Abstract
Infective endocarditis is defined as an infection of the endocardial surface of the heart. Its intracardiac effects include severe valvular insufficiency, which may lead to intractable congestive heart failure and myocardial abscesses. This disease still carries a poor prognosis and a high mortality. A severe case of infective endocarditis with its complications is presented. A man with aortic prosthetic valve due to earlier aortic stenosis and corrected aortal coarctation and implanted pacemaker presented with prolonged unexplained fever, malaise, sweating, weight loss (15 kg/4 months) and lumbar pain. He was treated with broad-spectrum antibiotics prior IE diagnosis was considered. Echocardiogram showed aortic vegetations and possible periaortal abscess formation. Nonspecific inflammation parameters were high positive. Cultures were constantly negative. His condition had deteriorated suddenly, and he had presented with worsening of cutaneous vasculitis, subacute glomerulonephritis and subsequent acute respiratory distress syndrome and septic shock. This patient survived with residual bilateral necrosis of the feet and toxic peroneal paresis. At the end transthoracic echocardiogram showed enlarged heart chambers, LV mild dilated and concentric hypertrophy with ejection fraction about 40%, degenerative postinflammatory mitral valve changes, mild mitral regurgitation and tricuspid regurgitation, postinflammatory aortic root fibrosis and moderate aortic valve stenosis (AVPG max 50,9 mmHg, AVPG mean 24 mmHg) with no pericardial effusion. Initial suspicion of Q fever was definitely excluded by serological testing showing nonspecific IgM positivity, probably rheumatoid factor related. © 2012 All rights reserved

Keywords: Endocarditis lenta, prosthetic valve infection, septic shock, false positive Q-fever

Introduction
Infective endocarditis (IE) is an interesting disease because of its constant incidence and mortality rate despite advances in both diagnostic and therapeutic procedures. The diverse nature and evolving epidemiological profile of IE ensure it remains a diagnostic challenge (1). Despite improvements in medical and surgical therapy, IE is still associated with a severe prognosis and remains a therapeutic challenge (2). Different sets of diagnostic criteria have been used to direct and standardize case definitions both in clinical practice and in scientific work (3). The clinical history of IE is highly variable according to the causative microorganism, the presence or absence of preexisting cardiac disease, and the mode of presentation. Thus, IE should be suspected in a variety of very different clinical situations. It may present as an acute, rapidly progressive infection, but also as a subacute or chronic disease with low grade fever and nonspecific symptoms which may thwart or confuse initial assessment. The current in-hospital mortality rate for patients with IE is 15% to 20% with 1-year mortality approaching 40% (3). Once a disease of young adults with mostly rheumatic valve disease, IE now has new predisposing factors – valve prostheses, degenerative valve sclerosis, intravenous drug abuse – associated with increased risk for bacteremia, resulting in health care-associated IE. Leading causative organism shifted from predominantly streptococci to predominantly staphylococci. According to microbiological findings, the following categories are proposed:
1. IE with positive blood cultures (oral streptococci, enterococci, staphylococci)
2. IE with negative blood cultures because of prior antibiotic treatment (oral streptococci or coagulase-negative staphylococci)
3. IE frequently associated with negative blood cultures (HACEK group Gram-negative bacilli)
4. IE associates with constantly negative blood cultures (Coxiella burnetii, Bartonella, Chlamydia, Tropheryma whipplei) (1).

The true prevalence of Q fever may be underestimated because this disease can be asymptomatic in infected individuals. Endocarditis is the most common manifestation of chronic Q fever (4). The risk of transformation from acute Q fever to endocarditis is 40%. C. Burnetii anti-phase IgG titers of > 800 are considered to be a major criteria for the diagnosis of endocarditis (5). Most cases of Q fever are initially misdiagnosed, which directly results in patients’ multiorgan involvement (6). Currently, treatment with long-term tetracycline and quinolone regimen for at least 4 years is recommended. Patients are considered cured when IgG antibodies to C. Burnetii phase I are < 800 and IgM and IgA antibodies are < 50 (7).

According to Duke criteria evidence of endocardial involvement and typical blood culture are regarded as major criteria, while a predisposing cardiac condition or recent history of injecting drug abuse, the presence of temperature of 38.0 or more, defined vascular and immunological phenomena, blood cultures intermittently positive for microorganisms, and echocardiographic findings consistent with IE but not meeting major criteria are regarded as minor criteria. The disease is designated as definite IE if a combination of 2 major criteria, 1 major and 3 minor criteria, or 5 minor criteria is observed. The disease is also categorized as definite IE if histopathologic or microbiological evidence of IE is obtained at surgery or autopsy. Furthermore, an episode of suspected IE is rejected if a firm alternate diagnosis is found, the symptoms of the patient resolve with antimicrobial therapy for 4 days or less, or surgery or autopsy is performed within 4 days after commencing antimicrobial therapy and no pathologic evidence of IE is obtained. Finally, the case is classified as possible if it can neither be rejected nor designated as definite IE (8).

Among IE caused by the most frequent microorganisms, IE caused by Staphylococcus aureus affecting left-sided valves carries the worst prognosis and has a high prevalence of embolic episodes and neurologic involvement. It is also well known that prosthetic valve IE has a poorer prognosis than native valve IE (9).

**Case report**

In November 2011 a 51-year-old man was admitted to General Hospital Sarajevo because of high fever, sweating, high erythrocyte sedimentation rate and back pain. Three months prior to admission he has started complaining of pain around inferior scapula angle, profuse night sweats and prolonged fever (about 38°C) and has lost weight (15 kg during this time). He was given paracetamol and antibiotics (he is allergic to penicillin).

The patient was born with a congenital heart disease – coarctation of the aorta (corrected in 1980 y in Geneva) and he underwent to replacement of a stenotic bicuspid aortic valve in 2007. and three years after he has been implanted a pacemaker. Six months prior to admission pacemaker revision was necessary because of an inflammation at the generator pocket. On admission to hospital he had no significant symptoms and fever was not documented. He had normal hemodynamics and had no peripheral or renal signs of systemic infection. Transesophageal echocardiogram (TEE) examination ten days prior to hospitalization showed no signs of prosthetic valve or electrode infections. Heart auscultation revealed mechanical aortic valve click. Transthoracal echocardiogram (TTE) on admission showed vegetations on aortic prosthetic valve and possible periaortic abscess formation (Figure 1). Laboratory investigation showed a total white blood cell count of 9,5x10^9, hemoglobin level of 117 g/l, platelet count of 405x10^9, erythrocyte sedimentation rate was 97 mm/h, fibrinogen level and C reactive protein concentration were constantly elevated and rheumatoid factor (RF) was positive. Rheumatologic testing was conducted and serological testing for Q fever was ordered. The tests revealed positive anti-nuclear antibodies (ANA) antibodies and F2-IgM Coxiella Burnetii-antibody. Initial therapy with Hiramycin 2x100mg
was started and the patient was advised to return for follow-up in two weeks and for retesting for Q fever. In this period he was constantly afebrile and that may led away from bacterial IE diagnosis. In January 2012 the patient was admitted to KCUS-Heart Center for reevaluation and repeated fever. On admission he presented with difficulty walking due to swollen ankles with petechial-purpuric rash and vesicular-bullous blister around medial malleolus. INR was 2.75 and TTE revealed vegetations on mechanical valve. Serologic testing for Q fever revealed F2-IgM and IgG positive. The patient was redirected to Clinic for Infectious Diseases. He was prescribed Vancomycin 2x1 g, Gentamycin 2x80mg, Rifampycin 2x300 mg. TTE showed diffuse partially mobile vegetations on the ventricular and atrial side of the mitral valve (MV) with mild mitral regurgitation (MR), aortic regurgitation (AR) and tricuspid regurgitation (TR). TEE showed three mobile vegetations on the ventricular side of the aortic valve (AV) and on the atrial side of the anterior leaflet of the MV. Cardiosurgeon did not suggest any surgical treatment. However, his condition deteriorated suddenly, and he presented with worsening of cutaneous vasculitis, subacute glomerulonephritis and subsequent acute respiratory distress syndrome (ARDS) and septic shock. Chest auscultation was significant for basal bilateral fine crackles. Chest x-ray showed progressive bilateral infiltrative changes. He was intubated and mechanically ventilated for six days. Antibiotic therapy was changed to Doxycyclin 2x100 mg, Tienam 3x1 g, Funzol 1x400 mg and finally Linezolid 2x600 mg. Third serologic testing results showed F2-IgM positive, F1-IgG and F2-IgG negative. It was concluded that it was a false positive reaction and Q fever was definitely excluded. In addition our patient developed left femoral vein thrombosis and lymphoedema in his right arm with possible superficial vein thrombosis. TEE showed vegetation on artificial valve but patient was hemodynamically insufficient and no definitive surgical therapy was indicated. After stabilization he was discharged from Intensive Care Unit and sent back to Heart Center. Subsequent laboratory investigation showed high cytoplasmic (classical) antineutrophil cytoplasmic antibodies (c-ANCA) which led to suspect Wegener's granulomatosis and corticosteroid therapy was administrated (Medrol 1x12 mg). It was not conclusive because of no evidence of upper respiratory involvement. At the end TTE showed enlarged heart chambers, LV mild dilated and concentric hypertrophy with ejection fraction about 40%, degenerative postinflammatory MV changes (figure 2), mild MR and TR, postinflammatory aortic
root fibrosis (Figure 4) and moderate AV stenosis (AVPG max 50.9 mmHg, AVPG mean 24 mmHg) (Figure 3) with no pericardial effusion. Because of bilateral necrosis of the feet plastic surgeon recommended surgical treatment. The patient was discharged with bilateral toxic peroneal paresis treated with gabapentin.

**Discussion**

We presented a case of culture-negative IE with multiple episodes of recurrent fever, vegetation formation on the prosthetic aortic valve, thromboembolic incidents through the whole body and subsequent complication development. Initial suspicion of Q fever was definitely excluded by serological testing showing nonspecific IgM positivity, probably RF related. Later Wegener’s granulomatosis diagnosis was dismissed because no evidence of upper respiratory tract involvement was found. IE has showed to be a great challenge to diagnose because of its non-specific symptomatology. Patients may therefore present to a variety of specialists who may consider a range of alternative diagnoses including chronic infection, rheumatologic and autoimmune disease, or malignancy. Classic textbook signs may still be seen in the developing world, although peripheral stigmata of IE are increasingly uncommon elsewhere, as patients generally present at an early stage of the disease. However, vascular and immunological phenomena such as splinter hemorrhages, Roth spots, and glomerulonephritis remain common, and emboli to the brain, lung or spleen occur in 30% of patients and are often the presenting feature (2). In a febrile patient, the diagnostic suspicion may be strengthened by laboratory signs of infection, such as elevated C-reactive protein or sedimentation rate, leukocytosis, anemia, and microscopic hematuria. TTE/TEE are now ubiquitous and their fundamental importance in diagnosis, management, and follow-up of IE is clearly recognized. Echocardiography must be performed rapidly, as soon as IE is suspected. Three echocardiographic findings are major criteria in the diagnosis of IE: vegetation, abscess, and new dehiscence of a prosthetic valve (1). The sensitivity of TTE ranges from 40 to 63% and that of TEE from 90 to 100%. However, diagnosis may be particularly challenging in IE affecting intracardiac devices, even with use of TEE. Identification of vegetations may be difficult in the presence of preexisting severe lesions (mitral valve prolapse, degenerative calcified lesions, prosthetic valves), if vegetations are very small (<2 mm), not yet present (or already embolized), and in non-vegetant IE. In cases with an initially negative examination, repeat TTE/TEE must be performed 7–10 days later if the clinical level of suspicion is still high. Multislice computed tomography (CT) has recently been shown to give good results in the evaluation of IE-associated valvular abnormalities, as compared with TEE, particularly for the assessment of the perivalvular extent of abscesses and pseudoaneurysms (1). The American Heart Association encourages acquiring blood cultures promptly when diagnosing infective endocarditis. In fact, a positive blood culture is a major diagnostic criterion for infective endocarditis. Most patients with infective endocarditis will yield a positive culture. However, low-grade bacteremia (less than 50
colony-forming units per milliliter of blood) is a common occurrence. In these cases of low-grade bacteremia, the administration of antibiotics before obtaining blood cultures may affect bacterial growth in the sample and hinder the ability to appropriately tailor therapy to the offending pathogen (10). Bacterial culture is integral to microbiological practice, since it enables empirical treatments to be refined to agents that may be less toxic, cheaper, or more effective (11). Blood culture negative infective endocarditis (BCNIE) occurs in 2.5–31% of all cases of IE, often delaying diagnosis and the initiation of treatment, with profound impact on clinical outcome. BCNIE arises most commonly as a consequence of prior antibiotic administration, underlying the need for withdrawing antibiotics and repeat blood cultures in this situation. An increasingly common scenario is infection by fastidious organisms with limited proliferation under conventional culture conditions, or requiring specialized tools for identification. These organisms may be particularly common in IE affecting patients with prosthetic valves, indwelling venous lines, pacemakers, renal failure, and immunocompromised states (1). Cardiac device related infective endocarditis (CDRIE) is defined as an infection extending to the electrode leads, cardiac valve leaflets, or endocardial surface. CDRIE must be suspected in the presence of unexplained fever in a patient with a cardiac device (CD). In the majority of patients, CDRIE must be treated by prolonged antibiotic therapy associated with device removal (1). Surgical treatment is used in approximately half of patients with IE because of severe complications. Reasons to consider early surgery in the active phase, i.e. while the patient is still receiving antibiotic treatment, are to avoid progressive heart failure (HF) and irreversible structural damage caused by severe infection and to prevent systemic complications (1). Perivalvular extension of IE is the most frequent cause of uncontrolled infection and is associated with poor prognosis and high likelihood of need for surgery. Perivalvular complications include abscess formation, pseudoaneurysms, and fistulae. Surgery is indicated when fever and positive blood cultures persist for several days (7–10 days) despite an appropriate antibiotic regimen and when extra-cardiac abscesses (splenic, vertebral, cerebral, or renal) and other causes of fever have been excluded. Embolic events are a frequent and life-threatening complication of IE related to the migration of cardiac vegetations. The decision to operate early for prevention of embolism must take into account the presence of previous embolic events, other complications of IE, the size and mobility of the vegetation, the likelihood of conservative surgery, and the duration of antibiotic therapy (1).

Conclusion

Signs and symptoms of an IE can be very unspecific making the diagnosis, treatment and prognosis challenging. The presented case of a prolonged, initially unexplained febrile state was treated with broad-spectrum antibiotics without previously taking the appropriate samples for cultures that reduced the chances of identifying causative microorganism. We believe that contamination was made by superficial dermal Staphylococcus at the time of CD implantation. Good response to Linezolid therapy leads to believe that probably causative organism is Staphylococcus aureus which had spread hematogenously to most vulnerable prosthetic aortic valve (PAV) and then on to MV giving clinical presentation of endocarditis lenta. Metastatic abscesses and distal necrosis in an septic environment can be very serious subsequent events. This interesting case of false positive Q fever can be explained with positive RF which is also an IgM molecule and is positive in 50% cases of systemic infections. Detailed early evaluation and interdisciplinary action is a key point to correct diagnosis and early treatment of IE before metastatic and local serious complications. Different course of action might bring faster diagnosis and better survival rate with patients' fewer consequences in the future.

Conflict of interest

Authors declare no conflict of interest.
References