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【 CASE REPORT 】

Intracranial Hemorrhaging Following *Cardiobacterium hominis* Endocarditis

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Abstract:
Acute infectious endocarditis (IE) is a complex disease that presents as a serious clinical condition associated with a high mortality rate, especially due to intracranial hemorrhaging (ICH). The most common causative organism is *Staphylococcus aureus.* We herein report a patient with ICH following subacute IE with a positive blood culture for *Cardiobacterium hominis*. A review of the existing literature revealed that acute IE associated with *Cardiobacterium* has been reported to cause ICH in only seven previous cases. Prolonged culture-specific antibiotic therapy along with extended surveillance of blood culture is therefore essential for timely intervention.

Key words: infectious endocarditis, HACEK, stroke, valvular disease, blood culture

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Introduction

Acute infectious endocarditis (IE) is a rare and complex disease that presents as a serious clinical condition associated with a high mortality rate. Acute IE is most commonly caused by *Staphylococcus aureus, Streptococcus viridans,* or *Streptococcus bovis*, and the incidence of IE caused by other bacteria is low (1). The HACEK group of organisms is particularly rarely etiologically responsible for IE, with 0.8-6% of IE cases reported to be due to HACEK organisms in recent population-based studies. According to the International Collaboration on Endocarditis Prospective Cohort Study, the rates of hospital mortality and heart failure due to HACEK endocarditis (HE) were less than those of non-HE (2). Visceral bleeding, such as hemoperitoneum or intracranial hemorrhaging (ICH), which is associated with poor outcomes, warrants emergency intervention.

We herein report a patient with *Cardiobacterium hominis* endocarditis and ICH caused by cerebral pseudoaneurysm who underwent emergency craniotomy and prolonged antibiotic therapy. In addition, we provide a review of the literature on other reported cases of *Cardiobacterium*-induced acute IE with ICH.

Case Report

A 63-year-old man was admitted to the hospital with a fever of 38.4℃, headache and left hemispatial neglect after a road traffic rear-end collision caused by sudden hemispatial neglect. Five years earlier, the patient had undergone aortic valve and mitral valve replacements with biological and mechanical valves, respectively, at another hospital, because he had developed severe aortic regurgitation due to bicuspid valve and mitral regurgitation due to A1 prolapse and annular dilatation. One week before the accident, he experienced throat pain without a fever and took a pain-killer (loxoprofen sodium) only on the first day. He had no recent history of dental treatment or oral infections.

His physical examination revealed the following: Glasgow Coma Scale score, E3V5M6; blood pressure, 143/76 mmHg; heart rate, 88 beats/min; respiratory rate, 24 breaths/min; body temperature, 37.8℃; and pupil diameter, 4 mm. He had no evidence of traffic accident-related injuries, heart

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murmur, or bleeding into the skin or conjunctiva. Laboratory tests revealed the following: white blood cell count, 8,300/μL (reference, 4,000-8,000/μL); platelet count, 11.8×10^4/μL (reference, $14\text{-}34\times10^4$/μL); hemoglobin, 9.8 g/dL (reference, 11.0-17.0 g/dL); prothrombin time-international normalized ratio, 3.23; D-dimer, 3.6 μg/mL (reference, <0.30 μg/mL), C-reactive protein, 7.1 mg/dL (reference, <0.30 mg/dL); creatinine, 1.23 mg/dL (reference, 0.60-1.20 mg/dL); and estimated glomerular filtration rate, 47.1 mL/min/1.73 m^2 (reference, 60.0< mL/min/1.73 m^2). Initial cranial computed tomography (CT) revealed a subcortical ICH in the right parietal lobe (Fig. 1). Contrast-enhanced CT of the brain revealed extravasation of the contrast medium into the hematoma and cerebral aneurysm arising from the terminal branch of the right middle cerebral artery (Fig. 2). Contrast-enhanced CT of the entire body did not reveal any infarction in the spleen, liver or kidneys or any aneurysm formation. Transthoracic echocardiogram (TTE) revealed mild mitral regurgitation and left ventricle dilatation but did not shown any vegetations or paravalvular abscesses on the mitral or aortic valves. The patient was negative for rheumatoid factor as well.

The patient was suspected of having sepsis caused by IE and was started on meropenem (2 g; Meropen®, Sumitomo Dainippon Pharma, Tokyo, Japan) as empirical antibiotic therapy after two sets of blood culture samples were obtained. He was then transferred to our emergency center for the treatment of ICH and the evaluation of IE. The patient met three of the minor modified Duke criteria, including valvular disease, a fever above 38℃ and ICH with infectious cerebral aneurysm (3). Cranial CT revealed an increase in the hematoma size; therefore, cerebral angiography was performed under general anesthesia prior to emergency craniotomy because of his coagulopathy, which revealed a small cerebral aneurysm arising from the terminal branch of the right middle cerebral artery (Fig. 3). Subsequently, he underwent emergency evacuation and decompression of the ICH in the emergency room.

The patient's initial blood cultures revealed Gram-negative bacilli at 6 days and *C. hominis* at 20 days after the onset. Therefore, the patient met one major criterion and three minor modified Duke criteria and was diagnosed with definitive IE. A transesophageal echocardiogram revealed hyperplasia of the anterior mitral valve but did not detect any vegetations or paravalvular abscess twenty days after hospitalization. He was administered meropenem (6 g/day) and vancomycin hydrochloride (2 g/day) for a period of 7 days from the time of symptom. After the administration of meropenem for 16 days, between days 8 and 23 after the symptoms had first manifested, the patient was switched to ceftriaxone sodium hydrate (2 g/day) on day 23 for 20 days based on the results of antibiotic susceptibility testing. The initial aneurysm and new aneurysmal formation were not detected by contrast-enhanced CT performed after antibiotic therapy, and blood cultures were negative thereafter. During hospitalization, TTE performed three more times revealed no change in the hyperplasia of the anterior mitral valve. Therefore, the patient was discharged from the hospital for rehabilitation 60 days after admission with a modified Rankin Scale score of 2, and further follow-up was conducted by the hospital where the patient had previously undergone cardiac surgery.

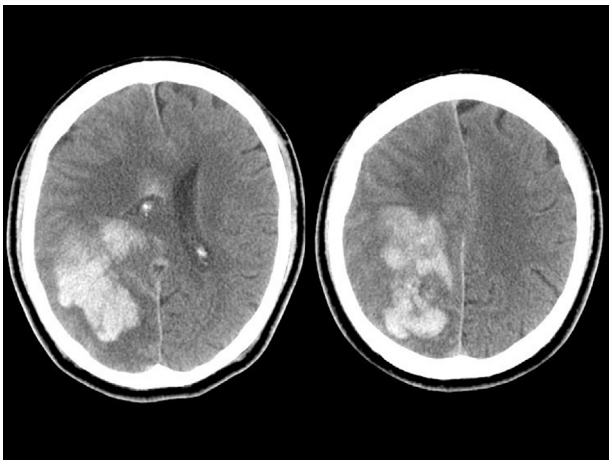

Figure 1. Cranial computed tomography.

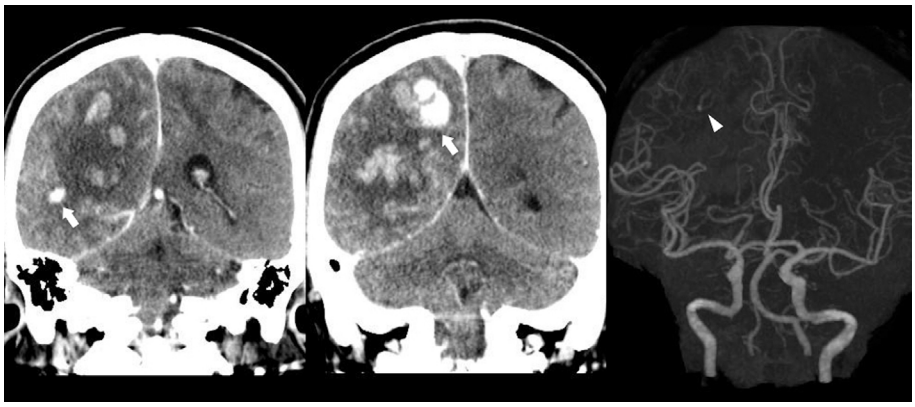

Figure 2. Contrast-enhanced computed tomography of the head revealing a subcortical hematoma with contrast medium extravasation.

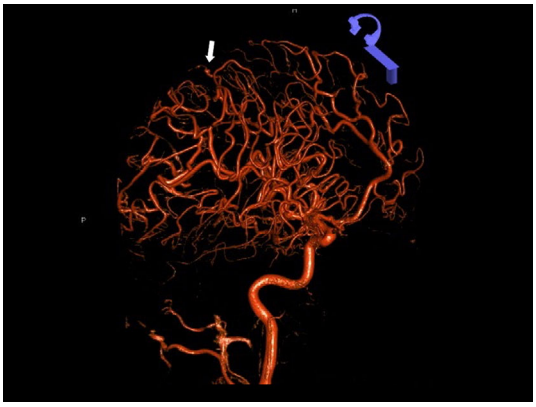

Figure 3. Cerebral angiography showing an aneurysm arising from the distal branch of the middle cerebral artery (arrow).

Table 1. Review of Published Works on Intracranial Hemorrhage Following Unusual Infective Endocarditis among the Japanese Population.

HACEK organisms	Number
Haemophilus spp.	
Haemophilus parainfluenzae	-
Aggregatibacter spp.	
Aggregatibacter segnis	1
Cardiobacterium spp.	
Cardiobacterium hominis	1*
Eikinella corrodens	-
Kingella spp.	-
Non-HACEK Gram-negative organisms	
Arcanobacterium spp.	
Arcanobacterium haemolyticum	1
Unusual Gram-positive organisms	
Rothia spp.	
Rothia aeria	1
Rothia dentocariosa	1

* present case

Discussion

C. hominis, a slow-glowing anaerobic Gram-negative bacillus, is a well-known commensal bacterium of the oral cavity. *Cardiobacterium hominis* bacteremia is accompanied by IE in 95% of cases. Wormser et al. noted that no history of dental treatment or oral infections was reported in half of cases with *C. hominis* bacteremia (4). Chentanez et al. reviewed 13 cases of *C. hominis* IE and reported that the mean time from the appearance of symptoms to the diagnosis was 108 days (5). Furthermore, the growth of *C. hominis* is very slow; two weeks are necessary for it to grow in a blood culture, and the culture is sometimes negative (6, 7). In the present case, the patient had a history of valve replacement due to severe vulvar diseases five years ago. However, he had no recent history of dental procedures or oral infections and developed a cold without a fever only one week before the hospital admission. On arrival at the previous hospital, he met three of the criteria for systemic inflammatory response syndrome and showed a quick sequential organ failure assessment score of 2. Therefore, the differential diagnosis included severe infection or sepsis, and the cause of the infection was considered to be IE based on the minor modified Duke criteria. Therefore, empiric broad spectrum therapy was initiated. Importantly, the blood cultures revealed Gram-negative bacilli after 6 days, and the use of meropenem could not be de-escalated until the detection of *C. hominis* at 20 days after the start of symptoms.

We searched the literature using the ICHUSHI and the PubMed databases for original articles and case reports published in Japanese and English language, respectively, with the keywords "infectious endocarditis", "HACEK", and "*Cardiobacterium*" and excluded ICH cases that occurred within one week of cardiac surgery. To date, only four case reports involving four patients with ICH following unusual IE were identified among the Japanese studies (8-11), summarized in Table 1. Only one patient who suffered from ruptured mycotic aneurysm was diagnosed with HE (*Aggregatibacter segnis*), and the interval from the onset to the isolation of the organism was over two weeks. Another patient suffered from ICH due to non-HE by *Arcanobacterium haemolyticum*, whereas hemorrhagic infarction caused by *Rothia* spp. was reported in two patients (9, 10). A search of the English literature revealed seven patients with ICH following IE with *Cardiobacterium* spp., including five and two cases with *C. hominis* and *C. valvarum*, respectively (Table 2) (12-18). Among these seven cases, three patients experienced subarachnoid hemorrhaging (*C. hominis* and *C. valvarum* in one and two patients, respectively), whereas four patients with *C. hominis* IE experienced subcortical hematoma. The duration for the detection of *Cardiobacterium* spp. ranged from three to four days after incubation in three cases. This review of the literature illustrates the limited number of reports on ruptured infectious or mycotic cerebral aneurysms caused by IE due to *Cardiobacterium* spp. To our knowledge, this is the first report of a patient with ICH caused by *C. hominis* IE among the Japanese population.

Mycotic aneurysm is considered to involve an infectious break in the wall of an artery with the formation of a blind, saccular outpouching (19). Pathological findings include acute or chronic inflammation, acute suppurative inflammation, abscess formation and bacterial clumps found in the excised aneurysm. The most common causative organism is *S. aureus,* which is a major cause of acute IE. These aneurysms are extremely fragile and can rupture, which is often considered life-threatening and carries a high mortality rate, although the aneurysm is relatively small. Visceral infarction associated with IE is rarely detected in clinical practice because of the nonspecific clinical presentation. Although stroke occurs as a complication in a higher percentage of HE cases than in non-HE cases, hemorrhagic stroke is more

Table 2. Review of Published Works on Regarding Intracranial Hemorrhage Following Infective Endocarditis Caused By *Cardiobacterium* spp.

Reference	Age	Sex	Risk factors	Clinical presentation	Organism	Findings of TEE	Type of ICH	Cerebral aneurysm	Empirical antibiotics therapy	Duration for detection of species after incubation
12	41	F	AV replacement, pulmonary autograft	Dyspnea, myalgia, and malaise	*Cardiobacterium hominis*	AV vegetations	Subcortical hematoma (6 cm)	NA	CFTX, GM	4 days
13	37	M	Dental procedure	Headache, nausea, vomiting, and worsening disorientation	*Cardiobacterium valvarum*	AV vegetations	SAH	Solo	VM, CFT, GM	3 days
14	49	M	Aortic valvotomy	Headache and aphasia	*Cardiobacterium hominis*	AV vegetations	Subcortical hematoma (3 cm)	Multiple	AMP, GM	NA
15	63	F	VSD	Headache, slurred speech, and vomiting	*Cardiobacterium valvarum*	MV and VSD vegetations	SAH	Solo	PCG, cloxacillin, GM	4 days
16	35	F	AV replacement	Headache, myalgia, arthralgia, and nausea	*Cardiobacterium hominis*	NA	Subcortical hematoma (2 cm×3 cm)	Solo	CFT	NA
17	65	M	Hepatosplenomegaly	aphasia	*Cardiobacterium hominis*	NA	Subcortical hematoma (7 cm×4 cm)	Solo	AMP	NA
18	33	M	Rheumatic heart disease	Malaise, chilly sensation, and erythema nodusum	*Cardiobacterium hominis*	NA	SAH	NA	PCG, Streptomycin	NA
Present case	63	M	AV replacement, MV repair	Headache, and visual field defect	*Cardiobacterium hominis*	MV hyperplasia	Subcortical hematoma (7 cm×4 cm)	Solo	MPEM	20 days

AMP: ampicillin, AV: aortic valve, CFT: ceftazidime, CFTX: ceftriaxone, GM: gentamycin, ICH: intracranial hemorrhage, MV: mitral valve, NA: no available, PCG: penicillin G, SAH: subarachnoid hemorrhage, TEE: transesophageal echocardiography, VM: vancomycin, VSD: ventricular septal defect

frequent than embolic stroke in patients with HE. Spontaneous resolution with prolonged culture-specific antibiotic therapy, along with surveillance imaging for IE, is the most important approach (20). We recently reported that catheter-based hemostasis before surgical treatment was effective in patients with continuous hemorrhaging caused by ruptured mycotic aneurysms (21). In the current case, hemorrhaging from the aneurysm was noted to have stopped during angiography, so craniotomy was performed in the emergency room.

In conclusion, prolonged culture-specific antibiotic therapy along with surveillance with extended blood cultures are critical for timely intervention in patients with ICH following *C. hominis* IE.

Informed consent: Written informed consent was obtained from the patient for publication of the case history and the accompanying images.

The authors state that they have no Conflict of Interest (COI).

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