CASE REPORT

Probable hepatic tuberculosis masquerading as Klatskin tumour in an immunocompetent patient

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SUMMARY

A 55-year-old immunocompetent woman was presented with features of obstructive jaundice and a clinoradiological picture suggestive of a hilar cholangiocarcinoma (Klatskin tumour). However, caseating granulomatous lesion associated with miliary nodules were revealed intraoperatively. The lesion responded to standard antituberculous therapy. This unusual presentation highlights the considerable diagnostic challenge in such case.

BACKGROUND

Mycobacteria are a family of small, rod-shaped bacilli that generally can be classified into *Mycobacterium tuberculosis* (TB) complex, *Mycobacterium leprae* and non-tuberculous mycobacterium (NTM). TB and NTM are frequently manifested as pulmonary diseases. However, they can be presented in other extra-pulmonary sites, including solid organs.

The present case demonstrated a caseating granulomatous lesion at the region of the hepatic duct confluence causing proximal biliary ductal dilations associated with miliary nodules. No definite proof of tuberculosis obtained via culture or PCR analysis. Nonetheless, the lesions responded to the standard antituberculous treatment regime. In view of the fact that the present case took place in the region where TB was endemic (Incidence of tuberculosis in Malaysia was 80/100 000 people in 2012) and the granulomatous lesion showed some areas of caseation, the lesion was diagnosed as probable hepatic TB. NTM is a potential differential diagnosis in the present case. Historically thought to cause disease exclusively in immunocompromised individuals, NTM are now recognised as major pathogens in immunocompetent individuals as well.¹ However, dissemination to solid organ as localised and miliary nodules by NTM is mainly found in patients with advanced HIV disease or other severe immunosuppression.²

Hepatic TB alone is a rare entity and accounts for less than 1% of all cases of TB.³ In general, hepatic TB may present as diffuse involvement (granulomatous hepatitis or miliary) or localised form (tuberculoma or tubercular abscess).⁴ Clinoradiological manifestations of localised hepatic TB may mimic malignant lesions, leading to erroneous clinical diagnosis. We highlight the need of considering mycobacterial infection as a differential diagnosis of lesion at the porta hepatis of the liver particularly in areas endemic for the disease.

CASE PRESENTATION

A 55-year-old immunocompetent female patient was presented with a 3-week history of jaundice, epigastric discomfort, fever and tea-coloured urine. There were associated loss of appetite and loss of weight. No history of diabetes mellitus or previous exposure to tuberculosis was found. No exposure to farm animals or a history of drinking unpasteurised milk was found. The blood pressure (124/86), pulse rate (78 bpm) and temperature were normal (36.8°C). The physical examination revealed icterus and non-tender vague epigastric mass. Otherwise, no hepatosplenomegaly or palpable lymphadenopathy was found. The rest of systemic examinations were within normal limits.

INVESTIGATIONS

Liver function test showed obstructive picture with elevated total bilirubin (149 µmol/L) and alkaline phosphatase (687 U/L). Tumour marker of CA 19-9 was elevated (850 U/mL). The erythrocyte sedimentation rate was significantly raised (>120 mm/h). The routine full blood profile, haemoglobin, platelet and white cell counts and their subcomponents, was within normal limits.

The chest radiograph was normal. Ultrasound abdomen showed dilated intrahepatic ducts (figure 1) with normal common bile duct. No obvious focal liver lesion was seen. However, contrasted CT of the abdomen revealed an ill-defined hypodense mass with a focus of calcification at the hepatic duct confluence causing proximal intrahepatic duct dilation (figure 2). There was associated portal lymphadenopathy (figure 3) with the largest lymph node measured as 2.3×3.0 cm. Common bile duct and pancreatic duct were not dilated.

DIFFERENTIAL DIAGNOSIS

Prior to intraoperative and histopathological findings, provisional diagnosis of Klatskin tumour with lymph node metastases was made in view of the age group, usual location and appearance associated with high CA19-9 level.

TREATMENT

Prior to the surgery, a plastic stent (10 Fr) was inserted into the intrahepatic duct confluence via endoscopic retrograde cholangiopancreatography to release the obstruction. In view of clinical diagnosis of Klatskin tumour, central hepatectomy was planned. Intraoperatively, there were porta hepatic lesion and numerous pale yellowish miliary nodules over the liver surface associated with multiple necrotic coeliac and portal nodes. No bowel lesions or

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Figure 1 Images of liver sonography. (A) Intercostal and (B) subcostal views showing 'double barrel sign' where dilated intrahepatic ducts (arrows) are seen as second tubular structures parallel to the intrahepatic portal vein branches.

involvement of the Peyer's patches were noted during the surgery. Hepatic tuberculosis was suspected during the surgery. Tissue specimen of the porta hepatic lesion was obtained for histopathological study and culture.

The histopathological findings of the specimen from the porta hepatic lesion demonstrated lymphoplasmacytic infiltration of the portal tracts and intrahepatic bile ducts. Multiple confluent granulomas were detected which were surrounded by lymphocytes and rim of fibroblasts. Some of the granulomas demonstrated central necrosis in keeping with caseating granulomatous inflammation suspicious of TB. No malignancy or cirrhosis was noted. The Ziehl-Neelsen staining showed no evidence of acid-fast bacilli (AFB). The culture result was negative for mycobacteria.

A Mantoux test was performed and showed induration size of 40 mm in diameter. In view of tuberculosis being the most frequently encountered caseating granulomatous lesion in an immunocompetent patient in our practice, an empirical antituberculous therapy was initiated. Screening for HIV was performed and confirmed negative.

OUTCOME AND FOLLOW-UP

The patient was treated with antituberculous drugs (akurit 4; combination of rifampicin 150 mg, isoniazid 75 mg, ethambutol

275 mg and pyrazinamide 400 mg) and the follow-up abdominal CT performed after 4 months revealed resolution of the intrahepatic lesion and reduction of the intrahepatic duct dilation. The lymphadenopathy was also significantly less comparatively, indicating response to treatment. The response towards antituberculous therapy virtually excluded other granulomatous lesions caused by fungal or other non-infectious granulomatous disease.

DISCUSSION

Extra-pulmonary sites of TB infection commonly include lymph nodes, pleura and osteoarticular areas.⁵ However any organ can be involved. Isolated hepatic TB is extremely rare.³ The diagnosis of pulmonary TB is easily established but patients of hepatic TB may pose a diagnostic dilemma due to the non-specific clinical symptoms and imaging features.

The clinical symptoms of hepatic tuberculosis may include abdominal pain, low-grade fever, hepatosplenomegaly, loss of weight and loss of appetite. Jaundice is extremely rare and may occur as a result of biliary obstruction by localised liver lesion, enlarged porta hepatic lymph nodes or biliary stricture secondary to peri-portal inflammation.⁶ In addition, hepatic tuberculosis is associated with elevated liver enzymes in only about 25% of cases.⁶ In the present case, biliary obstruction was demonstrated due to compression by localised granulomatous

Figure 2 Axial images (A and B) of abdominal contrast-enhanced CT showing an ill-defined hypodense macronodular lesion (curved arrows) with a focus of calcification (arrow head) at the hepatic confluence causing the right and left intrahepatic duct dilation (arrows).

Figure 3 Coronal image of abdominal contrast-enhanced CT showing multiple enlarged portal lymph nodes (arrows).

lesion at the hepatic duct confluence associated with elevated serum levels of liver enzymes and CA 19-9.

The presence of associated pulmonary TB by chest X-ray will help in the diagnosis but negative chest X-ray should not rule it out. Chest X-ray was reported negative for pulmonary tuberculosis in 35% of cases of hepatic tuberculosis.⁴ Diffuse hepatic involvement is usually accompanied by pulmonary TB. However, it was not seen in this case. The frequency of positive AFB smear in hepatic tuberculosis is low, ranging from 0% to 45%.⁷ In addition, only 10% of cultures yield a positive result.⁷ Hence, AFB negative should not divert from the diagnosis, especially in areas where TB is endemic. Histopathological finding of caseating granulomatous disease, which responded to antituberculous therapy, is supportive of hepatic TB as the diagnosis in this case.

Mantoux test is one of the common investigations in patients who are suspected of having tuberculosis. The reaction is read by measuring the diameter of the induration across the forearm in millimeters. Various factors in the host and inherent in the test lower its specificity and sensitivity.⁸ Hence, the results of this test must be interpreted carefully, along with the patient's clinical context. The measurement of the induration that is interpreted as positive depends on the risk factors. A low-risk patient must have a larger induration size for a positive result than a high-risk patient. High-risk groups include immunosuppression (HIV, organ transplant, long-term corticosteroid therapy and end-stage renal failure), recent contacts of active tuberculosis cases and persons with nodular or fibrotic changes on chest radiograph consistent with old healed TB.⁸ Some patients may react to the Mantoux test even though they are not infected with *M tuberculosis*. The causes of these false-positive reactions may include incorrect method of tuberculin skin test administration, incorrect bottle of antigen used, cross reactivity by NTM infection and previous BCG vaccination.⁸ Some authors described that the skin indurations of >15 mm in patient with no risk factors are more likely to be the result of the tuberculous infection than due to previous BCG vaccination or environmental mycobacterial infection.⁸⁻⁹ It is also imperative to know that the Mantoux test itself is unable to differentiate latent from active infection and there is no correlation between the size of induration and the likelihood of current active TB disease.⁸ In the present case, the strongly positive Mantoux test (>40 mm) suggested that the disease was probably caused by TB, but further work up in an attempt to confirm the diagnosis was still necessary as the possibility of a concurrent latent infection was still there.

Three forms of hepatic TB were described, namely diffuse miliary TB, granulomatous hepatitis and localised form.⁴ The localised form includes solitary or multiple tuberculomas and tuberculous abscesses with or without bile duct involvement causing obstructive jaundice.⁴ Miliary form is the commonest type of hepatic tuberculosis and is thought to involve haematogenous dissemination via the hepatic artery.¹⁰ In the present case, there were mixed localised and miliary lesions; a large lobulated localised lesion was found at the porta hepatis depicted on abdominal contrasted CT. The miliary nodules, on the other hand, were only visible intraoperatively.

On abdominal contrasted CT, appearance of localised hepatic TB varies from a hypodense mass with or without postcontrast rim enhancement to a heterogeneous density with necrotic centre.⁶ Miliary lesions may also be detected as multiple small hypodense lesions, but it is extremely difficult to find non-calcified lesion with less than 0.5 cm in diameter.¹¹ Liver calcification may be seen in association with hepatic TB and usually they are multiple, small, discrete and scattered in both lobes of the liver.⁴ Nonetheless, the presence of calcification is non-specific and can be seen in other liver lesions including histoplasmosis, hepatoma and metastatic liver disease. The abdominal contrasted CT, in the present case, demonstrated poorly enhancing hypodense lesion at the hepatic duct confluence with dilation of the intrahepatic biliary duct proximal to it. From imaging standpoint, combinations of diffuse dilation of intrahepatic duct and abrupt cut-off just beyond hepatic duct confluence with hypodense mass at the confluence of hepatic ducts are in favour of Klatskin tumour.⁶ Hence, in this case, the initial provisional diagnosis was wrongly made.

Klatskin tumours are cholangiocarcinomas localised in the bifurcation of the common hepatic bile duct in the liver hilum. Tumour marker of CA 19-9 is elevated in up to 85% of patients with cholangiocarcinoma.¹² However, it may also be elevated in obstructive jaundice without malignancy, severe hepatic injury from any cause, pancreatitis and other pancreatic and gastric malignancy.¹² Despite the relatively low sensitivity and specificity, CA 19-9 may be useful in conjunction with other diagnostic modalities where diagnostic doubt exists and it may be useful for the differential diagnosis of cholangiocarcinoma but further studies are needed. Percutaneous biopsies and brushings for cytology are generally associated with a relatively low sensitivity (<50%).¹³ For patients with potentially curable and resectable disease, open or percutaneous biopsy is not recommended due to the risk of tumour seeding.¹² Considering that the preoperative histological diagnosis of a Klatskin tumour can be extremely difficult, histopathological confirmation may not be necessary prior to proceeding with surgical intervention.¹³ Hence, resection of Klatskin mimicking lesions that cannot be differentiated by clinical presentation or imaging modalities may be unavoidable in some cases. However, firm diagnosis, which may require biopsies are needed prior to treating an operable lesion with 'palliative' intubational techniques and radiation therapy.¹⁴ In addition, over treatment such as extended liver resection, vascular reconstruction and liver transplantation should also be avoided if the benign lesion has not been ruled out.¹⁴

NTM are referring to a group of mycobacteria, which do not cause tuberculosis or Hansen's disease. NTM are free-living organisms that are ubiquitous in the environment but has the potential to cause disease in human, particularly if the immune system is suppressed. There are more than 120 identified mycobacterial species known to cause disease in human and there is no evidence of human-to-human or animal-to-human transmission, hence regarded as non-communicable disease.¹⁵ Like TB, NTM

can cause a wide array of clinical diseases including chronic pulmonary infections, lymphadenitis, soft tissue and osteoarticular infections and disseminated disease.¹ Disseminated disease is commonly found in patients with advance HIV disease or severe immunosuppression, for instance, due to organ transplantation, haematological malignancies and chronic steroid use. Disseminated disease caused by NTM may be presented as single or multiple granulomatous lesions that mimic neoplastic process.¹ The overlapping clinical presentations of the disease caused by TB make the diagnosis of NTM difficult. In addition, this entity is often overlooked in area where tuberculosis is endemic. The treatment of NTM disease is seldom straightforward. Depending on the species of the NTM, the infection may show response, partial response or resistant to the standard antituberculous therapy.¹⁵ The availability of newer Macrolides, such as clarithromycin and azithromycin have become the cornerstone therapy for NTM.¹⁵ Although effective, these agents should not be used as monotherapy to prevent the risk of resistance.

Mycobacterial infection has protean manifestation and may demonstrate clinical features that overlap with several conditions including malignancies and other infections. Clinicoradiological presentation mimicking Klatskin tumour as demonstrated in the present case is a very rare entity.

Learning points

- ▶ Hepatic tuberculosis (TB) or NTM may show overlap of clinical and biochemical features with several conditions including malignancies.
- ▶ Radiological appearance of hepatic TB or NTM may pose a diagnostic challenge, particularly in the localised form.
- ▶ Hepatic TB should be considered as a differential diagnosis of lesion at the porta hepatis of the liver with proximal biliary ductal dilation particularly in areas endemic for the disease.

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