The Diagnostic and Therapeutic Significance of Antimicrobial Antibody Titer in the Bacteremia

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Antimicrobial antibody titer (AMT) in the sera was determined in 5 patients with infective endocarditis (IE), 8 with septicemia without endocarditis, 3 with fungemia, and 4 with false-positive blood culture. AMT in cases of IE in the early stage of clinical course was over 350 and decreased to less than 50 with clinical improvement following appropriate antibiotic therapy. AMT in cases of septicemia without endocarditis was over 20 and less than 200 and the titer in patients with false-positive blood culture was less than 10. AMT in cases of fungemia without endocarditis ranged from 200~800.

INFECTIONE endocarditis (IE) and septicemia are serious infectious diseases. The differentiation of these two disorders is often based on clinical or relatively nonspecific laboratory parameters. Distinguishing between these two specific diseases is of therapeutic importance. The presence of circulating antimicrobial antibodies in patients with IE has been documented!¹⁻³

Our observation of the patients with an elevated antimicrobial antibody titer (AMT) in cases of persistent IE and the high serum antibody titers against the infecting organism led to the prospective examination of a series of patients with IE. The objective of our study was to determine whether or not the AMT against the infecting organism might aid in differentiating between septicemia with IE and without, and to determine the duration of antibiotic therapy required for patients with IE.

MATERIALS AND METHODS

Serial sera were collected from 5 patients with

IE whose diagnosis was ascertained by isolation of the same pathogen from multiple blood cultures taken on one day or from serial blood cultures taken over 2 or more days. These patients had clinical features including fever, cardiac murmur and, frequently, echocardiographic valvular vegetation. For comparison, sera were collected from 8 patients with septicemia without IE, 3 with fungemia, and 4 with a false-positive blood culture. Serum antimicrobial antibodies against the infecting organisms were examined using an indirect immunofluorescence assay.

Overnight cultures on blood agar of the isolated organism were used to prepare whole cell antigen suspensions. The smears were fixed with acetone. Serum specimens were diluted two-fold by a phosphate buffered saline solution, pH 7.2, starting at one in 10. Volumes of 0.1 ml of serum dilutions were added to circles containing bacterial cell antigen and incubated in a wet chamber at 36°C for 30 min. The serum was then washed off with buffer and the slide was immersed in fresh buffer for 5 minutes. Conjugate, fluorescein labelled rabbit anti-human immunoglobulin (obtained from Boehringer-Werke), diluted 1 in 8 in buffer, was added to cover the smear

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Fig.1. Left: AMT positive one. α -hemolytic streptococcus was incubated with AMT positive serum, and subsequently with fluorescent antiserum to immunoglobulin. Right: AMT negative one. α -hemolytic streptococcus was incubated with AMT negative serum, and subsequently with fluorescent antiserum to immunoglobulin. $\times 300$

and the slide was incubated in the moist chamber for 30 min at 36°C . The conjugated antiserum was analyzed for purity by immunoelectrophoresis. The highest dilution of the serum

showing a fluorescence of more than moderate brightness (Fig. 1) was taken as the end point of serum AMT. Negative smears were checked by phase contrast microscopy to confirm the

Fig.2. Schematic presentation of clinical course of Case Y.H. Abbreviations: CEX = cephalixin, CTZ = ceftazidime, EM = erythromycin, ABPC = ampicillin, S.T. = sulfamethoxazole-trimethoprim, SM = streptomycin

presence of bacteria in the field examined.

RESULTS

Four of 5 patients with IE had an AMT of 350 to 2000 at the time of admission and the AMT values fell progressively with antibiotic therapy and clinical improvement. Follow-up studies show these 4 patients to be doing well with no evidence of relapse. One of 5 patients with IE had an AMT of 3200 at the time of admission and the AMT levels fell to 500 following antibiotic therapy. But thereafter the titer remained at the level of 500 and the signs of left ventricular failure increased. The patient died 52 days after the admission, despite antibiotic therapy and negative blood culture results. In the postmortem autopsy, a ring abscess and vegetation were present on several chordae tendineae of the mitral valve. These results suggest that the AMT remained high so long as bacterial antigens were present in the myocardial lesions, regardless of negative blood culture results.

The following case report of IE serves to illustrate important features of the therapeutic program used in our study.

Case Y. H. The patient, a 36 year-old housewife, was transferred to Kyoto University Hospital for treatment of systemic lupus erythematosus. The patient's hospital course is summarized in Fig. 2. Three blood cultures were positive for enterococcus in November, 1978. The patient had been treated with cephalexin, and then ampicillin and culfamethoxazole-trimethoprim therapy was substituted for cephalexin. Subsequent blood cultures were negative. The serum obtained in November, 1978 showed an AMT of 500. When blood cultures were negative, AMT in serum became less than 50. In March of 1979, when she again developed fever, 4 successive blood cultures were positive for enterococcus. Ampicillin therapy was prescribed, but the blood cultures remained positive. After 2 weeks, streptomycin was prescribed. Then, she became afebrile and blood cultures were negative. AMT in serum during positive blood cultures were between 100 and 800, and became less than 50 when blood cultures were negative and she was afebrile.

The 8 septicemic patients without IE had an AMT of 20 to 200 and the sepsis disappeared with appropriate antibiotic therapy. There were no evidence of IE in the subsequent examination in all 8 patients with septicemia. Four patients,

whose blood cultures were judged to be contaminated, had an AMT of less than 10.

DISCUSSION

Although significant advances have been made in understanding the pathogenesis, antimicrobial chemotherapy and surgical treatment of infective endocarditis, nevertheless, certain issues concerning the management of endocarditis remained unresolved. The optimal dose and duration of antimicrobial therapy for most forms of endocarditis have not been precisely determined. Some workers recommended the use of bactericidal antibiotics given parenterally for a period of 4–6 weeks^{4,5} but this treatment is often insufficient. Then, there is a need for further precise methods that identify optimal antibiotics and the bacterial antigens persistence in the endocardial lesions. A practical observation in our study was that, in cases of bacterial endocarditis, when the AMT decreased to less than 50 with antibiotic therapy, the endocarditis could be considered subsided. But a patient in whom the AMT did not decrease to less than 50 with antibiotic therapy, died from mitral valve rupture considered to be of infective origin. The values of AMT may allow for a reasonably rapid decision on optimum duration of antibiotic therapy in the IE. And the AMT in the patients with IE was over 350 and these values were significantly higher than those seen in cases of septicemia without IE. Moreover, AMT can be useful to determine whether positive blood cultures signified a bacteremia or a false positive one. AMT in the 4 cases of false positive blood cultures was less than 10, and AMT in 8 cases of septicemia without IE was over 20 and less than 200. We conclude that assessment of AMT for infecting bacteria may contribute to the therapy of IE and may help to diagnose whether or not the bacteremia is associated with endocarditis and to establish criteria differentiating contamination from positive blood culture results.

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