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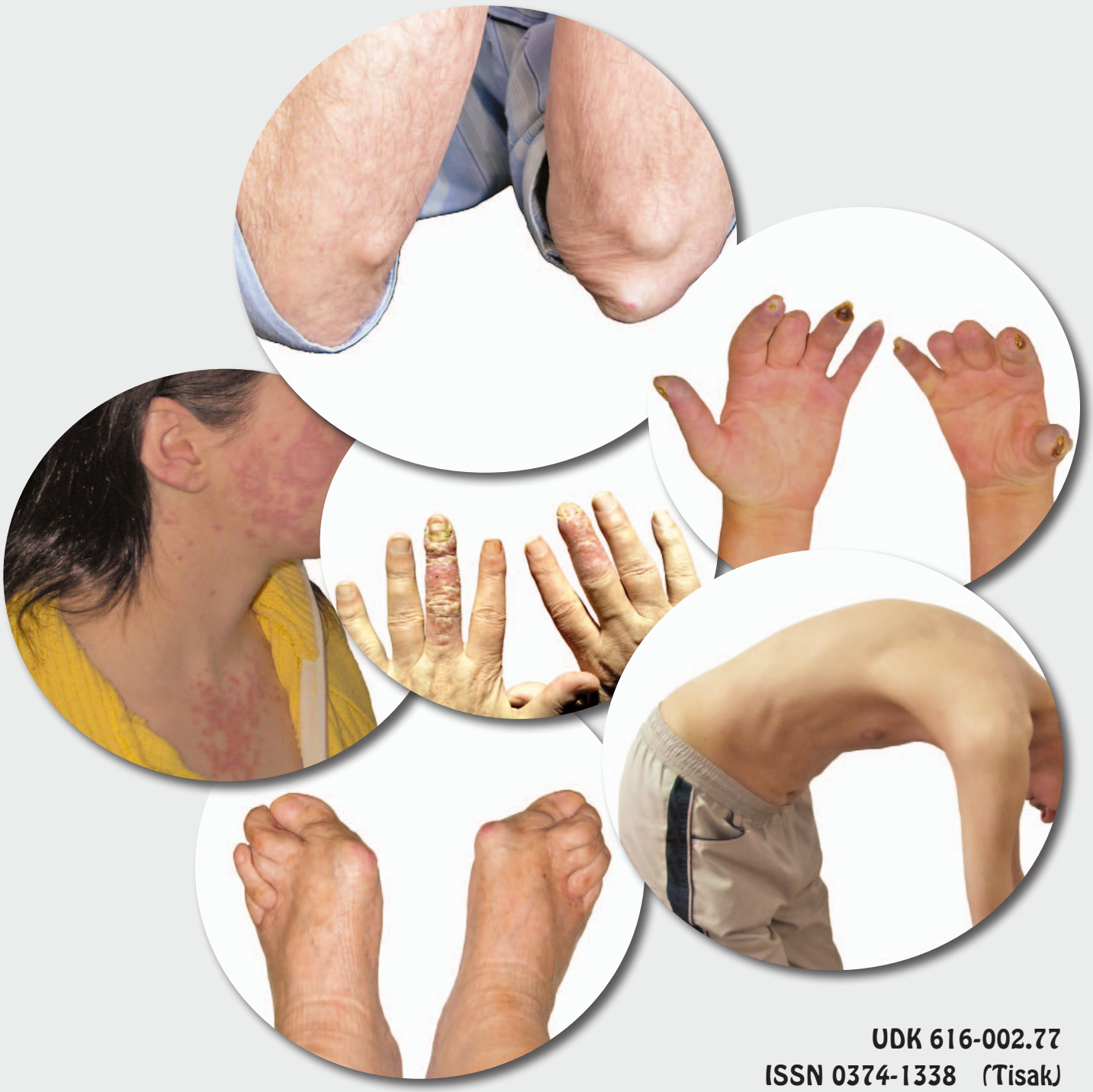

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Reumatizam objavljuje uvodnike, znanstvene radove, stručne radove, kratka priopćenja, pregledne radove, prethodna izvješća i prikaze bolesnika. Časopis obavještava reumatologe o novostima u kliničkom i nekliničkom djelokrugu rada.

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ORIGINAL SCIENTIFIC ARTICLE ORIGINALNI ZNANSTVENI RAD

CORRELATION OF CLINICAL AND HISTOPATHOLOGICAL FINDINGS IN PATIENTS WITH CLINICALLY SUSPECTED PRIMARY SJÖGREN SYNDROME

POVEZANOST KLINIČKIH I PATOHISTOLOŠKIH NALAZA U BOLESNIKA SA SUSPEKTNIM PRIMARNIM SJÖGRENOVIM SINDROMOM

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Abstract

Introduction. Association of clinical and diagnostic findings is important in making correct diagnosis in patients with primary Sjogren's syndrome. The aim of this study was to evaluate the correlation of minor salivary gland biopsy, serological findings and sialometry, as components used to classify primary Sjögren's syndrome. *Materials and methods.* Thirty-six patients with subjective symptoms of possible primary Sjögren's syndrome underwent minor salivary gland biopsy and sialometry. Clinical and laboratory data were retrieved from the clinical files. We compared and correlated biopsy results, serological findings and salivary flow rate between Sjögren and non-Sjögren patients. Patients were classified into two groups, twenty-eight cases (77.8%) had a diagnosis of primary Sjögren's syndrome and eight cases (22.2%) did not fulfill the classification criteria for diagnosis. *Results.* Primary Sjögren's syndrome diagnosis strongly correlated with "positive" biopsy (rho= 0.93, p<0.001), serological findings (rho= 0.38, p=0.023) and negatively correlated with saliva flow rate (rho= –0.51, p=0.002). "Positive" biopsy results were in negative correlation with saliva flow rate (rho= –0.41, p=0.012), but in a stronger correlation with patients below the diagnostic flow rate cutoff (≤0.1 ml/minute, rho= 0.46, p=0.005). *Conclusion.* In conclusion, unstimulated whole salivary flow rate ≤0.1 ml/minute is highly predictive of "positive" biopsy and can be used as a supplemental method to biopsy in diagnosing the oral component of primary Sjögren's syndrome.

Key words: Sjögren's syndrome; Sialometry; Salivary; Gland; Biopsy; Classification

Sažetak

Uvod. Povezanost kliničkih i dijagnostičkih nalaza važna je u postavljanju točne dijagnoze primarnoga Sjögrenovog sindroma. Cilj ovog istraživanja bio je procijeniti korelaciju nalaza biopsije malih žlijezda slinovnica, seroloških nalaza i sijalometrije kao klasifikacijskih kriterija za dijagnozu primarnoga Sjögrenovog sindroma. *Materijali i metode.* U ovu studiju bilo je uključeno 36 pacijenata sa subjektivnim simptomima koji odgovaraju primarnom Sjögrenovom sindromu. Svim bolesnicima učinjena je biopsija malih žlijezda slinovnica i sijalometrija. Iz medicinske dokumentacije prikupljeni su klinički i laboratorijski podatci. Uspoređeni su rezultati biopsije, seroloških nalaza i brzine izlučivanja

sline u pacijenata sa Sjögrenovim sindromom i pacijenata koji ne ispunjavaju klasifikacijske kriterije za Sjögrenov sindrom. Bolesnici su razvrstani u dvije skupine; njih 28 (77,8 %) je ispunjavalo klasifikacijske kriterije za dijagnozu primarnoga Sjögrenovog sindroma, a osam (22,2 %) ih nije ispunjavalo klasifikacijske kriterije za dijagnozu. *Rezultati.* Rezultati analize pokazali su pozitivnu korelaciju dijagnoze primarnoga Sjögrenovog sindroma i „pozitivne" biopsije (rho = 0,93, p < 0,001) i seroloških nalaza (rho = 0,38, p = 0,023) te negativnu korelaciju s brzinom izlučivanja sline (rho = –0,41, p = 0,012). Rezultati „pozitivne" biopsije bili su u negativnoj korelaciji s brzinom izlučivanja sline (rho = –0,41, p = 0,012) dok je jača korelacija utvrđena kod pacijenata s nalazom ispod dijagnostičke razine brzine izlučivanja (≤ 0,1 ml/min, rho = 0,46, p = 0,005). *Zaključak.* Zaključno, nestimulirana brzina izlučivanja sline ≤ 0,1 ml/min objektivizirana sijalometrijom snažan je prediktor „pozitivne" biopsije te se može upotrebljavati kao dodatna metoda uz biopsiju u dijagnostici oralne komponente primarnoga Sjögrenovog sindroma.

Ključne riječi: Sjögrenov sindrom; Sijalometrija; Biopsija; Žlijezda; Slinovnica; Klasifikacija

INTRODUCTION

Primary Sjögren's syndrome (pSS) is a chronic, lymphoproliferative, autoimmune disease affecting exocrine glands. The main features of the disease are dry mouth (xerostomia) and dry eyes (xerophthalmia) resulting from immune-mediated damage and dysfunction of the salivary and lacrimal glands (1, 2). The disease can be of varying intensity, from milder forms involving oral and ocular dryness, fatigue and pain, to more severe systemic conditions affecting multiple organs (3). Patients are at increased risk of developing lymphoma, particularly non-Hodgkin's lymphoma, compared with the general population (4). Thus, the appropiate and timely diagnosis is important due to clinical follow-up of the possible complications.

The disease occures in all age groups; however it mainly affects women, at ratio of 9:1 (5). The diagnosis of pSS commonly requires a multidisciplinary approach, including rheumatologists, oral medicine specialists, ophthalmologists and it relies on interpreting and integrating all aspects of the patient's medical history, clinical and laboratory testing and clinical experience of the physician (6, 7). The optimal management of pSS is not yet clear and the current treatments are mainly symptomatic.

The development of classification criteria for use in clinical practice as well as studies have occupied the scientific literature for many decades. Misdiagnosis of pSS is common and numerous studies have shown great variation in the frequency of pSS. Approximately half of all patients are thought to be undiagnosed (8). That makes it one of the least understood inflammatory diseases in current clinical practice. Although various classification criteria for pSS have been proposed, a revised version of the European criteria proposed by the American-European Consensus Group (AECG) has been the most widely used classification set (9). The revised version includes six criteria, four of the six criteria are necessary to confirm the diagnosis of pSS, among which should be either a „positive" histopathological finding or the presence of autoantibodies (anti-SSA and/or anti-SSB) (10). In daily clinical practice,

UVOD

Primarni Sjögrenov sindrom (pSS) kronična je, limfoproliferativna, autoimuna bolest koja zahvaća egzokrine žlijezde. Glavne su značajke ove bolesti suhoća usne šupljine (kserostomija) i očiju (kserofralmija) koje su posljedica imunološki posredovanog oštećenja i disfunkcije žlijezda slinovnica i suznih žlijezda (1, 2). Bolest može biti različitog intenziteta, od blažih oblika koji uključuju suhoću usne šupljine i očiju, umor i bol do težih oblika sistemskih bolesti koje zahvaćaju više organa (3). U usporedbi s općom populacijom, osobe koje boluju od primarnoga Sjögrenovog sindroma imaju povećan rizik od razvoja limfoma, osobito ne-Hodgkinovog limfoma (4). Stoga je odgovarajuća i pravovremena dijagnoza bitna zbog kliničkog praćenja bolesnika u slučaju razvoja mogućih komplikacija.

Ova bolest zahvaća sve dobne skupine, no češće se javlja u žena i to u omjeru 9:1 (5). Dijagnoza primarnoga Sjögrenovog sindroma (pSS) obično zahtijeva multidisciplinarni pristup koji uključuje više različitih stručnjaka, poput reumatologa, specijalista oralne medicine, oftalmologa i oslanja se na tumačenje i integraciju svih aspekata bolesnikove povijesti bolesti, kliničkih i laboratorijskih ispitivanja te kliničkog iskustva liječnika (6, 7). Optimalna metoda liječenja primarnoga Sjögrenovog sindroma (pSS) još uvijek nije jasno definirana, a terapije koje se danas upotrebljavaju uglavnom su simptomatske.

Razvoj klasifikacijskih kriterija te istraživanja za primjenu u kliničkoj praksi teme su koje se u znanstvenoj literaturi obrađuju već desetljećima. Pogrešna dijagnoza primarnoga Sjögrenovog sindroma (pSS) uobičajena je, a brojna istraživanja pokazala su i izrazita odstupanja u učestalosti pojave pSS-a. Smatra se da u otprilike 50% slučajeva bolest ostaje nedijagnosticirana (8). To je čini jednom od upalnih bolesti koje najmanje razumijemo u današnjoj kliničkoj praksi. Iako su predloženi različiti klasifikacijski kriteriji za pSS, najviše se upotrebljava klasifikacija utvrđena u revidiranoj verziji europskih kriterija koje je predložila organizacija *American-European Consensus Group* (AECG) (9). U revidiranoj verziji navodi se šest kriterija. Četiri od tih šest

the only reliable „gold" standard for the diagnosis of pSS is the clinical judgement of an experienced physician confirmed with objective complementary tests.

Minor salivary gland biopsy (MSGB) is widely accepted and currently remains the best method for diagnosing the salivary gland damage (11), but it is not a *sine qua non* criterion for diagnosis of pSS. Histopathological finding of lymphocytic sialoadenitis is highly informative, but represents an invasive diagnostic method. Focal lymphocytic infiltrates of minor labial salivary glands are considered target-organ specific for pSS, but it may also be present in other autoimune diseases as well as in aquired immunodeficiency syndrome (AIDS) (12, 13, 14). External factors such as smoking and medications have also been suggested to influence the focal lymphocytic infiltrates (15).

The anti-SSA and/or anti-SSB autoantibodies are considered typical among pSS patients. Depending on different laboratory methods, anti-SSA and/or anti-SSB autoantibodies are detected in about 50% to 70% of patients with pSS (16). It is well known that negative serology results occur in 10% to 50% of patients with pSS and correlate with a milder form of the disease (17). The presence of autoantibodies (anti-SSA and/or anti-SSB) have been included in all classifications and usually precede MSGB on routine pSS diagnosis.

The approach to the definition of glandular involvement in pSS is constantly evolving, but in daily practice, clinicians tend to use less invasive diagnostic methods. Thus having access to less invasive but sensitive confirmatory tests that complement existing immunological and/or histopathological findings would be a great advantage. The objective assessment of oral and ocular dryness could be one of such complementary tests. Current literature suggests good agreement between ocular component and pSS, but the previous results regarding xerostomia are inconclusive and possibly confusing. Evaluation of xerostomia in patients with clinically suspected pSS is a diagnostic challenge. Sialometry results can vary considerably because xerostomia can be a side effect of numerous medications (antidepressants, antihistamines, diuretics, etc.) or previous treatment (e.g., radiotherapy of the head and neck) (18).

Sialometry is widely applied in diagnosing xerostomia. Several methods for collecting saliva have been reported. Salivary flow measurement is simple and quick diagnostic method, needs no special equipment and was shown to have good reproducibility. Sialometry has a sensitivity (56.1%) and specificity (80.7%) that is lower than the sensitivity (84.4%) and specificity (86.2%) of MSGB (19); however, sialometry, unlike MSGB, is completely uninvasive diagnostic method. Unstimulated whole saliva (UWS) flow rate ≤0.1 ml/

potrebno je za potvrdu dijagnoze pSS-a, a moraju uključivati pozitivan patohistološki nalaz ili prisutnost autoantitijela (anti-SS-A i/ili anti-SS-B) (10). U svakodnevnoj kliničkoj praksi jedinim pouzdanim „zlatnim" standardom za dijagnozu pSS-a smatra se klinička prosudba iskusnog liječnika potvrđena objektivnim komplementarnim ispitivanjima.

Biopsija malih žlijezda slinovnica (engl. *minor salivary gland biopsy*, *MSGB*) široko je prihvaćena i trenutačno najbolja metoda za dijagnozu oštećenja žlijezda slinovnica, ali nije *condicio sine qua non* za dijagnozu pSS-a. Patohistološki nalaz limfocitnog sijaloadenitisa pruža mnogo informacija, ali predstavlja invazivnu dijagnostičku metodu. Fokalni infiltrati limfocita malih labijalnih žlijezda slinovnica smatraju se ciljnim organom specifičnim za pSS, ali mogu biti prisutni i kod drugih autoimunih bolesti, kao i kod sindroma stečene imunodeficijencije (AIDS) (12, 13, 14). Također se smatra da vanjski čimbenici poput pušenja i uzimanja lijekova utječu na fokalne infiltrate limfocita (15).

Anti-SS-A i/ili anti-SS-B autoantitijela tipična su za bolesnike koji boluju od pSS-a. Ovisno o različitim laboratorijskim metodama, anti-SS-A i/ili anti-SS-B autoantitijela otkrivaju se u otprilike 50 – 70% bolesnika koji boluju od pSS-a (16). Poznato je da se negativni serološki rezultati javljaju u 10 – 50% bolesnika koji boluju od pSS-a te da su u korelaciji s blažim oblikom bolesti (17). Pretrage za utvrđivanje prisutnosti autoantitijela (anti-SS-A i/ili anti-SS-B) uključene su u sve klasifikacije i obično se izvode prije biopsije malih žlijezda slinovnica u rutinskoj dijagnostici pSS-a.

Pristup definiciji zahvaćenosti žlijezda u pSS-u stalno se razvija, ali u svakodnevnoj praksi kliničari su više skloni upotrebljavati manje invazivne dijagnostičke metode. Stoga bi pristup manje invazivnim, ali osjetljivim potvrdnim ispitivanjima koja bi se obavljala kao komplementarna uz postojeće imunološke i/ili patohistološke nalaze bio jako koristan. Objektivna procjena suhoće usne šupljine i očiju mogla bi biti jedno od takvih komplementarnih ispitivanja. U novijoj literaturi ističe se povezanost između očne komponente i pojave pSS-a, ali raniji rezultati u vezi s kserostomijom nepotpuni su i zbunjujući. Procjena kserostomije u bolesnika sa suspektnim pSS-om postupak je koji predstavlja pravi dijagnostički izazov. Rezultati sijalometrije mogu pokazivati značajna odstupanja jer kserostomija može biti nuspojava uzimanja brojnih lijekova (antidepresivi, antihistaminici, diuretici itd.) ili prethodnih terapija (npr. radioterapija glave i vrata) (18).

Sijalometrija se u velikoj mjeri primjenjuje u dijagnostici kserostomije. U literaturi se navode razne metode za prikupljanje sline. Mjerenje izlučivanja sline jednostavna je i brza dijagnostička metoda koja ne zahtijeva uporabu posebne opreme i za koju je dokazano da ima dobru ponovljivost. Osjetljivost (56,1%) i

minute is one of the classification criteria for the diagnosis of pSS (10, 20, 21).

In the study by Liquidato *et al.*, authors concluded that both isolated MSGB and sialometry can be used in screening patients with clinically suspected pSS because those diagnostic methods have shown no difference in sensitivity. If there are limitations in the classification of patients, the combination of a „positive" histopathological finding and sialometry increases the chance of making a correct diagnosis (22).

The main objective of our study was to retrospectively evaluate correlation between MSGB, serological findings and sialometry in patients with clinically suspected pSS.

SUBJECTS AND METHODS

This is a retrospective study involving patients with subjective complaint of oral and ocular dryness who were examined at the Department of Internal Medicine, Clinical Hospital Centre „Sestre milosrdnice", Zagreb in a period of three years. Clinical oral examination with appropriate diagnostic tests was performed at the Department of Oral Medicine, School of Dental Medicine, University of Zagreb and classification was made based on revised AECG criteria (10). The symptoms of ocular and/or oral dryness or various extraglandular symptoms were the initial reason for specialist consultation and raised suspicion of pSS.

The study was conducted after approval by the Ethics Committee of the Clinical Hospital Centre „Sestre milosrednice" regarding the retrospective collection of data. After signing the informed consent, the patients were included in the study. The study was performed in accordance with the World Medical Association, Declaration of Helsinki (23).

The diagnosis of pSS was made by experienced rheumatologists in collaboration with oral medicine specialists and ophthalmologists. Patients were classified into two groups, pSS group and non-pSS group. Primary Sjögren's syndrome was diagnosed based on revised AECG classification criteria, considering the results of the 6-item screening questionnaire for oral and ocular dryness, ocular test (Schirmer's test), measurement of timed UWS flow rate, MSGB, presence of autoantibodies (anti-SSA and/or anti-SSB), and expert clinical judgement (10). Non-pSS group included patients who have not been diagnosed with pSS because they were not fulfilling the revised AECG diagnostic criteria. Only patients who underwent MSGB were included in the study after signing informed consent.

Exclusion criteria were: non signing informed consent; patients with radiation-induced xerostomia, sarcoidosis-associated xerostomia, current use of anticholinergic drugs; patients with history of secondary SS,

specifičnost (80,7%) sijalometrije niže su od osjetljivosti (84,4%) i specifičnosti (86,2%) biopsije malih žlijezda slinovnica (19), no, za razliku od biopsije malih žlijezda slinovnica, sijalometrija je u potpunosti neinvazivna dijagnostička metoda. Nestimulirana brzina izlučivanja sline ≤ 0,1 ml/min jedan je od klasifikacijskih kriterija za dijagnozu pSS-a (10, 20, 21).

U istraživanju koje su proveli Liquidato i sur. autori su zaključili da se i izolirana biopsija malih žlijezda slinovnica i sijalometrija mogu upotrebljavati u probiru bolesnika sa suspektnim pSS-om jer te dijagnostičke metode nisu pokazale razliku u osjetljivosti. Ako postoje ograničenja u klasifikaciji bolesnika, kombinacija „pozitivnoga" patohistološkog nalaza i sijalometrije povećava vjerojatnost za postavljanje točne dijagnoze (22).

Glavni cilj našeg istraživanja bio je retrospektivno procijeniti korelaciju između biopsije malih žlijezda slinovnica, seroloških nalaza i sijalometrije u bolesnika sa suspektnim pSS-om.

ISPITANICI I METODE

Ovo je retrospektivna studija koja uključuje bolesnike sa subjektivnim pritužbama na suhoću usne šupljine i očiju koji su tijekom razdoblja od tri godine bili pregledani u Klinici za unutarnje bolesti KBC-a Sestre milosrdnice u Zagrebu. Klinički pregled usne šupljine s odgovarajućim dijagnostičkim pretragama obavljen je na Zavodu za oralnu medicinu Stomatološkog fakulteta Sveučilišta u Zagrebu, a klasifikacija je izvršena na temelju revidiranih AECG kriterija (10). Simptomi suhoće usne šupljine i/ili očiju ili razni ekstraglandularni simptomi bili su primarni razlog za savjetovanje sa specijalistom te su upravo oni izazvali sumnju na pSS.

Studija je provedena nakon odobrenja Etičkog povjerenstva KBC-a Sestre milosrdnice u pogledu retrospektivnog prikupljanja podataka. Nakon potpisivanja informiranog pristanka bolesnici su uključeni u istraživanje. Studija je provedena u skladu s Helsinškom deklaracijom Svjetskoga liječničkog udruženja (23).

Dijagnozu pSS-a postavili su iskusni reumatolozi u suradnji sa specijalistima oralne medicine i oftalmolozima. Bolesnici su razvrstani u dvije skupine: pSS skupinu i ne-pSS skupinu. Primarni Sjögrenov sindrom dijagnosticiran je na temelju revidiranih AECG klasifikacijskih kriterija, uzimajući u obzir rezultate probirnog upitnika od 6 stavki koji je uključivao suhoću usne šupljine i očiju, test suhog oka (Schirmerov test), mjerenje brzine izlučivanja sline (UWS), biopsiju malih žlijezda slinovnica (MSGB), prisutnost autoantitijela (anti-SS-A i/ili anti-SS-B) te kliničku procjenu stručnjaka (10). U ne-pSS skupinu svrstani su bolesnici kojima nije dijagnosticiran pSS jer nisu ispunjavali revidirane AECG dijagnostičke kriterije. U studiju su bili uključeni samo bolesnici kojima je učinjena biopsija

hepatitis C virus (HCV) infection, human immunodeficiency virus (HIV) infection, pre-existing lymphoma, graft-versus-host disease (GvHD); patients without clinical, laboratory and histopathological findings.

The results of clinical, laboratory and histopathological findings were stored in medical files. The data collected included age, gender, family history, body mass index (BMI), subjective symptoms of xerostomia and xerophthalmia, ocular tests, cerebrovascular risk factors (hypertension, *diabetes mellitus* (DM), smoking, hyperlipidemia), as well as history of other comorbidities. The time (in months) from the initial onset of symptoms to the diagnosis of pSS was also recorded as well as information of previous or current use of immunosuppressants before the MSGB.

Clinical oral examination included measurement of UWS flow rate according to a sialometry protocol (20, 24). Patients were asked to refrain from eating, drinking, smoking and brushing their teeth for at least two hours prior to saliva sampling. Saliva was collected in graduated tubes for five minutes using the spitting method. The UWS flow rate ≤0.1 ml/minute indicated reduced secretion of salivary glands (10, 20, 21).

Minor salivary gland biopsy was performed from the inner surface of the lower lip mucosa under local anesthesia at the Department of Oral Medicine, School of Dental Medicine, University of Zagreb. Histopathological analysis of MSGB was performed at the Department of Pathology and Cytology, University Hospital Centre Zagreb. A "positive" biopsy finding is a classification criteria that highly indicates pSS and refers to the presence of focal lymphocytic sialoadenitis with a focus score ≥1 at 4 mm^2 of glandular tissue (1 focus is a cluster of 50 CD4 + cells) (25).

We also used EULAR Sjögren's Syndrome Patient Reported Index (ESSPRI) to measure perception of patients' symptoms (26). It is a very simple questionnaire to assess disease symptoms and activity on a 10-point scale for pain, fatigue and dryness. The scores from three questions are added together, resulting in a total score that varies from 3 (very mild symptoms) to 30 (maximum symptoms). With good construct validity, it is used as an outcome measure in clinical trials (27).

Statistical analysis was performed using MedCalc version 11.4 software. The normal distribution of continuous variables was assessed by the Kolomogrov-Smirnov test. The continuous variables are expressed as mean ± standard deviation (SD) or median (interquartile range) as appropriate. Categorical variables are expressed as a number (%). Student's t-test was used to compare mean values between groups where the distribution was normal. Mann-Whitney nonparametric test was used when the distribution of values was not normal. The significance level (P value) for all analyses was defined as P <.05. The correlation be-

malih žlijezda slinovnica i to nakon potpisivanja informiranog pristanka.

Kriteriji isključenja bili su: nepotpisivanje informiranog pristanka; bolesnici koji boluju od kserostomije uzrokovane zračenjem, kserostomije povezane sa sarkoidozom, koji trenutačno uzimaju antikolinergike, bolesnici koji u anamnezi imaju sekundarni Sjögrenov sindrom, infekciju virusom hepatitisa C (HCV), infekciju virusom humane imunodeficijencije (HIV), bolesnici s već postojećim limfomom, oni koji imaju bolest presatka protiv primatelja (GvHD) te bolesnici bez kliničkih, laboratorijskih i patohistoloških nalaza.

Rezultati kliničkih, laboratorijskih i patohistoloških nalaza pohranjeni su u medicinskoj dokumentaciji. Prikupljeni podatci uključivali su dob, spol, obiteljsku anamnezu, indeks tjelesne mase (BMI), subjektivne simptome kserostomije i kseroftalmije, očne pretrage, rizične čimbenike cerebrovaskularne bolesti (hipertenzija, *diabetes mellitus* (DM), pušenje, hiperlipidemija) te anamnezu drugih komorbiditeta. Također je zabilježeno vrijeme (u mjesecima) od početne pojave simptoma do dijagnoze pSS-a, kao i informacije o prethodnoj ili trenutačnoj primjeni imunosupresiva prije biopsije malih žlijezda slinovnica.

Klinički pregled usne šupljine uključivao je mjerenje brzine izlučivanja sline (UWS) u skladu s protokolom sijalometrije (20, 24). Bolesnici su zamoljeni da se suzdrže od jela, pića, pušenja i pranja zubi najmanje dva sata prije uzimanja uzorka sline. Slina je sakupljena metodom pljuvanja u graduirane epruvete tijekom razdoblja od pet minuta. Brzina izlučivanja sline ≤ 0,1 ml/min ukazuje na smanjeno lučenje žlijezda slinovnica (10, 20, 21).

Biopsija malih žlijezda slinovnica izvedena je s unutarnje strane sluznice donje usne, u lokalnoj anesteziji, na Zavodu za oralnu medicinu Stomatološkog fakulteta Sveučilišta u Zagrebu. Patohistološka analiza biopsije malih žlijezda slinovnica provedena je na Kliničkom zavodu za patologiju i citologiju KBC-a Zagreb. Rezultat „pozitivne" biopsije klasifikacijski je kriterij koji s velikom točnošću ukazuje na pSS i odnosi se na prisutnost fokalnoga limfocitnog sijaloadenitisa s brojem fokusa ≥ 1 na 4 mm^2 žljezdanog tkiva (nakupina od 50 CD4 + stanica čini jedan fokus) (25).

Također smo upotrebljavali indeks subjektivnih bolesnikovih tegoba Europske lige protiv reumatizma (engl. *European League Against Rheumatism Sjögren's syndrome patient report index*, dalje u tekstu: ESSPRI) za mjerenje percepcije simptoma bolesti u bolesnika (26). To je vrlo jednostavan upitnik za procjenu simptoma bolesti i aktivnosti na skali od 1 do 10 prema kojoj bolesnici procjenjuju subjektivni osjećaj boli, umora i suhoće. Bodovi iz tri pitanja zbrajaju se te se time dobiva ukupan rezultat u rasponu od 3 (vrlo blagi simptomi) do 30 bodova (najteži simptomi). Zbog

tween clinical, serological and histological findings was analysed using Spearman correlation coefficient.

RESULTS

A total of 56 MSGB were performed at the Department of Oral Medicine, School of Dental Medicine, University of Zagreb. Of the initial number of patients, 36 patients (34 female and 2 male) were included in the study because they met the inclusion criteria. Twenty patients were excluded due to lack of clinical or/and laboratory findings or presence of other exclusion criteria.

The mean age of the patients was 53.4 years (ranging from 23 to 77 years) and 34 patients were female (94.4%). According to the revised AECG criteria, 36 patients were divided into two groups, a pSS group (n=28; male/female: 2/26) and a non-pSS group (n=8; male/female: 0/8). Patients in the non-pSS group had subjective oral and ocular dryness but did not meet the diagnostic criteria for pSS diagnosis because they had negative serology and/or histopathological findings that were not consistent with the revised AECG diagnostic criteria. Eighteen patients (64.3%) did not meet serological criteria for the diagnosis of pSS but met the histopathologic criteria. The demographic, clinical and laboratory characteristics of pSS and non-pSS patients are showed in Table 1.

The results showed that the two groups shared most of the features similarly. There are statistically significant differences between these two groups in BMI and obesity. Proportion of obese patients in the pSS group was higher than in the non-pSS group (71.4% *vs* 12.5%, p=0.005). There was a higher proportion of smokers in the pSS group (17.9% *vs* 0%, p=0.566), although it was not statistically signifficant. The time from onset of symptoms to diagnosis of pSS ranged from 1 to 84 months, with a mean of 36 months. Two (5.6%) of a total of 36 patients underwent immunosuppressive therapy prior to MSGB.

The perception of symptoms was similar among the groups according to the ESSPRI assessment (Table 2). It is very interesting to notice that the perception of pain measured by the ESSPRI questionnaire was statistically significant lower (p=0.041) in the pSS group than in the non-pSS group, but we must take into account the small number of patients included in interpreting the results. Studies with a larger number of patients are needed to make relevant conclusions.

Serological testing was performed in all 36 patients. At least one autoantibody (anti-SSA or anti-SSB) was positive in 14 patients (38.9%) (Table 1). The frequency of anti-SSA autoantibodies in the pSS group was statistically significant higher than in the non-pSS group (42.9% *vs* 0%, p=0.033), while the frequency of anti-

dobre konstruktivne valjanosti ovaj se upitnik upotrebljava za mjerenje rezultata u kliničkim ispitivanjima (27).

Statistička analiza provedena je pomoću softvera *MedCalc* (verzija 11.4). Normalna raspodjela kontinuiranih varijabli procijenjena je pomoću Kolomogrov-Smirnovljeva testa. Kontinuirane varijable izražene su kao srednja vrijednost ± standardna devijacija (SD) ili medijan (interkvartilni raspon, IQR) prema potrebi. Kategoričke varijable izražavaju se u brojčanom obliku (%). Studentov t-test upotrijebljen je za usporedbu srednjih vrijednosti između skupina u kojima je raspodjela bila normalna. Mann-Whitneyjev neparametrijski test upotrijebljen je u slučajevima u kojima raspodjela vrijednosti nije bila normalna. Razina značajnosti (p-vrijednost) definirana je kao p <,05 za sve analize. Povezanost kliničkih, seroloških i histoloških nalaza analizirana je s pomoću Spearmanovog koeficijenta korelacije.

REZULTATI

Na Zavodu za oralnu medicinu Stomatološkog fakulteta Sveučilišta u Zagrebu provedeno je ukupno 56 biopsija malih žlijezda slinovnica. Od početnog broja bolesnika u istraživanje je uključeno njih 36 (34 žene i 2 muškarca) koji su zadovoljili kriterije uključenja. Dvadeset bolesnika isključeno je zbog nedostatka kliničkih i/ili laboratorijskih nalaza ili prisutnosti drugih kriterija isključenja.

Prosječna dob bolesnika bila je 53,4 godine (u rasponu od 23 do 77 godina), a od ukupnog broja bolesnika njih 34 bilo je ženskog spola (94,4 %). Prema revidiranim AECG kriterijima, 36 bolesnika podijeljeno je u dvije skupine, pSS skupinu (n = 28; broj muškaraca / broj žena: 2/26) i ne-pSS skupinu (n = 8, broj muškaraca / broj žena: 0/8). Bolesnici u ne-pSS skupini imali su simptom subjektivne suhoće usne šupljine i očiju, ali nisu ispunjavali dijagnostičke kriterije za dijagnozu pSS-a jer su imali negativne serološke i/ili patohistološke nalaze koji nisu bili u skladu s revidiranim AECG dijagnostičkim kriterijima. Osamnaest bolesnika (64,3%) nije zadovoljilo serološke kriterije za dijagnozu pSS-a, ali je zadovoljilo patohistološke kriterije. Demografske, kliničke i laboratorijske karakteristike bolesnika koji boluju od pSS-a i bolesnika koji ne boluju od pSS-a prikazane su u tablici 1.

Rezultati su pokazali da obje skupine imaju većinu sličnih karakteristika. Između ove dvije skupine postoje statistički značajne razlike u indeksu tjelesne mase i pretilosti. Udio pretilih bolesnika u pSS skupini bio je veći nego u ne-pSS skupini (71,4% prema 12,5%, p = 0,005). Skupina pSS imala je veći udio pušača (17,9% prema 0%, p = 0,066), iako taj broj nije bio statistički značajan. Vremensko razdoblje od pojave simptoma

Table 1. Demographic, clinical and laboratory characteristics of pSS group according to the revised AECG criteria
Tablica 1. Demografske, kliničke i laboratorijske karakteristike pSS skupine prema revidiranim AECG kriterijima

Variable / Varijabla	Patients with pSS (n=28) / Bolesnici koji boluju od pSS-a (n = 28)	Non-pSS patients (n=8) / Bolesnici koji ne boluju od pSS-a (n =28)	p value* / p-vrijednost*
Age, mean (SD) / Dob, srednja vrijednost (SD)	63.9 (13.0)	67.5 (10.0)	0.472
Age at diagnosis, mean (SD) / Dob pri postavljanju dijagnoze, srednja vrijednost (SD)	52.3 (12.6)	57.6 (11.4)	0.285
Gender – Female / Spol – ženski	26 (92.9%)	8 (100%)	1
Immunotherapy / Imunoterapija	7 (25%)	1 (12.5%)	0.651
History of cardiovascular diseases / Bolesnici koji u anamnezi imaju kardiovaskularne bolesti	17 (60.7%)	3 (37.5%)	0.422
Smoking / Pušenje	5 (17.9%)	0 (0.0%)	0.566
Exercise / Fizička aktivnost	10 (35.7%)	2 (25.0%)	0.691
BMI, mean (SD) / Indeks tjelesne mase (BMI), srednja vrijednost (SD)	26.5 (4.1)	23.4 (2.0)	**0.006**
Overweight / Pretilost	20 (71.4%)	1 (12.5%)	**0.005**
Hyperlipidemia / Hiperlipidemija	9 (32.1%)	3 (37.5%)	1
Diabetes mellitus	11 (39.3%)	2 (25.0%)	0.682
Hypertension / Hipertenzija	13 (46.4%)	6 (75.0%)	0.236
"positive" MSGB / „Pozitivna" biopsija malih žlijezda slinovnica	27 (96.4%)	0 (0.0%)	< **0.001**
anti-SSA / anti-SS-A	12 (42.9%)	0 (0.0%)	**0.033**
anti-SSB / anti-SS-B	10 (35.7%)	2 (25.0%)	0.691
Either anti-SSA or SSB / Anti SS-A ili anti-SS-B	12 (42.9%)	2 (25.0%)	0.441
Saliva flow, median (IQR) / Brzina izlučivanja sline, medijan (IQR)	0.1 (0.04 – 0.2)	0.48 (0.3 – 0.6)	**0.003**
Low saliva flow / Niska brzina izlučivanja sline	21 (75.0%)	1 (12.5%)	**0.003**

Legend / Legenda: pSS – primary Sjögren's syndrome / primarni Sjögrenov sindrom; AECG: American-European Consensus Group
** Fischer's exact test and t-test were used, significant differences indicated in bold / Upotrebljavani su Fisherov test i t-test, značajne razlike označene su podebljanim slovima*

SSB autoantibodies was similar in both groups (35.7% *vs* 25.0%, p=0.69).

Mann–Whitney test showed that UWS flow rate was statistically significant lower in pSS group (mean UWS flow rate 0.148 +/– 0.147 *vs* 0.463 +/– 0.259 ml/minute, p=0.003). Unstimulated whole salivary flow rate is an objective diagnostic test to assess the involvement of the salivary glands. It was performed in all patients (n=36). The results of 22 (61.1%) patients showed hyposalivation according to the revised AECG diagnostic criteria for diagnosing pSS (abnormal UWS flow rate ≤ 0.1 ml/ minute) (Table 1). In the pSS group, 75% of patients had low UWS flow rate (*vs* 12.5% in non-pSS group). The results of UWS flow rates are presented in Figure 1. The difference is statistically significant (Mann–Whitney test p=0.003).

The correlation between histopathological and serological findings, salivary gland involvement and clinical features were assessed by Spearman rank correlation. As expected, pSS diagnosis strongly correlated

do dijagnoze pSS-a bilo je u rasponu od 1 do 84 mjeseca, a u prosjeku je iznosilo 36 mjeseci. Dva (5,6%) od ukupno 36 bolesnika uzimala su imunosupresivnu terapiju prije biopsije malih žlijezda slinovnica.

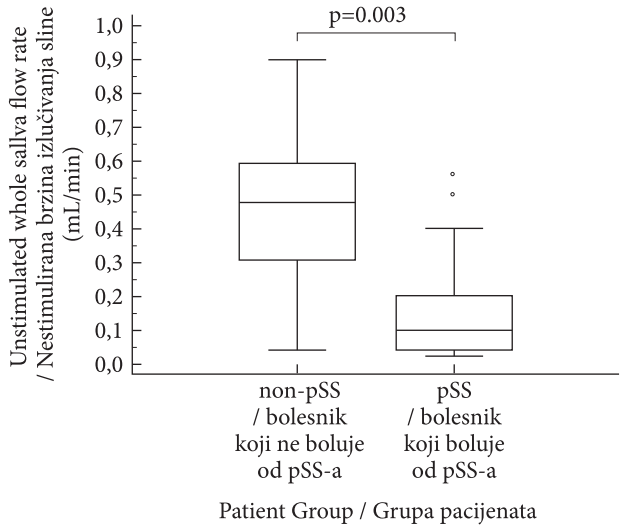
Prema ESSPRI upitniku za procjenu, percepcija simptoma bolesti u obje skupine bila je slična (tablica 2). Zanimljivo je da je percepcija boli mjerena ESSPRI upitnikom statistički značajno niža (p = 0,041) u pSS skupini nego u ne-pSS skupini, ali moramo uzeti u obzir mali broj bolesnika uključenih u tumačenje rezultata. Za donošenje relevantnih zaključaka potrebno je provesti studije s većim brojem bolesnika.

Svih 36 bolesnika podvrgnuto je serološkim ispitivanjima. Najmanje jedno autoantitijelo (anti-SS-A ili anti-SS-B) bilo je pozitivno kod 14 bolesnika (38,9%) (tablica 1). Učestalost anti-SS-A autoantitijela u pSS skupini bila je statistički značajno veća nego u ne-pSS skupini (42,9% prema 0%, p = 0,033), dok je učestalost anti-SS-B autoantitijela bila slična u obje skupine (35,7% prema 25,0%, p = 0,69).

Table 2. Results of ESSPRI measurements in the pSS and non-pSS groups.
Tablica 2. Rezultati ESSPRI mjerenja u pSS i ne-pSS skupini

Self-reported measure / Mjera samoprocjene	Patients with pSS (n=28), Median (IQR) / Bolesnici koji boluju od pSS-a (n = 28), Median (IQR)	Non-pSS patients (n=8), Median (IQR) / Bolesnici koji ne boluju od pSS-a (n = 8), Median (IQR)	p value* / p-vrijednost*
Dryness score / Ocjena suhoće (prema bodovnoj skali)	8 (7.5 – 9)	8 (7 – 9)	0.533
Pain score / Ocjena boli (prema bodovnoj skali)	5 (5 – 7)	6.5 (6 – 8)	**0.041**
Fatigue score / Ocjena umora (prema bodovnoj skali)	5 (4 – 7)	6.5 (6 – 8)	0.070
Total score / Ukupan rezultat	19 (16 – 22)	21 (20 – 22.5)	0.147

Legend / Legenda: pSS – primary Sjögren's syndrome / primarni Sjögrenov sindrom
ESSPRI: European League Against Rheumatism Sjögren's syndrome patient report index
** Mann-Whitney test, significant p-values highlighted in bold / Mann-Whitneyjev test, značajne p-vrijednosti istaknute su podebljanim slovima*



Legend / Legenda: pSS – primary Sjögren's syndrome / primarni Sjögrenov sindrom

Figure 1. Unstimulated whole saliva flow rate in pSS and non-pSS patients
Slika 1. Nestimulirana brzina izlučivanja sline u bolesnika koji boluju od pSS-a i bolesnika koji ne boluju od pSS-a

with MSGB (rho=0.93, p<0.001), BMI (rho=0.41, p=0.013), the presence of anti-SSA autoantibody (rho=0.38, p=0.023) and negatively correlated with UWS flow rate (rho= –0.51, p=0.002) and ESSPRI pain score (rho= –0.35, p=0.037). Also, positive MSGB results were in negative correlation with UWS flow rate (rho= –0.41, p=0.012) but in a stronger correlation with patients below the diagnostic flow rate cutoff (≤0.1 ml/minute, rho=0.46, p=0.005). The detection of either autoantibody (anti-SSA or anti-SSB) was not in correlation with other parameters but both were correlated well with diagnosis (rho= –0.48, p=0.003 and rho= –0.42, p=0.011, for A and B, respectively).

It is interesting to note that diagnostic criteria did not correlate statistically significant with ESSPRI scores or most demographic or clinical parameters. A good

Mann-Whitneyjevim testom utvrđeno je da je brzina izlučivanja sline statistički značajno niža u pSS skupini (prosječna brzina izlučivanja sline 0,148 +/– 0,147 prema 0,463 +/– 0,259 ml/minuti, p = 0,003). Nestimulirana brzina izlučivanja sline objektivna je dijagnostička pretraga za procjenu zahvaćenosti žlijezda slinovnica. Ova je pretraga obavljena na svim bolesnicima (n = 36). Kod 22 (61,1%) bolesnika rezultati pretraga ukazali su na hiposalivaciju prema revidiranim AECG dijagnostičkim kriterijima za dijagnozu pSS-a (abnormalna brzina izlučivanja sline ≤ 0,1 ml/min) (tablica 1). U pSS skupini kod 75% bolesnika utvrđena je niska brzina izlučivanja sline (u odnosu na 12,5% u ne-pSS skupini). Rezultati brzine izlučivanja sline prikazani su na slici 1. Razlika je statistički značajna (Mann-Whitney test, p = 0,003).

Povezanost patohistoloških i seroloških nalaza, zahvaćenosti žlijezda slinovnica i kliničkih slika procijenjena je Spearmanovim koeficijentom rang korelacije. Očekivano, dijagnoza pSS-a bila je u snažnoj korelaciji s biopsijom malih žlijezda slinovnica (rho = 0,93, p < 0,001), indeksom tjelesne mase (rho = 0,41, p = 0,013), prisutnošću anti-SS-A autoantitijela (rho = 0,38, p = 0,023) i u negativnoj korelaciji s brzinom izlučivanja sline (rho = –0,51, p = 0,002) i ocjenom boli prema bodovnoj skali upitnika ESSPRI (rho = –0,35, p = 0,037). Također, rezultati „pozitivne" biopsije malih žlijezda slinovnica bili su u negativnoj korelaciji s brzinom izlučivanja sline (rho = –0,41, p = 0,012), dok je jača korelacija utvrđena kod pacijenata s nalazom ispod dijagnostičke razine brzine izlučivanja (≤ 0,1 ml/minuti, rho = 0,46, p = 0,005). Otkrivanje bilo kojeg autoantitijela (anti-SS-A ili anti-SS-B) nije bilo u korelaciji s drugim parametrima, ali su oba autoantitijela bila u dobroj korelaciji s dijagnozom (rho = –0,48, p = 0,003 i rho = –0,42, p = 0,011, za A i B).

Zanimljivo je da dijagnostički kriteriji nisu bili u statistički značajnoj korelaciji s ESSPRI ocjenama ili većinom demografskih ili kliničkih parametara. Dobra ne-

negative correlation was observed only for anti-SSA and anti-SSB autoantibodies and the age of the patient at the time of diagnosis (rho= –0.48, p=0.003 and rho= –0.42, p=0.011 for A and B, respectively). ESSPRI pain and fatigue scores correlated between themselves (rho= 0.73, p<0.0001) but neither correlated with ESSPRI dryness score. Interestingly the dryness score correlated well with patient BMI (rho= 0.57, p=0.0003). Additionally, exercising was negatively correlated with both ESSPRI fatigue (rho –0.37, p=0.026) and ESSPRI total scores (rho= –0.41, p=0.014) indicating that it can alleviate some of the subjective symptoms and improve overall self-perception.

DISCUSSION

The objective of our study was to retrospectively evaluate correlation between MSGB, serological findings and sialometry in patients with clinically suspected pSS. From our experience, in early stage pSS can be misdiagnosed as burning mouth symptoms. Several reports frequently show a delay in the diagnosis of pSS that can range from 3 to 11 years (18.). Already in early stage of disease patients have reduced UWS flow rate, sometimes even without salivary gland ultrasonography abnormalities (28). Using UWS flow rate may improve the timely diagnosis of the disease and should be part of the classification criteria for diagnosing pSS.

The fact that multiple classification criteria for pSS are available could introduce some confusion in clinical trials and research, resulting in different cohorts of patients and in non-comparable results (29, 30). It is interesting to mention that in the classification criteria of the American College of Rheumatology (ACR) (31) the oral component is completely left out. Many medical experts in this field did not agree with such classification criteria (29). In order to develop international consensus on classification criteria, the ACR-EULAR (European League Against Rheumatism) criteria were introduced, endorsed by both ACR and EULAR (21, 32).

The MSGB has been standardized as one of major parameter used in a composite of criteria to provide reliable sensitivity and specificity for the classification of pSS (10, 21, 31). It is an invasive diagnostic method and there is no algorithm or any recommendation when to indicate MSGB. Unfortunately, there are no clear guidelines when MSGB is indicated in the treatment of patients with pSS. There is no data in the available literature on how rheumatologists use MSGB results in daily clinical work. Patients with clinically suspected pSS are preselected for having difficulty with their oral mucosa, thus, any operative intervention in the oral area should be undertaken only with good reason. Given the diversity of classification criteria used throughout the years, the lack of experience with MSGB, inconsistent interpretation of results and pa-

gativna korelacija uočena je samo za anti-SS-A i anti-SS-B autoantitijela i dob bolesnika pri postavljanju dijagnoze (rho = –0,48, p = 0,003 i rho = –0,42, p = 0,011 za A i B). Ocjene boli i umora prema bodovnoj skali upitnika ESSPRI bile su u međusobnoj korelaciji (rho = 0,73, p < 0,0001), ali niti jedna od njih nije bila u korelaciji s ocjenom suhoće prema bodovnoj skali upitnika ESSPRI. Zanimljivo je da je ocjena suhoće bila u dobroj korelaciji s indeksom tjelesne mase bolesnika (rho = 0,57, p = 0,0003). Nadalje, fizička aktivnost bila je u negativnoj korelaciji s ocjenom umora prema bodovnoj skali upitnika ESSPRI (rho = –0,37, p = 0,026) i ukupnim rezultatom upitnika ESSPRI (rho = –0,41, p = 0,014), što ukazuje na to da fizička aktivnost može ublažiti neke od subjektivnih simptoma i poboljšati opću samopercepciju.

RASPRAVA

Cilj našeg istraživanja bio je retrospektivno procijeniti korelaciju između biopsije malih žlijezda slinovnica, seroloških nalaza i sijalometrije u bolesnika sa suspektnim pSS-om. Prema našem iskustvu, pSS se u ranoj fazi može pogrešno dijagnosticirati kao simptom sindroma pekućih usta. U raznim izvješćima često se ukazuje na kašnjenje u dijagnozi pSS-a koje može varirati od 3 do 11 godina (18). Već u ranoj fazi bolesti bolesnici imaju smanjenu brzinu izlučivanja sline, ponekad čak i bez abnormalnosti ultrazvuka žlijezda slinovnica (28). Čimbenik brzine izlučivanja sline može poboljšati pravovremenu dijagnozu bolesti i trebao bi biti uključen u klasifikacijske kriterije za dijagnosticiranje pSS-a.

Činjenica da su dostupni razni kriteriji klasifikacije za pSS mogla bi unijeti određenu dozu pomutnje u klinička ispitivanja i istraživanja, što bi rezultiralo različitim skupinama bolesnika i neusporedivim rezultatima (29, 30). Zanimljivo je da je u klasifikacijskim kriterijima organizacije *American College of Rheumatology* (ACR) (31) oralna komponenta potpuno izostavljena. Mnogi medicinski stručnjaci u ovom području nisu se složili s takvim kriterijima klasifikacije (29). S ciljem postizanja međunarodnog konsenzusa o kriterijima klasifikacije uvedeni su kriteriji ACR-EULAR (Europska liga protiv reumatizma) koje su odobrile obje prethodno navedene organizacije – ACR i EULAR (21, 32).

Biopsija malih žlijezda slinovnica standardizirana je kao jedan od glavnih parametara koji se upotrebljava u skupu kriterija kako bi se osigurala pouzdana osjetljivost i specifičnost za klasifikaciju pSS-a (10, 21, 31). To je invazivna dijagnostička metoda i ne postoji algoritam niti ikakva preporuka kada postaviti indikaciju za biopsiju malih žlijezda slinovnica. Nažalost, ne postoje jasne smjernice koje bi određivale kada bi trebalo postaviti indikaciju za biopsiju malih žlijezda slinovnica u liječenju bolesnika s pSS-om. U dostupnoj literaturi nema podataka o tome kako reumatolozi upotrebljavaju rezultate

tient benefit, it is hard to assess in which cases it would be convenient to have MSGB in defining diagnosis of pSS. From our experience, in select clinical situations, the diagnosis of pSS can be made based on noninvasive tests i.e., it can be confirmed by positive serology findings (anti-SSA and/or anti-SSB). Clearly, dryness of the exocrine glands and serologic markers are not a complete replacement for tissue diagnosis, which does provide additional data that may be helpful in certain clinical situations.

Over the past years, salivary gland ultrasound has gained more attention. It was proven to be effective for the detection of typical structural abnormalities in pSS (33, 34). Parotid gland ultrasound can be directly compared to parotid and submandibular glands histopathology (35). Salivary gland ultrasound has a good sensitivity and high specificity, it appeared to mirror dysfunction of the salivary glands, even at the early stages of the disease (36). It is non-invasive, relatively inexpensive, easily accessible and quick (37). Despite the potential of salivary gland ultrasound in diagnosis and classification of pSS, the value of salivary gland ultrasound to assess disease activity and disease progression needs to be established (38).

There are many methods of measuring salivary gland function, although not all of them are practical and adaptable for clinical trials (28, 39). As a measure of salivary gland function, the UWS flow rate has been adopted as one validated measure for the revised AECG and ACR-EULAR criteria for pSS (10, 21). It provides great sensitivity and specificity in differentiating patients with pSS from non-pSS patients. It is simple to administer and non-invasive, needs no special equipment, has a good reproducibility and reflects the physiologic state of the gland. The results of our study showed statistically significant correlation between "positive" biopsy score and clinically reduced (≤0.1 ml/minute) saliva secretion (rho= 0.461, p=0.0047). Our results illustrate the correlation between MSGB, which shows morphological changes, and UWS flow rate, representing the functional aspect. Therefore, UWS flow rate may serve as a noninvasive surrogate biomarker of inflammation and fibrosis as well as an indicator of treatment success in patients with pSS. Unstimulated whole salivary flow rate reflects the basal saliva flow. It should be included in all pSS trials to document glandular parenchymal damage and its possible deterioration over time in pSS. Considering the statistical correlation between a "positive" biopsy score and the serological findings, it was noted that there was not statistically significant correlation between these two parameters (p=0.10). Our results reaffirm that "positive" histopathology finding is a requirement for the diagnosis of pSS in the absence of anti-SSA autoantibodies (22, 40, 41). We highly recommend that physi-

biopsije malih žlijezda slinovnica u svakodnevnoj kliničkoj praksi. Bolesnici sa suspektnim pSS-om odabrani su postupkom predselekcije na temelju postojanja poteškoća s oralnom sluznicom, stoga se svaki operativni zahvat u oralnom području treba obavljati samo ako za to postoji dobar razlog. S obzirom na raznolikost kriterija klasifikacije koji su se upotrebljavali tijekom godina, nedostatak iskustva s postupkom biopsije malih žlijezda slinovnica, nedosljedno tumačenje rezultata i koristi za bolesnike, teško je procijeniti u kojim bi slučajevima bilo korisno upotrebljavati biopsiju malih žlijezda slinovnica u postavljanju dijagnoze pSS-a. Prema našem iskustvu, u odabranim kliničkim slučajevima dijagnoza pSS-a može se postaviti na temelju neinvazivnih testova, odnosno može se potvrditi pozitivnim serološkim nalazima (anti-SS-A i/ili anti-SS-B). Jasno je da suhoća egzokrinih žlijezda i serološki markeri ne mogu u potpunosti zamijeniti tkivnu dijagnozu koja pruža dodatne podatke koji mogu biti korisni u određenim kliničkim slučajevima.

Proteklih godina pažnja znanstvene zajednice sve je više usmjerena na ultrazvuk žlijezda slinovnica. Ova metoda pokazala se učinkovitom za otkrivanje tipičnih strukturnih abnormalnosti u pSS-u (33, 34). Ultrazvuk parotidnih žlijezda može se izravno usporediti s patohistologijom parotidnih i submandibularnih žlijezda (35). Ultrazvuk žlijezda slinovnica ima dobru osjetljivost i visoku specifičnost te se čini da odražava disfunkciju žlijezda slinovnica, čak i u ranim stadijima bolesti (36). Ova je metoda neinvazivna, relativno jeftina, lako dostupna i brza (37). Unatoč potencijalu koji ultrazvuk žlijezda slinovnica ima u dijagnostici i klasifikaciji pSS-a, potrebno je utvrditi njegovu vrijednost za procjenu aktivnosti bolesti i progresije bolesti (38).

Postoje razne metode mjerenja funkcije žlijezda slinovnica, iako nisu sve praktične i pogodne za klinička ispitivanja (28, 39). Budući da se upotrebljava kao metoda za mjerenje funkcije žlijezda slinovnica, brzina izlučivanja sline usvojena je kao valjana mjera za revidirane AECG i ACR-EULAR kriterije za dijagnozu pSS-a (10, 21). Ta metoda omogućuje veliku osjetljivost i specifičnost u razlikovanju bolesnika koji boluju od pSS-a i onih koji ne boluju od pSS-a. Jednostavna je za primjenu i neinvazivna, ne zahtijeva uporabu posebne opreme, ima dobru ponovljivost i odražava fiziologiju žlijezde. Rezultati našeg istraživanja pokazali su statistički značajnu korelaciju između „pozitivnog" rezultata biopsije i smanjenog (≤ 0,1 ml/min) lučenja sline (rho = 0,461, p = 0,0047). Naši rezultati ukazuju na korelaciju između biopsije malih žlijezda slinovnica, koja pokazuje morfološke promjene, i brzine izlučivanja sline, koja predstavlja funkcionalni aspekt. Stoga, brzina izlučivanja sline može poslužiti kao neinvazivni zamjenski biomarker u slučajevima upale i fibroze, kao i pokazatelj uspješnosti u liječenju bolesnika s pSS-om. Nestimulirana brzina izlučivanja sline odražava brzinu izlučivanja bazalne sline. Taj čimbenik

cians should consider performing MSGB in patients with glandular dysfunctions and negative serology. Evidence-based algorithms need to be developed in screening patients who have dryness of the exocrine glands to prevent delaying the diagnosis of pSS, and to avoid unnecessary MSGB in patients who already have oral complications. In patients diagnosed with pSS, objective diagnostic tests for ocular and oral dysfunction should be performed regularly to monitor salivary gland function over time. Future studies aimed at developing effective screening and treatment algorithms are needed to improve the quality of life of these patients. In that respect, continuing research in understanding the underlying etiopathogenesis and possibly incorporating genetic and genomic alterations, might prove beneficial in constructing improved criteria for this complex disorder.

We acknowledge some limitations of our study. The study was conducted in a single center with a retrospective nature. The study was performed at the Clinical Hospital Center „Sestre milosrdnice", which belongs to tertiary health care. Patients with various diseases were included in the study and we performed MSGB and UWS flow rate in all patients. Being a single-centre study, the number of patients included was limited and most importantly, the control group was represented by patients clinically suspected for pSS but diagnosed with non-pSS, which is a heterogeneous entity. However, patients with xerostomia (non-pSS patients) had all undergone MSGB, which to date, remains a cornerstone for pSS diagnosis. It is not possible to exactly determine how many patients with clinically suspected pSS were not biopsied and therefore not included, a factor which could therefore have had an influence on the results. The limited number of cases and the long time interval for the indication of the MSGB and UWS flow rate in some cases under pSS investigation may have modulated the results. Eight of our patients were receiving immunosuppressive therapy, which can downregulate the production of autoantibodies and also altered some histological parameters. Because of the retrospective nature of the study we were not able to evaluate the temporality of the autoantibody presentation. Thus, prospective carrying out of other serological tests (rheumatoid factor, C3, C4, cryoglobulins) would have improved the validity of the clinical judgment and possibly modified the sensitivity of the classification criteria. The methods adopted for ocular staining varied among the participating institutions, forcing us to modify certain items in some criteria.

In conclusion, in our study according to the revised AECG classification criteria only „positive" histopathological findings, reduced saliva secretion and existence of anti-SSA autoantibody confirmed to have a significant diagnostic value in detecting pSS patients. Also,

treba uključiti u sva ispitivanja pSS-a u svrhu dokumentiranja oštećenja parenhima žlijezda i njegova mogućeg pogoršanja do kojeg s vremenom može doći u slučaju bolesnika koji boluju od pSS-a. Uzimajući u obzir statističku korelaciju između „pozitivnog" rezultata biopsije i seroloških nalaza, uočeno je da ne postoji statistički značajna korelacija između ova dva parametra ($p = 0,10$). Naši rezultati potvrđuju da je „pozitivan" patohistološki nalaz uvjet za postavljanje dijagnoze pSS-a u odsutnosti anti-SS-A autoantitijela (22, 40, 41). Naša je preporuka da liječnici razmotre provođenje postupka biopsije malih žlijezda slinovnica u bolesnika s disfunkcijama žlijezda i negativnom serološkom analizom. Algoritme utemeljene na dokazima potrebno je razviti u probiru bolesnika koji imaju simptom suhoće egzokrinih žlijezda kako bi se spriječilo odgađanje dijagnoze pSS-a i kako bi se izbjegla nepotrebna biopsija malih žlijezda slinovnica u bolesnika koji već imaju oralne komplikacije. U bolesnika s dijagnozom pSS-a potrebno je redovito provoditi objektivne dijagnostičke pretrage za disfunkciju očiju i usne šupljine u svrhu praćenja funkcije žlijezda slinovnica tijekom određenog razdoblja. U budućnosti je potrebno provesti studije usmjerene na razvoj učinkovitih algoritama za probir i liječenje ove bolesti kako bi se poboljšala kvaliteta života ovih bolesnika. U tom pogledu, daljnje provođenje istraživanja vezanih za razumijevanje temeljne etiopatogeneze te mogućnost uključivanja čimbenika poput genetskih i genomskih promjena mogli bi se pokazati korisnim u postavljanju poboljšanih kriterija za ovaj složeni poremećaj.

Priznajemo da u sklopu naše studije postoje i određena ograničenja. Studija je provedena u jednom bolničkom centru te je po svojoj prirodi retrospektivna. Provedena je u Kliničkom bolničkom centru Sestre milosrdnice koji je zdravstvena ustanova na tercijarnoj razini. U studiju su uključeni bolesnici s raznim bolestima te su na svim bolesnicima provedeni postupci biopsije malih žlijezda slinovnica i brzine izlučivanja sline. Budući da je ova studija provedena u jednom bolničkom centru, broj bolesnika koji su u nju uključeni bio je ograničen i, što je najbitnije, predstavnici kontrolne skupine bili su bolesnici sa suspektnim pSS-om, ali kojima nije dijagnosticiran pSS, što je heterogeni entitet. No, svim bolesnicima koji boluju od kserostomije (bolesnici koji ne boluju od pSS-a) bila je učinjena biopsija malih žlijezda slinovnica, koja je i dandanas temeljni postupak za dijagnozu pSS-a. Nije moguće točno utvrditi broj bolesnika sa suspektnim pSS-om kojima nije učinjena biopsija i koji stoga nisu uključeni u studiju, što je čimbenik koji bi sigurno utjecao na rezultate. Čimbenici poput ograničenog broja slučajeva i dugoga vremenskog intervala za postavljanje indikacije za postupke biopsije malih žlijezda slinovnica i brzine izlučivanja sline možda su utjecali na konačne rezultate u nekim slučajevima u kojima se tek trebalo utvrditi postojanje dijagnoze pSS-a. Osam bole-

UWS flow rate appears to be a useful aid in diagnosis of pSS. Unstimulated whole salivary flow rate ≤0.1 ml/minute is highly predictive of "positive" MSGB and can be used as a supplemental method to MSGB in diagnosing the oral component of pSS. As a non-invasive, easy to perform, inexpensive method it might be good monitoring tool to follow the progress of the disease.

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snika iz naše studije uzimalo je imunosupresivnu terapiju koja može smanjiti proizvodnju autoantitijela i također promijeniti neke histološke parametre. Budući da je ova studija bila retrospektivna, nismo bili u mogućnosti procijeniti vremensko razdoblje prikaza autoantitijela. Stoga bi prospektivno provođenje drugih seroloških pretraga (reumatoidni faktor, C3, C4, krioglobulini) poboljšalo valjanost kliničke procjene i možda modificiralo osjetljivost klasifikacijskih kriterija. Ustanove koje su sudjelovale u provođenju studije upotrebljavale su različite metode za bojenje okularne površine, zbog čega smo morali modificirati određene stavke u nekim kriterijima.

U konačnici možemo zaključiti da je u našoj studiji prema revidiranim AECG klasifikacijskim kriterijima potvrđeno da samo „pozitivni" patohistološki nalazi, smanjeno lučenje sline i postojanje anti-SS-A autoantitijela imaju značajnu dijagnostičku vrijednost u otkrivanju bolesnika koji boluju od pSS-a. Nadalje, možemo zaključiti da je brzina izlučivanja sline korisna metoda koja može pomoći u dijagnozi pSS-a. Nestimulirana brzina izlučivanja sline ≤ 0,1 ml/min snažan je prediktor „pozitivne" biopsije te se može upotrebljavati kao dodatna metoda uz biopsiju u dijagnostici oralne komponente primarnoga Sjögrenovog sindroma. Budući da se radi o neinvazivnoj i jeftinoj metodi koja je jednostavna za izvođenje, ona može biti korisna za praćenje progresije bolesti.

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REFERENCES / LITERATURA

1. Vitali C, Bombardieri S, Moutsopoulos HM, Balestrieri G, Bencivelli W, Bernstein RM i sur. Preliminary criteria for the classification of Sjögren's syndrome. Results of a prospective concerted action supported by the European Community. Arthritis Rheum. 1993;36(3):340–7.
2. Fox R. Sjögren's syndrome. The Lancet. 2005;366:321–31.
3. Ng W, Bowman S. Primary Sjogren's syndrome: too dry and too tired. Rheumatology (Oxford). 2010;49(5):844–53.
4. Nocturne G, Mariette X. B cells in the pathogenesis of primary Sjögren syndrome. Nat Rev Rheumatol. 2018;14(3):133–45.
5. Psianou K, Panagoulias I, Papanastasiou AD, de Lastic AL, Rodi M, Spantidea PI i sur. Clinical and immunological parameters of Sjögren's syndrome. Autoimmun Rev. 2018;17(10):1053–64.
6. Cartee DL, Maker S, Dalonges D, Manski MC. Sjögren's syndrome: oral manifestations and treatment, a dental perspective. J Dent Hyg. 2015;89(6):365–71.
7. Holdgate N, St. Clair E. Recent advances in primary Sjogren's syndrome. F1000Res. 2016;5:1412.
8. Kassan S, Moutsopoulos H. Clinical Manifestations and Early Diagnosis of Sjögren Syndrome. Arch Intern Med. 2004;164(12):1275.
9. Rasmussen A, Ice JA, Li H, Grundahl K, Kelly JA, Radfar L i sur. Comparison of the American-European Consensus Group Sjögren's syndrome classification criteria to newly proposed American College of Rheumatology criteria in a large, carefully characterised sicca cohort. Ann Rheum Dis. 2013;73(1):31–8.
10. Vitali C, Bombardieri S, Jonsson R, Moutsopoulos HM, Alexander EL, Carsons SE i sur. Classification criteria for Sjogren's syndrome: a revised version of the European criteria proposed by the American-European Consensus Group. Ann Rheum Dis. 2002;61(6):554–8.
11. Vitali C, Bombardieri S, Moutsopoulos HM, Coll J, Gerli R, Hatron PY i sur. Assessment of the European classification criteria for Sjögren's syndrome in a series of clinically defined cases: results of a prospective multicentre study. The European

Study Group on Diagnostic Criteria for Sjögren's Syndrome. Ann Rheum Dis. 1996;55(2):116–21.

12. Greenspan J, Daniels T, Talal N, Sylvester R. The histopathology of Sjögren's syndrome in labial salivary gland biopsies. Oral Surg Oral Med Oral Pathol. 1974;37(2):217–29.
13. Lindhal G, Hedfors E. Lymphocytic infiltrates and epithelial HLA-DR expression in lip salivary glands in connective tissue disease patients lacking sicca: a prospective study. Br J Rheumatol. 1989;28(4):293–8.
14. Guellec D, Cornec D, Jousse-Joulin S, Marhadour T, Marcorelles P, Pers JO i sur. Diagnostic value of labial minor salivary gland biopsy for Sjögren's syndrome: a systematic review. Autoimmun Rev. 2013;12(3):416–20.
15. Stone DU, Fife D, Brown M, Earley KE, Radfar L, Kaufman CE i sur. Effect of tobacco smoking on the clinical, histopathological, and serological manifestations of Sjögren's syndrome. PLOS ONE. 2017;12(2):e0170249.
16. Oni C, Mitchell S, James K, Ng WF, Griffiths B, Hindmarsh V i sur. Eligibility for clinical trials in primary Sjögren's syndrome: lessons from the UK Primary Sjögren's Syndrome Registry. Rheumatology (Oxford). 2016;55(3):544–52.
17. Luo J, Xu S, Lv Y, Huang X, Zhang H, Zhu X i sur. Clinical features and potential relevant factors of renal involvement in primary Sjögren's syndrome. Int J Rheum Dis. 2019;22(2):182–90.
18. Lee Y, Song R, Yang Y, Eun Y. Prevalence and Predictors of Sjögren's Syndrome in Patients with Burning Mouth Symptoms. J Oral Facial Pain Headache. 2018;32(1):91–6.
19. Vitali C, Moutsopoulos H, Bombardieri S. The European Community Study Group on diagnostic criteria for Sjögren's syndrome. Sensitivity and specificity of tests for ocular and oral involvement in Sjögren's syndrome. Ann Rheum Dis. 1994;53 (10):637–47.
20. Navazesh M. Methods for Collecting Saliva. Ann N Y Acad Sci. 1993;694:72–7.
21. Shiboski CH, Shiboski SC, Seror R, Criswell LA, Labetoulle M, Lietman TM i sur. 2016 American College of Rheumatology/ European League Against Rheumatism classification criteria for primary Sjögren's syndrome: A consensus and data-driven methodology involving three international patient cohorts. Ann Rheum Dis. 2017;76(1):9–16.
22. Liquidato B, Filho I. Evaluation of sialometry and minor salivary gland biopsy in classification of Sjögren's Syndrome patients. Braz J Otorhinolaryngol. 2005;71(3):346–54.
23. World Medical Association Declaration of Helsinki. Ethical Principles for Medical Research Involving Human Subjects. JAMA. 2013;310(20):2191.
24. Navazesh M, Kumar S. Measuring salivary flow: challenges and opportunities. J Am Dent Assoc. 2008;139:35S–40S.
25. Daniels TE, Cox D, Shiboski CH, Schiødt M, Wu A, Lanfranchi H i sur. Associations between salivary gland histopathologic diagnoses and phenotypic features of Sjögren's syndrome among 1,726 registry participants. Arthritis Rheum. 2011;63 (7):2021–30.
26. Cho HJ, Yoo JJ, Yun CY, Kang EH, Lee HJ, Hyon JY i sur. The EULAR Sjogren's syndrome patient reported index as an independent determinant of health-related quality of life in primary Sjogren's syndrome patients: in comparison with non-Sjogren's sicca patients. Rheumatology (Oxford). 2013;52(12): 2208–17.
27. Seror R, Theander E, Brun JG, Ramos-Casals M, Valim V, Dörner T i sur. Validation of EULAR primary Sjögren's syndrome disease activity (ESSDAI) and patient indexes (ESSPRI). Ann Rheum Dis. 2015;74(5):859–66.
28. Jousse-Joulin S, Milic V, Jonsson MV, Plagou A, Theander E, Luciano N i sur. Is salivary gland ultrasonography a useful tool in Sjögren's syndrome? A systematic review. Rheumatology (Oxford). 2016;55(5):789–800.
29. Cornec D, Saraux A, Cochener B, Pers JO, Jousse-Joulin S, Renaudineau Y i sur. Level of agreement between 2002 American–European Consensus Group and 2012 American College of Rheumatology classification criteria for Sjögren's syndrome and reasons for discrepancies. Arthritis Res Ther. 2014;16 (2):R74.
30. Goules AV, Exarchos TP, Pezoulas VC, Kourou KD, Venetsanopoulou AI, De Vita S i sur. Sjögren's syndrome towards precision medicine: the challenge of harmonisation and integration of cohorts. Clin Exp Rheumatol. 2019;118(3):175–84.
31. Shiboski SC, Shiboski CH, Criswell L, Baer A, Challacombe S, Lanfranchi H i sur. American College of Rheumatology classification criteria for Sjögren's syndrome: a data-driven, expert consensus approach in the Sjögren's International Collaborative Clinical Alliance Cohort. Arthritis Care Res (Hoboken). 2012;64(4):475–87.
32. Billings M, Amin Hadavand M, Alevizos I. Comparative analysis of the 2016 ACR-EULAR and the 2002 AECG classification criteria for Sjögren's syndrome: Findings from the NIH cohort. Oral Dis. 2018;24(1–2):184–90.
33. Carotti M, Salaffi F, Di Carlo M, Barile A, Giovagnoni A. Diagnostic value of major salivary gland ultrasonography in primary Sjögren's syndrome: the role of grey-scale and colour/ power Doppler sonography. Gland Surg. 2019;8(S3):S159–67.
34. Devauchelle-Pensec V, Zabotti A, Carvajal-Alegria G, Filipovic N, Jousse-Joulin S, De Vita S. Salivary gland ultrasonography in primary Sjögren's syndrome: opportunities and challenges. Rheumatology (Oxford). 2019;kez079.
35. Mossel E, Delli K, van Nimwegen JF, Stel AJ, Kroese FGM, Spijkervet FKL i sur. Ultrasonography of major salivary glands compared with parotid and labial gland biopsy and classification criteria in patients with clinically suspected primary Sjögren's syndrome. Ann Rheum Dis. 2017;76(11):1883–9.
36. Baldini C, Luciano N, Tarantini G, Pascale R, Sernissi F, Mosca M i sur. Salivary gland ultrasonography: a highly specific tool for the early diagnosis of primary Sjögren's syndrome. Arthritis Res Ther. 2015;17(1):146.
37. Ramsubeik K, Motilal S, Sanchez-Ramos L, Ramrattan L, Kaeley G, Singh J. Diagnostic accuracy of salivary gland ultrasound in Sjögren's syndrome: A systematic review and meta-analysis. Ther Adv Musculoskelet Dis. 2020;12:1759720X20973560.
38. van Ginkel MS, Glaudemans AWJM, van der Vegt B, Mossel E, Kroese FGM, Bootsma H i sur. Imaging in primary Sjögren's syndrome. J Clin Med. 2020;9(8):2492.
39. Liu S, Chen W, Wang M, Wu T, Dong L, Pan C i sur. Quantitative analysis of parotid gland secretion function in Sjögren's syndrome patients with dynamic magnetic resonance sialography. Korean J Radiol. 2019;20(3):498.
40. Pereira D, Vilela V, dos Santos T, Pires F. Clinical and laboratorial profile and histological features on minor salivary glands from patients under investigation for Sjögren's syndrome. Med Oral Patol Oral Cir Bucal. 2014;19(3):e237–41.
41. Liapi A, Horisberger A, François S, Ribi C. Sjögren's syndrome: when to suspect and how to confirm? Rev Med Suisse. 2016; 12(513):698–702.

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PROFESSIONAL PAPER STRUČNI RAD

CLINICAL MANIFESTATIONS OF POLYMYALGIA RHEUMATICA – A SINGLE CENTRE EXPERIENCE

KLINIČKA OBILJEŽJA REUMATSKE POLIMIALGIJE – ISKUSTVA JEDNOG CENTRA

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Abstract

Introduction. Polymyalgia rheumatica (PMR) is a chronic inflammatory rheumatic disease that occurs mainly in patients over the age of 50. It is characterised by pain and stiffness in the shoulder and pelvic girdle and neck. Some patients develop giant cell arteritis (GCA). The aim of our study was to present clinical characteristics of PMR patients diagnosed in the period from January 2015 to July 2020 at the Division of Rheumatology and Clinical Immunology, Split University Hospital Centre, Croatia. *Materials and methods.* We analysed available medical records of patients diagnosed with PMR in accordance with the 2012 EULAR/ACR classification criteria. Methods of descriptive statistics were used in the analysis. Forty-nine PMR patients were included in the study. The mean age of patients was 77, and 67.35% of included patients were female. *Results.* The most frequent PMR manifestation was joint pain, which was documented in 91.84% patients, followed by fever in 28.57% cases. GCA was diagnosed in 6 cases (12.24%). The most common comorbidities were arterial hypertension (73.47%), followed by type 2 diabetes (38.78%). In 3 cases (6.12%) the malignant disease was diagnosed in the period of one year before and after the diagnosis of PMR. All patients received glucocorticoid therapy (GC) and remission was achieved in 45 (91.84%) cases. *Conclusion.* In conclusion, PMR is a disease which commonly affects the elderly, and it is successfully treated with GC. As expected, the most common symptom was joint pain, and the most common comorbidity was arterial hypertension. We did not find a higher prevalence of malignant diseases, so PMR should not be viewed as part of the paraneoplastic syndrome, which was also confirmed by the results of the recently conducted studies.

Keywords: Polymyalgia rheumatica; Comorbidity; Paraneoplastic syndrome

Sažetak

Uvod. Reumatska polimialgija (lat. *polymialghia reumatica* – PMR) je kronična upalna reumatska bolest koja se javlja uglavnom kod bolesnika starijih od 50 godina. Najčešće se prezentira bolovima i ukočenošću u području ramenog i zdjeličnog obruča te vrata. U pojedinih bolesnika dolazi do razvoja arteritisa divovskih stanica (engl. *Giant Cell Arteritis* – GCA). Cilj ovoga istraživanja jest prikazati kliničke karakteristike bolesnika kojima je dijagnosticirana PMR u razdoblju od početka 2015. godine do srpnja 2020. godine na Zavodu za reumatologiju i kliničku imunologiju Kli-

ničkoga bolničkog centra (KBC-a) Split. *Materijali i metode.* U istraživanje su uključeni bolesnici kojima je dijagnosticirana PMR prema EULAR/ACR klasifikacijskim kriterijima iz 2012. godine. Podatci su prikupljeni pregledom dostupne medicinske dokumentacije. U analizi rezultata korištene su metode deskriptivne statistike. Ukupno je dijagnosticirano 49 bolesnika s PMR-om. Prosječna dob je 77 godina, a prevladavaju osobe ženskog spola (67,35%). *Rezultati.* PMR se najčešće manifestirala bolovima u zglobovima (u 91,84% bolesnika) te febrilitetom (u 28,57% bolesnika). U 6 bolesnika (12,24%) je naknadno dijagnosticiran GCA. Najčešći pridruženi komorbiditeti bili su arterijska hipertenzija (73,47%) i šećerna bolest tipa 2 (38,78%). U troje bolesnika (6,12%) maligna bolest je dijagnosticirana u periodu od jednu godinu prije i nakon postavljanja dijagnoze PMR-a. Liječenje glukokortikoidima (GC) provedeno je u svih bolesnika, a u njih 45 (91,84%) postignuta je remisija bolesti. *Zaključak.* Zaključno, PMR je bolest koja se javlja u starijoj životnoj dobi i uspješno se liječi GC. Najčešća klinička prezentacija u naših bolesnika bila je bol u zglobovima, dok je najčešći komorbiditet bila arterijska hipertenzija. Nije potvrđeno da je PMR paraneoplastična bolest, što se poklapa s podatcima dostupnim iz literature.

Ključne riječi: Reumatska polimialgija; Komorbiditeti; Paraneoplastički sindrom

INTRODUCTION

Polymyalgia rheumatica (PMR) is a chronic inflammatory rheumatic disease manifested by pain in the shoulder and pelvic girdle and neck, morning stiffness, and increased acute phase reactants such as C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR). Joint effusion is often present in shoulder and hip joints. This disease most commonly occurs in people over the age of 50 and its incidence increases with ageing (1,2).

Approximately 10 – 16% of PMR patients develop giant cell arteritis (GCA) (3). This is the most common form of large blood vessel vasculitis which predominantly affects the extracranial branches of the carotid arteries and aorta, and is followed by symptoms such as headache, fever and / or vision loss (3, 4). A clear aetiology of PMR is yet to be defined, but it is thought that the main cause of immune system modulation is associated with ageing in genetically predisposed individuals (3, 5). Given that the incidence of PMR increases in old age, when the incidence of malignancy also increases, PMR has long been considered part of paraneoplastic syndromes, but this has not been clearly confirmed (6–8).

One of the characteristics of this disease is an excellent therapeutic response to low doses of glucocorticoids (GC).

The aim of this study was to determine the clinical manifestations of PMR in patients treated at the Division of Rheumatology and Clinical Immunology of the Split University Hospital Centre, the frequency and type of comorbidities and the response to the therapy used.

SUBJECTS AND METHODS

The study included patients with a clear diagnosis of PMR in accordance with the 2012 EULAR / ACR classification criteria, who were treated at the Division of

UVOD

Reumatska polimialgija (lat. *polymialghia reumatica* – PMR) je kronična upalna reumatska bolest koja se manifestira bolovima u vratu, ramenom i zdjeličnom obruču, jutarnjom zakočenosti, povišenim reaktantima akutne upale kao što su C-reaktivni protein (CRP) i sedimentacija eritrocita (SE). Često su prisutni izljevi u zglobovima ramena i kukova. Gotovo isključivo se javlja u osoba starijih od 50 godina, a incidencija raste povećanjem životne dobi (1, 2).

U 10–16% bolesnika s PMR-om razvija se arteritis divovskih stanica (engl. *Giant Cell Arteritis* – GCA) (3). To je vaskulitis velikih krvnih žila s predominantnim zahvaćanjem ekstrakranijalnih ogranaka karotidnih arterija i aorte te posljedičnom glavoboljom, febrilitetima i/ili ispadima vida (3, 4). Jasna etiologija PMR-a još nije definirana, smatra se da je glavni uzrok modulacija odgovora imunološkog sustava povezana sa starenjem u genetski predisponiranih pojedinaca (3, 5). S obzirom na to da incidencija PMR-a raste u starijoj životnoj dobi, kada raste i incidencija zloćudnih bolesti, PMR se dulje vrijeme smatrala dijelom paraneoplastičnih zbivanja, što međutim nije jasno potvrđeno (6–8).

Jedna od značajki ove bolesti jest izvrstan terapijski odgovor na niske doze glukokortikoida (engl. *Glucocorticoids*, skr. GC).

Cilj ovog istraživanja bio je utvrditi klinička obilježja PMR-a u bolesnika liječenih na Zavodu za reumatologiju i kliničku imunologiju Kliničkoga bolničkog centra (KBC-a) Split, učestalost i vrstu komorbiditeta te odgovor na primijenjenu terapiju.

ISPITANICI I METODE

U istraživanje su uključeni bolesnici s jasnom dijagnozom PMR-a prema EULAR/ACR klasifikacijskim kriterijima iz 2012. godine, koji su liječeni na Zavodu za reumatologiju i kliničku imunologiju KBC-a Split (9).

Pregledana je dostupna medicinska dokumentacija bolesnika koji su liječeni ambulantno ili stacionarno u

Rheumatology and Clinical Immunology, Split University Hospital Centre (9).

We analysed available medical records of patients who have received outpatient or inpatient care in the period from January 2015 to July 2020. Apart from the demographic data, the manifestations of the disease and its duration were recorded as well. In addition to that, comorbidities and the occurrence of malignant neoplasms were recorded, as well as symptoms that would indicate the occurrence of GCA. The therapy used in the treatment of patients, the response to therapy used, the number of patients in remission, the number of patients who have experienced relapse and the number of patients with active disease were analysed. Methods of descriptive statistics were used in the analysis. The collected data were analysed in Microsoft Excel.

RESULTS

The study included 49 PMR patients. Out of the total number of patients, 33 (67.35%) were female and 16 (32.65%) were male. The mean age of patients was 77, ranging from 62 to 92, and the mean age at diagnosis was 74.5. The mean age for the diagnosis of PMR was 76 for women, and 71.5 for men. The cohort analysis revealed that the average duration of the disease was 2.5 years, with the average duration of the disease being slightly longer in women (2.79 years) than in men (1.88 years).

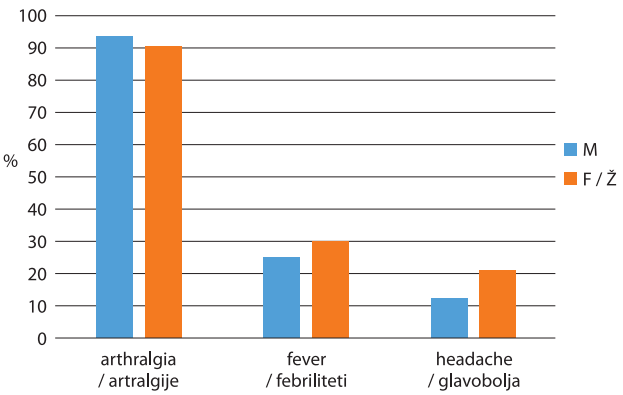
PMR manifested as joint pain in 91.84% of patients, fever (37.5 °C, axillary temperature) in 28.57% of patients, while headaches were recorded in 18.37% of patients (Figure 1). At the time of diagnosis, all patients reported pain and stiffness in the shoulders and shoulder girdle muscles, while 33 patients (67.4%) reported pain and stiffness in the hips and pelvic girdle muscles. Hand pain was recorded in 18 patients (36.7%), and knee pain was recorded in 13 patients (26.5%). A total of 43 patients (87.8%) reported significant morning stiffness lasting over 30 minutes. The headaches reported did not have GCA-specific characteristics, and patients with early-onset headaches did not meet the GCA criteria. None of the patients had positive antibodies to citrullinated proteins, while rheumatoid factor was detected in low titre in four patients (8.2%). Regarding the values of inflammatory parameters, the average value of erythrocyte sedimentation rate (ESR) at the time of diagnosis was 61 ± 25 mm/hr, and the average value of CRP was 74 ± 61.7 mg/dl. After treatment with low doses of glucocorticoids, the values decreased significantly and the average value of the last recorded ESR was 18 ± 13 mm/hr, and CRP 7.7 ± 4.4 mg/dl. As part of the diagnosis of PMR, ultrasound examination of the shoulder joints was performed in 10 patients (20.4%). The most common comorbidities

razdoblju od siječnja 2015. godine do srpnja 2020. godine. Osim demografskih podataka, zabilježeni su simptomi kojima se bolest prezentirala te trajanje bolesti. Uz to su evidentirani komorbiditeti i pojava zloćudnih novotvorina te simptomi koji bi upućivali na pojavu GCA. Analizirana je terapija kojom su bolesnici liječeni, odgovor na terapiju, udio bolesnika koji su u remisiji te udio onih koji su imali relaps bolesti ili je bolest još uvijek aktivna. U analizi su korištene metode deskriptivne statistike. Dobiveni podatci su analizirani u programu *Excel Microsoft Office*.

REZULTATI

U istraživanje je uključeno 49 bolesnika s PMR-om. Od ukupnog broja bolesnika njih 33 (67,35%) su bile žene, a 16 muškarci (32,65%). Prosječna životna dob oboljelih bila je 77 godina, uz raspon od 62 do 92 godine, a prosječna dob u trenutku postavljanja dijagnoze bila je 74,5 godine. U žena je u prosjeku dijagnoza PMR-a bila postavljena u dobi od 76 godina, a u muškaraca u dobi od 71,5 godina. Za analiziranu kohortu prosječno trajanje bolesti bilo je 2,5 godine, s tim da je u žena prosjek trajanja bolesti nešto dulji (2,79 godine) nego u muškaraca (1,88 godine).

PMR se u 91,84% bolesnika manifestirala bolovima u zglobovima, febrilitetom (37,5°C mjereno aksilarno) u njih 28,57%, dok su u 18,37% bolesnika evidentirane glavobolje (slika 1). Svi su bolesnici u trenutku dijagnoze navodili bolove i ukočenost u ramenima i mišićima ramenog obruča, dok su 33 bolesnika (67,4%) navela bolnost i ukočenost u kukovima i mišićima zdjeličnog obruča. U 18 bolesnika (36,7%) evidentirani su bolovi u šakama, a u 13 bolesnika (26,5%) evidentirani su bolovi u koljenima. Ukupno 43 bolesnika (87,8%) navelo je značajnu jutarnju zakočenost u trajanju preko 30 minuta. Zabilježene glavobolje nisu imale obilježja karakteristična za GCA, a bolesnici s glavobo-



Legend / Legenda: M – males / muški, F/Ž – females / ženski

FIGURE 1. Main presenting symptoms of polymyalgia rheumatica (PMR)
SLIKA 1. Glavni prezentirajući simptom reumatske polimijalgije (PMR)

Legend / Legenda:
M – males / muški, FŽ – females / ženski

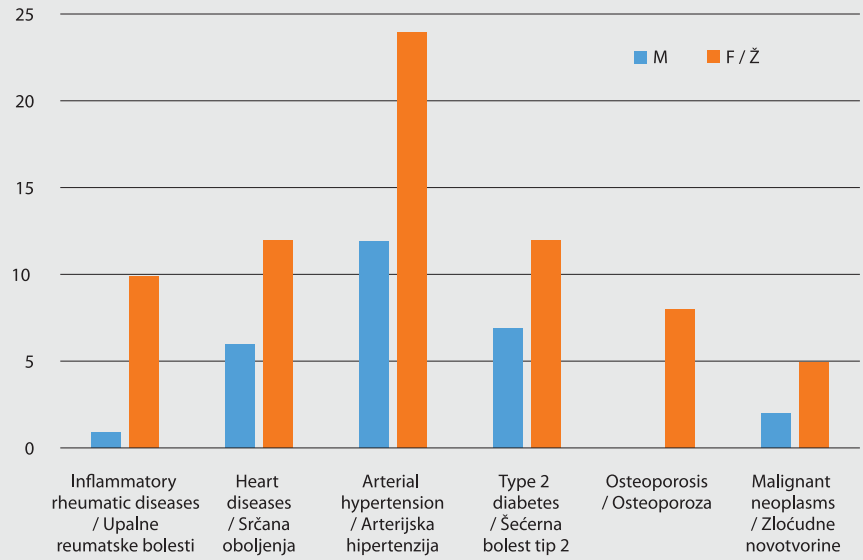


FIGURE 2. Comorbidities in patients with polymyalgia rheumatica (PMR)
SLIKA 2. Komorbiditeti u bolesnika s reumatskom polimijalgijom (PMR)

were arterial hypertension, found in 73.47% of cases, type 2 diabetes, found in 38.78% of cases, and various heart diseases such as ischemic or dilated cardiomyopathy, found in 36.73% of cases (Figure 2). Osteoporosis was recorded in 8 patients (16.33%). When it comes to concomitant inflammatory rheumatic diseases, GCA was diagnosed in 6 patients through additional diagnostic processing, while seronegative polyarthritis was diagnosed in three patients, rheumatoid arthritis was diagnosed in one patient and generalised osteoarthritis was diagnosed in one patient as well. Most cases of concomitant inflammatory rheumatic diseases as well as osteoporosis have been reported in women (Figure 2). Five patients had a previous diagnosis of malignancy at the time of diagnosis of PMR. In three of them, the malignancy occurred more than five years before the diagnosis of PMR. The most commonly diagnosed malignancies were breast cancer, which was diagnosed in three patients, malignant melanoma, which was diagnosed in one patient and smouldering multiple myeloma, which was also diagnosed in one patient. In two patients, the malignancy was diagnosed after the diagnosis of PMR, and these malignancies included cases of renal cell carcinoma and essential thrombocythemia.

All patients received oral glucocorticoid therapy at the time of data analysis. The initial daily dose of methylprednisolone was 12 to 16 mg. Synthetic antimalarials were used as treatment in 20.41% of cases, while methotrexate was used in 14.29% of cases, mostly in cases with concomitant inflammatory rheumatic diseases. Azathioprine was used for the treatment of concomitant GCA in one patient. In 47 (95.92%) patients, remission of PMR was achieved at the time of analysis, and the remaining two patients had recently been diagljama na početku bolesti nisu zadovoljavali kriterije za GCA. Niti jedan bolesnik nije imao pozitivna protutijela na citrulinirane proteine, dok je u njih četvero (8,2%) pronađen reumatoidni faktor u niskom titru. Što se tiče vrijednosti upalnih parametara, prosječna vrijednost sedimentacije eritrocita (SE) prilikom postavljanja dijagnoze bila je 61±25/h, a prosječna vrijednost CRP-a 74±61,7 mg/dl. Nakon provedenog liječenja niskim dozama glukokortikoida vrijednosti su se značajno snizile te je prosječna vrijednost posljednje zabilježene SE bila 18±13/h, a CRP 7,7±4,4 mg/dl. U sklopu dijagnoze PMR-a, ultrazvučni pregled ramenih zglobova napravljen je u 10 bolesnika (20,4%). Najčešće pridružene bolesti bile su arterijska hipertenzija, nađena u 73,47% slučajeva, šećerna bolest tipa 2 u 38,78%, a različita srčana oboljenja kao što su ishemijska ili dilatativna kardiomiopatija u 36,73% slučajeva (slika 2). Osteoporoza je bila zabilježena u 8 bolesnika (16,33%). Od pridruženih upalnih reumatskih bolesti u 6 bolesnika je dodatnom obradom dijagnosticiran GCA, seronegativni poliartritis u tri bolesnika, reumatoidni artritis u jednoga te generalizirani osteoartritis u jednoga bolesnika. Većina popratnih upalnih reumatskih bolesti kao i osteoporoza zabilježena je u žena (slika 2). Pet bolesnika imalo je već ranije postavljenu dijagnozu zloćudne bolesti u trenutku postavljanja dijagnoze PMR-a; u njih troje zloćudna bolest se javila više od pet godina prije dijagnoze PMR-a. Najčešće dijagnosticirane zloćudne bolesti bile su karcinomi dojke u tri bolesnice te maligni melanom u jednoga i asimptomatski multipli mijelom u još jednoga bolesnika. U dvoje bolesnika maligna bolest je dijagnosticirana nakon postavljanja dijagnoze PMR-a, a radilo se o karcinomu bubrega i esencijalnoj trombocitemiji.

Svi bolesnici su bili na terapiji peroralnim glukokortikoidima u trenutku analize podataka. Početna doza

nosed with PMR. Relapse was reported in two (4.08%) cases.

DISCUSSION

The results of our study confirmed that PMR is more common in women, like most inflammatory rheumatic diseases, and the most common symptom was joint pain (10). Given that this is a condition that commonly affects the elderly population, a high incidence of arterial hypertension is expected (11, 12). It is known that long-term glucocorticoid therapy may lead to the occurrence of new or dysregulation of existing diabetes in these patients, and in the case of prolonged treatment there is an increased risk of osteopenia and / or osteoporosis progression. Also, long-term use of glucocorticoids promotes accelerated atherosclerosis, despite the known fact that adequate control of systemic inflammation in inflammatory rheumatic diseases has a protective effect on the vascular endothelium (13–17). The incidence of osteoporosis, heart disease, and type 2 diabetes, despite relatively long-term glucocorticoid therapy, has been reported in approximately one-third of our patients. Similar results were presented in the study conducted by Shbeeb et al. after analysing the connection between glucocorticoid therapy and the occurrence of these comorbidities in patients with PMR. According to this study, the incidence of diabetes, atherosclerosis, and osteoporosis is similar in patients with PMR who received glucocorticoid therapy and the control group (18). Based on these data, it can be concluded that relatively small doses of glucocorticoids used in the treatment of PMR suppress systemic inflammation with a relatively low incidence of adverse effects and have a protective effect on inflammation-mediated endothelial and bone damage (19, 20).

A group of Italian authors showed, on a relatively small number of subjects, that 12.5 mg of prednisolone per day is a sufficient dose for the start of PMR treatment (21). These data indicate a good efficacy of glucocorticoid therapy in the treatment of PMR, which has also been confirmed in the case of our patients. The duration of glucocorticoid therapy should be at least 1–3 years, and in patients with high CRP and / or ESR levels, long-term treatment with minimal doses of prednisolone is recommended to prevent relapse (22, 23).

One of the aims of our study was to determine how often PMR occurs with malignancies. In the group of our patients, we recorded only three cases of malignancies that occurred in the period of one year before or after the diagnosis of PMR. One patient was diagnosed with multiple myeloma one year before she was diagnosed with PMR, while two other patients were diagnosed with essential thrombocythemia or kidney cancer several months after being diagnosed with PMR. Therefore, in our group of patients, PMR proved

bila je 12 do 16 mg metilprednizolona dnevno. Sintetskim antimalarikom liječeno je 20,41%, a metotreksatom 14,29% bolesnika, uglavnom s pridruženim upalnim reumatskim bolestima. U jednog bolesnika primijenjen je azatioprin za liječenje pridruženog GCA. U 47 (95,92%) bolesnika postignuta je remisija PMR-a u trenutku analize, a u preostala dva bolesnika radilo se o nedavno dijagnosticiranoj PMR. Relaps je zabilježen u dvoje (4,08%) bolesnika.

RASPRAVA

Rezultati našeg istraživanja potvrdili su da se PMR češće javlja u žena, poput većine upalnih reumatskih bolesti, a najčešći simptomi bili su bolovi u zglobovima (10). S obzirom na to da se radi o starijoj populaciji, očekivana je visoka učestalost arterijske hipertenzije (11, 12). Poznato je da dugotrajna terapija glukokortikoidima može dovesti do pojave nove ili disregulacije postojeće šećerne bolesti kod ovih bolesnika, a u slučaju produljenog liječenja raste rizik pogoršanja osteopenije i/ili osteoporoze. Također, dugotrajna primjena glukokortikoida potiče ubrzanu aterosklerozu, usprkos poznatoj činjenici da adekvatnom kontrolom sustavne upale u upalnim reumatskim bolestima ima protektivno djelovanje na krvožilni endotel (13–17). Učestalost osteoporoze, srčanih oboljenja i šećerne bolesti tipa 2, unatoč relativno dugotrajnoj terapiji glukokortikoidima, zabilježena je u otprilike trećine naših bolesnika. Slične rezultate prikazali su Shbeeb i sur. nakon analize povezanosti terapije glukokortikoidima i pojavnosti navedenih komorbiditeta u oboljelih od PMR-a. Prema toj studiji pojavnost šećerne bolesti, ateroskleroze i osteoporoze slična je u oboljelih od PMR-a koji su liječeni glukokortikoidima i u kontrolnoj skupini (18). Na temelju ovih podataka može se zaključiti da relativno male doze glukokortikoida koje se koriste u liječenju PMR-a suprimiraju sustavno upalno zbivanje uz relativno nisku učestalost štetnih učinaka te da protektivno djeluju na upalom posredovano oštećenje endotela i kostiju (19, 20).

Grupa talijanskih autora pokazala je na relativnom malom broju ispitanika da je 12,5 mg prednizolona dnevno dovoljna doza za početak liječenja PMR-a (21). Ovi podatci ukazuju na dobru učinkovitost terapije glukokortikoidima u liječenju PMR-a, što je potvrđeno i u naših bolesnika. Trajanje terapije glukokortikoidima trebalo bi biti barem 1–3 godine, a u bolesnika s povišenim nalazima CRP-a i/ili SE preporuča se i dugotrajnije liječenje minimalnim dozama prednizolona, čime se prevenira pojava relapsa bolesti (22, 23).

Jedan od ciljeva našeg istraživanja bio je ustanoviti koliko često se PMR javlja uz maligne bolesti. U skupini naših bolesnika zabilježili smo samo tri zloćudne bolesti koje su se pojavile u periodu od jedne godine prije ili nakon postavljanja dijagnoze PMR-a. Jednoj bolesnici je dijagnosticiran multipli mijelom jednu godinu prije

to be a paraneoplastic syndrome in only three patients, while malignancies that were diagnosed several years before the diagnosis of PMR can hardly be considered in this context. Since the elderly population was analysed in this study, we expected a more frequent occurrence of malignancies (24, 25), which in the end was not recorded. Therefore, we cannot state with certainty that PMR can be viewed as part of the paraneoplastic syndrome, which has also been concluded in some of the recently published reviews (7, 26). The suspected paraneoplastic syndrome should be confirmed by the atypical clinical features of PMR, which include, for example, the absence of prolonged morning stiffness, therapeutic response to glucocorticoids, or the absence of radiologically confirmed bursitis of the shoulders and hips (26). However, in a 2018 review by Partington et al., the connection of PMR with the occurrence of malignancies, especially haematological ones, was not rejected. In summary, a connection with malignancies was confirmed in seven studies, while in nine of the analysed studies no connection between PMR and malignancies was found (27). Two of our patients with malignancies that were diagnosed in the same period as PMR presented with typical clinical features which, in addition to pain and stiffness in the shoulder and pelvic girdle, manifested by hand swelling and pain with typical prolonged morning stiffness with a good response to glucocorticoid therapy. Further population research is needed to define a clear connection between PMR and occult malignant neoplasms.

The main challenge in the diagnosis of PMR is the early recognition of GCA symptoms to prevent the occurrence of disease complications such as vision loss. In addition to that, patients with concomitant GCA require higher doses of glucocorticoids (23). Literature data show that the incidence of GCA in PMR patients is 10 – 16%, which is in accordance with our results (3, 28). When it comes to other cases of concomitant inflammatory rheumatic diseases, three cases of seronegative arthritis, one case of rheumatoid arthritis and one case of generalised osteoarthritis have been reported, which is also in line with the current knowledge of the incidence of these diseases in PMR patients (26).

The disadvantage of this study is the small number of patients included, due to the fact that we have analysed data from only one hospital centre and performed only descriptive statistical analysis. In addition to that, it is a retrospective study based on the review of medical records, with no control group.

In conclusion, PMR is an inflammatory rheumatic disease which affects the elderly and is more common in women. In our group of patients, no significantly higher connection of the disease with the occurrence of malignancies nor with other inflammatory rheumatic diseases was found. Prospective population re-

nego joj je postavljena dijagnoza PMR-a, dok je kod još dva bolesnika dijagnosticirana esencijalna trombocitemija odnosno karcinom bubrega nekoliko mjeseci nakon što je dijagnosticirana PMR. Prema tome, u našoj skupini bolesnika PMR se pokazala kao paraneoplastični sindrom u svega tri bolesnika, dok zloćudne bolesti koje su utvrđene više godina prije dijagnosticiranja PMR-a teško možemo razmatrati u tom kontekstu. Budući da je analizirana populacija starije životne dobi, očekivali smo učestaliju pojavu zloćudnih bolesti (24, 25), koja u konačnici ipak nije zabilježena. Stoga PMR ne možemo sa sigurnošću smatrati dijelom paraneoplastičkog sindroma, što je zaključak i nedavno objavljenih preglednih članaka (7, 26). Sumnju na paraneoplastično zbivanje trebala bi pobuditi atipična klinička slika PMR-a, koja na primjer uključuje izostanak produžene jutarnje zakočenosti, terapijskog odgovora na glukokortikoide ili izostanak radiološki potvrđenog burzitisa ramena i kukova (26). Ipak, u preglednom članku Partingtona i sur. iz 2018. godine nije odbačena povezanost PMR-a s pojavom malignih oboljenja, pogotovo hematoloških. Sumarno, povezanost s malignim bolestima potvrđena je u sedam studija, dok u devet analiziranih studija nije pronađena povezanost PMR-a s malignim bolestima (27). Naša dva bolesnika sa zloćudnim bolestima koje su dijagnosticirane u periodu kada je postavljena i dijagnoza PMR-a prezentirala su se tipičnom kliničkom slikom koja se osim bolovima i ukočenošću u ramenom i zdjeličnom obruču manifestirala i oticanjem i bolovima u šakama uz pojavu tipične produžene jutarnje zakočenosti, s dobrim odgovorom na liječenje glukokortikoidima. Buduća populacijska istraživanja potrebna su kako bi se definirala jasna povezanost PMR-a s okultnim malignim neoplazmama.

Glavni izazov u dijagnostici PMR-a je rano prepoznavanje simptoma GCA kako bi se spriječile komplikacije ove bolesti kao što je gubitak vida. Uz to, bolesnici s pridruženim GCA zahtijevaju više doze glukokortikoida (23). U literaturi se navodi da učestalost GCA u oboljelih od PMR-a iznosi 10–16%, što odgovara i našim rezultatima (3, 28). Od ostalih pridruženih upalnih reumatskih bolesti zabilježena su tri slučaja seronegativnog artritisa, po jedan slučaj reumatoidnog artritisa i generaliziranog osteoartritisa, što je također u skladu s dosadašnjim saznanjima o pojavnosti ovih bolesti u oboljelih od PMR-a (26).

Nedostatak je ove studije mali broj uključenih bolesnika, budući da su analizirani podatci iz samo jednog centra te je provedena samo deskriptivna statistička obrada. Osim toga, radi se o retrospektivnoj studiji koja se temelji na pregledavanju medicinske dokumentacije, dok nije bilo kontrolne skupine.

Zaključno, PMR je upalna reumatska bolest starije životne dobi koja se češće javlja u žena. U našoj skupini bolesnika nije utvrđena značajno viša povezanost bolesti s malignim bolestima kao ni s drugim upalnim reu-

search is needed to define a clear connection between PMR and malignant neoplasms.

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matskim bolestima. Prospektivna populacijska istraživanja potrebna su kako bi se definirala jasna povezanost PMR-a s malignim neoplazmama.

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REFERENCES / LITERATURA

1. Raheel S, Shbeeb I, Crowson CS, Matteson EL. Epidemiology of polymyalgia rheumatica 2000–2014 and examination of incidence and survival trends over 45 years: A population-based study. Arthritis Care Res (Hoboken). 2017;69(8):1282–5.
2. Partington RJ, Muller S, Helliwell T, Mallen CD, Sultan AA. Incidence, prevalence and treatment burden of polymyalgia rheumatica in the UK over two decades: a population-based study. Ann Rheum Dis. 2018;77(12):1750–6.
3. Salvarani C, Cantini F, Hunder GG. Polymyalgia rheumatica and giant-cell arteritis. Lancet. 2008;372(9634):234–45.
4. Buttgereit F, Dejaco C, Matteson EL, Dasgupta B. Polymyalgia Rheumatica and Giant Cell Arteritis: A Systematic Review. JAMA. 2016;315(22):2442–58.
5. Guggino G, Ferrante A, Macaluso F, Triolo G, Ciccia F. Pathogenesis of polymyalgia rheumatica. Reumatismo. 2018;70(1):10–17.
6. Coelho S, Magalhães H, Correia J, Magalhães A, Lourenço P. Polymyalgia rheumatica and pulmonary adenocarcinoma: A case report and literature review. Porto Biomed J. 2017;2(3):93–5.
7. Muller S, Hider S, Helliwell T, Partington R, Mallen C. The real evidence for polymyalgia rheumatica as a paraneoplastic syndrome. Reumatismo. 2018;70(1):23–34.
8. Manzo C, Natale M. Polymyalgia rheumatica and cancer risk: the importance of the diagnostic set. Open Access Rheumatol. 2016;8:93–5.
9. Dasgupta B, Cimmino MA, Maradit-Kremers H i sur. 2012 provisional classification criteria for polymyalgia rheumatica: a European League Against Rheumatism/American College of Rheumatology collaborative initiative. Ann Rheum Dis. 2012; 71(4):484–92.
10. Kermani TA, Warrington KJ. Polymyalgia rheumatica. Lancet. 2013;381(9860):63–72.
11. Lionakis N, Mendrinos D, Sanidas E, Favatas G, Georgopoulou M. Hypertension in the elderly. World J Cardiol. 2012;4(5): 135–47.
12. Filipovský J. Arterial hypertension in the elderly. Vnitr Lek. 2018;64(11):987–92.
13. Nashel DJ. Is atherosclerosis a complication of long-term corticosteroid treatment? Am J Med. 1986;80(5):925–9.
14. Willenberg T, Diehm N, Zwahlen M, Kalka C, Do DD, Gretener S i sur. Impact of long-term corticosteroid therapy on the distribution pattern of lower limb atherosclerosis. Eur J Vasc Endovasc Surg. 2010;39(4):441–6.
15. del Rincón I, O'Leary DH, Haas RW, Escalante A. Effect of glucocorticoids on the arteries in rheumatoid arthritis. Arthritis Rheum. 2004;50(12):3813–22.
16. Arida A, Protogerou AD, Kitas GD, Sfikakis PP. Systemic inflammatory response and atherosclerosis: The paradigm of chronic inflammatory rheumatic diseases. Int J Mol Sci. 2018; 19(7):1890.
17. Bartoloni E, Alunno A, Valentini V, Luccioli F, Valentini E, La Paglia GMC i sur. Targeting Inflammation to Prevent Cardiovascular Disease in Chronic Rheumatic Diseases: Myth or Reality? Front Cardiovasc Med. 2018;5:177.
18. Shbeeb I, Challah D, Raheel S, Crowson SC, Matteson EL. Comparable Rates of Glucocorticoid-Associated Adverse Events in Patients With Polymyalgia Rheumatica and Comorbidities in the General Population. Arthritis Care Res (Hoboken). 2018;70(4):643–7.
19. Verhoeven F, Prati C, Maguin-Gaté K, Wendling D, Demougeot C. Glucocorticoids and endothelial function in inflammatory diseases: focus on rheumatoid arthritis. Arthritis Res Ther. 2016;18(1):258.
20. Fenton CG, Webster JM, Martin CS, Fareed S, Wehmeyer C, Mackie H i sur. Therapeutic glucocorticoids prevent bone loss but drive muscle wasting when administered in chronic polyarthritis. Arthritis Res Ther. 2019;21(1):182.
21. Cimmino MA, Parodi M, Montecucco C, Caporali R. The correct prednisone starting dose in polymyalgia rheumatica is related to body weight but not to disease severity. BMC Musculoskelet Disord. 2011; 12:94.
22. Muratore F, Pipitone N, Hunder GG, Salvarani C. Discontinuation of therapies in polymyalgia rheumatica and giant cell arteritis. Clin Exp Rheumatol. 2013;31(78):86–92.
23. Albrecht K, Huscher D, Buttgereit F, Aringer M, Hoese G, Ochs W i sur. Long-term glucocorticoid treatment in patients with polymyalgia rheumatica, giant cell arteritis, or both diseases: results from a national rheumatology database. Rheumatol Int. 2018;38(4):569–77.
24. Ershler WB. Cancer: a disease of the elderly. J Support Oncol. 2003;1(2):5–10.
25. Cinar D, Tas D. Cancer in the elderly. North Clin Istanb. 2015; 2(1):73–80.
26. Chatzigeorgiou C, Mackie SL. Comorbidity in polymyalgia rheumatica. Reumatismo. 2018;70(1):35–43.
27. Partington R, Helliwell T, Muller S, Abdul Sultan A, Mallen C. Comorbidities in polymyalgia rheumatica: a systematic review. Arthritis Res Ther. 2018;20(1):258.
28. Manzo C. Incidence and Prevalence of Polymyalgia Rheumatica (PMR): The Importance of the Epidemiological Context. The Italian Case. Med Sci (Basel). 2019;7(9):92.

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PROFESSIONAL PAPER STRUČNI RAD

CLINICAL AND LABORATORY FEATURES OF IgA VASCULITIS WITH GASTROINTESTINAL INVOLVEMENT: A 12-YEAR EXPERIENCE OF THE REFERRAL CENTRE FOR PAEDIATRIC AND ADOLESCENT RHEUMATOLOGY OF THE REPUBLIC OF CROATIA

KLINIČKE I LABORATORIJSKE ZNAČAJKE IgA VASKULITISA S GASTROINTESTINALNOM ZAHVAĆENOŠĆU: DVANAESTOGODIŠNJE ISKUSTVO REFERENTNOG CENTRA ZA PEDIJATRIJSKU I ADOLESCENTNU REUMATOLOGIJU REPUBLIKE HRVATSKE

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Abstract

Introduction. IgA vasculitis (IgAV) is the most common systemic vasculitis in childhood. More than half of IgAV patients experience gastrointestinal involvement which usually occurs in the form of abdominal pain, nausea and vomiting, and up to 5% of patients may develop serious complications such as intussusception, intestinal perforation and / or acute bleeding. The aim of our study was to determine the clinical and laboratory features of gastrointestinal involvement in IgAV. *Materials and methods.* Retrospective analysis of IgAV patients' data, who were diagnosed and treated at the Referral Centre for Paediatric and Adolescent Rheumatology of the Ministry of Health of the Republic of Croatia, in the period from 2009 to 2020, and who experienced gastrointestinal involvement. Differences between categorical variables were examined using the $\chi 2$ test, and between the numerical ones using the Mann-Whitney U-test. *Results.* IgAV was diagnosed in 216 patients, 116 boys and 100 girls. Gastrointestinal involvement was detected in 94 patients (43.5%), the age range at diagnosis was 6.75 (5.2 – 9), and the M : F ratio was 1.68 : 1. The most common clinical sign of gastrointestinal involvement in IgA vasculitis was abdominal pain which occurred in 45 patients (47.9%). Abdominal pain was most often located in the periumbilical region (62.5%). One patient developed ileocolic intussusception. The incidence of generalised purpuric rash ($p = 0,023$) and nephritis ($p = 0,001$) was higher in patients with gastrointestinal involvement compared to a group of patients without gastrointestinal involvement. This group of

patients had statistically significantly higher values of leukocyte count (p = 0,021) and lower values of erythrocyte sedimentation rate (p = 0,039) and total serum proteins (p = 0,002). In the majority of cases, patients with gastrointestinal involvement were male (p = 0,019), their length of stay (LoS) in the hospital was longer (p < 0,001) and they had a higher frequency of relapses (p = 0,011). *Conclusion.* In conclusion, gastrointestinal symptoms in IgAV are most often self-limiting, while complications are rare. We observed that, in most cases, patients with gastrointestinal symptoms were males, with longer length of stay in the hospital, and a higher frequency of nephritis and relapses.

Key words: Henoch-Schönlein purpura; Vasculitis; Gastrointestinal tract; Children; Adolescents

Sažetak

Uvod. IgA vaskulitis (IgAV) najčešći je sistemski vaskulitis dječje dobi. U više od polovice bolesnika s IgAV-om dolazi do zahvaćanja gastrointestinalnog sustava najčešće u vidu bolova u trbuhu, mučnine i povraćanja, a u do 5% bolesnika mogu se razviti ozbiljne komplikacije poput intususcepcije, perforacije crijeva i/ili akutnog krvarenja. Cilj istraživanja bio je utvrditi kliničke i laboratorijske značajke zahvaćenosti gastrointestinalnog sustava u IgAV-u. *Materijali i metode.* Retrospektivna analiza podataka bolesnika s IgAV-om, dijagnosticiranih i liječenih u Referentnom centru za pedijatrijsku i adolescentnu reumatologiju Ministarstva zdravstva RH u razdoblju od 2009. do 2020. godine, koji su imali zahvaćen gastrointestinalni sustav. Razlike između kategorijskih varijabla ispitane su pomoću $\chi 2$ testa, a one između numeričkih Mann-Whitneyevim U-testom. *Rezultati.* IgAV je dijagnosticiran u 216 bolesnika, od toga 116 dječaka i 100 djevojčica. Gastrointestinalni sustav bio je zahvaćen u 94 bolesnika (43,5%), raspon dobi u trenutku dijagnoze bio je 6,75 (5,2–9) godina, a omjer M:Ž 1,68:1. Najčešći klinički znak zahvaćanja gastrointestinalnog sustava u IgA vaskulitisu bila je bol u trbuhu koju je imalo 45 bolesnika (47,9%). Bolovi u trbuhu bili su najčešće locirani periumbilikalno (62,5%). Jedan bolesnik razvio je ileokoličnu invaginaciju crijeva. Učestalost generaliziranoga purpuričnog osipa (p=0,023) i pojave nefritisa (p=0,001) bila je veća u bolesnika sa zahvaćenim gastrointestinalnim sustavom u usporedbi sa skupinom bolesnika bez zahvaćenog gastrointestinalnog sustava. Ta skupina bolesnika imala je statistički značajno veći broj leukocita (p=0,021) te niže vrijednosti sedimentacije eritrocita (p=0,039) i ukupnih proteina (p=0,002). Bolesnici sa zahvaćenim gastrointestinalnim sustavom češće su bili muškog spola (p=0,019), imali su dulje trajanje hospitalizacije (p<0,001) i veću učestalost relapsa (p=0,011). *Zaključak.* Zaključno, gastrointestinalni simptomi u IgAV-u najčešće su samoograničavajući, a komplikacije rijetke. Uočili smo da su bolesnici s gastrointestinalnim simptomima IgA vaskulitisa češće muškog spola, imaju duže trajanje hospitalizacije te veću pojavu nefritisa i relapsa.

Ključne riječi: purpura, Schoenlein-Henoch, vaskulitis, gastrointestinalni sustav, djeca, adolescenti

INTRODUCTION

IgA vasculitis (IgAV), formerly known as Henoch-Schönlein purpura (HSP), is a systemic, IgA-mediated vasculitis that mainly affects children but can also occur in adults (1). It is the most common vasculitis in childhood, with an average annual incidence in the Republic of Croatia of 6.79 per 100,000 children (2). According to the 2008 EULAR/PRINTO/PRES criteria, the diagnosis of IgAV requires the presence of palpable non-thrombocytopenic purpura with at least one of four other symptoms or signs of the disease: abdominal pain, histopathological signs of leukocytoclastic vasculitis with predominant IgA deposition, arthritis/arthralgia, and renal involvement in the form of haematuria and / or proteinuria (1,3). In children diagnosed with IgAV, gastrointestinal involvement usually occurs within a week of the onset of purpuric rash and can sometimes occur up to two weeks prior to the onset of rash (4). According to our literature review, gastrointestinal involvement ranges between 50% and 75% (4–7), and it is most often manifested by abdomi-

UVOD

Henoch-Schönleinova purpura (HSP) ili IgA vaskulitis (IgAV), kako se danas naziva, sistemski je, IgA-posredovan vaskulitis koji uglavnom zahvaća djecu, ali se može pojaviti i u odraslih (1). To je najčešći vaskulitis dječje dobi s prosječnom godišnjom incidencijom u Republici Hrvatskoj od 6,79 na 100.000 djece (2). Prema EULAR/PRINTO/PRES kriterijima iz 2008. za dijagnozu IgAV-a neophodno je postojanje palpabilne netrombocitopenične purpure uz prisutnost barem još jednog od četiriju simptoma ili znaka bolesti: bol u trbuhu, patohistološki znakovi leukocitoklastičnog vaskulitisa s predominantnim IgA depozitima, artritis/artralgije i zahvaćanje bubrega u vidu hematurije i/ili proteinurije (1,3). U djece s IgAV-om zahvaćenost gastrointestinalnog sustava obično nastupi unutar tjedan dana nakon pojave purpuričnog osipa, a katkad može prethoditi osipu i do dva tjedna (4). Prema dostupnim literaturnim podatcima, zahvaćenost gastrointestinalnog sustava kreće se između 50% i 75% (4–7), a klinički se najčešće očituje bolovima u trbuhu, mučninom,

nal pain, nausea, vomiting, and blood and mucus in the stool (4–6). Abdominal pain is most often located in the periumbilical region and in the epigastrium, it intensifies after meals, and is caused by submucosal haemorrhage and intestinal oedema, which results in the exudation of interstitial fluid and blood into the lumen of the gastrointestinal tract (4–6). Although IgAV is most often a self-limiting disease that resolves spontaneously, up to 5% of patients may experience serious gastrointestinal complications, most commonly intussusception, intestinal perforation, and major haemorrhage (4–7). The importance of early recognition of these complications is that they also require surgical intervention, because otherwise they could be life-threatening and even fatal (4,5). Numerous laboratory, microbiological, ultrasound and radiological tests are used in the diagnosis of IgAV with gastrointestinal involvement, in addition to the clinical features which are the key element in making the diagnosis. This study includes 94 IgAV patients with gastrointestinal involvement, who were treated at the Department of Paediatrics of the University Hospital Centre Zagreb in the last 12 years. The aim of this study is to present and compare the clinical and laboratory features, treatment methods, disease course and outcome in the case of IgAV patients with gastrointestinal involvement compared to other IgAV patients.

SUBJECTS AND METHODS

A retrospective study was conducted involving patients diagnosed with IgAV in the period from January 2009 to June 2020 at the Division of Clinical Immunology, Allergology and Rheumatology, Department of Paediatrics, University Hospital Centre Zagreb, Referral Centre for Paediatric and Adolescent Rheumatology of the Ministry of Health of the Republic of Croatia. All patients were under the age of 18 and met the EULAR/PRINTO/PRES criteria for the diagnosis of IgAV (3). Epidemiological, clinical, and laboratory data on IgAV patients were collected from a database based on medical records, which enabled the long-term follow-up of patients. The research was approved by the Ethics Committee of the University Hospital Centre Zagreb and the School of Medicine, University of Zagreb. Demographic data included age at diagnosis of IgAV, sex, and date of diagnosis. Clinical data included the length of stay in the hospital (LoS), the presence of previous infection, the order of onset of symptoms, the prevalence of purpuric rash, organ involvement, type of medication, outcome, and number of relapses. Disease relapse was defined as the recurrence of symptoms and signs characteristic of IgAV after an asymptomatic period of at least one month. The laboratory findings that were analysed included inflammatory markers (erythrocyte sedimentation rate, C-reactive protein and ferritin), complete

povraćanjem te krvlju i sluzi u stolici (4–6). Bolovi u trbuhu najčešće su smješteni periumbilikalno i u epigastriju, pojačavaju se nakon jela, a uzrok im je submukozno krvarenje i edem probavne stijenke, što dovodi do izlaska intersticijske tekućine i krvi u lumen probavne cijevi (4–6). Premda je IgAV najčešće samoograničavajuća bolest koja i spontano prođe, u do 5% bolesnika mogu se javiti ozbiljne komplikacije vezane uz gastrointestinalni sustav, među kojima su najčešće intususcepcija, perforacija crijeva i masivno krvarenje (4–7). Važnost ranog prepoznavanja navedenih komplikacija jest u tome što one zahtijevaju i kiruršku intervenciju, jer u suprotnom može doći do životne ugroze bolesnika pa i smrtnog ishoda (4,5). U dijagnostici IgAV-a s gastrointestinalnom zahvaćenošću, uz kliničku sliku kao ključnu u postavljanju dijagnoze, koriste se brojne laboratorijske, mikrobiološke, ultrazvučne i radiološke pretrage. U ovom radu prikazujemo 94 bolesnika s IgAV-om u kojih je bio zahvaćen gastrointestinalni sustav, a liječili su se u Klinici za pedijatriju Kliničkoga bolničkog centra Zagreb u posljednjih 12 godina. Cilj rada je prikazati i usporediti kliničku sliku, laboratorijske značajke, liječenje, tijek bolesti i ishod IgAV-a s gastrointestinalnom zahvaćenošću u odnosu na preostale bolesnike s IgAV-om.

ISPITANICI I METODE

Provedeno je retrospektivno istraživanje u koje su uključeni bolesnici kojima je u razdoblju od siječnja 2009. do lipnja 2020. dijagnosticiran IgAV u Zavodu za kliničku imunologiju, reumatologiju i alergologiju Klinike za pedijatriju Kiničkoga bolničkog centra Zagreb, Referentnom centru za pedijatrijsku i adolescentnu reumatologiju Ministarstva zdravstva Republike Hrvatske. Svi bolesnici bili su mlađi od 18 godina i zadovoljili su EULAR/PRINTO/PRES kriterije za dijagnozu IgAV-a (3). Epidemiološki, klinički i laboratorijski podatci o bolesnicima s IgAV-om prikupljeni su iz baze podataka temeljene na medicinskoj dokumentaciji, čime je omogućeno dugoročno praćenje bolesnika. Istraživanje je odobrilo Etičko povjerenstvo Kliničkoga bolničkog centra Zagreb i Medicinskog fakulteta Sveučilišta u Zagrebu. Demografski podatci uključivali su dob pri dijagnozi IgAV-a, spol i datum dijagnoze. Klinički podatci uključivali su trajanje hospitalizacije, postojanje prethodne infekcije, redoslijed pojave simptoma, rasprostranjenost purpuričnog osipa, zahvaćenost organa, vrstu lijekova, ishod i broj relapsa. Relaps bolesti definiran je kao ponovna pojava simptoma i znakova karakterističnih za IgAV nakon asimptomatskog razdoblja u trajanju od najmanje jednog mjeseca. Od laboratorijskih nalaza analizirani su upalni pokazatelji (sedimentacija eritrocita, C-reaktivni protein i feritin), kompletna krvna slika, biokemijske pretrage krvi (kreatinin, ureja, ukupni proteini), koagulacijske

blood count, biochemical blood tests (creatinine, urea, total protein test), coagulation tests (fibrinogen, D-dimer test, prothrombin time test [PT]) and activated partial thromboplastin time [aPTT]) and immunoassays (immunoglobulin classes [IgA, IgG, IgM], antistreptolysin titre [ASOT], total complement measurement [CH50] and complement components C3 and C4). We analysed the presence of haematuria in urine, defined as > 5 erythrocytes in urine sediment, and/or the presence of proteinuria, defined as ≥ 2+ protein in a qualitative urine test strip analysis with the first morning urine sample. In the case of patients with a pathological finding of the first morning urine sample, 24-hour urine protein test was performed. In the 24-hour urine protein test, proteinuria was defined as > 0.15 g/day of total protein excretion. Faecal calprotectin levels and the presence of occult bleeding were analysed in stool samples. Microbiological tests performed on patients with a history of infection included a nasopharyngeal swab. Radiological tests performed on patients with gastrointestinal symptoms included abdominal colour Doppler ultrasound of the ileocecal region.

The data are presented in tabular form, and data preparation was performed using Microsoft Excel. Continuous variables for values that do not have a normal distribution are shown as the median and interquartile range (25 to 75 percentiles), and categorical variables are shown as percentages. Differences between numerical variables in univariate analysis were analysed using the Mann-Whitney U-test, and between the categorical variables using the $\chi 2$ test. Statistical significance was set at $p < 0.05$.

RESULTS

In the period from January 2009 to June 2020, 216 patients (116 boys and 100 girls) with IgAV were diagnosed at the University Hospital Center Zagreb. The median age (range) at diagnosis was 6.5 (4.5 – 8.4), and the ratio of boys to girls was 1.16 : 1. Purpuric rash was detected in all patients, 155 patients (71.8%) had arthritis/arthralgia, 94 patients (43.5%) experienced gastrointestinal involvement, 45 patients (20.8%) experienced renal involvement, and incidence of scrotal involvement was recorded in 14 boys (12.1%). Two patients (0.9%) developed life-threatening complications such as respiratory distress syndrome and intussusception. In 116 patients (53.7%) the initial presenting symptom of IgAV was purpuric rash, in 66 patients (30.6%) it was arthritis and/or arthralgia, and in 34 patients the initial symptoms were gastrointestinal ones (15.7%). Purpuric rash was generalised in 94 patients (43.5%), and 9 patients (4.2%) experienced severe cutaneous changes in the form of ulcerations and necrosis. The median (range) of renal disease was 4 (0 – 18) days from the diagnosis of IgAV, and renal biopsy was performed in

pretrage (fibrinogen, D-dimeri, protrombinsko vrijeme [PV] i aktivirano parcijalno tromboplastinsko vrijeme [APTV]) te imunološke pretrage (razredi imunoglobulina [IgA, IgG, IgM], antistreptolizinski titar [ASTO], razina ukupnog komplementa [CH50] i komponente komplementa C3 i C4). U urinu je analizirana prisutnost hematurije, definirane kao >5 eritrocita u sedimentu urina i/ili prisutnost proteinurije definirane s ≥2+ proteina u kvalitativnom pregledu urina test-trakom u prvom jutarnjem uzorku urina. U bolesnika s patološkim nalazom prvog jutarnjeg uzorka urina učinjeno je određivanje proteina u 24-satnom urinu. Proteinurija u 24-satnom urinu definirana je kao >0,15 g/dU sveukupno izlučenih proteina. U uzorcima stolice analizirana je razina fekalnog kalprotektina i prisutnost okultnog krvarenja. Mikrobiološke pretrage u bolesnika s anamnezom infekcije uključivale su obrisak nosne sluznice i ždrijela. Od radioloških pretraga u bolesnika s gastrointestinalnim simptomima učinjen je UZV trbuha s obojenim doplerom ileocekalne regije.

Podatci su prikazani tablično, a priprema podataka je izvršena pomoću *Microsoft Office Excela*. Kontinuirane varijable za vrijednosti koje nemaju normalnu distribuciju prikazane su kao medijan i interkvaritilni raspon (od 25 do 75 centile), a kategoričke varijable prikazane su u postotcima. Razlike između grupa u univarijantnoj analizi za numeričke podatke analizirane su pomoću Mann-Whitneyjevog U-testa, a za kategoričke pomoću X^2 testa. Statistička značajnost postavljena je na $p<0,05$.

REZULTATI

U razdoblju od siječnja 2009. do lipnja 2020. u Kliničkom bolničkom centru Zagreb dijagnosticirano je 216 bolesnika s IgAV-om, odnosno 116 dječaka i 100 djevojčica. Medijan (raspon) dobi u trenutku dijagnoze bio je 6,5 (4,5–8,4) godina, a omjer dječaka prema djevojčicama iznosio je 1,16:1. Svi bolesnici imali su purpurični osip, 155 bolesnika (71,8%) imalo je artritis/artralgije, 94 bolesnika (43,5%) imalo je zahvaćen probavni sustav, 45 bolesnika (20,8%) imalo je zahvaćene bubrege, a u 14 dječaka (12,1%) bio je zahvaćen skrotum. Dvoje bolesnika (0,9%) imalo je po život opasne komplikacije u vidu respiratornoga distresnog sindroma i invaginacije crijeva. IgAV je u 116 bolesnika (53,7%) započeo purpuričnim osipom, u 66 bolesnika (30,6%) artritisom i/ili artralgijama, a u 34 bolesnika (15,7%) gastrointestinalnim simptomima. Purpura je u 94 bolesnika (43,5%) bila generalizirana, a 9 bolesnika (4,2%) imalo je teže kožne promjene u vidu ulceracija i nekroza. Medijan (raspon) pojave bubrežne bolesti bio je 4 (0–18) dana od dijagnoze IgAV-a, a biopsija bubrega učinjena je u 23 bolesnika (10,6%). U većini slučajeva IgAV-u je prethodila infekcija (64,8%)

23 patients (10.6%). In most cases, IgAV was preceded by an infection (64.8%) with the most common isolated causes: *Streptococcus pyogenes* (34.4%), *Staphylococcus aureus* (27.8%) and *Streptococcus pneumoniae* (18%). The largest number of patients was diagnosed in winter (31%) and in autumn (26.4%), and the median (range) length of stay (LoS) in the hospital was 10 (5 – 13) days. The most commonly used drugs were glucocorticoids (59.7%) and non-steroidal anti-inflammatory drugs (54.6%). The recurrence of symptoms and signs of IgAV after an asymptomatic period of at least one month was recorded in 31 patients (14.3%).

Gastrointestinal involvement was detected in 94 patients (59 boys and 35 girls). The median age (range) at diagnosis was 6.75 (5.2 – 9), the ratio of boys to girls was 1.68 : 1, and the median length of stay in the hospital was 12 (8 – 16.5) days. In 34 patients (36.2%) gastrointestinal symptoms were preceded by purpuric rash with a median (range) of 3 (2 – 5) days before the onset of the purpuric rash. In 18 patients (19.1%), the purpuric rash and gastrointestinal symptoms occurred simultaneously, while in 42 patients (44.7%), the purpuric rash preceded gastrointestinal symptoms with a median (range) of 3 (1 – 4.25) days before the onset of gastrointestinal symptoms. The most common clinical sign of gastrointestinal involvement in IgA vasculitis was abdominal pain which occurred in 45 patients (47.9%). The other most frequent symptoms included abdominal pain with positive occult bleeding in 22 patients (23.4%) and visible gastrointestinal bleeding (haematemesis, melena, hematochezia) in 16 patients (17%). 10 patients (10.6%) experienced positive occult bleeding without any other symptoms and/or signs of gastrointestinal involvement. One patient developed a severe complication in the form of ileocolic intussusception due to which a surgical procedure had to be performed. Abdominal pain was most often located in the periumbilical region (62.5%) and in the epigastrium (25%). In most cases (62.8%), no abnormalities were detected during the abdominal ultrasound, while in other cases signs of mesenteric lymphadenitis (22.3%) and bowel wall thickening with oedema (14.9%) were detected. In one patient, ileocaecocolic intussusception was detected during the abdominal ultrasound.

Comparing the laboratory findings of IgAV patients, in the group with gastrointestinal involvement, a statistically significant difference in the number of leukocytes (10.8 x 10^9/ L compared to 10.54 x 10^9/ L, p = 0.021), which was higher, was observed, as well as the difference in the values of erythrocyte sedimentation rate (15 mm/hr compared to 20 mm/hr, p = 0.039) and total serum proteins (68 g/L compared to 71 g/L, p = 0.002), which were lower in relation to the group without gastrointestinal involvement. No statistically significant differences were observed in other laboratory

s najčešće izoliranim uzročnicima: *S. pyogenes* (34,4%), *S. aureus* (27,8%) i *S. pneumoniae* (18%). Najveći broj bolesnika dijagnosticiran je zimi (31%) i u jesen (26,4%), a medijan (raspon) trajanja hospitalizacije iznosio je 10 (5–13) dana. Najčešće primjenjivani lijekovi bili su glukokortikoidi (59,7%) i nesteroidni protuupalni lijekovi (54,6%). Ponovnu pojavu simptoma i znakova IgAV-a nakon asimptomatskog razdoblja u trajanju od barem mjesec dana imao je 31 bolesnik (14,3%).

Gastrointestinalni sustav bio je zahvaćen u 94 bolesnika, odnosno 59 dječaka i 35 djevojčica. Medijan (raspon) dobi prilikom dijagnoze bio je 6,75 (5,2–9) godina, omjer dječaka prema djevojčicama 1,68:1, a medijan trajanja hospitalizacije 12 (8–16,5) dana. U 34 bolesnika (36,2%) gastrointestinalni simptomi su prethodili purpuri s medijanom (rasponom) od 3 (2–5) dana prije pojave purpure. U 18 bolesnika (19,1%) purpura i gastrointestinalni simptomi javili su se istodobno, dok je u 42 bolesnika (44,7%) purpura prethodila gastrointestinalnim simptomima s medijanom (rasponom) od 3 (1–4,25) dana prije pojave gastrointestinalnih simptoma. Najčešći klinički znak zahvaćanja gastrointestinalnog sustava u IgAV-u bila je bol u trbuhu koju je imalo 45 bolesnika (47,9%). Sljedeći po učestalosti bili su bolovi u trbuhu s pozitivnim okultnim krvarenjem koje je imalo 22 bolesnika (23,4%) i vidljivo krvarenje iz probavnog sustava (hematemeza, melena, hematokezija) koje je imalo 16 bolesnika (17%). Pozitivno okultno krvarenje bez ikakvih drugih simptoma i/ili znakova zahvaćanja gastrointestinalnog sustava imalo je 10 bolesnika (10,6%). U jednog bolesnika nastala je teška komplikacija u vidu ileokolične invaginacije crijeva, zbog čega je učinjen kirurški zahvat. Bolovi u trbuhu najčešće su bili locirani periumbilikalno (62,5%) i epigastrično (25%). UZV trbuha najčešće je bio uredan (62,8%), zatim sa znacima mezenterijskog limfadenitisa (22,3%) i zadebljanja stijenki crijeva uz edem (14,9%). U jednog bolesnika UZV trbuha pokazao je ileocekokoličnu invaginaciju crijeva.

Uspoređujući laboratorijske nalaze bolesnika s IgAV-om, u skupini sa zahvaćenim gastrointestinalnim sustavom uočena je statistički značajna razlika u broju leukocita (10,8 x 10^9/L u odnosu na 10,54 x 10^9/L, p=0,021) koji je bio viši te u vrijednostima brzine sedimentacije eritrocita (15 mm/h u odnosu na 20 mm/h, p=0,039) i ukupnih serumskih proteina (68 g/L u odnosu na 71 g/L, p=0,002) koje su bile niže u odnosu na skupinu bez zahvaćenog gastrointestinalnog sustava. U preostalim laboratorijskim nalazima nisu uočene statistički značajne razlike. Uočena je statistički značajna razlika u učestalosti generaliziranoga purpuričnog osipa (53,2% u odnosu na 37,7%, p=0,023) kao i pojave nefritisa (30,8% u odnosu na 13,1%, p=0,001) u bolesnika s gastrointestinalnim simptomima. U bolesnika

Table 1. Demographic, clinical and laboratory features in patients with IgA vasculitis with and without gastrointestinal involvement

Tablica 1. Demografske, kliničke i laboratorijske značajke u bolesnika s IgA vaskulitisom sa zahvaćenim gastrointestinalnim sustavom i bez njega

Parameters / Parametri	IgAV patients with GI symptoms / IgAV bolesnici s GI simptomima (N=94)	IgAV patients without GI symptoms / IgAV bolesnici bez GI simptoma (N=122)	p-value* / p-vrijednost*
DEMOGRAPHIC / DEMOGRAFSKI			
Age (in years): median (IQR) / Dob (godine): medijan (IR)	6.7 (5.2–9.0)	6.2 (4.5–7.7)	0.638[b]
Sex (M : F ratio) / Spol (omjer M:Ž)	59:35	57:65	**0.019**[a]
CLINICAL / KLINIČKI			
Length of stay in the hospital (in days): median (IQR) / Hospitalizacija (dani): medijan (IR)	12 (8.0–16.5)	9 (6–11)	**<0.001**[b]
Infection / Infekcija: n (%)	54 (57.4%)	86 (70.5%)	**0.046**[a]
Generalised purpuric rash / Generalizirana purpura: n (%)	50 (53.2%)	46 (37.7%)	**0.023**[a]
Joints / Zglobovi: n (%)	62 (65.9%)	93 (76.2%)	0.096[a]
Kidneys / Bubrezi: n (%)	29 (30.8%)	16 (13.1%)	**0.001**[a]
Time from the diagnosis until the onset of renal disease (in days): median (IQR) / Vrijeme od dijagnoze do pojave bubrežne bolesti (dani): medijan (IR)	4 (0–18)	3 (0–8.7)	**<0.001**[b]
Non-steroidal anti-inflammatory drugs / Nesteroidni antireumatici: n (%)	38 (40.4%)	80 (65.6%)	**<0.001**[a]
Glucocorticoids / Glukokortikoidi: n (%)	74 (78.7%)	55 (45.1%)	**<0.001**[a]
Immunosuppressive drugs / Imunosupresivi: n (%)	8 (8.5%)	4 (3.3%)	0.096[a]
Antihypertensive drugs / Antihipertenzivi: n (%)	16 (17%)	4 (3.3%)	**<0.001**[a]
Relapse / Relaps: n (%)	20 (21.3%)	11 (9%)	**0.011**[a]
LABORATORY / LABORATORIJSKI			
ESR (mm/hr): median (IQR) / SE (mm/h): medijan (IR)	15 (10.8–24.8)	20 (10.5–33.5)	**0.039**[b]
CRP (mg/L): median (IQR) / CRP (mg/L): medijan (IR)	7.5 (2.4–14.8)	5.5 (1.6–14.2)	0.779[b]
Erythrocytes (1012/L): median (IQR) / Eritrociti (10^{12}/L): medijan (IR)	4.7 (4.5–5.1)	4.6 (4.42–4.98)	0.888[b]
Haemoglobin (g/L): median (IQR) / Hemoglobin (g/L): medijan (IR)	129 (120–137)	127 (118–131)	0.083[b]
Leukocytes (109/L): median (IQR) / Leukociti (10^9/L): medijan (IR)	10.8 (8.0–14.3)	10.54 (8.2–12.5)	**0.021**[b]
Thrombocytes (109/L): median (IQR) / Trombociti (10^9/L): medijan (IR)	360 (297–437)	355.5 (277.3–423.5)	0.230[b]
Creatinine (µmol/L): median (IQR) / Kreatinin (µmol/L): medijan (IR)	45.0 (33.3–60.0)	42.5 (32.3–56.3)	0.542[b]
Urea (mmol/L): median (IQR) / Ureja (mmol/L): medijan (IR)	3.9 (3.2–4.7)	4.1 (3.5–4.7)	0.158[b]

findings. A statistically significant difference was observed in the frequency of generalised purpuric rash (53.2% compared to 37.7%, p = 0.023) as well as the occurrence of nephritis (30.8% compared to 13.1%, p = 0.001) in patients with gastrointestinal symptoms. IgAV nephritis was 1.81 times more common in patients with gastrointestinal symptoms (29 patients compared to 16 patients, p = 0.001), and haematuria was twice as common (27.6 % compared to 10.6%, p = 0.001). Patients with gastrointestinal symptoms were more often treated with glucocorticoids (78.7% compared to 45.1%, p < 0.001), while non-steroidal anti-inflammatory drugs were not used as often (40.4% compared to 65.6%, p < 0.001) compared to patients

u kojih su se pojavili gastrointestinalni simptomi 1,81 puta češće je došlo do razvoja nefritisa u sklopu IgAV-a (29 bolesnika u odnosu na 16 bolesnika, p=0,001), a dva puta češći bio je nalaz hematurije (27,6% u odnosu na 10,6%, p=0,001). Bolesnici s gastrointestinalnim simptomima češće su liječeni glukokortikoidima (78,7% u odnosu na 45,1%, p<0,001), a manje nesteroidnim protuupalnim lijekovima (40,4% u odnosu na 65,6%, p<0,001) u usporedbi s bolesnicima koji nisu imali zahvaćen gastrointestinalni sustav. Primjena imunosupresiva bila je dva puta veća, a antihipertenziva iz skupine inhibitora angiotenzin konvertaze čak četiri puta veća u odnosu na bolesnike bez gastrointestinalnih simptoma. Bolesnici s gastrointestinalnim manifesta-

Table 1. Continued / *Tablica 1. Nastavak*

Parameters / Parametri	IgAV patients with GI symptoms / IgAV bolesnici s GI simptomima (N=94)	IgAV patients without GI symptoms / IgAV bolesnici bez GI simptoma (N=122)	p-value* / p-vrijednost*
Ferritin (ng/mL): median (IQR) / Feritin (ng/mL): medijan (IR)	70.5 (48.9–93.4)	67.4 (48.6–105.5)	0.968[b]
PT: median (IQR) / PV: medijan (IR)	0.98 (0.87–1.09)	1.03 (0.94–1.10)	0.984[b]
aPTT (s): median (IQR) / APTV (s): medijan (IR)	25.0 (23.0–26.7)	25.9 (24.5–27.9)	0.400[b]
Fibrinogen (g/L): median (IQR) / Fibrinogen (g/L): medijan (IR)	3.3 (2.7–4.0)	3.4 (2.9–4.0)	0.624[b]
D-dimer test (µg/L): median (IQR) / D-dimeri (µg/L): medijan (IR)	2.46 (0.71–4.89)	2.12 (0.99–4.23)	0.803[b]
Total protein test (g/L): median (IQR) / Ukupni proteini (g/L): medijan (IR)	68 (65.00–71.25)	71 (67–74)	**0.002**[b]
Albumin test (g/L): median (IQR) / Albumini (g/L): medijan (IR)	37.9 (34.7–40.6)	39.2 (36.5–42.6)	0.384[b]
IgA (g/L): median (IQR) / IgA (g/L): medijan (IR)	1.99 (1.31–2.63)	1.84 (1.37–2.36)	0.674[b]
IgG (g/L): median (IQR) / IgG (g/L): medijan (IR)	9.39 (7.61–11.44)	10.11 (8.62–12.33)	0.516[b]
IgM (g/L) median (IQR) / IgM (g/L) medijan (IR)	0.84 (0.68–1.12)	0.97 (0.74–1.31)	0.568[b]
ASOT: median (IQR) / ASTO: medijan (IR)	135.5 (32.3–417.3)	202 (37.0–452.5)	0.294[b]
C_3 (g/L): median (IQR) / C_3 (g/L): medijan (IR)	1.26 (1.08–1.38)	1.31 (1.16–1.43)	0.575[b]
C_4 (g/L): median (IQR) / C_4 (g/L): medijan (IR)	0.25 (0.20–0.30)	0.25 (0.20–0.32)	0.818[b]
Faecal calprotectin (µg/g): median (IQR) / Fekalni kalprotektin (µg/g): medijan (IR)	24 (20.0–72.5)	30 (20–49)	0.718[b]
24-hour urine protein test (g/day): median (IQR) / 24-satna proteinurija (g/dU: medijan (IR)	0.11 (0.07–0.30)	0.09 (0.06–0.16)	0.772[b]
Haematuria > 5 erythrocytes per high-power field and / or 2+ on a dipstick test: n (%) / Hematurija >5 eritrocita u vidnom polju i/ili 2+ na *dipstick* testu: n (%)	26 (27.6%)	13 (10.6%)	**0.001**[a]
Positive faecal occult blood test (+/–): n (number) / Stolica pozitivna na okultno krvarenje (+/–): n (broj)	48	0	N/A

IQR/IR: interquartile range / interkvartilni raspon; IgAV: IgA vasculitis / IgA vaskulitis; GI: gastrointestinal / gastrointestinalni; ESR/SE: erythrocyte sedimentation rate / sedimentacija eritrocita; CRP: C-reactive protein / C-reaktivni protein; PT/PV: prothrombin time / protrombinsko vrijeme; aPTT/APTV: activated partial thromboplastin time / aktivirano parcijalno tromboplastinsko vrijeme; IgA: immunoglobulin A / imunoglobulin A; IgG: immunoglobulin G / imunoglobulin G; IgM: immunoglobulin M / imunoglobulin M; ASOT/ASTO: anti-streptolysin O titre / antistreptolizinski titar; C_3: complement component C_3 / C_3 komponenta komplementa; C_4: complement component C_4 / C_4 komponenta komplementa; NSAIDs/NSAID: non-steroidal anti-inflammatory drugs / nesteroidni protuupalni lijekovi; N/A: not applicable / nije primjenjivo

*Podatci su prikazani kao medijan (interkvartilni raspon) i u postotcima, statistička značajnost postavljena na *P<0,05 / Data was presented as the median range (interquartile range) and in percentages, statistical significance was set to *p < 0.05; [a]χ^2 test, [b]Mann-Whitney U-test/ Mann-Whitneyjev U-test*

without gastrointestinal involvement. The use of immunosuppressive drugs was twice as high, and the use of antihypertensive drugs from the group of angiotensin-converting enzyme (ACE) inhibitors was as much as four times higher than in patients without gastrointestinal symptoms. Patients with gastrointestinal manifestations had a lower incidence of infections that preceded the occurrence of IgA vasculitis (57.4% compared to 70.5%, p = 0.046). The incidence of IgAV relapse in patients with gastrointestinal symptoms was 1.81 times higher compared to patients without gastrointestinal involvement (21.3% compared to 9%, p = 0.011). When it comes to demographic parameters, a statistically significant difference was observed in gas-

cijama imali su manju pojavnost infekcija koje su prethodile pojavi IgA vaskulitisa (57,4% u odnosu na 70,5%, p=0,046). Učestalost relapsa IgAV-a u bolesnika s gastrointestinalnim simptomima bila je 1,81 puta veća u usporedbi s bolesnicima bez zahvaćenosti gastrointestinalnog sustava (21,3% u odnosu na 9%, p=0,011). Od demografskih pokazatelja uočena je statistički značajna razlika u zahvaćanju gastrointestinalnog sustava u muškog spola (62,7% u odnosu na 46,7%, p=0,019) (tablica 1).

RASPRAVA

U ovom retrospektivnom istraživanju koje je provedeno tijekom dvanaestogodišnjeg razdoblja u Klinici za

trointestinal involvement in males (62.7% compared to 46.7%, p = 0.019) (Table 1).

DISCUSSION

In this retrospective study, which was conducted during a twelve-year period at the Department of Paediatrics of the University Hospital Centre Zagreb, the clinical and laboratory features of IgA vasculitis patients with gastrointestinal involvement were analysed. Gastrointestinal symptoms are present in most IgAV patients, and their incidence ranges from 50% to 75% (4–7). In addition to that, acute complications that can occur with this disease are most often associated with gastrointestinal involvement, and they can also be life-threatening and require surgical treatment (4,5,8). Our study shows that the number of patients with gastrointestinal symptoms falls within the average range described in other studies (43.5%) (9 – 11). In observing patients with gastrointestinal symptoms, a statistically significant difference was observed in the more frequent involvement of male patients (p = 0.019), which is in line with the data reported in the reviewed literature (4,12,13). Patients with gastrointestinal involvement had a higher incidence of generalised purpuric rash, that is, purpura occurring on both extremities (14–16). The most significant results in the clinical sense are related to the fact that patients with gastrointestinal symptoms were more often prone to developing IgAV nephritis, which is the most important chronic complication of the disease that can result in chronic kidney failure in 1 – 15% of patients (17–20). In our cohort of patients, the incidence of nephritis was 1.81 times higher in the group of patients who had at least one gastrointestinal symptom. Another connection between the gastrointestinal system and kidneys was the higher incidence of microhematuria in patients with gastrointestinal symptoms, who were more frequently treated with glucocorticoids, immunosuppressive drugs and antihypertensive drugs and had a longer length of stay in the hospital (p < 0.001) (4,12). The connection between gastrointestinal and renal involvement in IgAV has been described in some studies, but the results are ambiguous (13,18,21,22). The pathophysiological mechanism that could explain the increased incidence of nephritis in patients with gastrointestinal symptoms remains unknown. However, from this observation it is important to point out that patients who have experienced gastrointestinal manifestations may have a higher risk of developing nephritis. In this regard, the issue of the optimal length of follow-up of these patients has not yet been resolved to ensure the timely separation of the patients who have developed nephritis (18). In the treatment of IgAV patients with gastrointestinal involvement, there are conflicting opinions of various authors (23–25) about the use of glucocorticoids. Accordpedijatriju Kliničkoga bolničkog centra Zagreb analizirane su kliničke i laboratorijske značajke bolesnika s IgA vaskulitisom koji su imali zahvaćen gastrointestinalni sustav. Gastrointestinalni simptomi prisutni su u većine bolesnika s IgAV-om, a njihova se učestalost prema literaturnim podacima kreće između 50% i 75% (4–7). Osim toga, upravo su sa zahvaćanjem gastrointestinalnog sustava najčešće povezane akutne komplikacije koje se pojavljuju u ovoj bolesti, a koje mogu dovesti do životne ugroze bolesnika te zahtijevati kirurško liječenje (4,5,8). Iz našeg je istraživanja razvidno da je broj bolesnika s gastrointestinalnim simptomima u okviru prosjeka koji je opisan i u drugim istraživanjima (43,5%) (9–11). Uočena je statistički značajna razlika u češćem zahvaćanju muškog spola u bolesnika s gastrointestinalnim simptomima (p=0,019), što je u skladu s literaturnim podatcima (4,12,13). Bolesnici sa zahvaćenim gastrointestinalnim sustavom imali su veću pojavu generaliziranoga purpuričnog osipa, odnosno purpure proširene na oba ekstremiteta (14–16). Klinički najznačajniji rezultati vezani su uz činjenicu da su bolesnici u kojih su se pojavili gastrointestinalni simptomi u konačnici češće razvili nefritis u sklopu IgAV-a, što je najvažnija kronična komplikacija bolesti koja može rezultirati kroničnim zatajenjem bubrega u 1–15% bolesnika (17–20). U našoj kohorti bolesnika učestalost nefritisa bila je 1,81 puta veća u skupini bolesnika koji su imali barem jedan gastrointestinalni simptom. Druga povezanost između gastrointestinalnog sustava i bubrega očitovala se u većoj učestalosti mikrohematurije u bolesnika s gastrointestinalnim simptomima, a ti su bolesnici češće liječeni glukokortikoidima, imunosupresivima i antihipertenzivima te su imali dulje trajanje hospitalizacije (p<0,001) (4,12). Povezanost zahvaćanja probavnog sustava i bubrega u IgAV-u opisana je u nekim istraživanjima, ali rezultati nisu jednoznačni (13,18, 21,22). Patofiziološki mehanizam kojim bi se objasnila povećana učestalost nefritisa u bolesnika koji su imali prisutne gastrointestinalne simptome nije poznat. No, iz ovog opažanja važno je istaknuti kako bi bolesnici u kojih su se pojavile gastrointestinalne manifestacije mogli imati veći rizik za razvoj nefritisa. S tim u svezi, još nije riješeno pitanje optimalne duljine praćenja ovih bolesnika kako bi se na vrijeme izdvojili oni u kojih je došlo do pojave nefritisa (18). U liječenju bolesnika s IgAV-om koji imaju zahvaćen gastrointestinalni sustav postoje oprečna razmišljanja različitih autora (23–25) o primjeni glukokortikoida pa tako prema jednima glukokortikoidi značajno smanjuju bol, trajanje hospitalizacije i sprječavaju nastanak komplikacija (24), dok drugi nisu primijetili značajno smanjenje rizika u ponovnom javljanju gastrointestinalnih simptoma (25). Prema preporukama SHARE (engl. *Single-Hub Access for Pediatric Rheumatology in Europe*) glukokortikoidi su indicirani kratkotrajno i/ili u slučajevima ozbiljnoga

ing to some, glucocorticoids significantly reduce pain, length of stay in the hospital and prevent the development of complications (24), while others did not notice a significant reduction in risk of recurrence of gastrointestinal symptoms (25). According to the recommendations of the SHARE initiative (Single-Hub Access for Paediatric Rheumatology in Europe) glucocorticoids are indicated for short-term use and/or in cases of severe gastrointestinal bleeding (26). Out of a total of 94 patients with gastrointestinal symptoms, 74 (78.7%) were treated with glucocorticoids, and 20 of them had a recurrence of IgAV, most often in the form of purpuric rash, so, in our experience, the short-term use of glucocorticoids in patients with severe gastrointestinal manifestations proved to be effective. In addition to the fact that our patients with gastrointestinal involvement were more often treated with glucocorticoids, they also received antihypertensive therapy with angiotensin-converting enzyme (ACE) inhibitors, as the majority of patients in this group were those with nephritis, and, according to the recommendations of the SHARE initiative, it is advisable to use this type of therapy in all patients who have developed proteinuria as a result of nephritis due to the beneficial effect on the prevention or limitation of secondary glomerular disease (26). Clinical manifestations of gastrointestinal involvement in IgA vasculitis most often include nausea, vomiting and abdominal pain (cramping), which is most often present in the periumbilical region and the epigastrium (3–5). Furthermore, in our patient cohort, the clinical features of most of our patients, 67 of them (31%), included abdominal pain in the periumbilical region. Gastrointestinal bleeding occurred in 48 patients (22.2%), which is also within the expected frequency of this manifestation, which otherwise occurs in the range from 18 to 52% (4–7,12). Bleeding was mostly occult, and the follow-up of patients with positive occult bleeding lasted for the next six months, with no cases of recurrence of blood in the stool. In 34 patients (15.7%) gastrointestinal symptoms had occurred prior to the onset of the characteristic purpuric rash, with a median of three days, similar to other studies, although the gastrointestinal symptoms may precede the onset of purpura by up to two weeks (4,5,8,27– 29). This is often a differential diagnostic problem because it mimics the acute abdomen, which often includes surgical intervention (8,27,29). Only one patient (0.5%) had to undergo surgery, as he developed ileocaecocolic intussusception, so, it can be concluded that the most severe gastrointestinal complications in our study were extremely rare. In the reviewed literature, intussusception is mentioned as the most common complication related to the gastrointestinal system with an incidence of 0.7–13.6% (4,5). Among the imaging tests, an ultrasound and a CT scan are the most used methods (4–6,30). According to

gastrointestinalnog krvarenja (26). Od 94 naša bolesnika s gastrointestinalnim simptomima njih 74 (78,7%) liječeno je glukokortikoidima, a od toga ih je 20 imalo ponovnu pojavu IgAV-a i to najčešće u vidu purpure, tako da se prema našim iskustvima kratkotrajna primjena glukokortikoida u bolesnika s težim gastrointestinalnim manifestacijama pokazala učinkovitom. Osim što su naši bolesnici sa zahvaćenim gastrointestinalnim sustavom češće liječeni glukokortikoidima, oni su češće primali i antihipertenzivnu terapiju inhibitorima angiotenzin konvertaze, budući da su se u toj skupini bolesnika češće nalazili oni s nefritisom, a prema preporukama SHARE poželjno je takvu terapiju uključiti u svih bolesnika u kojih se u sklopu nefritisa pojavila proteinurija radi povoljnog učinka na prevenciju ili ograničavanje sekundarnoga glomerularnog oštećenja (26). Klinički se zahvaćanje gastrointestinalnog sustava u IgA vaskulitisu najčešće očituje mučninom, povraćanjem i grčevitim bolovima u trbuhu koji su najčešće locirani epigastrično i periumbilikalno (3–5), a i u našoj kohorti bolesnika najveći broj, njih 67 (31%), imao je kliničku sliku periumbilikalnih bolova u trbuhu. Gastrointestinalno krvarenje pojavilo se u 48 bolesnika (22,2%), što je također u okviru očekivane učestalosti ove manifestacije koja se inače pojavljuje u rasponu od 18 do 52% (4–7,12). Krvarenje je većinom bilo okultno, a bolesnici s pozitivnim okultnim krvarenjem praćeni su kroz sljedećih šest mjeseci, pri čemu niti u jednom slučaju nije došlo do ponovne pojave krvi u stolici. U 34 bolesnika (15,7%) gastrointestinalni simptomi prethodili su pojavi karakterističnoga purpuričnog osipa, s medijanom od tri dana, slično kao i u ostalim istraživanjima, iako gastrointestinalni simptomi mogu prethoditi pojavi purpure i do dva tjedna (4,5,8,27–29). Navedeno često predstavlja i diferencijalno-dijagnostički problem jer oponaša akutni abdomen koji onda nerijetko uključuje i kiruršku intervenciju (8,27,29). Samo jedan bolesnik (0,5%) liječen je kirurški, budući da je razvio ileocekokoličnu invaginaciju crijeva, pa se prema tome može zaključiti da su najteže gastrointestinalne komplikacije u našem istraživanju bile iznimno rijetke. U literaturi se kao najčešća komplikacija vezana uz gastrointestinalni sustav upravo i spominje intususcepcija s učestalošću 0,7–13,6% (4,5). Od slikovnih pretraga najčešće korištene metode jesu ultrazvučna i CT dijagnostika (4–6,30). Prema većini autora, ultrazvučna dijagnostika je prvi izbor u otkrivanju crijevnog vaskulitisa među slikovnim metodama zbog svoje neinvazivnosti i sigurne primjene, što je osobito važno u dječjoj populaciji (4,5,30). Znakovi zadebljanja crijevne stijenke uz edem sluznice ultrazvučno izgledaju poput ograničenih hipoehogenih polumjeseca, a obojenim doplerom u zahvaćenom dijelu crijeva detektira se smanjeni protok (4,5,30). Još jedna prednost ultrazvuka jest mogućnost procjene količine intraabdominalne tekućine i

most authors, diagnostic ultrasound is the first choice in the detection of intestinal vasculitis among other imaging methods due to its non-invasiveness and safe use, which is especially important in the paediatric population (4,5,30). Signs of bowel wall thickening with mucosal oedema appear on ultrasound as limited hypoechoic crescents, and colour Doppler is used for the detection of low flow in the involved part of the intestine (4,5,30). Another advantage of ultrasound is its ability to assess the amount of intra-abdominal fluid and to perform early detection of complications such as intussusception (4–6). Ultrasound has proved to be useful in the diagnostic procedure involving our patient with ileocaecocolic intussusception as well. The largest number of patients in our study had an ultrasound finding that showed no abnormalities, which corresponds to the results of other authors (4,6), followed by mesenteric lymphadenitis, which is also a common finding (4,5). Among the laboratory findings, it was observed that patients with gastrointestinal involvement had a statistically significantly higher number of leukocytes, which can be interpreted as a systemic response with leukocyte migration to the site of intestinal inflammation (7,18,28). Furthermore, significant differences were observed in terms of lower values in erythrocyte sedimentation rate and total protein in this group of patients. Lower total protein values have previously been described by Nagamori et al., and this finding could be associated with higher intestinal protein permeability due to intestinal vasculitis, but it could also be related to greater loss of protein and albumin through the kidneys, as most of these patients had nephritis (31). Although calprotectin is an important biomarker of inflammation, as it is released from neutrophils that migrate to the site of intestinal inflammation and then excreted in the stool (12,32), our study did not show a statistically significant difference in faecal calprotectin between the two groups (p = 0.377). The follow-up of patients with gastrointestinal symptoms lasted for six months and during that period all of them have recovered.

To conclude, most gastrointestinal symptoms in IgAV are self-limiting and often resolve spontaneously or with short-term drug use. Our study has confirmed that severe, life-threatening complications of IgAV are rare. However, the patients who developed gastrointestinal symptoms were also more prone to developing nephritis, the most important chronic complication of IgAV. Also, in our group of IgAV patients, patients with gastrointestinal symptoms were more often male, with a longer length of stay in the hospital, they were more often treated with glucocorticoids and antihypertensives, and had a higher incidence of relapse. This calls for caution and raises the question of the need for longer clinical follow-up of these patients to detect and ranog uočavanja komplikacija poput intususcepcije (4–6). I u slučaju našeg bolesnika s ileocekokoličnom invaginacijom crijeva ultrazvuk se pokazao korisnim u dijagnostici. Najveći broj bolesnika u našem istraživanju imao je uredan ultrazvučni nalaz, što odgovara i rezultatima drugih autora (4,6), potom mezenterijski limfadenitis koji je također čest nalaz (4,5). Među laboratorijskim nalazima uočeno je da su bolesnici sa zahvaćenim gastrointestinalnim sustavom imali statistički značajno veći broj leukocita, što se najvjerojatnije može protumačiti kao sustavni odgovor uz migraciju leukocita na mjesto crijevne upale (7,18,28). Nadalje, uočene su značajne razlike u smislu nižih vrijednosti u brzini sedimentacije eritrocita i ukupnih proteina u navedenoj skupini bolesnika. Snižene vrijednosti ukupnih proteina ranije su opisali Nagamori i sur., a taj bi se nalaz mogao povezati s većom propusnošću crijevne sluznice za bjelančevine uslijed vaskulitisa crijeva, ali možda i s većim gubitkom bjelančevina i albumina putem bubrega, s obzirom na to da su ti bolesnici češće imali nefritis (31). Iako je kalprotektin važan biomarker upale, budući da se oslobađa iz neutrofila koji migriraju na mjesto crijevne upale i potom izlučuje u stolici (12,32), u našem istraživanju nije zabilježena statistički značajna razlika u vrijednostima fekalnog kalprotektina između dviju skupina (p=0,377). Bolesnici s gastrointestinalnim simptomima praćeni su kroz šest mjeseci tijekom kojih je u svih došlo do oporavka.

Zaključno, većina gastrointestinalnih simptoma u IgAV-u jest samoograničavajuća pa često i spontano prestaje ili uz kratkotrajnu primjenu lijekova. Naše istraživanje je potvrdilo da su teške, po život opasne komplikacije IgAV-a rijetke. Međutim, bolesnici u kojih su se pojavili gastrointestinalni simptomi u konačnici su češće razvili nefritis, najvažniju kroničnu komplikaciju IgAV-a. Također, u našoj skupini bolesnika s IgAV-om bolesnici s gastrointestinalnim simptomima češće su bili muškog spola, imali su dulje trajanje hospitalizacije, češće su liječeni glukokortikoidima i antihipertenzivima te su imali veću pojavu relapsa. To nalaže oprez i otvara pitanje za potrebom duljega kliničkog praćenja ovih bolesnika kako bi se na vrijeme otkrile i počele liječiti moguće komplikacije bolesti.

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begin the treatment of the possible complications of the disease in time.

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REFERENCES / LITERATURA

1. Jelušić M, Frković M. Vasculitides in childhood. Reumatizam. 2016;63(Suppl 1):80–5. [in Croatian]
2. Šapina M, Frković M, Šestan M, Sršen S, Ovuka A, Batnožić Varga M i sur. Geospatial clustering of childhood IgA vasculitis and IgA vasculitis-associated nephritis. Ann Rheum Dis. 2021; 80(5):610–16.
3. Ozen S, Pistorio A, Iusan SM, Bakkaloglu A, Herlin T, Brik R i sur. EULAR/PRINTO/PRES criteria for Henoch-Schonlein purpura, childhood polyarteritis nodosa, childhood Wegener granulomatosis and childhood Takayasu arteritis: Ankara 2008. Part II: Final classification criteria, Ann Rheum Dis. 2010;69(5):798–806.
4. Chen SY, Kong MS. Gastrointestinal manifestations and complications of Henoch-Schönlein purpura. Chang Gung Med. 2004;27(3):175–81.
5. Ebert EC. Gastrointestinal manifestations of Henoch-Schönlein purpura. Dig Dis Sci. 2008;53(8):2011–9.
6. Chang WL, Yang YH, Lin YT, Chiang BL. Gastrointestinal manifestations in Henoch-Schönlein purpura: a review of 261 patients. Acta Pædiatr. 2004;93(11):1427–31.
7. Makay B, Altug˘ Gücenmez Ö, Duman M, Ünsal E. The relationship of neutrophil-to-lymphocyte ratio with gastrointestinal bleeding in Henoch-Schönlein purpura. Rheumatol Int. 2014;34(9):1323–7.
8. Choong CK, Beasley SW. Intra-abdominal manifestations of Henoch-Schönlein purpura. J Paediatr Child Health. 1998;34 (5):405–9.
9. Karadağ ŞG, Tanatar A, Sönmez HE, Çakmak F, Kıyak A, Yavuz S i sur. The clinical spectrum of Henoch-Schönlein purpura in children: a single-center study. Clin Rheumatol. 2019; 38(6):1707–14.
10. Dolezalová P, Telekesová P, Nemcová D, Hoza J. Incidence of vasculitis in children in the Czech Republic: 2-year prospective epidemiology survey. J Rheumatol. 2004;31(11):2295–9.
11. Riancho-Zarrabeitia L, Santurtun A. Cutaneous vasculitis in children: A nationwide epidemiological study in Spain. F1000Res. 2017;6:1527.
12. Paek Young E, Yong Yi D, Kang B, Choe BH. Fecal calprotectin as a marker of gastrointestinal involvement in pediatric Henoch-Schönlein purpura patients: a retrospective analysis. BMC Pediatr. 2020;20(1):374–81.
13. Ekinci RMK, Balci S, Melek E, Karabay Bayazit A, Dogruel D, Altintas DU i sur. Clinical manifestations and outcomes of 420 children with Henoch Schönlein purpura from a single referral center from Turkey: A three-year experience. Mod Rheumatol. 2020;30(6):1039–46.
14. Johnson EF, Lehman JS, Wetter DA, Lohse CM, Tollefson MM. Henoch-Schönlein purpura and systemic disease in children: retrospective study of clinical findings, histopathology and direct immunofluorescence in 34 paediatric patients. Br J Dermatol. 2014;172(5):1358–63.
15. Demircioğlu Kılıç B, Demir Kasap B. Determination of risk factors in children diagnosed with Henoch-Schönlein purpura. Arch Rheumatol. 2018;33(4):395–401.
16. Hočevar A, Tomšić M, Jurčić V, Perdan Pirkmajer K, Rotar Ž. Predicting gastrointestinal and renal involvement in adult IgA vasculitis. Arthritis Res Ther. 2019;21(1):302–8.
17. Oni L, Sampath S. Childhood IgA vasculitis (Henoch Schönlein purpura)-advances and knowledge gaps. Front Pediatr. 2019;7:257.
18. Ozturk K, Cakan M. Initial manifestations and short term follow-up results of Henoch-Schönlein purpura in children: A report from two centers. North Clin Istanb. 2020;7(4):341–7.
19. Kawasaki Y, Ono A, Ohara S, Suzuki Y, Suyama K, Suzuki J i sur. Henoch-Schönlein purpura nephritis in childhood: pathogenesis, prognostic factors and treatment. Fukushima J Med Sci. 2013;59(1):15–26.
20. Chen JY, Mao JH. Henoch-Schönlein purpura nephritis in children: incidence, pathogenesis and management. World J Pediatr. 2015;11(1):29–34.
21. Chan H, Tang YL, Lv XH, Zhang GF, Wang M, Yang HP i sur. Risk factors associated with renal Involvement in childhood Henoch-Schönlein purpura: a meta-analysis. PLoS One. 2016; 11(11):0167346.
22. Taner Elmas A, Tabel Y. Platelet counts in children with Henoch-Schönlein purpura – relationship to renal involvement. J Clin Lab Anal. 2016;30(1):71–4.
23. Gonzalez-Gay MA, Llorca J. Controversies on the use of corticosteroid therapy in children with Henoch-Schönlein purpura. Semin Arthr Rheum. 2005;35(3):135–7.
24. Ronkainen J, Koskimies O, Ala-Houhala M, Antikainen M, Merenmies J, Rajantie J i sur. Early prednisone therapy in Henoch-Schonlein purpura: a randomized, double-blind, placebo-controlled trial. J Pediatr. 2006;149(2):241–7.
25. Huber AM, King J, McLaine P, Klassen T, Pothos M. A randomized, placebo-controlled trial of prednisone in early Henoch Schönlein purpura. BMC Med. 2004;2:7.
26. Ozen S, Marks SD, Brogan P, Groot N, de Graeff N, Avcin T i sur. European consensus-based recommendations for diagnosis and treatment of immunoglobulin A vasculitis – the SHARE initiative. *Rheumatology (Oxford). 2019;*58(9):1607–16.
27. Teng X, Gao C, Sun M, Wu J. Clinical significance of fecal calprotectin for the early diagnosis of abdominal type of Henoch-Schönlein purpura in children. Clin Rheumatol. 2018;37(6): 1667–73.
28. Hong J, Yang HR. Laboratory markers indicating gastrointestinal involvement of Henoch-Schönlein purpura in children. Pediatr Gastroenterol Hepatol Nutr. 2015;18(1):39–47.
29. Cull DL, Rosario V, Lally KP, Irving R, Cull L, Mahour GH. Surgical implications of Henoch-Schönlein purpura. J Pediatr Surg. 1990;25(7):741–3.
30. Ge Y, Liu S. Ultrasound, X-ray, computed tomography and clinical tests for diagnosis of abdominal purpura in children: A retrospective study. Exp Ther Med. 2020;19(6):3559–64.
31. Nagamori T, Oka H, Koyano S, Takahashi H, Oki J, Sato Y i sur. Construction of a scoring system for predicting the risk of severe gastrointestinal involvement in Henoch-Schönlein purpura. Springerplus. 2014;3:171.
32. Kanik A, Baran M, Ince FD, Cebeci O, Bozkurt M, Cavusoglu D i sur. Faecal calprotectin levels in children with Henoch-Schönlein purpura: is this a new marker for gastrointestinal involvement? Eur J Gastroenterol Hepatol 2015;27(3):254–8.

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CASE REPORT PRIKAZ BOLESNIKA

INTESTINAL VASCULITIS AS A MANIFESTATION OF DIFFERENT SYSTEMIC AUTOIMMUNE DISEASES TREATED AT THE SPLIT UNIVERSITY HOSPITAL CENTRE DURING A 10-YEAR PERIOD

VASKULITISI CRIJEVA KAO OČITOVANJA RAZNIH SUSTAVNIH AUTOIMUNIH BOLESTI LIJEČENI U KLINIČKOM BOLNIČKOM CENTRU SPLIT U DESETOGODIŠNJEM RAZDOBLJU

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Abstract

Introduction. The most common types of vasculitis that involve the gastrointestinal tract (GIV) are immune complex-mediated in systemic lupus erythematosus (SLE), Sjögren's syndrome (SS), mixed connective tissue disease (MCTD), and IgA vasculitis (IgAV). GI manifestations are rarely the leading symptom of systemic vasculitis. Only 1 – 5% of rheumatoid arthritis (RA) patients develop symptoms of gastrointestinal tract vasculitis (GIV), while up to 40% of them have GI symptoms. GIV is a rare but life-threatening complication in patients with SLE with a prevalence of up to 2.5%. The leading symptoms in patients with GIV include abdominal pain, nausea, vomiting, diarrhoea, small bowel obstruction, and profuse GI bleeding. The objective of this study was to describe the incidence and clinical manifestations of GIV in patients with various systemic autoimmune (AI) diseases who were treated at Split University Hospital Centre over a 10-year period. *Materials and methods.* A retrospective study was conducted by analysing medical records of patients diagnosed with GIV and treated for SLE, SS, MCTD, vasculitis syndrome, IgAV, and RA between January 2009 and December 2018. Only patients with anamnestic data in relation to abdominal pain or endoscopic and/or radiographic findings of GIV were included in the study. *Results.* Out of a total number of 12 patients with a confirmed diagnosis of GIV, 9 were male. Eight of them had vasculitis with gastrointestinal involvement (GIV) in IgAV, 2 patients had GIV in SLE, 1 patient had microscopic polyangiitis (MPA), and one patient had primary SS. In 6 cases, GIV was diagnosed by an MSCT of the abdomen, in one case it was diagnosed by a PET-CT scan, in another case it was diagnosed through histopathological findings, and in 4 cases it was diagnosed through endoscopic findings. The leading symptom in 4 patients was abdominal pain with nausea and vomiting, 2 had profuse GI bleeding, 1 had fatigue without GI symptoms, and the remaining patients' clinical features included acute abdomen with visible radiographic thickening of the bowel wall with oedema and stratification with ascites. GIV was the cause of death of one patient with SLE. Others had a good or moderate response to treatment with glucocorticoids and immunosuppressants. *Conclusion.* In conclusion, GIV is a rare manifestation of systemic AI diseases, but the clinical features can be very severe and lead to a fatal outcome, especially if it is not diagnosed at an early stage and treated with aggressive immunosuppressive therapy.

Key words: Vasculitis; Gastrointestinal; Mesenteric; IgA vasculitis; Autoimmune diseases

Sažetak

Uvod. Najčešći vaskulitisi gastrointestinalnog trakta (GIV) su oni posredovani imuno-kompleksima u sistemskom eritemskom lupusu, Sjögrenovoj bolesti, miješanoj bolesti vezivnog tkiva, IgA-vaskulitisu (IgAV). Gastrointestinalne (GI) manifestacije rijetko su vodeći simptom sustavnih vaskulitisa. Samo 1–5% bolesnika s reumatoidnim artritisom razvija kliničku sliku vaskulitisa gastrointestinalnoga trakta (GIV), dok ih do 40% ima GI simptome. GIV je rijetka, ali životno ugrožavajuća komplikacija u bolesnika sa sistemskim eritemskim lupusom (SLE), s prevalencijom do 2,5%. Vodeći simptomi u bolesnika s GIV-om su bol u trbuhu, mučnina, povraćanje, proljev, opstrukcija tankog crijeva i obilno GI krvarenje. Cilj ovog rada bio je ispitati učestalost i klinička očitovanja GIV-a u bolesnika s različitim sustavnim autoimunim (AI) bolestima liječenih u KBC-u Split u desetogodišnjem razdoblju. *Materijali i metode.* Retrospektivno su analizirani podatci iz medicinske dokumentacije bolesnika koji su se liječili od SLE-a, Sjögrenovog sindroma (SjS), miješane bolesti vezivnog tkiva (MCTD), sindroma vaskulitisa, IgA-vaskulitisa (IgAV) i i RA, a imali su anamnestičke podatke o boli u trbuhu ili endoskopske ili/i radiografske znakove GIV-a, u razdoblju od 1/2009. do 12/2018. *Rezultati.* Od ukupno 12 bolesnika s potvrđenom dijagnozom GIV-a, 9 su bili muškarci. Osam ih je imalo GIV u sklopu IgAV-a, dvije bolesnice u sklopu SLE-a, MPA jedna bolesnica, primarnog SS-a jedan bolesnik. U 6 slučajeva GIV je dokazan MSCT-om trbuha, u jednom PET-CT-om, u jednom patohistološki, a u 4 slučaja endoskopski. Vodeći simptom u četvoro bolesnika bila je bol u trbuhu s mučninom i povraćanjem, dva su imala su obilno GI krvarenje, jedna bolesnica je imala umor bez GI simptoma, a preostali kliničku sliku akutnog abdomena s radiološki verificiranim edemom i raslojavanjem stijenke crijeva uz ascites. GIV je bio uzrok smrti jedne bolesnice sa SLE-om. Ostali su imali dobar ili umjeren odgovor na liječenje glukokortikoidima i imunosupresivima. *Zaključak.* Zaključno, GIV je rijetka manifestacija sustavnih AI bolesti, ali klinička slika može biti vrlo teška i dovesti do fatalnog ishoda te je nužna brza dijagnoza i agresivno imunosupresivno liječenje.

Ključne riječi: Vaskulitis; Gastrointestinalni; Mezenterijalni; IgA-vaskulitis; Autoimune bolesti

INTRODUCTION

Systemic autoimmune (AI) diseases can cause various gastrointestinal (GI) disorders, some of which may be the first symptom of the disease and some a consequence of underlying disease treatment (1). Rare but potentially fatal GI manifestations of AI diseases, which require timely and rapid care, are vasculitides of the GI tract (gastrointestinal vasculitis, GIV). Vasculitis is an inflammation of the walls of blood vessels with or without necrosis and granuloma. The diagnosis of different forms of GIV is based on a combination of clinical features and available tests (endoscopy, computed tomography (CT), magnetic resonance imaging (MRI), histopathology diagnosis). It is crucial to make a correct diagnosis given the different approaches to treatment, but also the prognosis that varies greatly depending on the type of disorder (2). GI blood vessels can be affected in various types of vasculitis affecting large, medium and small blood vessels and those of variable size according to the 2012 Revised International Chapel Hill classification (Table 1) (3). The GI tract (GIT) may be the primary site of involvement of several systemic vasculitides: Henoch–Schönlein purpura (IgA vasculitis, IgAV), polyarteritis nodosa (PAN), eosinophilic granulomatosis with polyangiitis (EGPA), microscopic polyangiitis (MPA), granulomatosis with polyangiitis (GPA), Behçet's disease, systemic lupus erythematosus (SLE), mixed connective tissue disease (MCTD), systemic sclerosis (SSc). The most common types of vasculitides that involve the GIT tract are: SLE, MCTD and IgAV (2). GIV is almost just

UVOD

Sistemske autoimune (AI) bolesti mogu uzrokovati čitav spektar različitih gastrointestinalnih (GI) poremećaja od kojih neki mogu biti prvi simptom bolesti, a neki posljedica liječenja osnovne bolesti (1). Rijetke, ali potencijalno fatalne GI manifestacije AI bolesti, koje zahtijevaju pravodobno i brzo zbrinjavanje, upravo su vaskulitisi GI trakta (engl. *gastrointestinal vasculitis*, GIV). Vaskulitis je upala stijenke krvne žile s nekrozom i granulomom ili bez njih. Dijagnoza različitih oblika GIV-a temelji se na kombinaciji kliničke slike i dostupnih pretraga (endoskopija, kompjuterizirana tomografija [engl. *computed tomography*, CT], magnetska rezonancija [engl. *magnetic resonance imaging*, MRI], patohistološka dijagnostika [PHD]). Od ključne je važnosti postaviti ispravnu dijagnozu s obzirom na različite pristupe u liječenju, ali i prognoze koji se uvelike razlikuju ovisno o vrsti poremećaja (2). GI krvožilje može biti zahvaćeno kod raznih tipova vaskulitisa koji pogađaju velike, srednje i male krvne žile te one promjenjive veličine sukladno Chapel Hill klasifikaciji revidiranoj 2012. (tablica 1) (3). GI trakt (GIT) može biti primarno mjesto zahvaćanja nekoliko sistemskih vaskulitisa: Henoch-Schönleinova purpura (IgA-vaskulitis, IgAV), nodozni poliarteritis (engl. *polyarteritis nodosa*, PAN), eozinofilna granulomatoza s poliangiitisom (engl. *eosinophilic granulomatosis with polyangiitis*, EGPA), mikroskopski poliangiitis (engl. *microscopic polyangiitis*, MPA), granulomatoza s poliangiitisom (engl. *granulomatosis with polyangiitis*, GPA),

Table 1. Classification of vasculitis according to 2012 Chapel Hill Classification (according to reference no. 3)
Tablica 1. Klasifikacija vaskulitisa prema reviziji Chapel Hill klasifikacije iz 2012. godine (prema referenciji br. 3)

Large-vessel vasculitis / Vaskulitis velikih krvnih žila	Giant cell arteritis / Gigantocelularni (temporalni) Takayasu's arteritis / Takayasuov arteritis
Medium-vessel vasculitis / Vaskulitis srednje velikih krvnih žila	Polyarteritis nodosa / Nodozni poliarteritis
Small-vessel vasculitis / Vaskulitis malenih krvnih žila	Kawasaki disease / Kawasakijeva bolest ANCA-associated vasculitis / ANCA-vaskulitis – Microscopic polyangiitis (MPA) / mikroskopski poliangiitis (MPA) – Granulomatosis with polyangiitis (GPA) / Granulomatoza s poliangiitisom (GPA) – Eosinophilic granulomatosis with polyangiitis (EGPA) / Eozinofilna granulomatoza s poliangiitisom (EGPA) Immune complex vasculitis / Vaskulitis imunih kompleksa – Anti-glomerular basement membrane (anti-GBM) disease / Anti-GBM vaskulitis – Cryoglobulinemic vasculitis / Krioglobulinemički vaskulitis – IgA vasculitis (Henoch-Schönlein) / IgA-vaskulitis (Henoch-Schönlein) – Hypocomplementemic urticarial vasculitis (HUV) (anti-C1q vasculitis) / Hipokomplementemički urtikarijalni vaskulitis (anti-C1q-vaskulitis)
Variable-vessel vasculitis / Vaskulitis različito velikih krvnih žila	Behçet's disease / Behçetova bolest Cogan's syndrome / Coganov sindrom
Single-organ vasculitis / Vaskulitis jednog organa	Cutaneous leukocytoclastic angiitis / Kožni leukocitoklastički angiitis Cutaneous arteritis / Kožni arteritis Primary CNS vasculitis / Primarni vaskulitis SŽS-a Isolated aortitis / Izolirani aortitis Others / Drugo
Vasculitis associated with systemic disease / Vaskulitis udružen sa sistemskom autoimunosnom bolešću	Lupus vasculitis / Lupusni vaskulitis Rheumatoid vasculitis / Reumatoidni vaskulitis Sarcoid vasculitis / Vaskulitis u sarkoidozi Others / Drugo
Vasculitis associated with systemic disease / Vaskulitis udružen s drugim bolestima	Hepatitis C virus-associated cryoglobulinemic vasculitis / Krioglobulinemički vaskulitis uz infekciju HCV-om Hepatitis B virus-associated vasculitis / Vaskulitis uz infekciju HBV-om Syphilis-associated aortitis / Aortitis udružen sa sifilisom Drug-associated immune complex vasculitis / Vaskulitis imunih kompleksa uzrokovan lijekovima Drug-associated ANCA-associated vasculitis / ANCA-vaskulitis uzrokovan lijekovima Cancer-associated vasculitis / Vaskulitis uz malignu bolest Others / Drugo

Legend / Legenda: ANCA – antineutrophil cytoplasmic antibodies / antineutrofilna citoplazmatska antitijela; GBM – glomerular basement membrane / glomerularna bazalna membrana; CNS / SŽS – central nervous system / središnji živčani sustav; HCV – hepatitis C virus / virus hepatitisa C; HBV – hepatitis B virus / virus hepatitisa B.

as often induced by drugs and GI infections (due to glucocorticoid [GC]-induced immunosuppression) (4). The pathophysiological mechanism of most gastrointestinal vasculitides (GIVs) is immune-mediated by the deposition of autoantibody and antigen complexes or antibody complexes, as well as the direct action of antibodies. In some cases, a cell-mediated allograft rejection reaction occurs (1,4). In case of some diseases, such as Takayasu's arteritis (TAK) or polyarteritis nodosa (PAN), the pathophysiological mechanism is still not completely clear (4).

The clinical course as well as pathological changes in GIV are highly variable and depend on the type of vascular lesions (localised or diffuse) of the GI tract. Accordingly, GIT lesions in vasculitis include ulcers, submucosal oedema, haemorrhage, paralytic ileus, mesen-

Behçetova bolest, sistemski eritemski lupus (engl. *systemic lupus erythematosus*, SLE), miješana bolest vezivnog tkiva (engl. *mixed connective tissue disease*, MCTD), sistemska skleroza (engl. *systemic sclerosis*, SSc). Od navedenih, GIT najčešće zahvaćaju: SLE, MCTD i IgAV (2). Gotovo jednako često GIV je induciran lijekovima te GI infekcijama (uslijed glukokortikoidno [GK] uzrokovane imunosupresije) (4). Patofiziološki mehanizam većine GIV-a je imunološki posredovan odlaganjem kompleksa autoprotutijela i antigena ili samih protutijela, kao i direktnim djelovanjem protutijela. U nekim slučajevima dolazi do stanično posredovane reakcije odbacivanja alotransplantata (1,4). Za neke bolesti, poput Takayasuova arteritisa (TAK) ili nodoznog poliarteritisa (PAN), patofiziološki mehanizam još uvijek nije u potpunosti jasan (4).

teric ischaemia, bowel obstruction, and perforation (5,6,7). Clinical manifestations range from abdominal pain (sometimes cramping), which usually gets worse after eating, to obvious signs of intestinal ischaemia or bowel perforation with diffuse and constant abdominal pain, slow peristalsis, guarding and distension, and signs of peritoneal irritation. GI bleeding, often occult, hematochezia, and less frequently melena or rectorrhagia, are common occurrences. Non-specific symptoms such as nausea, vomiting or diarrhoea may also occur. Furthermore, pancreatitis, cholecystitis or appendicitis may rarely occur (8).

GIT involvement in large-vessel vasculitis is not a common occurrence. Takayasu's arteritis is a type of vasculitis that commonly affects the celiac plexus and hepatic or mesenteric arteries, with clinically significant consequences in about 16% of patients, while only 4% of patients develop mesenteric ischaemia (4,9). Half of patients with polyarteritis nodosa (PAN) develop GIV, which can manifest as acute abdominal pain, GI bleeding, infarction, peritonitis, cholecystitis, appendicitis, and perforation (4). Up to 60% of patients with Kawasaki disease may have GI symptoms (abdominal pain, vomiting), but these symptoms are severe in only 4.6% of patients (10).

When it comes to antineutrophil cytoplasmic antibody (ANCA)-associated vasculitides (AAV), GIT involvement is more common in eosinophilic granulomatosis with polyangiitis (EGPA) (35 – 50%) in comparison with microscopic polyangiitis (MPA) (5 – 30%) or granulomatosis with polyangiitis (GPA) (5 – 10%). The leading GI symptoms in patients with EGPA are abdominal pain, bloody diarrhoea (30 – 58%), vomiting, ileus, anorexia, GI bleeding (29%), and odynophagia. Patients with GPA have similar symptoms, with possible intestinal perforation and/or ischaemia and granulomatous hepatitis or pancreatitis. Symptoms of GIV in patients with MPA range from abdominal pain, nausea, vomiting, and diarrhoea to, rarely, ischaemic colon ulcers, peritonitis, and bowel perforation (2,4).

GI symptoms in IgAV are varied and very common (50 – 85% of patients) and they include: diarrhoea, vomiting, abdominal pain, obstruction, perforation, distension, intussusception, haematemesis, melena, and hematochezia. The inferior part of the duodenum is predominantly affected. In approximately 14% of cases, GIV is the first manifestation of IgAV (11,12). There are two types of GIV in Behçet's disease that can develop in 3 – 50% of patients. If small blood vessels are affected, inflammation of the intestinal mucosa with ulcerations occurs, and if large-vessel vasculitis develops, ischaemia and infarction of the bowel wall can occur (13,14).

Various GI manifestations may occur in patients with SLE (up to 40%), including lupus peritonitis, non-

Klinički tijek kao i patološke promjene u GIV-u jako su varijabilni te ovise o vrsti oštećenja GI krvožilja (lokalno ili difuzno). Sukladno tomu, lezije GIT-a u vaskulitisu uključuju ulkuse, submukozni edem, krvarenje, paralitički ileus, ishemiju mezenterija, opstrukciju crijeva i perforaciju (5,6,7). Kliničke manifestacije variraju od boli u trbuhu (ponekad grčevite), koja se obično pogoršava nakon jela, do očitih znakova ishemije ili perforacije crijeva uz difuznu i konstantnu trbušnu bol, usporenu peristaltiku„defans" i distenziju te znakove peritonealnog nadražaja. GI krvarenje, često okultno, hematokezija te rjeđe melena ili rektoragija, učestale su pojave. Također se mogu pojaviti i nespecifični simptomi poput mučnine, povraćanja ili proljeva. Nadalje, rijetko može doći i do pojave pankreatitisa, kolecistitisa ili apendicitisa (8).

Zahvaćenost GIT-a u vaskulitisima velikih krvnih žila nije česta pojava. GIV u sklopu TAK-a najčešće zahvaća celijačni pleksus te hepatalne ili mezenterične arterije, s klinički značajnim posljedicama u oko 16% bolesnika, dok se u svega 4% bolesnika razvija ishemija mezenterija (4,9). U polovice oboljelih od PAN-a dolazi do razvoja GIV-a koji se može očitovati kao akutna trbušna bol, GI krvarenje, infarkcija, peritonitis, kolecistitis, apendicitis i perforacija (4). Do 60% bolesnika s Kawasakijevom bolešću može imati GI simptome (trbušna bol, povraćanje), ali ti su simptomi ozbiljni samo kod njih 4,6% (10).

Među vaskulitisima udruženim s antineutrofilnim citoplazmatskim antitijelima (engl. *ANCA associated vasculitis*, AAV) zahvaćenost GIT-a je češća u EGPA (35–50%), u usporedbi s MPA (5–30%) ili GPA (5–10%). Vodeći GI simptomi u bolesnika s EGPA su trbušna bol, krvavi proljevi (30–58%), povraćanje, ileus, anoreksija, GI krvarenje (29%) te odinofagija. Slične simptome imaju i bolesnici s GPA uz moguću perforaciju ili/i ishemiju crijeva te granulomatozni hepatitis ili pankreatitis. Simptomi GIV-a u bolesnika s MPA kreću se u rasponu od trbušne boli, mučnine, povraćanja i proljeva do, rijetko, ishemijskih ulkusa kolona, peritonitisa i perforacije crijeva (2,4).

GI simptomi u IgAV-u su raznovrsni i vrlo česti (50–85% bolesnika): proljev, povraćanje, grčevita bol u trbuhu, opstrukcija, perforacija, distenzija, intususepcija, hematemeza, melena, hematokezija. Dominantno je zahvaćen donji dio duodenuma. U otprilike 14% slučajeva, GIV je prva manifestacija IgAV-a (11,12). Dva su tipa GIV-a u Behçetevoj bolesti koja se mogu razviti u 3–50% oboljelih. Ukoliko su zahvaćene male krvne žile, dolazi do upale crijevne mukoze s ulceracijama, a ukoliko se radi o vaskulitisu velikih krvnih žila može doći do ishemije i infarkta crijevne stijenke (13,14).

U bolesnika sa SLE-om mogu se javiti raznovrsne GI manifestacije (do 40%), uključujući lupus peritonitis,

necrotising pancreatitis, GIV, and complications of the aforementioned conditions. According to current data, lupus mesenteric vasculitis (LMV) occurs in 10% of patients. Its mortality rate is up to 2.5%, and its prevalence is highest in patients who are in active disease period (2,4). Despite the fact that 10 – 38% of patients with rheumatoid arthritis (RA) have different GI symptoms, only 1% of them develop GIV (15). In patients with primary Sjögren's syndrome (SjS), involvement of the entire GIT is possible. Common symptoms include epigastric pain, dyspepsia and nausea. Other GI manifestations include jejunitis, sigmoiditis, and inflammatory bowel disease (16). Some of the GI presentations of vasculitis include the following: large-vessel vasculitis can cause extensive bowel infarctions as well as infarctions of other organs, while small-vessel vasculitis mostly affects intramural arteries causing focal, segmental ischaemia and ulcerations (8). Despite the increased survival rate of patients with GIV due to advanced treatments (various immunosuppressive therapies and surgical interventions), GI manifestations of AI diseases continue to pose a medical challenge, both in their timely recognition and early care.

The objective of this study was to describe the incidence and clinical manifestations of GIV in patients with various systemic autoimmune (AI) diseases who were treated at the Split University Hospital Centre over a ten-year period.

SUBJECTS AND METHODS

This retrospective cohort study was conducted at the Division of Rheumatology and Clinical Immunology of the Split University Hospital Centre. The patients' medical records were downloaded from the electronic database of the Division of Rheumatology and Clinical Immunology, covering the period from 1 January 2009 to 31 December 2018. Research criteria included anamnestic data on abdominal pain or endoscopic and/or radiographic findings of intestinal vasculitis. GI involvement is defined as GI manifestations present at the time of diagnosis of vasculitis, after other causes of GI symptoms have been ruled out. The aforementioned GI manifestations include: abdominal pain, nausea or vomiting, diarrhoea, bowel obstruction, intussusception, intestinal bleeding, ulceration and perforation, pancreatitis, and bowel infarction. Based on a detailed review of medical records, GIV symptoms were documented in 12 patients. The following diagnostic methods were used in making the diagnosis: multi-slice computed tomography (MSCT), positron emission tomography-computed tomography (PET-CT), endoscopy of the upper gastrointestinal tract, colonoscopy, MR enterography, and histopathology of the GIT mucosa (Table 3). Patients were treated for SLE, SjS, MCTD, IgAV and vasculitis.

ne-nekrotizirajući pankreatitis, GIV te komplikacije navedenih stanja. Prema dosadašnjim podatcima, u 10% bolesnika pojavljuje se lupus mezenterični vaskulitis (engl. *lupus mesenteric vasculitis*, LMV) čija je stopa smrtnosti do 2,5%, a prevalencija mu je najviša u onih s aktivnom bolešću (2,4). Unatoč tomu što 10–38% bolesnika s reumatoidnim artritisom (RA) ima različite GI simptome, samo u njih 1% razvija se GIV (15). U bolesnika s primarnim Sjögrenovim sindromom (SjS) moguća je zahvaćenost cijeloga GIT-a. Uobičajeni simptomi su epigastrična bol, dispepsija te mučnina. Ostale GI manifestacije uključuju jejunitis, sigmoiditis te upalnu bolest crijeva (16). Kada saberemo GI prezentacije sindroma vaskulitisa, vaskulitisi velikih krvnih žila mogu uzrokovati opsežne intestinalne infarkte, kao i infarkte drugih organa, dok vaskulitisi malih krvnih žila većinom pogađaju intramuralne arterije uzrokujući fokalnu, segmentalnu ishemiju te ulceracije (8). Unatoč sve boljem preživljenju bolesnika s GIV-om zahvaljujući naprednim načinima liječenja (različita imunosupresivna terapija i kirurške intervencije), GI manifestacije AI bolesti i dalje predstavljaju medicinski izazov, kako u njihovom pravovremenom prepoznavanju, tako i u što ranijem zbrinjavanju.

Naš je cilj bio ispitati učestalost i klinička očitovanja crijevnog vaskulitisa u bolesnika s različitim sustavnim AI bolestima liječenih u Kliničkom bolničkom centru Split u desetogodišnjem razdoblju.

ISPITANICI I METODE

Ova retrospektivna studija kohorte provedena je u Zavodu za reumatologiju i kliničku imunologiju KBC-a Split. Medicinski podatci o bolesnicima preuzeti su iz elektronske baze podataka Zavoda, obuhvaćajući vremenski period od 1. siječnja 2009. do 31. prosinca 2018. godine. Kriteriji pretrage uključivali su anamnestičke podatke o boli u trbuhu ili endoskopske ili/i radiografske znakove vaskulitisa crijeva. GI zahvaćenost definirana je kao GI manifestacije prisutne u trenutku dijagnosticiranja vaskulitisa, nakon što su isključeni ostali uzroci GI simptoma. Navedene GI manifestacije odnose se na: bol u trbuhu, mučninu ili povraćanje, proljev, intestinalnu opstrukciju, intususepciju, intestinalno krvarenje, ulceracije i perforaciju, pankreatitis, infarkt crijeva. Na temelju detaljnog pregleda medicinskih kartona, 12 bolesnika je imalo dokumentirane dokaze GIV-a. Pri postavljanju dijagnoze, korištene su sljedeće dijagnostičke metode: višeslojni CT trbuha (engl. *multi-slice computed tomography*, MS-CT), PET-CT (engl. *positron emission tomography–computed tomography*, PET-CT), endoskopija gornjeg dijela GIT-a, kolonoskopija, MR enterografija, PHD sluznice GIT-a (tablica 3). Bolesnici su se liječili od SLE-a, SjS-a, MCTD-a, IgAV-a i sindroma vaskulitisa.

Table 2 Summarised results of the variables of interest in patients with gastrointestinal vasculitis
Tablica 2. Zbirni prikaz rezultata parametara od interesa u bolesnika s vaskulitisom gastrointestinalnoga trakta

Patient sex and age / Spol i dob bolesnika	Underlying disease / Osnovna bolest	Leading symptom / Vodeći simptom	Endoscopy / Endoskopija	Multi-slice CT / Višeslojni CT	Histopathology finding / PHD	Other methods / Ostale metode	Treatment / Liječenje	Treatment response / Odg. na terapiju
M, 45 years of age / 45. god.	IgAV	Acute abdomen / Akutni abdomen	Hyperemia of the mucous membranes of the oesophagus, stomach and bulbus / Hiperemija sluznice ezofagusa, želuca i bulbusa	Inflammation of jejunal wall / Upala stijenke jejunuma	Ileum: lamina propria permeated with inflammatory infiltrate and eosinophils / Ileum: lamina proprija prožeta upalnim infiltratom i eozinofilima	MR enterography: jejunal wall thickening / MR enterografija: zadebljanje stijenke jejunuma	GC / GK, AZA	Good / Dobar
M, 57 years of age / 57. god.	IgAV	Abdominal pain, nausea / Bol u trbuhu, mučnina	Hyperemia of the antrum / Hiperemija antruma	–	–	–	GC / GK	Good / Dobar
M, 64 years of age / 64. god.	IgAV	Acute abdomen / Akutni abdomen	Erosive gastritis / Erozivni gastritis	Inflammation of the wall of the ileum, caecum and ascending colon and sigmoid colon / Upala stijenke ileuma, cekoascendesa i sigme	–	–	GC / GK, AZA	Moderate / Umjeren
M, 44 years of age / 44. god.	IgAV	Abdominal pain / Bol u trbuhu	Gastric hyperemia and erosion / Hiperemija i erozije želuca	–	Mucosa with normal glands / Mukoza s pravilnim žlijezdama	–	GC / GK, AZA	Good / Dobar
M, 44 years of age / 44. god.	IgAV	GI bleeding / GI krvarenje	Gastritis and duodenitis, mucosal hyperemia / Gastroduodenitis, hiperemija sluznice	–	–	–	GC, chloroquine / GK, KLOROKIN	Good / Dobar
M, 22 years of age / 22. god.	IgAV	Abdominal pain / Bol u trbuhu	Hyperemia of the gastric mucosa / Hiperemija sluznice želuca	–	–	–	GC / GK	Good / Dobar
M, 20 years of age / 20. god.	IgAV	Abdominal pain, vomiting / Bol u trbuhu, povraćanje	Hyperemic mucosa of the antrum / Hiperemična sluznica antruma	–	–	–	GC / GK	Good / Dobar
M, 60 years of age / 60. god.	IgAV	Acute abdomen / Akutni abdomen	Erosive gastritis / Erozivni gastritis	Dilated small bowel loops with closed loop torsion / Dilatirane vijuge TC-a, torzija, „Cloosed loop“	–	–	GC / GK, AZA	Moderate / Umjeren

Table 2 Continued
Tablica 2. Nastavak

Patient sex and age / Spol i dob bolesnika	Underlying disease / Osnovna bolest	Leading symptom / Vodeći simptom	Endoscopy / Endoskopija	Multi-slice CT / Višeslojni CT	Histopathology finding / PHD	Other methods / Ostale metode	Treatment / Liječenje	Treatment response / Odg. na terapiju
F / Ž, 23 years of age / 23. god.	SLE	Acute abdomen / Akutni abdomen	Erosive gastritis / Erozivni gastritis	Stratification of the bowel wall / Raslojavanje stijenke crijeva	Jejunum: mucosal necrosis, inflammatory infiltrate and submucosal haemorrhage / Jejunum: nekroza sluznice, upalni infiltrat i krv podsluznice	–	GC / GK, CYC, IVIG	Adverse / Nepovoljan
F / Ž, 31 years of age / 31. god.	SLE	GI bleeding / GI krvarenje	Hyperemic mucosa of the antrum, erosions / Hiperemija sluznice antruma, erozije	–	–	–	GC / GK, CYC	Good / Dobar
F / Ž, 54 years of age / 54. god.	MPA	No symptoms / Bez simptoma	–	–	–	PET-CT: FDG uptake in the colon / PET-CT: signal FDG duž crijeva	GC / GK, AZA, MTX, CYC, RTX	Moderate / Umjeren
M, 78 years of age / 78. god.	Primary SS / primarni SS	Acute abdomen / Akutni abdomen	–	Congestion and mesenteric oedema / Kongestija i edem mezenterija	–	–	GC / GK, CYC, IVIG	Moderate / Umjeren

Legend / Legenda: CT – computed tomography; PHD – histopathology diagnosis / patohistološka dijagnostika; MR – magnetic resonance / magnetska rezonancija; IgAV – IgA vasculitis / IgA-vaskulitis; SLE – systemic lupus erythematosus / sistemski eritemski lupus; MPA – microscopic polyangiitis / mikroskopski poliangiitis; SS – Sjögren's syndrome / Sjögrenov sindrom; GI – gastrointestinal / gastrointestinalno; GC / GK – glucocorticoid / glukokortikoid; AZA – azathioprine / azatioprin; CYC – cyclophosphamide / ciklofosfamid; IVIG – intravenous immunoglobulins / intravenski imunoglobulini; RTX – rituximab / rituksimab.

In terms of descriptive statistics methods for statistical analysis, an arithmetic mean with standard deviation or a median with interquartile range for continuous variables were used, as well as frequency (percentages) for categorical variables. The analysis was performed using the MedCalc computer programmes (MedCalc Software, Ostend, Belgium).

RESULTS

The diagnosis of gastrointestinal vasculitis was confirmed in 12 patients, of whom 9 were men (75%). The median age at diagnosis of GIV was 45.2 ± 23.3 years. The results of our research are summarised in Table 2. Eight patients (67%) had GIV in IgAV. Other patients with vasculitis also had underlying conditions such as SLE (2 patients), MPA (1 patient), and primary SS (1 patient). The leading symptom in four patients was abdominal pain with nausea and vomiting, 2 patients had profuse GI bleeding, one patient had fatigue without GI symptoms, and the remaining patients' clinical features included acute abdomen with visible radiographic thickening of the bowel wall with oedema and stratification with ascites. Diagnostic methods are listed in Table 3. In six (50%) cases, vasculitis was detected by an MSCT of the abdomen (three patients with IgAV, two patients with SLE, one patient with SS), in one case it was detected by a PET-CT scan, in one case through histopathological findings, and in four cases through endoscopic findings. CT of the abdomen showed thickening and stratification of the bowel wall, followed by inflammation of the wall of the jejunum, ileum, caecum and ascending colon and sigmoid colon, and dilated bowel loops (Figure 1). In one patient, CT showed congestion and mesenteric oedema (Figure 1). Endoscopy of the upper GIT was performed in 10 (83%) patients, and abnormalities were detected in all of them. The abnormalities were mostly related to hyperemia and mucosal erosions (Figure 1). In one patient with IgAV, MR enterography was subsequently performed through which jejunal loops with bowel wall thickening along with a misty mesentery sign with swollen lymph nodes were detected (Figure 1). Finally, GI biopsies were performed in three patients, and a pathological finding was detected in two of them. Inflammatory infiltrate of the lamina propria of the ileum was detected in a patient with IgAV, and in a patient with SLE who died as a result of GIV, gangrene of the small intestine with acute peritonitis (mucosal necrosis of the jejunum with accumulation of mixed inflammatory infiltrate and blood in lamina propria and bleeding through the rest of the wall with thrombotic microangiopathy and fibrinoid necrosis of the blood vessels) was detected (Figure 1).

All patients were treated with glucocorticoids (GCs) (methylprednisolone administered intravenously or a

Za statističku analizu od metoda deskriptivne statistike korištena je aritmetička sredina sa standardnom devijacijom ili medijan s interkvartilnim rasponom za kontinuirane varijable te frekvencija (postotci) za kategorijske varijable. Korišten je računalni program *MedCalc* (*MedCalc Software*, Ostend, Belgium).

REZULTATI

U 12 bolesnika je potvrđena dijagnoza crijevnog vaskulitisa, od čega su 9 bili muškarci (75%). Srednja životna dob pri postavljanju dijagnoze GIV-a iznosila je 45,2 ± 23,3 godina. Rezultati našeg istraživanja zbirno su prikazani u tablici 2. Osam bolesnika (67%) imalo je GIV u sklopu IgAV-a. U ostalim vaskulitisima, u podlozi je bio SLE (2 bolesnice), MPA (1 bolesnica), primarni SS (1 bolesnik). Vodeći simptom u četvoro bolesnika bila je bol u trbuhu s mučninom i povraćanjem, dvojica su imala obilno GI krvarenje, jedna bolesnica je imala umor bez simptoma od strane GI sustava, a preostalih pet bolesnika kliničku sliku akutnog abdomena s radiološki verificiranim edemom i raslojavanjem stijenke crijeva uz ascites. Dijagnostičke metode prikazane su u tablici 3. U šest (50%) slučajeva vaskulitis je dokazan MS-CT-om trbuha (tri bolesnika s IgAV-om, dvije bolesnice sa SLE-om, jedan bolesnik sa SS-om), u jednom PET-CT-om, u jednom patohistološki, a u četiri slučaja endoskopski. CT-om trbuha prikazana su zadebljanja i raslojavanje stijenke crijeva, potom upala stijenke jejunuma, ileuma, cekoascedensa i sigme te dilatirane crijevne vijuge (slika 1). U jedne bolesnice CT-om se prikazala kongestija i edem mezenterija (slika 1). Endoskopija gornjeg dijela GIT-a izvršena je u 10 (83%) bolesnika, i kod svih su uočene abnormalosti, većinom hiperemija i erozija sluznice (slika 1). U jednog bolesnika s IgAV-om naknadno je učinjena i MR enterografija kojom su se utvrdile zadebljane stijenke vijuge jejunuma uz zamućen mezenterij s uvećanim limfnim čvorovima (slika 1). Naposljetku, GI biopsije su obavljene u tri bolesnika, otkrivši patološki nalaz u dva. U bolesnika s IgAV-om dokazan je upalni infiltrat lamine proprije ileuma, a u bolesnice sa SLE-om, koja je preminula od posljedica GIV-a, utvrđena je gangrena tankog crijeva s akutnim peritonitisom (nekrotična sluznica jejunuma uz kolekciju miješanoga upalnog infiltrata i krvi u lamini propriji te krvarenja kroz ostatak stijenke uz trombotičnu mikroangiopatiju i fibrinoidnu nekrozu krvnih žila) (slika 1).

Svi bolesnici su liječeni GK (intravenskim metilprednizolonom ili peroralno prednizonom u dozi od 0,5 do 1 mg/kg) uz postupnu redukciju doze. Početna doza metilprednizolona od 80 mg ordinirana je u osam bolesnika (pet bolesnika s IgAV-om, dvije bolesnice sa SLE-om te u bolesnika s SS-om). U preostalih četvero

dose of 0.5 – 1 mg/kg of prednisone administered orally) with gradual dose reduction. An initial dose of methylprednisolone of 80 mg was administered to eight patients (five patients with IgAV, two patients with SLE, and one patient with SS). In the remaining four patients, treatment was initiated with a dose of prednisone of 60 mg, administered orally (three patients with IgAV and one patient with MPA). In four patients with IgAV, azathioprine (AZA) at a dose of 150 mg/day was introduced, and in one patient chloroquine (250 mg/day) was introduced. Other patients with IgAV had an excellent response to treatment with moderate doses of GCs. In patients with SLE, in addition to GC therapy, cyclophosphamide therapy was administered (CYC) at a dose of 500 mg/m^2 of body surface area, and in one patient intravenous immunoglobulins therapy was administered (IVIG) at a dose of 0.4 mg/kg. CYC and IVIG therapy was administered to patients with SS as well, at the same doses as in patients with SLE. A satisfactory response to treatment was achieved in three patients; however, one patient with SLE died as a result of mesenteric vasculitis (after repeated surgical interventions – bowel resection). A patient with MPA who was treated with all of the aforementioned drugs had a satisfactory response to treatment (Table 2).

Table 3. Diagnostics of gastrointestinal vasculitis
Tablica 3. Dijagnostika vaskulitisa gastrointestinalnoga trakta

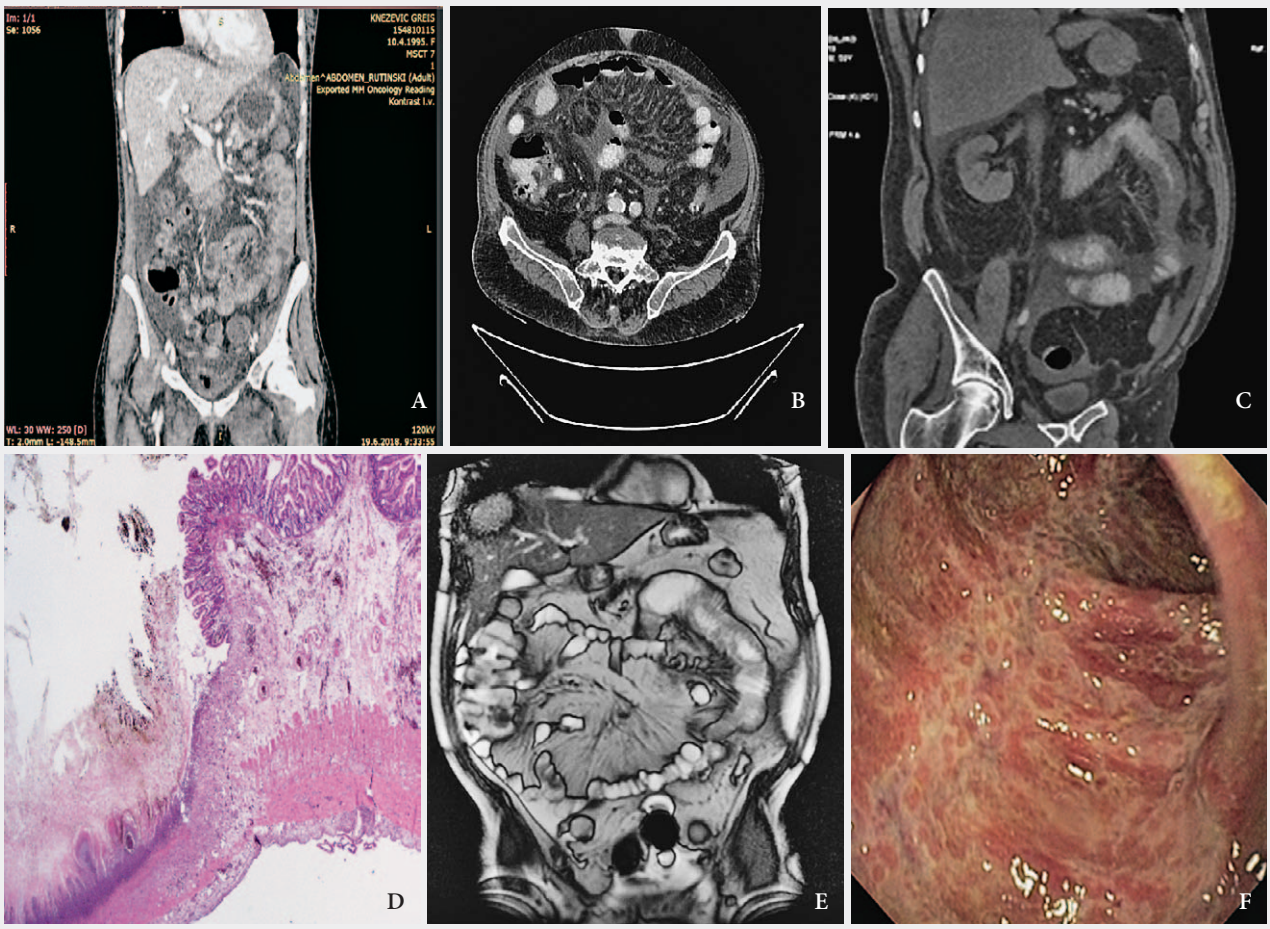
Diagnostic methods / Dijagnostičke metode	GI patients / GI bolesnici (N=12)
Multi-slice CT / Višeslojni CT	5
Small bowel wall inflammation / Upala stijenke tankog crijeva	2
Dilatation small bowel wall with torsion / Dilatacija stijenke tankog crijeva uz torziju	1
Stratification of the bowel wall / Raslojavanje stijenke crijeva	1
Congestion and mesenteric oedema / Kongestija i edem mezenterija	1
MR enterography / MR enterografija	1
Jejunal wall thickening / Zadebljanje stijenke jejunuma	1
PET-CT	1
FDG uptake in the colon / Signal FDG duž crijeva	1
Endoscopy of the upper GIT / Endoskopija gornjeg GIT-a	10
Hyperemia and mucosal erosions / Hiperemija sluznice i erozije	7
Erosive gastritis / Erozivni gastritis	3
Histological finding / Histološki nalaz	3
No abnormalities detected / Uredan nalaz	1
Infiltration of inflammatory cells and eosinophils / Infiltracija upalnih stanica i eozinofila	1
Infiltration of inflammatory cells with vascular fibrosis / Infiltracija upalnim stanicama uz fibrozu krvnih žila	1

Legend / Legenda: CT – computed tomography; MR – magnetic resonance / magnetska rezonanca; PET-CT / PET CT – positron emission tomography with computed tomography / pozitronska emisijska tomografija s kompjutoriziranom tomografijom; FDG – fluorodeoxyglucose / fluorodeoksiglukoza; GIT – gastrointestinal tract / gastrointestinalni trakt.

DISCUSSION

The treatment of patients with GIV in systemic AI diseases still poses a serious challenge because GI system involvement is a rare but very serious complication of the underlying disease that can significantly affect its possible outcomes. Given that clinical symptoms are very diverse and non-specific, and that abdominal pain may be the first, early symptom of bowel perforation, rheumatologists should always approach patients who report newly occurring GI complications with caution (1). To the best of our knowledge, no controlled randomised clinical trials have been conducted on this topic. All data were obtained from a series of case reports, retrospective studies, and a systematic literature review. If GIV presents with clinical features of acute abdomen or GI bleeding, the recommendation for treatment is the use of GCs as the first-line therapy with some of the following immunosuppressants: cyclophosphamide (CYC), methotrexate (MTX), azathioprine (AZA), intravenous immunoglobulins (IVIG), rituximab (RTX), chloroquine (1,2,4). The results of our study showed that GIV most often occurs in IgAV and has the best response to therapy, which is consistent with most data to date (11,12). Remission was achieved in most patients and GIT involvement was not associated with an adverse outcome and relapse of IgAV, which is inconsistent with the results of another study in which GI involvement at the time of diagno-

bolesnika liječenje je započeto s peroralnom dozom prednizona od 60 mg (tri bolesnika s IgAV-om te jedna bolesnica s MPA-om). U četvero bolesnika s IgAV-om, uz redukciju doze GK, u terapiju se uveo azatioprin (engl. *azathyoprin*, AZA) u dozi od 150 mg dnevno, a u jednog bolesnika klorokin (250 mg/dn). Ostali bolesnici s IgAV-om postigli su odličan odgovor na liječenje samo sa srednjim dozama GK. U bolesnica sa SLE-om, uz GK, provedena je terapija ciklofosfamidom (engl. *cyclophosphamide*, CYC) u dozi od 500 mg/m^2 tjelesne površine, a u jedne i intravenskim imunoglobulinima (engl. *intravenous immunoglobulin*, IVIG) u dozi od 0,4 mg/kg tjelesne težine. Terapija s CYC-om i IVIG-om u istim dozama kao i u SLE-u ordinirana je



Legend / Legenda: a) multi-slice CT of GIV in patient with SLE shows oedema and stratification of the bowel wall (target sign) / višeslojni CT GIV-a u bolesnice sa SLE-om prikazuje edemi i raslojavanje stijenke crijeva (target sign); b) multi-slice CT in patient with SS shows free fluid perihepatic space, perisplenic space, paracolic gutter and interstitial space with mesenteric congestion / višeslojni CT u bolesnika sa SS-om prikazuje slobodnu tekućinu perihepatalno, perispenično, parakolično i interstinalno uz kongestiju mezenterija; c) multi-slice CT in patient with IgAV shows dilated small bowel loops with torsion and congestion of the associated mesentery; two transition points collapsed into dilated loops: closed loop / višeslojni CT u bolesnika s IgAV-om prikazuje dilatirane vijuge TC uz torziju istih i kongestiju pripadajućeg mezenetrija; dva prelaska kolabiranih u dilatirane vijuge: „closed loop"; d) small bowel histopathology in patient with SLE (hematoxylin and eosin staining, 20x magnification) shows full-thickness necrosis of the bowel wall, as well as complete necrosis of serosa / PHD tankog crijeva u bolesnice sa SLE-om (bojenje hemalaunom i eozinom, povećanje 20x) prikazuje nekrotičnu stijenku u cijeloj debljini, kao i potpunu nekrozu seroze; e) MR enterography of the GIV in patient with IgAV shows jejunal loops with bowel wall thickening; one of the loops is fixed; misty mesentery sign with swollen lymph nodes / MRI enetrografija GIV-a u bolesnika s IgAV-om prikazuje vijuge jejunuma zadebljane stijenke; jedna od vijuga fiksirana; mezenterij zamućen s uvećanim limfnim čvorovima; f) endoscopy of the upper GIT in patients with IgAV shows hyperemia and mucosal erosion / endoskopija gornjeg dijela GIT-a u bolesnika s IgAV-om prikazuje hiperemiju i eroziju sluznice.

Figure 1. Imaging (different techniques) of gastrointestinal vasculitis in patients with autoimmune diseases
Slika 1. Slikovni prikaz (različite tehnike) gastrointestinalnoga vaskulitisa u bolesnika s autoimunim bolestima

sis, along with joint involvement, was associated with more frequent relapses. The reason for this is the impartiality in the selection of subjects in this study (children and adults, cutaneous, renal and joint manifestations of the disease, different treatment protocols) (17). In our study, the subjects were individuals ≥ 18 years of age with predominantly cutaneous and GI symptoms who had a good response to treatment, i.e., who have achieved remission. With regard to GIV in SLE, lupus mesenteric vasculitis (LMV) is known to occur in up to 10% of patients, with the highest prevalence being in i u bolesnika sa SS-om. U tri bolesnika postignut je zadovoljavajući odgovor na liječenje, međutim jedna bolesnica sa SLE-om je preminula od posljedica mezenterijalnog vaskulitisa (nakon opetovanih operativnih zahvata – resekcije crijeva). U bolesnice s MPA provedena je terapija svim navedenim lijekovima sa zadovoljavajućim odgovorom (tablica 2).

RASPRAVA

Zbrinjavanje bolesnika s GIV-om u sklopu sistemskih AI bolesti i dalje predstavlja pravi izazov zbog toga

patients in active disease period. Typical manifestations of lupus enteritis include focal or diffuse thickening of the bowel wall, bowel dilatation, and ascites, which provide visible radiographic signs such as the "target sign" and "comb sign": increased bowel wall volume, thickening and multiplication of mesenteric blood vessels, and high adipose tissue density. First-line therapy includes administration of high doses of GCs, administered intravenously, and in refractory cases CYC therapy is administered as well. In patients with obvious signs of peritonitis and highly suspected intestinal perforation or ischaemia, surgical treatment should not be delayed (18). In one of our patients, all the aforementioned treatment methods were used with IVIG, but there was a fatal outcome, while in other patients a good response to treatment was achieved. According to data found in literature, the prognosis of LMV varies and depends on the extent of ischaemia, and better outcomes can be achieved with early administration of high doses of GCs, CYC, or RTX (19). In patients with primary SS, systemic vasculitis extremely rarely affects the GIT, and it may be linked to associated cryoglobulinemia. If ischaemia or bowel infarction are present, the condition is life-threatening. If GC therapy or immunosuppressants prove to be inefficient, surgical intervention is required (20). GIT is rarely affected in MPA; however, it is a very serious manifestation of the disease with possible severe consequences. Although there are no clear treatment recommendations, intravenous GCs with immunosuppressants (CYC or RTX) are administered in most cases (21). Survival rates differ in various studies, but recent data suggest that mortality is the same in patients with MPA regardless of GI tract involvement (21–23).

Patients with GIV who were treated in our university hospital centre had a good response to treatment and the outcome was fatal in only one patient. We believe that the reason for the favourable outcomes is the timely diagnosis and rapid therapeutic intervention, but longer follow-ups with more subjects are required in order to find out whether the survival rate has really improved over the last few years. Since these are rare disorders, successful treatment of these patients requires a range of diagnostic and laboratory procedures, as well as good cooperation between experts in a multidisciplinary team (rheumatologists, gastroenterologists, radiologists, pathologists and surgeons). Diagnosis is made based on clinical suspicion and imaging methods because there is no specific test for the detection of GIV in systemic AI diseases.

Our study is limited due to retrospective nature of data collection, which is why there are certain shortcomings. In addition to that, other limitations include the relatively small number of patients and the fact that

što je zahvaćenost GI sustava rijetka, ali vrlo ozbiljna komplikacija osnovne bolesti koja može značajno utjecati na ishod. S obzirom na to da su klinički simptomi vrlo raznoliki i nespecifični te kako bol u trbuhu može biti prvi, rani simptom perforacije crijeva, reumatolozi uvijek s oprezom trebaju pristupiti bolesnicima koji navode novonastale GI smetnje. (1) Prema našim saznanjima do sada nije provedeno ni jedno kontrolirano randomizirano kliničko ispitivanje na navedenu temu. Svi podatci dobiveni su iz serija prikaza slučajeva, retrospektivnih studija i sustavnog pregleda literature. Ukoliko se GIV prezentira kliničkom slikom akutnog abdomena ili GI krvarenjem, preporuka za liječenje je primjena GK kao prve linije uz neki od imunosupresivnih lijekova: ciklofosfamid (engl. *cyclophosphamide*, CYC), metotreksat (engl. *methotrexate*, MTX), AZA, IVIG, rituksimab (engl. *rituximab*, RTX), klorokin (1,2,4). Rezultati naše studije pokazali su kako se GIV najčešće javlja u sklopu IgAV-a te ima najbolji odgovor na terapiju, što je u skladu s većinom dosadašnjih podataka (11,12). U većine bolesnika postignuta je remisija te zahvaćenost GIT-a nije bila povezana s lošijim ishodom i relapsom IgAV-a, što se pak ne podudara s rezultatima jednoga drugog istraživanja u kojem je zahvaćenost GI sustava u trenutku postavljanja dijagnoze, zajedno sa zglobnom zahvaćenošću, bila povezana s češćim relapsom. Razlog navedenome je nepristranost pri izboru ispitanika u navedenom istraživanju (djeca i odrasli, kožne, bubrežne i zglobne manifestacije bolesti, različiti protokoli liječenja) (17). U našem istraživanju ispitanici su bili osobe ≥ 18 godina s dominantno kožnim i GI simptomima s dobrim odgovorom na provedeno liječenje, odnosno postizanjem remisije. Što se tiče GIV-a u sklopu SLE-a, poznato je da se LMV javlja u do 10% bolesnika, s najvišom prevalencijom u bolesnika s aktivnom bolešću. Tipična obilježja lupusnog enteritisa uključuju fokalno ili difuzno zadebljanje stijenke crijeva, dilataciju crijeva i ascites koji daju prepoznatljiva radiološka obilježja „znak mete" i „znak češlja" (engl. *target and comb's signs*): povećani volumen stijenke crijeva, zadebljanje i umnažanje mezenterijalnih krvnih žila i povišeni denzitet masnoga tkiva. Prva linija liječenja su visoke doze intravenskih GK, a za refraktorne slučajeve primjenjuje se i CYC. U bolesnika s očitim znakovima peritonitisa i visokom sumnjom na perforaciju ili ishemiju crijeva kirurški pristup se ne smije odgađati (18). U jedne naše bolesnice provedene su sve navedene mjere liječenja uz IVIG-e, međutim došlo je do smrtnog ishoda, dok je u druge bolesnice postignut dobar odgovor na provedeno liječenje. Prema literaturnim podacima, prognoza LMV-a varira i ovisi o opsegu ishemije, a bolji ishodi se mogu postići ranom primjenom visokih doza GK, CYC-a ili RTX-a (19). U bolesnika s pri-

this study was conducted in a single hospital centre. Despite the descriptive analysis, with all the inherent bias associated with this type of research, we have tried to gain useful insights in order to improve the identification and treatment of patients with GIV in various AI diseases.

CONCLUSION

GIV is a rare manifestation of systemic AI diseases, but the clinical features can be very severe and lead to a fatal outcome, especially if it is not diagnosed at an early stage and treated with aggressive immunosuppressive therapy. However, additional studies are needed to identify factors that influence the prognosis and treatment outcome of these disorders, as well as clear recommendations and guidelines for the treatment of these patients.

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marnim SS-om, sistemski vaskulitis iznimno rijetko zahvaća GIT, i može ga se povezati s pridruženom krioglobulinemijom. Ako su prisutni ishemija ili infarkt crijeva, stanje je opasno po život. Ukoliko se terapijom GK ili imunosupresivima ne postigne učinak, potreban je kirurški zahvat (20). GIT je rijetko zahvaćen u MPA, međutim radi se o vrlo ozbiljnoj manifestaciji bolesti s moguće teškim posljedicama. Iako ne postoje jasne preporuke za liječenje, većinom se primjenjuju intravenski GK s imunosupresivima (CYC ili RTX) (21). Stopa preživljenja se razlikuje u nekoliko studija, ali noviji podatci ukazuju kako je smrtnost jednaka u bolesnika s MPA bez obzira na zahvaćenost GI trakta (21-23).

Bolesnici s GIV-om u našem centru imali su dobar odgovor na provedeno liječenje te je u samo jednom slučaju došlo do smrtnog ishoda. Mišljenja smo kako je razlog dobrim ishodima pravodobno postavljanje dijagnoze i brza terapijska intervencija, ali potrebna su dulja praćenja s većim brojem ispitanika koja bi pokušala odgovoriti je li zaista poboljšana stopa preživljenja tijekom posljednjih nekoliko godina. Budući da se radi o rijetkim poremećajima, za uspješno liječenje ovih bolesnika potreban je čitav niz dijagnostičkih i laboratorijskih postupaka, kao i dobra suradnja multidisciplinarnog tima (reumatolozi, gastroenterolozi, radiolozi, patolozi i kirurzi). Dijagnoza se postavlja temeljem kliničke sumnje i slikovnih metoda jer ne postoji nijedna specifična pretraga za dokazivanje GIV-a u sklopu sistemskih AI bolesti.

Ograničenje našeg istraživanja jest retrospektivnost prikupljanja podataka, zbog čega postoje određene nedostatnosti. Također, ograničenja su i relativno mali uzorak bolesnika te provođenje istraživanja u samo jednom centru. Unatoč deskriptivnoj analizi, uza svu inherentnu pristranost koja se veže uz takvu vrstu istraživanja, pokušali smo izvući korisne spoznaje u svrhu poboljšanja prepoznavanja i liječenja bolesnika s GIV-om u sklopu različitih AI bolesti.

ZAKLJUČAK

Crijevni vaskulitis je rijetka manifestacija sistemskih AI bolesti, ali klinička slika može biti vrlo teška i dovesti do fatalnog ishoda te je nužna brza dijagnoza i agresivno imunosupresivno liječenje. Međutim, dodatne studije su nužne kako bi se identificirali čimbenici koji utječu na prognozu i ishod liječenja ovih poremećaja, kao i jasne preporuke i smjernice za zbrinjavanje ovih bolesnika.

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REFERENCES / LITERATURA

1. Cojocaru M, Cojocaru IM, Silosi I, Vrabie CD. Gastrointestinal manifestations in systemic autoimmune diseases. Maedica (Bucur). 2011;6(1):45–51.
2. Ahn E, Luk A, Chetty R, Butany J. Vasculitides of the gastrointestinal tract. Semin Diagn Pathol. 2009;26(2):77–88.
3. Jennette JC, Falk RJ, Bacon PA, Basu N, Cid MC, Ferrario F i sur. 2012 revised international Chapel Hill Consensus conference nomenclature of vasculitides. Arthritis Rheum. 2013;65(1):1–11.
4. Chetty R, Serra S. A pragmatic approach to vasculitis in the gastrointestinal tract. J Clin Pathol. 2017;70(6):470–5.
5. Jennette JC, Falk RJ, Andrassy K, Bacon PA, Churg J, Gross WL i sur. Nomenclature of systemic vasculitides. Proposal of an international consensus conference. Arthritis Rheum. 1994;37(2):187–92.
6. Jennette JC, Falk RJ. Small-vessel vasculitis. N Engl J Med. 1997;337(21):1512–23.
7. Ha HK, Lee SH, Rha SE, Kim JH, Byun JY, Lim HK i sur. Radiologic features of vasculitis involving the gastrointestinal tract. Radiographics. 2000;20(3):779–94.
8. Soowamber M, Weizman AV, Pagnoux C. Gastrointestinal aspects of vasculitides. Nat Rev Gastroenterol Hepatol. 2017;14(3):185–94.
9. Schmidt J, Kermani TA, Bacani AK, Crowson CS, Cooper LT, Matteson EL i sur. Diagnostic features, treatment, and outcomes of Takayasu arteritis in a US cohort of 126 patients. Mayo Clin Proc. 2013;88(8):822–30.
10. Colomba C, La Placa S, Saporito L, Corsello G, Ciccia F, Medaglia A i sur. Intestinal Involvement in Kawasaki Disease. J Pediatr. 2018;202:186–93.
11. Audemard-Verger A, Pillebout E, Guillevin L, Thervet E, Terrier B. IgA vasculitis (Henoch–Shönlein purpura) in adults: diagnostic and therapeutic aspects. Autoimmun Rev. 2015;14(7):579–85.
12. Pillebout E, Verine J. Henoch–Schönlein purpura in the adult. Rev Med Interne. 2014;35(6):372–81.
13. Vaiopoulos AG, Sfikakis PP, Kanakis MA, Vaiopoulos G, Kaklamanis PG. Gastrointestinal manifestations of Behçet's disease: advances in evaluation and management. Clin Exp Rheumatol. 2014;32:140–8.
14. Zeidan MJ, Saadoun D, Garrido M, Klatzmann D, Six A, Cacoub P. Behçet's disease physiopathology: a contemporary review. Auto Immun Highlights. 2016;7(1):4.
15. Bartels C, Bell C, Rosenthal A, Shinki K, Bridges A. Decline in rheumatoid vasculitis prevalence among US veterans: a retrospective cross-sectional study. Arthritis Rheum. 2009; 60(9):2553–7.
16. Asherson R, Font J, Ramos-Casals M, Rodes J. Digestive involvement in systemic autoimmune diseases. U: Asherson R, ur. Handbook of systemic autoimmune diseases. Amsterdam: Elsevier Ltd.; 2008, str. 1–295.
17. Calvo-Río V, Hernández JL, Ortiz-Sanjuán F, Loricera J, Palmou-Fontana N, González-Vela MC i sur. Relapses in patients with Henoch-Schönlein purpura: Analysis of 417 patients from a single center. Medicine (Baltimore). 2016; 95(28):e4217.
18. Yuan S, Ye Y, Chen D, Qiu Q, Zhan Z, Lian F i sur. Lupus mesenteric vasculitis: clinical features and associated factors for the recurrence and prognosis of disease. Semin Arthritis Rheum. 2014;43(6):759–66.
19. Hatemi I, Hatemi G, Çelik AF. Systemic vasculitis and the gut. Curr Opin Rheumatol. 2017;29(1):33–8.
20. Doyle MK. Vasculitis associated with connective tissue disorders. Curr Rheumatol Rep. 2006;8(4):312–6.
21. Eriksson P, Segelmark M, Hallböök O. Frequency, Diagnosis, Treatment, and Outcome of Gastrointestinal Disease in Granulomatosis with Polyangiitis and Microscopic Polyangiitis. J Rheumatol. 2018;45(4):529–37.
22. Mahr A, Katsahian S, Varet H, Guillevin L, Hagen EC, Höglund P i sur. Revisiting the classification of clinical phenotypes of anti-neutrophil cytoplasmic antibody-associated vasculitis: a cluster analysis. Ann Rheum Dis. 2013;72(6): 1003–10.
23. Guillevin L, Lhote F, Gayraud M, Cohen P, Jarrousse B, Lortholary O i sur. Prognostic factors in polyarteritis nodosa and Churge-Strauss syndrome. A prospective study of 342 patients. Medicine (Baltimore). 1996;75(1):17–28.

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CASE REPORT PRIKAZ BOLESNIKA

LATE-ONSET OF SYSTEMIC SCLEROSIS – CASE REPORT AND LITERATURE REVIEW

SISTEMSKA SKLEROZA KOD STARIJEG BOLESNIKA – PRIKAZ BOLESNIKA I PREGLED LITERATURE

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Abstract

Systemic sclerosis most commonly occurs in middle-aged patients. Younger or older people are rarely affected. It is very rare in people over the age of 80. In older patients, different clinical and laboratory characteristics of the disease, as well as a different therapeutic response are expected, in comparison to younger patients. Therefore, we present the case of an 84-year-old patient with systemic sclerosis, as well as a literature review in relation to this topic.

Key words: Systemic sclerosis; Geriatrics; Glucocorticoids

Sažetak

Sistemska skleroza se najčešće javlja u bolesnika srednje životne dobi. Rjeđe obolijevaju mlađe ili starije osobe, a vrlo rijetko se javlja u osoba starijih od 80 godina. U starijih bolesnika možemo očekivati drugačija klinička i laboratorijska obilježja bolesti kao i terapijski odgovor u odnosu na mlađe bolesnike. Stoga, u ovom radu prikazujemo 84-godišnjeg bolesnika sa sistemskom sklerozom, uz pregled literature o ovoj temi.

Ključne riječi: Sistemska skleroza; Gerijatrija; Glukokortikoidi

INTRODUCTION

Systemic sclerosis (SSc) is a systemic inflammatory rheumatic disease characterised by the presence of fibrosis of the skin and internal organs and obliterative vasculopathy in addition to immune system disorders. The disease usually occurs in women between the ages of 30 and 50, while it is a less common occurrence in

UVOD

Sistemska skleroza (SSc) sistemska je upalna reumatska bolest koju uz imunološke abnormalnosti karakterizira prisutnost fibroze kože i unutarnjih organa te obliterirajuća vaskulopatija. Bolest se obično javlja u žena u dobi između 30 i 50 godina, dok je u muškaraca i u osoba starije životne dobi znatno rjeđa. Istraživanja

men and the elderly. Studies have shown that clinical features differ between patients who develop the disease at a younger age compared to geriatric patients (1).

Elderly patients have an increased risk of developing pulmonary hypertension, heart and kidney failure, and pronounced muscle weakness and functional impairment. While comparing the laboratory findings of older and younger patients, high levels of alkaline phosphatase (ALP) and low levels of creatinine kinase (CK) were observed in older patients, as well as a high percentage of anti-centromere antibodies and low level of U1RNP antibodies, which were observed in immunological findings. On the other hand, elderly patients tend to have a mild form of Raynaud's phenomenon as well as a lower risk of developing digital ulcers (2).

There is no doubt that high life expectancy in patients with SSc is associated with a poor prognosis, but it is important to note that most geriatric patients have other comorbidities which, in addition to the age factor, increase the risk of adverse outcomes and mortality.

In this paper, we shall present the case of an 84-year-old patient who came for a check-up due to pain and swelling of the small wrist joints with significantly reduced functional ability, and who was eventually diagnosed with SSc.

CASE REPORT

An eighty-four-year-old patient was referred for specialist treatment due to symptoms such as swelling and pain in his fingers and Raynaud's phenomenon, which appeared several months ago. Various conditions such as arterial hypertension, coronary heart disease (after recovery from myocardial infarction) and scalp sarcoma surgery which occurred several years ago (without chemotherapy) were known from the patient's medical history.

The clinical examination revealed abnormalities such as diffuse swelling of the fingers ("puffy fingers"), arthritis of the small wrist joints and both wrists, sclerodactyly, skin tightening of the upper extremities and chest, and all of these symptoms were enough to diagnose SSc based on the clinical features. Extremely high levels of inflammatory markers were observed in laboratory findings (ESR = 102 mm/hr, CRP = 81 g/L). Subsequent immunological findings included a positive antinuclear antibody finding with positive centromere-specific fluorescence (> 1: 640). The CK finding was in the normal range (21 U/L). Capillaroscopy revealed the presence of megacapillaries and pathological bleeding, which indicated an active scleroderma pattern. Pulmonary function tests showed reduced diffusion capacity for carbon monoxide (DLCO = 57%), and multi-slice computed tomography (MSCT) findings of the chest did not show a distinct interstitial pattern. The echocardiogram showed signs of ischemic

su pokazala da se klinička obilježja razlikuju između bolesnika kod kojih se bolest pojavi u mlađoj dobi u odnosu na gerijatrijske bolesnike (1).

U starijih bolesnika povećan je rizik za nastanak plućne hipertenzije, srčano i bubrežno oštećenje, a izraženija je mišićna slabost i funkcionalna onesposobljenost. U laboratorijskim nalazima, u odnosu na mlađe bolesnike, u starijih bolesnika uočene su više vrijednosti alkalne fosfataze (ALP) i niže vrijednosti kreatinin kinaze (CK), a u imunološkim nalazima veći postotak pozitivnih protutijela na centromere i manja prisutnost U1RNP protutijela. S druge strane, bolesnici starije životne dobi obično imaju blaži oblik Raynaudovog fenomena kao i manji rizik za nastanak digitalnih ulceracija (2).

Nedvojbeno je da je visoka životna dob u bolesnika sa SSc-om povezana s lošijom prognozom, ali važno je naglasiti da većina gerijatrijskih bolesnika ima pridružene i druge komorbiditete koji zajedno sa životnom dobi sami po sebi povisuju rizik lošijeg ishoda i smrtnosti.

U ovom radu prikazujemo bolesnika u dobi od 84 godine koji se javio na pregled zbog bolova i oteklina malih zglobova šaka uz značajno reduciranu funkcionalnu sposobnost, a kojemu je u konačnici dijagnosticiran SSc.

PRIKAZ BOLESNIKA

Osamdesetčetverogodišnji bolesnik upućen je na specijalističku obradu zbog pojave oteklina i bolova prstiju šaka te Raynaudovog fenomena unatrag nekoliko mjeseci. Iz ranije anamneze bila je poznata arterijska hipertenzija, koronarna bolest srca (stanje nakon preboljelog infarkta miokarda) te operacija sarkoma na vlasištu prije više godina (bez provedene kemoterapije).

U kliničkom pregledu dominirale su difuzne otekline prstiju šaka (engl. "*puffy fingers*"), artritis malih zglobova šaka i obaju ručnih zglobova, sklerodaktilija, zategnutost kože gornjih ekstremiteta i prsnog koša, što je bilo dovoljno da se već na osnovi kliničke slike postavi dijagnoza SSc-a. U laboratorijskim nalazima zabilježene su izrazito povišene vrijednosti rekatanata upale (SE=102 mm/h, CRP= 81 g/L). U naknadno pristiglim imunološkim nalazima bila su visoko pozitivna antinuklearna protutijela s pozitivnom fluorescencijom na centromere (>1:640). Nalaz CK je bio uredan (21 U/L). Kapilaroskopski, prisutne su megakapilare te zone patološkog krvarenja, što je upućivalo na aktivni sklerodermijski uzorak. Testovi plućne funkcije pokazali su smanjen difuzijski kapacitet za ugljični monoksid (DLCO=57%), a nalaz kompjuterizirane tomografije (MSCT) toraksa nije pokazao značajan intersticijski uzorak tipičnih promjena. Ultrazvukom srca zabilježeni su znakovi ishemijske kardiomiopatije uz održanu ejekcijsku frakciju, dok nije nađeno indirektnih znakova plućne hipertenzije. Radiografska pasaža jednjaka

cardiomyopathy with preserved ejection fraction, while no indirect signs of pulmonary hypertension were detected. The barium swallow test of the oesophagus showed no abnormalities, the chest MSCT showed no signs of oesophageal dilatation, the patient had no pronounced gastrointestinal disturbances, and did not agree to the recommended endoscopy. Tumour markers and abdominal magnetic resonance imaging showed no signs of associated active malignancy. Therapy was initiated by administering low doses of methylprednisolone (8 mg of methylprednisolone for two weeks, followed up with a dose of 4 mg for 5 months and ultimately a dose of 4 mg every other day) and peripheral vasodilators (amlodipine). There was an excellent clinical response to this therapy, in addition to the regression of peripheral arthritis and swelling of the fingers, as well as the regression of skin thickening. Normalisation of inflammatory parameters is observed in laboratory findings. At the follow-up appointments, the patient was in good general condition, his functional status was normal, and he was able to perform all normal daily activities. We continue to carry out the follow-up of this patient.

DISCUSSION

This paper presents the case of a patient who was diagnosed with SSc at the age of 84. Through this case report, it can be concluded that the clinical and laboratory characteristics of SSc, according to the data found in the reviewed literature, were different in the case of our geriatric patient compared to younger patients. SSc is a disease that most commonly occurs in the working age population, although its incidence has been reported in both younger and older patients. A relatively small number of cases in which patients were diagnosed with SSc late in life has been described in literature so far.

Hügle et al. have conducted a study which included 8554 patients with SSc. Out of the total number of patients, only 123 of them (1.4%) were older than 75, and the results showed that the elderly patients were more likely to have a limited type of SSc and a higher prevalence of anti-centromere antibodies. The modified Rodnan skin score and the prevalence of pulmonary fibrosis did not differ significantly between the two groups (3). According to the 2013 ACR/EULAR classification criteria, the skin thickening of the fingers of both hands extending proximal to the metacarpophalangeal joints is sufficient for the patient to be classified as having SSc. In the case of our patient, it was determined at the first clinical examination that there were enough elements to raise suspicion of SSc. Other manifestations of the disease that collectively confirm the diagnosis of SSc (score ≥9) include: skin thickening of the fingers, fingertip lesions, telangiectasia, abnormal

bila je uredna, MSCT toraksa nije pokazao dilataciju jednjaka, bolesnik nije imao izraženih gastrointestinalnih smetnji, a nije bio sklon preporučenoj endoskopskoj obradi probavnog trakta. Tumorski markeri i magnetska rezonancija abdomena nisu pokazali znakova pridružene aktivne maligne bolesti. Započeta je terapija niskim dozama metilprednizolona (8 mg metilprednizolona kroz dva tjedna, zatim nastavljeno 4 mg kroz 5 mjeseci i nakon toga nastavljeno 4 mg svaki drugi dan) i perifernim vazodilatatorima (amlodipin). Na navedenu terapiju nastupio je odličan klinički odgovor, regresija perifernog artritisa i oteklina prstiju šaka, kao i regresija kožnog zadebljanja. U laboratorijskim nalazima prati se normalizacija upalnih parametara. Na kontrolama je bolesnik dobroga općeg stanja kao i funkcionalnog statusa, obavlja sve uobičajene aktivnosti. Bolesnik je u našem daljnjem praćenju.

RASPRAVA

U ovom radu prikazan je bolesnik kojemu je u 84. godini postavljena dijagnoza SSc-a. Prikazom slučaja može se zaključiti da su kliničko-laboratorijska obilježja SSc-a, sukladno podatcima iz literature, i kod našeg gerijatrijskog bolesnika bila različita u odnosu na bolesnike mlađe životne dobi. SSc je bolest koja se najčešće javlja u radno aktivnoj populaciji, iako je njezina pojavnost opisana i kod mlađih i starijih pacijenata. U literaturi je do sada opisan relativno mali broj bolesnika koji su od SSc-a oboljeli u starijoj životnoj dobi.

Hugle i sur. proveli su istraživanje na 8.554 pacijenta sa SSc-om, od kojih su samo 123 bolesnika (1,4%) bili stariji od 75 godina i pokazali su kako stariji bolesnici češće imaju limitirani oblik bolesti i veću prevalenciju antitijela na centromere. Modificirani Rodnanov kožni zbroj i prevalencija plućne fibroze nisu se značajno razlikovali između dvije skupine (3). Prema ACR/EULAR kriterijima iz 2013. godine, zadebljanje kože prstiju obje ruke proksimalno od metakarpofalangealnih zglobova dovoljno je za klasifikaciju pacijenta za dijagnozu SSc-a. U našeg bolesnika temeljem kliničkog pregleda bilo je dovoljno elemenata da se već prvim pregledom postavi temeljita sumnja na SSc. Ostale manifestacije bolesti čijim se zbrajanjem određuje potvrda dijagnoze bolesti (skor ≥9) jesu: zadebljanje kože prstiju, lezije vrškova prstiju, telangiektazije, kapilaroskopski abnormalne kapilare ležišta noktiju, plućna arterijska hipertenzija i/ili intersticijska bolest pluća, Raynaudov fenomen i autoantitijela povezana sa SSc-om (4). U našeg bolesnika bila je prisutna sklerodaktilija, Raynaudov fenomen, u laboratorijskim nalazima visoko pozitivna protutijela na centromere, dok je nalaz kapilaroskopije pokazao aktivan sklerodermijski uzorak.

Prema objavljenim podatcima, plućna hipertenzija dijagnosticirana ultrazvukom i kateterizacijom desnog srca češća je u bolesnika s kasnim početkom bolesti,

nailfold capillaries (detected through capillaroscopy), pulmonary arterial hypertension and/or interstitial lung disease, Raynaud's phenomenon and SSc-related autoantibodies (4). Our patient had sclerodactyly and Raynaud's phenomenon, a positive anti-centromere antibody finding (a type of anti-nuclear antibodies) was revealed through laboratory findings, while capillaroscopy revealed an active scleroderma pattern.

According to the published literature data, pulmonary hypertension diagnosed with an echocardiogram and right heart catheterisation are more common in patients with late onset of the disease, while the risk of digital ischemia is lower in these patients. The prevalence of anti-U1RNP antibodies is significantly lower in elderly patients (2). The ultrasound showed no signs of pulmonary hypertension in our patient, and according to the data found in the literature, the anti-U1RNP antibodies were negative. Despite the Raynaud's phenomenon and an active scleroderma pattern (revealed through capillaroscopy), digital ulcerations were not present in our patient.

Gastrointestinal involvement is relatively high in patients with SSc. In a study conducted by Alba et al., patients with early onset of the disease have been shown to have a higher prevalence of oesophageal involvement (72% of early-onset patients compared to 56% of late-onset patients). After correction for the population effects of age and sex, mortality was shown to be higher in younger patients (1). The patient from this case report had no gastroenterological disorders or symptoms or signs typical of SSc, the barium swallow test of the oesophagus showed no abnormalities, and the chest MSCT showed no signs of oesophageal dilatation.

In our patient, high levels of alkaline phosphatase (ALP) and relatively low levels of creatinine kinase (CK) were recorded, in accordance with the data found in the literature (5).

Although it seemingly appeared like a typical clinical presentation of SSc, our patient's case required additional caution and differential diagnosis, primarily due to the presence of extremely high inflammatory markers and pronounced Raynaud's phenomenon, which could indicate an associated malignancy. It is important to note that Raynaud's phenomenon could be one of the initial manifestations of an associated malignancy (6).

An earlier diagnosis of a malignancy that was cured several years ago is unlikely to be associated with the development of SSc, and our patient has not been treated with chemotherapy or other drugs that would be associated with the development of SSc.

It is interesting to note that in the treatment of our patient, a low dose of glucocorticoids led to a complete regression of clinical symptoms as well as an improvement in skin manifestations, i.e., it resulted in an almost complete remission of the disease.

dok je rizik od digitalne ishemije u tih bolesnika manji. Prevalencija anti-U1RNP antitijela znatno je rjeđa u bolesnika u starijoj dobi (2). U našeg bolesnika nije bilo ultrazvučnih znakova za plućnu hipertenziju, a sukladno podatcima iz literature anti-U1RNP protutijela bila su negativna. Unatoč prisutnom Raynaudovom fenomenu i kapilaroskopski aktivnom sklerodermijskom uzorku kod našeg bolesnika nisu bile prisutne digitalne ulceracije.

Zahvaćanje gastrointestinalnog sustava relativno je visoko u bolesnika sa SSc-om. U studiji Albe i sur. pokazano je da bolesnici s ranim početkom bolesti imaju veću prevalenciju zahvaćenosti jednjaka (72% pacijenata sa ranim početkom u usporedbi s 56% kod kasnog početka). Nakon korekcije za dob i spol, pokazalo se da je smrtnost veća kod mlađih bolesnika (1). Ovdje prikazani bolesnik nije imao gastroenterološkihsmetnji odnosno simptoma ili znakova tipičnih za SSc, nalaz pasaže jednjaka bio je uredan, a na MSCT-u toraksa nije se vidjelo dilatacije jednjaka.

U našeg bolesnika zabilježene su više vrijednosti ALP-a i relativno niže vrijednosti CK-a, a sukladno podatcima iz literature (5).

Iako naizgled tipična klinička prezentacija SSc-a, u našeg bolesnika bio je potreban dodatan oprez i diferencijalna dijagnostička obrada, a prvenstveno zbog prisutnih izrazito visokih upalnih biljega i izraženog Raynaudova fenomena, koji bi mogli upućivati i na pridruženu malignu bolest, a čija prva manifestacija može biti upravo Raynaudov fenomen (6).

Ranija dijagnoza izliječene maligne bolesti prije više godina vjerojatno nema poveznice s razvojem SSc-a, a naš bolesnik nije liječen kemoterapijom ili drugim lijekovima koji bi bili povezani s nastankom SSc-a.

Zanimljiv je podatak da je u liječenju našeg bolesnika niska doza glukokortikoda dovela do potpune regresije kliničkih simptoma kao i poboljšanja kožnih manifestacija, odnosno gotovo do remisije bolesti.

Planira se daljnja redukcija odnosno pokušaj isključivanja glukokortikoida, a u slučaju nepovoljnoga kliničkog odgovora razmotrit će se primjena drugih imunosupresiva čija primjena nije limitirana u starijih bolesnika, ali potrebna je prilagodba doze lijekova bubrežnoj i jetrenoj funkciji uzimajući u obzir sve pridružene komorbiditete kod starijih bolesnika.

Za razliku od povoljnog tijeka bolesti i dobrog odgovora na terapiju koji smo imali u našeg bolesnika, SSc kasnije pojavnosti uglavnom se povezuje s agresivnijim oblikom bolesti (3).

Veća prevalencija ekstrakutanog zahvaćanja organa u početku bolesti i ranija pojava sistemskih manifestacija u starijih osoba vjerojatno je razlog ranijeg započinjanja obrade i postavljanja dijagnoze (1,2,7). Potrebno je obratiti pozornost i na skupinu mlađih pacijenata s blažim simptomima koji su u početku klasificirani

Further reduction or an attempt of discontinuation of glucocorticoid therapy is planned, and in case of an adverse clinical response, other immunosuppressants, whose use is not limited in elderly patients, will be considered. However, the dose of these immunosuppressants should be adjusted in order to be in accordance with the renal and hepatic function, taking into account all comorbidities that may occur in elderly patients.

In contrast to the mild course of the disease and the good response to therapy we had in our patient, late-onset SSc is mainly associated with a more aggressive form of the disease (3).

The higher prevalence of extracutaneous organ involvement at the onset of the disease and the earlier occurrence of systemic manifestations in the elderly is the probable reason for the earlier initiation of treatment and diagnosis (1,2,7). Attention should also be paid to the group of younger patients with mild symptoms who were initially classified as cases of undifferentiated connective tissue disease and who tend to develop features of SSc later in life (8).

Although systemic sclerosis most often occurs in middle-aged people, its occurrence has also been reported in elderly patients. Clinical and laboratory characteristics as well as response to therapy are different in younger and older patients. There is no doubt that high life expectancy in patients with SSc is associated with a poor prognosis, but it is important to note that most geriatric patients have other comorbidities which, in addition to the age factor, increase the risk of adverse outcomes and mortality.

A relatively small number of cases with SSc onset in patients over the age of 80 has been described in literature so far. Our patient's case report enables a better exchange of clinical experiences, facilitation in differential diagnosis and a diagnostic and therapeutic algorithm in patients with late-onset SSc. It is particularly interesting to note that the administration of low doses of glucocorticoids in our patient has produced satisfactory results in terms of cutaneous manifestations of the disease, in addition to having a beneficial effect on peripheral joints. In addition to being significant in terms of scientific contribution, this patient's case report can also contribute to additional research into the pathophysiological mechanisms of the onset and progression of this disease in geriatric patients.

Conflict of interest statement: The authors declare no conflict of interest.

kao nediferencirana bolest vezivnog tkiva, a koji tek kasnije razvijaju značajke SSc-a (8).

Iako se sistemska skleroza najčešće javlja u osoba srednje životne dobi, njezina pojavnost zabilježena je i u starijih bolesnika. Kliničko-laboratorijska obilježja kao i odgovor na terapiju različiti su između mlađih i starijih bolesnika. Nedvojbeno je da je visoka životna dob u bolesnika s SSc-om povezana s lošijom prognozom, ali važno je naglasiti da većina starijih bolesnika ima pridružene i druge komorbiditete koji zajedno sa životnom dobi sami po sebi povećavaju rizik od lošijeg ishoda i smrtnosti.

U literaturi je do sada opisan ralativno mali broj bolesnika u kojih se SSc manifestirala u dobi iznad 80 godina. Prikaz našeg bolesnika omogućuje bolju razmjenu kliničkih iskustava, olakšanje u diferencijalnoj dijagnostici i dijagnostičko-terapijski algoritam u bolesnika s SSc-om starije životne dobi. Od posebnog je interesa da je uz povoljan učinak na periferne zglobove primjena niskih doza glukokortikoda u našeg bolesnika polučila dobre rezultate na kožne manifestacije bolesti. Osim stručnog doprinosa, prikaz ovog bolesnika može pridonijeti i dodatnim istraživanjima u patofiziološkim mehanizmima nastanka i progresije ove bolesti kod gerijatrijskih bolesnika.

Izjava o sukobu interesa: Autori izjavljuju da nisu u sukobu interesa.

REFERENCES / LITERATURA

1. Alba MA, Velasco C, Simeón CP, Fonollosa V, Trapiella L, Egurbide MV i sur. Early- versus late-onset systemic sclerosis: differences in clinical presentation and outcome in 1037 patients. Medicine. 2014;93(2):73–81.
2. Manno RL, Wigley FM, Gelber AC, Hummers LK. Late-age onset systemic sclerosis.J Rheumatol. 2011;38(7):1317–25.
3. Hügle T, Schuetz P, Daikeler T, Tyndall A, Matucci-Cerinic M, Walker UA i sur. Late-onset systemic sclerosis-a systematic survey of the EULAR scleroderma trials and research group database. Rheumatology. 2011;50(1):161–5.
4. van den Hoogen F, Khanna D, Fransen J, Johnson SR, Baron M, Tyndall A, et al. 2013 classification criteria for systemic sclerosis: an American college of rheumatology/European league against rheumatism collaborative initiative. Ann Rheum Dis. 2013;72(11):1747–55.
5. Weng HH, Ranganath VK, Oh M, Park GS, Khanna D, Clements PJ i sur. Differences in presentation of younger and older systemic sclerosis patients in clinical trials. Clin Exp Rheumatol. 2010;28(5 Suppl 62):ii 10–4.
6. Sutic A, Gudelj-Gracanin A, Morovic-Vergles J. Raynaud' phenomen-first sign of malignancy: case report. Acta Med. Croatica.2014;68(3):295–8.
7. Perez-Bocanegra C, Solans-Laque R, Simeon-Aznar CP, Campillo M, Fonollosa-Pla V, Vilardell Tarres M. Age-related survival and clinical features in systemic sclerosis patients older or younger than 65 at diagnosis. Rheumatology. 2010;49 (6):1112–7.
8. Valentini G, Vettori S, Cuomo G, Iudici M, DAbrosca V, Capocotta D et al. Early systemic sclerosis: short-term disease evolution and factors predicting the development of new manifestations of organ involvement. Arthritis Res Ther. 2012;14(4):R188.

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MUSCLOSKELETAL DISORDERS AND DISEASES IN PIANISTS
Lessons from the past and messages to young people

Iva Bartolić, Ladislav Krapac

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Medicinska naklada, the leading specialized publishing house in Croatia in the field of medicine, recently, in February 2021, published a new book entitled *MUSCULOSKELETAL DISORDERS AND DISEASES IN PIANISTS* – Lessons from the past and messages to young people. The book is the result of many years of joint work of Iva Bartolić, Master of Music and Ladislav Krapac, specialist of physical and rehabilitation medicine, subspeciality in rheumatology, Prim. Ph D.

The book presents a detailed account starting with the history of medicine in music and an account of the anatomy of the hand and the playing apparatus.

The special value of this book is given by the author's own experience and a detailed description of the problems she encountered as well as the possibilities of solving them. Also, an overview of the causes of the most common diseases and their clinical picture is presented (overexertion syndromes, ischemia, tendinitis and tenosynovitis, De Quervain's disease, upper thoracic orifice syndrome, cubital and carpal tunnel syndrome, chronic degenerative problems, painful syndromes of the spine). The book also includes chapters on recovery from injuries and prevention of future injuries. Everything is accompanied in detail by appropriate illustrations, making a clear and understandable presentation of the above issues, with reference to domestic and foreign results of relevant research.

Musicians are a particularly vulnerable group for musculoskeletal disorders as parts of this system are prone to wear and injury due to constant use. As a first step in solving the problem, its (preferably timely or as early as possible) recognition is necessary. Therefore, this book, which was written in collaboration with the medical profession, is aimed at musicians of all ages and levels of education. The importance of prevention is especially emphasized, and a reminder is also given of the risk factors that we can influence.

From the reviews of academician Vida Demarin, professor Darko Breitenfeld Ph D. and doctor of medicine Mislav Pap, who is also an academic musician, on the cover of the book are highlighted their common opinions on the great need and importance of such a handbook for musicians, performers and their professors.

Generations, not only pianists, but musicians in general, can certainly be recognized in the topics covered in this book. But as the author herself states in the introduction, this handbook is not only intended for young musicians and their parents, but also for music professors, as well as computer scientists. It can also be very useful to doctors of various specialties: school medicine, occupational medicine, physical medicine, family medicine, rheumatologists, neurologists, surgeons, orthopedists, traumatologists.

Accompanied by rich bibliographic data, this manual will help interested pianists and other musicians to solve health problems that hinder them in their work on a daily basis. In conclusion, it can be said that the history of this topic has not been forgotten, and we hope that the future is more clearly illuminated, for the benefit and satisfaction of its readers.

The book can be ordered from Medicinska naklada at https://www.medicinskanaklada.hr/mišićno-koštani-poremećaji-i-bolesti-kod-pijanista at a price of 168.00 kn with a delivery time of 3 to 5 days.

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MIŠIĆNO-KOŠTANI POREMEĆAJI I BOLESTI KOD PIJANISTA
Pouke iz prošlosti i poruke mladima

Iva Bartolić, Ladislav Krapac

Izdavač: Medicinska naklada
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„Medicinska naklada“, vodeća specijalizirana nakladnička kuća u Hrvatskoj za područje medicine, nedavno je, u veljači 2021., izdala novu knjigu naslova *MIŠIĆNO-KOŠTANI POREMEĆAJI I BOLESTI KOD PIJANISTA – Pouke iz prošlosti i poruke mladima*. Ova knjiga rezultat je dugogodišnjeg rada i suradnje Ive Bartolić, magistre muzike i prim. dr. sc. Ladislava Krapca, specijalista fizikalne i rehabilitacijske medicine, subspecijalista reumatologije.

U knjizi se iznosi detaljan prikaz zdravstvenih problema koji se javljaju kod glazbenika te se obrađuju teme od povijesti medicine u glazbi do anatomije ruke i sviračkog aparata.

Osobno iskustvo autorice, detaljni opisi problema s kojima se susrela i načini njihova rješavanja ono su što ovu knjigu čini posebno vrijednom. Knjiga također sadrži pregled uzroka najčešćih bolesti i njihove kliničke slike (sindromi prenaprezanja, ishemija, tendinitis i tenosinovitis, De Quervainova bolest, sindrom gornjega torakalnog otvora, sindrom kubitalnog i karpalnog tunela, kronični degenerativni problemi, sindrom bolnih leđa). Nadalje, knjiga sadrži i poglavlja o oporavku od ozljeda i prevenciji budućih ozljeda. Svako poglavlje popraćeno je odgovarajućim ilustracijama, čime se omogućuje jasniji i razumljiviji prikaz navedenih problema, s osvrtom na rezultate bitnih istraživanja provedenih u sklopu domaćih i stranih projekata.

Glazbenici su skupina koja je posebno podložna mišićno-koštanim poremećajima upravo zbog toga što su dijelovi mišićno-koštanog sustava skloniji trošenju i ozljedama zbog neprekidne uporabe. Prvi korak u rješavanju ovog problema upravo je njegovo prepoznavanje (po mogućnosti pravovremeno ili u najranijem mogućem stadiju). Stoga je ova knjiga, koja je napisana u suradnji sa stručnjacima iz područja medicine, posvećena glazbenicima svih dobi i razina obrazovanja. U ovom djelu posebno se ističe važnost prevencije te se iznosi i podsjetnik na rizične čimbenike na koje je moguće utjecati.

Na koricama knjige izdvojeni su dijelovi iz recenzija akademkinje Vide Demarin, prof. dr. sc. Darka Breitenfelda i Mislava Papa, dr. med., koji je ujedno i akademski glazbenik, u kojima se ističe njihovo zajedničko mišljenje o velikoj potrebi za ovakvim priručnikom te o njegovoj važnosti za glazbenike, izvođače i njihove profesore.

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Reumatizam (Rheumatism) is the platinum open-access peer-reviewed biannual journal of the Croatian Society for Rheumatology. The journal publishes practice guidelines, editorials, original research, reviews, expert opinion pieces, case reports, letters, interviews, meeting reports, and news items. Priority is given to evidence-based research reports in rheumatology, physical medicine and rehabilitation, orthopedics, and allied health specialties to provide the readership with new scientific information on diagnostic and therapeutic procedures as well as comprehensive care for patients with autoimmune and autoinflammatory rheumatic diseases.

Although the journal primarily serves the interests of rheumatologists and physiatrists from Croatia and other Adriatic-Ionian countries, the editors welcome high-quality submissions from all over the world. The aim of the journal's internationalization is to publicize the best rheumatology research and practice, and monitor the progress in rheumatology and allied health professions in Croatia and neighboring countries.

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Reumatizam publishes the following types of peer-reviewed articles: practice guidelines, editorials, original research, reviews, expert opinion pieces, case reports, letters, interviews, meeting reports, and news items.

Editorial: 1200 words maximum; up to 1 figure or table; up to 20 references; 3–6 Medical Subject Heading (MeSH) keywords of the National Library of Medicine of US; unstructured abstract up to 300 words (if applicable).

Original Research: 6,500 words maximum; up to 6 figures and 6 tables; unlimited number of references; 3 – 6 keywords; structured abstract up to 300 words (except for articles on the history of medicine that may have an unstructured abstract).

logija.org) ili u dogovoru s urednikom u papirnatom obliku (u računalnom ispisu), zajedno s elektroničkom verzijom na CD-u, DVD-u, USB-*sticku* na adresu: *Reumatizam*, Uredništvo, Klinika za reumatologiju, fizikalnu medicinu i rehabilitaciju, Klinički bolnički centar Sestre milosrdnice, Vinogradska 29, 10000 Zagreb, Hrvatska.

Uredništvo časopisa slijedi upute Međunarodnog odbora urednika medicinskih časopisa – Preporuke za provedbu, prikazivanje, uređivanje i objavljivanje radova u medicinskim časopisima (*International Committee of Medical Journal Editors* (ICMJE) – *Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals*; http://www.icmje.org/icmje-recommendations.pdf) i Svjetske udruge medicinskih urednika (*World Association of Medical Editors* – WAME; http://www.wame.org). Za tekstove na engleskom jeziku preporučuje se da autori koji nisu izvorni govornici engleskog jezika potraže savjet stručnjaka radi točnog i kvalitetnog prijevoda. Izdavač može osigurati takvu uslugu uz plaćanje.

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Reumatizam objavljuje ove vrste radova kod kojih je potrebna recenzija : kliničke smjernice, uvodnike, originalne znanstvene radove, pregledne radove, stručne radove, kratka/preliminarna priopćenja, pregledne radove i dobro dokumentirane prikaze bolesnika (s pregledom literature).

Uvodnik (*Editorial*): maksimalno 1200 riječi; do 1 slike ili tablice; do 20 referencija; 3 – 6 MeSH ključnih riječi; nestrukturirani sažetak do 300 riječi (ako je primjenjivo).

Practice Guidelines, Review and Expert Opinion articles: 6,000 words maximum; up to 5 figures and 5 tables; unlimited number of references; 3 – 6 keywords; structured abstract up to 300 words (except for articles on the history of medicine that may have an unstructured abstract).

Letters (Short or Preliminary Communication, Brief Report): 1,500 words maximum; up to 3 figures or tables; up to 15 references; 3 – 6 keywords.

Case Report (Case Based Review): 6,000 words maximum; up to 5 figures or tables; unlimited number of references; 3–6 keywords; unstructured abstract up to 300 words.

Erratum: enables correction of errors made in writing, printing, or publication process of an article. To be sent to: *Reumatizam*, Uredništvo, Klinika za reumatologiju, fizikalnu medicinu i rehabilitaciju, Klinički bolnički centar Sestre milosrdnice, Vinogradska 29, 10000 Zagreb, Croatia, or via email: glavni-urednik-reumatizam@reumatologija.org and urednik-reumatizam@reumatologija.org.

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Reumatizam publishes articles in Croatian, including the title, abstract, keywords, and table and figure titles and legends in English, or articles in English (American standard), including the title, abstract, keywords, and table and figure titles and legends in Croatian. The writing style should be clear and concise. Articles should be structured following the EQUATOR Network principles (http://www.equator-network.org).

The text should be typed in 12-point font, on white A4 paper (210 x 297 mm), double-spaced, with a maximum of 30 lines per page, including the title page, abstract, text, acknowledgments, conflict of interest statement, references, tables, and legends. The left margin should be 35 mm, and the right, top and bottom margins 25 mm each. All the pages, including the title page, should be numbered in the bottom right corner.

Measurements, if needed, should be reported using the International System of Units (SI). Names that can be abbreviated should be spelled out in full followed by the abbreviation in parentheses at the first mention, and referred to only in the abbreviated form further in the text. Latin names should be italicized, with the full name at the first mention, and only the abbreviated form further in the text. Drugs should be referred to by their generic names, and trade names, if necessary, may follow in parentheses, with the manufacturer's name. Manufacturers of specific instruments or reagents (name and location) should be given in parentheses.

Except for reviews and letters to the editor, manuscripts should include the following: a title page (on a separate page), abstract and keywords (on a separate page), the main text (with the following sections: introduction, participants and methods, results, discussion, and conclusion), acknowledgments, funding, conflict of interest statement, references, list of tables, list of figures, tables and figures.

Title page

The title page should include the article title (concise, clear, and informative) both in Croatian and in English, and the full name of each author, followed by the full name of the author's affiliation, with full postal address (street, city, and country) of the institution. If the article was prepared by several authors of various affiliations, all authors should be linked to their corresponding affiliation(s) using superscript numerals after their respective names, and preceding the institution name.

This should be followed by the name, surname, and full contact address of the corresponding author responsible for the correspondence related to the article, with his/her telephone and fax numbers, and e-mail address.

Abstract and keywords

The second page should include the abstract, both in English and Croatian, of up to 300 words, providing the purpose of the study/research, materials (participants) and methods, results, and conclusions.

Originalni rad (*Original Research Article*): maksimalno 6500 riječi; do 6 slika i 6 tablica; neograničeni broj referencija; 3 – 6 ključnih riječi; strukturirani sažetak do 300 riječi (izuzetak su radovi iz povijesti medicine koji mogu imati nestrukturirani sažetak).

Kliničke smjernice (Practical Guidelines), pregledni radovi (Review) i radovi temeljeni na mišljenju eksperata (Expert Opinion Articles): maksimalno 6 000 riječi; 5 slika i 5 tablica; neograničeni broj referencija; 3-6 ključnih riječi, strukturirani sažetas sa do 300 riječi (izuzetak su radovi iz povijesti medicine koji mogu imati nestrukturirani sažetak).

Kratko priopćenje (*Short Communication*, *Brief Report*): maksimalno 1500 riječi; do 3 slike ili tablice; do 15 referencija; 3 – 6 ključnih riječi.

Prikaz bolesnika(*Case Based Review)* maksimalno 6000 riječi; do 5 slika ili tablica; neograničeni broj referencija; 3 – 6 ključnih riječi; nestrukturirani sažetak do 300 riječi.

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PRIPREMA RADA / RUKOPISA

U časopisu *Reumatizam* objavljuju se članci na hrvatskom jeziku, s naslovom, sažetkom, ključnim riječima te s naslovom i legendom tablica i slika na engleskom jeziku ili članci na engleskom jeziku (*UK spelling*), s naslovom, sažetkom, ključnim riječima te s naslovom i legendom tablica i slika na hrvatskom jeziku. Stil pisanja treba biti jasan i jezgrovit. Radovi trebaju biti strukturirani sukladno principima EQUATOR Networka (http://www.equator-network.org).

Tekst treba biti napisan slovima veličine 12 točaka na bijelom papiru formata A4 (210 × 297 mm) s dvostrukim proredom, s najviše 30 redaka po stranici, uključujući i naslovnu stranicu, sažetak, tekst, zahvale, izjavu o sukobu interesa, referencije, tablice i legende. Lijeva margina treba biti široka 35 mm, a desna margina te gornji i donji rub 25 mm. Sve stranice, uključujući naslovnu, trebaju imati redni broj u donjem desnom kutu.

Pri potrebi izražavanja podataka rabe se SI mjerne jedinice. Kod naziva koji se mogu pisati kraticom pri prvom je pojavljivanju potrebno napisati puni naziv, s kraticom, a u daljnjem tekstu samo kraticu. Latinski nazivi pišu se načinom Italic, i to puni naziv kod prvog pojavljivanja u tekstu, a u daljnjem tekstu navodi se kratica. Lijekovi se navode generičkim imenom, a ako je nužno, može se u zagradi navesti tvorničko ime, s imenom proizvođača. Proizvođače specifičnih instrumenata ili reagensa (naziv i lokacija) treba navesti u zagradi.

Izuzev preglednih radova i pisama uredniku radovi trebaju imati slijedeće elemente: naslovna stranica (posebna stranica), sažetak i ključne riječi (posebna stranica), glavni tekst rada (s dijelovima: uvod, ispitanici i metode, rezultati, rasprava i zaključak), zahvale, financiranje, izjava o sukobu interesa, literatura, popis tablica i slika te tablice i slike.

Naslovna stranica

Na naslovnoj stranici trebaju biti naslov rada (sažet, jasan i informativan) na hrvatskom i engleskom jeziku te puno ime svakog od autora. U sljedećem retku treba navesti puni naziv ustanove, ulicu i broj, grad i državu. Ako su u izradi rada sudjelovali autori iz različitih ustanova, za svakog od njih poslije imena i prezimena te prije navoda ustanove treba napisati odgovarajući broj u superskriptu.

Slijede ime i prezime te puna adresa autora za dopisivanje u vezi s radom, njegov/njezin telefonski broj, broj faksa i e-mail adresa.

The abstract should emphasize new and important aspects of the study, or observations. Below the abstract, three to six keywords or short terms should be listed, both in Croatian and in English, to help index the article. The keywords may be published with the abstract. Terms from the Medical Subject Headings (MeSH) list of the National Library of Medicine of US should be used for the keywords. General and plural terms, and multiple concepts (e.g., using "and", "or") should be avoided. The abstract should not include references.

Introduction

The introduction provides a brief outline of the context/background of the topic, as well as the purpose and rationale for conducting the study/research. It is recommended to cite only relevant references, which should be well-balanced and recent (not older than 10 years, if possible). At the end, the objective(s) of the study/research should be stated clearly and precisely. No data from the paper or conclusions should be given in the introduction.

Materials and methods

This section provides details about how the study/research was conducted: the place and time, as well as the eligibility criteria for selecting the experimental or observational participants (or laboratory animals), with all their important characteristics. The author(s) should provide a detailed outline of the study (e.g., a randomized–controlled study, an observational study, a prospective/retrospective study, etc.), the data collection methods applied, the meaning of the descriptors, and explain and identify the methods, devices (including the manufacturer's name in parentheses), and procedures, sufficiently detailed to enable others to reproduce the results. References should be given for established methods, and new or substantially modified methods should be described in detail, stating the reasons for using them, and evaluating their limitations.

Generic names should be used for drugs and chemicals. All measurements should be given in SI units. In Croatian texts a decimal comma should be used, and in texts in English a decimal point.

Ethics / Ethical standards

Studies involving human subjects or animals should have received the approval of the respective ethics committee. The work described should have been carried out in accordance with the ethical standards of an institutional or national committee responsible for experiments involving human subjects, as well as with The Code of Ethics of the World Medical Association (Declaration of Helsinki 1964 and its revisions) for experiments involving humans http://www.wma.net/en/30publications/10policies/b3/index.html; EU Directive 2010/63/EU and for animal experiments http://ec.europa.eu/environment/chemicals/lab_animals/legislation_en.htm. Also, it should be stated explicitly that informed consent was obtained from all participating adult subjects or from parents or legal guardians for minors or incapacitated adults, together with the manner in which informed consent was obtained (i.e., oral or written).

Participants' names and/or surnames should not appear, particularly in figurative/illustrative materials.

Statistics

Statistical methods should be described in detail, to enable a knowledgeable reader with access to the original data to verify the reported results. Where possible, findings should be quantified and presented with appropriate indicators of measurement error or uncertainty. The statistical software used should be specified.

Results

Results should be presented in a logical sequence in the text, tables, and figures. In this section, the results are not interpreted nor are their implications discussed. In addition to absolute numbers

Sažetak i ključne riječi

Druga stranica treba sadržavati sažetak na engleskom i hrvatskom jeziku (do 300 riječi) u kojem su navedeni cilj studije/istraživanja, materijal (ispitanici) i metode, rezultati i zaključci.

U sažetku valja naglasiti nove i važne aspekte studije ili opservacije. Ispod sažetka autori trebaju navesti tri do šest ključnih riječi ili kratkih pojmova na hrvatskom i engleskom jeziku koji će pomoći pri indeksiranju članka. Ključne riječi se mogu objaviti uz sažetak. Za ključne riječi treba se koristiti pojmovima iz popisa *Medical Subject Headings* (MeSH) Indexa Medicusa. Općenite, množine i mnogostruke koncepte (primjerice uz uporabu „i", „ili") treba izbjegavati. Sažetak ne smije sadržavati navode referencija.

Uvod

U uvodu se ukratko navode kontekst/pozadinsko znanje o temi, svrha i razlog provođenja studije/istraživanja. Preporučuje se navesti samo relevantne referencije, koje trebaju biti uravnotežene i recentne (po mogućnosti ne starije od 10 godina). Na kraju treba jasno i točno navesti cilj/-eve studije/istraživanja. U uvodu se ne navode podatci iz rada niti zaključci.

Materijal i metode

Navode se detalji provedbe studije/istraživanja: gdje i kad je provedena, na koji je način učinjen odabir i sve važne karakteristike ispitanika (ili laboratorijskih životinja) koje su studirane ili opservirane. Treba detaljno specificirati nacrt studije (npr., randomizirana-kontrolirana studija, opservacijska studija, prospektivna/retrospektivna itd.), način prikupljanja podataka, značenje deskriptora te objasniti, identificirati metode, aparate (s nazivom proizvođača u zagradi) i postupke, dovoljno detaljno kako bi se rezultati mogli reproducirati. Za poznate metode treba navesti referencije, a nove metode ili metode koje su znatnije modificirane detaljno opisati, navodeći razlog njihove primjene i procjene njihovih ograničenja.

Za lijekove i kemikalije moraju se rabiti generička imena. Sve veličine trebaju biti izražene u SI jedinicama. U tekstovima na hrvatskom jeziku rabi se decimalni zarez, a u tekstovima na engleskome decimalna točka.

Etika / Etički standardi

Radovi koji uključuju ljude ili životinje trebaju imati odobrenje od odgovarajućeg etičkog povjerenstva. Takav rad treba biti proveden sukladno etičkim standardima intitucije ili nacionalnom povjerenstvu odgovornom za eksperimente koji uključuju ljude i s Etičkim kodeksom udruge World Medical Association (Helsinška deklaracija iz 1964. i njezine kasnije inačice) za istraživanja koja uključuju ljude http://www.wma.net/en/30publications/10policies/b3/index.html; EU Direktiva 2010/63/EU I za istraživanja na životnjama http://ec.europa.eu/environment/chemicals/lab_animals/legislation_en.htm. Također, treba jasno navesti da je dobiven informirani pristanak od strane svih odraslih ispitanika ili od strane roditelja ili zakonskih skrbnika za maloljetne ispitanike ili nesposobne odrasle osobe, kao i način na koji je taj pristanak dobiven (npr. usmeno ili pismeno).

Imena i /ili prezimena ispitanika ne smiju biti obznanjena, naročito u grafičkim/slikovnim materijalima.

Statistika

Treba iscrpno opisati statističke metode kako bi se obrazovanom čitatelju koji ima pristup originalnim podatcima omogućilo da potvrdi navedene rezultate. Gdje god je to moguće zaključke treba kvantificirati i prezentirati odgovarajućim indikatorima pogrješke ili odstupanja od mjerenja. Treba navesti upotrijebljeni računalni program.

Rezultati

Rezultati se izlažu logičnim slijedom u tekstu, tablicama i slikama. U ovom se dijelu rezultati ne tumače niti se raspravlja o njiho-

and percentages, it is necessary to include the results of statistical analysis, by stating, for example, P values or other parameters. All the data from the tables or figures should not be repeated in the text, but rather only the most important observations should be emphasized or summarized. Redundant tables and figures (e.g., presenting the same data in different formats) should be avoided, as should the use of figures and tables when it is better to include the data in the textual part (e.g., when there is insufficient data for tables or figures).

Discussion

Most of this section is the interpretation of results. New and important aspects of the study, and its implications, should be emphasized. It is not recommended to repeat in detail data or any other material given in the Introduction or in the Results section. Own findings should be compared with the findings of other studies/research, showing the similarities and differences. It is also important to explain the significance of the results obtained, their limitations, and implications for future research, avoiding, however, making statements and drawing conclusions not completely confirmed by the obtained data. When necessary, new hypotheses may be given, but clearly labelled as such.

Conclusions

The main conclusions are drawn based on the author's or authors' own results (3 – 5 sentences maximum).

Abbreviations

Only standard abbreviations should be used. The spelled-out abbreviation followed by the abbreviation in parentheses should be used at the first mention unless the abbreviation is a standard unit of measurement. Abbreviations should be avoided in the manuscript title.

Symbols

Symbols used in the text should be explained. A detailed list of symbols may be given in an appendix.

Tables

Tables should be presented on a separate page. They should not be submitted as images/photographs. Each table should have a title and be numbered consecutively in the order it appears in the text. Tables should be self-explanatory and as simple as possible. Table legends should be given below the table, and may include a reference to data in the table indicated by a superscript figure or letter. Results presented elsewhere in the article (e.g., in an illustration), should not be repeated in the table. If a table originating from other sources is used, permission for such publication should be obtained from the respective publisher/author.

Figures / Illustrations

All figures should be professionally drawn or photographed. Letters, numbers, and symbols on figures should be clear enough to remain legible when the figure is reduced for publication. Figure titles and descriptions are considered to be a part of the text, and not part of the figure/illustration. Each figure/illustration should be numbered consecutively according to the order in which it appears in the text, and have a clear mark showing which is the upper side. Figures/illustrations should appear in a quality appropriate for print publication. Photocopied images or photographs are not suitable for reproduction. If submitted in electronic format, figures/illustrations should be in a high resolution TIFF or JPEG file format, a minimum of 1,500 pixels wide. Figures/illustrations submitted in other formats may be accepted only with the prior consent of the editorial board. The editorial board reserves the right not to publish any figures/illustrations that fail to meet the above requirevim implikacijama. Uz apsolutne brojeve i postotke potrebno je uključiti rezultate statističke analize, navođenjem obično p-vrijednosti ili drugog parametra. U tekstu se ne ponavljaju svi podatci iz tablica ili slika, već se naglašavaju ili sažimaju samo bitna opažanja. Potrebno je izbjegavati suvišne tablice i slike (npr. prikaz istih podataka u različitim formatima) ili uporabu slika i tablica u slučaju kada je informacije bolje uključiti u tekstualni dio (npr. kada nema dovoljno podataka za tablice ili slike).

Rasprava

Većina ovog dijela odnosi se na interpretaciju rezultata. Potrebno je naglasiti nove i bitne aspekte studije te implikacije koje iz nje proistječu. Ne preporučuje se detaljno ponavljati podatke ni bilo koje druge materijale koji su navedeni u uvodnom dijelu ili u dijelu s rezultatima. U dijelu za raspravu treba usporediti vlastite rezultate s rezultatima iz drugih studija/istraživanja te navesti sličnosti i razlike. Također, važno je objasniti značenje dobivenih rezultata, njihova ograničenja i implikacije vezane uz buduća istraživanja, ali uz izbjegavanje izjava i zaključaka koji nisu potpuno potvrđeni dobivenim podatcima. Kad je potrebno, mogu se navesti nove hipoteze uz jasno naglašavanje da su nove.

Zaključci

Na osnovi vlastitih rezultata izvode se glavni zaključci (maksimalno 3 – 5rečenica).

Kratice

Treba rabiti samo standardne kratice. Puni pojam za koji se rabi kratica mora biti naveden pri prvoj uporabi kratice u tekstu, osim ako je riječ o standardnim kraticama mjernih jedinica. Kratice treba izbjegavati u naslovu rada.

Simboli

U tekstu se simboli moraju objasniti. U dodatku se može navesti iscrpan popis simbola.

Tablice

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[Example] Journal article, continuous pagination:

2. Ritchlin CT. From skin to bone: translational perspectives on psoriatic disease. J Rheumatol. 2008;35:1434–7.

[Example] Supplement article:

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[Example] Book (editors):

5. Isenberg DA, Maddison PJ, Woo P, Glass D, Breedveld FC, editors. Oxford textbook of rheumatology. 3rd ed. New York: Oxford University Press; 2004.

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6. Vasey FB, Espinoza LR. Psoriatic arthritis. In: Calin A, editor. Spondyloarthropathies. Orlando: Grune and Stratton; 1984. pp. 151–85.

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7. Matucci Cerinic M, Pignone A. The early diagnosis of rheumatoid arthritis (RA). Reumatizam. 1997;44(Suppl):1.

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8. Babić-Naglić Đ. Fizička aktivnost i vježbe [Physical activities and exercises]. In: Ivanišević G, editor. Talasoterapija, kineziterapija i aromaterapija u Hrvatskoj [Thalassotherapy, kinesitherapy and aromatherapy in Croatia]. Proceedings of the 14th Lošinj School of Natural Remedies; 2013 Sep 6–7; Veli Lošinj, Croatia. Zagreb: Hrvatski liječnički zbor; 2013, pp. 49–55. Croatian.

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2. Ritchlin CT. From skin to bone: translational perspectives on psoriatic disease. J Rheumatol. 2008;35:1434–7.

[Primjer] Članak iz suplementa:

3. Gladman DD, Antoni C, Mease P, Clegg DO, Nash P. Psoriatic arthritis: epidemiology, clinical features, course, and outcome. Ann Rheum Dis. 2005;64(Supl 2):ii14–7.

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nadian Conference on Research in Rheumatic Diseases; 1970 Oct 15–17; Toronto, Canada. Toronto: University of Toronto Press; 1972.

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[Example] Journal article on the Internet, with a DOI:

11. Vivar N, Van Vollenhoven RF. Advances in the treatment of rheumatoid arthritis. F1000Prime Rep. 2014 May 6;6:31. doi: 10.12703/P6-31. PubMed PMID: 24860653; PubMed Central PMCID: PMC4017904.

[Example] Book/monograph on the Internet:

12. Chen Q, editor. Osteoarthritis – diagnosis, treatment and surgery [Internet]. Rijeka: InTech; 2012. Available from: http://www.intechopen.com/books/osteoarthritis-diagnosis-treatment-and-surgery. [2013 Oct 8].

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13. Hrvatsko reumatološko društvo [Internet]. Zagreb: Croatian Society for Rheumatology of the CMA; c2014. Available from: http://www.reumatologija.org/Pocetna.aspx. [cited: 2014 Apr 1].

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[Primjer] Mrežna stranica:

13. Hrvatsko reumatološko društvo [Internet]. Zagreb: Hrvatsko reumatološko društvo HLZ-a; c2014. Dostupno na: http://www.reumatologija.org/Pocetna.aspx. [Pristupljeno: 1. 4. 2014.].

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