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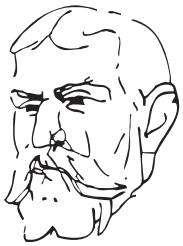

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ORIGINAL ARTICLE

BUCCAL CELL MICRONUCLEI AMONG PATIENTS WITH ORAL LEUKOPLAKIA

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ABSTRACT

The aim: The purpose of research was to evaluate the efficiency of micronucleus test in buccal cells for the diagnosis of oral leukoplakia.

Materials and methods: We have conducted a comprehensive clinical and laboratory examination of 155 patients with oral leukoplakia. It was conducted histological examination leukoplakia mucosal sites, to assess the buccal epithelium cell micronucleus test was carried out.

Results: Histological evaluation of the material was made according to the classification of leukoplakia WHO (2005). They are established 10 (14%) sites unmodified mucosa, 10 (14%) of the samples hyperkeratosis without atypia, 14 (19%) biopsies hyperkeratosis SIN1, 15 (21%) of hyperkeratosis SIN2, 10 (14%) -- SIN3 and 13 (18 %) of the cases of squamous cell carcinoma. Micronuclei, whose appearance is caused by violation of differentiation of epithelial cells, were found in patients with leukoplakia, the detection of micronuclei almost equally high as in patients with leukoplakia SIN2, and with SIN3 (a difference of 1.3 times ($p < 0,05$, $rxy = + 0.271$)), and consequently the probability of occurrence of tumoral diseases of the oral mucosa or malignancy existing large.

Conclusions: Thus, on the background of the general increase in proliferative activity of epithelial cells with increasing SIN, for each treatment group revealed the appearance of micronuclei in buccal cells. And the frequency of micronuclei and the fourth type of increases with hyperplasia, indicating an increase in the likelihood of malignancy and cancer of the oral mucosa in patients with leukoplakia SIN3.

KEY WORDS: Leukoplakia, hyperplasia, epithelial cells, micronuclei, buccal epithelium

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INTRODUCTION

A timely and effective diagnostic of the oral mucosa neoplastic lesions remains a serious challenge of dentistry. Annually registered in the world are nearly 400,000 cases of malignant tumors in the oral cavity, Ukraine recording more than 4,000 new cases [1].

Apparently, an effective clinical diagnostic of the oral cavity malignant tumors based on tracing of precancerous diseases should not cause major difficulties, since the oral cavity is easily accessible for examination and palpation. However, in spite of this, 40-90% of patients begin the treatment in late stages (III - IV) of the disease and only about 20% - in early (I - II) stages. Accordingly, a 5-year survival of patients with cancer of the oral mucosa (stage I and II) by applying radiation, surgical and combined methods of treatment is attained in 65-85% of cases, while the ratio for stage III patients is of only 11-40%. Therefore, treatment results depend on an early detection of tumors, a timely diagnostic and treatment of precancerous diseases. The most frequent diagnostic errors occur in this stage of tumor development [1].

Leukoplakia is the most common precancerous lesion of the oral mucosa [1, 2]. It is a type of mucous keratosis, which is characterized by chronic course and lesions of the oral mucosa and red border of lips [3]. At pathologicoanatomic examination, in case of clinical diagnosis of «leukoplakia», in 80-85% of cases hyperkeratosis with hyperplasia of basal and spinous layers of the epithelium is detected, hyperkeratosis with different degree of dysplasia is detected in 5--15% of cases, while squamous cell carcinoma is detected in 2--5% of cases [4].

Development of leukoplakia is caused by various polyetiologic factors. Among them one can mention mechanical, chemical and thermal injuries. Approximately 70-90% of cases of oral leukoplakia lesions are associated with smoking. Also there is a direct correlation between the frequency, duration of smoking and the development of leukoplakia [5, 6].

In recent decades, active work has been carried out to study the factors influencing the stability of human genetic material using a micronucleus test in the buccal epithelium. Currently, the influence of gender, age, genotype, anthropogenic pollution of the environment, diseases of various etiologies, immunological status of a person, psychophysical characteristics on the incidence of disorders in exfoliating cells of the oral cavity has been investigated. The widespread use of this method of analysis is due to its relative simplicity, speed and low cost, as well as the lack of the need for special equipment for cell cultivation. In addition, the buccal epithelium is a kind of "mirror" reflecting the state of the whole organism [1].

THE AIM

Objective of our study was to evaluate the effectiveness of the micronucleus test in buccal epithelial cells for the diagnosis of oral leukoplakia.

MATERIALS AND METHODS

To achieve this goal, a comprehensive clinical and laboratory examination was carried out of 155 patients with leukoplakia of the oral cavity, who applied to the Department of Therapeutic Dentistry of the National Medical University named after A.A. Bogomolets, including 68 men (43.9%) and 87 women (56.1%). The age of the patients ranged from 25 to 70 years and averaged 46.6 ± 2.63 years.

The localization of leukoplakia was determined according to individual areas of the oral mucosa: 1) tongue, 2) floor of the mouth, 3) lip, 4) hard palate, 5) soft palate, 6) cheek, and 7) in several areas simultaneously.

The histological examination of leukoplakia areas of the mucous membrane was carried out to confirm the diagnosis. According to the WHO classification (2005), the following types were distinguished: squamous cell hyperplasia (leukoplakia without atypia), low degree of dysplasia, moderate degree of dysplasia and high degree of dysplasia. For the last three types of leukoplakia, the concept of Squamous Intraepithelial Neoplasia (SIN) was introduced from 1 to 3, depending on the severity of dysplasia [10,11].

The micronucleus test was performed to assess buccal epithelial cells. Before preparing smears, the patients rinsed their mouths with water twice. A sterile spatula was scraped from the mucous membrane of both cheeks above the line of closing of the teeth. The taken material was suspended on a defatted glass slide and smears were prepared. The prepared preparations of exfoliating epithelial cells of the oral mucosa were dried in air and fixed with a May-Grunwald fixative. After fixation, the smears were stained according to Pappenheim (azure-2-eosin). Analyzed under a microscope in transmitted light at a magnification of 900x. All cells on the glass were counted for the presence of micronuclei and the proportion of different types of micronuclei was estimated. Well-expanded, undamaged, separately lying epithelial cells were analyzed without overlap or with little overlap in the monolayer. Cells containing numerous microorganisms on the surface were excluded from the analysis. Micronuclei (MN) were counted in cells with nuclei with a distinct and continuously smooth border, implying the presence of an intact nuclear membrane. We counted the number of cells with micronuclei per 2000 cells satisfying the described characteristics. Micronuclei were identified as rounded chromatin bodies with a continuous smooth edge, lying in the cytoplasm separately from the nucleus in the same plane with it and having the same chromatin pattern and color intensity [1].

There were 4 types of micronuclei:

Type 1 - 1 small MN (1/40 of the size of the main nucleus), located at a short distance from the main nucleus, formed by a detached chromosome fragment.

Type 2 - 1 MN measuring 1 / 15–1 / 10 of the size of the main nucleus, consisting of small fragments detached from chromosomes, or of 1–2 large fragments of chromosomes.

Type 3 - MNs of this type are several small formations from 2 to 10 in number and the size of microkernels of types 1 and 2.

Type 4 is one large MN up to 1/4 of the main nucleus, consisting of several (1-3) whole chromosomes and / or many fragments of other chromosomes [1].

The data obtained in the course of the study were subjected to statistical processing. The reliability of the revealed differences in the studied parameters was assessed using the Mann-Whitney test for independent samples.

RESULTS

In a complex clinical and laboratory study of 155 patients with a clinical diagnosis of leukoplakia of the oral mucosa.

Histological evaluation of the material has been performed according to the WHO (2005) classification of leukoplakia. 10 (14%) sites of unaltered mucosa, 10 (14%) samples of hyperkeratosis without atypia, 14 (19%) biopsy specimens of hyperkeratosis SIN1, 15 (21%) – hyperkeratosis SIN2, 10 (14%) - SIN3 and 13 (18%) cases of squamous cell carcinoma were evidenced.

Squamous hyperplasia was characterized by an increased number of cells in the basal and spinous layers. No sign of cellular and tissue atypia was revealed.

SIN1 leukoplakia was characterized by an intense proliferation of keratinocytes, with symptoms of minor cellular atypia and nuclear polymorphism in the lower third of the epithelium.

Characteristic to SIN2 leukoplakia was the location of the pathological process not only in the lower, but also in the middle third of the epithelial layer. Cellular and nuclear polymorphism was more pronounced, and hyperchromatism was observed, along with a higher nuclear-cytoplasmic coefficient and amount of mitosis in the basal layer. In some cases, changes in the tissue architectonics, appearing as epidermal "loop-shaped" outgrowths, hyperkeratosis, were revealed.

The SIN3 leukoplakia characteristic was the change of more than 2/3 of the epithelium height, expressed to a greater extent by all these signs of displasia, and the increased number of nucleoli in cells with nuclear hyperplasia. Cells polymorphism was determined, and sometimes parakeratosis with foci of erosion was observed. Inflammatory phenomena, accompanied by a dense infiltration of lymphocytes with an admixture of plasma cells, were intensified.

Histologic investigation of squamous cell carcinoma of the oral mucosa revealed disorderly arranged complexes of typical squamous cells with invasive growth in the deep lying layers of the submucosa. Manifested in varying degrees, characteristic for cellular atypia was the change in cell size and shape, in the nuclei, nuclear-cytoplasmic ratio, and the presence of polyploid forms of pathological mitosis.

When studying smears from the oral mucosa, the presence of micronuclei in epithelial cells was detected only in patients

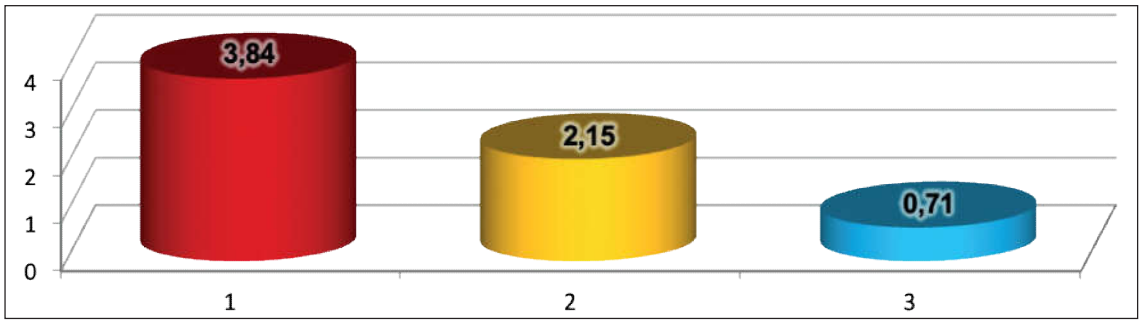

Fig. 1. The number of micronuclei in epithelial cells in patients with leukoplakia
1 – SIN1; 2 – SIN2; 3 – SIN3.

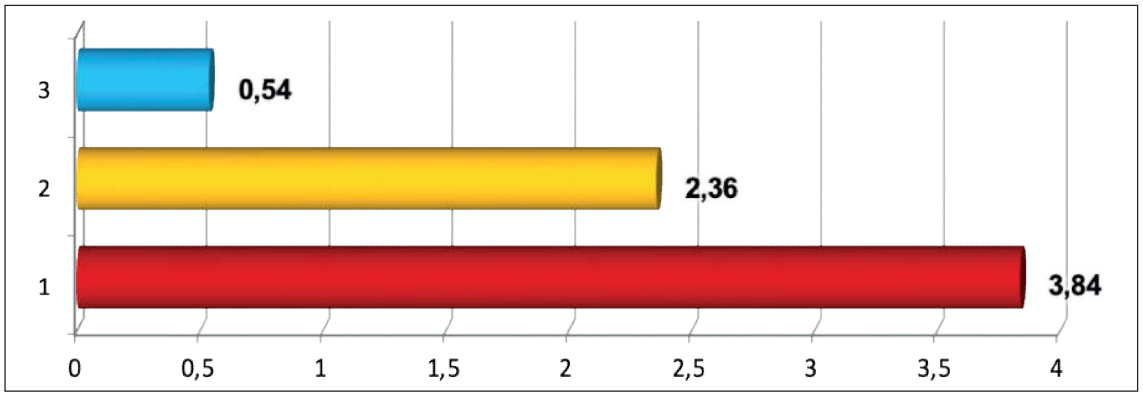

Fig. 2. Frequency of occurrence of micronuclei in epithelial cells in patients with leukoplakia
1 – Hyperplasia; 2 – SIN1; 3 – SIN3.

Table I. Frequency of micronuclei in epithelial cells of the oral mucosa in patients with leukoplakia

Groups	Micronuclei,%				
	1 type	2 type	3 type	4 type	Σ
SIN1	-	-	-	-	-
SIN2	0,025±0,01	-	-	0,075±0,02	0,1±0,02
SIN3	0,07±0,02	0,021±0,01	0,015±0,01	0,164±0,01	0,27±0,02
Σ	0,095±0,01	0,021±0,01	0,015±0,01	0,239±0,02	0,37±0,02

Table II. Frequency of micronuclei in epithelial cells of the oral mucosa in patients with leukoplakia

Groups	Micronuclei,%				
	1 type	2 type	3 type	4 type	Σ
SIN1	0,045±0,01	0,01±0,01	0,006±0,01	0,1±0,02	0,16±0,02
SIN3	0,05±0,01	0,011±0,01	0,009±0,01	0,139±0,02	0,21±0,02

with leukoplakia of the SIN1, SIN2 and SIN3 groups. In 21.6 ± 5.3% of patients with SIN3 and SIN2 leukoplakia, micronuclei were found in the epithelial cells of the oral mucosa; in patients with squamous cell hyperplasia, this phenomenon was not found (rxy = + 0.737) (Fig. 1).

More often micronuclei were found in patients with SIN3 leukoplakia - 2.7 times more than in patients with SIN2 leukoplakia ($p < 0.001$, rxy = + 0.812). In patients with SIN2 and SIN3 leukoplakia, micronuclei were found 1.3 times more often than in patients with SIN1 leukoplakia ($p < 0.05$, rxy = + 0.271).

The analysis of the occurrence of various types of micronuclei (intensity) among all studied showed that the most common micronuclei of types 1 and 4 are found, with type 4 micronuclei (in total) 2.5 times more than type 1 micronuclei ($p < 0.001$) (Fig. 2).

In patients with SIN3 leukoplakia, type 4 micronuclei were detected 3 times more often than all the others ($p < 0.01$), and in patients with SIN2 leukoplakia - 1.6 times as compared to the other three types of micronuclei combined (Table I).

The ratio of micronuclei types among patients with leukoplakia is as follows: type 4 micronuclei quantitatively prevails over all other types in patients with SIN2 leukoplakia by 1.6 times ($p < 0.05$), in patients with SIN3 leukoplakia - by 2 times ($p < 0.01$) (Table II).

DISCUSSION

Many forms of oral mucosa diseases and red border of the lips characterized by chronic relapsing course, occur with severe clinical symptoms, can provoke the development of systemic diseases, and lead to a reduction of dental quality of life [5]. Many chronic diseases of the oral mucosa have a high oncogenic potential [4]. According to experts [5, 6], the share of oncological diseases of the maxillofacial

region is accounted for 2.4% of all malignant neoplasms, and «coarse» and standardized mortality rates from malignant tumors of the maxillofacial area (lip, tongue, salivary glands, other and unspecified parts of the oral cavity, oropharynx) in Ukraine are amounted to 8.88 and 5.64 per 100 000 population [7]. A high percentage of detection of malignant tumors of the maxillofacial region in the III and IV stages of cancer indicates a lack of alertness at the dentists. Early detection of precancerous lesions of the maxillofacial region should become an integral part of medical and dental checkups. [1].

The purpose of recent studies now is prevention and early diagnosis of malignant lesions because of expensive therapeutic and rehabilitating procedures of these lesions [8]. Buccal cells form the primary barrier for the ingestion and inhalation route. They are capable of metabolizing proximate carcinogens to reactive products [9].

Micronuclei are acentric chromosomal fragments and separate whole chromosomes that were lost during mitosis [10]. An indicator of genetic disorders in interphase nuclei can be the sum of the observed protrusions of the "broken egg" or "tongue" type [11]. The "broken egg" protrusion looks like a micronucleus connected to the nucleus by a nucleoplasm bridge, while a "tongue" protrusion is an egg on two nucleoplasm bridges [12,10]. Moreover, micronuclei in buccal epithelial cells can serve as adequate indicators for determining the level of xenogeneic intoxication and the adaptive status of an organism [13]. In another work, describes an increase in the frequency of occurrence of micronuclei in epithelial cells of the buccal mucosa as a result of the action of exogenous factors, that is, in areas with a high content of toxic substances in the air and soil [14]. The above changes in the epithelium of the oral cavity are cytogenetic disorders, and also indicate an inflammatory process in the body [15,16]. Moreover, in healthy individuals, all observed changes can be attributed to biological aging and natural death of epithelial cells of the oral cavity [17,18].

In our present study, analysis of the prevalence and frequency of micronuclei in patients by gender showed a significant difference (in men compared to women) for both indicators. The prevalence of micronuclei in epithelial cells of the oral mucosa in men is 2.4 times higher ($p < 0.01$, $rxy = + 0.571$), and the frequency is 3.2 times higher ($p < 0.01$, $rxy = + 0.658$), which may be indirectly related to the more common habit - tobacco smoking (smoking intensity, degree of tobacco strength, smoking culture, oral hygiene).

Comparison of the frequency of micronuclei among patients of different ages showed an insignificant difference (1.3 times), that is, the frequency of micronuclei slightly increases with increasing age ($p < 0.05$).

Thus, micronuclei, the appearance of which is caused by impaired differentiation of epithelial cells, were detected in patients with leukoplakia, and the detectability of micronuclei is almost equally high in both patients with SIN2 leukoplakia and SIN3 (the difference is only 1.3 times ($p < 0.05$, $rxy = + 0.271$)), and, consequently, the likelihood of neoplastic diseases of the oral mucosa or malignancy of the existing ones is high.

CONCLUSIONS

Thus, against the background of a general increase in the proliferative activity of epithelial cells with an increase in SIN, the appearance of micronuclei in the cells of the buccal epithelium was revealed for each study group. Moreover, the frequency of occurrence of micronuclei and their fourth type increases with increasing hyperplasia, which indicates an increase in the likelihood of malignancy and the development of cancer of the oral mucosa in patients with SIN3 leukoplakia.

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The Authors declare no conflict of interest.

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