Novel treatment (new drug/intervention; established drug/procedure in new situation)

Thrombolysis is an appropriate treatment in lead-associated infective endocarditis with giant vegetations located on the right atrial lead

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Summary

CD endocarditis is a potentially lethal complication after implantation of permanent pacemakers or implantable cardioverter-defibrillators. Complete extraction of the hardware along with antibiotic treatment is the standard therapy. However, there is no standard procedure in the treatment of lead-associated infective endocarditis with large thrombotic vegetations. The authors present the case of a 60-year-old patient with a large vegetation located on the right atrial lead. Due to a high surgical and thromboembolic risk, especially of acute massive pulmonary embolism, the patient received recombinant tissue plasminogen activator to dissolve the thrombus under echocardiographic monitoring. The thrombotic masses were substantially reduced after thrombolysis. Therefore, standard transvenous extraction of the leads could be performed and high risk cardiac re-operation could be avoided.

BACKGROUND

Cardiac device (CD) endocarditis is a rare, but potentially lethal complication after the implantation of pacemakers (PMs) or implantable cardioverter-defibrillators (ICDs). Death rates of 30 to 35% have been reported.¹ Electrode lead endocarditis occurs in 1 to 7% of PM- and ICD-implantations.²⁻³ In some cases large thrombotic vegetations can develop on the leads. These vegetations cause a high thromboembolic risk of acute pulmonary embolism during transvenous lead extraction.⁴⁻⁵

Usually a combined treatment including surgery and antibiotics is the best approach for successful eradication of the infection. But the death rates are still up to 12.5%.⁶⁻⁸ Several clinical trials have shown that a pharmacological treatment without explantation of the entire hardware is obsolete. No standard procedure has been defined so far regarding the treatment of large thrombotic vegetations in CD endocarditis.

Therefore, thrombolytic therapy under echocardiographic monitoring might be an option to prevent the high risk of pulmonary embolism and can help to avoid open heart surgery.⁹⁻¹⁰

CASE PRESENTATION

A 60-year-old male presented with fevers and weight loss of 20 kilograms in the past 3 months in a general hospital. His medical history included a three-vessel coronary artery disease undergoing coronary artery bypass graft surgery in 1993. In addition the patient was treated by a cardiac resynchronisation therapy (CRT) due to an impaired left ventricular function (ejection fraction 35%), severe dyspnoea (New York Heart Association III), a left bundle branch block (QRS 140 ms) and a stable sinus rhythm in 2009. The CRT-ICD had been implanted with one lead in the right ventricle, one in the right atrium and an epimyocardial lead on the left ventricle.

The patient was diagnosed with a lead-associated infective endocarditis and was transferred to our university hospital for ICD-explantation.

INVESTIGATIONS

The physical examination showed no heart murmurs, a normal pulmonary status and no signs of septic embolism. He presented with fevers up to 39.5°C with a respiratory rate of 21 breaths/min and a pulse rate of 100 beats/min. The blood pressure was 110/80 mm Hg. The ECG showed a ventricular paced rhythm. His white blood cell count was 22960 cells/μl with an elevated C reactive protein of 27mg/dl. He also suffered from anaemia with a haemoglobin of 8.9 g/dl. A chest x-ray showed an enlarged cardiac silhouette, the lung fields were clear. Transthoracic (TTE) and transoesophageal (TEE) echocardiography revealed three vegetations, two small masses measuring 6×12 mm and 6×9 mm respectively, and one large adherent thrombotic vegetation (36×41 mm) on the right atrial lead prolapsing into the right ventricle and reaching the vena cava superior (figure 1A,B). There were no signs of a right ventricular overload or pulmonary hypertension. The abdominal ultrasound did not reveal any signs of embolism in the abdomen. Several sets of blood cultures were collected, which revealed *Propionibacterium acnes*, an uncommon finding in infective endocarditis.

TREATMENT

After an empiric intravenous antibiotic therapy including vancomycin 1 g per day and gentamycin 240 mg per day, the antibiotic regimen was changed according to the antibiogram of the detected *P acnes* to rifampicin 600 mg per day and daptomycin 700 mg per day intravenously.

An emergency surgery was not indicated due to the stable clinical condition of the patient.

Figure 1 (A, B) Transthoracic apical four chamber view demonstrates a large vegetation (24×46 mm) in the right atrium adherent on the right atrial lead with protrusion in the right ventricle (A). Transoesophageal echocardiography shows three vegetations, two small masses 6×12 mm and 6×9 mm and one large mass (36×41 mm) adherent on the atrial lead and reaching into the vena cave superior (B). (C, D) Transoesophageal and transthoracic echocardiography shows slightly reduced thrombotic mass on the right atrial lead after the first thrombolysis with 50 mg recombinant tissue plasminogen activator over 2 h. (E, F) After the second thrombolysis transthoracic echocardiography does not show any vegetations in the apical four chamber view (E). Transoesophageal echocardiography confirms that the large vegetation on the right atrial lead is dissolved, thrombotic masses remain in the vena cava superior measuring 10×20 mm which means a significant reduction of the thrombotic mass in the right atrium after lysis (F).

Primary transvenous extraction of the leads would have gone along with a high risk of fulminant septic pulmonary embolism due to the large thrombotic mass in the right atrium and the vena cava superior.^{11 12} Open heart surgery was discussed, but was considered to be a high risk intervention as well, as a median thoracotomy would have meant a cardiac re-operation with increased perioperative mortality. Right lateral thoracotomy was the third option, but the perioperative risk was not substantially less than in the other procedures.

Therefore, we decided to perform an intravenous thrombolysis with recombinant tissue plasminogen activator (rtPA) using a dosing regimen of two infusions of 50 mg, each given over 2 h. The thrombolysis was performed under echocardiographic monitoring. Anticoagulation was conducted with unfractionated PTT-adjusted heparin administered intravenously (aim 70–80 s).

Echocardiography showed a reduction of the thrombotic material on the lead as well as in the vena cava superior during thrombolysis. After the first administration of rtPA the large thrombotic mass on the atrial lead was slightly reduced in size and measured 26×39 mm (figure 1C,D). After the second thrombolysis there was

no vegetation detected on the lead in TTE (figure 1E). TEE confirmed these findings and revealed substantially reduced thrombotic material (10×20 mm) in the vena cava superior. The large vegetation on the lead was dissolved (figure 1F). The systolic pulmonary artery pressure was elevated at 40 mm Hg after thrombolysis. The right ventricle was slightly enlarged with 33 mm as a sign of pulmonary embolism during lysis. The patient however, did not suffer from dyspnoea and was haemodynamically stable during the treatment.

As infection parameters and fevers slightly increased after thrombolysis, probably due to bacteremia and septic pulmonary embolism, penicillin G 5 000 000 units per day were added to the antibiotic regimen.

After effective thrombolysis standard transvenous extraction of the right atrial and right ventricular lead was successfully performed as well as the explantation of the ICD. After explantation of the device, the ICD-pocket did not show any pathological findings or clinical signs of infection. The pocket was rinsed thoroughly with nebacetin-solution. The left epimyokardial lead was disconnected and isolated with a lead-end-cap-kit to be left in the ICD-pocket. A specimen for culture

was obtained and showed *Bacillus* species, which were determined to be caused by secondary contamination.

The patient was referred to the general hospital after successful extraction of the ICD system. The oral anti-coagulation with phenprocoumon was initiated with an international normalised ratio aim of 2 to 3.

OUTCOME AND FOLLOW-UP

The patient received antibiotics intravenously for 4 weeks. As infection parameters decreased, the patient was discharged from the general hospital and an oral antibiotic treatment with amoxicillin 875 mg and clavulanic acid 125 mg was recommended for another 2 weeks.

A follow-up examination after 2 weeks showed slightly increased infection parameters and the patient was admitted to the general hospital again. CT scan revealed pneumonia of the right upper and lower lobe possibly due to septic embolism and a subtotal embolism of the right and left lower pulmonary artery. During the following days the inflammatory parameters normalised without another antibiotic treatment. Until today any further follow-up examinations showed negative blood cultures, no vegetations in echocardiography, no fevers and no signs of infection. Re-implantation of the CRT-ICD device was not performed yet as left ventricular function had improved and the patient showed permanent atrial fibrillation.

DISCUSSION

CD infection results in serious morbidity with prolonged hospital stays, repeated procedures of device extraction and re-implantation.¹³ There is a high rate of relapsing bacteraemia. Reported death rates for CD endocarditis without device extraction range from 31 to 66%, compared to 8 to 12.5% in patients in whom the hardware was extracted, followed by prolonged antibiotic therapy.¹⁴

Surgical therapy with exploration of the right chambers and the pulmonary arteries under full cardiopulmonary bypass containing lead extraction and embolectomy is the classic treatment⁶⁻⁸ of CD infection with large thrombotic vegetations, if transvenous extraction cannot be performed. Current guidelines suggest early cardiac surgical intervention, especially if a prosthetic intracardiac device is involved.¹⁰

In our case primary surgical intervention was associated with a high perioperative morbidity and mortality due to the large thrombotic mass on the atrial lead and due to the fact of cardiac re-operation.

We considered the risk of septic embolism in case of a transvenous removal of the right atrial lead to be extremely high. Taken into account the size of the vegetation, primary extraction could have led to massive pulmonary embolism with consecutive haemodynamic instability and cardiogenic shock.

Thrombolysis in CD endocarditis with large thrombotic vegetations is rarely discussed in the literature, but there are some data about lysis of free-floating right heart thrombi. Free-floating right heart thrombi are a rare phenomenon and have a dismal prognosis. Retrospective analysis in this clinical trial compared the outcome of patients after thrombolysis with rtPA, intravenous heparin therapy alone, surgical embolectomy on cardiopulmonary bypass and interventional techniques. Outcome

was poor in the heparin group. Early thrombolysis and embolectomy improved the clinical outcome.⁴ Similar to pulmonary embolism or other thrombi in the right heart, thrombolysis may be advocated first in CD endocarditis with masses on the leads before transvenous extraction to avoid pulmonary embolism.¹⁵⁻¹⁷ It may favourably affect the clinical outcome of patients with large vegetations.¹⁸ There are also other advantages of this procedure like accelerated thrombus lysis and pulmonary reperfusion, reduction of pulmonary hypertension and the reduction of clots in several locations at the same time.¹⁷ Finally, it is a simple, rapid and widely applicable treatment, which can be administered at the bedside of any intensive care unit. Three lytic drugs have been approved by the FDS of the United States in cases of severe pulmonary embolism and in cases of thrombi in the right heart: urokinase, streptokinase and rtPA.

We chose rtPA because of its faster haemodynamic improvement, its fibrin specificity and its short half-life, so that surgical treatment still can be performed in the case of haemodynamic instability. We used rtPA with an intravenous regimen of twice 50 mg over 2 h.¹⁷

We also recommend that patients should be admitted to an intensive care unit, because cardiogenic shock or sudden death can occur and mechanical ventilation may be required. Monitoring by TTE¹⁹ is useful during thrombolytic administration to assess the outcome of the thrombus and the right ventricle function. Transoesophageal examination²⁰ is rarely mandatory, but we performed it in this case before and after lysis as TTE did not show all the vegetations on the leads and in the vena cava superior.^{4 19 20}

Early surgery with complete device extraction and an early intravenous antibiotic therapy clearly remains the classic treatment in CD endocarditis. However, the individual risks of the single patient must be taken into account. Therefore it might be advisable in some cases to perform thrombolysis first.²¹⁻²³

Learning points

- ▶ Complete extraction of the CD should be considered as standard therapy for most patients with CD endocarditis in combination with antibiotic treatment.
- ▶ In case of large vegetations on the leads thrombolytic therapy might be an additional treatment option to avoid open heart surgery and fulminant pulmonary embolism, and should be performed before standard transvenous lead extraction.
- ▶ Thrombolysis should be administered under echocardiographic controls to monitor the size of the thrombotic material and the right ventricular function in case of acute pulmonary embolism.

Competing interests None.

Patient consent Obtained.

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