Clinicopathological analysis of oral mucous autoimmune disease: A 27-year study

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Abstract

Objectives: The aim of the present study was to analyze the main clinical and histopathological features of autoimmune diseases with oral manifestations such as oral lichen planus (OLP); mucous membrane pemphigoid (MMP); pemphigus vulgaris (PV) and erythema multiforme (EM).
Study design: Retrospective review of 5770 files from the Oral Pathology Laboratory of São José dos Campos Dental School, São Paulo State University (UNESP) comprising a 27-year period from 1974 to 2000.
Results: The cases accounted for 64 (1.10%) of 5770 anatomopathological examinations performed over the study period. Among the autoimmune diseases diagnosed, 49 (76.56%) were OLP, 6 (9.37%) were MMP, 5 (7.82%) were EM and 4 (6.25%) were PV. Descriptive statistical analysis was used.
Conclusion: The initial manifestations of most autoimmune diseases occur in the oral mucosa. An earlier diagnosis and proper therapeutic protocol will delay the dissemination of the lesions, thus greatly contributing to a better prognosis and quality of life of the patient.

Key words: *Autoimmune diseases, lichen planus, pemphigoid, mucous membrane, pemphigus, erythema multiforme.*

Introduction

A detailed clinical examination of the oral mucosa of an asymptomatic patient can be the best opportunity for the early diagnosis of an autoimmune disease, since many autoimmune diseases show their primary signs in the mouth. Although vesicles and bullae are associated with a large number of non-related conditions, i.e., herpes infections, bullous lichen planus, EM and thermal burns, autoimmune diseases comprise a specific group of diseases in which these lesions primarily occur. Early detection and treatment of autoimmune vesiculobullous diseases, sometimes showing a severe evolution (e.g. PV), allows the control of their dissemination and involvement of skin and/or other body organs (1-10).

Vesiculobullous, erosive or ulcerative disorders affecting the oral mucosa or gingivae can be very difficult to diagnose clinically. It is crucial to establish the diagnosis of diseases such as PV clearly and as early as possible to provide adequate treatment (4-5). Bullae may occur in multiple areas of the mucosa or skin and a biopsy is essential for a correct histopathological diagnosis. A biopsy is necessary in the case of doubt regarding the nature of vesiculobullous lesions in the mouth; therefore, anatomopathological features are essential for the correct diagnosis of the diseases studied (2).

In the clinical and histopathological study of mucous lesions of autoimmune conditions such as PV, MMP, EM and OLP, observation of the representative findings

of each disorder permits the correct diagnosis and, consequently, suitable treatment (1-10).

The aim of the present study was to analyze the main clinical and histopathological aspects of oral autoimmune diseases over a period of 27 years.

Materials and Methods

The present study is based on a retrospective review of 5770 files from the Oral Pathology Laboratory, Department of Biosciences and Oral Diagnosis, São José dos Campos Dental School, São Paulo State University comprising a 27-year period from 1974 to 2000. The inclusion criteria considered all cases diagnosed as OLP, MMP, PV and EM. Each case was evaluated with respect to age, gender, ethnic origin, and location and symptoms of the lesions. The majority of case files contained the necessary data for analysis. The hematoxylin and eosin-stained sections of all included cases were reviewed. Descriptive statistical analysis was used to summarize the demographic and clinical features of the study group.

Results

The lesions studied accounted for 64 (1,10%) cases of all anatomopathological examinations (5770) performed at the Oral Pathology Laboratory comprising a 27-year period from 1974 to 2000. Among a total of 64 autoimmune diseases, 49 (76,56%) were OLP, 6 (9,37%) were MMP, 5 (7,82%) were EM and 4 (6,25%) were PV. Diagnosis related to the gender, evolution time of the lesions and location is shown in Table 1.

- *Oral Lichen planus*

Most cases of OLP (50%) occurred between the 4th and 5th decades of life, with the oldest patient being 65 years of age and the youngest 16 years. No age information was available for two cases, and the mean age of the other three patients was about 40 years. OLP was more frequent in female and white patients (Table 1). Analysis of the clinical data showed that OLP lesions usually manifested as papules or plaques (83%), frequently with a reticular aspect (57%), and 41% of the patients reported some painful symptoms. The most affected anatomical site was the buccal mucosa (62%), followed by the alveolar mucosa (19%), tongue (14%) and lips (2%) (Table 1). Histopathological analysis of the OLP biopsies revealed infiltration of inflammatory cells with a predominance of lymphocytes characteristically distributed as a localized band underlying the epithelium in 97% of cases, hydropic degeneration of the basal cell layer with loss of the distinct limits of the epithelial/connective tissue interface in 90%, hyperkeratosis in 55%, hyperorthokeratosis in 26%, acanthosis and hyperplasia in 35%, and a sawtooth configuration of the rete pegs in 28%.

- *Mucous membrane pemphigoid*

MMP lesions showed no gender (Table 1) or ethnic origin preference. The disease was diagnosed in 50% of patients in the 5th and 6th decades of life, in two patients (33%) in their eighties and in one patient in his twenties. The evolution of the disease ranged from 1 to 11 months in four patients (Table 1), while no information was available for the other patients.

Clinical manifestations of MMP included ulcerated lesions (100%) and a positive Nikolsky's sign (50%). There were visible bullae in about 33% of patients and some reported painful symptoms. The alveolar mucosa was the most affected area, followed equally by the lips and buccal and soft palate mucosa. More than one area was involved in one patient. Histological analysis showed subepithelial bullae and a chronic inflammatory infiltrate with eosinophils in all cases. Epithelial atrophy and exocytosis were observed in four microscopic samples.

- *Erythema multiforme*

EM was diagnosed in five white patients (4 females and

Table 1. Diagnosis related to the gender, evolution time of the lesions and location.

Diagnosis	Gender	Evolution time of lesions	Location
OLP	43 woman 6 man	8 between 1 and 5 months, 3 between 6-11 months, 9 more than 12 months and 29 NI	30 buccal mucosa, 9 alveolar mucosa, 7 tongue, 1 lips
MMP	3 woman 3 man	2 between 1 and 5 months, 2 between 6-11 months, 2 NI	6 alveolar mucosa, 1 lips, 1 buccal mucosa, 1 soft palate mucosa
EM	4 women 1 man	3 less than 1 months, 2 more than 12 months	3 skin, 2 hard palate mucosa
PV	2 woman 2 man	2 between 1 and 5 months, 1 between 6-11 months, 1 more than 12 months	3 buccal mucosa, 3 alveolar mucosa, 3 soft palate mucosa, 1 tongue, 1 lips

1 male). The age of the patients was mentioned in only two cases, both in their forties. The evolution of the disease was less than 1 month in three cases and more than 12 months in the other two. Concerning the anatomical location, three samples were obtained from the skin and one from the hard palate (Table 1).

Frequently reported clinical aspects of these lesions (5) included generalized erythema (100%), aspect of recurring erythema (75%), and the presence of bullae (50%). Histologically, a perivascular inflammatory cell infiltrate was characteristically observed in all cases, while intracellular edema, spongiosis, hyperkeratosis and cleavage between the epithelium and connective tissue were noted in only 25% of the cases.

- *Pemphigus vulgaris*

PV only affected individuals in the 4th decade of life, with prevalence in whites (75% of cases). The most affected anatomical sites included buccal, alveolar and soft palate mucosal areas, corresponding to 75% of all biopsies. In several patients more than one area was affected, such as tongue and lips (Table 1). The evolution time of the disease ranged from one month to more than one year (Table 1). Ulceration of the lesions was observed in all samples studied (100%) and bullae were noted in 75% of cases, with painful symptoms being reported by only 50% of the patients. Histological analysis of all samples studied showed development of intraepithelial vesicles, acantholysis and "Tzanck cells" in 75% of cases and a perivascular inflammatory infiltrate in 50%.

Discussion

Vesiculobullous lesions comprise a group of skin and mucosal diseases with distinct macro- and microscopic features. An objective clinical exam and meticulous anamnesis will permit the detection of these diseases in preliminary stages. The histopathological analysis of the lesions, which usually begin in the oral epithelium, is essential for a correct diagnosis. It should be emphasized that an early diagnosis will allow proper treatment, delaying or even preventing the dissemination of the lesions as observed in PV (1-10). The relative frequency of OLP, MMP, EM and PV on the reviewed records of the Oral Pathology Laboratory between 1974 and 2000 was 49:6:5:4, respectively.

OLP was more frequent than the other diseases studied. Our results confirm those reported by Silverman et al (11) and Zegarelli and Sabbagh (12) who, in addition to its higher prevalence, observed that OLP especially affects white adult females. The high prevalence of OLP in middle-aged women suggests that the disease might be associated with the hormone disturbances typical of this age group (11). The hypothesis of these authors is supported by others (6,13-14) linking mucosal changes to autoimmune factors (15), since lymphocytes are predominant in this disease. In addition, the effectiveness of corticotherapy may prove this theory to be correct (10).

The long period of evolution of the disease can be explained by the lack of symptoms of the lesions, which go unnoticed by the patient. Pain motivates the patient to seek a specialized service, a fact explaining the large number of patients reporting pain in the present study. The buccal mucosa was the site most frequently affected by the disease in agreement with the results reported by Ingafou et al (16) and Buajeeb et al (17). Clinicians can observe the presence of keratotic, pinhead sized, white, slightly elevated papules, discrete or arranged in reticular or plaque-like configurations. Essential histological aspects for the diagnosis of OLP are mononuclear inflammatory infiltration with a predominance of lymphocytes arranged in a band-like pattern beneath the epithelium and hydropic degeneration of the basal cell layer, accompanied by a loss in brightness of the distinct limits between the epithelium and connective tissue. Hyperparakeratosis rather than hyperorthokeratosis is associated with these lesions in the oral mucosa as seen in the present study. Cases showing the above mentioned histopathological characteristics could be diagnosed as OLP.

Analysis of the clinical data obtained from patients with MMP confirms the preferred occurrence of these lesions in the oral mucosa of patients older than 40. The time between the onset of symptoms and diagnosis was relatively short, probably because of the patients' discomfort caused by bullae, ulcerations and subsequent pain. These data agree with those reported by Silverman et al (14), Lamey et al (18) and Siegel and Anhalt (19) who showed the alveolar and buccal mucosa, lips and soft palate mucosa to be the most affected areas. A positive Nikolsky's sign is an important feature which, combined with other aspects, may lead to the diagnostic hypothesis of MMP. The most appropriate area for a biopsy is not an erosion region, which generally has lost the epithelium, but a vesicular or perilesional lesion. A gingival biopsy should be avoided since chronic inflammation of the gingiva may confuse the histological aspects (1). Histological analysis of the cases demonstrated the characteristic findings of MMP, such as sub-basal layer cleavage at the union between the epithelium and connective tissue and chronic inflammatory cell infiltration with the presence of eosinophils (14,18-19).

EM comprises a group of mucocutaneous disorders characterized by variable degree of mucosal and cutaneous blistering and ulceration. The exact pathogenesis of EM is unknown (20). Diagnosis usually entails excluding other similar diseases by careful review of the clinical history and detailed clinical examination. EM is often associated with preceding herpes simplex virus (HSV) infection. Aside from HSV infection, a wide variety of other viral, fungal and bacterial infections have also been implicated in triggering EM (20). However, food additives, chemicals, and drugs have also been reported as triggering factors (7). It has been suggested that an immunologically mediated (i.e., lymphocytic) reaction to an infectious agent or drugs

leads to skin and mucosal lesions at the dermal-epithelial junction (20). Microscopically, EM is characterized by keratinocyte necrosis, intracellular edema of the epithelium in the prickle cell layer, acanthosis, and a perivascular inflammatory cell infiltrate with a thin basement membrane adhered to the epithelium (4,20).

PV seems to be a disease whose early diagnosis in the oral mucosa may significantly change the course and progression of the disease (2-3,9-10). Oral lesions occur during an early stage when the oral epithelium largely expresses desmoglein 3 (2-4,9). The disease can affect all age groups (3-6, 21-22). In the present study all patients were between 32 and 39 years of age. There was no gender preference, as also reported in the study of Camacho-Alonso et al. (4), Robinson et al. (23). The evolution of the disease showed a wide variation, ranging from 1 month to 3 years. Femiano et al. (8) reported five cases of patients with PV who were clinically diagnosed as possibly suffering from recurrent aphthous stomatitis. Patients rarely report the intraoral formation of vesicles or bullae, and these lesions can seldomly be identified by clinical examination because of their thin, friable roof (6,22,24). The significant involvement of the buccal, alveolar and palatine mucosae agrees with the reports of Scully et al. (22) and Robinson et al. (23). The present histological findings agree with those described in the literature for PV (6,18,21). The diagnosis of PV requires the combination of clinical and histopathological findings, as well as immunohistochemical tests when available. According to Black et al. (2), histological and immunohistochemical analysis of biopsies obtained from perilesional tissue is essential for the diagnosis of PV. PV is associated with an autoimmune reaction resulting from the presence of circulating IgG class autoantibodies directed against desmosome components, which leads to the formation of bullae on the skin and on mucous membranes (23). The etiology of PV is uncertain and a genetic predisposition has been suggested (2,22). The early diagnosis of oral PV lesions facilitates the treatment and control of the disease.

Conclusions

Autoimmune diseases with oral manifestations are not common in the population studied. Since the initial manifestations of most of these diseases occur in the oral mucosa, an earlier diagnosis and proper therapeutic protocol will delay the dissemination of these lesions, greatly contributing to a better prognosis and quality of life of the patient.

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