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TERAPIJA REKURENTNIH ORALNIH ULCERACIJA KOD PACIJENATA SA HIV-om

MANAGEMENT OF RECURRENT APHTHOUS STOMATITIS IN HIV

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Sažetak

Uvod: *Danas je infekcija virusom humane imunodeficijencije (HIV) česti zdravstveni problem. Ljudi sa HIV-om žive duže i potrebno im je zbrinjavanje oralnih manifestacija ove bolesti. To je i razlog zašto je rad sa pacijentima sa HIV infekcijom prisutan u svakodnevnoj stomatološkoj i medicinskoj praksi. Iako rekurentne oralne ulceracije (rekurentni aftozni stomatitis; RAS) povezane sa HIV-om predstavljaju mali procenat oralnih lezija, one su jedno od najbolnijih stanja usne duplje.*
Cilj: *rada je da se ukaže na terapijske mogućnosti RASa i unapređenje zdravlja kod osoba sa HIVom*
Zaključak: *Jednom kada se postavi dijagnoza RAS-a, izbor specifičnog načina lečenja individualan je i uvek treba uzimati u obzir potencijalne neželjene efekte primenjenih lekova. Važno je smanjiti bol i postići dugotrajnu remisiju.*

Ključne reči: *HIV rekurentni aftozni stomatit, RAS, terapija, oralne ulceracije*

Abstract

Introduction: *Today, human immunodeficiency virus (HIV) infection is often health problem. People with HIV are living longer and more of them are seeking care for the oral complications of this disease. This is the reason why the management of HIV infection is regular in the dental and medical everyday practice. Although HIV-related recurrent aphthous stomatitis (RAS) constitute a small percentage of oral lesions they are one of the most painful conditions of the oral cavity.*
The aim: *is to point out the therapeutic possibilities and health improvement in people with HIV.*
Conclusion: *Once a diagnosis of RAS is reached, the choice of a specific treatment modality is individual and the potential side effects of drugs should always be taken into account. It is important to reduce pain and achieve a prolonged remission.*

Key words: *HIV, recurrent aphthous stomatitis, RAS, therapy, oral ulcers*

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Uvod

Infekcija virusom humane imunodeficijencije (HIV) predstavlja globalni zdravstveni problem i broj obolelih od HIV-a raste[1]. HIV infekcija utiče na više aspekata društva i menja zdravlje ljudi. Danas osobe sa HIV-om žive duže i sve se češće javljaju stomatologu radi lečenja oralnih manifestacija bolesti. Ovo i jeste razlog zbog koga se lečenje obolelih sa HIV infekcijom danas često u svakodnevnoj stomatološkoj i medicinskoj praksi[2].

Oralne manifestacije HIV-a dobro su poznate i više od 80% osoba zaraženih HIV-om ima simptome ili znakove koje stomatolog može uočiti u usnoj duplji. Usna duplja igra važnu ulogu u nadgledanju napredovanja HIV bolesti uočavanjem oralnih HIV manifestacija[3]. Najčešća HIV oportunistička oralna infekcija je oralna kandidijaza. Takođe primećuje se to da Kapošijev sarkom ima veliku prevalenciju u Africi i Latinskoj Americi, a histoplazmoza je česta kod osoba zaraženih HIV-om na Tajlandu. Oralne ulceracije povezane sa HIVom, kao što su rekurentni aftozni stomatitisa (RAS) afte, virusne i tuberkulozne infekcije, nespecifični i neoplastični ulkusi iako čine mali procenat oralnih lezija kod ovih pacijenata predstavljaju jedne od najbolnijih stanja usne duplje i smanjuju kvalitet života pacijenta. Od svih ulceracija, RAS su najčešće oralne ulceracije sa učestalošću od 1% u Brazilu do 14% u Južnoj Africi[4]. Osim toga, prevalencija ostalih specifičnih oralnih lezija poput kandidijaze, vlasaste leukoplakije i Kapošijevog sarkoma niža je kod pacijenata na antiretrovirusnoj terapiji i može sugerisati to da su neka od ovih oralnih stanja rezultat kasnog početka antiretrovirusne terapije i potrebna su dalja istraživanja u ovoj oblasti[5].

Pregled

RAS se javlja kod 25% opšte populacije. Najčešće se javlja u toku puberteta, a učestalost i težina kliničke slike smanjuje se sa godinama. Klinička slika RAS-a podeljena je u tri osnovna stadijuma. Prodromalni stadijum razvija se u prvih 48 sati u vidu peckanja na mestu gde će se razviti ulceracija. U sledećoj fazi, razvija se papula praćena bolom, okružena reaktivnim eritematoznim haloom. U trećem ulcerativnom stadijumu razvija se jasno definisana ulceracija veličine 1 mm - 3 mm, praćena bolom. Ova faza traje nekoliko nedelja, kada započinju regeneracija epitela, prekrivanje uceracije i smanjenje bola[5].

Introduction

Human immunodeficiency virus (HIV) infection is an overall health problem. The number of persons living with HIV is growing[1]. HIV infection influences multiple aspects of society and modulates health. Today, people with HIV are living longer and more of them are seeking care for the oral complications of this disease. This is the reason why the management of HIV infection is regular in the dental and medical everyday practice[2].

Oral HIV manifestations are well defined and more than 80% of HIV infected persons have symptoms or signs that are visible to dentists. The oral cavity plays an important role in supervising the progression of HIV disease through the occurrence of HIV manifestations[3]. The most common HIV opportunistic infection is oral candidiasis. It is also noticed that Kaposi's sarcoma has a high prevalence in Africa and Latin America and histoplasmosis is often in HIV infected persons in Thailand. HIV-related oral ulcers encounter a small percentage of oral lesions like recurrent aphthous stomatitis (RAS), viral, tuberculous, non-specific and neoplastic ulcers. They are one of the most painful conditions of the oral cavity and reduce the quality of patient's life. RAS are the majority of oral ulcerations with the frequency from 1% in Brazil to 14% in South Africa[4]. The prevalence of specific oral lesions like candidiasis, hairy leukoplakia and Kaposi's sarcoma is lower among patients on antiretroviral therapy and could suggest that some of this oral conditions are the result of late antiretroviral therapy initiation and should be further investigated[5].

Review

RAS affects up to 25% of the general population. The onset is usually during adolescence and diminishes in frequency and severity with age. The clinical features of RAS are divided into three major stages. Prodromal stage develops in the first 48 hours with a tingling sensation at the site where the ulceration will develop. In the next stage a papule develops with increasing pain. The papule is surrounded by a reactive erythematous halo. During the third ulcerative stage, papule ulcerates and aching, defined, oval 1-3 mm ulcer develops. This stage lasts to several weeks when epithelial regeneration, coverage of the ulcer and lessening of pain begins[5].

Najčešće korišćena *klasifikacija* RAS-a zasniva se na težini bolesti i povezanosti sa sistemskim faktorima. "Obične afte" nisu povezane sa sistemskim faktorima i javljaju se samo 2 do 4 puta godišnje. "Kompleksne afte" povezane su sa sistemskim faktorima, ili rekurentnim oralnim i genitalnim ulceracijama, ili je oboljenje konstantno aktivno sa novostvorenim lezijama koje se razvijaju kako stare lezije nestaju. Ove složene ulceracije u novijoj literaturi nazivaju se "lezije slične aftama". Najčešće bolesti povezane sa RAS-om su Behčetova bolest, Kronova bolest, ulcerozni kolitis, enteropatija osetljiva na gluten, HIV infekcija i ciklička neutropenija[5].

Starija klasifikacija RAS-a zasiva se na kliničkom izgledu bolesti. Prema ovoj klasifikaciji RAS je podeljen u tri oblika: *minor, major* i herpetiformni. Danas postoji i poseban dodatni entitet – aftozne ulceracije povezane sa HIV-om (Tabela 1).

Minor afte (minor aftozne ulceracije) čine 75% do 85% svih aftoznih lezija. Manje su od 10 mm, obično zarastaju u roku od 14 dana bez ožiljaka i lokalizuju se na nekratiniziranoj mukozi (labijalna ili bukalna sluzokoža, pod usne duplje, ventralna strana jezika).

Major afte (*periadenitis mucosa necrotica recurrens;* PMNR; Suttonova bolest) čine 10% svih aftoznih lezija. Simptomi su mnogo bolniji. PMNR polako zarasta, može trajati i do nekoliko meseci i obično ostavlja ožiljak po zarastanju. Češće se javlja na usnama, mekom nepcu i sluzokoži, koja prekriva manje pljuvačne žlezde.

Herpetiformne afte retko se javljaju i čine do 10% svih aftoznih lezija. One se vide kao mnogobrojne (do 100) manje od 3 mm, zaobljene, bolne lezije koje su vrlo slične onima kod intraoralnog herpes simpleks virusa. Javljaju se na oralnoj sluzokoži, spajaju se i stvaraju mnogo veće ulceracije. Obično traju do mesec dana, a u nekim slučajevima mogu ostaviti ožiljak po zarastanju[5].

HIV- povezane aftozne ulceracije

Kao i minor RAS, HIV aftozne lezije povezane sa HIV-om vide se kao manje ulceracije (po broju manjem od 5) lokalizovane na nekratinizovanoj mukozi. Često su šire od 10 mm i mogu trajati i do nekoliko meseci[6]. Uočeno je da samo 3% bolesnika zaraženih HIV-om imaju aftozne ulceracije i da ovi pacijenti ne pripadaju ni jednoj, određenoj etničkoj grupi, ni jednom, određenom polu. Ipak, kod njih broj CD4+ je ispod 100 ćelija/ml što može biti važno za diferencijalno dijagnostičko isključenje nekih specifičnih infekcija i maligniteta.

The most common used RAS classification is based on disease severity and association with systemic factors. "Simple aphthosis" is not associated with systemic factors and occurs only 2–4 times per year. "Complex aphthosis" is associated with systemic diseases, either recurrent oral and genital ulcers are present, or disease is continuously active with new lesions developing as older lesions heal. These complex ulcers are called "aphthous-like lesions." The most common diseases connected with RAS are Behcet disease, Crohn disease, ulcerative colitis, gluten-sensitive enteropathy, HIV infection and cyclic neutropenia[5].

Former RAS classification is based on clinical appearance of the disease. According to this, RAS are divided in three forms: minor, major and herpetiform. Nowadays, there is a special additional entity – HIV associated aphthous ulcers (Table 1).

Minor aphthae (mild aphthous ulcers) make up 75-85% of all aphthous lesions. They are smaller than 10 mm, usually heal within 14 days without scar and are localized on the nonkeratinized mucosa (labial or buccal mucosa, floor of the mouth, ventral border of the tongue).

Major aphthaes (periadenitis mucosa necrotica recurrens; PMNR; Sutton's disease) make up 10% of all aphthous lesions. The symptoms are more painful. PMNR tend to heal slowly and can last up to several months, usually leaving a scar. They have a predilection for the lips, soft palate and mucosa overlying the minor salivary glands.

Herpetiform aphthae are rare and make up to 10% of all aphthous lesions. They are multiple (up to 100) smaller than 3 mm, rounded, painful and very similar to lesions of intraoral herpes simplex. They occur throughout the oral mucosa, fuse and produce much larger ulcers. Usually they last up to 1 month and in some cases may leave a scar[5].

HIV- associated aphthous ulcers

Like RAS minor, HIV-associated aphthous ulcers are five or fewer in number and localized on nonkeratinized mucosa. They are often wider than 10 mm and can persist to several months[6]. It was noticed that only 3% HIV-infected patients have aphthous ulcers and they do not fall into any ethnic group or gender. Nevertheless, these patients have CD4 + counts below 100 cells/ml that can be important to exclude some specific infections and malignancy.

Tabela 1. Poređenje kliničkih oblika RAS
Table 1. Comparison of clinical features of RAS

Lezija **Lesion**	**Veličina** **Size**	**Broj** **Number**	**Trajanje** **Duration**	**Vrsta sluzokože** **Type of mucosa**
Minor	< 10 mm	1-5	7-14 dana/days	Nekeratinizirana Nonkeratinized
Major	> 10 mm	1-10	Nedelje do meseci Weeks to months	Nekeratinizirana Nonkeratinized
Herpetiformne **Herpetiform**	< 10 mm	> 10	7-14 dana/days	Nekeratinizirana Nonkeratinized
HIV-povezane **HIV-associated**	> 10 mm	1-5	Nedelje do meseci Weeks to months	Nekeratinizirana Nonkeratinized

Aftozne lezije povezane sa HIV-om klinički su slične major aftama, ali su trajnije i otporniji na lečenje čak i tetraciklinom i kortikosteroidima. Postoje neka razmatranja toga da su major afte povezane sa HIV-om zapravo minor afte koje se javljaju kod HIV pozitivnih pacijenata. Takođe, duboke ulceracije kod HIV pozitivnih pacijenata nazvane su NOS (ne definisane ulceracije), a u slučaju ekspozicije kostiju NUS (nekrotizirajući ulcerozni stomatitis). U većini slučajeva, NOS ulceracije na mekim tkivima predstavljaju NUS bez zahvatanja kosti ili obrnuto[7].

Smatra se da mnoge ulceracije kod HIV pozitivnih pacijenata predstavljaju infekciju virusom herpes simpleks (HSV) i kao takve uspešno se leče talidomidom. Potvrđeno je da sistemska terapija talidomidom ima najbolju efikasnost u RAS terapiji HIV seropozitivnih pacijenata i smernice za propisivanje ovog leka leka detaljno su dokumentovane u podacima iz literature. Ipak, treba istaći da je talidomid kontraindikovan kod pacijenata sa poliradikulopatijom ili encefalopatijom budući da može zakomplikovati kliničko stanje pacijenta.

Etiologija RAS i HIV

RAS je veoma čest poremećaj oralne sluzokože i može biti uzrokovan raznim etiološkim faktorima. Iz ovih razloga, histopatološkim pregledom postavlja se definitivna dijagnoza. Trajanje, učestalost i mesto javljanja ulceracija obično su modifikovano delovanjem sistemskih faktora. Kod HIV pozitivnih pacijenata može se javiti širok dijapazon oralnih ulceracija, a njihova precizna etiologija i uloga virusa obično ostaju nejasni.

HIV-associated aphthous ulcers are clinically similar to major RAS, but are more persistent and resistant to treatment even with tetracycline and steroids. There are some considerations that HIV-associated major aphthous ulcers are conventional RAS just present in HIV-positive patients. Also, deep ulcerations in HIV-positive patients are named NOS (not otherwise specified ulcers), and in case of bone exposure NUS (necrotizing ulcerative stomatitis). The most of the cases of NOS ulcers in the soft tissues represent NUS without involving bone, or vice versa[7].

It is considered that many ulcers in HIV patients represent herpes simplex virus (HSV) infection and such lesions are successfully treated with thalidomide. It is confirmed that systemic thalidomide therapy has the best efficacy in the RAS of HIV seropositive patients therapy and guidelines for prescribing such medication are well documented in the literature data. However, thalidomide is contraindicated in patients with polyradiculopathy or encephalopathy because it may complicate the clinical condition of the patient.

RAS aetiology and HIV

RAS is a very common disorder of the oral mucosa and can be caused by multifarious etiological factors. For these reasons, histopathological examination warrants a definitive diagnosis. Usually, duration, frequency and site of ulcers are specified by the underlying systemic condition. In HIV-positive patients wide spectrum of oral ulcerations may be present and their precise aetiology and the role of viruses usually remain unclear.

U svakodnevnoj praksi, kada su ulceracije kod RAS velike i kada zarastaju polako nakon primenjene rutinske terapije, lekari bi trebalo da uzmu u obzir testiranje pacijenta na HIV i pored činjenice da samo mali broj pacijenata sa HIV bolešću ima RAS[8].

Imuna patogeneza i etiologija RAS-a tek trebaju biti potpuno razjašnjeni. Pretpostavlja se da su predisponirajući faktori za nastanak RAS-a trauma, stres, hormonska neravnoteža i preosetljivost na hranu. Takođe, poznato je da je kod RAS-a infiltracija epitela T-limfocitima zapravo odgovor na neki neidentifikovani antigen povezan sa keratinocitima, i da je smrt keratinocita posredovana diferencijacijom citotoksičnih T-ćelija i proizvodnjom tumor nekrozis faktora-α (TNFα)[9].

Kod bolesnika sa HIV-om koji imaju mali broj CD4 T-limfocita i tešku kliničku sliku HIV-a obično se razvijaju duboke, bolne, nekrotične ulceracije zbog izraženog poremećaja imunološke ravnoteže i lokalnog sloma imunološke regulacije. Ulceracije su obično prisutne na sluzokoži i ždrelu i izazivaju tešku disfagiju i disartriju[6].

Terapija RAS-a

Lečenje RAS-a zavisi od broja lezija, veličine, trajanja i učestalosti recidiva. Svaka specifična vrsta lečenja zasniva se na potrebama pacijenta i mora uzeti u obzirkorist i potencijalne neželjene efekte lekova[10]. Prvi korak u terapiji RAS-a je detaljno uzimanjeanamneze vezane za simptome i istoriju bolesti. Treba uraditi detaljne analize krvi kako bi se isključio nedostatak gvožđa ili vitamina B_{12}. Jednom kada se postavi definitivna dijagnoza RAS-a pacijent treba da dobije uputstva o stanju i očekivanom ishodu iz svakog od različitih ponuđenih načina lečenja[11].

Dijetalne i opšte mere

Pacijenti često navode da je određena hrana odgovorna za nastanak RAS-a i preporučuje se njeno izbegavanje. Obično se pacijentima savetuje da izbegavaju tvrdu hranu, orašaste plodove, kiselu hranu ili pića, slane obroke, alkoholna i gazirana pića. Takođe treba izbegavati sredstva za čišćenje zuba koja sadrže natrijum-lauril-sulfat[11].

In everyday practice when RAS ulcers are large and heal slowly even after applied routine therapy, clinicians should consider HIV testing even small number of patients with HIV disease has RAS[8].

The immune pathogenesis and aetiology of RAS has yet to be fully elucidated. It is suggested that the predisposing RAS factors are trauma, stress, hormonal imbalance and food hypersensitivity. It is also known that in RAS, the infiltration of the epithelium by T lymphocytes is in response to some unidentified keratinocyte-associated antigen when keratinocyte death is mediated by the differentiation of cytotoxic T cells and involves the production of tumour necrosis factor-α (TNFα) by these leucocytes[9].

In in HIV patients with low CD4 T-lymphocyte counts and severe HIV disease deep, painful, necrotic ulcers usually develop due to immune imbalance and the local breakdown in immunoregulation. Ulcers are usually present on the buccal and pharyngeal mucosae and cause profound dysphagia and dysarthria[6].

Treatment of RAS

Treatment of RAS depends on the number of lesions, size, duration and frequency of recurrences. Every specific treatment modality is based on the patient's needs and must take into account drug's potential side effects and benefits[10]. The first step in RAS therapy is in-depth patient interview about symptoms and disease history. Blood tests should be performed in order to rule out iron or vitamin B_{12} deficiency. Once a diagnosis of RAS is established as part of informed consent, the patient should receive instruction about the condition and the expected outcome from each of the various treatment plans offered[11].

Dietary and general measures

Food that has often been reported by patients to be responsible for the causation of RAS should be avoided. Usually, patients are instructed to avoid hard food, nuts, acidic foods or drinks, salty meals, alcoholic and carbonated beverages. Also, teeth cleaning products containing sodium lauryl sulphate should be avoided[11].

Lokalna terapija

Lokalni anestetici mogu ublažiti simptome i smanjiti trajanje RAS-a. Obično se lokalno primenjuju: lidokain kao gel (Xylocaine 2% gel, Lidocaine 2% gel) ili sprej (Xylocaine sprej), polidokanol kao pasta (Solcoseryl zubna pasta), i benzokain kao pastile (Dolo-Dobendan pastile). Lokalni anestetici se mogu primeniti direktno na leziju u obliku rastvora (2% rastvor Xylocaina), kombinovanih preparata (sprej Acoin pumpice) ili gotovih sredstava za ispiranje usta (Ezafluor)[11].

Antiseptički i antiinflamatorni lekovi mogu da smanje trajanje RAS-a. Sredstva za ispiranje usta koje sadrže hlorheksidin (Chlorhexidine gluconate sol. 2%) smanjuju učestalost, trajanje i težinu RAS-a. Zubne paste i vodice za ispiranje usta sa triklosanom (Rutisept extra 0,1%) i dekspantenolom (Panthenol sprey, Bepanthen sol.) predstavljaju novu lokalnu antiinflamatornu i analgetsku terapijsku opciju[11].

Lokalno primenjeni tetraciklin smanjuje trajanje i bolnost RAS-a. Korišćenjem tetraciklin-hidrohlorida u obliku praha može se izbeći problem stabilnosti vodenog rastvora tetraciklin-hidrohlorida. Male kapsule napunjene tetraciklin-hidrohloridom (250 mg) mogu se uzimati sa 5 ml vode kao sredstvo za ispiranje usta. U trudnoći treba izbegavati tetraciklin, a 5-aminosalicilna kiselina može se lokalno koristiti tri puta dnevno[11].

U slučajevima sa nedovoljnim uspehom lokalnih anestetika i antiinflmatornih lekova, obično se koriste lokalni kortikosteroidi. Oni smanjuju zapaljensku reakciju i smanjuju trajanje RAS-a. Triamcinolon-acetonid u orabazi (Kenalog) ili pronizon u pasti (Dontisolon D) mogu se koristiti jednom ili dva puta dnevno, kao opcija lečenja. Kombinacija lokalnog anestetika tokom dana i triamcinolonske paste noću, takođe se može koristiti, jer mnogi literaturni podaci ističu njihovu efikasnost. Dugotrajna upotreba lokalnih kortikosteroida ne preporučuje se zbog mogućeg razvitka lokalnih gljivičnih infekcija. U slučaju bolnih i veoma dubokih ulceracija, obično se preporučuje intralezijsko davanje kortikosteroida (Triamcinolon 10 mg/ml u dozi od 0,1 ml do 0,5 ml po leziji)[12,13].

Topical therapy

Local anaesthetics can relieve symptoms and decrease the duration of the RAS. Usually are locally applied: lidocaine as a gel (Xylocaine 2% gel, Lidocaine 2% gel) or a spray (Xylocaine spray), polidocanol as a paste (Solcoseryl dental paste), and benzocaine as lozenges (Dolo-Dobendan lozenges). Local anaesthetics can be applied directly on the lesions in a form of a solution (Xylocaine 2% solution), a combination preparations (Acoin pump spray) or a ready-made mouthwashes (Ezafluor)[11].

Antiseptic and anti-inflammatory therapeutics can decrease the duration of the RAS. Chlorhexidine-containing mouthwashes (Chlorhexidine gluconate sol. 2%) cut down the incidence, duration and the severity of the RAS. Toothpastes and mouthwashes with triclosan (Rutisept extra 0.1%) and dexpanthenol (Panthenol spray, Bepanthen sol.) are thenew local antiinflammatory and analgesic treatment option[11].

Locally applied *tetracycline* decreases the duration and soreness of the RAS. Tetracycline hydrochloride in a form of a powder avoids the stability problem of tetracycline hydrochloride watery solution. Small capsules filled with tetracycline hydrochloride (250 mg) can be taken with 5 ml water as a mouthwash. In pregnancy, tetracycline should be avoided and 5-aminosalicylic acid locally used thrice daily[11].

In cases with inadequate success of local anaesthetics and anti-inflammatory agents combination local steroids are usually used. They reduce the inflammatory reaction and decrease the duration of RAS. Triamcinolone acetonide in orabase (Kenalog) or prednisolone in a paste (Dontisolon D) can be used once or twicedaily as a treatment option. The combination of a local anaesthetic during daytime and triamcinolone paste at night can also be used as many literature data emphasize its efficiency.Long-term use of local steroids is not suggested because of local fungal infections. In case of painful very deep ulcerations the use of intralesional injection of steroids (Triamcinolon 10 mg/ml in a dose of 0.1–0.5 ml per lesion) is usually recommended[12,13].

Sistemska terapija

Holhicicin je predstavljen kao nova terapijska opcija zbog svoje sposobnosti da inhibira hemotaktičku aktivnost neutrofila. Obično se nakon njegove primene smanjuje broj i trajanje ulceracija. Preporučuje se primena holcicina (1 do 2 mg / dan oralno) u trajanju najmanje 4nedelje do 6 nedelja, a recidivi RAS-a uobičajeni su nakon prestanka terapije. U teškim slučajevima RAS-a koji su rezistentni na monoterapiju holhicicinom, preporučuje se kombinacija pentoksifilina, pronizona, imunosupresiva ili interferona alfa. Holhicicin se ne sme koristiti tokom trudnoće i preporučuje se primena kontraceptivnih sredstava kod žena u trajanju od 3 meseca, a kod muškaraca i do 6 meseci nakon prestanka terapije ovim lekom[12].

Sistemski kortikosteroidi često se koriste u kombinaciji sa drugim imuno-supresivnim lekovima. Pronizon (10–30 mg / dan) se propisuje u slučajevima dubokih bolnih ulceracija u istoj dozi i trajanju kao i kod HIV negativnih bolesnika sa RAS-om. Kortikosteroidi se mogu koristiti tokom trudnoće, u periodu do jednog meseca[12].

Dapsone (100–150 mg/dan) inhibira povećanu hemotaktičku aktivnost neutrofila. Nažalost, često se javljaju brzi recidivi nakon prekida terapije. Terapiju treba sprovoditi veoma oprezno, jer se mogu javiti hemoliza, methemoglobulinemija i agranulocitoza kao ozbiljne nuspojave. Iz ovih razloga preporučuje se povremeno davanje i askorbinske kiseline[14].

Thalidomid se koristi kao sredstvo za ispitivanje lečenja RAS-a povezanog sa HIV-om, uprkos njegovoj teratogenosti. Propisane doze talidomida su široke: od niskih (50 mg/dan) do visokih (200 mg/dan). Nažalost, kao i kod primene dapsona, recidiv se javlja oko 3 nedelje nakon prestanka terapije. Takođe, njegova primena ima brojne očekivane nuspojave poput privremenih cerebralnih simptoma (glavobolja, letargija, kserostomija, zatvor). Zbog mogućih teških oštećenja ploda ne može se koristiti tokom trudnoće i neophodna je primena kontraceptivnih sredstava za vreme lečenja ovim lekom[15].

Pokazalo se da je *levamisol* efikasan (150 mg/dan, tri uzastopna dana) protiv RAS-a, iako njegova upotreba mora biti veoma pažljiva zbog rizika od agranulocitoze pa se preporučuje pažljivo nadgledanje pacijenta[15].

Systemic therapy

Colchicine is introduced as a new therapeutic option because of the neutrophil's chemotactic activity inhibition. Usually, a decreased number and duration of ulcers is present after its administration. At least 4-6 weeks (1 to 2 mg/day orally) of Colchicine application is recommended and recurrence of RAS is common following cessation of therapy. In severe RAS cases, resistant to monotherapy with colchicine, combination with pentoxifylline, prednisolone, immunosuppressants or interferon alpha can be applied. Colchicine should not be used during pregnancy. A contraceptive method should be applied in women for 3 months and in men up to 6 months after cessation of therapy[12].

Systemic corticosteroids are often used in combination with other immunosuppressive drugs. Prednisolone (10–30 mg/day) is prescribed in cases of deep painful ulcers with the same doses and duration as in HIV-negative patients with RAS. Corticosteroids can be used during pregnancy and for a period up to 1 month[12].

Dapsone (100–150 mg/day) inhibits the enlarged neutrophil chemotactic activity. Unfortunately, rapid relapse often occurs after discontinuation of therapy. Its application must be very careful because haemolysis, methaemoglobulinemia and agranulocytosis are its serious side-effects. For these reasons an intermittent administration of ascorbic acid is advisable[14].

Thalidomide is used as an investigational agent for the treatment of RAS associated with HIV despite its teratogenicity. The prescribed thalidomide doses are wide: from low (50 mg/day) to high (200mg/d). Unfortunately, like in dapsone application the recurrence occurs in about 3 weeks after cessation of therapy. It has numerous expected side-effects like temporary cerebral symptoms (headache, lethargy, xerostomia, constipation). Due to severe congenital defects it cannot be used during pregnancy and adequate contraception is necessary[15].

Levamisol is shown to beeffective(150 mg/day three successive days) against RAS although its usage must be very vigilant due to the risk of agranulocytosis and close patient monitoring is therefore recommended[15].

Mogu se koristiti *antimetaboliti*, poput azatioprina i metotreksata. Azatioprin (1 do 2 mg/kg/dan) smanjuje učestalost i ozbiljnost RAS-a, kontraindikovan je tokom trudnoće i dojenja zbog mogućih nuspojava, poput neplodnosti i oštećenja jetre, može ometati rast i ne preporučuje se deci. Za vreme primene ovog leka, neophodno je svaka 3 meseca kontrolisati krvnu sliku i funkciju jetre. U teškim slučajevima RAS-a može se pažljivo koristiti i metotreksat (7,5 do 20 mg/nedeljno). Dugotrajna terapija ovim lekom zahteva praćenje krvne slike i funkcije jetre svakog meseca, jer može doći do teške depresije koštane srži i poremećaja funkcije jetre[16].

Imunomodulatori poput ciklosporina A (3 do 6 mg/kg/dan) inhibiraju aktivaciju T-ćelija. Efikasni su u oko 50% pacijenata sa RAS-om i mogu se koristiti kao monoterapija ili u kombinaciji sa kortikosteroidima. Ne sme se naglo prestati sa njihovom primenom jer može doći do ponovne pojave RAS-a. Ne mogu se koristiti tokom trudnoće i dojenja i kod pacijenata sa bubrežnom insuficijencijom[17].

Alkilirajuća sredstva poput hlorambucila i ciklofosfamida mogu se koristiti u slučajevima teškog RAS-a. Hlorambucil (2-8 mg/dan) inhibira funkciju B- i T-ćelija i utiče na značajno smanjenje ulceracija, a u kliničkoj praksi je potvrđeno potpuno odsustvo lezija nakon njegove primene[17].

Interferon alfa (Roferon A) je veoma uspešan u lečenju RAS-a, a potpuna remisija ulkusa obično se postiže nakon primene velikih doza leka. Niske doze preporučuju se samo kao terapija za održavanje kada se lečenje visokim dozama pokazalo uspešno u periodu od mesec dana do 4 meseca. Paracetamol (500 mg, oralno, 1 sat pre i posle injekcije) može se dodatno koristiti jer smanjuje sporedne efekte terapije koji se javljaju u vidu simptoma sličnih gripu na početku terapije i zavise od doze primenjenog leka. Nažalost, u mnogim slučajevima dolazi do brzog recidiva RAS-a nakon prekida terapije ovim lekom[18].

Fizikalna terapija. U mnogim slučajevima pacijent sa HIV-om zahteva složenu interdisciplinarnu terapiju i sistemski pristup lečenju bolesti. Obično je pored standardne anti-HIV terapije, potrebna dodatna terapija kako bi se eliminisale ulceracije. Terapija laserima male snage (LLLT) može se primeniti zbog njenih specijalnih efekata poput biostimulativnog, analgetskog i anti-inflamatornog dejstva, što izaziva dodatno smanjenje bola. Dobro je poznato da LLLT poboljšava oralno zdravlje,

Anti-metabolites like azathioprine and methotrexate can be used. Azathioprine (1 to 2 mg/kg/day) reduces the incidence and severity of RAS. It is contraindicated during pregnancy and lactation due to its possible side-effects like infertility and liver damage. It may interfere with growth and is not recommended for children. Blood picture every month and liver function every 3 months should be carefully monitored. In severe RAS methotrexate (7.5 to 20 mg/week) can be efficiently but carefully used. Long-term therapy requires monitoring of blood picture and liver function every month, because severe bone marrow depression and liver function abnormalities may occur[16].

Immunomodulators like Cyclosporine A (3 to 6 mg/kg/day) inhibit T-cell activation. They are effective in about 50% of patients with RAS and can be used as a monotherapy or in combination with steroids. Rapid dose reduction is forbidden because it can lead to rebound phenomenon. They cannot be used during pregnancy, nursing and renal insufficiency[17].

Alkylating agents like chlorambucil and cyclophosphamide can be used in cases of severe RAS. Chlorambucil (2–8 mg/day) inhibits B- and T-cell function and shows marked improvement of ulcerations. Clinical practice has confirmed complete absence of lesions after chlorambucil administration[17].

Interferon alpha (Roferon A) is very successful in the treatment of RAS. Usually, complete remission of ulcers is achieved after administration of high doses. Low doses are recommended as a maintenance therapy when treatment with high doses is successful in the first 1 to 4 months. Paracetamol (500 mg orally 1 h before and after the injection) can be additionally used as it decreases the initial dose-dependent flu-like symptoms as a side-effect. Unfortunately, in many cases there is a rapid RAS recurrence following discontinuation of therapy[18].

Physical therapy. In many cases HIV patient requires complexmultispecilizing therapy and systemic approach to treatment of the disease. Usually, an additional therapy is necessary to solve the problem of ulcers. The low-intensity laser therapy (LLLT) can be applied because of its special effects like biostimulation, analgesia, and reduction of inflammation which leads to reduction in pain after laser treatment. It is well known that LLLT improves oral health allowing the feeding and giving the time required for the patient's body to have a positive response to the medication[19].

obezbeđujući nesmetanu ishranu pacijenta što omogućava organizmu da pozitivno reaguje na lekove[19]. Upotreba LLLT-a kod RAS-a važna je alternativna terapija kod HIV pozitivnih pacijenta koja izaziva regresiju lezija i poboljšava kvalitet života pacijenata[20].

Zaključak

Infekcija virusom humane imunodeficijencije (HIV) veliki je globalni zdravstveni problem, a oralne ulceracije povezane sa HIV-om predstavljaju rani nalaz bolesti. Ove ulceracije smanjuju kvalitet života pacijenta i dobar su pokazatelj napredovanja bolesti i imunosupresije. Neophodno je bolje informisati stomatologe o oralnim manifestacijama i lečenju ove bolesti.

Lečenje RAS-a kod pacijenata zaraženih HIV-om zavisi od težine bolesti i učestalosti recidiva. Važno je smanjiti bol i postići dugotrajnu remisiju. Izbor načina lečenja individualan je, a uvek je potrebno uzeti u obzir i potencijalne neželjene efekte lekova.

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The use of LLLT in RAS is an important alternative therapy in HIV patient causing the regression of lesions and improvement of the quality of life of this patients[20].

Conclusion

Human immunodeficiency virus (HIV) infection is a major global health problem and HIV-related oral ulcers are an early finding of the disease. They reduce the quality of patient's life and are useful markers of disease progression and immunosuppression and dentists should be better informed about the oral manifestations and treatment of this disease.

Treatment of RAS in HIV infected patients depends on the severity of the disease and the frequency of recurrences. It is important to reduce pain and achieve aprolonged remission. The choice of a specific treatment modality is individual and the potential side effects of drugs should always be taken into account.

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