Diagnostics and treatment of recurrent endocarditis - case report

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ABSTRACT

Infective endocarditis is an inflammation of the inner surface of the heart, which is most commonly caused by bacteria and may lead to severe complications. A 44-year-old male patient was admitted due to suspected recurrent infective endocarditis (IE). The patient had a history of infections with Staphylococcus aureus etiology in 2014, 2015, and 2018, including IE affecting the mitral valve, sepsis after a dental procedure and septic shock. On examination, the patient presented a diastolic murmur 4/6 (Levine Scale) over the apex of the heart. The enlargement of the left atrium and left ventricle was detected in the transthoracic echocardiogram. Laboratory tests revealed elevation of the C-reactive protein and the presence of Methicillin-sensitive Staphylococcus aureus in blood culture. The patient was treated with vancomycin. Single photon emission tomography and computed tomography with technetium-99m-hexamethyl propylene amino-oxime-labeled leukocytes (99mTc- HMPAO-SPECT/CT) were performed, revealing no abnormalities. Patients with the first incident of endocarditis are at risk of recurrence and of developing additional complications. Early diagnosis and treatment of infective endocarditis are vital.

Keywords: recurrent endocarditis, Staphylococcus aureus, sepsis, septic shock

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INTRODUCTION

Infective endocarditis (IE) is a rare but one of the most lethal infectious diseases [1]. Its prevalence in the general population is about 3.19-9.3 episodes per 100,000 inhabitants yearly [1]. In-hospital mortality is as high as 24%, along with a 1-year mortality rate that exceeds 30% [2].

The incidence of recurrent endocarditis is estimated to range from 2% to 31%. Bacterial infection is responsible for the etiopathogenesis of IE in most cases, while the microorganism most commonly identified is *Staphylococcus aureus* [1,3]. The symptoms are mainly fever, found in more than 95% of IE patients, chills, malaise and fatigue.

The diagnosis of IE is based on the patient’s clinical presentation supported by consistent microbiologic findings and the documentation of IE-related cardiac lesions by imaging techniques [2,4]. Modified Duke criteria are used to assess the probability of diagnosing IE [3,4,5,6] .

The new European Society of Cardiology (ESC) Guidelines for managing endocarditis were published on August 25, 2023 [4,7] providing an update on the criteria above.

Definitions of the 2023 European Society of Cardiology modified diagnostic criteria of infective endocarditis [4,7]:
The major criteria are:
1. Positive blood cultures for IE:
   a. Typical microorganisms consistent with IE from 2 separate blood cultures;
   b. Microorganisms consistent with IE from persistently positive blood cultures;
   c. Single positive blood culture for Coxiella burnetti or antiphase I Immunoglobulin G antibody titer >1:800;
2. Imaging positive for IE:
   a. Valvular, perivalvular/periprosthetic and foreign material anatomic and metabolic lesions characteristic of IE detected by any of the following imaging techniques:
   a. Echocardiography (Transthoracic (TTE) and Transesophageal TOE).
   b. Cardiac Computed Tomography.
   c. [18F]-FDG-PET/CT(A) (Fluorodeoxyglucose positron emission tomography/CT(A), computed tomography (angiography)).
   d. WBC SPECT/CT (white blood cell single photon emission tomography/computed tomography).

The minor criteria are:
1. Predisposing conditions (i.e., predisposing heart condition at high or intermediate risk of IE or PWIDs)
2. Fever defined as temperature >38°C
3. Embolic vascular dissemination (including those asymptomatic detected by imaging only):
   a. Major systemic and pulmonary emboli/infarcts and abscesses.
   b. Haematogenous osteoarticular septic complications (i.e. spondylodiscitis).
   c. Mycotic aneurysms.
   d. Intracranial ischaemic/haemorrhagic lesions.
   e. Conjunctival hemorrhages.
   f. Janeway’s lesions.

4. Immunological phenomena:
   a. Glomerulonephritis.
   b. Osler nodes and Roth spots.
   c. Rheumatoid factor.

5. Microbiological evidence:
   a. Positive blood culture but does not meet a major criterion as noted above.
   b. Serological evidence of active infection with organism consistent with IE.

The recommended treatment of IE includes aminoglycosides, and in the case of *staphylococcal* endocarditis, anti-*staphylococcal* penicillins if the isolates are methicillin-susceptible (alternative, cefazolin) and vancomycin for methicillin-resistant isolates (alternative, daptomycin) [7-8]. For *staphylococcal* prosthetic valve endocarditis, consider including gentamicin in the first 2 weeks or rifampicin for the entire treatment period, i.e., 6 weeks, to enhance treatment [9]. In patients stabilized after initial intravenous treatment, it is safe to change treatment to oral [10].

CASE REPORT

A white European man, 44 years old, who had recurrent hospitalizations for IE and had MSSA (methicillin-sensitive *Staphylococcus aureus*) in his body. He was chronically suffering from severe atopic dermatitis (AD) and hypertension. In 2014, the first episode of IE occurred. It involved a native mitral valve with *Staphylococcus aureus* etiology. The echocardiography revealed a 2x1.5 cm vegetation on the anterior mitral valve leaflet and prolapse of the anterior mitral valve leaflet. He was treated in the hospital for 6 weeks with vancomycin along with simultaneous gentamicin administration for one week. The antibiotic therapy was effective, as demonstrated by the clinical state and the resolution of the vegetation. In 2015, the patient underwent a dental procedure without antibiotic prophylaxis, resulting in subsequent *staphylococcal* sepsis. Scintigraphy of inflammatory foci with labeled leukocytes was performed, reporting an inflammatory focus within the right palatine tonsil. Retreatment with vancomycin with gentamicin was applied.

In 2018, the patient participated in a clinical trial for severe AD. After administration of two doses of nemolizumab (a humanized monoclonal antibody against interleukin-31 receptor A, which demonstrates great efficiency in reducing pruritus
and to a lesser degree, dermatitis associated with AD), he relapsed with fever, which progressed to sepsis. The man was hospitalized in an intensive care unit for septic shock - treated with vancomycin and meropenem.

In March 2022, the patient presented in the hospital emergency department with symptoms of inflammation and a fever of up to 38 degrees Celsius. He was admitted to the Cardiology Department.

During the hospitalization, blood cultures revealed the presence of Methicillin-sensitive Staphylococcus aureus (MSSA). Transesophageal echocardiography did not show vegetation. The result was comparable to previous examinations. Laboratory tests showed as follows: leukocytes - 21,900/μl (standard 4,000-10,000/μL), C-reactive protein – 248 milligram/liter (mg/L) (normal <5 mg/L), procalcitonin 2.18 nanogram/milliliter (ng/mL) (normal <0.05ng/mL). It was decided to begin antibiotic therapy following the result of the antibiogram. Vancomycin 1 gram (g) twice a day was administered, improving the clinical condition and regression of inflammatory parameters.

After the patient's condition was initially stabilized, further cardiac diagnostics were considered to be necessary, mainly due to the patient's history of recurrent MSSA infections.

Therefore, after ten days of hospitalization, the patient was transferred to a higher reference-level unit.

On admission, the patient was in good general condition, hemodynamically stable, with no fever. He denied having any stenocardia symptoms or exertional dyspnea. On physical examination, there were no features of stasis in the pulmonary or peripheral circulation, the heart rate was regular, 90/min with properly accented tones, and a diastolic murmur 4/6 (Levine Scale) over the apex of the heart. Auscultation of the lung fields finds a symmetrical alveolar murmur. Skin on the hands, especially the right hand, is scarred, scaly, and rough with deformed fingers. In laboratory tests: the C-reactive protein was elevated 8.1mg/L (normal <5.0mg/L), N-terminal pro-B-type natriuretic peptide 70pg/mL (normal <125pg/mL), procalcitonin <0.05ng/mL (normal). Methicillin-sensitive Staphylococcus aureus was detected in blood culture. Transthoracic echocardiography showed slightly enlarged dimensions of the left atrium and left ventricle with preserved systolic function, normal transvalvular pressure gradients, prolapse of the anterior mitral valve leaflet with a moderate eccentric regurgitation along the posterolateral atrial wall, and normal appearance of the other valves. Duplex Doppler ultrasound of the cephalic arteries showed standard spectra and flow velocities.

Figure 1. The single-photon emission and computed tomography with technetium99m-hexamethylpropyleneamineoxime—labeled leukocytes (99mTc-HMPAO-SPECT/CT) had no pathological findings.
Patient was continued to be treated with targeted antibiotic therapy - vancomycin 2g per day due to the detection of Methicillin-sensitive Staphylococcus aureus in the bloodstream. During hospitalization, the vancomycin was changed to 3 grams per day due to the low level of antibiotic in the blood test. As a result of the appropriate treatment, the patient did not develop any complications.

The single-photon emission tomography and computed tomography with technetium99m-hexamethylpropylamineoxime-labeled leukocytes (99mTc-HMPAO-SPECT/CT) were performed during the hospitalization. No pathological uptake of radiolabeled leukocytes in the cardiac region was observed, showing an excellent response to ongoing treatment. The examination is presented in Figure 1.

DISCUSSION

Treatment of recurrent endocarditis is extremely important and must be implemented as soon as possible to avoid the development of severe complications such as embolism, metastatic infections, damage to heart valves, heart failure, arrhythmia and conduction disturbances, as well as kidney failure [11]. Patients who have had IE at least once are at risk of recurrence, particularly if they remain carriers of the bacterium that caused it, in this case Staphylococcus aureus [12].

The new European Society of Cardiology (ESC) Guidelines for the management of endocarditis change the definition of the disease considering the ESC-modified diagnostic criteria, which include, in a broader way than before, the results of diagnostic imaging procedures including echocardiography, tomography, PET (positron emission tomography) scan and scintigraphy [7]. Recommendations for prophylaxis were also modified by expanding the indications to include new patient groups, including patients after valve repair procedures performed from percutaneous access, with LVADs (Left Ventricular Assist Devices), and after heart transplantation. The guidelines have also been widened to include other groups of procedures and dental interventions, which have so far appeared as the sole ones. Current guidelines also introduce other imaging methods into clinical practice: leukocyte-labeled SPECT, PET, CT (computed tomography), and MRI (magnetic resonance imaging). Patient treatment algorithms have also been revised. Oral ambulatory treatment of selected patients with uncomplicated conditions from the 10th day of antibiotic therapy is safe. It is associated with reduced mortality at both 6-month and 5-year follow-up. Recommendation classes have also been raised for many surgical indications, emphasizing the prevention of embolic complications in the patients described.

Antimicrobial treatment should be in line with current recommendations for best clinical outcome. The decision to treat with vancomycin at a dose of 1g twice a day complied with guidelines for the treatment of IE [8]. In addition, it should be emphasized that during hospitalization, blood levels of the antibiotic were also measured, and when they proved to be insufficient, the dose of vancomycin was increased to 1g three times a day. Furthermore, inflammatory markers were continuously monitored and decreased significantly (C-reactive protein decreased from 248mg/L to 8.1mg/L (normal <5mg/L) and procalcitonin from 2.18ng/mL to normal <0.5mg/mL), which most clearly confirms the effectiveness of the treatment [13].

Moreover, this case demonstrates the importance of cooperation between smaller hospitals and those with more significant experience and diagnostic capabilities. A patient suffering from a severe infection caused by the same pathogen for the fourth time should be consulted, as presented, by a multi-specialized panel. Additionally, performing tests such as transthoracic echocardiography and 99mTc-HMPAO-labeled leukocyte SPECT/CT in such a patient allows an exact assessment of the patient's condition. It greatly facilitates making decisions on further conservative or invasive treatment [14]. In the present case, echocardiography was the study of choice to evaluate the heart valves for visible vegetation and abnormalities in their function. Considering the absence of visible vegetation on ECHO examination, 99mTc-HMPAO-labeled leukocyte SPECT/CT was performed. This allowed a confident decision to leave the patient on conservative treatment.

The analysis of this case raises at least one issue of concern. Any dental procedure in post-IE patients must be performed under antibiotic prophylaxis [15]. The lack of antibiotic protection can lead to severe complications such as IE recurrence or sepsis in the presented patient [16].

Additionally, the severe form of AD that the presented patient suffered from is a rare predictor of developing IE [17]. Patients with atopic dermatitis have a high rate of skin surface colonization of Staphylococcus aureus [18], which is also the main microorganism causing infective endocarditis [19]. Therefore, the treatment of AD is of such importance in the prevention of IE. However, special attention should be paid to such patients when qualifying for anti-Interleukin-31 receptor A monoclonal antibody treatment to prevent serious consequences such as sepsis.

CONCLUSION

Patients who develop endocarditis for the first time need to be treated with particular caution, as they are at risk of recurrence, as demonstrated in this case. Prevention of IE and carrying out a detailed
diagnosis and early inclusion of treatment are essential in managing the patient as they reduce the need for invasive treatment and the occurrence of complications and, in some cases, mortality.

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**Conflicts of interest**

There are no conflicts of interest to declare.

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