Internal Medicine
The Japanese Society of Internal Medicine
doi: 10.2169/internalmedicine.1196-18
Intern Med 57: 3663-3666, 2018
http://internmed.jp

【 CASE REPORT 】

Bacteremia Possibly Caused by *Helicobacter cinaedi* and Associated with Painful Erythema in Rheumatoid Arthritis with Malignant Lymphoma

Shunichi Fujita[1], Hiroaki Hayashi[2], Shoko Kodama[1], Tomoyuki Mukai[1] and Yoshitaka Morita[1]

Abstract:
We herein report the case of a 69-year-old woman with rheumatoid arthritis (RA) and malignant lymphoma who developed *Helicobacter cinaedi* bacteremia after starting rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) chemotherapy. She had a recurrent fever and painful erythema for 13 months before the diagnosis was made. This delayed diagnosis was attributable to the underlying RA, which typically presents with various cutaneous manifestations and elevated C-reactive protein levels. The erythema on the thighs, abdomen, and left forearm improved following treatment with intravenous aminobenzyl penicillin; she received antibiotics for six weeks. This case emphasizes the importance of recognizing this opportunistic infection in immunocompromised patients.

Key words: *Helicobacter cinaedi*, painful erythema, rheumatoid arthritis, malignant lymphoma

(Intern Med 57: 3663-3666, 2018)
(DOI: 10.2169/internalmedicine.1196-18)

Introduction

Patients with rheumatoid arthritis (RA) may develop a variety of specific or nonspecific cutaneous manifestations. When rheumatologists encounter RA patients with painful erythema on the extremities, the differential diagnosis for this cutaneous condition can be particularly challenging. It may include cellulitis, neutrophilic panniculitis, diffuse fasciitis, or neutrophilic dermatosis with Sweet's syndrome (1-5). However, it is also necessary to consider *Helicobacter cinaedi* bacteremia-associated erythema in rheumatoid disease (6-9), even though this opportunistic infectious disease is rare. Indeed, there are very few reports of this complication in the rheumatology literature.

We herein report a case of RA with malignant lymphoma in a patient with recurrent painful erythema associated with *H. cinaedi* bacteremia.

Case Report

A 69-year-old woman with a 7-year history of RA was admitted to our hospital in October 2015 for recurrent painful swelling and redness of both thighs and the abdomen. She had received a diagnosis of gastric diffuse large B-cell lymphoma (DLBCL) in March 2014, and the methotrexate (12 mg/week) she had been taking was stopped because of the possibility of methotrexate-associated lymphoproliferative disorder. Since discontinuation of methotrexate failed to lead to remission of the gastric DLBCL, she was then started on rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) chemotherapy in September 2014. Two weeks after the first administration of R-CHOP, she developed painful erythematous swelling of the left thigh (Fig. 1). Laboratory findings were C-reactive protein (CRP) 2.26 mg/dL and white cell count 6,400/μL. A skin biopsy revealed inflammatory infiltrate of lymphocytes in the dermis and subcutaneous adipose tissue without evidence of vasculitis (Fig. 2). No bacteria were observed mi-

[1]Department of Rheumatology, Kawasaki Medical School, Japan and [2]Department of Dermatology, Kawasaki Medical School, Japan
Received: March 15, 2018; Accepted: June 5, 2018; Advance Publication by J-STAGE: August 24, 2018
Correspondence to Dr. Yoshitaka Morita, morita@med.kawasaki-m.ac.jp

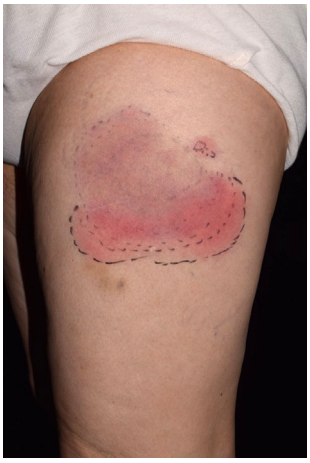

Figure 1. **Painful erythema on the left thigh, with the area of erythema marked in black ink to assess the clinical progress.**

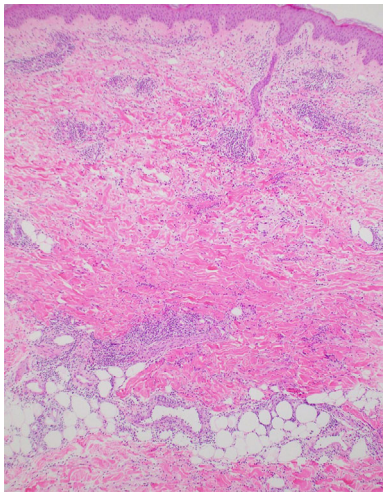

Figure 2. **A skin biopsy specimen shows inflammatory infiltrate of lymphocytes in the dermis and subcutaneous adipose tissue without evidence of vasculitis.**

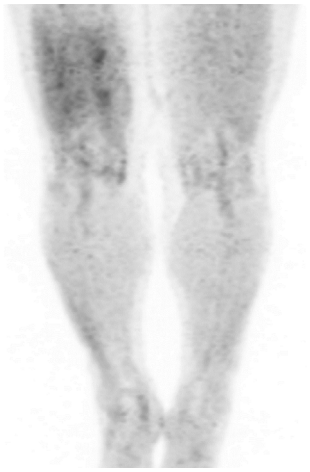

Figure 3. **Positron emission tomography-computed tomography images show an increased ^{18}F-fluoro-2-deoxyglucose uptake in the right thigh.**

croscopically in the tissue specimen.

The erythema improved spontaneously two weeks later, so the second round of R-CHOP was administered. However, three weeks after the second round of R-CHOP, she developed painful erythema on both thighs. The serum CRP level was 4.22 mg/dL, so she was treated empirically with moxifloxacin for 5 days. After a brief improvement, the third round of R-CHOP was administered. R-CHOP chemotherapy was repeated every three to four weeks for four cycles, and a subsequent two cycles of rituximab monotherapy were added. During these cycles, she received 14 days' treatment of garenoxacin twice in December 2014 and March 2015 for her fever and chronic painful erythema on both thighs. However, despite these treatments, she did not show a marked response, and her CRP level remained high.

Positron emission tomography-computed tomography was performed in April 2015 after the last rituximab administration. This showed an increased ^{18}F-fluoro-2-deoxyglucose uptake in the right thigh (Fig. 3), with no other abnormalities in the visceral organs. Given that the painful erythema in the thigh might have been associated with RA, she underwent a trial of prednisolone 20 mg/day but was only partially responsive, and she developed new painful erythematous lesions on the skin of the abdomen and left forearm and was thus admitted for a further investigation in October 2015.

On an examination, her temperature was 36.3℃, blood pressure 142/99 mmHg, and pulse 87 beats/min. A skin examination revealed painful erythema on both thighs, the abdomen, and the left forearm. A physical examination of the chest was unremarkable. Laboratory investigations revealed a CRP level of 6.25 mg/dL, hemoglobin of 12.2 g/dL, white blood cell count of 9,400/μL, and platelet count of 9.3×10^4/μL. Rheumatoid factor and anti-cyclic citrullinated peptide antibody were both positive at 21 IU/mL and 32.9 U/mL, respectively. Serum complement C3 and C4 were elevated at 125.6 mg/dL and 36.7 mg/dL, respectively. Hep-2 antinuclear antibody and antineutrophil cytoplasmic antibodies were negative. An interferon gamma release assay for tuberculosis was negative.

Two sets of blood culture tests were performed, and aerobic bottles from both sets were positive for growth of a Gram-negative spiral bacillus after four days' incubation. A thinly spread colony was found 4 days after the start of subcultures, consisting of growth on 5% sheep blood agar plates upon immediate incubation under wet microaerophilic conditions. Growth occurs at 35℃ but not at 25 or 42℃. The bacteria isolated was presumed to be *H. cinaedi* based on the morphology and growth features. Treatment with intravenous aminobenzyl penicillin (ABPC) at 8 g/day improved the erythema on the thighs, abdomen, and left forearm. This bacterium was not detected in the blood culture nine days after starting ABPC, and the patient received antibiotics for six weeks. Two years later, she remains clinically well without recurrence of the infection or malignant lymphoma.

Discussion

H. cinaedi is a Gram-negative enterohepatic spiral bacillus that inhabits the intestinal tracts of mammals (10). Several cases of human *H. cinaedi* infections have been reported in immunocompromised patients, such as those following organ transplantation or with human immunodeficiency virus infection or cancer (10-12). Although the exact mechanism has not been identified, *H. cinaedi* bacteremia is often accompanied by skin manifestations, such as cellulitis and erythema nodosum-like eruptions (11), which have been reported to develop through bacterial translocation from the intestines into the circulation (13).

It is likely that R-CHOP chemotherapy was associated with the onset of this opportunistic infection in our patient, although recently there have been some reports describing patients with rheumatic diseases who developed *H. cinaedi* infection as an opportunistic pathogen (7, 8, 11). Therefore, RA itself or the previous treatment with methotrexate might have been involved in the development of disease in our case.

We should note that a definitive diagnosis of *H. cinaedi* infection should be based on a gene analysis (14). Since nucleotide sequencing or species-specific polymerase chain reaction was not performed in our case, the isolated Gram-negative spiral bacterium was not identified as a specific bacterium within the genus *Helicobacter*. However, the organism had several morphological and growth features characteristic of *H. cinaedi*. It appeared as a thinly spread colony and showed no hemolysis on sheep blood agar. Furthermore, the bacterium grew at 35℃ and but not 25℃ or 42℃ (15). Based on these morphological and growth features, we suspected that the isolated bacterium was very likely *H. cinaedi*.

The unique but regrettable point of this case is that it took an extremely long time before a diagnosis of *H. cinaedi* bacteremia could be made. Our patient developed painful erythema in September 2014, which was two weeks after the first administration of R-CHOP chemotherapy. She was diagnosed with *H. cinaedi* infection in October 2015. Since she had been having a recurrent fever and chronic skin manifestations during this period, it is likely that the bacteremia had been ongoing for 13 months. We should have considered *H. cinaedi* infection as the cause of the recurrent fever and erythema earlier in the course of the disease. However, her underlying RA, which can present with various skin manifestations and elevated CRP (1-5), as well as the short-term use of oral antibiotics resulted in a delayed diagnosis. Since *H. cinaedi* is a low-virulence bacterium (16, 17), our patient fortunately did not develop serious complications. Infectious aortic aneurysm has been reported in some patients with *H. cinaedi* bacteremia (17, 18), although this fortunately did not occur in our case.

The ideal duration or choice of antibiotic therapy for *H. cinaedi* bacteremia has not been established. This organism is reportedly resistant to various antibiotics, including macrolides and quinolones (6). Furthermore, frequent cases of recurrence after stopping antibiotics have been reported (16). We therefore treated our patient with intravenous antibiotics for a sufficiently long period of six weeks, which proved successful. This case emphasizes the importance of recognizing this opportunistic infection in patients with rheumatic disease. Infection with this pathogen should be suspected in cases of painful erythema of unidentified etiology.

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

References

1. Chua-Aguilera CJ, Moller B, Yawalkar N. Skin manifestations of rheumatoid arthritis, juvenile idiopathic arthritis, and spondyloarthritides. Clin Rev Allergy Immunol **53**: 371-393, 2017.
2. Yoshida Y, Kiryu H, Furue M, Nakayama J, Matsuda T. Rheumatoid neutrophilic dermatitis. J Dermatol **30**: 255-256, 2003.
3. Gay-Crosier F, Dayer JM, Chavaz P, Hauser C. Rheumatoid neutrophilic dermatitis/sweet's syndrome in a patient with seronegative rheumatoid arthritis. Dermatology **201**: 185-187, 2000.
4. Iwata K, Arinuma Y, Nakayama H, et al. An autopsy case of necrotizing fasciitis with rapidly progressive purpura caused by hemolytic streptococcal infection in a patient with rheumatoid arthritis. Mod Rheumatol **21**: 669-672, 2011.
5. Yamamoto T. Cutaneous necrobiotic conditions associated with rheumatoid arthritis: important extra-articular involvement. Mod Rheumatol **23**: 617-622, 2013.
6. 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.
7. Kikuchi H, Asako K, Tansho S, et al. Recurrent *Helicobacter cinaedi* cellulitis and bacteremia in a patient with systemic lupus erythematosus. Intern Med **51**: 3185-3188, 2012.
8. Nishida R, Shimono N, Miyake N, et al. *Helicobacter cinaedi* bacteremia mimicking a flare of systemic lupus erythematosus. Intern Med **56**: 725-728, 2017.
9. Minauchi K, Takahashi S, Sakai T, et al. The nosocomial transmission of *Helicobacter cinaedi* infections in immunocompromised patients. Intern Med **49**: 1733-1739, 2010.
10. Kiehlbauch JA, Tauxe RV, Baker CN, Wachsmuth IK. *Helicobacter cinaedi*-associated bacteremia and cellulitis in immunocompromised patients. Ann Intern Med **121**: 90-93, 1994.
11. Shimizu S, Shimizu H. Cutaneous manifestations of *Helicobacter cinaedi*: a review. Br J Dermatol **175**: 62-68, 2016.
12. Matsumoto T, Goto M, Murakami H, et al. Multicenter study to evaluate bloodstream infection by *Helicobacter cinaedi* in Japan. J Clin Microbiol **45**: 2853-2857, 2007.
13. Araoka H, Baba M, Okada C, et al. First evidence of bacterial translocation from the intestinal tract as a route of *Helicobacter cinaedi* bacteremia. Helicobacter 23, 2018 [Epub ahead of print].
14. Oyama K, Khan S, Okamoto T, et al. Identification of and screening for human *Helicobacter cinaedi* infections and carriers via nested PCR. J Clin Microbiol **50**: 3893-3900, 2012.
15. 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.
16. Uckay I, Garbino J, Dietrich PY, Ninet B, Rohner P, Jacomo V. Recurrent bacteremia with *Helicobacter cinaedi*: case report and review of the literature. BMC Infect Dis **6**: 86, 2006.

17. Kushimoto K, Yonekura R, Umesue M, et al. Infected thoracic aortic aneurysm caused by *Helicobacter cinaedi*. Ann Vasc Dis **10**: 139-142, 2017.

18. Unosawa S, Niino T. An infected abdominal aortic aneurysm caused by *Helicobacter cinaedi*. Ann Vasc Dis **8**: 318-320, 2015.