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CASE REPORT

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Management of generalized severe periodontitis using full-mouth disinfection and systemic antibiotics in a leukemic patient before stem cell transplantation: A case report

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Abstract

The full-mouth disinfection protocol implemented in this case can be integrated into established protocols for treating severe periodontitis in the context of a hematological malignancy, without any interference with the cancer treatment.

KEYWORDS

acute lymphoblastic leukemia, full-mouth disinfection, severe periodontitis, stem cell transplantation

1 | INTRODUCTION

Oral infection is a contributor to morbidity and mortality in leukemic patients. Full-mouth disinfection, which terminates subgingival debridement within a short period, is applicable and effective in combination with antimicrobial agents in treating leukemic patients with severe periodontitis as an oral infection removal procedure prior to stem cell transplantation.

Hematopoietic stem cell transplantation (SCT) is a curative therapy for hematologic malignancies. Standard pre-transplantation therapeutic approaches, including high-dose chemotherapy, total body irradiation, and SCT, greatly improve the prognosis of leukemic patients. At multiple phases during SCT, patients are at risk of contracting infectious diseases due to profound and prolonged neutropenia.[1] The US National Cancer Institute indicated that odontogenic infection is a potential source of systemic infections that should be eliminated by dental treatment.[2,3] However, no definitive criteria for extraction or preservation of infected teeth that do not affect hematological treatment have been established for recipients with severe infections, including patients with hematological malignancies.

Here, we present a case of acute lymphoblastic leukemia with severe periodontitis prior to SCT that was treated with a regimen involving full-mouth disinfection (FMD).

2 | CASE REPORT

A 38-year-old man diagnosed with acute lymphoblastic leukemia and scheduled to undergo chemotherapy, total body irradiation, and SCT was referred to our department for odontogenic infection screening. After evaluation of his clinical oral condition, dental X-ray photographs, and the presence of periodontitis-related bacteria by quantitative polymerase chain reaction (qPCR), a diagnosis of generalized severe periodontitis (generalized periodontitis stage IV, grade C) was made. The patient had already received intravenous antimicrobial infusion for febrile neutropenia (FN) on admission to the hospital; however, periodontitis-related bacteria were

detected (Table 1). When the leukocyte count was low, we only followed the oral hygiene instructions. To remove dental plaque and supragingival calculus, scaling procedures on the gingival margin were performed at the time of recovery from FN after induction of chemotherapy. To prevent bacteremia and septicemia after SCT, FMD was considered to remove the infectious source via completion of scaling and root planing (SRP) within the limited dental treatment window of only 1 week, covering all periodontally infected teeth (Figure 1). Before the initiation of chemotherapy, oral hygiene instructions were provided to the patient to avoid risk of infection from dental foci. In the neutropenic phase, during chemotherapy and immunosuppression, oral care was provided to reduce oral complications including oral mucositis and acute periodontitis. Since his first visit to our department, the patient was expected to develop chemotherapy-induced FN and oral mucosal disorders. We thus provided the patient with thorough oral hygiene instructions aiming to quantitatively reduce the source of infection in the mouth. Specifically, the patient was instructed on the toothbrush Bass technique regarding the toothbrush and interdental brush cleaning methods. Oral assessments were performed based on an oral assessment guide,[4] and the information was shared with the physician and nurses. A nonirritating moisturizer was used for xerostomia.

TABLE 1 Quantitative evaluation of periodontitis-related bacteria in the deepest periodontal pocket of the patient

	Baseline (count)	Seven months after FMD (count)
Total bacteria	30 000	<1000
Porphyromonas gingivalis	570	<10
Tannerella forsythia	1300	<10
Treponema denticola	1100	<10
Fusobacterium nucleatum	2000	<10

The patient achieved complete remission following induction of chemotherapy consisting of cyclophosphamide vincristine, prednisolone, daunorubicin, and L-asparaginase and consolidation chemotherapy consisting of doxorubicin, vincristine, and prednisolone. The myelosuppression grades of these chemotherapies were categorized as severe and moderate, respectively.[5] Procalcitonin (PCT) levels were measured when fever and febrile neutropenia (FN) were present. PCT was predominantly higher (7.4 ng/mL) in the presence of FN and septic shock during the first round of chemotherapy on day −116. Otherwise, the PCT was not predominant during the pretransplant oral care and at 1 month after the transplant, which is the focus of this study (Figure 1). Blood cultures were performed at the time of fever, and the only positive results between the time of admission and 1 month after transplantation were obtained from day −116 to day −111. At that time, FN and septic shock were both present, and the patient was positive for *Corynebacterium striatum* and *Staphylococcus haemolyticus*. No oral bacteria were found. Mechanical debridement for severe periodontal disease was then scheduled during the non-neutropenic period after chemotherapy induction and consolidation. The day on which SCT was performed was designated day 0. To gain sufficient healing time of SRP for debridement of the periodontal deep pocket before SCT and to avoid reinfection from an untreated site to the treatment site in this case, we planned for FMD combined with systemic antimicrobial therapy, which could effectively be used to treat patients who had been diagnosed with generalized severe periodontitis in a short period of time.[6] After the first round of chemotherapy, we considered performing the procedure if the white blood cell count was

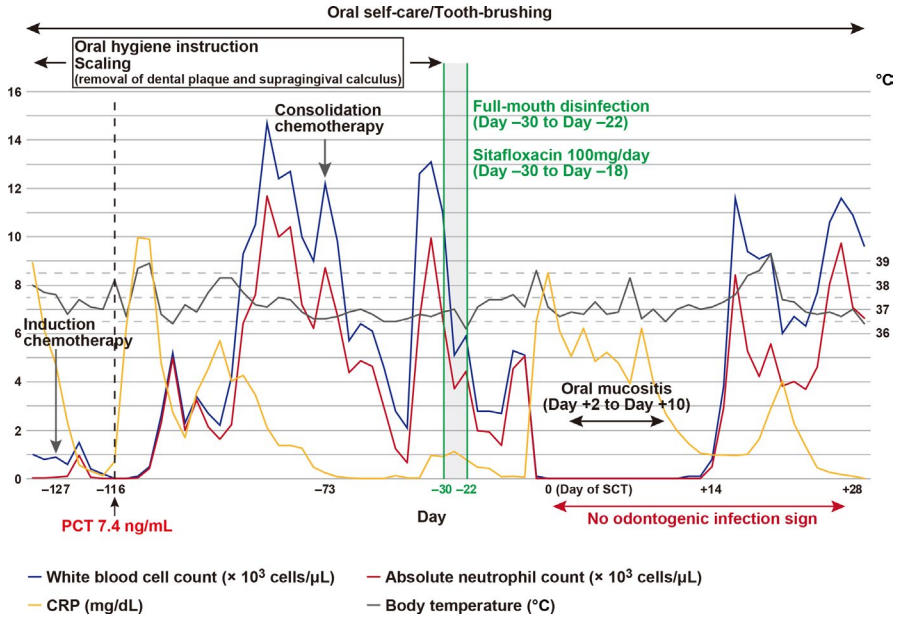

FIGURE 1 Treatment timeline. The patient was a 38-year-old male hematopoietic stem cell transplant (SCT) recipient with generalized severe periodontitis

normal. However, after consulting with the hematologist, we decided to schedule the consolidation chemotherapy; thus, the medical team considered the time when the consolidation chemotherapy was finished, the white blood cell and absolute neutrophil counts had recovered, there was no febrile neutropenia, and there was enough time for the wound to heal after FMD. As a result of this discussion, we treated for severe periodontitis in a short period from day −30 to day −22. FMD was performed from days −30 to −22 for debridement of all periodontal pockets by SRP with Gracey curettes. We performed SRP for tooth numbers 36, 37, 38, 46, 47, and 48 on day −30 (Federation Dentaire Internationale System); tooth numbers 14-18 and 24-28 on day −27; tooth numbers 31, 32, 33, 35 and from 41-44 on day −24; and finally, tooth numbers 13, 21, 22, and 23, on day −22. During FMD, the patient was treated with sitafloxacin (100 mg/day for 14 days) to prevent bacteremia/septicemia, periodontopathic bacterial infection, and fever, which are possible adverse complications induced by FMD.[7] Both body temperature and C-reactive protein (CRP) level were stable during FMD period, with a maximum body temperature of 37.0°C and maximum CRP concentration of 1.13 mg/dL (Figure 1). Allogeneic peripheral blood SCT was performed with myeloablative conditioning on day 0. The graft contained $CD34^+$ cells at 2.66×10^6/kg. Myeloablative conditioning was based on total body irradiation at 12 Gy in six fractions on day −8 to −6, administered in combination with cytarabine 2000 mg/m^2/day on days −5 to −4 and cyclophosphamide 60 mg/kg/day on days −3 to −2. In the nadir phase, the physician and nurses checked the patient's condition including oral conditions daily using the oral assessment guide to score the patient's voice, swallowing, lips, tongue, saliva, mucous membranes, gums, teeth, and dentures.[4] The records confirmed that there was no odontogenic infection. From day + 6, we also performed the same assessment after SCT. No acute exacerbation of periodontitis was detected. Oral mucositis was present from days + 2 to + 10. The attended hematologists and nurses shared this patient's treatment plan, the patient's condition, and oral assessment through conferences and we discussed the treatment plan with them. Seven and 13 months after FMD (6 and 12 months after SCT), the microbiological and clinical parameters of periodontitis, as demonstrated by the O'Leary plaque control record, decreased from 95% to 19%. Additionally, bleeding on probing (BOP), an indicator of periodontal inflammation (including gingivitis), decreased from 81.6% to 7.5% (Table 2). Probing depth (PD), defined as the distance from the bottom of the periodontal pocket to the gingival cuff, also improved. Deeper periodontal pockets indicate greater alveolar bone resorption. PD ≥4 mm and PD ≥7 mm significantly reduced after FMD from 98.3% to 4.6% and from 31.6% to 0%, respectively; the mean PD reduced from 6.1 to 2.5 mm (Table 2). At 13 months after FMD, gingival inflammation was effectively reduced (Figure 2 A,B), the teeth affected by severe periodontitis were preserved, alveolar bone was regenerated (Figure 2C,D), and functional occlusion was achieved without tooth extraction. Furthermore, qPCR data revealed no periodontitis-related bacteria in the deepest periodontal pocket during the initial examination (Table 1).

TABLE 2 Clinical characteristics of the patient at baseline and 13 mo after FMD

Characteristics	Baseline	13 mo after FMD
Plaque control record (%)	95	19
BOP (mean %)	81.6	7.5
PD ≥4 mm (mean %)	98.3	4.6
PD ≥7 mm (mean %)	31.6	0
PD (mm; mean)	6.1	2.5

Abbreviations: BOP, bleeding on probing; FMD, full-mouth disinfection; PD, probing depth.

3 | DISCUSSION

We have demonstrated a case in which FMD was effective in treating generalized severe periodontitis without interfering with chemotherapy or SCT. Moreover, FMD effectively removed infectious sources and SRP was completed within only a few days throughout the entire jaw using antimicrobial agents. Upon re-evaluation after SCT, we confirmed improvement of the periodontal status, bone regeneration at the resorption site, and observed no odontogenic infectious complications.

Full-mouth disinfection with systemic antimicrobial therapy was conducted on this patient for three reasons: (a) The patient was diagnosed with acute lymphoblastic leukemia, indicating immunodeficiency; (b) intensive chemotherapy, total body irradiation, and SCT were scheduled at the first visit; and (c) intensive periodontal treatment reportedly reduces the occurrence of febrile neutropenia, significantly reducing CRP levels.[8] Before administering the conditioning regimen preceding hematopoietic SCT, the period available for dental treatment, including tooth extraction and periodontal basic therapy, is limited due to the development of neutropenia and thrombocytopenia. Moreover, the conventional method of nonsurgical periodontal therapy consists of SRP, which involves the debridement of periodontal pockets in the jaw quadrants (Q-SRP).[9,10] However, as most periodontopathic bacteria exist in periodontal pockets as well as in several other oral mucosal sites, including the saliva,[11] the treated periodontal pockets could be reinfected from the untreated regions[12] during Q-SRP. Quirynen et al[7,13] suggested a one-stage FMD protocol instead of the conventional strategy with consecutive debridement per quadrant over a 1-2-week interval. On the contrary, Herrera and colleagues have suggested that antimicrobials should be administered

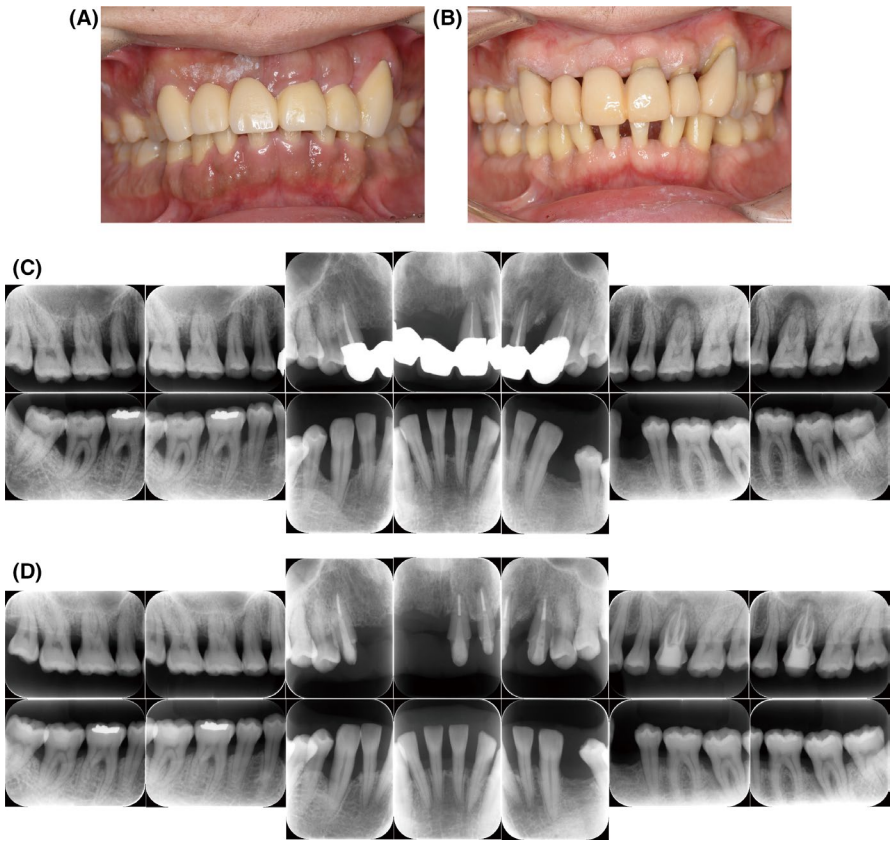

FIGURE 2 Oral evaluation and dental radiographic images. The patient was a 38-year-old male hematopoietic stem cell transplant (SCT) recipient with generalized severe periodontitis. A, Intraoral image at the initial visit. B, Intraoral image after SCT and full-mouth disinfection (FMD). C, Radiographic images at the initial visit. D, Radiographic images after SCT and FMD

immediately after the end of debridement and that debridement should be terminated in as short a time as possible, that is, within 1 week.[14] Yashima et al[15] found that if the SRP was completed within 1 week of maintaining the effective concentration of the antimicrobial agent (azithromycin), the clinical fungicidal efficacy of SRP was comparable to that of one-stage full-mouth SRP. Thus, termination of SRP within 1 week under antimicrobial administration would be equivalent in clinical efficacy to SRP within 24 hours. Furthermore, in practice, SRP below the gingival margin of the entire jaw in 1 day is known to be burdensome for patients and to cause a high frequency of fever.[7] Therefore, we planned to complete the SRP within approximately 1 week in this case while monitoring the patient's physical condition and response on the dental chair. Systematic review and meta-analysis[16] have revealed that FMD combined with systemic administration of amoxicillin and metronidazole improved the clinical and microbiological outcomes significantly and effectively. These combined periodontitis treatments have not been approved in Japan. However, in our study, we systemically administrated sitafloxacin, which has been reported as significantly effective against periodontopathic bacteria.[17,18] Leukemic patients with pancytopenia and hematopoietic dysfunction are often immunodeficient, with difficulty in maintaining hemostasis, which increases the risks of postoperative infection and hemorrhage. Hence, it is preferable to conduct these treatments when patients attain normal hematopoiesis after the nadir phase, in which remission induction and consolidation chemotherapy suppress tumor cells. Thus, a desirable disinfection protocol includes (a) postinduction and consolidation chemotherapy; (b) following exit from the nadir phase, administration of antibiotics in combination with oral care; and (c) completion (with epithelialization) of the indicated dental surgical treatments before pretreatment (chemotherapy and total body irradiation) for SCT. Another study showed that reduced frequency of FN coincided with periodontal treatment.[19] These studies clearly demonstrate the importance of periodontal management in patients with leukemia and periodontal disease.

In our case, adverse events induced by dental treatment did not occur before or after SCT. Leukemic patients with severe odontogenic infection can experience infections within the periodontal deep pockets. For instance, a prospective observational study indicated that patients with periodontal inflammation had bacteremia more often than those with healthy periodontal tissue and that bleeding on probing was related to bacteremia.[20] These conditions may lead to bacteremia and septicemia before and after the SCT immunodeficient phase. Moreover, previous studies have shown that periodontal disease is associated with markedly elevated hospital charges, longer hospital stays, and higher rates of infectious complications in SCT recipients.[21] Furthermore, significantly lower frequencies of both oral and systemic infections were observed in patients undergoing chemotherapy

that completed all dental treatments compared with those who did not. However, this difference was dependent on the chemotherapy grade.[5,22]

Hence, dental treatment should be implemented prior to, during, and following SCT and chemotherapy. To this end, FMD can be integrated into existing protocols and regimens for hematology treatment without interfering with SCT. Furthermore, the lack of periodontitis-related bacteria as detected by qPCR after FMD combined with systemic antimicrobial therapy suggests that FMD with systemic antimicrobial therapy may alter the oral microbiome of patients with severe periodontitis to a more desirable state.[6,16] However, the establishment of pre- and post-SCT protocols based on individual patients' oral condition is required to prevent oral adverse events. Overall, FMD can be performed rapidly and before SCT, providing effective oral care and improving the condition of leukemic patients with severe periodontitis.

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CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

AUTHOR CONTRIBUTIONS

SM: provided clinical oral care, conducted full-mouth disinfection, collected and analyzed the data, and primarily wrote the manuscript. KT: analyzed data and revised the manuscript. YM and MN: provided clinical oral care and analyzed the data. NH and SU: provided clinical oral care and commented on the manuscript. JK: performed the SCT, clinical care, and commented on the manuscript. TM and TN: contributed to writing, reviewing, and editing the manuscript.

DATA AVAILABILITY STATEMENT

The datasets used and analyzed during this study are available from the corresponding author on reasonable request.

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