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Case Report

Brucellosis Causing Thrombotic Thrombocytopenic Purpura Confirmed by Low ADAMTS13 Levels. Report of Two Cases and Literature Review

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Abstract

Thrombotic Thrombocytopenic Purpura (TTP) is a life-threatening thrombotic microangiopathy that has been reported in association with several diseases and infectious complications. Several cases of TTP had been reported in patients with brucellosis, but none of them was confirmed to have low ADAMTS13 level.

We report 2 patients with brucellosis presenting with TTP. In both patients, ADAMTS13 levels were confirmed to be below 5% and after appropriate therapy with antimicrobials and Therapeutic Plasma Exchange (TPE), normal blood indices and blood levels of ADAMTS13 were restored. To our knowledge, these are the first 2 cases of TTP associated with brucellosis that were confirmed to have low ADAMTS13 levels.

Keywords: Brucellosis; Thrombotic thrombocytopenic purpura; Therapeutic plasma exchange; ADAMTS13; Antimicrobial therapy

Introduction

TTP is a rare but rather severe and potentially fatal disease that is characterized by the following pentad: Coombs negative microangiopathic hemolytic anemia, thrombocytopenia, neurological abnormalities, renal dysfunction or failure, and fever [1-6]. TTP can either be hereditary or acquired [2,4]. Acquired TTP is immune-mediated with autoantibodies directed against ADAMTS13 which is a metalloproteinase responsible for cleavage of Von Willebrand Factor (VWF) that induces platelet aggregation [1-4,6]. TTP causes formation of disseminated platelet thrombi in the arterioles and capillaries leading to end-organ ischemia and damage to vital organs such as: brain, heart and kidneys [1-6]. The diagnosis of TTP is based on clinical presentation as well as laboratory results and is confirmed by documentation of severe ADAMTS13 deficiency with ADAMTS13 levels < 10% [4,6]. Treatment of TTP consists of: (1) Therapeutic Plasma Exchange (TPE) to replace ADAMTS13 and to remove VWF and ADAMTS13 antibodies from the circulation; (2) immunosuppressive therapies such as glucocorticoids and rituximab; and (3) caplacizumab which is a humanized nanobody that targets the A1 domain of VWF thus preventing the interaction with platelet glycoprotein Ib-IX-V receptor and the ensuing microvascular thrombosis [1-4,6]. If left untreated, TTP carries a mortality rate (MR) of > 90%. However, the introduction of TPE in the management of TTP has reduced MR to < 20% [2,6].

Case Presentations

Case number (1)

On 31/10/2020, an 18 years old Saudi male was admitted to King Fahad Specialist Hospital (KFSH) in Dammam with 2 weeks History Of (H/O) fever, night sweats, headache, fatigue, low back pain and generalized body aches in addition to red urine for 2 days. There was no H/O dyspnea, chest pain, cough, gastrointestinal symptoms, or other neurological manifestations. He gave H/O raw milk ingestion and there was family H/O brucellosis. The patient was known to have type 1 diabetes mellitus on insulin therapy. He denied H/O taking herbal medications. His physical examination on admission revealed: temperature: 37.8°C, heart rate: 82/minute, blood pressure: 118/82 mmHg, and respiratory rate of 16/minute. There was no: external palpable lymphadenopathy, leg edema, jaundice, or neck stiffness. There was tenderness over lumbosacral area. There was no abdominal tenderness but the spleen and the liver were just palpable, chest was clear, and examination of both cardiovascular and neurological systems showed no abnormality. Complete Blood Count (CBC) revealed: White Blood Cell (WBC) count: $5x10^9$/L, Hemoglobin (Hb): 10g/dL, Platelet (PLT) count: $20x10^9$/L. Renal, hepatic and coagulation profiles were normal. Serum haptoglobin was low, while Coombs test was negative. Peripheral Blood Smear (PBS) showed 20 schistocytes per power field, and no blasts or dysplastic changes (Figure 1). Serum

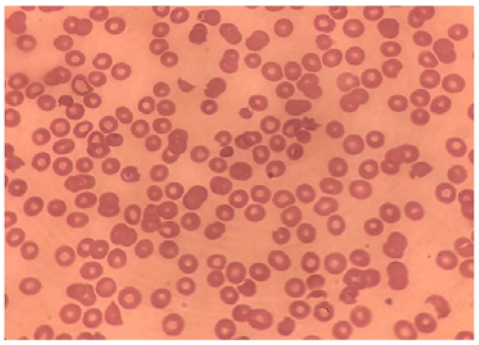

Figure 1: Peripheral blood smear showing severe thrombocytopenia and schistocytosis.

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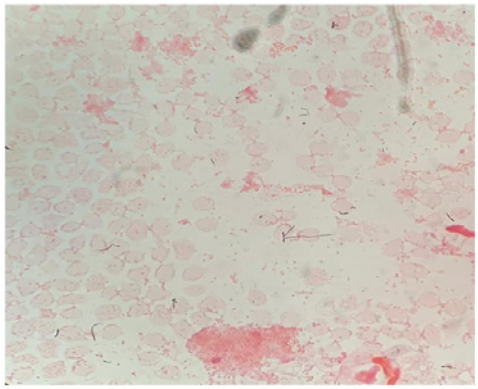

Figure 2: Bone marrow culture showing small Gram-negative coccobacilli.

Lactic Dehydrogenase (LDH) level was 900unit/liter (U/L). Blood cultures were negative but cultures of Bone Marrow (BM) aspirate grew Gram negative coccobacilli that were identified as Brucellae (Figure 2). Serum IgM for Brucella was negative while serum IgG was positive. Antibody agglutination was 1:1280 for Brucella(B.) abortus and 1:2560 for B.melitensis. Viral, hepatitis and autoimmune screens were negative. Covid-19 screen was also negative. ADAMTS13 level was < 5%. Chest X ray and echocardiography showed no abnormality.

Soon after admission and knowing the results of CBC and PBS, the patient was commenced on daily TPE for 3 days. After confirming the diagnosis of brucellosis, the patient was commenced on: oral doxycycline 100mg twice daily and ciprofloxacin 750mg twice daily orally for a total duration of 6 weeks. To control his blood glucose level, the patient was commenced on sliding scale of insulin for few days then he was shifted back to twice daily insulin injections. Few days later, the patient started to improve clinically, his PLT count started to increase considerably, while schistocytes on the blood smear and serum LDH level started to decrease gradually. One week after admission, the patient was discharged in an excellent clinical condition and was given regular follow-up at the outpatient clinics. Two weeks later, blood counts and serum LDH level normalized and 6 weeks after discharge, blood level of ADAMTS13 went up to 80%. Thereafter, the patient continued to have follow-up every 3 months. Meanwhile, he remained stable clinically without relapse of his TTP or brucellosis as reflected by his laboratory results. He was last seen at OPD in January 2022: he was asymptomatic and his physical examination revealed no abnormality at all. His CBC showed: WBC: $4.6x10^9$/L, Hb: 12.9g/dL, and PLT count of $304x10^9$/L. His serum LDH was 142 U/L. No new medication was started and the patient was given a new follow-up appointment.

Case number (2)

A 42 years old Saudi lady was admitted to KFSH in Dammam on 1/12/2020 with H/O fever, headache, fatigue, nausea, and dizziness for 3 weeks in addition to red urine and minor gum bleeding for 2 days. There was no H/O dyspnea, abdominal pain, diarrhea, seizures or other neurological manifestations. She gave H/O raw milk ingestion. The patient was not known to have any medical or surgical illnesses and she was not on any regular medication. Her physical examination on admission showed: temperature: 37.4°C, heart rate: 96/minute, blood pressure: 118/82 mmHg, and respiratory rate of 18/minute.

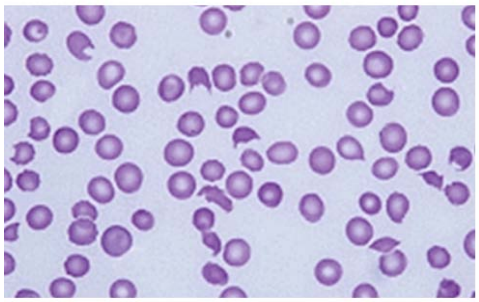

Figure 3: Peripheral blood smear showing severe thrombocytopenia and schistocytosis.

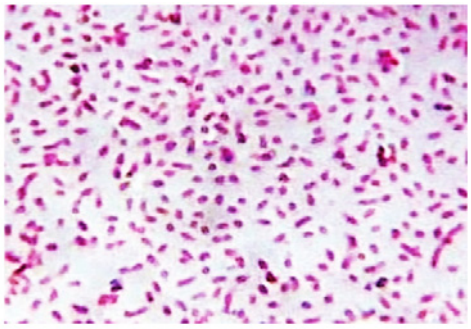

Figure 4: Blood culture showing Gram negative coccobacilli.

There was no: external palpable lymphadenopathy, leg edema, jaundice, neck stiffness, joint swelling or tenderness. There was no abdominal tenderness or palpable organomegaly, chest was clear, and examination of both cardiovascular and neurological systems showed no abnormality. CBC revealed: WBC count: $3.9x10^9$/L, Hb: 9.6g/dL, and PLT count: $10x10^9$/L. Renal, hepatic and coagulation profiles were normal. PBS showed thrombocytopenia and 10 schistocytes per power field (Figure 3). Serum LDH was 320U/L. Blood cultures grew Gram negative coccobacilli that were identified as B.melitensis (Figure 4). Serum IgM for Brucella was positive while serum IgG was negative. Brucella antibody agglutination was 1: 1280. Viral, hepatitis and autoimmune screens were negative. Covid-19 screen was also negative. ADAMTS13 level was < 5%. Chest X ray and echocardiography showed no abnormality.

Soon after admission and knowing the results of CBC and PBS, the patient was commenced on daily TPE. After obtaining the results of blood cultures, the patient was commenced on intramuscular gentamicin 240mg/day and oral doxycycline 100mg twice daily. As the plasmic score of TTP was 6.0, the patient was given 1 dose of rituximab and one week of oral prednisolone 1mg/kg/day. Few days after starting TPE, the patient started to improve clinically reflecting the improvement in blood indices. However, more improvement was obtained after commencing antimicrobial therapy for brucellosis. Ten days after admission, the patient became very well and she was discharged oral ciprofloxacin 750mg twice daily and doxycycline 100mg twice daily for 5 more weeks. Later on, the patient continued to have regular follow-up at the outpatient clinic. Five months after diagnosis of brucellosis and TTP, her CBC showed: WBC: $8.48x10^9$/L, Hb: 10.6g/dL, PLT: $380x10^9$/L. Repeat ADAMTS13 assay showed

normal level. Throughout her follow-up, the patient sustained her clinical and laboratory improvement without evidence of relapse of her TTP or brucellosis.

Discussion

Brucellosis is a zoonosis that can be transmitted to humans by domestic and wild animals [5,7-12]. The distribution of brucellosis is global but the infection is endemic in the Mediterranean, Middle East, Indian Subcontinent, Mexico and parts of Central and South America [8-10]. The causative organism is a Gram-negative, non-spore-forming, aerobic, non-motile, and non-encapsulated coccobacillus [9-12].Several species including *B. melitensis*, *B. abortus*, *B. suis*, and *B. canis* are pathogenic to humans [9,10,12]. Brucellosis is transmitted to humans by: (1) consumption of unpasteurized milk and other dairy products; (2) direct contact with infected animal products and inhalation of infected aerosolized particles; and (3) transfusion of blood products and stem cells [7,9,10]. The incubation period of brucellosis is 1-6 weeks but can be as long as several months [9-11]. The clinical manifestations of brucellosis include: fever or pyrexia of unknown origin, night sweats, chills and rigors, anorexia, malaise, weakness, weight loss, headache, arthralgia, myalgia, low backache, tenderness over lumbosacral spine, swollen and tender joints, nausea, vomiting, abdominal pain, dizziness, cough, dyspnea, epistaxis, dyspepsia, hemoptesis, jaundice, mouth ulcerations, various cutaneous eruptions, jaundice, external lymphadenopathy, hepatomegaly, splenomegaly, and epididemo-orchitis. Additionally, brucellosis can be complicated by: (1) endocarditis, myocarditis, pericarditis, and pericardial effusions; (2) meningoencephalitis, cranial nerve palsies, stroke, paraplegia, subdural hematoma, sudarachnoidalhemorrhage, coma, and convulsions; (3) spondylitis, sacroilitis, osteomyelitis, and paravertebral abscess; and (4) disseminated infection, relapses, and chronic brucellosis [7-9,11].

The hematological complications of brucellosis include: (1) anemia of chronic illness, hemolytic anemia that maybe autoimmune and Coombs positive; (2) leukopenia or leukocytosis, neutropenia, lymphocytosis or lymphocytopenia;(3) thrombocytopenia that may be isolated, severe, and immune; (4) bicytopenia, and pancytopenia; (5) reticulocytosis; and (6) disseminated intravascular coagulation, and bleeding diathesis [7,9,11,13-39]. The BM in brucellosis may be normocellular, hypocellular or even hypercellular and examination of the BM may reveal: hyperplasia of erythroid elements, left shift of granulocytic series, increased megakaryocytes, and hemophagocytosis. Also, BM biopsy may show infiltration by: eosinophils, plasma cells, histiocytes, as well as granulomas that are neither necrotic nor calcified [9,11,14,19-22,27,28,30,32,35,36,38].

The diagnosis of brucellosis is made on clinical grounds and confirmed by: (1) culture of Brucella organisms from: blood which is the gold standard for the laboratory diagnosis of brucellosis, BM, and other body fluids such as cerebrospinal fluid and pleural fluid; (2) serological testing including: Rose Bengal test, enzyme-linked immunosorbent assay, Coombs test, immunocapture and rapid slide agglutination assays, and fluorescence polarization assay; (3) molecular tests such as polymerase chain reaction [9,12,22,30,32,38,40-45]. However, WBC count, C-reactive protein, and neutrophil count can be used as valuable markers in the preliminary diagnosis of brucellosis. Additionally, neutrophil-to-lymphocyte, lymphocyte-to-monocyte, and platelet-to-lymphocyte ratios can predict complications as well as specific organ involvement in individuals having brucellosis [8,9,11,40,45-47].

Several antimicrobial regimens have been employed in the treatment of brucellosis including the following groups of antibiotics in various combinations: (1) trimethoprim-sulfamethoxazole; (2) doxycycline, tetracycline and tigecycline;(3) ciprofloxacin, and ofloxacin; and (4) gentamicin, and streptomycin [9,12,40,43,45,48-53].Treatment is usually given for 6 weeks except in complicated infections that require prolonged treatment for upto 3 months [9,12,48,49,52,53]. Control or eradication of brucellosis requires several elements including: control of animal disease, pasteurization of milk, and vaccination of animals [9,12,54,55].

Brucellosis has been reported in pregnancy and in patients with: hematologic malignancies such as acute leukemia, myelodysplastic syndrome, multiple myeloma, polycythemiarubra vera, and myelofibrosis; solid tumors such as lung carcinoma, prostatic carcinoma, ovarian cancer, hepatocellular carcinoma, and neurological tumors; human immunodeficiency virus; end-stage renal disease, rheumatoid arthritis, pulmonary fibrosis, liver cirrhosis, and chronic osteoarthritis; and recipients of solid organ as well as hematopoietic stem cell transplantation [5,9,11,22,38,52,53]. Systemic infection with different microorganisms such as bacteriae, viruses, and fungi may mimic the clinical manifestations of TTP [56].

Several cases of TTP had been reported in patients with brucellosis [3,5,57-64]. However, none of the reported cases of brucellosis and TTP was tested for ADAMTS13 [3,5,57-59,61-64]. The reported patients having both TTP and brucellosis presented with: fever, generalized purpuric skin lesions, bleeding from various sites, malaise, pallor, jaundice, mental confusion, headache, and reduced level of consciousness [5,57-59,61-64]. The laboratory investigations of these patients showed: pancytopenia, microangiopathic hemolytic anemia with red blood cell fragmentation of PBS, increased erythrocyte sedimentation rate and serum LDH level, renal dysfunction, reticulocytosis, and negative Coomb test and their BM examinations showed: hemophagocytosis, enhanced megakaryopoiesis and erythropoiesis, in addition to multiple granulomas [5,57-59,62-64]. TTP in the reported patients with brucellosis responded well to: (1) appropriate antimicrobial therapies such as rifampicin, doxycycline, trimethoprim-sulfamethoxazole; and (2) plasma infusion or TPE in addition to methylprednisolone [3,5,57-59,61-63].

Our patients presented had bleeding tendency due to thrombocytopenia in addition to clinical manifestations consistent with brucellosis. Their investigations confirmed that both of them had TTP and brucellosis. Their treatment consisted of TPE for the TTP component and antimicrobial therapy for their brucellosis. Their ADAMTS13 levels were very low at presentation and they normalized weeks after receiving appropriate treatment, while none of the previously reported cases of TTP and brucellosis was confirmed to have low ADAMTS13 level. Additionally, the diagnosis of brucellosis in our patients was confirmed by having positive BM cultures in the first patient and positive blood cultures in the second one.

Conclusion

It is essential to start appropriate treatment for TTP as soon as

it is strongly suspected. Additionally, thorough investigations for a secondary cause of TTP including infections such as brucellosis should be made promptly. Appropriate management of both TTP and brucellosis will lead to successful outcome.

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