A case of histopathologically confirmed infective endocarditis with no vegetations observed during preoperative diagnosis

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Abstract An 81-year-old woman on maintenance hemodialysis (HD) was admitted to the hospital with fever and repeated positive blood cultures for coagulase-negative staphylococci. The patient had a history of aortic valve replacement for aortic valve stenosis (AS). Although one major criterion and two minor criteria from the Duke criteria were met and therefore infective endocarditis (IE) was suspected for this case, no definitive diagnosis was made. Vegetations were not observed on the transesophageal echocardiography, but AS was prominent. The patient was refractory to antibiotic therapy using vancomycin, and blood cultures did not convert to negative. To treat the suspected IE and AS, aortic valve replacement was performed. Although vegetations were not observed in the resected valve, gram-positive cocci were found in clusters, and a histopathological diagnosis of IE was made. The postoperative blood culture converted from positive to negative, and the patient was subsequently discharged from the hospital. While relative risk of IE is high in HD patients, a definitive diagnosis of IE may be difficult due to calcification of the valve and valve replacement. In HD patients with bacteremia, suspicion of IE should be aggressively pursued if other sources of infections are negative, and if the patient is refractory to medical treatment, surgical treatment may be necessary.

Keywords Infective endocarditis · Hemodialysis · Aortic valve stenosis · Coagulase-negative · Staphylococci

Introduction

The relative risk of infective endocarditis (IE) is as high as 16.9 in hemodialysis (HD) patients compared with the general population, as valve calcification caused by abnormal calcium–phosphorus metabolism induces valve abnormalities, vascular access is available, and immune function is compromised due to renal failure [1]. The mortality rate for IE among HD patients is relatively high: approximately 30 % within 30 days of hospitalization in patients with poor prognosis [1]. Here, we report a case in which vegetations were not observed during the preoperative diagnosis, but where a definitive diagnosis of IE was made histopathologically.

Case report

An 81-year-old woman on maintenance HD for 26 years, due to chronic glomerulonephritis, was initially admitted to the hospital with fever starting 3 months prior, elevated C-reactive protein levels, and identified methicillin-susceptible coagulase-negative staphylococci (CNS) in blood cultures.

The patient had a history of aortic valve replacement for aortic valve stenosis (AS) at the age of 72 years. A biosynthetic valve was selected in a manner most consistent with the patient's wishes. She also has serious allergies to β -lactam and fluoroquinolone antibiotics.

No apparent source of infection was detected, and the patient received vancomycin for 14 days and was

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discharged. After discharge, the patient experienced repeated fever, and blood cultures were found to be positive, prompting suspicion of IE. The patient received vancomycin for 28 days; however, no improvement was observed, and the patient was subsequently hospitalized.

On admission, the patient had a fever of 38.2 °C. Bulbar conjunctiva hemorrhage or rash on the legs and arms were not noted. No neurological abnormalities were found. Systolic regurgitant murmurs (Levine III/VI) were audible at the right sternal border in the 2nd intercostal space. Analysis of sampled blood revealed an elevated inflammatory reaction. The results of blood tests are shown in the table below (Table 1).

A strain pattern was noted on electrocardiograms. Head computed tomography (CT) and magnetic resonance

imaging (MRI) did not reveal cerebral infarction or abscess formation. Chest and abdominal CT did not confirm the apparent source of infection, and a spine MRI also did not show abscess formation. Valve calcification was prominent, and infectious vegetations were not obvious on the transthoracic/transesophageal echocardiography; however, severe AS was observed (Fig. 1). The mean aortic valvular pressure gradient was 74.5 mmHg.

Because the patient had repeated CNS-positive bacteremia during a short period of time and other sources of infection were unlikely, IE was suspected. The case met one of the major criteria for blood cultures and two of the minor criteria for predisposition and fever according to the Duke criteria, further suggesting IE. However, a definitive diagnosis was not made.

While antibiotic therapy with vancomycin was continued even after hospital admission, blood culture results remained positive. Because the patient had severe allergies to multiple antimicrobial agents, changing the medication was considered risky. Aortic valve replacement was performed to treat the suspected IE and AS. In the resected valve, no vegetations were found macroscopically. However, gram-positive cocci were found in clusters histopathologically, and a diagnosis of IE was made (Fig. 2).

The postoperative blood culture converted to negative, and antibiotic therapy with vancomycin was continued. The patient was discharged with a favorable prognosis. General clinical course is shown in Fig. 3.

Table 1 Laboratory data at the time of admission

TP (g/dL)	5.8	Na (mEq/L)	140
Alb (g/dL)	2.8	K (mEq/L)	5.2
T-Bil (mg/dL)	0.7	Cl (mEq/L)	103
AST (IU/L)	19	Ca (mg/dL)	8.7
ALT (IU/L)	7	Pi (mg/dL)	4.4
ALP (IU/L)	288	WBC (/μL)	7980
LDH (IU/L)	244	Hb (g/dL)	10.8
γ-GTP (IU/L)	40	Plt ($\times 10^4/\mu\text{L}$)	15.6
CK (IU/L)	18	PT-INR	1.08
BUN (mg/dL)	50.4	PT (s)	12.8
Cr (mg/dL)	9.18	APTT (s)	31.6
CRP (mg/dL)	14.4	D-D (μg/mL)	4.8

TP total protein, Alb albumin, T-Bil total bilirubin, AST aspartate aminotransferase, ALT alanine aminotransferase, ALP alkaline phosphatase, γ-GTP gamma-glutamyl transpeptidase, CK creatine kinase, BUN blood urea nitrogen, Cr creatinine, CRP C-reactive protein, Na sodium, K potassium, Cl chloride, Ca calcium, Pi inorganic phosphate, WBC white blood cell, Hb hemoglobin, Plt platelet, PT-INR prothrombin time-international normalized ratio, PT prothrombin time, APTT activated partial thromboplastin time, D-D D-dimer

Discussion

In Japan, the number of patients with end-stage renal failure (ESRD) is increasing, with approximately 310,000 ESRD patients currently on HD. The leading cause of death in this population is cardiac failure, followed by infections

Fig. 1 **a** Calcification of the aortic valve (arrow) and mitral valve (arrowhead) were prominent on transthoracic echocardiographic images, but no warts were apparent. **b** Transesophageal echocardiographic images showed prominent calcification of the aortic valve (arrow), but no warts were apparent

Fig. 2 Aggregation (arrow) of gram-positive cocci is observed in the resected valve (hematoxylin-eosin stain, $\times 40$)

and malignant neoplasms [2]. As such, for immunocompromised ESRD patients, the treatment of infectious diseases is crucial.

The relative risk of IE is high in HD patients [1]. HD patients are prone to developing calcification of the valve [3], and the incidence of valve replacements is high [4]. Calcification and artifacts from replaced valves make detection of vegetations difficult. Therefore, ruling out IE based on echocardiography alone is difficult. However, when negative conversion of cultures is not observed, urgent surgery is indicated for IE [5].

In the present case, it took 5 weeks from admission of this time to perform the operation. Severe AS for which surgery was indicated was observed. Although AS was

prominent and IE was suspected, hemodynamics of the patient was stable and no septic embolisms was detected. Since emergency surgical intervention was not necessary at that time, medical treatment was selected. However, blood culture results were consistently positive. Therefore, aortic valve replacement was performed for the suspected IE and AS, and a histopathological diagnosis of IE was subsequently made. The odds ratio of embolization was 2.80 in the presence of a vegetation larger than ten millimeter [6]. Generally, the presence of septic embolization is a risk of poor prognosis. Since the present patient had no septic embolizations and vegetations, favorable prognosis was achieved.

Why detecting vegetations on echocardiography is so difficult in HD patients is unclear; it may be due to cardiac valvulopathy and artifacts from valve replacements, or to the fact that detectable vegetations are less likely to form in HD patients in the presence of valve calcification and replaced valves—or both. In some cases, as in the present case, macroscopically detectable vegetations are not formed, and bacterial bodies may instead be histopathologically verified.

CNS mostly form normal flora of the skin and its pathogenesis is not always invasive. However, CNS possesses the abilities to form biofilm and adhere to prosthetic surfaces [7]. According to recent study, CNS bloodstream is related to prosthetic device-associated infection in immunocompromised patients [8]. The microbiological characteristics, forming biofilm, may be associated with refractory to medical treatment and not forming vegetations.

In patients with bacteremia that do not have a definitive diagnosis but where IE is suspected and for whom other

Fig. 3 Clinical course: although the patient was suffering from repeated fever and consistent positive blood culture, the fever abated and the blood culture converted to negative after operation

CNS: coagulase negative staphylococci, CRP: C-reactive protein

sources of infections are negative, surgical treatment should be considered if the patient is refractory to medical treatment.

In HD patients, the detection of vegetations on echocardiography and a definitive diagnosis of IE may be difficult, or similar to this case, vegetations may not be formed at all.

Therefore, in dialysis patients with bacteremia, suspicion of IE should be aggressively pursued if other sources of infections are negative. If the patient is refractory to proper antibiotic therapy, surgical treatment should be considered, especially the patients without vegetations and embolizations as in the present case.

Compliance with ethical standards

Conflict of interest All the authors have declared no competing interest.

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