

# Life-threatening oral mucositis following chemotherapy in a pediatric patient

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## Abstract

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## Title page

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Life-threatening oral mucositis following chemotherapy in a pediatric patient

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## Abstract

Pediatric patients undergoing chemotherapy may present upper airway obstruction due to severe oral mucositis. Although completely reversible, its clinical course correlates with the course of neutropenia and may be complicated. Thus, airway management in these patients must be determined on an individual case basis.

## Keywords

Mucositis, chemotherapy, upper airway obstruction, neutropenia, pediatric

## Main text

### 1. Introduction

Mucositis is a common adverse effect in pediatric patients receiving chemotherapy for hematological malignancies<sup>1</sup>. However, severe mucositis leading to upper airway obstruction is rare and literature regarding this topic is scarce. It is an impending oncologic emergency and clinicians should be aware of the clinical course and management of this life-threatening complication.

### 2. Case Presentation

A 10-year-old, 34 kg female with no significant medical history was admitted with recently diagnosed acute myeloid leukemia. She was treated with etoposide 150 mg/m<sup>2</sup>/dose on days 1-5, cytarabine 200 mg/m<sup>2</sup>/dose on days 6-12, mitoxantrone 5 mg/m<sup>2</sup>/dose on days 6-10, and triple intrathecal therapy on day 6 as induction therapy (JPLSG AML-05 protocol<sup>2</sup>). Following chemotherapy, her course was complicated by continued febrile neutropenia and oral mucositis. Broad spectrum antibiotics including meropenem, teicoplanin, and caspofungin with granulocyte colony-stimulating factor (G-CSF) was initiated. As multiplex polymerase chain reaction proved positive for *Herpes simplex* viral infection, acyclovir was added. She complained of severe throat pain and dysphagia due to worsening mucositis and required continuous infusion of morphine.

On day 24, the patient complained of increasing throat pain and difficulty breathing. She was found sitting up in bed, leaning forward, drooling. Pan-inspiratory stridor and mild effort of breathing was observed on physical examination. She was alert with her vital signs otherwise stable. Examination on nasolaryngoscopy revealed extensive desquamation of the oropharyngeal mucosa and multiple, confluent ulcerative lesions with significant edema extending down to the arytenoid cartilage (Fig. 1). The patient was taken to the operating room for elective intubation with otolaryngology team on standby for tracheostomy placement. A size 5.0 mm internal diameter endotracheal tube was successfully inserted by video laryngoscopy with anesthesia maintaining spontaneous ventilation.

The patient was then transported to the pediatric intensive care unit. As infection being considered as an aggravating factor, antimicrobial agents and G-CSF was continued, and granulocyte transfusion from paternal donor was attempted.

On day 28, she developed significant spontaneous bleeding from the gingiva and the oropharyngeal ulcers, resulting in hemorrhagic shock. Platelet transfusions and vasoconstrictors were warranted for resuscitation. Nasolaryngoscopy revealed further aggravation of the ulcerative lesions with active oozing and worsening edema of the oropharyngeal tissues showing complete obstruction of the retropharyngeal space. Packing of the oropharyngeal space was performed as electrocoagulation of bleeding vessels failed to control bleeding.

Surgical tracheostomy was considered taking the above finding into account. After thorough discussion with the oncologists and the otolaryngologists a decision was made to wait for resolution of neutropenia considering the elevated risk of procedure in the nadir phase and expected improvement of mucositis following recovery of neutrophil counts.

On day 29, absolute neutrophil count exceeded 500 / $\mu$ L and G-CSF was discontinued. Her bleeding was well controlled. On day 31, defervescence was achieved. On day 32, improvement of the ulcerative lesions and airway swelling was confirmed on nasolaryngoscopy. Adequate leakage around the endotracheal tube was verified. The patient was able to cough, swallow efficiently requiring minimum ventilatory support. Extubation was successful on first attempt. Repeated blood cultures obtained throughout her course were found to be negative. Her course after extubation was uneventful.

### 3. Discussion

Oral mucositis (OM) is a common adverse event in patients receiving chemotherapy. Its clinical manifestation ranges from mild erythema and soreness to extreme pain and ulceration, significantly affecting patient's quality of life<sup>3</sup>. Specific drug therapy has been associated with an increased risk of developing mucositis; etoposide is excreted in the saliva which increases its oral toxicity<sup>1</sup>. In rare cases, severe OM can result in significant edema of the upper airway leading to airway obstruction<sup>4</sup>.

Pediatric patients are more prone to develop OM with increased severity<sup>5</sup>. Its prevalence is reported to exceed 90% among children under 12 years old receiving chemotherapy for hematological malignancies compared with 40% in the adult counterparts<sup>1</sup>. This has been attributed to the greater number of mitoses in the basal epithelium in younger patients, making the epithelial cells more vulnerable to cytotoxic effects<sup>6</sup>. The duration of OM in the pediatric population tends to be shorter reflecting their greater healing capacity<sup>6</sup>.

Pediatric patients with severe OM are at greater risk of airway compromise due to their narrower airway<sup>6</sup>. The exact prevalence of upper airway complications in the pediatric patients following chemotherapy is unknown. One study reported that 10.5% of the pediatric patients following bone marrow transplantation required mechanical ventilation, of which upper airway obstruction due to mucositis accounted for 13%<sup>7</sup>.

Typically, OM develops 10-14 days after initiation of chemotherapy and heals within 2-4 weeks, consistent with the clinical course of neutropenia<sup>8</sup>. Neutropenia has been reported to play a key role in the development of OM. Severity of OM is associated with the degree of neutropenia, and resolution coincides with granulocyte recovery<sup>8</sup>. This is assumed to be a result of neutropenia leading to impaired mucosal defence and repair<sup>8</sup>.

Management of OM is crucial as it provides a portal for potentially life-threatening infection<sup>8</sup>. Previous studies have shown that the risk of infection increases with increasing grade of OM<sup>8</sup>. As most patients with OM develop neutropenic fever, broad spectrum beta-lactam with combination of antifungal and antiviral agents is commonly used as a standard treatment to cover gram-negative bacteria, *Coagulase-negative Streptococci*, *Streptococcus viridans*, *Candida albicans* and *Herpes simplex*<sup>6, 9, 10</sup>. However, fever remains unexplained in 30-50% of neutropenic patients with no evidence of infection<sup>11</sup>. Furthermore, fever persists for 4-5 days or even longer in approximately 30% of cases despite adequate microbial treatment directed at bacteria and fungi<sup>11</sup>. In these cases, fever may not be necessarily related to infection and may be a manifestation of the inflammatory process contributed by the mucositis itself<sup>9, 11</sup>. In a report examining patients receiving chemotherapy for treatment of acute leukemia, inflammation was shown to be correlated with the occurrence of mucositis. The inflammatory response is elicited by formation of reactive oxygen species due to DNA damage of the epithelial cells, followed by amplification of proinflammatory and inflammatory cytokine release triggered by various microbial motifs (Pathogen-associated molecular patterns) released from invading microorganisms and damaged tissues (Damage-associated molecular patterns) through the distorted mucosal barrier, manifesting systemic fever and further tissue damage<sup>11</sup>.

In the current case, the patient remained febrile despite treatment with broad spectrum antibiotics, antifungal and antiviral agents lacking evidence of infection. Regarding her prompt defervescence coinciding with recovery of mucositis, her fever may have been a manifestation of the inflammation of mucositis, irrelevant of infection. Currently no guideline is provided regarding the use of G-CSF on mucositis due to insufficient evidence<sup>12</sup>. Yet, the possibility of infection could not be discarded in this circumstance and treatment with broad-spectrum antimicrobials combined with G-CSF was continued.

In the current case, the patient was successfully extubated following recovery of mucositis but required

prolonged mechanical ventilation. Determination whether to perform tracheostomy in this case was difficult considering its completely reversible pathology.

Airway management with intubation possesses a significant risk of complete airway obstruction and death in case of accidental extubation, mandating deep sedation (paralysis may be considered) and prolonged mechanical ventilation which significantly delays patient recovery.

Placement of a tracheostomy provides a secure airway and enables safe management of the patient with further advantages of improved patient comfort, reduced sedative requirements and early patient recovery. Although surgical tracheostomy in the presence of severe immunosuppression and thrombocytopenia is not a contraindication, it may be associated with increased risk of surgical complications. Studies regarding this topic are scarce, especially in the pediatric population and do not support a recommendation<sup>13-15</sup>.

Thus, airway management in these patients must be determined prudently regarding the expected duration of neutropenia, weighting the risks and benefits on an individual case basis.

#### **4. Conclusion**

Pediatric patients undergoing chemotherapy may require intubation and mechanical ventilation due to airway compromise as a complication. The clinical course of oral mucositis is consistent with the course of neutropenia and may require prolonged intubation. Determination whether to perform tracheostomy in these circumstances is difficult due to the essentially reversible pathology of this complication. Thus, airway management of these patients should be determined on an individual case basis.

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#### **Disclosure**

None.

#### **Conflict of Interest**

The authors have no conflict of interest to declare.

#### **Author Contributions**

K.T. drafted and revised the initial manuscript; N.T., K.S., A.T., D.T., N.N., S.N. critically revised the manuscript for important intellectual content. All authors read and approved the final manuscript.

#### **Ethical approval**

Informed consent was obtained from the patient and her parents for publication of this case report. Approval of the institutional ethics committee was obtained in advance to submission.

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## Figure captions

Fig.1

Nasolaryngoscopy revealed significantly swollen, erythematous arytenoid cartilages with extensive desquamation.

