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Name of Journal: *World Journal of Clinical Cases*

Manuscript NO: 73168

Manuscript Type: CASE REPORT

***Mycobacterium tuberculosis* bacteremia in an HIV-negative patient with liver cirrhosis: A case report**

Lin ZZ *et al.* *Mycobacterium tuberculosis* bacteremia

Abstract

BACKGROUND

With the increasing prevalence of HIV, the incidence of *Mycobacterium tuberculosis* (*M. tuberculosis*) bacteremia has also increased. As a common affliction of AIDS patients, *M. tuberculosis* infection is associated in these patients with severe sepsis and high mortality. In contrast, *M. tuberculosis* bacteremia is rarely seen in HIV-negative patients, and *M. tuberculosis* has never been reported from the blood of patients with liver cirrhosis.

CASE SUMMARY

We evaluated a 55-year-old Chinese male patient who had been admitted to the hospital with abdominal distension of unknown cause of one-week duration, accompanied by diarrhea, shortness of breath, and occasional fever. Based on these indicators of abnormal inflammation and fever, we suspected the presence of an infection. Although evidence of microbial infection was not found in routine clinical tests and the patient did not show typical clinical symptoms of infection with *M. tuberculosis*, next-generation sequencing of blood samples nevertheless demonstrated the presence of *M. tuberculosis*, which was subsequently isolated from blood samples grown in conventional BacT/ALERT FA blood culture bottles.

CONCLUSION

Our findings demonstrate that HIV-negative liver cirrhosis patients can also be infected with *M. tuberculosis*.

Key Words: Mycobacterium tuberculosis; Bacteremia; HIV; Liver cirrhosis; High-throughput nucleotide sequencing; Case report

Lin ZZ, Chen D, Liu S, Yu JH, Liu SR, Zhu ML. Mycobacterium tuberculosis bacteremia in an HIV-negative patient with liver cirrhosis: A case report. *World J Clin Cases* 2022; In press

Core Tip: Our findings are interesting in two ways. First, although *M. tuberculosis* bacteremia is a common occurrence in AIDS patients, it has rarely been reported from HIV-negative patients. We report here, however, a case of *M. tuberculosis* bacteremia in an HIV-negative patient diagnosed with liver cirrhosis. This finding should alert physicians to consider the possibility of *M. tuberculosis* bacteremia in patient populations not usually considered to be vulnerable to such infections. Second, our successful use of next-generation sequencing for detection of *M. tuberculosis* in the blood should be of interest to physicians as a tool for early detection of microbial infection.

INTRODUCTION

Despite intense worldwide efforts for treatment and prevention of this disease by the medical community, tuberculosis remains ⁵one of the most common causes of death from a single infectious pathogen. China has the third-highest burden of tuberculosis in the world, after India and Indonesia [1]. *Mycobacterium tuberculosis* can directly invade the human gastrointestinal tract, respiratory tract, and skin. It can also infect other parts of the body through spread of this bacterium from the primary lesions through the blood. *M. tuberculosis* bacteremia is commonly found in AIDS patients, and it can also

occur in patients with malignant tumors, diabetes, and rheumatic diseases [2]. However, *M. tuberculosis* has been rarely reported in patients with liver disease. In this report, we describe an HIV-negative, cirrhotic patient with *M. tuberculosis* bacteremia.

CASE PRESENTATION

Chief complaints

A 55-year-old man reported persistent abdominal distension of one week duration, with no obvious underlying cause; the distension was accompanied by diarrhea, shortness of breath, and occasional fever.

History of present illness

The patient showed no symptoms of illness other than the one-week duration of persistent abdominal distension with diarrhea, shortness of breath, and occasional fever.

History of past illness

Medical records indicated a two-year history of abnormal liver function without treatment.

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Personal and family history

The patient had a history of smoking and alcohol abuse. There was no family history of other diseases.

Physical examination

Physical examination of the skin showed the evidence of spider nevi, jaundice of skin or sclera, and facial features associated with liver disease, but no evidence of palmar erythema. Auscultation revealed abnormal breath sounds over both lungs and a decreased breath sounds over the right lower lung. Examination of the abdomen

showed abdominal distension but no tenderness or rebound pain, splenomegaly, or percussion pain in the liver area. There were also no signs of asterixis.

Laboratory examinations

Laboratory analysis of blood samples indicated abnormal liver function: total bilirubin, 221.52 $\mu\text{mol/L}$; direct bilirubin, 138.76 $\mu\text{mol/L}$; indirect bilirubin, 82.8 $\mu\text{mol/L}$; total protein, 48.9 g/L; albumin, 21.6 g/L; alanine aminotransferase, 57 U/L; aspartate aminotransferase, 73 U/L; C-reactive protein, 34 mg/L; serum amyloid A, 92 mg/L; procalcitonin, 1.820 ng/mL; total lymphocyte count, 220/ μL ; HBsAg, 0.00 IU/mL; HBsAb, 29.19 mIU/mL, HBeAg, 0.38 S/CO; HBeAb, 1.30 S/CO; HBcAg, 8.88 S/CO; hepatitis A antibodies IgM, negative; HCV antibody, negative; hepatitis D antigen, negative; hepatitis D antibody, negative; hepatitis E antibody IgM, negative; hepatitis E antibody IgG, weakly positive; cytomegalovirus antibody IgG, positive; cytomegalovirus antibody IgM, negative; coxsackie virus antibody IgG, positive; coxsackie virus antibody IgM, negative; antinuclear antibody, negative; antimitochondrial antibody, negative; anti-Ro-52 antibody, negative; anti-mitochondrial antibody type 2, negative; anti-SSA antibody, negative; anti-SSB antibody, negative; anti-CENP-B antibody, negative; antihistone antibodies, negative; anti-Jo-1 antibody, negative; anti-Sm antibody, negative; anti-Scl-70 antibody, negative; anti-soluble liver antigen/pancreas antigen antibody, negative; anti-smooth muscle antibody, negative; anti-liver and kidney microsome antibodies, negative; anti-PM-Scl antibody, negative; anti-PCNA antibody, negative.

Examination of ascites fluid showed a positive Rivalta test; ascites cell counts showed $1.6 \times 10^9/\text{L}$ nucleated cells, 76% of which were neutrophils, 10% mononuclear macrophages, 12% lymphocytes, and 2% mesothelial cells. Conventional cultures of the patient's blood and ascitic fluid were negative for bacterial growth; sputum culture did not show any pathogenic bacteria. However, screening for microbial pathogens in blood samples with next generation sequencing demonstrated the presence of *M. tuberculosis* infection in this patient (Figure 1). The presence of acid-fast bacilli in these samples was

confirmed by blood smears (Figure 2A) and by fluorescence microscopy (Figure 2B) of blood cultured in conventional BacT/ALERT FA blood culture bottles. Blood cultured on Lowenstein-Jenden medium yielded white colonies, which were identified as *M. tuberculosis* by MALDI-TOF MS (France, Bio-Mérieux). (Figure 3)

Imaging examinations

Computed tomography (CT) scans showed abdominal (Figure 4) and pelvic effusion and bilateral pleural effusion, with greater effusion in the right pleura. Multiple patchy high-density shadows were seen in both lungs, with blurred borders. Although there were no obvious signs of swollen lymph node shadows in the mediastinum, there were multiple areas of inflammation in both lungs (Figure 5). CT scans indicated liver cirrhosis and multiple cystic foci in the liver.

FINAL DIAGNOSIS

Chronic liver failure, spontaneous bacterial peritonitis (SBP), pulmonary infection, pleural effusion, ascites.

TREATMENT

The patient was treated with supplementary oxygen delivered by a nasal cannula. He was also treated with spironolactone (40mg, three times a day) and torasemide (10mg, once a day) for diuretic therapy and magnesium isoglycyrrhizinate (200mg, once a day) for hepatoprotective therapy. To control the large volume of ascites, the patient's excess fluid was treated by abdominal puncture drainage, and the infection was treated with piperacillin sulbactam (6g, every 12 h), biapenem (300mg, every 6 h) and micafungin (150mg, once a day).

OUTCOME AND FOLLOW-UP

Although the patient was in severe condition at high risk of respiratory and cardiac arrest at any time, he discharged himself from the hospital against medical advice.

DISCUSSION

Bacteremia is a serious systemic infectious disease. The most commonly observed pathogen in bacteremia is *Escherichia coli*, followed by *Klebsiella pneumoniae* and *Staphylococcus aureus* [3].

There have been fewer reports of *M. tuberculosis* bacteremia, which is usually diagnosed by a *M. tuberculosis*-positive blood culture. With the increasing number of AIDS patients, however, the incidence of *M. tuberculosis* bacteremia has also been gradually increasing [4]. Among AIDS patients, *M. tuberculosis* bacteremia is a common and life-threatening disease [5, 6], and it is often associated with severe sepsis [7, 8] and high mortality [9] in these patients. The common symptoms of AIDS patients infected with *M. tuberculosis* bacteremia include fever, lymphopenia, pulmonary symptoms, weight loss, and cough with sputum [2, 10].

Compared to AIDS patients, there have been fewer reports of *M. tuberculosis* bacteremia in HIV-negative patients [11, 12]. Chiu *et al.* have pointed out that the incidence of *M. tuberculosis* bacteremia in HIV-positive patients is significantly higher than that in HIV-negative patients [10]. *M. tuberculosis* bacteremia can also occur in other immunocompromised patients, such as those with malignant tumors, diabetes, and rheumatic diseases [2].

Cirrhosis of the liver is an immunocompromised condition that increases the vulnerability of patients to various infections [13]. The most common bacteremia pathogens in patients with liver cirrhosis include *Enterobacter*, *Enterococcus*, and *Streptococcus* [14]. Compared with non-cirrhotic patients, cirrhotic patients with bacteremia show significantly higher mortality as well as greater risk of morbidity and longer hospital stays [3].

Several less common pathogens are also more prevalent and more virulent in patients with liver cirrhosis. Studying liver patients in a hospital in France, Campillo *et al.* [14] found that methicillin-resistant *S. aureus* (MRSA) bacteremia is present in 35% of patients with liver cirrhosis. Citing several studies in Scandinavia and the United States,

Bunchorntavakul and Chavalitdharnrong^[15] reported that patients with liver cirrhosis show an increased incidence and heightened virulence of *M. tuberculosis* infection, which frequently manifests as peritonitis. However, there have been very few reports of *M. tuberculosis* bacteremia in patients with liver cirrhosis.

The clinical symptoms of the patient in this study included pulmonary abnormalities, abdominal distension, and occasional fever, and lymphopenia, similar to the reports of Chiu *et al.* in HIV-negative patients^[10]. Our patient did not show any of the typical symptoms of *M. tuberculosis* infection such as cough, sputum expectoration, fatigue, or night sweats. However, use of next generation sequencing to screen the patient's blood samples for microbial pathogens revealed infection with *M. tuberculosis*. *M. tuberculosis* was later isolated from samples of the patient's blood grown in conventional BacT/ALERT FA blood culture bottles, thus confirming the sequencing results. We were unable to determine whether the primary disease of *M. tuberculosis* in this patient was an intrapulmonary or extrapulmonary infection because both ascites and blood cultures eventually showed growth of *M. tuberculosis* and *M. tuberculosis* can spread to different sites in the bloodstream. Although the patient's conventional sputum culture showed no abnormal colony growth, it was possible that laboratory culture time was insufficient to obtain *M. tuberculosis*.

In 2005, Hanscheid *et al.* reported that *M. tuberculosis* can grow in conventional BacT/ALERT FA blood culture bottles, which can be used to reliably diagnose *M. tuberculosis* bacteremia^[16]. However, because of sparse subsequent reports, few clinicians are aware that *M. tuberculosis* can grow in conventional BacT/ALERT FA blood culture bottles. Our detection of *M. tuberculosis* in the patient's blood with next-generation sequencing indicates that the use of advanced technologies can also greatly assist in clinical testing for elusive or unknown pathogens.

The findings presented here can raise the awareness of doctors to the possibility that even HIV-negative patients, including HIV-negative patients with liver cirrhosis, may develop *M. tuberculosis* bacteremia.

CONCLUSION

Although *M. tuberculosis* bacteremia is a common occurrence among AIDS patients, there have been very few reports of HIV-negative cirrhosis patients with *M. tuberculosis* bacteremia. We have shown that next-generation sequencing of pathogenic microorganisms can be used when the cause of infection cannot be found by routine laboratory tests. After sequencing indicated the presence of *M. tuberculosis* in patient blood in this clinical case, later isolation of *M. tuberculosis* from blood samples grown in ordinary blood culture media further confirmed the sequencing results.

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