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Procjena parodontnog statusa oboljelih od kronične limfocitne leukemije u ranom stadiju

Evaluation of Periodontal Parameters in Patients with Early Stage Chronic Lymphocytic Leukemia

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Sažetak

Svrha rada: Procjenjivao se parodontni status ispitanika s KLL-om u ranom stadiju i uspoređivao s parodontnim statusom zdravih ispitanika u kontrolnoj skupini te analizirala veza između parodontoloških i hematoloških parametara bolesnika s KLL-om. **Materijali i metode:** Pregledano je 60 ispitanika: 30 oboljelih od KLL-a – u stadiju Rai 0 (ispitna skupina) te 30 zdravih osoba iste životne dobi (kontrolna skupina). Kriteriji za isključivanje bili su: postojanje neke druge sistemske bolesti ili stanja (npr. dijabetes), već provedena parodontna terapija, liječenje antibioticima tijekom posljednja tri mjeseca i uzimanje lijekova. Socijalno-demografski podatci prikupljeni su upitnikom. Ispitanicima s najmanje osam zuba obavljen je kompletan parodontološki pregled i određeni su API, PBI, PPD, REC i CAL. Medicinski podatci oboljelih od KLL-a preuzeti su iz njihove medicinske dokumentacije, a hematološki parametri očitani su iz nalaza krvne pretrage. **Rezultati:** Skupine su se međusobno razlikovale s obzirom na dob, broj zuba i učestalost odlazaka stomatologu ($p < 0,05$). Ispitanici s KLL-om imali su značajno veće prosječne vrijednosti parodontoloških indeksa (API 0,81 ± 0,18; PBI 2,72 ± 0,68; PPD 3,40 ± 0,53; REC 1,95 ± 0,87; CAL 4,37 ± 0,80) u odnosu prema ispitanicima iz kontrolne skupine (API 0,69 ± 0,15; PBI 1,9 1± 0,45; PPD 2,51 ± 0,40; REC 0,99 ± 0,54; CAL 3,00 ± 0,58). Koeficijenti korelacije između dobi i parodontoloških indeksa bili su statistički značajni za dob i REC ($r = 0,357$; $p < 0,01$) te dob i CAL ($r= 0,295$; $p < 0,05$). Dob nije bila statistički značajan kovarijat za CAL ($F = 2,205$; $p > 0,05$), nego samo za REC ($F = 4,601$; $p < 0,05$). Nakon statističkog uklanjanja utjecaja dobi, razlika u REC-u između KLL-a i kontrolne skupine ostala je statistički značajna ($F = 19,732$; $p < 0,01$; $eta^2 = 0,287$). Nije dokazana statistički značajna veza između parodontoloških i hematoloških parametara kod oboljelih od KLL-a ($p > 0,05$). **Zaključak:** Rezultati ovog istraživanja pokazali su da su oboljeli od KLL-a imali lošiji parodontni status negoli zdravi ispitanici. Uzročno-posljedična veza između parodontoloških i hematoloških parametara nije dokazana.

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Uvod

Leukemija je zloćudna hematološka bolest pri kojoj se pojavljuju nekontrolirane proliferacije krvotvornih tkiva, što rezultira značajnim porastom broja cirkulirajućih nezrelih i nefunkcionalnih bijelih krvnih stanica (blasta). Ova bolest nastaje iz hematopoetske matične stanice u kojoj se dogodio poremećaj diferencijacije i proliferacije (1).

Leukemije se u osnovi dijele prema vrsti zahvaćenih stanica na limfoidne ili mijeloidne, a prema kliničkom tijeku bolesti na akutne ili kronične (2). Kronična limfocitna leukemija (KLL) klinički je heterogena bolest B-limfocita za koju je svojstvena B-klonska ekspanzija s blokom u sazrijevanju. KLL je najčešća pojedinačna vrsta leukemije kod odraslih osoba u zapadnim zemljama i uglavnom se pojavljuje u starijoj životnoj dobi (3). Uzrok nije poznat. Unatoč tomu

Introduction

Leukemia is a malignancy of hematologic origin caused by proliferating white blood cell-forming tissues, resulting in a marked increase in circulating immature or abnormal white blood cells (blasts). Leukemia arises from a hematopoietic stem cell characterized by a disordered differentiation and proliferation of neoplastic cells (1).

Leukemia can be classified as lymphoid or myeloid, according to the cell lineage, and as acute or chronic, according to the evolution of the disease (2). Chronic lymphocytic leukemia (CLL) is a clinically heterogeneous disease originating from B lymphocytes that may differ in activation, maturation state, or cellular subgroup. CLL is the most common form of adult leukemia in Western countries and primarily a disease of the elderly (3). No etiologic factors have been iden-

što otprilike 20 posto ispitanika s KLL-om ima krvne srodnike s istom ili sličnom limfoidnom zloćudnom bolesti, genetska poveznica nije znanstveno potvrđena (4).

Početak KLL-a često je asimptomatski, a na bolest se obično posumnja nakon slučajnoga nalaza limfocitoze tijekom rutinskoga pregleda krvne slike. Dijagnoza se postavlja ako je broj B-limfocita veći od 5 x 10^9/L dulje od šest mjeseci. Stanice neoplastičnoga klona nastaju poliklonalnom ekspanzijom CD5 + B-limfocita djelovanjem određenoga mutagenog sredstva i tvore monoklonsku populaciju. Imunološki fenotip KLL-stanica karakterizira jaka ekspresija staničnih biljega CD5, CD19 i CD23, te slabija ekspresija markera CD20 i CD79b (5).

Klasifikacija bolesti u kliničke stadije obavlja se na temelju fizikalnog pregleda bolesnika i nalaza krvne slike. Dva najčešće korištena sistema za klasificiranje KLL-a su Rai i Binet. Oba pridonose preciznijem određivanju prognoze bolesti. Očekivano vrijeme preživljavanja osoba s KLL-om u zadnjem stadiju bolesti jest između jedne i dvije godine, a kod osoba s početnim stadijem očekuje se preživljenje dulje od 10 godina (6). Ostali prognostički čimbenici kojima se procjenjuje rizik progresije bolesti jesu visoke serumske razine ß2-mikroglobulina i biljega CD23, kratko vrijeme podvostručenja broja limfocita (< 6 mjeseci) i difuzna infiltracija koštane srži (7).

Oralne manifestacije leukemije može imati 65 posto bolesnika, a uključuju bljedilo oralne sluznice zbog anemije, pojavu petehija i ekhimoza na sluznici, te pojačano gingivalno krvarenje zbog trombocitopenije. Kao posljedica infiltracije gingivalnog tkiva leukemijskim stanicama, nastaju hiperplastične promjene na desnima koje se klinički manifestiraju progresivnom proliferacijom interdentalnih papila, slobodne i pričvrsne gingive, a češće su u slučaju akutnih negoli kroničnih leukemija (1).

Poremećaj imunosnog sustava jedna je od glavnih manifestacija kronične limfocitne leukemije. Bolesnici s KLL-om imaju sniženu razinu imunoglobulina već u ranom stadiju bolesti, što ih čini podložnijima za razvoj bakterijskih infekcija. Zato kliničkim tijekom bolesti dominiraju simptomi vezani za oslabljenu funkciju imunosnog sustava: sklonost banalnim, ali rekurirajućim, ili ozbiljnim infekcijama, te autoimuni poremećaji (8, 9). Neadekvatan stanični i humoralni imunosni odgovor domaćina nastaje kao posljedica kvantitativnoga i kvalitativnog poremećaja imunosnih stanica (10).

Na antigeni podražaj oboljeli od KLL-a reagiraju smanjenom sekrecijom protutijela jer im je broj zdravih B-limfocita znatno smanjen (11). Smanjena je i sekrecija svih imunoglobulina (IgG, IgA, IgM), a osobito IgG3 i IgG4 (12). Smatra se da humoralna imunost, osobito antitijela IgG i IgA, ima važnu obrambenu zadaću u patogenezi parodontne bolesti, pa se može pretpostaviti da će osobe sa sniženom razinom ovih imunoglobulina biti sklonije razvoju parodontitisa u odnosu na one s normalnim vrijednostima. Kako leukemija napreduje, tako hipogamaglobulinemija postaje sve izražena. No česta je i u početnim fazama bolesti. Prema podatcima iz jedne studije, 73 posto ispitanika s KLL-om u stadiju Rai 0 imalo je snižene vrijednosti barem jedne vrste imunoglobulina (13).

tified for CLL. Approximately 20% of patients with this disease have relatives with CLL or another lymphoid malignancy, although no genetic linkage has been identified (4).

Patients with CLL are generally asymptomatic at presentation and the diagnosis is often made incidentally when lymphocytosis is noted at the time of routine evaluation. The presence of B-cell lymphocytosis of at least 5 × 10^9/L for 6 months or longer is diagnostic for CLL. CLL cells arise from polyclonal expansion of CD5+ B lymphocytes, which are transformed into a monoclonal population by mutational agents. Immunophenotyping of CLL cells shows expression of CD5, CD19, and CD23, as well as dim expression of CD20 and CD79b (5).

The clinical staging of CLL is based on physical examination and complete blood counts. The two widely used staging systems are Rai and Binet. With both staging systems, patients with the most advanced stage have a predicted survival time of 1 to 2 years, while patients with the earliest stage of disease have a median survival time of more than 10 years (6). In addition to clinical staging, traditional prognostic factors for stratifying the risk of disease progression have included high serum levels of β_2-microglobulin and soluble CD23, short lymphocyte doubling time (<6 months), and diffuse bone marrow infiltration (7).

Local symptoms and findings of leukemia in the oral cavity, which can be found in 65% of patients with leukemia, include paleness of the oral mucosa due to underlying anemia, with presence of petechiae, ecchymosis and gingival hemorrhage or gingival bleeding due to underlying thrombocytopenia. Infiltration of the gingival tissue with leukemia cells cause gingival hyperplasia which is characterized by progressive enlargement of the interdental papillae as well as the marginal and attached gingiva. Gingival hyperplasia is more common in acute than chronic leukemia (1).

Chronic lymphocytic leukemia is characterized by a dysregulated immune system. All patients have reduced immunoglobulin levels, even in early stages, and this is associated with an increased frequency and severity of infection. The clinical course in CLL is dominated by events associated with immune dysfunction, manifested predominantly as an increased susceptibility to infection and/or autoimmunity (8, 9). There are both quantitative and qualitative defects in immune effector cells that result in abnormal cellular and humoral-mediated immune responses (10).

Production of immunoglobulin from normal B cells and antibody response to different antigens are significantly reduced in CLL patients (11). All 3 classes (IgG, A and M) are affected, although predominantly IgG3 and IgG4 (12). The humoral immune response, especially IgG and IgA, is considered to have a protective role in the pathogenesis of periodontal disease, so it can be assumed that these patients would be much more susceptible to periodontitis. The severity of hypogammaglobulinemia in CLL patients tends to increase with the duration and stage of disease. However, in one study, 73% of patients with Stage 0 CLL were found to have diminished levels of at least one serum immunoglobulin, indicating that this is a significant finding even in early stages (13).

Nadalje, kod oboljelih od KLL-a pojavljuju se i poremećaji staničnoga imunosnog odgovora (posredovanog T-limfocitima, NK-stanicama, neutrofilima i monocitima). Nastaje poremećaj sekrecije, skladištenja i transporta citotoksičnih molekula unutar CD8 + T-limfocita, što onemogućuje pravilno funkcioniranje T-limfocita u procesu prezentacije antigena B-limfocitima (14). Ove promjene pridonose nesposobnosti T-limfocita da započnu, održe i uspješno privedu kraju odgovarajuću imunosnu reakciju oboljelih. Osim narušene funkcije T-limfocita, pojavljuju se i poremećaji fagocitoze, migracije i kemotaksije NK-stanica, neutrofila (PMN) i monocita (15). Studije koje su izučavale imunosnu reakciju unutar parodontoloških lezija, jasno su definirale neutrofile kao stanice koje čine prvu crtu obrane domaćina i koje, u normalnim okolnostima, ograničavaju štetno djelovanje parodontopatogena (16, 17). Pritom oni ne djeluju samostalno, nego u korelaciji s antitijelima i sustavom komplementa, pri čemu svi zajedno čine važnu okosnicu u borbi protiv gram-negativnih mikroorganizama, glavnih uzročnika parodontne bolesti.

S druge strane, kod imunokompromitiranih bolesnika, kao što su oboljeli od KLL-a, inficirani parodont može djelovati kao fokalno žarište različitih sistemskih infekcija. Ulcerirani epitel umjerenoga, pa čak i blagog, parodontitisa mjesto je ulaska bakterija u sistemsku cirkulaciju ovih imunokompromitiranih bolesnika. Učestalost parodontitisa kod oboljelih od KLL-a nepoznata je i u većini slučajeva podcijenjena. Naime, zbog izostanka tipičnih simptoma gingivitisa (crvenilo, oteklina, bol) i slabijega imunosnog odgovora, parodontitis se kod tih bolesnika može lako previdjeti (18). Uz procjenu parodontološkog statusa, nužno je utvrditi stupanj oralne higijene već na početku bolesti kako bi se izbjegle neželjene komplikacije u kasnijim fazama kada počinje razvoj ozbiljnije neutropenije (19,20). Pokazalo se da pravodobno stomatološko zbrinjavanje onkoloških bolesnika smanjuje rizik od pojave oralnih komplikacija te pridonosi njihovoj kraćoj hospitalizaciji (21). Adekvatna oralna higijena umanjuje rizik od razvoja oralnog mukozitisa, febrilnih epizoda i bakterijemije (22). Parodontna terapija provedena u intervalima između kemoterapijskih ciklusa značajno smanjuje pojavu febrilne neutropenije tijekom kemoterapije i transplantacije koštane srži (23).

Svrha ovog istraživanja bila je procijeniti parodontni status bolesnika u ranom stadiju KLL-a i usporediti ga s parodontnim statusom zdravih ispitanika iste životne dobi u kontrolnoj skupini, te analizirati vezu između parodontoloških i hematoloških parametara kod ispitanika s KLL-om.

Ispitanici i postupci

U istraživanje su bili uključeni oboljeli od KLL-a koji su se od rujna 2013. do prosinca 2014. godine javili na kontrolni pregled u Zavod za hematologiju Klinike za internu medicinu Kliničkog bolničkog centra Sestre milosrdnice u Zagrebu, a zadovoljavali su kriterije za uključivanje u studiju. Svima njima (ispitna skupina, n = 30) hematolog je u skladu s valjanim kriterijima (5) dijagnosticirao kroničnu limfocitnu leukemiju (stadij Rai 0). Svi ti ispitanici bili su u sustavu re-

Furthermore, the cellular immune response (mediated by T cells, NK cells, neutrophils and monocytes) is also impaired in CLL patients. Specifically, production, storage and transportation of cytolytic molecules in CD8+ T-cells are faulty, which means that interaction with B cells in the process of antigen presentation is impaired (14). These changes all contribute to the inability of T cells to successfully initiate, maintain and complete an immune response in patients with CLL. NK cells, neutrophils (PMNs) and monocytes are also defective in their phagocytic and bactericidal function as well as in migration and chemotaxis (15). Studies of host response in periodontal disease have clearly identified the PMNs as the key protective cells, which, under normal circumstances, limit the extent of damage by periodontal pathogens (16, 17). The PMNs do not act alone, but as part of a neutrophil-antibody- complement axis that exerts a protective role against the gram-negative microorganisms that are the major pathogens of periodontal disease.

On the other hand, the infected and inflamed periodontium can act as a focus for systemic infection in patients with impaired immune system such as those with CLL. Moderate to severe periodontitis represents putative origins of systemic infection in those immunocompromised patients.

The incidence of periodontal disease in patients with CLL is unknown, but probably underestimated. Periodontal disease can easily be overlooked, primarily because symptoms of gingival inflammation may be minimal with reduced erythema, swelling, and pain in sites of infection (18). A thorough assessment of the level of oral hygiene and of periodontal condition should be performed early in the workup for any patient in whom profound and prolonged neutropenia is anticipated in order to avoid later complications in these patients (19,20).

In cancer patients, oral and dental pretreatment has been shown to decrease the length of hospital stay, and to be associated with reduced oral complications (21). Good oral hygiene has been reported to reduce the risk of mucositis and decrease the risk of fever or bacteremia (22). Periodontal treatment in the intervals between chemotherapy cycles reduces febrile neutropenia in subsequent courses of chemotherapy and hematopoietic transplantation (23).

The aim of this study was to assess periodontal conditions in patients with early stage CLL and to compare it with the periodontal status of age matched healthy controls and also to analyze the relationship between periodontal and hematological parameters in CLL patients.

Patients and methods

Between September 2013 and December 2014 all consecutive CLL patients visiting the Department of Hematology, Clinic of Internal Medicine, University Hospital Centre (UHC) "Sestre Milosrdnice" in Zagreb who matched the inclusion criteria were informed of the purpose of this study and were asked to participate in it. All CLL patients included in this study (test group, n=30) had been diagnosed by the hematologist with CLL (Rai 0) in accordance with the recent

dovitih kontrolnih pregleda, te u skladu sa smjernicama za liječenje KLL-a nisu primali nikakvu terapiju (5).

Zdravi ispitanici iz kontrolne skupine bili su iste životne dobi (n = 30) i u istom vremenskom razdoblju dolazili su stomatologu na Odjel za dentalnu i oralnu patologiju s parodontologijom Stomatološke poliklinike Zagreb.

Kriteriji za isključivanje ispitanika iz obje skupine bili su: sistemske bolesti ili stanja za koja se zna da su rizični čimbenik za razvoj parodontitisa (npr. dijabetes), prije provedena parodontološka terapija, antibiotska terapija tijekom posljednja tri mjeseca i uzimanje medikamenata za koje se zna da mogu utjecati na razvoj parodontne bolesti.

Prije pregleda, svi ispitanici uključeni u istraživanje potpisali su informirani pristanak za dobrovoljno sudjelovanje, nakon što su detaljno obaviješteni o načinu i ciljevima istraživanja. Istraživanje je provedeno u skladu s Helsinškom deklaracijom, a odobrilo ga je Etičko povjerenstvo Stomatološkog fakulteta Sveučilišta u Zagrebu, Etičko povjerenstvo KBC-a Sestre milosrdnice i Etičko povjerenstvo Stomatološke poliklinike Zagreb.

Parodontološki pregled ispitanika obavio je specijalist parodontolog koji je prošao kalibraciju mjerenja. Ispitanicima s osam i više zuba (KLL n = 24; kontrola n = 28) izmjerene su dubine sondiranja parodontnih džepova (PD), recesije gingive (REC) i gubitak kliničkoga pričvrstka (CAL). Mjere su izražene u milimetrima i zaokružene na najbliži cijeli milimetar. Određeni su i sljedeći parodontološki indeksi: aproksimalni indeks plaka (API, Lange, 1986.) i indeks krvareće papile (PBI, Saxer i Mühlemann, 1975.). Parodontološki pregled obavljen je standardnom graduiranom parodontološkom sondom (Aesculap, DB766R, UPM, B. Braun, Njemačka) i stomatološkim zrcalom. Ispitanicima kojima su pronađene patološke promjene parodonta savjetovano je da se jave specijalistu parodontologu radi daljnjeg pregleda i obrade.

Podatci o dobi, spolu, indeksu tjelesne mase (BMI), stupnju obrazovanja, mjesečnom dohotku, pušenju i konzumaciji alkohola, prikupljeni su posebnim upitnikom.

Medicinski podatci oboljelih od KLL-a preuzeti su iz njihove medicinske dokumentacije, a hematološki parametri očitani su iz krvnih nalaza učinjenih na dan pregleda. Svi krvni nalazi obrađeni su u biokemijskom laboratoriju KBC-a Sestre milosrdnice.

Za analizu podataka korišten je statistički program IBM SPSS Statistics version 17,0 (SPSS INC., Chicago, IL, SAD). U svrhu deskriptivnih analiza, za kontinuirane varijable korištene su aritmetičke sredine (M), standardne devijacije (SD) i raspon (tj. minimalne i maksimalne vrijednosti), a za kategorijske varijable korištene su frekvencije (f) i postoci (%). Normalnost distribucije hematoloških i parodontoloških mjera KLL-a i kontrolne skupine testirana je Kolmogorov-Smirnovljeviim testovima koji su pokazali da su unutar skupina sve mjere normalno distribuirane. Značajnosti razlika između KLL-a i kontrolne skupine testirane su Studentovim t-testom za kontinuirane varijable, a χ^2- testom za kategorijske varijable. **P** vrijednosti manje od 0,05 smatrane su značajnima.

criteria (5). They were on a regular recall schedule for CLL and without any therapy because they did not meet the established criteria for initiating appropriate treatment (5).

During the same period of time, age-matched controls (control group, n=30) were selected from the Department of Dental and Oral Pathology with Periodontology, Dental Polyclinic Zagreb. They were informed about the nature and the purpose of the study and afterwards asked to participate.

The exclusion criteria for both groups were: presence of other systemic disease or condition (e.g. diabetes) which are known as risk factors for periodontitis, the history of treatment for periodontitis, use of antibiotics during the last 3 months, use of medications which are known to be risk factors for periodontitis.

All subjects included in this study signed a written informed consent prior to examination. The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee for Research at the School of Dental Medicine, University of Zagreb, University Hospital Centre "Sestre Milosrdnice" and Dental Polyclinic Zagreb.

Periodontal parameters were evaluated by one experienced and calibrated examiner. Participants with at least 8 teeth (CLL n=24; control n=28) underwent a full mouth examination which assessed the periodontal probing depth (PD), gingival recession (REC) and clinical attachment loss (CAL). Measurements were made in millimeters and were rounded to the nearest whole millimeter. Approximal Plaque Index (API, Lange, 1986) and Papilla Bleeding Index (PBI, Saxer and Mühlemann, 1975) were also recorded for each subject. Periodontal examination was performed with standard graduated periodontal probe (Aesculap, DB766R UPM, B. Braun, Germany) and dental mirror. Patients who were diagnosed with pathological conditions were advised to seek consultation and treatment from a specialist.

Information about age, gender, body mass index (BMI), educational level, monthly income, smoking and alcohol consumption was obtained by means of a questionnaire.

Medical data for CLL patients were collected from the patients' records, while hematological data were obtained from the hemogram performed on the same day as the clinical examination. All blood counts were processed by the laboratory at the UHC "Sestre Milosrdnice".

Software used for data analysis was IBM SPSS Statistics version 17.0. (SPSS Inc., Chicago, IL, USA). For the purpose of descriptive analysis, arithmetic mean (M), standard deviation (SD) and range (i.e. minimum and maximum values) were used for continuous variables, while frequencies (f) and percentages (%) were used for categorical variables. Normality of distribution of hematological and periodontal measures within CLL and control group was tested by Kolmogorov-Smirnov tests showing that all measures were normally distributed within groups. Significance of differences between CLL and control group was tested by Student's t-test for continuous variables and Chi-Square test for categorical variables. P values below 0.05 were considered significant.

Rezultati

Tijekom istraživanja pregledano je ukupno 60 ispitanika (27 muškaraca, 33 žene), od kojih 30 ispitanika s KLL-om – stadij Rai 0 (17 muškaraca, 13 žena) i 30 sistemski zdravih ispitanika u kontrolnoj skupini (10 muškaraca, 20 žena). Ispitanici s manje od osam zuba (6 ispitanika s KLL-om i 2 ispitanika iz kontrolne skupine) isključeni su iz daljnje parodontološke evaluacije. Socijalno-demografski podatci sudionika istraživanja prikazani su u tablici 1. Svi ispitanici bili su starije životne dobi (67,9 ± 10,1 godina). Tako je prosječna dob ispitanika u KLL-skupini bila 70,8 ± 9,9 godina, a u kontrolnoj je iznosila 65 ± 9,6 godina. Studentov t-test za kontinuirane varijable pokazao je da je razlika u dobi između KLL-a i kontrolne skupine bila statistički značajna (p = 0,026), tj. ispitanici iz KLL-skupine bili su statistički znatno stariji od ispitanika iz kontrolne skupine. Prosječan broj zuba po ispitaniku u KLL-skupini iznosio je 10,2 ± 7,3, a u kontrolnoj 18,5 ± 7,5. Razlika u broju zuba po ispitaniku između dviju skupina bila je statistički značajna (p < 0,01), tj. ispitanici iz kontrolne skupine imali su više zuba u odnosu prema ispitanicima iz KLL-skupine. Statistički značajna razlika među skupinama zabilježena je i s obzirom na učestalost odlazaka stomatologu (p = 0,04). Samo 10 posto pregle-

Results

A total of 60 participants (27 men, 33 women) were examined during the research: 30 patients with CLL Rai 0 (17 men, 13 women) and 30 systemically healthy subjects from the control group (10 men, 20 women). 6 participants from the CLL group and 2 from the control group had less than 8 teeth and they were excluded from further periodontal evaluation. The socio-demographic data are shown in Table 1. All participants were of older age (67.9± 10.1 years). The average age of patients in the CLL group was 70.8±9.9 years, while in the control group the average age was 65±9.6 years. Student's t-test for continuous variables showed that the difference in age between the groups was statistically significant (p=0.026), that is, participants of the CLL group were older than those in the control group. The average number of teeth per subject in the CLL group was 10.2±7.3 and in the control group it was 18.5±7.5. The difference in the number of teeth per subject between the two groups was statistically significant (p<0.001), meaning that the participants in the control group had more teeth than those in CLL group. A statistically significant difference between the groups was also observed considering the frequency of dental checkups (p=0.04). Only 10% of the examined patients with CLL sta-

Tablica 1. Socijalno-demografski podatci sudionika istraživanja
Table 1 The socio-demographic data of the research participants.

	Ukupno • Total (N=60)			KLL • CLL (N=30)			Kontrolna • Control (N=30)			Razlika • Difference	P
Dob* • Age*	67.90	(± 10.06)	48 - 90	70.77	(± 9.86)	54 - 90	65.03	(± 9.57)	48 - 82	2.286	.026
Spol, *f (%)*§ • Gender, *f (%)*§											
M	27	(45%)		17	(56.7%)		10	(33.3%)		3.300	.069
Ž • F	33	(55%)		13	(43.3%)		20	(66.7%)			
BMI*	27.46	(± 3.38)	20.1 - 36.3	27.52	(± 3.62)	20.8 - 36.3	27.39	(± 3.18)	20.1 - 32	.140	.889
Broj zuba* • Number of teeth*	14.35	(± 8.43)	0 - 30	10.20	(± 7.30)	0 - 20	18.50	(± 7.45)	0 - 30	-4.358	.000
Odlasci stomatologu, *f (%)*§ • Dental checkups, *f (%)*§											
< 1 x godišnje • < 1 x per year	27	(45%)		17	(56.7%)		10	(33.3%)		4.209	.040
1 x godišnje • 1 x per year	22	(36.7%)		10	(33.3%)		12	(40%)			
2 i više x godišnje • >= 2 x per year	11	(18.3%)		3	(10%)		8	(26.7%)			
Stručna sprema, *f (%)*§ • Educational level, *f (%)*§											
NSS • low	8	(13.3%)		5	(16.7%)		3	(10.1%)		.605	.739
SSS • medium	38	(63.3%)		18	(60%)		20	(66.7%)			
VSS • high	14	(23.3%)		7	(23.3%)		7	(23.3%)			
Dohodak mjesečni, *f (%)*§ • Monthly income, *f (%)*§											
ne ostvaruje • without income	6	(10%)		2	(6.7%)		4	(13.3%)		1.969	.374
<5000 kn	41	(68.3%)		23	(76.7%)		18	(60%)			
5000-10000 kn	13	(21.7%)		5	(16.7%)		8	(26.7%)			
Pušenje, *f (%)*§ • Smoking, *f (%)*§											
ne puši • non-smoking	48	(80%)		25	(83.3%)		23	(76.7%)		1.174	.556
do 1 kutije dnevno • up to 1 box per day	11	(18.3%)		5	(16.7%)		6	(20%)			
> 1 kutije dnevno • > 1 box per day	1	(1.7%)		0	(0%)		1	(3.3%)			
Alkohol, *f (%)*§ • Alcohol consumption, *f (%)*§											
ne konzumira • do not consume	51	(85%)		25	(83.3%)		26	(86.7%)		1.520	.468
< 6 pića tjedno • < 6 drinks per week	8	(13.3%)		5	(16.7%)		3	(10%)			
> 6 pića tjedno • > 6 drinks per week	1	(1.7)		0	(0%)		1	(3.3%)			

* aritmetička sredina M (± standardna devijacija SD), raspon = minimum-maksimum, test razlike (t-test), značajnost (p) • arithmetic mean M (± standard deviation SD), range=minimum-maximum, difference test (t-test), significance (p)
§ frekvencije (f), postotci (%), test razlike (χ^2test), značajnost (p) • frequencies (f), percentages (%), difference test (χ^2test), significance (p)

danih ispitanika s KLL-om navelo je da odlazi stomatologu dva i više puta na godinu, a u kontrolnoj skupini taj je postotak bio znatno veći (26,7 %). Skupine se nisu statistički značajno razlikovale s obzirom na spol, indeks tjelesne mase, stupanj obrazovanja, mjesečni dohodak, pušenje i konzumaciju alkohola. Većina ispitanika imala je srednju stručnu spremu (63,3 %), te je ostvarivala prosječan mjesečni dohodak manji od 5000 kuna (68,3 %). Ispitanici su uglavnom bili nepušači (80 %) i nisu konzumirali alkohol (85 %).

Vrijednosti promatranih hematoloških parametara ispitanika s KLL-om prikazane su u tablici 2. Broj bijelih krvnih stanica značajno je povećan (leukociti ukupni: 30,46 ± 23,06 x 10^9/L; limfociti: 24,71 ± 22,52 x 10^9/L) u odnosu na normalne vrijednosti (leukociti ukupni: 3,4 – 9,7 x 10^9/L; limfociti: 1,19 – 3,35 x 10^9/L). Nekontrolirana proliferacija limfocita smanjuje volumni udjel neutrofila u perifernoj krvi (21,45 ± 11,57 %; ref. int.: 44 – 72 %), iako njihov apsolutni broj ostaje u granicama normalnih vrijednosti (4,66 ± 1,48 x 10^9/L; ref. int.: 2,06-6,49 x 10^9/L).

Ispitanici s KLL-om imali su statistički značajno više prosječne vrijednosti promatranih parodontoloških indeksa (API, PBI, PPD, REC, CAL) negoli oni u kontrolnoj skupini (tablica 3.). U KLL-skupini prosječna izmjerena vrijednost aproksimalnog indeksa plaka iznosila je 0,81 ± 0,18, indeksa krvareće papile 2,72 ± 0,68, dubine sondiranja 3,40 ± 0,53, recesije gingive 1,95 ± 0,87 i gubitka kliničkog pričvrstka 4,37 ± 0,80. U kontrolnoj skupini prosječna izmjerena vrijednost aproksimalnog indeksa plaka iznosila je 0,69 ± 0,15, indeksa krvareće papile 1,91 ± 0,45, dubine sondiranja 2,51 ± 0,40, recesije gingive 0,99 ± 0,54 i gubitka kliničkog pričvrstka 3,00 ± 0,58. Prema Cohenovu kriteriju, veličina utjecaja dobivene razlike među grupama kategorizirana je kao srednji utjecaj za API (0,72), te kao velik utjecaj za PBI (1,41), PPD (1,90), REC (1,33) i CAL (1,96). Parodontoted that they visited their dentist two or more times a year, while in the control group the percentage was much higher (26.7%). Groups did not differ significantly according to gender, BMI, educational level, monthly income, smoking and alcohol consumption (p>0.05). Most of the participants had a high school education (63.3%) with average monthly earnings less than 5000 Kuna (68.3%). The majority of participants were non-smokers (80%) and did not consume alcohol (85%).

The values of the observed hematological parameters in patients with CLL are shown in Table 2. The number of white blood cells is significantly increased (total leukocytes: 30.46±23.06x10^9/L; lymphocytes: 24.71±22.52x10^9/L) compared to normal values (total leukocytes: 3.4-9.7x10^9/L; lymphocytes: 1.19-3.35x10^9/L). Uncontrolled proliferation of lymphocytes leads to a decrease in the volume fraction of neutrophils in the peripheral blood (21.45 ±11.57%; ref. int.: 44-72%) although their absolute number remains within normal range (4.66 ±1.48x10^9/L; ref. int.: 2.06-6.49x10^9/L).

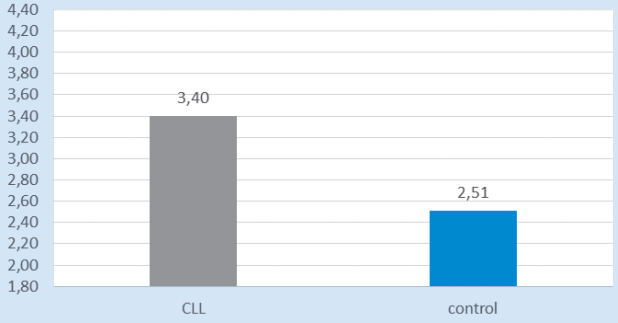
The patients with CLL had significantly higher average values of the observed periodontal indices (API, PBI, PPD, REC, CAL) compared to the control group (Table 3). In the CLL group, the mean value of Approximal Plaque Index was 0.81±0.18, Papilla Bleeding Index 2.72±0.68, periodontal probing depth 3.40±0.53, gingival recession 1.95±0.87 and clinical attachment loss 4.37±0.80. In the control group, the mean value of Approximal Plaque Index was 0.69±0.15, Papilla Bleeding Index 1.91±0.45, periodontal probing depth 2.51±0.40, gingival recession 0.99±0.54 and clinical attachment loss 3.00±0.58. According to Cohen's criteria, the size of the impact of differences obtained between groups was categorized as medium impact for API (0.72) and as great impact for PBI (1.41), PPD (1.90), REC (1.33) and CAL (1.96). Periodontal status of patients in the CLL group was

Tablica 2. Hematološki parametri ispitanika iz KLL-skupine
Table 2 Hematological parameters for CLL patients.

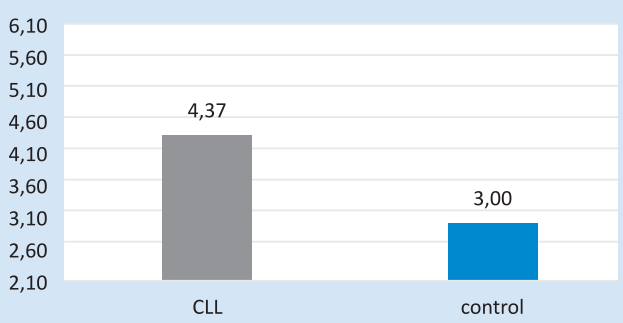
	Referentni interval • Reference interval	Raspon • Range	M ± SD
Gamaglobulini (g/L) • Gammaglobulins (g/L)	8 – 13.5 g/L	4.9 - 14.7	8.64 ± 1.85
ß2-mikroglobulin (mg/L) • ß2-microglobulin (mg/L)	do 3 mg/L	1.7 - 3.9	2.44 ± 0.48
LDH (U/L 37°C)	124 – 241 U/L 37°C	89 - 374	195.07 ± 56.45
Leukociti ukupni (x109/L) • Leukocytes total (x109/L)	3.4 – 9.7 x10^9/L	6.2 - 105.5	30.46 ± 23.06
Limfociti (x109/L) • Lymphocytes (x109/L)	1.19 – 3.35 x10^9/L	5.2 - 97.6	24.71 ± 22.52
Neutrofili (x109/L) • Neutrophils (x109/L)	2.06 – 6.49 x10^9/L	0.9 - 9.1	4.66 ± 1.48
Neutrofili (%) • Neutrophils (%)	44 – 72	5.0 - 44.5	21.45 ± 11.57
Trombociti (x109/L) • Platelets (x109/L)	158 – 424 x10^9/L	119 - 309	183.90 ± 47.61

Tablica 3. Usporedba parodontoloških parametara KLL i kontrolne skupine
Table 3 Comparison of periodontal parameters between CLL and control group.

	KLL • CLL (N=24)	Kontrolna • Control (N=28)	t-test (df=50)	p	Cohen d	95% CI
API	0.81 ± 0.18	0.69 ± 0.15	-2.569	.013	0.72	-0.21 to -0.03
PBI	2.72 ± 0.68	1.91 ± 0.45	-5.180	.000	1.41	-1.13 to -0.50
PPD	3.40 ± 0.53	2.51 ± 0.40	-6.886	.000	1.90	-1.15 to -0.63
REC	1.95 ± 0.87	0.99 ± 0.54	-4.684	.000	1.33	-1.35 to -0.56
CAL	4.37 ± 0.80	3.00 ± 0.58	-7.136	.000	1.96	-1.75 to -0.98



Slika 1. Usporedba dubine sondiranja (PPD) među grupama
Figure 1 Comparison of Periodontal Probing Depth (PPD) between groups.



Slika 2. Usporedba gubitka kliničkog pričvrstka (CAL) među grupama
Figure 2 Comparison of Clinical Attachment Level (CAL) between groups.

loški status ispitanika KLL-skupine bio je značajno lošiji u usporedbi sa statusom ispitanika iz kontrolne skupine, što se jasno vidi iz izmjerenih prosječnih vrijednosti dubine sondiranja i gubitka kliničkoga pričvrstka u svakoj grupi (slika 1., slika 2.).

Budući da je razlika u dobi ispitanika između KLL-skupine i one kontrolne bila statistički značajna (p = 0,026; ispitanici KLL-skupine bili su u prosjeku 5,7 godina stariji od ispitanika kontrolne skupine), izračunati su koeficijenti korelacije između dobi i parodontoloških indeksa (tablica 4.). Rezultati su pokazali da su koeficijenti korelacije bili statistički značajni samo između dobi i recesije gingive (r = 0,357; p < 0,01), te između dobi i gubitka kliničkoga pričvrstka (r = 0,295; p < 0,05). Stoga je analizom kovarijance provjeren utjecaj dobi kao kovarijata u razlikama gubitka kliničkog pričvrstka i recesije gingive između ispitanika s KLL-om i onih iz kontrolne skupine. U razlici gubitka kliničkog pričvrstka između tih dviju skupina dob se nije pokazala statistički značajnim kovarijatom (F = 2,205; p > 0,05) (tablica 5.), a u razlici recesije gingive jest (F = 4,601; p < 0,05). No nakon statističkog uklanjanja utjecaja dobi, razlika u recesiji gingive između tih dviju skupina ostala je statistički značajna (F = 19,732; p < 0,01; eta^2 = 0,287) (tablica 6.). S obzirom na to da su ispitanici iz KLL-skupine imali statistički značajno lošiji parodontološki status negoli oni u kontrolnoj skupini, testirana je korelacija između njihovih izmjerenih parodontoloških indeksa i hematoloških nalaza. Matrica Spearmanovih rho koeficijenata korelacije pokazala je da kod ispitanika iz KLL-skupine nema statistički značajne povezanosti između parodontoloških i hematoloških parametara (tablica 7.).

significantly worse in comparison to the status of the control group participants, which is clearly evident from mean values of PPD and CAL in each group (Figure 1, Figure 2).

Since the age difference between the CLL and the control group was statistically significant (p=0.026; CLL patients were in average 5.7 years older than control group participants), the correlation coefficients between age and periodontal indices were calculated (Table 4). The results showed that the correlation coefficients were statistically significant only between age and gingival recession (r=0.357; p<0.01) and between age and clinical attachment loss (r=0.295; p<0.05). Therefore, the analysis of covariance was used to test the impact of age as covariate in clinical attachment loss and gingival recession differences between the CLL and the control group. Age was not a statistically significant covariate in clinical attachment loss difference between the CLL and the control group (F=2.205; p>0.05) (Table 5). In gingival recession difference between the CLL and the control group, age was a statistically significant covariate (F=4.601; p<0.05). However, after the removal of the statistical effect of age, the difference in gingival recession between the CLL and the control group remained statistically significant (F=19.732; p<0.01; eta^2=0.287) (Table 6). Since the CLL patients had a significantly worse periodontal status compared to control group participants, the correlation between the periodontal indices and hematologic findings of these patients was tested. Matrix of Spearman's rho correlation coefficients showed no statistically significant association between periodontal and hematological parameters in CLL patients (Table 7).

Tablica 4. Utjecaj dobi na parodontološke parametre
Table 4 Influence of age on the periodontal parameters.

	Dob • Age	PI	PBI	PPD	REC	CAL
Dob • Age	-					
PI	.164	-				
PBI	.209	.404**	-			
PPD	.210	.533**	.761**	-		
REC	.357**	.287*	.378**	.628**	-	
CAL	.295*	.477**	.670**	.939**	.857**	-

*p<.05; **p<.01

Tablica 5. Utjecaj dobi na vrijednosti CAL-a
Table 5 Influence of age on CAL values.

Zavisna varijabla: CAL • Dependent Variable: CAL						
Izvor • Source	**Zbroj kvadrata tip III • Type III Sum of Squares**	**Stupnjevi slobode (df) • df**	**Sredina kvadrata • Mean Square**	**F**	**Sig.**	**Parcijalna eta² • Partial Eta Squared**
Korigirani model • Corrected Model	25.226[a]	2	12.613	27.181	.000	.526
Konstanta (intercepta) • Intercept	7.687	1	7.687	16.566	.000	.253
dob • age	1.023	1	1.023	2.205	.144	.043
Grupa • group	21.060	1	21.060	45.383	.000	.481
Pogreška • Error	22.738	49	.464			
Total	733.236	52				
Korigirani total • Corrected Total	47.964	51				

Tablica 6. Utjecaj dobi na vrijednosti REC-a
Table 6 Influence of age on REC values.

Zavisna varijabla: REC • Dependent Variable: REC						
Izvor • Source	**Zbroj kvadrata tip III • Type III Sum of Squares**	**Stupnjevi slobode (df) • df**	**Sredina kvadrata • Mean Square**	**F**	**Sig.**	**Parcijalna eta² • Partial Eta Squared**
Korigirani model • Corrected Model	14.004[a]	2	7.002	14.888	.000	.378
Konstanta (intercepta) • Intercept	.002	1	.002	.005	.946	.000
dob • age	2.164	1	2.164	4.601	.037	.086
Grupa • group	9.281	1	9.281	19.732	.000	.287
Pogreška • Error	23.047	49	.470			
Total	143.386	52				
Korigirani total • Corrected Total	37.051	51				

Tablica 7. Matrica Spearmanovih rho koeficijenata korelacije između parodontoloških i hematoloških parametara
Table 7 Matrix of Spearman's rho correlation coefficients between periodontal and hematological parameters.

	PI	**PBI**	**PPD**	**REC**	**CAL**	**gamaglob. • gammagl.**	**ß2mikrogl • ß$_2$microgl.**	**LDH**	**leukociti • leukocytes**	**limfociti • lymph.**	**neutrofili • neutroph.**	**trombociti • platelets**	**TTM**
PI	-	.345*	.457**	.326*	.445**	.278	.367	-.002	.027	-.025	.014	-.163	.109
PBI		-	.725**	.509**	.700**	-.195	-.144	-.362	.199	.119	.104	.051	.259
PPD			-	.692**	.956**	.093	.051	.111	.068	.044	-.105	.017	.173
REC				-	.853**	-.082	-.025	.114	-.164	-.125	-.176	.204	-.051
CAL					-	.102	.115	.175	-.055	-.056	-.170	.137	.032
gamaglobulini • gammaglobulins						-	.624**	.119	.042	-.008	.161	-.050	-.011
ß2-mikroglobulin • ß2-microglobulin							-	.053	.091	.057	.106	.122	.059
LDH								-	-.257	-.243	-.030	.146	-.300
leukociti • leukocytes									-	.982**	.423*	-.093	.949**
limfociti • lymphocytes										-	.309	-.128	.952**
neutrofili • neutrophils											-	.332	.325
trombociti • platelets												-	-.084
TTM													-

*p < .05; **p < .01;
LDH = laktat-dehidrogenaza • lactate dehydrogenase; TTM = ukupna tumorska masa • total tumor mass

Rasprava

U ustima bolesnika s leukemijom česte su oralne manifestacije te zloćudne bolesti. Hiperplastične promjene na desnima najčešće nastaju zbog infiltracije leukemijskih stanica u gingivalno tkivo (24, 25, 26). Abdullah i suradnici dijagno-

Discussion

Oral manifestations of leukemia are common findings in leukemic patients. Usually, they show hyperplastic gingival changes caused by the infiltration of leukemic cells in the gingival tissue (24, 25, 26). Abdulah et al. diagnosed hyper-

sticirali su hiperplastične promjene na gingivi kod 16 od ukupno 72 bolesnika s akutnom leukemijom (27). Leukemijski gingivalni infiltrati ne pojavljuju se kod bezubih bolesnika, što upućuje na to da važnu ulogu u njihovoj patogenezi imaju lokalni čimbenici kao što su karijes, zubni kamenac i loša oralna higijena (28). Gingivalna hiperplazija i upalne promjene parodontnog tkiva znatno su izraženije kod bolesnika s lošijom oralnom higijenom. Proučavajući oralni status 73 oboljela od akutne mijeloične leukemije, Shankarapillai i suradnici ustanovili su da tri četvrtine njih od ukupnoga broja pregledanih ima nezadovoljavajuću oralnu higijenu (29). Dokazali su statistički značajan negativan utjecaj razine akumuliranoga plaka na razvoj parodontne bolesti i gingivalnih hiperplastičnih promjena kod bolesnika s leukemijom. Rezultati našeg istraživanja također su pokazali da ispitanici s kroničnom limfocitnom leukemijom imaju lošiju oralnu higijenu (API = 81 % ± 1,8 %) od onih iz kontrolne skupine (API = 69 % ±1,5 %), što se može povezati s lošijim parodontnim statusom ispitanika s KLL-om.

Specifični imunosni odgovor domaćina, orkestriran odgovarajućim antitijelima, ima važnu ulogu u prevenciji razvoja parodontne bakterijske infekcije. Schenck i suradnici dokazali su da visoke razine salivarnih IgA, čija je aktivnost usmjerena protiv bakterija u dentalnom plaku, mogu spriječiti razvoj gingivitisa (30). U sklopu preglednoga rada o imunosnim aspektima parodontne bolesti, obavljena je metaanaliza staničnog infiltrata parodontne lezije (31). Pokazalo se da plazmatske stanice čine 50 posto staničnoga infiltrata, B-limfociti 18 posto, a samo pet posto ukupnog staničnog infiltrata čine polimorfonukleari i makrofagi. Unutar parodontne lezije B-limfociti bili su zastupljeni u znatno većoj mjeri od T-limfocita, što upućuje na to da B-limfociti imaju važnu zadaću u patogenezi parodontitisa kao antigen prezentirajuće stanice. Nadalje, uočeno je da je broj plazmatskih stanica i B-limfocita znatno veći u lezijama uznapredovalog parodontitisa negoli u lezijama umjerenoga ili blagoga. Meyer i suradnici proveli su presječno istraživanje na trima grupama imunokompromitiranih bolesnika: uključili su 46 osoba sa sistemskim lupusom, 48 transplantiranih osoba i 53 s akutnom leukemijom (32). Autori su zabilježili veću prevalenciju oralnih manifestacija (uglavnom ulcerativnih i eritematoznih promjena) kod imunokompromitiranih bolesnika (50 %) u odnosu na zdrave ispitanike iz kontrolne skupine (26 %). Nije utvrđena statistički značajna veza između nađenih patoloških promjena i promatranih imunoloških parametara. Ipak, kod bolesnika s leukemijom utvrđene su statistički značajno veće vrijednosti parodontoloških indeksa nevezano za dob bolesnika, što se podudara s rezultatima našeg istraživanja. Druga presječna studija, koju su proveli Angst i suradnici, obuhvaćala je 37 ispitanika s različitim vrstama leukemije, a proučavala je utjecaj trombocitopenije na gingivalno krvarenje (33). Rezultati su pokazali da je utjecaj niske razine trombocita na gingivalno krvarenje bio vrlo slab, te da statistički nije bio značajan. No zaključili su da ovako mali uzorak ima nisku statističku snagu, te da je nužno provesti istraživanje na znatno većem uzorku ispitanika kako bi rezultati bili relevantniji. Zato su isti autori godinu dana poslije proveli novu presječnu studiju koja je obuhvaćala 68 oboljelih od leukemije

plastic gingival changes in 16 out of 72 patients with acute leukemia (27). Leukemic gingival infiltrates do not occur in edentulous patients, which suggest that an important role in their pathogenesis represent local factors such as tooth decay, dental calculus and poor oral hygiene (28). Gingival hyperplasia and inflammation of periodontal tissues are much more pronounced in patients with poor oral hygiene. Shankarapillai et al. examined 73 patients suffering from acute leukemia and they found that ¾ of examined patients have poor oral hygiene (29). They proved a statistically significant negative effect of the level of accumulated plaque on development of periodontal disease and gingival hyperplasia in patients with leukemia. Our findings also showed that patients with CLL have slightly weaker oral hygiene (API: 81%) compared to the control group (API: 69%), which can be related to worse periodontal status in patients with CLL.

Specific antibody response plays an important role in preventing infection and promotes recovery from periodontal diseases. Schenck et al. reported that high levels of salivary IgA directed against bacteria in dental plaque might protect against the development of gingivitis (30). In a review on aspects of adaptive host response in periodontitis, a meta-analysis was made with regard to the cell composition in periodontitis lesions (31). Plasma cells represent about 50% of cells, B cells about 18%, while PMN cells and macrophages represent less than 5% of all cells. The proportion of B cells in periodontal lesion is larger than that of all T cells, which implies that B cells serve as important antigen-presenting cells in periodontitis. In the review of literature, it was further observed that in both chronic and aggressive forms of periodontitis the proportions of plasma cells and B cells appear to be larger in lesions obtained from sites representing severe periodontitis than in lesions from areas with moderate or mild periodontitis. In a cross-sectional study, Meyer et al. evaluated three groups of immunocompromised patients: 46 patients with systemic lupus, 48 patients who underwent transplantation and 53 patients with acute leukemia (32). The authors observed a higher prevalence of oral manifestations (mostly ulcers and erythema) in immunocompromised patients (50%) compared to the controls (26%). No association between the periodontal parameters and laboratory data was observed. However, in agreement with the results of our research, statistically significant higher levels of periodontal indices were found in leukemic patients compared to controls, irrespective of the patient's age. Another cross-sectional study, conducted by Angst et al., included 37 patients with different types of leukemia in which authors studied the effect of thrombocytopenia on gingival bleeding (33). The results showed that the impact of low levels of platelets on gingival bleeding was very low and was not statistically significant. The authors concluded that the lack of correlation between periodontal inflammatory parameters and platelet count might be explained by the limited number of patients which may have been insufficient to express a real correlation. Therefore, a year later the same authors conducted a new cross-sectional study that included 68 patients with leukemia (34). The results were similar to those of the previous study and yet once again no statistically significant relationship

(34). Rezultati su bili slični onima iz prijašnje studije, te ni ovaj put nije dokazana statistički značajna veza između parodontoloških i hematoloških parametara. Analiza među grupama pokazala je veći gubitak kliničkoga pričvrstka kod bolesnika s kroničnim oblicima leukemije u odnosu na bolesnike s akutnim leukemijama, no autori su ovakav nalaz povezali s njihovom starijom životnom dobi, jer nije potvrđena veza promatranoga kliničkog parametra s njihovim hematološkim nalazom. Naše istraživanje dokazalo je da su oboljeli ispitanici imali značajno lošiji parodontni status od zdravih ispitanika iz kontrolne skupine i nakon uklanjanja utjecaja dobi, ali nije dokazana statistički značajna veza između parodontoloških i hematoloških parametara kod oboljelih od KLL-a.

Zaključak

Rezultati ovog istraživanja pokazali su da oboljeli od KLL-a imaju lošiji parodontni status od zdravih ispitanika iz kontrolne skupine. Poremećaji imunosnog sustava čine oboljele od KLL-a visokorizičnima kad je riječ o razvoju različitih oportunističkih infekcija, a postojeća parodontna infekcija kod njih je potencijalno bakterijsko žarište. Laine i suradnici dokazali su veću incidenciju febrilnih epizoda tijekom kemoterapijskih ciklusa kod bolesnika s neliječenim parodontitisom negoli kod bolesnika sa zdravim parodontom (35). Stoga bi svakako trebalo istaknuti važnost pravodobnoga parodontološkog zbrinjavanja bolesnika kod kojih se očekuje liječenje visokim dozama kemoterapeutika, kako bi se spriječile neželjene komplikacije i poboljšao ishod terapije. Iako su ispitanici s KLL-om imali lošiji parodontni status od onih iz kontrolne skupine, veza između njihovih parodontoloških i hematoloških nalaza nije dokazana. Razlog može biti premalen uzorak za istraživanje, pa bi trebalo obaviti daljnja ispitivanja na većem broju ispitanika.

Sukob interesa

Autori nisu ni u kakvom sukobu interesa.

between periodontal and hematological parameters had been proven. The analysis between the groups showed greater clinical attachment loss in patients with chronic forms of leukemia compared to those with acute leukemia. But the authors linked such finding with the age of these patients, since causal relationship between hematological parameters and clinical attachment loss was not confirmed. We found that CLL patients had a significantly worse periodontal status compared to control healthy participants, even after removing the impact of age, but there was no statistically significant association between periodontal and hematological parameters in CLL patients.

Conclusion

The results of this research showed that the patients with CLL had worse periodontal status compared to healthy subjects of the control group. Immune system disorders put CLL patients in higher risk for the development of various opportunistic infections and existing periodontal infection represents a potential bacterial focus. Laine et al. have shown a higher incidence of febrile episodes during chemotherapy cycles in patients with untreated periodontal disease compared to those with healthy periodontium (35). Therefore, the importance of timely periodontal care of patients in whom treatment with high doses of chemotherapeutic agents is expected must be emphasized in order to prevent unwanted complications and to improve the outcome of treatment. Although the patients with CLL had worse periodontal status compared to controls, a causal relationship between periodontal and hematological parameters was not proved. This may be due to small sample size on which the research was conducted; hence future research should include a larger number of patients in order to accomplish stronger statistical power.

Conflict of interest

The authors deny any conflicts of interest.

Abstract

Objective: To assess periodontal conditions in patients with early stage CLL and to compare it with the periodontal status of age matched healthy controls and to analyze the relationship between periodontal and hematological parameters in CLL patients. **Materials and Methods:** 60 subjects were examined: 30 patients with CLL Rai 0 (test group) and 30 age-matching healthy individuals (control group). The exclusion criteria were: presence of other systemic disease or condition (e.g. diabetes), history of treatment for periodontitis, use of antibiotics during the last 3 months, use of medications. Socio-demographic data were obtained by means of a questionnaire. Participants with at least 8 teeth underwent a full mouth examination assessing API, PBI, PPD, REC and CAL. Medical data for CLL patients were collected from the patients' records, while hematological data were obtained from the hemogram. **Results:** Difference between groups was statistically significant for age, number of teeth and frequency of dental checkups ($p<0.05$). Patients with CLL had significantly higher average values of periodontal indices (API 0.81±0.18; PBI 2.72±0.68; PPD 3.40±0.53; REC 1.95±0.87, CAL 4.37±0.80) compared to the control group (API 0.69±0.15; PBI 1.91±0.45; PPD 2.51±0.40; REC 0.99±0.54; CAL 3.00±0.58). The correlation coefficients between age and periodontal indices showed statistically significance between age and REC ($r=0.357$; $p<0.01$), and age and CAL ($r=0.295$; $p<0.05$). Age was not statistically significant covariate for CAL ($F=2.205$; $p>0.05$), only for REC ($F=4.601$; $p<0.05$). After the removal of the statistical effect of age, the difference in REC between CLL and control group remained statistically significant ($F=19.732$; $p<0.01$; $eta^2=0.287$). Statistically significant association between periodontal and hematological parameters in CLL patients was not found ($p>0.05$). **Conclusion:** The results of this study showed that patients with CLL had worse periodontal status compared to healthy subjects. Causal relationship between periodontal and hematological parameters was not proved.

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