

Oral premalignant lesions: epidemiological and clinical analysis in the northern Polish population

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Abstract

Introduction: Leukoplakia is the most common potentially malignant condition of the oral cavity.

Aim: Epidemiological and clinical analysis of patients with oral leukoplakia (OL) diagnosed and treated in the Department of Maxillofacial and Oral Surgery, Medical University of Gdansk.

Material and methods: The study was retrospective and prospective. Among 55 911 patients diagnosed and treated in the Department in 1999–2009, 204 people with OL were selected. The material includes 104 women and 100 men with an average age of 58.1. Most of the patients were in the age group of 50–70 years, average age was 58.1.

Results: The most common concomitant disease was diabetes. More than 88% of the patients declared occurrence of OL predisposing development factors (50.49% – cigarette smoking). Three hundred and twenty foci of OL were found among patients. Homogeneous OL dominated (72.05%). Multifocal OL was diagnosed in 58.3% of patients. The most common location of lesions was buccal mucosa (52.2%). Cancers developed on the basis of OL in 7 patients (3.43%). The percentage of malignant transformation was 12.19% for untreated patients and 1.41% for treated patients. The floor of the oral cavity was proven to be the location of the highest risk of oral squamous cell carcinoma. Patients with diabetes may be more likely to develop OL. The risk of malignant transformation is relatively high. In our material it was equal to 3.43%.

Conclusions: Cigarette smoking is the most important factor, which can influence the effectiveness of treatment.

Key words: leukoplakia, oral premalignant lesion, epidemiology.

Introduction

Potentially malignant diseases of the oral mucosa, with the risk of conversion to squamous cell carcinoma (oral squamous cell carcinoma – OSCC), are described in the literature as ‘pre-cancer’, ‘precursor lesions’, ‘pre-malignant’, ‘intraepithelial neoplasia’, and ‘potentially malignant’. At the moment, according to the World Health Organization (WHO), lesions and conditions of the oral mucosa, which may undergo malignant transformation are defined as a potentially malignant disorder (PMD) [1]. Early diagnosis and implementation of appropriate treatment of PMD is crucial in preventing OSCC. There are 5 conditions described as potentially malignant disorders – erythroplakia, lichen planus, oral submucosus fibrosis, actinic cheilitis and leukoplakia. The term ‘erythroplakia of the oral mucosa’ (oral erythroplakia – OE) describes

red discs, which in a clinical and histopathological examination, do not correspond to any defined disease [2]. The OE may resemble many diseases of the oral cavity such as candidiasis, tuberculosis, histoplasmosis, pemphigus, amelanotic melanoma and Kaposi’s sarcoma. The OE occurs in 0.02–0.83% of the population, usually among elderly and middle-aged men. The clinical picture of OE includes well-demarcated red discs with a smooth or granular surface. Sometimes concave changes can be observed, rarely nodular lesions are present. The soft palate, floor of the mouth and buccal mucosa are reported to be the most frequent locations of OE. Etiology and pathogenesis of OE are not fully recognised. It is assumed that a significant number of OE cases are associated with cigarette smoking, tobacco chewing and alcohol abuse [3–5]. Histopathology reveals atrophic

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stratified epithelium; features of dysplasia or squamous cell carcinoma can be present. The percentage of neoplastic transformation of OE ranges from 14% to 50% [6]. Surgical removal of the lesions seems to be the most effective treatment. Cryosurgery or laser therapy may be useful in the treatment of OE without presence of dysplasia or with low-grade dysplasia. The incidence of oral lichen planus (OLP) is estimated at 0.4–2.5%. The clinical picture includes reticulate, papular, plaque-like, erosive, atrophic and bullous lesions. Polymorphic eruptions can often occur. Malignant transformation of OLP is recorded in 1% of cases; the development of OSCC is more likely to occur in erosive, atrophic and plaque-like lesions [7]. The mechanism of malignant transformation remains unknown. Induced therapy depends on the presence or absence of dysplasia. Oral submucous fibrosis (OSF) occurs in Southern Asia. Lesions in the course of OSF are associated with chewing areca nut and betel palms. Alkaloids present in the seeds, which affect the deposition and degradation of collagen, are crucial in pathogenesis of OSF. Neoplastic transformation is recorded in 0.5% of cases [8]. Actinic cheilitis (AC) is observed more often in elderly men with fair skin (I and II skin phototype), who are particularly exposed to ultraviolet radiation [9, 10]. In the initial stage of the disease, redness and swelling of the lips with desquamation of the epithelium can occur. Over time, erosions and scrub covered ulcers may develop. Choice of appropriate treatment depends on the result of histopathological examination. Leukoplakia is the most common potentially malignant lesion within the oral epithelium. The name derives from Greek and is a combination of the words: λευχο (leuko – white) and πλακος (plakos – patch). Oral leukoplakia (OL) is defined as a white shield with an uncertain risk of malignant transformation by excluding other known diseases or disorders that are not connected with an increased risk of cancer [11]. The OL is a clinical term made by exclusion. It does not have a characteristic histopathological picture, there are no references to the presence or absence of dysplasia. The term 'leukoplakia' is used as a clinical or histopathological term. Leukoplakia occurs in a population with a frequency of 0.2–11.7% and is subject to geographic and ethnic variations. The average global incidence rate is estimated at around 2% [12]. The average age of patients with OL is 60 years old and is close to the average age of patients with oral cancer. Men suffer from OL three times more often than women, although among young patients the ratio is 1 : 1. Nevertheless, there are also reports of more frequent occurrence among women [13]. This might be associated with a higher prevalence of smoking among women compared to the past decades. Aetiology of OL is still not fully recognised. Local predisposing factors include chemical factors (tobacco, alcohol) – which are crucial ones, mechanical factors (chronic trauma), thermal factors (burns after eating hot food) and electrogalvanic (burns resulting from the local elec-

trical potential difference between metals present in the oral cavity), UV radiation, viral infections (human papillomavirus), bacterial and fungal infections (chronic candidiasis). Systemic predisposing factors include hormonal imbalance, excessive secretion of the gastric juice, diabetes, decreased salivation, Plummer-Vinson syndrome and vitamin deficiencies [14]. The endogenous and exogenous OL development factors mentioned above should be treated more as promotion than causal ones. In about 14% of patients with OL no obvious reason for the disease can be found. Clinically there are two types of OL: homogenous (includes flat, white coloured changes) and non-homogenous (includes white and red coloured lesions (erythro-leukoplakia) as well as verrucous leukoplakia where white coloured and uneven surface dominate). A subtype of verrucous leukoplakia is proliferative verrucous leukoplakia, which is characterized by multifocal lesions, resistance to treatment and frequent conversion into OSCC (70%) [15]. Over 2/3 of all changes are present in three locations: the lips, buccal mucosa and gingiva [16] and are usually localized on mucous membrane near the occlusal surfaces of lateral teeth (Kiesow zone), often symmetrically. Lesions located on the gums include the entire surface of toothless alveolar or are linear, often separated from the alveolar rim. The OL occurs much less frequently on the lower surface of the tongue and the floor of the mouth. However, in these places dysplasia often coexists, which in consequence leads to malignant transformation of such lesions. To date, the classification of OL proposed by van der Waal has been used [17]. It includes the size of OL, its clinical picture (homogenous/non-homogenous) and histopathology (presence/absence of dysplasia) (Table 1). Large, non-homogenous lesions with dysplasia are more likely to undergo malignant transformation.

The presence and severity of dysplasia are based on an assessment of architectural abnormalities and atypia of cells. The main dysplasia classifications are the WHO classification system, squamous intraepithelial neoplasia (SIN) system, Ljubljana classification of squamous intraepithelial lesions. According to WHO, low-grade dysplasia (mild dysplasia) determines the changes which involve only the lower 1/3 epithelium thickness, moderate dysplasia corresponds to the occupation of the epithelium in 2/3 of its thickness, high-grade dysplasia (severe dysplasia) is diagnosed when abnormal cells are located in the superficial layers of the epithelium (more than two thirds of epithelium). Carcinoma *in situ* means that the entire thickness of epithelium is involved. The stage of dysplasia remains a largely subjective assessment of the pathologist examining the preparation and depends on the condition of the section and its technical processing. According to SIN classification of squamous intraepithelial neoplasia, there are three types of changes. In comparison to the WHO staging, SIN 1 corresponds to low-grade dysplasia, SIN 2 applies to moderate dysplasia, SIN 3 includes

both high-grade dysplasia and carcinoma *in situ*. The histological classification of epithelial proliferative lesions of Ljubljana includes benign and premalignant lesions. Benign lesions include simple hyperplasia and abnormal hyperplasia. The premalignant changes consist of two groups: atypical hyperplasia with features of stimulation, which has a low risk of malignant transformation and carcinoma *in situ*, which has a high risk of malignant transformation. The presence of non-homogenous leukoplakia in a clinical trial, and dysplasia in the histopathological examination remain the most significant risk factors for malignant transformation, which ranges from 0.13% to 17.5%. The average annual rate of malignant transformation in Western countries for all types of OL is assumed at 1% [11]. The probability of dysplasia or carcinoma correlates with the appearance of macroscopic changes. Nodular leukoplakia and especially verrucous leukoplakia, have a higher risk of developing dysplasia than homogeneous leukoplakia in the early stages of development. Transition into invasive squamous cell carcinoma is the most probable in proliferative verrucous leukoplakia. According to various authors, the frequency of malignant transformation varies between 70% and 100% [18]. The choice of treatment method depends on the clinical stage of OL, presence or absence of dysplasia in histopathological examination. In the case of initial clinical diagnosis of OL (suspicion of leukoplakia), the therapeutic procedure aims to eliminate the possible causative factors (removal of mechanical and chemical injuries, cessation of tobacco and alcohol consumption, correction of various irregularities in biochemistry examination). A 2–4-week period of observation is necessary. In absence of improvement during the observation period and in patients with OL without any etiological factors, histopathological diagnosis should be performed. The choice of treatment depends on absence or presence of dysplasia. Dysplasia entitles to surgical treatment.

The main purpose of this study was epidemiological and clinical analysis of patients with oral leukoplakia diagnosed and treated in the Department of Maxillofacial and Oral Surgery, Medical University of Gdansk and determining the risk of squamous cell carcinoma development in patients with oral leukoplakia.

Aim

Leukoplakia is the most common potentially malignant condition of the oral cavity. An increasing number of oral cancer cases, low social awareness and therapeutic difficulties resulted in clinical and epidemiological research. The main purpose of this study was epidemiological and clinical analysis of patients with OL diagnosed and treated in the Department of Maxillofacial and Oral Surgery, Medical University of Gdansk.

Table 1. Classification of OL according to van der Waal

L Size of OL	L1	Lesion ≤ 2 cm
	L2	Lesion of 2–4 cm
	L3	Lesion ≥ 4 cm
	Lx	Size of lesion not specified
P Histopathological picture	P0	No dysplasia
	P1	Dysplasia
	PX	Presence of dysplasia not specified
C Clinical presentation	C1	Homogenous leukoplakia
	C2	Non-homogenous leukoplakia

Stage of leukoplakia	Evaluation of leukoplakia based on histopathological examination	Evaluation of leukoplakia based on clinical manifestation
I	L1, P0	L1, C1
II	L2, P0	L2, C1
III	L3, P0, L1, L2, P1	L3, C1, L1, L2, C2
IV	L3, P1	L3, C2

Material and methods

The study was performed at the Department of Maxillofacial and Oral Surgery, Medical University of Gdansk (Head of the Department Professor Adam Włodarkiewicz) in 2005–2009. Among 55 911 patients diagnosed and treated in the clinic in 1999–2009, 204 people with OL were selected. The material includes 104 women and 100 men with the average age of 58.1 years. The study was retrospective and prospective. In the retrospective part, epidemiological and clinical evaluation of the treatment of patients, who were diagnosed and treated between 1999 and 2004 was performed. However, in this period of time patients with OL were treated with cryosurgery and surgery. Prospective studies were conducted in 2005–2009. At that time, besides the above-mentioned therapies, topical 0.05% tretinoin cream was applied. In each case of OL, the diagnosis was confirmed by histopathological examination. Each patient carried out sanitation of the oral cavity in order to eliminate factors sustaining the disease. The clinical diagnosis involved WHO criteria for potentially malignant disorders and the classification of leukoplakia by Axell and four-stage classification of van der Waal. The moment when changes occur was defined; special attention was paid to risk factors, medications and chronic diseases. Photographic documentation was performed using a digital camera (Kodak). A full course of therapy and follow-up period over 6 months was completed by 178 patients (87.25% qualified for treatment). In the case of failure or relapse of OL after topical 0.05% tretinoin treatment, cryosurgery or surgery was performed. Relapse after

cryosurgery treatment was treated again with cryosurgery or was surgically removed. These results relate to the treatment of 178 cases. Treatment with a cream containing 0.05% tretinoin (Locacid, Pierre-Fabre) was used in 74 cases. Patients used the topical cream on the affected area twice a day. They prolonged its contact with the mucous membrane acting with an occlusive swab or spatula. In the case of irritation, smearing 5% Solcoseryl paste (ICN Polfa Rzeszow) or stopping the application for 24–48 h were recommended. Topical treatment was used for at least 8 weeks. Cryosurgery was performed in 63 patients. All procedures were performed under local anaesthetic infiltration of 2% lignocaine using Cryo-S engine with nitrous oxide as a cooling medium. All procedures were performed by spraying, using two cycles of freezing of 40 s each, with an interval of 2–3 min between them. In the case of multifocal changes, multi-step treatment with 2–3 weeks' interval between the visits was taken. In the case of pain, over-the-counter nonsteroidal anti-inflammatory drugs and 5% Solcoseryl paste (ICN Polfa Rzeszow) were recommended after the surgery. Forty-one patients underwent surgical treatment. The surgeries were performed under local anaesthetic infiltration of 2% lignocaine with noradrenaline. Excisions were performed within borders of clinically visible changes. Depending on the location and size of the lesions, cavities were closed in a linear way, covered with a graft or allowed to cover with granulation tissue. Patients were monitored at 2, 4, 6 and 8 weeks and then every 6 months. No significant side effects or complications during the treatment which could interrupt the therapy were observed. Recuperation was assumed when changes clinically subsided. Partial regression was assumed for relief of at least 50% of the changes. Other changes were classified as no improvement/relapse. The appearance of new lesions in the adjacent area was regarded as a relapse.

Statistical analysis

All calculations were performed using the statistical package Statistica 8.0 (StatSoft, Inc. In 2008), and Microsoft Excel 2003. To assess the statistical significance of differences in the results, χ^2 tests were used (depending on the size of the samples and the expected numbers an original method of Pearson, test with Yate's correction or Fisher's exact test were used). In all statistical tests, the level of statistical significance was $p < 0.05$.

Results

Among 55 911 patients, lesions clinically resembling OL (manifested as white spots or discs) were observed in 256 patients (4.35%). Among these 256 patients, the diagnosis was the following: leukoplakia in 204 patients (79.69%), reactive keratosis – 29 (11.33%), lichen planus – 10 (3.91%), candidiasis – 9 (3.52%), and squamous cell carcinoma – 4 (1.56%). The reactive keratosis was usually associated with biting mucous membrane or friction (Figure 1). In these cases, recovery occurred after removal of irritants.

In 4 cases (1.56%), histological examination revealed squamous cell carcinoma (Figure 2). The OL was diagnosed in 204 people. Table 2 shows the age and sex distribution of patients with OL. Over 63% of the patients were in the age group of 50–70 years. The average age was 58.1 (59.4 for women and 56.7 for men).

Ninety-four patients (46.08%) reported concomitant diseases. The most common disease was diabetes – 24 patients (11.76%). Factors predisposing to the development of OL were reported by 181 patients (88.72%), while cigarette smoking was the most common factor (50.49%) (Table 3). In patients younger than 40 years old, the percentage of smokers was 88.88%.

In 204 patients, 320 foci of OL were found. Homogenous leukoplakia (Figure 3) was noted in 147 patients

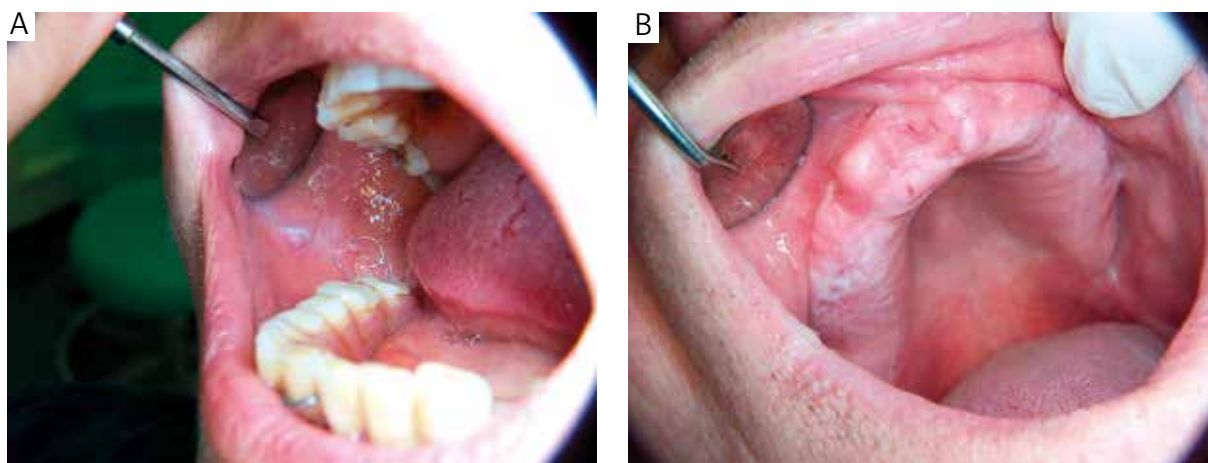


Figure 1. Reactive keratosis caused by biting (A) and friction (frictional keratosis) – toothless gums (B)

(72.05%), non-homogenous leukoplakia (Figure 4) in 57 patients (29.95%). In 85 (41.7%) patients, there was unifocal leukoplakia (Figure 5), multifocal leukoplakia (Figure 6) in 119 patients (58.3%).

The most common location of the lesions was buccal mucosa (52.2%). Table 4 shows the distribution of changes location. Lesions localized on the lip occurred significantly more often in men ($p = 0.05$).

According to van der Waal's classification, the largest group of patients was classified into stage I and II. In 7 cases, the presence of dysplasia was noted (including 2 with a high grade dysplasia) (Tables 5, 6).

Cancers developed on the basis of OL were diagnosed in 7 patients (3.43%) (Figures 7–9). In 5 cases, these were patients who did not start or discontinued treatment (26 patients), whereas in 2 cases, the treatment was ineffective. In most cases, the reason for the next medical consultation were pain and burning sensation associated with food intake. The percentage of malignant transformation of OL into OSCC was 12.19% in patients who gave up therapy. In treated and systematically observed patients the percentage of transformation was 1.41%.

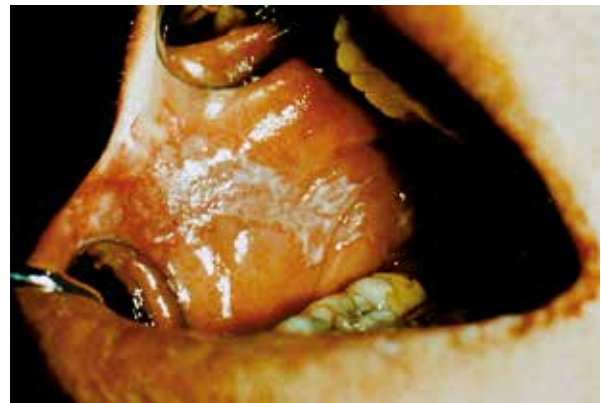


Figure 2. The SCC is manifested as white disks and patches within the buccal mucosa

The highest percentage of malignant transformation was noted for lesions situated on the floor of the mouth (13.3%). Table 7 shows information about patients including the location of OL within which OSCC developed (Figures 7–9).

Table 2. Distribution of age and gender of the patients with OL

Gender	Age							Total
	20–30	31–40	41–50	51–60	61–70	71–80	81–90	
Female	2 (1.0%)	6 (2.9%)	10 (4.9%)	38 (18.6%)	30 (14.7%)	12 (5.9%)	6 (2.9%)	104
Male	2 (1.0%)	8 (3.9%)	17 (8.3%)	37 (18.1%)	24 (11.8%)	10 (4.9%)	2 (1.0%)	100
Total	4 (2.0%)	14 (6.9%)	27 (13.2%)	75 (36.7%)	54 (26.5%)	22 (10.8%)	8 (3.9%)	204

Table 3. Distribution of factors predisposing to the development of OL

Gender	Cigarettes	Alcohol	Trauma	Spices	Prosthesis
Female	59 (28.92%)	50 (24.51%)	29 (14.22%)	13 (6.37%)	24 (11.76%)
Male	44 (21.57%)	33 (16.18%)	30 (14.71%)	11 (5.39%)	17 (8.33%)
Total	103 (50.49%)	83 (40.69%)	59 (28.93%)	24 (11.76%)	41 (20.09%)



Figure 3. Clinical manifestation of homogeneous leukoplakia of buccal mucosa



Figure 4. Heterogeneous leukoplakia of buccal mucosa



Figure 5. Unifocal OL of the tongue



Figure 6. The clinical manifestation of multifocal OL

Table 4. Distribution of changes location

Gender	Cheek	Tongue	Floor of the mouth	Lower gum	Upper gum	Lip	Palate	Diffused
Female	91 (28.4%)	12 (3.8%)	21 (6.6%)	33 (10.3%)	13 (4.1%)	3 (0.9%)	5 (1.6%)	1 (0.3%)
Male	76 (23.8%)	8 (2.5%)	9 (2.8%)	28 (8.8%)	9 (2.8%)	8 (2.5%)	2 (0.6%)	1 (0.3%)
Total	167 (52.2%)	20 (6.3%)	30 (9.4%)	61 (19.1%)	22 (6.9%)	11 (3.4%)	7 (2.2%)	2 (0.6%)

Table 5. Distribution of OL according to the classification of van der Waal on the basis of the clinical picture

Gender	I	II	III	IV
Female	94 (29.4%)	44 (13.8%)	36 (11.3%)	5 (1.6%)
Male	64 (20.0%)	31 (9.7%)	42 (13.1%)	4 (1.3%)
Total	158 (49.4%)	75 (23.5%)	78 (24.4%)	9 (2.9%)

Table 6. Distribution of leukoplakia according to the classification of van der Waal on the basis of the histological picture

Gender	I	II	III	IV
Female	106 (33.1%)	53 (16.6%)	19 (5.9%)	1 (0.3%)
Male	86 (26.9%)	42 (13.1%)	13 (4.1%)	0 (0.0%)
Total	192 (60.0%)	95 (29.7%)	32 (10.0%)	1 (0.3%)

Discussion

Leukoplakia, the most common pre-cancerous condition of the oral cavity, is quite often the subject of research investigations. According to the literature, OL affects from 0.2% to 11.7% of the population [19]. Such significant differences are due to dissimilarities in the incidence of pathology in the defined age, ethnic and social group. Axell [20] conducted epidemiological studies on a group of 20 333 Swedes aged over 15 years old; OL was found in 3.6% of patients. In the Dutch material of Hogewind and van der Waal [21], the percentage was 1.4% (1000 patients). In the Italian material of Campisi *et al.* [22], OL was diagnosed in 13.8% of men over 40 years old. Cebeci *et al.* [23], after analysing the results of 5000

routine dental examinations, diagnosed OL only in 0.4% cases. Tokajuk *et al.* [24] conducted an epidemiological research in the north-east region of Poland. Among 591 patients aged over 55, OL was diagnosed in 7.4% of cases. In a study of Knyszalska-Karwan [25], OL was detected in 5.75% of the patients aged 15–80 years old. The presented differences are due to at least two reasons. First, the analysis relates to different age groups. Secondly, because of the nonspecific clinical manifestation, some of mucosal abnormalities, in which dysplasia is never or very rarely present, are included in OL. In the recent years, there has been a tendency to exclude these changes from the group of leukoplakia. Unfortunately, in practice this is not always possible. Some authors believe



Figure 7. OSCC *in situ* (T1S0) – the floor of the mouth growing on the basis of OL (patient 2)



Figure 8. OSCC of the tongue (T2N1) growing on the basis of OL (patient 7)

that changes like reactive keratosis may constitute up to half of all the pathologies of the oral mucosa [18, 26, 27]. In our material, these changes were observed in 11.33% of patients. The literature emphasizes a three times higher incidence of OL in men; in the material of Cebeci *et al.* [23], the male to female ratio was 4 : 1. Our own results, as well as other Polish reports, do not confirm this information; the male to female ratio was 1 : 1 [13]. The reason for such a ratio might be a high percentage of smoking women in Poland as well as their higher health awareness. Results relating to the age of patients are similar to these in the literature [13]. More than 76% of patients were over 40 years old – the average age was 58 years. In the age group under 50 years, predominance of women was observed. Bouquot [28], after analysing 23 616 white Americans, diagnosed OL in 8% of men and 2% of women over 70 years old. In the material of Bizoń-Wróblewska *et al.* [29], in patients over 30 years old, OL was the second most common (after lichen planus) disease of the oral mucosa. While in patients in the age group of 40–50 years, it was the dominant change. The impact of smoking on the incidence of OL is now indisputable. In Hungarian studies, the percentage of smokers was 82–100% [30]. Morger *et al.* [31], in a study of 615 Swiss army recruits, showed a statistically higher incidence of pathology of the oral mucosa, including OL, among smokers and alcohol abusers. Depending on the social habits related to the use of tobacco, there is a connection between OL and smoking pipes and cigars, chewing black tobacco, betel. It is assumed that about 30% of the Polish society is addicted to cigarette smoking [32, 33]. In our study, smokers constituted more than 50% of patients. In the group of patients under 40 years old, this percentage was 80%. Apart from the fact of smoking, the number of smoked cigarettes is important. Banoczy and Rigo [34] assume that among 104 patients with OL, 13.5% did not smoke, 9.6% smoked 10 cigarettes per day while

76.9% more than 10 cigarettes. Alcohol abuse, especially high percentage alcohol, is also a predisposing factor for OL and oral cancer. It is believed that in the carcinogenesis process tobacco acts both at the initiation and promotion stage, however alcohol only acts at the promotion stage. Carcinogenic effects of these two factors do not add up, but multiply [33]. The role of alcohol as an independent factor for OL and OSCC development is not as well documented as tobacco. In 2006, Maserejian *et al.* [35] conducted a prospective study among 41 458 people and proved that the risk of developing OL is dependent on the amount of alcohol regardless of the tobacco. The proposed mechanism of alcohol action involves a direct effect on the mucous membrane (facilitating penetration of carcinogens, action causing atrophy) and systemic (immunosuppression, damage of liver detoxification function, mutagenic action of its metabolites). In our



Figure 9. OSCC of buccal mucosa (T2N1) growing on the basis of OL (patient 5)

Table 7. Information about seven patients diagnosed with OSCC developing on the basis of OL. Treated and systematically observed patients are marked bold

No.	Gender	Age	Location of OL/SCC	Van der Waal – clinical	Van der Waal – histological	Smoking	Time from diagnosis of OL and SCC [years]	Histological type of cancer	Stage of cancer
1	F	59	FM	III	II	+	5	SCC G2	T2N1
2	F	63	FM	III	II	+	2	SCC G2 (in situ)	T1SNO
3	F	54	FM	III	III	+	6	SCC G1	T2N1
4	F	66	FM	III	II	+	3	SCC G2	T1N0
5	M	54	C	II	II	+	5	SCC G2	T2N0
6	M	55	L	II	II	+	4	SCC G1	T2N0
7	M	62	T	II	II	+	6	SCC G2	T2N1

F – female, M – male, FM – floor of the mouth, C – cheek, L – labia, T – tongue

study, more than 40% of patients admitted to alcohol drinking more than twice per week. It is estimated that about 16% of the population in Poland abuse alcohol. The results connected with coexisting diseases, especially diabetes are very interesting from a clinical point of view. It is assumed that about 5% of the Polish society is suffering from this disease. In our study this percentage is much higher. Our observations confirm the hypothesis of some researchers that the development of diabetes predisposes to OL. Albrecht *et al.* [36] proved a high prevalence of OL in diabetics in comparison with a control group (6.2% vs. 2.2%). Dietrich *et al.* [14] demonstrated that patients with diabetes have a twice higher risk of OL development compared with the healthy population. The pathomechanism of OL formation in diabetics is probably associated with the weakening of the protective role of mucous membrane due to its atrophy, reduced secretion of saliva and pH reduction. It should be noted that the elevated blood glucose level increases the amount of free radicals and reduces antioxidant potential of tissues [37]. Other factors which play a potential role in the aetiology of OL include nutritional deficiencies (especially vitamins), hormonal disorders, chronic injury and inflammations [38, 39]. Our results have proven the role of chronic injuries that have been demonstrated in more than 28% of patients and were often associated with dysfunctional prosthesis. In our study homogenous leukoplakia dominated (72%), what is compatible with other reports [13, 20, 21]. The most common location was the cheek mucosa as well, as in Petkowicz's (60.4%) [13] and other authors' studies [40]. From the clinical point of view, the connection between OL and oral cancer is the most important. It is estimated that about 50% of oral squamous cell carcinomas develop on the basis of OL [18, 33]. This fact is extremely important because of oral cancer prevention. Unfortunately, little attention is paid to the prevention of this disease, in contrast to breast, prostate,

uterine and colon cancer. This seems to be an inappropriate approach since the oral cancer is the eighth most common cancer in Poland and accounts for 2.5% to 4% of all cancer cases [18, 33]. In our material, dysplasia or carcinoma in lesions clinically corresponding to OL was found in 11 cases (5.29%). This percentage is lower than that presented in the literature (15.6–39.2%) [41]. These differences are probably caused by a non-homogenous classification of changes. Waldron and Shafer [42] analyzed retrospectively 3256 biopsies taken from changes corresponding to OL. Invasive cancer was found in 3.1% of cases, carcinoma *in situ* or high-grade dysplasia in 4.6%, while low-grade and moderate dysplasia in 12.2%. In our study, this percentage was 1.92%, 0.96%, 2.88%, respectively. In our study, the proportion of cancers developed on the basis of OL is lower (1.92%) than in the literature reports (5–6%) [18, 33]. There are interesting observations about the risk of OL malignancy. Within 5 years, neoplastic transformation on the basis of OL was observed in 7 patients (3.43%). In 5 cases, patients did not start or discontinued treatment (12.2%). In two cases, treatment was ineffective (1.4%). This information suggests that treatment of OL reduces the risk of cancer. We observed less clinical progression of cancer among treated patients. This information is compatible with the literature, where malignant transformation of OL is estimated at 4–6% [33]. Our observations confirm the fundamental role of tobacco in the pathogenesis of oral cancer. All of patients with cancer were smokers. In the Uruguayan studies, De Stafani *et al.* [43] proved that the relative risk (RR) of oral cancer development among non-smokers was 1, while among smokers 4.2. The authors also found that the risk among people who have given up smoking is lower in comparison to active smokers (2.2 vs. 5.7). Merletti *et al.* [44] observed that the RR increases with the number of smoked cigarettes (from 4.4 to 6.2). Shiu *et al.* [45] conducted a cohort study of

neoplastic transformation on the basis of OL in the Taiwanese population. The authors found that smoking and chewing betel predispose to the development of OL, while only betel is associated with malignant transformation. They also claimed that the abandonment of habits reduces the risk of OL and oral cancer [45]. Despite the extensive campaign, the problem of addiction to tobacco is extending, especially in developing countries. It is estimated that in 2000, 4.9 million people died from diseases connected with cigarette smoking, in 2020 it will be probably 10 million [46]. Unfortunately, the awareness of patients is insufficient, the vast majority of patients in our study did not discontinue or returned to the habit. It is difficult to predict the clinical behaviour and course of OL. It is known that the probability of dysplasia correlates with morphology of lesions (especially with thickness). The risk of malignant transformation in the case of verrucous leukoplakia ranges from 70% to 100% [3, 18, 33]. The location of changes is significant. The most common places susceptible to malignant transformation are the floor of the oral cavity, bottom and side surfaces of the tongue, and soft palate [3, 18, 33, 42]. Our results show the highest percentage of malignant transformation within the floor of the mouth. Another prognostic factor may be molecular tests. It was proven that in the case of loss of heterozygosity (LOH) within chromosome 3p and/or 9p, the risk of malignant transformation increases 3.8 times, whereas the additional loss of loci 4q, 8p, 11q, 17p multiplies the risk 33 times. Genetic studies have proven that the process of carcinogenesis involves not only clinically visible change but is far wider [33].

Conclusions

Most of the patients were 50–70 years old (average 58.1). The most common coexisting disease was diabetes. The OL predisposing factors were reported by 88% of the patients (tobacco smoking 50.49%). There were 320 OL lesions, and homogenous leukoplakia dominated (72.05%). Multifocal OL was diagnosed in 58.2% of the patients. The most common lesion location was buccal mucosa (52.2%). According to van der Waal's classification, most patients were classified as stage I and II. Malignant transformation on the basis of OL was diagnosed in 7 patients (3.43%). The percentage of malignant transformation among untreated patients was 12.9%, while among treated patients – 1.41%. The highest risk of OSCC development was proven to be the floor of the mouth.

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