Case Report

Thrombophlebitis and Deep Vein Thrombosis Caused Due to Subacute brucellosis

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Brucellosis is a disease caused by bacteria of the genus brusella, which is caused by fever, sweating, weight loss, joint pain and often enlarging spleen and liver. Brucellosis is a systemik infectious disease. Brucellosis keeps the most common bone, CNS, heart, lung, spleen, liver, testes, bladder, kidney, prostate and skin. Brucellosis may effect circulatory system as well. It may appear as pericardit, myocardit and endocardit in circulatory system. It would rarely occur thrombophlebitis. Therefore, we presented a case of brucellosis characterized with thrombophlebitis.

Keywords: Brucella, Thrombophlebitis – DVT

INTRODUCTION

Brucella bacteria are intracellular parasites and they are gram-negative, immobile, spore-free, cocobacillous, 0.5-2 micron microorganisms. Brucellosis is a disease caused by bacteria of the genus brusella, which is caused by fever, sweating, weight loss, joint pain and often enlarging spleen and liver. Brucellosis can be acute or chronic.1 Brucellosis is a systemik infectious disease. Brucellosis keeps the most common bone, CNS, heart, lung, spleen, liver, testes, bladder, kidney, prostate and skin.2

Brucellosis may effect circulatory system as well. It may appear as pericardit, myocardit and endocardit in circulatory system. It would rarely occur thrombophlebitis. Brucellosis is an insidious onset infectious disease caused by bacteria of the genus brusella.1 Chronic brucellosis is chronic due to the acute cases and it is found out later.1,2

In the classification proposed by Gotuzzo4 and accepted today, brucellosis is divided into three categories in terms of clinical process.

1-Acute brucellosis: up to 8 weeks of onset
2-Subacute brucellosis (Ondulan form): Between 8 and 52 weeks of age
3-Chronic brucellosis: the onset is 52 weeks longer.

Patients complain of fever, fatigue, excessive sweating, loss of appetite and joint aches. The fever is of decidious type and usually occurs with dizziness after lunch and may rise to 38-39C and falls into the night with plenty of sweating.1,2

Etiology is unclear in 40% of thrombophlebitis. Brucellosis is a rare condition that causes thrombophlebitis in the circulatory system.5,6 Thrombophlebitis can usually be seen in varicocele, infusion phlebitis, mendor thrombophlebitis, thrombophlebitis migrans, infectious-septic thrombophlebitis.7

The most definite method for brucellosis is the production of microorganisms in culture. If there is no proliferation, a standard tube agglutination test (Wright) is used to diagnose titers above 1/160.1 Tetracycline (T) - Streptomycin (S) Yada T-Rifampicin (R) combinations can be used in treatment.1,7

Combinations of quinolones and trimethoprim tetracycline have also been used but the nuch rate is high.9

The Wright test, which is the most commonly used serologic diagnosis of brucellosis, may have false negative results in the early stages of the disease. It is recommended to dilute the patient's serum at high titers to avoid negative prognostic outcome of the patient with low serum dilution due to excess antibody in the patient serum (inhibition of agglutination at low dilutions due to excess antibody or excess serum antibody).8,9

Agglutination in the prezonal phenomenon may be masked by in the case of high titre antibodies especially low dilutions of serum. Often seen in 1/20 dilution, it is rare in 1/80 or more dilutions.10,11 The Wright test is inadequate for the detection of unagglutinated antibodies. The Coombs test is a test to determine the incomplete, blocked or nonagglutinable IgGs continuation of wright test.
The added anti-human globulin in the medium enables the real seropositivity to occur by establishing bridges between the antibodies. The frequency of blocking antibodies that cause false negative results with wright in Brucella serology is high enough to be negligible. For this reason, it is recommended to confirm wright results with other serological methods such as CT or ELISA.

CT, a cumbersome and time-consuming test, is a good method for detecting complicated and chronic patients but can be negative by about 7% when compared to ELISA. For this reason, eliza testing should be performed in patients who are negative for wright and coombs test.

In a study conducted by Gültekin and colleagues, CT was negative in three (3.5%) patients and IGG was detected by ELISA. The ELISA is a method that determines the levels of Brucella specific IGG, IGM and IGA antibodies, clinical interpretation is an easier and removes the factors that cause false negative / positives in the STA test.

ELISA is a rapid, highly sensitive, specific and reliable method that profiles the immunoglobulin classes in the case of acute and chronic brucellosis. Total and specific immunoglobulins (IGG, IG M, IGA) can be detected rapidly by ELISA with high sensitivity and specificity (4-6 hours). The advantages of the ELISA test are that they are not affected by blocking antibodies, they are quantitative, they are objective, they are easy to apply.

Vascular complications of brucellosis are rare; the arteries are more affected than veins. Arterial complications of brucellosis include aneurysm formation in diverse arteries, such as the aorta, brachial, tibiofemoral, and cerebral arteries, with or without underlying endocarditis. Vein thrombosis is a rare vascular complication in acute brucellosis.

THE CASE

45 years old male patient was admitted to our hospital with complaints of high fever, malaise, night sweats and pain in his right leg. His history revealed that he was examined and treated by departments of internal medicine, physical therapy-rehabilitation and cardiovascular surgery for his right leg pain since ten weeks, but did not respond to various treatments.

Laboratory investigations performed by the most recently admitted department, cardiovascular surgery outpatient clinic revealed negative results for rose bengal, protein C, protein S and anti-thrombin 3. Following identification of local heat and redness of the right leg, a diagnosis of thrombophlebitis was suggested and antibiotic therapy with combination of amoxicillin-clavulanic acid and ciprofloxacin was initiated.

He was consulted to our Infectious Diseases Department when his body temperature was measured as 39°C in his control examination. The patient also reported that he was drinking raw sheep milk. Physical examination in our clinic revealed fever of 39.4°C, dilated veins in the right leg and tenderness in calf muscles.

At the anterior aspect of the right leg, an area with redness, longitudinally 20 cm in length, was identified. No organomegaly was existed. Laboratory examinations revealed the following results: white blood cell count 6,800 cells/mm³ (neutrophils, 44%), platelet count 312,000/mm³, erythrocyte sedimentation rate 20 mm, and C-reactive protein 43 mg/dL. Results of other routine biochemical blood tests were all normal.

The patient was hospitalized with preliminary diagnosis of “fever of unknown origin”. ECG, PA chest X-ray, abdominal ultrasound and urinalysis were normal. An anteroposterior X-ray of the pelvis showed grade I sacroilitis of the right sacroiliac joint Urine and blood cultures grew no microorganisms.

Negative results were obtained for rose bengal, Wright and Gruber-Widal tests and treatment with Ceftriaxone 2x1 gr iv was initiated. The Coombs test was negative. In his 3rd day of treatment, his body temperature was 39°C. Brucella Ig M and IgG tests were requested with the Elisa method. Since Brucella Ig M and IgG tests by Eliza method revealed positive results, a lower extremity venous system Doppler USG was performed and fresh thrombi, completely obliterating the lumens of deep veins of the right lower extremity, were detected.

Since diagnosis were thrombophlebitis related to brucella and deep vein thrombosis (DVT), Ceftriaxone treatment was terminated and combination of doxycycline and rifampicin was started. The patient was consulted to Department of Cardiovascular Surgery. Following confirmation of diagnoses of thrombophlebitis related to brucella and DVT, Heparin was added to the treatment regimen. At the 10th day of doxycycline and rifampicin treatment, redness of the right leg disappeared.

Treatment for brucella lasted for 3 months; anticoagulant treatment lasted for a total of 4 months, first two weeks with Heparin and with Clexane thereafter. Doppler USG performed at the end of 4th month showed no thrombus. First year follow-up examination did not reveal any recurrence of brucella and thrombophlebitis.

DISCUSSION

We present a case of brucellosis that can not be diagnosed because of wright and coombs tests negative findings and complicated with DVT on the right leg for eight weeks. In the classification proposed by Gotuzzo and accepted today, brucellosis is divided into three categories in terms of clinical process.

1-Acute brucellosis: up to 8 weeks of onset
2-Subacute brucellosis (Ondulan form): Between 8 and 52 weeks of age
3-Chronic brucellosis: the onset is 52 weeks longer

According to this classification, Our case was classified as subacute brucellosis because the time from the onset of symptoms to the diagnosis was 10 weeks. The Wright test is inadequate for the detection of unagglutinated antibodies. The Coombs test is a test to determine the incomplete, blocked or nonagglutinable IgGs continuation of wright test. The added anti-human globulin in the medium enables the real seropositivity to occur by establishing bridges between the antibodies.

CT, a cumbersome and time-consuming test, is a good method for detecting complicated and chronic patients but can be negative by about 7% when compared to ELISA. For this reason, eliza testing should be performed in patients who are negative for wright and coombs test.

In a study conducted by Gültekin and colleagues, wright CT was negative in three (3.5%) patients and IGG was detected by ELISA.

In our case also the wright and coombs tests were negative and the diagnosis was made with elisa. In our case, based on the history of ingestion raw sheep milk, fever associated with myalgia and night sweats, the presence of sacroilitis, and a positive Elisa test, a diagnosis of acute Brucella infection associated with a DVT in the left leg was made. Tetracycline (T) - Streptomycin (S) Yada T-Rifampicin (R) combinations can be used in treatment.
Combinations of quinolones and trimethoprim-tetracycline have also been used, but the nuchal ratio is high. In this case, the patient was treated with rifampicin 900 mg/day, doxycycline 200 mg/day and low molecular weight heparin and clexane. The treatment durations for anticoagulant was extended to 4 months (first two weeks with Heparin and with Clexane thereafter) and for brucellosis was extended to 3 months.

Doppler USG performed at the end of 4th month showed no thrombus or DVT. First year follow-up examination did not reveal any recurrence of brucella or thrombophlebitis. First year follow-up examination did not reveal any recurrence of brucella or thrombophlebitis.

Vascular complications of Brucella infection have rarely been reported in the medical literature. By searching MEDLINE, nine cases of deep vein thrombosis (DVT) associated with acute brucellosis have been reported.

Vein thrombosis is a rare vascular complication in acute brucellosis. In 1973, Romem et al. reported the first case of brucellosis complicated with central vein thrombosis. Since this publication, eight further cases of vein thrombosis due to brucellosis have been reported.

Table 1 shows demographic data and clinical and laboratory findings of the eight case reports of brucellosis complicated with vein thrombosis. Thrombosis was detected in the central retinal vein, portal vein, cerebral vein, and the lower limb veins. Acute brucellosis was associated with DVT in the legs in five patients (four men, one woman).

The diagnosis of DVT in the leg was diagnosed before the onset of other clinical features of brucellosis in one case concomitant with the diagnosis of brucellosis in two cases. In our case the duration between DVT diagnosis and the occurrence of brucellosis clinical features was 10 weeks. One patient had a history of brucellosis.

In 2013 in Tunisia, Koubaa et al. published a case of thrombosis in the left leg vein of a 45-year-old male patient. Thrombophlebitis associated with brucellosis is rare but can cause death with the cause of pulmonary embolism.

Gregersen ve Lund have published, a 53-year-old woman, indicating phlebitis in the patient and that the patient had died of brucellosis.

Wohlwill reported a 67-year-old female patient who died of brucellosis with pulmonary embolism. The main branch of pulmonary artery has been blocked by embolism in this patient's autopsy.

Winters et al. Published a case of brucellosis that detected thrombosis in pulmonary venules. In this case, pulmonary embolism-related death proved in otopside.

Spink has published a case showing thrombophlebitis in two patients with brucellosis and a case showing that she lives despite embolism in one of the patients.

Iglesias and Nunez have published a case showing thrombophlebitis in a patient with B.melitensis endocarditis but no pulmonary embolism.

Mechanisms by which brucellosis may cause DVT include induction of inflammation by the infectious process in adjacent tissues, direct endothelial damage, granulomatous endophlebitis, compression from a local soft tissue mass or abscess, induction of a transient hypercoagulable state, and an immune reaction in the vessel wall to a Brucella antigen.

In the present case, protein C, protein S, and antithrombin III levels, and activated protein C resistance activity were normal, and no antiphospholipid antibodies were detected. In this case, there was no infectious process in adjacent tissues, no direct endothelial damage, no local soft tissue mass or abscess. Therefore, in this case, it is possible that granulomatous endophlebitis or a possible immune reaction in the vessel wall to a Brucella antigen was responsible for the patient's DVT.

Table 1: Summary of all reported cases of deep vein thrombosis with brucellosis.

<table>
<thead>
<tr>
<th>Author</th>
<th>year</th>
<th>country</th>
<th>gender</th>
<th>age</th>
<th>vein thrombosis</th>
<th>serology</th>
<th>antibiotic therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Romem et al(20)</td>
<td>1973</td>
<td>Israel</td>
<td>NM</td>
<td>NM</td>
<td>central retinal vein</td>
<td>NM</td>
<td>NM</td>
</tr>
<tr>
<td>Gregory et al(21)</td>
<td>1990</td>
<td>Spain</td>
<td>NM</td>
<td>NM</td>
<td>portal vein</td>
<td>NM</td>
<td>NM</td>
</tr>
<tr>
<td>Zaidan et al(22)</td>
<td>1999</td>
<td>S.arabia</td>
<td>f</td>
<td>23</td>
<td>cerebral ven (sagital sinüs)</td>
<td>1/320</td>
<td>R+D+TS</td>
</tr>
<tr>
<td>Marfil Rivera et al(23)</td>
<td>1986</td>
<td>Mexico</td>
<td>f</td>
<td>18</td>
<td>lower limb</td>
<td>NM</td>
<td>T(NM)</td>
</tr>
<tr>
<td>Memish et al(24)</td>
<td>2001</td>
<td>Saudi Arabia</td>
<td>m</td>
<td>41</td>
<td>right leg</td>
<td>1/1280</td>
<td>R+D</td>
</tr>
<tr>
<td>Odeh et al(25)</td>
<td>2000</td>
<td>Israel</td>
<td>m</td>
<td>52</td>
<td>right leg</td>
<td>1/160</td>
<td>R+D</td>
</tr>
<tr>
<td>Sen et al(26)</td>
<td>2011</td>
<td>turkey</td>
<td>f</td>
<td>43</td>
<td>left leg</td>
<td>1/320</td>
<td>R+D</td>
</tr>
<tr>
<td>Gul et al(27)</td>
<td>2008</td>
<td>turkey</td>
<td>m</td>
<td>21</td>
<td>right leg</td>
<td>1/400</td>
<td>R+D</td>
</tr>
<tr>
<td>Koubaa et al(28)</td>
<td>2013</td>
<td>Tunisia</td>
<td>m</td>
<td>45</td>
<td>left leg</td>
<td>1/640</td>
<td>R+D</td>
</tr>
</tbody>
</table>

(F=female, M=małe, R=rifampicin, D=doxycycline, TS=trimethoprim-sulfamethoxazole, T=tetracycline, NM=not mentioned.)

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CONCLUSION

DVT is a rare complication of brucellosis. Vascular involvement in the form of allergic vasculitis can be seen in cases of brucellosis.

CT is a good method for detecting complicated acute and chronic patients but can be negative by about 7% when compared to ELISA. For this reason, eliza testing should be performed in patients who are negative for wright and coombs test.16

Wright, a frequently preferred method for serological diagnosis of brucellosis, can lead to the reporting of false negative results since it cannot detect the presence of blocking antibodies. Although it is time consuming and laborious to detect blocking antibodies, methods such as CT or ELISA testing, a valuable test, should be routinely used, especially in laboratories in endemic regions. It is difficult to interpret 1/40 and 1/80 titers with Wright. When interpreting the titers at this value, the results from more sensitive methods such as the ELISA method should also be considered. Determination of antibodies only in the IgG or IgM type by ELISA method results in some cases not being detectable. Therefore, if an ELISA is used at the end of the diagnosis, it will be more appropriate to investigate specific immunglobulins together.

The present case and the others reported previously suggest that brucellosis must be considered in patients suffering with DVT, particularly in patients from Brucella endemic areas.

Also, although wright and coombs tests are negative in the thrombophlebitis and DVT cases with complaints of ongoing fever, fatigue, sweating as the infection of Brucella is widespread in our country, brucellosis must be considered in the differential diagnosis and in such cases the elisa test must be studied.

Note: No potential conflict of interest relevant to this article is reported.

REFERENCES