Brucella endocarditis

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Abstract

Brucella Endocarditis requires a high level of suspicion for proper diagnosis and treatment. Although rare, affecting – depending on the series presented - less than 2% of patients with Brucellosis – is the most devastating complication of the disease, and the cause of up to 80% deaths. The aortic valve is the most commonly affected (75%), followed by the mitral valve. Despite medical treatment, cardiac surgery with valve replacement is usually needed. The authors report a case of mitral valve *Brucella* Endocarditis in a 42-year-old man with stroke and transient monoclonal gammopathy, successfully treated with medical treatment alone. The doses and duration of medical treatment are discussed, as well as the association between *Brucella* Endocarditis and transient monoclonal gammopathy, based on a literature review.

Key words: *Brucella*, Endocarditis, Transient monoclonal gammopathy.

Introduction

Brucella Endocarditis occurs in less than 2% of all cases of Brucellosis, yet it is the main cause of death related to the disease[1,2], accounting for 80% of mortality.[3-7] *Brucella* is the agent responsible for 4% of endocardites.[8] It is a gram-negative intracellular cocobacillus.[4] Four species are known to be responsible for the infection in humans: *Brucella abortus* (beef cattle), *Brucella melitensis* (goats, sheep, camels), *Brucella suis* (swine) and *Brucella canis* (dogs).[4,5] The most frequent etiology of cases of human Brucellosis is due to *Brucella melitensis,* the most virulent form of *Brucella spp*.[4] There are descriptions of the disease from the time of Hippocrates, but it was not until 1887 that the microorganism was isolated, by David Bruce, a doctor with the British Army, in the spleens of five patients who had died from the disease in Malta.[7] It is a zoonosis acquired through handling infected animals, as well as the ingestion of milk or contaminated (non pasteurized) dairy products.[4,9] The main mechanisms by which the infection is acquired are conjunctival, respiratory, cutaneous and digestive seeding.[10] The incidence of *Brucella* bacteremia is higher during Spring and Summer, and lower in the Winter months, a fact which is attributed to the higher number of animal births during these times, and the increased number visits to rural areas, with the consequent consumption of unpasteurized dairy products.[11] The incubation period is difficult to determine, but in general is 2 to 10 weeks.[4] Brucellosis may appear in acute form, as a febrile syndrome, or it may have a more insidious development, with a wide range of symptoms. Also known as Malta Fever, Crimea fever or undulant fever, it exists worldwide, especially in the Mediterranean basin, in the Arabian Peninsula, on the Indian subcontinent, and in parts of Mexico and Central and South America. Hemocultures are irregularly positive (17-96% of patients)[9] particularly if antibiotic treatment has already been initiated.[4] In the absence of bacteriological confirmation, with isolation of the agent, serological tests are used to obtain a presumptive diagnosis.[11,12] The reference test in the diagnosis is Wright's serum agglutination test,[4,10] which tests for the presence of the anti-o-polysaccharide antibody. Titers of 1:160 or higher are diagnostic,[4,10] with values ≥1:320 being considered by some works as ideal in the predictive value in the diagnosis.[12] Other tests exist for confirmation of the disease, such as complement fixation reaction and the indirect immunofluorescence test. The latter can assist in the diagnosis when the Wright reaction is negative. There are some authors who consider it to be more sensitive, although its positivity is more delayed.[1] In an emergency service, the use of the Rapid serum agglutination test with Bengal Rose buffered antigen – may have high diagnostic value in the presence of a characteristic epidemiological history,

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particularly outside an endemic environment, since it shows rapid results, enabling immediate initiation of the therapy.

Clinical case

42-year-old male, Caucasian, worker in an animal feed factory and resident in Milharado in the District of Torres Vedras. In July 2001, the patient began complaining of lumbalgias, myalgias and fever (39ºC axillary temperature) particularly in the evenings, accompanied by sweating and hot flushes. Patient had no complaints affecting the other organs and systems. Family history irrelevant and personal history included sporadic contact with animals, but no consumption of unpasteurized dairy products during the last six months.

In October 2001, patient was referred to the Internal Medicine consultancy due to persistence complaints. On objective examination, he presented fever (axillary temperature = 37.5ºC) and hepatosplenomegaly. For results of the laboratory tests see *Table I:* Laboratory Evolution. Normal urinary sediment. Rapid agglutination test with Bengal Rose buffered antigen-positive. Wright's serum agglutination test, positive 1:320. Serological markers for VIH1e2 and for hepatitis A, B, C negative. Abdominal echography confirmed the presence of hepatosplenomegaly. Radiography of the lumbosacral column revealed narrowing of intervertebral space L3-L4. CT scan of the lumbosacral column confirmed narrowing of intervertebral space L3-L4 due to a degenerative process, without excluding a possible coexistent infectious/inflammatory condition. MNR of the lumbosacral column showed L3-L4 intervertebral degenerative process, without evidence of infection or inflammation.

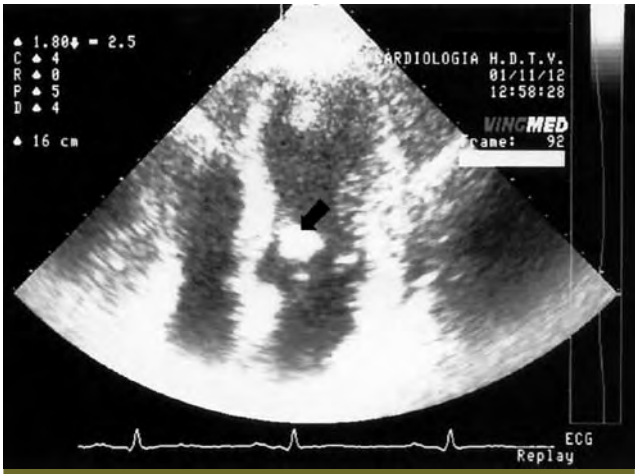
Following a diagnosis of Brucellosis, therapy was initiated with Rifampicin 900mg/day and Doxycycline 200mg/day. An excellent initial response was obtained, with apyrexia on the 5th day and progressive improvement of the pain complaints. On the 18th day of therapy, food vomiting occurred, with return of the fever, and the patient was admitted in hospital (November 2001). On objective examination: axillary temperature = 38.2ºC, hepatosplenomegaly, tachycardia 109bat/min, without audible murmurs. (See *Table I*): Rapid agglutination test with Bengal Rose buffered antigen - positive, Wright's serum agglutination test 1:1280, indirect immunofluorescence for *Brucella*

TABLE I

Laboratory evolution

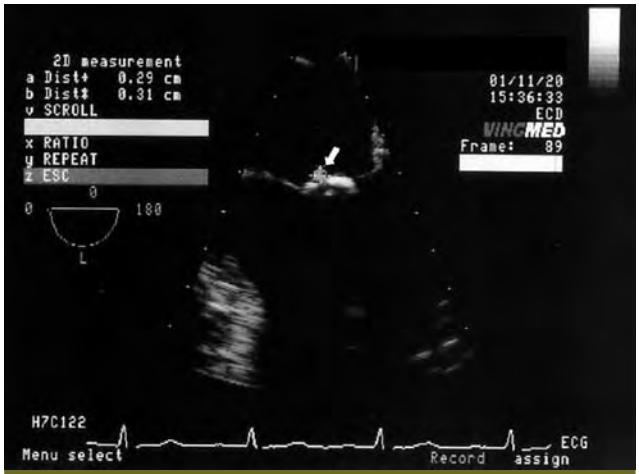
	October 2001	November 2001
Hemoglobulin	11.3g/dL	9.7g/dL
MCV	93 γm^3	96 γm^3
MCHC	33.8g/dL	35 g/dL
Leukocytes	4.7X10^3/mm^3	7.7 X10^3/mm^3
Neutrophils	55%	67%
Lymphocytes	32%	21%
Platelets	215X10^3/mm^3	
INR	1.1	1.0
AST	60U/L	18 U/L
ALT	108U/L	8 U/L
ESR	90mm 1st hour	80 mm 1st hour
Total Proteins		9.5g/dL
IgG (700-1600)		2831mg/dL
IgA (70-400)		298 mg/dL
IgM (40-230)		286 mg/dL
Albumin		3.1g/L
α 1 Globulin		0.4g/L
α 2 Globulin		1.0g/L
β Globulin		1.2g/L
γ Globulin		3.8g/L

in the serum 1:640, hemocultures and uroculture negative. Serum and urinary immunoelectrophoresis: hypergammaglobulinemia (IgG e IgM). Radiographies of the skeleton without lytic lesions. Myelogram and bone biopsy normal. Transthoracic Echocardiogram (mode M and BD)- (12 November 2001): mitral valve vegetation; slight mitral insufficiency *(Fig. 1)*. Transesophageal echocardiogram (mode M and BD)- (20 November 2001): confirmed a 6x9mm mass, joined to the anterior mitral valve leaflet with two small zones of around 3mm plus filiforms, and erratic movement in the auricular surface of the valve; image compatible with mitral vegetation; small flow of mitral regurgitation *(Fig. 2 and 3)*. During hospitalization, patient continued therapy with Rifampicin 900mg/day and Doxycycline 200mg/day (over a period of 5



Transthoracic echocardiogram: mitral valve vegetation.

FIG. 1



Transesophageal echocardiogram: mitral valve vegetation.

FIG. 2

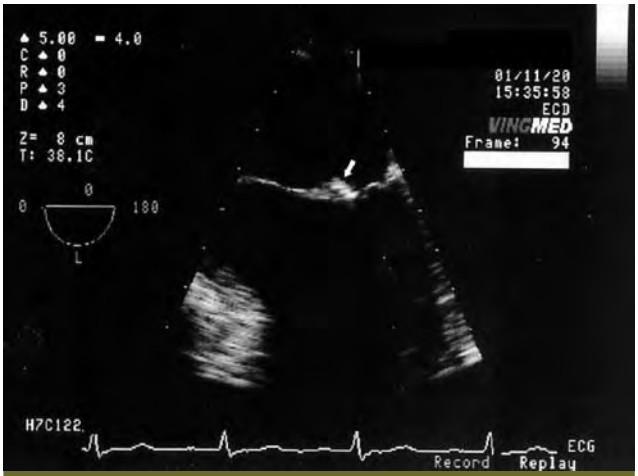
weeks) with good clinical and imagiological response. Apyrexia emerged on the 11th day. Transthoracic control echocardiogram (mode M and BD)- (29 November 2001): light mitral insufficiency; no evidence of vegetation *(Fig. 4)*. As a complication, on the 20th day of admittance, an episode of left palpebral ptosis was observed, with left deviation of the labial commissure, lasting around 12 hours. Cranial CT scan was carried out 48 hours after the episode, which was normal, as was the study of blood viscosity (Couette viscosimeter) which although at the upper limit, was within the interval considered normal.

Due to the apyrexia and the clinical-imagiological response, the patient was discharged on the 32nd day after admittance, with the following diagnoses: 1. *Brucella* Endocarditis 2. Monoclonal gammopathy and 3. Transitory ischemic accident. Therapy with Rifampicin 900mg/day and Doxycycline 200mg/day was maintained for 12 months. In the follow-up at the Internal Medicine clinic, at 6 months, patient was asymptomatic without hepatosplenomegaly, with indirect immunofluorescence in the serum for *Brucella 1:320* and normal serum and urinary immunoelectrophoresis. At 12 months, patient remained asymptomatic, Wright's serum agglutination test 1:32, indirect immunofluorescence in the serum for *Brucella 1:32*, transthoracic echocardiogram (mode M and BD): slight mitral insufficiency; no evidence of any vegetation. At 24 months of follow-up, normal clinical and laboratory situation continued. Patient was discharged from the Internal Medicine clinic with final diagnoses of 1. *Brucella Endocarditis* 2. Transitory monoclonal gammopathy and 3. Transitory ischemic accident.

Discussion

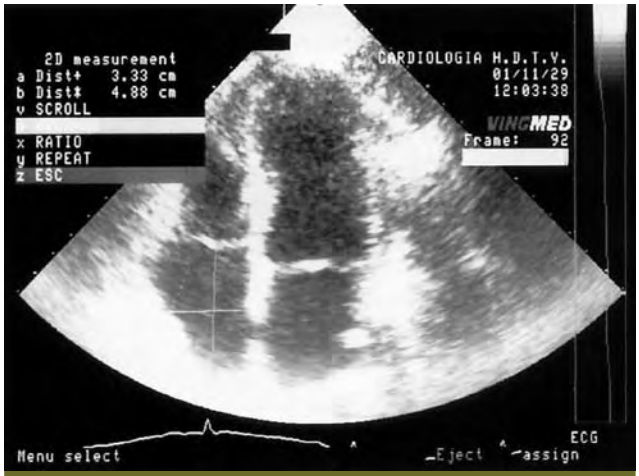
The diagnosis of infectious Endocarditis has been difficult, with the pathology often manifesting itself in a hidden form.[13] 20-30% of cases did not present any predisposing factors such as previous valvular lesions.[13] Men are more frequently affected than women (1.7:1).[14]

In this clinical case, the diagnosis of endocarditis required a high level of suspicion based on the clinical evolution and laboratory data. In the presence of recurrence, and in the presence of a diagnosis of endocarditis, the epidemiological history is fundamental.[4,10] In the case presented, the patient reported contact with cattle, albeit sporadic. With fever being the most frequent sign and symptom[14] it may present in an acute form as a febrile syndrome, or its onset may be insidious. The fever is undulant, although this characteristic is not pathognomonic of the pathology.[10] Given that an infection, as a complication, is the materialization hepatosplenomegaly and adenomegalies, through the activation of the reticuloendothelial system, they may also emerge as the laboratory parameters which indicate infection. White blood cell counts are generally normal or low.[3,5] Sedimentation speed, although it may be high, is attributed low im-



Transesophageal echocardiogram: mitral valve vegetation.

FIG. 3



Transesophageal echocardiogram: without vegetation; slight mitral insufficiency.

FIG. 4

portance in the diagnosis.[5] Osteo-joint manifestations occur in 20-60% of patients.[7,15] Focalized complaints justify investigation for exclusion of a process of spondylodiscitis and/or osteomyelitis.

Diagnosis was made by clinical suspicion and laboratory confirmation with particular emphasis on the positivity of the Rapid agglutination test with Bengal Rose buffered antigen – and the Wright's serum agglutination test. Its immediate use is important. Because the result is rapid, the start of therapy may be immediate until the indirect Immunofluorescence for *Brucella* in the serum is available. Start of treatment with double therapy is now recommended with Doxycycline 200mg/day and Rifampicin 600-900mg/day or streptomycin[4,5,12] although some authors suggest triple therapy.[9,16]

The therapy was initially carried out with good response. With the start of vomiting and reappearance of fever, failure of the therapy, secondary effects of the treatment, and complications of the disease or possible concomitant pathology were accepted. The transitory ischemic accident and hypergammaglobulinemia led to the question of the possibility of hematologic disease with possible associated hyperviscosity syndrome, which were excluded. Although the culture exams (blood and urine) and chest teleradiography were normal, the persistence of clinical data, namely hepatosplenomegaly, and laboratory data, such as worsening of the anemia and maintenance of the high speed of sedimentation, lead to a hypothesis of the existence of a possible complication which requires investigation.

Given that endocarditis it the most feared complication of Brucellosis, it must be considered. Although two thirds of patients have prior valvular disease, including the presence of valvular prostheses, the remaining third have no relevant history.[4,17] The appearance of a heart murmur or alterations in the characteristics of an existing murmur are verified in a way that enables a timely diagnosis. Transthoracic echocardiogram (mode M and BD) showed the existence of mitral valve vegetation. Although in *Brucella* Endocarditis it is the aortic valve that is most frequently affected (75%)[9] in this case only the mitral valve was involved. The transeosophagic echocardiogram enabled us to better characterize the vegetation identified in the transthoracic echocardiogram, and exclude the involvement of other valves. In the case presented, although it is reported that the transesophageal echocardiogram is the most sensitive and specific, and is capable of detecting vegetations smaller than 10mm[13] diagnosis was possible from the transthoracic echocardiogram. Valvular vegetations, which in *Brucella* Endocarditis are mostly of appreciable dimensions,[4] may result in tissue destruction, embolic events and immunocomplexes.[13] Systemic embolization may occur in 22-50% of cases of endocarditis[9] involving the central nervous system in 60-65%.[13,14]

During hospitalization, the complaints of palpebral ptosis and deviation of the labial comissure led us

to investigate a possible cerebral embolic event, which was excluded by the normal results of the cranial CT image. Although hyperviscosity syndromes are mostly related to lymphoplasmocytary disturbances which secrete IgM[18], the normal blood viscosity enabled us to exclude this hypothesis. With the clinical evolution and the objective examination altered within 24 hours, a diagnosis of transitory ischemic accident - one of the possible vascular manifestations in the SNC[10] – was made. The subsequent normalization of protein and immunoglobulin levels, in the presence of normal protein electrophoresis and serum and urine immunoelectrophoresis, led to a diagnosis of transitory monoclonal gammopathy, which is usually described as being associated with inflammatory/ infectious processes[19] There are few cases reported in the literature in which, like this case, the endocarditis is associated with *Brucella*.[20,21] The duration of the treatment is uncertain[9] and unlike the case presented, surgery is usually also necessary.[4,9,22] Given that *Brucella* is highly destructive for the valves[4,14] the combination of medical and surgical treatment in patients with hemodynamic involvement results in a lower mortality rate.[8,13] The non-existence of cardiac insufficiency, valvular prosthesis or incipient extravalvular involvement, as well as the short period of the disease until the start of treatment, are characteristics currently exhibited by patients who respond well to conservative treatment.[23] One should bear in mind that for the suspension of antibiotic treatment, the laboratory results and clinical evolution of the patient which should be totally asymptomatic[9], which is confirmed after 6 to 12 months of follow-up.

Conclusion

The interest of this clinical case is based on four distinct factors: the rare involvement of the cardiac valves, especially the mitral valve, in Brucellosis; the good evolution, despite this involvement, only with medical treatment, the fact that there are no recent references in the literature relating to Brucellosis, and above all, *Brucella*endocarditis, with transitory monoclonal gammopathy and the complication of transitory ischemic accident which, occurring concomitantly with monoclonal gammopathy, imposes a differential diagnosis with possible hyperviscosity syndrome. ■

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