Hepatobiliary Tuberculosis - Therapeutic Challenge

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ABSTRACT

Liver can be involved in all forms of tuberculosis (i.e. pulmonary, extra-pulmonary and miliary). Evidence of hepatic involvement is granulomas and non-specific hepatic lesions. Primary pulmonary tuberculosis has some evidence of liver involvement. Most patients with hepatobiliary tuberculosis present with non-specific symptoms, but few percentage of patients present with hepatomegaly, fever, abdominal pain, jaundice and biochemical abnormalities including elevated alkaline phosphatase, transaminases, hyperbilirubinemia. Abdominal ultrasound and computed tomography play an important role in the diagnosis. Liver biopsy is essential to the diagnosis and demonstration of *M. tuberculosis* by culture of liver tissue.

With the advent of acquired immunodeficiency syndrome (AIDS) epidemic incidence of new cases are coming up and as many as 2/3rd of patients with AIDS with extra-pulmonary tuberculosis. Atypical mycobacteria especially Mycobacterium avium complex play an important role in the course of AIDS, in respect of liver involvement.

Reported cases of tuberculosis in the liver transplant recipient are observed.

Therapy of tuberculosis in hepatobiliary involvement is same without such involvement. Mortality rate is variable. Patients with M. avium intracellular complex infection remains poor.

INTRODUCTION

Involvement of liver in patient with tuberculosis has been described more than 100 years. Earliest descriptions of liver in tuberculosis was published in Guy's hospital be Thomas Addison in 1836.[1]

During the middle of 19th & 20th century autopsy studies demonstrated granulomas and other vareties of lesions in liver of patients of tuberculosis.[2,3] Though reports of isolated hepatobiliary tuberculosis published infrequently[4,5] still different detailed review of cases come up to give proper importance to the clinical spectrum of the disease.

Klatskin[6] demonstrated that as many as 2/3rd of the patients with primary pulmonary tuberculosis have evidence of liver involvement. Hepatic granulomas have been found in the tune of 80% of patients with chronic pulmonary tuberculosis and this was confirmed by autopsy studies of patients dying of chronic pulmonary tuberculosis.[7] In miliary infection hepatic lesion is described in about 90% of patients.[8]

Primary hepatic tuberculosis is a well described syndrome in which hepatic involvement dominates the clinical picture.[9] With advent of acquired immunodeficiency syndrome (AIDS) epidemic, incidence of new cases of tuberculosis are coming up[10] and as many as 2/3rd of the patients. of AIDS with extra-pulmonary tuberculosis occurs. Atypical mycobacteria, especially *Mycobacterium avium* complex play as important role in the course of AIDS, in respect to liver involvement.[11,12]

SPECTRUM OF HEPATOBILIARY TUBERCULOSIS

Liver can be involved in all forms of tuberculosis (i.e. pulmonary, extra-pulmonary and miliary). In addition to that infection confirmed predominantly to the liver or biliary tract where tuberculosis is endemic.

Various hepatic lesions are regularly associated with tuberculosis e.g., Granulomas, Kupffer cell hyperplasia, sinusoidal infiltration, caseous necrosis and steatosis, amyloidosis & additional lesions associated with adverse drug effects.

Histopathological Spectrum of Hepatobiliary Tuberculosis

a. Granulomas
b. Granulomatous hepatitis
c. Tuberculomas
d. Caseous necrosis
e. Tuberculous abscess
f. Cholangitis
g. Cholecystitis
h. Fulminant hepatic failure

Table 1 : Shows hepatic function test & biochemical abnormalities in tuberculosis

Series	Abnormal BSP retention	Elevated Alkaline	Bilirubin	Elevated SGOT/SGPT	Increased Globulin
Klatskin & Yesner	75%	69%	100%		67%
Seiefe et al	14.3%	14.3%			50%
Korn et al	85.7%	40.9%	26.7%		75%
Alvarez & Carpio	55%	75%	65%	35%	81%

i. Non-specific changes
   - Fatty changes
   - Focal necrosis
   - Kupffer cell hyperplasia
   - Sinusoidal inflammation
   - Free acidophilic bodies
   - Portal fibrosis
   - Giant hepatocytes
   - Amyloidosis
   - Peliosis hepatis

j. Coincidental lesions
   - Alcoholic liver disease & cirrhosis
   - Viral hepatitis
   - Nodular regenerative hyperplasia
   - Hemosiderosis

k. Hepatotoxicity secondary to ATD therapy

   BCG–induced granulomatous hepatitis

   Drug-induced hepatitis (INH, PAS, rifampicin, pyrazinamide)

   Drug-induced fibrosis

Evidence of Hepatic involvement

a. Granulomas:

Prevalence – Prevalence of hepatic granulomas (tubercles) in biopsy specimen from patients with tuberculosis ranged from 0-100%. Pulmonary tuberculosis involve liver less common than miliary tuberculosis in the tune of 20% in pulmonary as compared to 68% in miliary tuberculosis.

Liver biopsy also shows less frequently with pulmonary tuberculosis than miliary tuberculosis. Identification of organism (mycobacteria) in patients with pulmonary tuberculosis range from 0-20%, as compared miliary tuberculosis 20-50% in several series,[7,13] caseation is thought to occur with miliary cases and rarity of caseation in hepatic granulomas leads to difficulty in demonstration of acid fast bacilli (AFB).

Increased yield of hepatic granulomas is possible by fluorescent staining technique.[14] False estimate percentage of granulomas suggest previous ATD therapy as complete resolution is expected by ATD therapy.

Character of Granulomas

Tuberculous lranulomas are composed of mononuclear (epithelioid) cells, surrounded by lymphocytes with or without Langerhan's multinucleated giant cells.

They range in size from 0.5mm microgranulomas to 12cm tuberculomas but are generally 1-2mm in diameter. Central necrosis of tubercle may also develop. It is granular and cheesy hence the term caseous. Caseous necrosis occurs with more regularity in miliary tuberculosis than in other forms of disease.

b. Non-specific hepatic lesions

a. Kupffer cell hyperplasia
b. Sinusoidal dilatation
c. Fatty change
d. Focal Necrosis
e. Periportal fibrosis
f. Acidophilic bodies
g. Glycogen nuclei
h. Amyloid
i. Siderosis

Biochemical Abnormalities in Tuberculosis

Biochemical evidence of hepatic dysfunction in tuberculosis has been observed in large number of cases, although in general the biochemical values themselves correlate poorly with specific type of hepatobiliary tuberculosis.

Abnormal serum protein levels are characteristic of tuberculosis.

CLINICAL SYMPTOMS

Most patients with hepatic tuberculosis manifest no symptoms specifically refer to hepatobiliary tract but present with non-specific symptoms e.g. fever, malaise, fatigue, night sweats, anorexia and weight loss. Patients with prominent hepatic complaints represent a minority of patients with hepatic tuberculosis and these patients may present with abdominal pain, jaundice or ascites.

LABORATORY FEATURES

Most common specific hepatic biochemical abnormalities are elevations of serum alkaline phosphatase and γ-glutamyl transpeptidase levels.

Alkaline phosphatase level was abnormal in more than 75% and about 92% in patients of Philipines and South African series. Causes are due to intrahepatic granulomas and extrahepatic biliary tree by tuberculosis and extrahepatic CBD obstruction by tuberculosis lymph node at porta.

- Transaminase levels may also be elevated in about 70% patients.
- Hyperbilirubinemia can be seen in patients with hepatic tuberculosis in about 20% of patients.
- Alteration of albumin / globulin ratio is common.

Table 2 : Shows : Liver function alteration in hepatic involvement of tuberculosis[15]

	No. of Patients	Percentages
Serum bilirubin	3	4.22
SGOT	5	7.00
SGPT	2	2.81
Alkaline Phosphatase	2	2.18

- Hypoalbuminemia and hyperglobulinemia present in approx 80% of patients in hepatobiliary tuberculosis.

Imaging

Non-specific findings are observed on radiography in hepatobiliary tuberculosis. Older series suggest most patients with hepatobiliary tuberculosis on chest X-Ray suggest tuberculosis,[16] but in modern series abdominal tuberculosis had concomitant pulmonary disease is much less common and in tune of approx 10% of patients. Thus absence of pulmonary disease no longer excludes the diagnosis of hepatobiliary tuberculosis. But on the other hand extra-pulmonary presentation of tuberculosis in AIDS patients has increased incidence.

Liver calcification highly suggestive of hepatobiliary tuberculosis. Alvarez[16] and Maglinte at al[18] reported hepatic calcification in approx 50% of patients with hepatobiliary tuberculosis. Multiple chalky or powdery calcification in the liver and nodal calcifications along the course of common bile duct are highly suggestive of hepatobiliary tuberculosis and differ reliably from other form of liver calcification.[17,18]

Liver is diffusely involved by small nodules ranging from 0.5 – 2mm in size in miliary tuberculosis. Macronodule or pseudotumour are found in rare condition where nodule is larger than 2mm in size. These larger nodules mimic neoplasm.

Abdominal ultrasound is used in initial imaging as universally accepted initial imaging modality in hepatic diseases though technitium-sulfa colloid scan used earlier.

Computed tomography provide a detailed of hepatic parenchyma. Endoscopic retrograde cholangiography (ERCP) and percutaneous transhepatic cholangiography (PTCA) provide direct visualization of biliary tree and commonly used in jaundiced patients with hepatobiliary tuberculosis.

In patients with obstructive jaundice, obstruction is found at porta hepatitis in about 80% and in distal common bile duct in about 14% patients. Biliary involvement range from mild narrowing to severe irregular tortuous stricture with proximal dilatation.

Fan et al[19] described involvement of biliary epithelium by tuberculosis confirmed by choledochoscopic biopsy from common hepatic duct stricture and also observation of AFB from bile aspiration during ERCP, and stent replacement in narrowed segment.

Congenital Tuberculosis

Liver is often involved in congenital tuberculosis. This is defined as tuberculosis acquired by fetus in intrauterine life, liver is involved in 80% of patients.[20] Specific signs are hepatomegaly and jaundice.

Table 3 : Shows incidence of hepatic granuloma

Authors	No of patients. Studied	Granuloma percentage	Type of Tuberculosis
Klatskin & Yesner R.	4	100	M
Haex & Vam Bick	189	93	P&E
Matev et al	22	68	M&MAT
Buckingham et al	22	40	E
Von Oiders havsen et al	93	25.3	M
Ban	59	20.3	P
Vonolder Hausen et al	248	19.2	P
Seife et al	17	13	P
Arora et al	50	12	P&E
Van Buchem	9	0	P
Gupta et al	71	18.3	P&E

Local Hepatic Tuberculosis (Primary Tuberculosis)

Involvement of hepatobiliary tract by tuberculosis, either without apparent involvement elsewhere or only with local lymph node and splenic involvement termed primary or local hepatic tuberculosis.[21]

Local Hepatic Tuberculosis (Primary Tuberculosis)

The liver is usually extensively involved in local hepatic tuberculosis. Symptoms and signs, laboratory abnormalities and imaging studies are similar to those of miliary tuberculosis. Pathogenesis of local hepatic tuberculosis is unclear. Tubercle bacillus is thought to reach liver via hepatic artery or portal vein or lymphatics.

Percutaneous liver biopsy confirm diagnosis in about 67% of patients and laparoscopy yields about 92% which appear as cheesy white, irregular nodules.

Biliary Tuberculosis

Obstructive jaundice rarely results in hepatobiliary tuberculosis. Fan et al[19] described biliary stricture as a result of granulomatous involvement of the biliary epithelium. Tuberculous cholangitis is rare, may result from rupture of caseating granuloma from the portal tract into bile duct. Clinical features resemble bacterial cholangitis with upper quadrant pain, fever and jaundice. Tuberculosis involvement of gallbladder is also rare. Gallbladder tumor caused by hepatobiliary tuberculosis is also described.[22]

Acquired Immunodeficiency Syndrome and Hepatobiliary Tuberculosis

AIDS patients show high incidence of TB which run an aggressive course also extra-pulmonary involvement is common.

Approx, 50% of AIDS patients are diagnosed with TB. In the setting of AIDS and extra-pulmonary TB, hepatic involvement is common.

Table 4 : Shows Clinical features of Hepatic Tuberculosis

Hepatomegali	91%
Fever	75%
Wt loss	64%
Abdominal pain	52%
Splenomegali	39%
Digestive symptoms	33%
Night sweats	25%
Jaundice	12%

Atypical mycobacteriosis, in particular *Mycobacterium avium-intracellular* complex infection is commonly found in patients with AIDS, both produces AFB-positive hepatic granulomatous disease, comparative incidence of *M. tuberculosis* verses *M. avium-intracellular* complex in various series differ greatly. The infection with *M. tuberculosis* occur relatively early in the course of AIDS reflecting less immunosuppression, relatively good response to antituberculosis chemotherapy (and where as disseminated *M. avium-intracellular* complex suggest severe immunosuppression). *M. avium-intracellular* complex infection conversely responds poorly to prolonged multidrug regimens.

Tuberculosis in liver transplant patients

- Higgins et al[23] reported TB in five of 2380 liver transplant recipients and only one patients showed tuberculin test response.
- Severe isoniazid associated hepatitis requiring liver transplantation has been reported
- Salizzoni et al[24] recommend routine preoperative screening for TB by tuberculin skin testing, with prophylactic treatment of patients with positive results.

DIAGNOSIS

Hepatobiliary TB should be considered in patients with compatible symptoms and signs and biochemical evidence of liver disease. Imaging studies may suggest biliary or pseudotumoral hepatic involvement

Liver biopsy is essential for the diagnosis and demonstration of *M. tuberculosis* by culture of liver tissue makes the diagnosis most certain. Positive cultures may be obtained even in absence of granulomas or AFB on histologic examinations.

Presence of hepatic caseating granulomas containing AFBs in highly suggestive of *M. tuberculosis* infection. PCR detection of *M. tuberculosis* has potential for diagnostic sensitivity and accuracy. Sensitivity of PCR is about 58% in the diagnosis of hepatic granulomas, and specificity is about 96%.

TREATMENT

Therapy of hepatobiliary TB is same in patients without such involvement. First-line antituberculosis agents are the mainstay of current regimen. Second-line agents should be used in patients with demonstrable resistant to first-line drugs or those who cannot tolerate the medications.

Isoniazid, rifampicin and pyrazinamide for 6 months is curative in absence of resistance.

The therapy of patients with AIDS and TB may be complicated by interaction between rifampicin and antiretroviral therapy. In that situation rifabutin may be substituted

Hepatic toxicity is common in currently used antituberculous agents. Patients with hepatic TB and whose liver function abnormalities are often present at the beginning may create diagnostic dilemma as therapy progresses. In such situation liver biopsy clarifies the issue whether worsening hepatic parameter represent progression of hepatic TB or due to drug toxicity. Jaundice due to biliary obstruction treated by biliary drainage either by percutaneous or endoscopic access. Surgical decompression is rarely necessary.

PROGNOSIS & CONCLUSION

Hepatobiliary TB is a treatable infection. Definite microbiological diagnosis without drug resistance and compliance with good regimen is effective. Patients with hepatobiliary TB may have a worse prognosis than without involvement. This may be due to fact that hepatobiliary involvement is a result of wide- spread and advanced disease

Hersch[23] showed mortality rate of 75% in jaundiced patients with hepatic TB.

Alvarez and Carpio[16] showed overall mortality rate is about 12%.

Situation of hepatic TB and AIDS is problematic successful therapy of TB does not affect the progressive immunosuppression owing to human immunodeficiency virus infection.

Lastly the prognosis of patients with *M. avium-intracellular* complex infection remains poor.

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