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# Oral ulcers in hematological malignancy patients undergoing chemotherapy: is it chemotherapy or neutropenia?: a case report and review of the literature

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# Abstract

**Background** Chemotherapy can cause oral complications either directly, by inducing mucosal degeneration, or indirectly, through myelosuppression leading to neutropenia. Neutropenia, a common side effect, is often associated with multiple oral ulcers.

**Case presentation** A 39-year-old Arabic Syrian man with acute myelogenous leukemia developed neutropenia following his initial chemotherapy course, resulting in oral ulcers. A complete blood count confirmed chemotherapy-induced neutropenia, and the clinical presentation supported the diagnosis of neutropenic ulcers. The patient's chemotherapy regimen was temporarily halted, and a topical corticosteroid paste containing triamcinolone acetonide was applied three times daily for 7 days. This treatment led to significant regression of the ulcers. The patient provided written informed consent after receiving a detailed explanation of the study's objectives, procedures, and privacy considerations.

**Conclusion** Topical corticosteroid treatment effectively promoted significant regression of neutropenic ulcers in this case.

Keywords Neutropenic ulcer, Neutropenia, Oral ulcer, Chemotherapy-induced neutropenia

# Introduction

Hematological malignancies comprise a diverse group of cancers arising from the uncontrolled proliferation and malignant transformation of hematopoietic cells. These malignancies vary significantly in incidence, etiology, prognosis, and mortality rates. Globally, they rank as the fifth most prevalent cancer type, accounting for approximately 6.5% of all cancer cases and the second leading cause of cancer-related mortality [1–7]. They are broadly classified into myelocytic and lymphocytic subtypes on the basis of cell lineage [3, 5], with leukemias and lymphomas being the most common types worldwide [1, 2, 6, 7].

The management of hematological malignancies depends on factors such as disease subtype, patient age, and comorbidities. Treatment options include chemotherapy, radiotherapy, stem cell transplantation, and supportive care [8-10]. Among these, chemotherapy remains the primary treatment modality, exerting cytotoxic effects on rapidly dividing cells by disrupting DNA



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and RNA synthesis, causing DNA damage, and interfering with mitotic spindle formation [11–17]. It employs various agents, including alkylating agents, antimetabolites, antimitotics, and certain antibiotics [9, 11]. However, owing to its nonselective nature, chemotherapy not only targets malignant cells but also affects rapidly proliferating normal cells, particularly within the hematopoietic system, leading to a range of adverse effects [11–14, 16–20].

One of the most serious complications of chemotherapy is neutropenia, resulting from bone marrow suppression. Neutropenia increases the susceptibility to infections and other complications [21-26], as neutrophils play a crucial role in immune defense, acute inflammatory responses, and tissue repair [27-31]. In patients with hematological malignancies receiving myelosuppressive chemotherapy, the oral mucosa is especially vulnerable to toxicity owing to its high cellular turnover, distinct microbiome, presence of odontogenic infection foci, and exposure to physiological trauma [13, 18, 32-36]. The combination of neutropenia and immune suppression disrupts oral hemostasis, predisposing patients to oral complications such as mucositis and ulceration [13, 32-34], which significantly impact quality of life and treatment adherence [35]. This article explores the etiology and management of neutropenic ulcers, presenting a case report of a patient with acute myelogenous leukemia who developed multiple painless oral ulcers following a chemotherapy-induced neutropenia. Future research is needed to develop more effective strategies for preventing and managing oral mucositis, ultimately improving patient outcomes and chemotherapy efficacy.

## **Case presentation**

A 39-year-old Syrian male of Arabic descent, diagnosed with acute myelogenous leukemia (AML), underwent his initial chemotherapy at Al-Bairouni University Hospital, Damascus's primary oncology center. The induction regimen followed the standard 7+3 protocol, consisting of cytarabine for 7 days and anthracycline for 3 days. Three days after initiating chemotherapy, the patient developed moderate neutropenia [absolute neutrophil count (ANC):  $0.9 \times 10^9$ /L]. Complete blood count (CBC) also revealed a reduced red blood cell count (2.31×10<sup>12</sup>/L) and platelet count (11×10<sup>9</sup>/L).

Two days after neutropenia onset, a clinical oral examination identified a painless ulcer covered by a pseudofibrinous membrane on the lower labial mucosa. Initially measuring  $1.5 \text{ cm} \times 1$  cm, the ulcer exhibited an erythematous halo and edema (Fig. 1A). After 1 week, it expanded to 2 cm $\times 1.5$  cm, developing necrotic edges while remaining painless (Fig. 1B). In addition, a 1



Fig. 1 Displays an ulcer located on the lower lip. A The ulcer after 5 days of neutropenia with a pseudo-fibrinous membrane and an erythematous halo. The ulcer appears nonhemorrhagic, painless, and measures approximately 1.5 cm × 1 cm in size. B The ulcer on the lower lip after 12 days of neutropenia. There is evident growth in the size of the ulcer and the presence of necrotic tissue. C Reduction in the size of the ulcer on the lower lip, taken 7 days after initiating the topical treatment

 $cm \times 1.5$  cm necrotic ulcer was observed on the left buccal mucosa (Fig. 2A).

To manage the ulcers, the patient was prescribed topical corticosteroids and antiseptic mouth rinses [37]. Chlorhexidine 0.02% was used as a mouthwash twice daily, and a topical paste containing triamcinolone acetonide (Denti-Cort) in Orabase was applied three times daily for 7 days (Fig. 3). Upon reevaluation, the ulcers showed significant regression, with no pain or bleeding (Figs. 1C and 2B).

The patient provided written informed consent after receiving a thorough explanation of the study objectives, procedures, and privacy considerations.

## Discussion

The introduction of chemotherapy in the 1940s led to the recognition of mucositis as a significant adverse effect. Initially termed stomatitis, its pathogenesis was not fully understood until six decades later, prompting the adoption of the term "mucositis" in 2007 to describe lesions caused by cytotoxic chemotherapy [38]. Mucositis can

affect multiple segments of the gastrointestinal tract, including the oral cavity, where it presents as oral mucositis (OM). OM typically develops 4–16 days after initiating a high-dose chemotherapy and persists for 10-14 days post-treatment [13, 35]. It is characterized by inflammation, epithelial damage, ulceration, and impaired cell regeneration, leading to mucosal atrophy. Clinically, OM manifests as erythema, a burning sensation, swelling, and mucosal desquamation, ultimately leading to ulcer formation [12, 13, 19, 35, 38, 39]. These crater-like ulcers, covered by pseudo-fibrinous tissue with indistinct edges, indicate complete epithelial loss and partial soft tissue involvement [13, 40]. OM is a common chemotherapy complication, affecting approximately 40% of patients, often resulting in severe pain, functional impairment, and treatment delays, which negatively impact quality of life [35, 38].

The development of mucositis occurs through a five-phase process, influenced by cytokine activity, chemotherapy-induced cytotoxicity, oral microbiome composition, and bone marrow status [38, 41, 42].

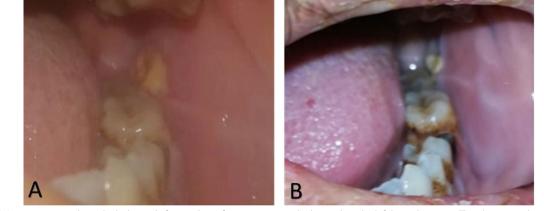


Fig. 2 A A new necrotic ulcer which showed after 12 days of neutropenia, and is located on the left buccal mucosa. The ulcer is painless, non-bleeding, and measures approximately 1 cm × 1 cm in size. B A notable decrease in the size of the ulcer on the left buccal mucosa



Fig. 3 Shows the topical medication containing triamcinolone acetonide in Orabase, which was utilized in the treatment

- 1. Inflammatory/vascular (initiation) phase: Chemotherapy-induced damage to epithelial and submucosal cells triggers the release of reactive oxygen species (ROS). ROS cause DNA damage, apoptosis, and vascular impairment leading to early mucosal injury [35, 38].
- 2. Epithelial phase: Free radicals disrupt DNA strands, inducing apoptosis. Activation of nuclear transcription factor kappa B (NF-kB) stimulates the release of pro-inflammatory cytokines, further impairing cell regeneration and mucosal integrity [35, 38].
- 3. Signal formation and transmission: Transcription factors activate the ceramide apoptosis pathway, exacerbating programmed cell death. Macrophages and matrix metalloproteinases further degrade tissue structure, while tumor necrosis factor-alpha (TNF $\alpha$ ) accelerates mucosal damage [35].
- 4. Ulcerative phase: Damage to oral epithelial stem cell results in ulcer formation, particularly during periods of neutropenia. These ulcers are highly susceptible to secondary infection, increasing the risk of bacteremia or sepsis [35, 38].
- 5. Healing phase: Epithelial regeneration and microbiome restoration occur around day 15 or 16 postchemotherapy, coinciding with peripheral blood recovery [35].

In chemotherapy patients, oral ulcers can result from neutropenia, direct chemotherapy toxicity, or infections [37]. Neutropenic ulcers are particularly concerning, as studies indicate a high prevalence of oral ulcers in neutropenic patients undergoing chemotherapy [43]. These ulcers are deep, irregularly shaped, and covered by a yellow pseudo-fibrin membrane, often exhibiting necrosis. While pain is a common symptom, some patients may experience reduced pain sensitivity due to chemotherapy-induced peripheral neuropathy [37, 40, 42, 44–46].

The diagnosis of OM is primarily clinical, based on characteristic ulcerative lesions, erythema and mucosal atrophy. In cases where superinfection is suspected, complementary diagnostic tests—such as cultures for candida, polymerase chain reaction (PCR) for herpes simplex virus, and bacterial cultures—may be necessary to confirm secondary infections. In addition, a CBC can be useful in identifying neutropenia and thrombocytopenia, both of which may predispose patients to more severe OM manifestations [42]. In this patient's case, the diagnosis of neutropenic ulcers was established on the basis of the clinical presentations and laboratory findings, confirming neutropenia.

Currently, there is no standardized protocol for the management of OM; however, treatment generally

consists of local and systemic interventions aimed at pain relief, inflammation control, infection prevention, and tissue regeneration [13, 35, 42, 47, 48]

- 1. Pain management
  - Topical or systemic analgesics: lidocaine gel is commonly used to provide localized pain relief in ulcerated regions [47].
  - Cryotherapy: the application of ice chips during chemotherapy administration may reduce pain and inflammation by decreasing mucosal blood flow and limiting chemotherapy exposure to the oral epithelium [42].
- 2. Anti-inflammatory and healing agents
  - Topical corticosteroids (e.g., triamcinolone acetonide) help reduce inflammation and promote healing [47].
  - Biological response factors such as granulocyte colony stimulating factor (G-CSF) have been investigated for their potential role in mucosal regeneration [42].
  - Antioxidants (e.g., glutamine and honey-based formulations) may facilitate mucosal repair by reducing reactive oxygen species [42].
- 3. Antimicrobial and infection control strategies
  - Antiseptic mouthwashes (e.g., chlorhexidine 0.02%) help prevent secondary infections, as chlorhexidine exhibits bactericidal, fungicidal, and virucidal properties [48].
  - Topical or systemic antibiotics may be required if bacterial superinfection is suspected.
  - Antifungal or antiviral medications are used when fungal or viral infections are present.
- 4. Non-pharmacological interventions
  - Low level laser therapy (LLLT) has shown promise in reducing severity of OM and promoting healing [42].
  - Oral care protocols (soft-bristled toothbrushes, saline rinses, and adequate hydration) are essential in preventing OM progression [42].
- 5. Management of neutropenic ulcers
  - Corticosteroids (topical or systemic) help reduce inflammation and promote healing.

- Antiseptics and antibiotics are often necessary to prevent infections, particularly in immunocompromised patients.
- Neutrophil recovery is a critical factor, as ulcers typically heal once neutrophil counts normalize [49, 50].

In this case, the patient's oral ulcer characteristics were consistent with neutropenic ulcers, and treatment with topical corticosteroid led to a significant improvement. The absence of pain was likely attributable to chemotherapy-induced neuropathy [13]. The prescribed regimen included chlorhexidine 0.02% mouthwash (twice daily) for antisepsis and infection prevention, and triamcinolone acetonide-based topical paste (Denti-Cort) (three times daily for 7 days) to reduce inflammation and promote healing. This therapeutic approach resulted in ulcer regression without complications; early identification and timely intervention are essential for optimal patient outcomes.

This case report highlights an effective treatment strategy for chemotherapy-induced neutropenic ulcers. It provides practical insights for healthcare professionals managing oral complications in patients with cancer and contributes to the clinical understanding of neutropenic ulcer evaluation and treatment. Despite various available therapeutic strategies, evidence supporting their efficacy remains variable across patient populations. Future clinical research is required to optimize treatment protocols, compare different inventions, and explore novel management strategies for chemotherapy-associated oral ulcerations.

The novelty in this case lies in distinguishing neutropenic ulcers as a specific subset of chemotherapyrelated oral mucosal damage. While oral mucositis is well-documented, this report emphasizes the need for early clinical recognition of neutropenic ulcers, especially in patients with severe neutropenia, to guide timely interventions. Furthermore, although corticosteroids are commonly used for oral mucositis, their role in neutropenic ulcers remains poorly established. This case demonstrates successful ulcer regression following treatment with triamcinolone acetonide-based paste in Orabase, suggesting topical corticosteroids as a potential first-line therapy in this subset of patients. In addition, the adjunctive use of chlorhexidine 0.02% mouthwash was beneficial owing to its bactericidal, fungicidal, and virucidal properties. This aligns with emerging research suggesting that modulation of the oral microbiome may influence mucositis severity and ulcer healing. Overall, this case provides a real-world example of an effective, noninvasive treatment strategy that can be integrated in routine oncology care.

## Conclusion

This case report highlights the oral complications associated with chemotherapy, emphasizing the importance of vigilant monitoring and timely intervention in managing neutropenic ulcers. The use of topical or systemic corticosteroids, antiseptics, or antibiotics has proven effective in reducing inflammation and promoting healing. Early identification and prompt treatment of neutropenic ulcers are crucial for preventing complications and ensuring patient outcomes.

#### Abbreviations

AML Acute myelogenous leukemia

- ANC Absolute neutrophil count
- CBC Complete blood count
- NFkB Nuclear transcription factor kappa B
- OM Oral mucositis
- ROS Reactive oxygen species
- TNFa Tumor necrosis factor-alpha

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#### Author contributions

Fatima AlZahraa Al Beesh: conceptualization, investigation, validation, visualization, and writing—original draft. Nafiza Martini: writing—review and editing. Siham Suleiman: conceptualization, supervision, validation, visualization, and writing—review and editing. Abeer Aljoujou: conceptualization, supervision, validation, visualization, and writing—review and editing.

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#### Availability of data and materials

The datasets generated during the current study are available from the corresponding author on reasonable request.

### Declarations

#### Ethics approval and consent to participate

The Scientific Research Committee of the Faculty of Dentistry of Damascus University obtained the necessary regulatory approvals to conduct the research, and the study was registered with number 154 on 27 September 2021. Written informed consent was obtained after receiving a comprehensive explanation of the study objectives, procedures, and considerations regarding patient privacy. This study is registered in the ISRCTN with the number 17585958. Informed consent was obtained from the patient.

#### **Consent for publication**

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

#### **Competing interests**

The authors have no relevant interests to disclose.

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