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Severe oral infection caused by *Pseudomonas aeruginosa* effectively treated with methylene blue-mediated photodynamic inactivation

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ABSTRACT

P. aeruginosa is a gram-negative bacterium present in nosocomial infections with high morbidity and mortality. This microorganism is frequently resistant to antibiotics, leading to clinical complications. In the present report, we described a clinical case of a patient with severe oral lesions caused by *P. aeruginosa*, which was refractory to antibiotics treatment and presented positive clinical outcomes after some sessions of antimicrobial photodynamic inactivation (API) mediated by methylene blue dye. We discuss the potential of API for *P. aeruginosa* refractory infections and possible resistance mechanisms of this microorganism to different API protocols.

1. Introduction

Pseudomonas aeruginosa is a Gram-negative bacterium commonly observed in nosocomial infections, associated with high morbidity and mortality. The treatment of these infections has become a challenge because this pathogen has a great ability to develop antibiotics resistance, mainly against, quinolones, and β-lactams. Antimicrobial photodynamic inactivation (API) for *P. aeruginosa* has been indicated for some localized infections. In general, the antimicrobial photodynamic protocols include several photosensitizers combined with nanoparticles and other substances, to enhance the bactericidal effect. The outcomes of these therapies are rarely described clinically. Herein, we present a clinical case of an oncologic patient with severe oral infection of *P. aeruginosa* treated with API using a routine protocol with methylene blue dye and red light.

2. Case report

In February 2018, a 37-year-old female patient, under chemotherapy for a recurrent colon adenocarcinoma, reported an intense oral pain and difficulties for mastication and swallowing after four cycles of folinic acid, fluorouracil, and irinotecan. During the previous month, she underwent a subtotal colectomy and terminal ileostomy due to an important colonic occlusion and distension secondary to the tumor recurrence. An intraoral exam revealed multiple and extensive necrotic areas in the gingiva of the upper and lower alveolar ridge. Intense erythema and edema were also noted in the entire oral mucosa (Fig. 1A). Neutrophils count (11,573 cells/mm^3) and serum reactive C protein (PCR) value (364 mg/L) were high. The patient had severe body weight loss. Clinical and laboratory exams suggested an oral bacterial infection. Microbiological culture of oral lesions and central venous catheter confirmed the presence of *P. aeruginosa*. A biopsy in the oral cavity revealed an intense suppurative inflammatory process, with epithelial erosion and necrosis. The antibiogram of the catheter samples revealed susceptibility to amikacin, cefepime, ceftazidime, ciprofloxacin, gentamicin, imipenem, meropenem, and tobramycin. Endovenous cefepime (2000 mg/8 h), vancomycin (1000 mg/12 h), and anidulafungin (100 mg/day) were immediately initiated, the central catheter was removed, and the chemotherapy was discontinued. Mouthwash with a non-alcoholic solution of chlorhexidine 0.12% was also prescribed. After 4 days of the antibiotic treatment, the patient exhibited a significative reduction on the serum PCR (13.3 mg/L), suggesting that the infection was controlled. In the oral cavity, the pain had reduced, but the lesions did not exhibit a positive outcome (Fig. 1B). On the contrary, discrete mobility of the lower central incisors was noted. An orthopantomography exam revealed mild bone resorption in the incisor region. Due to the severity of the oral lesions, surgical intervention for removing the necrotic debris was considered. However, facing the high risk for gingival retraction after the surgical debridement, it was decided to initiate an API using an aqueous solution of methylene blue dye (0.01%) (Chimiolux 10, DMC, Sao Carlos, Brazil), incubated directly in the oral mucosa for 5 min, followed by

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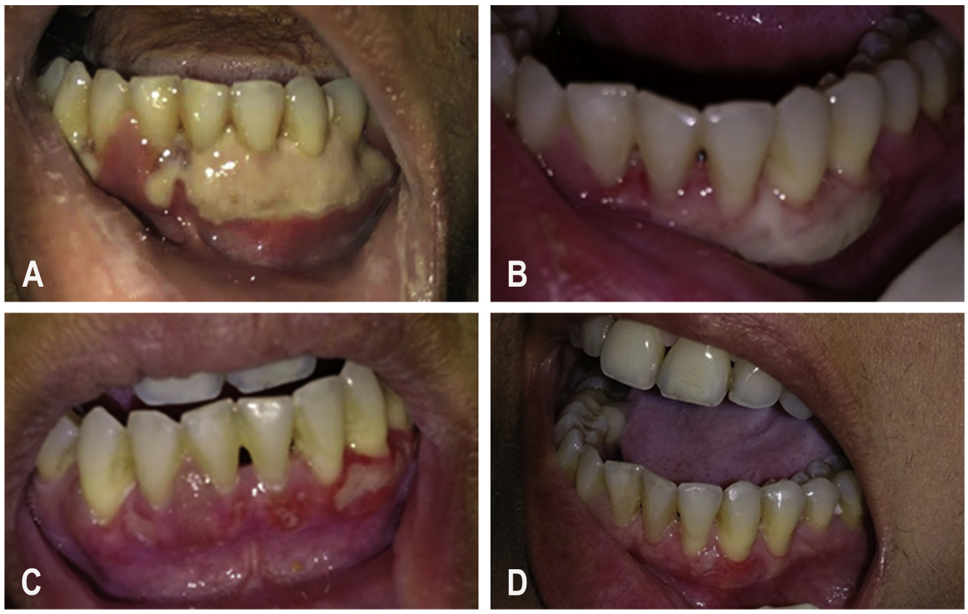

Fig. 1. Intraoral aspect of the lesions induced by *P. aeruginosa* infection. A: Extensive ulcerative and necrotic areas in the oral mucosa of the lower alveolar ridge. B: Maintenance of necrotic areas in the gingiva after 4 days of systemic antibiotic therapy and oral rinses with chlorhexidine. Gingival retraction and lower central incisor mobility were also presented. C: After 2 weeks of antimicrobial photodynamic inactivation (API) with methylene blue dye and red light. The lesions exhibited an advanced healing process. D: After 3 weeks of API, the lesions had a complete remission. A mild gingival retraction was presented, but the central incisor recovered its original attachment.

low-level laser irradiation (660 ± 10 nm, 100 mW, 80 s, 0.04 cm^2 spot area, 8 J, sweep mode) applied in all of the necrotic and ulcerative areas. One daily session of API was performed for six consecutive days, as an adjuvant treatment for systemic antibiotics (Fig. 1C). The patient re-started the chemotherapy after 10 days of antibiotic therapy. At this period, the API was performed on alternate days, associated to low-level laser therapy (660 nm ± 10 nm, 100 mW, 10 s, 0.04 cm^2 spot area, continuous mode, 1 J per point) for prevention of oral mucositis derived from the chemotherapy. The oral infection showed complete remission, and the marginal gingiva recovered its original anatomy, with a minimal retraction (Fig. 1D). There were no side effects derived from the API. Unfortunately, after completing chemotherapy, the patient died due to the tumor recurrence without any sign of infection.

3. Discussion

The oral cavity can be a reservoir for *P. aeruginosa* in debilitated patients, mainly in those hospitalized in intensive care units and exposed to invasive procedures (e.g., catheters and devices for mechanic ventilation). Patients with chronic diseases, such as chronic renal disease [1] and cystic fibrosis [2], are also exposed to a high risk of *P. aeruginosa* oral infection. Although with lower frequency, chemotherapy-derived neutropenia, disruption of mucosa barrier (mainly due to mucositis), the presence of surgical wounds, and nutritional imbalance are also risk factors for *P. aeruginosa* dissemination [3]. Loss of mucosal barrier integrity and surgical wounds can induce a gastrointestinal *P. aeruginosa* translocation to extraluminal sites, originating severe infections in other sites [4]. 5-FU, capecitabine, cyclophosphamide, ifosfamide, cisplatin, carboplatin, and taxanes are some chemotherapy agents that cause intestinal mucositis [3] and can be related to *P. aeruginosa* infection. During the chemotherapy, our patient exhibited a severe body weight loss, suggesting a nutritional imbalance. As she did not have important neutropenia during this period, the oral infection was attributed to the intestinal resection and the nutritional disturbances.

Multiple mucoid and non-mucoid *P. aeruginosa* strains, with distinct antibiotic susceptibilities, have been described in the oral cavity [2]. In these cases, osteomyelitis and loss of dental attachment can be presented, leading to a non-conservative surgical intervention that can culminate in gingiva, bone, and tooth losses [1].

In the present case, although the antibiogram of samples obtained from the catheter did not indicate resistance to the tested antibiotics, we noted that the oral lesions did not respond adequately to the systemic antibiotics. It seems likely that the presence of heterogenous *P. aeruginosa* strains in the oral cavity [2], which can differ from those localized in the catheter and other sites of the body, contributed to the persistence of the oral lesions. Based on the clinical outcomes in the oral cavity, we decided to adopt API as a topical adjuvant treatment, which promoted the healing of the oral lesions after multiple consecutive sessions.

Other clinical reports showed the efficacy of API for the eradication of *P. aeruginosa*. APIs mediated by ALA [5] and methylene blue dye [6] had a high bactericidal effect and promoted healing of chronic skin ulcers infected by *P. aeruginosa*. On the other hand, some *in vitro* studies have shown that methylene blue-mediated API can induce the selection of persistent *P. aeruginosa* subpopulation (surviving cells after the API, but without resistance to antimicrobials) [7], and modification of efflux-pump expression on the *P. aeruginosa* outer membrane [8]. Although more *in vitro* and clinical studies need to be conducted, these facts might interfere with the methylene blue-mediated API efficacy.

In summary, the API protocol adopted in this clinical report, as an adjuvant treatment to the systemic antibiotics, eliminated *P. aeruginosa* infection in the oral cavity and avoided invasive interventions. More clinical studies should be conducted to confirm the API efficacy for *P. aeruginosa* eradication, and to establish the ideal protocol for immunosuppressed patients.

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