Case report

Appearance of Multi-Drug-Resistant Opportunistic Bacteria on the Gingiva during Leukemia Treatment—A case report

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Running title: Multi-drug-resistant opportunistic bacteria on gingiva

One-sentence summary of key findings: The gingiva in patients undergoing leukemia treatment acts as sites of proliferation and reservoirs for multi-drug-resistant opportunistic bacteria.

Abstract

***Background*:**

Dentists generally recognize the importance of periodontal treatment in patients with leukemia, with the most attention paid to preventing development of odontogenic infection, while the worst type of infection is by multi-drug-resistant bacteria for physicians. Here, we report a patient with an abnormal increase of multi-drug-resistant opportunistic bacteria in the gingiva during hematopoietic cell transplantation (HCT).

***Methods*:**

A 53-year-old woman receiving HCT for leukemia had an insufficient blood cell count for invasive periodontal treatment before HCT. Even brushing caused difficulties with hemostasis. Therefore, frequent pocket irrigation and local minocycline administration were performed.

***Results*:**

The multi-drug-resistant opportunistic bacterium *Stenotrophomonas maltophilia* was first detected in phlegm 2 days before HCT, and then detected in a gingival smear and a blood sample 7 and 11 days after HCT, respectively. The patient developed sepsis on day 11, and died 14 days after HCT. Frequent irrigation and local antibiotic application were ineffective against *S. maltophilia* on the gingiva. Inflammatory gingiva without scaling and root planing showed bleeding tendency, and this interfered with wiping out of this bacterium.

***Conclusions*:**

The gingiva in patients undergoing leukemia treatment acts as sites of proliferation and reservoirs for multi-drug-resistant opportunistic bacteria. Severe systemic infection by multi-drug-resistant bacteria in such leukemic patients may also involve the gingiva. To prevent abnormal increases in such bacteria on the gingiva, scaling and/or root planing before chemotherapy, which reduces bleeding on brushing during the neutropenic period caused by chemotherapy, may contribute to infection control in such patients, although it was impossible

in this case.

Key words: leukemia, gingiva, multi-drug-resistant bacteria, compromised patients

Introduction

Acute myeloid leukemia (AML) is a heterogeneous clonal disorder of hematopoietic progenitor cells, and is the most common type of malignant myeloid disorder in adults[1]. Treatment for AML consists of induction chemotherapy followed by a number of cycles of consolidation chemotherapy. The goal of induction chemotherapy is to achieve complete remission by eliminating leukemic cells from the bone marrow, while consolidation chemotherapy is necessary to prevent relapse after remission. Hematopoietic cell transplantation (HCT) can be used as post-remission therapy[2].

Oral and systemic infections arising from the oral cavity are significant problems in cancer patients treated with intensive chemotherapy regimens, including HCT[3]. Pre-existing periodontal infections may induce fever and microorganisms may spread systemically in patients with hematological malignancy during chemotherapy[4-7]. From the viewpoint of physicians involved in the treatment of leukemia patients, infection by multi-drug-resistant bacteria is the worst type of infection.

Here, we report the appearance of multi-drug-resistant opportunistic bacteria on the gingiva in a patient receiving HCT. This case showed that the gingiva in patients undergoing leukemia treatment acts as sites of proliferation and as reservoirs for multi-drug-resistant opportunistic bacteria.

Case Description and Results

Patient

The patient was a 53-year-old Japanese woman who developed AML at 51 years of age. Despite repeated consolidation therapy, her leukemia relapsed and she was referred to the Department of Hematology, Okayama University Hospital, for treatment. Umbilical cord HCT was planned, and she was referred to the Department of Periodontics and Endodontics for oral examination and treatment, if necessary, by her physician 40 days before HCT. Her medical history was not remarkable except for the leukemia.

Clinical oral findings on first oral examination

The first oral examination was performed 40 days before HCT. The patient's blood cell counts were as follows: WBC, 4,900/μl (1.5% neutrophils); Plt, 29,000/μl; CRP, 0.4 mg/dl. The gingival appearance is shown in Fig. 1. Although attachment loss was not remarkable, redness, hypertrophy, and deep pockets with probing depths ranging from 4 to 6 mm were observed around the inter-dental gingiva. Radiographic examination was not available as she could not leave the biological clean room due to her severely immunocompromised condition. However, the possibility of existing odontogenic infections other than periodontitis was very low because she had no third molars and no visible dental caries. In addition, tooth restorations in this patient were small and limited to the occlusal fissure.

Oral diagnosis and treatment planning

Based on the clinical findings, a diagnosis of mild chronic periodontitis was made. However, gingival hypertrophy associated with leukemic cell infiltration caused deep periodontal pockets. Therefore, the patient was judged to be at high risk of developing

systemic infection from periodontitis.

Total-body irradiation and high-dose chemotherapy were planned from days –7 to –5 and –4 to –3 prior to HCT, respectively. These two therapies are generally referred to as the conditioning regimen for HCT. This therapy causes reduction of normal WBC count to ~0/μl along with that of leukemic cells, resulting in an extremely immunocompromised condition. Her severe neutropenia was estimated to continue for about 4 weeks until engraftment.

Scaling and/or pocket curettage could not be performed prior to HCT because the patient's neutropenia and thrombocytopenia were very severe. Even brushing of the inflamed gingiva was difficult due to the deficiency of hemostasis. To reduce the bacterial counts in the periodontal pocket without invasive procedures, pocket irrigation with 0.2% povidone iodine was performed every day, and 2% minocycline slow releasing ointment (Periocline®; Sunstar Inc., Osaka, Japan) was applied once a week. Bacterial counts in the periodontal pockets in the 13 buccodistal region and 31 buccomesial region were monitored. The methods used for isolation and detection of total and three major periodontal bacteria, *Actinobacillus actinomycetemcomitans*, *Prevotella intermedia*, and *Porphyromonas gingivalis*, were described previously[8].

Clinical course

Gingival appearances during our observation periods are shown in Fig. 2A–C. The patient's CRP, WBC, and neutrophil counts are shown in Fig. 3.

Before the conditioning regimen for HCT, WBC counts increased, and gingival hypertrophy around the interdental area became severe. Hypertrophic gingiva almost covered the tooth crown and caused deep pockets. High fever >39.0ºC continued from 14 days before HCT. CRP value was also elevated to 18.9 mg/dl. No infection other than periodontitis was

found. Frequent pocket irrigation and application of minocycline ointment to the periodontal pockets were continued. Systemic antibiotic treatment was also performed as summarized at the end of this section. However, CRP value showed a marked reduction from 18.9 to 3.2 mg/dl due not to the antibiotics but to high-dose chemotherapy and total-body irradiation. Reducing WBC along with the number of leukemic cells led to the disappearance of gingival hypertrophy, as shown in Fig. 2C.

After total-body irradiation, at –4 days before HCT, the CRP value was elevated again (Fig. 3), although the patient's leukemic cells had disappeared. From this stage, WBC count remained at ~0/μl. The CRP value became very high, ranging from 13.1 to 21.8 mg/dl. High fever >39.0ºC continued. Throughout the period of the conditioning regimen and HCT, bacterial counts in the periodontal pockets showed no remarkable increase (Fig. 4).

Seven days after HCT, white smears appeared on the gingiva around the tooth margins despite frequent irrigation (Fig. 5). This could be wiped out, but inflammatory gingiva without scaling or root planing showed a bleeding tendency, and this interfered with the wiping out of such smears. Platelet count remained low at 5,000~10,000/μl. Detection of bacteria by culture revealed that the white smears consisted of opportunistic bacteria, *Stenotrophomonas maltophilia* and *Enterococcus faecalis*, which had been detected in phlegm 2 days before HCT. Eleven days after HCT, sepsis caused by *S. maltophilia* and *Pseudomonas aeruginosa* occurred, and the patient died 14 days after HCT. All these bacteria showed high levels of resistance to many antibiotics. Among the bacteria detected, *S. maltophilia* was common to phlegm, gingiva, and blood samples, and the antibiotic sensitivity patterns were almost the same in each isolate (Table 1).

The antibiotics used in this patient were as follows: days –16 to –8: meropenem; days –7 to +1: cefepime; days +2 to +12: biapenem; days +8 and +9: gentamicin; days +9 to +14: clindamycin.

Discussion

No systemic infection other than periodontitis was discovered in this patient before the conditioning regimen for HCT. We attempted to perform continuous irrigation without invasive procedures due to her severe neutropenia and thrombocytopenia. However, the main cause of high fever and CRP appeared to be the leukemia itself, as high-dose chemotherapy and total-body irradiation markedly reduced CRP.

After total-body irradiation, the CRP value was again elevated, although her leukemic cells had disappeared. Thus, in this case, infection was strongly suspected. Due to her high fever and CRP, many types of antibiotics were used in this patient, and this could have led to microbial substitution. The multi-drug-resistant opportunistic bacterium *S. maltophilia* was first detected in phlegm 2 days before HCT, and was then detected in a smear on the gingiva and in a blood sample 7 and 11 days after HCT, respectively. We speculated that all these bacteria were of the same origin, as the antibiotic sensitivity patterns of the three isolates were very similar. *S. maltophilia* might reach the gingiva from the respiratory tract. The visible growth of *S. maltophilia* on the patient's gingiva could be wiped out, but it caused difficulties in hemostasis. Frequent irrigation and local application of antibiotics were ineffective against *S. maltophilia*, probably because of the antibiotic resistance of the biofilm, although major periodontal bacteria were maintained at clinically acceptable levels and were not systemically causal. It has been reported that allogenic BMT is a significant risk factor for *S. maltophilia* with antibiotic-resistant bacteremia[9].

In this case, inflammatory gingiva without scaling or root planing interfered with keeping the gingiva clean by brushing or wiping out throughout the HCT period, even through white smears consisting of multi-drug-resistant bacteria appeared, because the bleeding tendency could cause the risk of bacteremia and difficulty in hemostasis. Scaling and root planing before chemotherapy can reduce gingival inflammation and enable removal of the

biofilm that may consist of multi-drug-resistant bacteria by brushing or wiping out during the neutropenic and thrombocytopenic period. A case was reported in which successful periodontal treatment was performed to maintain good gingival condition without any bleeding even though the platelet count was very low (around 5,000/μl)[10]. Although scaling and root planing could not be performed in this case, many patients have WBC and platelet counts sufficient to allow such periodontal treatments before chemotherapy.

Dentists generally recognize the importance of periodontal treatment in patients with hematological malignancy, and most attention is paid to prevention of the development of odontogenic infection itself during the neutropenic period. On the other hands, for neutropenic patients undergoing HCT, the worst type of life-threatening bacterial infection is that by multi-drug-resistant bacteria. The patient reported here showed inflammatory gingiva without scaling or root planing before chemotherapy and bleeding tendency, and this interfered with wiping out of multi-drug-resistant opportunistic bacteria that may appear during the severe neutropenic period caused by chemotherapy. It is not clear whether this unusual infection comprised of such bacteria was either the cause of death in this case or was confined to the oral cavity as a reservoir. However, there is at least concern regarding the direct and/or indirect influences of these bacteria (*e.g.*, aspiration pneumonia or focal infection) on the patient's life and death. Therefore, effort should be made to prevent abnormal increases in number of multi-drug-resistant bacteria on the gingiva. Scaling and root planing before chemotherapy may reduce inflammation of the gingiva, which may reduce the bleeding caused by brushing even in the neutropenic period. Prevention of abnormal increases in multi-drug-resistant bacteria on the gingiva by scaling and/or root planing before chemotherapy, which would allow intensive brushing during the neutropenic period, may contribute to infection control in such patients.

In conclusion, the gingiva in patients undergoing leukemia treatment acts as sites of

proliferation and as reservoirs for multi-drug-resistant opportunistic bacteria. Severe systemic infection by multi-drug-resistant bacteria in such leukemic patients may also involve the gingiva.

Acknowledgments

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Figure legends

Fig. 1 Gingival appearance at first oral examination (40 days before HCT)

Redness, hypertrophy, and deep pockets with probing depths ranging from 4 to 6 mm were observed around the interdental gingiva. The possibility of odontogenic infection other than periodontitis was very low because the patient was missing the third molars and had no visible dental caries, in addition, restorations were small and limited to occlusal fissures. The patient's hematology was as follows: WBC: 4,900/μl (1.5% neutrophils); Plt: 29,000 /μl; CRP: 0.4 mg/dl.

Fig. 2 Changes in gingival appearance before HCT

A: Day –40, at first oral examination. B: Day –15, before total-body irradiation. C: Day 0, the day of hematopoietic cell transplantation.

Fig. 3 Changes in CRP value, WBC, and neutrophil counts

TBI: total-body irradiation, HDC: high-dose chemotherapy.

Fig. 4 Changes in bacterial counts in the periodontal pockets

Bacterial counts of the periodontal pockets at the 13 buccodistal region and 31 buccomesial region were monitored on days –40, –8, and +1 relative to HCT. Throughout the period of the conditioning regimen and HCT, periodontal bacteria showed no remarkable increase in number.

Fig. 5 White smears appeared on the gingiva around the tooth margins 7 days after HCT

Detection of bacteria by culture revealed that the white smear consisted of *Stenotrophomonas maltophilia* and *Enterococcus faecalis* with high levels of resistance to many antibiotics.

Table

Table 1. Sensitivity to major antibiotics of *S. maltophilia* detected in phlegm, gingival smear, and blood sample.

day of detection	sample	MIC (μg/ml)					
		piperacillin (Penicillin)	cefozopran (Cephem)	amikacin (Aminoglycoside)	minocycline (Tetracycline)	ciprofloxacin (Kinolon)	imipenem (Penem)
–2	phlegm	>16	16	16	2	>8	>16
+7	gingiva	>16	16	4	2	>8	>16
+11	blood	>16	16	8	2	>8	>16

Fig. 1

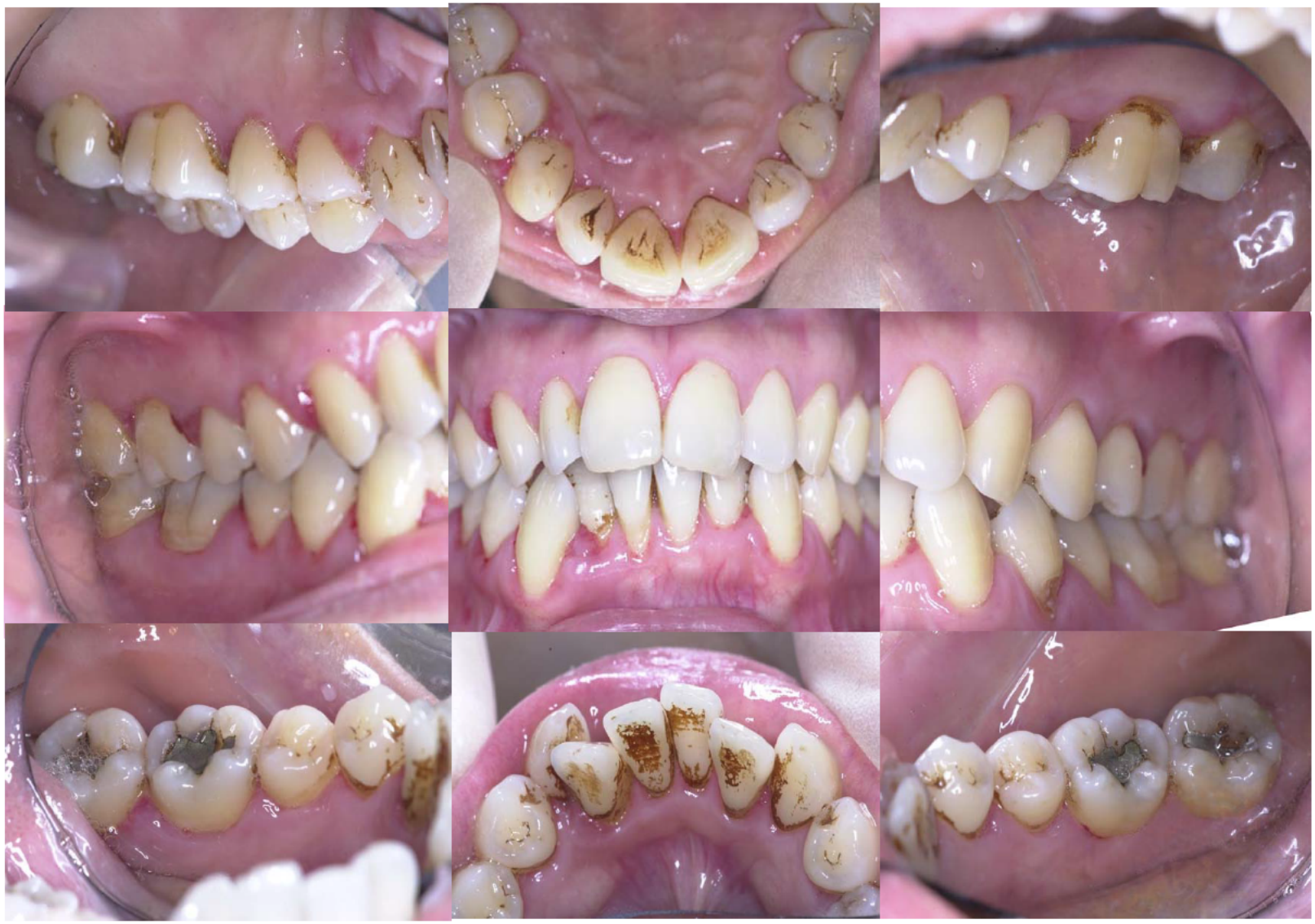

Fig. 2

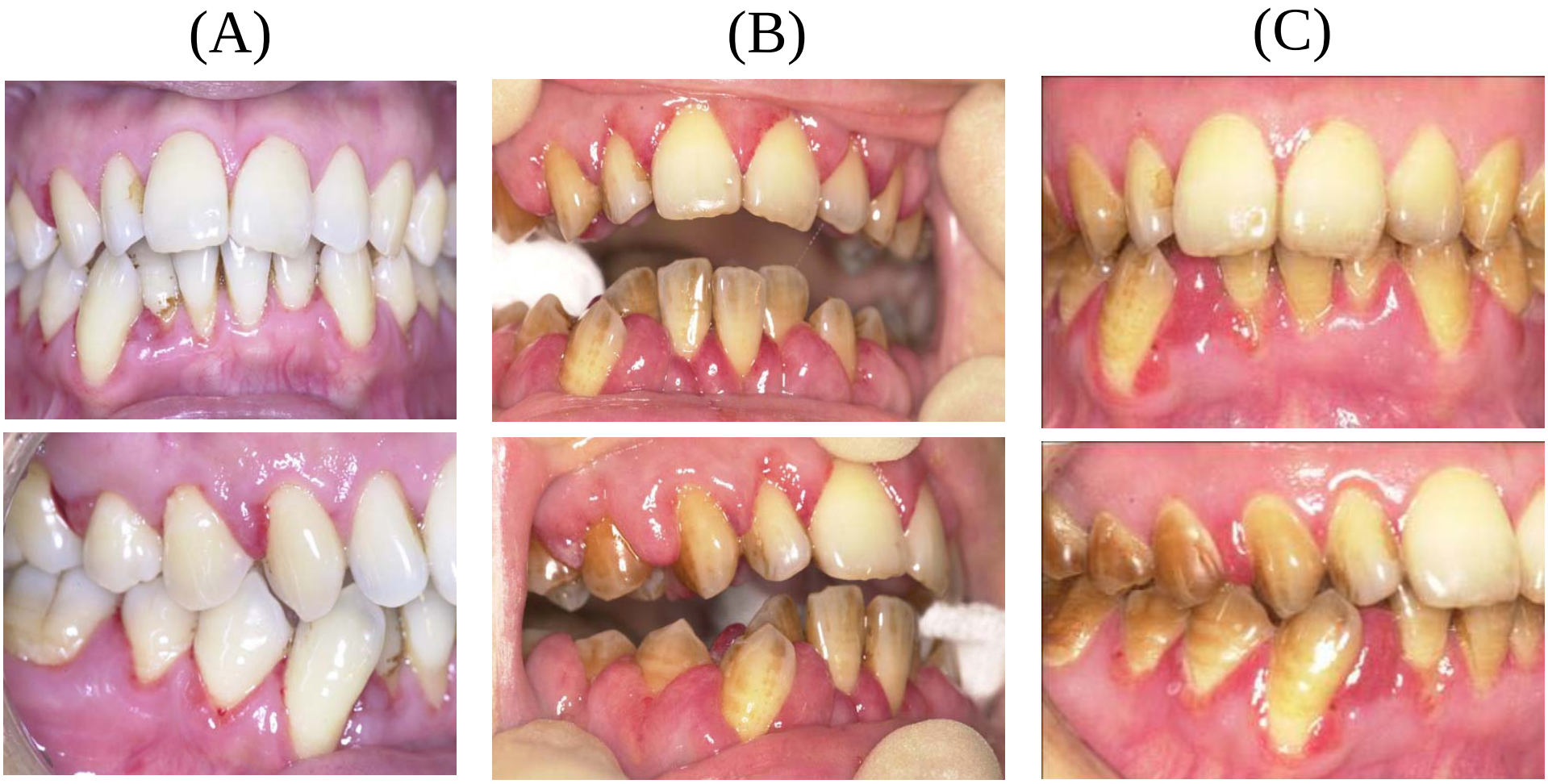

Fig. 3

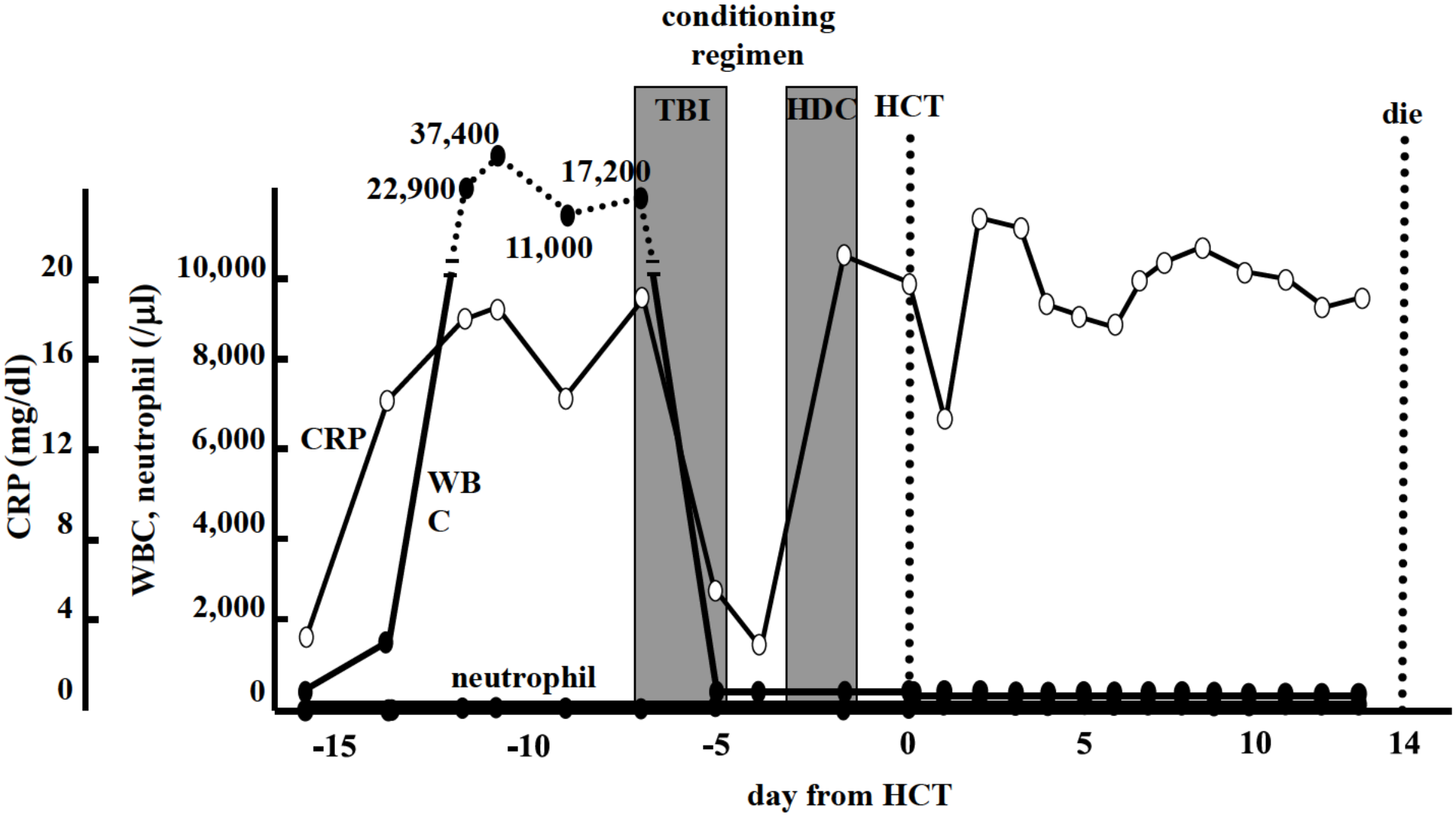
conditioning regimen
TBI
HDC
HCT
die
37,400
22,900
17,200
11,000
CRP
WBC
neutrophil
CRP (mg/dl)
WBC, neutrophil (/μl)
20
16
12
8
4
0
10,000
8,000
6,000
4,000
2,000
0
-15
-10
-5
0
5
10
14
day from HCT

Fig. 4

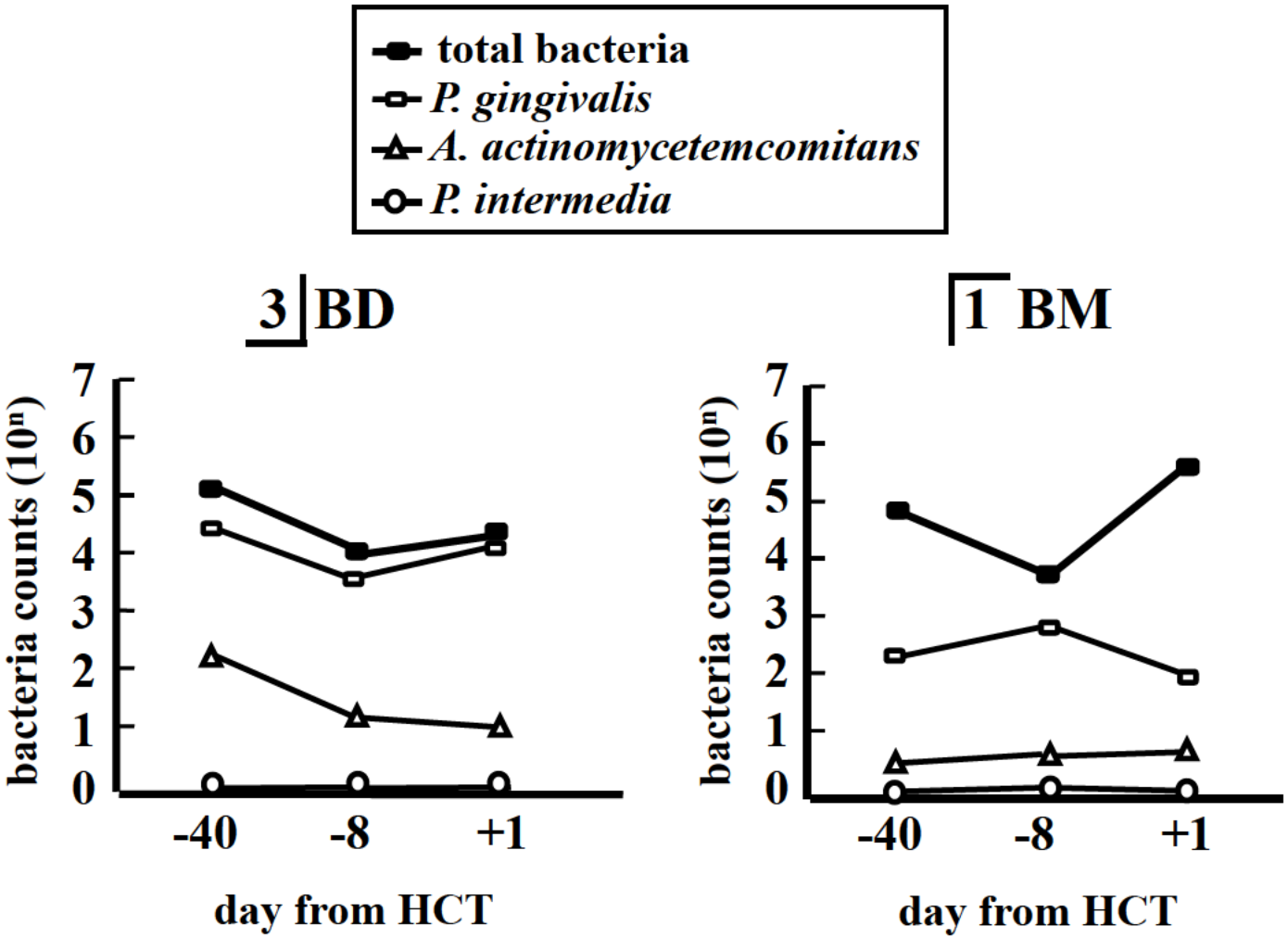
total bacteria
P. gingivalis
A. actinomycetemcomitans
P. intermedia
3 BD
1 BM
bacteria counts (10ⁿ)
0
1
2
3
4
5
6
7
-40
-8
+1
day from HCT

Fig. 5