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Population-based cohort study to assess the gingival lesions in 1319 patients with lichen planus

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Abstract

Aims: Oral lichen planus (OLP) is a chronic immune disease. In this paper, we evaluated the overall characters, clinical presentation, and outcome of gingival lesions in OLP Italian patients.

Methods and Results: A retrospective cohort study was accomplished: a total of 1319 charts were investigated, of whom 922 were female (69.9%): 617 patients (46.8%) manifested white lesions and 702 red ones (53.2%). While most patients had several oral sites of involvement, the gingiva was the unique location in 103 cases. Symptoms were reported in 480 patients (36.4%): 286 patients with erosive OLP, 103 with atrophic form, and 91 with a white form. Long-lasting surveillance showed that only 40 patients (3.03%) had a total clinical signs remission. Regarding OLP medical treatment provided, patients attending less frequently a dental office underwent more often a specific therapy.

Conclusions: To the best of our knowledge, this is the biggest collections of patients with gingival OLP ever described; exclusive gingival lesions are, however, rare and unlikely to undergo a malignant transformation. Moreover, gum lesions seemed to anticipate the appearance of oral lesions and a higher rate of OLP therapy was observed in patients with less frequent dental check-ups and oral hygiene instructions.

KEYWORDS
clinical characters, dental care, gingiva, oral lichen planus, outcome

1 | INTRODUCTION

Oral lichen planus (OLP) is a chronic inflammatory disorder, affecting almost 2% of the population. It is likely a Th1 cell-mediated inflammatory disease with indeterminate etiology (Yang et al., 2021).

The oral appearances of OLP have been widely assessed (Carbone et al., 2009; Eisen et al., 2005) and different clinical types categorized: reticular, plaque-like, papular, atrophic, erosive, and bullous. Some patients could manifest peculiar gingival lesions; the so called desquamative gingivitis (DG) usually displays as epithelial desquamation, erythema, and painful erosions or ulcerations, unconnected to, but possibly aggravated by, local plaque accumulation

(Arduino et al., 2017). However, no data are available on the extent to which the immune host-response and bacterial-elicited inflammation independently contributes to the growth, in gingival crevicular fluid levels, of inflammatory biomarkers in subjects with DG due to OLP (Romano et al., 2019). It has been stated that OLP patients tend to manifest with higher plaque accumulation which may additionally exacerbate the condition; in theory, plaque control may than increase the quality of life of OLP patients and a recent systematic review has stated that enhancements in patient-reported outcomes can occur because of oral hygiene instructions (Albaghli et al., 2021).

Various medications have been used to treat OLP-related symptoms and erosive lesions: the first-line treatment are high-potency

topical corticosteroids, but the management is frequently empirical and the results for clinical response inconclusive (Lodi et al., 2020).

To the best of our knowledge, the clinical outcome of patients with gingival OLP lesions has never been documented over a long period of time. Only another paper from Italy has evaluated the OLP gingival features in a big cohort, but without a follow-up estimation (Mignogna et al., 2005). Besides, most of the related papers are of limited evidence with fewer cases (Bornstein et al., 2008; Camacho-Alfonso et al., 2007; Eisen, 1994), or others mainly focused on the periodontal status (Ertugrul et al., 2013; Mergoni et al., 2019; Rai et al., 2016; Ramón-Fluixá et al., 1999).

In this retrospective article, we detailed the features of patients with gingival OLP, also differentiating those who have had regular access to dental facilities over the years, to evaluate if the regular dental follow-up could have favored the clinical outcome.

2 | MATERIALS AND METHODS

2.1 | Design and data collection

A retrospective cohort study was performed on patients with OLP diagnosed between January 1988 and December 2020 in Northern Italy.

Data collected at baseline have been recently described (Arduino et al., 2021): smoking status, alcohol consumption, clinical aspect of the lesions, sites of involvement, and HCV status. Screening for HCV with an anti-HCV antibody test was performed in every patient since beginning of 1991 as a part of routine investigations for new patients. In case of positive result, current infection was confirmed with a qualitative HCV RNA test. Patients who were already in follow-up before HCV diagnostic tests were available for clinical use, namely between 1988 and 1991, were re-contacted and screened during routine appointments.

Subjects had to be resident in Piedmont region, Northwest Italy.

Outcome events were collected from a computerized database (Carbone et al., 2009), and four authors (P.G.A., A.G., D.K., and R.B.) gathered all the patient data. Included patients were those with a follow-up of at least 12 months. The length of the disease and treatment delivered were detailed. Moreover, the reported frequency of dental visits, when patients underwent dental cleaning and hygiene instructions, were described as follow: more than once a year, once a year, less than once a year. This information was recalled at each follow-up visit.

Treatment was usually commenced with the goal of controlling reported symptoms with minor and negligible side effects (Carbone et al., 2009). For patients with symptomatic forms, a procedure of topical and/or systemic corticosteroids therapy, commonly in association with anti-fungal therapy, was carried out; if subjects underwent at least one treatment during the follow-up period, they were classified as "therapy positive" (Arduino et al., 2021).

Follow-up visits were conducted with a frequency established on the clinical feature and the need for treatment; generally, patients with white forms were seen twice a year for the first 2 years and then once; patients with red forms were regularly seen every 6 months; patients on therapy were usually seen each 2 months (Carbone et al., 2009).

2.2 | Diagnostic criteria for inclusion

Only adult patients, with gingival detectable lesions at baseline, were enrolled; if patients manifested other related oral lesions, those were recorded according to the site of involvement (buccal mucosa, palate, tongue, lips).

Oral lichen planus were clinically divided in: (a) "white form," which included the papular, reticular, and plaque forms; (b) "red form," which included all the atrophic or erosive lesions, irrespective of a simultaneous presence of a white form (Gandolfo et al., 2004).

All patients underwent incisional biopsy. The final diagnosis of OLP had to be based on both clinical (a) and histological microscopic (b) criteria (van der Meij & van der Waal, 2003): (a) presence of characteristic bilateral clinical signs [papular and/or reticular lesions (Wickham striae) alone or in association with atrophic or erosive lesions], not related to oral amalgam restorations or drug intake; (b) existence of a well-defined band-like zone of cellular infiltration confined to the superficial part of the connective tissue, mainly consisting of lymphocytes; signs of "liquefaction degeneration" in the basal cell layer; lack of epithelial dysplasia.
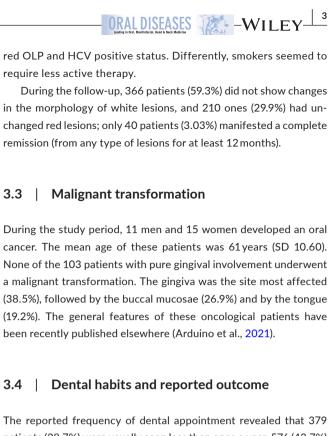
2.3 | Statistical analysis

Means and standard deviations or medians and interquartile ranges were used to describe continuous variables distribution, while frequencies and percentages were employed to depict categorical factors. Patients were compared in terms of demographic, clinical presentation, sites involved, treatment, and dental office attendance. Differences were investigated using T-test or Wilcoxon–Mann–Whitney test or Chi-squared test. All statistical analyses were performed using R software (version 4.1.2) and a p-value <0.05 was considered statistically significant.

3 | RESULTS

3.1 | Patient characteristics at first visit

The study sample was extrapolated from 3173 OLP cases recently described (Arduino et al., 2021); a total of 1319 records were finally analyzed, of whom 922 were female (f:m = 1.43:1). Most of the patients were non-smoker (86.2%). Regarding the liver profile, 79 (6%) patients resulted infected with hepatitis C virus. According to clinical OLP grouping, 617 patients (46.8%) had white forms and 702 red ones (53.2%) (Figures 1 and 2, respectively). While most patients had multiple oral sites of involvement, the gingiva was

FIGURE 1 Case of diffuse white gingival lichen planus.

FIGURE 2 Case of diffuse red gingival lichen planus (typical case of desquamative gingivitis).

the unique site in 103 cases. Considering the total sample size of 3173, 41.6% manifested gingival and oral lesions and 3.2% exclusive gingival lesions. The demographic and clinical features of total subjects are detailed in Table 1. Comparing subjects with only gum involvement with those with other oral manifestations, the former was younger and less often smokers ($p = 0.0008$ and $p = 0.015$, respectively).

3.2 | Clinical follow-up changes and treatment outcome

Symptoms were reported in 480 patients (36.4%), mainly in those with red lesions: 286 with erosive OLP, 103 with atrophic form, and 91 with a white form. Those requiring treatment were 448, and only 23 of them with exclusive gingival lesions (Table 1): this suggests that patients with pure gingival disease required significant less therapies ($p = 0.009$). Table 2 reported in more details the differences between patients who underwent a specific treatment and those who were merely followed-up over the period. Female patients required more treatment, as well as those with

red OLP and HCV positive status. Differently, smokers seemed to require less active therapy.

During the follow-up, 366 patients (59.3%) did not show changes in the morphology of white lesions, and 210 ones (29.9%) had unchanged red lesions; only 40 patients (3.03%) manifested a complete remission (from any type of lesions for at least 12 months).

3.3 | Malignant transformation

During the study period, 11 men and 15 women developed an oral cancer. The mean age of these patients was 61 years (SD 10.60). None of the 103 patients with pure gingival involvement underwent a malignant transformation. The gingiva was the site most affected (38.5%), followed by the buccal mucosae (26.9%) and by the tongue (19.2%). The general features of these oncological patients have been recently published elsewhere (Arduino et al., 2021).

3.4 | Dental habits and reported outcome

The reported frequency of dental appointment revealed that 379 patients (28.7%) were usually seen less than once a year, 576 (43.7%) once a year, and 364 (27.6%) more than once a year, with no statistical differences regarding gender, age, type of lichen, or only gingival involvement. Regarding the need of OLP treatment during the follow-up period, patients attending less frequently a dental office underwent more often a specific therapy ($p < 0.001$) (Table 3, Figure 3).

4 | DISCUSSIONS

To date, this is the biggest case series of patients with OLP gingival lesions ever reported; the clinical features of these subjects shared some similarities with those previously reported, but we also found some novel findings.

Considering a total population of 3.173 patients, gingival lesions have been identified in almost 42% of cases, habitually associated also with diffuse oral involvement. This is very similar to what reported from Mignogna et al. (2005). Whilst gingiva is frequently affected in OLP, the pure gingival involvement is quite rare, previously reported with a frequency of around 8% of cases (Eisen, 2002; Mignogna et al., 2005) up to 10% (Scully & El-Korm, 1985); differently, we found only 3.2% of subjects with exclusive gingival lesions.

Oral lichen planus usually affects female subjects more than twice than male ones (Eisen, 2002; Xue et al., 2005), and our cohort also confirmed this. Notably, patients with pure gingival involvement were statistically younger than those other oral lesions, possibly suggesting that gingival signs could appear at earlier stage.

As previously detailed (Camacho-Alfonso et al., 2007), white forms were the most recurrently reported in pure gingival lesion, and the most common gingival location was the concurrent involvement of the attached and marginal gingiva.

TABLE 1 Demographical and clinical features of considered OLP gingival patients

	Total cases	Pure gingival involvement (with no other oral lesions)	Others	*p*-Value
Number	1319	103	1216	
Gender				
Male	397 (30.1%)	31 (30.1%)	366 (30.1%)	1[a]
Female	922 (69.9%)	72 (69.9%)	850 (69.9%)	
Age (mean±SD)	58.89 ± 11.76	55.72 ± 12.42	59.15 ± 11.67	0.008[b]
Clinical form				
White	617 (46.8%)	54 (52.4%)	563 (46.3%)	0.231[a]
Red	702 (53.2%)	49 (47.6%)	653 (53.7%)	
FU (median [IQR])	72.00 [36.00, 144.00]	36.00 [12.00, 96.00]	84.00 [36.00, 144.00]	<0.001[c]
Smoking status				
Positive	182 (13.8%)	6 (5.8%)	176 (14.5%)	0.015[a]
Negative	1137 (86.2%)	97 (94.2%)	1040 (85.5%)	
OLP therapy	448 (33.9%)	23 (22.3%)	425 (35%)	0.009[a]
HCV status				
Positive	79 (6%)	5 (4.9%)	74 (6.1%)	0.613[a]
Negative	1240 (94%)	98 (95.1%)	1142 (93.9%)	

Abbreviations: FU, months of follow-up.

[a]Chi-squared test.

[b]*T*-test.

[c]Wilcoxon–Mann–Whitney test.

As reported previously, OLP patients usually do not have specific risk factors for oral cancer, (Eisen, 2002), for instance, more than 85% of our cases were no smokers.

In the current study, oral discomfort was present in only in 36% of total cases, likely because of the large number of white OLP, typically presenting without symptoms; this also agrees with previous data from our group (Carbone et al., 2009).

The most employed and useful agents for the treatment of gingival OLP are topical corticosteroids (Lodi et al., 2005). More than 30% of our patients have been treated, and more than 40% of them needed more than one medication course. Usually, HCV positive patients manifested more often red lesions and needed to be treated more. The most common medication was clobetasol, used roughly in 80% of the treated subjects, mainly alone. In our experience, patients with gingival lesions due to OLP should be managed similarly to those with diffuse oral involvement. However, lately it has been stated that OLP patients tend to present with plaque accumulation which may increase the lichenoid lesions; for this reason, a proper plaque control may improve the patients' quality of life (Albaghli et al., 2021; Romano et al., 2019). More recent evidence suggested a significant relationship between the severity of periodontal disease and the presence of OLP (Nunes et al., 2022). Improvements in disease and patient-reported outcomes have been reported because of oral hygiene instruction in patients with gingival manifestations of OLP (Albaghli et al., 2021); moreover, it has been demonstrated that plaque control could be successful in improving the clinical features and painful symptoms of oral lichen planus with gingival involvement (Salgado et al., 2013).

For the first time ever, we have reported that patients with gingival OLP, attending less frequently a dental office, required more often a specific active therapy for their oral disease. We did not evaluate in detail which type of dental treatment were offered during the follow-up but usually patients were provided with oral hygiene sessions and instructions. It could be speculated that regular hygiene control could be beneficial also for lesions due to localized autoimmune diseases, which are not strictly plaque related. However, even if with limited evidence, it has been reported in a recent systematic review that the structured plaque control appeared to be successful in improving signs and related pain in case of desquamative gingivitis (Cabras et al., 2019).

Another quite interesting issue was that none of the 103 patients with pure gingival involvement underwent a malignant transformation. This is completely different form gingival cases with proliferative verrucous leukoplakia, in which the possibility to develop cancer from the affected gingival tissues is very high (Ramos-García et al., 2021).

A strength in our work was the length of the follow-up period, that allow us to obtain valuable data on the clinical progression of gingival OLP lesions, the necessity of treatment and the eventual complications of the disease. As reported in patients with diffuse oral OLP (Carbone et al., 2009; Silverman et al., 1985; Thorn et al., 1988), we can endorse the chronic nature of the gingival involvement, with a small percentage of subjects who have shown comprehensive and permanent healing (3.03%), and the vast majority that has shown long lasting clinical manifestations. As other retrospective

TABLE 2 Differences between treated and untreated OLP patients

	Overall	Untreated cases	Treated cases	*p*-Value
Number	1319	871	448	
Gender				
Male	397 (30.1%)	281 (32.3%)	116 (25.9%)	0.017[a]
Female	922 (69.9%)	590 (67.7%)	332 (74.1%)	
Age (mean ± SD)	58.89 ± 11.76	58.46 ± 11.87	59.71 ± 11.51	0.065[b]
Clinical form				
White	617 (46.8%)	541 (62.1%)	76 (17.0%)	<0.001[a]
Red	702 (53.2%)	330 (37.9%)	372 (83.0%)	
FU (median [IQR])	72.00 [36.00, 144.00]	60.00 [24.00, 126.00]	108.00 [48.00, 180.00]	<0.001[c]
Smoking status				
Positive	182 (13.8%)	133 (15.5%)	49 (10.9%)	0.031[a]
Negative	1137 (86.2%)	738 (84.7%)	399 (89.1%)	
HCV status				
Positive	79 (6%)	33 (3.8%)	46 (10.3%)	<0.001[a]
Negative	1240 (94%)	838 (96.2%)	402 (89.7%)	
More than 1 series of therapy needed				
Positive	—	—	185 (41.3%)	—
Negative	—	—	263 (58.7%)	

Abbreviations: FU, months of follow-up.

[a]Chi-squared test.

[b]*T*-test.

[c]Wilcoxon–Mann–Whitney test.

TABLE 3 Differences between groups with diverse patterns of dental office attendance

	Less than once a year	Once a year	Greater than once a year	*p*-Value
Number	379	576	364	
Gender				
Male	108 (28.5%)	191 (33.2%)	98 (26.9%)	0.087[a]
Female	271 (71.5%)	385 (66.8%)	266 (73.1%)	
Age (mean ± SD)	59.25 ± 11.81	58.57 ± 11.58	59.16 ± 11.94	0.616[b]
Clinical form				
White	157 (41.4%)	288 (50.0%)	172 (47.3%)	0.067[a]
Red	222 (58.6%)	288 (50.0%)	192 (52.7%)	
Pure gingival involvement				
Yes	30 (7.9%)	43 (7.5%)	30 (8.2%)	0.909[a]
OLP therapy				
Yes	163 (43.0%)	174 (30.2%)	111 (30.5%)	<0.001[a]

[a]Chi-squared test.

[b]*T*-test.

evaluation, our works have some limitations; for instance, the reporting of the frequency of OLP being limited to the gingiva may be biased by the duration of follow-up, even if all the clinical changes have been reported in the clinical charts. However, new data about the clinical outcome of gingival OLP have been added.

5 | CONCLUSIONS

This is the biggest group of gingival OLP patients with extended follow-up ever reported. We can confirm the chronic nature of the gingival involvement, with only 3% of spontaneous remissions,

FIGURE 3 Case of a patient not regularly attendant a dental office.

independently of the treatment given. Gingival OLP lesions share similarities with oral OLP lesions, but exclusive gingival lesions are however rare and unlikely to undergo a malignant transformation. Possibly, the gingiva lesions anticipate other oral involvement, and this must be valued by general dentists and periodontologists. As already reported, maintaining a good degree of oral hygiene, and being regularly checked may contribute to a reduction in reported symptoms and therefore to less possibility of immunosuppressive treatments. As most of the patients have a chronic disease, they need to be reviewed for many years by proper trained oral clinicians, and primary dental healthcare employees.

AUTHOR CONTRIBUTIONS
Paolo G. Arduino: Conceptualization; writing – original draft. **Alessio Gambino:** Writing – review and editing. **Alessandra Macciotta:** Data curation; formal analysis. **Giorgia El Haddad:** Data curation. **Davide Conrotto:** Data curation. **Mario Carbone:** Conceptualization; data curation. **Marco Carrozzo:** Formal analysis; writing – review and editing. **Roberto Broccoletti:** Data curation; formal analysis; investigation.

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CONFLICT OF INTEREST
No conflict of interest is declared.

PEER REVIEW
The peer review history for this article is available at https://publons.com/publon/10.1111/odi.14398.

DATA AVAILABILITY STATEMENT
The data sets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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