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【 CASE REPORT 】

Hemolytic Anemia in a Patient with Subacute Bacterial Endocarditis by *Cardiobacterium hominis*

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Abstract:

Hemolytic anemia is a rarely occurring manifestation of native valve infective endocarditis. We herein report an afebrile patient with hemolytic anemia caused by *Cardiobacterium hominis* endocarditis. A 60-year-old Japanese man had a history of aortic root replacement and the gradual onset of general fatigue. He had hemolytic anemia. Blood cultures detected *C. hominis*. A transthoracic echocardiogram showed aortic valve vegetation and periannular abscess with perforation of the non-coronary cusp. Intravascular hemolysis recovered after antimicrobial therapy, surgical removal of the vegetation and abscess, and aortic valve replacement. Subacute endocarditis should be considered if patients develop hemolytic anemia with signs of chronic inflammation without a fever.

Key words: *Cardiobacterium hominis*, intravascular hemolysis, infective endocarditis

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Introduction

Anemia has been shown to frequently accompany infective endocarditis (1). Although rare, there have been reports of hemolytic anemia associated with native valve infective endocarditis (2-9). In addition, some patients with infective endocarditis do not become febrile. In fact, febrile patients account for 87.8% in cases of infective endocarditis caused by staphylococci, streptococci and enterococci and 76.2% in cases caused by other microorganisms (10).

We herein report an afebrile patient with *Cardiobacterium hominis* endocarditis that manifested as hemolytic anemia with a high titer of C-reactive protein (CRP).

Case Report

A 60-year-old man experienced the gradual onset of general fatigue associated with anemia over a 3-month period. He was referred to our general internal medicine department by a cardiac surgeon for investigations into the underlying cause of his anemia. Five years prior to the presentation, he had undergone valve-sparing aortic root replacement for aortic regurgitation (AR). More recently, he had undergone a series of dental procedures, including extraction of decayed teeth one month before the current presentation. He had also undergone esophagogastroduodenoscopy and colonoscopy four weeks before the referral as part of an evaluation for anemia, which showed no evidence of gastrointestinal bleeding. He had not taken any antimicrobials, including after the recent dental procedures.

The patient was afebrile (35.4°C, his normal temperature averaged 36.5°C), and his blood pressure was 111/56 mmHg, heart rate 79/min, respiratory rate 16/min, and SpO_2 98% (ambient air). His weight was 71.7 kg, his height was 169 cm, and his body mass index was 25.1 kg/m^2. His oral cavity was dirty, and his dentures were loose. An ophthalmic exam showed no abnormalities, including Roth spots. A head and neck examination did not reveal conjunctival petechiae or enlarged lymph nodes. A cardiac examination showed a grade IV/VI holosystolic murmur that was maximal at the left lower sternal border. His lungs were clear on auscultation, and an abdominal examination was unremarkable, without hepatosplenomegaly. No skin lesions were recognized, including Janeway lesions and Osler's nodes. A neurological examination was also unremarkable.

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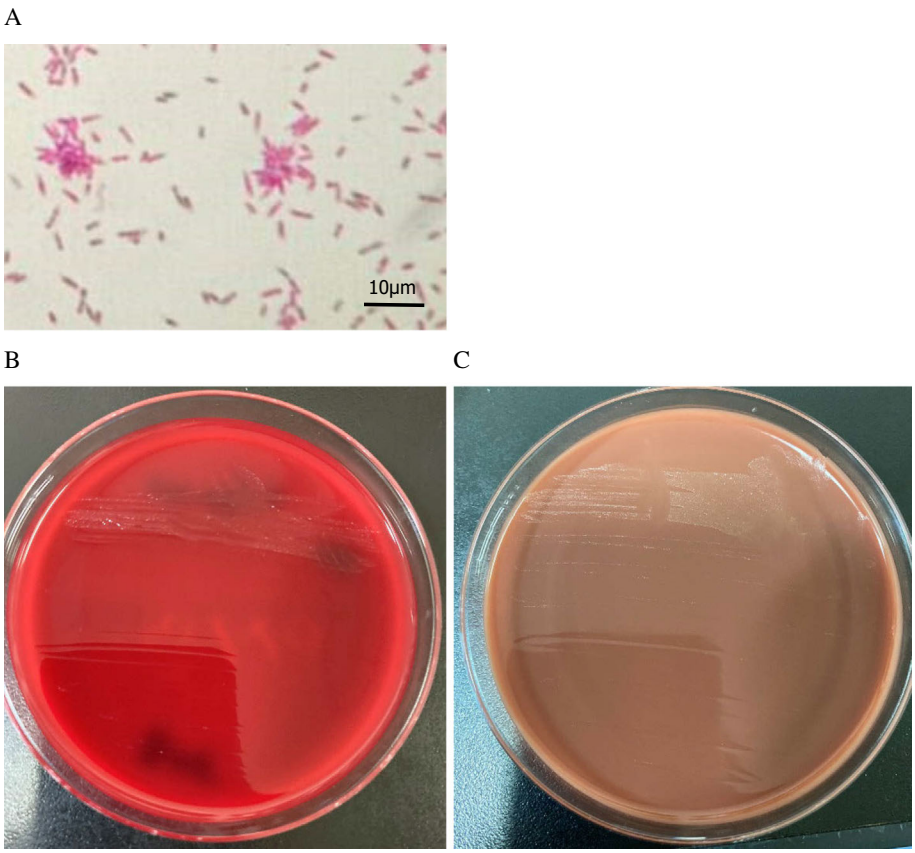

Figure 1. Blood culture yielded Gram-negative bacilli and bacterial colonies on the culture media. Gram-negative bacilli were positive on Gram staining (×1,000) (A), and bacterial colonies grew on blood agar (B) and chocolate agar (C).

Initial laboratory studies showed a significantly normocytic anemia (hemoglobin 9.4 g/L, mean cell volume 88.9 fL, white cell count of 8,330/mm^3 with 70.0% neutrophils and 23.0% lymphocytes, platelet count of 21.8×10^9/L, red cell distribution width of 16%, and a reticulocyte production index of 0.9%). Schistocytes were shown in a peripheral blood smear. A coagulation screen showed elevated fibrinogen and D-dimer levels (prothrombin time 13.2 seconds, activated partial thromboplastin time 34.7 seconds, fibrinogen 476 mg/dL, D-dimer 2.8 μg/mL, and antithrombin III 88.8%). Liver function tests (albumin 3.6 g/L, total bilirubin 0.8 g/dL, alkaline phosphatase 15 U/L and alanine transaminase 12 U/L) were normal. The CRP level was 5.2 mg/dL, lactate dehydrogenase (LD) was elevated to 532 U/L (normal range 106-211) and haptoglobin was decreased to 10 mg/dL (19-170). The electrolyte screen was normal (sodium 138 mmol/L, potassium 4.3 mmol/L, chloride 102 mmol/L). The serum iron level was 27 μg/dL (54-200), and the total iron binding capacity was 244 μg/dL (240-430) while the unsaturated iron binding capacity was 217 μg/dL (180-280). Direct Coombs test was negative. A urinalysis revealed occult blood 3+ and a red blood cell count of 20-29/high-power field without proteinuria.

Due to concerns of an underlying malignant pathology, such as malignant lymphoma or leukemia, or inflammatory disease, such as tuberculosis or sarcoidosis, bone marrow aspiration and a biopsy were performed one week before admission, and a random skin biopsy (left chest wall, right abdominal wall, and left femur) was performed two days before admission, but the results were unremarkable.

Contrast-enhanced computed tomography 1 week before admission showed a small amount of pleural effusion and splenomegaly (spleen length, 12 cm) with no evidence of mycotic aneurysm, abscess, or embolism. Given the patient's clinical course with fatigue, weight loss and elevated CRP levels, two sets of blood cultures were obtained three days before admission to investigate the possibility of infective endocarditis. After 41 hours, blood culture yielded Gram-negative bacilli, identified as *C. hominis* (Fig. 1). Using blood samples, 16S ribosomal ribonucleic acid (rRNA) gene-targeting polymerase chain reaction (PCR) of the strain was positive, and the corresponding 1365-bp sequence showed 100% homology with *C. hominis* NCTC 10426.

The patient was admitted to our institute for antibiotic therapy 23 days after the referral. Both a transthoracic echocardiogram (TTE) and transesophageal echocardiogram showed vegetation (6×22 mm) in the non-coronary cusp (NCC) of the aortic valve, a perivalvular abscess extending from the NCC/left coronary cusp (LCC) commissure to the NCC anulus, and a perforation in the NCC along with moderate aortic regurgitation (regurgitant volume: 49.5 mL and regurgitant fraction: 33.5%) (Fig. 2). He was diagnosed with

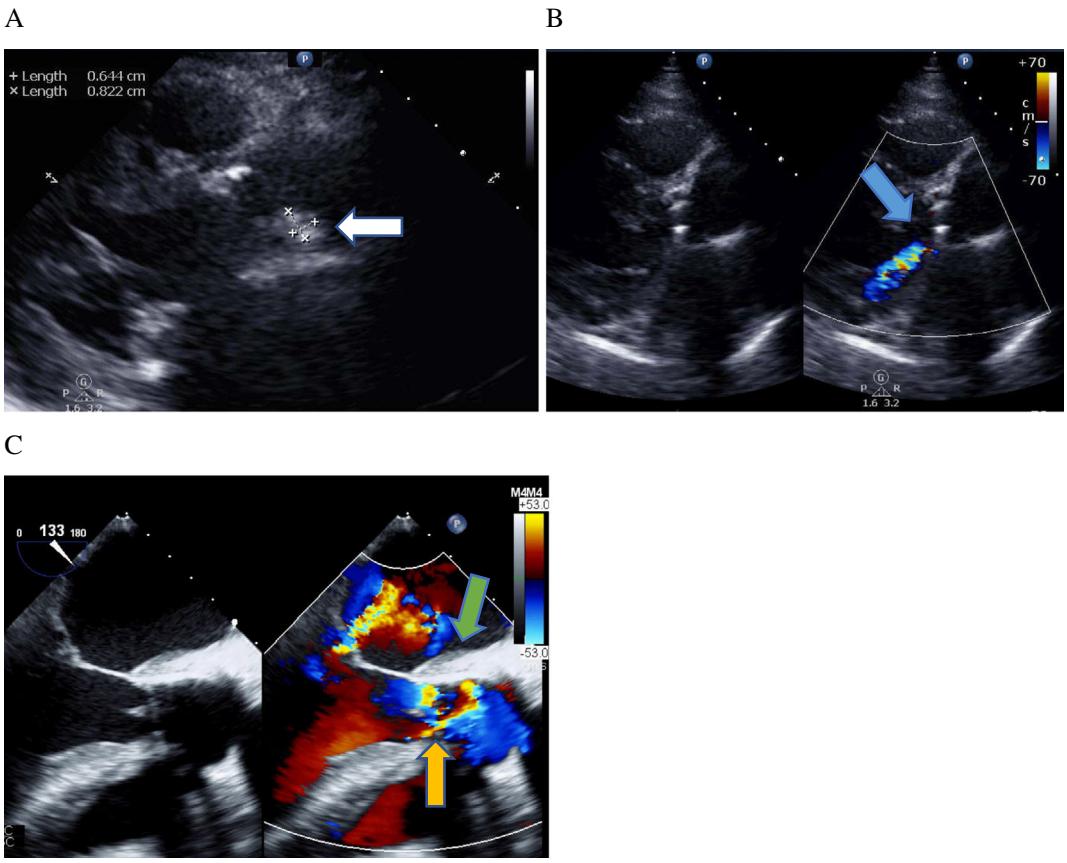

Figure 2. **A transthoracic long-axis view of the aortic valves and transesophageal long-axis view of the aortic valves. A long-axis view showing large vegetations on the aortic valves (white arrow) (A). Color Doppler reveals perforation due to tissue destruction (blue arrow) (B). A transesophageal echocardiogram showing non-coronary cusp perforation (yellow arrow) and vegetation along with degeneration of the mitral-aortic intervalvular fibrosa (green arrow) (C).**

infective endocarditis caused by *C. hominis* according to the modified Duke criteria (11).

The patient then underwent emergent aortic valve replacement. Red blood cells were transfused in surgery. Vegetation was attached to the aortic valve NCC and perforation of the NCC was observed. There was abscess formation just below the commissure of the NCC/LCC. In addition, a fistula was formed from the left ventricle to the posterior side of the septal cusp of the tricuspid valve. In the right coronary cusp valve ring, an abscess-like mass was recognized. Pathological studies showed mild vitrification, hydropic degeneration of the aortic valve tissue accompanying granulation, and fibrin precipitation (Fig. 3A). In the fibrin mass, a large amount of bacilli were present (Fig. 3B, C).

After emergent surgery, the patient underwent six weeks of single-agent therapy of intravenous ceftriaxone (CTRX), 2 g daily. Antimicrobial susceptibility testing was performed for the strain using the broth microdilution method (Dry Plate Eiken Chemical, Tokyo, Japan) according to the Clinical and Laboratory Standards Institute guidelines (12). The isolate was susceptible to ampicillin, CTRX, carbapenems, and fluoroquinolones (Table). Two sets of blood cultures that were obtained on the first day were positive, and those obtained postoperatively on day five of admission were negative. We therefore administered six weeks of antibiotic therapy counting from day five.

Five days after the surgery, brain magnetic resonance imaging (MRI) was performed to search for cerebral embolism, which revealed multiple acute lacunar infarctions (Fig. 4). On the same day, a TTE revealed the absence of abscesses in the aortic valves, with only a tiny amount of vegetation in the right ventricle. The clinical course of the patient was good, so we continued CTRX. The hemogram improved with hemoglobin of 10.5 g/dL, LD of 225 U/L, and haptoglobin of 36 mg/dL, which was taken ten days after the surgery. The peripheral blood smear was also normal. The patient was discharged one month after admission with no further complications (Fig. 5). After he completed the therapy, infective endocarditis did not reoccur during the six-month observation period.

Discussion

Among HACEK microorganisms (*Haemophilus* species, *Aggregatibacter* species, *Cardiobacterium hominis*, *Eikenella corrodens* and *Kingella* species), *C. hominis* has a relatively low virulence. *C. hominis* bacteremia accompanies infective endocarditis in 95% of cases (13), although the onset is in-

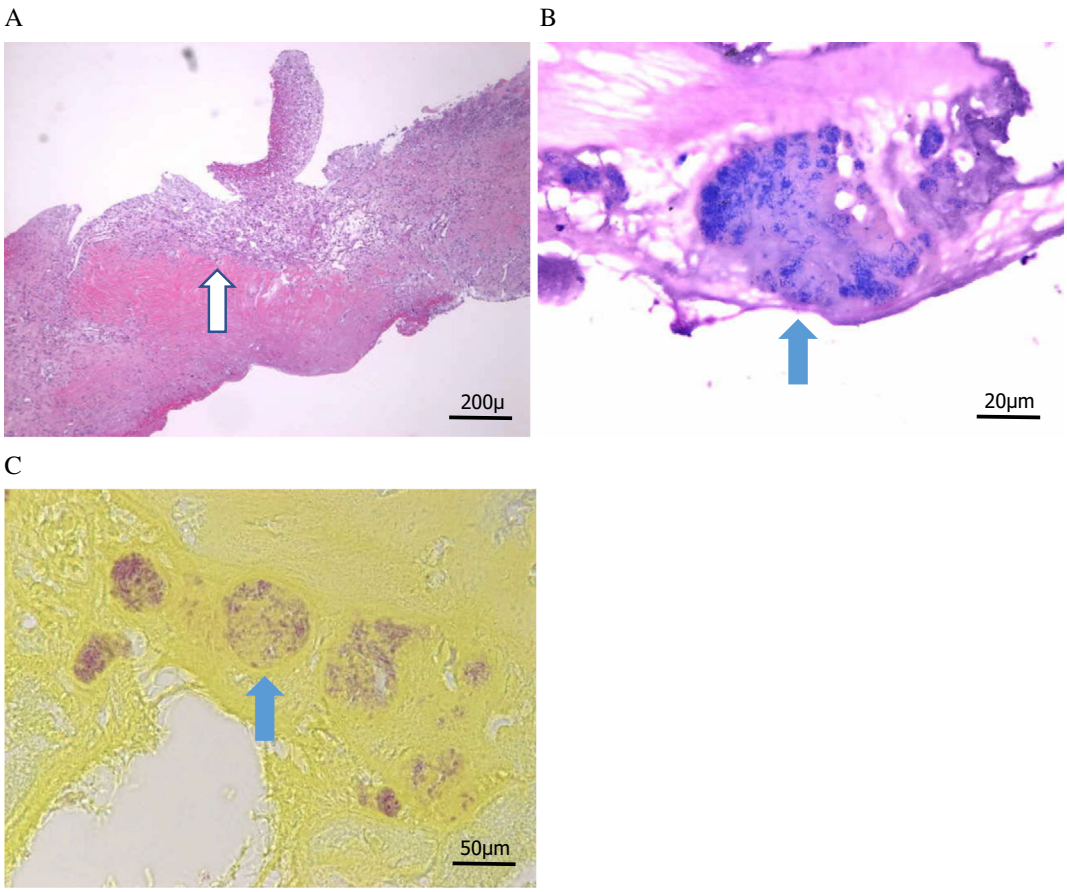

Figure 3. **Surgical pathology of the aortic valve tissue. Overview of the aortic valve with inflammation (white arrow) (A) and adherent vegetation containing microorganisms with Hematoxylin and Eosin staining (blue arrow) (B), which were found to be Gram-negative bacilli (blue arrow) (C).**

sidious with a prolonged subacute course. Diagnosis of infective endocarditis is sometimes difficult because of the indolent clinical course with non-specific symptoms. A longer duration of symptoms has been reported to occur with *C. hominis* endocarditis than with other HACEK organisms (14). In one report, systemic symptoms preceded the eventual diagnosis of infective endocarditis by as much as 12 months (15). Our patient was afebrile but had a subacute course of hemolytic anemia and general fatigue.

Hemolytic anemia was an unusual feature that initially directed attention away from infective endocarditis (4). Anemia accompanying infective endocarditis is generally normochromic and normocytic without reticulocytosis. Fragmentation hemolysis occurs rarely in patients with infective endocarditis (2). Regarding the pathophysiologic mechanism of hemolysis, previous literature has suggested the involvement of shearing stress, hypersplenic sequestration, production of anti-erythrocyte antibodies, and production of circulating immune complexes (4, 16, 17). Powerful turbulent flow caused by vegetation and abnormal valve structures produces shearing stress on the red blood cells. Hypertrophy of the reticulo-endothelial system with hypersplenic sequestration can result in extravascular hemolysis (4). Invading microorganisms can produce anti-erythrocyte antibodies by cross-reaction with erythrocytes, leading to their destruction in the spleen. Thrombotic thrombocytopenic purpura (TTP)-like syndrome has been described with thrombocytopenia, hemolytic anemia, and neurologic and renal impairment in cases with high levels of circulating immune complexes (18, 19). Our patient showed the presence of schistocytes, but there was no thrombocytopenia, and Coombs test was negative. Signs of intravascular hemolysis, such as the fragmented red blood cells and low level of haptoglobin and hemosiderinuria, improved after surgery and antimicrobial therapy. Our patient did not have accompanying hyperbilirubinemia, even with hemolysis. In cases with intravascular hemolysis, unconjugated bilirubin can also be produced, but most free hemoglobin is filtered through the kidneys and flows into the urine (20). This is the reason why only a small amount of the total bilirubin was produced in our patient. Turbulent flow through the fistula in the septum and perforation hole in NCC along with vegetation were likely the mechanisms underlying the intravascular hemolysis in this patient (9).

C. hominis has a strong association with aortic valve infection, and it frequently induces embolic complications involving the peripheral and central nervous system (CNS) (13). Our patient also had cerebral emboli but recovered without any CNS complications. The early detection to ensure the consequent early management is crucial for preventing embolic complications in patients with *C. hominis*

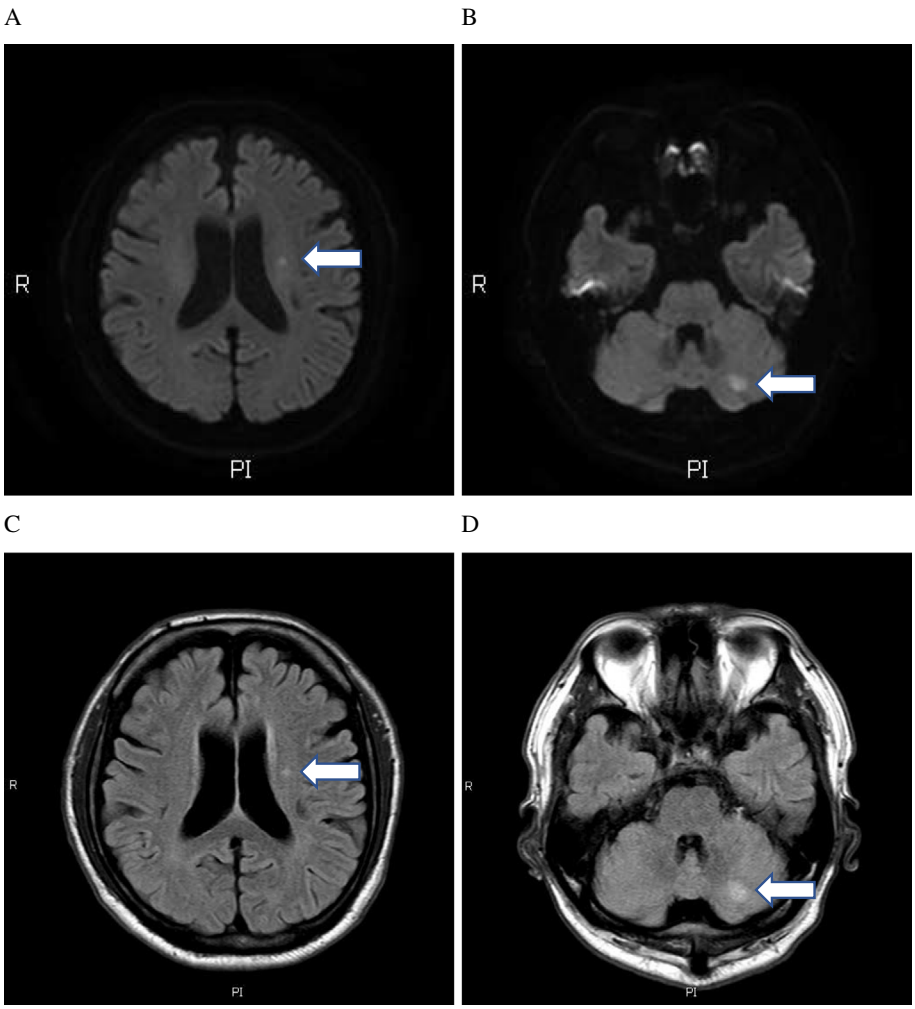

Figure 4. **Magnetic resonance imaging (MRI) of the brain on diffusion-weighted imaging and fluid-attenuated inversion recovery (FLAIR) imaging. A small, high signal (white arrow) in the left corona radiata and cerebellar hemisphere on diffusion-weighted imaging (A, B) and a high signal in the same area (C, D) on fluid attenuated inversion recovery imaging, suggesting acute lacunar infarctions.**

Table. **Antimicrobial Susceptibility of *Cardiobacterium Hominis* Isolated from Blood Culture.**

Drug	MIC (μg/mL)	Category
PCG	0.12	S
Ampicillin	≤0.12	S
Ampicillin/Sulbactam acid	≤0.25	S
Ceftriaxone	0.25	S
Imipenem	≤0.06	S
Meropenem	≤0.06	S
Levofloxacin	≤1	S

MIC: minimum inhibitory concentration, S: susceptible

endocarditis. It is therefore imperative to obtain blood cultures with a low threshold and incubate them over long periods in patients at high risk of this microorganism. *C. hominis* usually resides in the oropharynx as normal indigenous flora. Reported key risk factors for HACEK infection include previously known heart disease, prosthetic valve, poor dentition, and recent dental work (10, 21). Our patient had a history of valve-sparing aortic root replacement and poor dentition.

Regarding the treatment of *C. hominis* endocarditis, the antimicrobial susceptibility and tissue penetration must be considered. Although rare, *C. hominis* produces β-lactamase, which makes it resistant to penicillin. Our patient, who had CNS embolisms, was managed with ceftriaxone, which has excellent penetration to the cerebrospinal fluid. Our patient's clinical course went well with the lacunar lesions scarred on follow-up brain MRI without exacerbation of CNS embolisms, although the dose of CTRX can generally be set at 4 g per day in cases involving CNS lesions.

To our knowledge, there have been no other reports of cases of hemolytic anemia in patients with endocarditis caused by *C. hominis* in the English literature. Subacute endocarditis should be considered in patients with risk factors for HACEK infection and hemolytic anemia. Even without a fever, signs of chronic inflammation should not be overlooked.

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

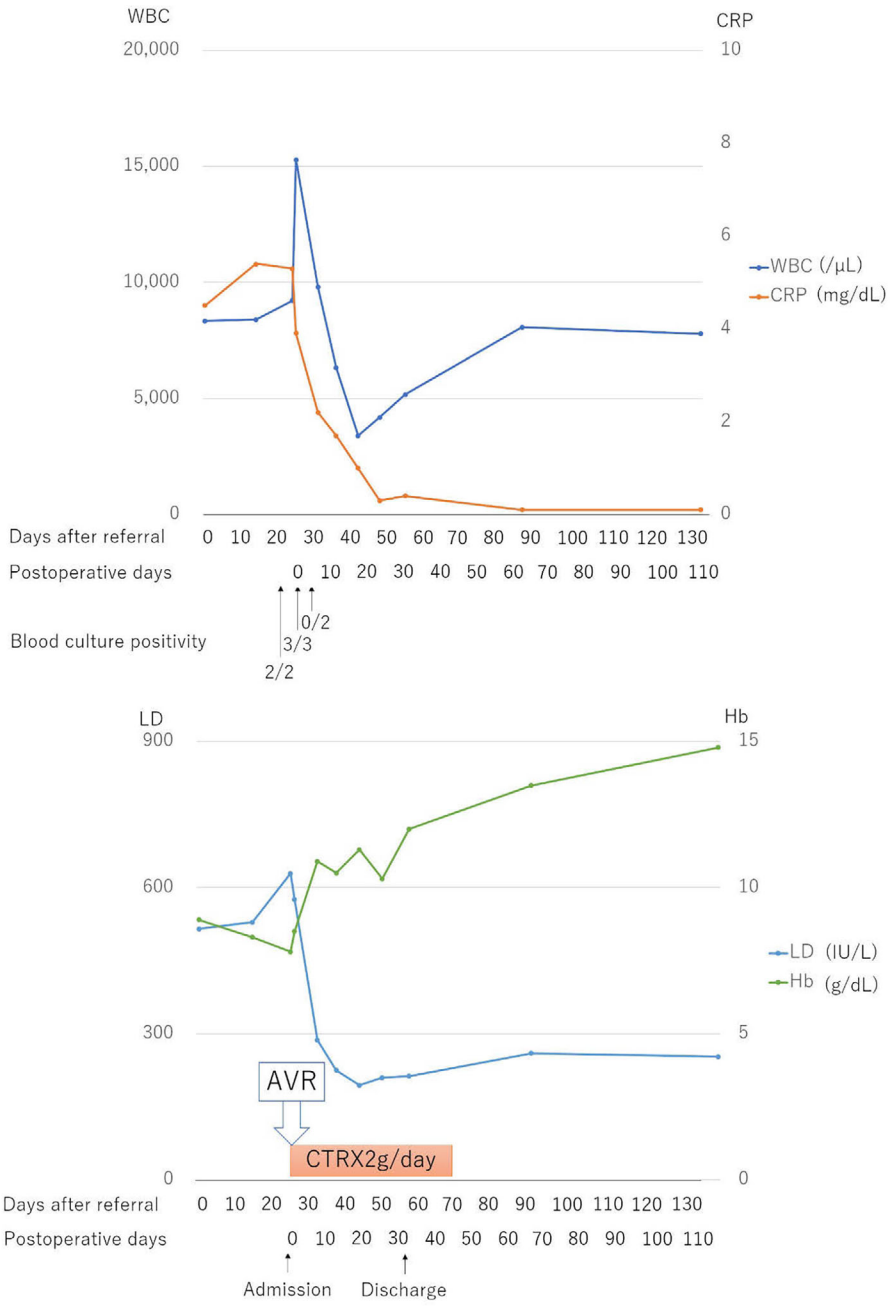

Figure 5. **The patient's therapeutic course. CTRX: ceftriaxone, AVR: aortic valve replacement**

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