CASO CLÍNICO / *CLINICAL CASE*

Febre persistente com hemoculturas negativas

Persistent fever with negative blood cultures

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/ Resumo

A síndrome febril persistente, sem causa etiológica aparente, pode constituir um desafio, mas a história clínica cuidada muitas vezes ajuda no diagnóstico. Apresentamos o caso de um homem de 73 anos, com endocardite de válvula protésica, após dois episódios de possível endocardite infeciosa, nos seis meses anteriores. As hemoculturas foram repetidamente negativas, assim como o ecocardiograma transtorácico. Os estudos serológicos para os agentes mais comuns eram negativos. Finalmente, o ecocardiograma transesofágico mostrou um abscesso periaórtico e foi identificado DNA de *Coxiella burnetii* no sangue periférico. No mesmo dia, iniciou-se uma associação de doxiciclina com lexofloxacina, tendo o doente melhorado sustentadamente. Foi proposta reintervenção para substituição da bioprótese valvular, mas, devido ao alto risco cirúrgico, optou-se por não submeter o doente a nova cirurgia. Ao fim de dois anos de antibioterapia, foram suspensos os fármacos, mantendo-se o doente em vigilância, sem sinais clínicos ou analíticos de recidiva. Este caso sublinha a importância de se identificar o agente de uma endocardite infeciosa, já que as recidivas são frequentes quando os antibióticos não são dirigidos ao agente em causa.

Palavras-chave: Endocardite; Válvula protésica; *Coxiella burnetii*; Febre persistente

/ Abstract

Febrile illness without an initially obvious aetiology can be challenging, but a careful clinical history can enlighten the diagnosis. We present a case of a 73-year-old male with a prosthetic valve endocarditis, after two possible infective endocarditis in the previous six months. Blood cultures were repeatedly negative, as was transthoracic echocardiogram. Blood serologies were not helpful. Finally, a transoesophageal echocardiogram revealed a periaortic valve abscess and DNA of **Coxiella burnetii** *was identified in peripheral blood. In the same day, an association of doxycycline and levofloxacin was initiated, with sustained improvement. Prosthetic valve replacement was considered but postponed because of high surgical risk. Both antibiotics were stopped two years after the diagnosis. The patient is in close follow-up without evidence of clinical or analytical relapse. This case stresses the importance of identifying the agent of an infective endocarditis, as relapses are common when antibiotics are not directed to the culprit microorganism.*

Keywords: *Endocarditis; Prosthetic valve;* **Coxiella burnetii***; Persistent fever*

/ Introduction

Febrile illness without an initially obvious aetiology can be challenging in patients with several comorbidities. Many exams can be ordered, but a careful clinical history and physical examination are crucial, mainly when the symptoms do not seem to fit. In most patients with persistent fever, distinguishing characteristics will lead to the diagnosis or the fever will ultimately vanish spontaneously. Fever of unknown origin (FUO) is defined as temperature equal or superior to 38.3ºC, for more than three weeks, that remains undiagnosed after a hospital work-up. FUO can be classified in four groups: infectious, malignant/neoplastic, rheumatic/inflammatory and miscellaneous disorders, such as drug fever or familial periodic fever syndromes. There is no standard approach to this diagnostic challenge. Individual risk factors and epidemiologic data will determine the most useful tests. Nonspecific tests often provide useful diagnostic clues.[1]

Infective endocarditis is one of the possible aetiologies for persistent fever, but usually it is diagnosed in less than three weeks. Patients with a prosthetic heart valve are at increased risk for endocarditis, as are patients with previous infective endocarditis.[2]

Blood cultures are the mainstay for the diagnosis of infective endocarditis. Guidelines from the European Society of Cardiology and American Heart Association recommend that, at least, three sets should be taken with half-hour of interval, as it will detect 96% of the episodes of bacteraemia.[2,3] The detection rate can exceed 99% with four blood cultures.[3] Despite this, etiologic diagnoses cannot be obtained in 5 to 69.7% cases of infective endocarditis (highly variable by country), the so named blood culture–negative infective endocarditis. Up to 74% of these cases arises because of previous antibiotic therapy.[4] When true blood culture–negative infective endocarditis is being considered, agents such a fungi or fastidious bacteria should be tested according to epidemiology and risk factors of the patient. The European Society of Cardiology guidelines for infective endocarditis suggests systematic serological testing for *Coxiella burnetii*, *Bartonella* spp., *Aspergillus* spp., *Mycoplasma pneumonia*, *Brucella* spp. and *Legionella pneumophila*, according to local epidemiology, followed by specific polymerase chain reaction (PCR) assays for *Tropheryma whipplei*, *Bartonella* spp. and fungi (*Candida* spp. and *Aspergillus* spp.).[2] Blood PCR can also be considered for the diagnosis of more common bacteria, that normally grow in blood cultures, in patients who received recent antibiotic courses.[4,5]

/ Case description

A 73-year-old man was admitted to our medical ward after ten days of low-grade fever and night sweats. He was prescribed cefixime the week before, because of productive cough, with no improvement.

Two years before, he was submitted to aortic valve replacement with a bioprosthetic valve, because of severe aortic stenosis, and coronary artery bypass graft. His post-operative period was complicated by post-pericardiotomy syndrome, that eventually was resolved, and he was doing well until six months before this presentation.

At that time, the patient was admitted in another hospital for persistent fever. There was no identified agent on blood cultures, no signs of endocarditis in transthoracic echocardiogram (no information about transoesophageal echocardiography), but a new zone of renal infarction was noted on computed tomography (CT) scan. He received gentamicin and vancomycin during 4 weeks for

infectious endocarditis, with resolution of fever. After this hospitalization, he never recovered from kidney injury, developing stage 4 chronic kidney disease.

Two months after this hospitalization, he was readmitted in a second hospital for persistent fever. Methicillin-resistant *Staphylococcus haemolyticus* were isolated in blood cultures (no information about the timing of collection and number of blood cultures) and echocardiogram showed a periaortic valve abscess. Gentamicin and linezolid were started and the patient had a new surgery where bioprosthetic valve was replaced. No agent was isolated in the culture of valve tissue. Because of new evolving pancytopenia, linezolid was replaced by daptomycin (total treatment time was between 6 to 8 weeks). Patient recovered progressively until the present admission. A recent ambulatory echocardiogram reported a small periprosthetic leak, without other relevant valvular abnormalities, vegetations or dysfunction.

His past medical history was relevant for hypertension, diabetes mellitus, that was controlled with diet, and prostatic benign hyperplasia. He had undergone cholecystectomy, after acute lithiasic pancreatitis, and appendicectomy, in the remote past. When he was 20-years-old, he received treatment for malaria, at the war in Angola. He had previous smoking habits (30 pack-years), drank moderate quantities of alcohol and did not use illicit drugs. His medications included aspirin, perindopril, dutasteride and tamsulosin; he had no known allergies.

He was a retired teacher that lived all his life in a city, but frequently spent some weekends in a farm house with dogs, chickens and sheep. He had not travelled outside Portugal for more than ten years.

In the emergency department of our hospital, the patient reported a feeling of fever and nights sweats, occasionally, in the last year, even when he was at home between hospitalizations. His cough was low productive. He denied headache, sore throat, dyspnea, thoracic or abdominal pain, nausea, vomiting, diarrhea, dysuria, arthralgias or rash. On physical examination, the temperature was 38.0°C, the pulse 58 beats per minute, the blood pressure 127/56 mm Hg, the respiratory rate 18 breaths per minute, and the oxygen saturation 99% while he was breathing ambient air. The patient was emaciated but did not appear acutely ill. Pulmonary auscultation was unremarkable, but a systolic ejection murmur (grade 2/6) was noted in the precordium. The abdomen was non-distended, with normal bowel sounds and no tenderness on palpation. The spleen was palpable. There were no skin lesions or lymphadenopathy.

Blood tests were relevant for anemia (8.8 g/dL), leukopenia (3560/µL), thrombocytopenia (59 000/µL), mild C-reactive protein elevation (28 mg/L) and erythrocyte sedimentation rate of 97 mm/h, hyponatremia of 128 mEq/L, with no other electrolyte abnormality, and creatinine of 2.7 mg/dL (similar to the last blood tests). Blood levels of glucose, liver enzymes, lactic acid, lactate dehydrogenase, creatine phosphokinase, thyroid-stimulating hormone and urinalysis were normal.

Chest radiograph was normal. Abdominopelvic ultrasound revealed homogeneous splenomegaly, disclosing other relevant findings. Electrocardiogram showed sinus bradycardia (54 bpm) with a first-degree atrioventricular block. After blood cultures were collected, patient was admitted in our medical ward. As he was stable, no antibiotic was initiated at this time.

New transthoracic echocardiogram exposed the already known mild-to-moderate periprosthetic leak, without sign of endocarditis. Antibodies for human immunodeficiency virus and antinuclear antibodies were negative. Blood cultures were repeatedly negative (a total of three sets were collected in different days), while the patient had fever, normally at the afternoon, once to twice a day (maximum of 38.7ºC). Blood levels of C-reactive protein, cell-counts and renal function were steady. As the patient was stable, antibiotics were postponed.

Computed tomography (CT) scan of chest, abdomen and pelvis revealed a new peripheral splenic infarction, an old renal infarction zone and splenomegaly and mild homogeneous hepatomegaly, with no masses, adenomegaly or other relevant findings. Respiratory samples were persistently negative for acid-fast bacilli or *Mycobacterium tuberculosis* DNA (and later, cultures for mycobacteria were negative). Polyclonal hypergammaglobulinemia was noted on serum protein electrophoresis and immunofixation. Bone marrow examination showed nonspecific reactive findings.

Non-palpable purpura on his feet developed during hospital stay. At this time, rheumatoid factor antibodies were positive.
The results from serologic testing for antibodies to phase II *Coxiella burnetii* antigens were reported, by the laboratory, as ambiguous (assay for phase I antibodies were not available), so blood was collected for detection of *C. burnetii* by DNA amplification. Wright reaction, antibodies for *Bartonella* spp, *Mycoplasma spp*, *Legionella*, cytomegalovirus and parvovirus B19 were negative.

Finally, a transoesophageal echocardiogram was made, that revealed a periaortic valve abscess and the periprosthetic leak, without vegetations or relevant prosthesis dysfunction. At the same time, *Coxiella burnetii* DNA identification on peripheral blood was positive.

Modified Duke criteria for definitive endocarditis diagnosis was met, with positive results only for *Coxiella burnetii*, in a patient that had contact with sheep. This agent could also explain the pancytopenia and splenomegaly, even though bone marrow examination didn't have the typical findings of this infection.

An association of doxycycline 100mg q12h and levofloxacin 500mg q48h (dose adjusted to renal function) was initiated, with sustained apyrexia and progressively lower C-reactive protein.

Patient global condition improved with time, and valve replacement was postponed because of the high surgical risk. High titters of phase I antibodies were measured in the first ambulatory consultation, in another hospital, two months after the antibiotic therapy was started, and were progressively lower during the next months. Both antibiotics were stopped two years after the diagnosis. The patient is still on follow-up, with regular echocardiogram and *Coxiella burnetii* phase I antibodies, in another hospital, with no evidence of clinical or analytical relapse after one year without antimicrobial therapy.

/ Discussion

This patient had an intriguing sequence of prosthetic valve endocarditis in a relatively short period of time. Even though the previous events were not treated at our hospital, criteria for possible infective endocarditis were met, despite the negative or unreliable report of microbiological studies in both. Nevertheless, signs and symptoms of infective endocarditis were, at least, temporarily resolved after antibiotic administration. In our hospital, blood cultures were repeatedly negative, but cefixime course was terminated a few days before admission and could have spoiled those attempts to isolate an agent, as antibiotic administration is the main cause of blood culture negative infective endocarditis.[4]

The suspicion for infectious endocarditis was present from the beginning. However, as there was pancytopenia, splenomegaly, night sweats and fever, we initially also suspected of an hematological implication, that complementary exams ruled out. Infection by *Mycobacterium tuberculosis* was another strong possibility. We didn't test the patient for malaria as we didn't think that a so persistent low-grade fever without other dysfunctions, several decades after the primary infection, would be explained by this disease.

Depending on local epidemiology, *Coxiella burnetii* is a not so rare cause of endocarditis.[5] Moreover, modified Duke criteria for the diagnosis of infective endocarditis includes, as a major criterion, a single positive blood culture for *Coxiella burnetii* or anti–phase I IgG antibody titter ≥1:800.[6] As there are few laboratories providing kits for anti–phase I IgG antibodies, DNA detection by polymerase chain reaction (PCR) can be an alternative. Usually, this is done directly in the valve tissue, although there are case reports of such use in peripheral blood.[7]

Anti-phase II IgG antibodies titter for *Coxiella burnetii* are recommended just for the diagnosis of acute infection. For chronic infection anti-phase II antibodies are unreliable as those titters can remain high, can become lower with time or be in an intermediate ambiguous value, as our patient. But this titter was a clue, that made us ask the laboratory for an assay phase I antibodies and, because it was not possible, to ask for DNA detection by PCR. Later, the high titters of phase I antibodies, ordered in another hospital, reinforced the diagnosis of chronic infection.[8,9]

This patient had sporadic contact with sheep and dogs that gave the epidemiologic context for *Coxiella burnetii* and *Bartonella henselae*. *C. burnetii* can survive for long periods of time in the environment, can be transmitted by aerosol and is highly infectious.[8] Therefore, close contact with animals is not required to be infected with this microorganism.

In this case, there were some abnormalities that pointed to *C. burnetii*: history of endocarditis with negative blood cultures, splenomegaly and hepatomegaly, relative bradycardia, pancytopenia, polyclonal gammopathy and high erythrocyte sedimentation rate.[1,8]

Actual guidelines state that patients with endocarditis (by *C. burnetii*) should receive doxycycline (100 mg twice daily) and hydroxychloroquine (200 mg three times daily) for at least 24 months for prosthetic valve infections.[9,10] We preferred an alternative regimen with levofloxacin instead of hydroxychloroquine, because plasma levels of hydroxychloroquine should be monitored when high doses of hydroxychloroquine are used for a very long time in patients with chronic kidney disease, and patient follow-up would be in another hospital. At that time, the adverse effects of levofloxacin appeared, to us, potentially less toxic than hydroxychloroquine, and with easier posology for the patient. There is more recent evidence that this regimen can be a safe alternative.[10]

In addition to medical treatment, a surgical strategy is recommended for prosthetic valve endocarditis complicated by abscess formation with difficult-to-treat organisms. Patients with good response to antibiotics and seem to be at high surgical risk, can be managed conservatively with close follow-up.[2]

We cannot be sure that the previous episodes of infection were caused by *C. burnetii*, but these sequence of infections in six months in a patient with risk factors for chronic *C. burnetii* infection, made us think that those were episodes of relapses of this agent.[9] Antimicrobial therapy with vancomycin and gentamicin were used in the first episode. This is an appropriate empiric regimen for community acquired native valves or prosthetic valves endocarditis (more than one year after surgery), but the four-week duration may have been too short, in a patient with a prosthetic valve. The duration also depends of the causing microorganism[2], that was not identified in the first episode. In the second episode, gentamicin and linezolid or daptomycin were used, directed to methicillin-resistant staphylococci. Of all these agents, only linezolid is known to have *in vitro* bacteriostatic activity against *C. burnetii*.[11] But even non-clinical significant bacteriostatic activity of other agents could have decreased the infective load of *C. burnetii*, as the prosthetic valve replacement probably did. Quinolones, rifampin, macrolides and cotrimoxazole are alternative treatments for *C. burnetii*, that we don't know for

sure if they weren't used between those hospitalizations.[12] It is also possible that the patient has had a coinfection with *C. burnetii* and other agent, such as methicillin-resistant *Staphylococcus haemolyticus*, as described in 6.5% of patients with *C. burnetii* endocarditis in previous studies.[13]

This case stresses the importance of identifying the agent of an infective endocarditis and the use of other tools, such as serological testing and DNA amplification, when microorganism don't grow in blood cultures. Some patients with indication for surgery, but with high surgical risk, can survive with medical treatment only.

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