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【 CASE REPORT 】

Acquired Hemophilia A Presenting with Infectious Aortic Aneurysms Due to an Underlying *Helicobacter cinaedi* Infection

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Abstract:

Acquired hemophilia A (AHA) is a bleeding disorder caused by the acquired appearance of inhibitor for factor VIII. Approximately half of all patients with AHA have some type of underlying disease. We herein report the case of a 72-year-old Japanese man with AHA who presented with infectious aortic aneurysms due to an underlying *Helicobacter cinaedi* infection. To our knowledge, this is the first report of AHA triggered by a bacterial infection; however, there may be similar cases that remain undiagnosed because this pathogen is difficult to identify. Clinicians should consider the possibility of *H. cinaedi* as a causative pathogen in patients presenting with a fever of unknown origin.

Key words: acquired hemophilia A, *Helicobacter cinaedi*, infectious aortic aneurysms

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Introduction

Acquired hemophilia A (AHA) is a bleeding disorder caused by the acquired appearance of inhibitor for factor VIII (FVIII) that results in sudden and severe bleeding, such as subcutaneous bleeding and intramuscular bleeding. Serious bleeding, which is associated with a mortality rate of 7.9-42%, is not uncommon (1-4). Since approximately 50% of AHA patients have some type of underlying disease, such as autoimmune disease, or a malignant neoplasm, it is important to search for the underlying diseases at the time of onset.

We herein report the case of a patient with AHA who presented with infectious aortic aneurysms due to an underlying *H. cinaedi* infection.

Case Report

A 72-year-old Japanese man underwent percutaneous coronary intervention for ischemic heart disease in September 2019. Aspirin, prasugrel hydrochloride, lansoprazole, rosuvastatin calcium, and enalapril maleate were continued as treatments for ischemic heart disease and dyslipidemia. He had no history of either any hemorrhagic episodes or a family history of bleeding disorders. In March 2020, he had difficulty moving due to arthralgia, which had persisted for three days. After that, he became weak and had great difficulty moving. He was referred to our hospital because of severe anemia with an acute course. A physical examination on admission revealed the following: body temperature, 37.6℃; heart rate, 74 bpm; and blood pressure, 116/70 mmHg. His oxygen saturation was 96% while breathing room air. Clear consciousness. There were no abnormal heart sounds or breath sounds. No joint swelling or lower leg edema was observed. Purpura was found from the lower jaw to the precordium. The laboratory findings are shown in Table 1. Severe anemia and an activated partial thromboplastin time (APTT) prolongation were noted. The hemoglobin level at two weeks before referral was 12.3 g/dL. A cross-mixing test showed a downwardly convex curve, but prolongation of the 2-hour value was observed (Fig. 1). Later, a marked decrease in FVIII activity and the presence of FVIII inhibitor were found. As a close examination for high C-reactive protein (CRP), 2 sets of blood cultures and urine cultures were performed but they were negative. Some

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Table 1. Laboratory Data at the Onset of Acquired Hemophilia A.

Complete blood cell count		Blood chemistry		Serological test	
White blood cell	7.5×10^9 /L	Total protein	5.5 g/dL	C-reactive protein	7.85 mg/dL
Neutrophil	77.9 %	Albumin	2.7 g/dL	Immunoglobulin G	1,104 mg/dL
Lymphocyte	14.1 %	Aspartate aminotransferase	22 U/L	Immunoglobulin A	179 mg/dL
Monocyte	6.8 %	Alanine aminotransferase	22 U/L	Immunoglobulin M	134 mg/dL
Basophil	0.4 %	Lactate dehydrogenase	295 U/L	Complement 3	122 mg/dL
Eosinophil	0.8 %	Alkaline phosphatase	162 U/L	Complement 4	28 mg/dL
Hemoglobin	6.4 g/dL	γ-glutamyl transpeptidase	20 U/L	Antinuclear antibody	<×40
Platelet count	288.0×10^9 /L	Total bilirubin	0.9 mg/dL	Rheumatoid factor	<5.0 IU/mL
		Urea nitrogen	22 mg/dL	Proteinase 3-ANCA	<1.0 U/mL
Coagulation test		Creatinine	1.09 mg/mL	Myeloperoxidase-ANCA	<1.0 U/mL
PT	10.9 s	Creatine phosphokinase	699 U/L		
APTT	81.9 s	Troponin I	11.0 pg/mL	Bacterial culture test	
Fibrinogen	498 mg/dL	Ferritin	713 ng/mL	Blood culture (2 sets)	negative
FDP	8.3 μg/mL	Glucose	88 mg/dL	Urine culture	negative
FVIII activity	<1 %				
FVIII inhibitor	14 B.U.				

PT: prothrombin time, APTT: activated partial thromboplastin time, FDP: fibrinogen and fibrin degradation products, FVIII: factor VIII, B.U.: Bethesda units, ANCA: anti-neutrophil cytoplasmic antibody

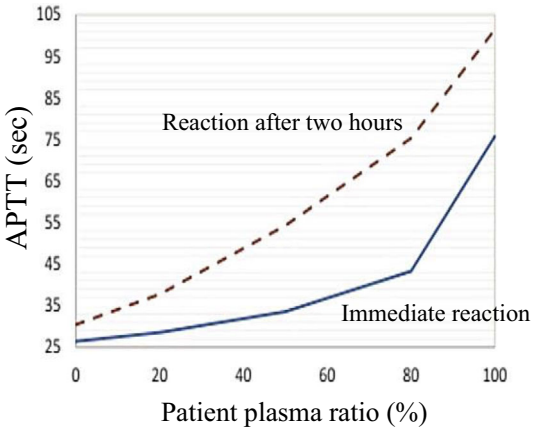

Figure 1. A cross-mixing test showed a downwardly convex curve, but a prolongation of the two-hour value was observed. APTT: activated partial thromboplastin time

autoantibodies were also measured, but all were negative. Contrast-enhanced computed tomography (CE-CT) screening for causes of anemia performed in April 2020 revealed suspected non-communicating aortic dissection with ulcer-like projection (ULP) in the descending thoracic aorta, which had not been observed six months previously (Fig. 2a). There were no findings suggestive of malignant neoplasms. Furthermore, upper and lower gastrointestinal endoscopy revealed no findings suggestive of malignant neoplasms. AHA was diagnosed based on the findings of purpura, a decreased FVIII activity and the presence of FVIII inhibitor. The clinical course is shown in Fig. 3. Under a diagnosis of AHA, immunosuppressive therapy was initiated with prednisolone (PSL; 60 mg) and cyclophosphamide (CY; 100 mg). Aortic dissection was followed with strict blood pressure control. On the 8th hospital day, sudden swelling of both forearms and an exacerbation of anemia were observed, and activated Eptacog alfa (recombinant activated factor VII; rFVIIa) was administered as hemostasis therapy due to a high suspicion of intramuscular bleeding. Since cellulitis could not be ruled out, cephalexin was also given temporarily. On the 32nd day after the start of PSL, the APTT level decreased to almost the normal range, and the FVIII inhibitor disappeared. On the other hand, high CRP levels, fatigue and weight loss continued, and the patient's albumin level further decreased. Positron emission tomography (PET)/CT using ^{18}F-fluorodeoxyglucose (FDG) was performed in June 2020, and it showed an abnormal FDG uptake in the aortic walls corresponding to the dissection (Fig. 2b). Thereafter, CE-CT in July 2020 revealed an increase in the size of the thoracic descending aorta, infrarenal aorta, and the origins of the bilateral common iliac arteries (Fig. 2c). Each showed saccular protrusion and a minimal FDG uptake was observed in each lesion by retrospective interpretations (Fig. 2b). At this time, the possibility of an infectious aneurism, not aortic dissection, was considered. A blood culture test was performed again, and 1 of the 2 sets was positive for *H. cinaedi*. When blood culturing was performed again 7 days later, the same bacteria were detected; *H. cinaedi* was also detected in a fecal culture. Enhanced magnetic resonance imaging of the thoracolumbar spine showed no evidence of infectious spondylitis, and transthoracic echocardiography showed no evidence of infective endocarditis.

Ceftriaxone [2 g, intravenous (IV)] was administered every 24 hours and was changed to meropenem (2 g, IV) every 8 hours based on an antimicrobial susceptibility test (Table 2). Soon after the administration of these antibiotics, the CRP level rapidly normalized, and the fatigue, weight loss, and hypoalbuminemia also improved. No exacerbations of the aortic aneurysms were observed thereafter. Systemic drug eruption due to meropenem occurred, and was therefore changed to minocycline (100 mg, IV, every 12 hours)

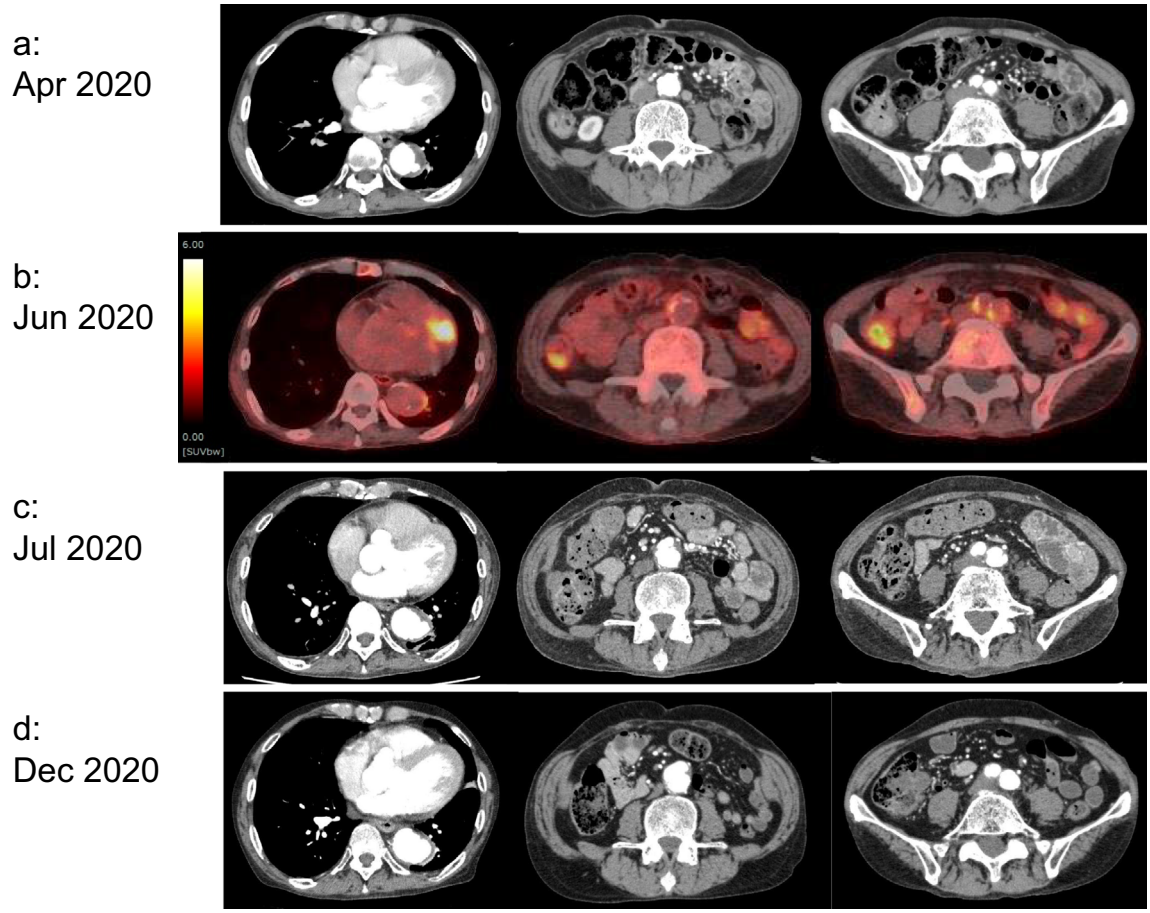

Figure 2. **Contrast-enhanced computed tomography (CE-CT) and positron emission tomography (PET)/CT using ^{18}F-fluorodeoxyglucose (FDG) throughout the clinical course. (a) A non-communicating aortic dissection with an ulcer-like projection in the descending thoracic aorta was suspected based on the CE-CT findings in April 2020. (b) FDG-PET/CT in June 2020 showed a minimal uptake in the walls of the aorta and the bilateral common iliac arteries. (c) CE-CT in July 2020 revealed an increase in the size of the thoracic descending aorta, infrarenal aorta, and the origins of the bilateral common iliac arteries, and infectious aneurysms were suspected at this time. (d) CE-CT in December 2020, after five months of treatment with antibiotics, showed no further increase in the size of the aneurysms.**

and gentamicin (180 mg, IV, every 24 hours), and the dose of PSL was temporarily increased. After a total of six weeks of these intravenous antibiotics, oral minocycline was started and has been continued until the present time. CY for AHA was discontinued due to cytopenia, and the PSL dosage was gradually reduced to 2 mg. The patient remained negative for FVIII inhibitor.

The aneurysms were followed-up by CE-CT, and at five months after the administration of antibiotics targeting *H. cinaedi*, (December 2020), no further size increase has been observed. Finally, the multiple arterial lesions were clinically diagnosed as infectious aneurysms due to *H. cinaedi*.

Discussion

In our case, CRP had already been elevated since the onset of AHA, and the patient was later diagnosed with *H. cinaedi* infection, and the CRP level rapidly normalized with antibiotics. It was considered that *H. cinaedi* infection had already occurred at the onset of AHA and it was the therefore deemed to be the underlying disease of AHA.

H. cinaedi is a Gram-negative spiral rod that causes gastroenteritis, cellulitis, arthritis and bacteremia (5). This bacterium was first isolated from rectal cultures from homosexual men in 1984 (6). For the next 10 years, it was considered to be a bacterium identified only in immunocompromised patients. Recently, however, it has been reported to cause arterial infections in immunocompetent patients (7-9). The bacterium has also been reported to promote atherosclerosis through chronic infection (10-12). In the present case, at the onset of AHA, an arterial infection developed despite an immunocompetent state. Even in immunocompetent patients, it is necessary to be alert for infection with this bacterium. Many patients infected by *H. cinaedi* do not display any symptoms other than a fever (5). The bacteremia usually grows slowly and it has been reported to likely be overlooked in approximately 50% of cases when the duration of blood culture monitoring was limited to 5 days (13). In the

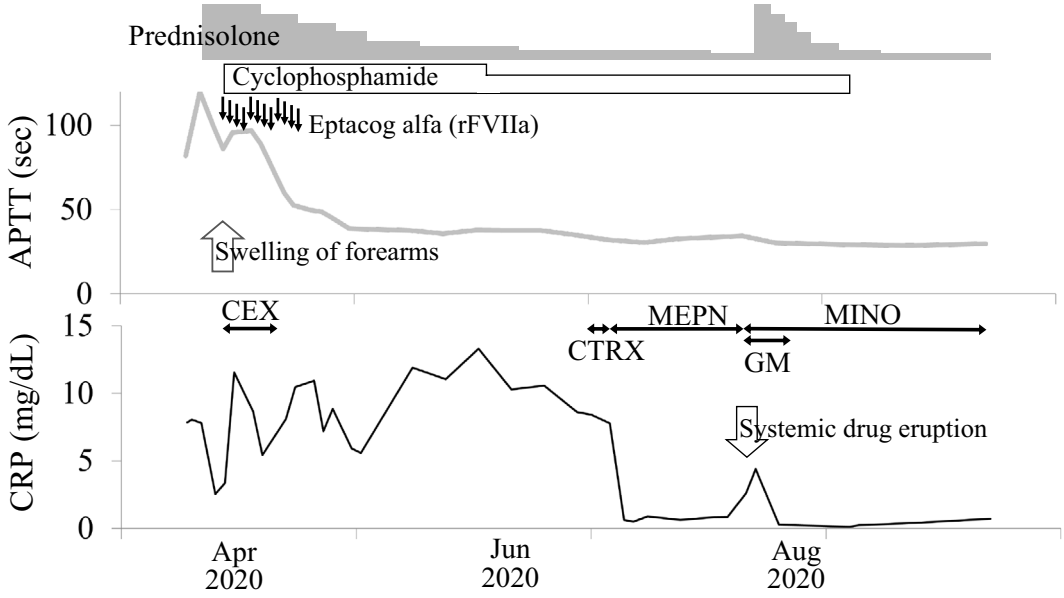

Figure 3. **The clinical course. APTT: activated partial thromboplastin time, CRP: C-reactive protein, rFVIIa: recombinant activated factor VII, CEX: cephalexin, CTRX: ceftriaxone, MEPN: meropenem, MINO: minocycline, GM: gentamicin**

Table 2. **Antimicrobial Susceptibility Test for *Helicobacter cinaedi*.**

		Minimum inhibitory concentration (μg/mL)
Penicillins	Ampicillin	8
	Amoxicillin	4
	Carbenicillin	8
	Piperacillin	4
	Piperacillin/Tazobactam	4
Cephalosporins	Cefepime	8
	Ceftriaxone	4
Carbapenems	Imipenem	0.06
	Meropenem	0.06
Aminoglycosides	Gentamicin	0.25
	Kanamycin	0.5
Tetracycline	Tetracycline	0.06
Macrolides	Erythromycin	>64
Quinolones	Ciprofloxacin	8
	Levofloxacin	4
	Moxifloxacin	0.5
Metronidazole	Metronidazole	>64
Chloramphenicol	Chloramphenicol	0.5

Judgment was made after 72 hours of microaerobic culture at 37°C. The measured concentration range was 0.06 to 64 g/mL.

present case, it is possible that this bacterium could not be identified by blood culturing at the onset of AHA because it is difficult to identify and because the amount of bacterium was small. Due to immunosuppressive therapy for AHA, the amount of bacterium increased, and it may have been identified by blood culturing that was performed again later. Because *H. cinaedi* is difficult to identify, there may be similar cases that remain undiagnosed. Even in immunocompetent patients, clinicians should suspect *H. cinaedi* as a causative pathogen in patients with a fever of unknown origin. One the other hand, it cannot be ruled out that the infection in the present case may have developed after the immunosuppressive therapy for AHA.

In our case, aortic dissection with ULP in the thoracic descending aorta was initially suspected. Subsequently, a slow increase in the sizes of some parts of the arteries was observed during the course, despite strict blood pressure control. Considering the possibility of infectious aneurysms, FDG-PET/CT showed an abnormal uptake in the arterial walls corresponding to the saccular protrusion. Infectious

aneurysms often show an extremely high uptake of FDG (14). Even though the FDG uptake is not direct evidence of infection, the degree of the uptake of FDG that was observed in our case, which was not so high, may be due to the characteristics of *H. cinaedi* infections, which often follow a chronic clinical course.

Since AHA is associated with various underlying diseases, it is considered that there are various pathogenic mechanisms. To our knowledge, this is the first report of AHA triggered by a bacterial infection; however, several other autoimmune diseases are closely associated with a bacterial infection, including autoimmune thrombocytopenia (ITP) with *Helicobacter pylori* infection (15) and Guillain-Barré syndrome with *Campylobacter jejuni* infection (16). In *H. pylori*, which belongs to the same genus as *H. cinaedi*, cross-reactivity between platelet-associated immunoglobulin G and *H. pylori* cytotoxin-associated gene A (CagA) protein was shown in *H. pylori*-positive ITP patients, suggesting that molecular mimicry by *H. pylori* CagA protein is involved in the pathogenesis of ITP (17).

Another hypothesis is that the aortic aneurysm itself may have caused AHA, and the *H. cinaedi* infection may only have contributed to the exacerbation of the aortic aneurysm. One of the pathogenic mechanisms that causes AHA is the breakdown of immune tolerance to endogenous FVIII (18). One of the causes of the breakdown of immune tolerance is the danger signal theory, wherein the "danger signal" from cells damaged by tissue destruction or inflammation induces an abnormal immune response (19). There are some reports of AHA developing after surgery (20, 21). In these cases, surgically invaded tissue may have issued a "danger signal", causing the breakdown of immune tolerance and thereby inducing the development of AHA. Similarly, in our case, the tissue invaded by the aortic aneurysm may have issued a "danger signal", thus leading to the onset of AHA.

In conclusion, we experienced a case of AHA in which the infectious aneurysms due to *H. cinaedi* infection were present as an underlying disease. To our knowledge, this is the first report of AHA triggered by a bacterial infection; however, there may be other similar cases that remain undiagnosed because this pathogen is difficult to identify. Clinicians should be aware that *H. cinaedi* is a possible causative pathogen in patients with a fever of unknown origin.

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

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