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Case Report

Recurrent Fever due to *Helicobacter cinaedi* Infection during R-CHOP Chemotherapy in Diffuse Large B-Cell Lymphoma: Case Report and Literature Review

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Erythema · Fever · *Helicobacter cinaedi* · Chemotherapy

Abstract
Fever due to *Helicobacter cinaedi* bacteremia under chemotherapy has not been widely recognized among clinicians. We experienced a 72-year-old man with diffuse large B-cell lymphoma, who was complicated with *H. cinaedi* bacteremia-induced fever under R-CHOP chemotherapy. We summarized 6 cases including ours, suggesting that fever without neutropenia developing around day 6 from starting chemotherapy is a possible symptom caused by *H. cinaedi* bacteremia. We should discriminate fever due to *H. cinaedi* bacteremia if fever emerged before myelosuppression in the course of chemotherapy.

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Introduction

Helicobacter cinaedi is a Gram-negative spiral bacillus inhabiting the intestinal tracts of humans [1, 2]. This organism can easily cause bacteremia with fever, especially in immunocompromised individuals. *H. cinaedi* bacteremia has been attributed to this organism's strong ability of bacterial translocation from the intestinal tracts to the vascular system. The cases due to *H. cinaedi* bacteremia in patients receiving chemotherapy have been reported [3–7]. In some of these cases, the diagnosis of *H. cinaedi* bacteremia was delayed not only because *H. cinaedi* is difficult to isolate by blood culture, but also because this pathology has not been widely recognized among clinicians.

Here, we describe a unique case in which a patient with diffuse large B-cell lymphoma (DLBCL) developed recurrent fever due to *H. cinaedi* bacteremia during R-CHOP chemotherapy. In addition, we investigated the clinical and laboratory features of *H. cinaedi* bacteremia-induced fever in patients receiving chemotherapy for malignant lymphoma by reviewing previous cases.

Case Report

A 72-year-old Japanese man was diagnosed with splenic DLBCL (stage IV) in April 2018 at the Department of Hematology, Kita-Harima Medical Center, and 8 cycles of R-CHOP therapy (375 mg/m^2 rituximab on day 1, 50 mg/m^2 doxorubicin on day 2, 750 mg/m^2 cyclophosphamide on day 2, 1.4 mg/m^2 vincristine on day 2, and 100 mg prednisolone on days 2–6) every 3 weeks were planned.

The first cycle of chemotherapy was started in the hospital setting (Fig. 1A). Prophylactic daily subcutaneous administration of granulocyte colony-stimulating factor, filgrastim (75 μg/day), was performed from day 4 to day 12 to reduce the incidence of febrile neutropenia (FN). On day 6, the patient developed high fever (38.8°C), nausea, vomiting, sore throat, and loss of appetite. Laboratory investigations showed an elevated white blood cell (WBC) count of 23,780/mm^3 (normal, 3,500–9,700/mm^3), along with a marked increase in neutrophil and decrease in monocyte percentages to 95.8% (normal, 38–74%) and 0.3% (normal, 2–10%), respectively. The concentration of C-reactive protein (CRP) was within normal limits. Neither chest X-ray nor urine findings showed any abnormality. Treatment with intravenous piperacillin/tazobactam (PIPC/TAZ) (18 g/day) was given for 5 days from day 7, with marked improvement in clinical symptoms within 3 days. Intravenous PIPC/TAZ was changed to oral levofloxacin hydrate (LVFX) (500 mg/day for 3 days) on day 12. Blood culture performed on day 7 was negative after culturing the sample for 5 days. Blood culture was performed using an automatic blood culture system (BACTEC FX; Nippon Becton Dickinson Co., Ltd., Minato City, Japan) with aerobic and anaerobic resin bottles. Retrospectively, FN was ruled out since absolute neutrophil count did not decrease below 500 during the entire course of the chemotherapy cycle. However, the cause of the fever remained unknown.

The second cycle of chemotherapy was commenced from day 1 to day 3 of admission (Fig. 1B). Subcutaneous injection of granulocyte colony-stimulating factor, pegfilgrastim (3.6 mg), was administered on day 4. Nausea and chills and high fever (38.0°C), respectively, appeared on days 5 and 6. Laboratory investigations on day 6 showed an elevated WBC count of 16,550/mm^3, along with marked increase in neutrophil and decrease in monocyte percentages to 99.7% and 0%, respectively. CRP was elevated to 3.06 mg/dL (normal, 0–0.3 mg/dL). Based on a suspicion of bacterial infection, oral LVFX (500 mg/day) was prescribed. Several asymptomatic erythematous lesions appeared on the trunk and upper extremities on day 8 (Fig. 2A, B). Intravenous PIPC/TAZ (18 g/day) therapy was started on the same day,

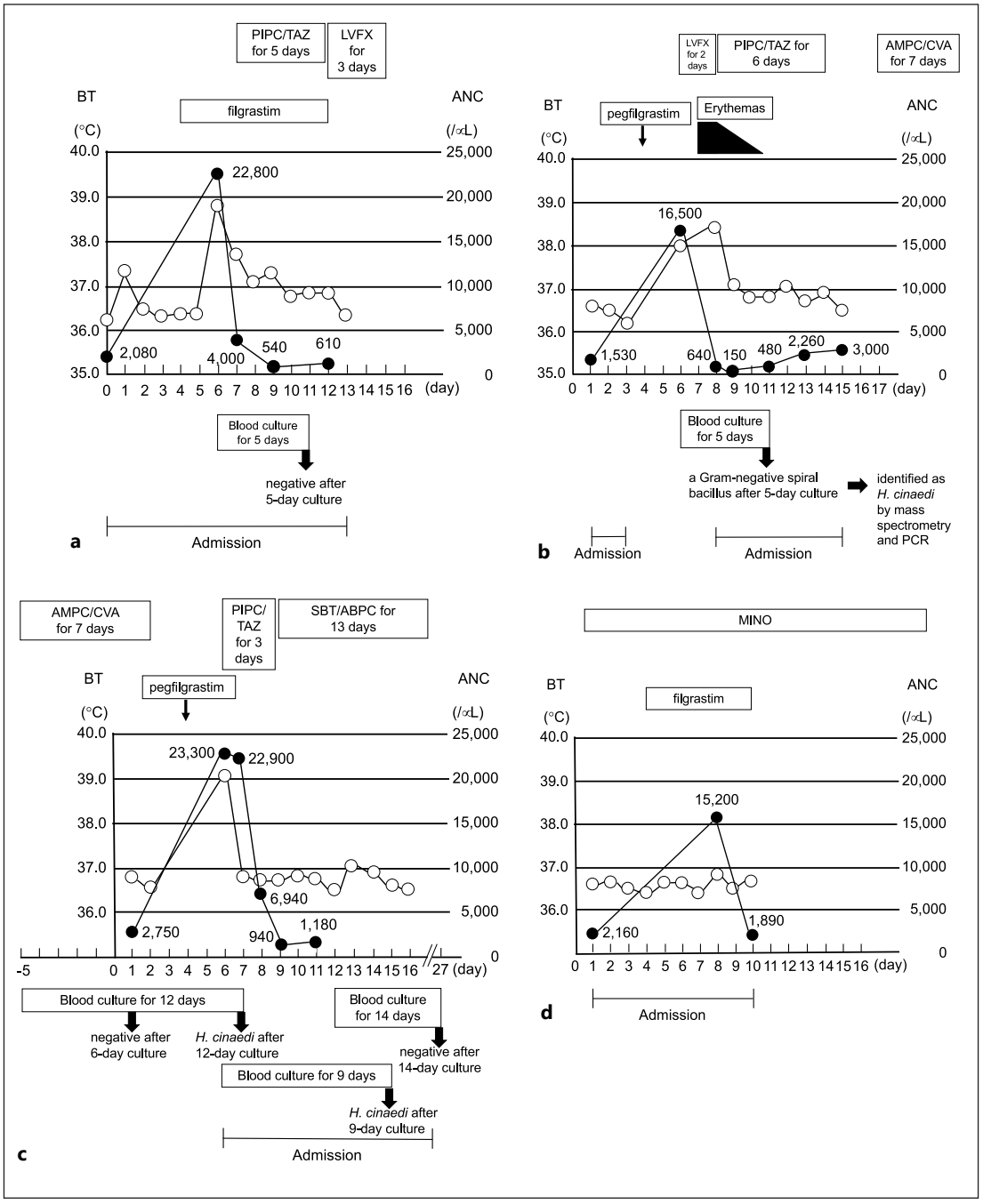

Fig. 1. Clinical course of the first (**A**), second (**B**), third (**C**), and fourth (**D**) cycles of R-CHOP chemotherapy. The white and black circles indicate BT and ANC, respectively. The vertical line shows the BT, and the horizontal line represents ANC. BT, body temperature; ANC, absolute neutrophil count.

while oral LVFX was discontinued. The antibiotic therapy promptly improved clinical symptoms. Furthermore, the erythematous lesions completely disappeared within 3 days. The patient was discharged after 6 days of treatment with intravenous PIPC/TAZ. Simultaneously, however, a Gram-negative spiral bacillus was isolated from the aerobic blood culture bottle after a 5-day culture, while anaerobic culture was negative. Subculture of the positive blood broth was performed on blood agar plates for 2 days in a microaerobic (5% O_2, 5–10% H_2)

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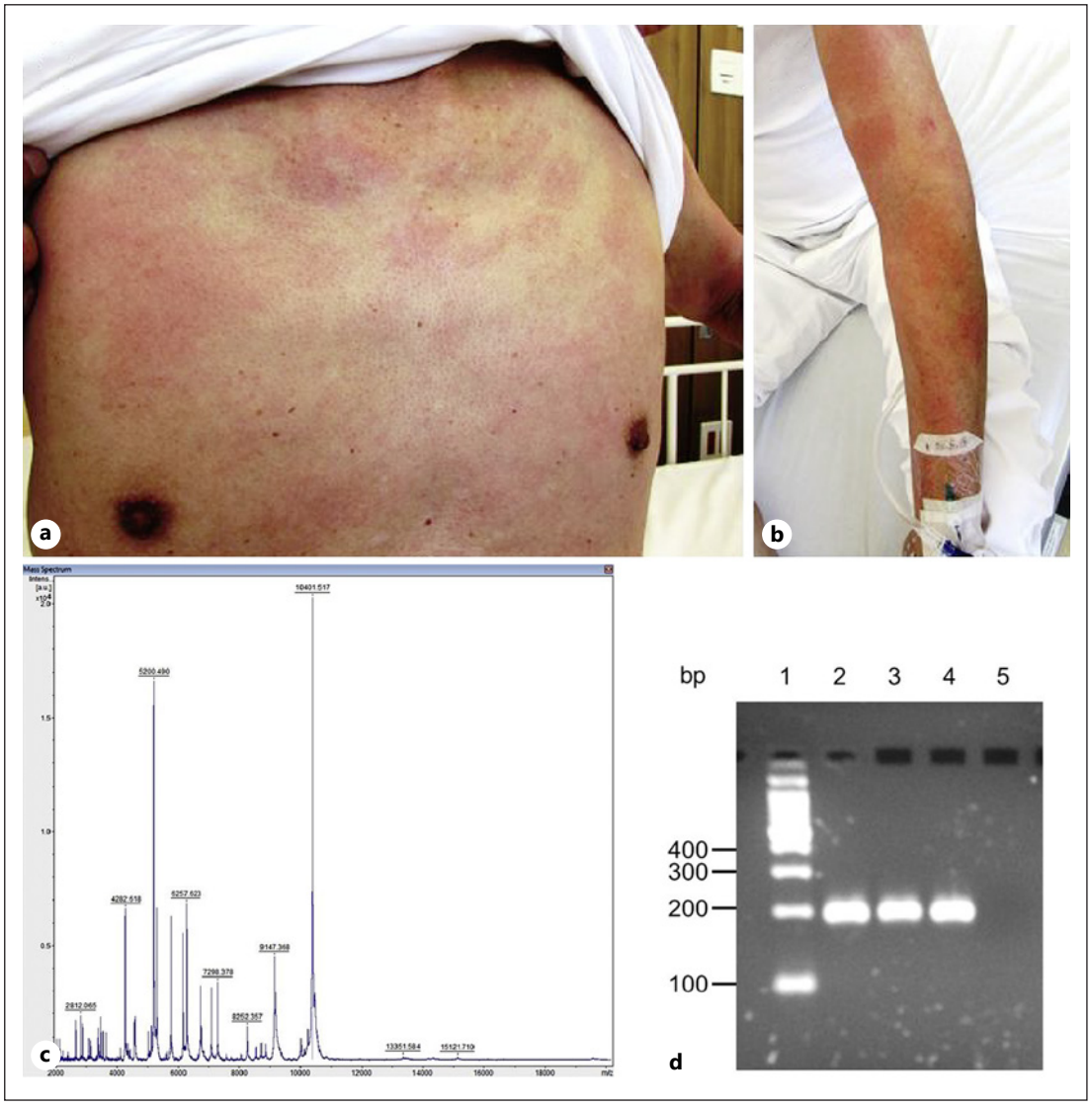

Fig. 2. Clinical appearance of skin lesions that appeared during the second cycle of R-CHOP therapy. Multiple erythematous lesions with irregular shape were seen on the chest (**A**) and left upper limb (**B**). **C** Identification of *H. cinaedi* by MALDI-TOF mass spectrometry. The protein composition of isolated bacterial cells from subculture of the positive blood culture was analyzed by MALDI-TOF mass spectrometry as described previously [8, 9]. The vertical axis shows the relative intensities of the ions (in arbitrary units), and the horizontal axis shows mass-to-charge (m/z) ratios. The identification score was analyzed using the integrated pattern-matching algorithm of the MALDI Biotyper 3.0 software (Bruker Corp., Karlsruhe, Germany). An identification score of >2 is useful for identification at the species level, and a score between <2 and >1.7 is useful for identification at the genus level. A score of <1.7 is considered to be unreliable for identification. The patient's identification score was 1.93. **D** Identification of *H. cinaedi* by PCR. Total DNA from 10 μL of the patient's blood (lanes 2 and 3) was subjected to PCR analysis (using the forward primer AGGGATTCCACAAAGTGAGC and the reverse primer TCTTGTCCTGTGCGTTCATC to amplify the gyrB gene region, which is specific to *H. cinaedi*) as described previously [4]. Lanes 1, 4, and 5 show the 100-bp size marker, positive control (DNA from *H. cinaedi*) band of 195 bp, and negative control (DNA from *H. pylori*), respectively. MALDI-TOF, matrix assisted laser desorption/ionization time of flight; PCR, polymerase chain reaction.

atmosphere at 35°C, resulting in the formation of thinly spread film-like colonies. A positive colony from the subculture was analyzed by matrix-assisted laser desorption/ionization time of flight mass spectrometry [8, 9] (Fig. 2C). The identification score was 1.93, strongly suggesting that the organism constituting the positive colonies was *H. cinaedi*. Later, the organism was further identified as *H. cinaedi* by polymerase chain reaction (PCR) (Fig. 2D), as previously described [4]. Based on these results, it was concluded that the fever and skin eruption were caused by *H. cinaedi* bacteremia.

Before starting the third cycle of chemotherapy, amoxicillin clavulanate (AMPC/CVA) (1,500 mg/day for 7 days) was prescribed against *H. cinaedi*, and blood culture was started from 6 days before day 1 (day 17 of the second cycle). After confirming that the blood culture was negative after a 6-day culture, the third cycle of chemotherapy with dose reduction (80%) was started (Fig. 1C). Subcutaneous injection of pegfilgrastim (3.6 mg) was performed on day 4. On day 6, the patient developed fever (39.1°C) and chills and was seen at the emergency department. Laboratory investigations showed an elevated WBC count of 23,620/mm^3, along with marked increase in neutrophil and decrease in monocyte percentages to 98.9% and 0%, respectively. The CRP level was high, at 4.16 mg/dL. Referring to the history of fever during the previous 2 chemotherapy cycles, we administered intravenous PIPC/TAZ (18 g/day) after admitting the patient, resulting in rapid improvement of clinical symptoms within 2 days. In addition, blood culture was performed on the same day. However, blood culture performed before the start of the third cycle of chemotherapy yielded a Gram-negative spiral bacillus on day 7 of the third cycle after a 12-day culture, and the bacillus was suspected to be *H. cinaedi* based on the fact that similar bacillus detected by blood culture during the second cycle had been identified as *H. cinaedi*. Thus, the patient was diagnosed as having *H. cinaedi* bacteremia, and intravenous PIPC/TAZ was changed to intravenous sulbactuam/ampicillin (SBT/ABPC) (12 g/day) on day 9. Blood culture performed on day 6 also yielded a Gram-negative spiral bacillus after a 9-day culture. Intravenous SBT/ABPC therapy was administered for 13 days, followed by oral AMPC/CVA (1,500 mg/day) therapy for 7 days. Blood culture performed from day 12 was negative after a 14-day culture.

The fourth cycle of dose-attenuated (80%) R-CHOP chemotherapy was commenced on an inpatient basis (Fig. 1D). Oral minocycline hydrochloride (MINO) (100 mg/day) was prescribed from day 1 to prevent *H. cinaedi* bacteremia. Daily subcutaneous administration of filgrastim (75 μg/day) was performed from day 4 to day 10. This cycle could be finished without fever or skin eruptions.

The subsequent fifth and sixth cycle of dose-attenuated (80%) chemotherapy was performed. Oral MINO was continued. Subcutaneous injection of pegfilgrastim (3.6 mg) was administered. He had no fever due to *H. cinaedi* infection during the clinical course. Blood culture performed on day 9 of the fifth cycle of chemotherapy was negative after a 14-day culture. Since positron emission tomography-computed tomography performed during the sixth cycle of R-CHOP chemotherapy showed no abnormalities in the visceral organs, he was subsequently followed up without any treatment. No recurrence of DLBCL has been seen during the 2-year follow-up period.

Discussion

This report presents a unique case of recurrent fever due to *H. cinaedi* bacteremia without neutropenia during R-CHOP chemotherapy. Since we had some difficulty in distinguishing *H. cinaedi* bacteremia-induced fever from FN-induced fever in the present case, we tried to seek clinical and laboratory clues that might help differentiate *H. cinaedi* bacteremia-induced fever from FN-induced fever by summarizing the present and 5 previously reported cases of *H. cinaedi* bacteremia-induced fever [3–7] (Table 1).

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Table 1. Summary of reported cases of *H. cinaedi* bacteremia during chemotherapy for malignant lymphoma

Patient number	Age, gender	Disease	Day of fever onset	Neutropenia on the day of fever onset	Skin eruption	Reference
1	53, female	B-cell lymphoma	nd	nd	Pink macular rash developed during the second cycle	Uçkay et al. [3]
2	65, male	Malignant lymphoma	Days 10 and 6 of the second and third cycle, respectively	nd	Cellulitis developed with fever during the second cycle	Minauchi et al. [4]
3	70, male	Diffuse large B-cell lymphoma	Days 6, 7, and 8 of the fourth, fifth, and sixth cycle	No neutropenia	None	Ono et al. [5]
4	63, male	Follicular lymphoma	Day 6 of the second and third cycle. Day 5 of the fourth cycle	No neutropenia	None	Minauchi et al. [6]
5	69, female	Diffuse large B-cell lymphoma	nd	nd	Painful erythema	Fujita et al. [7]
6	72, male	Diffuse large B-cell lymphoma	Day 6 of the second to fourth cycle	No neutropenia	Asymptomatic multiple erythematous areas together with developing fever during the second cycle	Present case

nd, not described.

Among the 6 cases, 4 cases (patients 2, 3, 4, and 6) had accurate information available related to the day of fever onset. Patient 2 had fever on day 10 and day 6 in the second and third cycles, respectively. Patient 3 had fever on days 6, 7, and 8 in the fourth, fifth, and sixth cycles, respectively. The remaining 2 patients (patients 4 and 6) developed fever on day 5 or 6. These results suggest that *H. cinaedi* bacteremia-induced fever during chemotherapy tends to develop around day 6, which seems to be earlier than the usual times of myelosuppression. In addition, among the 6 cases, 3 cases (patients 3, 4, and 6) had information on neutrophil or WBC counts at the onset of fever. Importantly, none of these 3 patients had neutropenia when they had *H. cinaedi* bacteremia-induced fever, indicating that lack of neutropenia is a feature of fever caused by *H. cinaedi* bacteremia.

It has been revealed that *H. cinaedi* bacteremia is sometimes accompanied by skin eruptions. Most of the previously reported skin eruptions developed with fever [4, 10–15]. These skin eruptions were considered to be secondary bacterial involvement of the skin through hematogenous spread from the gastrointestinal tract. They have been described as "cellulitis" in most cases, since they develop as one to a few erythematous macules on the extremities, together with pain or tenderness, which is a common clinical finding of cellulitis. Among the 6 cases in Table 1, 4 patients (patients 1, 2, 5, and 6) developed erythematous skin eruptions with fever. The presence of erythematous skin eruption at the onset of fever seems to be a characteristic sign of *H. cinaedi* bacteremia.

The diagnostic process for *H. cinaedi* bacteremia consists of isolation of a Gram-negative spiral bacillus suggestive of *H. cinaedi* from blood by blood culture and identification of the organism as *H. cinaedi*. Isolation of the organism from blood is just as difficult as it is for other *Helicobacter* species, except for *H. pylori* [1]. The major reason for the difficulty in the isolation of *H. cinaedi* from blood is that *H. cinaedi* requires a longer culture period for its detection than that required for common bacterial strains. Specifically, it takes 6 days on average and up to 10 days in some cases to detect *H. cinaedi* in blood culture bottles, while common bacterial strains can be cultured in 2–3 days. Since the blood culture period is usually set at 5 days in many facilities, it is presumed that *H. cinaedi* bacteremia tends to be overlooked in many cases. In the present case, it took 5–12 days to detect the Gram-negative spiral bacillus suggestive of *H. cinaedi* in blood in the second and third cycles, respectively, supporting what has been said so far about the days required to detect *H. cinaedi* in blood culture, as described above. Definitive identification of *H. cinaedi* is achieved by gene amplification techniques, such as PCR and subsequent sequencing [4, 5, 11, 12]. Furthermore, recently, the usefulness of mass spectrometry for identification and diagnosis of *H. cinaedi* has been reported [8, 9].

Once *H. cinaedi* bacteremia is suspected, treatment should be started even before confirmation of the diagnosis by definitive isolation and identification of *H. cinaedi*. Although the treatment of *H. cinaedi* infection has not been standardized, various antibiotic agents, including carbapenems, aminoglycosides, tetracyclines, penicillins, and cephalosporins, alone or in combination, have been successfully used for treating infections caused by *H. cinaedi* [2–7]. Since *H. cinaedi* has low virulence, the symptoms caused by this bacterium, such as fever and skin eruption, resolve after 2 or 3 days of therapy with these antibiotics [2]. However, approximately 30–60% of patients have recurrent symptoms due to the possible presence of residual *H. cinaedi* in the intestines [2, 12]. Thus, it is recommended that treatment should be continued for prolonged periods after blood culture becomes negative, especially in immunocompromised patients. On the other hand, for patients with FN, initial antibiotic monotherapy for a few days, including an antipseudomonal beta-lactam (such as cefepime), a carbapenem (i.e., meropenem, imipenem, or cilastatin), or PIPC/TAZ, has been established. Thus, the management of patients with fever caused by *H. cinaedi* bacteremia is somewhat different from that of patients with FN without *H. cinaedi* infection. Aota et al. [6] reported a case in which MINO was effective in preventing *H. cinaedi* bacteremia-induced recurrent fever in a patient with follicular lymphoma receiving R-CHOP therapy. Based on their report, in the present case, prophylactic administration of MINO was performed during the fifth and sixth cycles of R-CHOP therapy to prevent *H. cinaedi* bacteremia, resulting in the absence of occurrence of *H. cinaedi* bacteremia in these cycles. The present case strongly suggests the usefulness of MINO for prevention of *H. cinaedi* bacteremia. In conclusion, we should discriminate fever due to *H. cinaedi* bacteremia if fever emerged before myelosuppression in the course of chemotherapy.

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Statement of Ethics

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. No ethical review board approval is required for this publication.

Conflict of Interest Statement

The authors declare that they have no conflicts of interest.

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Author Contributions

K.T. and K.K. developed the original idea and analyzed the data. T.F. provided dermatologic decision. K.O. and T.N. performed laboratory analysis. M.O. and T.S. prepared this manuscript.

Data Availability Statement

All data generated during this study are included in this article. Further enquiries can be directed to the corresponding author.

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