Case Report

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Necrotizing Periodontal Disease Following Chemotherapy for Refractory Diffuse Large B-Cell Lymphoma: A Case Report and Review of Literature

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Despite the latest developments in chemotherapeutic regimens and protocols to reduce chemotherapy-related adverse side-effects, some appear unavoidable and could be severe enough to impair the patient's quality of life. The most common oral side effects of chemotherapy are oral mucositis, jaw osteonecrosis, oral infections caused by bacteria, fungi, and viruses, dental anomalies, hyposialia, xerostomia, and taste changes. These side effects have negative impacts on the patient's oral intake and nutrient status. We report a 43-year-old man with refractory B-cell non-Hodgkin lymphoma (NHL) who began chemotherapy in September 2005 at E-Da Hospital. After his fifth cycle of chemotherapy, multiple necrotic gingival lesions appeared accompanied by severe pain. The patient was referred to the dental department and diagnosed with necrotic periodontitis, which is a rare and atypical necrotizing periodontal disease with a sudden onset and rapid progression within a few days. The disease is characterized by dislodgement of necrotic tissue from the marginal gingiva together with rapid bone destruction. This report aims at highlighting the importance of interdisciplinary cooperation through which physicians familiar with necrotizing periodontitis disease (NPD) could help in making timely diagnosis that allows prompt treatment.

Key words: necrotizing periodontitis disease, necrotizing ulcerative periodontitis, chemotherapy, B-cell lymphoma, non-hodgkin lymphoma (NHL)

Introduction

Diffuse large B-cell lymphoma (DLBCL) is the most common type of non-Hodgkin lymphoma (NHL). Approximately 1/3 of DLBCL patients will develop refractory disease or experience relapse, which remains a major cause of morbidity and mortality. Although high-dose chemotherapy and stem cell transplantation may be beneficial to those refractory to initial treatment and those experiencing disease relapses, certain side effects in the oral cavity remain a significant morbidity in this patient population. A review of the literature showed an association of primary

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non-Hodgkin's lymphoma and other malignancies with periodontal problems in immunocompromised patients, including drug-induced gingival enlargement and poor oral hygiene that contribute to further periodontal diseases. In contrast to these conditions, necrotizing periodontal disease (NPD), which is a rarer but more serious disease entity, does not present with typical features of gingivitis or medication-related gingival enlargement.[1]

With sudden onset and rapid progression, NPD is one of the most severe inflammatory periodontal disorders that requires urgent treatment. NPD appears to encompass different stages of necrotic gingivitis (NG).[2] A previous study reported a wide variation in the prevalence of NG in different populations.[3] Besides, although it can be observed in both adults and children, there are regional differences in age distribution.[3] Among the general population who attend dental clinics, the prevalence of NG ranges from 0.51% to 3.3%; while the prevalence was higher during the Second World War (3.96% – 20.6%) according to a US military survey than that in recent studies (0.11% – 6.19%), it was reported to be higher in developing countries than in developed countries.[4]

Although the specific mechanism is still unclear, NPD is often associated with immunodeficiency. Nevertheless, clinical reviews of the relationship between NPD and chemotherapy remain rare. Through the current case report, we hope to better understand chemotherapy-induced NPD and explore the potential improvement in the quality of patient care through cooperation between oncologists and dentists.

Case Report

Case presentation

A 43-year-old man diagnosed with refractory B-cell NHL received three courses of chemotherapy from 2001 to 2004 at another hospital. In September 2005, he started a new course of chemotherapy in the Hematology-Oncology department of our institute (E-Da Hospital, a tertiary referral hospital) for five cycles that consisted of vincristine, adriamycin, cyclophosphamide, prednisone, and etoposide. After the fifth cycle of chemotherapy, the patient developed multiple severely painful necrotic gingival lesions for which we were consulted by the oncologist for evaluation.

History taking and physical examination showed a malnourished and weak individual who also experienced insomnia and major depressive symptoms. Oral examination revealed poor oral hygiene with generalized plaque and calculus deposition along the gingival margins. In addition to two main ulcerative gingival lesions covered with whitish pseudomembrane, necrosis of dental papilla with an erythematous base was noted. One lesion was 25 mm × 10 mm on the upper buccal gingiva, while the other was 15 mm × 10 mm on the lower labial gingiva (Fig. 1A). The patient complained of extreme pain and halitosis. According to the patient, this was a recurrent attack with similar but aggravated symptoms. Serum biochemical analysis revealed leukopenia with a white blood cell count of only 270 cells/mm^3 and a reduced proportion of neutrophils three days before his dental visit.

Clinical management

Full-mouth supragingival scaling was performed with an ultrasonic scaler on his first dental visit except over the lesion areas which were gently wiped with wet cotton swabs to remove the superficial necrotic slough and debris. In addition, a free necrotic bone fragment was removed from the upper arch lesion. Close to the lesion sites, the gingival sulcus was irrigated with chlorhexidine. After the procedure, chlorhexidine mouth rinse (0.12%) was prescribed twice a day for two weeks. The patient was given instructions to improve his dental hygiene and to avoid smoking, alcohol consumption, and irritating food. The medical team continued to provide

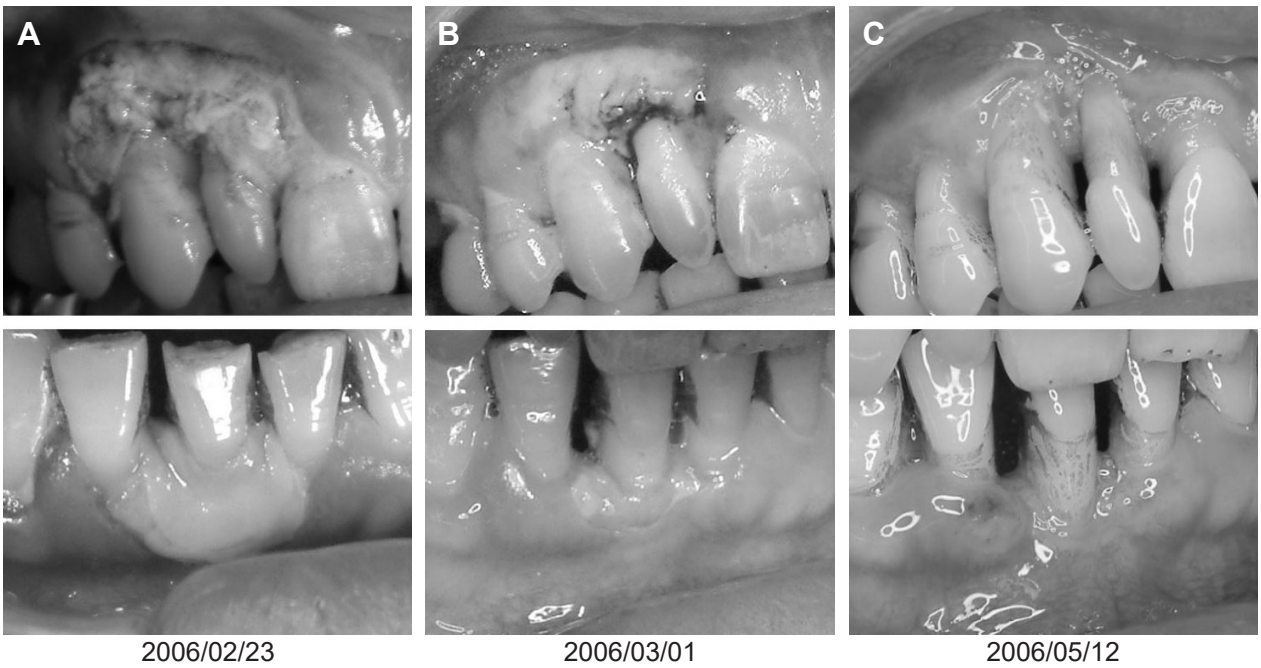

Fig. 1 Clinical records of the necrotizing periodontal disease lesions (A) first examination (B) 1 week after initial conservative local debridement and 0.12% chlorhexidine irrigation on (C) 3 months follow up after periodontal treatment, the symptoms and signs significantly released.

the patient with nutritional supplements and supportive care.

After three days, his oral hygiene and pain were signficantly improved. Patient education included the suggestions of using a soft toothbrush and rinsing the oral cavity with chlorhexidine mouthwash (0.12%) twice a day.

Further improvements in pain and oral hygiene as well as shrinkage of the ulcerative lesions were noted after one week (Fig. 1B). After two months, the ulcerative lesions healed and the patient was symptom-free (Fig. 1C). Regular dental clinic follow-ups were suggested every three months.

Discussion

An immunocompromised status from chemotherapy or leukemia, malnutrition, psychological stress, poor oral hygiene, smoking, and a previous history have been reported to be predisposing factors for NPD.[1] Despite the common belief that more than one factor is required for development of the disease, there was a wide variation in the results of previous studies.[5]

The stages of NPD are defined according to the extent of disease involvement (Table 1). Papillary necrosis, bleeding, and pain are the typical clinical features of the condition. Other signs and symptoms include halitosis, pseudomembranes, regional lymphadenopathy, fever, and rapid alveolar bone loss.[4]

Bacteriology research has indicated that *Prevotella intermedia, Treponema, Selenomonas,* and *Fusobacterium* species usually predominate in NPD lesions, whereas the typical periodontitis-related pathogens, *Porphyromonas gingivalis* and *Tannerella forsythia*, were less frequently found.[6] In addition, viruses such as herpes viruses, especially cytomegalovirus and Epstein-Barr virus type 1, may play a role in the pathogenesis of necrotizing periodontal diseases.[3]

Despite the lack of evidence supporting that chemotherapy-induced neutrophil deficiency may induce NPD, there is a strong correlation between NPD and severe immunodeficiency.[7] Besides, antineoplastic agents would interrupt the process of cell replication for cancer cells and some healthy cells with a

Table 1. Proposal of classification for necrotizing periodontal diseases (NPD) from American Academy of Periodontology 2017 World Workshop Consensus report Severity.

	Severity	Clinical features
NG	The least severe	• Acute onset, symptomatic ulceration and necrosis area limited to gingival tissue only without loss of periodontal attachment. • Low grade fever, cervical lymphadenopathy may progress to NP or NS (particularly in debilitated patient).
NP		• Acute onset, patients may have history of NG or periodontitis. • Loss of periodontal attachment and bone. • Destruction of the extraoral area if more severely. • In severely immunocompromised patients, a bone exposure and sequestrum may be present.
NS		• Acute onset and rapidly progress. • Destruction beyond mucogingival junction (MGJ). • Larger areas of osteitis and bone sequestrum. • It may extend the entire alveolar ridge, causing oral deformity.
Noma	The most severe	• Most severe form, also called "cancrum oris". • A severe intraoral and extraoral destructive, perforation through the skin. • One of the most devastating human diseases.

NG: Necrotizing gingivitis; NP: Necrotizing periodontitis; NS: Necrotizing stomatitis.

high turnover rate such as mucosal cells of the gingiva and throat. The resulting loss of protective function of the oral mucosa predisposes to infection from opportunistic pathogenic bacteria as a side effect of chemotherapy.[1]

In the present case, the diagnosis of NPD was primarily based on clinical findings (Table 1). The extent of tissue necrosis was limited to the buccal mucosa without lingual involvement or extension beyond the mucogingival junction. Destruction of gingival and bone tissues was noted in both lesions. Laboratory studies showed a persistently low neutrophil count that dropped below 500 cell/mm^3 one week before NPD onset (Fig. 2). The associated hemorrhoidal bleeding, genital ulcers, herpes simplex, insomnia, and major depression may predispose the patient to intense psychological stress and immunosuppression.

We also differentiated the diagnosis of NPD from vesicular-bullous diseases as well as primary or recurrent herpetic gingivostomatitis.[2] Table 2 lists the important clinical features for differential diagnosis. The clinical features and the presence of risk factors were sufficient to establish the diagnosis of NPD, which was confirmed by the clinical improvement observed two days after the initial treatment. Because of the severity and prolonged duration of neutropenia as well as the disproportionate destruction of the periodontium in our patient, we suspected the diagnosis of NPD resulting from chemotherapy-induced immunodeficiency.

The aim of treatment during the acute stage is to remove irritating local factors, including dental plaque, calculus, and superficial necrotic tissues. Systemic metronidazole has been identified as the first-line antibiotic for the treatment of NPD.[4] However, this patient was admitted to our hospital due to a neutropenia-related infection. Because he was already taking antibiotics, we did not prescribe any additional antibiotic regimens.

Patient-centered care and interprofessional practice are important components of current medical care. Chemotherapeutic regimens are being improved not only to improve prognosis but also toreduce the incidence of complications. Although oral complications are not life-threatening, they decrease oral intake and increase patients' sufferings fromrepeated oral mucosal ulcers and pain from mucositis during the entire period of chemotherapy. Oral ulcers and severe pain of unknown etiology require immediate medical attention to prevent NG from progressing to NPD.

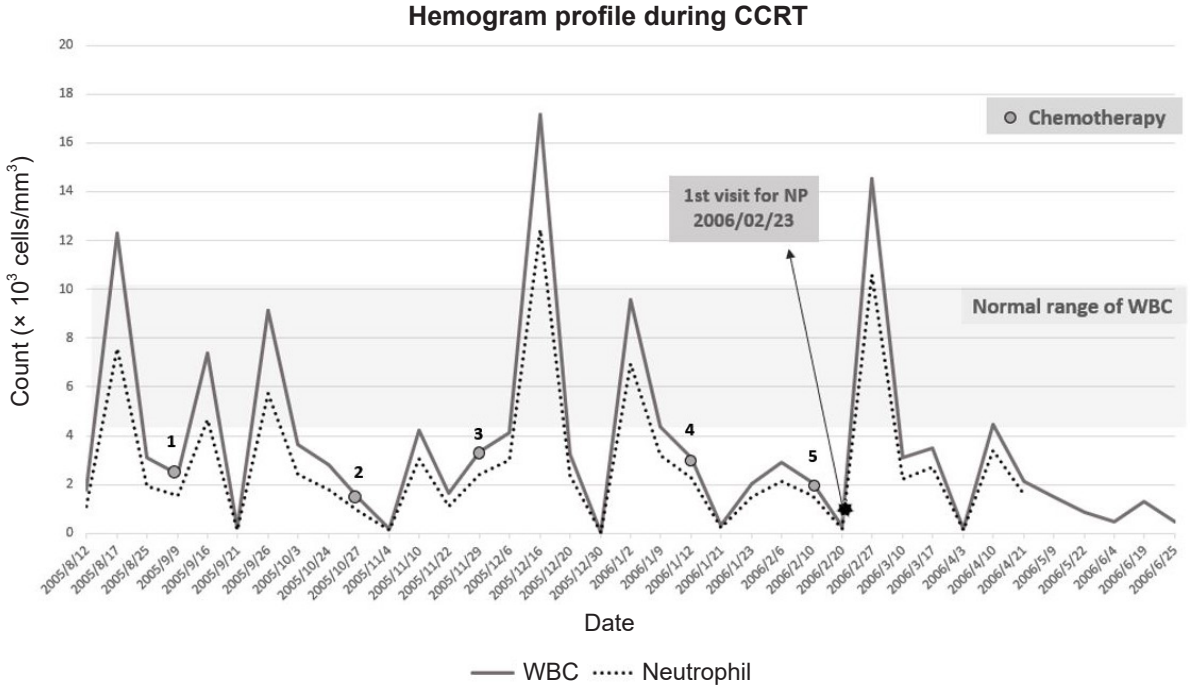

Fig. 2 Changes in white blood cell (WBC) and neutrophil counts during concurrent chemoradiotherapy (CCRT). Note the extremely low WBC count on 2006/02/20 after the fifth cycle of chemotherapy (2006/02/10) when necrotizing periodontal disease (NPD) occurred and the patient was referred to dental department on 2006/02/23.

Table 2. Important clinical features for differential diagnosis between primary herpetic gingivostomatitis (PHG) and necrotizing periodontal disease (NPD).

	PHG	NPD
Etiology	Herpes simplex virus	Bacteria
Age	Frequently children	10 – 30 years
Site	Gingiva and entire oral mucosa	• Interdental papillae • Rarely outside gingiva • Localized or multiple sites
Symptoms	• Multiple vesicles which disrupt • Fibrin-covered ulcerations • Fever	• Ulcerations, necrotic tissue leaving small round and a yellowish—white plaque • Moderate fever may occur
Duration	1 – 2 weeks	1 – 2 days if treated
Contagious	Yes	No
Healing	No permanent destruction	Destruction of periodontal tissue remains

Before chemotherapy, a thorough dental clinical and radiographic examination is needed. The dentist could eliminate active or potential sources of infection such as dental calculi and teeth with poor prognoses.[4] Patients must also be informed of the potential impact of the oral complications of chemotherapy. More importantly, educating the patient or caregivers about oral hygiene maintenance is considered the most effective preventive measure.[8]

During and after chemotherapy, the use of antimicrobial rinses such as 0.12% chlorhexidine mouth wash may achieve local decontaminationby eliminating most gram-positive and certain gram-negative bacteria,[9] thereby reducing gingival inflammation and the risk of thrombocytopenia-induced bleeding.[10] Besides,

encouraging regular dental follow-ups can also help patients to maintain the stability of the oral health environment.

Conclusion

Patients undergoing chemotherapy may experience complications in the oral cavity that could adversely affect their quality of life. Although most of these complications are unavoidable, some clinical measures can be taken to minimize the negative impact. Appropriate and timely periodontal treatment to enhance oral hygiene and patient compliance are essential. Moreover, interprofessional cooperation between oncologists and dentists is necessary for providing a successful all-round treatment for this patient population.

Author Contributions

Conceptualization, Wen-Hui Chen & Po-Yuan Hsiao; Data Curation and Writing-Original Draft: Po-Yuan Hsiao; Writing-Review & Editing and supervision: Wen-Hui Chen.

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Conflicts of Interest

The authors declare no conflict of interest.

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