CME Article

Hepatobiliary tuberculosis

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ABSTRACT

Tuberculosis (TB) infection is still common today and remains an important cause of morbidity and mortality. Abdominal TB is one of the most prevalent forms of extra-pulmonary manifestations, and collectively refers to gastrointestinal, splenic, pancreatic, hepatobiliary and abdominal lymphadenopathy involvement. The manifestation can be nonspecific, and mimics many conditions, including malignancies. Biliary involvement is extremely rare. It can directly involve or be a result of external compressions or extension from adjacent organs. Strictures can be simple or multiple and isolated or complex. Radiologically, it is difficult to exclude cholangiocarcinoma. Hepatic involvement is more common and is categorised as the miliary or isolated local type. Both can be further sub-divided into nodular or diffuse forms. The manifestations range from abscesses and tuberculomas to hepatic calcifications. Calcifications range from small isolated specks to gross calcification with or without hepatic atrophy.

The diagnosis of hepatobiliary TB (HBTB) can be difficult. Ultrasonography and computed tomography are the main radiological investigations. Endoscopic retrograde cholangiography is important in the management of biliary TB. It is often important to look for the involvement of other organs and consider the coexistence of other pathologies such as malignancies. This pictorial essay reviews some of the HBTB infections that have been encountered in our tertiary referral centre.

Keywords: bile ducts, diagnostic imaging, endoscopy, hepatic tuberculosis, strictures, tuberculoma, tuberculosis

Singapore Med J 2010; 51(9): 744-751

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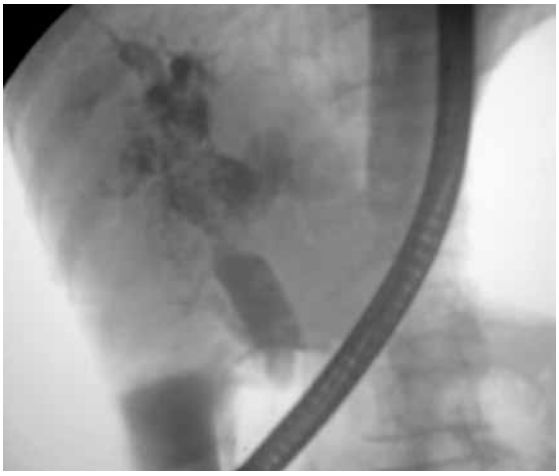


Fig. 1 ERCP image shows complex strictures in the hilar region with both intrahepatic radicals being involved at multiple sites in an elderly man who presented with symptoms of fever, anorexia, weight loss and progressive jaundice. The patient was managed with single stent placement in addition to anti-TB therapy.

INTRODUCTION

Tuberculosis (TB) infection is a common disease and an important cause of morbidity and mortality, especially in underdeveloped and developing nations. An estimated two billion people have latent TB, with an estimated 7–8 million new cases being detected worldwide every year. Despite the availability of effective therapy, two million affected individuals succumb to this infection annually, particularly in underdeveloped nations. Patients in immunocompromised states, such as those with human immunodeficiency virus (HIV) or acquired immunodeficiency syndrome (AIDS), are particularly susceptible to TB infections, both pulmonary and extra-pulmonary.[1] However, in this group of patients, extra-pulmonary involvement predominates.

TB infection can affect any organ. Abdominal TB is one of the most prevalent forms of extra-pulmonary manifestations. Abdominal TB collectively refers to the involvement of the gastrointestinal tract, hepatobiliary system, pancreas, spleen, abdominal lymph nodes and other abdominal organs.[2] Overall, the prevalence has been shown to correlate with the severity of pulmonary TB (PTB). One study showed that among those with abdominal TB, the small bowel was the most commonly affected site (33.8%), followed by the peritoneum (30.7%), large bowel (22.3%), liver (14.6%) and the upper gastrointestinal tract (8.5%).[3] However, it is believed that the liver is affected in most cases of miliary TB.

The manifestations of hepatobiliary TB (HBTB) are nonspecific and resemble other diseases such as malignancies and infections. Nonspecific presentations

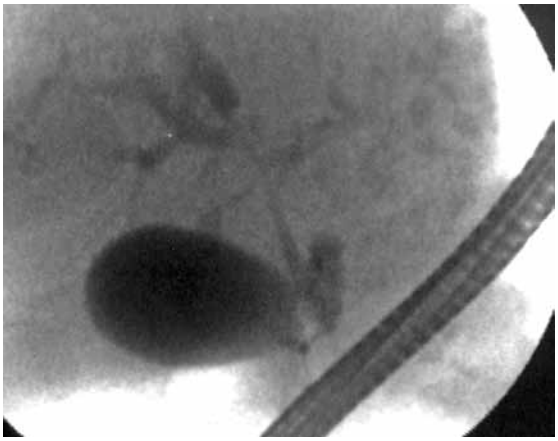


Fig. 2 ERCP image shows hilar stricture with resultant dilated intrahepatic dust in a man with nonspecific symptoms of TB infection and obstructive jaundice. Brushing was positive for acid fast bacilli. Management included biliary stenting and anti-TB treatment.

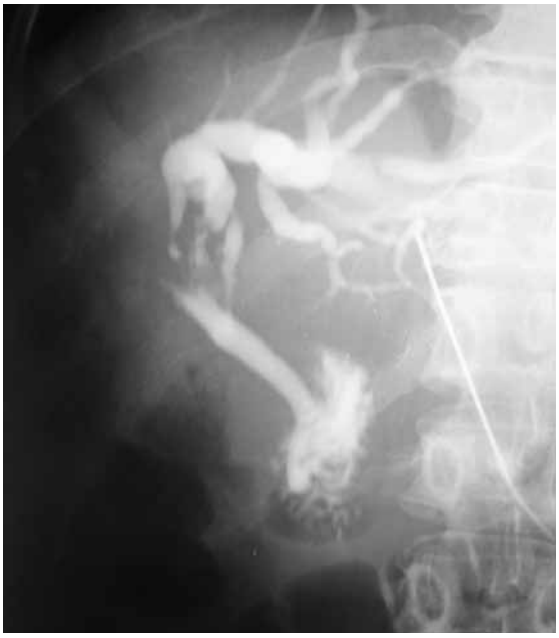


Fig. 3 PTC in a patient who failed ERCP cannulation of the biliary system shows a long hilar stricture with resultant dilatation of the left intrahepatic duct. The right intrahepatic duct is not visualised, indicating involvement of the right intrahepatic duct with complete obstruction. This patient was managed with multiple biliary stent placement and the standard anti-TB regime.

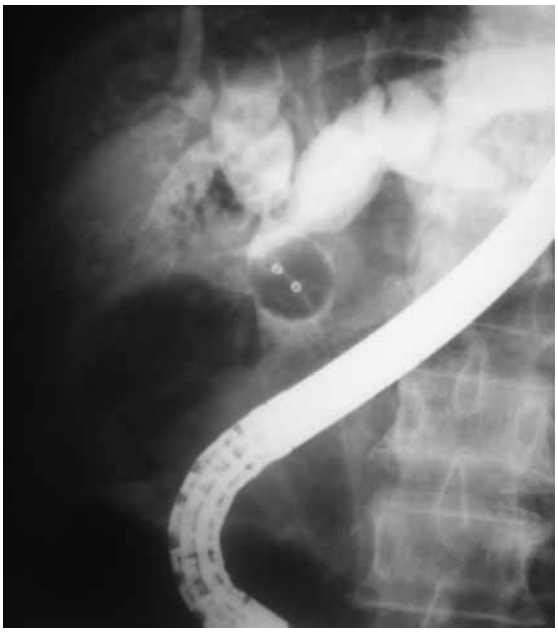


Fig. 4 ERCP balloon cholangiogram shows complex hilar strictures with resultant right and left intrahepatic ducts, with gross dilatations. The patient was managed with anti-TB treatment and prolonged stenting.

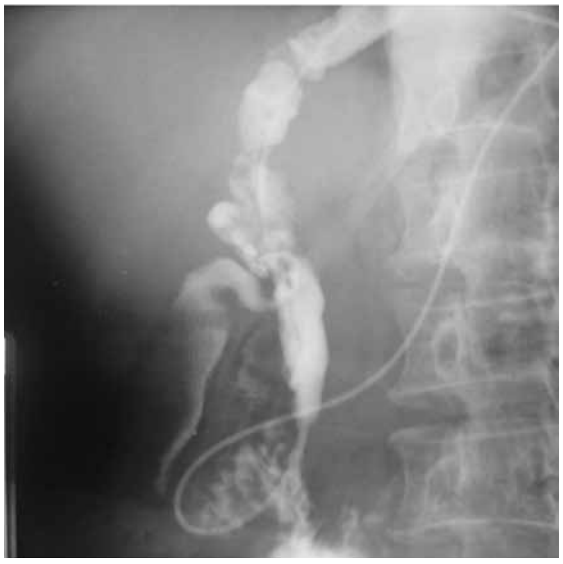


Fig. 5 Nasobiliary drainage tube cholangiogram shows multiple strictures, one located in the distal common bile duct and the others in the common hepatic ducts, with resultant common bile duct and intrahepatic duct dilatations.

that are common to all TB infections and other conditions, such as fever, weight loss and anorexia, are also common. Therefore, diagnosis can be difficult, resulting in delayed treatment. The evaluation of suspected cases can be divided into three stages. The first two stages involve clinical and radiological evaluations, and usually provide indirect evidence of the presence and location of the involvements. Confirmation is required in the more invasive third stage, where tissues samples are obtained for histological and microbiological evaluations. Radiological imaging such as ultrasonography (US) and computed tomography (CT), complemented by endoscopic evaluations such as endoscopic retrograde cholangiography (ERCP) and endoscopic ultrasonography (EUS), are the mainstay of investigations. Tissue samplings are directed by these investigations. As the involvement of other organs is common, it is particularly important to look for it.[4]

Knowledge and awareness of the spectrum of manifestations and investigative findings are important,

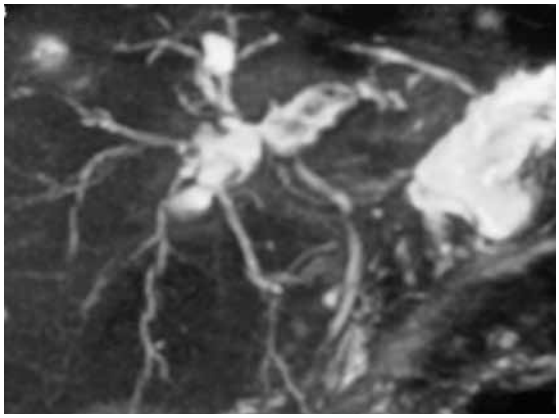
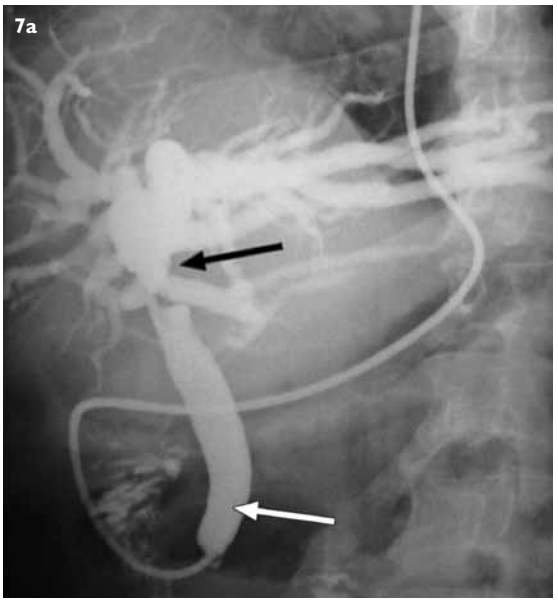


Fig. 6 MRCP image of a patient with hepatic involvement, with resultant multiple biliary strictures from multiple granulomas. The patient required prolonged biliary stenting as a result of recurrent intermittent cholangitis.



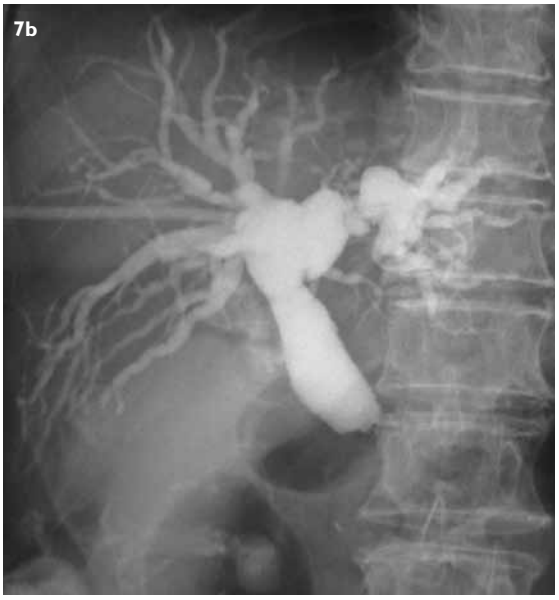


Fig. 7 (a) Nasobiliary drainage tube cholangiogram in an elderly man shows two levels of obstructions. Both the intrahepatic ducts and common bile ducts were dilated. The hilar stricture was due to biliary TB (black arrow) and distal common bile duct stricture secondary to early ampullary carcinoma (white arrow). This patient also had evidence of pulmonary and bone TB. (b) An elderly woman presented with weight loss, anorexia, fever and progressive jaundice. Investigations showed dilated common hepatic and intrahepatic ducts on US and CT imaging. Attempted ERCP failed due to tight stricture and distorted duodenal anatomy. PTC showed dilated systems with a stricture in the distal common hepatic duct. Brushing and biopsy of stricture were negative for malignancies. Bile aspirate was positive for acid fast bacilli. The patient was treated with anti-TB therapy and prolonged biliary stenting and remained well, but repeat imaging showed the persistence of stricture and lymphadenopathy with central necrosis. Repeat percutaneous biopsy showed adenocarcinoma.

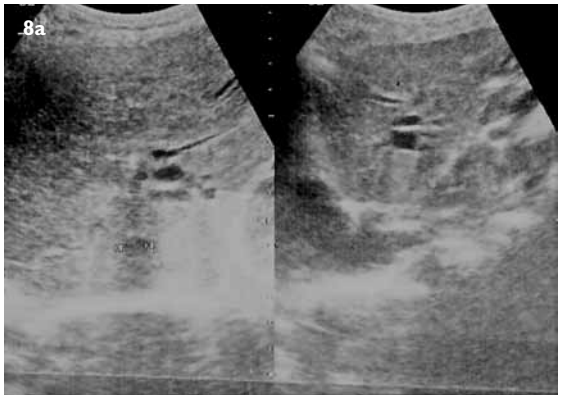
as the timely diagnosis of extra-pulmonary TB remains a challenge in some cases.[5] This pictorial essay reviews the radiological imaging findings of proven HBTB infections encountered in our tertiary referral centre. None of our patients had concomitant HIV/AIDS.

BILIARY TUBERCULOSIS

Biliary TB (BTB) is rare, and the first case of isolated BTB was only recognised and reported in 1989. To date, less than 20 cases have been reported in the English literature.[6] In some settings, the annual incidence of BTB has been reported to be 0.0%–0.1% of all TB infections.[7] The pathogenesis of BTB includes direct biliary contaminations from swallowed mycobacterium, extension from adjacent affected structures and rarely, by haematogenous spread. Usually, evidence of other organ involvement is observed.

BTB can occur due to primary biliary involvement or due to compression of the biliary tree by affected adjacent organs such as affected lymph nodes or hepatic granuloma. Primary biliary involvement ranges from the involvement of small to large ducts, resulting in stricture formations.[8,9] These strictures can be categorised into isolated strictures or the more common complex multiple strictures that usually involve the hila region (Figs. 1–5). Biliary involvement by hepatic granuloma tends to be associated with multiple and complex strictures (Fig. 6). These complex multiple strictures resemble primary sclerosing cholangitis, and can be difficult to distinguish from cholangiocarcinoma, regardless of whether the biliary involvement is localised or diffuse. Occasionally, other findings that may potentially lead to biliary obstructions, such as stone diseases, are also present. It is also important to consider the coexistence of underlying malignancy (Fig. 7).[6]

Biliary involvement in patients with HIV/AIDS commonly manifests as granulomatous hepatitis, resulting in cholestatic liver enzymes. This is due to predominant small duct involvement, and imaging findings typically show hepatomegaly without many ductal abnormalities



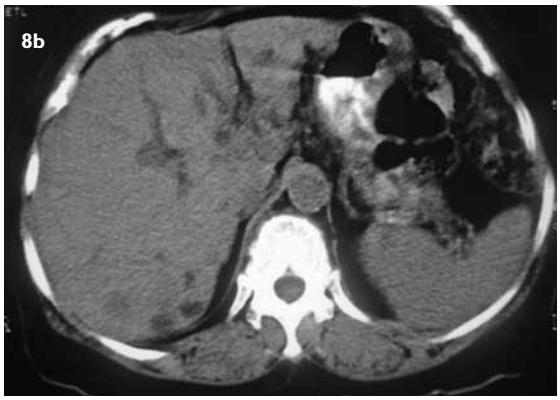


Fig. 8 A middle-aged woman presented with nonspecific symptoms of fever, weight loss and sweating. (a) US image shows multiple hypodense lesions in both lobes of the liver. Percutaneous biopsy was positive for acid fast bacilli. The hepatic lesions resolved with a six-month course of anti-TB treatment. (b) CT image shows multiple hypodense lesions of early hepatic TB involvement.

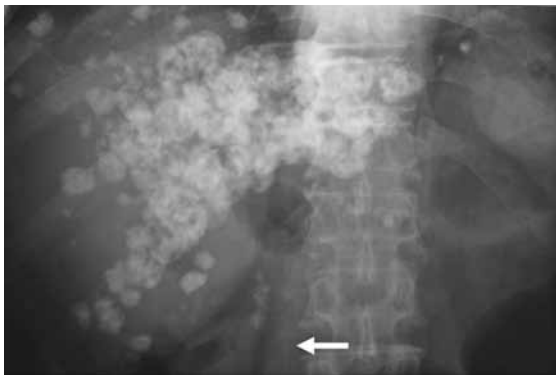
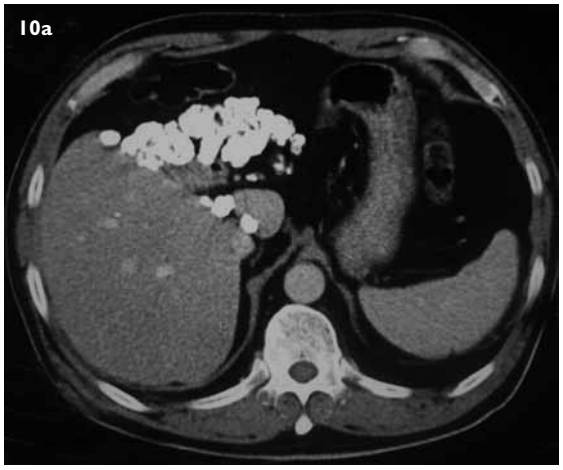
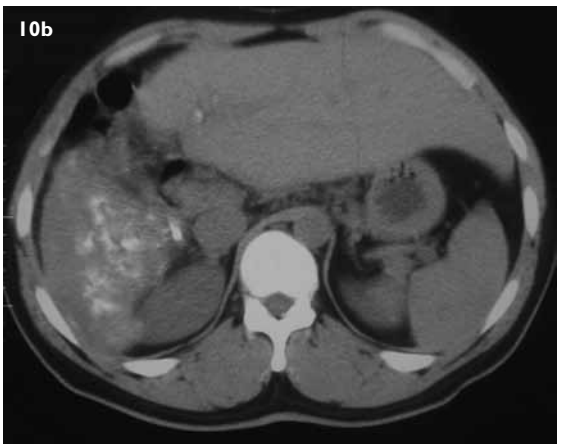


Fig. 9 Plain abdominal radiograph image of a man who presented with nonspecific abdominal pain shows gross hepatic popcorn-like calcifications. US revealed calcifications mainly on the left system with grossly dilated common bile duct, common hepatic ducts and intrahepatic ducts with stones. This patient was previously treated for pulmonary TB 18 years ago. Calcification outside of the liver (arrow) is noted. CT imaging confirmed bile duct wall calcifications.





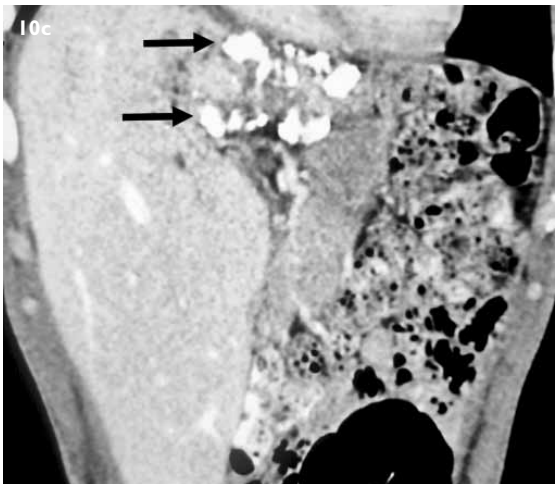


Fig. 10 CT images show (a) atrophic and calcified left hepatic lobe. The calcifications appear to be discrete round nodules corresponding to calcification of granulomas (nodular form) and (b) hepatic calcifications in the right lobe with glandular atrophy and hypertrophied left lobe. (c) Reformatted coronal CT image shows atrophic left lobe with gross calcification (arrows) in a young man with proven hepatic tuberculosis.

or dilatations.[10] Apart from the nonspecific symptoms common to all TB infections, clinical presentations include obstructive jaundice, chronic abdominal pain, hepatomegaly, splenomegaly and even complications of chronic liver diseases. Ascites and other abdominal symptoms may be present if there is concomitant peritoneal or intestinal involvement. Prolonged biliary obstruction can lead to secondary biliary cirrhosis.

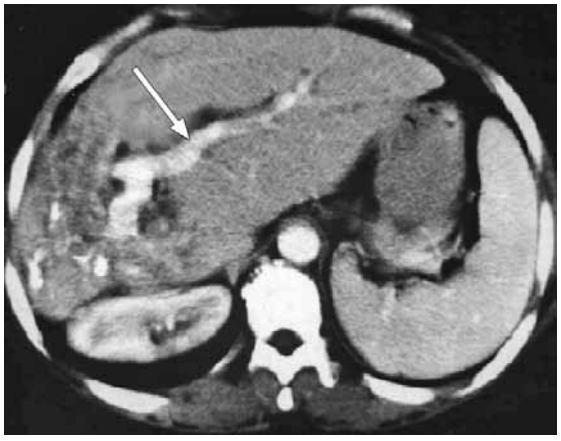
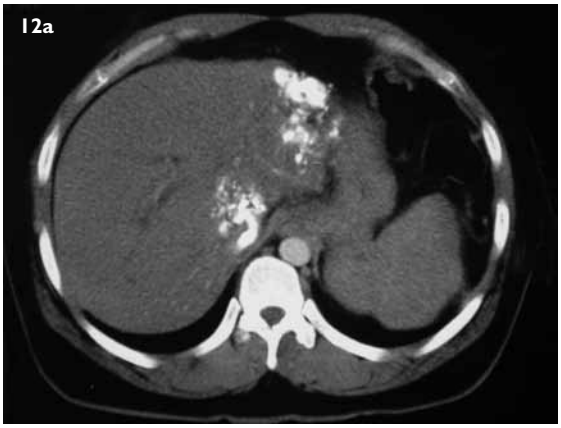


Fig. 11 CT image shows hepatic calcifications in the atrophic right lobe and ductal dilatation (arrow).



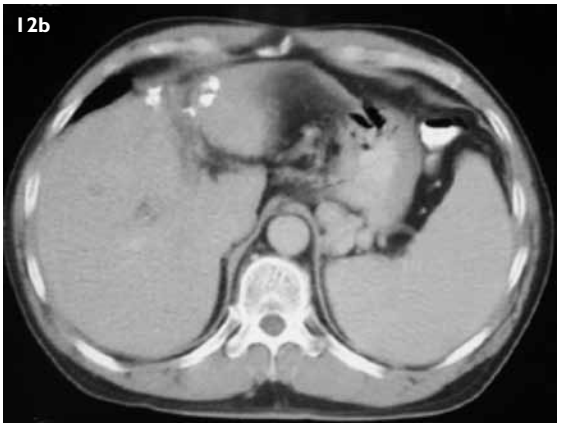


Fig. 12 (a) CT image shows fine calcifications in a young man with previous hepatic involvement. The type of calcifications is finer (in contrast to the patient in Figs. 9 & 10). (b) CT image of an elderly man who presented with weight loss, fever, anorexia and abdominal pain shows hepatic calcifications (localised form) in segments 4 and 5. This patient was diagnosed with active TB of the ascending colon and was managed with anti-TB treatment, but his disease was complicated by multiple intra-abdominal sepsis with resultant portal vein thrombosis and gastric variceal bleeding. The patient eventually died of sepsis and variceal bleeding.

Imaging of the biliary tree can be performed with US, CT, ERCP, magnetic resonance (MR) or magnetic resonance cholangiopancreatography (MRCP) imaging. All imaging modalities have their own advantages and usually complement one another. As the findings are often non-diagnostic, the main aim is to acquire tissue for diagnosis. EUS is now becoming an important diagnostic and therapeutic tool. ERCP has the advantage of allowing the placement of biliary stents to decompress the obstructed systems, in addition to bile and tissue samplings. More invasive modalities, such as percutaneous transhepatic cholangiography (PTC) or surgery, may be required. Imaging findings consist mainly of biliary dilatations, strictures and other concomitant findings such as hepatic calcifications or tuberculoma. In isolated biliary involvement, imaging typically shows biliary dilatation proximal to the strictured area, a finding that is common to biliary obstructions of other aetiologies. In complex involvement, imaging may only show localised dilatations or no dilatations at all. However, it is important to consider TB if there are findings of hepatic calcifications.

Management includes biliary drainage and standard anti-TB therapy. Isolated strictures can be easily managed with biliary stenting. However, these strictures may be fibrotic and tight. Sequential placement of multiple plastic stents has been shown to be effective, as the stents serve as biliary drainage and a dilator. The management of multiple or complex strictures is more challenging and requires combination therapies that are endoscopic, percutaneous or surgical.

HEPATIC TUBERCULOSIS

Hepatic TB (HTB) is rare but more common than BTB. As in all TB infections, the involvement of other organs is common. Despite the scarcity of reports in the literature, HTB is reported to occur in 50%–80% of patients who are dying of PTB.[11] In autopsy studies, this rate approaches 90%. Therefore, hepatic involvement is possibly under-diagnosed and under-reported in clinical practice. It has also been reported that concomitant splenic involvement is common in patients with HTB, particularly in patients with HIV/AIDS. However, in our local setting, splenic involvement is uncommon, and to date, we have not encountered any cases.

HTB manifestations can be broadly divided into two types: the more common miliary type and the less common local type. Each of these can be further divided into diffuse and nodular types. The pathogenesis of miliary manifestations is due to haematogenous spread of the mycobacterium via the hepatic arteries, resulting in granulomatous hepatitis, and this is characterised by diffuse hepatic involvement. The patients usually show evidence of miliary PTB. This manifests as diffuse

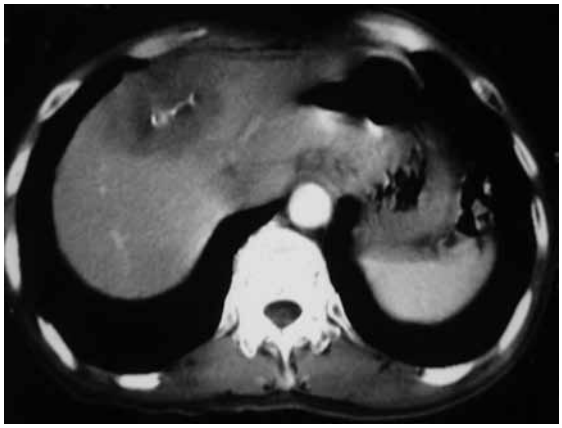


Fig. 13 CT image shows a hypodense lesion in the right lobe with central calcifications (local form) in an elderly man who presented with a long history of right upper quadrant pain and weight loss who was investigated for suspected hepatocellular carcinoma as he was also suffering from chronic hepatitis B. Serum alpha fetoprotein was normal. The patient declined biopsy of the lesion, with resultant delayed diagnosis. The diagnosis of TB infection was made only when the patient represented with bleeding per rectum, and colonoscopy showed ileoceacal tumours that turned out to be TB. The patient remained well after treatment without further bleeding.

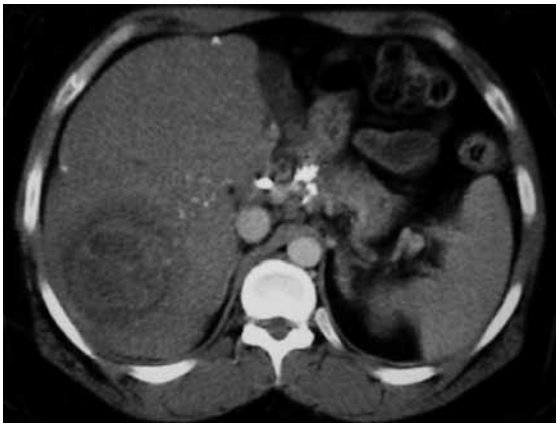


Fig. 14 CT image of a young man who was evaluated for a long history of abdominal pain, fever, weight loss and anorexia shows specks of calcifications (diffuse form) and a lesion in segment 8 of the liver. The patient was initially treated for pyogenic liver abscess, and a biopsy was done when the lesion failed to regress. This isolated *Staphylococcus auerus* and mycobacterium tuberculosis. The patient completed a course of anti-TB treatment but developed biliary obstructions secondary to healed granulomas. Chronic biliary obstruction had led to secondary biliary cirrhosis.

hepatic enlargement and abnormal cholestatic liver function test with disproportionate elevated serum alkaline phosphatase compared to serum bilirubin. Liver histology usually reveals multiple granulomas with or without caseation. Radiological imaging usually does not reveal any ductal dilation despite the cholestatic liver function test. This is due to predominant small duct disease.

In the acute stages, hepatic imaging may show multiple small lesions resembling abscesses or metastases (Fig. 8). Healing of these granulomas can lead to calcifications. Therefore, the presence of calcification usually indicates healed lesions, and biopsy of these lesions is often non-contributory and of a low yield. However, it is important to consider the reactivation of latent infections in patients with imaging findings that are consistent with previous TB infection (Fig. 9). Glandular atrophy or associated duct dilatations (Figs. 10 & 11) may also be observed. The patterns of calcifications differentiate the diffuse from the nodular form (Figs. 9 & 12). Patients are often treated for miliary TB without many symptoms due to hepatic involvement. However, acute liver failure has previously been reported.[11]

The local type occurs through the spread of the mycobacterium via the portal vein from the intestine. This explains the common association of hepatic involvement in patients with bowel TB. In contrast to the miliary type, there is less evidence of pulmonary involvement. These lesions may appear as abscesses, space occupying lesions that resemble either hepatocellular carcinoma or metastatic diseases (Figs. 13 & 14).

Both the miliary and local types are more common in patients with HIV/AIDS. The radiological manifestations resemble those of patients without HIV/AIDS. The management of HTB is mainly medical, with standard anti-TB therapy unless there is concomitant ductal involvement. In cases of concomitant biliary involvement, biliary decompression will be required.

EXTRA-HEPATOBILIARY TB INVOLVEMENT

As the involvement of other organs is common, it is particularly important to look for the presence of TB infection in other organs, especially in the chest. CT imaging, bronchoscopy and bronchoalveolar lavage may be required, as routine radiography may not be sensitive enough. It is necessary to search for the presence of gastrointestinal, peritoneal and omental involvement in patients suspected to have HBTB.

CONCLUSION

This pictorial essay underscores the varied manifestations of HBTB and the importance of knowledge about it due to its different manifestations and investigative findings. As the treatment for TB infections is standardised, timely and accurate diagnosis is vital. Suggestive symptoms, such as anorexia, abdominal pain, weight loss, fever and obstructive jaundice in patients with risk factors, laboratory investigation findings of elevated erythrocyte sedimentation rates, anaemia and hypoalbuminaemia, should heighten suspicion for HBTB in patients presenting with hepatobiliary problems. Common

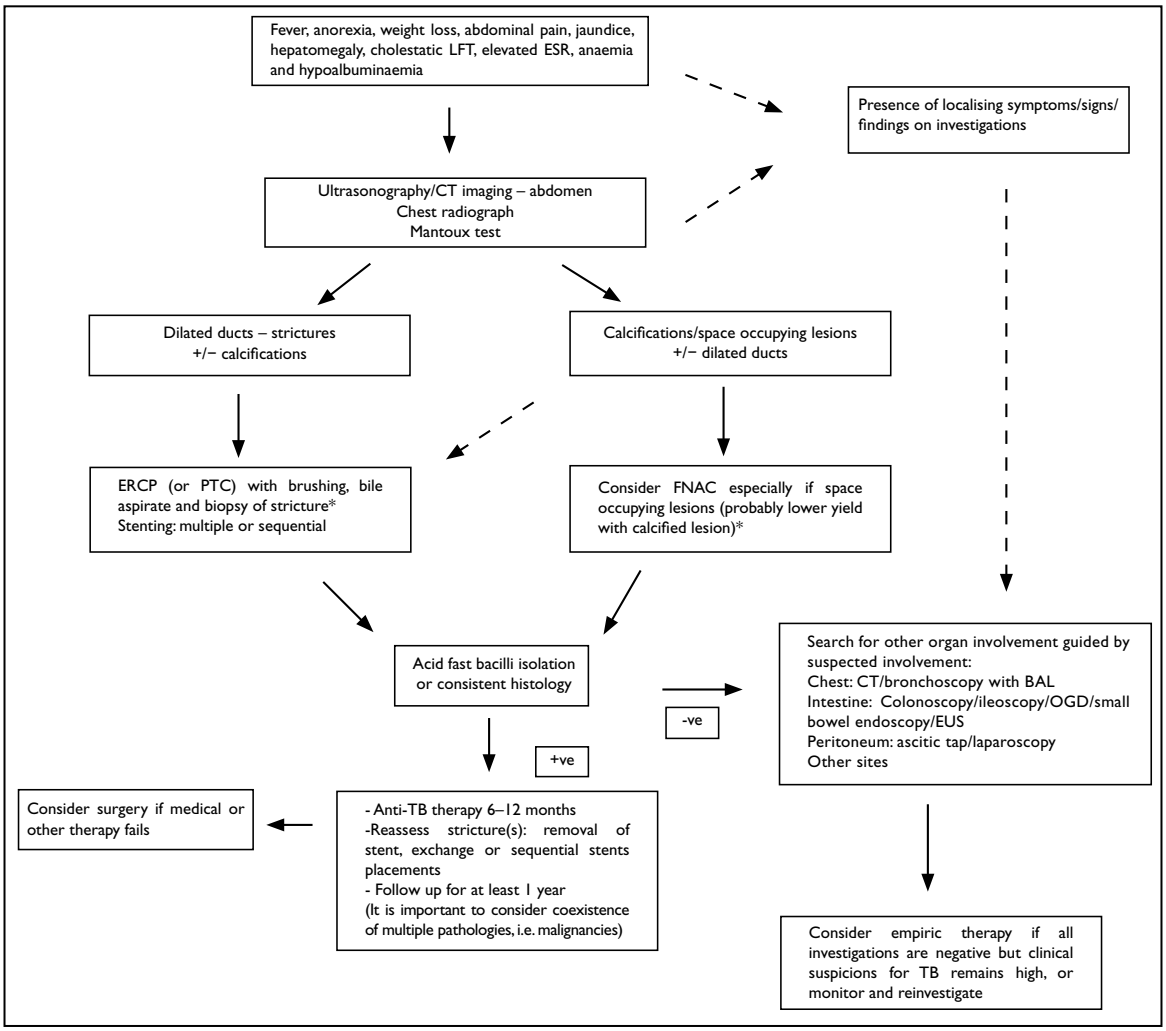


Fig. 15 Algorithm for investigations of patients with suspected hepatobiliary tuberculosis.
* Consider using PCR or adenosine deaminase if the facility is available.
BAL: bronchoalveolar lavage: ERCP: endoscopic retrograde cholangiopancreatography; ESR: erythrocyte sedimentation rate; EUS: endoscopic ultrasonography; FNAC: fine needle aspiration cytology; LFT: liver function test; PTC: percutaneous transhepatic cholangiography

findings include calcifications, mass lesions that resemble abscesses or tumours, dilated ducts that can be singular, simple, multiple or complex. Evaluations for the possible involvement of other organs are important. A proposed algorithm for the investigations of patients with suspected HBTB is shown in Fig. 15.

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SINGAPORE MEDICAL COUNCIL CATEGORY 3B CME PROGRAMME
Multiple Choice Questions (Code SMJ 201009B)

	True	False
Question 1. Regarding hepatobiliary tuberculosis:		
(a) Hepatobiliary tuberculosis is a part of abdominal tuberculosis.	☐	☐
(b) Severity of involvement is not correlated with pulmonary involvement.	☐	☐
(c) Manifestations are nonspecific and may result in a delayed diagnosis.	☐	☐
(d) Evaluation can be divided into three stages.	☐	☐
Question 2. Regarding biliary tuberculosis:		
(a) Stricture formation is a common manifestation.	☐	☐
(b) Strictures are usually isolated.	☐	☐
(c) Biliary strictures can resemble cholangiocarcinoma or primary sclerosing cholangitis.	☐	☐
(d) Prolonged stenting alone is an acceptable therapy.	☐	☐
Question 3. Regarding hepatic tuberculosis:		
(a) Hepatic involvement is as common as biliary involvement.	☐	☐
(b) Hepatic involvement has been reported to occur in up to 90% of patients who are dying of pulmonary tuberculosis.	☐	☐
(c) Hepatic involvement can be broadly categorised as miliary or local type.	☐	☐
(d) The miliary type is often associated with venous spread.	☐	☐
Question 4. In the evaluation of hepatobiliary tuberculosis:		
(a) Preliminary investigations provide useful clues to the line of investigation.	☐	☐
(b) Definitive diagnosis does not require isolation of the mycobacterium.	☐	☐
(c) Concomitant malignancies need to be considered.	☐	☐
(d) CT imaging is the best modality for detecting hepatic calcifications.	☐	☐
Question 5. Regarding hepatobiliary tuberculosis:		
(a) In biliary involvement, ultrasonography may be normal in early involvement.	☐	☐
(b) Early hepatic involvement may resemble hepatic abscess.	☐	☐
(c) Hepatic atrophy is not a complication of hepatic tuberculosis.	☐	☐
(d) Secondary biliary cirrhosis is a recognised complication.	☐	☐

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SUBMISSION INSTRUCTIONS:
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RESULTS:
(1) Answers will be published in the SMJ November 2010 issue. (2) The MCR numbers of successful candidates will be posted online at www.sma.org.sg/cme/smj by 15 November 2010. (3) All online submissions will receive an automatic email acknowledgment. (4) Passing mark is 60%. No mark will be deducted for incorrect answers. (5) The SMJ editorial office will submit the list of successful candidates to the Singapore Medical Council.

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