Acquired Hemophilia A Presenting with Infectious Aortic Aneurysms Due to an Underlying *Helicobacter Cinaedi* Infection: A Case Report

Anna Matsuoka¹, Yuya Sasaki¹, Ai Kubodeta², Kiyohito Hayashi², Ryo Shimizu², Akira Toriihara¹, Akira Nakamura⁴, Keiichi Furukawa⁴ and Hiroaki Tanaka²

**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

(Intern Med Advance Publication)  
(DOI: 10.2169/internalmedicine.7517-21)

**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, rosvastatin 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°C; 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 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, cephalixin 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 18F-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) 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 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 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.

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

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

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

Acknowledgement
The authors would like to thank Yoshiaki Kawamura of Department of Microbiology, School of Pharmacy, Aichi Gakuen University for performing the antimicrobial susceptibility test.

References
1. Hay CR, Brown S, Collins PW, Keeling DM, Liesner R. The diagnosis and management of factor VIII and IX inhibitors: a guideline from the United Kingdom Haemophilia Centre Doctors Organisation. Br J Haematol 133: 591-605, 2006.
2. Collins PW, Hirsch S, Baglin TP, et al. Acquired hemophilia A in the United Kingdom: a 2-year national surveillance study by the United Kingdom Haemophilia Centre Doctors’ Organisation. Blood 109: 1870-1877, 2007.
3. Collins P, Baudo F, Knoebel P, et al. Immunosuppression for acquired hemophilia A: results from the European Acquired Haemophilia Registry (EACH2). Blood 120: 47-55, 2012.
4. Borg JV, Guillet B, Le Cam-Duchez V, Goudemand I, Levesque H. Outcome of acquired haemophilia in France: the prospective SACHA (Surveillance des Auto antiCorps au cours de l’Hémosthèle Acquise) registry. Haemophilia 19: 564-570, 2013.
5. Kawamura Y, Tomida J, Morita Y, Fujii S, Okamoto T, Akaike T. Clinical and bacteriological characteristics of Helicobacter cinaedi infection. J Infect Chemother 20: 517-526, 2014.
6. Fennell CL, Totten PA, Quinn TC, Patton DL, Holmes KK, Stamm WE. Characterization of Campylobacter-like organisms isolated from homosexual men. J Infect Dis 149: 5866, 1984.
7. Nakao S, Hagiya H, Kimura K, et al. Helicobacter cinaedi-associated Carotid Arteritis. Acta Med Okayama 72: 189-192, 2018.
8. Matsuo T, Mori N, Mizuno A, et al. Infected aortic aneurysms caused by Helicobacter cinaedi: case series and systematic review of the literature. BMC Infect Dis 20: 854, 2020.
9. Suematsu Y, Morizumi S, Okamura K, Kawata M. A rare case of axillofemoral bypass graft infection caused by Helicobacter cinaedi. J Vasc Surg 61: 231-233, 2015.
10. Khan S, Okamoto T, Enomoto K, et al. Potential association of Helicobacter cinaedi with atrial arrhythmias and atherosclerosis. Microbiol Immunol 56: 145-154, 2012.
11. Khan S, Rahman NN, Okamoto T, et al. Promotion of atherosclerosis by Helicobacter cinaedi infection that involves macrophage-driven proinflammatory responses, Sci Rep 4: 4680, 2014.
12. D’Elios MM, Vallese F, Capitani N, et al. The Helicobacter cinaedi antigen CAIP participates in atherosclerotic inflammation by promoting the differentiation of macrophages in foam cells. Sci Rep 7: 40515, 2017.
13. Araoka H, Baba M, Kimura M, Abe M, Inagawa H, Yoneyama A. Clinical characteristics of bacteremia caused by Helicobacter cinaedi and time required for blood cultures to become positive. J Clin Microbiol 52: 1519-1522, 2014.
14. Mikail N, Benali K, Dossier A, et al. Additional diagnostic value of combined angio-computed tomography and 18 F-fluorodeoxyglucose positron emission tomography in infectious aortitis. JACC Cardiovasc Imaging 11: 361-364, 2018.
15. Gasbarrini A, Franceschi F, Tartaglione R, Landolfi R, Pola P, Gasbarrini G. Regression of autoimmune thrombocytopenia after eradication of Helicobacter pylori. Lancet 352: 878, 1998.
16. Yuki N, Yoshino H, Sato S, Miyatake T. Acute axonal polyneuropathy associated with anti-GM1 antibodies following Campylobacter enteritis. Neurology 40: 1900-1902, 1990.
17. Takahashi T, Yuiji T, Shinozuka K, et al. Molecular mimicry by Helicobacter pylori CagA protein may be involved in the pathogenesis of H. pylori-associated chronic idiopathic thrombocytopenic purpura. Br J Haematol 124: 91-96, 2004.
18. Lacroix-Desmazes S, Navarrete AM, Andre S, Bayry J, Kaveri SV, Dasgupta S. Dynamics of factor VIII interactions determine its immunologic fate in hemophilia A. Blood 112: 240-249, 2008.
19. Matzinger P. Tolerance, danger, and the extended family. Annu Rev Immunol 12: 991-1045, 1994.
20. Ushiki M, Koike M, Akiyama T, et al. Acquired hemophilia A with rectus abdominis muscle and intrapelvic hematomas after aortic arch replacement. Rinsho Ketsueki (Journal of Japanese Society of Hematology) 52: 8-13, 2011 (in Japanese).

21. Khan UZ, Yang X, Masroor M, Aziz A, Yi H, Liu H. Surgery-associated acquired hemophilia A: a report of 2 cases and review of literature. BMC Surg 20: 213, 2020.