

Brucellosis With Multi-Organ Involvement in a Patient With History of Composite Aortic Graft and Hepatitis B

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Abstract- The brucellosis with multi-organ involvement in a patient with a history of the composite aortic graft (Bentall procedure) and Hepatitis B infection is rare. A 35-year-old man presented to us with fever and loss of consciousness. Four years ago, he was IDU and underwent cardiac surgery because of endocarditis. Recently lumbar spondylodiscitis was diagnosed. The Wright (1/320) and Coombs Wright tests (1/640) were positive. After CNS imaging, lumbar puncture was done. The CSF pleocytosis was lymphocyte dominant. In cardiac echocardiography, large vegetation on prosthetic aortic valve leaflets was seen. The brain MRI was reported abnormal. Treatment of brucellosis started with Ceftriaxone, Doxycycline, Rifampin and Gentamycin. After 4 days, he became oriented, and fever was disappeared then we continued the treatment for 16 days. The patient discharged and followed by daily phone calls. As symptoms of abdominal pain and jaundice were presented on the fifth day, he re-admitted. The patient expired because of hepatorenal and cardiac insufficiency. Drug side effects, activation of Hepatitis B and embolism of cardiac vegetation to other organs were suspected causes of death. We do not suggest medical therapy without cardiac surgery in such cases. When combination therapy is necessary for brucellosis in an HBsAg-positive patient, hepatitis virus activity should be assessed by HBV-DNA PCR and the dose of drugs with known hepatotoxic effects such as rifampin and co-trimoxazole should be adjusted. Combination therapy with quinolones instead of hepatotoxic drugs is one of our suggestions.

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Introduction

Brucellosis is the most common zoonotic bacterial infection in human. Fever, myalgia and arthralgia of the large joints are main symptoms. This disease most frequently involves osteoarticular system (1), but other organs like the heart and central nervous system can be involved (2). There are reports of multi-organ involvement by brucella in patients with heart instruments. Left side of the heart is more affected in these patients (2,3), but the experience in a patient with history of composite graft of aortic root by Bentall procedure (composite graft of the aortic root, ascending aorta, aortic valve, with re-implantation of the coronary arteries into the graft) and Hepatitis B positive antigen is rare.

Sharifkazemi and colleagues reported a 40-year-old veterinarian with a history of treated brucellosis and relapse of infection on aortic composite graft (4). But their patient was negative for hepatitis B and treated by

reoperation in involved graft and antibiotic therapy.

Antibiotic therapy without operation or reoperation of involved heart valves or grafts is not recommended as it had poor outcomes in previous studies (3).

Drug side effects and drug interactions can cause bad outcomes in the treatment of patients. Rifampin is one of the main drugs in the treatment of brucellosis. This drug has some side effects and can cause elevated liver enzymes. But its hepatotoxicity is not common unless the patient has a baseline hepatic dysfunction (5).

We present a case of brucellosis with spondylodiscitis, meningitis, endocarditis and positive hepatitis B antigen that had a composite aortic graft. Treatment of this case was intricate and experiences about such cases were insufficient.

Case Report

The patient was a 35-year-old man from Khorram-Abad city presented to the emergency department (ED)

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of Imam Khomeini hospital complex with fever (39.5° C oral) and loss of consciousness. He had a history of low back pain from 4 months ago. The back pain had not responded to conservative therapy. As fever and weight loss were added to his symptoms and because of point tenderness of lumbar vertebrae, lumbar spine MRI was done, and spondylodiscitis of L2-L3 with disk destruction was diagnosed (Figure 1). Since the Wright Test (1/320) and Coombs Wright (1/640) were positive, brucellosis was diagnosed, and treatment with Streptomycin and Doxycycline was started in an outpatient clinic. Some hours after the injection of the first dose of Streptomycin the consciousness of patient was decreased and he had an episode of seizure, then his family transferred him to our hospital.



Figure 1. Spondylodiscitis of L2-L3 with disk destruction

He had a history of Intravenous Drug Use (IDU) with Temgesic® (buprenorphine) about 5 years ago. After diagnosis of spleen abscess due to aortic valve endocarditis, splenectomy had been done for him about 4 years ago. Aortic root replacement (Bentall procedure) with anaortic homograft (23 mm) had been done. His blood and valve tissue cultures and brucellosis serology were negative in that admission, but Hepatitis B antigen (HBS Ag) was positive. He had been discharged with good condition and had been followed for two years with no complication and has had Carvedilol 6.25 mg tablet twice daily in last 4 years.

In ED of our hospital, vital signs were as follows: 39.5°c oral, BP 100/60 mmHg, PR: 80/min and RR: 30/min. His weight was 78 kg. He was agitated and disoriented. Two episodes of tonic clonic seizure happened in the hospital and controlled with Diazepam (5mg, IV) and Phenytoin (1 gr/stat then 125 mg TDS) infusion. Neck stiffness was found. Urine toxicology

was negative for opiates and amphetamines and positive for benzodiazepines.

Lumbar puncture was done, and treatment of brucellosis meningitis started with Ceftriaxone (2 g/Bid/IV), Doxycycline (100 mg/Bid/PO) and Rifampin (300 mg/TDS/PO) plus Phenytoin.

Echocardiography was done due to the history of a prosthetic heart valve that revealed a large vegetation on aortic valve leaflets (36×11 mm) resulting to jets moderate aortic regurgitation (Figure 2). The brain CT scan did not show any lesion (Figure 3).

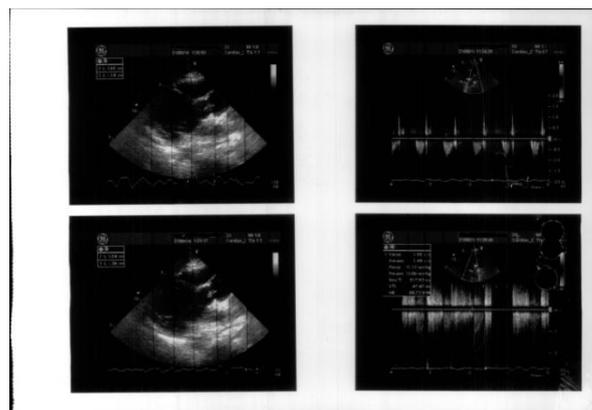


Figure 2. A large vegetation on aortic valve leaflets

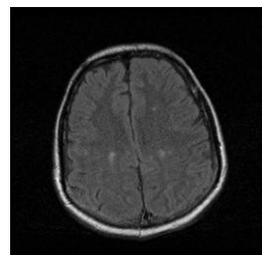


Figure 3. Multiple nonspecific signal changes in white matter of Centrum semiovale

CSF analysis (Volume=2 ml, colorless, clear, CSF Glucose=62 mg/dl/Blood sugar=93 mg/dl, Protein=139 mg/dl, LDH<10U/L, RBC=70 cell/mm², WBC=46 cell/mm², Poly=40 cell/mm², lymph=6 cell/mm²) done.

Other laboratory tests results on admission were: Urea (86 mg/dl), Cr (1.3 mg/dl), ALT (85 U/L), AST (72 U/L) Alkaline phosphatase (248 U/L), Bilirubin (Total 1.9/Direct 1 mg/dl), LDH (863U/L) INR 1, PTT (28 sec), PT (12 sec).

The brain MRI reported multiple nonspecific signal changes in white matter of Centrum semiovale, but after IV contrast injection no evidence of abnormal enhancement was seen.

As the diagnosis of *Brucella* endocarditis was

Brucellosis with multi-organ involvement

suspected, Gentamycin 240 mg/IV/Daily was added to previous drugs. After 4 days of treatment, his consciousness was improved, he was oriented, and fever was disappeared.

Cardiac surgery consultation was done, and the patient was not a candidate for reoperation of aortic homograft because "he likely would not have survived surgery," as a cardiac surgeon was written. Then medical treatment continued with monitoring of liver enzymes and serum creatinine.

After sixteen days of antibiotic therapy the patient was in very good condition, and liver and kidney conditions were acceptable (Urea (18 mg/dl), Cr (0.6 mg/dl), ALT (116 U/L), AST (170 U/L) Alkaline phosphatase (382 U/L), Bilirubin (Total 2.6/Direct 1.4 mg/dl), INR 1.26, PTT (26 sec), PT (13.5 sec)). Blood and CSF culture were negative. Then we decided to discharge him as the cardiac surgeons did not plan to re-operate him. He was discharged with Rifampin/300 mg/Bid, Doxycycline /100mg/Bid, Trimethoprim-Sulfamethoxazole 400-80 mg /Bid, Phenytoin 100 mg/tid, Naproxen 500 mg/Daily, and Carvedilol 6.25/Bid all of them per oral.

We followed the patient daily. Alarm signs were educated to him and his family. After five days of discharge, he started to yellow discoloration of the sclera and a pain in right upper quadrant of the abdomen. Patient advised admitting as soon as possible. Less than 24 hours he was admitted again with loss of consciousness, generalized edema and icter without fever (Urea (83 mg/dl), Cr (3 mg/dl), ALT (1005 U/L), AST (1350 U/L) Alkaline phosphatase (400 U/L), Bilirubin (Total 12.9/ Direct 10 mg/dl), INR 6.6, PTT (>120 sec), PT (>36 sec)). His vital sign was BP: 85/55 mmHg, PR: 80, T: 36.2 oral and RR: 28/min. After one day, the patient underwent endotracheal intubation because of respiratory distress and decreased blood oxygen saturation (O₂sat:74%). Unfortunately, after two days of admission, the patient expired because of hepato-renal and cardiac insufficiency. His family did not consent for diagnostic autopsy.

Discussion

We reported a 35-year-old man with aortic valve homograft and positive Hepatitis B antigen that presented to us with *Brucella meningitis* and spondylodiscitis. He finally diagnosed as endocarditis of aortic valve homograft and treated with a four drug regimen. Unfortunately, the patient expired because of hepatitis and acute kidney injury.

In our knowledge, there are few reports of *Brucella*

endocarditis on a composite graft of aortic root after Bentall procedure (4). Moreover, there is no report of *Brucella* with multi-organ involvement in a patient with a prosthetic cardiac valve that is Hepatitis B positive antigen simultaneously. Outcomes of treatment for such a patient are valuable.

Drug side effects, activation of Hepatitis B and embolism of cardiac vegetation to other organs such as liver and kidney are suspected causes and differential diagnosis of deterioration and death in our patient.

At first, our patient has presented symptoms of neurobrucellosis. We documented his CNS involvement by CSF analysis and a brain MRI. It is shown in other studies that CSF analysis is helpful for diagnosis of neurobrucellosis especially when a neurological symptom is present (6). Treatment with Rifampin, Doxycycline, and Ceftriaxone started because it is shown that these drugs achieve high drug levels in the CSF (6). But, *Brucella* endocarditis needs both medical and surgical treatment. Cardiac surgeons did not advise reoperation of the prosthetic valve because our patient was at high risk for such complex surgery. Then we continued medical therapy. Vegetations are usually large in *Brucella* endocarditis, and surgical removal of vegetation reduces the risk of septic emboli and involvement of other organs (3). It is shown that endocarditis is present as a complication in about 1% to 2% of patients with brucellosis, but it is the main cause of death in more than 80% of cases (7). Moreover, in about 80% of cases aortic valve is involved (3). *Brucella* endocarditis following Bentall operation is life threatening if untreated as shown in a previous report (4) and we experienced.

Hepatitis B positive antigen was a point of challenge in our patient. His basal liver enzymes were higher than normal, and it was controversial about the Rifampin consumption. Unfortunately, there was no previous experience and report then we started drug according to pharmacotherapy service advices. Unfortunately, we did not check the viral load and the status of hepatitis B activity in our patient. Risk factors such as age, sex, and genetic factors are found to have a role in drug-induced hepatic toxicity. Moreover, concomitant drug use and diseases are the most important risk factors for drug-induced hepatitis. Hepatitis B is one of these viral diseases (8). It is necessary to assess the activity of Hepatitis B in such patients. Hence, attention to medical history can help the physician to reduce the risk of death in high-risk patients.

Severe liver injury and hepato-renal syndrome due to rifampin alone is rare and hepatic injury following

rifampin monotherapy usually appears following first 2 to 4 weeks of treatment course (5). In addition, the drug-induced liver injury is not a common phenomenon following administration of ceftriaxone as a third-generation cephalosporin. Ceftriaxone can cause biliary sludge and symptoms of cholecystitis (9). Moreover, there are reports of ceftriaxone-induced toxic hepatitis (10).

Hepatotoxicity of doxycycline in comparison to other tetracyclines is low (11). There is a report of acute fatal hepatitis in a patient who received doxycycline plus naproxen and levofloxacin for *Mycoplasma pneumonia* (12). We were prescribed naproxen to our patient for his back pain.

Co-trimoxazole is one of the treatment options for brucellosis that prescribed to our patient (13). This drug can cause cholestatic or mixed hepatocellular-cholestatic injury because of sulfonamide component (11). Anti-epileptic drugs like phenytoin can uncommonly cause hepatotoxic reactions, and trimethoprim can increase the serum phenytoin level.

It is reported that measurement of antibodies against cytochrome P450 and liver-kidney microsome (anti-LKM) could help the physician to demonstrate drug-induced hepatotoxicity (10).

Quinolones like ofloxacin and ciprofloxacin are the alternative drugs in combination therapy of brucellosis. As the hepatotoxic effect of these drugs is lower than others, we suggest quinolones in combination therapy for similar cases (11,14).

This patient expired from severe hepatocellular injury. The cause of liver injury could be due to concomitant drugs usage rifampin, co-trimoxazole, doxycycline, phenytoin, and naproxen. Of course, chronic HBV infection exacerbated liver injury. The laboratory findings in time of discharge showed mild evidence of drug hepatotoxicity. In our opinion patient should not be discharged from the hospital. Transient stopping of drugs and restarting other drugs with lower potential of hepatotoxicity could be beneficial. Also, the replacement of phenytoin with levetiracetam and cease using naproxen could be helpful.

In conclusion, we do not suggest medical therapy without cardiac surgery in such cases. When combination therapy is necessary for brucellosis in an HBsAg-positive patient, hepatitis virus activity should be assessed by HBV-DNA PCR and the prescribed dose of drugs with known hepatotoxic effects such as rifampin and co-trimoxazole should be adjusted. Combination therapy with quinolones instead of hepatotoxic drugs is one of our suggestions.

References

1. Sanaei Dashti A, Karimi A. Skeletal Involvement of *Brucella melitensis* in Children: A Systematic Review. *Iran J Med Sci* 2013;38:286-92.
2. Buzgan T, Karahocagil MK, Irmak H, Baran AI, Karsen H, Evirgen O, et al. Clinical manifestations and complications in 1028 cases of brucellosis: a retrospective evaluation and review of the literature. *Int J Infect Dis* 2010;14:469-78.
3. Sasmazel A, Baysal A, Fedakar A, Bugra O, Ozkokeli M, Buyukbayrak F, et al. Treatment of *Brucella* endocarditis: 15 years of clinical and surgical experience. *Ann ThoracSurg* 2010;89:1432-6.
4. Sharifkazemi MB, Moarref AR, Rezaian S, Rezaian GR. *Brucella* endocarditis of pseudoaneurysm of an aortic composite graft. *J Cardiovasc Ultrasound* 2013;21:183-5.
5. Fountain FF, Tolley EA, Jacobs AR, Self TH. Rifampin hepatotoxicity associated with the treatment of latent tuberculosis infection. *Am J Med Sci* 2009;337:317-20.
6. Yetkin MA, Bulut C, Erdinc FS, Oral B, Tulek N. Evaluation of the clinical presentations in neurobrucellosis. *Int J Infect Dis* 2006;10:446-52.
7. Keshtkar-Jahromi M, Razavi SM, Gholamin S, Keshtkar-Jahromi M, Hossain M, Sajadi MM. Medical versus medical and surgical treatment for brucella endocarditis. *Ann ThoracSurg* 2012;94:2141-6.
8. Kaplowitz N. Drug-induced liver injury. *Clin Infect Dis* 2004;38:S44-8.
9. Bickford CL, Spencer AP. Biliary sludge and hyperbilirubinemia associated with ceftriaxone in an adult: case report and review of the literature. *Pharmacotherapy* 2005;25:1389-95.
10. Peker E, Cagan E, Dogan M. Ceftriaxone-induced toxic hepatitis. *World J Gastroenterol* 2009;15:2669-71.
11. Andrade RJ, Tulkens PM. Hepatic safety of antibiotics used in primary care. *J Antimicrob Chemother* 2011;66:1431-46.
12. Carrascosa MF, Lucena MI, Andrade RJ, Caviedes JR, Lavin AC, Mones JC, et al. Fatal acute hepatitis after sequential treatment with levofloxacin, doxycycline, and naproxen in a patient presenting with acute *Mycoplasma pneumoniae* infection. *Clin Ther* 2009;31:1014-9.
13. Kamali Aghdam M, Davari K, Eftekhari K. Recurrent Epistaxis and Bleeding as the Initial Manifestation of Brucellosis. *Acta Med Iran* 2016;54:218-19.
14. Alavi SM, Alavi L. Treatment of brucellosis: a systematic review of studies in recent twenty years. *Caspian J Intern Med* 2013;4:636-41.