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CASE REPORT

Acute necrotizing ulcerative gingivitis associated with *Stenotrophomonas Maltophilia*, a case report

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Abstract:

The aim of this study was to report a case of Acute Necrotizing Ulcerative Gingivitis (ANUG) related to chemotherapy toxicity and infection by Stenotrophomonas maltophilia bacterium, until then only one case of ANUG associated with this bacterium has been described in the literature. Female patient, 20 years old, diagnosed with poorly differentiated neuroendocrine carcinoma, undetermined primary site, was treated with etoposide and cisplatin. She presented halitosis, desquamative necrotic gingival tissue, with pseudomembrane formation compatible with ANUG related to chemotherapy toxicity and infection by Stenotrophomonas maltophilia bacterium. The Standard Operational Protocol for Oral Care (Oral SOP) adapted by VIDAL, AKL (2012), with topical application of oral sodium bicarbonate solution, 0.12% chlorhexidine digluconate, and hydrogen peroxide 10 volumes diluted with water, presenting tissue recovery. Early diagnosis and appropriate treatment with a multiprofessional team are decisive measures in the prognosis of pathogen infection and in the patient's quality of life.

Keywords: Dental care, Gingivitis, Necrotizing Ulcerative Stenotrophomonas maltophilia, Immunocompromised host.

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INTRODUCION

The emergence of new microorganisms resistant to multiple drugs, the increase in nosocomial infections, and the morbidity and mortality of these infections emphasize the importance of monitoring and controlling these microorganisms. Infections acquired in the hospital are associated with worse outcomes, with high mortality rates, and longer stay in the intensive care unit (ICU) and in the hospital[1].

Stenotrophomonas maltophilia, an aerobic gram-negative bacillus, present in the environment, is a multidrug-resistant opportunistic pathogen that often causes nosocomial infections in immunosuppressed or immunocompromised patients. *S. maltophilia* is not a highly virulent pathogen, but has emerged as an important nosocomial pathogen associated with high mortality rates[2].

This bacterium can cause serious infections, including pneumonia, bloodstream infections, endocarditis, meningitis, mucocutaneous and soft tissue infections, and septemias[3-5]. Risk factors for *S. maltophilia* infection include underlying malignancy, presence of internal devices, chronic respiratory disease, immunocompromised host, prior use of antibiotics, and prolonged hospitalization[6,7].

Acute necrotizing Ulcerative Gingivitis (ANUG) acquired different names over time, "ulceromembranous gingivitis", "gingivitis of Vincent", "trench mouth", and lastly known as necrotizing ulcerative gingivitis, it is characterized by necrosis and ulceration of the interproximal papillae with pseudomembrane formation, pain, bleeding, sudden onset, fetid odor, elevated body temperature, malaise, and metallic taste. The surfaces of the lesions are covered with a gray or grayish-yellow pseudomembrane that is easily removed leaving an ulcerated surface. In severe cases, it may spread to periodontal support tissues, leading to necrotizing ulcerative periodontitis[8].

The etiology of GUN is complex, it is an opportunistic bacterial infection which is predominantly associated with spirochetes, however some predisposing factors are associated with GUN, such as poor oral hygiene, smoking, immunocompromised patients, underlying disease, emotional stress or fatigue[8,9].

The most common predisposing factors for necrotizing periodontal diseases are those that alter the host immune response, although usually more than one factor is necessary for initiating the disease. Systemic conditions that have shown a positive association with necrotizing periodontal diseases include infection with HIV or with diseases affecting leukocytes, chemotherapy, malnutrition, measles, chickenpox, tuberculosis, herpetic gingiva-stomatitis, malaria, or diabetes[10].

The treatment is based on the treatment of the acute phase; treatment of the preexisting condition and corrective treatment of the disease sequelae; supportive or maintenance phase. The treatment of the acute phase can be performed through a careful superficial debridement, use chemical plaque-control formulations, such as chlorhexidine-based mouth rinses (0.12%, twice daily), 3% hydrogen peroxide diluted 1:1 in warm water, and other oxygen releasing agents, which not only contribute to the mechanical cleaning of the lesions but also provide the antibacterial effect of oxygen against anaerobes[10]. Another modality of treatment that releases highly reactive cytotoxic oxygen, is photodynamic therapy (PDT), which assists in the process of bacterial cell death[11].

The objective of this study was to report a case of Acute Necrotizing Ulcerative Gingivitis (ANUG) related to chemotherapy toxicity and *Stenotrophomonas maltophilia* infection in a patient with poorly differentiated neuroendocrine carcinoma of an undetermined primary site. The patient signed the Informed Consent Form (07264818.7.0000.5207), consenting to the disclosure of his case and information for academic, scientific purposes.

In this case report it is possible to identify the need to favor access to dental procedures, as well as the multidisciplinary and integral care to hospitalized patients in order to make available to the patient the benefits of health-promoting dentistry.

CASE REPORT

Female patient, 20 years old, single, melanoderma, was admitted to the Ovídio Montenegro Pavilion at the Oswaldo Cruz University Hospital of the University of Pernambuco (POM/HUOC/UPE), in April 2019, with symptoms of greenish and bitter vomiting, associated with loss of appetite, loss of 30 kg in 7 months, greenish stools and urine with occasional bloodshed. In addition to episodes of fever and pain in the right hypochondrium radiating to the back, which cease with the use of tramadol. It had positive epidemiology for schistosomiasis, negative for Chagas and leishmaniasis, denies smoking, former alcoholic, neonatal jaundice due to blood incompatibility with maternal blood.

Total abdomen ultrasound was performed in February 2019, which showed enlarged liver, with

multiple images of heterogeneous texture, the largest were 16.4 x 15 cm occupying the left lobe, the entire epigastric region, extending to the left hypochondrium and the other 22 x 14.2 cm located in segments VI, VII and VIII. Chest X-ray performed on March 2019 found no changes.

Contrast-enhanced upper abdominal computed tomography was performed in April 2019, which showed regular contoured liver, sharp volumetric increase by several heterogeneous nodular formations with areas of necrosis inside, with poorly delimited contours, the largest in the left lobe 16 x 13 cm and the right lobe 14 x 12 cm, undetermined.

A biopsy was performed in May, whose pathological report showed poorly differentiated carcinoma, with possibilities of hepatoblastoma and neuroendocrine carcinoma. Immunohistochemistry was requested, whose report showed poorly differentiated neuroendocrine carcinoma, undetermined primary site.

RCCS was referred to the Oncology Center (CEON) at the Oswaldo Cruz University Hospital to conduct a palliative chemotherapy in the face of advancing staging (stage IV). Chemotherapy was started in June 2019, with Etoposide 100 mg/m² and cisplatin 25 mg/m², at 28-day intervals, after first cycle patient was discharged. The Standard Operational Protocol for Oral Care (Oral SOP) adapted by VIDAL, AKL (2012)[8] was instituted from the first day of chemotherapy, preventively, using a toothbrush with small head and soft bristles, non-abrasive toothpaste, mouthwash with sodium bicarbonate oral solution (8/8h), mouthwash with 0.12% chlorhexidine digluconate (12/12h) and mouthwash with oral nystatin solution (100,000 IU) four times daily.

However, after 13 days, the patient was admitted to the Intensive Care Unit (ICU) of the Oswaldo Cruz University Hospital, with worsening of the general condition, presenting asthenia, bleeding and gingival bruising. Admission examinations showed thrombocytopenia (12.000), neutrophilia, impaired renal function (urea level: 244 mg/dL) and liver function (direct bilirubin levels: 6.4mg/dL; aspartate transaminase levels: 54U/L), in addition to of jaundice and fever episodes.

Blood cultures showed *Escherichia coli*, and urine culture was negative. Meropenem and vancomycin antibiotic therapy and acyclovir were started. Platelet infusion and hemodialysis were performed. RCCS remained under intensive care for 6 days, and after improvement of renal failure, she was discharged from the ICU and was referred to the Oncology Center of the Oswaldo Cruz University Hospital ward for continued treatment.

On the second day of admission to the oncology ward, after discharge from the ICU, the intraoral clinical examination showed halitosis, desquamative necrotic gingival tissue with pseudomembrane formation compatible with acute necrotizing ulcerative gingivitis (ANUG), as well as ulcerative areas in the upper and lower vestibule and lower lip (Figures 1, 2).

Oral cavity swab was performed on the same day of injury identification, to research and analyze bacterial or fungal infections that could be associated with ulcerative

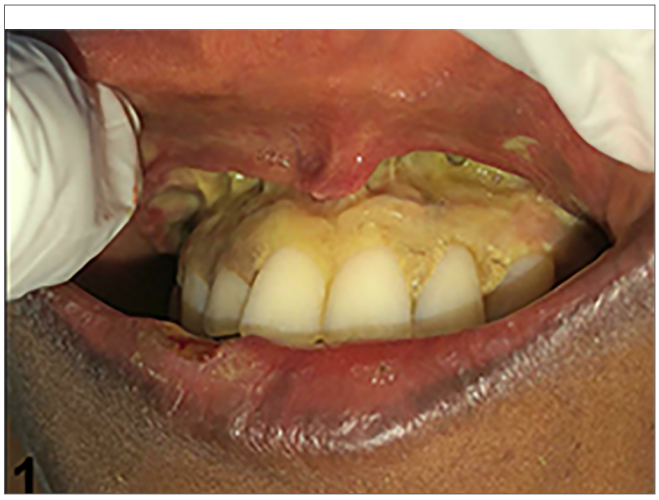

Figure 1. Intraoral clinical appearance showing acute necrotizing ulcerative gingivitis (ANUG) related to chemotherapy toxicity and S. maltophilia infection. Ulcerated tissue, desquamative necrotic, presence of pseudomembrane in upper gum and vestibule of mouth.

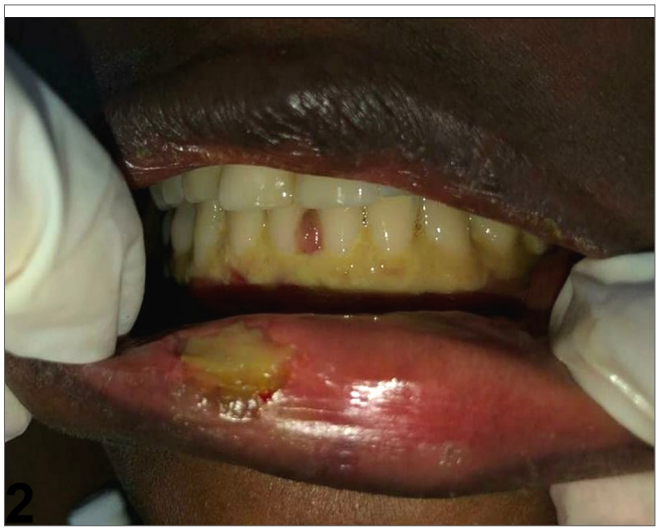

Figure 2. Intraoral clinical appearance showing acute necrotizing ulcerative gingivitis (ANUG) related to chemotherapy toxicity and S. maltophilia infection. Ulcerated tissue, desquamative necrotic, presence of pseudomembrane in lower gum and lip.

gingivitis. Oral care was initiated immediately in the bed of cancer ward of the Oncology Center, with changes in the oral care protocol (SOP - Oral)[8]: topical application of oral sodium bicarbonate solution (8/8h), 0.12% chlorhexidine digluconate (12/12h), and hydrogen peroxide 10 volumes (12/12h) diluted with water. Due to permanence of fever, polymyxin b and fluconazole were started. The oral swab result was released after 7 days of collection, and identified only the presence of *Stenotrophomonas maltophilia* bacteria, as well as its antibiotic resistance, and precautionary contact measures were instituted, but there was no change in the medication protocol.

The patient presented a drop in her general state after 12 days of discharge from the ICU, presenting Performance Status grade 4 on the functional capacity scale (Zubrod scale). Palliative sedation with morphine, continuous infusion, was instituted to control symptoms. Regarding ANUG, the patient presented significant improvement, with the presence of tissue renewal and significant reduction of necrotic areas 15 days after the beginning of oral care with topical application of oral sodium bicarbonate solution (8/8h), 0.12% chlorhexidine digluconate (12/12h), and hydrogen peroxide 10 volumes (12/12h) diluted with water (Figure 3, 4). Patient died 15 days after sedation with morphine, continuous infusion.

DISCUSSION

Treatment of neuroendocrine carcinoma using chemotherapy usually incorporates a combination of a platinum and etoposide compound[12]. Platinum-based chemotherapy is a first-line standard therapy for various cancers. However, the adverse effects of cisplatin, such as nausea, vomiting, myelosuppression, renal failure,

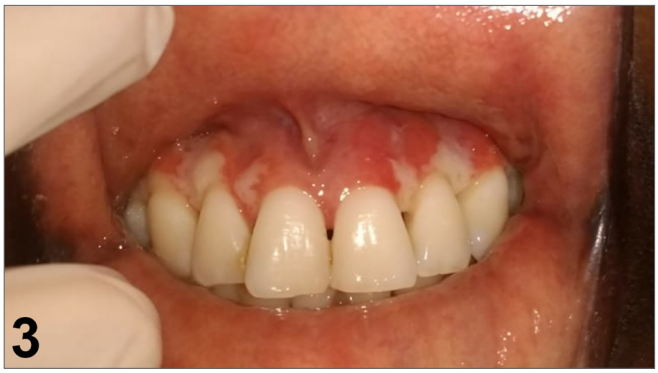

Figure 3. Intraoral clinical appearance after 17 days of the Standard Operational Protocol for Oral Care (Oral SOP). Upper arch gingival tissue with large area of tissue repair.

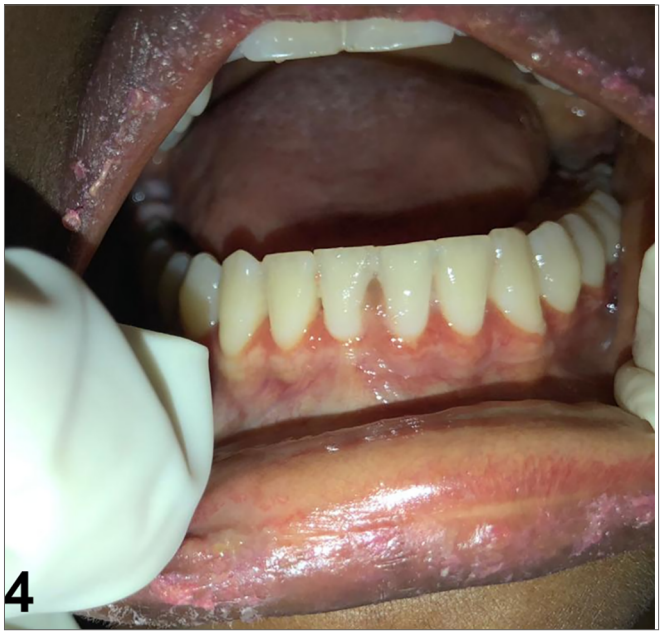

Figure 4. Intraoral clinical appearance after 17 days of the Standard Operational Protocol for Oral Care (Oral SOP). The lower arch complete tissue repair occurred, as well as in the lower lip.

transient elevations of liver and bilirubin enzymes may be severe and require hospitalization[13,14].

Similarly, etoposide may cause myelosuppression, nausea, vomiting, allergic reactions, hepatotoxicity (increase in serum bilirubin levels and concentrations of aspartate transaminase and alkaline phosphatase) and nephrotoxicity, manifested by increased urea levels and hyperuricemia[15]. In the reported case, the patient presented these high rates, characterizing a severe toxicity to etoposide and cisplatin chemotherapy.

Acute necrotizing ulcerative gingivitis (ANUG) is characterized by painful ulceration of the gingival surfaces, covered by pseudomembrane and necrotic tissue. There may be bleeding, foul odor, metallic taste, fever and lymphadenopathy. Immunosuppression is cited as a primary risk factor for its development and may be directly related to poor nutrition, decreased T lymphocyte count, psychological stress, poor oral hygiene, or smoking[16,17]. ANUG case has been reported in the literature associated with immunosuppression caused by the combination of etoposide and cisplatin chemotherapy, with complete healing after 6 weeks[17].

S. maltophilia has emerged as a significant cause of morbidity and mortality in hospitalized patients, causing bacteremia and other serious infections, including pneumonia, meningitis, mucocutaneous infections and others[18]. One study observed that only

10% of *S. maltophilia* infections affected skin and soft tissue lesions[19].

Skin lesions manifest mainly in the form of metastatic cellulitis, primary cellulitis, gangrenous cellulitis, soft tissue necrosis and mucocutaneous ulcers, which may progress to septicemia[4,18,20,21]. Only eight cases were reported of *S. maltophilia* infection with lesions in the oral cavity and were characterized as infected ulcers in the gum, lip and oral mucosa[18,22,23]. Of these cases, only one reported by Miyairi (2005) showed the development of necrotizing ulcerative gingivitis caused by the bacterium *S. maltophilia* in an immunocompromised patient with prior chemotherapy[23].

The case presented in 2005 provides histopathological evidence of *S. maltophilia* infection in gingival tissue and suggests that these opportunistic bacteria may play a significant role in the pathogenesis of ANUG in immunocompromised patients[23]. Alteration of systemic immunity due to nutritional deficiency or chemotherapy, associated with changes in local immunity from viral infection or disruption of oral mucosa by cytotoxic chemotherapy, may allow selective growth of a variety of pathogenic bacteria.

This is the second reported case of ANUG associated with *S. maltophilia*, and adds to the results found in the previous study. RCCS presented necrotizing ulcerative areas, with pseudomembranes throughout the gingival tissue, in the vestibule and lower lip mucosa.

Studies have shown the occurrence of mucocutaneous *S. maltophilia* infection in patients with one or more underlying comorbidities, being the most frequent ones: cardiac, pulmonary diseases and malignancies. In addition, they had immunosuppression, usually associated with chemotherapy, and received one or more broad-spectrum antibiotics to control concomitant infections[18-20].

These studies corroborate the data found in the case report in view of immunosuppression resulting from chemotherapy and antibiotic therapy for previous treatment of bloodstream infection with meropenem, vancomycin, polymyxin B.

The treatment of *S. maltophilia* infection is controversial, but studies have found total resistance to imipenem, susceptibility rate of 57% for ciprofloxacin, 86% for moxalactam and 98% for trimethoprim / sulfamethoxazole. Thus, the drug of choice for the treatment of infections with this organism is trimethoprim / sulfamethoxazole[7,19,24]. RCCS remained under antibiotic therapy previously proposed for bloodstream infection, and no specific therapy was adopted due to its low Performance Status (grade 4).

Dental follow-up in the multidisciplinary oncology team helps to minimize and / or control the risk of cancer sequelae, such as infections that may hinder or prevent continuity of treatment, negatively impacting the patient's quality of life[25]. In conjunction with medical treatment, the oral topical care, with sodium bicarbonate solution, 0.12% chlorhexidine digluconate, and hydrogen peroxide, was able to recover oral mucosa with significant reduction of necrosis and pseudomembrane areas.

The present case contributes to increase the recognition of this organism as a potential oral pathogen in immunocompromised patients and to direct a more adequate diagnosis and treatment for these cases.

CONCLUSION

S. maltophilia infection, in the development of necrotizing ulcerative gingivitis, should be considered in immunocompromised patients and, especially, those receiving broad spectrum antimicrobial therapy. Early diagnosis and appropriate treatment with a multidisciplinary team, including oral care, are important measures in controlling the infection and improving the patient's quality of life.

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