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An autopsy study of pathology of liver in tuberculosis

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Abstract

Background: Hepatic tuberculosis (TB) is an uncommon manifestation of tuberculosis. The term hepatobiliary TB refers to either isolated hepatic or hepatobiliary involvement with other organ involvement

Methods: A five year autopsy study conducted of 236 adult cases of tuberculosis. Clinical details of all cases were obtained from hospital records. Sections from the liver were processed routinely and histopathological findings along with Clinical & biochemical findings were analysed in detail.

Results: Commonest age group affected was 31 to 40 years of age with a male: female ratio of 1.29:1. Fever was present in (56.6%). Hepatomegaly along with abdominal pain was significantly associated with Hepatic involvement by TB. Pulmonary and extra pulmonary tuberculosis was seen in 177 and 59 cases respectively. Liver involvement was mainly secondary except in one case. The spectrum of histopathological changes of the liver showed epitheliod cell granulomas in (41.5%), fatty changes in (46.6%), inflammation in (16.5%) and fibrosis in (3.8%) cases. On comparing the liver TB and non-liver TB cases, it was found that fatty changes were more common but there was no difference in the degree of fibrosis in the two groups. Comparing liver function tests, available in 213/236 cases, 61% were abnormal. Deranged AST (65%), ALT (62.05%) & ALP (57. 05%) was seen in hepatic TB cases.

Conclusion: Liver involvement was mainly in the form of secondary tuberculosis. Fever, hepatomegaly, abdominal pain, fatty change and caseating granulomas along with deranged liver enzymes are significantly associated with hepatic involvement in cases of tuberculosis.

Keywords: Autopsy, Liver, Tuberculosis, Fatty change, Hepatomegaly, Alkaline phosphatase

Introduction

Tuberculosis (TB) is a common infection in developing countries of Asia and Africa.[1] Though pulmonary TB is the most frequent presentation, extra-pulmonary diseases, involving lymph node, gastrointestinal tract, peritoneum, brain are not infrequent. Hepatic involvement has been described in 90% of milliary TB, 75% of extra-hepatic TB and 25% of pulmonary TB.[2]

The incidence of TB underwent resurgence in the 1980s, and the World Health Organization (WHO) estimates that 8.7 million people develop active TB disease and 1.4 million die from TB annually.[3,4] While the incidence of active TB likely peaked in 2004, the proportion of extra-pulmonary TB cases continues to rise.[5,6] The HIV/AIDS pandemic, coupled with poor health care delivery in many resource-limited countries, has fuelled the resurgence of TB.[7] HIV/AIDS has also contributed to the relative rise in extra-pulmonary TB rates,[8] with decreasing CD4 counts.[9] Over 50% of HIV and TB co-infected people present with extra-pulmonary involvement, which includes hepatic TB.[10]

Tuberculous involvement of liver as a part of disseminated tuberculosis is seen in up to 50-80% cases, with the increasing resurgence of TB, the incidence of hepatic TB has also been increasing.[11,12]

The first recorded case of hepatic TB was reported in 1858 by Dr. John Syer Bristowe, an English physician.[13] In 1905, more than 20 years after Koch's discovery of the TB bacillus, Dr. Rolleston and McNee had classified hepatic TB into milliary (disseminated) and local (isolated) forms.[14]

The term hepatobiliary TB refers to either isolated hepatic, biliary, or hepatobiliary involvement with other organ system involvement. Hepatic tuberculosis has been categorised as milliary, local, and biliary in the literature. The terms used to describe hepatobiliary system involvement with TB include tuberculous pseudotumor, tuberculous cholangitis, tuberculous liver abscess, tuberculous hepatitis, and tuberculous cholangitis.[15-24]

Materials and Methods

This study consisted of 236 adult autopsies over a period of 5 years during January 2010 to December 2015. All cases showing evidence of tuberculosis at autopsy (either pulmonary or extra pulmonary or both) were included in the study. Patients with history of alcoholism, diabetes and on hepatotoxic drug treatment along with cases showing only healed foci of tuberculosis were excluded. The diagnosis of tuberculosis was done by microscopic examination, presence of caseating epitheliod cell granuloma or presence of Acid Fast Bacilli (AFB) as evidence of tuberculosis. Detailed clinical history obtained from clinical record. Gross appearance of liver, its weight, dimensions, different gross appearances were recorded. After formalin fixation, four random section and

sections from suspicious lesions of liver were taken. All the sections were processed routinely and stained with H&E staining; special stain- Masson Trichrome was done for assessment of fibrosis, ZN stain to demonstrate AFB.

Study was done in two groups, (a) one in which there is involvement of liver by TB (Liver TB) in the form of granulomas as a part of disseminated or milliary TB or primary hepatic TB and (b) another where there is no liver involvement, where no granulomas were seen but either pulmonary or other organ of body show evidence of TB i.e. (No Liver TB). These findings also compared between pulmonary and extra- pulmonary TB, wherever possible. The spectrum of histopathological changes of the liver studied was as 1) specific changes like granulomas, either caseating or non caseating granulomas, and 2) non- specific changes like fatty change, sinusoidal congestion, inflammation, hepatic fibrosis & necrosis. These changes in liver were graded according to the severity. Fatty change was graded by the semi quantitative grading system as per Mofrad et al:[25]

Grade I	10-30% Hepatocytes Showing Fatty Change
Grade II	30-60% Hepatocytes Showing Fatty Change
Grade III	More Than 60% Hepatocytes Showing Fatty Change

Severity of fibrosis was staged as per Brunt et al[25]

Grade I	Zone 3 Or Pericellular Or Perisinusidal Fibrosis
Grade II	Stage I With Portal Fibrosis
Grade III	Stage II With Bridging Fibrosis
Grade IV	Cirrhosis

Other features noted were presence of inflammation; necrosis and all the pathological findings were compared between two groups as with Liver TB and without Liver TB.

Also were studied liver function tests viz, Serum Bilirubin along with AST, ALT and ALP. The findings were compared between cases with liver TB and without liver TB, as well as between patients who had taken anti-tubercular treatment (AKT) and who had not taken AKT

Results

Total 236 cases of tuberculosis at autopsy were studied. Commonest age group affected was 31-40 (57cases) years closely followed by 21-30 years (54 cases) of age. Youngest patient was of 18 years female and oldest being 79 years male. Male preponderance was noted with a male: female ratio of 1.29:1.

Almost all patients had more than one signs and symptoms. Fever was the commonest symptom (56.4%), followed by hepatomegaly (46.4%). (Table 1)

Table 1: Comparison of Clinical Features

Clinical features	Total (%)	Liver TB (%)	No Liver TB (%)
Fever	133 (56.4)	36.2%	63.8
Hepatomegaly	110 (46.6)	58.3	41.7
Abdominal Pain	76 (32.2)	63.6	36.4
Weight Loss	75 (31.8)	45.5	54.5
Anorexia	59 (25)	50	50
Jaundice	23 (9.8)	70	30

It was seen that, hepatomegaly, abdominal pain & jaundice were frequently seen associated in cases when there is hepatic involvement by TB. While fever, weight loss were seen commonly in cases where there was no direct liver involvement by TB. Thus Hepatomegaly was significantly associated with hepatic tuberculosis (p value=0.0012). When compared between patients with hepatic TB and no liver TB, hepatomegaly and abdominal pain symptoms were statistically significant in cases with hepatic tuberculosis (p value= 0.0023).

Total of 117/236 (84.8%) were of pulmonary TB and extra-pulmonary TB in 59 (15.2%) cases respectively. Out of 236 tuberculosis cases, tuberculosis of liver i.e. direct involvement of liver by TB was seen in 98 (41.5%) of cases while in 138(58.5%) of cases there was no evidence of Hepatic TB, but lung or other organ of body showed evidence of TB. Out of 98 cases of hepatic TB, 63 were seen either as part of disseminated or milliary type of pulmonary TB. Abdominal tuberculosis, tuberculous meningo-encephalitis & genitourinary TB contributed to 35 cases of extra pulmonary TB. Total 59.3% (35/59) of extra pulmonary TB and 35.6% (63/117) of pulmonary TB showed secondary involvement of liver as Hepatic TB, most common type of extra-pulmonary tuberculosis was Abdominal TB (32 /35 cases) leading to hepatic TB. (Fig. 1)

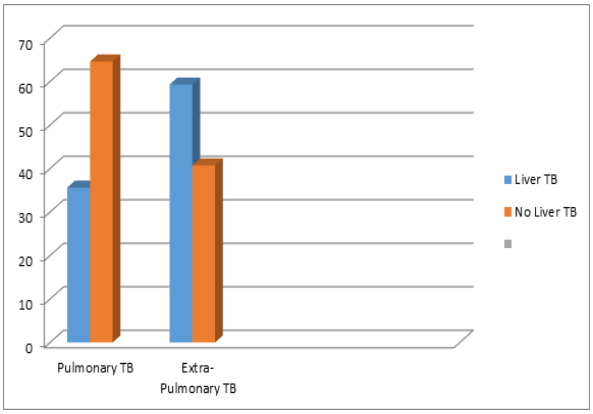

Fig. 1: Incidence of Liver involvement by TB in Pulmonary & Extra- pulmonary TB

Out of 236 cases of tuberculosis, 10 were of maternal mortality. Among these, 7/10 were of pulmonary TB and 3 being extra-pulmonary (2Tuberculous meningitis and 1 of abdominal TB. Out of these, 2 cases of disseminated pulmonary Koch's and one case of abdominal TB showed granulomas in liver.

Amongst these hepatic TB cases, caseating epitheliod granulomas were seen in 82.7% of cases while 17.3% showed non caseating granulomas. Granulomas were located within the parenchyma and peri portal areas. In pulmonary TB cases, granulomas were present predominantly within parenchyma (58/63 cases i.e. 92.1%); while peri portal granulomas were seen commonly with extra- pulmonary TB (85.7%).

The non- specific changes were seen as, sinusoidal congestion & dilatation in (67.8%), fatty changes in (46.6%), inflammation in (16.5%), necrosis in (10.6%) cases and fibrosis in (3.8%). (Table 2)

Table 2: Comparison of different histopathological findings between Liver TB & no Liver TB group

	Fatty change (n=110)	**Sinusoidal congestion & dilatation (n=160)**	**Inflammation (n=39)**	**Necrosis (n=25)**	**Fibrosis (n=9)**
Hepatic TB (n= 98)	57.4%	71.4%	16.7%	16.3%	9.5%
No Hepatic TB (n=138)	37.3%	24.6%	16.4%	6.5%	4.9%

Fatty change was seen in 110/236 cases of tuberculosis. Out of 98 cases with hepatic TB, 57.4% of cases showed fatty change, with Grade III as common (30.6%) grade. While Non hepatic TB involvement cases, fatty change was seen in in 37.7% cases, while Grade I being common grade (18.1%).

Sinusoidal congestion & dilatation was seen in 160 cases, with mild in 12 cases, moderate in 24 cases and severe in 19 cases.

Out of 39 cases of inflammation, 23 cases were of without hepatic involvement, mainly being mild inflammation (13/23 i.e. 56.5%). In hepatic TB, inflammation was present in 16.3% (16/98) cases, mainly of moderate (14/16 i.e. 87.5%). None of case showed severe inflammatory response. Out of these 39 cases, 30 cases showed predominantly mononuclear infiltration mainly by lymphocytes and plasma cells and 9 cases had mixed inflammation by neutrophils, lymphocytes, and plasma cells.

Fibrosis was seen in 9 cases, and no fibrosis seen in 96.2% of cases. Among these 77.8% were in range of Stage I & II, while 22.2% were of Stage III & IV. There was no much statistical difference between the two groups with or without hepatic TB.

Out of 25 cases of necrosis, 17 showed focal necrosis, 12/17 being pulmonary TB cases. Sub massive necrosis was seen in 7 cases while one case showed massive necrosis of liver.

Liver function tests (LFT) were available in 213 /236cases. Total 130 (61%) cases had deranged LFTs. Out of 130 deranged LFTs, 74(56.9%) cases were of Hepatic TB. In cases of hepatic TB with deranged LFTs, AST was deranged in 65%, ALT in 62.05%, Prothrombin in 60%, ALP in 57.05% and Bilirubin in 17.5% of cases. (Table 3)

Table 3: Comparison of Liver function tests in various groups

Liver function test (LFT)				
Normal (83=39%)		Abnormal (130=61%)		
Liver TB	**No Hepatic TB**	**Liver TB**		**No Hepatic TB**
21(25.3)	62(74.7)	74(56.9)		56(43.1)
	BILI	**AST**	**ALT**	**ALP**
Liver TB (74)	17.5%	65	62.05	57.05
No Hepatic TB (56)	14.8	37.7	34.4	19.7

Comparing LFTs between Hepatic TB cases and No hepatic TB cases, Deranged ALP was very much significantly associated with hepatic tuberculosis.

Out of 213 available LFTs, 160 patients were not taking AKT while 53 patients were on AKT. Out of these 160 patients without AKT, 65.6% showed deranged LFTs, of which 54 cases were of hepatic TB. Deranged ALP was significantly associated with hepatic tuberculosis without AKT.

In 53 LFTs of cases which were on AKT, 20 cases showed deranged LFTs, with 5 cases showed necrosis.

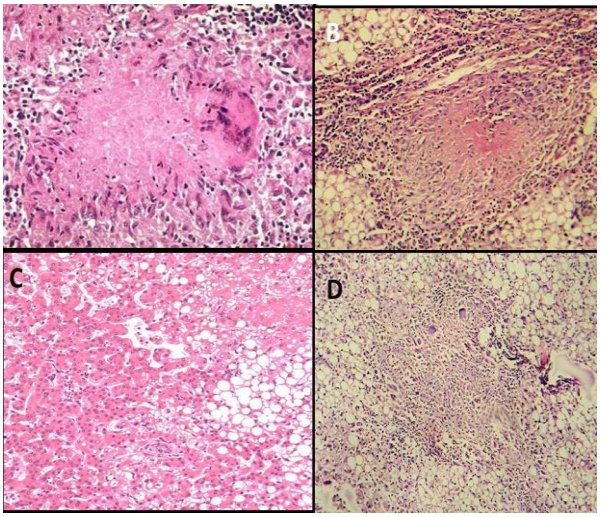

Fig. 2: Histological changes viz. A) Caseating granulomas in parenchyma, B) Peri-portal granulomas; C) Grade I fatty change in Non Hepatic TB cases; D) Grade III fatty change seen in Hepatic TB

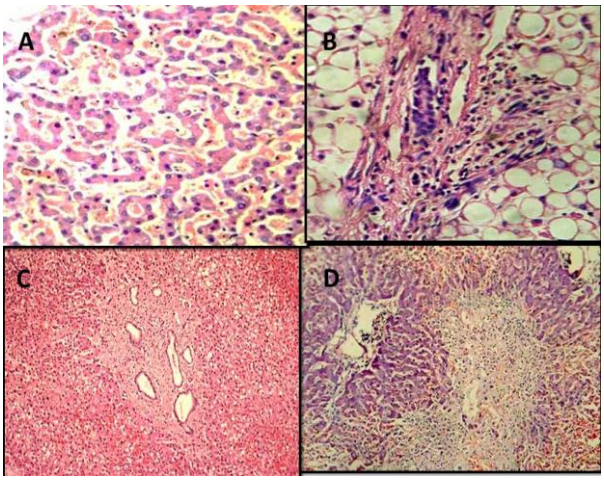

Fig. 3: Other Non-specific changes like A) Sinusoidal congestion & dilatation; B) Portal Mild Inflammation, C) Grade II fibrosis and D) Submassive necrosis seen in Hepatic TB with AKT

Discussion

The demographic study showed that 74.2% of cases between 21-60 years of age group with male predominance. The male to female ratio was 1.29:1. This is consistent with study by Nayak et al, Gupta et al and Amarapurkar et al.[25]

The clinical manifestations of hepatobiliary TB are those of the extra hepatic disease, hepatic involvement is usually asymptomatic. In most of the series, hepatomegaly is the commonest finding, being present in 70-96% of patients. The right upper quadrant or non-specific abdominal pain appeared to be the symptom present in 65-87% of patients. Other common presenting symptoms in several series were fever of unknown origin, anorexia and weight loss, present in 55-90% of patients. In several series fever was present in more than 50% of patient's.[20] In our study, patients presented with more than one symptom, hence there was overlap of symptoms. We compared symptoms with or without liver involvement; it was found that Fever was most common symptom in both the groups. Abdominal symptoms like abdominal pain, anorexia, diarrhoea were common in cases of liver involvement. Hepatomegaly is significantly associated with Liver involvement. These findings are similar to Amarapurkar.[25]

Jaundice was seen in cases which are comparable to Alvarez,[15] Amarapurkar.[25] In our study, 53 cases had history of intake of anti- tubercular drugs, out of which 8 cases showed presence of jaundice. Some of them had completed the full course of AKT while others being defaulters. However the clinical details were not available we could not analyse changes due to anti tubercular treatment in detail. Jaundice is an uncommon presentation, being present in 20-35% of patients. The presence of jaundice suggests biliary involvement, and the biochemical profile may simulate extra hepatic biliary obstruction. Jaundice may be due to enlarged lymph nodes compressing bile ducts or anti tubercular drug induced liver toxicity.[20] (Table 4)

Table 4: Clinical features in Hepatic TB - comparison data

Author	N	Signs and Symptoms (%)				
		Hepatomegaly	Fever	Abd pain	Wt loss	Jaundice
Hersch (1964)[26]	143	74	97	55	83	22
Alvarez (1983)[15]	130	96	65	45	55	35
Essop (1984)[27]	96	80	70	66	--	11
Maharaj (1987)[28]	41	95	63	46	61	15
Chien (1994)[14]	22	50	64	59	32	18
Vilaichone (2004)[29]	20	80	100	60	60	20
Yu (2004)[30]	12	33	67	83	42	17
Tai (2008)[31]	10	10	30	40	20	0
Present (2016)	236	46.6	56.4	32.2	31.8	9.8

The clinical classification and nomenclature of hepatic TB is confusing in the literature. However, Reed divided it into three forms: tuberculosis of the liver associated with generalized tuberculosis, milliary tuberculosis of the liver, and primary tuberculoma or abscess of the liver.[5] In our study, we adopted Reed's classification. According to his classification, 58 cases belong to tuberculosis of the liver associated with generalized tuberculosis and the other 39 cases are of milliary TB and one case of primary tuberculoma or abscess of the liver. This single case was of large tubercular abscess involving the right lobe of liver. No other organ in body showed tuberculosis; hence it was labelled as case of primary tubercular abscess of liver, which is extremely rare. In spite of a high prevalence of tuberculosis, very few cases of primary tuberculosis of liver have been reported in India. Olive et al in 1990 reviewed world literature and found that since 1950; only 21 cases of isolated tuberculoma or tubercular abscess of the liver have been reported, showing the rarity. Essop et al[27] & Alvarez et al[15] have shown that tuberculous involvement of the liver is usually secondary and is mainly in the form of milliary tuberculosis similar to our study. (Table 5)

Table 5: Prevalence of Primary and Secondary involvement of liver by Tuberculosis

Author	N	Milliary / Secondary TB(%)	Local / Primary TB(%)
Hersch (1964)[26]	143	90	10
Essop (1984)[27]	96	90	10
Chien (1994)[14]	22	70	30
Amarapurkar et al (2008)[11]	38	39	61
Tai (2008)[31]	10	60	40
Hwang et al. (2009)[32]	12	67	33
Present (2016)	236	99	01

Total of 4.2% cases were of maternal mortality. Jashnani et al[33] and Panchabhai TS et al[34] had maternal deaths due to tuberculosis in 2.2% & 7.9% cases respectively.

The final diagnosis of hepatic TB, local as well as diffuse, rests on histopathological evidence of caseating granuloma or demonstration of acid fast bacilli (AFB) on smear or culture of biopsy specimen. The granulomas are composed of epithelioid cells surrounded by lymphocytes, with or without Langhans' type multinucleated giant cells. Epithelioid granuloma formation in hepatic TB can be demonstrated in 80-100% of cases. Granuloma formation has also been reported in brucellosis, coccidioidomycosis and Hodgkin's disease, but occurrence of these conditions is high in the western hemisphere, while TB is the commonest cause of granuloma formation in India. Caseation, a hallmark finding of TB granulomas, is present in 33-100% of liver biopsy specimens from various series.[20,25,27] In our study, 98 cases of hepatic TB, caseating granulomas were seen in 82.7%. Out of these, 49 cases showed granulomas in hepatic parenchyma, 19 in peri-portal areas and 30 in both parenchymal and peri-portal areas. Generally caseating epithelioid cell granuloma, non-portal in location is characteristic of tuberculosis. Overall AFB positivity in our study was seen 29% of cases. It is well known fact that AFB positivity for mycobacterium is low. Survival of tuberculous bacilli is considered low in the liver as compared to the lung, may be due to low concentration of oxygen in the organ.[25]

In our study, Sinusoidal congestion and dilatation was seen 67.8% of cases. There is no known correlation between tuberculosis and sinusoidal congestion. Sinusoidal congestion in tuberculosis was also studied by Bowry et al (40%) and Ban et al (20%). It has been observed that sinusoidal dilatation in liver biopsy should prompt a thorough search for a tumor or a disease associated with granulomas.[25]

While considering other histological changes, fatty change was found in 46.6%. In tuberculosis, protein malnutrition, anorexia and starvation and also may be tuberculous toxicity. It has always been matter of controversy whether fatty change is directly due to tuberculosis or not. Some of the authors have considered the fatty change to be just coincidental and may be attributed to alcoholism, malnutrition and anorexia. Ban B compared the liver changes in pulmonary tuberculosis and non tuberculous lesions of lung. He found that fatty infiltration is more marked in tuberculosis despite the anorexia was more marked in non tuberculous cases and he attributes this to toxicity due to tuberculosis.[25]

Inflammation was present in 39.8% of cases, moderate degree (61.5%) in most of the cases. Buckingham et al called it as non- specific reactive hepatitis. Various studies have reported inflammation varying from 20-35%, similar to our study.[25]

The correlation between tuberculosis and cirrhosis had not yet been convincingly proved. Rolleston and Mc Nee state that tuberculosis of liver or some other part of the body may result in fibrosis of liver but true cirrhosis does not occur. There are few studies showing that various granulomatous diseases like sarcoidosis and brucellosis may also lead to cirrhosis. The incidence of liver fibrosis in tuberculosis ranges from 5-33%. In our study, there were 9 cases of fibrosis, which further were graded based of severity. There were only

2 cases of cirrhosis, chronic alcoholism and malnutrition being the underlying cause of cirrhosis in these patients.[25]

While comparing the histopathological spectrum of changes in cases of tuberculosis with or without hepatic granuloma, we found that fatty change and sinusoidal congestion were common in cases with liver tuberculosis than in cases without liver TB. There was no statistical difference in sinusoidal congestion, fibrosis amongst two groups. Mukherjee et al found inflammation associated with granuloma in 68% of cases, which he has attributed to toxaemia, malnutrition and hypoxia of tuberculosis.[25]

Laboratory Features and Diagnostic AIDS Although liver function tests, which included aspartate aminotransferase (AST), alanine aminotransferase (ALT), total protein, albumin globulin (A:G) ratio and alkaline phosphatase (ALP) were abnormal in 35-80% of the cases reported by Alvarez,[15] especially among those patients with obstructive jaundice, these were nonspecific and were not diagnostic of hepatobiliary TB. Abnormalities in the ALT and AST were seen in 91-94% of the jaundiced group in the reported series and in only 5% of the non-jaundiced group. Essop et al[27] reported elevated ALT and AST in 70% of their cases.[27] Alkaline phosphatase was elevated in almost all of the patients in the jaundiced group compared to only 60% in the non-jaundiced group as reported by Alvarez.[15] On the other hand, the alkaline phosphatase was elevated in 90% of Hersch's[26] series, while the Essop et al.[27] reported normal alkaline phosphatase in 17% of the cases in his series. Alterations in A: G ratios were common. Hypo-albuminaemia and hyper-globulinaemia were present in approximately 80% of patients with hepatobiliary TB.[15,26,27,28] In general, abnormalities in the liver function tests in hepatobiliary TB, particularly aminotransferases, gamma-glutamyl transpeptidase and alkaline phosphatase confirm the presence of hepatic involvement, but are not diagnostic of hepatobiliary TB. (Table 6)

Table 6: Abnormal liver function tests in hepatic tuberculosis

	Abnormal AST & ALT (%)	Abnormal ALP(%)
Alvarez and Carpio[15] (n=130)	35	75
Essop et al.[27] (n=96)	70	83
Maharaj et al[28] (n=41)	-	87
Huang et al[24] (n=5)	-	60
Chaudhary et al[20] (n=5)	-	50-87
Present study (n=236)	65	57

ALT, Alanine aminotransferase; AST, aspartate amino-transferase; ALP alkaline phosphatase

Chaudhary[20] stated that Biochemical clues to the presence of hepatic TB are non-specific. Liver function tests including aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, gamma-glutamyltranspeptidase, total protein and albumin-globulin ratio, although found to be elevated in 30-80% of patients, were non-specific and were not diagnostic of hepatobiliary TB.[11]

In our study, deranged AST, ALT and ALP were significantly associated with Hepatic TB.

Conclusions

Hepatic TB is an extra pulmonary expression of active TB disease, and the incidence has likely increased during the era of HIV/AIDS. Clinicians in TB-endemic regions should have a high index of suspicion in patients presenting with hepatomegaly, fever, and elevated liver enzymes (ALT, AST& ALP). Abdominal radiography and ultrasound, CT scan should be preferred if available. Liver biopsy with histology showing Fatty change and sinusoidal dilatation should prompt for vigilant search of TB granulomas and mycobacterial culture is the most specific test for diagnosing hepatic TB.

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