CASE REPORT

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Vasculitic Neuropathy Secondary to Disseminated Brucellosis Manifesting as Bilateral Foot Drop

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Abstract

Brucellosis is a bacterial zoonosis of global concern prevalent in countries having major shares in the livestock segment. It is often underdiagnosed due to its misleading clinical picture. Half-a-million cases are estimated globally, with population at risk of 2.4 billion. The disease encompasses a wide spectrum of clinical manifestations involving many organ systems. Neurological involvement occurs in up to 10% of cases and is a rare sequelae of brucellosis. We present the case report of a 19-year-old lady with disseminated brucellosis who developed bilateral foot drop as a manifestation of vasculitic polyneuropathy.

Key words: Neurobrucellosis, foot drop, vasculitic neuropathy.

Introduction

Brucellosis is a zoonotic infection caused by bacteria of the genus *Brucella* and is a major public health concern in many parts of the world, including India where it is endemic in several states. It has a diverse range of clinical manifestations depending upon the organs involved. Common symptoms include fever, night sweats, chills, headache and musculoskeletal symptoms. Neurobrucellosis is a rare complication of Brucellosis that occurs in less than 5% of the patients with disease[1]. It is a severe and potentially life-threatening condition that affects both central and peripheral nervous systems affecting the brain, spinal cord, and nerves. Bacteria invade the nervous system through bloodstream or by direct extension from an adjacent infected area. Common symptoms include headache, fever, lethargy, depression, meningoencephalitis, intracerebral abscess, cranial nerve deficits, myelitis, and radiculitis. In severe cases, patients may develop seizures, coma or permanent neurological deficits.

The transmission of brucellosis occurs through direct or indirect contact with infected animals such as cattle, goats and pigs, or their derived products including milk, meat, cheese, or ice cream. Brucellosis is acquired by ingestion, inhalation, mucosal or percutaneous exposure. In India, where livestock sector is a significant contributor to the economy, prevalence of brucellosis remains high[2]. Close proximity of humans and animals, poor hygiene practices, and lack of awareness contribute to the spread of the disease.

As healthcare personnel, it is essential to recognise the clinical manifestations of brucellosis and to consider it in the differential diagnosis, especially in patients with a history of exposure to animals or their products. Pancytopenia, polyneuropathy, and foot drop, as observed in this case report, are rare presentations of brucellosis and require prompt evaluation and management.

Case report

A 19-year-old lady, presented to the emergency department with a history of fever and joint pains for two months associated with weakness of both lower limbs for 20 days. The fever was insidious in onset, intermittent in nature, initially low grade, which subsided with medication. However, for the past one month, the patient experienced high grade continuous fever (102° - 103° F) associated with chills, night sweats, and non-projectile vomiting. She also developed a reddish-pink maculopapular exanthem predominantly over the trunk. There was a history of generalised weakness, fatigue, headache, vomiting and shortness of breath on exertion. She also reported a four to five kilogram weight loss in the last two months. Joint pains predominantly involved both large and small joints symmetrically and were not relieved by rest. Weakness of both lower limbs developed insidiously, making it difficult for the patient to walk and perform daily household activities for the last 10 days. It was also associated with numbness in both feet. The patient had no significant past medical history or family history. The patient reported a history of exposure to domestic animals, which included cattle and she was actively involved in the care of these animals.

On physical examination, the patient was febrile (102° F) with pallor, tachycardia and level II, III, IV group of cervical

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lymphadenopathy. Her body mass index (BMI) was significantly low (15.6 kg/m^2). Musculoskeletal examination revealed acute, bilaterally symmetrical polyarthritis involving both large and small joints, predominantly hip and knee joints and flexion contracture of the lower limbs at hip and knee with bilateral foot drop (Fig. 1 and 2). On neurological examination, higher mental functions were normal. Motor examination revealed a flexion attitude at bilateral hip and knee joints with reduced bulk and tone in the bilateral lower limbs. Power was assessed around all joints and found to be in the range of 0/5 to 3/5 in all movements at the hip, knee and ankle joints. Sensory system examination revealed loss of both superficial and deep sensations in bilateral foot in a non-dermatomal fashion pointing towards polyneuropathy. All the sensations above the ankle joints were normal. There was no evidence of cerebellar, autonomic or meningeal involvement. Abdominal examination revealed mild epigastric tenderness. The liver was enlarged, non-tender, with a liver span of 15 cm, smooth surface, rounded margins and soft in consistency. The spleen was not palpable. The cardiovascular and respiratory systems were normal on examination.

Laboratory investigations (Table I) revealed severe anaemia with a haemoglobin level of 5.5 g/dL, leukocytosis with a total leukocyte count of 12.80 x $10^3/\mu L$, and a platelet count of 108 x $10^3/\mu L$. The reticulocyte production index was

Fig. 1: *Bilateral foot drop.*

Fig. 2: *Flexion contracture and deformity at bilateral hip and knee joints.*

calculated at 0.45, indicating reduced erythropoiesis. Tests for viral markers including HIV, HBsAg, and anti-HCV were negative, while serum erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) were found to be significantly elevated. Smear for malarial parasite, dengue serology, typhoid antibodies, anti-streptolysin O titres were negative and were done to rule out the sequelae of common tropical infections prevalent in our area. Liver and kidney function tests were unremarkable. A chest radiograph revealed areas of increased opacity in bilateral upper and middle lung zones. Ultrasound abdomen showed hepatomegaly (liver size 16.5 cm) and splenomegaly (spleen size 12.5 cm). She was started on intravenous ceftriaxone 1 gm 12 hourly, intravenous paracetamol 1 gm 8 hourly, proton pump inhibitors (PPIs) and intravenous fluids.

Her haemoglobin remained consistently low even after transfusing two units of packed cell volume with no improvement in fever spikes, and hence antibiotics were upgraded to intravenous piperacillin and tazobactam 4.5 gm 6 hourly on day four of admission, followed by the addition of intravenous vancomycin 1 gm 12 hourly on the sixth day. The patient developed blackish discoloration of the right great and second toes for which Doppler ultrasonography of the lower extremity arteries and coagulation profile were done and found normal except for D-dimer, which was significantly elevated (1,321 ng/mL, normal reference range: <250 ng/mL). The patient was treated along the lines of disseminated intravascular coagulation (DIC). Blood cultures and 2D echocardiography were done to rule out infective endocarditis and were unremarkable. By day 11, there was no progression in toe discoloration, and the coagulation profile was normal.

The patient continued to have fever spikes despite antibiotics. A contrast-enhanced computed tomography

(CECT) scan of the chest and abdomen was done to rule-out any collection or other sources of infection. CECT chest showed bilateral mild-to-moderate pleural effusion with underlying linear areas of atelectasis and ground-glass opacities in the posterior segment of bilateral upper, superior, and basal segments of bilateral lower lobes, along with multiple subcentimetric sized lymph nodes in the pre and paratracheal regions (Fig. 3 and 4). Bone marrow aspiration and biopsy were also conducted to investigate the possibility of tuberculosis, lymphoma, or haemophagocytic lymphohistiocytosis. However, the results were inconclusive, showing erythroblastopenia and a hypocellular marrow. The patient was continued on the same antibiotics.

Table I: Laboratory investigations of the patient on presentation.

Lab parameter	Observed value	Normal reference range
Haemoglobin	5.5 g/dL	11.0 - 16.0 g/dL
Total leukocyte count	12.80 x 10^3/μL	4.00 - 10.00 x 10^9/L
Absolute platelet count	108 x 10^3/μL	100 - 300 x 10^9/L
ESR	132 mm/1st hour	≤20 mm/hr
CRP	76.09 mg/L	<5 mg/L
Blood urea	57 mg/dL	10 - 50 mg/dL
Serum creatinine	0.5 mg/dL	0.7 - 1.3 mg/dL
Aspartate amimotransferase	41 U/L	Upto 40 U/L
Alanine amiontransferase	27 U/L	Upto 40 U/L
Alkaline phosphatase	67 U/L	39 - 117 U/L
Serum Protein	6.4 g/dL	6 - 8 g/dL
Serum Albumin	3.3 g/dL	3.8 - 4.4 g/dL
Total Bilirubin	0.7 mg/dL	0.2 - 0.8 mg/dL
Direct Bilirubin	0.2 mg/dL	0 - 0.2 mg/dL
Indirect Bilirubin	0.5 mg/dL	0.2 - 0.7 mg/dL
Anti-Streptolysin O titre	60 IU/ml	Less than 200 IU/mL

The patient's fever improved subsequently and touched baseline on day 21 of admission, and a repeat neurological examination showed improvement in power around bilateral knee and hip joints. But the patient still experienced difficulty walking without support. Further, a high stepping gait was observed in the right lower limb more than the left lower limb. A magnetic resonance imaging (MRI) scan of the spine and bilateral sacroiliac joints was done to rule out sacroiliitis or compressive neuropathy, which were unremarkable. Nerve conduction studies were performed and revealed prolonged latency and reduced amplitude of compound motor action potentials in bilateral tibial and peroneal nerves. Sensory nerve action potentials showed

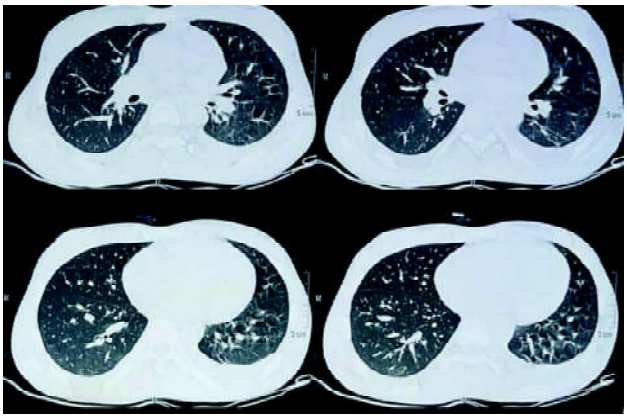

Fig. 3: *Bilateral mild-to-moderate pleural effusion with underlying linear areas of atelectasis and ground-glass opacities in the posterior segment of bilateral lower lobes.*

decreased amplitude and velocity with prolonged peak latency in bilateral sural nerves. F-wave latencies were prolonged in bilateral tibial and peroneal nerves. The results were consistent with bilateral sensorimotor polyneuropathy involving deep peroneal, sural, and tibial nerves.

Sural nerve biopsy was performed which revealed a florid acute axonal breakdown with perivascular and interstitial inflammation suggestive of inflammatory neuropathy consistent with vasculitic neuropathy. Based on her history and a strong clinical suspicion, Brucella serology titres were sent which revealed positive Brucella IgM antibodies with a value of 13.62 (reference positive was >11.0), and the patient thereafter was started on streptomycin 750 mg intramuscular (IM) once daily, oral doxycycline 100 mg twice daily and oral rifampicin 600 mg once daily. The patient was also started on oral prednisolone 40 mg once daily for one month and gradually tapered over the next two months. She remained afebrile and took discharge on request on oral rifampicin 600 mg once daily, oral doxycycline 100 mg twice daily, oral acetaminophen 650 mg once daily and oral iron supplementation. Antibiotics were continued for the next three months and regular physiotherapy was advised along with customised braces for foot drop.

Subsequently, cytopenias improved dramatically. The patient could walk without support after two months. The power of the muscles around bilateral ankle joints improved from 1/5 to 3/5 two months post-treatment. She continued to have right-sided foot drop after six months of therapy for which she was on regular physiotherapy. After one year of therapy, the patient completely recovered with no residual weakness or deformity. Hence, a final diagnosis of disseminated brucellosis was made. Various complications secondary to brucellosis were seen in our patient which included hepatosplenomegaly, lymphadenopathy

(reticuloendothelial), anaemia, leucocytosis, lymphopenia, thrombocytopenia, DIC (haematological), polyarthritis, flexion contracture (musculoskeletal), pleural effusion (pulmonary), foot drop and sensorimotor polyneuropathy (neurological).

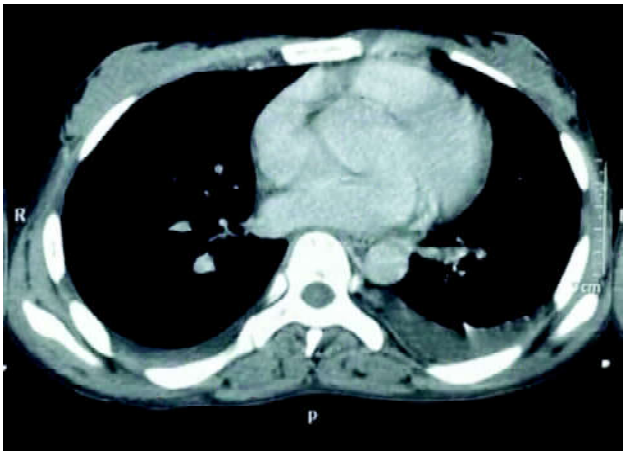

Fig. 4: *Multiple sub-centimetric sized lymph nodes in the pre and paratracheal regions.*

Discussion

Brucellosis is considered a difficult and deceptive disease in India, with musculoskeletal symptoms commonly observed and reported. Our patient showed signs and symptoms of disseminated brucellosis, including pleural effusion. There were haematological manifestations secondary to bone marrow suppression leading to anaemia, leucocytosis, thrombocytopenia, and DIC. The patient also showed signs of hepatosplenomegaly and lymphadenopathy with cutaneous involvement. Despite various case studies on brucellosis, neurobrucellosis remains a rarer manifestation of the disease.

The pathophysiology of neurobrucellosis, though not well studied, has three hypotheses. The first hypothesis suggests that the bacterium directly damages the nervous system. The second hypothesis proposes that the release of harmful cytokines or endotoxins by the immune system in response to the infection causes damage of nerves. The third hypothesis proposes that the inflammatory response mounted by the immune system to the Brucella antigen within the nervous system causes nerve damage[3]. In a large European case series, 82 patients had neurological involvement among 648 confirmed cases of brucellosis, with the most common manifestations being radiculopathies of the legs (41.46%), neck rigidity (46.34%), agitation (25.6%), behavioural disorders (18.3%), disorientation (19.5%) and stroke (1.22%). Cranial nerve involvement was also reported (24.4%)[4].

Foot drop and polyneuropathy are exceptionally rare presentations of neurobrucellosis. In a Turkish study by Inayat *et al*, foot drop was observed in only 0.09% of cases[5]. There are also case reports of permanent paralysis or hemiparesis secondary to brucellosis. Early diagnosis and prompt treatment play crucial roles in determining the prognosis of the disease in a patient. Neurological manifestations are likely to be reversed if diagnosed at an early stage. Doxycycline, rifampicin, and third-generation cephalosporins should be considered both standard and first choice medications for neurobrucellosis.

The diagnosis of brucellosis requires both clinical and serological aids. Common diagnostic tests include antibody detection against lipopolysaccharide, such as standard tube agglutination tests (SAT) and enzyme-linked immunosorbent assays (ELISA). Other tests include Brucella DNA detection by polymerase chain reaction, indirect immunofluorescence, the Wright agglutination test, the Rose Bengal test and bone marrow culture. Cerebrospinal fluid (CSF) Brucella antibody titre is an important diagnostic modality besides culture. CSF Brucella titres >1:8 demonstrated a sensitivity of 94% and a specificity of 96%[5].

The recommended treatment for uncomplicated brucellosis in adults is a combination of doxycycline and an aminoglycoside, with doxycycline-rifampicin and doxycycline- cotrimoxazole serving as alternative regimens. Quinolones may also be considered. For children under eight years old, cotrimoxazole plus rifampicin administered for six weeks may be the optimal treatment choice. For complicated cases or neurobrucellosis, a triple drug regimen of ceftriaxone-rifampicin-doxycycline is given in non-pregnant adults, while in pregnant women, ceftriaxone-rifampicin-cotrimoxazole is used. The duration of therapy is extended for four to six months in cases of meningitis or endocarditis. The use of corticosteroids can be a double-edged sword since the pathogenesis of polyneuropathy can be multifactorial, including sepsis, multiorgan failure, vasculitis, systemic inflammatory response syndrome (SIRS), malnutrition, prolonged immobilisation, critical illness polyneuropathy, or a deranged metabolic profile. In this case, the patient responded well with an improvement in disability.

The relapse rate after treatment for brucellosis ranges from 5 to 15 per cent[6]. Typically, relapse occurs within the first six months after the completion of treatment, although it can occur up to 12 months later. There are various causes for the same, like an inadequate antibiotic regimen or duration of therapy, a lack of adherence, or localised foci of infection. Hence, regular follow-up, at least for two years from the time of diagnosis is crucial.

Various ways to prevent brucellosis include avoiding

unpasteurised dairy products, wearing protective clothing, washing hands thoroughly after handling animals or animal products and vaccinating animals, particularly livestock against brucellosis. Thus, by educating individuals who are at risk of contracting the disease, the disease burden can be reduced thereby limiting its spread. The response to treatment can take time, as seen in this case, but nonetheless with appropriate testing and treatment, this uncommon complication was managed.

Conclusion

India comprises one of the largest livestock population in the world and brucellosis is a common and often neglected zoonotic disease. It must be considered as an important differential diagnosis in pyrexia of unknown origin and polyarthralgia. It often mimics the signs and symptoms of tuberculosis and hence often missed by the physicians. Importantly, neurobrucellosis is a rare but a lethal complication of brucellosis, manifestations ranging from cranial nerve palsies and neuropathies to fatal strokes.

Timely identification, swift diagnosis and rapid intervention can prevent irreversible manifestations of brucellosis. It is recommended to encourage active collaboration between health and veterinary services. At the same time, it is crucial to be aware of its clinical manifestations, modes of transmission and treatment options. Improving awareness among the general population, implementing effective control measures in the livestock sector and strengthening diagnostic and treatment facilities can help reduce the burden of brucellosis in India.

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