CASE REPORT

ORAL PEMPHIGUS VULGARIS IN OLD WOMAN: CONDUCTS OF A CHALLENGING CASE

PÊNFIGO VULGAR ORAL EM IDOSA: CONDUTAS DE UM CASO DESAFIADOR

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Resumo

A doença pênfigo é uma enfermidade autoimune que dependendo do nível de acometimento epitelial, pode ser classificada em pênfigo vulgar, vegetante, eritematoso e foliáceo. Além desses, há também o denominado pênfigo paraneoplásico, que ocorre especialmente em casos que há vínculo a neoplasias malignas com destaque para os linfomas. Somente os tipos vulgar e vegetante podem afetar a mucosa oral, sendo o pênfigo vulgar o mais prevalente. O mecanismo fisiopatológico da doença é caracterizado pela ação de autoanticorpos contra as proteínas desmogleínas dos desmossomos encontrados nas células epiteliais, desencadeando assim, a formação de fendas intraepiteliais e bolhas. O manejo dos pacientes com pênfigo vulgar oral é bastante desafiador, especialmente em casos de indivíduos idosos e portadores de comorbidades. O presente trabalho objetiva discutir aspectos contemporâneos do pênfigo vulgar oral e elucidar o caso de uma idosa acometida pela doença, destacando toda a propedêutica utilizada no seu atendimento e o tratamento empregado, com o uso de corticoides sistêmicos e acompanhamento constante da condição da paciente, uma vez que o pênfigo vulgar é uma doença que não tem cura.

Palavras-chave: Pênfigo. Doenças Autoimunes. Mucosa Bucal.

Abstract

Pemphigus is an autoimmune disease that, depending on the level of epithelial involvement, can be classified into pemphigus vulgaris, vegetans, erythematosus and foliaceus. In addition to these, there is also the so-called paraneoplastic pemphigus, which occurs especially when there is a link to malignant neoplasms with emphasis on lymphomas. Only the vulgaris and vegetans types can affect the oral mucosa, with pemphigus vulgaris being the most prevalent one. The pathophysiological mechanism of the disease is characterized by the action of autoantibodies against the desmoglein proteins of the desmosomes found in the epithelial cells, thus triggering the formation of intraepithelial clefts and blisters. The management of patients with oral pemphigus vulgaris is quite challenging, especially in cases of older individuals and patients with comorbidities. This study discusses contemporary aspects of oral pemphigus vulgaris and elucidate the case of an old woman affected by the disease, highlighting all the propaedeutics used in her care and the treatment employed, with the use of systemic corticosteroids and constant follow-up of the patient's condition, since pemphigus vulgaris is a disease that has no cure.

Keywords: *Pemphigus. Autoimmune Diseases. Oral Mucosa.*

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INTRODUCTION

The term pemphigus has Greek origin and refers to the formation of intraepithelial blisters related to a group of autoimmune diseases that affects both the skin and mucosa of affected individuals (1). Pemphigus encompasses a range of variants, such as pemphigus vulgaris, vegetans, foliaceus and erythematosus (2). In addition to these, there is also the so-called paraneoplastic pemphigus that is associated with malignant neoplasms, especially lymphomas (3). Of the variants of pemphigus, the vulgaris and vegetans types are the only ones with oral manifestations, with pemphigus vulgaris being more frequent in the mouth (2). In this context, it is noteworthy that the oral cavity is the first place where the disease manifests and the last place where lesions disappear (4, 5).

The cause of pemphigus vulgaris is not fully known, and there are some medications associated with its appearance, such as antihypertensives, antibiotics and anticonvulsants (6-8). The pathophysiology of the disease involves a type II hypersensitivity reaction, in which autoantibodies act against antigens present in epithelial cell desmosomes, called desmogleins 1 and 3. As a consequence, an acanthosis process occurs, characterized by the separation of the spinous layer of the epithelium, with the formation of intraepithelial clefts (9,10). Pemphigus vulgaris manifests itself especially in patients aged 40 to 60 years, with some studies showing a slight predilection for women, although most studies suggest a balance between the sexes. Those descendent of Jews, from South Asia and the Mediterranean, seem to be more prone to the disease (9,11,12). Lesions on the oral mucosa and skin are seen, so that skin lesions manifest as vesicles or blisters that rupture rapidly, leaving an unprotected erythematosus area, mainly affecting the skin of the trunk (11,12). Ocular involvement is less frequent, manifesting as bilateral conjunctivitis. Other mucous membranes may be affected, such as the mucous membranes of the oropharynx, esophagus, genital, anal and conjunctival mucosa (13,14).

Lesions in the oral cavity of pemphigus vulgaris are the most common, presenting as irregular erosions or ulcers of various sizes and locations, which may cause dysphagia and body weight loss (1). Patients report pain and the previous occurrence of vesicles and blisters that are not normally possible to be identified during clinical examination, due to being very friable and thin, easily breaking and exposing the underlying tissue. Several sites of the mouth can be affected, especially the palate, labial mucosa, jugal mucosa, belly of the tongue and gums, which become sensitive to spicy foods, alcoholic beverages and extreme temperatures (15). The free gingival margin and the lateral edge of the tongue, due to constant brushing and friction, tend to have larger and more intensely symptomatic lesions. Ulcerations can have varying sizes and the Nikolsky's sign, although not pathognoconic of this disease is a useful test in the diagnosis and can be performed on both the skin and the oral mucosa (16).

Because it is a mucocutaneous disease characterized by the manifestation of vesicles and blisters, pemphigus vulgaris has a differential diagnosis with several other autoimmune diseases, such as mucous membrane pemphigoid, erythema multiforme, erosive lichen planus, recurrent aphthous ulcerations and others (17, 18). The diagnosis of the disease usually occurs by perilesional incisional biopsy in the mucosa, and direct immunofluorescence is considered the gold standard for diagnosis, with the marking of autoantibodies next to the desmosomes between epithelial cells (19). It is noteworthy that in the early stages of the disease, before suprabasilar separation and Tzanck cells occur, immunofluorescence may be the only diagnostic means of biopsy of the removed tissue. Optionally, indirect immunofluorescence can also be used in the diagnosis, with the identification of circulating autoantibodies in the patient's plasma (1,3). Generally speaking, microscopy of the biopsied perilesional tissue reveals an intraepithelial separation above the basal cell layer, characterizing intraepithelial clefts. Keratinocyte acantolysis is seen, in addition to floating Tzanck cells and an infiltrate of chronic inflammatory cells in the underlying connective tissue. Tzanck cells are characterized by having a polygonal shape, being rounded, with cytoplasm less visible around the nucleus (1).

The treatment for pemphigus vulgaris is complex and usually involves the use of corticosteroids, in addition to immunosuppressants and analgesics. For intraoral lesions, corticosteroids in manipulated orabase such as ointments should be encouraged. After the start of corticosteroid treatment in the 1950s, mortality levels decreased significantly from 5 to 10% (20-22). In the context of pemphigus vulgaris therapy, it is essential to emphasize the importance of periodic and frequent follow-up that professionals should have in order to limit the manifestations of the disease and at the same time minimize the side effects of drugs as much as possible (23-26). Therefore, considering the use of corticosteroids and immunosuppressants in a systemic way, blood pressure measurement, blood glucose and calcium levels, liver function, renal function and complete blood count are just some of the various parameters and types of care needed for patients who use these drugs continuously (4). Thus, a multidisciplinary team is essential in the management of these individuals, encouraging them to maintain a healthy life with the practice of frequent physical exercises and a balanced and healthy diet.

Given the above, this study presents a clinical case of an older patient affected by pemphigus vulgaris with oral manifestations, highlighting all the conducts involving the onset of the treatment, with the therapy implemented and the periodic proservation of the patient.

CASE REPORT

Patient E.P.L., female, leukoderma, 80 years old, showing a certain frailty, attended the Program of Specific Care for Dental Diseases (PROCEDE) of the School of Dentistry at the Federal University of Uberlândia (FOUFU) for the first time in November 2016, complaining of a lot of pain and burning in the mouth, especially the tongue, associated with great difficulty in eating and with approximately 2 months of duration. The patient showed a previous biopsy report performed on the tongue that was inconclusive, informing only "inflammatory reaction." The patient could not associate the advent of the lesions with any medication or different substance used and in the medical and family history collected, so there was nothing contributory to explain the appearance of the lesions. (Figure 1. A-B-C-D).

Intraoral examination showed that she was a total toothless patient with total upper and lower prostheses, with the presence of extensive erosions and ulcerations located mainly on the lateral edges and dorsum of the tongue, which was erythematosus, as can be seen in Figure 1-B. It also presented ulcerations in the tonsillian column and soft palate of the right side, anterior lip and lower lip mucosa (Figure 2. A-B-C-D). No lesions were identified on the skin or other mucous membranes of the body. In view of the clinical findings exposed, autoimmune diseases such as pemphigus vulgaris, erosive lichen planus, pemphigoid membranes or lupus erythema, in addition to pernicious anemia, were considered. Then, perilesional incisional biopsies were performed on the labial mucosa and tongue. The patient was instructed to improve her oral hygiene, avoid the ingestion of spicy and citrus foods, she was also referred to a clinical physician for evaluation and dismissal of lesions in other mucous membranes of the body. In the same session, blood pressure was measured with the patient showing to be normotensive, and the following laboratory tests were also requested: antinuclear factor, complete blood count, glycemia, various electrolytes, dyslipidemic evaluation, hepatic transaminases, vitamin B12 and prescribed mouthwash of betamethasone elixir 0.5mg/5ml, three times a day.

Upon returning, seven days after the initial appointment, her laboratory tests were analyzed showing non-reactive antinuclear factor and the other parameters within the normal range. In addition, the histological description showed areas of alternating hyperplasia and atrophy in the epithelial tissue, as well as areas of spongiosis predominantly in middle and parabasal layers, leukocyte exocytosis with eventual formation of microabscesses, focus of suprabasal cleavage, with retention of parabasal layers to the lamina itself. In the lamina itself, there is a dense mononuclear inflammatory infiltrate, vascular ectasia, and intense generalized edema, being therefore compatible with pemphigus vulgaris (Figures 2. A-B-C). The patient reported some improvement in symptomatology, with the use of topical corticoste-

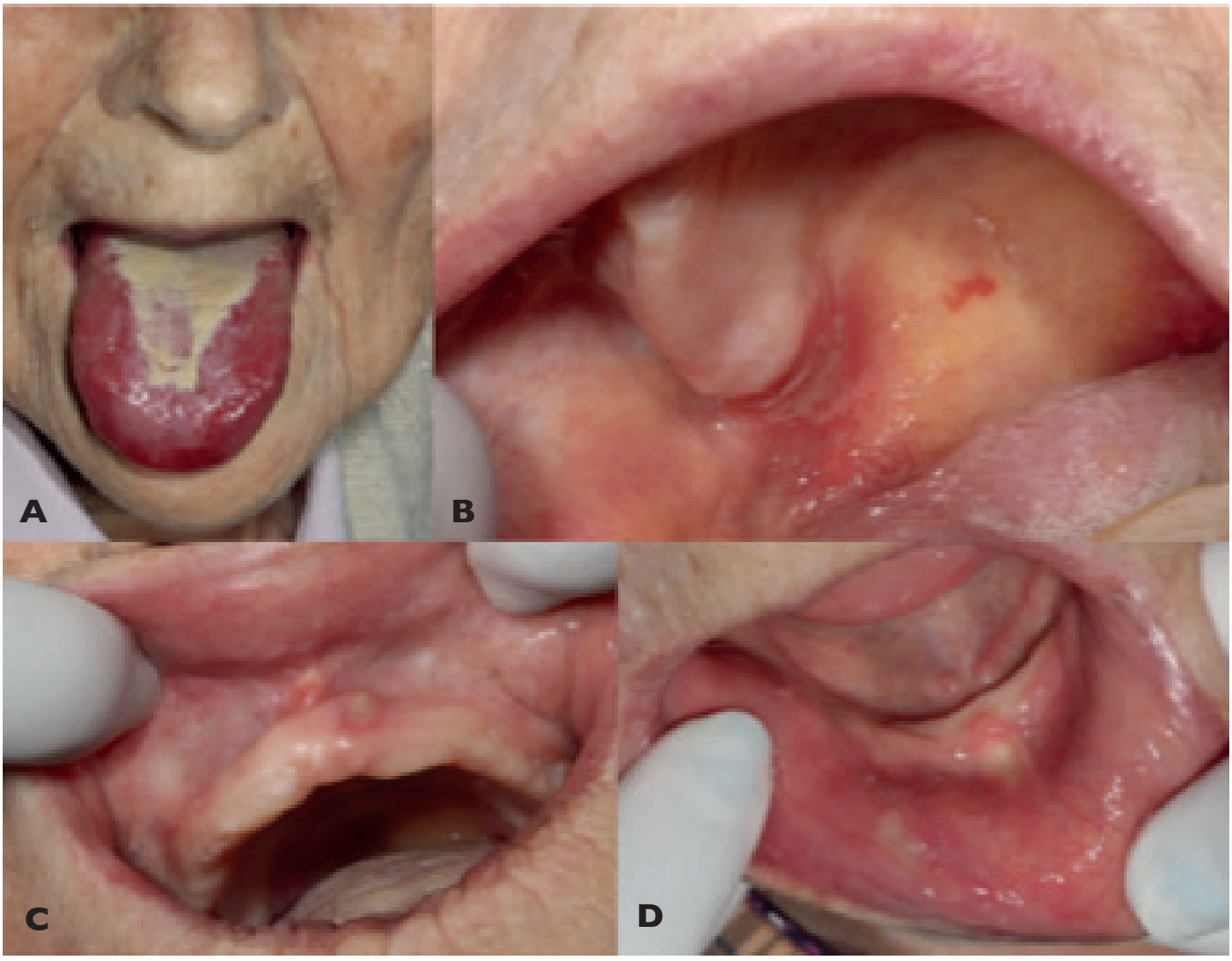

Figure 1 - (A), (B), (C) and (D) - Initial clinical aspect - Erythematosus and swollen lingual dorsum; region of the tonsillian column and soft palate with erythematous and necrotic areas; ulceration in the vestibular alveolar edge; ulceration in mucosa of the lower lip.

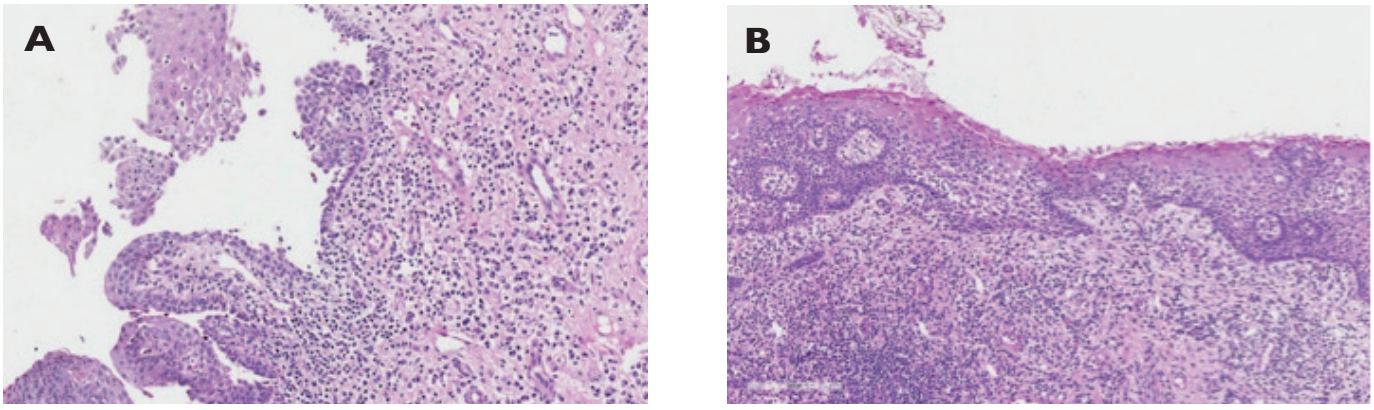

Figure 2 - (A) and (B) - Nonkeratinized stratified squamous epithelium, presenting acantholysis and spongiosis. The lamina itself presented dense and diffuse inflammatory infiltrate consisting mainly of lymphocytes and plasmocytes. Coloring: Hematoxylin and Eosin increase. Figure B shows the detachment of the epithelium above the basal and parabasal layers, forming an intraepithelial cleft, with acantholytic cells inside. Coloring: Hematoxylin and Eosin decrease.

roids; however, the lesions persisted, as well as difficulty to feed. So the team decided on the use of systemic corticosteroid therapy. For this, the patient, completed a medical history form directed to the use of systemic corticosteroids, being negative for any comorbidity, and a prophylaxis against strongyloidiasis was performed due to the high dose that would be used of corticosteroids with ivermectin 6mg, being 1.5 initial tablet and another after 7 days, in addition to vitamin D 1000 IU/day + calcium 1200 mg/day, as a way to minimize bone losses during treatment. The patient was recommended to use 40 mg of prednisone daily, divided into 2 doses, with the first 20 mg tablet ingested at 8:00 a.m. for 14 days. Finally, considering that the patient was no longer a smoker or an alcoholic, we recommended some weekly physical activity, in addition to avoiding the use of anti-inflammatory drugs and any type of vaccination in the period, due to the corticosteroid therapy. Given the relative symptomatic relief, topical corticosteroids were jointly maintained.

In a follow-up after one week of the second appointment, i.e., 15 days after the initial appointment, the patient showed almost total improvement of all initial lesions, with the restoration of normal feeding and persistence only of bilateral erasions in the tongue (Figure 3. A-B-C-D). Then, we proceeded a gradual removal of 5 mg of prednisone every fifteen days, in addition to checking blood pressure, weight and blood glucose in all sessions, until the medication was completely discontinued. After three months of therapy, the patient did not present any remaining lesions and new laboratory tests were requested to verify if there was any harm caused by the use of systemic corticosteroid therapy, all of which were within the normal range. At six months of follow-up, the patient reported very discreet lingual burning, which motivated the return of the daily use of prednisone and betamethasone elixir for 2 weeks, accompanied by vitamin D and calcium supplementation, resulting in a new remission of the lesions. At 10 months of follow-up, the patient showed white plaques compatible with pseudomembranous candidiasis,

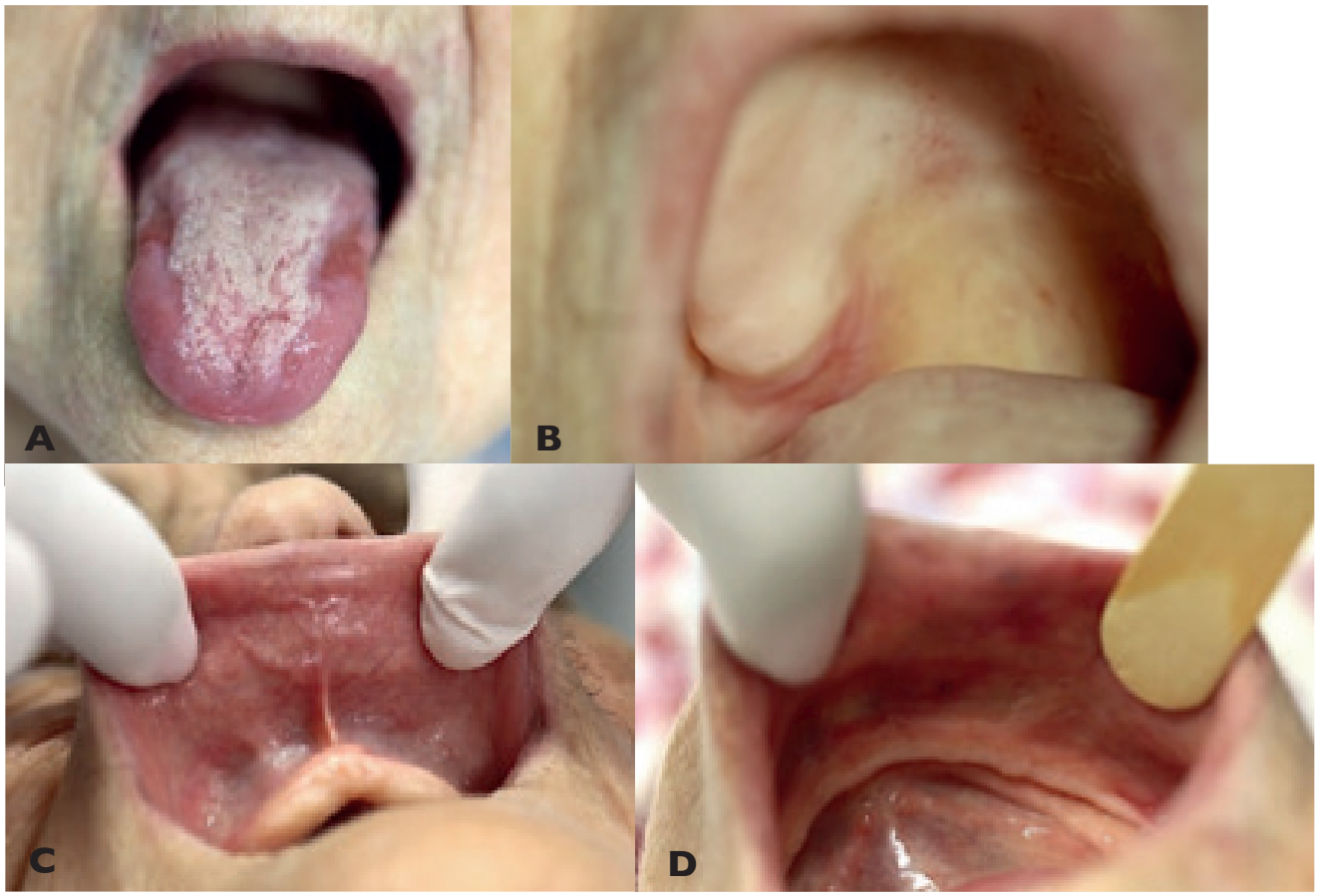

Figure 3 - (A), (B), (C) and (D) - Aspect of the lesions after one week of treatment — Lingual dorsum; tonsillar pillar and soft palate; upper alveolar rim; lower lip.

which justified the use of topical and systemic antifungal — nystatin 100,000 IU/ml mouthwash for 2 weeks and fluconazole 100 mg – 1 tablet per week for 2 weeks (Figure 4. A-B-C). After one year and four months, a second recurrence occurred with ulceration on the oral floor, erosions on the lateral edges and keratosis on the lower lip, causing the team to opt for a dose of 15 mg daily prednisone for another 14 days associated with the entire pharmacological protocol and guidelines, resulting in further remission of the lesions. Finally, after 3 years of follow-up, the patient is well, asymptomatic, in continuous follow-up and following the recommendations given at the beginning of the corticosteroid therapy.

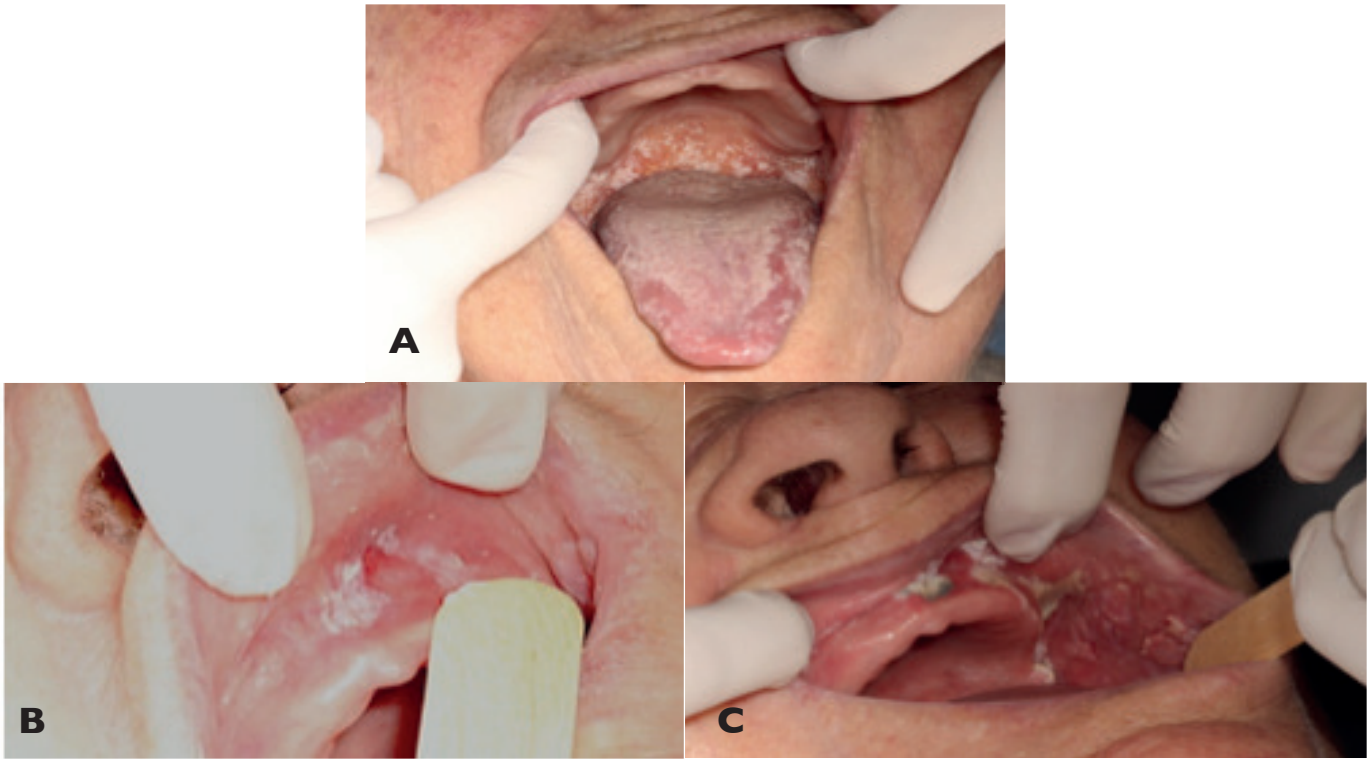

Figure 4 - (A), (B) and (C) - At 10 months of follow-up there was pseudomembranous candidiasis — involvement of the soft palate; extensive plaques affecting jugal mucosa and upper vestibule; detachment of the plates by wooden spatula.

DISCUSSION

Pemphigus vulgaris is a type II immune-mediated hypersensitivity mucocutaneous disease, whose etiology may be genetic, where antibodies act against desmoglein autoantigens 1 and 3, located in the desmosomes that connect epithelial cells, triggering epithelial detachments and resulting in the formation of vesicles, blisters, erosions and ulcerations. The destruction of the adhesion factors of the prickly cells of the suprabasal layer, present in pemphigus vulgaris is referred to as acantholysis (1, 9, 10). It is a disease with high morbidity and mortality when untreated, especially in older individuals, with diverse comorbidities and complications caused by the therapy employed. Some drugs such as antihypertensives, antibiotics and anticonvulsants have been associated with the onset of the disease (6-8).

Oral manifestations of the disease are often the first to appear and the last to disappear, usually causing considerable discomfort and pain to patients (4, 5). Palate, jugal mucosa, lip, gum and belly of the tongue are some of the sites possibly affected by the disease, which initially presents itself as vesicles that quickly rupture triggering the formation of various erosions and/or ulcerations (15). Skin and other mucous membranes, such as the ocular one, may also be affected and diagnosis occurs most commonly from 30 to 50 years of age (13, 14, 23). This case report shows an 80-year-old woman who reported never having had similar manifestations in the

oral cavity, presenting no other manifestation on the skin or on other body mucosa at the time of diagnosis. Tonsillar pillar, alveolar rim, lip and especially back and lateral edges of the tongue were affected, especially the tongue that is not a common site of manifestation of this disease and was the main cause of the search for care.

Oral pemphigus treatment usually involves the use of corticosteroid drugs of topical and systemic action (27). Topical medications should preferably be used as the first attempt at treatment, given their small potential to cause side effects (28, 29). However, systemic corticosteroid therapy implies a number of deleterious effects on patients, especially if used in the long term, such as increased blood pressure levels, hyperglycemia, osteopenia and immunosuppression (30). Older patients with comorbidities, such as chronic non-communicable diseases, are particularly vulnerable to this type of drug, and there should be much caution and follow-up during therapy. In this case, although the patient did not have comorbidities, she showed a certain physical weakness due to her 80 years. Although topical corticosteroid therapy and nutritional and oral hygiene guidelines improved symptoms, they were insufficient for the remission of lesions, justifying the use of systemic glucocorticoids. Thus, before using the drugs, the patient had to undergo a broad laboratory evaluation and also a prophylaxis against possible parasitic infection – strongyloidiasis – and osteopenia/osteoporosis (4). Moreover, in all follow-up visits the patient had her blood pressure, blood glucose and weight measured, besides being instructed to have a healthier diet, perform physical exercises and avoid the associated use of anti-inflammatory drugs. Every three months, all laboratory tests were repeated for adequate patient monitoring. Pemphigus vulgaris, similar to other autoimmune diseases, hardly has a definitive cure and thus the patient follows the scheduled returns and clinical follow-ups (23-26).

CONCLUSION

Pemphigus vulgaris is an autoimmune disease often diagnosed by important primary manifestations in the oral cavity. The dentist is fundamental in the management of this pathology and should be prepared for unusual cases such as the one presented in this report about an 80-year-old patient with tongue lesions.

The authors declare no conflict of interest.

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