

A Case of Systemic Lupus Erythematosus with Peripheral Neuropathy Misdiagnosed as Brucellosis

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Abstract

Brucellosis and systemic lupus erythematosus are two diseases with different origin and treatment targets characterized by multi-organ involvement particularly affecting central and peripheral nervous systems. It is known, that clinical symptoms of brucellosis are non-specific and can mimic many other diseases. Previously, it has been reported that slightly positive serological tests in some diseases (such as lymphoma, typhoid fever and malaria) have led to misdiagnosis of brucellosis. In our paper we report a case of systemic lupus erythematosus with bilateral “drop foot” misdiagnosed as brucellosis which recovered after appropriate treatment aimed at lupus.

Keywords: Brucellosis; Systemic lupus erythematosus; Peripheral neuropathy; Misdiagnosis

Introduction

Brucellosis is a zoonotic disease that is transmitted to humans by the consumption of infected animal products. Clinical symptoms of brucellosis are fluctuating fever, sweating, abdominal and joint pain that mimic many other diseases [1].

Systemic Lupus Erythematosus (SLE) is a chronic inflammatory autoimmune disease characterized by multi-organ system involvement [2]. Both SLE and brucellosis can affect the central and peripheral nervous systems [3,4].

In our case, a 35-year-old woman presented with peripheral neuropathy associated SLE, which had been misdiagnosed as brucellosis. As a result of appropriate treatment targeted to SLE, the patient recovered without neurological deficits.

Case Report

A 32-year-old female patient was followed with a diagnosis of brucellosis in the infectious diseases clinic. The Wright brucella agglutination test was positive in 1/80 dilution. The patient had a history of contact with livestock, in particular assisting in the birth of animals with her bare hands. About two years before, the patient had suffered from intervals of high fever, night sweating, muscle and joint pain but she did not visit any health care practitioner at this time. As the clinical symptoms and complaint were getting worse, she was admitted to the infectious diseases clinic about 8 months ago. The patient has been treated with rifampicin 600 mg/day, tetracycline 200 mg/day, patient's symptoms did not improve contrariwise the patient's condition escalated and worsen every single day, during the follow-ups drop foot appeared and the patient has been referred to our

clinic for further evaluation. In the previous two weeks, the patient had developed difficulty in walking and loss of foot dorsiflexion.

Physical examination was normal. There was edema on the patient's legs and ankles. In many circumstances, patient suffered from high body temperature reaching up to 40°C. She had a butterfly photosensitive malar rash on the face and erythematous papular lesions on both distal lower extremities (Figures 1 and 2).



Figure 1: A butterfly photosensitive malar rash on the face.



Figure 2: Erythematous papular lesions on both distal lower extremities.

The patient’s consciousness, orientation and cooperation were complete. Cranial nerve examination was normal. Revealed weakness (Medical Research Council Scale) of the tibialis anterior and gastrocnemius muscles was 2, feet dorsiflexion was 0 bilaterally. On the upper extremities, motor functions were preserved. Are flexia was noted on both knees and ankles. The pin-prick, vibration, deep proprioception and light touch sensations were decreased in the lower limbs. There was painful dysesthesia on the lower extremities bilaterally. There was no hyperalgesia or allodynia on the bilateral lower or upper extremities.

Nerve conduction studies showed sensory motor axonal peripheral neuropathy dominates in lower extremities. Additionally, needle electromyography examination showed no voluntary muscle activity from the tibialis anterior and extensor digitorum brevis muscle bilaterally. Results of electroneurographic examination presented in the Table 1.

	Distal Latency (ms)	Normal Range	Amplitude (mV, μ V)	Normal Range	Conduction Velocity (M/S)	Normal Range
L Ulnar (motor) Wrist-ADQ Elbow-Wrist	2.7 5.8	≤ 3.3	5.9 mV 5.0 mV	≥ 7.0	51.3	≥ 50
L Ulnar (sens) Digit 5-Wrist	2.4	≤ 3.4	8.9 μ V	≥ 10.0	47.5	≥ 37.5
L Median (motor) Wrist-APB Elbow-Wrist	3.1 6.1	≤ 3.8	3.4 mV 3.2 mV	≥ 4.3	50.9	≥ 49.7
L Median (sens) Digit 2-Wrist	2.7	≤ 3.4	7.6 μ V	≥ 12.8	46.3	≥ 39.5
R peroneal Ankle-EDB	No response					
L peroneal Ankle-EDB Fib head-EDB	3.3 6.7	≤ 5.5	0.4 mV 0.3 mV	≥ 3.6	44.1	≥ 40.9
R Tibial Ankle-Abd hal	3.1	≤ 5.8	1.2 mV	≥ 3.6	42.9	≥ 39.6
Knee-Ankle	7.9		1.1 mV			
L Tibial Ankle-Abd hal Knee-Ankle	2.8 7.1	≤ 5.8	1.8 mV 1.3 mV	≥ 3.6	43.8	≥ 39.6
R Sural Calf-Ankle	3.1 \leq	3.4	3.9 μ V	≥ 5	40.8	≥ 33.8
L Sural Calf-Ankle	No response					

Table 1: Results of the motor and sensory nerve conduction studies before the treatment. Abbreviations: R: Right; L:L; ADQ: Abductor Digiti Quinti; EDB: Extensor Digitorum Brevis; Fib: Fibula; abd hal: abductor hallucis, sens: Sensory.

Also, detailed ophthalmological examination of the patient, including best-correct visual acuity, slit-lamp biomicroscopy and fundoscopy, was performed for elimination conditions occurring with optic nerve or retinal pathologies. All tests were in the normal ranges.

Considering other medical conditions which may cause peripheral nerve involvement, we have realized the differential diagnosis for the foremost diabetes mellitus then the other metabolic disorders (kidney and liver function disorders), thyroid function disorders and its autoimmune diseases, vitamin B12, copper, zinc deficiencies, infectious causes (syphilis, Lyme, HBV, HCV and HIV), other

rheumatologic diseases (rheumatoid arthritis, Behçet's and Sjögren Diseases). Drug intoxication is also questioned but there were no history of recent drug use. All blood tests including liver, renal and thyroid functions, vitamin B12, folic acid, prothrombin time and activated partial prothrombin time, creatine kinase, and glucose were within the normal range. White blood cell count was 2300/ mm³ (normal range 4800 -10.000 mm³), hemoglobin level was 11.3 g/dL (normal range 14.0-18.0 g/dL), platelet count was 175.000/uL (normal range 150-450.000 /uL), serum sodium level was 129 mEq/L (normal range 135-148 mEq/L) and albumin level was 2.1 gr/dl (normal range 3,5-5,2 gr/dl). Erythrocyte sedimentation rate was 103 mm/hr (normal range 0-10) and C-reactive protein was 10.12 mg/dl (normal range 0-0.5 mg/dl). Urine analysis showed no proteinuria or haematuria and 24-hour urine micro protein creatinine ratio was normal range.

Rheumatologic blood tests showed high levels of antinuclear antibodies, as 1/5120 with cytoplasmic pattern, anti-ds DNA antibodies as 200 U/mL (normal range <20 U/mL), Anti Sm antibodies as 30 u/ml (normal range 0-25 u/ml) and Anti Ro antibodies as 24.9 u/ml (normal range 0-20 u/ml). Anticardiolipin antibodies were negative. Cerebrospinal Fluid (CSF) was examined; glucose, protein, and sodium levels were within normal ranges. There were no blood cells or atypical cells in the CSF. The rose Bengal test was negative in

the CSF, so a Wright agglutination test was not performed. Blood, CSF and bone marrow cultures were negative for brucellosis. Finally, the brucella genome was studied using the Polymerase Chain Reaction (PCR) method and negative results were obtained.

Brucellosis was excluded by clinical and laboratory findings and rheumatology consultation confirmed the diagnosis of SLE. According to the Systemic Lupus International Collaborating Clinics classification (SLICC) diagnostic criteria, the patient was diagnosed as SLE. The patient has received 1000 mg of methylprednisolone for 3 days followed by a treatment of 1 gr/kg (4 weeks). The treatment dose of steroid tapered gradually and slowly. Maintenance treatment of steroid continues with methylprednisolone at low dose of 10 mg/day. In addition to methylprednisolone, patient has received cyclophosphamide treatment (500 mg/m²) once a month intravenously. She responded well to high doses of corticosteroids, immunosuppressive treatment and regular rehabilitation programs. After follow-up for five weeks, she was discharged from hospital under appropriate medication without neurological deficits except the mild weakness at the foot dorsiflexion. Nerve conduction studies repeated 6 months after the first studies have shown values in normal range (Table 2).

	Distal Latency (ms)	Normal Range	Amlitude (mV, µV)	Normal Range	Conduction Velocity (M/S)	Normal Range
Ulnar(Motor) Wrist-ADQ Elbow-Wrist	2.6 5.8	≤ 3.3	9.7mV 9.0 mV	≥ 7.0	50.3	≥ 50
L Ulnar (sens) Digit 5-wrist	2.4	≤ 3.4	19.2 µV	≥ 10.0	47.5	≥ 37.5
L Median(mot) Wrist-APB Elbow-Wrist	2.6 7.1	≤ 3.8	5.4 mV 5.2 mV	≥ 5.0	52.9	≥ 49.7
LMedian (sens) Digit 2-wrist	2.6	≤ 3.4	19.6 µV	≥ 12.8	49.8	≥ 39.5
R peroneal Ankle-EDB Fib head-EDB	3.4 7.8	≤ 5.5	4.2 mV 3.9 mV	≥ 4.0	43.9	≥ 40.9
L peroneal Ankle-EDB	3.6	≤ 5.5	6.4 mV	≥ 4.0	43.2	≥ 40.9
Fib head-EDB	7.7		5.9 mV			
R Tibial Ankle-abd hal Knee-ankle	2.9 7.7	≤ 5.8	5.2 mV 4.9 mV	≥ 3.0	43.6	≥ 39.6
R Tibial Ankle-abd hal Knee-ankle	2.8 7.3	≤ 5.8	5.8 mV 5.3 mV	≥ 3.0	43.8	≥ 39.6
R Sural Calf-ankle	2.9	≤ 3.4	13.9 µV	≥ 10	40.8	≥ 33.8
L Sural Calf-ankle	2.6	≤ 3.4	9.8 µV	≥ 10	41.5	≥ 33.8

Table 2: Results of the motor and sensory nerve conduction studies 6 months after. Abbreviations: R: Right; L: Left; ADQ: Abductor Digniti Quinti; EDB: Extensor Digitorum Brevis; Fib: Fibula; abd hal: abductor hallucis, sens: Sensory; mot: Motor.

Discussion

Brucellosis is an endemic zoonotic disease caused by catalase and oxidase-positive, gram negative and unencapsulated coccobacillus [1]. Infection is often transmitted to humans by exposure to infected animal waste and unpasteurized milk and other dairy products. In our region the brucellosis is considered as an endemic disease due to the

fact that main occupation and source of income in the country region is the livestock [5]. Our patient is from the rural regions and the main occupation was the livestock; the patient had a previous history of working with cattle and sheep without wearing any protective means. In the light of the previous symptoms and patient's history despite the fact that the Wright agglutination test has come with a low positive titration patient has diagnosed with brucellosis.

Microorganisms may be taken in through injured skin or orally. The incubation period is usually 5-60 days but may extend up to several months. Afterwards, the bacteria settles in the nearest lymph node, blood, bone marrow, joints, nerves, brain or sexual organs and creates the disease [6]. The disease is characterized by non-specific symptoms such as fever, night sweating, anorexia, malaise and arthralgia. It may lead to complications affecting many systems and mimic many different diseases [1].

The diagnosis of brucellosis is made by clinical findings and laboratory tests. Such nonspecific laboratory findings as increased ESR, CRP, leukopenia/leukocytosis, thrombocytopenia/thrombocytosis, anemia and elevation of liver function tests may be monitored during different stages of the disease. Also, patients with brucellosis may suffer from high or subfebrile fever, night sweats, myalgia and weight loss [7].

Standard tube agglutination (Wright) test (SAT) is one of the most common serological tests used to diagnose the disease. This test was applied for the first time in 1897 by Wright [1,6]. Wright agglutination titers 1/160 or above are considered to be significant for active infection. The disadvantage of the test is its cross-reactions with antibodies against other gram-negative bacteria [8]. Also, this test sometimes is slightly positive in other diseases which mimic brucellosis clinically, such as malaria, non-Hodgkin's lymphoma and typhoid fever [9]. The Wright agglutination test was slightly positive (1/80) in our case.

A definitive diagnosis of brucellosis requires the isolation of the pathogen from blood, bone marrow and other body fluids. The culture isolation of brucella requires between 5-7 days. Especially in the early stages of the disease, there is a better chance of producing bacteria in cultures [10]. In our case bacteria was not detected in repeated blood, bone marrow and cerebrospinal fluid cultures.

Another diagnostic method is the screening of the genome of the bacteria by molecular methods. This method is more sensitive than culture isolation [11]. In our case, pathogen was not isolated by the PCR method.

Although the involvement of the musculoskeletal system has been reported in numerous studies, the prognosis of the disease is based on the extent of central nervous system damage. Central and peripheral nervous systems may be affected in both acute and chronic stages of disease. The symptoms of the disease are associated with a direct effect of bacilli, endotoxins and cytokines during the acute stage and immune related processes in the chronic stage of disease [3]. Neurological symptoms may be as non-specific as headache, dizziness and fatigue in the acute phase. Meningitis, meningoencephalitis, cranial nerve palsies, radiculoneuritis and peripheral neuropathies can be seen in 5-10% of patients in the chronic phase of the disease [12,13]. Peripheral nerve involvement is a rare complication of brucellosis. Clinical or subclinical involvement of peripheral nerves can be seen during the different phases of the disease. Polyradiculopathies, sciatic nerve involvement, lumbosacral neuritis, and acute or chronic polyneuropathies are examples of peripheral nervous system infiltrations. Purely motor, sensory or mixed manifestations have been reported in the previous studies [13].

After the beginning of antibiotic treatment, neurological changes are generally reversible. However, some authors have reported minor sequel [14,15]. It is well known that brucellosis may mimic many other diseases. Recent studies have drawn attention to the similarities between brucellosis and rheumatic diseases. In brucellosis, renal, skin

involvement and blood changes such as in rheumatic diseases can be seen [16-19]. Besides it is well known that antigens and antibodies like ANA and anti ds-DNA may appear and give positive serological results at the chronic stage of the brucellosis [20]. Thus further investigation realized for the differential diagnosis of brucellosis and SLE and as a result the previous misdiagnosis of brucellosis ruled out. SLE is an autoimmune disease characterized by multiple clinical manifestations [2].

The SLICC group revised and validated the American College of Rheumatology (ACR) SLE classification criteria in 2012 [4]. These criteria are divided into clinical and immunological criteria, and were used to diagnose our patient with SLE.

The frequency of neurological manifestations in patients with SLE ranges from 37- 90% [21].

The ACR has classified neuropsychiatric syndromes into three main categories: Diffuse psychiatric/neuropsychological syndromes; neurological syndromes of the central nervous system; and neurologic syndromes of the peripheral nervous system [22]. Although a central nervous system manifestation has been regarded as one of the main abnormalities of SLE, peripheral neuropathies are relatively rare, ranging from 10-21% [23]. Peripheral neuropathies in SLE may include axonal, sensory or sensory-motor polyneuropathy with acute or subacute onset, mononeuropathy multiplex, acute or chronic inflammatory demyelinating polyneuropathies, autonomic disorders and plexopathies [24-26].

In our case acute sensory motor axonal neuropathy was observed, which presented with bilaterally foot drop. In the literature, a few SLE patients have been reported as presenting with bilateral foot drop [25,27,28]. High-dose corticosteroids (methylprednisolone intravenous or oral prednisone), immunosuppressive (cyclophosphamide, methotrexate) and immune adsorption treatments are recommended [29]. Our patient responded well to high doses of corticosteroids, immunosuppressive treatment (intravenous cyclophosphamide) and regular rehabilitation programs.

Finally, many clinical and laboratory findings of brucellosis are similar to SLE. Thus, differential diagnosis of these diseases, which have very different treatment protocols, must be thorough especially in endemic areas for brucellosis.

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