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HEPATOBILIARY TUBERCULOSIS

Sol Z Alvarez

Section of Gastroenterology, Department of Medicine,
University of Santo Tomas Hospital, Manila, Philippines

Abstract The term hepatobiliary tuberculosis refers to the localized form of hepatic tuberculosis as a distinct clinical entity, with signs and symptoms related to the hepatobiliary tract. Its clinical features and the different diagnostic aids used in its diagnosis are reviewed. Plain abdominal radiographs showing diffuse hepatic calcifications seen in approximately 50% of cases are almost diagnostic for hepatobiliary tuberculosis. Liver biopsies guided either by ultrasound, computed tomography or laparoscopy, showing caseating granuloma usually establish the diagnosis. In the absence of caseation necrosis, a positive acid-fast bacillus (AFB) or culture for *Mycobacterium tuberculosis* is needed to establish the diagnosis. A polymerase chain reaction assay for the identification of *Mycobacterium tuberculosis* in liver biopsy specimens is a new development. Treatment is similar to that used for pulmonary tuberculosis. Quadruple therapy (using four anti-tuberculosis drugs) is recommended, generally for 1 year. For patients with obstructive jaundice, it is recommended to do MRCP first to outline the biliary tract, determine the site of the obstruction and then perform biliary decompression either by stent insertion during ERCP or by percutaneous transhepatic biliary drainage if stent insertion fails. Surgical decompression should be considered whenever feasible.

INTRODUCTION

Tuberculosis (TB) is known to involve the liver in different ways. Miliary TB of the liver is the most common and is said to occur in 50-80% of all patients dying of pulmonary TB.[1] Leader, in an extensive review of the world literature in 1952, documented only 80 cases of hepatic TB with large abscesses and nodules or tuberculomas and classified TB of the liver into miliary, which is part of generalized miliary TB and local, which he further divided into focal or nodular TB (to include tuberculous hepatic abscess and tuberculomas) and into the tubular form (involving intrahepatic ducts).[2] Since then, there have been isolated case reports of hepatic TB, particularly localized TB, referred to by different names ranging from tuberculous liver abscess,[3-10] tuberculous pseudotumour,[11-14] atypical hepatic TB,[15,16] primary hepatic TB,[17,18] tuberculous hepatitis,[19,20] tuberculous cholangitis and TB of the bile duct.[21] Inconsistencies in the nomenclature has created confusion, particularly with respect to the clinical features of specific forms of hepatic TB being referred to.

The author would like to classify hepatic TB into the following:

1. Miliary form, which is part of generalized miliary TB and usually has no signs or symptoms relevant to the liver.

2. Granulomatous disease (tuberculous hepatitis) due to TB, for those that present with unexplained fever, some with mild jaundice, with or without hepatomegaly, which, on liver biopsy, show caseating granuloma and improve with anti-tuberculous therapy.

3. Localized hepatic TB (with signs and symptoms relevant to the hepatobiliary tract): (i) without bile duct involvement, to include solitary or multiple nodules, tuberculoma and

tuberculous hepatic abscess; and (ii) with bile duct involvement causing obstructive jaundice, either by enlarged nodes surrounding the bile ducts or actual tuberculous processes in the ductal epithelium producing inflammatory strictures.

The term hepatobiliary TB as used in this article refers to the localized form of hepatic TB and is a distinct clinical entity with characteristic clinical features and gross appearance of the liver, with or without involvement of the biliary tract.

ETIOPATHOGENESIS AND PREVALENCE

Hepatobiliary TB, like any other extrapulmonary and gastrointestinal TB, is due to *Mycobacterium tuberculosis.* The organism reaches the hepatobiliary tract by the hematogenous route, from a tuberculous infection of the lungs (which may be active or inactive) via the hepatic artery.[22] In some cases, infection could reach the liver via the portal veins,[23-25] especially if there is concomitant TB of the gastrointestinal tract. The tubercle bacilli may also reach the liver through the lymphatics. Rupture of a tuberculous lymph node in the portal tract leading into the portal vein has also been mentioned as a route of infection.[23,26] Primary hepatic TB is probably rare, because even if there is no clinical or radiological evidence of TB elsewhere, pulmonary TB is discovered at autopsy in those patients who died, even if it is inactive.

Hepatobiliary TB has been seen commonly in the Philippines and among Filipino patients abroad. Some of the case reports in the world literature of localized hepatic TB, especially those causing obstructive jaundice, involved Filipino patients.[3,21,25,27] The author has no explanation why hepatobiliary TB occurs frequently among Filipinos but not among the Chinese living in the Philippines or in other Asian countries where tuberculosis is also common. Filipinos may have racial vulnerability to the tubercle bacilli.

CLINICAL FEATURES

Hepatobiliary TB has a 2:1 male preponderance with the majority falling within the 11-50-year-old age group[28] with a peak age incidence in the second decade of life in both sexes. The majority of localized hepatic TB reported in the literature occurs in the 30-50 year old age group.[5,8,11,21,25,27,29-31] More than half of the 130 cases reported by the author in 1983[28] were symptomatic for more than 1 year prior to admission. Abdominal pain appeared to be the most important symptom of hepatobiliary TB in several series. Abdominal pain was present in 45% of the patients in the jaundiced group reported mainly in the right upper quadrant, often associated with fever and chills. In the non-jaundiced group, abdominal pain was present in 39% of cases. Hersch, in a study of 200 black South African patients reported abdominal pain in approximately half of the patients in his series although localized hepatic TB was present only in 14% of the cases.[24] Fever was present in more than 60% in four large series.[19,24,28,32] Hepatomegaly was the most common finding present in 96% of the cases reported by the author.[28] The enlarged liver was nodular in 55% of cases simulating cancer of the liver and it was tender in 36% of cases simulating liver abscess.[28] Hersch reported hepatomegaly in 95% of his patients with localized hepatic TB, half of them with hepatic tenderness[24] while Essop *et al*[19] reported it in 80% and Maharaj *et al*[32] in 95% of their patients (Table 1). Splenomegaly was present in 25-57% of cases.[19,24,28,32] Jaundice was seen in 35% of the cases reported by the author.[28] It was obstructive in nature, simulating other conditions that exhibit extrahepatic biliary obstruction. Jaundice occured in a minority of patients in the other reports.

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 were abnormal in 35-80% of the cases reported by the author,[28] especially among those patients with obstructive jaundice, these were non-specific 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

Table 1. Outstanding signs and symptoms of hepatic tuberculosis in four large studies

	Prevalence (%)			
Signs and Symptoms	Alvarez and Carpio[28] (n= 130)	Essop et al.[19] (n = 96)	Hersch[24] (n = 200)	Maharaj et al.[32] (n=41)
Abdominal Pain	45	66	50	46
Fever	65	10	90	63
Weight Loss	55	-	75	61
Jaundice	35	11	15	14
Hepatomegaly	96	80	95	95
Nodular	55			
Tender	36	60	50	44
Splenomegaly	25	40	57	31

Table 2. Abnormal liver tests, radiographs and liver biopsy of hepatic tuberculosis in three large studies

	Prevalence (%)		
Diagnostic Aids	Alvarez and Carpio[28] (n=130)	Essop et al.[19] (n=96)	Maharaj et al[32] (n=41)
Abnormal ALT and AST	35	70	-
Abnormal alkaline phospatase	75	83	87
Abnormal albumin/ globulin ratio	81	63	95
Abnormal chest X-ray	65	75	78
Hepatic calcifications on plain abnormal radiographs	50	-	-
Liver biopsy			
caseating granuloma	67	83	51
AFB positive	7	9	59

ALT, Alanine aminotransferase; AST, aspartate amino-transferase; AFB, acid-fast bacillus.

Table 3: ERCP findings in hepatobiliary tuberculosis (n=26 patients)

	%
Hilar Obstruction	61.5
Segmental dilatation and constriction of the intrahepatic ducts	23.1
Beaded common bile duct	19.2
Obstruction at the common hepatic duct	11.5
Dilated common duct with areas of constriction	7.7
Prunning of the intrahepatic ducts	3.8

series[28] and in only 5% of the non-jaundiced group. Essop *et al.* reported elevated ALT and AST in 70% of their cases.[19] 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 the author.[28] On the other hand, the alkaline phosphatase was elevated in 90% of Hersch's series.[24] while the Essop *et al.*[19] reported normal alkaline phosphatase in 17% of the cases in his series. Alterations in A:G ratios were common. Hypoalbuminaemia and hyperglobulinaemia were present in approximately 80% of patients with hepatobiliary TB.[19,24,28,32] 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.

Chest X-rays showed abnormalities in 65% of the cases reported by the author[28] demonstrating pulmonary TB but were negative in 35% of cases. Maharaj *et al.* reported normal chest X-rays in 22% of cases.[32] Other reports with localized hepatic TB also reported normal chest X-rays (Table 2).[7,11,15,22]

Liver calcifications were noted in plain abdominal radiographs in 50% of the cases reported by the author,[28] (Fig. 1) but were rarely described in other reports. In all instances, the calcifications involved both lobes of the liver and in 98% of cases were 8-12 mm in size, small, discrete and scattered. Maglinte *et al.* described the pattern of calcification in hepatobiliary TB and compared it with those seen in histoplasmosis, hepatoma and metastatic liver disease and concluded that the calcifications seen in hepatobiliary TB can be differentiated from liver calcifications of other etiologies.[33]

Imaging techniques

Technetium-sulfa colloid liver scans have generally been replaced by ultrasonography and computed tomography (CT). Ultrasound of the liver showed hypo-echoic lesions and complex masses, particularly in those reports with tuberculous liver abscess, and could not be differentiated from carcinoma.[8,12,29-31] Liver calcifications can be detected earlier by ultrasound than by plain radiographs of the abdomen. Dilated intrahepatic ducts in obstructive jaundice can be demonstrated by ultrasound.

Computed tomographic scans of the liver can show solitary or multiple focal masses due to a large tuberculoma or tuberculous liver abscess, which can be difficult to differentiate from malignancy.[6,8,27,29-31,34] Computed tomography guided liver aspiration or biopsy can confirm the diagnosis. Liver calcifications can also be demonstrated by CT scan.

Liver biopsy

Percutaneous blind aspiration liver biopsy is useful in the diagnosis of the miliary form and tuberculous granulomatous disease of the liver, where there is a high chance of arriving at a correct diagnosis. In the localized form of hepatic TB, ultrasound-, CT- or laparoscopic-guided liver biopsy yields a higher success rate than blind aspiration liver biopsy. In the series reported by the author, the success rate in establishing the diagnosis of hepatobiliary TB with blind aspiration liver biopsy was only 67% compared to 92% for laparoscopic diagnosis and almost 100% with laparoscopic-guided liver biopsy.[28] The hardness of the tuberculous lesion, sometimes stony hard in hepatobiliary TB, is one reason why the yield from blind aspiration liver biopsy is not that high. Sometimes the biopsy needle barely penetrates the liver tissue and just pushes the liver away and inadequate tissue is obtained. A hard gritty sensation felt during liver biopsy, in the experience of the author is characteristic of hepatobiliary TB.

Histologically, the finding of caseating granuloma in the liver biopsy specimen is considered diagnostic of TB. However, it has also occasionally been reported in brucellosis,[35] coccidioidomycosis[36] and Hodgkin's disease,[37] but the clinical presentation is different.The finding of central caseation necrosis in a granuloma in liver biopsy specimens vary. The author found caseation necrosis in 67% of the cases reported,[28] while Essop *et al.*[19] reported

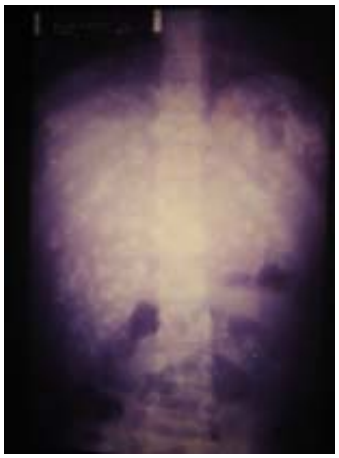


Figure 1 . Plain scout film of the abdomen showing diffuse hepatic calcifications in a patient with confirmed hepatobiliary tuberculosis

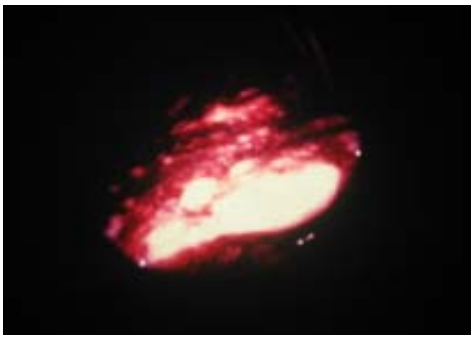


Figure 2. Laparoscopic view of the right lobe of the liver with confirmed hepatobiliary tuberculosis. Note the cheesy white irregular nodules representing tuberculoma at the surface, the biopsy of which showed caseating granuloma.

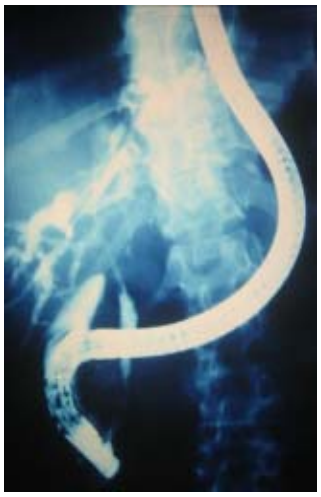


Figure 3. Endoscopic retrograde cholangiopancreatography of a patient with confirmed hepatobiliary tuberculosis

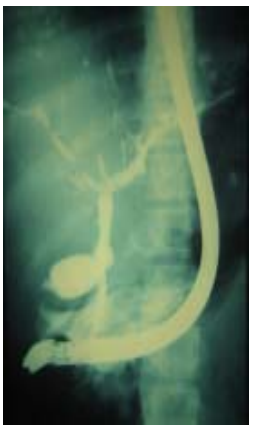


Figure 4. Endoscopic retrograde cholangiopancreatography of a patient with confirmed hepatobiliary tuberculosis showing multiple strictures at the intrahepatic ducts.

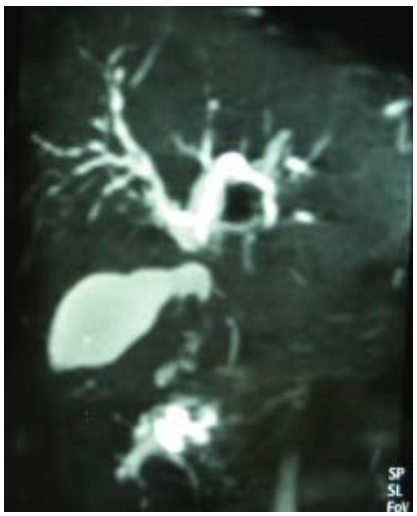


Figure 5. MRCP in a patient with hepatobiliary TB showing hilar obstruction, dilated intrahepatic ducts and normal CBD

83%, Maharaj *et al.*[32] 51 %, and Korn *et al.*[38] 30% in their series.

With a finding of non-caseating granuloma in the liver biopsy specimen, a test for acid-fast bacillus (AFB) and/or culture of *Mycobacterium tuberculosis* would be required. Acid-fast bacillus may be seen in tuberculous granulomas in 0-35% of cases.[39] The yield of positive culture for *Mycobacterium tuberculosis* is much lower.

Recently, Alcantara-Payawal *et al.*[40] developed a polymerase chain reaction (PCR) assay for identification of *Mycobacterium tuberculosis* in liver biopsy specimens with a diagnosis of hepatobiliary TB. They reported a 100% success rate for those with definitive diagnoses of TB (those with caseating granuloma) and 78% success rate for those with presumptive diagnosis of hepatobiliary TB, with an overall PCR assay positivity of 88%. This was favorably higher when compared with the use of the conventional method (AFB and culture) of 0-12%.

Laparoscopy

Before the era of ultrasonography and computed tomography, laparoscopy was used extensively as the main diagnostic aid in visualizing lesions on the surface of the liver and obtaining a direct vision liver biopsy. In the report of the author of 130 cases of hepatobiliary TB in 1983[28] where laparoscopy was carried out on 55 patients, a correct gross diagnosis of tuberculoma of the liver was made in 92% of cases. The author described the laparoscopic appearance of hepatobiliary TB (Fig. 2) as cheesy white, sometimes chalky white, irregular nodules of varying sizes, some of which resembled tumor masses. When combined with direct vision liver biopsy, the diagnosis of tuberculoma of the liver was established in 100% of cases. Bhargava *et al.* described laparoscopic findings of a case, which was confirmed with cytological and histological data.[41]

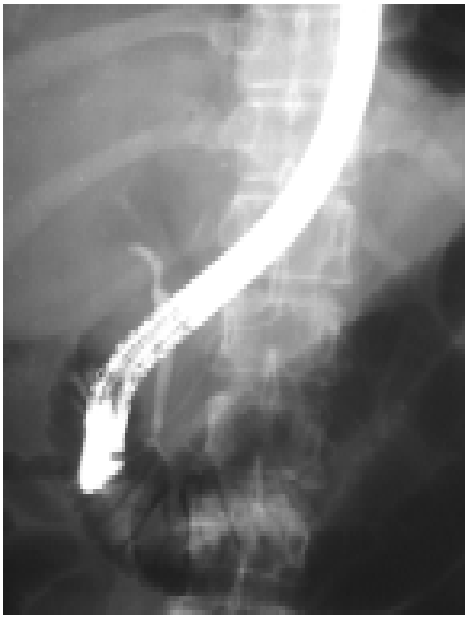
Endoscopic retrograde cholangiopancreatography and percutaneous transhepatic cholangiography

Visualization of the biliary tract is needed for patients with hepatobiliary TB presenting with obstructive jaundice. This can be accomplished by either endoscopic retrograde cholangiopancreatography (ERCP) or percutaneous transhepatic cholangiography (PTC). In the series reported by the author[28] where PTC was performed in 14 patients with hepatobiliary TB presenting with obstructive jaundice, the site of obstruction was located at the porta hepatis in eight (57%) patients. Maglinte and associates described cholangiographic findings in 22 patients with hepatobiliary TB and obstructive jaundice and localized the site of obstruction at the porta hepatis in 86% and at the distal common bile duct in 14% of patients.[33] The bile ducts involved showed irregular tortuous stricture with marked proximal dilatation. While the cholangiographic appearance is difficult to differentiate from malignancy, the presence of associated scattered hepatic calcifications favors the diagnosis of hepatobiliary TB. Sollano *et al.* reported the ERCP findings of 11 jaundiced patients with hepatobiliary TB and found hilar obstruction in 9 patients 4 of which were complete or tight, constriction at the proximal common bile duct was seen in 4 patients and at the hepatic ducts in 3 patients. [42]

Recently, the author described the ERCP findings in 26 patients with hepatobiliary TB presenting with obstructive jaundice.[43] Hilar stricture was the most common feature found in 61.5% of patients (Fig. 3). The common bile duct appeared beaded, with areas of dilatation and constriction in 19.2% of patients, while the intrahepatic duct was dilated in 26.9% and showed segmental dilatations and constrictions in 23% of patients (Fig. 4).

Biliary tract involvement in hepatobiliary TB in the majority of cases was due to enlarged tuberculous lymph nodes[28,44,45] located periductally at the hepatoduodenal ligament and at the porta hepatis, compressing the upper common hepatic duct and the common bile duct. Fan and associates described involvement of the biliary epithelium by TB, as confirmed by choledochoscopic biopsy of a common hepatic duct stricture.[21]

Figures 6a & 6b. ERCP of the same patient showing hilar obstruction (Fig 6a) with introduction of a stent through the hilar obstruction (Fig 6b)



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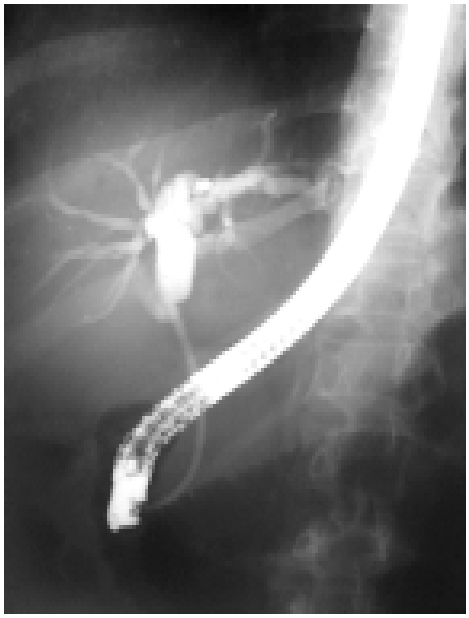

6b

DIAGNOSIS

The diagnosis of hepatobiliary TB in endemic areas/countries should be considered in any patient with chronic right upper quadrant pain associated with hepatomegaly, especially if accompanied by fever and weight loss. The presence of associated pulmonary TB by chest X-ray will help in the diagnosis, but a negative chest X-ray should not rule it out. The presence of an enlarged, hard nodular liver, especially if present for more than one year, will favor the diagnosis of hepatobiliary TB rather than malignancy. The presence of scattered hepatic calcifications by plain abdominal radiograph will, in all likelihood, be due to TB. Liver biopsy guided either by laparoscopy, ultrasonography or computerized tomography will establish the diagnosis if the caseating granuloma is seen. To confirm the diagnosis for a non-caseating granuloma, a positive AFB and/or culture for *Mycobacterium tuberculosis* would be needed. Identification of *Mycobacterium tuberculosis* by PCR is more successful than by the conventional method (AFB and culture).

In patients with chronic recurrent obstructive jaundice, especially when associated with an enlarged nodular liver and in those who have had the condition for more than one year, diagnosis of hepatobiliary TB should be highly entertained. Showing the presence of scattered hepatic calcifications by plain abdominal radiograph would favor the diagnosis.

The use of PTC or ERCP will localize the site of obstruction. Recently, the use of MRCP is as good as ERCP in visualizing the biliary tract and localizing the site of obstruction. It is non-invasive and should be the first one used reserving ERCP for therapeutic purposes such as stent insertion (Fig. 5 & 6).

ACQUIRED IMMUNODEFICIENCY SYNDROME AND HEPATOBILIARY TUBERCULOSIS

There has been a resurgence of TB in industrialized countries, primarily because of the acquired immunodeficiency syndrome (AIDS) with increasing incidence of extrapulmonary TB. Louie *et al.* reported that 50% of AIDS patients diagnosed with TB at the Bellevue Hospital in New York City had extrapulmonary involvement.[46] Recent reports documented the

rise of abdominal and hepatobiliary TB, especially in urban inner city populations.[47,48]

The impact of AIDS on TB in developing countries has not been felt as much as in industrialized countries, because TB has always been present and prevalent in Third World countries. All of the cases reported by the author and most cases of hepatobiliary TB reported in the literature are from human immunodeficiency virus (HIV)-negative patients. There are reports that AIDS patients may run an unusually aggressive course. Unusual forms of hepatic TB may be seen more commonly in patients with AIDS.[49] *Mycobacterium avium-intracellulare* (MAl) infection is commonly found in patients with AIDS and may involve the liver. This infection produces AFB-positive hepatic granulomas[50] and should be considered whenever a positive AFB is obtained from a liver biopsy specimen of an AIDS patient suspected to have hepatic TB.

TREATMENT AND PROGNOSIS

The treatment of hepatobiliary TB does not differ from that of pulmonary TB. At present, quadruple therapy (the use of at least *four* anti-tuberculous drugs) is recommended due to increasing incidence of drug resistant TB.[51] Isoniazid (INH), rifampicin, pyrazinamide (PZA) and ethambutol have been used. The duration of therapy is generally one year. The recent development of a PCR assay *for* identification of *Mycobacterium tuberculosis* can be used in the future to gauge response to treatment.

For those patients with obstructive jaundice, in addition to the use of anti-tuberculous treatment, biliary decompression should be done either by stent placement during ERCP, percutaneous transhepatic biliary drainage (PTBD) or by surgical decompression whenever feasible.[28]

The experience of the author with biliary stenting during ERCP is disappointing because of the tight hilar obstruction in most instances. In eleven patients with biliary stricture, the author was successful in inserting a stent and successfully decompressing the obstruction in only seven of the patients. Surgical decompression is attempted if there is a dilated proximal common bile duct or hepatic duct accessible for biliary enteric anastomosis.

PROGNOSIS

The author has shown good clinical responses with the use of anti-tuberculous treatments, INH, rifampicin and PZA in 67% of cases[28] with disappearance of abdominal pain and fever, reduction in the size of the liver and increases in appetite and weight gain. Good clinical responses have also been reported in tuberculous liver abscess after aspiration of the abscess plus anti-tuberculous treatment.[4,6-8] The author had four patients with recurrence of the symptoms after being asymptomatic and having discontinued the medications for one year. In the series reported by the author,[28] there was an overall mortality of 12% despite the use of anti-tuberculous therapy. One-third of the deaths were due to massive esophageal variceal bleeding from portal hypertension, secondary to the associated liver cirrhosis and not directly attributed to TB. Lately, some deaths have resulted from cholangitis in patients with obstructive jaundice, where decompression was unsuccessful. The patients who underwent successful decompression have remained asymptomatic for as long as 3-5 years following treatment.

Hersch in 1964 found a mortality rate of 75% in jaundiced patients with hepatic TB.[24] Essop et *al* reported a mortality rate of 42 %.[19] Hepatic failure is not a usual cause of death from hepatobiliary TB. There are only two reports in the literature of liver failure with hepatic encephalopathy leading to death[52, 53] one of whom had massive involvement of the liver with tuberculous granulomas. In the future, the use of the PCR assay for *Mycobacterium tuberculosis* may allow the assessment of the response and determine the duration of treatment needed for hepatobiliary TB.

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