Case Report

Combined *brucella melitensis* and *streptococcal viridans* endocarditis

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ABSTRACT

Infectious endocarditis is a potentially lethal inflammation of the hearts' inner lining invaded by microorganisms. The mortality from this illness increases as the number of infective organisms rises to 2, due to involvement of the left side of the heart. These microorganisms usually arise from the patient's own flora but can be acquired from the environment. Fever and heart murmurs are the principal clinical manifestations followed by a plethora of peripheral signs due to dissemination of microorganisms via the bloodstream. Echocardiographic imaging and sensitive culture techniques form the cornerstone of diagnosis. We report a patient with rheumatic heart disease who had combined *brucella melitensis* and *streptococcus viridans* endocarditis complicated by heart failure and an aortic root abscess. He was diagnosed on the basis of a history of prolonged fever and occupational risk as a shepherd, the presence of heart murmurs, positive blood cultures and echocardiographic evidence of aortic vegetations. He had an excellent response to intravenous antibiotic therapy combined with aortic valve replacement, which nowadays is regarded as the safest therapeutic approach for aortic valve endocarditis.

Keywords: Infective endocarditis, *brucella melitensis, streptococcus viridans*.

Saudi Med J 2002; Vol. 23 (1): 99-103

The current incidence of infective endocarditis (IE) is estimated as 7 cases per 100,000 population per year and continues to rise.[1] Surveys have indicated that up to 92% of cases of IE could be attributed to a dental origin.[2] At present mitral valve prolapse, degenerative valvular disease and rheumatic heart disease remain the most common predisposing conditions of IE and *streptococcus viridans* remains the most common cause of prosthetic and native valve IE.[3] Infective endocarditis due to brucella orgsanisms is a rare complication of brucellosis but the main cause of death related to this disease.[4] In this report we describe the diagnosis and management of combined infection with these organisms in our patient.

Case Report. ***Combined brucella melitensis and streptococcus viridans endocarditis.*** A 45-year-old Sudanese shepherd presented to the Accident and Emergency Department of Riyadh Medical Complex, Kingdom of Saudi Arabia in August 1999 complaining of generalized tiredness, fever and shortness of breath on exertion for the last 3 months. The dyspnoea was now present at rest and the fever had intensified over the week prior to his presentation. Six months ago he had been diagnosed to suffer from brucellosis and had been treated with a combination of tablets and injections for 6 weeks. Apart from several episodes of malaria in his home country of Sudan his past medical history was unremarkable, a history of rheumatic fever could not be obtained. He did not suffer from any allergies and was currently on paracetamol as the only medication. There were no chronic illnesses in his immediate family. He was the father of 4 children and had worked in the Kingdom of Saudi Arabia for the last 3 years as a shepherd for camels, drinking raw milk and handling them unprotected. The patient denied

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Received 22nd January 2001. Accepted for publication in final form 27th August 2001.

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any chest-pain or skin rash. Physical examination revealed a gravely ill looking patient with a temperature of 38°C, a collapsing pulse with a rate of 112/min, a blood pressure of 110/50 mmHg and a respiratory rate of 25/min. Notable was his pallor and the absence of any peripheral signs of endocarditis. Poor dental hygiene was present.

On examination of the cardiovascular system the jugular venous pressure was not raised, but the apex beat was shifted to the 6th intercostal space, there was an S3, a soft A2. Murmurs of a mitral regurgitation grade 3/6 and aortic regurgitation grade 3/6 were readily detectable. Inspiratory crackles were audible at the lung bases. Examination of the abdomen revealed no organomegaly and his central nervous system examination was normal. Urinalysis revealed microscopic haematuria with 8-12 red blood cells/high power field (HPF). The full blood count on admission showed a white blood cell count of 4.5 with normal differential and a hemoglobin level of 7.9g/dl, hematocrit 24.6, mean corpuscular volume 86.3, mean corpuscular hemoglobin 26.8 and a platelete count of 160 with an erythrocyte sedimentation rate 135 mm/first hour. Urea and electrolytes revealed a raised urea of 8.9 mmol/l and creatinine of 128 micromol/l with normal electrolytes and cardiac enzymes. Liver function tests apart from a raised alkaline phosphatase (ALP) 231 u/l were normal. Coagulation profile was normal. Serology showed a positive rheumatoid factor of 320 IU/ml, C-reactive protein of 12.8 mg/dl, and a *brucella melitensis* serum agglutination test (SAT) titre of 1/1280. *Brucella abortus* SAT titre was negative.

Blood cultures grew brucella species (sensitive to tetracycline, chloramphenicol, ciprofloxacin and imipenem with resistance to cotrimoxazole) and *streptococcus viridans* (sensitive to penicillins, cephalosporins, and erythromycin).

Electrocardiography showed sinus tachycardia and left ventricular hypertrophy by voltage criteria. The chest radiograph revealed left ventricular hypertrophy with pulmonary congestion. Echocardiography with color doppler showed dilated left atrium and ventricle with a left ventricular ejection fraction of 57% and a large vegetation on the right aortic valve cusp measuring 13.7 mm x 11.9 mm and a small vegetation on the posterior mitral leaflet. The patient was admitted with a diagnosis of IE complicated by left ventricular failure and commenced on penicillin G 4 million units intravenously every 6 hours and gentamicin 80 mg intravenously once daily along with medication to control his heart failure pending the result of an urgent transthoracic echocardiogram (TTE) since the probability of a *brucella endocarditis* (BE) was high. Following the finding of a large vegetation, the previous history of treatment for brucellosis and given his continued occupational risk, the treatment was revised on the 2nd hospital day and the patient was started on ampicillin 2 grams intravenously every 4 hours, streptomycin 750 mg intramuscularly daily, rifampicin 600 mg orally daily and doxycycline 100 mg orally twice daily. A dental referral confirmed the presence of advanced dental caries. The first blood culture was reported as growing *streptococcus viridans* on the 5th hospital day sensitive to the given antibiotics, followed on the 7th hospital day by a positive blood culture for brucellosis. A repeat TTE on the 10th hospital day revealed the vegetation on the aortic valve to be 8.3 mm x 15.5 mm in size, the vegetation on the posterior mitral leaflet was not seen anymore.

On day 28 of hospitalization the patient could be transferred to a tertiary care facility where repeat TTE confirmed the presence of only an aortic valve vegetation. The patient was subjected to a cardiac catheterization after which he underwent an aortic valve replacement with a size 25 free style stentless xenograft from Medtronic implanted as a full aortic root. Intraoperatively it was found that the aortic valve was thickened showing the typical appearance of a severe rheumatic valvulitis. There was a bicuspid rheumatic valve with rudimentary commissure. In addition there was the beginning of an abcess at the area below the commissure between the left and right coronary sinus. Transoesophageal echocardiography (TEE) postoperatively revealed a well functioning bioprosthesis with no aortic valve regurgitation. On the 32nd hospital day he was returned to Riyadh Medical Complex and continued on the same antibiotic regimen.

He was discharged in good health 2 weeks later on ampicillin 1 gm orally 4 times daily for one month, rifampicin 600 mg orally OD and doxycycline 100 mg orally 3 times daily which were to be continued for 2 months. On follow up 6 months and one year later the patient remained well with good prosthetic valve function, blood cultures remained negative, and his SAT titre for *brucellosis melitensis* was 1:320 at one year.

Discussion. The physical presence of inflammation inducing microorganisms in the endocardium defines the term IE.[5] The classification of IE based on the etiologic agent is the most logical approach since it gives an immediate outlook on the prognosis and course of the disease.[6] Since the etiologic agent is commonly inferred from the clinical presentation, the terms acute and subacute IE remain useful in our view, in the absence of nonbacterial endocarditis and polymicrobial infections. Spontaneous endocarditis was a term used most commonly with *streptococcal viridans* infections derived from the oral flora and occurs in 50% of the cases in previously damaged valves, yet only a minority of patients have a recent history of dental manipulation.[6]

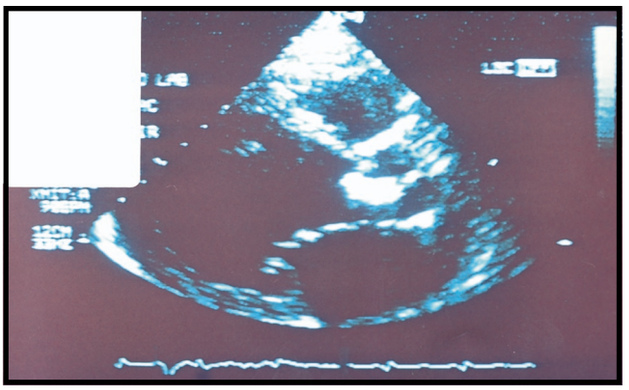

Figure 1 - Transthoracic echocardiogram long axis view of vegetation on the aortic valve.

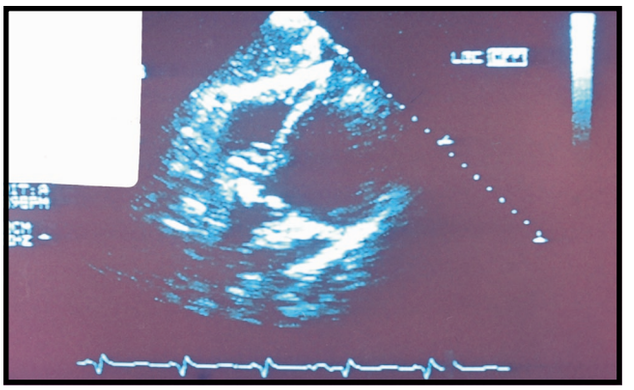

Figure 2 - Transthoracic echocardiogram apical view showing vegetation on aortic valve.

In the 1980s *viridans streptococci* were responsible for almost half the cases of IE[7] and they remained the most common cause of prosthetic valve and native valve endocarditis in the 90s.[3] Infective endocarditis due to unusual and gram-negative organisms especially when culture negative and in association with contact to mammals may suggest infection with brucella species.[8,9]

Another condition predisposing to IE is dental caries with which *viridans streptococci* are particularly associated as they constitute part of the oral flora.[10] There is evidence that dental caries is an ancient disease, which emerged when hunting was replaced with agriculture as the main source of food for survival.[11] Frequent consumption of fermentable carbohydrates that have a low oral clearance rate increases the risk for enamel caries.[12] Brucellosis on the other hand remains a major zoonosis worldwide where *brucella melitensis* has emerged as a cause of infection in cattle as well as in sheeps and goats.[13] In a prospective study of 400 cases in Kuwait raw milk ingestion was the major source of infection,[14] and a study of 500 cases in the Kingdom of Saudi Arabia revealed animal contact (74%) and raw milk ingestion (70%) as the main historical features.[15] Brucellosis can either be insidious or abrupt in onset and can infect virtually every organ system.[16] The virulence of the brucellae is thought to be essentially due to their capacity to survive and replicate within phagocytic cells.[17] In 1991 Baddour et al[18] noted that polymicrobial IE cases had greatly increased in the 1980s with a mean patient age of 36.5 years, a male to female ratio of 2:1, and an almost twice more likely chance of death (38.3% versus 20.8%) in patients infected with 2 organisms compared to 3 or more due to increased incidence of endocardial infections in the left side of the heart in the former.

In this case report we present a patient who was exposed to 3 risk factors of IE such as dental caries, brucellosis and rheumatic heart disease. The prolonged fever he had is usually associated with gram negative bacilli, a need for cardiac surgery an a higher mortality rate.[19,20] His presentation with heart murmurs occurs in over 85% of the cases[21] and over 90% of these patients will develop heart failure which nowadays is the leading cause of death of IE.[5] The diagnosis of a case of IE apart from a detailed history and physical examination requires the clinician to set up multiple blood cultures, order serological tests and to arrange an urgent echocardiogram which can be either TTE or TEE. Recently Durack et al[22] introduced clinical criteria based on blood cultures and echocardiography. All patients suspected of IE should at least undergo a baseline TEE to determine the size and location of the vegetation since TEE is more sensitive than TTE in detecting vegetations (90% versus 65%).[23]

In our patient TTE provided the rapid identification of a large vegetation on the aortic valve **(Figures 1 & 2).** Brucella endocarditis was suspected based on the occupational history and the known association of brucellosis with bulky vegetations.[24] On obtaining blood cultures and sending them to the laboratory it is important to inform the staff of a suspicion of brucellosis so that extended incubation, specific media and biohazard precautions can be employed.[15] While streptococci grow readily on blood agar, brucella species need incubation in liver infusion or glucose serum broth with CO_2 for a period of up to 6 weeks.[25]

Serological diagnosis of brucellosis encompasses several tests out of which the SAT and the 2-mercaptoethanol (2ME) agglutination are most commonly employed since a raised level of brucella agglutinin (with or without positive cultures of blood or tissues) in combination with potential exposure and consistent clinical features confirms the diagnosis.[15] Our patient had a significant SAT titre of 1:1280 and in endemic areas SAT titres considered significant are 1:320 or 1:640.[15] In a retrospective case study in the Kingdom of Saudi Arabia by Memish et al[26] of 160 patients with bacteraemic

brucellosis between 1983-1995 an agglutination antibody titre of ≥ 1:320 was observed. In nonendemic areas a SAT titre of 1:160 is sufficient to be considered significant[15] as was shown in a study by Young[27] which included the sera of 214 patients with suspected brucellosis out of which patients with active disease had SAT titres of ≥1:160.

Since most cases of IE involve infection with *viridans streptococci* in which aqueous penicillin or ceftriaxone are effective[28,29] the patient was commenced on the former in accordance with the guidelines of the American Heart Association.[30] Once daily gentamicin[31] was added to accelerate the clearing of the bacteremia.[29]

Streptococcal viridans endocarditis may be treated successfully in 2 weeks using a combination of penicillin and an aminoglycoside[32] however BE is the most devastating complication of brucellosis.[33] For the last 2 decades it has been known that BE has to be approached by combined medical and surgical treatment.[4,24,33-36] Conservative treatment can only be recommended in patients without congestive heart failure, no prosthetic valve, relatively mild extravalvular cardiac involvement and a somewhat shorter disease history until initiation of treatment as identified by a study of Cohen et al.[33]

Absolute indications for valve replacement during active IE in general include severe heart failure, the presence of an infecting organism that is not susceptible to available antimicrobial agents, and in patients with an infected valve, an unstable device.[38] The beginning of an aortic root abscess reconfirmed yet again the serious nature of BE and the fact that surgery is the safest therapeutic alternative for aortic valve localizations and it should be performed without delay, as emphasized by Chevalier et al[39] who reported a case of brucella pancarditis with abcess formation and fatal outcome.

Recently aortic allografts have been advocated instead of prosthetic valves in the treatment of active aortic valve endocarditis with associated periannular abcess due to a higher survival rate observed in a study by Knosalla et al,[40] and might be the approach in the future if confirmed by others. Antibiotic therapy should be continued for 2 months based on the recommendations for BE.[15] Overall polymicrobial IE has greatly increased and in our view should be suspected as soon as multiple risk factors for IE are present in a patient within the context of the right clinical setting.

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