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Cytological picture of the oral mucosa in patients with gastric and colon cancer

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Abstract: The incidence of malignant gastrointestinal cancers in Poland has been constantly growing, which has led to an intensification of the search for new markers of the early clinical stage of this disease. The oral cavity, as the first part of the gastrointestinal tract, has a very important role. The oral cavity presents symptoms of both typically stomatological and systemic diseases. Oral cancers, benign or malignant, may originate and grow in any of the tissues of the mouth, and within this small area they may be of varied clinical, histological and biological features. These can be lesions typically observed in the oral cavity, but also characteristic of cases where the symptoms occur both in the mouth and in other body parts. The aim of this study was to present a cytological picture of the oral mucosa in patients with gastric and colon cancer and to compare the cytological picture with that obtained from a group of patients with no cancer, using the Papanicolaou classification and the Bethesda system. The study was conducted in 126 patients treated surgically in the II General and Gastroenterological Surgery Clinic between 2006 and 2008. All patients were divided into two groups based on the type of lesions. In both of the studied groups, more than half of the patients did not present any abnormalities in the mucosa of the mouth, lips and cheeks in the physical examination. None of the patients had erosion, ulceration or lesions typical of leukoplakia or lichen planus. No malignant cells were detected in either of the studied groups, and there were no well-defined lesions found in the oral cavity that would distinguish the patients with gastrointestinal cancer. *(Folia Histochemica et Cytobiologica 2012, Vol. 50, No. 3, 375–380)*

Key words: oral mucosa, cytological picture, gastric cancer, colon cancer

Introduction

The incidence of malignant gastrointestinal cancers in Poland has been constantly growing, especially the colon and the pancreas. This has resulted in an intensification of the search for new markers of the early clinical stage of this disease. The oral cavity, as the first part of the gastrointestinal tract, plays a very important role. It receives food and allows for the intake of elements necessary for bodily functions. Obviously, other roles of the oral cavity are equally important, but these have already been described in numerous handbooks of human physiology. Unfortunately, as with every other organ, the oral cavity is constantly subjected to various disease processes. Most of the diseases are caused by local factors and can be easily diagnosed. In addition to the local factors, also systemic diseases and especially diseases and

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infections of the blood, the digestive tract and the skin, can give symptoms in the oral cavity [1, 2]. Except for the obvious, e.g. cancer, pemphigus, few diseases of the oral cavity are life threatening. Despite all this knowledge, early detection and following up with early treatment, especially of cancer, is still unsatisfactory, even though the oral cavity is easily accessible for clinical examination and diagnosis to every doctor, and particularly to dentists [3–7].

The possibility of conducting microbiological, biochemical or molecular tests gives hope for an early detection, especially of neoplastic and systemic diseases [8–10]. The available literature offers many reports on diseases of the oral mucosa in the course of systemic diseases and also of cancer. However, they mainly present a description of the local lesions in the course of a particular illness, whereas there is not much data on the evaluation of the state of the oral mucosa in patients with gastrointestinal tract cancer.

The oral cavity presents symptoms of both typically stomatological and systemic diseases. Oral cancers, benign or malignant, may originate and grow in any of the tissues of the mouth, and within this small area they may be of varied clinical, histological and biological features [11]. These can be lesions typically observed in the oral cavity, but also characteristic of cases where the symptoms occur both in the mouth and in other body parts [4].

The aim of this study was to present a cytological picture of the oral mucosa in patients with gastric and colon cancer. Additionally, we compare the cytological picture to that obtained from a group of patients with no cancer, using the Papanicolaou classification and the Bethesda system.

Material and methods

The study was conducted in 126 patients treated surgically in the II General and Gastroenterological Surgery Clinic of the Medical University of Bialystok between 2006 and 2008. All patients were divided into two groups based on the type of lesions. Group I consisted of patients with histopathologically confirmed gastrointestinal epithelial neoplasia. The group comprised 86 patients (35 females and 51 males, mean age 64.2 years, range 26.5–88). There were 50 patients with colon cancer and 36 patients with gastric cancer. Group II, a control group, consisted of 40 patients (19 females and 21 males, mean age 54.42 years, range 22–81) with benign, non-neoplastic lesions of gastrointestinal tract. They were hospitalized due to: abdominal hernia — 14, gallstones — 5, benign pancreatic lesions — 5, benign bowel lesions — 13, and nodular thyroid goiter — 3.

Most oral cavity cancers originate in the healthy mucosa, though some begin as clinically visible, potentially malignant lesions (erythroplakia, leukoplakia). One of the main pre-cancerous lesions is epithelial dysplasia — a term denoting a disturbance of cell maturation and proliferation. The dysplasia is divided into severity categories, with a high malignancy potential in the more severe, advanced, stages.

The studied groups of patients, after having their medical history taken, were thoroughly examined by a dentist (in accordance with a commonly accepted protocol). Next, a brush biopsy was performed from the inner lining of the right cheek using a sterile brush Cytobrush® Plus GT (Medscand Medical). In cases when pathological changes were noted in the right cheek, a smear was also collected from the inner lining of the left cheek. The obtained specimens were then placed on silanized glass slides and fixed with Fixocyt spray (POCH). In the laboratory, the Papanicolaou-stained smears were assessed according to the five-grade Papanicolaou classification of malignancy [10]. Additionally, the specimen was assessed according to the Bethesda system.

Results

Macroscopic picture of the oral cavity

In both of the studied groups, more than half of the patients did not present any abnormalities in the mucosa of the mouth, lips and cheeks in the physical examination. None of the patients had erosion, ulceration or lesions typical of leukoplakia or lichen planus. A comparable incidence of macroscopic changes was observed in the group of noncancerous patients i.e. the control group. The predominant pathological lesion was a coated tongue; additionally, we observed the following symptoms: a smooth tongue, a red tongue, angular cheilitis and *stomatitis prothetica*. These lesions need to be considered as secondary, resulting from deficiencies caused by a primary disease and by the *Candida* infections. Pathological changes observed in the physical examination of the mouth are presented in Table 1.

Cytological picture of the oral cavity

Cytology is a relatively simple, non-invasive study that helps to detect early stage neoplastic lesions [6]. It gives clinicians a picture of a cell at a particular moment of its changes. Specific meaning of cytology is seen when atypical cells are revealed and their presence suggests the need for histopathological examination [3, 5, 12].

Cytological picture of the oral cavity is shown in Table 2 (according to the Papanicolaou classification) and in Table 3 (according to the Bethesda system). In both of the studied groups, regardless of the system used for the diagnostic cytology, positive results were predominant (class I and II according to the Papani-

Table 1. Features of dysplasia

Disturbances of maturation	Disturbed proliferation
Irregular hyperplasia and/or atrophy	Loss of polarity of basal cells
Keratosis/parakeratosis	Basal cell hyperplasia
Drop-shaped rete ridges	Increased nuclear-cytoplasmic ratio
Irregular epithelial stratification	Enlarged nucleoli
Disturbed cell proliferation	Hyperchromatism
Cell keratinization	Increased number of mitoses
Reduced intercellular cohesion	Anisonucleosis
Cellular pleomorphism	Abnormal mitotic figures

Table 2. Grades of epithelial dysplasia and carcinoma *in situ*

Mild dysplasia	Atypical and immature basal cells extend from the basal layer to the lower third of the epithelium
Moderate dysplasia	Atypical and immature basal cells extend from the basal layer to the middle third of the epithelium
Severe dysplasia	Atypical and immature basal cells invade through the full thickness of the epithelium
Carcinoma *in situ*	Atypical and immature basal cells invade through the full thickness of the epithelium and the basal layer

Table 3. The Papanicolaou classification

Class I Normal	Absence of abnormal or atypical cells
Class II Normal/atypical	Atypical cells, but no evidence of malignancy
Class III Suspicious	Undefined — cytology suggestive of, but not conclusive for, malignancy
Class IV Suggestive	Cytology strongly suggestive of malignancy
Class V Indicative	Cytology conclusive for malignancy

Table 4. Cytology classification according to the Bethesda system

Normal smear result
ASC-US (atypical squamous cells of undetermined significance)
LSIL (low-grade squamous intraepithelial lesions)
HSIL (high-grade squamous intraepithelial lesions)
Invasive carcinoma

colaou test; normal smears and LSIL according to the Bethesda system). No malignant cells were detected in either of the studied groups. Additionally, there were no well-defined lesions found in the oral cavity that would distinguish those patients with gastrointestinal cancer.

Discussion

A macroscopic evaluation of the oral mucosa performed during the physical examination of the patients with gastrointestinal epithelial cancer, and patients from the control group, revealed similar results. No significant morphological changes were found that would distinguish those patients with cancer [13]. Regardless of the cancer location, the percentage of the detected pathological lesions was comparable between the groups of patients with gastric cancer and those with colon cancer. The detected pathological lesions were found in matching locations and affected the dorsum of the tongue, the corners of the mouth and the hard palate. Their intensity depends on the patient's body defense system and the effectiveness of hygienic treatments in the hospital environment [2, 6, 7].

A discussion of our own results is difficult because there is still not much data on the evaluation of the state of the oral mucosa in patients with gastrointestinal cancer. Fukushima et al. have presented patients with advanced gastric cancer who have diffuse changes in the angles of the lips, oral mucosa and esophagus of the type acanthosisnigricans [14].

Wijn et al. have pointed out that patients with familial adenomatous polyposis (FAP) include an increased risk of jaw osteomas, odontomas and supernumerary or unerupted teeth. Early diagnosis of FAP is crucial, and may be life saving. As oral signs usually precede gastrointestinal symptoms, the dentist may play an important role in the diagnosis of FAP [15].

The results of our study are comparable with those on oral cavity lesions in patients with cirrhosis [16] and ulcerative colitis [17] published by Knychalska-

Table 5. Macroscopic changes in the oral mucosa

	Group I Patients with cancer		Control group	
Pathological changes	**n = 86 (100%)**		**n = 40 (100%)**	
Stomatitis prothetica	2	2.33%	1	2.50%
Coated tongue	20	23.26%	8	20.00%
Red tongue	5	5.81%	0	0.00%
Smooth tongue	7	8.14%	3	7.50%
Fissured tongue	0	0.00%	3	7.50%
Angular cheilitis	3	3.49%	0	0.00%
Lichen planus, leukoplakia	0	0.00%	0	0.00%
Dryness, burning	3	3.49%	1	2.50%
Redness of the oral mucosa	2	2.33%	1	2.50%
Thinning of the oral mucosa	3	3.49%	0	0.00%
Erosion, ulceration	0	0.00%	0	0.00%
All changes	45	52.33%	17	42.50%
Patients with changes in the oral cavity	32	37.21%	14	35.00%
Patients with no changes in the oral cavity	54	62.79%	26	65.00%

Table 6. Microscopic changes in the oral mucosa according to the Papanicolaou classification

	Group I Patients with cancer		Control group	
Cytological picture	**n = 86 (100%)**		**n = 40 (100%)**	
Class I	24	27.90%	6	15.00%
Class II	42	48.84%	26	65.00%
Class III	9	10.47%	8	20.00%
Class IV	11	12.79%	0	0.00%
Class V	0	0.00%	0	0.00%
Dyskeratotic cells	29	33.72%	1	2.50%
Koilocytes	13	15.12%	2	5.00%
Candida	5	5.81%	2	5.00%

Table 7. Cytological picture of the oral cavity according to the Bethesda system

	Group I Patients with cancer		Control group	
Cytological picture	**n = 86 (100%)**		**n = 40 (100%)**	
Normal smear result	68	79.07%	31	77.50%
ASCUS	8	9.30%	7	17.50%
LSIL	10	11.63%	2	5.00%
HSIL	0	0.00%	0	0.00%
Invasive carcinoma	0	0.00%	0	0.00%
Dyskeratotic cells	29	33.72%	1	2.50%
Koilocytes	13	15.12%	2	5.00%
Candida	5	5.81%	2	5.00%

Table 8. Comparison of the systems for diagnostic cytology

The Bethesda system	The Papanicolaou classification
Within normal limits	I
Infection Reactive and reparative changes	II
ASCUS	No equivalent
LSIL	III
HSIL	III
HSIL	IV
Squamous cell carcinoma	V

Karwan. Malins and Baumgart have obtained similar results in many other chronic diseases of the digestive tract, especially inflammatory bowel disease. Similarly, uncharacteristic changes observed in the oral cavity are more frequent, and their nature depends primarily on nutritional deficiency, iron deficiency, vitamin B12, folic acid, used drugs or malabsorption syndrome [18, 19].

Comparing cytological pictures of patients with gastrointestinal tract cancer and the control group, it is difficult to draw simple conclusions if using the Papanicolaou classification [20]. Significant differences are observed in the percentage distribution of the particular Papanicolaou classes. At the same time, the number of dyskeratotic cells and koilocytes is different in both of the studied groups. However, when using the Bethesda system for diagnostic cytology, the differences observed between the two studied groups are less distinct. Due to a small number of lesions found in the studied patients, statistical tests were not used to evaluate the analyzed parameters. Substantial differences were observed in the percentage distribution of the results, but it is difficult to state whether they are statistically significant. Additionally, evaluation of cytological specimens was performed on the basis of systems for diagnostic cytology primarily created for the analysis of cervical smears. Evaluation of lesions in the oral cavity according to the Papanicolaou classification has previously been attempted [5, 12, 21]. The National Cancer Institute in Bethesda (USA) proposed replacing the Papanicolaou classification with another method called the Bethesda system [22]. The Bethesda system for reporting cervical/vaginal diagnoses was introduced to replace the numerical Papanicolaou class designations, thereby facilitating precise communications between cytopathologist and clinician.

Although this system is intended for the evaluation of cervical specimens, we attempted to use it to assess the specimen from the oral cavity, since the oral stratified squamous epithelium and the cervical stratified squamous epithelium are similarly built.

It is possible that cancerous lesions, due to an accompanying inflammatory reaction, can change the cytological picture, which is reflected in the comparison of the studied groups of patients. The number of abnormal smear results (class III and IV) is noticeably higher in patients with gastrointestinal epithelial neoplasia assessed according to the Papanicolaou classification. On the contrary, in the cytological assessment performed using the Bethesda system, these differences were not observed. It is not currently possible to select a classification that is more useful in stomatology, and so further studies are necessary.

In conclusion, we have not found any macro- or microscopic well-defined lesions of the oral cavity that would distinguish gastric from colon cancer patients.

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