Malignant transformation of oral lichen planus.

A retrospective analysis from 2003-2014: our experience

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Malignant transformation of oral lichen planus. A retrospective analysis from 2003-2014: our experience.

AIM: *The aim of the study is to describe both the clinical characteristics and the prevalence of Oral lichen planus (OLP) in a group of patients from a region of Southern Italy.*
MATERIAL AND METHODS: *Among the patients who referred to outpatient visit, 96 (35 men and 61 women) received diagnosis of OLP according to Van der Meij and Van der Wall criteria.*
RESULTS: *Nine of ninty-six cases observed developed squamous cell carcinoma (9,37%). The risk of malignant transformation was significantly higher among OLP patients who smoked (OR=2,5 P< 0,05), consumed alcohol (OR=3 P< 0,05), came from the province with a ratio province: city of 4,5:1 and had the reticular form (44.4%).*
DISCUSSION: *Oral lichen planus (OLP) is an oral subtype of lichen planus with a prevalence in the world population estimated between 0.22% and 5% and an incidence approximately of 2.2%. The analysis of our results revealed an important information about the prevalence of malignant transformation, which is 9.37%.*
CONCLUSION: *The transformation of the oral lichen planus may not be as rare as one would expect. The malignant transformation rates of OLP are underestimated due essentially to restrictive diagnostic criteria, inadequate follow-up periods, and/or low quality of studies. Close surveillance is mandatory to monitoring the growth and evolution of lesions in order to reduce the morbidity of OSCC.*

KEY WORDS: Malignant transformation, Oral lichen Planus, Squamous cell carcinoma of the oral cavity

Introduction

Lichen planus is a mucocutaneous chronic inflammatory disease affecting about 1% of the worldwide population [1] with higher incidence among women (female/male ratio 2: 1) and a high frequency in middle age with sporadic cases in very young or pediatric patients. Oral lichen planus (OLP) is an oral subtype of lichen planus with a prevalence in the world population estimated between 0.22% and 5% and an incidence approximately of 2.2%. In 1869 Erasmus Wilson was the first who described it, but its pathogenesis has not been completely understood yet. The main hypothesis refers to an immuno-pathological reaction mediated by T lymphocytes cells, induced by a series of exogenous agents, causing an alteration of the endogenous antigens and surface of oral mucosa keratinocytes [2]. This antigen's alterations in the membrane epithelial cells can be induced by biological, pharmacological or chemical agents. The most important factors that lead to these alterations are: local and systemic ones that are able to cause delayed cell-mediated hypersensitivity reactions, psycho-organic

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stress, autoimmunity phenomena, viral or bacterial infections (cytomegalovirus, herpes simplex type-1,4,6 virus, HBV, HCV, HPV) and systemic disorders (diabetes mellitus, arterial hypertension). Autoimmune phenomena include for example Hashimoto thyroiditis (first reported in 1994 3-9. Among the clinical features of the OLP, the most relevant one regards the frequent bilateral expression and dissemination in multiple oral districts. Oral lesions usually appear on the buccal or gingival mucosa, especially on lateral border and ventral surface of the tongue, retromolar trigone and soft palate-uvula complex. There are five clinically different sub-types of lesions, classified in two main groups: non-erosive atrophic forms (reticular, papular and plaque) and erosive atrophic forms (ulcerative and bullous) 10. Reticular one is the most frequent and common form while the erosive one is the most involved in the evolution to oral squamous cell carcinoma (OSCC).

There is still a debated question about the malignant potential evolution of OLP. The first case of OLP malignant transformation was reported in literature in 1910 by Hallopeau et al.; since then many sporadic cases of cancerization have been reported in literature [11]. The World Health Organization classified OLP among the potentially malignant disorders included in the category of Oral Precancerosis considering that the most serious complication could be OSCC according to Van der Meij and Van der Wall criteria [12-14]. Therefore, the adoption of dysplasia as an exclusion criterion could select cases at lower risk of malignant transformation, with a consequent underestimation of the malignant potential of this prevalent disease [11,15–17].

The aim of our study is to make a retrospective evaluation of the case histories related to the onset of squamous cell carcinomas of the oral cavity from pre-existent OLP lesions in patients treated at the Maxillofacial Surgery Unit of "Magna Graecia" University (Catanzaro -Italy), investigating on the influence of risk factors also related to lifestyle and living areas, in order to compare our results with the data reported in the literature.

Materials and Methods

This retrospective study analyzed 96 cases of patients affected by OLP and carcinomas arising from OLP assessed and treated at the Maxillofacial Surgery Unit of "Magna Graecia" University (Catanzaro-Italy) from 2003 to 2014. Patients data have been collected from our database.

In all cases the diagnosis was based on the analysis of clinical lesions and histopathological findings according to Van der Meij and Van der Wall criteria. The study included patients whose diagnosis after an histopathological analysis revealed an invasive carcinoma in the context of oral lichen lesions previously diagnosed as free from dysplastic alterations and / or identified by the onset of intraepithelial neoplasia. In order to evaluate the progression of the pathology and to investigate the presence of the non-genetic risk factors mentioned in literature, we collected patients clinical and anamnestic data such as gender, age at the time of the biopsy, city of origin, type of lesion, site of oral involvement, HCV infection, neoplasia diagnostic timing, history of previous carcinomas, other comorbidities (for example diabetes or hypertension). As regards behavioural risk factors that did not appear in the analyzed records, a telephone interview was carried out asking some questions to evaluate eating habits (consumption of coffee, soy, dairy products, spicy foods, gluten, red meat, high sugar intake) and voluptuous habits (smoking / alcohol). Patients who did not meet the clinical and histological criteria for OLP and OSCC from OLP were excluded from the analysis.

Statistic Analysis

To assess the risk of malignant transformation in the entire sample and compare it with risk factors, such as gender, smoking, alcohol, nutrition, injury type and location, an aggregated ODDS ratio (OR) was calculated together with a 95% confidence interval ($p < 0.05$).

Results

Among the patients who referred to outpatient visit 96 met the Van der Meij and Van der Wall criteria for the diagnosis of OLP. The male/ female ratio was 1: 1.74 (35 men and 61 women), although this difference is not statistically significant ($p < 0.05$). The average age of the onset of the disease was 59.06 years (range 31-88 years);

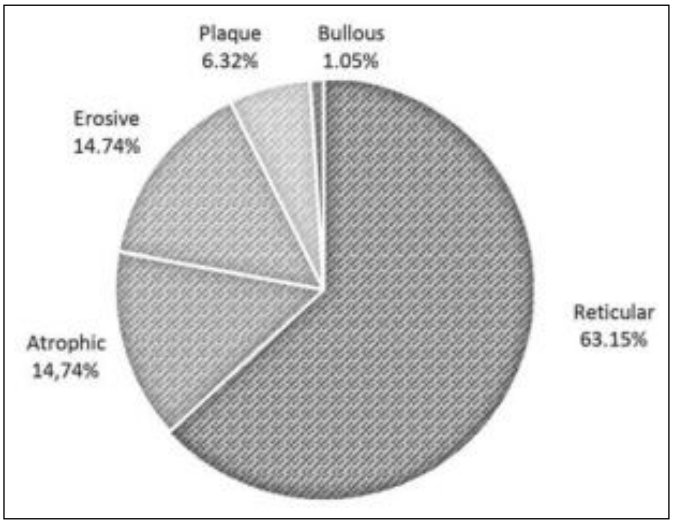

Fig. 1: Clinical appearance of the mucosal lesions at biopsy.

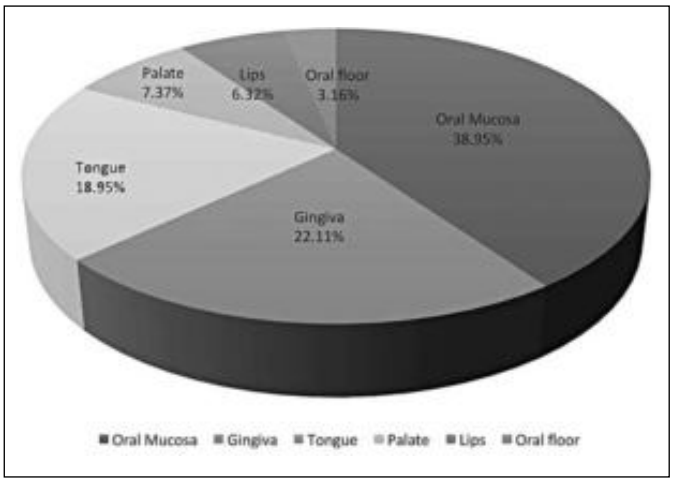

Fig. 2: Oral lichen planus (OLP) onset.

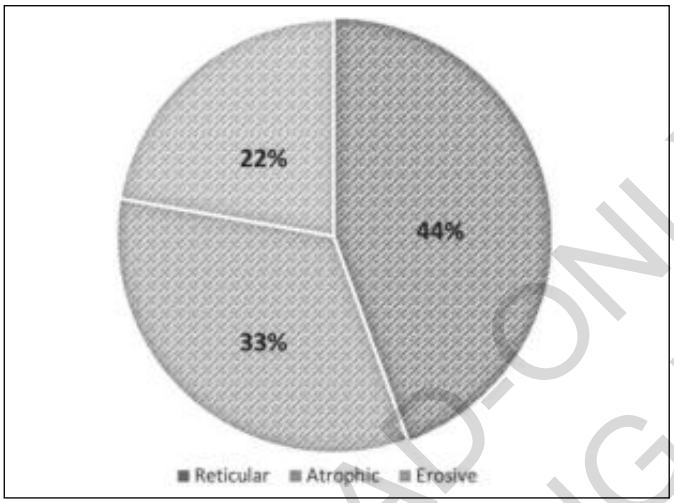

Fig. 3: Main clinical forms related to malignant transformation.

specifically, mean age for women was 60.29 while for men was 55.36. The prevalence of the type of lesions was: reticular (63.15%), erosive (14.74%), atrophic (14.74%), plaque (6,32%) and bullous (1.05%) (Fig. 1). OLP lesions have been diagnosed in different areas of the mucosa in the following order of frequency: oral mucosa (38,95%), gingiva (22.11%), tongue (18,95%), palate (7.37%), lip (6.32%) and oral floor (3.16%) (Fig. 2)

None of the patients suffered of HCV infection. Regarding the country of provenance, 75 of the 96 patients came from small towns in the provinces of Catanzaro (53.33%), Crotone (29.33%), Cosenza (17.33%), while only 21 came from the cities of Catanzaro (47.61%), Cosenza (28.57%) and Reggio Calabria (23.80%) (Table I). Therefore, the ratio province/city was 3.5: 1. As regards risk factors, 33 patients (34.7%) of which 10 women and 23 men were or are still smokers with an average of 15 sigarettes a day (p <0. 05), while 19 patients (20%) of which 3

TABLE I - *Demographical characteristics.*

	Provenance	OLP	OSCC on OLP (No)
City	Catanzaro	53,33%	1
	Cosenza	17,33%	1
	Crotone	29,33%	–
	Reggio Calabria	0%	–
Province	Catanzaro	47,61%	7
	Cosenza	28,57%	–
	Crotone	0%	–
	Reggio Calabria	23,80%	–
Ratio		3,5:1	4,5:1

TABLE II - *Epidemiology of oral lichen planus (OLP) malignant transformation.*

	Patients (number)	Mean age at the OLP onset patients	Cancer patients (number)	Mean age at theOSCC onset patients
Men	35	55,36	4	52,25
Women	61	60,29	5	73,8
Tot	96	59,06	9	64,27

women and 16 men taking alcohol with an average of 90 ml a day (p <0.05).

As regards nutrition habits, the results were almost homogeneous, with intake of dairy products 93,7%, gluten 96,8%, spicy foods 93,7%, red meat 95,8%, sugar-rich diet 95,8%, while soybean was intaken only by 4.2% (p> 0.05).

It was observed that 9 out of 96 selected patients developed squamous cell carcinoma, (5 women and 4 men). The male/ female ratio was 0.8: 1 (4 men and 5 women) (p> 0.05), while the average age at cancer diagnosis was 64.27 years; in particular for women it was 73.8 and for men 52.25 (Table II). The type of lesions included 4 reticular (44.4%), 3 atrophic (33.3%), 2 erosive (22.2%) respectively (Fig. 3). Regarding the affected sites, 3 lesions of the buccal mucosa (33%), 3 of the gingiva (33%) and 3 of the tongue (33%) have been detected. As risk factors, smoking (OR = 2.5 p <0.05) and alcohol (OR = 3, p <0.05) were present in the 4 male patients (44.4 %) while for the remaining percentages were dairy products 88%, gluten 100%, spicy foods 100%, red meat 88%, high sugar diet 88%, coffee 55% and soy 0% (p> 0.05). 7 out of 9 patients came from the Catanzaro province and 2 from the cities of Cosenza and Catanzaro. The province/ city ratio was 4.5: 1 (Table I). From the analysis of the total sample, the ODDS Ratio was 1.30 (p <0.05) regarding the comparison between the pathology and its evolution, while the correlation between transformation and risk factors was significant only in smoking and alcohol. However, considering the conflicting opinions in the literature and the exiguity of the sample, we reserve the right to further investigate the data.

Discussion

Our study focuses on the malignant transformation of the oral lichen planus. As known, the OLP is therefore divided into five main clinical types: reticular, atrophic, erosive/ulcerative, bullous and plaque [18,19]. The female/male ratio is 2:1, so it prevails in the female sex, while an age of onset usually around sixty years. The analysis of our results revealed an important information on the prevalence of malignant transformation, which is 9.37%; this clearly differs from the percentage mentioned in the literature, that is a range between 0.5% and 2%. Just the discovery of a such high incidence in our centre gave us the first input to investigate about this precancerosis malignant evolution in producing this article.

However, it should be remembered that there is much research from which emerge an higher transformation rate reaching and exceeding the 10% [20].

Therefore the severe criteria imposed for OLP diagnosis could underrate this transformation phenomena. In our case all included lesions, both OLP and oral squamous cell carcinoma (OSCC), have satisfied the clinical and histopathological inclusion criteria [21-22]. For OLP injuries the prevalence of women and the average onset age in the sixth decade of life is confirmed, even if it is slightly lower for men, around 55 years. The most frequent clinical form is confirmed to be the reticular one, while the most affected area is the oral mucosa. The percentages of food intake mentioned among the risk factors are very high and their correlation with the progression of the disease was not statistically significant. The intake of smoke and alcohol could have instead some more implications. It is well-documented that smoking can influence the malignant transformation of OLP through several mechanisms; among these are increased density in micro-vessel and enhancement of mesenchymal-epithelial transition factor (c-Met) expression. Likewise, it has been reported that alcohol increases the risk of oral malignancies by enhancing the permeability of oral mucosa and causing epithelial atrophy, which facilitates the penetration of carcinogens [23-25]. The carcinogenic effect of ethanol commonly occurs in case of daily ethanol intake higher than 45 ml [26].

Regarding the patients in which progression to OSCC occurred, however, the results differ from the national average and this may be a starting point for further research to more investigate in the possible reasons and factors of transformation. First of all, the male/female relationship changes: there is no clear superiority of the female gender; in fact we speak of an almost 1: 1 ratio. As regards the average age, it remains in the reference range with the particularity of the male age of 52 years (the youngest patient is 46 years old while the oldest one is 71 years old). This value is quite low compared to the standard and leads to the question if there is a particular risk factor that makes early transformation among men. All four men used to consume alcohol and smoke, and they also proved positive for food risk factors; there was no change in the food plan even after the diagnosis. Despite this, the result of the statistical tests did not prove significative these risk factors, with the exception of alcohol and smoking, probably due to the small reference sample. As regards the five women, on the other hand, the average age of malignant transformation was 73.8 years; this data coincide with the standard range. Another element that differs from literatureis the type of transformed lesions in the 9 patients; in fact, the main forms with malignant transformation are the erosive/ulcerative and the atrophic ones. In the sample under examination, however, the main transformed form is the reticular one with 4 cases, which normally has a very low probability of transformation; the atrophic one ranks second with 3 cases and finally the erosive one records 2 cases. As regards the sites of the oral mucosa, the tongue and the gingiva are the most affected by the tumor. Finally, we want to focus on two strictly interconnected aspects, the diagnostic times and geographical area of origin. These two aspects may lead to inadequate surveillance and the consequent delay in the diagnosis of oral carcinomas resulting from these lesions, having negative implications for survival, treatment costs and post-treatment quality of life [27]. These patients must be followed for a long period (even for a lifetime), even if there is no information to support the recommendations on the appropriate periodicity of the follow-up sessions. The geographic area of origin can also affect follow-up timing, in fact patients who live farther away from urbanized areas, although they are clearly informed of the potentially malignant nature of their lesions, hardly take part to follow-up programs [28]. Among these seven patients we found that the development of malignant transformation of OLP can occur both within and beyond five years from the diagnosis of OLP. In particular two 68 and 72 age women developed OSCC 5 years after the diagnosis of lichen. The other 5 patients developed OSCC after 4 years. The youngest of the sample (46 years old man) underwent transformation 3 years after the first diagnosis (no history of other carcinomas or comorbidities). About the other two patients from urban city, a man developed OSCC after 36 months and a woman after 52 months.

This is an important fact regarding the diagnostic timing of the pathology that was not intercepted in the initial phase since the patients never went to a specialistic visit neither to dentist nor a general doctor especially in the provinces.

Another aspect to evaluate is the geographical area of origin: 2 patients came from the urban cities of Catanzaro and of Cosenza, while 7 patients came from the provinces of Catanzaro. This data mainly support the thesis that the geographical area of origin, even if it is not completely representative of the socio-economic state of the individual, influences the state of health due

to the lower prevention mechanisms and the difficult access to specialist care. All 9 patients were treated surgically and closely followed-up to prevent the appearance of new neoplastic lesions [28-29].

Conclusion

According the data emerged from this retrospective study, it is clear that the transformation of the oral lichen planus may not be as rare as one would expect. It always remains a precancerous lesion with a lower risk of transformation, if compared to leukoplakia or erythroplakia, and with a favorable prognosis, nevertheless it should not be undervalued or underestimated because the lack of diagnosis could have effects on the patient's quality of life. In our investigation of the risk factors mentioned in literature, we did not found any big news in the lichen group as much as in the transformed group and, although the data are still insufficient, it can be considered a starting point for further investigations in which the spectrum of analyzed factors must be enlarged. The clear fact is that the age of transformation is lower than expected and that the lesions that would be least expected on the basis of location or type may be transformed. Therefore is very important to intercept at first the pathology and not to underestimate it. The medical team must monitor the injuries regularly by setting routine checks, which can be quarterly or half-yearly depending on the needs, and must invite the patient to follow all the instructions by modifying, for example, their food plan, especially if in the presence of an important symptomatology, and lifestyle, eliminating all those risk factors such as smoking and alcohol which has been seen to be potentially carcinogenic also for lichen. The other important fact regards the correlation that was found between the delay in diagnosis and the origin of the patients; this demonstrates that the knowledge of oral pathology and precancerous lesions, especially in the dental field, is still lacking. Dentist is the first figure of reference for various health conditions and must not be linked only to teeth diseases since the organ of relevance is the whole stomatognathic system, which includes the intraoral structures (tongue, palate, oral floor, mucous membrane buccal) but also extraoral region which must not be excluded from the diagnostic investigation. The ultimate goal of the scientific community is to standardize diagnostic criteria for both the OLP and its transformation, large, multicenter prospective studies will then be needed to validate these criteria, specify the risks and conditions of treatment and monitoring the OLP. Cancer incidence from OLP lesion seems to be underestimated because of the strict exclusion criteria generally imposed, excluding cases of epithelial dysplasia that could be represent indeed the evolution step from OLP to OSCC.

Riassunto

Il lichen planus è una malattia infiammatoria cronica mucocutanea che colpisce circa l'1% della popolazione mondiale con una maggiore incidenza nelle donne (rapporto 2: 1 femmina / maschio) e un'alta frequenza nella mezza età con casi sporadici in pazienti molto giovani o pediatrici. Il lichen planus orale (OLP) è un sottotipo orale di lichen planus con una prevalenza nella popolazione mondiale stimata tra lo 0,22% e il 5% e un'incidenza di circa il 2,2%. L'Organizzazione mondiale della sanità ha classificato l'OLP tra i disturbi potenzialmente maligni inclusi nella categoria delle precancerosi orali, considerando che la complicanza più grave potrebbe essere la trasformazione in carcinoma a cellule squamose (OSCC), secondo i criteri di Van der Meij e Van der Wall. Lo scopo del nostro studio è di fare una valutazione retrospettiva dei casi clinici relativi all'insorgenza di carcinomi a cellule squamose della cavità orale da lesioni OLP preesistenti in pazienti trattati presso l'Unità di Chirurgia Maxillo-Facciale dell'Università "Magna Graecia" (Catanzaro - Italia), indagando sull'influenza dei fattori di rischio legati anche allo stile di vita e alle aree di vita, al fine di confrontare i nostri risultati con i dati riportati in letteratura.
Sono stati arruolati 96 pazienti affetti da OLP afferenti alla nostra Unità di Chirurgia Maxillo-Facciale dell'Università "Magna Graecia" (Catanzaro-Italia) dal 2003 al 2014. Lo studio ha incluso pazienti la cui diagnosi dopo un'analisi istopatologica ha rivelato un carcinoma invasivo nel contesto di lesioni lichenoidi del cavo orale precedentemente diagnosticate come libere da alterazioni displastiche e / o identificate dall'insorgenza di neoplasia intraepiteliale. Al fine di valutare la presenza dei fattori di rischio non genetici menzionati in letteratura, abbiamo raccolto dati clinici e anamnestici dei pazienti come sesso, età al momento della biopsia, città di origine, tipo di lesione, sito di coinvolgimento orale, infezione da HCV ed altre comorbidità (ad esempio diabete o ipertensione), ed ancora abitudini alimentari (consumo di caffè, soia, latticini, cibi piccanti, glutine, carne rossa, elevato apporto di zucchero) e abitudini voluttuose (fumo / alcol). I pazienti che non rientravano nei criteri di Van der Meij e Van der Wall sono stati esclusi dall'analisi.
È stato osservato che 9 su 96 pazienti selezionati hanno sviluppato carcinoma a cellule squamose (5 donne e 4 uomini), con una prevalenza del 9,37%. Il rapporto maschio / femmina era 0,8: 1, mentre l'età media alla diagnosi del cancro era di 64,27 anni.
Per quanto riguarda i fattori di rischio quali alcool, fumo e fattori alimentari erano positivi anche se non statisticamente significativi. Un dato interessante è stato osservare, a differenza della letteratura, che la forma reticolare è stata quella che è andata maggiormente incontro a trasformazione maligna.
Inoltre, l'area geografica di origine dei pazienti (7 pazi-

enti provenivano dalle province e 2 dalla città) ha avuto un impatto importante nel ritardo della diagnosi. Probabilmente, la mancanza di campagne di prevenzione e, il difficile accesso alle cure specialistiche, nelle province calabresi rispetto alla città, potrebbe essere responsabile di un carente o addirittura assente follow-up di pazienti con OLP.
Infine, l'incidenza di cancro del cavo orale insorto su OLP sembrerebbe essere sottovalutata a causa di rigidi criteri imposti, escludendo la displasia epiteliale che potrebbe rappresentare, in effetti, il passaggio evolutivo dell'OLP all'OSCC.

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