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The Significance of Oral and Systemic Factors in Australian and Croatian patients with Oral Lichen Planus

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SUMMARY Oral lichen planus (OLP) is an immunologically T cell-mediated disease caused by an unknown stimulus. Despite intensive investigation its pathogenesis still remains unknown. A few possible associations between OLP and certain diseases such as thyroid and malignant diseases as well as specific medication intake have been proposed in the literature with inconsistent findings.

We aimed to investigate the profile of 163 Australian and 163 Croatian OLP patients with special regard to their systemic diseases, medication intake (with special regard to the drugs that metabolize through Cytochrome P450), OLP type and localization, as well as involvement of other body surfaces with lichen. We did not find any statistical significance with regard to the OLP presence and thyroid and malignant diseases. As expected, the reticular type of OLP was most prevalent, as well as involvement of the both buccal mucosas. There was no significant association with other oral diseases such as labial herpes. Simultaneous involvement of other body surfaces in patients with OLP does not seem to be prevalent. None of the medical conditions which were investigated had significant correlation with OLP neither in Australian nor in Croatian patients with OLP. Furthermore, the use of drugs which metabolize through Cytochrome P450 (CYP450) was not significantly correlated with OLP in either studied population. Therefore, we conclude that patients with OLP are not to be routinely screened for any systemic conditions.

KEY WORDS: oral lichen planus, systemic diseases, Croatia, Australia

INTRODUCTION

Oral lichen planus (OLP) is probably the second most common oral mucosal disease, affecting 0.5-2% of the general population (1). OLP is a T cell-mediated disease caused by a still unknown antigen. Certain diseases have been associated with OLP in the past, such as diabetes, hypertension, hepatitis C infection (HCV), thyroid disease, and malignant diseases. A connection between OLP and thyroid disease has been proposed, although data are scarce and limited to Siponen *et al.* (2) and Compilato *et al.* (3). The idea of paraneoplastic lichen planus mainly relies on the 12 case reports in patients with simultaneous OLP and malignant lesions (4,5). However, it is very unlikely that OLP patients should be routinely screened for malignant diseases in other parts of the body.

Table 1. Demographic data on patients with oral lichen planus (OLP)

	Australian patients	**Croatian patients**	Chi-Square	df	p
Gender					
Male	45 (27.6%)	40 (25.0%)	0.383	1	0.59
Female	118 (72.4%)	120 (75.0%)			
Type of OLP					
Reticular	117 (71.8%)	97 (60.6%)	4.493	1	**0.03**
Erosive	46 (28.2%)	63 (39.4%)			

Recently, Kragelund *et al.* (6) reported increased prevalence of medication intake which metabolize through Cytochrome P450 (CYP450).

New entities of OLP together with vulval/vaginal and penile involvement are being noted in the literature, and the true prevalence of this simultaneous involvement is yet to be established (7,8).

Therefore, the aim of this study was to assess the medical and oral profile of Australian and Croatian OLP patients, as well as OLP characteristics, with special regard to all known parameters which might contribute to development of OLP.

Furthermore, the rationale for comparing Australian and Croatian population was the fact that OLP presentation and correlation with systemic diseases varies between different geographic parts of the world.

MATERIALS AND METHODS

Australian patients with OLP were recruited from a private oral medicine practice in Brisbane, Australia. There were 163 patients with OLP between 34 and 92 years of age (mean 59.95 yrs). There were 118 women (72.4%) and 45 men (27.6%). In 63 patients, OLP was confirmed histologically when in doubt, in others OLP was diagnosed by one experienced oral medicine specialist. Medical history and use of medication was obtained from each participant. Medications were then analyzed regarding the mechanism of metabolizing through CYP450 according to the MIMS 2005.

Croatian patients with OLP were recruited from the Department of Oral Medicine in Zagreb, Croatia. There were 163 patients with OLP whose age range was 22-85 yrs, mean 56 yrs. There were 120 females (75%) and 40 males (25%). Patients from the both groups were Caucasian.

Every patient underwent clinical examination with special regard to type and localization of OLP as well as registration of other oral diseases.

We also investigated involvement of other body parts with lichen planus as reported by patients themselves and when indicated confirmed by other specialists. The Statistical program used was Statistica 7 (Statsoft, Tulsa, USA, 2005). Data was analyzed by means of descriptive statistics and Pearson Chi-square.

Table 2. Oral licen planus (OLP) presentation and localization in Australian patients and Croatian patients

	Australian patients	**Croatian patients**	Chi-Square	df	p
Presentation					
Unilateral	17 (10.4%)	10 (6.3%)	1.841	1	0.17
Bilateral	146 (89..6%)	150 (93.7%)			
Localization					
Buccal	58 (35.8%)	66 (41.2%)	15.409*	8	0.052
Tongue	7 (4.3%)	2 (1.2%)			
Gingiva	21 (12.9%)	8 (5%)			
Lips	2 (1.2%)	0 (0%)			
Buccal+gingiva	13 (8%)	29 (18.2%)			
Buccal+palatal	4 (2.6%)	6 (3.7%)			
Buccal+tongue	45 (27.9%)	41 (25.7%)			
Buccal+gingiva+tongue	9 (5.5%)	3 (1.9%)			
All localizations	3 (1.8%)	5 (3.1%)			

Table 3. Systemic diseases in Australian and Croatian patients with oral lichen planus

	Australian patients	**Croatian patients**	Chi-Square	df	p
SYSTEMIC DISEASES					
Hypertension					
yes	58 (35.6%)	66 (41.2%)	1.096	1	0.29
no	105 (64.4%)	94 (58.8%)			
Asthma					
yes	25 (15.3%)	9 (5.6%)	8.087	1	**0.004**
no	138 (84.7%)	151 (94.4%)			
Carcinoma					
yes	29 (17.8%)	6 (3.7%)	16.48	1	**0.001**
no	134 (82.2%)	154 (96.3%)			
Allergies					
yes	47 (28.8%)	7 (4.4%)	34.69	1	**0.0001**
no	116 (71.2%)	153 (95.6%)			
Thyroid diseses					
yes	15 (9.2%)	22 (13.7%)	1.64	1	0.199
no	148 (90.8%)	138 (86.3%)			
Diabetes					
yes	22 (13.5%)	14 (8.8%)	1.837	1	0.175
no	141 (86.5%)	146 (91.2%)			
Hepatitis C					
yes	4 (2.5%)	5 (3.1%)	0.001*	1	0.974
no	159 (97.%)	155 (96.2%)			

*=Yates correction

RESULTS

Table 1 presents data regarding the gender of OLP patients in both groups, as well as the type of OLP lesions. There is a significant difference between Australians and Croatians in the prevalence of OLP types, erosive OLP being more prevalent in the Croatian sample.

Table 2 shows OLP presentation and localization in Australian and Croatian patients. No significant differences between the two groups regarding OLP presentation and localizations could be found.

Table 3 presents systemic diseases found in both groups. No significant correlations regarding systemic diseases and OLP in either group could be found. However, there were significant differences between Australian and Croatian OLP patients regarding the prevalence of asthma, carcinoma, and allergies, i.e. Australians had increased incidence of these diseases in comparison with the Croatians.

Table 4 presents medications that metabolize through CYP 450 and those that do not in both groups of patients. Both groups of patients take more medications that do not metabolize through CYP450. However, Australian OLP patients take more non-steroidal anti-inflammatory drugs (NSAIDs), antacids and hormones that do metabolize through CYP450, when compared to Croatian OLP patients. A standardized list of drugs and diseases was made for each patient.

Table 5 shows involvement of other body surfaces with OLP in both studied groups. There were no significant differences regarding the involvement of other body surfaces between Australian and Croatian OLP patients. Additionally, involvement of other body surfaces was not significantly correlated with oral lichen.

DISCUSSION

Medical conditions

OLP has been described as a part of the paraneoplastic syndrome in some patients suffering from malignant neoplasms such as thymoma, lymphoma, histiocytoma, sarcoma, and breast carcinoma (4). Malignant disease was found in 29 Australian patients with OLP (17.8%) and in 6 Croatian patients with OLP (3.7%).

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Table 4. The use of drugs that do and do not metabolize in Australian and Croatian patients with oral lichen planus

	Australian patients	**Croatian patients**	Chi-Square	df	p
MEDICATIONS					
Cardiovascular					
yes	59 36.2%)	66 (41.3%)	0.869	1	0.351
no	104 (63.8%)	94 (58.7%)			
m-CYP450	39 (23.9%)	26 (16.2%)	2.96	1	0.085
nm-CYP450	124 (76.1%)	134 (83.8%)			
NSAID					
yes	31 (19 %)	18 (11.3%)	3.786	1	0.052
no	132 (81%)	142 (88.7%)			
m-CYP450	30 (18.4%)	15 (9.4%)	5.491	1	**0.019**
nm-CYP450	133 (81.6%)	145 (90.6%)			
Thyroid					
yes	13 (8%)	19 (11.9%)	1.376	1	0.241
no	150 (92%)	141 (88.1%)			
Reduce fat					
yes	27 (16.6%)	15 (9.4%)	3.689	1	0.055
no	136 (83.4%)	145 (90.6%)			
m-CYP450	24 (14.7%)	14 (8.8%)	2.776	1	0.096
nm-CYP450	139 (85.3%)	146 (91.2%)			
Antacid					
yes	25 (15.3%)	15 (9.4%)	2.646	1	0.104
no	138 (84.7%)	145 (90.6%)			
m-CYP450	24 (14.8%)	7 (4.4%)	9.967	1	**0.001**
nm-CYP450	139 (85.2%)	153 (95.6%)			
Psychiatric					
yes	26 (16%)	21 (13.1%)	0.519	1	0.471
no	137 (84%)	139 (86.9%)			
m-CYP450	24 (14.7%)	13 (8.1%)	3.99	1	0.046
nm-CYP450	139 (85.3%)	147 (91.9%)			
Hormones					
yes	22 (13.5%)	1 (0.6%)	18.328*	1	**0.001**
no	141 (86.5%)	159 (99.4%)			
m-CYP450	19 (17.8%)	0 (0%)	17.766*	1	**0.001**
nm-CYP450	144 (88.3%)	160 (100%)			

*=Yates correction, m-CYP450=metabolised through cytochrome P450, nm-CYP450= non metabolised through cytochrome P450

In some countries, an association between hepatitis C virus infection and OLP was reported, although these were probably accidental findings (9-11). However, in this study no association with hepatitis A, B, C virus infection could be established, as only 4 Australian patients with OLP out of 163 had a history of hepatitis (2.5%), and 5 out 163 (3.1%) Croatian patients with OLP.

No significant association between OLP and asthma, hypertension, diabetes, and allergies could be found in either studied population. However, there was a significant difference between Australian and Croatian patients with OLP regarding the prevalence of asthma, carcinoma, and allergies, i.e. Australians with OLP had increased prevalence of these diseases in comparison with Croatian patients.

It was also reported in the literature that patients with OLP have a more prevalent history of thyroid disease (2). However, only 15 Australian patients with OLP (9.2%) and 22 Croatian patients with OLP (13.7%) had thyroid disease. Therefore, we could not confirm the findings of the abovementioned authors, which is in accordance with Compilato *et al.* (3).

Table 5. Involvement of the other body surfaces with OLP in Australian and Croatian patients

	Australian patients	**Croatian patients**	Chi-Square	df	p
Oral mucosa	145 (89%)	142 (88.8%)	1.129	2	0.567
Oral mucosa+skin	15 (9.2%)	17 (10.6%)			
Oral+other mucosas	3 (1.8%)	1 (0.6%)			

Medication intake

Kragelund *et al.* (6) suggested that 91% of their patients with OLP were taking drugs which have inhibitory effect on CYPs. However, we were unable to confirm this finding, as 23.9% Australian patients and 16.2% of Croatian patients with OLP were taking cardiovascular agents that metabolize through CYP 450. Therefore, most cardiovascular agents that both groups were taking do not metabolize through CYP450. Additionally, there were no significant differences between Australians and Croatians regarding the number of cardiovascular agents taken.

However, 18.4% Australians with OLP were taking non-steroidal anti-inflammatory drugs which metabolize through CYP450 when compared to 9.4% Croatians, which is a significant difference.

Furthermore, Australians with OLP took significantly more antacids and hormones that metabolize through CYP450 when compared with the Croatians. Australians were taking more hormones in general when compared with the Croatians.

We could not confirm that use of drugs which metabolize through CYP450 is associated with OLP, as the majority of the Australian and Croatian patients were taking meds that do not metabolize through CYP450.

Lower rate of erosive OLP in Australian patients could not be correlated with NSAID use, as out of the 35 Australian patients with erosive OLP only 9 took NSAID.

Additional data regarding Australian OLP patients:

It is interesting to note that two patients had a history of reemergence of OLP – in one after cessation and return of OLP with repeated use of non-steroidal anti-inflammatory drugs (NSAID) (Vioxx®, NSAID, COX-2 inhibitors). Oral lichen planus started with hormone replacement therapy in one of our patients, with NSAID (Celebrex®, NSAID, COX-2 inhibitor) in another one, with asthma medication in a third one. In one patient, OLP resolved after Vioxx® cessation (NSAID, COX-2 inhibitor), in another after Celebrex® (NSAID, COX-2 inhibitor) cessation, after Metoprolol® (Betaloc®, beta-adrenergic blocking agent; metoprolol tartarate) cessation in a third, in a fourth after treatment of hemochromatosis, and in one it resolved spontaneously.

Gender, type and localization of OLP

In the Australian group, there were 118 women (72.4%) and 45 men (27.6%), and 120 (75%) women and 40 (25%) men in the Croatian group, which is consistent with other studies (12).

The most common presentation was reticular OLP (71.8%) in the Australian group as well as in the Croatian group (60.6%), and the difference between the two tested groups was statistically significant.

Most frequently, both buccal mucosas were involved, being the only site of involvement in 58 Australian patients (35.6%) and 66 Croatian patients (41.2%).

Involvement of other body surfaces

Skin involvement was found in 11.4% of cases in a study of Xue *et al.* (12). In our study, there were 15 Australian patients with that presented with skin lesions (9.2%), and 3 patients with vulval lesions (1.8%). Furthermore, there were 17 Croatian patients with simultaneous skin lesions (10.6%) and only one with involvement of other mucosa (0.6%).

Our results are not in concordance with Di Fede *et al.* (13), who reported that simultaneous vaginal/vulval lichen with OLP is seen in 75.6% patients. It seems that the prevalence was much lower in our patients. However, our patients did not undergo gynecological examination routinely, and knowledge that they had vulval lesions was recorded by taking a detailed medical history.

CONCLUSION

None of the medical conditions which were investigated had significant correlation with OLP neither in Australian nor in Croatian patients with OLP. Furthermore, the use of drugs which metabolize through Cytochrome P450 (CYP450) was not significantly correlated with OLP in either studied population. Therefore, we conclude that patients with OLP are not to be routinely screened for any systemic conditions.

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