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ORIGINAL ARTICLE

Periodontal status in oral mucous membrane pemphigoid: initial results of a case-control study

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OBJECTIVE: To evaluate the periodontal status of mucous membrane pemphigoid (MMP) patients and compare it with that of healthy controls.

METHODS: A prospective study was undertaken to examine the impact of gingival MMP lesions on the human periodontium of 29 patients. Parameters evaluated included full mouth plaque score (FMPS), full mouth bleeding upon probing scores, probing depths (PD), gingival recession, clinical attachment level (CAL), mobility score, furcation involvement, number of missing teeth and Machtei criteria.

RESULTS: All periodontal parameters recorded were increased in cases when compared to controls in univariate statistics. The mean differences between groups in PD (0.8 ± 0.2 mm, 95% CI 0.3–1.3), CAL (1.3 ± 0.4 mm, 95% CI 0.4–2.2), FMPS (41.0 ± 6.2%, 95% CI 28.7–53.4), FMBS (16.2 ± 6.6%, 95% CI 3.0–29.4) and tooth loss (2 ± 1 teeth, 95% CI 1–3) were all statistically significant ($P < 0.01$ for all). Substantial differences in domiciliary oral hygiene routines were observed ($P < 0.0001$). In multivariate models when FMPS was included as covariate the difference between groups in all clinical periodontal parameters was no longer statistically significant.

CONCLUSIONS: Our results showed that periodontal status is worse in MMP patients if compared with healthy controls due to a substantial difference in oral hygiene. Oral health should be promoted in MMP.

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Introduction

Mucous membrane pemphigoid (MMP) describes a heterogeneous group of chronic, inflammatory, sub epithelial blistering diseases that manifest macroscopically with a constellation of oral, ocular, skin, genital, nasopharyngeal, oesophageal, and laryngeal lesions. MMP is microscopically characterized by linear deposition of IgG, IgA or C3 along the epithelial basement membrane zone (BMZ) (Scully and Lo Muzio, 2008). It is well documented that scarring and loss of function are the foremost sequelae of the disease, with the exception of a subset of patients with mucous membrane disease restricted to the oral mucosa. The possible link between BMZ-specific autoantibodies and the scarring sequelae of the disease remains to be fully elucidated. Indeed circulating autoantibodies, only detectable in some MMP patients, target several BMZ components including the bullous pemphigoid antigens of 180 (BP180) and 230 (BP230) kDa, the a6b4 integrin, and laminin 5 (Chan *et al*, 2002).

The oral cavity and in particular the gingival tissue are the most common sites for MMP, accounting for 83–100% of all the MMP patients reported (Chan, 2001). The oral cavity can also be the only site of onset and manifestation of the disease. Gingival MMP is characterized by erythematous lesions, blisters, erosions, and ulcers, mainly located on the attached gingiva and palatal mucosa. The presence of epithelial desquamation, erythema, and erosive lesions on the gingival tissue is described as 'desquamative gingivitis' (DG) (Leao *et al*, 2008; Lo Russo *et al*, 2009). It has been suggested that DG could play a role in increasing the long-term risk for periodontal tissue breakdown at specific sites (Lo Russo *et al*, 2008; Schellinck *et al*, 2009); there is however scarce evidence to support such hypothesis.

The aim of this case–control study was therefore to examine and compare the periodontal status of individuals with gingival MMP compared to controls.

Patients and methods

Study population

A prospective case-control design was used to compare the periodontal status of individuals with MMP and age- and gender-matched controls. Twenty-nine unrelated Caucasians patients presenting with erosive and/or bullous oral lesions with DG, referred at the Oral Medicine Unit of the University of Turin (Italy) from November 2007 to November 2009, were included in this study as cases. The clinical diagnosis was confirmed in all cases by histopathological examination, which revealed the sub epithelial blistering process, and by direct immunofluorescence analysis.

Medical and present complaint histories were taken at the time of the first consultation by interview. Exclusion criteria included: (i) history of previous and/or current treatment for desquamative gingival lesions; (ii) history of previous periodontal therapy (surgical and non surgical); (iii) less than 18 teeth and (iv) pregnancy. Further patients with a positive history of diabetes mellitus and uncontrolled cardiovascular diseases, were also excluded.

A group of 30 controls, matched for age and gender, unrelated to cases were recruited among the population attending the University Hospital of Turin. All controls presented with no history of desquamative gingivitis related to MMP. All patients gave written informed consent and ethical approval was obtained by the local ethics committee at the Lingotto Dental School, University of Turin.

Clinical parameters

The oral clinical examination was performed by a single calibrated investigator (PGA), together with a comprehensive periodontal examination for the entire dentition, including the following criteria, as previously reported (Tricamo *et al*, 2006): full mouth plaque scores (FMPS), accomplished by having patients rinse after application of a disclosing solution; probing pocket depths (PD), defined as the distance from the free gingival margin to the base of the pocket; gingival recessions, recorded when the free gingival margin was apical to the cemento-enamel junction (REC); clinical attachment level (CAL) calculated from the formula (PD–REC); mobility score; full mouth bleeding upon probing scores (FMBS), considered positive if occurred within 20 s after the probe was removed following application of pressure with the probe tip; molar furcation involvement; number of missing teeth, determined by subtracting the number of teeth present from 32. All periodontal measurements were performed on six surfaces on each tooth (mesiobuccal, mid-buccal, disto-buccal, mesio-lingual, mid-lingual, and disto-lingual), using a manual periodontal probe (PCPUNC15: Hu-Friedy®, Chigago, IL, USA), and the readings were rounded up to the nearest 1 mm. Calibration of the examiner involved doubled full mouth PD/CAL measurements on 10 non study subjects. The examiner was judged to be reproducible if 90% of measurements were within 1 mm of agreement. A standardized digital sheet was used for systematic recording of the mentioned parameters as well as the presence and the exact location (site by site) of DG lesions (Lo Russo *et al*, 2009). Subjects were considered to be positive for periodontal disease if they have 2 or more teeth with CAL ≥6 mm and 1 or more sites with PD ≥6 mm (Machtei *et al*, 2000).

Oral hygiene domiciliary scores (DOH) were recorded as detailed in Table 1.

Table 1 Definition of oral hygiene domiciliary (DOH) scores

Score	*Daily number of teeth brushing*	*Use of flossing device*	*Cleaning of the tongue*
1	< 1	No	No
2	1	No	No
3	1	Yes	Yes
4	≥2	Yes	Yes

Statistical analysis

A sample size of 27 individuals per group would achieve 90% power to detect a difference of 1 mm in whole mouth PD between cases and controls (estimated group standard deviations of 1.1 mm) alpha = 0.05 using a two-sided two-sample *t*-test.

All data are reported as means and standard error unless otherwise stated. Differences in periodontal clinical parameters (PD, CAL, FMBS; FMPS) between groups and controls were analyzed by ANOVA. Categorical variables were computed with the χ^2 statistic test was used. Multivariate linear models were created to test differences in clinical periodontal parameters including as covariates: age, gender, smoking (categorized as current *vs* never), body mass index (BMI) (calculated as weight height^{-2} and presented in kg m^{-2}) and FMPS differences. We created a model 1 including only all demographic common covariates and model 2 fully adjusted for all covariates including FMPS. Linear correlation analyses were performed with Spearman rank test. *P*-values ≤ 0.05 were considered to be statistically significant. SPSS (SPSS for windows, version 17, SPSS inc, Chicago, IL, USA) statistical software was used.

Table 2 Clinical periodontal parameters of mucous membrane pemphigoid patients and healthy controlled patients

Variables (mean ± se)	*Cases*	*Controls*	P *value*[a]
Age	54.2 ± 2.7	51.7 ± 2.4	0.492
Female, *n* (%)	25 (86.2)	20 (66.7)	0.125[b]
Smoking current, *n* (%)	3 (10.3)	5 (16.7)	0.706[b]
BMI (kg m^{-2})	23.8 ± 0.6	22.4 ± 0.6	0.115
PD (mm)	3.2 ± 0.1	2.4 ± 0.2	0.001
CAL (mm)	3.1 ± 0.3	1.8 ± 0.3	0.006
FMPS (%)	79.2 ± 4.3	38.1 ± 4.4	< 0.0001
FMBS (%)	50.6 ± 4.8	34.4 ± 4.5	0.017
Tooth loss	4.6 ± 0.6	2.4 ± 0.5	0.01

FMPS, full mouth dental plaque scores; FMBS, full mouth gingival bleeding upon probing scores; BMI, body mass index; PD, probing depths; CAL, clinical attachment levels.
[a]Differences are calculated with ANOVA.
[b]Differences are calculated with chi-square test.

Results

Cases and controls demographic and clinical characteristics are presented in Table 2. Briefly both groups were comparable with regards to age, gender, smoking and BMI differences. The duration of oral DG symptoms before definitive diagnosis performed in our clinic varies from 4 to 72 weeks, leading to a mean delay of 24.5 weeks. On average, cases presented with 49.2 sites (range 18–96 sites) affected by DG, which corresponded to a mean of 36% of the total sites. All clinical periodontal parameters recorded were however increased in cases when compared to controls in univariate statistics. The mean differences between groups in PD (0.8 ± 0.2 mm, 95% CI 0.3–1.3), CAL (1.3 ± 0.4 mm, 95% CI 0.4–2.2), FMPS (41.0 ± 6.2%, 95% CI 28.7–53.4), FMBS (16.2 ± 6.6%, 95% CI 3.0–29.4) and tooth loss (2 ± 1 teeth, 95% CI 1–3) were all statistically significant ($P < 0.01$ for all). Substantial differences in domiciliary oral hygiene routines were observed (Figure 1a). Indeed cases presented with statistically significant lower scores in oral hygiene routine ($P < 0.0001$). The mean number of sites with furcation involvement or increased mobility did not differ between cases and controls (data not shown). Nevertheless, the frequency distribution of number of periodontal pockets deeper or equal to 2 and 3 mm was statistically significant higher in the cases compared to controls ($P < 0.01$) (Figure 1b).

PD and CAL differences were confirmed in multivariate model 1. Adjusted average PD values were 3.2 ± 0.2 mm and 2.3 ± 0.2 mm for cases and controls respectively ($P < 0.0001$, corrected model $F = 5.1$, $R^2 = 0.3$). However when FMPS was included in the model (Model 2) the difference between groups in PD was no longer statistically significant (3.0 ± 0.2 mm *vs* 2.8 ± 0.2 mm, $P = 0.5$, corrected model $F = 9.2$, $R^2 = 0.5$). Similar findings were observed when CAL differences were computed with both models. Briefly, CAL adjusted values in Model 1 were 2.8 ± 0.4 mm in cases and 1.5 ± 0.4 mm in controls ($P = 0.006$, corrected model $F = 3.0$, $R^2 = 0.1$) and in the fully adjusted Model 2 were 2.3 ± 0.3 mm and 2.8 ± 0.3 mm ($P = 0.3$, corrected model $F = 11.6$, $R^2 = 0.5$). Differences in FMBS were no longer statistically significant in Model 1 and therefore fully adjusted model (including FMPS) was not performed (data not shown). Tooth loss differences between study groups were similarly affected by multivariate adjustment (average difference in number of teeth was model 1 = cases 4 ± 1 compared to controls with 2 ± 1 teeth, $P = 0.015$, corrected model $F = 8.8$, $R^2 = 0.4$; model 2 = in cases 3 ± 1 compared to controls with 4 ± 1, *****$P = 0.4$, corrected model $F = 14.7$, $R^2 = 0.6$). Linear correlation analysis confirmed a strong positive linear correlation between FMPS with both PD (Figure 2a, $R = 0.6$, $P < 0.0001$) and FMBS (Figure 2b, $R = 0.7$, $P < 0.0001$) in both cases and controls.

According to the Matchei classification, 2 MMP patients met the proposed criteria for periodontitis, and

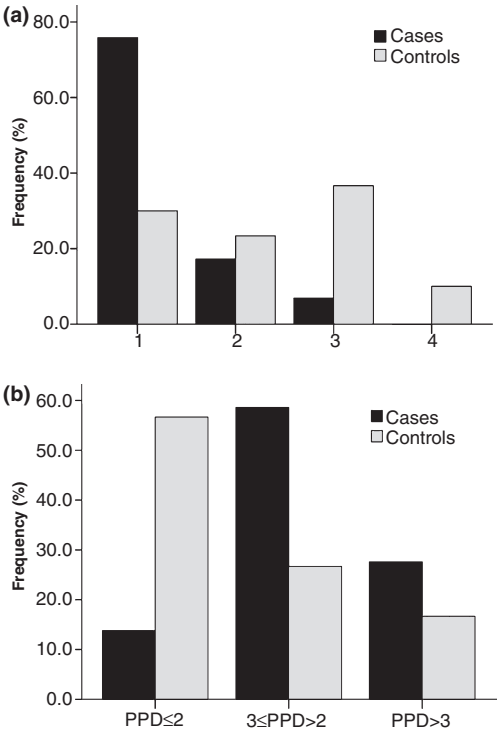

Figure 1 Bar chart of the frequency distribution of different oral hygiene domiciliary scores (**a**) and Probing Depths (PD) tertiles (**b**) between cases and controls

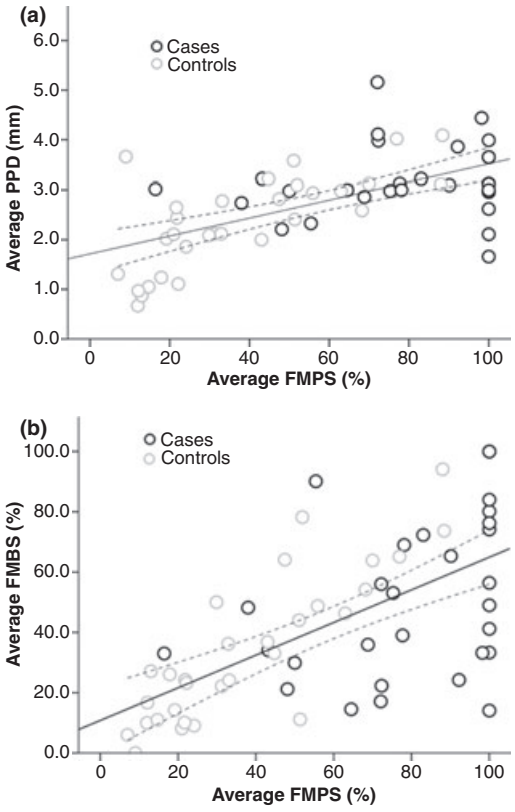

Figure 2 Scatter plots of linear correlation analyses between cases and controls in terms of Full mouth plaque scores (FMPS) with PD (**a**) and with full mouth gingival scores (FMBS) (**b**). Mean regression line (full line) and 95% confidence intervals (dotted lines) are also depicted

1 control subject met the criteria. This difference was not statistically significant as greatly affected by the limited number of cases (data not shown).

Discussion

This is the first study reporting the gingival status of individuals with histologically confirmed diagnosis of MMP compared to age and gender matched controls. The data presented is consistent with the notion that the periodontal status of MMP patients is worse than controls. The substantial differences in dental plaque levels however represent the most plausible cause behind these differences. Indeed both supragingival dental plaque levels were dramatically higher and oral hygiene routines worse in cases when compared to controls.

Previous evidence in support of our findings is scarce as only few studies have described the gingival status in patients with gingival MMP (Tricamo *et al*, 2006; Lo Russo *et al*, 2009; Schellinck *et al*, 2009).

The concepts of worsen dental plaque control and abundance of local etiological factors had been previously described and considered essential in the management of these patients. Indeed Lo Russo and co-workers reported on four patients with MMP and gingival involvement (Lo Russo *et al*, 2009). The analysis of their periodontal status resulted in no statistically significant differences like in our study; further they suggested that a trend of deeper probing PD might exist in sites where DG lesions are present. Recently, Schellinck and co-workers reported that patients with MMP appear to be more at risk than controls in developing or having an increased progression of periodontal disease (Schellinck *et al*, 2009). Consistent with our findings, recent reports showed that patients with MMP exhibit higher gingival bleeding scores, suggesting that more gingival inflammation was present (Tricamo *et al*, 2006; Schellinck *et al*, 2009).

It seems reasonable to believe that patients with DG resulting from MMP may have impaired capacity to perform efficient oral hygiene practices hence the increased gingival inflammation levels and periodontal breakdown. In addition, discomfort caused by gingival lesions could predispose patients to visit less their dentists on a regular basis. A similar phenomenon has been reported for patients with pemphigus vulgaris (Akman *et al*, 2008).

An alternative explanation could be that the increased gingival bleeding scores could be attributed to the erythema and edema proper to this type of lesions. MMP gingival lesions are usually persistent and painful, thus limiting efficient teeth brushing; this leads to plaque accumulation and could increase the possibility of long-term periodontal diseases.

Periodontitis is an infectious/inflammatory disease that affects the tooth-supporting tissue and including periodontal ligament and supporting bone, which if left untreated will ultimately result in tooth loss (Kornman *et al*, 1997; Schellinck *et al*, 2009). Although bacteria are considered necessary for triggering the initial periodontal infection, a susceptible host is also needed. The immune-inflammatory response that develops in the gingival and periodontal tissues in response to the chronic presence of plaque bacteria results in destruction of structural components of the periodontium leading, ultimately, to clinical signs of periodontitis (Kornman *et al*, 1997). Both the host and bacteria in the periodontal biofilm release proteolytic enzymes that cause tissue damage.

Hundreds or even thousands of microbial antigens evoke both humoral antibody-mediated and cell-mediated immune responses. These responses are usually protective, but a sustained microbial challenge in the presence of the forementioned risk factors results in the breakdown of both soft and hard tissues, mediated by cytokine and prostanoid cascades (Birkedal-Hansen, 1993; Pihlstrom *et al*, 2005).

Similar inflammatory process are also involved in the pathogenesis of MMP, which probably includes an autoantibody-induced complement mediated sequestration of leukocytes (neutrophils, mainly) resulting in release of great quantities of cytokine and leukocyte enzyme. This will eventually result in detachment of the basal cells from the BMZ, and possibly complement-mediated cell lysis. The exact mechanism is however not completely understood and could involve several inflammatory pathways (Bagan *et al*, 2005).

Our analysis did not include data on the exact duration of gingival lesions which is a common dilemma once DG is diagnosed and has been already reported for different types of DG (Lo Russo *et al*, 2009). Sometimes analysis of the oral symptoms is the only factor related to the history of the disease. However these are not always associated with DG and the extent of lesion may change over time. Thus, it is not possible to estimate the precise disease duration (Lo Russo *et al*, 2008).

Whether the presence of DG and MMP is a risk factor for developing more periodontal tissue breakdown or just a consequence due to the level of dental plaque could not be assessed based on our data. Indeed the study design does not allow us to appreciate the temporal relationship between DG and periodontitis. However our data is further strengthened by the multivariate analysis including most common periodontal tissue destruction risk factors/determinants (age, gender, smoking and BMI). Further research should be conducted to further evaluate the local gingival inflammatory response of these two category of patients with a particular interest at gene profiles signature and microbiological differences that could also serve to understand any possible mechanisms involved.

In conclusion, our result showed that patients diagnosed with MMP have higher levels of gingival and periodontal inflammation than healthy control patients. This was explained by the substantial differences in oral hygiene between the study groups.

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Author contributions

Arduino, Farci, Carbone, Carcieri and Broccoletti designed the study and organized patients' recruitment. Arduino, Farci and Carcieri examined patients and collected data. Tanteri, Gardino and Gandolfo revised the literature and participated in data analysis and paper drafting. Arduino, Carrozzo and D'Aiuto analysed data, drafted and edited the paper.

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