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"BRUCELLA ENDOCARDITIS INVOLVING NATIVE AORTIC VALVE: 2 CASE REPORTS AND REVIEW OF LITERATURE"

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ABSTRACT **Introduction:** Brucellosis is a zoonotic disease commonly found in the Mediterranean, Middle Eastern, and Southeast Asian regions. It is caused by bacteria of the genus Brucella and can be transmitted to humans from infected animals. Despite its rarity, the association of endocarditis with brucella infection (1-2% of cases) emphasizes the importance of considering brucellosis in the diagnosis of infective endocarditis, particularly in regions where the disease is endemic. Early recognition is key for appropriate management. The primary culprits in human brucellosis are Brucella melitensis, B. Abortus and B. suis, with B. canis being less common. Successful management of Brucella endocarditis typically involves a combination of medical and early surgical therapy for optimal outcomes. Early intervention is crucial in addressing the complexities associated with brucellosis-related endocarditis. **Case report:** We report two cases with brucella endocarditis developed on native aortic valve. The diagnosis of Brucella endocarditis in the reported cases was confirmed by positive blood cultures, serology, and the isolation of Brucella melitensis from the excised valve tissue. This multidimensional confirmation approach enhances the accuracy of diagnosis in cases of brucellosis-related endocarditis. **Conclusion:** Aortic valve involvement is often observed in Brucella endocarditis, and it remains the most common cause of death associated with the infection. The high mortality rate can be mitigated through early diagnosis and aggressive management. In the reported cases, endocarditis was the initial presentation without involvement of other organs, highlighting the importance of vigilance in detecting and treating brucellosis-related cardiac complications early.

KEYWORDS : Brucella endocarditis, Aortic valve, Brucella melitensis

INTRODUCTION:

Brucellosis is a zoonotic disease, and it is endemic to regions such as the Mediterranean, Middle Eastern, and Southeast Asian areas. The disease is transmitted from animals to humans, and awareness is crucial in these regions for effective prevention and management.[1] Brucellosis is caused by infection with Gram-negative coccobacillary organisms belonging to the Brucella family.

The primary mode of transmission to humans is through contact with fluids from infected animals and their products, with unpasteurized milk or milk products being a common source. Taking precautions in handling and consuming such products is crucial to prevent brucellosis transmission.[2] The three most common agents causing human brucellosis are Brucella melitensis, B. abortus, and B. suis. B. canis is less frequently involved in causing the infection. Being aware of these bacterial species is essential for accurate diagnosis and effective management of brucellosis cases.[4,5] The strains most frequently implicated with Brucella endocarditis are Brucella melitensis and B. abortus. These species of Brucella are more commonly associated with cardiac complications. Understanding the specific strains involved is crucial for targeted diagnosis and treatment in cases of brucellosis-related endocarditis.

Among the bacteria in the genus Brucella, B. melitensis is known for having the highest virulence and is associated with the most severe form of brucellosis in humans. This species tends to result in more significant clinical manifestations and complications compared to other Brucella species. Understanding the variations in virulence among Brucella strains is important for managing and treating brucellosis effectively.[6,7]

The clinical spectrum of human brucellosis is diverse, ranging from in-apparent or asymptomatic infection to severe disease with life-threatening complications. While Brucella endocarditis is a relatively rare occurrence (1-2% of cases), it plays a significant role in the mortality associated with brucellosis, accounting for up to 80% of Brucella-related deaths.[3] Aortic valve involvement is frequently observed in Brucella endocarditis, making it a critical and potentially fatal complication of the infection. Early diagnosis and management are essential in addressing these serious manifestations of brucellosis.[8,9]

We report two cases of Brucella endocarditis developed on a native aortic valve.

Case report-1:

A 50-year-old male farmer presented with the complaints of sudden onset breathlessness, chest pain, fever, chills, and rigors. His vital signs include a pulse rate of 80/min and blood pressure of 90/60mmHg. The presence of diastolic murmur in the pulmonary area on cardiac examination raised suspicion of a cardiac-related issue. Further diagnostic evaluation, including imaging and blood tests, was performed to determine the underlying cause and guide appropriate management.

Patient was initiated on Intravenous Magnex (cefperazone and sulbactum) 2gm every 8 hours and Intravenous Gentamicin 80mg every 8 hours after blood cultures were sent for suspected infective endocarditis. The Transesophageal Echocardiography (TEE) revealed calcific aortic valve with severe aortic regurgitation is significant. There were no vegetations, clots, or pulmonary embolism is notable but doesn't rule out infective endocarditis entirely. Further clinical correlation and monitoring were done.Computed Tomography (CT) angiogram of thoracic aorta showed severe aortic valve stenosis with LV hypertrophy. 11.9x19.7x17mm unruptured aneurysm arising from right sinus of valsalva was observed. Blood cultures sent to microbiology laboratory were sterile after five days of incubation.

The intraoperative findings during the surgical correction of the aneurysm and aortic valve stenosis by Bentall's procedure revealed significant cardiac involvement. Cardiomegaly was observed, with dilation of the right atrium, right ventricle, and left ventricle. The aortic valve exhibited thickening, severe aortic regurgitation, and vegetations over the valve, particularly in the commissural region between the right and left aortic cusps. There was an abscess cavity extending onto the left ventricle, and vegetations were present in the non-coronary aortic cusp region burrowing onto the right atrium. Aortic valve replacement was performed with a 21mm Biocor aortic valve. Postoperative care and monitoring were crucial for the patient's recovery.

The post-surgery repeat blood cultures and aortic valve tissue confirmed the presence of Brucella melitensis, emphasizing the importance of ongoing monitoring. The positive serum agglutination test (SAT) at a dilution of 1:320 further supports the diagnosis. Tablet Magnex was discontinued, and Tab Doxycycline was initiated at 100mg orally twice a day. Gentamicin was continued. The patient was successfully discharged in stable condition, continuing the prescribed therapy. Patient follow-up was done for 2 years and no complications were observed.

Case report-2:

A 40-year-old male farmer, presented with the complaints of fever, sudden onset of exertional breathlessness (NYHA II-III), and chest pain. The auscultation revealed an ejection systolic murmur in the aortic area and mid-diastolic murmur in the mitral area. 2D ECHO showed severe aortic regurgitation and a large vegetation on the aortic leaflet, strongly suggesting infective endocarditis of the aortic valve.

Given the patient's history of smoking and alcohol use, a comprehensive management plan, including antibiotic therapy and surgical intervention, was initiated.

The intraoperative findings showed congenital rheumatic heart disease (CRHD), severe aortic regurgitation (AR), and post-infective endocarditis (IE). The extensive involvement included cardiomegaly, left ventricular dilatation, dilated pulmonary artery, aortic dilation, bilateral pleural effusion, and moderate pericardial effusion. Notably, a large vegetation was identified on the right coronary cusp and non-coronary cusp, measuring about 1 cm x 1 cm. The valve tissue isolation of B. melitensis from the microbiology laboratory highlights the infective nature of the condition. The aortic valve replacement with a 23mm SJM non-rotatable valve. Close postoperative monitoring and appropriate antibiotic therapy facilitated uneventful patient's recovery.

Initiating Tab Doxycycline 100mg orally and Injection Gentamicin 80mg intravenously every 8 hours, along with conservative therapy, was a prudent choice for treating Brucella melitensis infective endocarditis. The microbiological workup, including blood cultures and excised valve tissue, confirmed the presence of B. melitensis. The efficient detection of Gram-negative coccobacilli in blood cultures, subsequent subculturing, and identification using the Vitek 2 system further characterized the organism. The routine antibiotic susceptibility testing is not needed due to the rarity of resistance plasmids in Brucella. Serological diagnosis, employing the standard tube agglutination test (SAT), confirmed the presence of antibodies against B. melitensis at a significantly high titer (≥1:320). Patient was discharged in stable hemodynamic condition. 2 year postoperative follow up showed no recurrence.

DISCUSSION:

Brucellosis, caused by the intracellular α2 proteobacteria gram-negative bacillus in the genus Brucella, has become the predominant infectious disease among zoonoses. Its transmission to humans often occurs through the consumption of infected, unpasteurized animal milk or direct contact with infected animals, particularly during events like handling aborted fetuses. The disease is more prevalent in rural areas, as observed in both cases where patients had a history of occupational exposure to cattle and hailed from rural regions. Definitive diagnosis involves considering the clinical presentation, repeated blood cultures, and serological tests. In our cases, the diagnosis was supported by clinical observations, positive serology tests, echocardiographic evidence of vegetations on the aortic valve, and the isolation of Brucella melitensis from both blood cultures and the excised valve tissue.

Brucella endocarditis is a rare but serious complication of brucellosis, contributing significantly to the mortality associated with the disease. While the overall mortality due to brucellosis is low (<1%), endocarditis is responsible for the majority of deaths (80%).[10] Cardiovascular complications in brucellosis encompass various issues such as endocarditis, myocarditis, pericarditis, aortic root abscess, thrombophlebitis leading to pulmonary aneurysm and pulmonary embolism.

The aortic valve is particularly prone to involvement, and cases may present with aortic root abscesses or aneurysms in up to 45% of cases.[10] The intracellular nature of Brucella poses a challenge for antimicrobial treatment as these agents struggle to penetrate eukaryotic cells where the bacteria reside. The microbe's tendency to cause tissue destruction, progressive ulceration, and an increased risk of embolism further complicates the management of Brucella endocarditis.[16]

The World Health Organization (WHO) recommends a combination treatment for acute brucellosis in adults, involving rifampicin at a dose of 600 mg and doxycycline at a dose of 100 mg. This combination therapy is typically prescribed for a minimum duration of 6 weeks. Adherence to the recommended treatment duration is crucial to ensure effective eradication of the Brucella infection and prevent relapses. [12]

In cases of Brucella endocarditis, the addition of Gentamicin at a dose of 3 mg/kg in 3 divided doses is a consideration for a duration of 2 weeks. Jacobs et al recommend a combination of antibiotic administration along with valve replacement as the most effective therapy. This multidimensional approach is often necessary to address the complexities of Brucella endocarditis and improve patient outcomes.[13]

It is noteworthy that in another study, 15 patients with Brucella endocarditis were successfully cured by medical treatment alone.[14] This underscores the potential effectiveness of antimicrobial therapy in certain cases, highlighting the importance of individualized treatment approaches based on the specific clinical scenario and patient response.

It is important to avoid single antibiotic therapy in order to minimize the risk of resistance development. Authors often recommend combining antibiotics like rifampicin and/or co-trimoxazole with doxycycline at higher dosages for effective treatment [9,13].

While some cases of Brucella endocarditis have been successfully treated with antibiotics alone, urgent or emergency cardiac surgery is generally required due to the potential progression of the infectious process leading to medically uncontrollable congestive cardiac failure. Surgery becomes necessary when conservative therapy fails over a reasonable period, especially in the presence of a hemodynamically significant valve lesion. However, in a report by Cohen et al 1 patient and 12 other patients in literature were cured by antibiotic therapy alone. [11]

The therapeutic approach in the described cases involved surgical treatment, specifically aortic valve replacement, along with antibiotic therapy. The antibiotic regimen included oral doxycycline 100 mg BD for a duration of 6 weeks and intravenous Gentamicin 80mg IV 8th hourly for 3 weeks, resulting in successful treatment. This combination allowed for stable discharges and positive outcomes in both cases.

The literature reveals a wide range in the duration of postoperative antibiotic therapy for Brucella endocarditis after surgery, ranging from 2 weeks to over a year. However, there is a consensus suggesting a minimum treatment period of at least 3 months post-surgery [15]. In our cases, postoperative antibiotic therapy was extended to 6 months, and fortunately, there were no relapses during the six-month follow-up period.

CONCLUSION:

Brucellosis presents a diagnostic challenge and is frequently under-diagnosed due to a lack of awareness. Clinicians, particularly in endemic regions, should approach the diagnosis of infective endocarditis with high suspicion for Brucella endocarditis. Early diagnosis is crucial for prompt and successful management of this infectious disease. In our cases, where endocarditis was the sole initial presentation without organ involvement, immediate surgical treatment followed by antibiotic therapy proved effective in successful management.

Financial Disclosure

Authors have no financial interests related to the material in the manuscript.

Conflict of interest:

The authors declare that they have no conflict of interest.

Compliance with Ethical standards:

The study is not funded by anyone and all procedures performed in the study were in accordance with the ethical standards of the institute and with the 1964 Helsinki declaration and its later amendments. Informed consent was obtained from all individual participants included in the study.

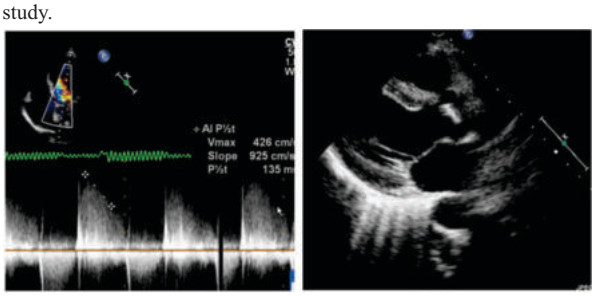

Figure-1: a)Transthoracic doppler signal showing severe aortic regurgitation b)Transthoracic echo showing large vegetation over aortic valve

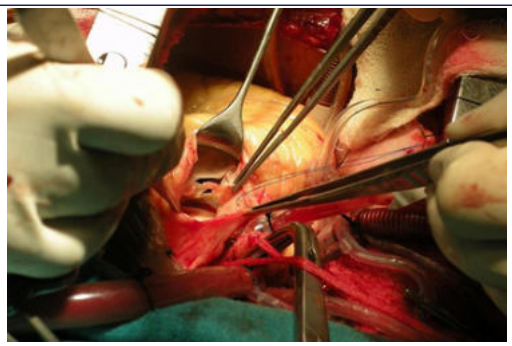

Figure 2: Intra operative photo with vegetations over aortic valve

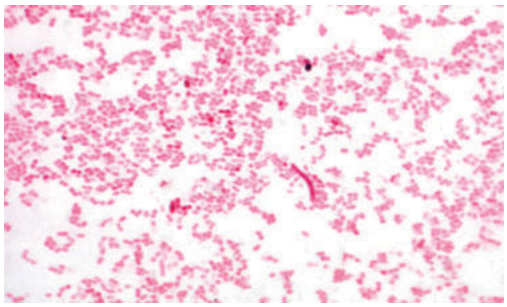

Figure:3 Grams stain showing Gram negative coccobacilli of B. melitensis

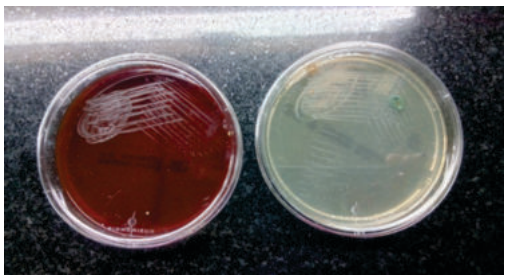

Figure:4 Colony morphology of *B. melitensis* on Blood agar and Chrome agar plates with pin point shiny grey colonies

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