REVIEW ARTICLE

Abdominal Tuberculosis

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Abstract

Abdomen is involved in 11% of patients with extra-pulmonary tuberculosis; The most common site of involvement is the ileocaecal region, other locations of involvement, in order of descending frequency, are the ascending colon, jejunum, appendix, duodenum, stomach, oesophagus, sigmoid colon, and rectum. Apart from the basic work up, Investigations like CT scan, EUS, Capsule endoscopy, Balloon enteroscopy, Ascitic fluid ADA, TB-PCR, GeneXpert, Laproscopy are being increasingly used to diagnose tuberculosis.Therapy with standard antituberculous drugs is usually highly effective for intestinal TB. Six-months therapy is as effective as nine-months therapy. Multi-Drug Resistance (MDR) has been observed in 13% of MTB isolates. The development of Drug Induced Hepatotoxicity (DIH) during therapy for TB is the most common reason leading to interruption of therapy. There are various guidelines for the management of TB post DIH. Surgery is usually reserved for patients who have developed complications or obstruction not responding to medical management.

Introduction

Tuberculosis is a disease which has affected mankind for many centuries. An early reference to probable intestinal tuberculosis was made in 1643 when the autopsy on Louis XIII showed ulcerative intestinal lesions associated with a large pulmonary cavity.[1]

John Hunter, described the microscopic tubercle" in the liver, the spleen, the uterus, the coats of the intestines, the peritoneum." He postulated that these tubercles probably arose from the lungs. This was followed by the description of a tubercle causing an ulcer in the mucous membrane of the intestine resulting in destruction of the wall and leading to intestinal phthisis.[2]

Incidence

Autopsies conducted on patients with pulmonary tuberculosis before the era of effective antitubercular drugs revealed intestinal involvement in 55-90 per cent cases, with the frequency related to the extent of pulmonary involvement. The abdomen is involved in 11% of patients with Extra-Pulmonary tuberculosis in this era of antituberculous treatment. Abdominal tuberculosis continues to be common in various parts of the world with large series being reported from Chile, Egypt, India, Iraq, Kuwait, Nigeria, Saudi Arabia. And Sudan.[3] Pimparkar found evidence of abdominal tuberculosis in 3.72% of 11,746 autopsies carried out in K.E.M. Hospital, Mumbai between 1964 to 1970.[4] Rathi et al in his study concluded that The HIV seroprevalence in the abdominal tuberculosis patients was 16.6% which was significantly higher compared with those with pulmonary tuberculosis (6.9%, $p < 0.05$).[5]

Aetiopathogenesis

Abdominal tuberculosis probably occurs due to reactivation of a dormant focus. This primary gastrointestinal focus is established as a result of haematogenous spread from a pulmonary focus acquired during primary infection in childhood. It may also be caused by swallowed bacilli which pass through the Peyer's patches of the intestinal mucosa and are transported by macrophages through the lymphatics to the mesenteric lymph nodes, where they remain dormant.[6]

The most common site of involvement is the ileocaecal region, possibly because of the increased physiological stasis, increased rate of fluid and electrolyte absorption, minimal digestive activity and an abundance of lymphoid tissue at this site. It has been shown that the M cells associated with Peyer's patches can phagocytise BCG bacilli.[7]

Pathology

Abdominal tuberculosis denotes involvement of the gastrointestinal tract, peritoneum, lymph nodes, and solid viscera, e.g. liver, spleen, pancreas, etc. The ileum and cecum are the most common sites of intestinal involvement and are affected in 75% of cases. Both sides of the ileocecal valve usually are

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Table 1: Clinical features

Site	Type	Clinical features
Small intestine	Ulcerative	Diarrhoea, malabsorption
	Stricturous	Obstruction
Large intestine	Ulcerative	Rectal bleeding
	Hypertrophic	Lump, obstruction
Peritoneal	Ascitic	Pain, distension
	Adhesive	Obstruction
Lymph nodes	-	Lump, obstruction

involved, leading to incompetence of the valve, a finding that helps distinguish tuberculosis from Crohn's disease. Other locations of involvement, in order of descending frequency, are the ascending colon, jejunum, appendix, duodenum, stomach, oesophagus, sigmoid colon, and rectum. Multiple areas of the bowel can be affected.[8]

Three types of intestinal lesions are commonly seen - ulcerative, stricturous, and hypertrophic, cicatricial healing of the ulcerative lesions resulting in strictures. Occlusive arterial changes may produce ischemia and contribute to development of strictures. These morphological types can coexist, e.g., ulcero-constrictive and ulcero-hypertrophic lesions. Small intestinal lesions are usually ulcerative or stricturous and large intestinal lesions are ulcero-hypertrophic. Colonic lesions are usually associated with ileocaecal or ileal involvement.[9]

Peritoneal involvement may be of either an ascitic or adhesive (plastic) type. The lymph nodes in the small bowel mesentery and the retro peritoneum are commonly involved, and these may caseate and calcify. Disseminated abdominal tuberculosis involving the gastrointestinal tract, peritoneum, lymph nodes and solid viscera has also been described.[10]

Clinical Features

The clinical presentation depends upon the site and type of involvement (Table 1).[11,12]

Table 2: Case series of intestinal tuberculosis

Symptoms	Mukewar et al	Makharia et al	Khan et al
Abdominal pain	80.6%	90.5%	93%
Weight loss	74.6%	83%	47%
Loss of appetite	62.7%	69.8%	52%
Fever	40.30%	41.5	64%
Diarrhoea	16.4%	37.7%	12%
Constipation	25%	49%	31%
Bleeding Per rectum	11.9%	16.9%	14%

Intestinal Tuberculosis

A recent series which highlights the intestinal tubeculosis provides a elaborate view of symptomatology of the colonic tuberculosis (Table 2).[13-15]

Tuberculous Peritonitis

In a series of 60 patients published by Chow et al the most common features were ascites (93 percent), abdominal pain (73 percent), and fever (58 percent).[16] The classic doughy abdomen is associated with the fibro-adhesive form of tuberculous peritonitis and is rarely seen.

Oesophageal Tuberculosis

It is rare, constituting about 0.3% of GI tuberculosis. In addition to constitutional symptoms, dysphagia, odynophagia and retrosternal discomfort or pain are common. Rarely, the patient may present with life-threatening complications such as broncho-oesophageal fistula or hematemesis. The middle third of the oesophagus is most commonly affected site near carina due to proximity to mediastinal lymph nodes.[17] Endoscopic mucosal biopsy has sensitivity of 22% as reported by Mokoena et al.[18]

Stomach Tuberculosis

Stomach and duodenal tuberculosis each constitute around 1 per cent of cases of abdominal tuberculosis. Primary and isolated gastric tuberculosis without evidence of lesions elsewhere is exceedingly rare due to the bactericidal properties of gastric acid, the scarcity of lymphoid tissue in the mucosa, and the rapid emptying of gastric contents. Usually involves the antral region, involvement of the pre pyloric region, fundus, have been reported, the presentation is usually of a non-healing ulcer or the hypertrophic lesion causing the gastric outlet obstruction.[19]

Duodenal Tuberculosis

Third part is the most commonly affected site in the duodenum. Duodenal lesion may be intrinsic (ulcerative, hypertrophic or ulcerohypertrophic) or extrinsic (i.e. compression of duodenum by enlarged periduodenal lymph nodes from the outside). The largest published series of duodenal tuberculosis reported 30 cases from India;[20] most patients (73%) had symptoms of duodenal obstruction. In a majority of these cases obstruction was due to extrinsic compression by tuberculous lymph nodes, rather than by intrinsic duodenal lesion. The remainder (27%) had a history of dyspepsia and were suspected of having duodenal ulcers. Two of these patients presented with hematemesis. Other reported complications by various authors are perforation,[21] fistulae (pyeloduodenal, duodenocutaneous, blind),[22] and obstructive jaundice by compression of the common bile duct.[23] Recently Mohite et al[24] from Mumbai reported a case of duodenal tuberculosis presenting with choledocho-duodenal fistula

Rectal Tuberculosis

Haematochezia is the most common symptom (88%) followed by constitutional symptoms (75%) and constipation (37%).[25] The high frequency of rectal bleeding may be because of mucosal trauma caused by scybalous stool traversing the strictured segment. Digital examination reveals an annular stricture. The stricture is usually tight and of variable length with focal areas of deep ulceration.[26]

Table 3: Differences between tuberculosis and Crohn's disease

Tuberculosis	Crohn's Disease
Mural thickening without stratification	Mural thickening with stratification in acute inflammation
Strictures concentric	Strictures eccentric
Fibrofatty Proliferation of mesentery very rare	Fibrofatty proliferation of mesentery
No vascular engorgement in the mesentery	Hypervascular mesentery
Hypodense lymph nodes with peripheral enhancement	Mild lymphadenopathy
High dense ascites	Abscesses

Investigations

Routine laboratory tests reveal mild anaemia and increased sedimentation rate in 50 to 80 percent of patients. The white blood count is usually normal.[27]

Ultrasonography

Ultrasound is useful for imaging peritoneal tuberculosis. The following features may be seen, usually in combination.[28]

i. Intra-abdominal fluid which may be free or loculated; and clear or complex. Fluid collections in the pelvis may have thick septa and can mimic ovarian cyst.

ii. "Club sandwich" or "sliced bread" sign is due to localized fluid between radially oriented bowel loops, due to local exudation from the inflamed bowel (interloop ascites)

iii. Lymphadenopathy may be discrete or conglomerated (matted). The echotexture is mixed Heterogenous, in contrast to the homogenously hypo echoic nodes of lymphoma. Small discrete anechoic areas representing zones of caseation may be seen within the nodes. Calcification in healing lesions is seen as discrete reflective lines. Both caseation and calcification are highly suggestive of a tubercular etiology, neither being common in malignancy related lymphadenopathy.

iv. Bowel wall thickening is best appreciated in the ileocaecal region. The thickening is uniform and concentric as opposed to the eccentric thickening at the mesenteric border found in Crohn's disease and the variegated appearance of malignancy.

v. Pseudo kidney sign – involvement of the ileocaecal region which is pulled up to a subhepatic position.

Table 4: Colonoscopic findings

Colonoscopic findings	Alvares et al	Misra SP et al	Singh V et al	Das HS et al
Ulceration	70%	92%	83%	47%
Nodularity	56%	88%	79%	42%
Deformed caecum and IC valve	40%	42%	55%	NA
Strictures	23%	25%	27%	14%
Polypoid lesions	14%	6%	5%	4.7%
Segmental involvement	19%	22%	19%	14%
Fibrous bands	7%	8%	NA	NA
Lesions mimicking carcinoma	16%	NA	20%	NA

CT Abdomen

The differential diagnosis usually includes Crohn's disease, lymphoma, or carcinoma. CT is the most helpful imaging modality to assess intraluminal and extra luminal pathology, and disease extent. The most common CT finding is concentric mural thickening of the ileocecal region, with or without proximal intestinal dilatation. MDCT showed that abdominal tuberculous lymphadenopathy involved predominately the mesenteric, upper and lower para-aortic, periportal, and pancreaticoduodenal regions. The diagnostic dilemma between the Crohn's disease and GI tuberculosis can be dealt to an extent with differences in Table 3.

Capsule Endoscopy and Enteroscopy

There is limited data regarding capsule endoscopy in intestinal TB. A few case reports have described capsule endoscopic features of intestinal TB as multiple scattered short, oblique or transverse mucosal ulcers with a necrotic base in the jejunum and ileum.[29] Cello *et al* [30] also found that ulcers of the small bowel in intestinal TB were characteristically shallow with extensive irregular "geographic" borders, were usually not larger than 1-2 cm and were transverse rather than longitudinal. However, it is difficult to differentiate CD from TB based on capsule endoscopic features alone.

A meta-analysis compared capsule endoscopy and double balloon enteroscopy in patients with suspected inflammatory lesions and found no statistically significant difference in their diagnostic yield[31] in a series of 106 cases of single balloon enteroscopy.

Colonoscopic Findings

The main differential diagnosis at endoscopy is Crohn's disease (CD). This distinction is important since the use of steroids for a misdiagnosis of CD may have disastrous consequences in patients with TB enteritis. The TB ulcers tend to be circumferential and are usually surrounded by inflamed mucosa. A patulous valve with surrounding heaped up folds or a destroyed valve with a fish mouth opening is more likely to be caused by TB than CD. The Colonoscopic findings in various series in patients of GI tuberculosis are high lightened in Table 4.[32-35]

Shah et al[36] has described the frequency of distribution of colonic TB based on the colonoscopy as follows: 32% disease confined to the ileocaecal region, 28% ileocaecal and contiguous involvement of variable lengths of the ascending colon, 26% segmental colonic tuberculosis with involvement of the ascending colon in 10%, transverse colon in 12%, and descending colon in 4%; 10% ileocaecal and non-confluent involvement of another part of the

Table 5: Histopathology in tuberculosis vs Crohn's disease

Tuberculosis granuloma	Granuloma in Crohn's disease
Caseating	Non-caseating
Organisms seen on AFB staining (5 to 15 % cases)	Not seen
5 or more granulomas in biopsies from one segment	infrequent (< 5) Granulomas in biopsies from one segment
Granulomas larger than 400 μm in diameter	Granulomas usually less than 200 μm in diameter
Granulomas located in the sub mucosa or in granulation tissue, often as palisaded epithelioid histiocytes, and disproportionate sub mucosal inflammation.	Granulomas located in the mucosa. Poorly organized and discrete or isolated. Micro granulomas, or aggregates of histiocytes and crypt-centred inflammation such as pericryptal granulomas and focally enhanced colitis is a feature.
Confluent granulomas	No confluent Granulomas
lymphoid cuff around granulomas	Not present

colon, and in 2% the entire colon was affected.

The ileo-caecal region is the most common site affected in either condition (TB and Crohn's), and colonoscopy with retrograde intubation of the ileum is the initial procedure of choice to differentiate. In patients with suspected or proven CD, ileocolonoscopy provided similar sensitivity (67% *vs.* 83%) but significantly higher specificity (100% *vs.* 53%) compared to video capsule endoscopy.[37] The diagnostic yield of histology increases with increasing number of biopsies from up to four segments in the colon. Endoscopic biopsies from segments upstream after dilating a stricture, and also from the normal looking ileum, increase the yield in patients with suspected TB.

USG Guided FNA

Suri et al[38] in his series performed FNAC in 30 patients with abdominal lymphadenopathy. 18 of the 31 FNACs (58%) revealed a positive diagnosis of abdominal tuberculosis

EUS FNA

Puri et al[39] considered this modality in whom image-guided node biopsy failed to establish diagnosis.EUS-FNA was successful in establishing a diagnosis in 90.8% of these patients; 76.1% were found to have tuberculosis.[1] Dhir et al[40] studied the utility of EUS-FNA in evaluating intra-abdominal lymph nodes of unknown etiology, in the setting of high endemicity of tuberculosis. Sensitivity, specificity, PPV and NPV for diagnosing tuberculosis via EUS-FNA were 97.1%, 100%, 100% and 96.9%, respectively.

Histopathology

Histopathology of tissue biopsy specimens in the setting of TB typically demonstrates granulomatous inflammation. Granulomas of TB characteristically contain epithelioid macrophages, Langhans giant cells, and lymphocytes. The centres of tuberculous granulomas often have characteristic caseation (cheese-like) necrosis; organisms may or may not be seen with acid-fast staining. The demonstration of above features strongly suggests Tuberculosis but it is not pathognomonic; culture is required to establish a laboratory diagnosis.[41] Alvares et al[42] in his study demonstrated well-formed granulomas in 23 patients (54%). 14 of the patients (61%) had caseation and 11 (48%) had confluence of the granulomas. Acid-fast bacilli were present in the biopsies from two patients (5%). Recently Ihama et al[43] demonstrated the diagnosis of intestinal tuberculosis using a monoclonal antibody to Mycobacterium tuberculosis. The antibody being to the CD 68 present in the granuloma.

One of the limitations of mucosal biopsies is that granulomas, the primary differentiating feature of TB from CD, are found in only 50%-80% of intestinal mucosal biopsies from patients with clinically confirmed TB[44] and in 15%-65% of mucosal biopsies from patients with CD[45].The differentiating features between the tuberculous Granuloma and Granuloma in Crohn's disease are highlighted in Table 5.

Score for Differentiation of CD and Intestinal Tuberculosis[xiv]

Makharia et al in his study has devised a score based on clinical endoscopy and histology for differentiating these CD and intestinal tuberculosis score = – 2.5 × involvement of sigmoid colon – 2.1 × blood in stool + 2.3 × weight loss – 2.1 × focally enhanced colitis + 7.

Where involvement of sigmoid colon, blood in stools, weight loss, and focally enhanced colitis were given a score of 1 if present and 0 if absent.

ROC analysis was performed on these scores to assess the ability of these features to discriminate between CD and intestinal tuberculosis. AUROC was 0.9089 (95 % CI 0.85 – 0.96). It means that about 91 % of the total subjects could be discriminated correctly by the scores. The score varied from 0.3 to 9.3. Higher score predicted greater likelihood of intestinal tuberculosis. Once the cut-off was set at 5.1, sensitivity, specificity, and ability to correctly classify the two diseases were 83.0, 79.2, and 81.1 %, respectively.

Ascitic Fluid ADA

Gupta et al[46] from India demonstrated an Ascitic ADA level of 30 units/L had a sensitivity of 100% and specificity of 94.1% for tubercular peritonitis. Liao et al[47] from Taiwan, China demonstrated that using 27 U/L as the cut-off value of ADA, the sensitivity and specificity were 100% and 93.3%, respectively, for detecting tuberculous peritonitis in patients with underlying chronic liver disease in the validation group. Kang SJ group[48] from South Korea demonstrated an ADA cut-off level

of 21 IU/L was found to yield the best results of differential diagnosis between tuberculous ascites and peritoneal carcinomatosis with; sensitivity, specificity, positive predictive value, and negative predictive value were 92.0%, 85.0%, 88.5% and 89.5%, respectively.

Quantiferon - TB Gold (QFT-G)

In May 2005, this new test was approved by the FDA for the diagnosis of latent TB. Quantiferon-TB gold (QFT-G) is a blood test that uses an interferon gamma release assay that measures the release of interferon gamma after stimulation in vitro by M. tuberculosis antigens. Most of the studies on this test have been performed on pulmonary TB. In a study looking at patients with active pulmonary TB, compared with PPD skin test, the sensitivity of the QFT-G was 62 and 86%, respectively.[49] In a review of meta-analysis[50] the pooled sensitivity, specificity, positive likelihood ratio, and negative likelihood ratio of IGRA for the diagnosis of ITB was 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) The AUC was 0.92[xlix]. IGRAs do not have high accuracy for the prediction of active TB, although use of IGRAs in some populations might reduce the number of people considered for preventive treatment. Several longitudinal studies show that incidence rates of active TB, even in IGRA-positive individuals in high TB burden countries, are low, suggesting that a vast majority (>95 percent) of IGRA-positive individuals do not progress to TB disease during follow-up.[51] The latest guidelines from the United States, Canada, the European Centre for Disease Prevention and Control (ECDC), the United Kingdom, and World Health Organization (WHO) do not support the use of QFT-G in the setting of active TB.

Anti-Saccharomyces Cerevisiae Antibody (ASCA)

The clinical, morphological, and histological features of intestinal tuberculosis and CD are so similar that it becomes difficult to differentiate between these two entities. The sensitivity of ASCA (IgG and IgA) in CD is 60%–80%, whereas the specificity is almost 90%.[52] ASCA IgG, a combination of ASCA IgA and IgG, and either ASCA IgA or ASCA IgG were positive in a similar number of patients with CD and intestinal tuberculosis and have no diagnostic value in differentiating these two diseases.[53]

T-cell Based Testing for Mycobacterium Tuberculosis (ELISPOT)

An FDA approved Enzyme-Linked Immunospot Assay (ELISPOT), measuring gamma producing T-cell responses to early secreted antigenic targets of mycobacterium tuberculosis, has shown promising results. Sharma et al[54] evaluated the diagnostic accuracy and cost-effectiveness of ascitic fluid interferon-gamma (IFN-gamma) and adenosine deaminase (ADA) assays in the diagnosis of tuberculous ascites. IFN-gamma and ADA assays showed equal sensitivity (0.97) and differed marginally in specificity (0.97 vs. 0.94). Difference in AUCs was not significant (0.99 vs. 0.98, p <0.62). For differentiating TB from non-TB ascites, optimal cut off points were 112 pg/mL for IFN-gamma and 37 IU/L for ADA.

Nucleic Acid Amplification

Nucleic Acid Amplification assays (NAA) are used to amplify the quantity of M. tuberculosis DNA in diagnostic specimens where organisms may be present in amounts too small to be seen by routine staining techniques. Two NAA tests were approved by the United States Food and Drug Administration as of 2012, but only for use with sputum or respiratory secretions obtained by bronchoscopy.[55] However in 2014 guidelines issued by the WHO the Gene Xpert has been validated for the extra pulmonary TB too

GeneXpert Assay

The GeneXpert MTB RIF assay is an automated nucleic acid amplification test that can simultaneously identify M. tuberculosis and rifampin resistance. Among 547 patients with suspected extra pulmonary TB in India and 1068 patients in Europe, the sensitivity and specificity of the Xpert assay were 81 and 99 percent, respectively.[56,57]

In a metanalysis of 12 studies (699 samples) that tested Xpert MTB/RIF using tissue samples from a site other than a lymph node, and compared the results against culture as a reference standard (10 studies had more than 10 samples). The estimates of sensitivity varied widely and ranged from 42% to 100%. The pooled estimate of sensitivity was calculated as 81.2% (95% CI, 67.7–89.9%). The pooled specificity was 98.1% (95% CI, 87.0–99.8%). The condition of the specimen (fresh versus frozen) did not appear to affect the performance of Xpert MTB/RIF. The five studies testing fresh specimens achieved a pooled sensitivity of 79% (95% CI, 64–94%). A further three studies used frozen specimens and had a pooled sensitivity of 76% (95% CI, 58–94%). The condition of the specimen (fresh or frozen) did not affect the specificity.[58]

Diagnosing TB in LN: metanalysis of fourteen studies that tested the accuracy of Xpert MTB/RIF on samples from lymph node biopsies or fine-needle aspiration (FNA) compared against culture as a reference standard. For the 11 studies with more than 10 samples (total, 849 samples) the estimates for sensitivity ranged from 50% to 100%. The pooled sensitivity across studies was 84.9% (95% CI, 72.1–92.4%); the pooled specificity was 92.5% (95% CI, 80.3–97.4%).

WHO recommendation 2013: Xpert MTB/RIF may be used as a replacement test for usual practice (including

conventional microscopy, culture or histopathology) for testing specific nonrespiratory specimens (lymph nodes and other tissues) from patients suspected of having extra pulmonary TB (conditional recommendation, very low- quality evidence).

Standards for TB care in INDIA WHO 2014: For all patients (adults, adolescents and children) with presumptive extra-pulmonary TB, appropriate specimens from the presumed sites of involvement must be obtained for microscopy/ culture and drug sensitivity testing (DST)/CB-NAAT/molecular test/ histo-pathological examination.

MTBDR Plus

It is a molecular probe capable of detecting rifampicin and isoniazid resistance mutations (rpoB gene for rifampicin resistance; katG and inhA genes for isoniazid resistance). In an evaluation of 536 smear positive specimens from patients at risk for MDR-TB in South Africa, the molecular probe was ≥99 percent sensitive and specific for multidrug TB resistance compared with standard DST; results were available in one to two days. Since the assay does not depend on culture, it yielded results even in specimens that were contaminated or had no growth. Molecular testing was successful even when the AFB smear was negative. Use of the assay can reduce time to initiation of therapy for MDR-TB.[59]

TB PCR

Makharia et al in his series of 53 patients with intestinal tuberculosis, 36 (67.9 %) had positive PCR for M. Tuberculosis.[14] In a study by Amarapurkar et al[60] PCR was positive in 21.6% cases of intestinal tuberculosis and 5% Crohn's disease. PCR assay showed high specificity (95%) for the diagnosis of intestinal tuberculosis. thus PCR assay is useful for rapid and accurate diagnosis of intestinal TB, and also helpful for differential diagnosis between intestinal TB and CD.

Ascitic Fluid Routine Microscopy and Culture

Tuberculous peritonitis should be considered in all patients presenting with unexplained lymphocytic ascites with a serum-ascites albumin gradient of <1.1 g/dL. Up to one-half of patients have underlying cirrhosis and therefore have a SAAG ≥1.1 The protein content of the ascitic fluid is usually >3.0 g/dL.[61]

Examination of an Acid fast stained smear of ascitic fluid has a disappointingly low yield. Direct smear for Ziehl-Neelson stain has a reported sensitivity of 0 to 6 percent.[62] In most series, the frequency of a positive ascites culture is disappointingly less than 20 percent. The utility of cultures is even more questionable when considering the delay of four to six weeks before a result is obtained. The delay can be associated with increased mortality.[63]

The Role of Laparoscopy

Bhargava et al[64] reported laparoscopic findings in 38 proven cases of peritoneal tuberculosis. The laparoscopic appearances can be classified into three types: thickened peritoneum with miliary yellowish white tubercles with or without adhesions (n = 25), only thickened peritoneum with or without adhesions (n = 8), and fibro adhesive pattern (n = 5). Biopsies were avoided from fibro adhesive lesions due to risk of complications. Visual diagnosis was accurate in 95% of patients. In comparison, in 27 (82%) of 33 patients, the examination enabled a histological diagnosis to be made on the basis of typical granuloma.

Management

Therapy with standard antituberculous drugs is usually highly effective for intestinal TB. Compliance with treatment is the main determinant of outcome and directly observed therapy is highly recommended.

Traditionally the 9 month AKT was given to the patients with abdominal Koch's however it is now proven that the 6-month therapy is as effective as 9-month therapy in patients with intestinal TB and may have the additional benefits of reduced treatment cost and increased compliance.[65]

In patients with newly diagnosed pulmonary TB, the "cure" rate after DOTS ranges from 75%-92%. Treatment success in extra pulmonary TB was 91% in one study, but this study did not further categorize extra pulmonary TB.[66] In a study by Mukewar et al[xiii] in colonic tuberculosis Majority of the ulcers (87.2%), nodules (84.6%), polypoid lesions (85.7%), luminal narrowing (76.2%), and ileo-cecal valve deformities (76.5%) resolved with anti-TB treatment after 4 weeks. However, biopsies were not taken from these patients during follow up thereafter nor was there any long term follow up of the treated individuals was a drawback of the study.

Drug resistance is increasingly common in strains of MTB and may contribute to recurrent or persistent disease in patients correctly diagnosed as having TB but not showing clinical, endoscopic or histological response to treatment with first line chemotherapy for TB. Multi-drug resistance (MDR) has been observed in 2.4% to 13.2% of strains of MTB isolated from newly diagnosed pulmonary TB patients and in 17.4% to 25.5% of previously treated patients.[15] Extensive drug resistance (XDR) is found almost exclusively in previously treated patients and accounts for about 6% of MDR TB.[67] Statistics regarding prevalence of MDR and XDR strains in intestinal TB are not available from India; however, in one series of 30 patients with colonic TB in Taiwan, 13% had MDR TB.[68]

Monitoring During Treatment

Treatment of patients with

tuberculosis requires careful monitoring for adverse drug effects. Since hepatotoxicity may be caused by INH, RIF or PZA, patients receiving antituberculous therapy with first-line drugs should undergo baseline measurement of hepatic enzymes (transaminases, bilirubin and alkaline phosphatase). In addition, testing for hepatitis B and C should be pursued for patients with epidemiologic risk factors.[69]

Hepatic Monitoring — Repeated monthly hepatic enzyme measurements are not necessary for patients with normal baseline results. They should be obtained in the following settings:

- Abnormal baseline results
- A drug reaction is suspected
- Liver disease (e.g. Hepatitis B or C, alcohol abuse)
- Pregnancy and the first three months postpartum
- Combination therapy including pyrazinamide in continuation phase

Patients must be educated about the symptoms of hepatic toxicity, including anorexia, nausea, vomiting, dark urine, icterus, rash, pruritus, fatigue, fever, abdominal discomfort (particularly right upper quadrant discomfort), easy bruising or bleeding, and arthralgias. Patients should be directly questioned at monthly visits for these symptoms. In addition, they should report any signs or symptoms that occur in the interval between the monthly visits immediately.

Hepatotoxicity may be caused by INH, RIF, or PZA. An asymptomatic increase in AST concentration occurs in nearly 20 percent of patients treated with the standard four-drug regimen; in most patients asymptomatic aminotransferase elevations resolve spontaneously. Occasionally there are also disproportionate increases in bilirubin and alkaline phosphatase; these are consistent with Rifampicin hepatotoxicity (Hepatic Adaptation).[70]

Drug-induced Hepatotoxicity (DIH)

The development of DIH during chemotherapy for TB is the most common reason leading to interruption of therapy[71] Wide variations have been found in the incidence of hepatotoxic reactions during short course chemotherapy from different countries, with the reported incidence being 3 per cent in the USA, 4 per cent in the UK, 11 per cent in Germany[72] 8-36 per cent in India,[73] anti-TB thus DIH is a relatively common problem. Acute viral hepatitis should be ruled out, especially in countries like India that are endemic for it. The factors predicting the DIH extrapolated from the PTB data are as follows

Age: Recent studies have noted patients older than 35 years are at 4 times increased risk to develop TB DILI.[74] Although DILI occurs less frequently in children than adults, it is by no means uncommon. DILI contributes to 4-8% and 8.7% paediatric cases in the west and India, respectively.[75]

Gender: Although women have traditionally been considered more susceptible to develop TB DILI, a recent report suggests that men outnumber women in the incidence of TB DILI. This likely reflects the demographic disparity where more men than women are under treatment for tuberculosis. However, female gender is a positive predictor of more severe liver disease including death.[76]

Hepatitis B: The risk of DILI is increased 4 fold in HBsAg carriers compared to non-carriers (34.9% vs. 9.4%, p<0.001) and 5 folds among the HCV infected individuals.[77]

Nutrition: The study by Rohit singla et al[74] identified Mid Arm Circumference (MAC), baseline serum protein and serum albumin as risk factors for anti-TB DIH with age > 35 yr., MAC < 20 cm, baseline hypoalbuminaemia being independent predictors of occurrence of anti-TB DIH on multivariate logistic regression.

Genetic polymorphism: the role of three enzymes important for metabolism of INH has been extensively investigated. They include, N-acetyltransferase 2 (NAT2) slow acetylators, CYP 2E1 A1/A1 and glutathione S-transferase depletion all three causing increased risk of TB DILI.[78]

Management of TB DILI

HR/HRZ are to be stopped. In general, in cases where there should be no interruption in therapy, three new drugs (e.g., an amino glycoside and two oral agents such as EMB and a fluoroquinolone) could be started until the transaminases concentration returns to less than two to three times the upper limit of normal (or to near baseline levels).

Thereafter, the first line medications can be restarted. Rifampicin should be restarted first. If there is no increase in hepatic transaminases after one week, INH may be restarted. If symptoms recur or hepatic transaminases increase, the last drug added should be stopped. All drugs to be started in maximum doses (American Thoracic Society).[79] British society guidelines[80] gives the following protocol, Isoniazid should be introduced initially at 50 mg/day, increasing sequentially to 300 mg/day after 2–3 days if no reaction occurs, and then continued. After a further 2–3 days without reaction rifampicin at a dose of 75 mg/day can be added, increasing to 300 mg after 2–3 days, and then to 450 mg (<50 kg) or 600 mg (>50 kg) as appropriate for the patient's weight after a further 2–3 days without reaction, and then continued. Finally, pyrazinamide is added at 250 mg/day, increasing to 1.0 g after 2–3 days and then to 1.5 g (<50 kg) or 2 g (>50 kg). A recent study from India evaluate the introduction of anti TB drugs according to different guidelines In this study the three treatment arms were as follows: arm I (n=58),

patients received maximum doses of INH, RIF, PZA simultaneously, arm II (n=59), patients received treatment as per ATS guidelines, i.e. RIF followed by INH after 7 days, followed by PZA after 7 days, all with maximum doses. In arm III (n=58), patients received sequential treatment with graded doses according to British Society Study (BTS) guidelines. The doses of INH, RIF and PZA were gradually escalated sequentially after the maximum dose of the preceding drugs was achieved. The authors concluded that the recurrence of DILI was similar between the three treatment arms, namely 8, 6, and 5 patients respectively (p=0.69).[81]

Surgical Management

Surgery is usually reserved for patients who have developed complications, including free perforation, confined perforation with abscess or fistula, massive bleeding, complete obstruction, or obstruction not responding to medical management. Obstruction is the most common complication; patients with multiple and/or long strictures are less likely to respond to medical therapy. Obstruction may be exacerbated during antituberculous therapy due to healing by cicatrisation.[82] The surgical resection should be conservative. Multiple small bowel strictures may be treated by stricturoplasty to avoid major resection.

An alternative may be colonoscopic balloon dilation, which can be used to manage readily accessible, short and fibrous tuberculous ileal strictures causing subacute obstructive symptoms. Although the experience is very limited, this technique appears safe and may obviate the need for surgery in this setting.[83]

Course of Action when the Diagnosis is Unclear

Many authorities recommend initiating antituberculous therapy if there is a high index of suspicion for ileocecal TB based upon clinical, radiologic, and endoscopic findings, despite nondiagnostic histological and/or bacteriological studies of biopsies.[84] Others suggest prompt diagnostic exploratory laparotomy in the absence of a definitive nonoperative diagnosis, since diseases such as CD, lymphoma, or malignancy can mimic TB in every way. In patients with compatible ileocecal lesions and a history of exposure to TB, strong positive PPD skin test, evidence of TB on chest x-ray, or those originating from an endemic region, Wagner et al favoured initiation of antituberculous therapy.[85] The vast majority of these patients will exhibit a rapid and improved response to medical therapy. Thus, if improvement is not seen within two weeks, laparotomy may be reconsidered.

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Book Review

Clinical Methods and Interpretation in Medicine

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Students and Doctors learn in differing ways. Some by listening, others by reading or looking at images. Dr. Saha's book provides the opportunity to assimilate all three methods. We can hear the author's voice in the text, we can read his words and the images, figures and tables provide excellent visual prompts.

The practice of Clinical Medicine is truly as much an art as a science. It is a wise clinician who realizes their limits and the need for constant and regular education. This book can do much to fill this requirement. It is comprehensive, clear and well structured. One can approach it by System or Symptom and dipping into it at random leads to a progressive wish to read more.

The book will be as valuable for the student as the more experienced clinician. It will be an excellent resource to which they will frequently return.

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