Acute Ischemic Stroke as a Presenting Feature of Brucellosis: A Case Report

Sir,

Brucellosis is a zoonotic disease caused by a gram-negative bacterial genus called “Brucella.”[1] It is transmitted to humans from infected animals mainly through food consumption (unpasteurized milk or cheese), contact of body fluids, tissues and, to some extent, by inhalation of aerosolized particles. Brucellosis presents with prolonged fever and other non-specific symptoms (headache, dizziness, arthralgia, night sweats). It is also called “Undulant fever” and “Malta fever” due to its remitting character.[2] People who are most likely to get exposed to infected animals are farmers, shepherds, dairy production personnel and veterinarians. The major prevalence is noted in countries like Mexico, Central and South America, Peninsula and Mediterranean areas whereas India and other developing countries are affected but to a lesser extent.[1]

Brucellosis is a systemic disease that can develop multi-organ complications. Among all cases of brucellosis, 30% patients develop focal complications, only 2% develop cardiac involvement (Brucella endocarditis),[3] only 2–6.5% present with CNS involvement (neuro-brucellosis, meningoencephalitis, ischemic stroke)[4] and very rarely it can cause vascular complications (arterial aneurysm, arterial thrombosis, deep vein thrombosis, cerebral vein thrombosis).[5]

We report a case of Brucella endocarditis with concomitant embolic stroke and acute arterial thrombosis who was successfully managed by long-term antibiotics, valve replacement surgery, and anticoagulation.

A 27-year-old male shepherd presented with sudden onset right upper limb and lower limb weakness with excruciating...
pain in the left lower limb. He had a preceding history of fever, chills, and generalized weakness for 20 days. General physical examination revealed moderate pallor with clubbing of digital nails. A regular right radial pulse with a blood pressure recording of 120/80 mm Hg was noted. All other peripheral pulses were normally palpable except left popliteal and dorsalis pedis pulse, which were not palpable. Neurologic examination revealed right-sided hemiparesis (power - right upper limb 3/5 and right lower limb 4/5 in all joints). Cardiac examination revealed a laterally displaced hyperdynamic apex beat with precordial pulsations. A holosystolic murmur in the mitral area was audible radiating up to the axilla suggestive of mitral valve regurgitation.

Pertinent laboratory reports were suggestive of leucocytosis, microcytic hypochromic anemia (hemoglobin 8.6 gm/dl), hypoalbuminemia (serum albumin 2.3 gm/dl), raised erythrocyte sedimentation rate (ESR) (65), normal creatinine, hematuria (1+), and proteinuria (1+). His magnetic resonance image (MRI) brain revealed acute left parietal region infarct with normal intracranial and neck vessel angiography. His 2D echocardiogram revealed severe mitral regurgitation with moderate mitral stenosis, with two large-sized (12 mm and 16 mm) vegetations in the tip and mid-body of the posterior mitral leaflet. Left lower limb arterial doppler study revealed complete thrombotic occlusion of the deep femoral artery (See Figure 1). Two blood cultures revealed Brucella melitensis growth after 72 hrs of aerobic incubation. Brucella antibody titres revealed Brucella IgG and IgM antibody titres greater than 1:160.

He was treated initially with empiric intravenous ceftriaxone 2 gm 12 hourly and gentamicin 3 mg/kg/day for 2 weeks. Once the blood culture was positive for Brucella, treatment with oral rifampicin 600 mg/day and doxycycline 100 mg/day for 6 weeks were initiated. He underwent mitral valve replacement surgery with removal of vegetation due to persistent fever, large vegetation, distal embolization, and persistent bacteremia. He gradually recovered with rehabilitation (modified Rankin scale 1 at 90 days). He was treated with oral anticoagulation with warfarin to keep prothrombin time (PT) 2.5 to 3.5 international normalized ratio (INR) post valve replacement surgery for secondary prevention of recurrent embolism.

Brucella endocarditis (BE) is a rare but severe complication of brucellosis, which requires appropriate treatment and extensive follow-up as it is responsible for up to 80% of deaths.[1] Prosthetic and abnormal valves are most commonly affected but native valves can also be affected (as seen in our case). Even with high clinical suspicions like prolonged fever, history of animal contact, and valvular vegetations on echocardiogram, it is not easy to diagnose BE due to low specificity of serological testing, isolation technique limitations, and high chances of negative culture results (mostly due to previous antibiotic exposures).[1,6] Certain complications like a myocardial abscess, left ventricular failure, septic embolization to other organs might be seen during BE[1] which can very well be prevented by initiating appropriate antimicrobials early.[7] Antimicrobials for brucellosis should be able to work in an acidic medium and penetrate the macrophages.[8] Monotherapy for less than 6 weeks is not advisable as it can lead to a higher relapse rate.[9] Therefore, WHO in 1986 recommended combination therapy with doxycycline and rifampicin for 6 weeks which was later replaced by a combination of tetracycline and streptomycin. Amongst different treatment combinations, WHO recommended that doxycycline and rifampicin combination (100 mg and 600 mg respectively for 6 weeks) is more favorable due to easy administration, cost-effectiveness and less adverse effects (ototoxicity and nephrotoxicity) as compared to aminoglycoside, but sometimes gentamicin (3 mg/kg for 2 weeks) can also be added in the treatment of Brucella endocarditis.[1,9] Medical treatment alone is suggested for cases with less cardiac involvement and no prosthetic valve[4,10] whereas medical treatment along with valve replacement surgery is the best treatment of choice in patients with severe cardiac involvement.[10] There are 16 cases of Brucella endocarditis reported with valvular involvement that were managed with only medical treatment and none of them had severe valvular involvement or other complications.[1]

It is rare for brucellosis to present with cardiac involvement but even rarer for BE to present with another system involvement like the central nervous system (CNS). To our knowledge, there are only four cases of Brucella endocarditis reported in the medical literature with ischemic stroke[3,4,11,12] and only two cases with peripheral artery involvement[5,10] (Table 1 for details). Our patient presented with BE with embolic ischemic...
stroke and concomitant acute peripheral arterial thrombosis, due to septic embolization to the brain and limb artery. In this regard, our case is unique as it had three systemic complications in a patient with brucellosis infection.

There are high chances of embolization during the first few days of antibiotic initiation (especially first 2 weeks) in IE. Administration of antiplatelet therapy does not reduce the risk of embolization in endocarditis patients. Using anticoagulation in patients with IE can be a double-edged sword. While anticoagulation is reported to be beneficiary in IE in presence of large vegetation (>10 mm), mitral valve involvement, atrial fibrillation or distal embolization, it is contraindicated in the other end in presence of acute ischemic stroke (for 2 weeks) for increased risk of hemorrhagic transformation of infarct and fresh hemorrhage due to mycotic aneurysms. This controversy in management has been noted in previous case reports of Brucella endocarditis, too. In one case of ischemic stroke, anticoagulation use was deferred following risk-benefit ratio analysis due to high risk of intracerebral hemorrhage whereas in another case, anticoagulant heparin was initiated immediately following ischemic stroke confirmation. Similar controversy exists in the management of BE patients with peripheral arterial thrombosis. One case reported with arterial thrombosis was treated with only medical management with classical regimen (rifampicin plus doxycycline plus trimethoprim-sulfamethoxazole) and additional acetylsalicylic acid whereas another case was treated with anticoagulant heparin for 10 days.

No consensus exists currently on the timing of initiating anticoagulation in IE in presence of cardio-embolic ischemic stroke. It is hypothesized that anticoagulants may not only reduce the risk of embolic events secondary to damaged heart valves but may also lead to reducing the size of vegetation as the vegetation as well as embolus have been found to consist of bacteria, fibrin, platelets, damaged tissues, and it is plausible for an anticoagulant to exert protective effect. Recent studies not only indicated an overall low risk of intracerebral hemorrhage due to warfarin but also a low incidence of ischemic stroke in IE patients taking anticoagulant. Our patient already had 2 embolic events and his left lower limb was at risk of gangrene in the absence of anticoagulation. Therefore, we decided in favor of initiating anticoagulation despite the risk of hemorrhagic transformation after discussion with the patient and family members.

Habib et al. have reported a better success rate in preventing embolic events by early surgical replacement of affected valve (within 2 weeks). Other indications of early surgical valve replacement in IE include large vegetation (>10 mm), regurgitant lesions, persistent bacteremia and distal embolization. Our case had all the above features and therefore, he required mitral valve replacement surgery, too in addition to antibiotics and anticoagulation. With the combination therapy, our patient had a good outcome despite all the complications and challenges in the care.

In conclusion, all patients with chronic fever should be thoroughly screened for brucellosis as well as endocarditis, especially when chronic contact exposure with farm animals is identified. Treatment of Brucella endocarditis with medical or surgical intervention should be prioritized based upon the degree of cardiac involvement, risk-benefits of using anticoagulation before and after embolic events should be assessed and patients should be managed appropriately to successfully prevent future embolization catastrophe.

**Declaration of patient consent**

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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**Conflicts of interest**

There are no conflicts of interest.

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**Table 1: Published Cases of Brucellosis Endocarditis with Embolic Stroke in the Literature**

| No | Age (years)/Gender | Symptoms | Valve affected | Imaging findings | Treatment | Reference |
|----|-------------------|----------|----------------|-----------------|-----------|-----------|
| 1  | 29/Male           | Right hemiparesis | Aortic valve | Left middle cerebral infarct | Doxycycline/rifampin/co-trimoxazole + valvular surgery | [3] |
| 2  | 35/Male           | Right hemiparesis with aphasia | Aortic valve and mitral valve | Left middle cerebral infarct | IV gentamicin, oral rifampin and oral doxycycline + valve replacement | [4] |
| 3  | 79/Female         | Left ataxic hemiparesis | Aortic and mitral valve | Left cerebellar infarct | Doxycycline, rifampicin, trimethoprim-sulfamethoxazole, gentamicin | [12] |
| 4  | 56/Male           | Right hemiplegia with sensory loss | Mitral valve and tricuspid valve | Left thalamo-capsular infarct | Doxycycline, rifampicin and co-trimoxazole with mitral valve replacement | [13] |

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*Letters to the Editor*
A case of Brucella endocarditis in association with subclavian artery thrombosis

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Letters to the Editor

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