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AĞIZ SUYU VƏZİSİNİN XOŞ- VƏ BƏDXASSƏLİ ŞİŞLƏRİ FONUNDA YARANAN SİALOLİTİAZIN MORFOLOJİ XÜSUSİYYƏTLƏRİ

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Xülasə. *Məqalədə ağız suyu vəzilərində daşların əmələ gəlməsinə səbəb olan amilləri müəyyənləşdirmək məqsədilə aparılmış tədqiqat haqqında məlumat verilmişdir. Tədqiqatda xoşxassəli və ya bədxassəli şişlərlə birlikdə biomineral törəmələri olan 20 ağız suyu vəzisi nümunəsindən istifadə edilmişdir. Strukturunda dəyişiklik olan vəzilərdə kalsifikatların yaranmasının patogenezini daha yaxşı aydınlaşdırmaq üçün histoloji və immunhistokimyəvi analizlər (kəskin və xronik iltihab markerlərinin və apoptozun inisiatorlarının öyrənilməsi ilə birlikdə), həmçinin sialolitlərin mikroelementlərə görə analizi aparılmışdır.*

Müəyyən edilmişdir ki, şiş prosesinin olduğu şəraitdə sialolitiazın yaranmasında iltihabi proses, pH səviyyəsinin dəyişməsi və mineral maddələrin müəyyən ardıcıllıqla çöküntüyə keçməsi kimi amillər iştirak edir.

Açar sözlər: *ağız suyu vəziləri, xoşxassəli şişlər, bədxassəli şişlər, qulaqaltı vəzi, sialolitiaz, kalsifikasiya, skanerləşdirici elektron mikroskopiya*

Ключевые слова: *слюнная железа, доброкачественная опухоль, злокачественная опухоль, околоушная железа, сиалолитиаз, кальцификация, сканирующая электронная микроскопия (СЭМ)*

Key words: *salivary gland, benign tumour, malignant tumour, parotid gland, sialolithiasis, calcification, calculus, scanning electron microscopy (SEM)*

THE MORPHOLOGICAL FEATURES OF SIALOLITHIASIS IN THE CONTEXT OF BENIGN AND MALIGNANT TUMORS OF THE SALIVARY GLAND

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The article provides information ab\out research conducted to identify the factors causing the formation of stones in salivary glands. The study utilized 20 tissue samples from salivary glands, encompassing both benign and malignant tumors with biomineral formations. For a more profound understanding of the pathogenesis of calcifications in structurally altered tissues, histological, immunohistochemical analyses (utilizing markers for acute and chronic inflammation, as well as to detect the initiation of apoptosis), and microelement analysis of sialoliths were conducted.

It was found that the formation of sialolithiasis in the presence of a tumorous process occurs due to structural tissue rearrangement amid inflammatory processes, changes in pH levels, and mineral deposition in a specific sequence.

Introduction. Sialolithiasis is the process of formation of biomineral structures (stones) in the salivary gland and its ducts, leading to swelling, pain syndrome, and persistence of the infectious process [1]. It affects approximately 1% of the world's population. Among the salivary glands, stones are most commonly found in the submandibular gland (69.5%), with a lower incidence in the parotid gland (36.8%) and other localizations (4.7%) [2]. The higher incidence of submandibular gland involvement can be explained as its pH is higher than that of other glands, it contains more mucin and calcium ions. The submandibular gland has a more complex anatomical structure compared to other glands (Wharton's duct has a length of approximately 5 cm and secretes saliva against gravity) [2].

According to Han H et al. (2015), it was found that 80.4% of sialolithiasis affects the submandibular ductal system (53% proximal, 37% distal, 10% intraparenchymal), while 19.6% affects the parotid ductal system (83% in Stensen's duct, 17% intraparenchymal) [3].

Calculus sialadenitis more frequently occurs in individuals aged 30-50 years, significantly less in children (3%), and in young individuals [3, 4]. There is also a trend towards an increase in the incidence rate with the age of patients, which may be due to reduced secretory activity of salivary glands, changes in the concentration of electrolytes in saliva composition, and disturbances in glycoprotein synthesis within the gland [2]. Cases are often encountered in practice where the process of stone formation is evident in several organs in one patient, such as in the kidneys, gallbladder, and salivary glands, indicating a disruption of the overall calcium metabolism in the body. Among systemic diseases with disturbances in calcium metabolism, gout can be distinguished, which may lead to stone formation in the salivary glands, where the stones consist primarily of uric acid [5], and multiple myeloma disease, accompanied by hypercalcemia due to bone tissue breakdown [6].

The primary treatment method for this pathology is surgical intervention and the removal of sialoliths, in most cases, with partial or total gland resection. This often leads to a significant reduction in baseline saliva production and the occurrence of xerostomia in more than half of the patients, significantly diminishing their quality of life [5].

The most significant cause of stone formation is partial or complete duct obstruction, which can be triggered by several factors. Among these, chronic sialadenitis holds the top position, along with gland cirrhosis, foreign bodies, strictures, diverticula, and stenoses of various origins [5, 7]. It is considered that partial obstruction is the most perilous because although saliva stasis occurs in complete duct occlusion, the secretory granules in the gland become depleted over time, rendering the saliva less lithogenic [5]. Additionally, the potential influence of factors such as smoking, dehydration, alcoholism, and the intake of certain medications (antidepressants, diuretics, and antipsychotic drugs) that lead to decreased saliva production is also considered [8,9,10].

It has been observed, moreover, that stones often form in the context of prolonged inflammation. Macrophages, the synthesis of active oxygen species, and oxidative stress are frequently found in the stone-forming zone, and further immune response contributes to initiating continued inflammation and calcium salt deposition [10]. Studies conducted on nephrolithiasis suggest that in patients with kidney stones, almost all major markers of chronic inflammation were elevated, including pro-inflammatory cytokines, acute-phase markers, adhesion molecules, myeloperoxidase (MPO), and more [11,12].

Since the mechanism of sialolithiasis development in the context of a tumorous process remains inadequately understood, the primary goal of our research is to conduct a biophysical analysis of the sialolith composition and a pathological examination of surrounding tissues to establish the mechanisms involved in the formation of biomolecular structures in structurally altered salivary gland tissues, as well as to determine the role of inflammation in this process.

Materials and methods

Bioethics Protocol. All studies were conducted following the Helsinki Declaration (6th edition, revised 2008, Seoul) and the Universal Declaration on Bioethics and Human Rights (2006).

The study included 20 tissue samples from structurally altered salivary glands with biomeneral formations. The selection criterion was the presence of stones in the gland tissue. All cases studied were represented by benign and malignant tumors of the salivary glands (10 samples for each), each showing calcifications. The sialoliths were obtained from male (5 cases) and female (15 cases) patients, aged between 22 and 77 years. The average age of the patients was 62.2 ± 6.95 years, with an average age of 68.2 ± 8.56 years for men and 60.3 ± 6.57 years for women. Among women, the frequency of benign tumors was 53.3% and malignant tumors was 46.7%. Among men, 40% of cases were benign and 60% were malignant.

Histological and Histochemical Research Methods. For histological analysis, the biological material was fixed in a 10% neutral buffered formalin solution for 24 hours. Subsequently, the material was processed using a histoprocessor and embedded in paraffin using the carousel-type apparatus 'ATM-4M' (Ukraine). Paraffin serial sections with a thickness of 4-5 µm were obtained using a rotary microtome Shandon Finesse 325 (Thermo Scientific). Deparaffinized sections were stained with hematoxylin-eosin and subjected to PAS reaction.

Immunohistochemical examination of salivary gland tissue. Serial sections with a thickness of 4-5 µm were obtained from histological paraffin blocks, applied onto adhesive SuperFrost slides (Thermo Scientific), and dried at 37°C for 18 hours. Deparaffinized sections underwent antigen retrieval by a thermal method, where the sections were heated in citrate buffer (pH 6.0) at a temperature of 95-98°C. The 'UltraVision Quanto Detection System HRP Polymer' (Thermo Scientific) was utilized for visualizing the immunohistochemistry (IHC) results. This system included the blocking of endogenous peroxidase activity using 3% hydrogen peroxide, nonspecific background staining suppression using 'Ultra V Block,' and amplification of the reaction with 'Primary Antibody Amplifier Quanto.' Diaminobenzidine (DAB) was used as the chromogen. The following antibody panel ('Thermo Scientific', USA) was used in the study (Table 1).

The antibodies were selected to detect the initiation of apoptosis processes (Bax) and the presence of acute (detection of neutrophils - MPO) or chronic (detection of macrophage cells - CD68) inflammation in structurally altered salivary gland tissues with calcifications.

In assessing the immunohistochemical reaction in salivary gland tissue analysis, the count of positively stained cells within a 1000 µm field of view was conducted using morphometric software 'SEO Scan Lab 2.0' and 'Zeiss Zen 2.0'. To ensure the quality control of the conducted IHC investigation, both active and passive control of the obtained results were carried out (utilizing tissue with previously established positive and negative reactions). The criteria for evaluating IHC results (positive reaction in %).

Scanning Electron Microscopy (SEM). The biological tissue displaying biomineralization phenomena was fixed in a 10% buffered formalin, embedded in a paraffin block. Then, 10-12 µm histological sections were obtained from the paraffin block and placed on a specimen holder made of spectrally pure graphite. To maximize adhesion of the biological material to the specimen holder and melt the paraffin, the sections were kept in a thermostat at 60°C for 30 minutes. To remove the paraffin, the samples were treated with xylene three times for 3-4 minutes each, then with 96% ethanol three times for 5-6 minutes, followed by rinsing with distilled water. Subsequently, the biological sample was additionally grounded with conductive tape wrapped around the specimen holder. The prepared samples were examined using a scanning electron microscope REMMA 100U with an energy-dispersive X-ray spectroscope (Selmi, Ukraine). Chemical analysis of the samples was carried out using energy-dispersive spectroscopy (EDS) and X-ray crystal diffraction spectrometry (XRC).

Statistical data analysis. The statistical analysis and data processing were performed using the software STATISTICA 10.0 (Version 13.3.704.5) and Microsoft Excel 2010 with the AtteStat 8 add-on. Results were considered significant with a probability level greater than 95% ($p < 0.05$) under the condition of $r_{exp} \geq r_{crit}$.

Factor analysis was chosen as the statistical method to identify the most significant factors and assess the degree of their influence. Factor analysis was used to identify latent variables that account for the presence of linear statistical relationships (correlations) among the observed variables.

Cluster analysis was performed using a hierarchical method in the form of a dendrogram to divide objects into relatively homogeneous clusters based on the considered set of variables, so that similar and closely related objects were grouped into one cluster, while distant objects were placed into different clusters.

Table 1

The antibody panel for IHC investigation

Antibody	Immunized animal	Clone	Dilution	Cellular localization
CD 68	Rabbit	Polyclone	1:200	Cytoplasm and membrane
MPO	Rabbit	Polyclone	1:200	Cytoplasm
Bax	Rabbit	Polyclone	1:200	Cytoplasm

Results

Macroscopic examination of sialoliths. Sialoliths were most commonly found in dilated salivary ducts. Typical sialoliths had an elongated oval shape, ranging in size from 0.3 to 2.0 cm in their largest dimension. Salivary gland calculi generally displayed a whitish-gray color, although some stones exhibited yellowish-brown and brownish hues. During histological examination, certain small calculi were identified within the salivary gland parenchyma. The average weight of sialoliths obtained from one patient was 0.95±0.87 g. The average mineral content in the sialoliths averaged 64.33%.

Histological examination of salivary gland tissues. The salivary glands exhibiting signs of sialolithiasis were enlarged, inflamed, congested, and edematous. Histological examination revealed chronic inflammation and sclerotic tissue changes, the systemic dilation of gland ducts, focal mixed-cell inflammatory infiltrates, and dyscirculatory changes. Certain calcifications were found within the surrounding connective tissue (Fig. 1).

Immunohistochemical examination. According to the results of the immunohistochemical examination (Fig. 1D), the main portion of Bax-positive cells was located in the glandular parenchyma (48.7%±19.1), and only 10%±17.4 found in the stroma. Staining was observed in the cytoplasm of tumor cells, whereas the normal cells (stromal cells, glandular cells, and infiltrating lymphocytes) were not immunostained. The CD68-positive cell expression showed a positive reaction in most cases, both in the stroma (23.7%±20.8) and in the parenchyma (26.1%±21.7). Staining was observed in both the cytoplasm and the membrane of the macrophage cells (Fig. 1C). The presence of MPO-positive cells was encountered in isolated instances (stroma – 2.5%±7.9, and in the parenchyma – 3.7%±8.3) (Fig. 1E).

Results of statistical data processing. During the factor analysis, a tendency was found linking the expression of CD68 in the stroma and parenchyma of the tumors (0.77 and 0.71, respectively) with the gender of the patients, both male and female.

During the cluster analysis, it was observed that there was no correlation between the gender of the patients and the development of the tumor process. However, a connection was identified between the expression of MPO and Bax, as well as between the age of the patients, the expression of apoptosis markers, and markers of acute and chronic inflammation.

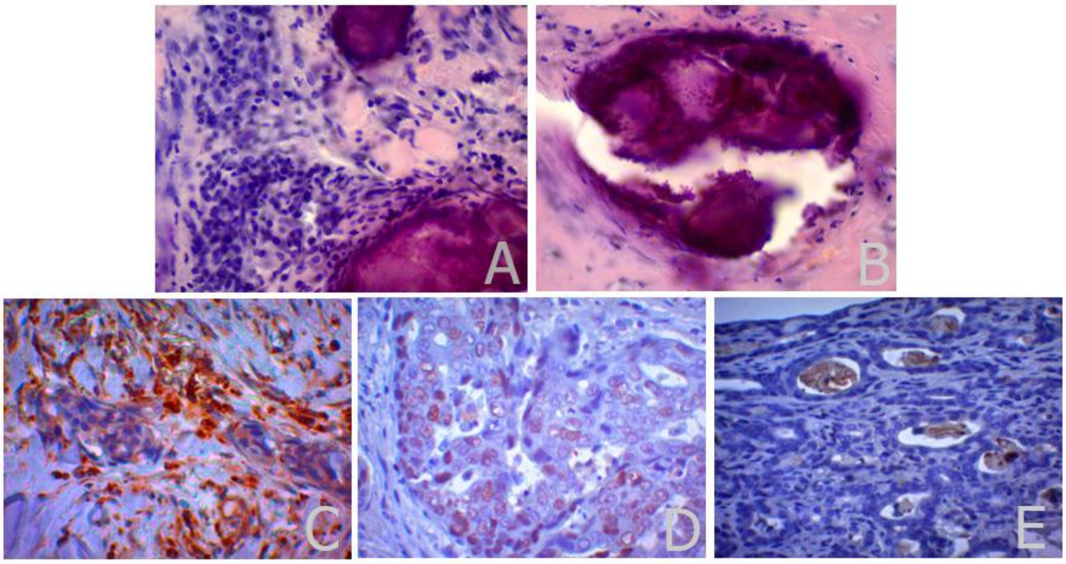

Figure 1. *Histological and immunohistochemical examination of the salivary gland with biomineralization. A. Inflammatory infiltrate around biomineral formations. H&E staining. B. Round-shaped calcifications. H&E staining. C. CD68 expression in the stroma and parenchyma of the gland. D. Bax expression in the gland's parenchyma. E. MPO expression in the gland's stroma. Visualized using DAB with hematoxylin Mayer nuclear counterstaining. Magnification 400X.*

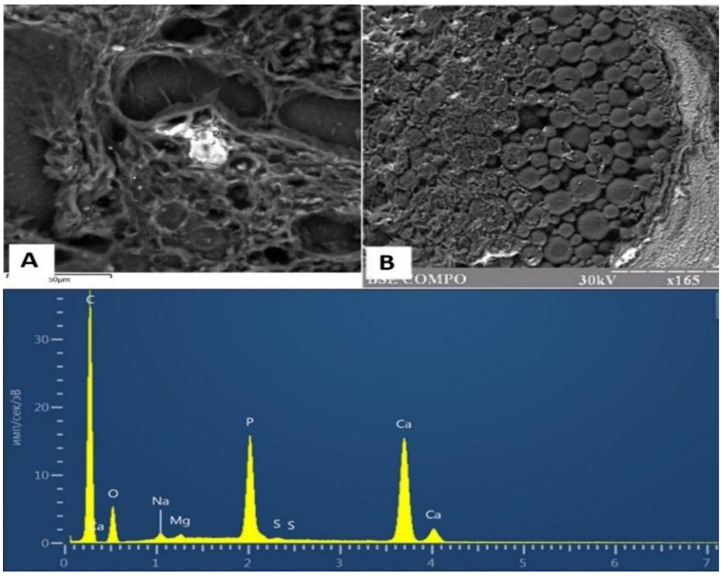

Figure 2. *Scanning Electron Microscopy of sialoliths with X-ray microanalysis. Carbon coating. A. Salivary gland tissue samples. A white calcification located periglandularly in the connective tissue. B. The surface of the sialolith section, showing cracks and ridges. Microcrystalline spheres on the section surface. The magnification and the marker are indicated in the lower right corner of the microphotograph. C. X-ray diffractogram from the microcrystal surface*

SEM Biomineral Research. During the SEM investigation with X-ray microanalysis of sections of salivary gland concrements embedded in epoxy resin, the study of the relief surface of sialoliths revealed circular deposition of minerals around the periphery of the concrement and a complex pattern of mineralization layers within its core. Upon detailed examination, surface irregularities such as folding, porosity, and cracks were evident in the relief of the sialoliths. Of particular interest are biomineral formations morphologically resembling spheres and globules (Fig. 2). Microanalysis was performed on the surface of these spherical microcrystals, identifying their composition as mainly calcium and phosphorus, proportionately aligning most plausibly with hydroxyapatite. In the electron microscopy analysis, the sialoliths were found to contain Ca – 11.66%, P – 6.39%, Na – 0.47%, Mg – 0.23%, and S – 0.14%. The stoichiometric ratio between calcium and phosphorus is 1.82 (Fig. 2).

Discussion.

The process of sialolithiasis occurring in the context of tumor growth is complex and involves several interrelated factors. Tumor growth leads to the destruction of the normal tissue architecture, creating favorable conditions for stone formation. This structural remodeling is associated with changes in the microenvironment, including an increase in the concentration of various substances involved in stone formation.

Many scientific studies indicate that sialoliths are composed of organic and inorganic components. The organic part of these stones includes glycoproteins, glycosaminoglycans, and cellular debris [2,5,13]. The inorganic part is primarily represented by calcium compounds (phosphates and carbonates in the form of hydroxyapatite) [12], as well as calcium and magnesium ions, which, along with other minerals such as iron, potassium, ammonium, and copper, account for about 20-25% [2,5].

In our research, the mineral composition of the sialoliths were similar. When studying hydroxyapatite, attention is usually paid to the ratio of calcium to phosphorus. The stoichiometric ratio of these elements is typically 1.67. However, this indicator can vary depending on the origin of the hydroxyapatite. In our sample, this ratio was 1.82 (Fig. 2). This deviation could be due to chemical group substitutions.

According to Williams M., Marchal F., et al., the formation of stones primarily requires an organic matrix, which comprises glycoproteins, cellular debris, and other organic remnants

[5,14,15]. This area, known as the nidus, is where organic residues accumulate. Over time, the inorganic components (phosphates, carbonates, and calcium salts) gradually precipitate onto this matrix. Evidence supporting this theory is that the organic component is typically found in the central part of the sialolith, with the inorganic part on the periphery [12]. This process might be intensified by tumor growth, as tumors could produce specific components that might be incorporated into the stone structure or alter the physicochemical properties of saliva, thus contributing to the formation and preservation of sialoliths.

The inflammatory process induces disturbances in the chemical balance of soluble components, increases saliva viscosity, and reduces its productivity, thereby promoting material deposition and triggering the sialolithiasis formation process [16]. Typically, calcifications develop in areas characterized by chronic inflammation and tissue necrosis [17,18]. Results from our immunohistochemical investigation also support this phenomenon.

A significant portion of cells showing positive Bax detection are situated in the gland's parenchyma, indicating the activation of apoptosis within the gland's tissue itself (Fig. 1D). Most of the analyzed samples revealed CD68-positive cells (macrophages), suggesting the presence of chronic inflammation in the area of calcification formation (Fig. 1C). The absence of MPO-positive cells (only a few cases) confirms that acute inflammation is not a contributing factor in the development of calcifications (Fig. 1E) [19,20].

The results of the cluster analysis, however, provide grounds to suggest that MPO expression intensifies the process of apoptosis, stimulating tissue self-damage and initiating the inflammatory process. Additionally, according to the results of the factor analysis, a correlation has been established between the presence of a benign or malignant tumor and the process of calcification (0.83) in the structurally altered tissues of the salivary gland.

In our view, the formation of concrements occurs in areas of necrosis and chronic inflammation due to changes in pH during these pathological processes. According to D.A. Chakkalaka et al., who studied the rate of bone mineralization relative to pH, they found that with an increase in pH levels, the processes of mineralization are accelerated [21]. During active (acute) inflammation, the microenvironment establishes an acidic pH, preventing the formation of calcifications. However, over time, acute inflammation transitions to a chronic state, leading to a pH shift towards alkaline conditions. This change results in the formation of dissociated salts in an alkaline environment, facilitating mineral deposition and activating the processes of sialolithiasis (Fig. 3). This is why calcifications are more frequently found in areas of chronic inflammation and necrosis [21-25].

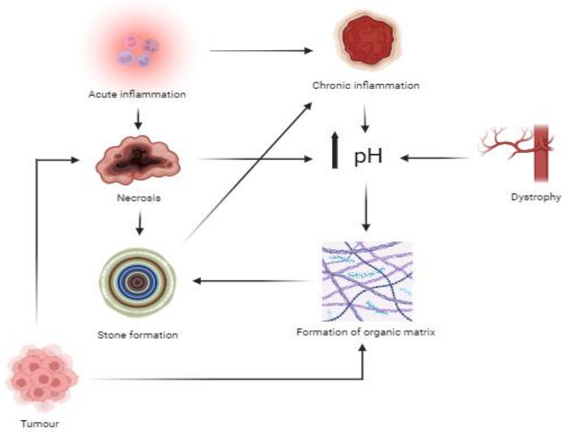

Figure 3. *Pathogenesis of stone formation in the context of tumorous processes*

Conclusions

1. The occurrence of sialolithiasis in the context of a tumorous process takes place due to the structural reorganization of tissue against the backdrop of inflammatory processes, pH level alterations, and mineral deposition.

2. The tissue surrounding the site of pathological biomineralization is characterized by the infiltration of macrophage cells (CD68) and activation of apoptosis (Bax). The expression of MPO, indicating acute inflammation, was observed only in isolated cases.

3. Based on the results of the cluster analysis, it could be inferred that the expression of MPO enhances the process of apoptosis, thus stimulating tissue damage and the inflammatory process, which, in turn, stimulates stone formation.

4. The results from electron microscopy revealed the following composition of sialoliths: Ca – 11.66%, P – 6.39%, Na – 0.47%,

Mg – 0.23%, S – 0.14%. The stoichiometric ratio of calcium to phosphorus is 1.82.

5. As per the results of the factor analysis, a correlation (0.83) was established between the presence of benign or malignant tumors and the process of calcification in structurally altered salivary gland tissues.

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МОРФОЛОГИЧЕСКИЕ ОСОБЕННОСТИ СИАЛОЛИТИАЗА НА ФОНЕ ДОБРОКАЧЕСТВЕННЫХ И ЗЛОКАЧЕСТВЕННЫХ ОПУХОЛЕЙ СЛЮННОЙ ЖЕЛЕЗЫ

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Резюме. В исследовании были использованы 20 образцов тканей слюнных желез, включая как доброкачественные, так и злокачественные опухоли, содержащие биоминеральные образования. Целью было выявление различных факторов, способствующих формированию камней в данных структурах. Для более глубокого понимания патогенеза образования кальцификатов в структурно измененных тканях проведены гистологический, иммуногистохимический анализ (с использованием маркеров острого и хронического воспаления, а также для выявления запуска процессов апоптоза) и микроэлементный анализ сиалолитов.

Установлено, что образование сиалолитиаза при наличии опухолевого процесса происходит вслідствие структурной перестройки ткани на фоне воспалительных процессов, изменения уровня pH и отложения минералов в определенной последовательности.

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