in the ATT regimens, are much safer. PZA has the potential to cause both dose-dependent and idiosyncratic type of DILI. PZA can also lead to hypersensitive reactions with eosinophilia, liver injury, and granulomatous hepatitis [19].

23.5 Fluoroquinolones (FQL)

FQL are used primarily as second-line agents to treat TB in the setting of multidrug-resistant cases or in patients where first-line agents cannot be used. Hepatotoxicity related to FQL is extremely uncommon and related to hypersensitivity type of reactions with eosinophilia and fever [20].

23.6 Clinical Features

The clinical features of ATT-related DILI have a wide spectrum of variation in terms of severity. The presentation can range from asymptomatic elevation of transaminases to acute hepatitis leading to acute liver injury and acute liver failure. A mild increase in aminotransferases while the patient is on ATT is seen in around 20% of

patients, and they are usually asymptomatic. This phenomenon is labeled as hepatic adaptation wherein the elevated transaminases normalize with the continuation of ATT drugs [5]. When symptomatic, the majority of patients have nonspecific symptoms like nausea, vomiting, and abdominal pain. In a study from a large TB center in the UK, ATT-related DILI was reported in 6.9% of patients. Around half the cases of DILI occurred within the first 2 weeks of starting ATT and 87.6% occurred within 8 weeks. The commonest symptoms among patients presenting with ATT-related DILI were nausea and vomiting in 54% of patients followed by abdominal pain in 18% and skin complaints in 17%. Clinical jaundice was noted in around 12% of patients [21]. In a study from Western India, 82 patients with DILI were evaluated, of which 49% were due to ATT drugs. The most common symptoms noted in this study were nausea and vomiting in around 90% of patients with DILI, followed by abdominal pain in 73% and anorexia in 69% of patients. The authors also showed that there was significantly higher mortality for patients with ATT-related DILI (17.5%) vs. those without (2.4%) [22]. In a pivotal study from South India, ATT was the etiology for DILI in 58% of all cases presenting with DILI (n = 313) over a period of 11 years, and ATT was the culprit in around 76% of cases of drug-induced acute liver failure (ALF) [4]. It was also noted in this study that the majority of the patients were relatively younger in age (mean age around 40 years). The mortality rate reported in this study was high (67%) among patients with ALF due to ATT. In another key study by Kumar et al [23], 1223 consecutive patients with ALF were evaluated, and ATT was determined to the etiologic agent in 70 (5.7%) patients. The authors noted that the median time duration of ATT intake before the onset of ALF was about 30 days. In comparison to patients having ALF due to hepatitis E virus (HEV) and non-A non-E etiology, patients with ATT-related ALF were older in age and had a lesser elevation of liver enzymes. The mortality rate was noted to be high among patients with ATT-ALF (67.1%). The authors suggested three factors that independently predicted mortality on the basis of their study - serum bilirubin ≥10.8 mg/dl, elevated prothrombin time (PT) (≥26 seconds), and the presence of high-grade (III/IV) hepatic encephalopathy at presentation [23]. It is thus vital to understand that ATT-related DILI can have a wide variation in its clinical presentation, which can range from the asymptomatic rise of transaminases and mild symptoms of nausea to severe acute liver injury and ALF.

23.7 Risk Factors for ATT-Related DILI

The factors mentioned below have been reported to influence the predilection of a patient with TB to develop ATT-related hepatotoxicity (Fig. 23.2):

(a) *Age*: Age has been incriminated as a risk factor to increased predisposition to ATT-related DILI in various studies. In a study assessing over 500 patients on standard ATT, a 3.5-fold higher risk for ATT-related DILI was observed in patients over the age of 60 years [1]. In another study, it was noted that PZA-related adverse effects and DILI were higher (2.6-fold times) in patients above

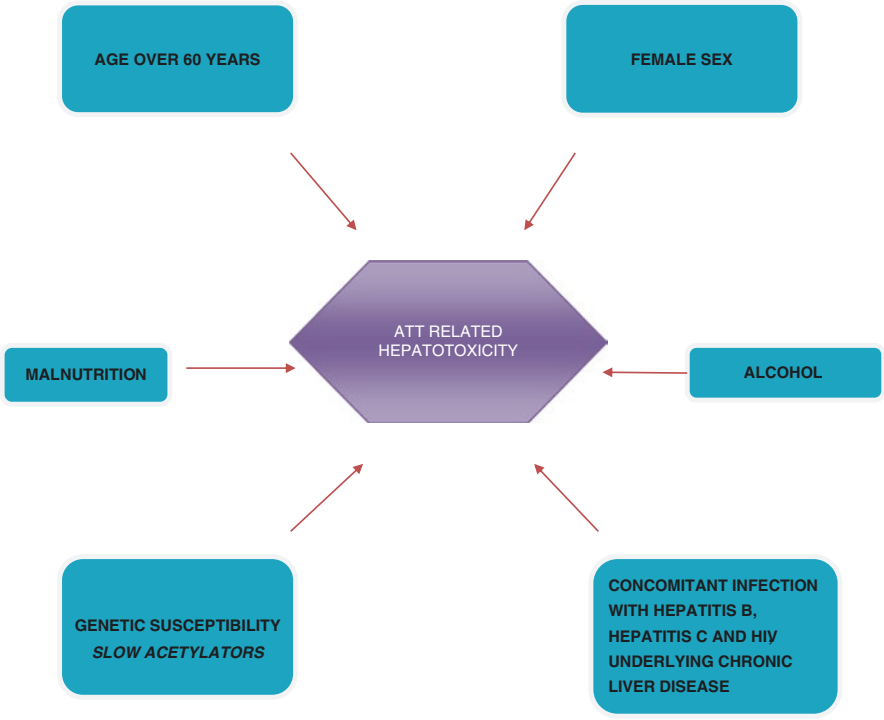

Fig. 23.2 Risk factors to develop ATT-related hepatotoxicity

60 years [24]. The incidence of INH-related DILI is noted to be higher among patients aged above 50 years [25, 26]. Data from another prospective clinical study noted that age over 35 years was an independent predictor to develop ATT-related DILI. Those aged less than 35 years had a 17% risk of ATT-related DILI when compared to 33% among patients who were over 35 years old [27].

The incidence of ATT-induced hepatitis reported in children from various parts of the world ranges from 1.8% to 6.5%, the variations being attributed to the regimen used, drug doses, diagnostic criteria, and type of surveillance, whether active or passive [28, 29]. With the recent increase in pediatric doses of rifampicin (to 10-20 mg/kg/day from previous 10 mg/kg/day) and isoniazid (to 10–15 mg/kg/day from previous 5 mg/kg/day) recommended for use in children, there are concerns about the increase in the incidence of liver injury. A recent Indian study reported an overall incidence of ATT-induced hepatotoxicity in children as 2.3%: 1.9% with old doses of ATT and 2.7% with revised doses; the increase was, however, not statistically significant [30].

(b) *Gender*: Various studies have reported that women have a higher predilection (fourfold higher risk) to develop ATT-related DILI when compared to men [31]. The activity of the cytochrome enzyme (CYP3A) is reported to be on the higher side in females which in part can explain this higher risk [32].

(c) *Nutritional status*: Several studies have noted a link between the presence of underlying malnutrition and increased risk of developing ATT-related DILI [33]. In a study by Warmelink et al., it was noted that patients who had a loss of weight of two kgs or more within a span of 4 weeks of ATT had a higher predilection to develop ATT-related DILI [34].

(d) *Alcohol intake:* Several studies have also linked alcohol consumption to a higher risk of ATT-related DILI. The propensity of alcohol to induce liver enzymes is the postulated mechanism for this link [35, 36].

(e) *Concomitant chronic viral infection:* Studies have linked a higher predilection of having ATT-related DILI in patients with underlying chronic hepatitis B (CHB) infection. In a study by Wang et al. [37], patients with CHB had a higher risk of developing ATT-related DILI when compared to patients who were uninfected (16% vs. 4.7% $p < 0.001$). This study also demonstrated that the degree of hepatotoxicity is linked directly to the viral load at the time of starting the ATT. Similar data have also been noted in those patients infected with chronic hepatitis C (CHC) infection. In a study from Miami, it was observed that 30% of patients with CHC infection developed ATT-related DILI when compared with 11% of uninfected patients. The authors similarly noted a trend to increased severity of DILI in those with higher hepatitis C viral load [38]. A study by Anand et al. noted that the presence of concomitant CHB and underlying chronic liver disease were significantly associated with the development of ATT-related DILI [39]. Human immunodeficiency virus (HIV) infection also increased the risk of ATT-related DILI. Various studies from the highly active antiretroviral therapy (HAART) era have noted the risk of ATT-related DILI to be around 4% to 27% among patients on ATT having concomitant HIV infection [40].

(f) *Presence of underlying liver disease:* The presence of underlying cirrhosis increases the risk for ATT-related DILI. ATT-related DILI in a patient with underlying cirrhosis can trigger an acute-on-chronic liver failure (ACLF), which carries a higher risk of mortality.

(g) *Genetic predisposition:* Polymorphisms of various genes coding for the enzymes involved in the drug metabolism have been linked to increased predisposition to ATT-related DILI. The prime candidates are genes linked to NAT2 and CYP2E1, which can lead to the formation of reactive drug metabolites and trigger hepatotoxicity. Studies have also shown that the presence of HLA-DQB1*0201 allele and the absence of HLA-DQA1*0102 allele were associated with a higher risk of ATT-related hepatotoxicity [35].

23.8 Pathophysiology

The pathophysiology of ATT-related hepatotoxicity can be understood as follows:

1. *The initiating event:* The factors leading to the higher formation of drug metabolites as resulting from phase I metabolism or factors which lead to reduced detoxification as a consequence of the failure of phase II metabolism are likely the key

inciting event. The reactive drug metabolites lead to cellular stress by overwhelming the antioxidant defense mechanism or binding with lipids, nucleic acids, or cellular enzymes. These metabolites can also lead to lipid peroxidation, which can lead to cell death [41]. The involvement of mitochondria is also considered a key link in the pathophysiology of DILI. When the mitochondrial respiratory chain is affected, it results in the depletion of adenosine triphosphate (ATP) which can, in turn, lead to the production of reactive oxygen species (ROS) [42].

2. *The immune response*: An innate immune response is known to propagate or inhibit an inflammatory process, and it thus plays a key role in deciding the fate of progression and severity of DILI. Innate immunity not only guides the production of cytokines involved in hepatic inflammation but also assist in liver regeneration. Inhibition of histone modification is another potential link mediating DILI. Histone acetylation is known to have a key role in gene transcription, and thus exhaustion and depletion of the enzyme histone acetyltransferase can result in the inhibition of hepatic regeneration and thus propagating DILI [43].

23.9 Diagnosis of ATT-Induced Hepatitis

ATT-induced hepatitis is diagnosed based on the international criteria developed for drug-induced hepatitis.

The criteria included are as follows: [5].

(a) Elevation of transaminases higher than 3 times the upper limit of normal (ULN) or 2 times the ULN of bilirubin in the presence of associated symptoms like anorexia, nausea, vomiting, pain in the right upper abdomen, and jaundice.
(b) Elevation of transaminases higher than 5 times the ULN without the presence of associated symptoms.

23.10 Management of ATT-Related DILI

The guidelines to manage and approach a patient with ATT-related DILI come from the British Thoracic Society (BTS) [44], the American Thoracic Society (ATS) [19], and the National Institute for Clinical Excellence (NICE), UK [45]. (Fig. 23.3). Revised National Tuberculosis Control Programme (RNTCP) from India has also issued its guidelines in 2019 for reinstituting ATT drugs after the diagnosis of ATT-related DILI [46].

(a) *Risk stratification*: It is apt to screen the patient for risk factors that lead to increased predisposition to ATT-related DILI. These include assessment of nutritional status, alcohol intake, and evaluating for the presence of superimposed co-infections with hepatitis B, hepatitis C, and HIV. It is imperative to rule out underlying chronic liver disease, which could increase the risk of ATT-related hepatotoxicity. Assessment of this risk–benefit ratio is extremely vital when planning to empirically start ATT.

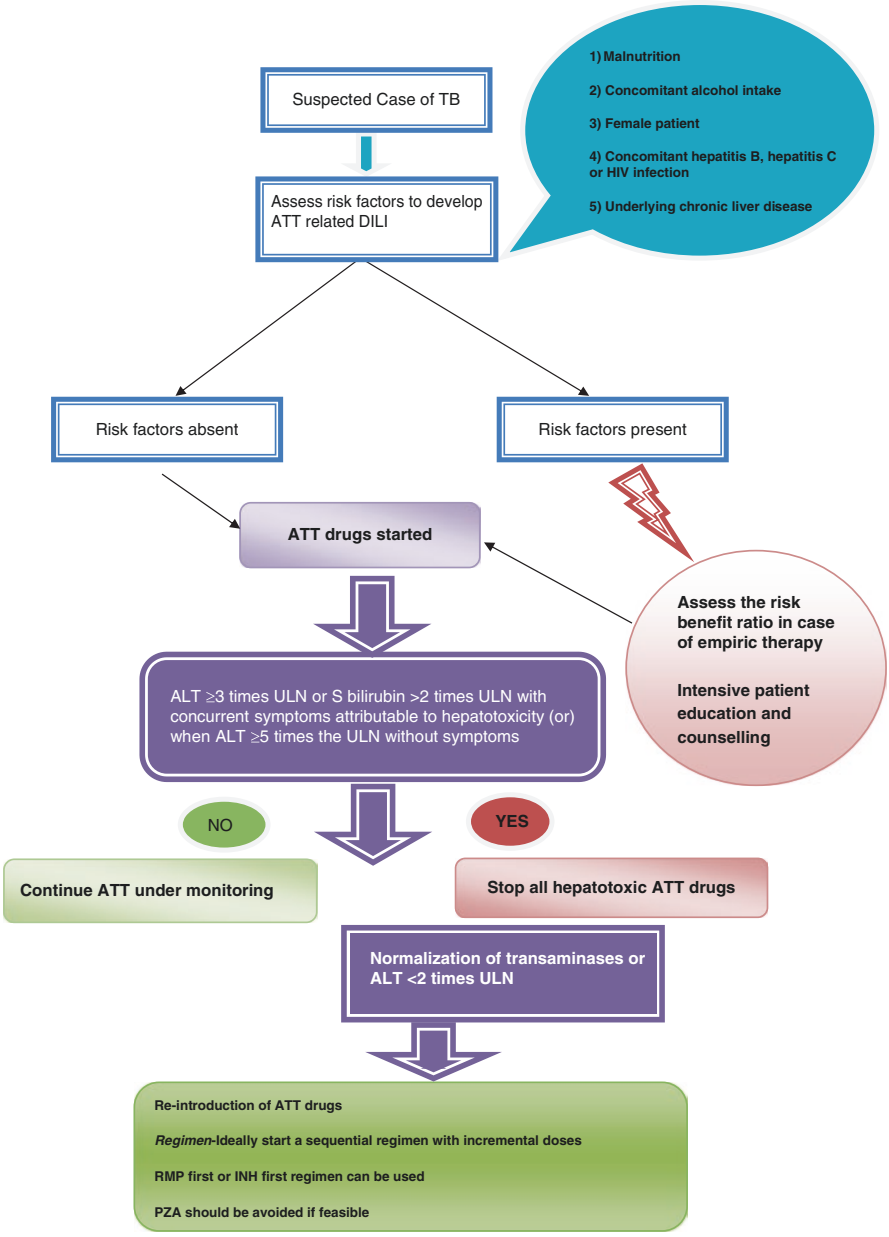

Fig. 23.3 Protocol to follow in case of ATT-related DILI

(b) *Immediate action:* Prompt withdrawal of ATT medications remains the cornerstone for the immediate management of ATT-related DILI. As mild elevations of transaminases would not justify stoppage of ATT (as they may be a consequence of hepatic adaptation), it is recommended that all the potential hepato-

toxic ATT drugs need to be stopped only when alanine aminotransferases (ALT) reach three times the ULN with concurrent symptoms attributable to hepatotoxicity or when the ALT becomes five times the ULN in the absence of associated symptoms [9]. Isolated hyperbilirubinemia without elevation of transaminases does not fulfill the definition of DILI by the DILI working group though the BTS guidance suggests careful monitoring and potentially stopping the hepatotoxic drugs [21, 44]. In patients where the clinical situation merits continual of ATT drugs, non-hepatotoxic drugs like FQL, cycloserine, ethambutol (ETH), and aminoglycosides can be considered. After the withdrawal of ATT drugs, the hepatotoxic anti-TB drugs need to be withheld till normalization of transaminases or at least till the ALT drops below two times the ULN [8].

(c) *Re-introductory regimens*: In view of the high efficacy of the first-line ATT drugs, it is imperative to consider them in the treatment regimen. It has been noted that the risk of having a repeat episode of ATT-related DILI is around 11% to 24% on re-exposure of the same drug regimen [47]. The BTS and ATS guidelines suggest reintroducing the ATT drugs one at a time; however, the World Health Organization (WHO) recommends starting all the drugs simultaneously and starting the drugs in a consecutive manner only in case of a repeat episode of ATT-related DILI. The RNTCP 2019 guidelines from India recommend adding the primary ATT drugs in a consecutive manner after the liver enzymes become less than 2 times ULN. It suggests starting with a full dose of rifampicin first, and the other ATT drugs are added (in full dose) every 3 days, with regular LFT monitoring. A new drug is reinstituted only if the ALT is less than twice the ULN [46].

An elegant study randomized 175 patients into 3 different regimens of reintroduction and noted no significant difference in the occurrence of ATT-related repeat DILI [47]. In another study by Tahaoglu et al. [48], the authors concluded that the incidence of ATT-related DILI was higher if the ATT drugs were re-initiated in a full-dose regimen (including pyrazinamide) when compared to a regimen which included a gradual reintroduction of anti-TB drugs without pyrazinamide. In a recent network meta-analysis to assess the impact of various re-introductory regimens on the risk of developing ATT-related hepatotoxicity, four randomized controlled trials with 577 patients were analyzed. It was shown that the sequential regimen with incremental doses of anti-TB drugs was linked to a significantly reduced risk of ATT-related hepatotoxicity when compared to the concomitant full-dose regimen. This meta-analysis also suggested that the re-introductory regimen using RMP first or INH first leads to similar rates of ATT-related hepatotoxicity [49]. With the current data, it would be acceptable to suggest that a sequential regimen with or without PZA rather than a concomitant regimen would be suitable as a re-introductory regimen especially in patients having a higher risk of developing ATT-related hepatotoxicity, e.g., those with malnutrition, concomitant hepatitis B, and hepatitis C infection [47]. Using an incremental dose strategy for RMP and INH, wherein one drug is started at a time using half its dose initially, it would be feasible to identify the drug responsible for hepatotoxicity if and when the transaminases get elevated. This incremental dose regimen would likely be less hepatotoxic

as the patient is not exposed to all the hepatotoxic drugs at full dose simultaneously. However, a longer time is required to attain the target dose of ATT drugs for the patient. There is currently no concrete evidence to suggest that 3 times per week regimen is less hepatotoxic than a daily regimen [50]. As INH and RMP are very efficacious in the management of TB, it is imperative that their use is considered in the ATT regimen whenever feasible.

Possible regimens would include [9]**.**

(i) *Regimen containing two hepatotoxic drugs:*
- Nine months of RMP and INH, plus ETH.
- Two months of RMP, INH, amikacin, or streptomycin and ETH, followed by six months of RMP and INH.
- Six to nine months of RMP, PZA, and ETH.

(ii) *Drug regimen with one hepatotoxic drug:*
- Two months of INH, ETH, and amikacin or streptomycin, followed by 10 months of INH and ETH.

(iii) *Drug regimen with no hepatotoxic drugs:*
- Eighteen to twenty-four months treatment with a combination therapy of ETH, FQL, cycloserine, and aminoglycoside or capreomycin can be considered.

23.11 ATT Regimen in Patients with Underlying Cirrhosis

The severity of DILI may be more severe when occurring in the setting of underlying cirrhosis. ATT-related DILI can trigger an ACLF in patients with underlying CLD, which can be associated with high mortality. In a recent study by Devarbhavi et al. [51], ATT was incriminated in the etiology of acute insult in 27.3% of patients who presented with drug-induced ACLF. The authors also noted that mortality was higher in patients with ACLF in whom the acute insult was related to drugs vs. those with non-drug-induced ACLF (46.5% vs. 38.8%). This data emphasizes the extreme vigilance which has to be taken in monitoring therapy with ATT drugs when used in patients with underlying cirrhosis. Table 23.2 provides a guide on the regimen to be used in patients with underlying cirrhosis based on the basis of Child–Turcotte–Pugh (CTP) score [52].

23.12 Role of Drugs in ATT-Related DILI

Withholding ATT drugs having hepatotoxic potential in case of development of ATT-related DILI is the primary step in the management of such patients. Baniasadi and colleagues evaluated the role of N-acetylcysteine (NAC) in preventing ATT-related DILI in an RCT, which compared ATT with NAC vs. ATT alone. The authors noted that hepatotoxicity related to anti-TB drugs occurred in 37.5% of patients in the group not receiving NAC and none in the group where

Table 23.2 ATT regimen in patients with underlying cirrhosis of liver

Child–Turcotte–Pugh score	ATT regimen to be used	Underlying liver disease
≤7 *CTP class A*	**2 hepatotoxic drug regimens can be used-** ϖNine months of therapy with RMP and INH, plus ETH (or) ϖTwo months of therapy with RMP, INH, and ETH, which is followed by seven months of RMP and INH [54]	**Stable liver disease**
8–10 *CTP class B*	**1 hepatotoxic drug regimen can be used-** ϖTwo months of therapy with INH (or) RMP with ETH and aminoglycoside, which is followed by ten months of therapy with INH and ETH [53]	**Advanced liver disease**
≥11 *CTP class C*	**No hepatotoxic drugs to be used** ϖEighteen to twenty-four months treatment using a combination of ETH, FQL, cycloserine, and aminoglycoside or capreomycin [53]	**Very advanced liver disease**

concomitant NAC was administered [53]. However, more studies are required to confirm the role of NAC in preventing ATT-related DILI, especially in patients with underlying risk factors.

23.13 Conclusion

TB continues to impose a significant healthcare burden in the world, and in India. Accurate diagnosis and prompt treatment remain the cornerstone to control the wrath imposed by this disease. As the first-line drugs used in the treatment of TB have a predilection for causing hepatotoxicity, identifying the high-risk patients and careful monitoring on therapy play a vital role in the early diagnosis and apt treatment. A knee-jerk reaction of stopping ATT drugs should not be done with a marginal rise in transaminases (hepatic adaptation) as, in most cases, they would normalize and prevent the development of drug-resistant tuberculosis. When specific stopping rules are attained, as mentioned above, stopping ATT drugs and continuing anti-TB medicines without hepatotoxic potential are recommended. A sequential regimen with incremental doses of drugs currently seems to be the norm in planning the re-introductory regimen, especially in patients having risk factors in developing ATT-related DILI.

Conflict of Interest None.

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Part VII

Miscellaneous

Pediatric Abdominal Tuberculosis

24

Rishi Bolia

Abbreviation

ADA	Adenosine deaminase
AFB	Acid-fast bacilli
ATB	Abdominal tuberculosis
ATT	anti-tubercular therapy
CBNAAT	cartridge-based nucleic acid amplification test
CD	Crohn's disease
FDC	Fixed drug combinations
FNAC	Fine needle aspiration cytology
GI	gastrointestinal
ITB	Intestinal tuberculosis
SAAG	serum ascitic albumin gradient
TB	Tuberculosis

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Key Points

1. Pediatric abdominal tuberculosis is primarily a disease of the developing world.
2. It can have a varied presentation, frequently mimicking other diseases. Abdominal pain, fever, and weight loss are the triad of symptoms most commonly seen.
3. Multiple abdominal sites are frequently involved in children.
4. Establishing the diagnosis can be challenging. A unique aspect about childhood tuberculosis is the history of contact with an infected person.
5. Doses of anti-tubercular drugs per mg body weight is higher in children as compared to adults. Treatment duration for pediatric abdominal TB is usually 9–12 months.

24.1 Introduction

Children have been neglected in the fight against tuberculosis (TB) for years. Of the ten million cases of tuberculosis recorded worldwide in the year 2018, an estimated 1.1 million were children, of which an estimated 205,000 children died [1]. An alarming 96% of these deaths occurred among children who were untreated which highlights the fact that tuberculosis in children is frequently unrecognized [2]. Apart from this, children also represent a significant but underappreciated proportion of the multi-drug-resistant TB burden with an estimated 30,000 children each year [3]. India has by far the highest burden of tuberculosis in children, which is not surprising considering its large size, demographic composition, and moderate tuberculosis prevalence [4].

Pulmonary tuberculosis is overall the commonest site of tubercular involvement in children, and abdominal tuberculosis has been reported to comprise 0.3–4% of all cases of tuberculosis. [5–7] This is likely an underestimate. An autopsy study of children who died from TB showed that 15.7% children had abdominal involvement. [8] Abdominal tuberculosis is relatively rare in children when compared to adults. It has been reported mainly from developing countries, especially the Indian subcontinent and is rare in developed nations. Delisle et al. in a review spanning 70 years (1946–2014) found only a total of 45 cases reported in the literature form Europe, North America, New Zealand and Australia. Even among these all patients except one were from high-risk populations, including aboriginals, foreign born and those with a history of recent travel to endemic countries. [8].

Abdominal TB occurs in four forms: tuberculosis of the abdominal lymph nodes, peritoneal tuberculosis, gastrointestinal tuberculosis and visceral tuberculosis and may occur as a result of hematogenous spread from a primary complex elsewhere, by the ingestion of the tubercle bacilli or by contiguous extension from other adjacent organs.

The protean clinical manifestations make it a challenge for the physicians to establish the diagnosis, even more so in the pediatric age group where a child's

inability to define their problems accurately contribute to this challenge. It is important to remember that abdominal TB in a child is not like TB in a miniature adult. There are many important differences in the disease presentation, site and type of the disease, diagnostic evaluation and treatment, which have been highlighted in the next few sections.

24.2 Clinical Features

Abdominal TB usually presents in childhood in the age—group of 9–14 years and does not have a predilection to any gender. [7, 9–14] (Table 24.1) It is often initially confused with other conditions, and the diagnosis is usually delayed. A median delay of 4–6 months in diagnosis has been reported in literature even from the endemic areas where there is a general awareness of this condition. The clinical spectrum depends on the site of involvement. It ranges from nonspecific symptoms to those that may mimic Crohn's disease. Overall, abdominal pain (61.5–81%), fever (31–90%), and weight loss (40–74%) are the most frequent findings on presentation [7, 9–14]. In patients of the pediatric age group, loss of body weight is defined as >5% weight loss in the preceding 3 months. In a child presenting with these triad of symptoms, one should suspect abdominal TB. Table 24.1 includes the clinical features noted in the major series of patients with pediatric abdominal tuberculosis.

In 33–37% patients, extra-abdominal symptoms including respiratory (cough, breathlessness, etc.), neurological (headache, seizures), genitourinary symptoms, cervical/axillary lymphadenopathy, and dermatological manifestations (erythema nodosum) may be present.

24.2.1 Disease Distribution

There is considerable variability in the distribution of the disease within the abdomen reported from different centers. The reason for this variability includes differences in clinical setting (secondary care center vs tertiary referral center) and the specialties (pediatrics vs pediatric gastroenterology vs pediatric surgeon) from which the data is published. Overall, the spectrum of disease in children is different from adults, in whom peritoneal and lymph nodal involvement is more common than gastrointestinal disease [9].

In the largest series of cases of pediatric abdominal TB reported from Chandigarh, lymph nodal involvement was overall the commonest [12] (Table 24.2). Involvement of multiple abdominal sites is common. In the series from Chandigarh, a substantial number (54%) had involvement of multiple sites with a combination of intestinal and lymph nodal involvement being the commonest. In an autopsy series of 24 children with ATB, it was found that, in 82% (14/17) cases of intestinal TB, the intestinal lesion extended to the peritoneum, while 2/7 children with presumed isolated peritoneal TB had evidence of disease arising from other abdominal sites,

Table 24.1 Clinical features of children with abdominal tuberculosis

	Turkey ($n = 35$)	Taiwan ($n = 10$)	India Lucknow ($n = 38$)	India Chandigarh ($n = 218$)	India Ajmer ($n = 125$)	Tunisia ($n = 13$)	Europe, North America, NZ & Australia ($n = 45$)
Mean age	9.7 ± 4.3 years	14.7 years	11 (4–16) Years	10 (0.25–12) Years	9.5 (2–14) Years	9.8 (7–14) Years	5–9 years–3 10–13 years–5 >14 years–11
Gender (M)	54.3%	40%	45%	54%	40%	23%	64%
Duration of symptoms	109 days (10 days– 3 years)	–	4.5 mths (15 days–5 years)	4 mths (0.5–36) months	54 day (7 days–9 months)	4.2 mths (4 days–1 year)	–
Fever	31.4%	90%	66%	76%	80%	31%	71%
Weight loss	40%	72%	71%	74%	58%	54%	68%
Anorexia	–	–	76%	66%	54%	54%	27%
Abdominal pain	62.9%	80%	66%	81%	80%	61.5%	76%
Abdominal mass	–	–	11%	6%	32%	15.4%	32%
Diarrhea	–	0%	18%	21%	14%	–	29%
Intestinal obstruction	–	0%	21%	16%	36%	7.7%	–
Abdominal distension	45.7	–	63%	43%	38%	61.5%	–
Doughy abdomen	–	–	–	27%	12%	–	–
Hepatomegaly	16.1%	–	42%	32%	6%	7.7%	–
Splenomegaly	16.1%	–	21%	15%	4%	16%	–
Ascites	74.3%	40%	47%	26%	44%	69%	68%
Extra-gastrointestinal symptoms	31.4%	100%	21%	21%	16%	16%	37%
Mortality	2.8%	10%	8%	–	0%	0%	9%

Table 24.2 Distribution of the disease within the abdominal cavity

	Turkey ($n = 35$)	India Lucknow ($n = 38$)	India Chandigarh ($n = 218$)	India Ajmer ($n = 125$)	Tunisia ($n = 13$)	Developed ($n = 45$)
Peritonitis	83%	24% (39.4%)	10.1% (35.3%)*	44%	38.4%	42%
Gastro-intestinal	14.3%	16% (39.4%)	16% (54.5%)	20%	–	49%
Lymph nodal	–	16% (39.4%)	17.9% (68.8%)	36%	7.7%	–
Visceral	–	5%	2% (8.2%)	–	–	–
Multiple sites	–	32%	54%	–	54%	–

(*)when those with involvement in multiple sites are also included

reiterating the fact that coexistence of TB at multiple sites of the abdomen is common in children [8]. Lymph nodal involvement varies from 7.7 to 68% of children with abdominal TB. The most commonly involved lymph nodes are the mesenteric nodes, peri-pancreatic, retroperitoneal, and omental nodes, and those along the celiac axis. However, it should be remembered that the presence of enlarged mesenteric lymph nodes alone does not mean that the child has abdominal TB as it is a common, non-specific finding in children. The diagnosis of TB should only be considered in the appropriate clinical context. The sonographic finding of oval and elongated lymph nodes with a short-axis diameter up to 10 mm in children should be considered a normal finding and should not be misdiagnosed as an early manifestation of tuberculosis [15].

Among children with intestinal TB (ITB), ileocecal involvement is the commonest and is seen in up to three-fourth of all children with ITB. Increased physiological stasis with a maximal period of contact, abundant lymphoid tissue, and minimal digestive activity in this region are reasons for this occurrence. The left-sided colon may be involved in ~40%. Clinical symptoms specific to ITB include abdominal pain (60%), diarrhea (40%), intestinal obstruction (20%), and blood in stools (10%) [16]. Growth failure is seen in up to 60%. The differentiation between ITB and Crohn's disease is often a challenge as microbiologic confirmation of ITB is possible only in around 40% cases. In a study by Singh et al., 20 children with ITB were compared with 23 children with CD. Features of subacute intestinal obstruction (20% vs 0%), ascites (30% vs 0%), and isolated ileocecal involvement (40% vs 8.7%) favored ITB. [16] The presence of blood in stool and left-sided colonic involvement were independent predictors of CD. On colonoscopy, the presence of deep, longitudinal ulcers with involvement of multiple segments is more suggestive of CD than TB. Perianal disease in children is seen exclusively in children with CD. This is in contrast to adults, where even though perianal disease is more common in CD it has been reported even in ITB. [16].

At times even after taking all the clinical, endoscopic, and biochemical parameters into account, it is not possible to conclusively differentiate between the two diseases. A therapeutic trial of anti-tubercular therapy (ATT) is safer than starting steroid in children in whom there is a diagnostic dilemma and up to one-third of children with CD receive ATT before a diagnosis of CD is made.

Overall, peritoneal involvement is reported in 35.3–83% of children with abdominal tuberculosis. Similar to adults, it includes the wet type (which is characterized by ascites formation), a dry fibrotic type (associated with a thickened peritoneum, adhesions, and omental thickening with little or no ascites), a mixed type (which is a combination of both), and abdominal cocoon (characterized by the presence of a membranous sac around the intestinal loops). Children with the wet type of peritoneal TB generally present with progressive diffuse or localized abdominal distension and pain in association with constitutional symptoms like fever, anorexia, and weight loss. Children with the dry fibrotic type or abdominal cocoon often present with features of abdominal pain and distension, vomiting, and constipation suggesting intestinal obstruction. In a series of 110 children with abdominal TB presenting to a pediatric surgical department with features of intestinal obstruction, an abdominal lump, or entero-umbilical fistula, 91% (n = 100) were found to have adhesive (dry fibrotic) peritonitis. Out of these 100 patients, 23 also had mesenteric lymph nodal involvement [17]. Abdominal cocoon is also known as subacute encapsulating peritonitis which is a known cause of intestinal obstruction although it is rare in children. In a small series of 17 children all presented with features of small bowel obstruction [18].

Visceral (hepatic, splenic) tuberculosis is usually associated with an active pulmonary disease or miliary tuberculosis and isolated involvement (<2%) is rare. Fever, weight loss, right or left hypochondriac pain, and hepatosplenomegaly are the most frequently observed clinical findings. Jaundice is a very rare manifestation of tuberculous liver involvement and may be caused by extra- or intrahepatic obstruction.

Tubercular involvement of the stomach, duodenum, and esophagus in children is hitherto rare [12].

24.2.2 Congenital TB

A rare form of tuberculosis in children is congenital TB. By 2005, only ~400 cases had been reported in the literature [19]. TB during pregnancy may lead to infection of the placenta or the genital tract, which may then be transmitted to the fetus either hematogenously from the placenta to the umbilical vein or by aspiration or ingestion of contaminated amniotic fluid. In infants in whom the mode of acquisition is transplacental, the primary complex develops in the liver, while in those in whom it occurs by the ingestion of infected material the primary is in the gastrointestinal (GI) tract. As it primarily involves the liver and GI tract, i.e., has abdominal involvement, it has been included in this chapter.

The Cantwell criteria is used for the diagnosis and is as follows [20]:

Proven tuberculosis lesions in the infant plus one of the following:

1. Lesions occurring in the first week of life
2. A primary hepatic complex

3. Maternal genital tract or placental tuberculosis
4. Exclusion of postnatal transmission by thorough investigation of contacts

The average age at the onset of congenital tuberculosis is 24 days (range, 1–84 days). The symptoms are often nonspecific and include fever, irritability, poor feeding, hepatosplenomegaly, and respiratory symptoms. It is particularly hard to diagnose because it is seldom distinguishable from other neonatal and congenital infections seen in this age group. A majority (60–70%) of mothers of patients have no symptoms of TB, which makes this condition even difficult to recognize. Most mothers are diagnosed with tuberculosis only after the child has been diagnosed with tuberculosis [20].

A high index of suspicion is needed for the diagnosis of congenital TB. Tuberculin testing is generally normal. Abdominal imaging (ultrasonography, CT) is a useful tool in diagnosing lesions in the liver and spleen. The sensitivity of liver biopsy for the diagnosis of congenital tuberculosis is 100%; however, it is an invasive test [21]. One may first try isolating the bacilli from other samples such as gastric aspirates, ascitic fluid (if present), pleural fluid (if present), and/or cerebrospinal fluid as the disease is often disseminated. A proportion (~50%) of patients may have an abnormal chest radiograph which may suggest the diagnosis.

Historically, the prognosis of congenital TB has been poor with up to 50% mortality seen. A delay in diagnosis being the most important reason for it [22]. However, with timely diagnosis and initiation of treatment, outcomes have improved.

24.3 Diagnosis

Establishing the diagnosis of abdominal tuberculosis can be challenging in children. The paucibacillary nature of the disease in children, difficulties in obtaining adequate samples for analysis, and the technical problems in obtaining proper imaging are some of the things that contribute to this difficulty.

Diagnostic tests can be divided into two categories:

1. *Test for definitive diagnosis*
   (a) Demonstration of acid-fast bacilli on smear or culture

   It is the most definitive method to diagnose tuberculosis. Samples are obtained depending on the site of involvement.
   - Ultrasound-guided fine-needle aspiration cytology (FNAC) of enlarged lymph nodes, focal lesions in the liver and spleen, omentum, and thickened bowel may have a yield of 45–58% [23, 24].
   - Endoscopic biopsies from the lesions has an AFB detection rate of 36.1%. Ileocolonoscopy in younger children can be challenging and can be done only in tertiary centers where appropriate expertise and equipment (pediatric colonoscopies) are available.
   - Demonstration of AFB in ascitic fluid is seen in only ~10% children [25]. Ascites with a low serum ascitic albumin gradient (SAAG) and lymphocytic predominance is a characteristic of tuberculosis.

- The rates of bacteriological confirmation have remained at ~50% from 1976 to 2019. It appears that the advances in the diagnostic modalities have not translated into higher microbiological yields [11].

(b) Histopathology showing tubercular granuloma
- Tissue obtained during endoscopy may demonstrate the presence of caseating granulomas on histology in ~60% of children with intestinal TB.
- Laparoscopy is an invaluable tool when the diagnosis is unclear, with a pick-up rate of 85%. Thickened peritoneum with miliary yellowish white tubercles with or without adhesions may be seen. However, it is invasive and is generally done only when the imaging features raise doubts about the possibility of a malignancy, since a lymphoma in a child can mimic TB in every way or there continue to be progressive symptoms even after initiation of anti-tubercular therapy, i.e., failure of a therapeutic trial.
- In children with hepatic involvement, a liver biopsy may help in confirming the diagnosis.

(c) Cartridge-based nucleic acid assay (CBNAAT).

In all children with suspected abdominal TB, the appropriate specimen from the involved site should be collected and subjected to CBNAAT. It is rapid and fully automated and is based on polymerase chain reaction that detects deoxyribonucleic acid directly from the clinical specimens. It can also detect rpoB gene mutations that confer rifampicin resistance. In adults it has a pooled sensitivity and specificity of 23% (95% CI16–32%) and 100% (95% CI 52–100%), respectively, for intestinal TB [26]. Pediatric data are lacking.

2. *Investigations that support the diagnosis*

(a) Radiology

An abnormal imaging plays a pivotal role in the diagnosis of abdominal TB and has the highest yield. However, caution should be exercised in the interpretation of the radiological findings and a diagnosis of TB should only be considered in the appropriate clinical context. This is especially true in children with isolated mesenteric lymph node enlargement where unwarranted treatment is rife.

(b) Chest X-ray—It is a useful adjunct in establishing the diagnosis of tuberculosis. A third of patients may not have pulmonary symptoms and are detected to have pulmonary involvement incidentally on a chest radiograph. Routine chest X-ray is a part of the evaluation in children with suspected ATB.

(c) Ultrasound abdomen/computed tomography—The most common findings in children with abdominal TB are enlarged intra-abdominal lymph nodes [27]. The upper para-aortic and mesenteric groups are more often involved in TB than in lymphoma. Presence of large and/or conglomerate lymph nodes with central hypodensity is suggestive of TB. However, they may be non-enhancing or show areas of calcification. Calcification does not imply inactivity. Ascites (septate ascites), bowel-wall thickening, omental thickening "caking," clumped bowel loops, and solid organ involvement (tubercular abscess, calcifications) are other features seen. CT is superior to US because

of the ability to identify all the features in a single study. This is especially so in the detection of caseating lymph nodes, high-density ascites, and bowel-wall thickening. Bowel thickening is considered less common in children than in adults.

(d) Demonstration of AFB from extra-gastrointestinal sites.

(e) In children with concomitant pulmonary involvement, gastric lavage samples have a detection rate of 40–92% [28]. The specimen is collected after 4–6 hours of fasting. Induced sputum by 3% nebulized saline is another alternative. Whatever method one chooses to use, one needs to collect at least two, preferably three, samples.

In children with concomitant peripheral lymphadenopathy, fine-needle aspiration cytology (FNAC) specimen may demonstrate AFB in 20–70% cases [29].

(f) Adenosine deaminase

ADA activity in the peritoneal fluid has been proved to be a simple and reliable method for early diagnosis of tuberculous peritonitis. Sensitivity and specificity levels over 90% have been reported [30, 31]. Similar observations about the utility of ADA (cutoff 36–40 IU/L) in the diagnosis of tubercular peritonitis have also been made,

(g) Mantoux test

Tuberculin skin tests (Mantoux test) are examined 48–72 h after the intradermal injection of five tuberculin units of a purified protein derivative. Positive results have been seen in 17–90% children with abdominal TB.

(h) Contact

A unique aspect about childhood tuberculosis is the hunt for an index case, i.e., history of contact with an infected person. It has been reported in up to 21–65% children with abdominal TB [11, 32]. Risk of acquiring TB in the child is directly proportional to the number of bacilli to which he or she is exposed. Contagiousness is generally limited to subjects with pulmonary disease and is greater among the patients with positive sputum microscopy test results. Subjects with cavitating TB and cough with expectoration are more bacilliferous and contagious.

(i) Response to a therapeutic trial

At times when the diagnosis cannot be established even after exhausting all investigative modalities, one may have to give anti-tubercular drugs and assess the response. The follow-up of these patients is of extreme importance, and demonstration of an objective response to therapy secures the diagnosis. In children with a diagnostic confusion between TB and CD and who were initiated on ATT, the demonstration of endoscopic healing of the ulcers at the end of ATT helps in confirming the diagnosis [12, 16]. A mere subjective response, i.e., the resolution of symptoms, is not enough as some patients with CD may also have symptomatic improvement. The diagnostic yield of all the investigations have been summarised in Table 24.3.

Table 24.3 Yield of various investigations for the diagnosis of pediatric abdominal tuberculosis

	Taiwan	India–Lucknow	India- Chandigarh $n = 218$				Tunisia	Developed
	$n = 10$	$n = 35$	GI	L	P	V	$n = 13$	$n = 45$
Bacteriological ¶	40%	47%	36.1%	29.3%	29.8%	44.4%	23%	73%
Histopathology	50%	19% ±	54.7%	45.3%	72.2%	72%	46%	18%
Radiology	100% (60%)§	94.5%	81.5%	89.3%	92.2%	100%	100%	–
ADA	–	82%	53.8%				–	– .
Abnormal chest X-ray	90%	16%	25.2%				15.3%	24%
TB contact	60%	21%	32.5%				7%	
Mantoux test	17%	45%	64.7%	68.7%	67.5%	72%	61%	90%

± in these patients histopathology alone helped in the diagnosis
¶ AFB on smear, culture, or polymerase chain reaction, CBNAAT
§- Ultrasound only
GI gastrointestinal, *L* lymph node, *P* Peritoneal, *V* Visceral

In children with peritoneal, visceral, or lymph nodal TB, a repeat imaging at the end of therapy showing an improvement/resolution of the imaging features is warranted for an objective assessment. It is suggested to follow up these patients for ~2 years after completion of therapy to look for a relapse of symptoms.

Based on these investigations, the diagnosis of tuberculosis can be

- *Definitive* [demonstration of AFB (in a tissue smear, histopathology, or culture), positive CBNAAT or caseous granulomas on histopathology, and/or unequivocal response to ATT].
- *Probable* [compatible clinical features + radiology features/positive Mantoux/history of contact/raised ADA/demonstration of AFB from extra-gastrointestinal sites].

24.4 Treatment

In recent years, the pharmacokinetics of all first-line TB drugs have been revisited and there has been an upward revision of the dosages needed for children [33]. This is because the pharmacokinetic data suggest higher dosages for maximizing the area under curve above the minimum inhibitory concentration. Also, pediatric patients show a rapid metabolism of isoniazid and require a higher mg/kg body weight dose when compared to adults. The current dosages as per the revised RNTCP guidelines have been tabulated in Table 24.4. Fixed drug combinations (FDC) that incorporate multi-drug therapy are preferred due to safe and simplified treatment and to do away with the possibility of missing one or more of the combination drugs. The FDCs consist of four weight bands for adolescents and adults (25 kg to >70 kg) and six weight bands in children (4 to 39 kg). Dispersible tablets are available for children. For a newly diagnosed child with abdominal TB, intensive phase consists of 8 weeks of

Table 24.4 Dosage for anti-tubercular dugs in children

	Range (mg/kg/d)	Average (mg/kg/d)	Maximum dose (mg)
Rifampicin	10–20	15	600 mg
Isoniazid	7–15	10	300 mg
Pyrazinamide	30–40	35	2000 mg
Ethambutol	15–25	20	1500 mg

isoniazid, rifampicin, pyrazinamide, and ethambutol. This is followed by 16–40 weeks of three drugs isoniazid, rifampicin, and ethambutol as a continuation phase.

The optimal duration of treatment for pediatric ATB is unclear. A shorter duration of treatment increases compliance and decreases the risk of toxicity of the drugs. However, it may also pose a risk for relapses. A review of three randomized controlled trials comprising 328 adult participants found a 6-month regimen (2-month intensive phase, 4-month continuation phase) to be efficacious, but whether it can be extrapolated to children or not is debatable [34]. Apart from including only adults, two of the three studies included only those who had intestinal tuberculosis, which may not be applicable to children where the majority have involvement of multiple abdominal sites. Moreover, the authors of the systemic review have conceded that the quality of evidence regarding the relapse estimate is very low, which is a cause for concern. Hence, more data are required before recommendations regarding the optimal treatment duration can be made. Till then treatment duration should be tailored according to the disease extent, treatment response, and treating physician's experience in managing such patients. Most centers treat for a total duration of 9–12 months. Anti-tubercular therapy-induced hepatotoxicity occurs less frequently in children than adults; it is by no means uncommon. It contributes to 4–8% and 8.7% pediatric cases of drug-induced liver injury in the West and India, respectively. It is important to keep it in the back of one's mind when evaluating a child on follow-up. [35].

Surgery is absolutely indicated when there is intestinal perforation. It constitutes ~15% of all children who present with perforating peritonitis to a tertiary center [36]. Partial intestinal obstruction, adhesive peritonitis, and entero-cutaneous fistulas are relative indications. In such children, it is prudent to first give a trial of ATT as a proportion of children may respond to it alone. In children with a tubercular enteric stricture, endoscopic dilatation may be attempted.

There has been a paradigm shift in the management, and the frequency of children who require surgery has gone down from 85–100% in the 1990s to 4% now.

24.5 Outcome

Most children respond well to therapy. Emergence of drug-resistant abdominal TB has recently been reported and should be considered in children who do not show an optimal response to anti-tubercular therapy. In a study from Mumbai, 12.5% children with abdominal TB had drug-resistant TB [37]. With a timely diagnosis,

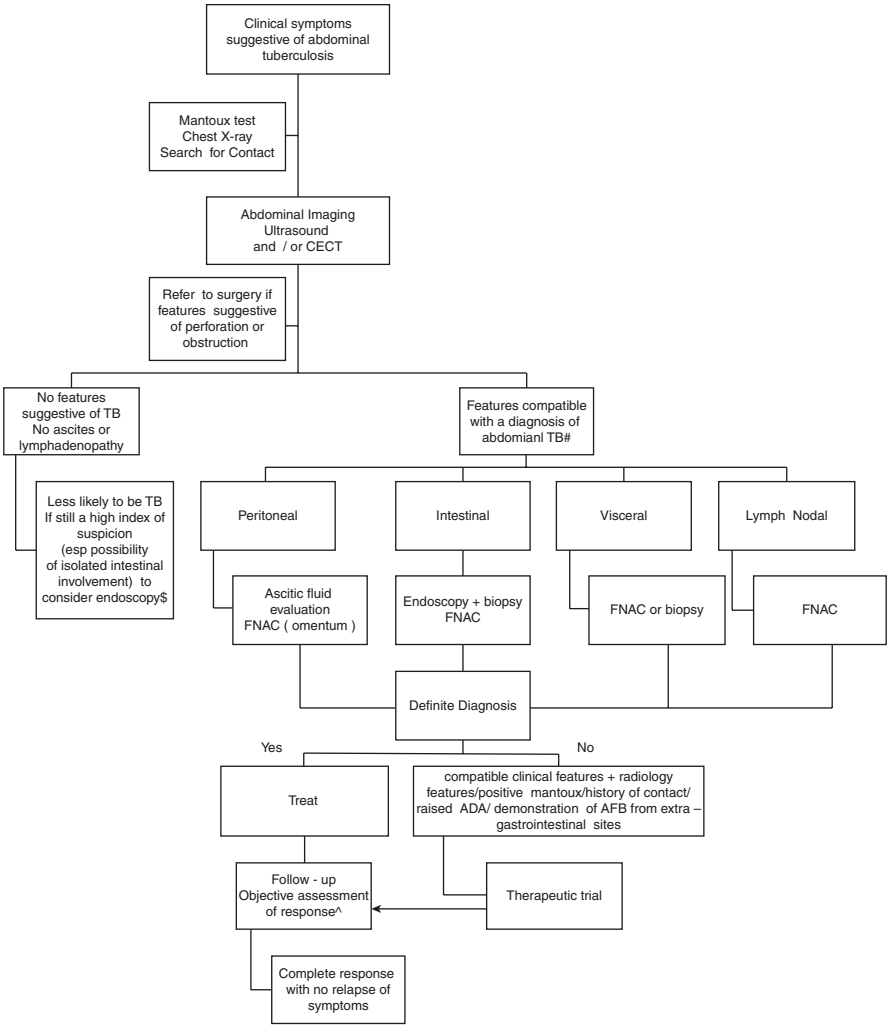

Fig. 24.1 Algorithmic approach to pediatric abdominal tuberculosis. #—ascites (free or loculated), high density (on CT) with or without multiple, thin, complete, and incomplete septae; (•) lymphadenopathy (mesenteric, peri-pancreatic, periportal, and para-aortic groups of lymph nodes) seen as conglomerate masses. (•) and/or as scattered enlarged nodes with hypoechoic or anechoic centers (on USG)/peripheral rim enhancement, non-homogenous enhancement (on CT); (•) bowel-wall thickening, peritoneal thickening and nodularity, adhesions, mesenteric thickening, and irregular soft tissue densities in the omental area; and (•) tiny, low-density foci or multiple low-attenuation, 1–3 cm round lesions scattered in the liver and/or spleen. $—Isolated intestinal involvement has the lowest diagnostic yield on imaging. ^—If the child continues to have symptoms, then the diagnosis needs to be revisited. If previous tissue diagnosis has been inconclusive, one may consider re-obtaining/ repeating it . At this point, one may consider a laparoscopy to obtain better tissue samples for diagnostic evaluation. In children in whom the diagnosis is definite, the possibility of drug resistance has to be considered. Some children with tubercular intestinal strictures may continue to have pain even after ATT in spite of healing of lesions. This needs to be tackled endoscopically/ surgically. *CECT* Contrast-enhanced computed tomography, *FNAC* Fine-needle aspiration cytology, *ADA* Adenosine deaminase

mortality is rare; however, in children in whom the diagnosis is considerably delayed, up to 10% mortality has been reported.

An algorithm for approaching a child with suspected abdominal TB has been given in Fig. 24.1.

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Immunodeficiency and Abdominal Tuberculosis

25

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Key Points

- Susceptibility to Tuberculosis depends on the host's immune response; any dysfunction leads to the progression of the disease.
- Human immunodeficiency virus infection, chronic kidney disease, chronic liver disease, malnutrition, use of immunosuppressants, and elderly age are risk factors for progression of latent Tuberculosis to disease or increased susceptibility to Tuberculosis.
- Management of Tuberculosis in patients of HIV would be to administer an appropriate regimen with minimal interaction of drugs in the proper time to prevent immune reconstitution.
- Screening for latent Tuberculosis before starting antiretroviral therapy or other immunosuppressants would help in minimizing the complications; Rifamycin based regimens can be used when tested positive for Latent Tuberculosis.

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25.1 Introduction

Tuberculosis is an opportunistic infection in humans and can be divided into active and latent tuberculosis. The global prevalence of tuberculosis infection is about 32%, out of which the majority are asymptomatic. The host's active immune response makes the host asymptomatic, although the organisms persist within. Any compromise of the immune system would predispose for reactivation of underlying latent disease. Susceptibility to tuberculosis is determined by the host's immune function irrespective of the active or latent phase. Control of infection requires a balance between immune-mediated eradication and limitation of inflammation. Dysfunction in immune regulatory mechanisms shifts the balance towards disease progression. Risk factors for immune dysregulation are human immunodeficiency virus (HIV) infection, malnutrition, chronic diseases like chronic liver disease, chronic kidney disease, substance abuse, elderly age, and use of immunosuppressive therapy. These risk factors are not mutually exclusive and can exacerbate each other.

Tuberculosis is known to be associated with increased morbidity and mortality among immunocompromised hosts. In this chapter, we give a brief description of various immunocompromised condition precipitating Tuberculosis.

25.2 Immunity to Tuberculosis

Mycobacterium tuberculosis enters the human body through droplet nuclei containing viable bacilli. These bacilli are usually trapped in the upper airways and propelled out by ciliated mucosal cells. Approximately 10% of these reach the alveoli. Alveolar macrophages phagocytize these bacilli, and this enhances the complement activation leading to opsonization of bacilli. Tuberculosis inhibits the lysis of phagosome by various mechanisms and prevents its self-destruction. In the initial stage, the bacilli disseminate widely through the lymph vessels to lung parenchyma and other organs and undergo growth inside the inactivated macrophages resulting in early granuloma formation.

In the next 2–4 weeks, host responds with a macrophage-activating cell-mediated response and tissue-damaging response. In most infected individuals, activated local macrophages stimulate T lymphocytes and release various lymphokines and effectively neutralize the bacilli. The central part of these lesions has necrotic material, and healing takes place gradually with fibrosis. The viable bacilli can be present in the necrotic tissue or stay dormant within the macrophage. In a minority of them, the above response is weak. It results in a delayed hypersensitivity reaction, leading to the destruction of the lesion and draining the necrotic debris to the environment through coughing. This debris contains lots of bacilli. Abdominal involvement is primarily due to Hematogenous spread from the primary focus.

Abdominal Tuberculosis is uncommon, making it approximately 5 per cent of all tuberculosis cases [1]. The mechanism of abdominal involvement can be by (a) swallowing of sputum causing direct seeding, (b) hematogenous spread, or (c) rarely due to consuming milk from cows affected with bovine TB.

25.3 Tuberculosis in Immunocompromised

Tuberculosis usually presents with localized involvement, commonly in the lungs. Still, it can sometimes present with dissemination to various organs like the brain, abdomen, and bones. Disseminated Tuberculosis is more common among immunocompromised individuals. Table 25.1 lists the different immunocompromised states associated with a high risk of developing tuberculosis infection. Tuberculosis in immunocompromised is associated with atypical manifestations, more extrapulmonary involvement, and rapid disease progression. Table 25.2 compares the differences and similarities between Tuberculosis in immunocompromised and immunocompetent individuals.

Table 25.1 High-risk tuberculosis groups

Human immunodeficiency virus
Tuberculosis after other forms of immune suppression
• Steroid therapy • Biologicals – Anti-TNF drugs – Anti-IL6 drugs • Solid organ transplant/HSCT • Autoimmune diseases
Other specific immunological factors
• Chronic disease – Diabetes mellitus – Malignancy – Chronic kidney disease – Chronic liver disease – Chronic obstructive lung disease • Substance abuse – Alcohol – Smoking • Malnutrition • Aging • Primary immunodeficiency/congenital disorders

Anti-TNF Anti-Tumor Necrosis Factor, *Anti-IL6* Anti-InterLeukin 6, *HSCT* Hematopoietic Stem Cell Transplant

Table 25.2 Characteristic features of Tuberculosis in immunocompromised and immunocompetent

	Immunocompromised	Immunocompetent
Presentation	Atypical features	Typical features
	Extrapulmonary involvement is common	Pulmonary involvement
	Disseminated disease is common	Localized
	Rapid progression	Latent or recovered
	More visceral lymphadenopathy	Less
	Tissue abscess	Less
Diagnosis	TST and IGRA less sensitive	More sensitive
Treatment	Drug interactions	Nil

TST Tuberculin Skin test, *IGRA* interferon-gamma release assay

25.4 Tuberculosis and HIV

25.4.1 Epidemiology

In 2018, an estimated 36.8 million adults and children lived with HIV or acquired immune deficiency syndrome (AIDS), out of which 1.3 million were newly infected with tuberculosis [2, 3]. It is estimated that HIV patients are at a 20-fold increased risk of developing Tuberculosis compared to the non-HIV population. Also, approximately one-third of all AIDS-related deaths were attributable to Tuberculosis.

25.4.2 Pathophysiology and Pathogenesis

CD4+ T lymphocytes are the main target of HIV, and macrophages act as sanctuaries for HIV-1. Both these cells also play a crucial role in the immunity against tuberculosis infection. Hence, patients with HIV are at increased risk of infection with Tuberculosis and are prone to disseminated tuberculosis. This results from impaired phagocytosis by macrophages infected with HIV and downregulation of classical Th1 cellular responses against tuberculosis bacilli [4, 5]. Biopsies taken from the tuberculin skin test site revealed decreased T lymphocyte recruitment among patients with HIV-tuberculosis coinfection compared to non-HIV tuberculosis patients [3] (Fig. 25.1).

25.4.3 Clinical Manifestations

Tuberculosis and HIV coinfected patients present with variable clinical features, and it largely depends on the phase of the illness. Even though pulmonary

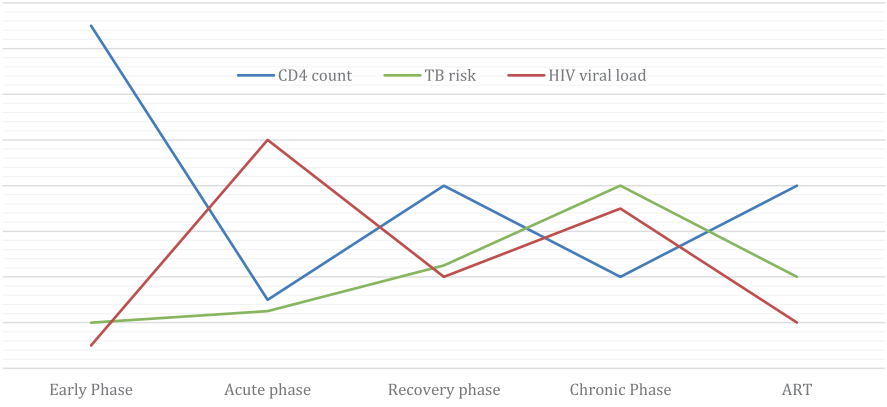

Fig. 25.1 Risk of Tuberculosis in the time frame of HIV. In the early phase of the disease, CD4 count falls drastically, and HIV viral load increases; once the patient starts recovering, Tuberculosis's risk increases gradually till Antiretroviral therapy is initiated; as ART is initiated, CD4 count increases and the risk of Tuberculosis decreases

involvement is the most common manifestation of Tuberculosis in HIV positive patients, atypical radiographic features like lower lobe involvement and less cavitation are more common in patients with advanced HIV infection. Extrapulmonary Tuberculosis is also seen in a higher number of patients with HIV infection. Among the extrapulmonary organs, lymphadenopathy, commonly the cervical and axillary lymph nodes, is the most commonly involved organ [6]. Abdominal Tuberculosis usually presents non-specific symptoms, including fever, night sweats, weight loss, pain abdomen, and diarrhea. On examination, they can have abdominal tenderness, ascites, and rarely lump abdomen. However, ascites were less common in HIV-tuberculosis coinfected patients than HIV seronegative patients [7]. Hence, a high index of suspicion should be kept for recognizing abdominal Tuberculosis.

25.4.4 Diagnosis

Screening for Tuberculosis is mandatory at the time of diagnosis of HIV [4]. Although there is no universally accepted screening tool for diagnosis among people living with HIV, various studies recommend historical questions like cough, fever, night sweats, or weight loss. In that case, a thorough examination and investigations should be performed to search for Tuberculosis focus [8].

The investigations to diagnose abdominal Tuberculosis in HIV infected patients are essentially the same as in non-HIV patients. Previous studies noted that abdominal Tuberculosis's radiological features among early HIV infection were similar to those noted in non-HIV patients [9]. But patients with advanced HIV infection had higher rates of splenomegaly, hepatomegaly, lymphadenopathy, biliary tract abnormalities, bowel wall edema, and ascites [10].

25.4.5 Treatment

The main aim of managing tuberculosis in patients of HIV would be to administer an appropriate regimen with minimal interaction of drugs with antiretroviral drugs. In most of the patients, the regimen and duration of ATT will be the same as that in non-HIV infected patients. For patients who are not started on antiretroviral therapy (ART), antitubercular therapy (ATT) should be imitated first. Subsequently, ART is to be initiated. National AIDS Control Organisation (NACO) technical guidelines on ART initiation state that ART is to be started between 2 weeks to 2 months of beginning ATT in ART naïve patients (Table 25.3). In patients with CD4 count less than 50 cells/microL, ART can be initiated within 2 weeks of starting ATT. Among patients who develop tuberculosis while on ART, certain modifications to ART or ATT regimens need to be made to maintain the drugs' efficacy and reduce the drug interactions. If the patient is receiving a nevirapine based ART regimen, it has to be changed to Efavirenz. In patients who are receiving protease inhibitor-based ART, rifampicin should be substituted with Rifabutin. In patients receiving raltegravir, an

Table 25.3 Treatment of HIV-TB coinfection as per NACO recommendations

CD4 count	Regimen
≥50 cells/μL	Start standard first-line ATT initially ($2H_7R_7Z_7E_7 + 4H_7R_7E_7$) Start ART as soon as ATT is tolerated (after two weeks before two months) ART regimen includes TDF + 3TC + EFV
<50cells/μL	Start standard first-line ATT initially ($2H_7R_7Z_7E_7 + 4H_7R_7E_7$) Start ART within two weeks after initiation of Antitubercular therapy

ATT Antitubercular therapy, *ART* Antiretroviral Therapy, *H* Isoniazid, *R* Rifampicin, *Z* Pyrazinamide, *E* Ethambutol, *TDF* Tenofovir, *3TC* Lamivudine, *EFV* Efavirenz, *NACO* National AIDS Control Organisation

Table 25.4 Drug interactions between Antitubercular and Antiretroviral therapy

Should not be co-administered	Rifampicin	Nevirapine	Decreases Nevirapine concentration
	Rifampicin	Indinavir	Decreases concentration of Indinavir by 80%
	Rifampicin	Lopinavir	Decreases the therapeutic effect of lopinavir significantly
	Rifampicin	Ritonavir	Loss of therapeutic effect and the possibility of development of resistance of ritonavir
Potential clinically significant interaction	Rifabutin	Efavirenz	Decreases concentration of Efavirenz by 38%; increases dose by 50%
	Rifabutin	Indinavir	Decreases Indinavir concentration and increases Rifabutin concentration; half the standard dose of Rifabutin and increase the dose of Indinavir
	Rifabutin	Lopinavir	Required close monitoring for development of uveitis or neutropenia
	Rifabutin	Ritonavir	Required close monitoring for development of uveitis or neutropenia
	Rifabutin	Maraviroc	Administered in the presence of protease inhibitor, the dose of Maraviroc decreased by 50%
	Rifampicin	Zidovudine	Coadministration causes decrease in zidovudine concentration by 43%
	Rifampicin	Maraviroc	Coadministration causes decrease in Maraviroc concentration by 60%–70%
	Rifampicin	Raltegravir	Decreases Raltegravir concentration by 40%
	Streptomycin	Tenofovir	No significant studies reporting adverse effects but both are nephrotoxic agents
	Isoniazid	Stavudine	Increased risk of distal sensory neuropathy

integrase inhibitor, based ART, either rifampicin should be substituted with Rifabutin, or raltegravir's dose should be increased from 400 mg twice a day to 800 mg twice a day. Table 25.4 lists the various drug interactions between drugs of ART and ATT regimens.

25.4.6 Immune Reconstitution Inflammatory Syndrome (IRIS)

IRIS describes a collection of inflammatory disorders associated with paradoxical worsening of the preexisting infectious process following ART initiation in HIV affected individuals [5, 6, 11]. The frequency of IRIS is between 10–25%. Mycobacterium tuberculosis is the most frequent infection implicated in IRIS. Still, it can also be found with *Cryptococcus neoformans*, cytomegalovirus, hepatitis C and B viruses. IRIS is more frequent among patients with CD4 count <50 cells/microL at ART initiation. It usually occurs within the first eight weeks, may occur as early as one week after therapy initiation or as late as 12 months after initiation. At the onset of IRIS, there is a significant decrease in HIV viral load and a more substantial increase in CD4 count [7, 12].

IRIS with Tuberculosis may present with clinical manifestations of lymphadenitis, pneumonitis, acute respiratory distress syndrome, hepatitis, CNS tuberculosis, gut perforation, new-onset serositis, renal failure, or epididymitis [6, 8]. Temporal correlation with the onset of ART and onset of symptoms can yield a clue. IRIS is usually self-limiting, and treatment depends on the severity of manifestations. Milder forms are managed with close observation without interrupting ART. In the localized form, minor surgical procedures like drainage from the local site are adequate. Antimicrobial therapy targeting the inciting pathogen would be required. Short-term corticosteroids or non-steroidal anti-inflammatory drugs can be given to decrease inflammation when it is secondary to non-replicating antigens. The usual prednisolone dose would be 1.5 mg/kg for two weeks, followed by 0.75 mg/kg for the next two weeks, followed by a taper. In severe and life-threatening IRIS manifestations, ART needs to be stopped.

25.5 Tuberculosis after Other Forms of Immunosuppression

25.5.1 Steroid Therapy

Corticosteroid therapy is a known risk factor for Tuberculosis's reactivation; however, the exact risk effect is not known [13, 14]. The risk is higher in patients receiving higher dose and long duration of corticosteroids. Studies on tuberculin skin test showed that corticosteroids at an amount of >15 mg/day for more than 2–4 weeks duration resulted in reduced reactivity to tuberculin antigen [15, 16]. The risk of tuberculosis reactivation is higher with systemic use of corticosteroids; Dong et al. have shown that the risk of tuberculosis reactivation was increased even with inhaled corticosteroid use [17]. Since the exact cutoff dose and duration of corticosteroids for tuberculosis reactivation are unknown, the decision on initiation of corticosteroid therapy and screening for latent tuberculosis before corticosteroid initiation needs to be individualized.

25.5.2 Tuberculosis after Biologics

Biologicals have changed the scenario in the management of rheumatological and some other autoimmune diseases. The main concern with them is the activation of latent Tuberculosis or contracting the fresh disease. TNF alpha inhibitors were commonly implicated, but sporadic cases of Tuberculosis were also reported with other biologicals like interleukin-6 inhibitors and anti-CD20 drugs.

25.5.2.1 Tumor Necrosis Factor-Alpha Inhibitor

TNF alpha is a proinflammatory cytokine produced by the macrophages, dendritic cells, and Th1 like cells when stimulated by *M. tuberculosis* bacilli. It has a vital role in macrophage activation, immune regulation, and formation of granulomatous inflammation [9, 10]. The use of TNF alpha inhibitors leads to an increased risk of serious infections, mainly intracellular opportunistic infections. All TNF alpha inhibitors have the risk for the development of Tuberculosis. Still, the highest risk is with infliximab and adalimumab [18]. The majority of these studies derive the conclusion from patients with rheumatoid arthritis where the disease perse imparts risk for Tuberculosis development. Tuberculosis onset is usually within the first six months after initiation of therapy. In the majority of the cases, it is due to the reactivation of latent infection [19–21]. Hence, it is essential to screen all patients for latent Tuberculosis before initiating TNF alpha inhibitors. As in all immunosuppressed conditions, there is a predisposition for extrapulmonary involvement with TNF alpha inhibitors.

25.5.3 Tuberculosis after Solid Organ Transplant/HSCT

Patients receiving solid organ transplantation or hematopoietic stem cell therapy are at increased risk of developing Tuberculosis due to the use of various immunosuppressive drugs. In recipients of solid organ transplant, the risk of developing Tuberculosis was estimated to be 20–74 fold compared with the general population [22]. The risk is present with all organ transplant types, but the highest risk was noted in lung transplant recipients. The risk of developing Tuberculosis is highest in the first year after transplant. Most of the infections occur within six months of transplant. Lungs are the most typical tuberculosis infection site among transplant recipients. Still, extrapulmonary and disseminated forms were reported in 16% and 23% of transplant recipients.

25.5.4 Tuberculosis and Autoimmune Diseases

Autoimmune conditions like rheumatoid arthritis, systemic lupus erythematosus, systemic sclerosis, and systemic vasculitis are associated with immune dysregulation. Hence, all autoimmune diseases are associated with an increased risk of

developing infections, including tuberculosis. Also, therapy for autoimmune diseases mainly consists of corticosteroids, cytotoxic agents, and other immunosuppressants. The use of these immunosuppressant drugs also increases the risk of developing tuberculosis in patients with autoimmune disease.

25.6 Other Specific Immunological Factors

25.6.1 Chronic Disease

25.6.1.1 Diabetes Mellitus

Multiple studies have shown that there is an association between uncontrolled diabetes mellitus and Tuberculosis [23]. Individuals with diabetes mellitus have three times more risk of developing Tuberculosis compared to non-diabetic patients [24]. Also, diabetes mellitus was associated with poor outcomes after treatment of Tuberculosis. In a systematic review, Baker et al. have shown diabetes increased the risk of secondary transmission, tuberculosis relapse and death during treatment. Although there is no literature regarding screening for diabetes in individuals developing Tuberculosis, screening may be warranted given the recent epidemic of diabetes mellitus.

25.6.2 Malignancy

There is an increased risk of the development of tuberculosis among persons suffering from malignancy. It is more commonly seen among individuals with hematological malignancies and with head and neck cancer [13, 25].

25.6.2.1 Chronic Kidney Disease

Chronic Kidney disease (CKD) is a significant risk factor for Tuberculosis. The increased risk is multifactorial, including uremia induced cellular immune dysfunction, CKD induced malnutrition, and vitamin D deficiency. In a study, tubercular peritonitis was shown to affect one-third of the patients on continuous ambulatory peritoneal dialysis. Apart from the increased risk, certain ATT drug dose modifications are required in patients with CKD. Ethambutol and fluoroquinolones dose needs to be reduced by 50% in patients with CKD, and streptomycin should be avoided in CKD patients.

25.7 Chronic Obstructive Lung Disease

Chronic Obstructive Lung disease is an established risk factor for pulmonary Tuberculosis, but it is unknown for abdominal tuberculosis. Nevertheless, the risk factors and therapy for COPD can interfere with antitubercular treatment.

25.7.1 Chronic Liver Disease

It is known that chronic liver disease is an immunosuppressed condition and theoretically associated with an increased risk of tuberculosis infection. However, limited data is documenting this increased risk. Only a few studies have shown that underlying cirrhosis was a risk factor for Tuberculosis. It is important to note that patients included in these studies were also consuming alcohol, which is a risk factor on its own. Cirrhosis is well recognized as a risk factor for peritoneal tuberculosis.

25.8 Substance Abuse

25.8.1 Smoking

Worldwide, approximately 1.3 billion people currently smoke cigarettes or use other tobacco products, with more than 900 million tobacco users living in developing countries [15]. Tobacco is the second major cause of death in the world. Multiple studies have shown that smoking is a risk factor for tuberculosis infection and disease. Still, its effect on abdominal tuberculosis is unknown [14, 16, 17]. Smoking impairs the response to antitubercular drugs and results in poor treatment outcome [26].

25.8.1.1 Alcohol

Alcohol consumption is a significant risk factor for the development of tuberculosis [27]. Alcohol impairs the immune system and increases susceptibility to both reactivations of preexisting disease and contracting a new infection [18]. It can impart a collateral insult by malnutrition, liver disease, and reduced utilization of medical facilities. A daily intake of alcohol >40 gm/day increases risk, and the risk rises linearly with every 10–20 gm of additional intake [28].

25.8.2 Malnutrition

Tuberculosis and undernutrition interact with each other. Persons with a low body mass index (<18.5 kg/m^2) have an increased risk of developing Tuberculosis [29]. Vitamin D plays a vital role in macrophage activation and mycobacterial growth restriction; hence, lower serum vitamin D levels appear to increase tuberculosis risk [30, 31].

25.8.3 Aging

Elderly age is a risk factor for developing Tuberculosis owing to the impaired immunity with aging. However, in developing countries, Tuberculosis is seen more

in young adults. The reason for this difference is not known. Still, factors like Malnutrition, substance abuse might contribute to the increased incidence in young adults.

25.8.4 Primary Immunodeficiency/Congenital Disorders

Primary immunodeficiency disorders (PIDs) associated with phagocyte and cell-mediated immune dysfunction commonly predispose to mycobacterial infections. Common PIDs associated with increased tuberculosis infection include severe combined immunodeficiency disease (SCID), chronic granulomatous disease (CGD), and Mendelian susceptibility to mycobacterial diseases (MSMD). Other than PIDs, congenital disorders like cystic fibrosis are also associated with an increased risk of tuberculosis infection in children.

25.9 Latent Tuberculosis and its Implications

The host defenses contain mycobacterium tuberculosis; it is either cleared from the individual or remains in the latent phase. During this phase, the individual is noninfectious and asymptomatic. This can be active at any time and more prone to activation during impaired immunity, as already described above. Hence, it is essential to rule out latent Tuberculosis before encountering any of the following conditions: HIV infection, patients waiting for a transplant, patients receiving chemotherapy, and those who need to be initiated on anti-TNF alpha therapy.

There are two main tests for diagnosis of Latent Tuberculosis (LTB), the Tuberculin skin test (TST) and the interferon-gamma release assay (IGRA) blood test. Tuberculin skin test interpretation—this test consists of an intradermal injection of tuberculin material (PPD—0.1 ml-5 tuberculin units) over the forearm, which stimulates a delayed type of hypersensitivity and causes an induration within 48–72 hours. The test is read by measuring the transverse diameter of the induration. Induration of 5 mm, 10 mm, 15 mm has a sensitivity of 98, 90, 50–60, respectively, and specificity increases as the cutoff increases.

The test is considered positive when the induration is

>15 mm in healthy individuals

>10 mm silicosis, CKD, Diabetes mellitus, malignancy

>5 mm HIV, Close contact of the contagious case, Immunosuppressed patients—TNF alpha inhibitors, chemotherapy, post-transplant, high dose steroid therapy

The test can be false negative either because of technical causes (improper storage of tuberculin material, improper administration, or wrong reading) or biological causes (active infection, HIV, recent vaccination, immunosuppressive drugs, immunosuppressive conditions, elderly individuals). Tests can be falsely positive because of infection by non-tubercular mycobacteria or BCG vaccination. When suspicion is strong and the test is negative, a test can be repeated or get IGRA.

Table 25.5 Treatment of latent tuberculosis

Rifamycin based regimens	
Rifampin	10 mg/kg once daily for four months
Isoniazid and rifampin	5 mg/kg and 10 mg/kg once daily, respectively, for three months
Isoniazid and Rifapentine	15 mg/kg and 750 mg, respectively, once weekly for three months
Isoniazid monotherapy regimens	
Isoniazid	5 mg/kg once daily for nine months or six months
Isoniazid	15 mg/kg twice weekly for nine months or six months

IGRAs are blood tests that measure the T cell release of interferon-gamma following stimulation by Mycobacterium tuberculosis antigen. In the IGRA test, the blood sample is incubated with antigens and controls. The test is conducted at a specific temperature, and results are available in 24 to 48 hours. Although there is no clear advantage of IGRA over TST, they can be used in individuals who have already received BCG vaccination. A positive IGRA test detects one or more specific antigens of mycobacterium tuberculosis which includes ESAT-6 and CFP-10. IGRAs have specificity >95% and sensitivity between 70–90% depends on the type of IGRAs. Tests are reported as positive, negative, or uninterpretable. Uninterpretable warrants repeat testing.

Patients with a positive test for LTB should be treated with either Rifamycin based regimens or isoniazid-based therapies in Table 25.5 [20, 32].

25.10 Conclusion

There is an increased risk of developing Tuberculosis in patients with underlying immunocompromise. The list of immunocompromised states are enormous, but common conditions associated with increased risk of tuberculosis reactivation include HIV, immunosuppressive drug use, uncontrolled diabetes, substance use like alcohol, and chronic diseases like renal failure, liver disease, transplant recipients, malignancy, and autoimmune diseases. Even though Tuberculosis's typical manifestations are common in patients with an underlying immunocompromised state, more patients present with atypical radiological features, extrapulmonary involvement, and disseminated Tuberculosis. Because of the atypical manifestations, a high suspicion is required for early diagnosis and treatment initiation. Tuberculosis treatment regimens grossly remain the same as in non-immunocompromised individuals. Some modifications to the ATT regimen or drugs dose and therapy duration may be needed in certain conditions.

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Conflict of Interest None.

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26 Diagnosis and Management of Drug-Resistant Abdominal Tuberculosis

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Abbreviations

ATT	anti tubercular treatment
Am	amikacin
Bdq	bendaquiline
CD	crohn's disease
CNS	central nervous system
CP	continuation phase
Cs	cycloserine
Cfz	clofazimine
Dlm	delamind
DILI	drug induced liver injury
DST	drug sensitivity testing
EP	extra pulmonary
Etm	ethambutol
Eto	ethionamide
FL	first line
FQ	fluoroquinolone
H	isoniazid
HIV	human immunodeficiency virus
IP	intensive phase
ITB	intestinal tuberculosis

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LJ	Lowenstein-Jensen
LC	liquid culture
LFT	liver function tests
LPA	line probe assay
MDR	multi drug resistant tuberculosis
Mfx	moxifloxacin
Mfxh	high dose moxifloxacin
MGIT	mycobacterium growth indicator tube
NTEP	national tuberculosis eradication program
Pza	pyrazinamide
PDR	poly drug resistant
PMDR	presumed multi drug resistant
R	rifampicin
RR	rifampicin resistant
SL	second line
SLI	second line injectable
Stm	streptomycin
TDR	totally drug resistant
TB	tuberculosis
WHO	world health organization
XDR	extensively drug resistant tuberculosis

Key points

- Multi-drug resistance (MDR) to antitubercular drugs is emerging as an important impediment to tuberculosis eradication programs.
- The data on drug resistance in gastrointestinal tuberculosis is sparse.
- Investigations helpful for the diagnosis of MDR TB and plan treatment are GeneXpert, Line probe assay, drug sensitivity testing.
- Regimens available to treat MDR TB are shorter WHO regimen, shorter oral bedaquiline-containing regimen, longer oral M/XDR-TB regimen.
- Pregnancy is not a contraindication for the treatment of drug-resistant TB but therapy needs modification.

> "The greatest disaster that can happen to a patient with TB is that the organisms become resistant to two or more of the standard drugs, through the selection of mycobacterial mutants that result from spontaneous chromosomal alterations"
>
> - Sir John Crofton

26.1 Introduction

Tuberculosis (TB) has remained a serious public health issue and a leading cause of mortality in countries with low socioeconomic status [1]. As per WHO, India accounts for up to 26% of world TB incidence in 2020 [2]. Even after the

availability of effective medications freely under national programs, prevalence of resistance is underreported. Moreover, resistance to existing drugs threatens the future of short-course chemotherapy regimens to first-line and second-line drugs. Most of literature available on drug resistance is on pulmonary tuberculosis. Data on drug resistance in abdominal tuberculosis is sparse. Another problem is that Crohn's disease (CD) mimics ITB very closely and may be misdiagnosed as drug-resistant TB or vice versa. Nowadays, CD is getting diagnosed more frequently in our country [3].

The first documented resistance to streptomycin was noted in the early 1940s. After it became widespread in the community, combination regimens were introduced using Para-Amino Salicylic acid (PAS) and Isoniazid (H). The first survey of drug resistance dates back to 1955–1956 in Great Britain, which documented streptomycin resistance for the first time. However, the first formal effort to compile global incidence of resistance was conceptualized by the World Health Organization (WHO) in 1994 [4]. The paradigm shift in testing policy was brought with the introduction of Drug Sensitivity Testing (DST). It remains a key tool in WHO's End TB strategy initiative. Given the disproportion between vast prevalence, notification, and lack of access to evidence-based medicine in proving resistance bacteriologically (overall TB notification 59% in 2019), many patients are deprived of optimal treatment. Even final outcomes are not reported.

26.2 Definitions

1. *Rifampicin resistant TB (RR-TB)*-A case, whose biological specimen is resistant to Rifampicin (R), detected using phenotypic or genotypic methods, with or without resistance to other anti-TB drugs. It includes any resistance to R, in the form of monoresistance, poly-resistance, MDR, or XDR.
2. *Multi-drug Resistance (MDR TB)*-A case, whose biological specimen is resistant to both H and R with or without resistance to other first-line anti-TB drugs. MDR-TB patients may have additional resistance to any/all fluoroquinolones (FQ) or any/all second-line injectables (SLI) antitubercular treatment (ATT).
3. *Presumed Multi-Drug Resistance (PMDR TB)* It is defined in the context of children. A child with poor response to first-line ATT, or contact with MDR TB, or children living with HIV or death in the household due to TB. This definition could be of relevance to abdominal tuberculosis not responding to standard ATT if the lack of response is documented objectively (see chapter on response to therapy).
4. *Poly-drug resistant TB (PDR-TB)*-A case, whose biological specimen is resistant to more than one first-line anti-TB drug, other than both H and R.
5. *Extensively Drug Resistance (XDR)*-A case whose biological specimen is resistant to INH and RIF amongst the first line, and one injectable drug and FQ amongst the second-line drugs.
6. *Total drug Resistance (TDR)*-Resistance to all first-line and second-line drugs [5].

26.3 Mechanisms for Drug Resistance

The genesis of drug resistance is often first explained by Mitchison's theory which emphasizes the role of poor compliance in the causation of resistance [6].

1. Selection of resistant strains during early bactericidal phase—After initiation of chemotherapy, few bacteria with at least a monoresistance could get selected in presence of inadequate inhibitory concentrations, inadequate dosing, or non-compliance.
2. Monotherapy resistance of dormant organisms during sterilization phase because most drugs may not act against dormant organisms or those in an acidic environment.
3. Sub-inhibitory drug concentrations during regrowth—low drug concentrations in this phase explain the selection of growth toward resistance strains.
4. Differential lag phases during regrowth—mutant strains lose suppression effects after completion of a drug regimen. Thus, the regrowth occurs after a shorter lag phase of another drug.

Thus, the above theory infers the importance of **compliance** and **adequate weight-based dosing**, sufficient enough **to achieve minimum inhibitory concentrations (MIC)** of each drug.

26.4 Real-World Data [1, 2]

- Incidence of MDR TB in newly diagnosed cases in world is 3.3%.
- Incidence of TB/lakh in 2019 in India—159/lakh population
- Estimated cases of TB in 2019 in India—193/lakh population
- Prevalence of MDR TB in 2020 in India—3.52 lakh cases
- Prevalence of XDR TB in 2020 in India—15,000 cases

26.5 Prevalence of Resistance in Abdominal TB

There are few studies on drug resistance in abdominal TB, mainly from Western India, Korea, and Taiwan. Most of them are retrospective and have employed different study protocols. Variation in the availability of culture methods, rapid diagnostic tests, and DST makes overall data heterogenous (refer Table 26.1). In most studies commonly preferred culture method was BACTEC MGIT 960 TB [7–9] Few studies were also done on LJ media, Ogawa, or Middlebrook as a culture method [10–12].

Table 26.1 Various studies on drug resistance in abdominal TB

	Udgirkar S et al. (2019)	Sonambekar A et al. (2017)	H Samant et al. (2013)	Bellam BL et al. (2019)	Kumar S et al. (2017)	Lin et al. (2009)	Ye et al. (2012)
State/Country	Mumbai, India	Mumbai, India	Mumbai, India	Chandigarh, India	New Delhi, India	Taipei, Taiwan	South Korea
Sample size	177	43	61	40	37	30	400
Intestinal TB cases	154 (79.9%)	43 (100%)	43 (70.4%)	25(62.5%)	37 (100%)	N/A	400 (100%)
Study design	Prospective	Retrospective	Retrospective	Retrospective	Prospective	Retrospective	Retrospective
Tests employed	GeneXpert PLUS_SPI MGIT 960 TB PLUS_ SPI DST	Only DST based	MGIT 960 TB PLUS_ SPI DST	GeneXpert	GeneXpert PLUS_SPI LJ culture	Onlyculturebased-LJ, Middlebrook, MGIT 960 TB	Seeplex PCR PLUS_SPI MGIT 960 TB/Ogawa/LJ
Culture Method	BACTEC MGIT 960 TB	BACTEC MGIT 960 TB	BACTEC MGIT 960 TB	–	LJ media	LJ, Middlebrook, MGIT 960 TB	MGIT 960 TB/ Ogawa/LJ
MDR (H PLUS_ SPI R) on DST	3 (11.5%)	6 (13.9%)	3 (5.4%)	1 (4%)	0	3 (75%)	2 (2.7%)
Cumulative R resistance (GeneXpert PLUS_SPI MGIT)	9 out of 61	6 out of 43	3 out of 18	0	0	N/A	2 (2.7%)
XDR	0	0	0	0	0	N/A	0
Overall resistant patients in GeneXpert or culture-positive cases	10/61 (16.3%)	10 (23.2%)	8/31 (25.8%)	0	0	3	13/74 (17.5%)

26.6 First-Line Drug Resistance

Samant et al. described resistance patterns in 18/61 (29.5%) patients with abdominal TB using DST. MDR TB was present in 3 (5.4%) cases [8]. Another study from the same center, by Sonambekar et al.; described drug resistance patterns in 43 cases. Ten cases (23.2%) had documented resistance to at least one first-line drug. The incidence of MDR TB was 13.3%. Limitation of both studies was being retrospective in nature and GeneXpert/TB PCR techniques were not employed [7, 8]. In another largest prospective study done by Udgirkar et al., where both MGIT (120 cases) and GeneXpert (136 cases) were performed, showed MDR in 3/26 patients on DST, while R resistance in 4/136 cases on GeneXpert [9]. Similar studies from PGIMER, Chandigarh and AIIMS, Delhi suggest that resistance is uncommon in North India, implying regional differences in Western and North India vis-à-vis prevalence of resistance [10, 11]. In cases with MDR TB, drug resistance apart from H and was noted in 4–14% of cases from the above studies. However, these patients did not fulfill the criteria of XDR [11].

In a large retrospective study from Korea (n = 400) with ITB, DST was performed in 74 cases. MDR TB was documented in 2.3%. Limitation of this study was the use of less sensitive Seeplex PCR (Seegen, Seoul, Korea), instead of GeneXpert and most of the cultures were done on less sensitive Ogawa and Lowenstein Jensen (LJ) media instead of BACTEC MGIT 960. They observed that drug resistance was more common in those having previous exposure to ATT [12]. None of the above studies had documented XDR [12, 13]. Overall MDR prevalence in above studies was variable. It was found 13% on DST, 13–15% on DST and GeneXpert combined. In a study from India on MDR TB, previous treatment with quinolone and injectable agents were associated with the development of MDR TB. Overall, most common resistance noted on DST, was for H. Mostly, it occurs in combination with other drugs, mainly R. Hence monoresistance to H is less common than MDR TB. H monoresistance was not associated with previous history of Koch's or consumption of ATT [14]. Like R, there is no direct method to diagnose H resistance. In western countries, H resistance occurs among 7.5% of new, and 12% in old cases [2].

26.7 Second-line Resistance

Amongst second-line drugs, fluoroquinolone (4–7%) and ethionamide (5–9%) are the most common drugs having resistance. Probability of resistance increases in presence of MDR TB. None of the above studies documented aminoglycoside resistance [7–15].

26.8 Investigation

Following are different investigations done for TB diagnosis:

1. Conventional culture methods (Lowenstein Jensen media, Ogawa media) which have low sensitivity and take a long time for growth (4–8 weeks). BACTEC MGIT 960 culture media has a rapid turnaround time of 8–10 days in multibacillary load samples to 4–6 weeks in paucibacillary sample.
2. Nucleic acid amplification test (NAAT).
   (a) GeneXpert RIF/MTB (Cepheid, CA, USA)- GeneXpert for rapid diagnosis of TB. It is a cartridge base Real-Time Polymerase Chain Reaction (RT-PCR) which also detects Rifampicin resistance (*rpoB gene*). It is a semi-quantitative test and has a rapid turnaround. Sensitivity of test is directly proportional to the bacterial load in a sample. This has been shown in a study from South Korea where the sensitivity of GeneXpert in smear-positive or culture-positive patients is higher as compared to smear-/culture-negative samples (98.6 v/s 63.1%) in pulmonary TB cases. In a metanalysis, pooled sensitivity of GeneXpert reported in ITB is 23% [16]. With the advent of new Xpert MTB/XDR tests, diagnosis of resistance for isoniazid, fluoroquinolones, second-line injectables and ethionamide, becomes quick and feasible.
   (b) Truenat MTB and Truenat MTB-Rif Dx (Molbio Diagnostics, Goa, India) are chip-based, micro real-time PCR-based NAAT for quick TB (procedural time 1 hour) and rifampicin resistance detection respectively.
   (c) Line probe assays (Hain test)—This test employs PCR and reverse hybridization techniques to detect mutations as compared to DST. Sensitivity of line probe ranges 85–92%, and specificity 98–100% to first- and second-line drugs, respectively. It provides results in 1–3 days (refer Table 26.2).
3. Urine Lateral Flow Lipoarabinomannan assay (LF LAM, Alere Determine TB LAM Ag, USA)—approved by WHO in 2015, in diagnosing high bacillary load patients with HIV. This test is not included under the National tuberculosis elimination program (NTEP).
4. Next-generation sequencing (NGS)—it is an expensive but rapid method of DST and overcomes many of the issues faced in conventional DST methods.

26.9 Management of MDR TB

Extrapulmonary TB should be treated using the same anti-tuberculous drug regimens as pulmonary TB disease. Regimens of 6, 9, and 18–24 months are all effective for extrapulmonary tuberculosis. In the case of Human Immunodeficiency

Table 26.2 LPA results and their clinical interpretation

Drug	Gene	Test results	Clinical interpretations
Rifampicin	rpoB	Resistance inferred or detected	R is not effective
Isoniazid	katG	Resistance to high-level H inferred or detected	H is unlikely to be effective even at high dose
	InhA	Resistance inferred low-level H inferred or detected	H at high dose is likely effective. Eto/Pto are not effective
Fluoroquinolones	gyrA	Resistance to Lfx and low-level Mfx inferred Resistance to Lfx and low-level Mfx detected	Lfx is not effective. Mfx could be used at higher dose.
		Resistance Lfx and high-level Mfx Detected	Lfx is not effective. Mfx could be used at higher dose.
	gyrB	Resistance to Lfx and low level Mfx inferred Resistance to Lfx and low-level Mfx detected	Lfx is not effective. Mfx could be used at higher dose.
Second-line injectable drugs	Rrs	Resistance inferred or detected	Am, Km, and Cm are not effective
		Resistance to Am inferred	Km and Cm are likely not effective.
	eis	Resistance inferred or detected	Am and Cm are likely effective. Km is not effective

Virus (HIV) co-infection, ATT should be started immediately, irrespective of the CD4 count. Treatment of tuberculosis in AIDS patients is the same as in patients without HIV infection, but multidrug-resistant tuberculosis is more common in patients with AIDS.

26.10 Grouping of Anti-TB Drugs and Steps for Designing Longer MDR-TB Regimen According to NTEP[1] and WHO (Refer Table 26.3)

Group A—Include all three medicines

Levofloxacin (Lfx) or Moxifloxacin (Mfx)
Bedaquiline (Bdq)
Linezolid (Lzd)

Group B—Add one or both medicines

Clofazimine (Cfz)
Cycloserine (Cs) or
Terizidone (Trd)

Table 26.3 Classification of Anti-tuberculosis drugs

First-line drugs	Second-line drugs	WHO classification	
Isoniazid (H)	Streptomycin (S)	Group1	Isoniazid, Rifampicin, Ethambutol, Pyrazinamide
Rifampicin (R)	Cycloserine (Cs)	Group2	Injectables: Streptomycin, Kanamycin (Km), Amikacin (Am)
Pyrazinamide (Z)	p-Aminosalicylic acid (PAS)	Group3	Quinolones—e.g., levofloxacin, moxifloxacin
Ethambutol (E)	Ethionamide (Eto)	Group4	Other bacteriostatic second-line drugs—e.g., Ethionamide, Prothionamide, Cycloserine, para-aminosalicylic acid
	Amikacin or kanamycin Capreomycin Levofloxacin (Lfx) Moxifloxacin (Mfx) Gatifloxacin	Group5	Agents with an unclear role—e.g., linezolid, amoxicillin–clavulanate, imipenem-cilastatin, high-dose isoniazid

[a]Drugs can be given in divided doses in a day in the event of intolerance

Group C—Add to complete the regimen and when medicines from Group A and B cannot be used

Ethambutol (E)
Delamanid (Dlm)
Pyrazinamide (Z)
Imipenem-cilastatin (Ipm-Cln) or Meropenem (Mpm)
Amikacin (Am) OR Streptomycin (S)
Ethionamide (Eto) or Prothionamide (Pto)
p-aminosalicylic acid (PAS)

26.11 Second-line Anti-TB Drugs

These agents are reserved for the treatment of drug-resistant TB. However, if sensitive, ethambutol, isoniazid and pyrazinamide, may also be used in MDR-TB regimens (streptomycin is now considered a second-line TB drug and used only as a substitute for amikacin when amikacin is not available or there is confirmed resistance to it).

26.12 Success Rates of Drug Regimens According to WHO World TB Report [2]

- Success rates in MDR TB reported are 57% overall [2].
- Success rates with injectable drug in MDR TB in 2018—60%.

- Success rate with injectable drug in XDR in 2017—34%.
- Success rates with Bedaquiline PLUS_SPI FQ PLUS_SPI injectable in XDR/MDR TB in 2016-17–71%.
- Success rates in XDR without Bedaquiline in 2016-18–29%.

26.13 Pretreatment Evaluation and Follow Up Investigations

At the time of starting treatment some baseline routine investigations should be done like chest X-ray, electrocardiogram, urine routine microscopy, pregnancy test, complete blood count, random blood sugar, liver function test, renal function test with electrolytes, HIV testing, thyroid profile. In addition to the above tests (except serum electrolytes) till injectable are continued following tests should be done:

- Audiometry—baseline and then every 2 months till second-line injectable (SLI) course is completed.
- Serum creatinine—baseline and then monthly till SLI course is completed.
- Repeated hepatic enzyme measurements—every 2 weeks for the first 3 months, then monthly.
  Additionally, for longer oral M/XDR-TB regimen
- Blood urea and serum creatinine—if Am needs to be added.
- Ophthalmologist opinion (for linezolid).
- Surgical evaluation for consideration after culture conversion is achieved.

26.14 Tailored Drug Regimens (Table 26.4)

26.14.1 Situation A: Treatment Algorithm H Mono/poly Drug-resistant (DR) TB Regimen

NTEP recommends screening every suspected case of TB for drug resistance. NTEP provides a regimen for various types of DR-TB. When rifampicin resistance is not detected, the patient is offered First-Line (FL) LPA for detecting resistance to H. If H resistance is detected, the patient is eligible for H mono/Poly DR-TB regimen. In such a scenario, Second Line (SL) LPA should be advised for detecting resistance to FQ, and Liquid Culture (LC) DST for Mfx (if resistant by SL LPA), Z, Lzd, and Cfz. H mono/poly DR-TB regimen is of 6 or 9 months duration, with no separate intensive/continuation (IP/CP) phase. Extensive disease, uncontrolled comorbidity, and extrapulmonary TB warrant extension of drug duration.

26.14.2 Situation B: Rifampicin Resistant TB (MDR/RR-TB)

According to NTEP, when rifampicin resistance is detected, the patient is offered first-line (FL) and second-line (SL) LPA. While FL LPA provides information on InhA mutations associated with Eto resistance, SL LPA provides information on

Table 26.4 Different MDR TB- anti-tuberculosis drug regimens and their comparison

	H mono/poly DR-TB regimen	Rifampicin resistant detected		
		WHO shorter MDR-TB regimen:	Shorter oral bedaquiline-containing MDR/RR-TB regimen	Longer oral M/XDR-TB regimen
Regimen	(6 or 9 months) Levofloxacin, Rifampicin, Pyrazinamide, Ethambutol	IP (4 months) Isoniazid, Pyrazinamide, Ethambutol, Kanamycin, Moxifloxacin, Ethionamide, Clofazimine CP (5 months) Pyrazinamide Ethambutol Moxifloxacin Clofazimine	IP (4–6 months) Isoniazid, Pyrazinamide, Ethambutol, Bendaquiline, Levofloxacin, Clofazimine, Ethionamide CP (5 months) Pyrazinamide, Ethambutol Levofloxacin, Clofazimine	(18–20 months) Levofloxacin, Linezolid, Clofazimine, Cycloserine, Bendaquiline (6 months or longer[a])
Duration	6 OR 9[a] months (no separate IP/CP phase)	9 months	9–11 months	18–20[b] months with no separate IP or CP
Dose	Weight based	Weight based	Weight based	Weight based

Footnote: IP/CP intensive/continuation phase
[a]Extensive disease, uncontrolled comorbidity, and extrapulmonary TB warrant extension of drug duration
[b] XDR treatment duration

resistance to Lfx, Mfx, and Am. Along with LPA, LC DST for Z, Mfx (if resistance detected by LPA), Lzd, Cfz, Bdq, and Dlm should be performed.

If FQ is sensitive and H resistance (either katG or InhA) is detected on LPA, a shorter oral bedaquiline containing MDR/RR-TB regimen can be started. In the case of both FQ and H resistance (due to mutations in both katG and InhA), the patient is eligible for a longer oral M/XDR-TB regimen.

26.14.3 WHO Shorter MDR-TB Regimen (see Table 26.4)

Certain variations exist between NTEP and WHO regimens. In the WHO regimen, if the continuation phase is prolonged, the injectable agent is only given three times a week after the fourth month.

26.14.4 Shorter Oral Bedaquiline-containing MDR/RR-TB Regimen

Shorter oral bedaquiline-containing MDR/RR-TB regimen is recommended for those MDR/RR-TB patients in whom resistance to the component drugs has been excluded or those who have not been previously treated for more than one month

with second-line drugs used in shorter oral bedaquiline-containing MDR/RR-TB regime.

26.14.4.1 Inclusion Criteria

1. DST based inclusion criteria:
   - Rifampicin resistance detected/inferred
   - MDR/RR-TB with H resistance detected/inferred based on InhA mutation only or based on KatG mutation only (not both)
   - MDR/RR-TB with FQ resistance not detected
2. Other inclusion criteria:
   - Children, aged 5 years to less than 18 years of age and weighing at least 15 kg
   - No history of exposure to previous treatment with second-line medicines in the regimen (Bdq, Lfx, Eto or Cfz) for more than 1 month

26.14.4.2 Exclusion Criteria

1. DST-based exclusion criteria:
   - MDR/RR-TB patients with H resistance detected with both KatG and InhA mutation
   - MDR/RR-TB patients with FQ resistance detected
2. Other exclusion criteria:
   - Intolerance to any drug or risk of toxicity from a drug in shorter oral bedaquiline containing MDR/RR-TB regimen (e.g., drug–drug interactions)
   - Extensive TB disease found in presence of bilateral cavitary disease or extensive parenchymal damage on chest radiography
   - In children aged under 15 years—presence of cavities or bilateral disease on chest radiography
   - Severe extrapulmonary TB (EP-TB) disease where there is a presence of miliary TB or TB meningitis or central nervous system (CNS) TB

26.14.5 Regimens and Duration

A shorter oral bedaquiline-containing MDR/RR-TB regimen of 9–11 months duration is recommended in eligible patients with confirmed MDR/RR-TB. The regimen consists of an initial phase of 4 months that may be extended up to 6 months and a continuation phase of 5 months, giving a total duration of 9–11 months. Bdq is used for a duration of 6 months. Neither replacement of drug (except the use of Am instead of Km) nor extension of treatment duration (beyond 11 months) is permitted.

26.14.6 Additional Considerations for the Use of Bendaquiline

26.14.6.1 Inclusion Criteria

- Bdq can be provided to adults and children aged 5 years to less than 18 years of age and weighing at least 15 kg.

- Patients with controlled stable arrhythmia can be considered after obtaining cardiac consultation.
- Pregnancy and lactating women

26.14.6.2 Exclusion Criteria

- Currently having an uncontrolled cardiac arrhythmia that requires medication
- Having any of the following QTc interval characteristics at screening:
  - QTc > 500 at baseline and normal electrolytes, ECG to be repeated after 6 hours and if both ECGs show QTc >500 then the patient should not be challenged with cardiotoxic drugs; and
  - History of additional risk factors for Torsades de Pointes, e.g., heart failure, hypokalemia, family history of long QT syndrome

26.14.6.3 Key Considerations for Newer Drugs

- If taking a light meal with Bdq and other anti-TB drugs, patients should not consume milk-containing products at the same time, as the calcium in these can decrease the absorption of FQs.
- Also, large fatty meals should be avoided, as these can impair absorption of some of the other anti-TB drugs (Cs, H, etc.).
- PPI should be avoided along with Bdq.
- Avoid the use of antacids as they decrease absorption of FQ.

26.14.7 Longer oral M/XDR-TB Regimen

26.14.7.1 Eligibility Criteria

Longer oral M/XDR-TB regimen is recommended for MDR/RR-TB patients who are excluded from shorter oral bedaquiline-containing MDR/RR-TB regimen including for the XDR-TB patients.

26.14.7.2 Regimen and Duration

All three Group A agents and at least one Group B agent should be included to ensure that treatment starts with at least four TB agents likely to be effective and that at least three agents are included for the rest of the treatment if Bdq is stopped.

If only one or two Group A agents are used, both Group B agents are to be included. If the regimen cannot be composed with agents from Groups A and B alone, Group C agents are added to complete it as recommended by WHO [2]. However, in India, the experts concurred to start with all 5 drugs of Group A and B and continue with 4 drugs in the latter part of the regimen (beyond 6–8 months) if the patient can tolerate the drugs.

- Longer oral M/XDR-TB regimen is of 18–20 months with no separate IP or CP.
- Once a patient is placed on a longer oral M/XDR-TB regimen for at least 4 weeks, normally that patient can no longer be switched to the shorter oral bedaquiline-containing MDR/RR-TB regimen, because this 4-weeks treatment would represent an exposure to second-line medicines.

Table 26.5 Replacement sequence of drugs to modify H mono/poly DR-TB regimen

Situation	Sequence of using replacement drugs
If Levofloxacin cannot be used	Replace with high dose Moxifloxacin, if SL-LPA pattern suggests. Do LC DST for detection of resistance to Moxifloxacin, pyrazinamide, Linezolid & Clofazimine
If Moxifloxacin (high dose) or Pyrazinamide cannot be used	Replace with Linezolid. If Linezolid also cannot be given, replace with Clofazimine PLUS_SPI Cycloserine
If both Moxifloxacin and Pyrazinamide cannot beused	Add 2 drugs of the 3—Linezolid, Clofazimine, Cycloserine in order of preference based on resistance, tolerability & availability
If Rifampicin resistance	Switch to appropriate shorter or longer regimen

- Dose of Lzd should be tapered to 300 mg after the initial 6–8 months of treatment.
- Bdq will be given for 6 months & extended beyond 6 months as an exception.
- Pyridoxine to be given to all DR-TB patients as per weight band.
- At least 4–5 drugs are to be used in the initial 6 to 8 months and at least 3–4 drugs in the last 12 months.
  Combined use of Bdq and Dlm in the regimen is recommended for those M/XDR-TB patients in whom an appropriate regimen cannot be designed using all 5 drugs from Group A and B.
  Replacement sequence of Group C drugs for longer oral M/XDR-TB regimen is recommended in the order of—delamanid, amikacin, pyrazinamide, ethionamide, PAS, ethambutol, penems.
- Dlm and Am should not be started in the final 12 months of treatment.
- Though Imp-Cln is fourth in the sequence of drugs of group C in WHO guidelines, it will only be used as the last resort for designing the regimens.
- For XDR-TB patients the duration of longer oral XDR-TB regimen would be for 20 months.

Replacement sequence of drugs to modify DR-TB regimen If there is additional resistance, intolerance, unavailability or contraindication of the component drugs then it requires to be replaced as per Table 26.5.

26.15 Pregnancy and Lactation

Pregnancy is not a contraindication for the treatment of drug-resistant TB but poses a great risk to both the mother and fetus. Second-line injectables are contraindicated throughout the pregnancy due to its effect on the eighth cranial nerve (auditory) of the fetus. Eto is contraindicated during the first 32 weeks of pregnancy due to teratogenic effects. For these reasons, shorter oral bedaquiline-containing MDR/RR-TB regimen cannot be administered in pregnancy with DR-TB. Bdq and Dlm both are not recommended during lactating period, unless the mother is willing to replace breastfeeding with formula feed.

26.16 Management of Hepatotoxicity During Treatment with Shorter/longer oral MDR-TB Regimen

1. Hepatotoxic drugs in the shorter oral bedaquiline-containing MDR/RR-TB regimen are H, Z, Eto, and Bdq. Hepatitis occurs rarely with the FQ. In patients with pre-existing liver disease with persistently abnormal liver function test, a shorter oral MDR/RR-TB regimen should be avoided due to the presence of H(h), Eto, and Z.
2. In case of longer oral MDR TB regimen withhold Bdq, Z, Eto, and PAS. Their introduction can be tried from lower doses of each drug with gradually increasing to full dose while monitoring the LFT and symptoms.
3. Where patient is not seriously ill and one can wait, the introduction of ATT can be done once enzyme levels are near normal. If enzymes are more than five times the upper limit of normal (ULN) with normal bilirubin or AST or ALT elevation > = 3× UNL accompanied by bilirubin > = 2× UNL or symptomatic patient, stop all hepatotoxic drugs and continue with at least three non-hepatotoxic medications (for example, the injectable agent, FQ and Cs/E).
4. Where patient is not seriously ill and one can wait, the introduction of ATT can be done once enzyme levels are near normal.
5. If hepatitis worsens or does not resolve with the three-drug regimen, then all drugs should be stopped.
6. Eliminate other potential causes of hepatitis (viral hepatitis and alcohol-induced hepatitis being the two most common causes).
7. Reintroduction strategies: If AST and ALT decrease to <= 2× UNL, restart full doses of withheld drugs in the allocated regimen gradually in the following order:
   (a) H, Z, Eto in case of Shorter MDR TB regimen.
   (b) BDQ, Z*, Eto* and PAS* in case of Longer MDR TB regimen.
   (a) Monitoring of AST and AST every 3 days after each reintroduction.
   (b) Ensure no deterioration before re-introducing the next drug.
8. Patient should be shifted to longer oral MDR TB regimen, if any drug needs to be permanently stopped in shorter MDR TB regimen. Also, if the patient is on longer MDR regimen, modify regimen from the replacement sequence if any drug is to be permanently stopped (Table 26.5).

26.17 New WHO Recommendations

A treatment regimen lasting 6–9 months, composed of bedaquiline, pretomanid, and linezolid (BPaL) may be used under operational research conditions in MDR-TB patients with TB that is resistant to fluoroquinolones, who have either no previous exposure to bedaquiline and linezolid or have been exposed for no more than 2 weeks [1, 2].

26.18 Areas of Future Research

In future, it is possible that mutant strains will outnumber the susceptible ones and will become dominant ones. This would be a totally challenging situation globally. Thus, even XDR TB does not seem to be a final product of resistance. There will be amplification of different resistance patterns which will permute and can jeopardize the scenario. Given the problem statement, drug sensitivity testing should be encouraged. Our country needs a multicenter prospective follow-up data describing outcomes. Research in newer diagnostic techniques for detecting drug resistance early needs more motivation and funding.

Conflict of Interest Nil

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