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Kobkan Thongprasom[1], Tin Panyawaraphon[2], Thanapat Pathomkulmai[2], Sahaphon Hungsaprug[2]

Razine folata i vitamina B_{12} kod Tajlanđana s oralnom lihenoidnom reakcijom povezanom s lijekovima

Folate and Vitamin B_{12} Levels in Thai Patients with Oral Lichenoid Related Drug

[1] Odjel oralne medicine Stomatološkog fakulteta Sveučilišta Chulalongkorn, Bangkok 10330, Tajalnd
Oral Medicine Department, Faculty of Dentistry, Chulalongkorn University, Bangkok 10330, Thailand
[2] Stomatološki fakultet Sveučilišta Chulalongkorn, Bangkok 10330, Tajland
Faculty of Dentistry, Chulalongkorn University, Bangkok 10330, Thailand

Sažetak
Pacijentima se propisuje sve više lijekova za liječenje sistemskih bolesti i za mnoge se zna da induciraju oralnu lihenoidnu reakciju (OLL). **Svrha** ovog istraživanja bila je analizirati povezanost OLL-a, lijekova i razine folata te vitamina B_{12}, a sudjelovalo je dvadesetero pacijenata kojima je kliničkim i histopatološkim pregledom dijagnosticiran OLL. **Ispitanici i postupci:** Ti ispitanici uspoređeni su s 24 zdrava sudionika. Svima je obavljena kompletna krvna slika, tipiziran hemoglobin, serum i folati crvenih krvnih stanica te serum i razina vitamina B_{12}. Kod pacijenta s OLL-om zabilježene su i analizirane sistemske bolesti te lijekovi koje su im ordinirali njihovi liječnici. **Rezultati:** Naši rezultati pokazuju da je samo 1/20 pacijenata s OLL-om (5 %) imao niske razine folata crvenih krvnih stanica, a samo jedan slučaj zabilježen je s niskom razinom serumskoga folata. U obje su skupine razine vitamina B_{12} bile u normalnim granicama. Nije bilo znatne razlike između folata crvenih krvnih stanica, serumskih folata ili razina vitamina B_{12} među pacijentima s OLL-om i kontrolne skupine ($p > 0,05$). Četvero ispitanika u skupini s OLL-om i troje iz kontrolne imali su hematokrit niži od 36 posto i definirani su kao anemični. **Zaključak:** Antihipertenzivi i antilipidemici bili su najčešći lijekovi ordinirani pacijentima s OLL-om, no nisu imali nikakav utjecaj na folate crvenih krvnih stanica, serumske folate ili na razinu vitamina B_{12}. Zbog toga što su uzimali više lijekova, pacijentima nismo mogli prekinuti terapiju da bismo potvrdili dijagnozu OLDR–a, pa smo se koristili terminom *OLL povezan s lijekovima*.

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Adresa za dopisivanje
Prof. Kobkan Thongprasom
Oral Medicine Department
Faculty of Dentistry
Chulalongkorn University
Bangkok 10330, Thailand
tel: +66-2-2188942
faks: +2-2188941
kobkan.t@chula.ac.th

Ključne riječi
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Uvod

Za liječenje svojih sistemskih bolesti pacijenti uzimaju sve više lijekova. No, za mnoge postoje podatci da uzrokuju oralne lihenoidne lezije (OLL) (1, 2). U nedavnim istraživanjima istaknuta je niska razina folata crvenih krvnih stanica kod pacijenata s oralnim lihenom planusom (OLP), stomatitisom, glositisom i pečenjem jezika (3, 4). OLL je oralna lezija histopatološki slična OLP-u, što razlikovanje čini teškim (2).Pacijenti s OLP/OLL-om obično se žale na bol, iritaciju, osjećaj pečenja i poremećaj osjeta okusa. OLP je najčešća uobičajena kronična bolest oralne sluznice koja uključuje staničnu imunosnu reakciju nepoznate etiologije, a OLL ima poznate uzročnike (5). Oralna lihenoidna reakcija na lijekove (OLDR) uzrokovana je lijekovima poput alopurinola, karbamazepina, klorokina, dapsona, ketokonazola, nesteroidnih protuupalnih lijekova (NSAID), propanolola i tetraciklina (6). Obje lezije – OLP i OLDR, teško je liječiti zbog njihove kronične prirode (5, 7). Postoji još jedna reakcija slična lihenu, a naziva se kontaktna oralna lihenoidna lezija (OLCL) koju uzrokuje doticaj s materijalima poput amalgama ili žive.

Introduction

Medications have been increasingly used by patients for the treatment of their systemic diseases. However, many drugs have been reported to induce oral lichenoid lesions (OLL) (1, 2). Recent studies reported that low red cell folate levels were found in patients with oral lichen planus (OLP), stomatitis, glossitis, and burning tongue (3, 4). OLL is an oral lesion that is histopathologically similar to OLP, which makes it very difficult to distinguish between these two lesions (2). OLP/OLL patients commonly complain of pain, irritation, burning sensation, or taste disturbance. OLP is the most common chronic oral mucosal disease involving a cell mediated immune response with an unclear etiology, whereas OLL has specific known causes (5). Oral lichenoid drug reaction (OLDR) is caused by drugs such as Allopurinol, Carbamazepine, Chloroquine, Dapsone, Ketoconazole, NSAIDs, Propanolol, and Tetracycline (6). Both OLP and OLDR are very difficult to treat because of their chronic nature (5, 7). In addition, there is another lichen-like lesion known as oral lichenoid contact lesion (OLCL), which is caused by con-

Nema dovoljno dokaza koji bi podupirali rutinsko uklanjanje amalgamskih restauracija ili zamjene amalgamskih ispuna u zubima da bi se dokazala dijagnoza ili odredila terapija (8, 9). Oralne lihenoidne lezije pojavljuju se u slučaju bolesti presatka i prijenosa na domaćina (OLL – GVHD), a nastaju ako su presađene alogenetske hematopoetske zametne stanice ili transplantirana koštana srž. Neklasificirani OLL oralna je lezija s eritematoznim promjenama na gingivi bez znakova *klasičnoga* OLP-a drugdje u usnoj šupljini, ili lezija koja izgleda poput lihena planusa ali joj nedostaje jedan ili više kliničkih nalaza, poput obostrane prisutnosti (10).

OLDR se može liječiti, a dijagnosticira se eliminacijom uzročnika, poput prekida terapije sumnjivim lijekom (1, 11). Bijele strije s eritematoznim ili ulcerirajućim područjima ili bez njih, histopatološki nalaz i povijest bolesti te korištenje lijekova, mogu biti dostatni za potvrdu dijagnoze OLDR-a. U našem istraživanju usredotočili smo se na nastanak oralnih lezija kod pacijenata s određenom terapijom, bez njezina prekida. Štoviše, pacijenti su uglavnom uzimali više lijekova i nisu mogli prekinuti terapiju da bi se potvrdila dijagnoza OLDR-a. U nedavnim istraživanjima istaknuto je da neke lezije, poput lihenoidne reakcije na lijekove, mogu na početku biti asimptomatske, ali tijekom godina postanu simptomatske pa je, za potvrdu dijagnoze, teško potvrditi povezanost početka uzimanja lijekova i razvoj (12). Zato smo se, kada su pacijenti s medikamentnom terapijom imali trajne lezije, koristili pojmom *OLL povezan s lijekovima*. Kako se sve više lijekova propisuje za liječenje sistemskih bolesti, terapiju OLP-a i OLL-a povezanog s lijekovima treba pozorno razmotriti. Primjereno liječenje takvih lezija može pacijentima poboljšati kvalitetu života.

Svrha ove studije bila je da prvi istražimo i izvijestimo o dosad neobjavljenim podatcima o odnosu OLL-a povezanog s lijekovima, lijekova, razine folata i vitamina B_{12}. Naši nalazi koristit će kliničarima u slučaju procjene terapije OLL-a povezanog s lijekovima.

Pacijenti i metode

U ovo istraživanje bilo je uključeno dvadesetero pacijenata koji su se javili u Kliniku oralne medicine Stomatološkog fakulteta Sveučilišta Chulalongkorn u Bangkoku. Oralne lezije dijagnosticirane su im pregledom usne šupljine, a potvrđene histopatološkom pretragom. Zabilježeno je također koliko dugo pate od oralnih lezija, vrste lezija, lijekovi i sistemske bolesti. U istraživanju je sudjelovalo 15 žena i petorica muškaraca u dobi od 40 do 76 godina (arit. sred. ± SD = 58,3 ±10,55). Tijekom oralnih pregleda pronađene su dvije ulcerativne lezije i 18 atrofičnih. U kontrolnoj skupini bila su 24 zdrava dobrovoljca ((Ž = 15, M = 9) bez oralnih lezija, osim zubnog karijesa i gingivitisa. Njihova dob bila je od 36 do 59 godina s arit. sred. ± SD = 47,92 ± 7,63 godina.

Protokol istraživanja odobrilo je Etičko povjerenstvo Klinike za oralnu medicinu Stomatološkog fakulteta Sveučilišta Chulalongkorn. Prije početka istraživanja svi su ispitanici potpisali informiranu suglasnost. Venska krv uzeta im je iz-

tact with materials such as amalgam or mercury. However, there is insufficient evidence to support the routine removal of amalgam restorations or replace amalgam filling to confirm the diagnosis or management of OLCL (8, 9). The oral lichenoid lesions in graft-versus-host disease (OLL-GVHD) are lesions that arise in recipients of allogeneic hematopoietic stem cell or bone marrow transplantations. Unclassified OLL is an oral lesion presenting as erythematous changes to the gingiva without the signs of "classic" OLP elsewhere in the oral cavity, or lesions that have a lichen planus-like aspect, but lack one or more characteristic clinical features, such as a bilateral presentation (10).

OLDR can be treated and its diagnosis confirmed by eliminating its cause, such as by withdrawing the suspected drug (1, 11). The presence of white striae with or without erythematous or ulcerative areas, histopathologic examination, and patients' medication history may not be sufficient to confirm the diagnosis of OLDR. In our study, we focused on oral lesions erupting in patients taking medications without withdrawing their medications. Moreover, the patients were taking multiple drugs and those drugs could not be withdrawn to confirm the diagnosis of OLDR. A recent report mentioned that some lesions such as lichenoid drug reaction may present asymptomatically initially but become symptomatic years later and then the relationship between the start of drug use and development of lesion is difficult to confirm for the diagnosis (12). Therefore, when patients taking medication had persistent lesions, we used the term OLL related drug instead.

Because medications have been increasingly used in patients with systemic diseases, treatment of OLP and OLL related drug should be carefully concerned. Appropriate treatment of such lesions will be helpful to improve the quality of life in those patients. Therefore, the aim of our study was to investigate the relationship between OLL related drug, medications, and folate and vitamin B_{12} levels which have not been investigated before. Hence, our findings will be useful for the clinician judgement in the treatment of OLL related drug.

Patients and methods

Twenty patients who enrolled in the Oral Medicine clinic at the Faculty of Dentistry, Chulalongkorn University were included in this study. Their oral lesions were diagnosed by oral examination and the diagnoses were confirmed by histopathological evaluation. The duration of their oral lesion, type of lesion, medications, and systemic diseases were recorded. The study group comprised 15 females and 5 males with ages ranging from 40–76 (mean± SD = 58.3 ±10.55) years. Oral examinations found 2 cases of ulcerative lesions and 18 cases of atrophic lesions. The control group consisted of 24 healthy volunteers (F=15, M=9) with no oral lesions apart from dental caries and gingivitis. The ages of the control group ranged from 36–59 years with a mean± SD = 47.92 ±7.63 years.

The study protocol was approved by the Ethics Committee for the use of human subjects, Faculty of Dentistry, Chulalongkorn University. Informed consent was obtained from

među devet i dvanaest sati, kako bi se smanjila diuralna varijacija.

Laboratorijski nalazi

Kako je već istaknuto, laboratorijska ispitivanja uključivala su kompletnu krvnu sliku, tipiziranje hemoglobina te razine folata crvenih krvnih stanica, serumskih razina folata i vitamina B_{12} (3). Kompletna krvna slika dobivena je standardnim metodama – korištenjem Coulterova brojača, a elektroforezom je tipiziran hemoglobin. Razine folata crvenih krvnih stanica, serumske razine folata i vitamina B_{12} određivale su se kompeticijskom vezujućom radiološkom pretragom. Razine folata crvenih krvnih stanica niže od 100 ng/ml, smatrale su se manjkom folata, 100 do 120 ng/ml bile su određene kao razine eritropoeza s manjkom folata, a 120 do 160 ng/ml kao folatno osiromašene (13). Serumske razine vitamina B_{12} niže od 150 pg/ml smatrane su niskima (14). Anemija je definirana kao stanje u kojem je hematokrit niži od 39 posto kod muškaraca i 36 posto kod žena. Makrocit je definiran kao aritmetička sredina korpuskularog volumena (MCV) iznad 100 fl, normocitemija za vrijednosti MCV-a od 80 – 96 fl i mikrocitemija MCV-a niža od 80 fl (15).

Statistička analiza

Za usporedbu skupina korišten je Hi-kvadrat test ili Fisherov egzaktni test. Određivanje statističke značajnosti postavljeno je na p manji od 0,05.

Rezultati

Aritmetičke sredine i rasponi razina folata crvenih krvnih stanica, serumskih folata i vitamina B_{12} u skupini ispitanika s OLL-om povezanim s lijekovima i u kontrolnoj skupini nalaze se u tablici 1. Analizirajući folate, uočeno je da ih je jedan ispitanik u skupini s OLL-om povezanim s lijekovima imao premalo (67 ng/ml). Razine folata crvenih krvnih stanica u skupini s OLL-om povezanim s lijekovima bile su u rasponu od 67 do 718 ng/ml s aritmetičkom sredinom ± SD = 289 ± 144,78 ng/ml. U kontrolnoj skupini razina folata crvenih krvnih stanica bila je u rasponu od 260 do 576 ng/ml, s aritmetičkom sredinom ± SD = 399.38 ± 85.8 ng/ml. Nije nađena statistički značajna razlika u razinama folata crvenih krvnih stanica između skupina (p > 0,05). Pronašli smo da je samo jedan ispitanik u skupini s OLL-om povezanim s lijekovima imao niske serumske vrijednosti folata (3,5 ng/ml) i nije bilo značajne razlike među skupinama (p > 0,05). Razine serumskog vitamina B_{12} u obje su skupine bile unutar normalnih granica.

Sedmero ispitanika u skupini s OLL-om povezanim s lijekovima i dvoje u kontrolnoj skupini imali su nizak hemoglobin. Četvero njih u skupini s OLL-om i troje u kontrolnoj imali su hematokrit niži od 36 posto i oni su definirani kao anemični.

Antihipertenzivi i hipolipidemici bili su najčešće korišteni lijekovi u skupini ispitanika s OLL-om povezanim s lijekovima, što je prikazano u tablici 2.

the patients and the control subjects before they participated in the study. Venous blood was drawn between 9.00 am and noon to minimize any effects of diurnal variation.

Laboratory investigation

The laboratory investigation included a complete blood count, hemoglobin typing, and serum and red cell folate and vitamin B_{12} levels determination as previously described (3). The complete blood count was performed by a standard method using a Coulter counter and the hemoglobin typing was analyzed by electrophoresis. Serum folate, red cell folate, and serum vitamin B_{12} levels were determined by competition binding radio assays. A red cell folate level below 100 ng/ml was defined as folate deficient, 100-120 ng/ml as folate deficient erythropoiesis, and 120-160 ng/ml as folate depletion (13). A serum vitamin B_{12} level less than 150 pg/ml was defined as low (14). Anemia was defined as a hematocrit of less than 39% for males and less than 36% for females. The macrocyte was defined as a mean corpuscular volume (MCV) above 100 fl, normocyte as MCV 80-96 fl and microcyte as MCV less than 80 fl (15).

Statistical analysis

The Chi-square test or Fisher's exact test was used to compare the groups. Statistical significance was established at p less than 0.05.

Results

The mean and range of the serum folate, red cell folate, and vitamin B_{12} levels in the drug related OLL and control groups are shown in Table 1. Folate analysis indicated that one subject in the OLL group had a folate deficiency (67 ng/ml). The red cell folate levels in the OLL related drug group ranged from 67–718 ng/ml with a mean ± SD =289±144.78 ng/ml. In the control group, the red cell folate levels ranged from 260–576 ng/ml with a mean±SD = 399.38 ± 85.8 ng/ml. However, there was no significant difference in red cell folate levels between the groups (p>0.05). We found that only one subject in the OLL related drug group demonstrated low serum folate (3.5 ng/ml) and there was no significant difference in serum folate levels between the groups (p>0.05). Serum vitamin B_{12} levels were within normal ranges in both groups.

Seven cases in OLL related drug and two cases in the control group showed low hemoglobin. Four subjects in OLL related drug group and three cases in the control group had low hematocrit, less than 36%, and these subjects were defined as anemic. Antihypertensives and hypolipidemics were the most common medications taken by patients with OLL related drug as shown in Table 2.

The histopathological examination of patients with OLL related drug found that the histopathological diagnoses of the oral lesions were varied with 7 subjects diagnosed with OLP/OLDR consistent with OLP in 5 cases, and with OLP in 3 cases, 3 subjects diagnosed with chronic nonspecific in-

Tablica 1. Obilježja prisutnosti folata crvenih krvnih stanica, serumskih folata i razine vitamina B_{12}, CBC profil kod pacijenata s OLL-om povezanim s lijekovima i kontrolne skupine
Table 1 Characteristics of presence red cell folate, serum folate and vitamin B_{12} levels, CBC profile in OLL related drug and control groups

Skupine • Groups		OLL (20)	Kontrola • Control (24)	p-vrijednost • P-value
Spol • Sex	Ženski • Female	15	15	
	Muški • Male	5	9	
Dob • Age (years)	Arit. sred. ± SD • Mean ± SD	58.3 ±10.55	47.92 ±7.63	
	(Raspon) • (Range)	(40 - 76)	(36 - 59)	
Vrsta oralne lezije • Oral lesions type	Ulcerativna • Ulcerative	2	-	
	Atrofična • Atrophic	18	-	
Folati crvenih krvnih stanica (ng/ml) • Red cell folate (ng/ml)	Arit. sred ± SD • Mean ± SD	289 ± 144.78	399.38 ± 85.8	
	(Raspon) • (Range)	(67-718)	(260 - 576)	
	Manjak folata • Folate deficiency	1	-	0.113
Serumski folati (ng/ml) • Serum folate (ng/ml)	Arit. sred ± SD • Mean ± SD	16.452 ± 10.46	16.80 ± 8.36	
	(Raspon) • (Range)	(3.5 - 40.03)	(6.09 - 28.91)	
	Niski serumski folati • Low serum folate	1	-	0.268
Vitamin B_{12} (pg/ml)	Arit. sred ± SD • Mean ± SD	532.53 ± 255.72	683.1 ± 214.80	
	(Raspon) • (Range)	(213.6 – 1,216)	(416.4 ±1,113)	
	Nizak vit. B_{12} • Low Vit B_{12}	-	-	NS
Hemoglobin (g/dl)	Arit. sred ± SD • Mean ± SD	12.74 ± 1.2	13.14 ± 0.83	
	(Raspon) • (Range)	(10.6 -15.7)	(11.8-15.2)	
	Nizak Hb • Low Hb	7	2	NS
Hematokrit (%) • Hematocrit (%)	Arit. sred ± SD • Mean ± SD	38 ± 3.43	37.92 ± 2.62	
	(Raspon) • (Range)	(31-46)	(35-45)	
	Nizak ct • Low Hct	4	3	NS

NS = Nije značajno • No significance

Tablica 2. Korišteni lijekovi u slučaju OLL-a povezanog s lijekovima
Table 2 Medications taking in OLL related drug

Lijekovi • Medications*		No
Antihipertenzivi • Antihypertensive	ACE inhibitor	6
	Beta blokator • Beta blocker	5
	Ca^+ blokatori kanala • Ca^+ channel blocker	4
	Diuretici • Diuretic	3
Hipolipidemici • Hypolipidemic	Statin	12
Hipoglikemici • Hypoglycemic	Metformin	3
	Glibenklamid • Glibenclamide	2
	Pioglitazon • Pioglitazone	1
	Vildagliptin	1
NSAID • NSAIDs	Aspirin	3
	Diklofenak • Diclofenac	1
	Celekoksib • Celecoxib	1
Antibiotik • Antibiotic	Rifampicin	1
	Levofloksacin • Levofloxacin	1
Antitiroidni lijek • Antithyroid	Tiroksin • Thyroxine	1
Ostali** • Others**		12

* Jedan pacijent uzima više od jednog lijeka • One patient taking more than one medication

** Ostali: alendronat, antacid, antihistaminici, antimikobaktericid, antivirusni, glukozamin itd. • Others: alendronate, antacid, antihistamine, antimycobacterial, antiviral, glucosamine etc.

Tablica 3. Histopatološki pregledi pacijenata s OLL-om povezanim s lijekovima
Table 3 Histopathological examination in patients with OLL related drug

Histopatološka dijagnoza • Histopathological diagnosis	Slučajevi • Cases
OLP/OLDR	7
Odgovara OLP-u • Consistent with OLP	5
OLP	3
Kronična nespecifična upala • Chronic non specific inflammation	3
OLDR	1
Normalna sluznica s hiperplastičnim epitelom • Normal mucosa with hyperplastic epithelium	1

Histopatološkim pregledom lezija pacijenata s OLL-om povezanim s lijekovima ustanovljeno je da je histopatološka dijagnoza oralnih lezija varirala – kod sedmero pacijenata dijagnosticiran je OLP/OLDR u suglasju s pet slučajeva OLP-a, u tri slučaja radilo se o OLP-u, a trojici pacijenata dijagnosticirana je kronična nespecifična upala. Zabilježen je i jedan slučaj OLDR-a i jedna normalna sluznica s hiperplastičnim epitelom (tablica 3.).

Rasprava

U ovom se istraživanju pri postavljanju dijagnoze oralne lezije većina naših pacijenata nije mogla sjetiti kada je točno počela njihova sistemska bolest, lijekova koje su uzimali ili drugih alternativnih lijekova koje im je propisao obiteljski liječnik. Dijagnoza OLDR-a može se potvrditi ukidanjem sumnjivoga lijeka. No u ovom istraživanju dijagnoza OLDR-a nije se mogla potvrditi i zato smo se koristili terminom *OLL povezan s lijekovima*. Općenito, teško je ukinuti sumnjivi lijek iz etičkih razloga, a u ovom istraživanju pacijenti su istodobno uzimali više njih. Sudionicima u ovom istraživanju dijagnoza je potvrđena oralnim i histopatološkim pregledom. Histopatološki nalazi uglavnom su potvrđivali OLP ili OLP/OLDR. Histopatološki rezovi pokazali su oralnu sluznicu prekrivenu parakeratiniziranim stratificiranim skvamoznim epitelom s degeneracijom bazalnih stanica. Unutar fibroznoga potpornog tkiva pronađena je limfocitna trakasta infiltracija s pojedinim plazmatskim stanicama i makrofazima. U novijim istraživanjima istaknuto je da histopatologija OLL-a pokazuje više eozinofila, plazmatskih stanica i granulocita u slučaju OLL-a u usporedbi s OLP-om (16). Zato bi za postavljanje dijagnoze OLP-a i OLL-a obvezno trebalo odrediti vrstu stanica u mononuklearnom infiltratu koji se može točnije povezati s pacijentovom povijesti bolesti i kliničkim značajkama. Jedan ispitanik imao je nalaz normalne sluznice s hiperplastičnim epitelom, no to se može pripisati djelomičnoj remisiji zbog lokalne steroidne terapije.

U ovom istraživanju pronašli smo samo jedan slučaj OLL-a povezanog s lijekovima s atrofičnom lezijom i nedostatkom folata (67 ng/ml), no serumska razina folata i vitamina B_{12} bila je normalna. Riječ je o ženi i ta je ispitanica imala hipertenzije dulje od tri godine. Njezin histopatološki nalaz i nalaz direktne imunofluorescencije iz oralne lezije bili su negativni te je postavljena dijagnoza lihenoidnog mukozitisa zajedno s lihenom planusom. Kad su joj vadili krv, uzimala je Amlodipin, Hydralazine HCl i Losartan. Dvije godine nakon toga dijagnosticiran joj je hipertiroidizam i liječena je Propiltiouracilom (PTU) i Propanololom. Njezin KKS i hemoglobin bili su unutar normalnih granica.

Nedavno istraživanje u Tajlandu o lijekovima pacijenata s oralnim lihenom planusom ili oralnom lihenoidnom reakcijom na lijek, pokazalo je da većina njih s oralnim lezijama uzima više od jednog lijeka. Najčešći su antihipertenzivi (17). Naše istraživanje također je pokazalo da većina naših pacijenata s OLL-om uzima više lijekova i to uglavnom antihipertenzive i hipolipidemike. Hipolipidemik statin uzimalo je u našem istraživanju svih 12 pacijenata s OLL-om povezanim s lijekovima. Naši slučajevi slični su već opisanima kod

flammation, 1 subject each with OLDR or normal mucosa with hyperplastic (Table 3).

Discussion

When diagnosing the oral lesions in our study, most of our patients could not remember the exact onset of their systemic diseases, the names of the medications they were taking or any alternative medications prescribed by their physicians. The diagnosis of OLDR can be confirmed by withdrawing the suspected drug. However, in our study, the diagnosis of OLDR could not be confirmed and the term OLL related drug was used instead. Indeed, it is impossible or very difficult to withdraw a suspected drug because of ethical considerations and furthermore, in the present study the patients were taking multiple drugs. The subjects in the study group had their diagnoses confirmed by both oral and histopathological examination. The histopathological findings in most cases were consistent with OLP or OLP/OLDR. The histopathological sections demonstrated oral mucosa covered by parakeratinized stratified squamous epithelium with basal cell degeneration. A band-like infiltration of lymphocytes with a few plasma cells and macrophages were observed within the subjacent fibrous connective tissue. A recent study revealed that the histopathology of OLL showed more eosinophils, plasma cells, and granulocytes in OLL compared with OLP (16). Therefore, to establish the histopathological diagnosis of OLP and OLL, it should be mandatory to define the type of cells in the mononuclear infiltrate, which can be associated more accurately with the patient's history and clinical features. One subject whose oral lesion was reported as normal mucosa with hyperplastic epithelium might be due to partial remission from topical steroid treatment.

In the present study, we only found one OLL related drug subject with an atrophic lesion and folate deficiency (67 ng/ml); however, her serum folate and vitamin B_{12} were normal. This subject had a history of hypertension for more than 3 years. The histopathological examination and direct immunofluorescence from this subject's oral lesion, which was negative, resulted in a diagnosis lichenoid mucositis, consistent with lichen planus. At the time of blood withdrawal, she was taking amlodipine, hydralazine HCl, and losartan. Two years later, this subject was diagnosed with hyperthyroidism and was treated with propylthiouracil and propanolol. However, her complete blood profile and hemoglobin pattern were within normal limits.

A recent study of medications in Thai patients with oral lichen planus or oral lichenoid drug reaction showed that most of the patients with oral lesions took more than one medication. Antihypertensive drugs were the most commonly used drugs by Thai patients with oral lesions (17). Our study also showed that most of our patients were taking mul-

kojih je statin također naveden kao uzročnik kožnih promjena i promjena na oralnoj sluznici poput OLL-a (18 – 20). Teško je konačno zaključiti kakav je odnos između oralnih lezija i ovih lijekova. Zato bi se na većem uzorku trebala istražiti povezanost uzimanja antihipertenziva i hipolipidemika s OLL-om povezanim s lijekovima.

Zanimljivo je da su svi pacijenti u ovom istraživanju imali normalnu razinu vitamina B_{12}. Ti nalazi mogu upućivati na to da lijekovi koje su uzimali ne utječu na metaboličke putove i metabolizam kobalamina.

Četvero sudionika iz skupine s OLL-om povezanim s lijekovima i troje iz kontrolne skupine bili su anemični, ali njihove razine folata crvenih krvnih stanica i serumskih folata te vitamina B_{12} bile su unutar normalnih granica. Mi smo definirali normalnima razine Hb-a – za ispitanike od 14 do 18 g/dl, a za ispitanice od 12 do 16 g/dl. Svih sedam žena imalo je hematokrit niži od 36 posto, no među skupinama nije nađena značajna razlika u anemiji.

Potrebna je velika skupina ispitanika da bi se objasnila povezanost lijekova s folatima, vitaminom B_{12} i anemijom.

tiple drugs rather than a single drug, particularly antihypertensives and hypolipidemics, which are the most common medications taken by patients with OLL. Regarding hypolipidemics, all 12 cases of OLL related drug in our study used statin group. Our cases are similar to the previous reports that statin has been implicated in causing cutaneous and oral mucosal involvement such as OLL (18-20). However, it is difficult to definitely conclude a relationship between the oral lesions and these medications. The relationship between taking antihypertensives or hypolipidemics and OLL related drug should be investigated in a large group study.

Interestingly, all the patients in the present study showed normal vitamin B_{12} levels. These findings may reflect that the medications taken by the patients in our study do not affect the pathway of cobalamin metabolism.

Four cases in OLL related drug and 3 cases in the control group had anemia but their red cell folate, serum folate and vitamin B_{12} were within normal limits. We define normal Hb level for males is 14-18 g/dl; that for females is 12 -16 g/dl. All 7 female cases had shown low hematocrit less than 36%. However, there was no significant difference in anemia between the two groups. A large group study is needed to clarify the folate, vitamin B_{12}, and anemia related medications.

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Conflict of interest

None declared

Abstract

Medications have been increasingly used by patients for the treatment of their systemic diseases. However, many drugs are reported to induce oral lichenoid lesions (OLL). **Aim:** The aim of our study was to investigate the relationship between OLL, medications, and folate and vitamin B_{12} levels. **Material and Methods:** Twenty Thai patients who were diagnosed with OLL by clinical and histopathological examination were included in this study. These subjects were compared with 24 healthy control subjects. Complete blood counts, hemoglobin typing, serum and red cell folate, and serum vitamin B_{12} levels were investigated. The medications taken and the systemic diseases of the Thai patients with OLL were recorded and analyzed. **Results:** Our results showed that only 1/20 patients with OLL (5%) had low red cell folate and only 1 case showed a low level of serum folate. Vitamin B_{12} levels were within normal range in both groups. There were no significant differences in red cell folate, serum folate, or vitamin B_{12} levels between the patients with OLL and the control group ($p>0.05$). Four cases in OLL and 3 cases in the control group had low hematocrit less than 36% and they were defined as anemic. **Conclusion:** Antihypertensives and hypolipidemics were the most common medications taken by patients with OLL; however, these drugs had no effect on red cell folate, serum folate, or vitamin B_{12} levels. Since the patients were taking multiple drugs and we could not confirm the diagnosis of OLDR by withdrawal of the drugs, we used the term OLL related drug instead.

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Address for correspondence
Prof. Kobkan Thongprasom
Chulalongkorn University
Faculty of Dentistry
Oral Medicine Department
Bangkok 10330, Thailand
Tel: +66-2-2188942
Fax: +2-2188941
kobkan.t@chula.ac.th

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