# Infectious Endocarditis without Marked Signs of Inflammation where High Sensitivity CRP Assay was Effective

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Abstract: A 26-year-old male was diagnosed as infectious endocarditis based on the findings bacteremia of methicillin resistant staphylococcus aureus (MRSA) and vegetation of mitral valve. Though infectious endocarditis is generally accompanied with high fever, increase in white blood cell count and rise in C-reactive protein (CRP), the patient displayed none of them except an abnormal rise of high sensitivity CRP. We, therefore, suggest the capability of high sensitivity CRP as a useful laboratory marker for diagnosis and treatment of infectious endocarditis, especially for such rare type of patient we described (J. Jpn. Coll. Angiol., 2003, 43: 369-373 )

Key words: High sensitivity CRP (hs-CRP), Infectious endocarditis, Methicillin resistant staphylococcus aureus (MRSA)

## Introduction

Infectious endocarditis is generally accompanied by high fever, elevated erythrocyte sedimentation rate and elevated CRP.<sup>1)</sup> In the present case, mild fever (37.0–37.9°C) and systemic malaise were seen, but white blood cell count, CRP and erythrocyte sedimentation rate remained normal throughout the management period. This is a rare case of infectious endocarditis without marked signs of inflammation. High sensitivity CRP assay is used to detect changes in CRP level in the range lower than conventional CRP assay. Therefore, we evaluated the usefulness of high sensitivity CRP (hs-CRP) assay in this case.

#### Case

A 26-year-old male had a fever around 39–40°C from July 29, 2000. He was transported to the nearby hospital as an emergency patient with decreased consciousness. He was diagnosed as having brain abscess and admitted to the hospital to receive mainly Cefotiam for about 3 months. Although he still had a mild fever, he was discharged on October 28 with almost normal inflammatory findings as

Department of Cardiology, Kinki University School of Medicine, Sakai Hospital, Osaka, Japan assessed by hematological examination. At this time, no cardiac murmur was audible, so echocardiography and blood culture were not conducted. The patient visited the nearby hospital because of persistent fever of 37°C or slightly higher. Systolic murmur was first noted by cardiac auscultation at this hospital and the patient was referred to our hospital on November 30. Echocardiography at our outpatient department on December 4 revealed a vegetation of 15 mm × 6 mm in diameter on the anterior leaflet of the mitral valve. He was diagnosed as infectious endocarditis and admitted to our department on the same day. His past medical history included atopic dermatitis and acute nephritis at age 5.

On admission, he was alert, the blood pressure was 136/ 78 mmHg, pulse rate was 98/min with regular rhythm, and body temperature was 37.4°C. His height was 184 cm and body weight was 63.4 kg. He had no signs of anemia and jaundice, no superficial lymphadenopathy. Levine III holosystolic murmur was audible at the left sternal edge in the 4th intercostal space. Respiratory sound was clear. He had no bleeding spots on fingers and toes. There was no splenohepatomegaly and no peripheral edema.

General laboratory data on admission are shown in Table.

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	Table General laboratory data on admission					
Hen	Hematological findings		Blood chemistry		Urine analysis	
WBC	; 7,100/mm <sup>3</sup>	TP	8.1 g/dl	pН	7.5	
Ne	utr 68.4%	Alb	4.4 g/dl	Protein	(-)	
Ly	mpho 19.7%	GOT	29 IU/I	Glucose	(-)	
Mono 4.5%		GPT	34 IU/I	Sediment	normal	
Eo	sino 7.0%	LDH	331 IU/I			
Ba	so 0.5%	СК	68 IU/I			
RBC	$461 \times 10^4$ /mm <sup>3</sup>	BUN	17 IU/I			
Hb	14.7 g/dl	CRE	0.9 mg/dl			
Ht	44.0%	Na	142 mEq/l			
Plt	$26.3  imes 10^4$ /mm <sup>3</sup>	К	4.2 mEq/l			
ESR	8 mm/h	CI	107 mEq/l			
		Glu	98 mg/dl			
		CRP	0.3 mg/dl			
		hs-CRP	2,700 ng/ml			

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There were no elevation in white blood cell count, CRP and erythrocyte sedimentation rate but the high sensitivity CRP level measured at the same time was 2,700 ng/ml. Plain chest x-ray showed cardiac enlargement and electrocardiogram showed no abnormal findings.

Echocardiography demonstrated a vegetation of 15 mm in diameter on the anterior leaflet of the mitral valve (arrow) with grade III mitral regurgitation. Left atrium and left ventricular diameters were slightly enlarged (**Fig. 1**). Magnetic resonance imaging (MRI) of the brain on admission showed high signal intensity area in bilateral cerebral cortex on T2weighted images, and enhanced MRI showed no active lesions. From these findings we concluded that his brain abscess had been completely cured on admission.

MRSA was detected by both arterial and venous blood culture performed on admission and was sensitive to Vancomycin. Intravenous administration of Vancomycin at a dose of 2 g/day was started from day 3 of admission. The body temperature during the administration was over 36°C but less than 37°C, the white blood cell count was normal, and the CRP was between 0.1 and 0.3 mg/dl. The high sensitivity CRP level measured on day 15 was 2,900 ng/ml but decreased to 900 ng/ml on day 43. Vancomycin was discontinued after 6 weeks of administration but the patient subsequently developed mild fever of 37°C. MRSA was detected again by both arterial and venous blood culture performed on day 50. A surgery was considered at this time, but since blood culture was negative for MRSA during Vancomycin therapy, we thought medical treatment would be effective and Vancomycin at a dose of 2 g/day was resumed on day 53 and was changed to intravenous Teicoplamin at a dose of 400 mg/ day from day 58. White blood cell count and CRP were both normal during the therapy except for high sensitivity CRP level of 5,400 ng/ml measured on day 78 and fever of 37.2°C with CRP of 0.6 mg/dl on day 92. Administration of Teicoplamin was then discontinued and blood culture was performed. MRSA was detected in the venous blood and the vegetation of the mitral valve noted by echocardiography was 12 mm  $\times$  6 mm in diameter, which showed no reduction. At this point, it was judged impossible to treat with medical therapy and was finally decided to conduct a surgery (Fig. 2). Mitral valvuloplasty was conducted on March 28, 2001.

It showed operative findings in the following. Adhesion of a vegetation to the anterior leaflet of the mitral leaflet was observed and rupture of chordae tendineae and destruction of anterior leaflet of the mitral valve possibly caused by infectious endocarditis were also observed. Blood culture was negative. 26 days after the operation he was discharged without any infectious signs. The patient was doing well one year after the operation and his high sensitivity CRP level



Figure 1 Two-dimensional echocardiography (A) demonstrates a vegetation of 15 mm in diameter on the anterior leaflet of the mitral valve (arrow). Color-flow Doppler (B) demonstrates severe mitral regurgitation.

decreased to 318 ng/ml.

### Discussion

Infectious endocarditis is a systemic infection that is characterized by an infectious focus in the endocardium called vegetation and presents diverse clinical symptoms. A fever, a symptom of this disease, ranges from mild fever (37.0–37.9°C) to moderate fever (38.0–38.9°C) and can exceed 39.0°C depending on the pathogen. Hematologically, patients with this disease usually show elevated white blood cell count, CRP and erythrocyte sedimentation

rate.<sup>1)</sup> In the present case, mild fever (37.0–37.9°C) and systemic malaise were seen, but white blood cell count, CRP and erythrocyte sedimentation rate remained normal throughout the management period. However, at the time of first visit, cardiac murmur was auscultated, MRSA was detected by blood culture, and vegetation was found in the mitral valve on echocardiogram, allowing us to make a diagnosis of infectious endocarditis in accordance with Duke's diagnostic criteria.<sup>2)</sup> Although *streptococci* and *Staphylococcus aureus* are often responsible for infectious endocarditis<sup>1,3)</sup> not a few cases with this disease caused by MRSA have been reported in recent years.<sup>4–6)</sup> Some cases of infectious endocarditis caused by MRSA were successfully cured by medical treatment alone.<sup>5)</sup> However, many cases of infectious endocardi







tis caused by this pathogen require surgery, because of severe inflammation and rapid progression.<sup>6)</sup> In the present case, marked fever and signs of heart failure were absent and other symptoms and signs of inflammation were not severe, although the disease had been caused by MRSA. It is known that infectious endocarditis is one of the factors responsible for brain abscess. It cannot be ruled out that infectious endocarditis had already been present in this patient during his stay at another hospital to receive treatment of brain abscess. However, the physicians and nurses of that hospital made no entry about cardiac murmur on the patient's medical records, and echocardiography and blood culture had not been performed at that hospital. Therefore, the causal relationship between brain abscess and infectious endocarditis in this case is unknown.

Inflammatory reactions associated with infection usually involve fever, acute reactions in the liver, increase in leukocytes, etc., which are caused by cytokines and other various substances produced as a result of host's response to microorganisms.<sup>7</sup> However, with severity of the infection, these reactions are less likely to take place. Likewise, these reactions are less likely to occur in patients with compromised immune function or on steroid therapy because of abnormalities of the bone marrow and the immune system, as well as in elderly people because of compromised host defense.<sup>7,8)</sup> The patient presented in this paper seems to have been susceptible to infection, since he had atopic dermatitis. However, he was not using any topical steroid on a daily basis, and he was young and free of underlying heart disease. Although the exact reason for the absence of marked inflammatory reactions in this case is unknown, it has been reported that fever was absent in a few percent of patients with infectious endocarditis.9) We cannot rule out the involvement of immune system in the pathogenesis of this case. However, it seems more likely that early administration of antibiotics was the primary cause for infectious endocarditis in this case.

Furthermore, we evaluated the usefulness of high sensitivity CRP assay. High sensitivity CRP assay is used to detect changes in CRP level in the range lower than conventional CRP assay. With conventional CRP assay, the lowest detectable level of CRP is 0.3 mg/dl. With high sensitivity CRP assay, the lower limit of measurement is about 200 ng/ ml.<sup>10)</sup> The upper limit of the normal range for high sensitivity CRP assay is 1,500 ng/ml, which is lower than that for conventional CRP assay, and the upper limit of the normal range for individuals below 39 years of age is 1,000 ng/ml or less. Thus, the normal range for high sensitivity CRP tends to be higher as the age advances.<sup>10, 11</sup>) We may therefore say that with conventional CRP assay, it is not possible to precisely determine the baseline level of CRP for healthy individuals, which means that it is not possible to detect early pathologic elevation in CRP. The usefulness of high sensitivity CRP as an early marker of infection has been pointed out for management of newborns, premature infants, etc. in whom the diagnosis of infection is not easy.<sup>11</sup> Following

the recent report suggesting that atherosclerosis can be viewed as chronic inflammation, CRP has begun to attract close attention as a risk factor for coronary artery diseases.<sup>11, 12</sup> It has been reported that the risk caused by CRP, as measured by high sensitivity assay, becomes higher in a concentrationdependent manner, and its risk is rated as very low when its level is below 700 ng/ml according to the five-grade risk rating system.<sup>11</sup>) The present case was a young patient without underlying heart disease and his CRP level remained low throughout the management period. However, the high sensitivity CRP level upon admission was 2,700 ng/ml, which suggests that the patient had developed infection earlier. During antibiotic therapy, he showed neither fever nor inflammatory symptoms. When antibiotics were discontinued, he developed mild fever and MRSA was detected by blood culture. These results suggest that antibiotic therapy was somewhat effective in this case. However, considering that the patient eventually underwent surgery and his high sensitivity CRP level decreased to 318 ng/ml after surgery, we may say that treatment with antibiotics alone did not suffice in this case.

## Conclusion

Since infectious endocarditis usually presents severe inflammatory reactions, high sensitivity CRP assay is not necessary for management of this disease. However, it was strongly suggested that when dealing with acute infection without marked signs of inflammation, as seen in newborns and in the present case, the time course of high sensitivity CRP level is useful as an indicator for determining the antibiotic dosing period and evaluating responses to treatment, etc.

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