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Vesiculobullous autoimmune diseases with oral mucosa manifestations: retrospective and follow-up study

Doenças autoimunes bolhosas com manifestação em mucosa oral: estudo retrospectivo e de acompanhamento

Rani Iani Costa GONÇALO[1]
ORCID iD 0000-0002-6762-135X
Mara Luana Batista SEVERO[1]
ORCID iD 0000-0001-8425-9869
Ana Miryam Costa de MEDEIROS[1]
ORCID iD 0000-0003-1839-1030
Patrícia Teixeira de OLIVEIRA[1]
ORCID iD 0000-0002-0641-1033
Éricka Janine Dantas Da SILVEIRA[1]
ORCID iD 0000-0003-2128-0147

ABSTRACT

Objective
To conduct a retrospective study on a series of cases of PV and BMMP with manifestations in the oral cavity in order to ascertain prevalence, sociodemographic characteristics, diagnostic maneuvers, treatment and follow-up.

Methods
This is a retrospective, descriptive study in which clinical data were collected from the medical records of all cases of PV and BMMP registered and diagnosed, between 1995 and 2015, in the Oral Diagnostic Service of the UFRN Department of Dentistry.

Results
The mean age of the total sample (n = 36) was 41.64, with females the most frequent (n = 26; 72.22%) and the cheek mucosa being the site most affected (n = 20; 27.40%). Eight patients (22.22%), including 5 cases of PV and 3 BMMP, were clinically reevaluated. All patients exhibited lesions at the time of follow-up. Prednisone (n=7; 87.5%) and clobetasol propionate (n=8, 100%) were the most widely used drugs in the systemic and topical treatment, respectively. The follow-up period ranged from 5 months to 5 years.

Conclusion
The clinical profile of patients in this study was similar to that evidenced in the literature. However, it was found that the oral lesions were more resistant to the treatment used on the patients evaluated.

Indexing terms: *Benign membrane mucous pemphigoid. Oral diagnosis. Pemphigus. Vesiculobullous skin diseases.*

RESUMO

Objetivo
Realizar um estudo retrospectivo em uma série de casos de PV e BMMP com manifestações em cavidade oral com o intuito de verificar suas prevalências, características sociodemográficas, diagnóstico, tratamento e acompanhamento.

Métodos
Trata-se de um estudo retrospectivo descritivo no qual os dados clínicos foram coletados a partir dos prontuários de todos os casos de PV e BMMP registrados e diagnosticados, entre 1995 e 2015, no serviço de Diagnóstico Oral do Departamento de Odontologia da UFRN.

Resultados
Da amostra total (n=36), a age média foi de 41,64 anos, sendo o sexo female o mais frequente (n=26; 72,22%) e a mucosa jugal o sítio mais afetado (n=20; 27,40%). Oito pacientes (22,22%), dos quais 5 são casos de PV e 3 de BMMP, foram reavaliados clinicamente. Todos os pacientes exibiram lesões no momento do acompanhamento, sendo a prednisona (n=7) e o propionato de clobetasol (n=8) os fármacos mais utilizados no tratamento sistêmico e tópico, respectivamente. O tempo de acompanhamento variou de 5 meses a 5 anos.

Conclusão
O perfil clínico dos pacientes da presente pesquisa foi semelhante ao da literatura. No entanto, verificou-se que as lesões orais foram mais resistentes ao tratamento empregado nos pacientes avaliados.

Termos de indexação: Penfigoide mucomembranoso benigno. Diagnóstico bucal. Pênfigo. Dermatopatias vesiculobolhosas.

[1] Universidade Federal do Rio Grande do Norte, Departamento de Odontologia. Av. Senador Salgado Filho, 1757, 59056-000, Lagoa Nova, Natal, RN, Brasil. Correspondência para / Correspondence to: EJD Silveira. E-mail: <ericka_janine@yahoo.com.br>.

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INTRODUCTION

Vesiculobullous diseases represent a heterogeneous group of dermatoses with widely varying clinical manifestations, which have been the subject of intense investigation in recent years. Although in the majority of cases these diseases are characterized primarily by the presence of vesiculobullous lesions, their etiology, pathogenesis, severity and trajectory may differ. These include common pemphigus or pemphigus vulgaris, paraneoplastic pemphigus and benign mucous membrane pemphigoid which, clinically, are very similar when present in the oral mucosa[1]. These diseases, characterized as mucocutaneous, have a significant impact on quality of life when compared to other conditions, as they can lead to pain and difficulty in eating and speech, depending on the extent of the ulceration[2].

Among the vesiculobullous diseases, pemphigus vulgaris (PV) and benign mucous membrane pemphigoid (BMMP) are prominent, and are characterized by the production of autoantibodies that are directed towards the constituents responsible for the adhesion of the epithelial cells to each other, as in the case of PV, or between the epithelium and the underlying conjunctive tissue, as with BMMP. Thus, this antigen-antibody reaction results in a pathological process clinically characterized by the appearance of blisters on the skin and/or mucosal surfaces[3-4].

In the oral mucosa, these diseases appear clinically in the form of blisters and ulcerations, which are also common to other diseases, which can complicate the process of diagnosis. According to Arundhathi et al.[5], the main diagnostic techniques for autoimmune bullous diseases are conventional histopathological analysis and direct or indirect immunofluorescence tests. However, these tests are not always readily available to patients.

The main objective of the treatment of autoimmune bullous diseases is the remission of the disease by reducing both the production of autoantibodies and inflammatory response. Due to the great clinical similarity between the two diseases, the principles for choice of treatment are based on the extent of the area affected by the lesion(s), the severity and the clinical progression[1].

It is of the utmost importance to conduct clinical-pathological studies based on the publication of data relating to the diagnosis, clinical characteristics, follow-up and treatment of patients suffering from these autoimmune bullous diseases since, based on analyses of case series, it is possible to broaden the understanding of the clinical procedures adopted in various specialist services.

Therefore, the aim of the present study was to perform a retrospective study in a series of cases of PV and BMMP with manifestations in the oral cavity including prevalence, sociodemographic characteristics, diagnostic maneuvers, treatment and follow-up period.

METHODS

This study was approved by the Research Ethics Committee at the Federal University of Rio Grande do Norte (UFRN) in the city of Natal, in the Brazilian state of Rio Grande do Norte, with opinion no. 1.134.789, dated June 26, 2015.

The study population comprised all the cases of autoimmune bullous disease recorded and diagnosed within the Stomatology Clinic of the Department of Dentistry at UFRN, between January 1995 and December 2015.

A convenience sample was intentionally chosen of 36 cases of patients suffering from autoimmune bullous diseases, comprising 25 cases of PV and 11 cases of BMMP. All were diagnosed by way of histopathological examinations.

The clinical data were collected from patient records and the completion of a data collection sheet previously drafted for this study, containing information such as sex, race, initial diagnosis date, age at the time of initial diagnosis, current age of patient and the presence of lesions on follow-up, as well as a list of lesions (location, form of diagnosis, clinical and histopathological diagnoses and treatment). From the initial diagnosis of the vesiculobullous diseases investigated, the aforementioned service procedure that a stomatology specialist may prescribe consists of topical corticosteroids or low level laser therapy (LLLT) when oral lesions are present, as described in table 2 and, in addition, where the patients are referred to a dermatologist, general clinic or, in the case of those suffering from BMMP, to the ophthalmologist. Systemic corticosteroids were prescribed for some patients in this study by their physicians and their doses were adjusted as the oral or skin lesions responded to treatment.

In the second stage, contact was made, where possible, with the patients themselves, and they were invited to present to the UFRN Department of Dentistry for a follow-up consultation.

The clinical data were then copied to tables in Microsoft Excel® 2007 and subsequently exported to version 20.0 of the statistical program SPSS®, where they were submitted to a descriptive analysis.

RESULTS

The clinical profile of 36 cases of autoimmune bullous lesions is detailed in Table 1. The mean age of the patients was 41.64 years, varying from 18 to 70 years. The mean age of individuals with BMMP was higher (42.72) than in those with PV (40.24). The female sex predominated (n= 26; 72.22%) in the sample as a whole and, separately, in the cases of PV (80%) and BMMP (54.55%).

Table 1. Demographic and clinical profile of the cases of autoimmune bullous lesions according to histopathological diagnosis. Rio Grande do Norte (RN), 2016.

	Total (n=36) %	PV (n=25) %	BMMP (n=11) %
Sex			
Female	26 (72.22%)	20 (80%)	6 (54.55%)
Male	10 (27.78%)	5 (20%)	5 (45.45%)
Age in years (mean)	41.64	40.24	42.72
Location of lesions			
Cheek mucosa	20 (27.40%)	16 (28.60%)	4 (23.52%)
Tongue (side edge)	13 (17.80%)	11 (19.64%)	2 (11.77%)
Tongue (dorsum)	4 (5.50%)	2 (3.57%)	2 (11.77%)
Alveolar ridge	3 (4.10%)	2 (3.57%)	1 (5.88%)
Retromolar region	3 (4.10%)	3 (5.35%)	0
Palate	7 (9.59%)	5 (8.92%)	2 (11.77%)
Gum	11 (15.06%)	7 (12.5%)	4 (23.52%)
Oropharynx	4 (5.50%)	2 (3.57%)	2 (11.77%)
Labial mucosa	8 (10.95%)	8 (14.28%)	0

Note: Caption: PV - pemphigus vulgaris; BMMP - benign mucous membrane pemphigoid.
Source: Oral Diagnostic Service and Oral Pathology Post-graduation Program - UFRN

All the patients had lesions in the oral cavity at the time of the initial diagnosis, the cheek mucosa being the site most affected, followed by the tongue (mainly on the lateral edges), gums, hard and soft palates, and in some cases dispersed throughout the oral mucosa. As for the clinical diagnosis, this was consistent with the histopathological findings of the lesions. Oral lichen planus, erythema multiforme and recurrent aphthous ulceration were the most prevalent differential diagnoses for PV and BMMP.

As far as the presence of skin alterations is concerned, eight patients (22.22%) exhibited lesions in a variety of locations, such as the arms, scalp and perioral region. In addition, 7 cases (19.44%) were affected in other mucosa: genital, nasal, ocular conjunctiva and pharyngeal.

The majority of the cases studied (n=30; 83.33%) did not include any information about symptomology, while five patients (13.88%) reported itching, burning mouth or pain when chewing and swallowing, and in one case (2.79%) no symptoms were reported.

Of the 36 cases studied, 8 (22.22%) were clinically reevaluated to check for the presence of lesions in the oral mucosa, symptomology, time since initial diagnosis, location of lesions and treatment. These patients are being monitored by the service. Of these, 5 had PV (62.5%) and 3 BMMP (37.5%). All the cases of PV or BMMP had lesions at the time of clinical reevaluation. The follow-up and treatment data for these 8 cases are described in Table 2 and the characteristics of some of the patients during follow-up can be viewed in figures 1 (A-F) and 2 (A-F).

The length of follow-up of patients varied from 5 months to 5 years. Depending on the severity of the lesions and the areas affected, the treatment consisted of the use of systemic corticotherapy and/or local action, the latter optionally combined with adjuvant therapies. Seven (87.5%) made use of prednisone, the drug of choice for systemic therapy, with a daily dosage varying according to the situation of the patient at the time of clinical reevaluation. Eight (100%) patients used, at some point in the treatment, 0.05% clobetasol propionate in the form of an elixir, being the most used topical steroid in our study, followed by 0.1 mg/ml dexamethasone elixir (n=3; 37.5%). In addition, for some of the patients (n=4; 50%), adjuvant therapies were employed such as laser therapy (n=2), which was effective in reducing the symptoms and the number of lesions, and the use of certain drugs, such as 0.125 mg/g fludroxycortide cream (n=1), for lesions of the lips or the perioral region; nystatin oral suspension (n=1), when there was associated candidiasis; dapsone (n=1) and azathioprine (n=2), the last two items being prescribed by dermatologists.

Table 2. Clinical/demographic data of treatment and follow-up of 8 cases of autoimmune bullous lesions. Natal, Rio Grande do Norte - 2016

Case	Sex	Age of patient diagnosed	Location of lesion	Clinical diagnosis	Histo-pathological diagnosis	Systemic treatment	Local treatment	Follow-up period
1	F	36	Skin; hard and soft palates; gums; cheek mucosa	PV	PV	azathioprine; prednisone (initially: 60 mg daily; currently: 40 mg daily)	dexamethasone elixir (0.1 mg/ml); fludroxycortide (0.125 mg/g); laser therapy; clobetasol propionate (0.05%) + nystatin	5 years
2	F	45	Skin (hands & arms); attached gum	PV; BMMP	PV	-	clobetasol propionate (0.05%)	2 and a half years
3	F	38	Side edge of tongue (R); dorsum of tongue; cheek mucosa	PV; BMMP; Recurrent aphthous ulcer	BMMP	prednisone (initially: 40 mg daily; Maintenance dose: 10 mg daily)	clobetasol propionate (0.05%); laser therapy	1 year
4	F	47	Skin, cheek mucosa, tongue, hard and soft palate; oropharynx, gums	BMMP/ PV	PV	dapsone; prednisone (initially: 60 mg daily; Maintenance dose: 5 mg daily)	clobetasol propionate (0.05%)	1 year
5	F	37	Cheek mucosa (R/L); lower and upper lips; side edge of tongue	Recurrent aphthous ulcer	PV	prednisone (20 mg daily)	dexamethasone elixir (0.1 mg/mg); clobetasol propionate (0.05%)	6 months
6	F	54	Cheek mucosa; palate and tongue	PV	PV	azathioprine; ranitidine; prednisone (initially: 60 mg daily; Maintenance dose: 5 mg daily)	dexamethasone elixir (0.1 mg/mg); clobetasol propionate (0.05%); artificial saliva.	1 year
7	F	60	Attached gum, ridge	Bullous angina; PV; BMMP	BMMP	prednisone 30 mg daily (reduction of 5 mg a day, every 5 day until weaned off)	Omcilon; clobetasol propionate (0.05%)	5 months
8	F	43	Lips, cheek mucosa, tongue, pharynx	Autoimmune lesion; Behçet's syndrome	PV	prednisone (dermatologist)	clobetasol propionate (0.05%)	4 years

Source: Oral Diagnostic Service and Oral Pathology Post-graduation Program - UFRN

DISCUSSION

Vesiculobullous diseases represent a heterogeneous group of mucosal dermatoses with quite varied manifestations. These diseases merit particular attention as some of them, such as PV and BMMP, can have a big impact on individuals' quality of life, influencing their social lives, as well as their physical and psychological wellbeing[6].

To arrive at a correct clinical procedure for these lesions, it is of paramount importance to obtain the correct diagnosis. According to Rameshkumar et al.[7], the diagnosis of mucocutaneous disorders is based on the natural history and clinical/ histopathological characteristics. According to these authors, despite the emergence of immunofluorescence techniques as a valuable tool for confirming these diseases, histopathological analysis is still regarded as the gold standard. The differentiation of PV and BMMP, based only on clinical aspects, is difficult due to the clinical similarity of these lesions, as both demonstrate positive Nikolsky signs. It is, therefore, necessary to perform a perilesional biopsy of the mucosa, similar to the

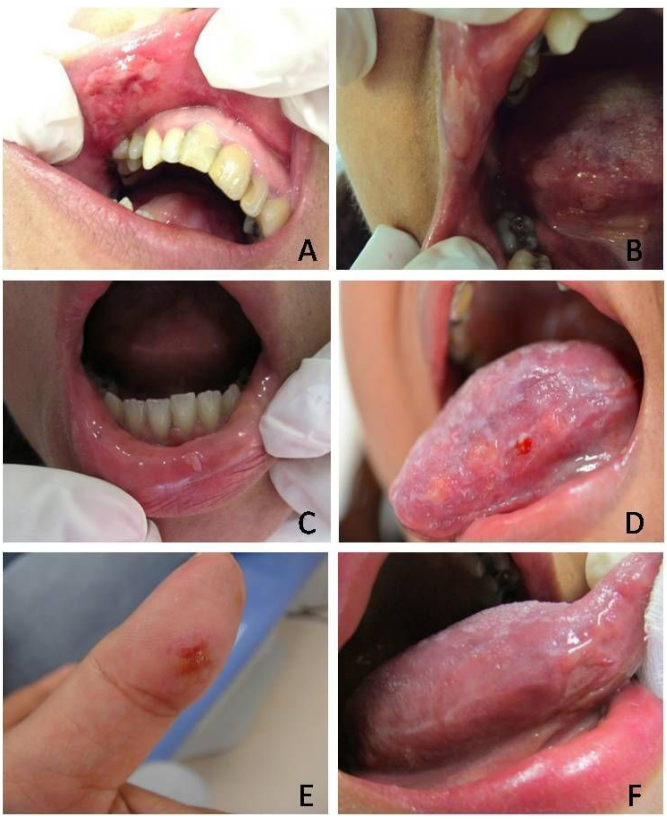

Figure 2. Clinical appearance of lesions in various locations in a patient suffering from Mucous Membrane Pemphigoid, resistant to clinical treatment. Note: A and B - Lesions in upper lip mucosa; C and D - Lesions in lower lip and tongue in 6th month of follow-up, evidencing a subtle clinical improvement; E and F - Evolution 2 years after start of treatment with the appearance of skin lesions and continuing lesions on tongue.

one used for the patients in the present study. However, when the histopathological characteristics are insufficient, an analysis of the lesion is recommended by means of direct immunofluorescence[5,8]. In all of the patients examined in the present study, the diagnosis was made based on the combination of clinical and histopathological aspects, since the patients did not have access to direct immunofluorescence techniques as the federal state in which the Service is located, does not possess a laboratory that can carry out this type of diagnostic technique.

With regard to demographic aspects, the literature states that vesiculobullous diseases show a greater tendency to affect women rather than men, in a proportion of 2:18. In the present study, bearing in mind the results obtained, it was noted that, in general, the female sex was most commonly affected (72.22%), approximately 2.5 times more than males. In a study conducted by Adolsomadi et al.[9] in the Dermatology Service in a city in Iran, a descriptive, retrospective review was conducted of the medical records of 1,560 patients diagnosed with pemphigus, of which 91.15% suffered from PV and the majority (56.95%) were female. However, other authors have described that these diseases can occur similarly in both sexes (10,1). One probable explanation for the higher incidence of these diseases in females is that women tend to seek help more readily, with the aim of prevention and/or cure. As for age, in the present study it was found that the average age was 40.24 and 42.72 for PV and BMMP, respectively. However, there is consensus in the literature that PV is more frequent between the 5th and 6th decades of life, while BMMP is more prevalent in the 6th to 8th decades of life[1,11-12].

Patients suffering from PV can be divided into 2 groups, those with lesions in the mucosa alone and those with involvement in both skin and mucosa, the oropharynx being the mucosal region most affected[13]. As for the patients clinically reevaluated in this study (n=8; 100%), all of them exhibited oral lesions at the time of this procedure, the cheek mucosa being the region most affected, followed by the tongue and gums, there being no involvement with any other mucous tissue, while three patients (37.5%) presented with skin lesions. Accordingly, it was observed that, in the patients assessed in the present study, impairment of the oral mucosa alone was greater than that of the skin and mucosa simultaneously. A similar outcome was seen in the study conducted by Abdolsomadi et al.[9], in a dermatology service, in which of 1,422 PV sufferers, 47% exhibited lesions only in the oral mucosa, with simultaneous involvement of skin and oral mucosa evidenced in 232 (16.3%) of these patients.

The study conducted by Ramos-e-Silva et al.[1] reported that the primary site affected in 50% of patients suffering from PV was the oral mucosa, mainly affecting the cheek mucosa, soft palate and lips, while other areas, such as the attached gum, which manifests itself in the form of desquamative gingivitis, were affected to a lesser extent. As far as BMMP is concerned, the oral mucosa is the site most affected, in around 90% of cases (the attached gum being the site most frequently affected), followed by the ocular membrane (65%)[1].

The majority of patients examined reported pain in the regions affected by the disease and emphasized, during anamnesis, that fruits like pineapple and lemon, and spicy foods, are related to an increase in symptoms and the appearance of lesions. Despite the fact that the etiology is still unknown, some factors may occasionally be linked to the appearance or aggravation of the disease, such as malignant conditions, pesticides, drugs, infections,

diet and stress[1,14].

PV and BMMP are not usually detected right away, and PV can be confused with other diseases that present with similar, clinical manifestations, for instance herpetic stomatitis, recurrent aphthous ulcerations, erosive lichen planus and pemphigoid[1,15]). As for BMMP, it is important to consider pemphigus vulgar, paraneoplastic pemphigus, Stevens-Johnson syndrome and systemic lupus erythematosus for differential diagnosis[16-17]. Comparing these data with the current study, it was found that oral lichen planus, erythema multiforme and recurrent aphthous ulceration were the most prevalent differential diagnoses for both of the diseases studied.

In the present study, 87.5% of the patients in follow-up made use of systemic corticotherapy, with prednisone being the principal drug of choice in a variety of doses. The mode of therapy employed will depend on the severity and progression of the disease. Being autoimmune diseases, treatment is carried out with the use of immunosuppressive agents, initially used in high doses to control the disease, and subsequently scaled back over the course of the treatment[3-4]. This rationale was adopted to treat the patients in this study.

Systemic therapy is used in more serious cases or when no improvement in condition is obtained using topical treatment, and consists of the use of corticosteroids, immunosuppressive agents and anti-inflammatory drugs, which may or may not be combined with topical agents. As in our study, prednisone was the corticoid of choice, being used until such time as the disease becomes less severe[1]. Higher doses, 120 mg a day for instance, result in a faster control of the disease, and there should be a progressive reduction in the dosage throughout the period of follow-up until complete remission of the lesions is achieved, thereby reducing the chances of recurrence[1-18].

As for topical treatment, this is recommended more when localized, milder lesions are observed, and can be carried out using clobetasol propionate (0.05%) in the form of a gel or elixir, rinsing with betamethasone elixir (0.1 mg/ml) or by means of intralesional injections of triamcinolone suspension[1]. The use of corticosteroids in the form of gel on the lesions is mainly recommended in cases of desquamative gingivitis, being particularly effective, while the intralesional injection of these drugs usually speeds up the healing process[8]. In the present study, clobetasol propionate (0.05%) and dexamethasone (0.1 mg/ml) were used, both in the form of an elixir, frequently recommended in combination with systemic corticoids, or used in isolation when, in the period of follow-up, the patients present with mild oral lesions.

For patients considered high risk, i.e. those with ocular and esophageal involvement, for example, and in cases refractory to the chosen therapy, it is necessary to use a more potent, systemic therapy, through the simultaneous use of corticosteroids and more potent immunosuppressants such as azathioprine, methotrexate, cyclosporine and cyclophosphamide. Immunomodulators, like dapsone and intravenous immunoglobulin, and biological agents such as rituximab (anti-CD20 monoclonal antibody) and inhibitors of tumor necrosis factor-alfa (TNF-α) can also be used[19-20]. Some of these immunosuppressive agents have been employed with the aim of reducing side effects associated with the long-term use of corticosteroids, such as hypertension, diabetes, osteoporosis and ocular damage, as they make it possible to reduce the dosage of these medications, in addition to intensifying the therapeutic response[8,18].

It is reported that the mortality rates are 70.5% before the establishment of systemic therapy with corticoids, just 21.4% with the use of corticosteroids and 3.7% when the corticoids are combined with other immunosuppressive drugs[14].

Another option for treating vesiculobullous disorders has been through the use of low-level laser therapy (LLLT), also known as photostimulation. This has been recommended as a treatment option in cases which are refractory to conventional therapy[21], since LLLT has the ability to promote the reduction or elimination of painful symptoms, as well as to reduce the number of lesions, by stimulating healing, which could produce better oral comfort[8,21-23].

In the study by Minicucci et al.[22], LLLT was used on two patients with PV. An improvement was observed as well as a reduction in the number of lesions after 7 to 10 sessions, with the patients reporting a reduction of around 70% in oral pain after the first session of laser therapy, and total remission after the third session.

Pavlić et al.[21], based on an evaluation in the literature on the effects of LLLT in the treatment of PV, suggested that this method was seen to be effective in the treatment of resistant oral lesions, observing significant and immediate analgesia, improved healing, as well as a reduction in discomfort and recurrence of the lesions over the course of patient follow-up. Consequently, confirming what has been seen in the literature, the use of low-level laser therapy has been considered effective in the present study, by reducing the symptoms and the number of oral lesions in patients who were subjected to the therapy

(n=2), although it did not reduce the recurrence of lesions.

As periods of aggravation and remission are common, with lesions that are found to be resistant to the treatment adopted in certain cases, the treatment of PV and BMMP is a challenge[24], one of the reasons for this being the fact that the clinical response to immunosuppression in patients in a more advanced stage of the disease, particularly in those with ocular involvement, is poor[3]. Depending on the initial severity and the chosen therapy, total remission of the disease may occur[1]. Oral lesions have proved more difficult to control and are therefore described as "the first to arrive and the last to leave". Moreover, the quicker the diagnosis and the start of corticotherapy, and in the proper dosage to induce the control of the disease, the greater the chance the patient will recover[25].

The main objective during the follow-up phase is to keep the disease under control with a minimum dosage of systemic corticoids. In addition, in order to prevent the side effects of this medication, it may be used on alternate days or even topical corticoids may be used, since the most common side effect of this is erythematous candidiasis and, in these cases, the use of adjuvants such as antifungal drugs can be considered in the treatment.

The rates of mortality and recurrence are lower in patients that only have oral mucosa lesions, as well as having a better prognosis (9). In the study by Robinson et al.[14], while trying to control PV, between 1 and 4 recurrences were observed in a period of two years. After this, the frequency of recurrence reduced to around once every four years. In the present study, none of the patients died during the follow-up period, neither as a result of the disease itself nor through the effects of immunosuppressive treatment. However, all the patients (n=8) experienced a recurrence of oral lesions over the course of the follow-up period, even when subjected to the chosen systemic and topic therapy.

CONCLUSION

In the present study, it was noted that all patients in follow-up had lesions in the oral mucosa, which reinforced the fact that these lesions were more resistant to treatment. Performing this type of study is very important as the studied lesions are often difficult to manage in the dental clinic and the dentist, in many situations, is responsible for its diagnosis as these lesions are, for the most part, the initial manifestation of these diseases. In this study, a number of limitations were found, such as the impossibility of contacting some of the patients, reduction in the number of patients for carrying out the follow-up and the lack of access to the technique of direct immunofluorescence.

The performance of a larger number of studies, focusing on the follow-up of oral lesions associated with autoimmune vesiculobullous diseases, is of the utmost importance so that it will be possible to obtain an understanding of the best way to control these lesions in the daily routine of the clinic.

Collaborators

RIC GONÇALO, selection and examination of the patients, data collection, writing of the article, data analysis, adequacy of the article to the RGO norms. MLB SEVERO, data analysis, organized the tables, adequacy of the article to the RGO norms and critical review of the article. AMC MEDEIROS, followed the patients of the study, decided their clinical management and performed critical review of the article. PT OLIVEIRA, followed the data analysis and performed critical review of the article. ÉJD SILVEIRA, followed the patients of the study and decided their clinical management, helped to write the manuscript, performed the orientation, critical review and approval of final version of the article as well.

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