







# Therapeutic challenges of oral mucositis in pediatric oncology

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## ABSTRACT

Neuroblastoma (NB) is a neoplasia of the sympathetic nervous system and the second most common extracranial malignant solid tumor in childhood. In antineoplastic therapy, oral complications can be observed in antineoplastic therapy, among them oral mucositis (OM). It is an acute mucosa inflammation resulting from the toxicity of chemotherapy drugs. This case report emphasizes the management of OM and its influence on the systemic condition and quality of life. A female patient, nine years old, presented a recurrence of metastatic NB after first-line treatment. She was admitted to the hospital unit for oncological therapy in the pediatric oncology ward, complaining of severe pain in the oral cavity and oropharynx associated with severe febrile pancytopenia. On physical examination, she presented dysphagia and severe weight deficit, which weakened the swallowing of her saliva. According to the World Health Organization (WHO), the intraoral exam revealed third-grade OM lesions on the lips, anterior gum, and oropharynx. Treatment consisted of removing local debris, cleaning the oral cavity with 0.12% chlorhexidine, and using a flexible, sterile cotton swab, aiming for daily local microbial control. In addition, photobiomodulation (660 nm, 50 mW, 2 J/cm<sup>2</sup>, 90 seconds) was applied to the erythematous and hemorrhagic bed, punctually in the areas of the lesion and sweeps in the oropharynx region (interspersed sessions). Racealphatocopherol acetate (vitamin E) was prescribed for antioxidant action and lip hydration. Concomitant with mucositis, the patient had severe febrile pancytopenia, requiring cefepime 150 mg/kg/day, with previous collection of blood cultures, granulocyte colony-stimulating factor, fluconazole, hydration, and nutritional support. Blood cultures were negative. The consequences of mucositis contributed to malnutrition and worsened quality of life. It is concluded that the interdisciplinary dental intervention enabled physical and emotional restoration, enabling a better quality of life for the patient.

**Keywords:** Stomatitis, Chemotherapy, Oral hygiene, Low-intensity light therapy, Vitamin E, Mucositis.

## INTRODUCTION

In Brazil and developed countries, childhood cancer already represents the leading cause of death (8% of the total) due to disease in children and adolescents aged 1 to 19 years, according to the National Cancer Institute. A series of impasses are presented to the patient and his family at the time of diagnosis, seeing that this child or adolescent will face a treatment that involves many procedures<sup>1</sup>.

Neuroblastoma (NB) is a malignant neoplasia from the sympathetic nervous system that presents itself as one of the most common types of cancer with high mortality in infancy, in metastatic patients<sup>2</sup>. It corresponds to 8% to 10% of cases of neoplasms in children, with a prevalence of one case in every seven thousand live births<sup>1</sup>.

NB has a highly heterogeneous clinical behavior, as in babies with a localized or metastatic disease can spontaneously regress without intervention. On the other hand, children diagnosed over one-year-old may succumb to the disease after months or years of therapy<sup>3</sup>. The clinical characteristics are variable and nonspecific, making clinical recognition difficult, leading to late diagnosis<sup>4</sup>.

To improve prognosis, patient stratification strategies were created based on presenting features and the tumor biology (age, stage, histology, N-MYC gene amplification status, tumor cell ploidy, and segmental chromosomal abnormalities) to guide the intensity of treatment protocols. The goal has been to decrease the number of interventions for low-risk patients to avoid long-term complications while targeting and increasing therapies for high-risk patients

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to improve overall survival. In asymptomatic low-risk patients with an estimated survival rate greater than 98%, the treatment is usually complete surgical resection, although observation may be possible in IVS staging. In intermediate-risk patients, in whom estimated survival can reach above 90%, moderate chemotherapy, according to the patient's response, is required along with resection. High-risk patients undergo multiple cycles of chemotherapy before surgery, followed by consolidation with myeloablative autologous hematopoietic stem cell transplantation and local radiation, and finally immunotherapy with differentiation therapy as a maintenance phase<sup>3</sup>.

In antineoplastic chemotherapy, oral complications can be observed, affecting the treatment and causing septicemia in some cases<sup>5</sup>. Mucositis is an acute inflammation of the digestive mucosa resulting from the toxicity of chemotherapeutic drugs. Among its consequences, pain is an important complication due to its intensity and impact, especially on the quality of life<sup>6</sup>. The clinical manifestations include erythema, atrophy, and/or ulceration of the oral mucosa. It occurs in 20% to 80% of patients receiving chemotherapy<sup>7</sup>. However, it is possible to prevent oral mucositis (OM), maintaining good oral health and reducing infectious outbreaks, in addition to obtaining an early diagnosis and treating these oral complications, preventing the development of a more serious clinical course that can negatively affect the treatment of the individual. This result requires the presence of a dental surgeon in the multidisciplinary cancer treatment team<sup>6</sup>.

The present study aims to discuss OM through a case report, exposing its clinical aspects, symptomatology, and influences on communication and nutrition, as well as the worsening of the systemic condition and possible interference in antineoplastic therapy.

## CASE REPORT

A female patient, nine years old, presented early recurrence of abdominal, midline NB, metastatic at diagnosis to left supraclavicular lymph node and posterior mediastinal lymph node, with amplified NMYC, after first-line treatment. Admitted to the Hospital Instituto Oncológico de Juiz de Fora for oncological treatment in the pediatric oncology ward, complaining of high-intensity pain in the oral cavity and oropharynx and associated with severe febrile pancytopenia secondary to second-line chemotherapy due to chest recurrence, with a posterior mediastinal mass. Upon diagnosis

and reassessment of the recurrence, the patient's bone marrow biopsy was negative, and scintigraphy with Metaiodobenzylguanidine (MIBG) was detected only in the abdomen. After 13 days of antineoplastic therapy with carboplatin and etoposide, she developed severe pain in the oral cavity and oropharynx, requiring hospitalization due to mucositis and severe febrile pancytopenia. This work was approved by the Research Ethics Committee of the Federal University of Juiz de Fora – Juiz de Fora, Minas Gerais, Brazil.

On physical examination, she presented dysphagia and severe weight loss, which deprived the patient to the point of preventing her from swallowing her saliva. Intraoral examination revealed OM grade 3 lesions, according to the World Health Organization (WHO), on the lips, anterior gingiva, and oropharynx (Figure 1).

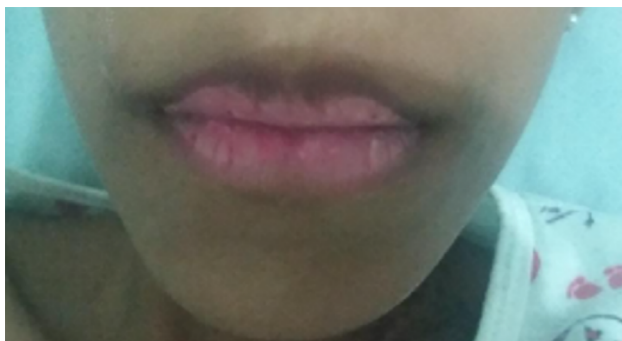
The case was discussed with the multidisciplinary team, and a treatment plan was established. It consisted of removing local debris under topical anesthesia with benzocaine. Hygiene of the oral cavity with chlorhexidine 0.12% using a flexible, sterile cotton swab adapted to perform gentle oral hygiene, aiming at local microbial control, daily. In addition, a photobiomodulation protocol (Photon Lase III-PL7336, DMC) was applied to the erythematous and hemorrhagic lesion at a 90° angle with the labial contact surface (660 nm, 50 mW, 2 J/cm<sup>2</sup>, 90 seconds) punctually in the areas of the lesion and in sweeping in the oropharynx region. The sessions were held on alternate days, from the initial evaluation, totaling 04 sessions. Racealphotocopherol acetate (vitamin E) was prescribed for antioxidant action and lip hydration (Figure 2). The mucositis presented by the patient caused a lot of pain and difficulty in swallowing, contributing to malnutrition and worsening the quality of life.

Concomitant to the mucositis, the patient had severe febrile pancytopenia with a white blood cell count of 100, hemoglobin 8.9 g/dL, and platelets 50,000/mm<sup>3</sup>, requiring the use of cefepime 150 mg/kg/day, administered every 8 hours with the prior collection of blood cultures, as well as the use of granulocyte colony-stimulating factor, Fluconazole, Filgrastim, hydration, and nutritional support. Blood cultures were negative. After seven days, there was total remission of the lesion and also physical and emotional restoration of the patient. There was no recurrence of oral mucositis (Figure 3). In this case, the patient was diagnosed with metastatic Neuroblastoma, at the age of nine, with amplification

of NMYC, five months after the recurrence, and thirteen months after the diagnosis, the patient died,



**Figure 1.** Clinical aspect in the initial evaluation, hemorrhagic crusted lesion on both lips.



**Figure 2.** Clinical aspect after four days of dental care. There is a lesion size reduction and an improvement in the appearance of the labial tissue.



**Figure 3.** Clinical aspect after 15 days of the beginning of dental care, with complete recovery of lip tissue.

due to the severity of the case, despite the cancer therapy for the high risk.

## DISCUSSION:

This case report addresses an important aspect of the multidisciplinary care of a patient undergoing antineoplastic therapy. Intraoral examination revealed extensive OM lesions on the lips, anterior gingiva, and oropharynx, preventing essential functions such as speaking, eating, and swallowing. It is known that OM is one of the main reactions due to toxicity secondary to chemotherapy, which manifests as erythematous, erosive, ulcerative, painful, and disabling lesions<sup>6-9</sup>. In addition to disabling speech, the patient had drooling associated with odynophagia. Healthy individuals have an unstimulated salivary flow of 0.22-0.82 mL/min<sup>10</sup>, therefore, the patient had an accumulation of approximately 31.2 mL/h of saliva in the oral cavity, causing intense discomfort.

An important element of this study is to demonstrate the importance of the dental approach in resonance with the entire team of professionals involved in patient care. The oral lesion, when suppressing the ability to eat, worsens the nutritional status and worsens the prognosis of the systemic disease<sup>11</sup>. Likewise, depriving speech impacts social and emotional aspects<sup>12</sup>. Thus, the presented therapeutic challenge aimed to reestablish the biopsychosocial balance through specific dental care.

The patient was diagnosed with OM grade 3 lesions by the presence of ulcers and ingestion ability of only liquid foods. The severity of OM can be classified clinically using several grading systems; however, the most used classification is the one

recommended by the WHO, which describes toxicities in patients undergoing chemotherapy, according to erythema and ulceration, pain, and swallowing ability<sup>13</sup>.

Along with oral lesions, dysphagia and severe weight loss were observed. One of the consequences of OM is pain<sup>6,14</sup>. Oral complications of antineoplastic therapy, such as dry mouth, dysphagia, and taste alteration, are also associated with a negative impact on nutrition and quality of life. Furthermore, in immunocompromised children, ulcerated lesions can be a gateway for microorganisms, leading to opportunistic infections and systemic dissemination<sup>8</sup>.

As for the chemotherapy protocol followed in the reported case, the use of Etoposide (group of plant-derived podophyllotoxins) and Carboplatin (group of alkylating agents) predisposed the appearance of OM, given the cytotoxic potential of these drugs<sup>15</sup>. Lesions develop as chemotherapeutic agents attack the rapidly dividing cells of the oral mucosa membrane. This destruction causes adverse effects, which vary according to dose, chemotherapy regimen, and patient susceptibility<sup>15,16</sup>.

For OM treatment, some monitoring possibilities are available, such as topical application of anesthetics, coating agents, cryotherapy, low-intensity laser therapy, pharmacological methods such as growth factors, vitamin supplementation, and an adequate diet<sup>9</sup>. In the present study, the therapeutic measures were control of oral hygiene, photobiomodulation, and prescription of vitamin E, which allowed total remission of the lesions after 7 days. The patient recovered the global white blood cell count after 28 days of treatment and hospital support, reaching a global white blood cell count of 3300 leukocytes per mm<sup>3</sup> and 55% neutrophils. Until the 19th day of hospitalization, she still had a global leukocyte count of 500 leukocytes/mm<sup>3</sup>, which reinforced the importance of dental therapy, with mucosal rehabilitation on the seventh day of hospitalization.

Local microbial control initially consisted of removing debris and cleaning the oral cavity with 0.12% chlorhexidine and a flexible, sterile cotton swab daily. Considering the severity of OM and its painful condition, brushing can become very uncomfortable, therefore, the chlorhexidine solution proves to be effective<sup>14</sup>. Adequate oral hygiene is recommended to reduce bacterial accumulation, prevent infections and provide comfort<sup>17</sup>.

Photobiomodulation was used in the present study from the initial evaluation, where the sessions

were held on alternate days. The results are consistent with the literature, which describes laser therapy as a promising therapeutic strategy whose efficacy is based on its analgesic, anti-inflammatory, and healing properties<sup>6</sup>. Such characteristics contributed to the remission of the lesions and their symptoms. The laser acts on cellular enzymes that would increase the oxidative chain mechanism in mitochondria (cellular power), which increases the production of adenosine triphosphate (ATP), producing intracellular reactive oxygen species<sup>8</sup>.

Targeting antioxidant action and hydration of the lips, vitamin E was prescribed because studies show benefits, such as preventing tissue damage, contributing to cell regeneration, generating an epithelialization effect on the mucosa, repairing the skin, protecting cells from oxidative stress, and strengthening the immune system<sup>18</sup>.

The medical team chose to prescribe antibiotic therapy with cefepime 150 mg/kg/day, administered every 8 hours, associated with fluconazole and granulocyte colony-stimulating factor, having previously initiated the dental procedure and maintained it for 10 days. Cefepime is a fourth-generation cephalosporin that belongs to a class of antibiotics known as beta-lactams indicated in the treatment of gram-positive and gram-negative bacterial infections<sup>19</sup>, with activity against *Pseudomonas aeruginosa* and first line in the treatment for severe febrile neutropenia. Patients undergoing chemotherapy with a nutritional deficit are at increased risk of bacteremia<sup>20</sup>.

Therefore, it should be noted that, in the face of a condition that affects the general condition of a critically ill patient, the great challenge is to find, in agreement with the multidisciplinary team, the most effective approach based on scientific evidence. Especially in the face of a severe illness process, well-being and pain relief restore dignity to the patient<sup>12</sup>. Thus, the motivation was to demonstrate that, through specific care, the local and systemic recovery of the patient is possible, contributing to their quality of life.

## CONCLUSION

This case discussed therapeutic measures that associated control of oral hygiene, photobiomodulation, and topical application of vitamin E to manage grade 3 oral mucositis in a pediatric oncology patient, which proved to be effective, acting in an analgesic, anti-inflammatory, and biomodulating way. The

interdisciplinary dental intervention enabled the remission of the lesion, restoration of the patient's quality of life, and control of the side effects of chemotherapy.

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