



# Treatment of life-threatening acute osteomyelitis of the jaw during chemotherapy: a case report

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Oral and maxillofacial infection is a common complication in patients undergoing chemotherapy. The treatment of oral diseases in such patients differs from that administered to healthy patients. This paper reports a case of acute osteomyelitis of odontogenic origin following a recent chemotherapy session. The patient's condition was life-threatening because of neutropenic fever and sepsis that developed during the inpatient supportive care. However, the patient showed prompt recovery within 40 days following the use of appropriate antibiotics and routine dressing, without the requirement for surgical treatment, except tooth extraction. As seen in this case, patients undergoing chemotherapy are more susceptible to rapid progression of infections in the oral and maxillofacial areas. Therefore, accurate diagnosis through prompt clinical and radiological examination, identification of the extent of infection, and assessment of the patient's immune system are crucial for favorable outcomes. It is also necessary to eliminate the source of infection through appropriate administration of antibiotics. In particular, a broad-spectrum antibiotic with anti-pneumococcal activity is essential. Proper antibiotic administration and wound dressing are essential for infection control. Furthermore, close consultation with a hemato-oncologist is necessary for effective infection management based on the professional evaluation of patients' immune mechanisms.

**Keywords:** Acute Osteomyelitis; Chemotherapy; Maxillofacial Abscess; Neutropenia; Oral Infection.

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## INTRODUCTION

The oral and maxillofacial area is vulnerable to infection during chemotherapy because of two factors [1]. Firstly, the turnover rate of cells, especially the epithelial cells in the oral mucosa, is fast; therefore, anticancer drugs may directly affect them [2]. The toxicity of anticancer drugs destroys the epithelium and provides an opportunity for bacterial invasion. The oral plaque and saliva are sources of oral bacteria that can cause opportunistic infections [3]. In a disease-free state,

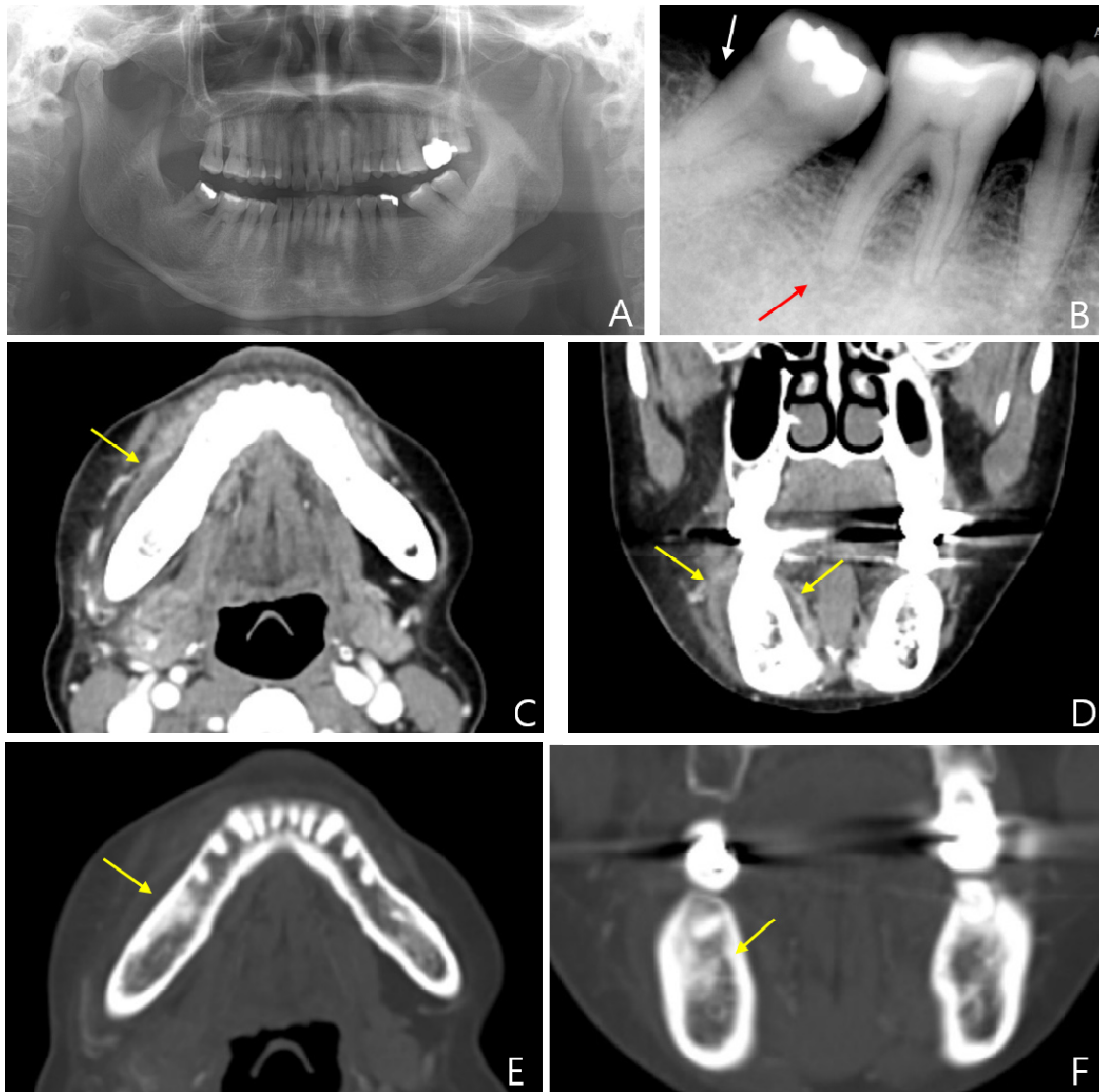
immune-mediated cellular defense and bacterial attack are balanced. With regards to dental treatment, bacteria that remain in the subgingival calculus or root canal after incomplete root canal treatment rarely cause acute infection in healthy patients. However, the number of immune cells decreases during chemotherapy, and infection can easily occur because of the disrupted attack-defense balance [4,5]. In addition, 40% of patients receiving chemotherapy develop oral complications [5]. Simple oral diseases in patients receiving chemotherapy can easily exacerbate to acute systemic events, such as sepsis and pneumonia; this suggests the importance of

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**Fig. 1.** (A) A panoramic radiography acquired on day 2 of hospitalization (November 20, 2019) shows no lesion. (B) An apical lesion of the mandibular right first molar is observed (red arrow) on a periapical radiography (November 25, 2019). Vertical absorption of the alveolar bone at the mandibular right second molar (white arrow) is also observed. (C, D) Computed tomography performed at first visit (November 19, 2019) shows small amount of abscess in the buccal and lingual side of the right mandible (yellow arrow). (E, F) Osteosclerosis is seen (yellow arrow) on the bone setting of computer tomography.

prompt and appropriate oral and maxillofacial infection management [4].

Surgical treatments for infection, such as incision and drainage, might not be contraindicated in patients undergoing chemotherapy because of their hematologic characteristics. Close clinical examination and noninvasive approaches, such as antibiotic administration, could be considered as alternatives. The National Comprehensive Cancer Network (NCCN) guidelines recommend broad-spectrum antibiotics with anti-pneumococcal

properties to manage infections during chemotherapy [6]. Conventional antibiotic options are aminoglycosides and antipseudomonal penicillin (ticarcillin/clavulanate, piperacillin/tazobactam) [7]. However, recent third and fourth generation cephalosporins (ceftazidime, cefepime) and carbapenem (meropenem) are considerable options owing to their strong antibiosis of aerobic gram-negative bacteria, including *Pseudomonas aeruginosa*, and to some extent, against Gram-positive cocci [8].

This study reports the case of acute osteomyelitis due

**Table 1.** Trend of clinical test results. From November 20, 2019, to November 21, 2019, leukocyte count showed a sharp decrease. White blood cell count showed a rapid rise after administration of 300 mcg of G-CSF

	Normal range	11/19	11/20 9 AM	11/20 6 PM	11/21 6 AM	11/21 4 PM	11/22	11/23	11/25	11/26	11/28	12/6	12/11	12/17
WBC	4-10 (x10 <sup>3</sup> /μl)	2.93	1.13	0.83	0.84	1.19	3.27	13.15	9.28		9.75	11.17	11.40	
ANC	1800-7000 (/μl)	2520	678	224	92	417	2289	10783	7238		6767	8109	7923	
Seg. Neut	50-75 (%)	80	52	22	8	18	60	69	72		69.4	72.6	69.5	
RBC	4-5.4 (x10 <sup>6</sup> / μl)	3.20	2.88	2.87	2.62	2.95	2.45	3.02	3.09		3.45	3.27	3.43	
Platelet	130-400 (x10 <sup>3</sup> /μl)	95	65	68	68	73	57	46	70		232	619	527	
GOT	0-40 (IU)	68	53	37	22		13		30		26	34	30	
GPT	0-40 (IU)	74	68	55	41		24		25		28	24	22	
hs-CRP	0-0.5 (mg/dL)	20.17	22.79	25.70	27.89	29.07	27.01		12.71		11.82	2.27	1.02	
BT	36.5 (°C)	37.6 (38.4)	37.3 (39.6)	38.9	37.3 (39.4)	39.3	38.9	36.9	37.7					
Antibiotics		Amoxi+ Metro	Amoxi+ Metro	Cefepem	Cefepem	Pip/tazo	Pip/tazo	Ceftrizone	Amoxi	Amoxi	Amoxi	Amoxi	Amoxi	Cefdinir
Blood/Pus Culture	negative	(+) <i>K. pneumoniae</i>		(-)					(-)				<i>C. braakii</i> <i>P. aeruginosa</i>	
Note		Sepsis				G-CSF			Ext (#46,47)				Bone exposure	
Admission		EM/OMS	OMS	OMS	OMS	OMS/HOM	HOM	HOM	HOM	HOM	DC		OMS	OMS
Outpatient													OMS	OMS

Amoxi, amoxicillin/clavulanate; Metro, metronidazole; Pip/tazo, piperacillin/tazobactam; Ext, extraction; EM, emergency medicine; OMS, oral and maxillofacial surgery; HOM, hemato-oncology medicine; DC, discharge; BT, body temperature

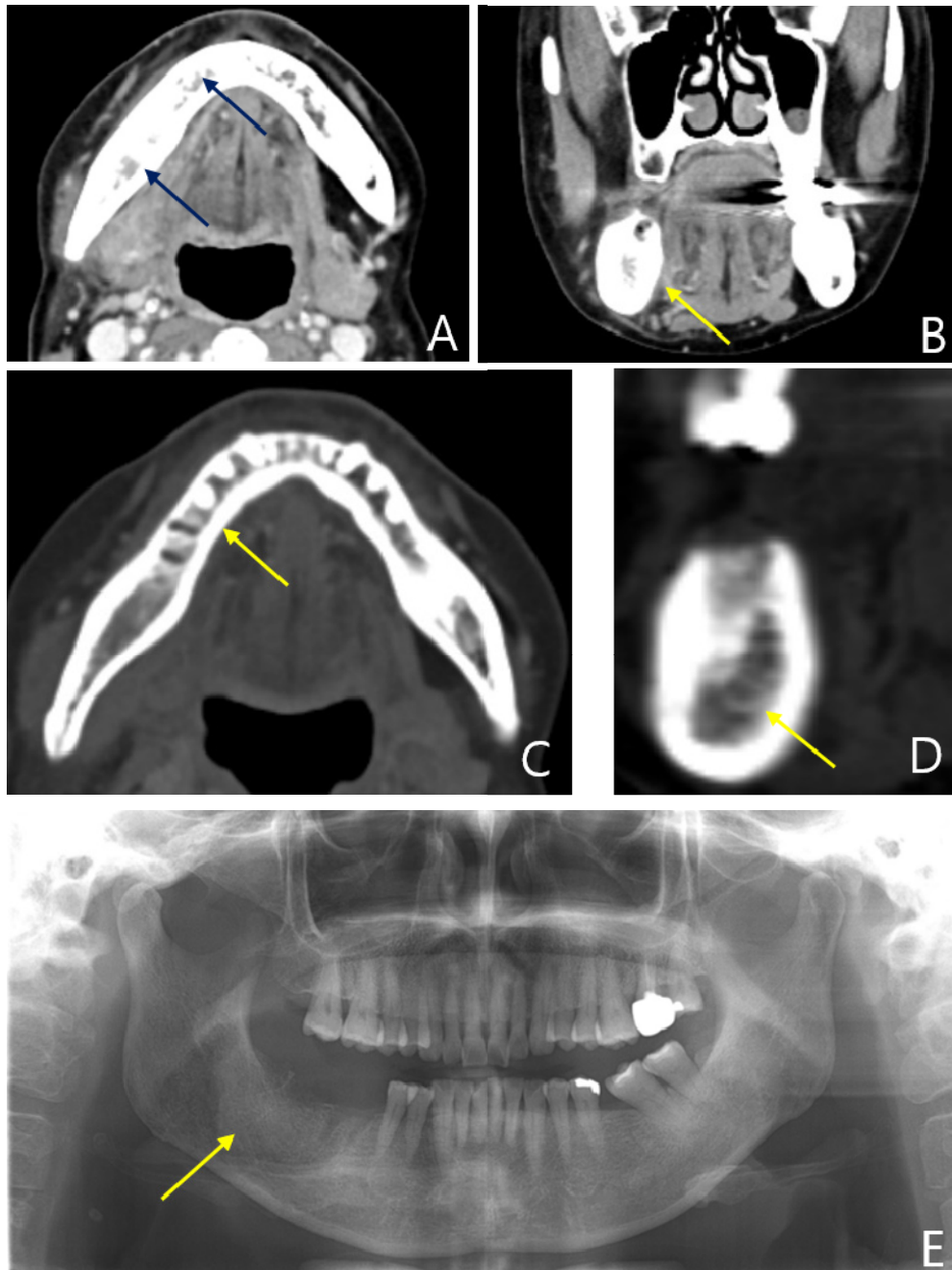
to odontogenic factor observed 5 days after the first cycle of chemotherapy for lung cancer. The patient reached a life-threatening condition because of fatal neutropenic fever and sepsis during the oral infection treatment. Moreover, gingival necrosis occurred, exposing over 3 cm of the mandibular bone. However, the patient recovered promptly within 40 days following treatment with appropriate antibiotics and routine dressing, without requiring any special surgical treatment except tooth extraction. Herein, we also summarize the standard treatment process for maxillofacial infections that occurs during chemotherapy.

## CASE REPORT

A 64-year-old woman underwent lower lobectomy on October 18, 2019, at the Department of Thoracic and Cardiovascular Surgery after diagnosis of stage III (pT2aN2M0) non-small-cell lung carcinoma and was scheduled for four cycles of adjuvant chemotherapy.

Five days after paclitaxel (207 mg) and carboplatin (300 mg) administration (November 12, 2019), she reported extreme pain in the lower jaw and the mandibular right first and second molars (November 17, 2019). Two days later (November 19, 2019), the patient visited the emergency room with right mandibular edema, fever, and limited mouth opening. An apical lesion was identified at the root tip of the mandibular right first molar, and the distal gingiva of the mandibular right second molar was covering the tooth crown due to the inflammatory edema (Fig. 1A, 1B).

Computerized tomography (CT) images showed signs of early abscess formation involving the right buccal space and acute osteomyelitis of the right mandible (Fig. 1C-F). At presentation to the Department of Oral and Maxillofacial Surgery later that day, the patient's high sensitivity CRP (hs-CRP) level was elevated to 20.17 mg/dL (normal, 0-0.5 mg/dL). However, complete blood count (CBC) results were normal. As only a week had passed since the administration of antineoplastic agents, and because the abscess was small, intravenous anti-



**Fig. 2.** (A, B) Computed tomography performed on day 21 from the first visit (December 21, 2019) shows a broad increase in the right mandibular bone marrow attenuation (black arrow) despite resolution of the abscess around the right mandible (yellow arrow). (C, D) Osteosclerosis is observed to expand anteriorly (yellow arrow). (E) As shown in a panoramic radiograph acquired on day 29 from the first visit (December 17, 2019), the right first and second molar were extracted (yellow arrow).

biotics (amoxicillin/clavulanate, 1.2 g t.i.d. intravenous [IV]; metronidazole, 500 mg t.i.d. IV) were administered.

On day 2 of hospitalization (November 20, 2019), the right buccal edema had reduced and mouth opening improved from 14 mm to 17 mm. However, fever (over 39°C) was observed temporarily. The absolute neutrophil

count (ANC) rapidly decreased from 2520 / $\mu$ L on the first day of hospitalization to 678 / $\mu$ L (normal, 1500-8000 / $\mu$ L) (Table 1). The 4th generation cephalosporin, Cefepime, was administered in view of the neutropenia. However, ANC further decreased to 224 / $\mu$ L after 9 hours, and the neutropenic fever persisted with a





**Fig. 3.** (A) A clinical photograph acquired on day 18 from the first visit (December 6, 2019). Necrotic gingiva (white arrow) and bone exposure are observed (black arrow) surrounding the tooth extraction site on the right mandible. Persistent suppuration is seen at the border between the extraction site and the necrotic lingual gingiva. (B) A clinical photograph acquired on day 26 from the first visit (December 14, 2019). The exposed area is seen to undergo re-epithelialization. (white arrow). (C) A clinical photograph acquired on day 40 from the first visit (December 28, 2019). The exposed area has completely healed into oral mucosa by deliberate secondary healing (white arrow). (D) A clinical photograph acquired on day 54 from the first visit (January 11, 2020). The secondary healed epithelium appears to have gradually connected with the surrounding tissue without distinct border.

maximum body temperature of 39°C. The result of the blood culture test performed on hospitalization day one were reported in the next afternoon as sepsis caused by Gram-negative bacilli (*Klebsiella pneumoniae*), without any sign of septic shock. All vital signs, except body temperature, remained stable.

On day 3 of hospitalization (November 21, 2019), ANC further decreased to 92 / $\mu$ L and the hs-CRP increased to 27.89 mg/dL. Body temperature persisted at 38-39°C. The patient was transferred to the Department of Hemato-Oncology ward for neutropenia treatment. After administration of granulocyte colony-stimulating factor (G-CSF; Filgrastim; 300 mcg), ANC rapidly increased to 417 / $\mu$ L. Based on the blood culture test result, the hemato-oncologist changed the intravenous antibiotic agent to piperacillin/tazobactam (4.5 g q.i.d.), an

empirical antibiotic. A follow-up blood culture was performed.

On day 5 of hospitalization (November 23, 2019), the patient's body temperature decreased to 36.9°C and the blood count was stable: white blood cells, 9280 / $\mu$ L; platelets, 70,000 / $\mu$ L; and absolute neutrophils, 6867 / $\mu$ L. Because the follow-up blood culture result showed no bacterial infection, we changed the antibiotic regimen to a third generation cephalosporin (ceftriaxone; 2 g t.i.d.).

On day 8 of hospitalization (November 26, 2019), the right mandibular first and second molars, suspected of causing the infection, were extracted. Treatment options other than tooth extraction, such as endodontic or periodontal treatments, were discussed with the patient; they were discarded owing to their relatively long treatment period, which would delay the patient's

**Table 2.** Selection of antibiotics against bacterial infection in patients undergoing chemotherapy (NCCN guidelines)

IV antibiotic therapy (typical monotherapy)	Consider oral antibiotic therapy for select low-risk patients
Cefepime (2 g, q8hr)	Ciprofloxacin (500 mg, q12hr) + amoxicillin/clavulanate (875 mg, q12hr)
Imipenem/cilastatin (500 mg, q6hr)	Moxifloxacin (400 mg, q.d.)
Meropenem (500 mg, q6hr)	Levofloxacin (500 mg, q.d.)
Piperacillin/tazobactam (4.5 g, q6-8hr)	
Ceftazidime (2g, q8hr)	

chemotherapy cycle, with the possibility of re-infection on resuming chemotherapy. Suppuration was confirmed from the tooth extraction site. As the patient's blood count was normal and because the infective bacteria were susceptible to amoxicillin/clavulanate, she was discharged with a prescription of amoxicillin/clavulanate (1 g, p.o., b.i.d.). The patient was instructed to do chlorhexidine gluconate and saline gargles, place a warm pack, and perform mouth opening exercises daily. The amount of mouth opening at discharge was 15 mm, and periodic dressing continued post-discharge at the outpatient clinic.

In the first week after discharge, follow-up panoramic CT showed resolution of the previously confirmed abscess. However, bone marrow attenuation increased than before in the wide area of the right mandibular body (Fig. 2). Gingival necrosis was observed around the extraction site, exposing more than 3 cm of the mandibular bone (Fig. 3A). The upper part of the exposed bone had an intense white color, in contrast to the pale-yellow color of the surrounding bone. Suppuration continued at the border between the extraction site and the necrotic lingual gingiva. The pus was collected and cultured. The amount of mouth opening improved from 15 mm to 43 mm. Oral amoxicillin/clavulanate therapy was continued, and dressing was performed twice a week. In the second week post-discharge, a consultation with the hemato-oncologist was planned to discuss chemotherapy resumption. Considering the fatal complication that occurred after the first cycle, a decision was made to cancel the remaining chemotherapy course. The exposed bone was undergoing epithelialization (Fig. 3B). In the third week, the pus culture was reported positive for *Citrobacter braakii* and *Pseudomonas aeruginosa*. Since *Citrobacter braakii* was resistant to amoxicillin/clavulanate, Cefdinir, a third-generation cephalosporin,

was administered instead. In the fourth week, the exposed 3 cm of the mandibular bone had re-epithelialized with mucosa and healed with secondary intention (Fig. 3C). The secondary healed epithelium gradually connected to the surrounding tissue without any distinct border (Fig. 3D).

## DISCUSSION

Patients undergoing chemotherapy are prone to acute infection and require careful evaluation based on appropriate clinical and blood tests. According to Vento et al. [6] and the NCCN guidelines (version 1.2020) [7], blood culture test is recommended before antibiotic therapy when patients undergoing chemotherapy have a body temperature of 38.3°C or higher, when there is neutrophil reduction ( $\leq 500 /\mu\text{L}$ ), or when an infection is suspected. In our case, bacteria were detected in the blood culture test performed at first visit, and sepsis was promptly diagnosed. Blood tests should include a total blood count with a differential test, a biochemistry panel, and liver function test (LFT) [6]. When a rapid hematologic change is expected, blood tests can be performed more than twice daily as performed for our patient, which could detect the sudden decrease in absolute neutrophil counts that enabled the provision of immediate treatment.

Hemato-oncology consultation and careful observation are necessary when a patient under chemotherapy shows febrile neutropenia. The mortality rate of hospitalized patients with febrile neutropenia is 6.8–20%, and accompanies pneumonia, sepsis and shock, eventually causing death [9]. Therefore, when infection occurs in patients undergoing chemotherapy, the NCCN guideline recommends treatment with broad-spectrum antibiotics that have anti-pneumococcal activity. Cefepime

(2 g, q8hr), imipenem/clastatin (500 mg, q6hr), meropenem (500 mg, q6hr), piperacillin/tazobactam (4.5 g, q6-8hr), ceftazidime (2 g, q8hr) for intravenous administration, and ciprofloxacin (500 mg, q12hr) + amoxicillin/clavulanate (875 mg, q12hr), moxifloxacin (400 mg, q.d.), and levofloxacin (500 mg, q.d.) in oral administration are recommended (Table 2) [6]. This comprehensive proposal for general infections does not specifically recommend the antibiotics for an intraoral infection. G-CSF is mainly used to prevent febrile neutropenia in cancer patients on myelosuppressive chemotherapy. This patient's ANC levels rose sharply after administration of G-CSF (300 mcg). The protocols of G-CSF administration are as follows. For patients presenting with febrile neutropenia, if risk factors of infection-related complications are present, therapeutic G-CSF should be considered. Filgrastim, tbo-filgrastim, filgrastim-sndz, or filgrastim-aafi may be administered in the therapeutic setting at a daily dose of 5 mcg/kg. Treatment should continue through postnadir recovery [10].

*Streptococcus spp*, *Pseudomonas spp*, *Veillonella spp*, *Bacteroid spp*, etc. were reported as the main species that cause odontogenic infection [11]. Moreover, prevalence of sepsis-causing Gram-negative bacteria, such as *Staphylococcus aureus*, coagulase-negative staphylococci, *Enterococcus spp*, and *Viridans streptococci*, are increasing [7]. These species compose normal bacterial flora in the oral cavity. Therefore, it is necessary to make effective selection of antibiotics against these strains in case of oral and maxillofacial infections.

Ciprofloxacin, a broad-spectrum antibiotic, when used alone is insufficient against gram-positive bacteria (*Viridans streptococci*) and anaerobic bacteria in the oral cavity [8]. Amoxicillin/clavulanate, the first-choice antibiotic agent for intraoral infections, is not suitable when used alone for patients undergoing chemotherapy, as it has insufficient anti-anaerobic and anti-pneumococcal activity. In conclusion, the combination of amoxicillin/clavulanate (875 mg, q12hr) and ciprofloxacin (500 mg, q12hr) seems appropriate for patients with oral and maxillofacial infection during their chemotherapy course.

In patients allergic to penicillin, amoxicillin/clavulanate can be changed to clindamycin (150 mg, q.i.d.) and administered as a combination (ciprofloxacin and clindamycin). Among the broad-spectrum antibiotics that can be administered intravenously, piperacillin/tazobactam, cefepime, imipenem/cilastatin, and meropenem have sufficient sensitivity against oral bacteria [12]. Our patient received cefepime and piperacillin/tazobactam, which effectively controlled the oral and maxillofacial infection.

As in the present case of osteomyelitis, cases of mandibular bone exposure after administration of certain drugs require accurate differential diagnosis from medication-related osteonecrosis of jaw (MRONJ). According to a 2014 position paper by American Association of Oral and Maxillofacial Surgeons (AAOMS), MRONJ must meet the following criteria: First, you must have a history of administering anti-resorptive or anti-angiogenic agents, either current or previous. Second, the intraoral or extraoral exposure of the bone should last more than 8 weeks in the maxillofacial region. Third, there should be no history of radiation therapy in the oral and maxillofacial area [13]. This case could not fulfill some of these criteria. Paclitaxel, a chemotherapeutic agent administered to the patient in the present case, acts on the microtubules and inhibits cell division. Carboplatin, the other agent, damages the DNA of cancer cells. Neither drug is an anti-resorptive agent or an anti-angiogenic agent. In addition, all exposed bones were epithelialized within less than 8 weeks, but within 40 days. Thus, this patient was diagnosed with acute osteomyelitis rather than MRONJ.

Osteomyelitis is subdivided into acute osteomyelitis, secondary chronic osteomyelitis, and primary chronic osteomyelitis under the Zurich classification system. Currently, the Zurich classification system is widely used for osteomyelitis of the jaws [14]. This classification system defines acute osteomyelitis as the onset of symptoms within 4 weeks. Although the duration suggested was arbitrary, the criteria is widely accepted [15]. The patient described in this report recovered within 4 weeks, without presenting advanced symptoms, such

as sequester formation or osteolysis. Therefore, the patient can be regarded to have recovered from acute osteomyelitis.

Before chemotherapy, patients are recommended to undergo thorough dental examination to eliminate any potential source of oral infection. Chronic and severe dental diseases were found in each 79% and 44% of patients in pre-chemotherapy dental assessment [16]. When an infection in the oral and maxillofacial region occurs because of a residual source in the oral cavity, it may be inevitable to change the whole anti-cancer treatment plan to settle the infection first. In the worst case, the infection can worsen and develop into a life-threatening condition, as reported herein. If a patient undergoing chemotherapy is suspected to have an oral and maxillofacial infection, it is important to quickly identify the extent of infection spread, and assess the ability of the patient's immune system through immediate clinical and radiological examinations. Proper antibiotic administration and wound dressing are essential in controlling the infection. Furthermore, close consultation with a hemato-oncologist is necessary for effective infection management based on the professional evaluation of patients' immune mechanisms.

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**Jun-Sang Park:** Methodology, Writing - review & editing  
**Choi-Ryang Lee:** Methodology, Writing - review & editing  
**Jae-ho Jeon:** Conceptualization, Data curation  
**Ik-Jae Kwon:** Conceptualization, Supervision  
**Hoon Myoung:** Supervision, Validation

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