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MUCOUS MEMBRANE PEMPHIGOID WITH ORAL MUCOSA MANIFESTATIONS: CASE REPORT

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Abstract: Mucous membrane pemphigoid represents a group of chronic mucocutaneous bullous diseases of autoimmune origin, in which tissue-bound autoantibodies cause the destruction of basement membrane components. Oral lesions are usually the first to be observed, but other sites may be involved, such as the conjunctival, nasal, esophageal, laryngeal and vaginal mucous membranes, as well as the skin. The clinical characteristic of the lesions are blisters or vesicles, which later rupture leaving an area of superficial ulceration. In general, this clinical manifestation is seen diffusely in the mouth, but may be limited to a specific site, the gums being the most frequent. Gingival involvement forms a clinical pattern called desquamative gingivitis, which can also be seen in other immune--mediated conditions such as erosive lichen planus and pemphigus vulgaris. It is therefore of the utmost importance for dentists to know the main oral manifestations of autoimmune diseases, as well as the various etiologies that desquamative gingivitis can present. The aim of this study is to report two clinical cases of mucous membrane pemphigoid, with oral and gingival manifestations, in order to help dentists diagnose and treat this pathology.
Keywords: Autoimmune diseases. Oral health. Laser. Pathology.

INTRODUCTION

Autoimmune diseases are marked by an exaggerated response by the body that leads to the destruction and dysfunction of tissues and organs. They are characterized by a failure to differentiate between what is proper and what is not proper to the body, causing the immune system to act against its own cells. A wide range of autoimmune diseases can affect the oral cavity, which can also be the primary site of other immune disorders affecting the skin and mucosa (Carvalho, 2022; Rocha, 2022).

The production of reactive forms of oxygen and nitrogen can damage cellular components and induce autoimmune responses, as these components play a role in regulating cellular functions. In prolonged periods of stress, inflammatory and/or immune activation, this production can increase, making the relationship between autoimmune diseases and the emotional factor clear (Rocha, 2022).

During the Covid-19 pandemic, autoimmune diseases have been in the spotlight due to the increase in cases. A retrospective cohort study carried out in Hong Kong between April 2020 and November 2022 concluded that Covid-19 patients have an increased risk of developing autoimmune diseases, such as: spondyloarthritis, rheumatoid arthritis, pemphigoid, Graves' disease, multiple sclerosis and vasculitis (Peng et al., 2023). This correlation is also observed in a medical article published in Spain, which reports a clinical case in which a patient presented with a clinical manifestation of bullous cutaneous pemphigoid after receiving the *COMIRNATY* vaccine (mRNA, Pfizer-BioNTech), both in the first and second doses (Lopez et al., 2021).

More studies need to be carried out to confirm or not this hypothesis linking the increased incidence of autoimmune diseases with Covid-19. However, health professionals should be aware of the possible autoimmune sequelae associated with Covid-19, as they may require careful clinical management.

Among the autoimmune diseases that affect the oral cavity, pemphigoid is of great importance. It is characterized by the action of an autoantibody against a component of epithelial cells called the hemidesmosome, responsible for the adhesion of epithelial cells to the basement membrane (Neville et al., 2024; T. S. Santos et al., 2010).

The most appropriate term to refer to the manifestation of pemphigoid is pemphigoid of the mucous membranes (PMM), and it is

also commonly called cicatricial pemphigoid. PMM usually affects individuals in adulthood, on average between 50 and 60 years old, and is more common in women (Neville et al., 2024;).

In terms of clinical characteristics, blistering or vesicular lesions are observed, which later rupture, leaving a superficially ulcerated area, stripped of mucosa. The blister phase is more commonly seen in cases of pemphigoid, as these are subepithelial, producing a thicker, more resistant layer. Oral lesions are seen in the majority of cases and are usually the initial site of the disease, but other sites can also be affected, such as the conjunctival, nasal, esophageal, laryngeal and vaginal mucous membranes and the skin (Neville et al., 2024; T. S. Santos et al., 2010).

In the oral cavity, PMM usually presents in a diffuse form, but it can also be limited to a certain location, with the gums being the most common, accounting for 83 to 100% of cases, followed by the ocular mucosa. Pemphigoid lesions generally leave scars, with the exception of those affecting the oral cavity, which can result in impaired vision and esophageal stenosis (Neville et al., 2024; Carvalho, 2022; Rocha, 2022).

The most significant complication of PMM is ocular involvement, which can occur in up to 25% of cases. The initial alteration is subconjunctival fibrosis, which can easily be detected by an ophthalmologist. With the progression of the disease and the body's repeated attempts to cure it, a scar forms between the bulbar conjunctiva, which lines the eyeball, and the palpebral conjunctiva, resulting in adhesions called symblepharon. The scars can obstruct the tear duct, resulting in poor tear production and increased keratin production, progressing to keratinization of the cornea and complete loss of vision, which can occur in 15% of cases (Neville et al., 2024; T. S. Santos et al., 2010).

When limited to the gingiva, it produces a clinical pattern called desquamative gingivitis, which is manifested by the presence of erythema, desquamation, erosion and ulceration in the free and adhered gingiva. It is currently used to describe a clinical manifestation and not a diagnosis, and can be seen in other pathologies, such as erosive lichen planus and pemphigus vulgaris, highlighting the importance of making a differential diagnosis (Neville et al., 2024; Silva, 2020).

Pemphigoid is rarely diagnosed at the first examination, but is considered a diagnostic hypothesis when the lesions persist for weeks to months and there is a negative response to drug therapy (Buonavoglia et al., 2019). To aid diagnosis, which is made difficult by the similar clinical manifestations between different pathologies, it is necessary to perform semi-technical maneuvers, such as Nikolsky's sign, and complementary tests, such as biopsy of the perilesional mucosa with subsequent microscopic analysis.

Pemphigus is a group of rare bullous autoimmune diseases that affect the skin and mucous membranes. Oral lesions often precede skin lesions or are the only manifestation of the disease. It usually affects adults aged between 40 and 70, with no gender predilection. It is characterized by the action of an autoantibody against a protein found in the desmosomes, which are responsible for adhesion between the epithelial cells of the oral and cutaneous lining, generating a process of acantholysis and resulting in the formation of suprabasilar blisters (Carvalho, 2022; Rocha, 2022).

With such similar clinical characteristics, histopathological and immunological findings are fundamental for confirming the diagnosis. Histologically, in cases of pemphigoid, a gap can be seen between the epithelium and the underlying connective tissue, caused by the destabilization of the epithelial cells of the basal layer with the basal membrane. In pemphigus, on the other hand, histology shows an intraepithelial separation, often leaving only

the basal cells. The cells of the spinous layer of the epithelium are separated and take on a rounded shape, thus being called Tzanck cells, used as a diagnostic marker for pemphigus (Rocha, 2022, Neville et al., 2024).

Serological diagnosis can be carried out using direct or indirect immunofluorescence. The former is used to detect autoantibodies that are adhered to tissues, while the latter evaluates antibodies that are circulating in the blood. In pemphigoid, direct immunofluorescence of the perilesional mucosa shows a continuous linear band in the basement membrane zone in around 90% of affected patients. Indirect immunofluorescence is positive in only 5 to 25% of cases, indicating a consistent absence of circulating autoantibodies. In cases of pemphigus, immunoreagents are deposited in the intercellular areas, between the cells of the surface epithelium, in almost all affected patients. In this case, indirect immunofluorescence is positive in 80 to 90% of cases, demonstrating the presence of circulating autoantibodies in the patient's serum (Rocha, 2022, Neville et al., 2024).

Immunoprecipitation studies are still used because, although diagnostic confirmation is often obtained by perilesional biopsy, it is not always possible to conclude whether it is pemphigoid or pemphigus (Rocha, 2022).

The recommended treatment aims to restore the patient's quality of life and prevent the lesions from evolving. Treatment must be individualized, as there is no defined protocol for treating pemphigoid. Multidisciplinary care is very important, and with regard to pemphigoid, ophthalmological follow-up is essential (Rocha, 2022; T. S. Santos et al., 2010).

The most commonly used therapeutic approach is the administration of topical or systemic corticosteroids, but the use of these drugs presents an increased risk of side effects and should only be prescribed to patients who have no medical contraindications. Therefore, other effective alternatives for the treatment of pemphigoid should be considered, such as low-intensity laser therapy, which can be used as an adjunct, due to its anti-inflammatory and analgesic effects and because it accelerates the regeneration of damaged tissues (Yilmaz et al., 2010; Rosalen, 2022).

This highlights the importance of the dental surgeon's knowledge of the clinical manifestations of mucous membrane pemphigoid, as well as the assessment of the patient as a whole, in order to establish clinical management.

OBJECTIVES

To report two clinical cases of pemphigoid of the mucous membranes, in order to assist the dental surgeon in the diagnosis and treatment of this pathology.

METHODOLOGY

This study was written by searching digital platforms such as PubMed, Cielo and Google Scholar. The case reports were based on the collection of data from the clinical records, images and complementary exams of patients diagnosed with mucous membrane pemphigoid, seen at a dental clinic in the city of Cascavel/PR. The proposed treatment was based on the current literature related to the oral pathology discussed and the laser protocol was taken from the book "Lasers in daily clinical practice" written by the author Ana Cecilia Aranha.

CASE REPORT 1

A 62-year-old male patient who had been smoking for 52 years, smoking four cigarettes a day, sought stomatological care. He did not report any relevant medical history, but it was possible to observe the presence of reddish and purple patches on his upper limbs, which he said were caused by gardening. The patient wore upper and lower full dentures, and intraoral examination revealed ulcers on the apex of the tongue (Figure 1), palate (Figure 2) and jugal mucosa (Figures 3 and 4), and whitish pla-

ques on the upper and lower edges (Figures 2, 3 and 4). During the examination, the whitish plaques on the alveolar ridge were scraped off and removed through this procedure, so the first diagnostic hypothesis was candidosis. Initial treatment was prescribed with ketoconazole 150mg once a day and chlorhexidine 0.12% without alcohol for 14 days.

Figure 1- Ulcers on the apex of the tongue.
Source: Authors, 2023.

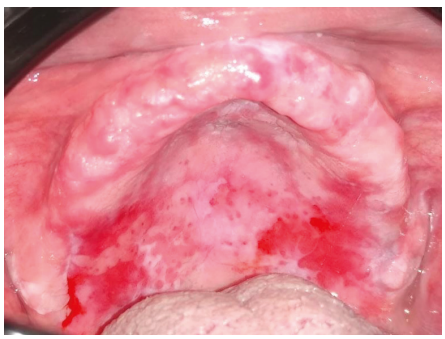

Figure 2 - Ulcers on the palate and whitish plaques on the upper alveolar ridge.
Source: Authors, 2023.

Figure 3 - Ulcers on the left jugal mucosa and whitish plaque on the lower alveolar ridge.
Source: Authors, 2023.

Figure 4 - Ulcers on the right jugal mucosa and whitish plaque on the lower alveolar ridge.
Source: Authors, 2023.

On his return visit, the patient reported blisters on his lips, which had already crusted over that day (Figure 5), and intraoral examination revealed a worsening of the clinical picture, with the presence of new lesions (Figures 6 and 7). At the doctor's appointment, the patient was prescribed Dexamethasone ointment to apply to the bullous lesions and inside the nose. The patient also reported a lot of pain when rinsing with Chlorhexidine 0.12% with alcohol, which the patient had mistakenly bought.

Figure 5 - Lesions on the upper lip, already in the crust stage.
Source: Authors 2023

Figure 6 - Lesions on the belly of the tongue.

Source: Authors, 2023.

Figure 7 - Lesions on the lower labial mucosa.

Source: Authors, 2023.

After 21 days of using ketoconazole, the patient still reported intense pain when eating. He also had extensive lesions on the jugal mucosa, lips and tongue. It was therefore necessary to perform an incisional biopsy of the lesions. Three samples were taken, one from the jugal mucosa on the right and the other two from the upper lip. They were then sent for histopathological analysis at UNIOESTE's LabPat.

On the day of the surgical procedure, Dexamethasone elixir 0.1mg/1ml was prescribed, to be swallowed five ml of the solution every eight hours for five minutes, for 15 days, and Prednisolone 20mg, one tablet every 12 hours for seven days, and then another seven days with one tablet a day.

The sutures were removed 15 days after surgery. The patient reported a significant reduction in pain, with no recurrence of the lesions (Figure 8). A laser therapy session was carried out, with red and infrared wavelengths and three joules of energy. The prescription for Prednisolone 10mg, one tablet a day, for seven days, and Dexamethasone elixir five ml, for mouthwash, every eight hours, for seven days, was maintained.

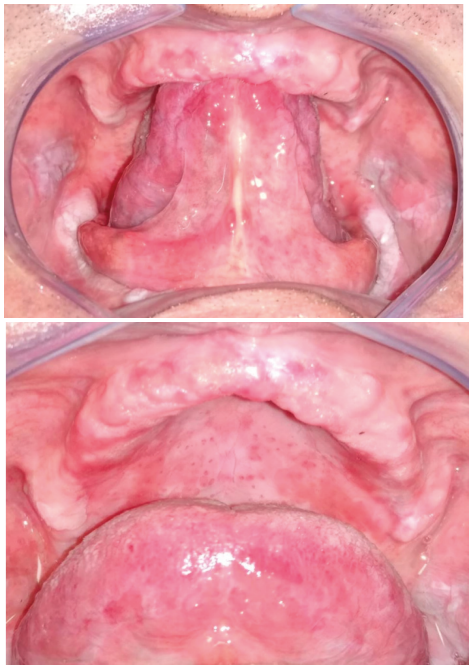

Figure 8 - Improvement in the clinical picture, with no new lesions.

Source: Authors, 2023.

The histopathological analysis of the samples collected resulted in a diagnosis suggestive of pemphigoid of the mucous membranes. The sample taken from the jugal mucosa on the right side showed "A fragment of mucosa lined by hyperkeratinized stratified sidewalk epithelium and the presence of a subepithelial cleft. The connective tissue is fibrous and associated with an intense chronic inflammatory infiltrate". On the right side of the upper lip, "Fragments of mucosa lined with hyperkeratinized stratified sidewalk epithelium and acanthotic. The connective tissue is fibrous with an intense subepithelial lymphocytic inflammatory infiltrate in bands."

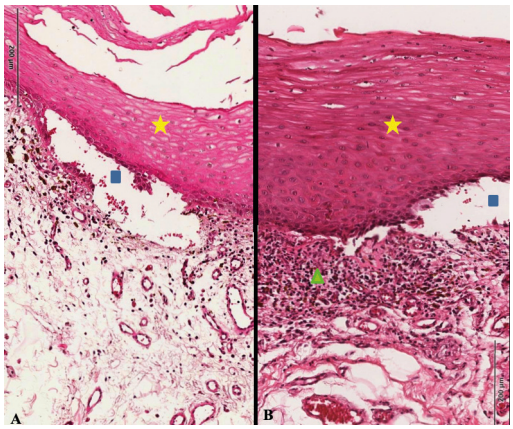

Figure 9 - Fragments of mucosa **A** and **B**, we can see "fraying" of the epithelial tissue (yellow star), formation of a "bubble" (blue square) and intense subepithelial conical inflammatory infiltrate (green triangle).
Source: LabPat.

After 21 days of using systemic and topical corticosteroids, the patient reported a significant improvement in pain and the lesions had healed. It was therefore decided to continue prescribing Prednisolone five mg, one tablet a day, for seven days.

After three months between appointments, the patient returned to the clinic reporting worsening of the lesions (Figures 10 and 11), but with a milder clinical picture compared to the time of diagnosis. Treatment was prescribed with Prednisolone 20mg for 10 days and Dexamethasone elixir for 15 days. At the same appointment, another session of laser therapy with a red wavelength and two joules of energy was carried out. The patient did not return for follow-up appointments.

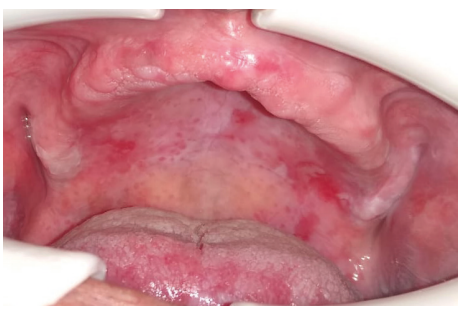

Figure 10 - Lesions on the palate.
Source: Authors, 2023.

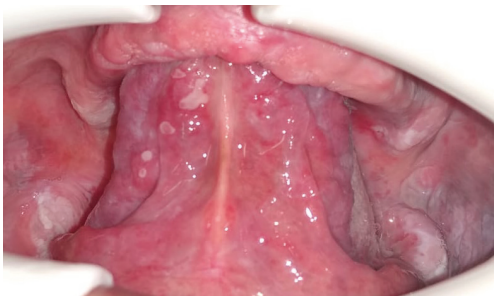

Figure 11 - Lesions on the belly of the tongue.
Source: Authors, 2023.

CASE REPORT 2

A 63-year-old male smoker with a history of pre-diabetes and atherosclerosis sought stomatological care complaining of gingival inflammation since 2020. He reported taking Trayenta to treat diabetes, Reconter for psychiatric purposes, Losartan and ASA. Intraoral examination revealed desquamative gingivitis in the lower anterior region (Figure 12), with a reddish color and whitish streaks, pain, and white plaques on the bilateral jugal mucosa (Figure 13). The primary diagnostic hypothesis was lichen planus, but a biopsy procedure was carried out for confirmation.

Figure 12 - Lower anterior region with desquamative gingivitis.
Source: Authors, 2022.

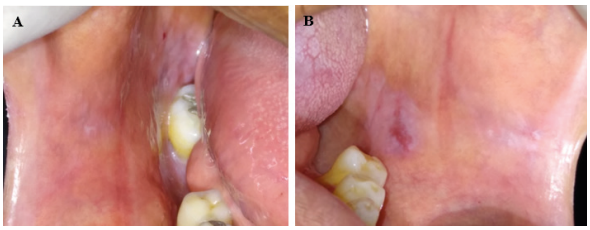

Figure 13 - Lesion on the right (A) and left (B) jugal mucosa.
Source: Authors, 2022.

Pre-operative medication included Amoxicillin 1g for antibiotic prophylaxis, due to the patient's pre-diabetes condition, and Dexamethasone 4mg. A perilesional incisional biopsy was performed on the altered gingival tissue (Figure 14) and the jugal mucosa on the left (Figure 15), and the samples collected were sent for histopathological analysis at UNIOESTE's LabPat. On the same day as the procedure, the Nikolsky maneuver was performed and the result was positive.

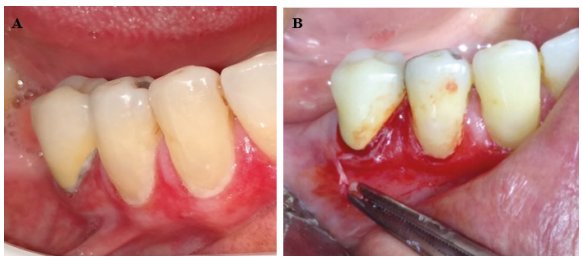

Figure 14 - A - Aspect of the gingival tissue near teeth 43, 44 and 45, prior to the biopsy. B - Transoperative biopsy of gingival tissue near teeth 44 and 45.

Source: Authors, 2022.

Figure 15 - Immediate postoperative period of the biopsy performed on the left jugal mucosa.

Source: Authors, 2022.

The histopathological analysis of the samples collected resulted in a diagnosis suggestive of pemphigoid of the mucous membranes. Histologically, a "fragment of mucosa lined by parakeratinized stratified sidewalk epithelium was observed. Stray epithelial fragments were observed at the level of the basal layer, as well as fragments of intensely inflamed connective tissue chronically".

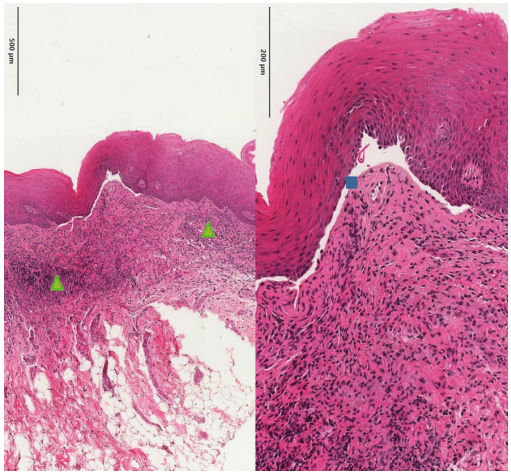

Figure 16 - In (A), we can see the intense subepithelial chronic inflammatory infiltrate (green triangle), in (B) the portion where there is detachment of the epithelium at the basal level (blue square).

Source: LabPat.

After 15 days, the patient returned to have the sutures removed and treatment started. Laser therapy with red and infrared wavelengths was proposed, with variations in the energy applied during the sessions. Treatment began at the same appointment with the first laser session, using two joules of energy.

The following day, the patient returned for the second laser session. First, dental biofilm removal was carried out, as the patient reported gingival sensitivity and pain compatible with six on a scale of zero to 10, which made hygiene difficult. Next, a red and infrared laser was applied, with three joules of energy.

In the third treatment session, the patient was instructed on oral hygiene before the laser was applied. The patient reported a sensitivity compatible with six on the pain scale. Clinically, the gums were red and erosive. The laser was applied in the same way as the previous session.

The energy used in the laser therapy sessions varied according to the sensitivity reported by the patient on the day of the appointment and the clinical condition observed. The red laser, with a wavelength of 660nm, was used to accelerate the healing of the lesions. The infrared laser, with a wavelength of 808nm, was used to reduce pain sensitivity by producing an analgesic action.

The treatment consisted of 11 laser sessions, in which the red laser was applied at between two and three joules of energy, and the infrared laser at between two and six joules of energy.

Twenty days after the last laser session, at a follow-up appointment, gingival integrity was observed (Figure 18) and the patient no longer reported any pain or sensitivity, so there was no need to apply the laser. The patient was referred for an ophthalmological assessment and returned after four months with results showing the integrity of the ocular mucosa.

Figure 17 - Four-month follow-up, with gingival integrity.
Source: Authors, 2023.

DISCUSSION

Pemphigoid of the mucous membranes is a chronic autoimmune disease that has a significant impact on the quality of life of affected individuals due to the pain that leads to difficulty in eating, speaking and oral hygiene. The clinical appearance of the lesions includes erosions, erythematous patches, blisters and involvement of the gingival mucosa, known as desquamative gingivitis. The sites most commonly affected by the disease in the oral cavity are the inserted gingiva, the palate and the buccal mucosa (Arduino et al., 2017 and Roma et al., 2020).

The clinical manifestations of this disease are similar to various oral pathogens, such as aphthous stomatitis, oral candidosis and erosive lichen planus, making a definitive diagnosis initially difficult. This is obtained through a combination of clinical findings, histopathological analysis and immunological findings (Neville et al., 2024; Roma et al., 2020).

In a study carried out by Arduino et al. (2017), 182 cases of PMM were analyzed and the characteristics found were reported. Of the cases, 151 had gingival involvement, of which 146 were vestibular and only 84 were palatal or lingual. It was also reported that less than 30% of patients had extraoral manifestations, the most common being ocular and cutaneous involvement, which was more frequent in male patients (Arduino et al., 2017).

In the same study, it was reported that only 62% of cases were positive for Nikolsky's sign, highlighting the importance of performing a biopsy to confirm the diagnosis (Arduino et al., 2017).

The professional's mastery of the surgical biopsy technique is extremely important in these cases, as the epithelial tissue in PMM cases is easily detached and can alter the sample, making it unsuitable for histopathological analysis. The most suitable area for biopsy is the perilesional region, so that the sample collected contains part healthy tissue and part altered tissue (Roma, et al., 2020).

Patients can be classified as low risk, when the lesions are restricted to the oral cavity, and high risk, when there is ocular, pharyngeal, laryngeal, esophageal and/or genital involvement. When low-risk, treatment can be conservative, prioritizing topical medications, while high-risk patients need more aggressive treatment, using systemic drugs. Among

the medications used, corticosteroids stand out for their effectiveness, but they also have side effects that should be considered before prescribing them, including mucosal atrophy and the reactivation of opportunistic diseases, such as candidosis and herpes simplex, due to the immunosuppression caused by these medications (Roma et al., 2020; Yilmaz et al., 2010; Rosalen, 2022).

Laser therapy is thus proving to be an excellent alternative for treating PMM. Lasers are non-ionizing electromagnetic radiation whose properties are monochromaticity, coherence and collimation. The most commonly used for treating oral lesions is the low-intensity laser (LLLT), which generally operates at wavelengths of 600 to 700nm or red, and 800 to 1000nm or infrared. LLLT promotes an anti-inflammatory, analgesic effect and has biomodulatory properties that aid tissue repair, which is why it has been used in the treatment of inflammatory and painful conditions (T. K. G. L. Santos et al., 2018).

Multidisciplinarity in cases of pemphigoid is important because of the possible aggravations the disease can cause. Thus, interaction between dentists, dermatologists, ophthalmologists, otorhinolaryngologists, urologists and gastroenterologists is necessary for a better therapeutic outcome (Roma et al., 2020; Rocha, 2022).

CONCLUSION

Because its clinical characteristics are similar to those of other diseases, the definitive diagnosis of pemphigoid is often delayed, as is the start of correct treatment. It is therefore clear that health professionals, especially dentists, need to know more about the subject in order to identify the initial clinical signs and reach an early diagnosis, thus preventing the disease from worsening.

Another aggravating factor is that patients discontinue treatment. Because it is a chronic inflammatory and autoimmune disease, with no possibility of a cure, only control of the signs and symptoms, it is common for patients not to attend follow-up appointments, returning only during periods of disease reactivity. Frequent follow-up of patients diagnosed with autoimmune diseases is crucial for controlling symptoms and improving the patient's quality of life.

The clinical cases reported in this study highlight the use of low-intensity laser in the treatment of pemphigoid, which can be used as an adjunct to topical and systemic drugs, but also as an alternative for patients who have contraindications to drug treatments. Laser therapy can be used to treat the disease and prevent new lesions by promoting local anti-inflammatory action and its biomodulatory effect, which aids tissue repair.

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