

CASE REPORT

A case of brucellosis complicated with fatal capillary leak syndrome

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Abstract: Brucellosis may involve multiple organs and progresses with complications. Brucella endocarditis, disseminated intravascular coagulopathy (DIC) and chronic renal insufficiency are rare complications of brucellosis. Capillary leak syndrome due to brucellosis is seen even more rarely and up to this date, only one case has been reported. Our case will probably be the second. In this article, a case of brucellosis associated with the development of DIC, infective endocarditis and capillary leak syndrome is presented. Although antimicrobial treatment with ceftriaxone, doxycycline and rifampicin in intensive care unit, the patient died. As the reporting of capillary leak syndrome due to brucellosis is very rare, this case is regarded as valuable to be presented and will serve to call attention to this issue (Ref. 15). Full Text in PDF www.elis.sk.

Key words: brucellosis, capillary leak syndrome, infective endocarditis, renal failure.

Currently, brucellosis is still an important zoonotic disease worldwide and especially in developing countries with half a million people being infected each year. Brucellosis may infect almost all of the organs and may cause various complications (1, 2). Capillary leak syndrome (CLS) is a rare medical condition where the number and size of pores in the capillaries are increased leading to a leakage of fluid from the blood to the interstitial fluid, resulting in dangerously low blood pressure, edema and multiple organ failure due to limited perfusion (3). Capillary leak syndrome due to brucellosis is seen even more rarely and up to this date, only one case has been reported (4). Our case will probably be the second. In this article, a case of brucellosis associated with the development of disseminated intravascular coagulopathy (DIC), brucella endocarditis, renal insufficiency and capillary leak syndrome is presented.

Case Report

A 69-year-old man was admitted to our clinic with symptoms of back and leg pain, chills and shivers, loss of appetite and difficulty in walking. His symptoms appeared two months ago and intensified progressively to the current state. A detailed medical history revealed that, 15 months ago he was admitted to our clinic with a diagnosis of brucella endocarditis and glomerulonephritis due to brucellosis. In echocardiographic evaluation performed during previous admission, aortic insufficiency and vegetation on

aortic valve was detected. Brucella standard tube agglutination test (SAT) was positive with a titer of 1/640 and *Brucella* spp. were isolated in his blood culture. Patient was treated with ceftriaxone, rifampicin and doxycycline for a month and clinical features resolved. He was also referred to cardiovascular surgery department for surgical evaluation. Patient rejected cardiac surgery. He was advised to continue treatment and return for follow-up. But he did not take the medical treatment regularly and stopped it. Fifteen months later on admission, his vital signs were the following: body temperature of 37.8 °C, pulse rate of 88/min and blood pressure of 130/80 mmHg. There was a murmur of 4/6 degrees in aorta. In addition to bilateral pretibial edema (++), petechial rash was seen on both legs and face. In laboratory evaluation, brucella SAT was positive with a titer of 1/640 and 2-mercapto-ethanol was designated as positive with a titer of 1/320. Urine analysis findings were as follows: density 1014, pH 6.5, protein 150 mg/dl, erythrocytes 3 (+). Haemogram showed white blood cells (WBC) 10800/mm³, Hb 12.4 g/dl, platelets 102000/mm³ and erythrocyte sedimentation rate as 13mm/h. Biochemical evaluations revealed C-reactive protein (CRP) 11.4 mg/L (normal: 0.1–0.5), urea 71 mg/dl, creatinine 1.9 mg/dl, albumin 2.5 g/dl, protein 6.2 g/dl, prothrombin time (PT) 14 s (normal 10–15), active partial thromboplastin time (aPTT) 41 s (normal 26–41) and INR 1.19 (normal: 0.8–1.22). Serological tests for viral hepatitis A, B, C, E, toxoplasmosis, infectious mononucleosis, herpes simplex virus, cytomegalovirus and human immunodeficiency virus, blood film for malaria, salmonella agglutination tests, and tuberculin test results were negative. Upon withdrawal of blood culture, treatment with ceftriaxone, rifampicin and doxycycline was initiated. Unfortunately the patient was intolerable to oral therapy and could not receive rifampicin and doxycycline regularly. Lumbosacral magnetic resonance imaging (MRI) of the patient showed spondylodiscitis of T11–12. Echocardiographic examination showed that vegetations seemed to per-

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sist. It was planned to apply trans-esophageal echocardiography which was rejected by the patient. One unit of albumin was given due to decrease in albumin and pretibial edema. Upon decrease in platelets ($68000/\text{mm}^3$), one unit of platelet was administered. Creatinine clearance was determined as 25 ml/min. Upon consultation with nephrology department, the patient was designated to be in a state of chronic renal insufficiency (CRI). Medical treatment was not successful in improving the clinical state of the patient. When free fluid was detected during abdominal ultrasonography, furosemide was added to treatment. Platelets and albumin continued to decrease while creatinine started to increase (3.37 mg/dl). Four units of albumin were administered within a few days. Albumin value was restored to a level of 3 g/dl. Upon repeated consultation with nephrology, patient was diagnosed with acute renal insufficiency (ARI) developing on a state of CRI. On 14th day of hospitalization, severe dyspnea and cough developed. In addition, there was edema in abdomen and thorax with symptoms of nausea, vomiting and headache. Blood pressure decreased to a level of 100/70 mm Hg. Following consultation with Pulmonary Diseases department, the patient was diagnosed as having bilateral pleural effusion and acute pulmonary edema. He was admitted to intensive care unit and salbutamol, ipratropium plus steroids were initiated. With the intention of elimination of the edema, the dose of furosemide was increased. Abundant leukocytes were seen in fluid extracted by thoracentesis and wright test of thoracentesis fluid was evaluated as positive with a titer of 1/1280. Simultaneous serum wright test was regarded as positive with a titer of 1/1280. On the following day, body edema of the patient increased and progressed to a state of anasarca. Laboratory values of the patient deteriorated further. Levels of following values decreased: WBC 6900 mm^3 , Hb 9.4 g/dl, platelets 51500 mm^3 and albumin 2g/dl. Other laboratory values were as follows: Urea 108 mg/dl, creatinine 3.37 mg/dl, PT 26 s, aPTT 59 s, Fibrinogen 67 mg/dL (normal: 150–400), D-Dimer 2.05 ug/mL (normal: 0–0.4). Following consultation with the department of Haematology, fresh frozen plasma (FFP) was initiated with a dose of 15 ml/kg to the patient who was diagnosed as having DIC. A total of 15 units of FFP was administered in three days. No growth was seen in thoracentesis fluid and second blood culture. After admission to intensive care unit, hallucinations and confusion was seen. Two units of albumin and one unit of platelet was administered. Anasarca type edema persisted. FFP was continued due to persistent elevation in PT and aPTT. The patient entered an anuric phase despite the treatment. Cardiopulmonary collabs developed on the next day and he was placed on mechanical ventilation which lasted for only one day, then the patient died.

Discussion

Human brucellosis has a wide clinical spectrum with specific and nonspecific symptoms. The most prominent symptoms of brucellosis are fever, sweats, malaise, anorexia, arthralgia and back pain (5). Our patient presented with similar symptoms. Even though various complications can be seen during the course of brucellosis, main involvement is in the musculoskeletal system.

Despite a high rate of general haematological complications, thrombocytopenia has been reported to occur in 1–8 % of patients with brucellosis (6). Although the mechanism of thrombocytopenia in brucellosis is not yet entirely known, it may be hypersplenism, bone marrow suppression due to septicemia, hemophagocytosis, granulomas and peripheral immune destruction of thrombocytes (6, 7). During the treatment, haematological conditions may deteriorate or new conditions may develop (8). In our case, initial platelet count was $102000/\text{mm}^3$ but it decreased to a level of $50000/\text{mm}^3$ after two weeks. On the following days, anemia developed. DIC development in brucellosis is rare. Dilek et al. reported only one case of DIC in both series in their trials (7). Therefore, DIC seen in our case is significant. In the last phase of the disease PT, aPTT, INR and D-dimer increased; following the decrease in platelets, a state of DIC was established.

In general, a combination of medical and surgical treatment is used in brucella endocarditis, which has a high rate of mortality. There are some reports which indicate that patients may be cured solely by medical therapy, provided that it is administered for an appropriate duration (9, 10). In our patient, clinical improvement was seen with medical treatment of one month during previous hospitalization. He was advised to continue medical treatment and to refer to cardiovascular surgery department for surgical evaluation. Unfortunately, the patient rejected surgical intervention and stopped medical treatment as well. Therefore he presented with a reactivated and deteriorated clinical condition. In patient's evaluation, increased and persistent aortic murmurs and vegetations were detected. In a previous study, cases of renal involvement accompanying infectious endocarditis (IE) were reported (11). Similarly in our patient, renal involvement and subsequent new complications developed following IE. Renal involvement in brucellosis may present with various conditions like interstitial nephritis, pyelonephritis, exudative glomerulonephritis, renal abscess, mixed cryoglobulinemia, and IgA nephropathy (12). Likewise in our patient, CRI developed following IE. Subsequently, complications increased to a multiple state. We believe that multiplicity of complications is not only due to virulence of brucella bacteria and host resistance but is also due to predisposition to a second complication which is triggered by a complication. As the number of complications increase, the prognosis of the disease deteriorates.

The main complication in our case was CLS. CLS is characterized by localized or diffuse edema, haemoconcentration, hypotension, hypovolemic shock and in some of the cases, with monoclonal gammopathy. Currently, etiology of CLS is not clear but it develops via increased permeability of capillary walls which is triggered by inflammatory processes and as a result, fluid and albumin leak from capillaries into interstitial tissue. Possible cause is vessel wall damage due to cytokins (interleukin 2, interleukin-6, IFN- γ and tumor necrosis factor) because IL-10, IL-12 and IFN-gamma play a role in intracellular infections and stimulate other cytokins (3, 13). The infection leads to acute and chronic inflammation related to the brisk interaction of Brucella-derived products, such as lipopolysaccharide with the host cells. In fact, Brucella lipopolysaccharide is reported to act as a virulence factor of the infection (8). In a number of trials carried out in patients with brucellosis,

IFN- γ , neopterin, IL-2-6-8-12 and TNF alfa were found to be significantly higher than in the control group (14). It seems that these cytokines play a role in the development of CLS syndrome, DIC and certain haematological disorders. Haemoconcentration, which is a feature of CLS is lacking in our case because brucella suppresses blood elements via the same mechanism. In association with this development, SAT titer was doubled. Clinical state of the patient deteriorated. ARI developed upon CRI. Stability of haemostasis was distorted. Hallucinations and confusion may be associated with cerebral edema but MRI could not be performed. In our case, with the decrease of blood pressure to 50 mm Hg, persistent decrease of albumin in spite of albumin therapy, development of anasarca type edema and finally, with cardiopulmonary collaps, CLS was fully established. Up to this date, IE was recognized as the major cause of brucellosis. In a trial which evaluated 9 brucellosis patients with IE complications, one patient died. Mortality rate was 11 % (15). Similarly, in another trial of 7 brucellosis patients with IE complications, one patient was lost and mortality rate was 14 % (16). On the other hand, in CLS cases, one of two patients is lost so that mortality seems to be around 50 %. In CLS developing upon various infections, while cases with a favorable prognosis have a mortality rate of 34 %, in cases admitted to intensive care units, mortality rate is reported to be 80 % (17). CLS mortality in general, even in cases with favorable prognosis, seems to be higher than the mortality in IE.

As a result, even though CLS is an extremely rare complication of brucellosis, it should be carefully considered during differential diagnosis due to its high mortality rate. We believe that CLS should be substituted instead of IE as the main cause of mortality but substantial number of further case reports are required on this subject.

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