Review Article

Hepatobiliary Tuberculosis

Sanjay Bandyopadhyay, Pranab K Maity

Abstract

Hepatobiliary tuberculosis refers to the localized form of hepatic tuberculosis and is a distinct entity in which hepatobiliary involvement overwhelmingly dominates the clinical picture. Presentations are often delayed, and manifestations can be nonspecific. Fever is the most common symptom followed by abdominal pain, and hepatomegaly is the most common abnormality found on clinical examination. Abnormalities of the liver function tests are non-specific and hence not diagnostic. Ultrasound or computed tomography reveals single or complex masses, and guided biopsy is diagnostic either by demonstrating caseating granuloma or the organism by staining and culture. Treatment is with standard first-line antituberculous drugs. Endoscopic stenting gives an excellent outcome for symptomatic biliary strictures. The outcome in patients infected with Human Immunodeficiency virus depends on the level of underlying immunosuppression.

Introduction

Tuberculosis is known to involve the liver in three different forms.1 1. Miliary form, which is part of generalized miliary tuberculosis, occurs in 50-80%, and usually has no signs or symptoms relevant to the liver. 2. Granulomatous disease (tuberculous hepatitis) that presents with unexplained fever, some with mild jaundice, with or without hepatomegaly, which, on liver biopsy, shows caseating granuloma and improves with anti-tuberculous therapy (ATT). 3. Localized hepatic tuberculosis (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.

Hepatobiliary tuberculosis refers to the localized form of hepatic tuberculosis and is a distinct entity in which hepatic (and biliary) involvement overwhelmingly dominates the clinical picture. Hepatobiliary tuberculosis is uncommon and accounts for less than 1% of all tuberculous infections.2

Pathogenesis

Normally the liver is an inhospitable place for tubercle bacillus owing to its low tissue oxygen tension.3 If the organism reaches the hepatobiliary tract via the hepatic artery from a tuberculous infection of the lungs (which may be active or inactive), it results in miliary tuberculosis.3 In some cases, however, infection could reach the liver via the portal vein especially if there is a concomitant involvement of the gastrointestinal tract. The tubercle bacilli may also reach the liver by lymphatic spread or due to rupture of a tuberculous lymph node in the portal tract. These latter cases result in localized hepatobiliary tuberculosis.3 This difference in pathogenesis may explain the observation that in miliary tuberculosis, lesions are concentrated near the hepatic veins, although in the local form, they are usually found periportally.4 The term primary hepatobiliary tuberculosis is inappropriate and the term ‘localized hepatobiliary tuberculosis’ may be preferred.

Table 1: Table showing outstanding clinical features, laboratory abnormalities and adverse outcome from seven large series of hepatobiliary tuberculosis

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The majority of localized hepatic tuberculosis reported in the literature occurs in the 30-50 years age group. Patients are symptomatic for more than one year prior to admission. The outstanding signs and symptoms of hepatobiliary tuberculosis from several widely-quoted series are shown in Table 1. Fever is the most common (50-90%) symptom followed by abdominal pain (45-66%, mainly in the right upper quadrant). Hepatomegaly is the most common abnormality found on clinical examination, and in one series, it was nodular in 55% and tender in 36% cases suggesting liver abscess. Less than one-third patients present with jaundice that is obstructive in nature, simulating other conditions that exhibit extrahepatic biliary obstruction. Pruritus is reported in 23%. Concomitant tuberculous peritonitis is found in 9-14%, producing abdominal distension and ascites.

A significant decline in liver function is unusual and acute liver failure is rare. The rarity of liver failure in hepatobiliary tuberculosis may be owing to the fact that the presence of tuberculous granulomas, even if massive, does not directly result in the extensive destruction of hepatocytes. The liver may be massively enlarged by the presence of granulomas, yet liver metabolic function remains normal.

The nodular form of localized hepatic tuberculosis is a distinct radiological entity. Two brilliant case series illustrated the difficulty in reaching the correct diagnosis, unsuspected in nearly all the cases and most often confused with carcinoma of the liver. A greater awareness of this rare entity may prevent needless surgical intervention.

Clinical Features

Investigations

Abnormalities of the liver function tests are non-specific and hence not diagnostic (Table 1). Alkaline phosphatase may be markedly elevated, particularly in those cases presenting with obstructive jaundice. Hypoalbuminaemia with polyclonal hyperglobulinaemia are present in approximately 80% patients. In general, abnormalities in liver chemistry parameters confirm the presence of hepatic involvement, but their levels have no correlation with the extent of involvement. More than two-thirds of cases show abnormalities in chest radiography, although concomitant active pulmonary tuberculosis is rare (less than 10%). Liver calcification is rare though one series had reported it to the extent of 50%. Calcifications seen in hepatobiliary tuberculosis can easily be differentiated from other causes of liver calcification. In hepatobiliary tuberculosis, large (8-12 mm in size) “chalky” and confluent hepatic calcifications involving both the lobes are seen. Other characteristic imaging finding is the nodal-type calcifications along the course of the common bile duct. Histoplasmosis is differentiated from tuberculosis by the presence of small, discrete, scattered calcifications. Benign tumors of liver may show popcorn calcification. Liver cysts show marginal calcification. Primary hepatocellular carcinoma are usually solitary and show irregular calcification if any. On the other hand calcification is unusual in hepatic metastasis.

Ultrasound of the liver shows hypoechoic lesions and complex masses mimicking primary or metastatic hepatic carcinoma or pyogenic abscess, particularly in those cases with tuberculous liver abscess (Figure 1). These lesions have been referred by a variety of names, including tuberculosis, macronodular tuberculosis or pseudotumoral tuberculosis. Liver calcifications can be detected earlier by ultrasound than by plain radiographs. Dilated intrahepatic ducts in obstructive jaundice can be demonstrated by ultrasound.

Computed tomography (CT) scan of the liver can show solitary or multiple focal masses due to a large tuberculoma or tuberculous liver abscesses, which can be difficult to differentiate from malignancy. CT-guided liver aspiration or biopsy can confirm the diagnosis. Liver calcifications can also be demonstrated by CT scan. Technetium-sulfur colloid liver scans have generally been replaced by ultrasonography and CT.

Percutaneous blind aspiration liver biopsy is more useful for the miliary form and tuberculous granulomatous disease of the liver, where the success rate of a correct diagnosis is better. In the localized form of hepatic tuberculosis, ultrasound-, CT- or laparoscopic-guided liver biopsy yields a higher success (nearly 100%) than blind aspiration liver biopsy (67%). A hard gritty sensation felt during liver biopsy is very suggestive but may also occur in malignancy. Histologically, the finding of caseating granuloma (found in 30-67%) in the liver biopsy specimen is considered diagnostic of tuberculosis. In the presence of non-caseating granuloma, a test for acid-fast bacillus (AFB) and/or culture of Mycobacterium tuberculosis would be required. AFB may be seen in tuberculous granulomas in 0-35% of cases. The yield of positive culture for Mycobacterium tuberculosis is much lower. The overall positivity of PCR assay for M tuberculosis in liver biopsy specimen is 88% (100% in those with caseating granuloma). This is favorably higher when compared with the conventional methods of AFB staining and culture (0-12%).

In presence of non-caseating granuloma in liver biopsy, distinction from sarcoidosis becomes difficult. Sarcoid granulomas are numerous, discrete, perportal in distribution, with asteroid bodies or Schaumann bodies, with thin rim of lymphocytes and with concentric hyalinized scar in old granulomas. Criteria which favor tuberculosis are the presence of Langhans’ giant cells, tendency to coalesce, no zonal predilection, destruction of reticulin framework, and irregular contour with a dense cuff of lymphocytes.

Prior to availability of ultrasonography and CT, 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. The finding of cheesy white, sometimes chalky white, irregular nodules of varying sizes (often resembling tumor masses) are diagnostic. Laparoscopy has a diagnostic yield of 88%, and combined with guided-biopsy, nearly 100%.

Presence of fatty liver is seen in 14 – 42% and amyloidosis in 0 – 10% cases. Other non-specific changes in liver biopsy include focal hepatocellular necrosis, Kupffer cell hyperplasia, lymphohistiocytic aggregates, nodular regenerative hyperplasia, mild periportal fibrosis and non-specific portal inflammation.
making stenting an ideal treatment.2 Percutaneous drainage compression tends to be at the hilum and is usually singular, may require multiple stent placements. Conversely, lymph node involvement or hepatic tuberculoma tend to be multiple and proximal dilatation.14,24 While this cholangiographic appearance involved shows irregular tortuous stricture with marked constriction.25 Obstruction is usually found at porta (67-86%) appear beaded (19% in one series), with areas of dilatation and constriction.25 Obstruction is usually found at porta (67-86%) or at distal bile duct (14-33%).25 Constriction at the proximal common bile duct or the hepatic ducts is rarely reported. Biliary tract involvement in the majority of cases is due to enlarged tuberculous lymph nodes located periductally at the hepatoduodenal ligament and at the porta hepatis (Figure 2).26 Direct tubercular involvement of biliary epithelium is rare,27 ERCP or PTC is restricted for use in jaundiced patients with therapeutic intentions.25

**Treatment**

Hepatobiliary tuberculosis is a treatable infection. Successful therapy, however, requires an accurate microbiologic diagnosis and compliance with a regimen of demonstrated efficacy.11 The treatment regimen does not differ from that of pulmonary tuberculosis. Initially, quadruple therapy (containing isoniazid, rifampicin, pyrazinamide and ethambutol) is recommended for at least two months due to increasing incidence of drug resistance.11 Total duration of therapy is generally one year. For those patients with obstructive jaundice, in addition to the use of ATT, biliary decompression should be done by stent placement during ERCP.28 Strictures resulting from biliary involvement or hepatic tuberculoma tend to be multiple and may require multiple stent placements. Conversely, lymph node compression tends to be at the hilum and is usually singular, making stenting an ideal treatment.2 Percutaneous drainage may be used as a temporary measure and later combined with endoscopic internalization of the stents. Surgery is attempted if there is dilated proximal common bile duct or hepatic ducts accessible for biliary-enteric anastomosis.1

Prognostic factors for adverse outcome include age younger than 20 years, acute presentation, coagulopathy, and high mean caseation score.8 The outlook of patients with AIDS is problematic. The level of underlying immunosuppression appears to be the most important variable influencing long-term survival in this group.29

A good clinical response is documented by reduction in the size of the liver, and increases in appetite and weight gain.2 Quadruple therapy results in response in 67%.5 Despite ATT, overall mortality varies from 12-42%,5,6 and may be as high as 75% in those with jaundice.7 Deaths usually results from disseminated disease, complications of portal hypertension (often due to underlying cirrhosis) or unrelieved cholangitis.1 Poor general condition of the patients, delayed presentation and adverse effects of drug therapy are important contributors to mortality.7 Hepatic failure is not a usual cause of death.20

**Special Issues**

**Hepatobiliary tuberculosis in HIV infection**

There has been a resurgence of tuberculosis in recent years, primarily because of acquired immunodeficiency syndrome (AIDS), and 50% of AIDS patients diagosed with tuberculosis have extrapulmonary involvement.31 AIDS patients may run an unusually aggressive course. Unusual forms of hepatic tuberculosis are more common as also high rate of disseminated disease, drug resistance and adverse drug reactions.11 The comparative incidence of M tuberculosis versus M avium-intracellulare complex in various series differs greatly owing to the fact that these infections occur in different stages of immunosuppression. Geographic, racial and socioeconomic factors may also influence these differences in comparative incidence.31

**Tuberculosis occurring in liver transplant patients**

Both pediatric and adult liver transplant recipients appear to be at risk because of their immunosuppressed state. The prevalence of new onset tuberculosis in liver transplant recipients is 0.7% over five year period. However, tuberculosis is a rare cause of hepatic granuloma in post-transplant patients.32 Of greater concern is the risk of hepatotoxicity associated with isoniazid therapy or prophylaxis. Hepatic enzyme abnormalities associated with drug therapy can be confused with transplant rejection.32

**Associated and coincidental hepatic lesions**

Nearly 30% patients dying of cirrhosis have demonstrable tuberculous infections.33 Korn et al suggested that the fatty changes in the liver in patients with hepatic tuberculosis may be the result of concomitant alcohol ingestion.19 Alcohol also increases the risk of hepatotoxicity from INH and other antituberculous therapy.34 Cirrhosis has been described as a possible risk factor for the development of drug-resistant tuberculosis.34 In patients with underlying liver disease, ofloxacin may be better than traditional antituberculous therapy.34

**Hepatic injury due to ATT**

INH causes acute hepatocellular jaundice in about 1% of all recipients, and at least 10% experience more trivial anicteric hepatic injury.34 Clinical features are indistinguishable from acute viral hepatitis.34 Case fatality rate may be as high as 10%.34 The mechanism appears to be metabolic idiosyncrasy rather than hypersensitivity. Risk factors are advanced age, female sex, alcoholism, concomitant use of other hepatotoxic drugs or rifampicin and pyrazinamide.34

rifampicin increases the likelihood of INH-induced hepatic injury but occasionally can itself produce acute idiosyncratic injury. It can also interfere with bilirubin uptake and excretion as a benign physiologic effect.

Pyrazinamide also potentiates hepatotoxicity of INH and rifampicin. Case fatality rate is higher (compared to those not receiving pyrazinamide) and the survival is inversely related to the time to onset of jaundice.24

**Tuberculosis of the gallbladder**

The gallbladder is an uncommon site of tuberculous infection.
The majority of patients are women over 30 years of age. Gallstones are present in more than two third of cases, and most commonly reported symptoms and signs include epigastric pain made worse by eating, and right hypochondriac tenderness. Most cases occur in association with other organ involvement, including tuberculous peritonitis. Treatment usually requires cholecystectomy in combination with ATT. Complications, such as, tuberculous abscess of the gallbladder requires prompt surgical attention.

Conclusion

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. Presentations are often delayed, and manifestations can be nonspecific. The diagnosis of hepatobiliary tuberculosis in endemic countries should be considered in any patient with prolonged fever and chronic right upper quadrant pain associated with hepatomegaly, especially if accompanied by weight loss. The presence of associated pulmonary lesions (active or inactive) by chest radiography along with scattered hepatic calcifications by plain abdominal radiograph will aid in the diagnosis. Liver biopsy done either during laparoscopy, ultrasound- or CT-guided biopsies 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 of 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 tuberculosis should be highly entertained. Nearly two-third of patients responds to standard ATT given for one year. With the emergence of AIDS epidemic, Physicians are likely to experience more aggressive, unusual forms of hepatobiliary tuberculosis with a higher rate of drug resistance and fatal outcome.

References