

Brucella Endocarditis

Presentation of two cases and literature review

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Among 77 patients surgically managed between January 1996-December 2000 for valve endocarditis, two cases of brucella endocarditis are reported. They both refer to endocarditis of native valve with preexisting stenosis in the first patient. Severe regurgitation of the valve was the main finding of the echocardiographic study, while blood cultures for brucella were positive in the first case. Replacement with mechanical valves was performed in these cases after 20 days of prompt antibiotic regimen, was continued for 2.5-5 months postoperatively. Postoperative course was uneventful and both patients are doing well 12 and 40 months respectively after the operation. Timing of the operation is critical. In hemodynamically stable patients, administration of a combination of antimicrobial agents for 3 weeks preoperatively is indicated in order to achieve sterilization. As positive blood cultures are not always present, diagnostic suspicion and therapeutic vigilance are mandatory for the successful management of brucella endocarditis.

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For the past few years, an important spectrum of microbes that are involved as causative factors in infective endocarditis have been studied. Among these microbes, the following are included: streptococcus viridans, streptococcus bovis, community staphylococcus aureus, as well as some enterococcus strains. Therefore, when typical infective endocarditis, that is due to such microorganisms is encountered, the diagnosis is facilitated by the continuous bacteremia that is observed. The responsible microorganism may be identified with the use of standard methods, materials and cultures.

Developments in molecular microbiology, in culture methods and in echocardiographic techniques have led to the discovery of microbes that constitute rare causes of infective endocarditis. Brucella is one of these microbes with a global incidence of less than 1%, although some series report percentages up to 10.9%. The observed difference is due to epidemiological factors, while a recently published

Greek series with a retrospective study of the last twenty years from different centers raises Brucella Endocarditis (BE) up to 4% over the total number of patients treated for endocarditis¹. Its particularity lies in the difficulty to eradicate it with pharmaceutical treatment only and the need for surgical valve replacement that is followed by long-term antibiotic treatment.

Among 77 patients surgically managed in our department for endocarditis, in the last five years, two patients with Brucella Endocarditis (BE) are included. These two cases are presented in this paper.

Case description

1st case: A sixty-three-year old male patient was admitted with high fever for the last five days (mainly in the afternoon reaching 39°C with chills), reporting weakness and fatigue over the last two months. From the patient's cardiological history, there was a diagnosed calcification and stenosis of the aortic valve, while from the

epidemiology history we noted the consumption of non pasteurized milk products, of private production. Clinically, on heart auscultation a 4/6 systolic murmur was observed, in the whole precordium, while on palpation of the abdomen, there was slight hepatomegaly. Laboratory examination indicated normal WBC (7000-7800) with type inversion (polymorphonuclears 40%, lymphocytes 49%), Ht 43.4%, platelets 142000, hepatic enzymes increase (transaminases and LDH) and microscopic hematuria. The strong suspicion of brucellosis was verified with Wright seroreaction that was positive in a dilution of 1:320, but mainly and primarily with positive *Brucella melitensis* blood cultures. In abdominal ultrasound, the liver showed increased echogenicity as in the case of diffuse disease and the spleen was enlarged (12.6 cm). Transthoracic echocardiography showed aortic valve vegetation, which was verified from the transesophageal echocardiography. From the third day of hospitalization, we administered to the patient ampicillin, gentamicin and doxycyclin i.v. to which we added, following positive blood culture, rifampin. Despite the indications of stabilization of the clinical condition with the recession of fever and the reduction of hepatic enzymes, progressive decrease of the hematocrit was observed to 28.2% with concurrent deterioration of the renal function (urea 77, creatinine 2.56) and continuous deterioration of his echocardiographic imaging. Twenty days later, two large mobile vegetations were found, while aortic valve regurgitation 3+/4+ and pressure gradient 50 mmHg, with co-existing mitral insufficiency 1-2+/4+ with 60 mm end-diastolic diameter of the left atrium, were recorded. Brain, chest and abdomen CT-scans excluded the existence of peripheral septic emboli. We decided to proceed to surgical treatment and the patient underwent aortic valve replacement with mechanical two-flap pyrolytic carbon valve St-Jude 21R. Valve culture was sterile. The post-operative course was completely normal and following two months of parenteral administration of antibiotics, the patient left the hospital with instructions for per os rifampin and ciprofloxacin for another 3 months. The patient is well 12 months after the surgery.

2nd case: A thirty-nine-year-old male presented with dyspnea in mild effort (NYHA III classification) weakness and fatigue on the ground of febrile condition with, chills and sweating, for the last 20 days. Within this period he had received antibiotics per os on an outpatient basis. On heart auscultation, 3/6 diastolic murmur of high frequency was observ-

ed, while on palpation of the abdomen, the liver was found enlarged 2-3 cm under the costal arch. Laboratory examination indicated mild anemia with Ht 32.5% and thrombocytopenia (platelets 100,000/mm³). Due to compatible epidemiological history, brucellosis was suspected, which was subsequently proved with Wright seroreaction (positive 1:320), while blood cultures were sterile. Cardiac ultrasound showed significant dilatation of the left ventricle with aortic valve failure of 3+/4+. Following parenteral administration of triple antibiotics regimen (doxycycline, netilmycin, rifampin) for 20 days, the patient underwent aortic valve replacement with a mechanical 23 R valve. Valve culture was sterile. The post-operative course was normal and parenteral antibiotic treatment for six weeks and per os antibiotic treatment for one month were administered to the patient. Forty months later, the patient is well and free of disease.

Discussion

BE constitutes a rare but severe complication of brucellosis. It is observed in less than 2% of brucellosis cases², yet it is the main cause of death from infection, being responsible for up to 80% of deaths³. Despite the administration of properly adjusted on a case-by-case basis pharmaceutical treatment, BE calls for emergency or immediate heart surgery, in the majority of cases, due to inability to control the infection and the progression shift to congestive heart failure⁴. The pre-existence of valvulopathy predisposes to valve involvement, while the valve that is most commonly affected is the aortic valve in 75% of the cases.

Although the diagnosis is relatively easy in endemic areas, high suspicion is needed when the incidence of brucellosis is low. The diagnosis will be based on epidemiological data in combination with positive cultures or serological reactions. Blood culture constitutes the only specific test, its sensitivity, however, varies from 17-85%, depending on the conditions of the culture, the antibiotic treatment and the time lapse between the onset of symptoms and the diagnosis. However, brucella positive blood culture is equivalent to endocarditis, when relative predisposing factors co-exist. Regular echocardiographic monitoring plays a primary role in these cases. Usual echocardiography findings include valve vegetations with possible accompanying ulcerations and abscesses. Cardiac and extracardiac complications may occur and they include annulus abscesses at the root of the aorta⁵ pericarditis and diffuse

intravascular coagulation². Peery and Belter reported 80% endocarditis and 43% myocardial abscesses in a total of 44 autopsies on individuals who died of brucellosis⁶.

The strains that are most often considered culprits for endocarditis are *Brucella melitensis* and *B. abortus*. A combination of pharmaceutical and surgical management is proven necessary. The intracellular nature of the microbe is responsible for the fact that anti-microbial agents cannot reach it, since they do not penetrate eukaryotic cells. On the other hand, the microbe causes tissue destruction, with a tendency for progressive ulceration and significant risk of embolism. At the same time with the surgical valve replacement, it is proposed to use a combination of aminoglycoside, rifampin and doxycyclin. The required duration of the treatment is unclear, although most clinicians suggest a 3-6 months regimen with rifampin, doxycyclin and an aminoglycoside for the first 2-6 weeks of treatment. Alternatively, an acceptable antibiotic, instead of rifampin, is cotrimoxazole². No resistance increase of the *B. melitensis* was observed with antibiotic administration over a period of 13 years from the material of 63 patients of Memish et al⁷.

Reports of conservative treatment of BE can be found in the literature. At this point, we consider it necessary to comment on two significant parameters:

- The causative factor in most of these cases was *Brucella abortus*. Given the endemic presence of *Brucella melitensis* in the Greek region and the, proven, more severe clinical image and course of the specific infection, we are led to a different therapeutic approach concept. This is reported by Hadjinikolaou et al.¹, who were in favor of aggressive strategies in the treatment of *Brucella melitensis* endocarditis (surgical operation within the first week from the start of antimicrobial treatment). Similar aggressive strategies are used by Keles et al.⁵, having, however, administered antibiotics for 6 weeks earlier.
- The absence of congestive heart failure or of a prosthetic valve, the relatively mild extravalvular involvement and the shorter course of the disease until the start of treatment, have been proposed as characteristics of those patients who are responding in a satisfactory way to conservative treatment⁸. In accordance, however, with the small experience of the two cases described, the early stage of the infection cannot be safely assessed on one hand;

on the other, the hemodynamic stability of the patient is subject to change even one month after the administration of a complete regime of the indicated therapeutic treatment. The main indication for surgical treatment is the existence of significant insufficiency of the affected valve, which deteriorates the hemodynamic condition of the patient. If we add to this, the unpredictable and largely uncontrolled course of the infection, due to the inability of effective eradication of the microbe, there almost always arises the need for surgical treatment. The basic examination used for the assessment and follow-up of patients is heart ultrasound, whose findings change rapidly, from one day to the other.

Valve cultures in both our cases were sterile. This result is in line with data from the 6 cases that Keles et al.⁵ reported, with negative valve cultures, but it is in disagreement with the respective data of the Greek series by Hadjinikolaou et al.¹, which 7 patients had positive cultures in heart tissues. This deviation must be attributed to the difference regarding the pre-operative administration of antibiotics for a time period sufficient to ensure valve and heart tissue sterilization. Of course, in the case of BE of the prosthetic mitral valve that was recently reported by Akinci et al., the prosthetic valve culture was positive for *Brucella abortus*, despite the fact that the patient had received a possibly insufficient antibiotic regime in the previous 3 months⁹.

Conclusions

Increased diagnostic and therapeutic vigilance is required for the timely and efficient treatment of BE. **Diagnostically**, a high degree of suspicion is required for patients with a history of consumption of non-pasteurized dairy products, occupation associated with animal breeding or simply of living in rural areas.

Therapeutically, surgical treatment with the replacement of the affected valve in combination with pharmaceutical treatment for a large period of time, are deemed necessary for the successful treatment of BE. The selection of the optimal time for surgical treatment is unclear. Provided that the patient's hemodynamic condition allows it, we opt for the administration of antimicrobial agents for approximately 20 days pre-operatively in order to achieve sterilization. Patients must be operated on earlier in

case of deterioration of their clinical condition, either due to the presentation of systemic manifestations (hemodynamic deterioration, sepsis, peripheral embolism, renal failure), or due to the increase of the size of the vegetations or development of abscess in the valve. However, since the hemodynamic condition may change rapidly and the mortality rate is high alertness for urgent treatment is needed. Blood culture positive for brucella dictates assessment by cardiac surgeon with the view of further treatment.

The time for post-operative administration of antibiotics varies depending on the case and is basically determined on a case-by-case basis. All chemotherapeutic combinations should be discontinued, not only when IgA antibodies become negative for brucella, but also when CRP becomes normal and the Wright seroreaction titer shows reduction below 1/64, which is maintained stable for a few weeks. In order to decide to discontinue antibiotics, we should consider the results of laboratory follow-up of the patient together with the clinical condition of the patient that must be absolutely symptom-free.

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