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SAVREMENI POGLED NA MEHANIZME EPITELIJALNE DIFERENCIJACIJE ORALNE MUKOZE U NORMALNIM I PATOLOŠKIM PROCESIMA

MODERN VIEW ON MECHANISMS OF EPITHELIUM DIFFERENTIATION OF THE ORAL MUCOSA IN NORMAL AND PATHOLOGICAL PROCESSES

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Sažetak

Uvod:*U svakodnevnoj kliničkoj praksi pacijenti koji traže stomatološku negu u slučaju oboljenja oralne sluzokože su jedna od najtežih kategorija pacijenata zbog komplikacija u dijagnostici i lečenju.*
Materijali i metode:*Pregled i analiza naučne i medicinske literature zasnovana na bazama podataka Scopus, Veb of Science, MedLine, PubMed, NCBI, čija starost ne prelazi 5 godina, uključujući pregledne radove i rezultate kliničkih ispitivanja.*
Rezultati:. *Promene na oralnoj sluznokoži mogu biti jako specifične. Kliničari mogu postaviti ispravnu dijagnozu i izgledom odrediti proceduru lečenja. Međutim, u većini slučajeva dijagnoza bolesti sa ovom anatomskom lokacijom je komplikovana, jer je klinička slika nespecifična i često su pridodati lokalni i opšti nepovoljni faktori. Za postavljanje tačne dijagnoze neophodan je detaljan klinički pregled i dodatne metode istraživanja. Dijagnoza bolesti oralne sluzokože zasniva se na pažljivoj proceni kliničkih i laboratorijskih podataka.*
Zaključak:*Uzimajući u obzir rasprostranjenost oboljenja oralne sluzokože, posebno je interesantno pitanje toka procesa diferencijacije epitela različitih anatomskih zona i mehanizama restrukturiranja ćelijskog sastava u patološkim procesima, koji objektivizuju dijagnozu, predviđaju tok bolesti i patogenetski potkrepljeni tretman.*

Ključne reči:*usna duplja, epitelne ćelije, upalni proces, parodontalna tkiva*

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Abstract

Background:*In everyday clinical practice, patients who seek dental care in case of oral mucosa diseases are one of the most difficult categories of patients due to difficulties in diagnosis and treatment.*
Materials and methods:*The review and analysis of scientific and medical literature based on the Scopus, Web of Science, MedLine, PubMed, NCBI databases, the study of which does not exceed 5 years, including literature reviews and the results of clinical trials.*
Results:*Changes in the oral mucosa can be clearly specific. Clinicians can make the correct diagnosis and determine the tactics of treatment by appearance. However, in most cases the diagnosis of diseases with this anatomical location is complicated, because the clinical picture is nonspecific and often burdened with additional local and general adverse factors. A detailed clinical examination and additional research methods are required to establish the correct diagnosis. Diagnosis of oral mucosa diseases is based on a careful assessment of clinical and laboratory data.*
Conclusions:*Taking into account the prevalence of diseases of the oral mucosa, of particular interest is the question of the course of the process of differentiation of the epithelium of various anatomical zones in the norm and the mechanisms of restructuring of the cellular composition in pathological processes, with the cops of objectifying the diagnosis, predicting the course of the disease and pathogenetically substantiated treatment.*

Key words:*oral cavity, epithelial cells, inflammatory process, periodontal tissues*

Uvod

Epitel pokriva 80% površine oralne sluzokože, čija je površina, kod odrasle osobe, oko 172 cm^2. Strukturu epitela karakteriše jasna pripadnost jednoj regiji. Prema morfo-funkcionalnim karakteristikama, istraživači razlikuju sledeće tipove oralne sluzokože: mastikatornu, pokrovnu i specijalizovanu[1].

Mastikatorna mukoza, koja se nalazi na tvrdom nepcu i desnima, uglavnom je uključena u mehaničku obradu hrane. Sastoji se od pločasto-slojevitog nekeratinizovanog epitela, bazalne membrane i submukozne baze, pokretne i elastične. Sluzokoža specija-lizovanog tipa pokriva dorzalnu površinu jezika, prekrivenu pločasto-slojevitim nekaratinizovanim i, na nekim mestima, keratinizovanim epitelom i bazalnom membranom, koju karakteriše prisustvo papila i specijalizovanih kvržica čula ukusa, koja je pričvršćena za mišićno tkivo, umereno pokretna i otporna na mehanički pritisak[2,3].

Cilj rada bila je analiza literatiurnih podataka, koji se bave proučavanjem savremenih pogleda na problem imunološkog statusa oralne sluzokože.

Materijali i metode

Pregled i analiza naučne i medicinske literature na osnovu baza podataka Scopus, Web of Science, MedLine, PubMed, NCBI, čija starost prelazi 5 godina, uključujući pregledne radove i rezultate kliničkih ispitivanja.

Rezultati i diskusija

Barijerna svojstva epitela oralne sluzokože pojačana su ćelijskom proizvodnjom brojnih peptida - katjonskim proteinima, kalprotektinom, b-efensinom i lingvalnim antimikrobnim peptidom, sa širokim spektrom antimikrobne aktivnosti[4,5]. Održavanje integriteta epitela i svojstava barijere obezbeđeno je kombinacijom tri međusobno uravnotežena procesa sa sinhronim tokom. To su: regeneracija: kontinuirano stvaranje ćelija u bazalnom sloju, usled podele slabo diferenciranih prekursora; diferencijacija – promena morfo-funkcionalnih karakteristika ćelija istovremeno sa njihovim pomeranjem u gornjim slojevima; deskvamacija – uklanjanje oštećenih ćelija (deskvamirane ljuske) sa površine epitela, koje na svojoj površini sadrže mikroorganizme.

Introduction

The epithelium covers 80% of the oral mucosa surface, the area of which in an adult is about 172 cm^2. The structure of the epithelium is characterized by a clear regionality. According to morphofunctional features, researchers distinguish the following types of mucosa: masticatory, lining and specialized[1].

The masticatory mucosa, located on the hard palate and gums, is involved mainly in the mechanical processing of food. It is represented by a stratified squamous keratinized epithelium and basement membrane, which is closely attached to the bone, less mobile, has high strength and low permeability. The lining mucosa covers the cheeks, lips, the floor of the mouth, the oral surface of the soft palate and the ventral surface of the tongue. It is represented by a stratified squamous non-keratinized epithelium, basement membrane and submucosal base, mobile and elastic. The mucous membrane of the specialized type covers the dorsal surface of the tongue, covered with stratified non–keratinized and in some areas – keratinized epithelium and basement membrane, characterized by the presence of special papillae and taste buds, adjacent to muscle tissue, moderately mobile and resistant to mechanical pressure[2,3].

The aim. Analysis of literary sources with the study of modern views on the problem of the immune status of the oral mucosa.

Materials and methods

The review and analysis of scientific and medical literature based on the Scopus, Web of Science, MedLine, PubMed, NCBI databases, the study of which does not exceed 5 years, including literature reviews and the results of clinical trials[4].

Results anddiscussion

The barrier properties of the oral mucosa epithelium are enhanced by its cells production of a number of peptides – cationic proteins, calprotectin, b-efensin and lingual antimicrobial peptide with a wide range of antimicrobial activity[5,6]. Maintaining the integrity of epithelium and barrier properties is provided by the combination of three mutually balanced processes with a synchronous course.

Ćelijski sastav skvamoznog poločasto-slojevitog epitela usne duplje je stereotipno epitelno tkivo i sadrži sve tipične elemente – bazalni, parabazalni (srednji) i orožao (površinski) sloj. Dakle, reč je o postepenoj diferencijaciji epiteliocita u epitelnom sloju, usled čega nastaju orožale skvame, koje se potom deskvamiraju[6].

Proteinski enzimi sadržani u citoplazmi bazalnih ćelija okruženi su vodenim medijumom, dok su u zrnastim epiteliocitima uronjeni u hidrofobnu supstancu – keratohialin. Prema nekim istraživačima[7], takav medijum inicira intramolekularno preuređivanje polipeptidnih lanaca filamenata.

Procesi keratinizacije pločasto-slojevitog epitela odvijaju se kroz sledeće faze: 1) formiranje tonofibrila; 2) formiranje tono-filamentnih elemenata; 3) stvaranje tonofibrilarno-keratohialinskih kompleksa; 4) formiranje orožalih skvama i njihova deskvamacija[8].

Prva faza keratinizacije javlja se u bazalnom i parabazalnom sloju. U citoplazmi epitelocita ovih slojeva nastaju tonofibrili prečnika 3 nm –5 nm, koji su strukturno povezani sa ribozomima. Kontakt bazalnih epitelocita sa membranom obezbeđen je poludezmozomalnim kontaktima; ćelije bazalnog i parabazalnog sloja povezane su pojedinačnim dezmozomima.

U drugoj fazi keratinizacije, u citoplazmi ćelija spinoznog sloja nastaju snopovi tonofibrila-tonofilamenata prečnika 7 nm – 8 nm. Poslednji formira dve konture u citoplazmi: jednu direktno oko jedra, a drugu na njenoj periferiji u blizini dezmozoma. Ova ultrastrukturna distribucija tonofilamentnih struktura u spinoznim ćelijama omogućava funkciju amortizacije[9]. Ćelije spinoznog sloja u kontaktu su jedna sa drugom kroz brojne dezmozome.

U trećoj fazi keratinizacije, u citoplazmi zrnastih epitelocita, nastaju keratinozomi ili Odlanderove granule, prečnika 100 nm – 400 nm. Keratinozomi su okruženi membranom i sadrže lamele sa keratohialinskim masama. Prema Bikovu[1], oni su poseban oblik lizozoma. Mase keratohialina, koje se oslobađaju keratinozom, zajedno sa snopovima tonofibrila, formiraju složene komplekse kerato-tonofilamenta. Tako je sinteza keratohialina u ćelijama zrnastog sloja praćena uništavanjem njihovog tonofibrilarnog matriksa.

U četvrtoj fazi keratinizacije formiraju se rožaste skvame, koje se naknadno deskvamiraju. Tako se ostvaruje zaštitna funkcija pločasto-slojevitog epitela. U stratum corneumu, na ultrastrukturnom nivou, postoje skvame sa paralelnom orijentacijom tonofibrilarnih struktura (A tip) i sa njihovim

These are: regeneration – the continuous formation of cells in the basal layer due to the division of poorly differentiated precursors; differentiation – change of morphofunctional characteristics of cells simultaneously with their displacement in the upper layers; desquamation – removal ofdamaged cells (desquamated scales) from the epithelium surface which contain microorganisms on its surface.

The cellular composition of the stratified squamous oral mucosa epithelium is stereotyped epithelial tissue and contains all the typical elements – basal, parabasal (intermediate) and corneal (superficial). Thus, it is a gradual differentiation of epitheliocytes in epithelial layer, as a result of which horny scales are formed and subsequently desquamated[7].

Protein enzymes contained in the cytoplasm of basal cells are surrounded by an aqueous medium, while in granular epitheliocytes they are immersed in a hydrophobic substance – keratohyalin. According to some researchers[8], such a medium initiates the intramolecular rearrangement of filaments polypeptide chains.

Keratinization processes in the stratified squamous epithelium occur in stages: 1) the formation of tonofibrils; 2) formation of tonofilament elements; 3) formation of tonofibrillary-keratohyalin complexes; 4) the formation of horny scales and their desquamation[9].

The first stage of keratinization occurs in the basal and parabasal layers. In the cytoplasm of epitheliocytes of these layers, tonofibrils with a diameter of 3–5 nm are formed, which are structurally connected with ribosomes. Contact of basal epitheliocytes with the membrane is provided by semi-desmosomal contacts, cells of basal and parabasal layers are connected by single desmosomes.

At the second stage of keratinization, bundles of tonofibrils – tonofilaments with a diameter of 7–8 nm are formed in the cytoplasm of the thorny layer cells. The last forms two contours in the cytoplasm: one directly around the nucleus, and the other on its periphery near the desmosomes. This ultrastructural distribution of tonofilament structures in thorny cells provides an amortization function[10]. The cells of the thorny layer are in contact with each other through numerous desmosomes.At the third stage of keratinization, keratinosomes or Odlander granules with a diameter of 100–400 nm are formed in the cytoplasm of granular epitheliocytes. Keratinosomes are surrounded by a membrane and contain lamellae with keratogialin masses. According to V.L.

okomitim ili tangencijalnim rasporedom (B tip).Međutim, u nekim rožnatim skvamama, piknotična jezgra, pa čak i pojedinačne mitohondrije, delimično su očuvane. Takve ljuske nazivaju se T-ćelije, a njihovo prisustvo ukazuje na nepotpun proces ortokeratoze[10,11].

Studija Brija[12] pokazuje da procese keratinizacije, koji se javljaju u pločasto-slojevitom epitelu oralne sluzokože, karakterišu brojne osobine, koje su povezane sa funkcijom anatomskog područja.

Ovo potvrđuje studija Choija[13] i ukazuje na to da je težina stratum corneuma, koju formiraju skvame, različita. U stratum corneumu gingive nalazi se veliki broj skvama, dok na obraznoj sluzokoži nisu tako izražene. Istovremeno, primećuje se umeren razvoj tonofilamentnih struktura u citoplazmi ćelija spinoznog sloja. Takve karakteristike višeslojne keratinizacije epitela obrazne sluzokože ukazuju na procese nepotpune keratinizacije u njemu.

Regulaciju procesa diferencijacije i proliferacije, kao i homeostaze epitelocita obezbeđuju ćelije intraepitelnog sistema makrofaga; naime to su Langerhansove ćelije i dendritične ćelije.

Eksperimentalno je dokazan funkcionalni odnos između Langerhansovih ćelija i keratinocita. Pored toga, izneta je teorija[14] o epidermalnoj proliferativnoj jedinici. Prema njoj, Langerhansova ćelija je centar diferona ili zasebna epidermalna proliferativna jedinica. Uz pomoć citoplazmatskih procesa, one dolaze u kontakt sa epitelocitima bazalnog i parabazalnog sloja unutar svog diferona, izazivajući njihov vertikalni anizomorfizam i regulišući procese proliferacije i specijalizacije. Zbog sinteze supstanci sličnih cejlonu, Langerhansove ćelije inhibiraju proliferativnu aktivnost bazalnih epitelocita. Svaki diferon ili svaka epidermalna proliferativna jedinica uključuje oko 20 ćelija, od kojih se polovina nalazi na nivou bazalnog i parabazalnog sloja. Diferon ima oblik vertikalnog stuba, čiji se gornji deo sastoji od rožnatih ljuski, a donji se oslanja na bazalnu membranu. Rožnate ljuske formiraju površinski sloj diferona. U ovom slučaju, tri skale tipa A povezuju se sa tri skale tipa B i zajedno sa T-ćelijama, na površini epitela, formiraju heksagonalne konture svake proliferativne jedinice.

Langerhansove ćelije pripadaju sistemu intraepitelnih makrofaga. Specifičnosti njihove ultrastrukturne organizacije, razvijeni citoplazmatski kompleksi, kao i prisustvo posebnih granula i lizozoma u citoplazmi, ukazuju na visoku funkcionalnu aktivnost ovih ćelija.

Bykov[1], they are a special form of lysosomes.

Keratogialin masses, which are released with keratinosis, together with bundles of tonofibrils form complex kerato-tonofilament complexes. Thus, the synthesis of keratohyalin in the cells of the granular layer is accompanied by the destruction of their tonofibrillary matrix.

In the fourth stage of keratinization, horny scales are formed, which are subsequently desquamated. Thus the protective function of a stratified squamous epithelium is realized. In the stratum corneum at the ultrastructural level there are scales with parallel orientation of tonofibrillar structures (A-type) and with their perpendicular or tangential arrangement (B-type). However, in some horny scales pyknotic nuclei and even single mitochondria are partially preserved. Such scales are called T-cells, their presence indicates an incomplete process of orthokeratosis[11].

The work of A. Bryja[12] shows that the keratinization processes that occur in the stratified squamous epithelium of the oral mucosa are characterized by a number of regional features that are associated with the function of the anatomical area.

This position is confirmed by the work of J. Choi[13] and indicates that the severity of the stratum corneum, which is formed by scales, is different. In the stratum corneum of the gums is determined by a large number of scales, while a similar layer of cheeks is almost not expressed. At the same time moderate development of tonofilament structures in a cytoplasm of cells of a prickly layer is observed. Such features of multilayered squamous epithelium keratinization of cheek indicate the processes of incomplete keratinization in it.

Regulation of differentiation and proliferation processes, as well as epitheliocyte homeostasis are provided by cells of the intraepithelial macrophage system, namely Langerhans cells and dendritic cells.

The functional relationship of Langerhans cells with keratinocytes has been experimentally proven. In addition, a theory [14] of the epidermal proliferative unit has been put forward. According to it, the Langerhans cell is the center of diferon, or a separate epidermal proliferative unit. With the help of cytoplasmic processes, they contact the epitheliocytes of the basal and parabasal layers within their diferon, causing their vertical anisomorphism and regulating the processes of proliferation and specialization.Due to the synthesis of keylon-like substances, Langerhans cells inhibit the proliferative activity of basal epitheliocytes.

Nedavna istraživanja[15,16]pokazala su to da su metabolički procesi u epitelnim tkivima oralne sluzokože hormonski zavisni. Receptori za brojne hormone, uključujući estradiol, koji se uglavnom nalazi u ćelijskim jezgrima parabazalnog i bazalnog sloja, otkriveni su u epitelocitima gingivalne mukoze.

U slučaju hormonskog prilagođavanja tokom menstrualnog ciklusa, razvijaju se morfo-funkcionalne promene u epitelu oralne sluzokože.

Razvoj ovih dinamičkih procesa može inicirati pojavu parodontopatije, u slučaju hormonske neravnoteže. Najčešće su ovi oblici atipični i agresivni[17].

Bae[18] prikazuje to da se tok procesa diferencijacije sluzokože usne duplje i usta odražava na biološku starost pojedinca – stepen starosnih promena bioloških sposobnosti organizma u svakoj fazi ontogeneze. U pozadini preranog starenja tela, stanje njegovih organa i sistema, kao i rizici od pojave i toka parodontalnog tkiva i bolesti sluzokože usne duplje značajno se razlikuju od onih kod fiziološkog starenja; prognoza se pogoršava, vreme oporavka kasni, uobičajeni načini lečenja su neefikasni, što dovodi do smanjenja kvaliteta života[19].

Prema statističkim podacima, procenat patoloških procesa na oralnoj sluzokoži kod poseta terapeutu varira od 0,5% do 0,9% svih primarnih poseta, u zavisnosti od starosti pacijenata.

Međutim, u svakodnevnoj kliničkoj praksi, pacijenti sa bolestima oralne sluzokože, koji zahtevaju stomatološku negu, jedan su od najtežih izazova u stomatološkoj praksi, zbog poteškoća u dijagnostici i lečenju. Zato je potraga za citološkim markerima, indikatorima stanja pojedinačne oralne sluzokože perspektiva, ne samo za poboljšanje kvaliteta dijagnoze i terapije zuba, već i za utvrđivanje opšteg stanja zdravlja pacijenata. Klinički je dokazano to da je sluzokoža najtačniji pokazatelj procene patoloških procesa u digestivnom traktu, imunološkog stanja organizma, opšteg nivoa aktivnosti i proliferacije ćelijskih sistema[20-22].

U mladosti, bolesti sluzokože usne duplje razvijaju se zbog smanjene salivacije i lokalne otpornosti tkiva, poremećaja procesa diferencijacije i keratinizacije u epitelnim ćelijama, kao i usled promene u mikrobiocenozi sluzokože.

U vezi sa prethodno navedenim, tokom lečenja bolesti oralne sluzokože, jako je važno uključiti skup dijagnostičkih i profilaktičkih mera, koje karakteriše minimalna invazivnost i dostupnost na prijemu, koje bi ubrzale obnavljanje sluzokože i mikrocirkulaciju[23],

Each diferon, or epidermal proliferative unit, includes about 20 cells, half of which are located at the level of the basal and parabasal layers. Diferon has the shape of a vertical column, the upper part of which consists of horny scales, and the lower rests on the basement membrane. Horny scales form the surface layer of diferon. In this case, three A-type scales connect with three B-type scales and together with T-cells on the surface of the epithelium form the hexagonal contours of the proliferative unit.

Langerhans cells belong to the system of intraepithelial macrophages. The peculiarities of their ultrastructural organization, namely the developed cyto-plasmic complexes, as well as the presence of specific granules and lysosomes in the cytoplasm, indicate high functional activity of these cells.

Recent studies[15,16] have shown that metabolic processes in the epithelial tissues of the oral mucosa are hormone-dependent. Receptors to a number of hormones, including estradiol, which are mainly found in the cell nuclei of the parabasal and basal layers, have been detected in the epitheliocytes of the gingival mucosa.

In the case of hormonal adjustment during the menstrual cycle, morphofunctional changes develop in the epithelium of the oral mucosa.

The development of these dynamic states can initiate the occurrence of periodontal disease in the case of hormonal imbalance. Most commonly these forms are atypical and aggressive[17].

The work of C.-Y. Bae[18], show that the course of the differentiation process of the mucous membrane of the oral cavity and mouth reflects the biological age of the individual – the degree of age-related changes in the biological capabilities of the organism at each stage of ontogenesis. At the background of premature body aging, the condition of its organs and systems, as well as risks of occurrence and course of periodontal tissues and oral mucosa diseases are significantly different from those of physiological aging, the prognosis deteriorates, recovery time is delayed,common treatment regimens are ineffective, resulting in reduced quality of life[19].

According to statistics, the percentage of pathological processes of the oral mucosa in the structure of visits to the therapeutic department varies from 0.5 to 0.9% of all primary visits depending on age.

However, in everyday clinical practice, patients who seek dental care with diseases of the oral mucosa are one of the most difficult problems in dentistry due to difficulties in diagnosis and treatment.

imajući u vidu istovremeno minimalne nuspojave u organizmu, u celini, i pružajući mogućnost dinamičkog praćenja istih.

Poslednjih godina, zahvaljujući praktičnoj implementaciji programa prevencije stomatoloških oboljenja[24], postoji tendencija njihovog smanjenja među decom, što otvara perspektivu poboljšanja zdravlja zuba u ovoj starosnoj grupi. Međutim, program prevencije, zapravo, ne odnosi se na odraslu generaciju i u bliskoj budućnosti nema razloga očekivati smanjenje incidencije među pacijentima starosti od 25 od 35 godina, kao i među još starijim pacijentima. Štaviše, zbog starenja stanovništva, među starima se očekuju posebni i najteži problemi stomatološke zaštite.

U lekarskoj praksi, pokazalo se[25,26]da promene u oralnoj sluzokoži mogu imati specifičan karakter, kada se samo na osnovu izgleda mogu dijagnostikovati i može se odrediti taktika lečenja. Međutim, u većini slučajeva, dijagnoza bolesti koje se javljaju na sluzokoži je komplikovana, jer je klinička slika nespecifična i često sa udruženim nepovoljnim lokalnim (loša higijena, trauma, sekundarna infekcija) i opštim (hipovitaminoza, somatska patologija) faktorima. Za postavljanje tačne dijagnoze, neophodan je detaljan klinički pregled i potrebne su dodatne metode istraživanja.

Dijagnostika većine oboljenja oralne sluzokože zasniva se na pažljivoj proceni kliničkih i laboratorijskih podataka. Efikasnost lečenja zavisi od tačne dijagnoze. Epitel oralne sluzokože tradicionalni je predmet citoloških studija, koji omogućava otkrivanje razvoja prekanceroznih i tumorskih procesa, poremećaja ćelijske diferencijacije i infektivnih lezija. Ovo ukazuje na to da citološka analiza zahvaćenih područja oralne sluzokože daje dragocene informacije o morfo-funkcionalnom stanju sluzokože u različitim lezijama[27].

Takve citološke metode istraživanja, kao što su printovi i ponovni printovi, prilično su pouzdane i imaju nekoliko prednosti u odnosu na biopsiju. One su minimalno invazivne, olakšavaju pribavljanje materijala, omogućuju postavljanje preliminarne dijagnoze procesa za 20 do 30 minuta, mogu se ponovo koristiti za praćenje dinamike procesa i procenu efikasnosti lečenja[25].

Tok diferencijacije epitela oralne sluzokože procenjuje se njenim citološkim pregledom. Prema citološkoj klasifikaciji, u epitelu oralne sluzokože nalaze se bazalne, parabazalne, srednje i površinske ćelije, a rožaste skvame nađene su u područjima koja su podvrgnuta keratinizaciji. U ćelijskom sastavu epitela sluzokože preovlađuju intermedijarne ćelije.

That is why the search for cytological markers-indicators of the individual oral mucosa state is perspective not only to improve the quality of diagnosis and correction of dental status, but also to determine the general health of patients. It is clinically proven that the mucous membrane is the most accurate indicator of the pathological processes assessment of the digestive tract, the immune status of the organism, the general level of activity and proliferation of cellular systems[20-22].

At young age, diseases of the oral mucosa develop at the background of reduced salivation and local tissue resistance, violation of the differentiation and keratinization processes in epithelial cells, as well as changes in the microbiocenosis of the mucous membrane.

In connection with the foregoing, during the treatment of oral mucosa diseases it becomes important to include in a set of diagnostic and prophylactic measures, which are characterized by minimally invasiveness and availability at the dental reception and would accelerate the renovation of the mucous barrier and microcirculation[23] having at the same time the minimum side effect on an organism as a whole and providing the possibility of dynamic monitoring.

In recent years, thanks to the practical implementation of a dental disease prevention program[24], there has been a tendency to reduce them among children, which opens the perspective of improving dental health in this age group. However, the prevention program does not actually cover the adult generation and in the near future there is no reason to expect a decrease in the incidence among patients aged 25-35 years and older. Moreover, due to the trend of aging population, special and the most difficult problems of dental care are expected among the elderly.

The clinician's work shows[25,26]that changes in the oral mucosa can have clearly specific character, when the treatment tactics can be diagnosed and determined just by the appearance. However, in most cases, the diagnostics of diseases that occur on the mucosa is complicated because the clinicalpicture is nonspecific and often burdened by additional adverse local (poor hygiene, trauma, secondary infection) and general (hypovitaminosis, somatic pathology) factors. A detailed clinical examination and additional research methods are required to establish a correct diagnosis.

Izgled površinskih ćelija odgovara maksimalnom nivou sazrevanja nekeratinizovanog epitela, a izgled rožastih skvama odgovara keratinizovanom epitelu. Sadržaj poslednjeg sloja epitela naglo se uvećava u slučaju hiperkeratoze. Poslednjih godina, razvijene su metode za procenu parametara, koji se odnose na epitelocite oralne sluzokože, korišćenjem sistema za automatsku analizu slike[29].

Promena prirode epitelne diferencijacije, koja je karakteristična za određeno područje oralne sluznokože, ukazuje na lokalne ili sistemske poremećaje. Prisustvo ćelijske atipije sa velikom verovatnoćom ukazuje na razvoj prekanceroznih i tumorskih promena oralne sluzokože i u 96% slučajeva omogućava pouzdano dijagnostikovanje ovih bolesti citološkim metodama. Promene u diferencijaciji epitela oralne sluzokože mogu takođe biti rezultat metaboličkih i hormonskih poremećaja, dejstva mehaničkih faktora i hemijskih supstanci[30,31].

Kod inflamatornih procesa, različite geneze u printovima sa sluzokože usne duplje, otkrivaju se manje diferencirane ćelije, sve do bazalne ćelije (I faza). U hiperkeratozi, naprotiv, ima više ćelija VI stadijuma[32].

U slučaju lichen planusa, citološki metod pregleda, po pravilu, otkriva veliki broj limfocita u zahvaćenom području, od kojih su mnogi aktivirani makrofagi, dok su plazma ćelije ređe.

Analizirajući literaturne podatke, vidimo da se citološka slika ćelijskih elemenata u patološkim procesima oralne sluzokože karakteriše određenim osobinama. Citogrami iz fokusa lezije, koji odražavaju dinamiku promena oralne sluzokože tokom njene epitelizacije, takođe su jedan od objektivnih testova za procenu opšteg stanja organizma[30].

Prilično često, radovi različitih autora predstavljaju kvantitativne podatke o korelaciji tipova ćelija u citološkim preparatima oralne sluzokože. Do ovakvih odstupanja došlo je čak i u slučajevima u kojima su autori koristili istu klasifikaciju epitelnih ćelija i proučavali slična područja oralne sluzokože. Glavni razlozi za takve razlike su različite metode fiksacije brisa i subjektivne procene citograma, kao i polne i starosne razlike, koje prethodnici nisu uzeli u obzir.

U tu svrhu, predloženi su različiti indeksi: nuklearno-piknotički (procenat ćelija sa piknotičnim jedrom), keratinizacija (procenat nenuklearnih ćelija) i eozinofilni (procenat ćelija sa eozinofilno-oksifilnom citoplazmom među površinskim ćelijama).

Diagnostics of most oral mucosa diseases is based on a careful assessment of clinical and laboratory data. The effectiveness of treatment depends on the correct diagnosis. The epithelium of the oral mucosa is a traditional object of cytological studies, which allows to reveal the development of precancerous and tumor processes, disorders of cell differentiation, infectious lesions. This indicates that the cytological analysis of imprints from the affected areas of the oral mucosa provides valuable information about the morphofunctional state of the mucosa in various lesions[27].

Such cytological research methods as prints and re-prints are quite reliable and have several advantages over biopsy. They are minimally invasive, make it easy to obtain material, make it possible to establish a preliminary diagnosis of the process in 20-30 minutes, can be reused to monitor the dynamics of the process and evaluate the effectiveness of treatment[25].

The course of differentiation of the oral mucosa epithelium is assessed by its cytological examination. According to the cytological classification, basal, parabasal, intermediate and superficial cells are selected in the oral mucosa epithelium, and horny scales in the areas that undergo keratinization. In the cellular composition of the mucosal epithelium, intermediate cells predominate. The appearance of surface cells corresponds to the maximum level of non-keratinized epithelium maturation, and the appearance of horny scales corresponds to the keratinized epithelium. The content of the last increases sharply in a case of hyperkeratosis. In recent years, methods to estimate the parameters of oral mucosa epitheliocytes using automatic image analysis systems have been developed[29].

A change in the nature of epithelial differentiation, which is normally characteristic of a certain area of the oral mucosa, indicates local or systemic disorders. The presence of cellular atypia sign with a high probability indicates the development of precancerous and tumor changes of the oral mucosa and in 96% of cases allows reliably diagnose these diseases by cytological methods. Changes in the differentiation of the oral mucosa epithelium may also be the result of metabolic and hormonal disorders, the action of mechanical factors and chemical substances[30,31]. At inflammatory processes of various genesis in imprints from a mucous membrane of an oral cavity less differentiated cells, up to basal (I stage) are revealed. In hyperkeratosis, on the contrary, there are more cells of VI stage[32].

Zbog praktične primene i dobijanja najpotpunijih i najobjektivnih citoloških karakteristika printova oralne sluzokože, preporučuje se korišćenje indeksa ćelijske diferencijacije, koji uzima u obzir ćelije u različitim fazama diferencijacije i citomorfometrijska metoda, koja se zasniva naprebrojavanju epitelnih ćelija različitih vrsta na citogramu. Citopatologija pokazuje: povećanu citoplazmatsku bazofiliju, distrofične i nekrobiotičke promene, "phaging". Na osnovu relativnih nekrobiotičkih indikatora broja izmenjenih ćelija, autori su predložili dva indeksa: indeks uništenja, koji odražava aktivnost procesa i upalno-destruktivni indeks, koji je u korelaciji sa intenzitetom i prirodom zapaljenskog procesa.

Poslednjih godina, brojne studije[5,7,28,29,34]pokazale su to da u etiologiji i patogenezi niza patoloških procesa oralne sluzokože značajnu ulogu ima mikrobiološki uticaj, posebno predstavnici saprofitskih i oportunističkih mikroflora. Najučestalije bolesti zuba nemaju specifičan etiološki patogen i razvijaju se kao posledica oportunističke proliferacije mikroflore u uslovima naglog smanjenja prirodnih zaštitnih faktora i adaptivnih reakcija organizma.

Naše kliničke studije pokazale su to[6,8,34,35]da je u današnje vreme značajan problem pravovremena dijagnostika dermatoza sa autoimunom komponentom, poput lichen planusa i akantolitičkog pemfigusa. Teškoće prilikom postavljanja dijagnoze nastaju zbog nedostatka jasnih kvantitativnih podataka o procentualnoj korelaciji epitelnih ćelija jedne regije, uzimajući u obzir starost i pol pacijenata, kao i stabilne citološke parametre ovih bolesti u pretkliničkoj fazi. Izolovana lezija oralne sluzokože čini 30% do 35% ukupnog broja slučajeva. Erozivno-ulcerativni i hiperkeratotični oblici lichen planusa su opcionalne prekancerozne lezije sa verovatnoćom transformacije u tumor od 7%.

In the case of lichen planus, the cytological method of examination, as a rule, reveals a large number of lymphocytes in the affected area, many activated macrophages, plasma cells are less common.

Analyzing the literature data, we see that the cytological picture of cellular elements in pathological processes of the oral mucosa is characterized by certain features. Cytograms from the focus of the lesion, reflecting the dynamics of changes in the oral mucosa during its epithelialization, is also one of the objective tests to assess the general condition of the organism[30].

Quite often works of various authors present quantitative data concerning the correlation of cell types in cytological preparations of the oral mucosa differ significantly. Such discrepancies occurred even in cases where the authors used the same classification of epithelial cells and studied similar areas of the oral mucosa. The main reasons for such differences are various methods of smears fixation and subjective assessment of cytograms, as well as gender and age differences, not taken into account by predecessors.

According to numerous studies, to increase the reliability and comparability of cytological studies results should refer to quantitative estimates, values that can be measured and expressed through quantitative indicators and, of course, in the dynamics of treatment.

With this purpose, have proposed various indices: nuclear-pyknotic (percentage of cells with pyknotic nucleus), keratinization (percentage of non-nuclear cells), eosinophilic (percentage of cells with eosinophilic-oxyphilic cytoplasm among superficial cells).

For the convenience of practical application and obtaining the most complete and objective cytological characteristics of the imprints of the oral mucosa, it is advisable to use the cell differentiation index, which takes into account the ratio of cells at different stages of differentiation, and a cytomorphometric method has been developed, which is based on counting the number of epithelial cells with signs of various types in the cytogram. cytopathology: increased cytoplasmic basophilia, dystrophic and necrobiotic changes, «phaging». Based on the relative necrobiotic indicators of the number of altered cells, the authors proposed two indices: the destruction index, which reflects the activity of processes, and the inflammatory-destructive index, which correlates with the intensity and nature of the inflammatory process.

In recent years numerous studies[5,6,8,25,26,30] have shown that in the etiology and

Zaključak

Analitički pregled literature pokazuje to da su mehanizmi poremećaja oralne epitelne homeostaze usko povezani sa procesima regeneracije, diferencijacije i deskvamacije i imaju vodeću ulogu u patogenezi oboljenja oralne sluzokože. Poslednjih godina, bilo je mnogo dijagnostičkih kriterijuma za primarne i sekundarne lezije oralne sluzokože, proučavana je mogućnost njihove kliničke primene, ali je efikasnost lečenja bolesti oralne sluznice još uvek nedovoljna. Postoji samo nekoliko studija o proceni procentualne korelacije epitelocita, ali one ne uzimaju u obzir starost i pol pacijenata. Tako je proučavanje procesa diferencijacije oralne sluzokože, uz dubinsku analizu citoloških karakteristika različitih anatomskih područja i morfoloških i citospecifičnih promena kod prisustva inflamatornog procesa u parodontalnim tkivima, relevantno i perspektivno područje istraživanja.

pathogenesis of a number of pathological processes of the oral mucosa a significant role belongs to the microbial factor, in particular representatives of saprophytic and opportunistic microflora. Most dental diseases don't have a specific pathogen and develop as a consequence of the opportunistic microflora proliferation in the conditions of sharp decrease in natural factors of protective and adaptive reactions of organism.

My/Our own clinical studies have shown[6,8,34,35] that a significant problem today is the timely diagnostics of dermatoses with an autoimmune component, such as lichen planus and acantholytic pemphigus. The difficulty of the diagnostic process is due to the lack of clear quantitative data about the regional percentage correlation of epithelial cells, taking into account the age and sex of patients, as well as stable cytological guidelines of these diseases in the preclinical stage. The isolated lesion of the oral mucosa is 30-35% of the total number of cases. Erosive-ulcerative and hyperkeratotic forms of lichen planus are optional precancerous lesions with a probability of tumor transformation of 7%.

Conclusion

Analytical review of the literature shows that the mechanisms of disturbance of oral epithelial homeostasis are closely related to the processes of regeneration, differentiation and desquamation and play a leading role in the pathogenesis of oral mucosa diseases. In recent years, there have been many diagnostic criteria for primary and secondary lesions of the oral mucosa, the possibility of their clinical application has been studied, but the effectiveness of treatment of diseases of the oral mucosa is still insufficient. There are only a few studies on the assessment of the percentage correlation of epitheliocytes in norm, but they don't take into account age and gender. Thus, the study of the differentiation processes of the oral mucosa with the in-depth analysis of cytological features of different anatomical areas in the norm and morphological and cytospecific changes in the presence of an inflammatory process in periodontal tissues, is a relevant and perspective area of research.

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