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ORIGINAL ARTICLE

Diagnosis and Treatment of Infective Endocarditis in Chronic Hemodialysis Patients[△]

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Key words: hemodialysis; infective endocarditis; clinical feature

Objective To analyze the clinical features of hemodialysis patients complicated by infective endocarditis.

Methods The clinical features of six such patients admitted to Peking Union Medical College Hospital during the year 1990 to 2009 were analyzed. All of them were diagnosed based on Chinese Children Diagnostic Criteria for Infective Endocarditis.

Results The average age of the six patients was 52.3 ± 19.3 years old. Four were males. Vascular accesses at the onset of infective endocarditis were as follows: permanent catheters in three, temporary catheters in two, and arteriovenous fistula in one. Three were found with mitral valve involvement, two with aortic valve involvement, and one with both. Five vegetations were found by transthoracic echocardiography, and one by transesophageal echocardiography. Four had positive blood culture results. The catheters were all removed. Four of the patients were improved by antibiotics treatment, in which two were still on hemodialysis in the following 14-24 months and the other two were lost to follow-up. One patient received surgery, but died of heart failure after further hemodialysis for three months. One was well on maintenance hemodialysis for three months after surgery.

Conclusions Infective endocarditis should be suspected when hemodialysis patients suffer from long-term fever, for which prompt blood culture and transthoracic echocardiography confirmation could be performed. Transesophageal echocardiography could be considered even when transthoracic echocardiography produces negative findings. With catheters removed, full course of appropriate sensitive antibiotics and surgery if indicated could improve the outcome of chronic hemodialysis patients complicated by infective endocarditis.

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OVER the decades, maintenance hemodialysis population is increasing rapidly. Infective endocarditis (IE) in maintenance hemodialysis was reported for the first time in 1966 by Brescia.¹ It is generally known that hemodialysis increases the morbidity of IE, and IE in turn is a significant contributor to the mortality in hemodialysis patients, just secondary to cardiovascular diseases.² To our knowledge, there have been only few reports on IE in hemodialysis patients in China, possibly due to the underestimation of such condition and ignorance of the diagnosis. Therefore, we reviewed the inpatients' medical records in the past twenty years (1990-2009) in Peking Union Medical College Hospital, finding only six diagnosed cases. Their clinical courses were reviewed according to the references to improve the awareness of this life-threatening condition in clinical practice.

PATIENTS AND METHODS

The medical records of Peking Union Medical College Hospital during the year 1990 to 2009 were retrospectively searched with the keywords of chronic hemodialysis and IE or subacute bacterial endocarditis.

Chinese Children Diagnostic Criteria for Infective Endocarditis were used,³ which are different from the revised Duke's criteria in some aspects. Its major clinical criteria include: (1) positive blood culture for IE (typical micro-organism for IE from two separate blood cultures such as *Streptococci viridans*, *Streptococcus bovis*, *Staphylococcus aureus* or *enterococci*); (2) evidence of endocardium involvement (positive echocardiogram for IE includes vegetation on valve, supporting structures, endocardium, vessels endothelium, or implanted material). And the five minor clinical criteria include: predisposing heart condition, including central catheter implementation and underlying heart diseases; fever $\geq 38^{\circ}\text{C}$ and anemia; positive blood culture not meeting the major criterion. Pathological criterion is vegetation on valve confirmed by pathology with active IE. Cases are defined clinically if they fulfill one major criterion plus two or more minor criteria, or only the pathological criterion.

Statistical analysis

Data were presented as means $\pm$ SD if applicable.

RESULTS

Six patients were identified in the review. The average age was 52.3 ± 19.3 years old. The average disease dura-

tion before starting dialysis was 19.2 ± 7.2 years. Except for one case diagnosed in 1999, all the cases were diagnosed between 2007 and 2009.

In all the cases, the onset of IE was manifested as fever. Vascular accesses at the onset were: permanent catheters in three, temporary catheters in two, and arteriovenous fistula in one. Three had mitral valve involvement, two had aortic valve involvement, and one had both. The vegetations were found by transthoracic echocardiography (TTE) in five, and by transesophageal echocardiography (TEE) in one. Four had positive blood culture findings. The catheters were consequently all removed. The conditions were improved by antibiotics treatment in four patients, two of which were still on hemodialysis in the following 14-24 months and the other two were lost to follow-up. One patient received surgery, but died after hemodialysis for another three months. One was well on maintenance hemodialysis for three months after surgery (Table 1).

DISCUSSION

Maintenance hemodialysis is a unique risk factor for IE. According to United States Renal Data System (USRDS) database, Abbott and Agodoa² found that the age-adjusted incidence ratio for endocarditis of hemodialysis patients to the general population was 17.86 : 1. The retrospective study by Nori et al⁴ showed that the incidence of IE in maintenance hemodialysis patients was 11 per 1 000 patient-years. Due to the peculiarity, some author proposed to add a fifth category in the nowadays accepted four category-classification (native valve IE, prosthetic valve IE, IE in intravenous drug users, and nosocomial IE).⁵

The risk factor was thought to lie in the altered calcium and phosphate metabolism in hemodialysis patients with subsequent micro-inflammatory state. Valvular and perivalvular involvement in end-stage renal disease (ESRD) is most commonly manifested as mitral annular calcification, and calcification of aortic valve and perivalvular structures. Compared with non-ESRD patients, valve calcification in ESRD patients occurs earlier, and mitral and aortic valves are often concomitantly involved.⁶

Bacteremia is very common in hemodialysis patients, and mainly related with repeated venous channel centesis.⁷ Some authors pointed out that the incidence of bacteremia in hemodialysis patients is related with access type, increasing in order of permanent native arteriovenous fistulae, synthetic grafts, central catheters with cuff or without cuff.⁸ Impaired immune system in hemodialysis patients is also accounted.⁷ Arteriovenous fistula was recommended as the first choice as vascular access to

Table 1. Clinical characteristics of six chronic HD patients complicated by infective endocarditis

Items	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
Gender	Female	Male	Female	Male	Male	Male
Age (yr)	43	80	61	53	22	55
Underlying disease	Systematic erythematosus lupus	Chronic glomerulonephritis	Chronic glomerulonephritis	Chronic glomerulonephritis	Systematic erythematosus lupus	Primary hypertension
Duration of fever	7 days	2 months	4 months	9 days	3 months	12 days
Access type	Permanent catheter in right internal jugular vein	Permanent catheter in right internal jugular vein	Arteriovenous fistula	Temporary catheter in right internal jugular vein	Permanent catheter in right internal jugular vein	Temporary catheter in femoral vein
Duration of access before onset	13 months	16 months	10 years	14 days	1 year	30 days
Valve involved	Mitral valve	Mitral valve+aortic valve	Aortic valve	Mitral valve	Aortic valve	Mitral valve
Vegetation size	2 mm×3 mm	Multiple, 16mm×6mm being the largest	4.9 mm×2.7 mm, 5.6 mm×4.9 mm	3 mm×6 mm	30 mm×9 mm	Not mentioned
Underlying heart disease	-	-	-	-	-	Rheumatic heart disease
History of cardiac operation	-	-	-	-	-	-
Cardiac catheterization	-	-	-	-	-	-
TTE detection of vegetation	Detected	Detected	Detected	Detected	Detected	Not detected
TEE detection of vegetation	Not done	Not done	Not done	Not done	Not done	Detected
Total times of blood culture	7	6	7	15	6	3
Positive blood culture	1	0	1	1	3	0
Pathogenic bacteria	<i>Klebsiella pneumoniae</i>	Negative	<i>Enterococcus gallinarum</i>	Methicillin resistant <i>Staphylococcus aureus</i>	Methicillin resistant <i>Staphylococcus epidermidis</i>	Negative
Culture of catheter tip	Negative	Negative	Inapplicable	Methicillin resistant <i>Staphylococcus aureus</i>	Methicillin resistant <i>Staphylococcus epidermidis</i>	Negative
Diagnostic criteria	Endocardial involvement (vegetation)+fever/microbiology/liable factor	Endocardial involvement (vegetation)+fever/liable factor	Endocardial involvement (vegetation)+fever/microbiology/liable factor	Endocardial involvement (vegetation)+fever/microbiology/liable factor	Pathology+endocardial involvement (vegetation)+fever/microbiology/liable factor	Endocardial involvement (vegetation)+fever/liable factor
Duration of intravenous antibiotics	4 weeks	6 weeks	7 weeks	7 weeks	8 weeks	4 weeks
Access change	Temporary catheter in femoral vein for 2 weeks, then shifted to arteriovenous fistula	Temporary catheter in femoral vein for 5 weeks, then shifted to arteriovenous fistula	Permanent catheter in internal jugular vein	Temporary catheter in internal jugular vein for 5 weeks, then shifted to arteriovenous fistula	Temporary catheter in femoral vein for 2 weeks, then shifted to arteriovenous fistula	Arteriovenous fistula
Surgery	Not indicated	Not indicated	Aortic prosthetic valve replacement	Refusal of peritoneal dialysis and surgery	Aortic prosthetic valve replacement	Not indicated
Follow-up	2 years	Lost	3 months	14 months	3 months	Lost
Outcome	Well in maintenance HD	-	Death due to heart failure	Well in maintenance HD	Well in maintenance HD	-

HD: hemodialysis; TTE: transthoracic echocardiography; TEE: transesophageal echocardiography; -: not available.

decrease the incidence of IE in Kidney Disease Outcome Quality Initiative (K/DOQI). Five patients in this study used central catheter, which indicates that central catheter might portend higher risk of IE. The reasons for such predominant use of central catheter are: failed establishment of arteriovenous fistula due to poor vascular condition in one patient, and poor pre-dialysis care so that timely establishment of arteriovenous fistula was delayed in the other four. Therefore, the importance of pre-dialysis care should be emphasized for chronic kidney disease patients.

Controversy exists about whether arteriovenous fistula employed as a long-term access would also cause IE. Doulton et al⁹ found 26.7% of IE in hemodialysis patients was caused by arteriovenous fistula infection. McCarthy et al¹⁰ studied thirteen IE patients due to access infection, among which only one patient was through arteriovenous fistula line. We suggest once hemodialysis patient with arteriovenous fistula access is suspected of IE, arteriovenous fistula infection should be ruled out first. If the result turns out negative, other potential infection sources should be searched with caution.

The most common microbes in hemodialysis patients with IE are *Staphylococcus aureus*, *enterococcus*, and *Streptococcus viridians*, while *Staphylococcus aureus* accounts for more than 75% of them.¹¹ One study showed more than 50% of hemodialysis patients were *Staphylococcus aureus* carriers, with the flora mainly located in their nasal cavity.¹² We recommend that hemodialysis patients should wear masks during the vascular access punctuating, which may be an effective way to avoid bloodborne contamination.

The current international diagnostic criterion of IE is Duke's criteria,¹³ the specificity of which was 99%, but the sensitivity was only over 80%.¹⁴ Spies et al¹⁵ showed 40 cases (6.8%) were hemodialysis patients after reviewing 581 cases of IE patients during eleven years in his cohort by adopting the revised Duke's criteria. Qian et al¹⁴ studied 93 cases with pathological proof, showing the sensitivity of the Duke's criteria was only 43%; however the sensitivity increased to 76% when applied to the Chinese Children Diagnostic Criteria for Infective Endocarditis.³ It is considered that the low rate of positive blood culture is the main reason of a decreased sensitivity of the Duke's criteria in Qian's cohort.¹⁴ There are some limitations in the Duke's criteria when applied to hemodialysis patients with IE.⁵ One item of the Duke's criteria requires the existence of bacteremia without any removable focus of infection, however the vascular access of the hemodialysis patients with

bacteremia of IE is often difficult to remove. Due to the impaired immune system of hemodialysis patients, fever is not as common as in the general population with IE. Furthermore, erythrocyte sedimentation rate, anemia, and the presence of hematuria are not reliable in hemodialysis patients to suspect IE.¹⁶

Consequently, the application of TTE and TEE in diagnosis of IE in hemodialysis patients is significant. TTE is more sensitive than TEE,¹⁷ as there is no interference of chest wall with higher conductive frequency, in detecting valve vegetation, perivalvular abscess, and prosthetic valve vegetation. It has been suggested that it is necessary to perform TEE when patient undergoing maintenance hemodialysis without any positive findings presents newly onset of congestive heart failure or clinical manifestations of IE, or for hypertensive patients with onset of intradialytic hypotension, and also patients with history of IE onset, valve operation, dialysis on catheters, microbe of IE carrying, or recurrent bacteremia after administration of antibiotics.^{15,18}

In this report, we adopted Chinese Children Diagnostic Criteria. If the patients received long-term antibiotics treatment, the blood culture might turn out false-negative even one week after withdrawal of antibiotics. The inappropriate blood culture sample collection might be the reason. In diagnosis of IE, blood sample is required to take for no less than three times with intervals of at least one hour; discontinuation of antibiotics is preferred for at least three days before sample collection if antibiotics was given temporarily; both aerobic and anerobic cultures are needed in each collection; 10 mL venous blood is needed for diagnosis in adults; and minimal inhibitory concentration of each available antibiotic must be measured.

Current guidelines for treatment of IE in the general population are also suitable for chronic hemodialysis patients, except for some controversial issues such as removal of catheters, the indication and timing of surgery.

Theoretically, Fernández-Cean et al¹⁹ showed the most effective way to eliminate the focus of infection is to remove the criminal catheter and shift to peritoneal dialysis, which could also help improve the prognosis. In the clinical practice, the antibiotics treatment must be prolonged if the catheter is the only way to accomplish blood purification.

In the study of Spies et al,¹⁵ the overall hospital mortality of hemodialysis with IE was 52%, the indicators of poor prognosis included fever on admission, few negative blood culture, bivalvular infective endocarditis, and more often valve replacement surgery. The perioperative mortality in their study was 73%. The high operative mortality

was attributed to more severe diseases of patients in this selected group, such as the poor response to antibiotics, recurrent embolism, and vegetation of larger than 10 mm. One case in the present report underwent the surgery after failure of antibiotics treatment and recurrent heart attacks. Some suggest patient to take surgery earlier rather than to waste the chance on an unsuccessful antibiotics therapy.²⁰

In order to improve the outcome, an intensive consultation with specialists of cardiac surgery and infectious disease should be conducted on an individual basis about the indication and timing of surgery.

In conclusion, patients with ESRD undergoing long-term hemodialysis are at an increased risk of developing IE. If a hemodialysis patient suffers from long-term fever, the possibility of IE should be considered. Blood culture with TTE or TEE if necessary should be applied to confirm diagnosis. On the basis of sensitive antibiotics treatment, removal of catheter and even surgery should be considered if the outcome is unfavorable. Clearly, a randomized, controlled trial is needed for the further clarification of the clinical uncertainty.

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