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Clinical and demographic overlaps among immunologically mediated oral diseases: a challenge for clinicians

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This study sought to assess and compare retrospective demographic and clinical data of oral lesions of *lichen planus, pemphigus vulgaris,* and mucous membrane pemphigoid from the records of the Department of Oral Pathology and Surgery, School of Dentistry, Universidade Federal de Minas Gerais, Brazil, covering a period of 55 years. Out of 25,435 specimens, these immunologically mediated diseases accounted for 301 (1.18%) cases, of which 250 (0.98%) were lichen planus, 27 (0.11%) were pemphigus vulgaris, and 24 (0.09%) were mucous membrane pemphigoid. Lichen planus presented mainly as white asymptomatic plaques on buccal mucosa. Pemphigus vulgaris was usually characterized by multiple symptomatic erythematous ulcers on the buccal mucosa. Painful ulcers and/or blisters on the gingiva were the most common presentation for mucous membrane pemphigoid. Desquamative gingivitis was noted for all 3 diseases, but mainly for mucous membrane pemphigoid. Overall, lesions were more frequent in white women >50 years.

Oral manifestations of immunologically mediated diseases are relatively rare, and the correct diagnosis can be a challenge for dentists as the lesions often share similar clinical and demographic features.

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Lichen planus, pemphigus vulgaris, and mucous membrane pemphigoid are the most frequent immunologically mediated mucocutaneous diseases with oral involvement. Frequently, the first manifestations of these systemic illnesses are plaques or vesiculobullous, ulcerative, and/or erosive oral lesions. It is noteworthy that the lesions in these 3 diseases and others (infectious and noninfectious) have similar clinical and demographic characteristics, therefore the identification of a disease based solely on oral lesions is a challenging issue for dentists, leading to a delay in the establishment of the correct diagnosis and suitable management of the patient. This is especially crucial considering that pemphigus vulgaris is a life-threatening disease with poor prognosis, and an early diagnosis is critical for successful treatment.[1-5]

In lichen planus, T lymphocytes are activated, leading to the destruction of the epithelial basal cell layer by apoptosis.[5,6] A possible association between lichen planus and infectious diseases, such as chronic hepatitis C, has been reported.[7] While still a matter of debate, lichen planus is considered as *at risk* for malignant transformation, according to the latest World Health Organization classification of tumors.[8-11]

Pemphigus vulgaris is a severe and life-threatening autoimmune chronic mucocutaneous disorder. In this condition, mainly IgG serum autoantibodies are raised against cadherin-type cell adhesion molecules of the squamous epithelium, generally desmoglein.[3] Oral lesions are a hallmark of pemphigus vulgaris and often herald the disease, being detected in almost every patient.[12-15] It is accepted that it has a fairly strong genetic background, with a higher prevalence in people from the Mediterranean and South Asia, and in certain ethnic groups, such as Ashkenazic Jews.[16]

In mucous membrane pemphigoid, the oral mucosa is often the first affected site, and it is exclusively involved in 85% of cases in the literature.[5,17,18] In addition, some patients may show systemic and severe complications, such as ocular involvement, which may culminate in symblepharon (adhesion between the eyelid and the eyeball) and blindness.[17,18]

The aim of this study was to retrospectively assess and compare the demographic data and clinical manifestations of oral lichen planus (OLP), oral pemphigus vulgaris (OPV), and oral mucous membrane pemphigoid (OMMP) from the Oral and Maxillofacial Pathology reference center of Minas Gerais, Brazil. The authors intended to provide relevant information about the similarities and differences among these diseases, allowing dentists to improve their ability to properly recognize the main clinical presentations of each.

Materials and methods

Biopsy charts were retrieved from the records of the Department of Oral Pathology and Surgery, School of Dentistry, Universidade Federal de Minas Gerais, Brazil. They comprised 25,435 cases from a period of 55 years. Cases with a histopathological diagnosis of OLP, OPV, or OMMP were considered for the study. H&E stained sections were re-examined according to current criteria.[5] Conflicting cases were reviewed by 2 experienced oral pathologists in order to reach a consensus. Cases showing clinical and histopathological features suggestive of lichenoid reaction were excluded.

Demographic data—gender, age, and skin color (white or nonwhite), along with the clinical features of the oral lesion (site, color, size, number of lesions, recurrence, evolution time, and symptoms)—were retrieved from the charts. Symptoms in oral lesions were defined as pain or a burning/itching sensation. The capacity in recognizing clinical presentations of OLP, OPV, or OMMP was evaluated comparing the clinical diagnostic hypotheses described in the charts with the final histopathological diagnosis. Descriptive statistical analysis was performed, and the study was approved by the Institutional Committee of Ethics in Research.

Table. Demographic and clinical data in number (%) regarding oral lesions of lichen planus (OLP), pemphigus vulgaris (OPV), and mucous membrane pemphigoid (OMMP).

	OLP 250 (83.1)	OPV 27 (8.9)	OMMP 24 (8.0)	Total 301 (100)
Gender				
Female	156 (62.4)	19 (70.4)	16 (66.7)	191 (63.5)
Male	93 (37.2)	8 (29.6)	8 (33.3)	109 (36.2)
NA	1 (0.4)	0	0	1 (0.3)
Age (years)				
10-19	7 (2.8)	0	0	7 (2.3)
20-29	23 (9.2)	2 (7.4)	4 (16.6)	29 (9.6)
30-39	56 (22.4)	7 (25.9)	3 (12.5)	66 (21.9)
40-49	63 (25.2)	7 (25.9)	3 (12.5)	73 (24.3)
50-59	50 (20.0)	6 (22.2)	5 (20.8)	61 (20.3)
60-69	25 (10.0)	4 (14.8)	5 (20.8)	34 (11.3)
70-79	8 (3.2)	0	3 (12.5)	11 (3.7)
80-89	1 (0.4)	0	0	1 (0.3)
NA	17 (6.8)	1 (3.7)	1 (4.2)	19 (6.3)
Skin color				
White	109 (43.6)	12 (44.4)	12 (50.0)	133 (44.2)
Nonwhite	127 (50.8)	14 (51.8)	11 (45.8)	152 (50.5)
NA	14 (5.6)	1 (3.7)	1 (4.2)	16 (5.3)
Site				
Buccal mucosa	183 (73.2)	18 (66.6)	5 (20.8)	206 (68.4)
Tongue	60 (24.0)	8 (29.6)	0	68 (22.6)
Gingiva	31 (12.4)	6 (22.2)	13 (54.1)	50 (16.6)
Lips	17 (6.8)	8 (29.6)	2 (8.3)	27 (9.0)
Retromolar area	12 (4.8)	4 (14.8)	0	16 (5.3)
Alveolar mucosa	10 (4.0)	3 (11.1)	3 (12.5)	16 (5.3)
Vestibular mucosa	7 (2.8)	2 (7.4)	1 (4.1)	10 (3.3)
NA	4 (1.6)	1 (3.7)	3 (12.5)	8 (2.7)

	OLP 250 (83.1)	OPV 27 (8.9)	OMMP 24 (8.0)	Total 301 (100)
Oral presentation				
Plaque	157 (62.8)	2 (7.4)	3 (12.5)	162 (53.8)
Ulcer	37 (14.8)	16 (59.2)	11 (45.8)	64 (21.3)
Macule	25 (10.0)	0	4 (16.6)	29 (9.6)
Papule	5 (2.0)	1 (3.7)	0	6 (2.0)
Blister	1 (0.4)	8 (29.6)	11 (45.8)	20 (6.7)
Tumor	1 (0.4)	0	0	1 (0.3)
NA	35 (14.0)	5 (18.5)	1 (4.2)	41 (13.6)
Desquamative gingivitis				
Yes	13 (5.2)	4 (14.8)	5 (20.8)	22 (7.3)
No	0	0	0	0
NA	237 (94.8)	23 (85.2)	19 (79.1)	279 (92.7)
Symptomatic				
Yes	37 (14.8)	21 (77.7)	16 (66.7)	74 (24.6)
No	172 (68.8)	0	5 (20.8)	177 (58.8)
NA	41 (16.4)	6 (22.3)	3 (12.5)	50 (16.6)
Lesion color				
Whitish	161 (64.4)	1 (3.7)	2 (8.3)	164 (54.5)
Erythematous	13 (5.2)	16 (59.2)	13 (54.2)	42 (14.0)
Whitish and erythematous	45 (18.0)	0	4 (16.7)	49 (16.3)
Pink	3 (1.2)	1 (3.7)	2 (8.3)	6 (2.0)
Blackened	7 (2.8)	0	0	7 (2.3)
Purple	0	1 (3.7)	0	1 (0.3)
NA	21 (8.4)	8 (29.6)	3 (12.5)	32 (10.6)

Abbreviation: NA, data not available.

Results

Autoimmune diseases accounted for 301 (1.18%) of the total (25,435) cases: OLP 250 (0.98%), OPV 27 (0.11%), and OMMP 24 (0.09%). Considering only the 301 autoimmune disease cases, 83.1% of the cases were OLP, 8.9% were OPV, and 8.0% were OMMP. Demographic and clinical data are summarized in the Table.

Oral lichen planus

Histopathological analysis of OLP revealed a squamous epithelium with para- or orthokeratinization, showing a typical degeneration of the basal layer, along with exocytosis. Immediately subjacent to the epithelium was a dense, band-like inflammatory infiltrate, composed predominantly of lymphocytes. Saw-toothed rete ridges and colloid (civatte) bodies could be seen in some cases (Fig. 1). The patients' age range was 16 to 81, with the highest prevalence between 40 and 60, and a mean age of 49.6. OLP affected mainly white women, with a female:male ratio of 1.68:1.[1]

Of the 250 cases diagnosed with OLP, the most affected site was the buccal mucosa, followed by the tongue and gingiva. Multiple lesions were noticed in 117 (46.8%) cases. Lesions were described as plaques in 157 (62.8%) cases, with a whitish color in 161 (64.4%) cases. Wickham striae (white or gray lines or dots often seen on the top of the papular rash and oral mucosal lesions in OLP) and desquamative (red, shredding, and/or ulcerative) gingivitis (DG) were reported in 36 (14.4%) and 13 (5.2%)

cases, respectively. In 26 (10.4%) cases, more than 1 clinical presentation was described simultaneously. For the 104 (41.6%) cases in which information about the size of the lesion was available, 56 (53.8%) of the lesions measured ≥10 mm, while 48 (46.1%) cases had lesions <10 mm. The presence of extraoral lesions was noticed in 11 patients, mainly in the face and upper limbs. In 125 (50%) of the 250 OLP cases, the evolution time was ≤1 year, and 42 (16.8%) were >1 year. In 83 (33.2%) cases, this information was unknown. Primary manifestations (76%) were more common than recurrences (12%). Symptoms were reported in 37 (14.8%) cases, and ulcerations were described in 37 (14.8%) patients.

OLP was the first clinical diagnostic hypothesis in 213 (85.2%) cases, while in 37 (14.8%) cases, this possibility was not considered by the specialists. In 58 (23.2%) cases, leukoplakia and hyperkeratosis were also mentioned as differential diagnoses. In 221 (88.4%) cases, the patient was referred by a general dentist or physician without any clinical diagnostic hypothesis.

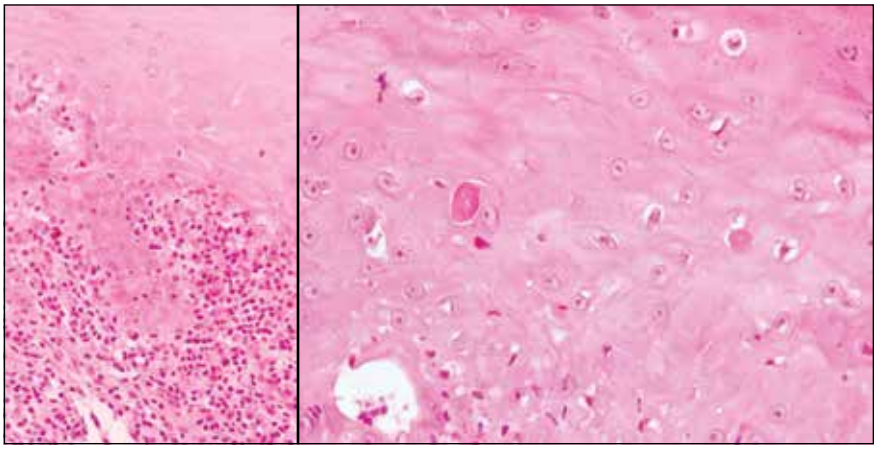

Fig. 1. Oral lichen planus. *Left.* The typical degeneration of the basal layer along with exocytosis and a dense band-like subepithelial lymphocytic inflammatory infiltrate (H&E, magnification 200X). *Right.* Civatte bodies (H&E, magnification 400X).

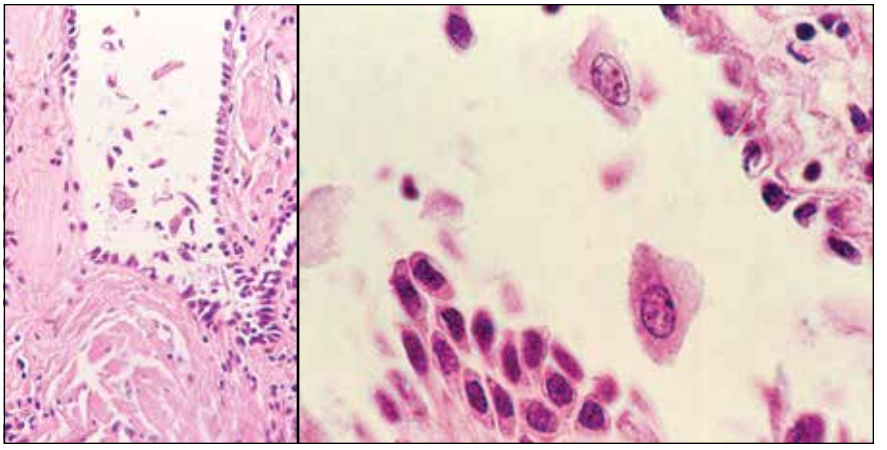

Fig. 2. Oral pemphigus vulgaris. *Left.* The intraepithelial suprabasilar cleft. Basal layer cells remain adherent to the underlying basement membrane zone (H&E, magnification 400X). *Right.* Acantholytic (Tzanck) cells in the cleft (H&E, magnification 1000X).

Oral pemphigus vulgaris

Histopathological features of perilesional biopsy specimens of OPV showed a characteristic intraepithelial suprabasilar clefting with acantholytic (Tzanck) cells, which tended to present a round shape. The basal layer cells remained adherent to the underlying basement membrane zone, and a mild to moderate chronic inflammatory infiltrate was usually seen in the connective tissue (Fig. 2). The patients' age range was 23 to 64, with the highest prevalence between 40 and 60, and a mean age of 44.8. White women were the most affected, with a female:male ratio of 2.38:1.

Of the 27 cases diagnosed with OPV, lesions were found mainly in the buccal mucosa, with DG reported in 4 (14.8%) cases. In 16 (59.2%) cases, dentists reported multiple lesions. However, in 11 (40.7%) cases, this information was unavailable. The most common clinical presentation was of an erythematous (red, swollen) ulcer. For the 11 (40.7%) cases in which information about the size of the lesion was available, 6 (54.5%) lesions were >10 mm in diameter, while 5 (45.5%) were ≤10 mm. The presence of a positive *Nikolsky's sign* (a "slipping away" of the skin; a common lesion in OPV) was observed in 3 (11.1%) cases. Extraoral manifestations could be seen in 9 cases: 3 (11.1%) each in the face, upper limbs, and genitals.

In 20 cases (74.0%), patients presented for treatment ≤6 months after the first symptoms appeared, and 2 cases (7.4%) presented >6 months. This information was missing in 5 (18.5%) charts. Primary lesions were more prevalent (88.9%) than recurrent ones (3.7%), with data unavailable in 7.4% of the cases. Symptoms were present in 21 (77.7%) cases.

Among the clinical diagnostic hypotheses, OPV was considered in 22 (81.5%) cases; neither OPV nor other immunologically-mediated diseases were diagnosed in 3 cases (11.1%). In 21 (77.8%) cases, neither the physician nor the general dentist who referred the patient made a diagnostic hypothesis.

Oral mucous membrane pemphigoid

Microscopic evaluation of a perilesional biopsy revealed a detachment of the epithelium from the lamina propria at the basement membrane, giving rise to

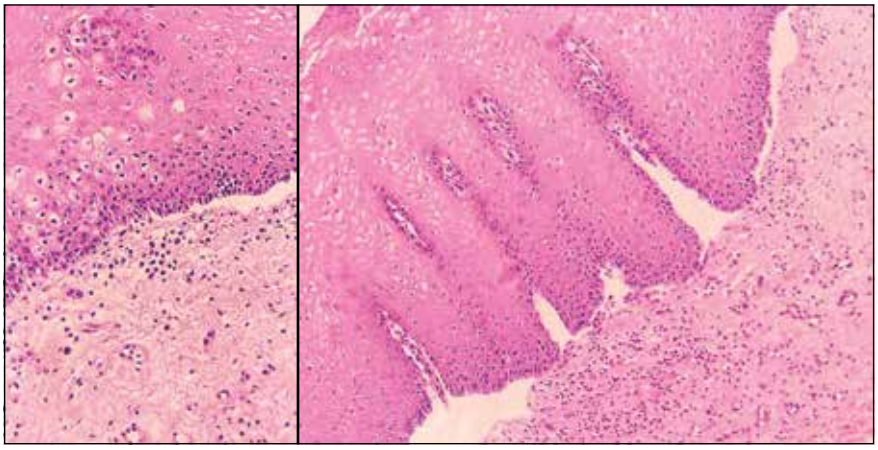

Fig. 3. Oral mucous membrane pemphigoid. *Left.* Perilesional biopsy showing a junctional separation of the basement membrane from the connective tissue (H&E, magnification 200X). *Right.* Closer view of the subepithelial split (H&E, magnification 400X).

a sub-basilar split, without acantholysis. A predominantly chronic inflammatory infiltrate could be observed in the connective tissue in all cases (Fig. 3). The patients' age range was 20 to 76, with a homogeneous distribution between 30 and 76 and a mean age of 49.9. Most cases of OMMP affected white women, with a female:male ratio of 2:1.

Of the 24 cases diagnosed with OMMP, gingival mucosa was involved in the majority of patients, with DG in 5 (20.8%) cases. Multiple lesions were observed in 13 (54.1%) cases, while single lesions were noticed in 11 (45.8%) patients. Ulcers and blisters were the main clinical manifestation, displaying erythematous (abnormal redness) in 13 (54.2%) cases. For the 5 (20.8%) cases in which information about the size of the lesion was available, lesions measured ≤10 mm in diameter.

Neither a Nikolsky's sign nor an extraoral involvement was reported in the OMMP cases. Search for treatment took place approximately 6 months after the beginning of the symptoms in 10 (41.6%) cases and <6 months in 8 (33.3%) cases. Data were not available in 6 (25%) charts. Manifestations were primary in 10 (41.6%) cases and recurrent in the other 10 (41.6%) cases. The data from the remaining 4 (16.7%) cases could not be assessed. Of the 16 (66.7%) cases with available information, all were symptomatic lesions.

At clinical evaluation, the hypothesis of OMMP was considered in 16 (66.7%) cases, while in 7 (29.1%) cases, this diagnosis was not considered. In 4 cases (16.6%), all 3 diseases (OLP, OPV, OMMP) were considered. In 19 (79.2%) cases, the physician or general dentist who referred the patient was not able to make a diagnosis.

Discussion

Immune-mediated mucocutaneous disease may present oral involvement, in which a pathological process promotes the loss of epithelial integrity. The primary etiology of these conditions is not fully understood, although the cellular and/or humoral immune responses are thought to play a central role. Such immune responses are directed against epithelial or connective tissue, in a chronic and recurrent pattern.[3,16,18,19] In the current study, we evaluated the 3 most frequent immunologically mediated diseases with oral manifestations: OLP, OPV, and OMMP.

Taken together, OLP, OPV, and OMMP accounted for 1.18% of all the assessed records in this study, and this prevalence is in accordance with other authors.[20,21] However, as our sample only included biopsy specimens, we believe that our results may be underestimated. This point has to be emphasized, as patients may not be aware of the presence of these diseases, such as the asymptomatic lesions of OLP.[22] It is also of note that in this study, OPV lesions were more frequent than OMMP ones, in contrast with the current literature.[16,21] However, in our study, the OPV female:male ratio was 2.38:1, in accordance with the literature regarding the gender predilection in OPV.[5,14] These findings have to be analyzed with caution, based on our relatively small sample. Additionally, patients with mucous membrane pemphigoid may not show an oral involvement.

In the present study, the most common description of OLP was white plaques on the buccal mucosa of white women >50 years of age. OPV usually appeared as multiple symptomatic erythematous ulcers on the buccal mucosa of white women >45 years of age. The general description for OMMP was painful ulcers and/or blisters on the gingiva of white women >50 years of age. These descriptions show that similarities among the demographic data of patients with OLP, OPV, and OMMP are often observed. Considering the prevalence of immune-mediated diseases in the general population, when seeing a patient with a probable oral immune-mediated lesion, a dentist can reasonably consider OLP first, followed by OMMP, then OPV. The careful evaluation of the lesion's presentation is pivotal to presume the correct clinical diagnosis. It also must be considered that the "classic" characteristics of each disease are not always observed in every patient. This is the reason the differential diagnosis may pose a clinical challenge.

Concerning the epidemiological features found in the present study, the higher prevalence of lesions in white patients must be interpreted with caution, as the study population exhibited a great race miscegenation.[23] The observed predilection for females has been extensively reported in the literature for OLP and OMMP, with Scully & Challacombe and Alkan et al reporting female:male ratios of 1.75:1 and 2:1, respectively.[18,24-27]

The mean age of onset of the 3 diseases were quite similar, so we can expect to see most patients at >50 years.[5,12,13,25,28-30] OLP seems to have an earlier onset in males, with little or no clinical significance, as proposed by other authors.[19,20] The study revealed that OLP affected a wider age range than OPV and OMMP. Immune-mediated diseases are relatively rare in childhood, however, the wide age distribution of

OLP, OPV, and OMMP allows for the possibility of seeing an oral immune-mediated lesion in patients at any age.[21,27] Health care professionals should be aware of these diseases and perform a careful examination of the patients' oral mucosa.

The most affected site of OLP and OPV was the buccal mucosa, while OMMP lesions occurred mainly in the gingiva. Indeed, DG is more prevalent in OMMP, although it is also reported in OLP and OPV. This supports the idea that when a patient presents only gingival involvement, while OMMP may be the first consideration, OLP and OPV have to be included as possibilities.[17,18,25,31-34] Some authors have stated that OLP is the main cause of DG.[35,36]

DG usually results from a pathological process that causes detachment or erosion of the epithelium from the underlying connective tissue of the oral mucosa. DG may be a clinical manifestation of several mucocutaneous diseases, most commonly OLP, OPV, and OMMD.[36] This is in accordance with our study, in which this feature was described for all the evaluated diseases. The correct diagnosis of the underlying disease in patients with DG requires careful clinical observation, detailed medical history, and histopathological examination of the lesions. In addition, other exams may be necessary, such as direct and indirect immunofluorescence.[34,36,37] Inflammatory periodontal disorders are the most common causes of alterations in gingival tissue. Nevertheless, when gingival diseases are nonresponsive to classic periodontal therapy, the diagnostic hypothesis of an immune-mediated disease must be considered.

The lesion itself appears quite commonly as white plaques in OLP, while ulcers were frequently seen in OPV and OMMP. The most common and easily recognized presentation of OLP comprises white reticular lesions, which helps distinguish OLP from OPV and OMMP.[9] Other lesions can mimic OLP, so it is important that all lesions with a clinical suspicion of OLP undergo a biopsy and histopathological examination, even those cases with the classic clinical presentation of OLP (bilateral white striae in buccal mucosa). Some erosive forms of OLP may be clinically misdiagnosed as other immune-mediated conditions.[9]

The presence of a blister may suggest OMMP rather than OPV. The subepithelial nature of OMMP blistering produces a thicker, longer lasting, and more well-defined lesion than those found with OPV, which may help in the proper diagnosis.[5]

Multiple lesions occur at similar rates (>50%) in OLP, OPV, and OMMP patients, showing the importance of carefully screening the oral mucosa of these patients at every appointment in order to provide the best clinical assistance and treatment.[25,30,38] According to the results of this study, the size of the lesion does not seem to be important for diagnosis.

Symptomatic lesions could be observed in these 3 diseases, although much less in OLP than in OPV and OMMP. Since the most common presentation of OLP does not include symptomatic lesions, the management of the patient may include only a strict follow-up.[10] Moreover, patients with OPV and OMMP may look for dental or medical assistance earlier, due to the presence of painful lesions. It is important to mention that 14.8% of OLP lesions were symptomatic as well, and the authors believe that this finding is probably related to the erosive forms of the disease.

The presence of a positive Nikolsky's sign may be helpful for diagnosis.[39] As extraoral involvement was reported in this study for OLP and OPV, dentists may investigate this possibility within their patients. Coexisting cutaneous and oral lesions of pemphigus vulgaris were reported in 9 (33.3%) cases, supporting the current literature, which states that in the majority of these patients, oral lesions can be the first manifestation of this life-threatening illness, likely preceding cutaneous lesions by months.[15,25] An investigation of extraoral involvement is warranted for the diagnosis and correct management of the patient, who may need a multidisciplinary approach.

A high index of agreement was observed between clinical hypotheses suggested by the specialists and the histopathological diagnoses. For OLP and OPV, matching results were found in 88.4% and 88% of the cases, respectively. For OMMP, this index was 69.5%. This difference is probably due to the high prevalence of DG in OMMP, in spite of its nonspecific nature for any immune-mediated disease. In some cases, non-autoimmune diseases were considered in the clinical diagnosis, especially among OLP cases (23.2%), in which leukoplakia and hyperkeratosis were common and reasonable hypotheses. The high accuracy reported herein may reflect a bias, as the majority of the patients were from the authors' own university department, although most of these patients were referred by physicians and general dentists without any diagnostic hypotheses. This fact reflects the inability of some physicians and general dentists to recognize the main clinical features of these immune-mediated disorders.

Conclusion

With the results of this study, it can be assumed that immune-mediated diseases with oral manifestations are relatively rare among oral lesions. To the authors' knowledge, the present study comprises the largest retrospective assessment of oral immunologically mediated diseases, in which data regarding the 3 diseases were retrieved and analyzed altogether. As those lesions can often present similar clinical features and demographic data, their precise recognition can be a challenge for dentists. A correct and early diagnosis is of paramount importance for a proper therapeutic decision and appropriate approach to the patient's treatment. For this matter, despite the emergence of new, promising drugs in the market, immunosuppressives (mainly corticosteroids) are still the mainstay of treatment, and their harmful side effects have to be seriously considered.[10,40]

Taking into account the relative low prevalence of oral manifestations of immune-mediated diseases, large epidemiological studies regarding these conditions are clearly needed. Moreover, to fill in patients' charts properly is essential to prevent research bias related to missing data and to provide more reliable information on this issue.

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