

Case Report

Disseminated tuberculosis diagnosed first as leptospirosis in immunocompetent patient

Erni J. Nelwan,¹ Juferdy Kuniawan,² Mirna N. Praptini,³ Herdiman T. Pohan¹

¹ Division of Tropical and Infectious Disease, Department of Internal Medicine, Universitas Indonesia, Jakarta, Indonesia

² Division of Hepatobilier, Department of Internal Medicine, Universitas Indonesia, Jakarta, Indonesia

³ Department of Internal Medicine, Faculty of Medicine, Universitas Indonesia, Jakarta, Indonesia

ABSTRAK

Tuberkulosis diseminata, lebih sering di diagnosis pada pasien dengan status imun yang lemah (immunocompromised). Manifestasi yang tidak khas menyebabkan penegakan diagnosis di klinik sering kali membutuhkan waktu. Studi ini melaporkan kasus tuberkulosis diseminata pada pasien imunokompeten; seorang wanita 42 tahun dengan tuberkulosis paru dan ekstraparu (tuberkulosis hati.) yang berhasil ditegakkan diagnosis nya melalui biopsi hati.

ABSTRACT

Disseminated tuberculosis, mostly seen in immunocompromised patient, can affect several organs. The diagnosis can be difficult due to various clinical manifestations. A case of disseminated tuberculosis of lung and liver that develops acutely is rare especially in immunocompetent patient. Here, we present a 42 year old immunocompetent woman with lung and hepatic tuberculosis which was confirmed by characteristics histopathological findings of the liver biopsy.

Keywords: acute onset, disseminated tuberculosis, immunocompetent

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Correspondence author: **Erni J. Nelwan**, ejnelwan@yahoo.com

Liver involvement in tuberculosis, though common both in pulmonary and extra-pulmonary tuberculosis, is usually clinically silent. Sometimes, signs and symptoms may be prominent in hepatic tuberculosis, and may appear as the initial or sole presenting feature of the disease. However, even in developing countries, liver tuberculosis accompanied by local symptoms is an uncommon entity. A study from South Africa showed that liver tuberculosis accounted for only 1.2% of all cases of tuberculosis diagnosed at a general hospital. Similarly in Indonesia, within the last 10 years, there is only one case of hepatic tuberculosis ever reported from national referral hospital.¹ Lack of familiarity with this condition was apparently responsible for the diagnosis of hepatic tuberculosis never been concluded in the past due to difficulty of diagnosing.² Since tuberculosis remains a potentially curable disease, an awareness of diagnosing this disease is very essential.³⁻⁵

CASE REPORT

A 42 year old woman was admitted with complaints of fever and yellowish skin since six days before admission. She had been well before. Physical and ultrasonographic examinations of the abdomen revealed hepatomegaly. Leukocyte was low and liver panel showed obstructive jaundice and high liver enzyme [aspartate aminotransferase (AST) at 429U/L and alanine transaminase (ALT) at 373U/L]. Patient was first diagnosed with leptospirosis due to contact with rats before and treated as leptospirosis first with ceftriaxone injections 2 grams qd for five days but there was no improvement in general condition and fever. The blood tests for any epidemiologically significant diseases revealed negative results (tuberculosis polymerase chain reaction, TUBEX test for typhoid fever, malaria antibody, and leptospira antibody). Oral amoxicillin-clavulanic acid was then added to the patient for three more days but patient status was still unchanged and the leukocyte kept declining. Antibiotic was changed to meropenem 1 gram q8h but fever remains. The source of infection was still unknown. Anti-hepatitis A virus (anti-HAV), HBsAg, anti-hepatitis C virus (anti-HCV), anti-human immunodeficiency virus (anti-HIV), gram staining of urine, throat swab, and blood culture were negative. The patient's CD4 was low (113 cells/ μ L).

After three days, intravenous (iv) levofloxacin 500 mg qd and iv metronidazole 500 mg q8h were added to patient's drug regimen but still no improvement. Patient was getting weaker and physical, laboratory, and ultrasonographic examinations of the abdomen revealed hepatomegaly that got bigger during hospitalization and no widening of intra- or extrahepatic ductals, but bilirubin was improved (total of 9.1 mg/dL to 3.7 mg/dL). Due to abdominal pain, patient intake was falling and albumin level also fell. The results of her blood tests showed bicytopenia (Hb 11.3g/dL to 8.4g/dL, and leukocyte 3,900/ μ L to 2,040/ μ L). Abdominal computed tomography (CT) scan showed a hepatomegaly and severe fatty liver. Patient was prepared to get liver biopsy and the antibiotics were changed to ertapenem 750 mg qd for seven days, still there was no improvement.

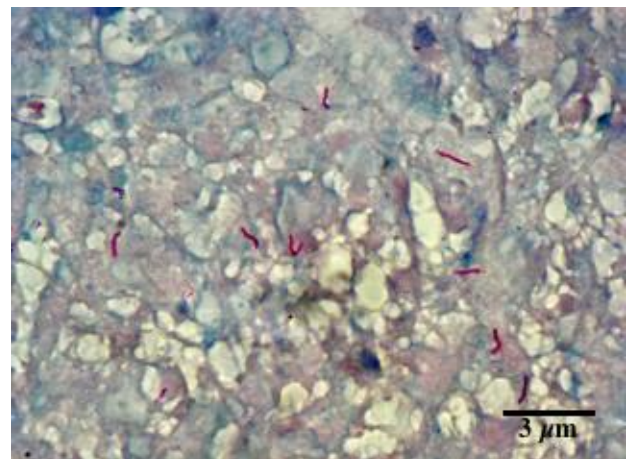


Figure 1. Liver biopsy, acid fast bacilli staining, 100x

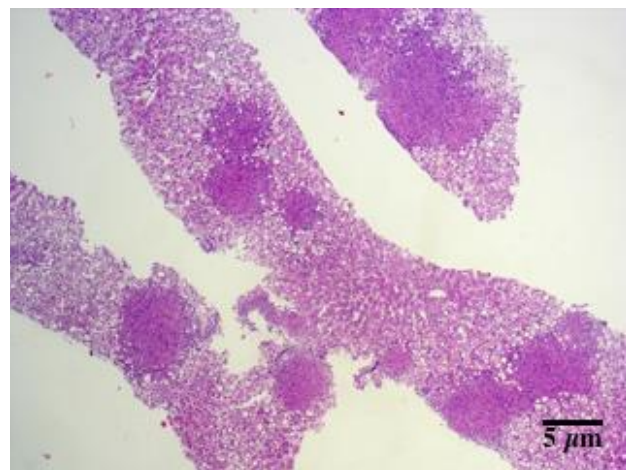


Figure 2. Liver biopsy, hematoxylin and eosin (HE) staining, 40x. Caseous necrosis and granuloma formation

Liver biopsy was performed on day 18. Pathologic examination of her liver showed caseous necrosis, granuloma formation, and a positive acid fast bacilli staining (Figures 1 and 2). Patient was diagnosed with millitary tuberculosis of the liver.

Repeated chest X-ray showed a change from normal to infiltration at both apices without any evidence of acid fast bacilli in sputum though repeated testing (Figure 3). Patient was diagnosed as having disseminated tuberculosis. We did not diagnose patient with pneumonia since clinical and laboratory data were not coherent (inconclusive Gram smear result).

Since the liver enzymes were still high (AST 215U/L and ALT 39U/L, bilirubin total of 6.9 mg/dL) and having lactate dehydrogenase (LDH) of 1,871U/L (normal value <215U/L) patient was given rifampicin 450 mg, isoniazide 300 mg, ethambutol 1,000 mg, streptomycin 750 mg as antituberculosis drugs. We gave no pyrazinamide out of concerns that patient also had malignancy besides tuberculosis although the routine malignancy markers came back negative [carcinoembryonic antigen (CEA), Ca 19-9, alpha-fetoprotein (AFP), and Ca 125]. After initiating the antituberculosis treatment for three days, her bilirubin increased and she fell into sepsis with procalcitonin reaching higher than 100ng/mL, so the antituberculosis therapy was changed to ethambutol, amikacin, moxifloxacin, tygecycline, and fluconazole. She was then getting better and the antituberculosis regimens were continued with ethambutol, moxifloxacin, and streptomycin. Patient was discharged at day-48 with bilirubin level significantly decreased and clinically much improved.

DISCUSSION

In all tuberculosis (TB) patients, disseminated TB is responsible for 1–3% cases, while liver tuberculosis is said to be around 1.2% of all cases or 80–100% of all disseminated TB.^{3,6,7} Epidemiological data in an endemic area in Iran showed that poor prognosis of disseminated TB often showed blood abnormalities such as low hemoglobin, leucocytes, and thrombocytes. Disseminated TB mortality rate was significantly higher in patients with diabetes, injection drug history and blood abnormalities. Old age (median

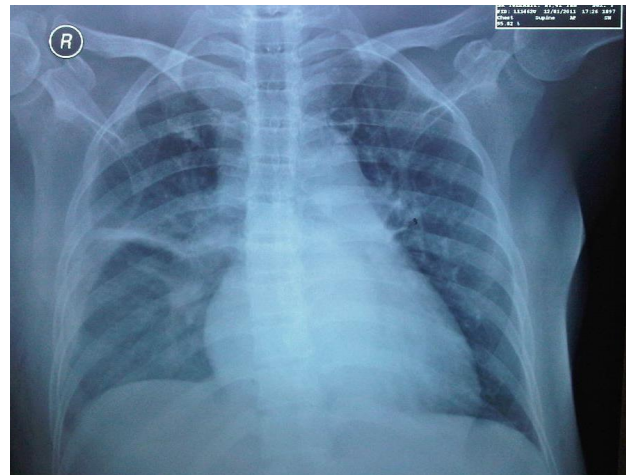


Figure 3. Chest X-ray day 19. Infiltration at both apices, positive kerley line on the right middle lobe lung

of 52.7 years; 20–76 years) was seen as another factor affecting liver TB survival.^{6,7}

This patient was first came with jaundice and fever. After narrowing the diagnosis, liver tuberculosis was considered as the primary causation. Liver tuberculosis was finally diagnosed from liver biopsy and staining. The positive result of biopsy, as can be seen in this patient, is rare.^{3,5}

Spreading to liver may occur either hematogenously or millitary TB or direct inoculation through the portal venous system from gastrointestinal (GI) lesions. If the spreading was from the lung or the hepatic artery, the liver TB form would be millitary and if it was from portal vein, the form would be focal TB.^{3,7}

Liver tuberculosis has three presentations. The first and most common presentation is diffuse hepatic involvement that is usually found together with lung or millitary tuberculosis. This presentation was found in more than half of pulmonary tuberculosis cadaver. The second presentation is diffuse hepatic infiltration (granulomatous hepatitis) that happens without any pulmonary involvement. In this presentation, symptoms of liver disease are usually absent. The third and rarest form is a focal/local tuberculoma or abscess.³ This case belongs to the second presentation of hepatic tuberculosis (granulomatous type) with unspecific pulmonary involvement at the initial that further shows an infiltrate at the apices of both lungs.

Even without caseation or necrosis or positive acid fast bacilli (AFB), histological finding of liver granulomas is a gold standard of TB diagnosis in Asia and Africa. The most common symptoms are fever (60–99%), weight loss and abdominal pain, shared almost the same percentages (45–80%), all were seen in this patient. More than 50% of the patients have hepatomegaly and splenomegaly. Jaundice is not usual for liver tuberculosis and only presents in 20–35% of patients. Biliary compression caused by porta hepatic nodes or pericholangitis or clogging of ruptured TB granuloma into the bile ducts ultimately resulted in jaundice with bilirubin values between 2.3 mg/dL and 5.8 mg/dL. In this patient improvement of bilirubin (total of 9.1 mg/dL to 3.7 mg/dL) was seen after administration of levofloxacin and metronidazole which has a potent anti-mycobacterial properties. Liver function tests are also non-specific but an elevated alkaline phosphatase level is the only test that is common and found in 50–87% of patients. Normal chest X-ray was seen in 75% of patients with isolated hepatic tuberculosis, while only two in 21 patients with local liver tuberculosis have abnormal chest X-ray finding.^{3,4,6,7} This case showed atypical signs of symptoms of hepatic tuberculosis.

Needle biopsy is a proposed method for diagnosis confirmation. More than 80% of hepatic tuberculosis case samples will reveal epithelioid granuloma formation; caseous necrosis in 30–83% and positive acid fast bacilli (AFB) staining in less than 60% of cases. There were also some non-specific features of tuberculosis that can be found histologically in high percentage of patient with fatty liver appearance, hyperplasia of Kupffer cell, focal necrosis and infiltration of inflammatory cell into the liver parenchyma. These unspecific features were also found together with specific tuberculosis lesions.^{6,8} Liver biopsy of this patient confirmed the diagnosis of hepatic tuberculosis which were shown by caseous necrosis, granuloma formation, and positive AFB staining.

For reasons that stay unanswered, AFB liver tissue results in several studies from India and Philippines have been inconclusive. Negative AFB was found in three series from India, despite the presence of caseous necrosis and epithelioid granulomas. Similarly, even guided percutaneous liver biopsy and laparotomy were successfully

performed in isolated liver TB, diagnosis could still be missed.⁸ With the fact of so many challenges in making definite diagnosis of hepatic tuberculosis, this patient was successfully diagnosed and treated.

None of common imaging modalities [ultrasound, CT, and magnetic resonance imaging (MRI)] is utilizable because the granulomas are usually too small (2 mm) to be seen by naked eyes, hence imaging is a modality that still needs scrutinizing by analyst. Diffuse hyperechogenicity, with a “bright liver or spleen” pattern could be seen by ultrasound. Multiple hypoechoic and hyperechoic nodules can occasionally be seen in the liver or spleen. After the disease worsened, calcification could occur and seen by imaging.^{3,6,8} This might explain the bright liver and no tubercle seen in ultrasound while CT scan of the abdomen revealed hepatomegaly and severe fatty liver. Therefore needle biopsy is very important in liver tuberculosis diagnosis.

The CT that was done in this patient was carried out on the concern of possible lymph node malignancy due to high lactate dehydrogenase (LDH). LDH itself can increase in liver disease (LDH-3 that can comprise up to 25% of total LDH) and lung disease (LDH-1 and LDH-2 that comprise up to 27% and 37% of total LDH, respectively), although the maximum level of LDH in disseminated TB was unknown.⁹

Other diagnosis to be considered beside hepatic millitary tuberculosis are metastases, lymphoma, sarcoidosis, and fungal infection. This was the reason why this patient was also tested for tumor markers, LDH, liver biopsy, and fungal staining in biopsy. The macronodular form can look similar to metastases, primary malignant tumor, or pyogenic abscess.⁶

Due to the nonspecific and wide characteristics of imaging manifestations, definitive diagnosis for hepatic tuberculosis consecutively starts with ultrasound or CT-guided biopsy (or even open biopsy) with subsequent staining for acid-fast bacilli, culture, and histology examinations. Furthermore, delicate technique of tissue biopsy by multiple passes through all the lesion may be required to yield positive result of histological and microbiological examination, so that the result can be granted as adequate.^{6,8}

Disseminated tuberculosis is treated with standard antituberculosis drugs (intensive phase, two months including isoniazide (INH), rifampicin, streptomycin, and pyrazinamide; intermittent phase, seven months including INH and rifampicin) are required.^{3-6,10} This can be challenging for some physicians in giving antituberculosis drugs to people with liver disease, hence liver tuberculosis.

The study of Essop et al¹¹ showed that when both isoniazide and rifampicin are used, it can decrease favorably mortality rates compared to regimen not using rifampicin (0% vs 17–50%). But still we gave no rifampicin to this patient due to high basal liver enzyme and because this may be due to the small number of samples and still good prognosis in several studies. We will follow the patient liver condition. The antituberculosis will be continued for at least one year.

Fluconazole was given to this patient due to prolonged use of antibiotics although the prevalence of candidaemia was just 5%. Intravenous broad spectrum antibiotics ($p < 0.001$), oral broad spectrum antibiotics ($p < 0.010$), and indwelling catheters ($p < 0.010$) were the three important risk factors of candidemia in TB patients.¹²

For patients that have obstructive jaundice, a magnetic resonance cholangiopancreatography (MRCP) order is first to determine problems in the biliary tract, knowing the site of obstruction to decompress then either by stent insertion during endoscopic retrograde cholangiopancreatography (ERCP) or by percutaneous transhepatic biliary drainage if stent insertion fails. Surgical decompression should be considered if needed.⁶ We did not decompress patient due to no visible obstruction in ultrasound or CT and when the bilirubin level rose, the patient condition got worsened. After assessing risk of infection due to MRCP/ERCP, we decided to do no decompression.

Mortality rate of liver tuberculosis was high (15–42%) and associated with young age, millitary TB, use of steroid, acquired immunodeficiency syndrome (AIDS), wasting, chronic end liver disease. About half of the patients with liver tuberculosis mortality in the Philippines study were due to respiratory failure and ruptured esophageal varices respectively. AIDS is also the main cause of death in patients with both AIDS and tuberculosis. Report on the drug induced hepatotoxicity is not

found in many studies of hepatic tuberculosis even with the use of rifampicin.^{6,7}

In conclusion, despite many challenges in diagnosing hepatic TB, the disease can be cured. Liver TB diagnosis can be a problem because there is no easy way to timely diagnose it since the gold standard is histological finding. Patient's symptoms, signs, and imaging manifestations are not typical. This case illustration wants to emphasize the importance of considering the diagnosis of disseminated tuberculosis in prolonged fever even in otherwise healthy adults.

Conflicts of Interest

The authors affirm no conflict of interest in this study.

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