

KUTANI B-ĆELIJSKI LIMFOM MARGINALNE ZONE KAO KOMPLIKACIJA DUGOGODIŠNJEG PRIMARNOG SJOGRENOVOG SINDROMA – MULTIDISCIPLINARNI DIJAGNOSTIČKI IZAZOV PRIMARY CUTANEOUS MARGINAL ZONE B-CELL LYMPHOMA COMPLICATING LONG-STANDING PRIMARY SJÖGREN'S SYNDROME – A MULTIDISCIPLINARY DIAGNOSTIC CHALLENGE

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Sažetak

Primarni Sjogrenov sindrom je hronična autoimuna egzokrinopatija koja nosi značajno povećan rizik od razvoja non-Hoćkinovog limfoma, posebno limfoma marginalne zone mukoza limfoidnog tkiva. Kutani B-ćelijski limfom marginalne zone predstavlja retku, spororastuću formu primarnog kutanog non-Hoćkinovog limfoma koja se javlja u sklopu autoimunih oboljenja, a njena udruženost sa primarnim Sjogrenovim sindromom je predmet sve većeg naučnog interesovanja. Prikazujemo slučaj pacijentkinje koja se 10 godina leči od primarnog Sjogrenovog sindroma (terapija hlorokinom od 1999. godine) kod koje su se januara 2024. godine javile kožne promene u vidu eritematoznih pečata na trupu. Nakon neuspeha lokalne kortikosteroidne terapije i opsežne dijagnostičke obrade koja je uključivala dve uzastopne biopsije kože sa imunohistohemijskom analizom, dijagnostikovao je kutani B-ćelijski limfom marginalne zone (CD20+, CD79a+, Bcl-2+, CD43+/-, Ki-67 ~5%). Biopsija koštane srži i multislajсна kompjuterizovana tomografija grudnog koša, abdomena i karlice nisu ukazali na sistemsku zahvaćenost. Dijagnoza je postavljena multidisciplinarnim pristupom uz saradnju dermatologa, reumatologa i hematologa. Ovaj slučaj naglašava koliko je važno da se posumnja na limfoproliferativne bolesti kod pacijenata sa primarnim Sjogrenovim sindromom koji razvijaju perzistentne kožne promene. Multidisciplinarni pristup, pravovremena rebiopsija i sveobuhvatna imunohistohemijska analiza su ključni za postavljanje tačne dijagnoze i adekvatno zbrinjavanje ove retke, ali klinički značajne povezanosti dveju bolesti.

Ključne reči: Sjogrenov sindrom; B-ćelijski limfom; B-ćelijski limfom marginalne zone; Non-Hodgkinov limfom; autoimunost; kožne bolesti; limfoproliferativni poremećaji; ishod lečenja

Abstract

Primary Sjögren's syndrome is a chronic autoimmune exocrinopathy associated with a significantly increased risk of developing Non-Hodgkin lymphoma, particularly extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue. Primary cutaneous marginal zone B-cell lymphoma represents a rare, indolent subtype of primary cutaneous Non-Hodgkin lymphoma that may occur in the setting of autoimmune diseases, and its association with primary Sjögren's syndrome has become an area of growing scientific interest. We present the case of a female patient with a 10-year history of primary Sjögren's syndrome treated with chloroquine therapy since 1999, who developed erythematous plaques on the trunk in January 2024. Following unsuccessful local corticosteroid therapy and extensive diagnostic evaluation including two consecutive skin biopsies with immunohistochemical analysis, Primary cutaneous marginal zone B-cell lymphoma was diagnosed (CD20+, CD79a+, Bcl-2+, CD43+/-, Ki-67 ~5%). Bone marrow biopsy and multislice computed tomography of the chest, abdomen, and pelvis showed no evidence of systemic in-

volvement. The diagnosis was established through a multidisciplinary collaboration between dermatologists, rheumatologists, and hematologists. This case highlights the importance of considering lymphoproliferative disorders in patients with primary Sjögren's syndrome who develop persistent skin lesions. A multidisciplinary approach, timely re-biopsy, and comprehensive immunohistochemical analysis are essential for establishing an accurate diagnosis and ensuring appropriate management of this rare but clinically significant association between two diseases.

Key words: Sjogren's Syndrome; Lymphoma, B-Cell; Lymphoma, B-Cell, Marginal Zone; Lymphoma, Non-Hodgkin; Autoimmunity; Skin Diseases; Lymphoproliferative Disorders; Treatment Outcome

Uvod

Primarni Sjogrenov sindrom (pSS) predstavlja hroničnu sistemsku autoimunu bolest egzokrinih žlezda čija je suštinska karakteristika limfocitna infiltracija žlezdanog tkiva, pri čemu pljuvačne i suzne žlezde trpe najveći udar imunološke disfunkcije. Klinički, manifestuje se suvoćom oka (keratoconjunctivitis sicca) i usne duplje (xerostomia) – uz česte sistemske manifestacije [1,2]. Prema epidemiološkim podacima, prevalencija pSS u opštoj populaciji kreće se između 0,05 i 4,8%, sa snažnom predominacijom kod žena u odnosu 9 : 1, a najveća učestalost se beleži u petoj i šestoj deceniji života [1].

Ono što pSS izdvaja od većine autoimunih bolesti jeste razvoj limfoproliferativne bolesti. Rizik od NHL kod pSS pacijenata je do 44 puta veći nego u opštoj populaciji prema ranijim studijama, dok savremene metaanalize procenjuju povećanje rizika na 10 do 14 puta [3–5]. Kumulativni rizik dostiže 9,8% u roku od 15 godina od postavljanja dijagnoze [3,5]. Ova asocijacija nije slučajna – hronična autoantigenska stimulacija B-limfocita, kontinuirana aktivacija signalnih puteva preživljavanja poput NF-κB i BCR signalizacije, kao i razvoj tercijarnih limfoidnih struktura unutar egzokrinih žlezda, predstavljaju ključne patogenetske korake na putu od autoimunosti do limfogeneze [2,6,7].

Kada se na toj putanji razvije limfom, dominantni histološki tip je limfom marginalne zone (MZL), najčešće u ektranodalnoj, MALT lokalizaciji (mucosa-associated lymphoid tissue), tipično u pljuvačnim žlezdama [5,8]. Kožna varijanta ovog entiteta – primarni kutani limfom marginalne zone (PCMZL) – predstavlja redak, ali jasno prepoznat kliničkopatološki fenomen koji prema najnovijim klasifikacijama Svetske zdravstvene organizacije (WHO 5th edition, 2022) i Međunarodnoj konsenzus klasifikaciji (ICC, 2022) zauzima posebno mesto među indolentnim limfoproliferativnim po-

Introduction

Primary Sjögren's syndrome (pSS) is a chronic systemic autoimmune disease of the exocrine glands characterized by lymphocytic infiltration of glandular tissue, predominantly affecting the salivary and lacrimal glands. Clinically, it manifests with keratoconjunctivitis sicca and xerostomia, frequently accompanied by systemic manifestations [1,2]. Epidemiological data estimate the prevalence of pSS in the general population between 0.05% and 4.8%, with a strong female predominance of 9:1, most commonly affecting individuals in the fifth and sixth decades of life [1,16].

What distinguishes pSS from most autoimmune diseases is its pronounced association with lymphoproliferative disorders. Earlier studies reported up to a 44-fold increased risk of NHL in pSS patients compared to the general population, whereas more recent meta-analyses estimate a 10–14-fold increase [11,13,23]. The cumulative risk reaches approximately 9.8% within 15 years after diagnosis [3,11,13,23]. This association is not incidental; chronic autoantigenic stimulation of B lymphocytes, continuous activation of survival pathways such as NF-κB and B-cell receptor (BCR) signaling, together with the formation of tertiary lymphoid structures within exocrine glands, represent key pathogenic mechanisms linking autoimmunity and lymphomagenesis [5,6,13,19].

Among lymphomas arising in pSS, marginal zone lymphoma (MZL) is the predominant histological subtype, most frequently occurring in extranodal MALT locations, particularly within salivary glands [3,13,34]. The cutaneous variant of this entity – primary cutaneous marginal zone lymphoma (PCMZL) – is a rare but well-recognized clinicopathological phenomenon classified by both the WHO 5th edition (2022) and the International Consensus Classification (ICC, 2022) as an indolent lymphoproliferative disorder with a

remećajima, sa specifičnim imunofenotipom i izuzetno povoljnom prognozom [9–11].

Postavljanje dijagnoze PCMZL u kontekstu dugogodišnjeg pSS klinički je izazov koji se ne sme potceniti. Inicijalne kožne promene lako bivaju pripisane benignim reaktivnim dermatozama ili kožnim manifestacijama samog autoimunog oboljenja, što dijagnostički proces može odložiti za nekoliko meseci [12,13]. Prikazujemo slučaj pacijentkinje sa dugogodišnjim pSS kod koje je, nakon višemesečnog dijagnostičkog puta, histopatološki i imunohistohemijski verifikovana dijagnoza PCMZL, bez znakova sistemske diseminacije.

Prikaz slučaja

Pacijentkinja starosti 65 godina, javila se na dermatološki pregled zbog perzistentnih kožnih promena lokalizovanih na trupu, koje je prvi put primetila dva meseca pre prve posete dermatovenerologu. U ličnoj anamnezi dominira podatak o sika sindromu (sicca) u sklopu Sjogrenovog sindroma, koji je dijagnostikovao pre deset godina i od tada se nalazi pod redovnim nadzorom reumatologa. Takođe, boluje od arterijske hipertenzije, koja je adekvatno regulisana medikamentnom terapijom, dok je zbog

characteristic immunophenotype and excellent prognosis [7,11,14].

Establishing the diagnosis of PCMZL in the context of long-standing pSS is clinically challenging and should not be underestimated. Initial skin lesions are often attributed to benign reactive dermatoses or cutaneous manifestations of the autoimmune disease itself, potentially delaying diagnosis for several months [17,18]. We present a case of a patient with long-standing pSS in whom PCMZL was histopathologically and immunohistochemically confirmed after a prolonged diagnostic process, without evidence of systemic dissemination.

Case Report

A 65-year-old female patient presented for dermatological evaluation due to persistent skin lesions localized on the trunk, first noticed two months before the initial dermatology consultation. Her medical history was notable for sicca syndrome associated with Sjögren's syndrome, diagnosed ten years earlier, for which she had been under regular rheumatologic follow-up. She also had adequately controlled arterial hypertension, glau-



Slika 1. Eritematozni infiltrirani plakovi na bočnoj strani trupa

Figure 1. Erythematous infiltrated plaques on the lateral trunk



Slika 2. Eritematozni plakovi na prednjoj strani trupa

Figure 2. Erythematous plaques on the anterior trunk

glaukoma pod stalnim oftalmološkim praćenjem. U anamnezi je prisutna i osteoporoza, za koju prima odgovarajuću terapiju.

Porodična anamneza nije ukazivala na prisustvo malignih niti autoimunih oboljenja. Negira pušenje i konzumaciju alkohola. Prvobitne promene na koži, pacijentkinja je inicijalno pripisala autoimunoj bolesti, međutim, zbog perzistiranja lezija dolazi na pregled kod dermatologa.

Na prvom pregledu kod dermatologa u lokalnom statusu beležimo par numularnih eritematoznih infiltriranih plakova na prednjoj strani trupa, koji su se u početku spontano povlačili, bez subjektivnih tegoba (pruritusa, peckanja ili bola). Na osnovu kliničke slike, uvodi se lokalna kortikosteroidna terapija. Par nedelja nakon primene, nije zabeleženo poboljšanje kožnih promena, što je bio povod za dalje dijagnostičko ispitivanje i hospitalizaciju.

Klinički najznačajniji laboratorijski parametri su: blago povišeni limfociti, snižena vrednost C4 komponente komplekta (0,07 g/L, referentna vrednost 0,10–0,40 g/L), povišen reumatoidni faktor (40 IU/mL) i visoko pozitivna ANA (6,80, referentna vrednost 1,00–1,20).

Negativni rezultati virusoloških analiza (HBV, HCV, HIV), negativni Quantiferon-TB

coma requiring continuous ophthalmologic monitoring, and osteoporosis treated with appropriate therapy.

Family history was negative for malignant or autoimmune diseases. The patient denied smoking and alcohol consumption. Initially, she attributed the skin lesions to her autoimmune disease; however, due to their persistence, she sought dermatological evaluation.

On initial examination, several nummular erythematous infiltrated plaques were observed on the anterior trunk. The lesions initially regressed spontaneously and were not associated with pruritus, burning, or pain. Based on the clinical presentation, local corticosteroid therapy was introduced. Several weeks later, no improvement was observed, prompting further diagnostic evaluation and hospitalization.

The most clinically significant laboratory findings included mildly elevated lymphocyte count, reduced C4 complement level (0.07 g/L; reference range 0.10–0.40 g/L), elevated rheumatoid factor (40 IU/mL), and strongly positive antinuclear antibodies (ANA 6.80; reference range 1.00–1.20).

Negative viral serologies (HBV, HCV, HIV), a negative Quantiferon-TB Gold test, negative skin swabs for bacteria, fungi, and dermatophytes, as well as negative ELISA testing for *Borrelia burgdorferi* (IgM and IgG), excluded infectious causes of the skin lesions.

During hospitalization, chest radiography revealed no active pathological pulmonary changes. Spirometry findings were normal. Mild elevation of the tumor marker CYFRA 21-1 (4.0 ng/mL; reference value <3.5 ng/mL) prompted pulmonology consultation, which found no evidence of bronchopulmonary malignancy.

Histopathological examination of the initial skin biopsy demonstrated skin tissue with epidermis of preserved morphology. Around sebaceous glands, and particularly around sweat glands, there was a pronounced predominantly lymphocytic, focally plasmacytic infiltrate forming a periappendageal sleeve-like pattern. Atrophic changes of eccrine glands were observed, along with mild perivascular lymphocytic infiltrates within the dermis. The hypodermis appeared morphologically unremarkable.

The initial histopathological findings were interpreted as compatible with autosensitiza-



Slika 3. Cikatrix na mestu biopsije i rebiopsije

Figure 3. Detail of lesion with scarification changes



Slika 4. Prvobitne promene periumbilikalno
Figure 4. Detail of the periumbilical region

Gold test, negativni brisevi kože na bakterije, gljivice i dermatofite, kao i negativna ELISA analiza na *Borrelia burgdorferi* (IgM i IgG) – isključeni su infektivni uzroci kožnih promena.

U toku hospitalizacije rađen je RTG grudnog koša koji je bio bez aktivnih patoloških promena u plućnom parenhimu. Spirometrija je bila uredna. Blago povišena vrednost tumorskog markera CYFRA 21-1 (4,0 ng/mL, ref. do 3,5 ng/mL) bila je povod za pulmološku konsultaciju koja nije ukazivala na postojanje bronhopulmonalnog malignog procesa.

Patohistološki nalaz učinjene biopsije kože opisuje isečak kože gde epiderm odgovarajuće morfologije uz sebacealne žlezde, a posebno oko znojnih žlezda pokazuje izražen, predominantno limfocitni, mestimično plazmocitni infiltrat u vidu periadneksalnog infiltrata-rukavca. Uočavaju se atrofične promene ekričnih žlezda. Perivaskularno u dermu prisutan lakostepeni limfocitni infiltrat. Hipoderm odgovarajuće morfologije.

Inicijalna patohistološka slika bila je ocenjena kao kompatibilna sa autosenzibilizacijom u okviru osnovne bolesti – Sjogrenovog sindroma. Ovaj nalaz, iako sugestivan za autoimunu genezu, nije isključivao rani limfom i bio je nedovoljan za definitivnu dijagnozu. Zbog perzistiranja kožnih promena, indikovana je



Slika 5. Promena periumilikalno desno
Figure 5. Erythematous lesion in the lower abdominal region

tion related to the underlying Sjögren's syndrome. Although suggestive of autoimmune etiology, these findings did not exclude early lymphoma and were insufficient for definitive diagnosis. Due to persistent lesions, re-biopsy was performed three months later, accompanied by an expanded immunohistochemical panel. Micromorphological and immunohistochemical findings confirmed the diagnosis of indolent primary cutaneous marginal zone B-cell lymphoma (PCMZL). The immunophenotype (CD20+, CD79a+, Bcl-2+, CD43+/-, negative for CD5, CD10, and Bcl-6, with low Ki-67 proliferation index of approximately 5%) was fully consistent with current WHO and ICC diagnostic criteria.

MSCT of the chest, abdomen, and pelvis revealed two micronodular pulmonary lesions with benign radiological characteristics in the right lung, stable and without signs of progression. No other pathological findings were identified in thoracic, mediastinal, or abdominal structures. Abdominal ultrasonography was unremarkable.

Ultrasound examination of the neck, axillary, and inguinal regions demonstrated hypoechoic lymph nodes in the right cervical region measuring approximately 23 × 9 mm

Tabela 1. Pregled laboratorijskih nalaza**Table 1.** Overview of laboratory findings

Parametar/Parameter	Vrednost/Value	Ref. vrednosti/Ref. value	Interpretacija/Interpretation
Leukociti/Leukocytes	<i>u ref. vred.</i> within range	4.0–10.0 × 10 ⁹ /L	<i>Uredan/Normal</i>
Limfociti/Lymphocytes	15.70 × 10 ⁹ /L	1.0–4.8 × 10 ⁹ /L	<i>Blago povišeni ↑/Slightly elevated ↑</i>
Eritrociti/Hb/Hct Erythrocytes/Hb/Hct	<i>u ref. vred.</i> within range	—	<i>Uredan/Normal</i>
Trombociti/Thrombocytes	<i>u ref. vred.</i> within range	150–400 × 10 ⁹ /L	<i>Uredan/Normal</i>
CRP/CRP	<i>u ref. vred.</i> within range	<5 mg/L	<i>Uredan/Normal</i>
C4 komplement C4 complement	0.07 g/L	0.10–0.40 g/L	<i>Snižen ↓/Decreased ↓</i>
Reumatoidni faktor (RF) Rheumatoid factor (RF)	40 IU/mL	0–30 IU/mL	<i>Povišen ↑/Elevated ↑</i>
ANA (antinuklearna at.) ANA (antinuclear at.)	6.80	1.00–1.20	<i>Značajno povišen ↑↑</i> <i>Significantly elevated ↑↑</i>
CYFRA 21-1/CYFRA 21-1	4.0 ng/mL	do 3.5 ng/mL	<i>Blago povišen ↑/Slightly elevated ↑</i>
Virusol. (HBV,HCV,HIV) Virusol. (HBV,HCV,HIV)	<i>Uredne/Normal</i>	<i>Negativan/Negative</i>	<i>Uredan/Normal</i>
Quantiferon-TB Gold Quantiferon-TB Gold	<i>Negativan</i> Negative	<i>Negativan/Negative</i>	<i>Uredan/Normal</i>
ELISA Borrelia IgM/IgG ELISA Borrelia IgM/IgG	<i>Negativan</i> Negative	<i>Negativan/Negative</i>	<i>Negativan/Negative</i>
Brisevi kože/Skin swab	<i>Negativan</i> Negative	<i>Sterilno/Sterile</i>	<i>Negativan/Negative</i>
Ostali tum. markeri Other tum. markers	<i>u ref. vred.</i> within range	—	<i>Uredan/Normal</i>

rebiopsija koja je nakon tri meseca učinjena sa proširenom imunohistohemijskom (IHH) obradom tumorskih markera. Mikromorfološki nalaz i rezultati imunohistohemijskih analiza odgovaraju dijagnozi indolentnog non-Hoćkinovog limfoma kože (Non-Hodgkin's Lymphoma – NHL) tipa kutanog B-ćelijskog limfoma marginalne zone (PCMZL). Postavljeni IHH profil (CD20+, CD79a+, Bcl-2+, CD43+/-, uz negativnost za CD5, CD10, Bcl-6 i niski Ki-67 ~5%) u potpunosti je konzistentan sa ovom dijagnozom prema aktuelnim klasifikacionim kriterijumima (WHO 5th edition, ICC 2022).

Na multislajсној компјутеризованој томографији (MSCT) grudnog koša, abdomena i male karlice u plućnom parenhimu desno primećene su dve mikronodularne promene be-

with predominantly pathological sonographic characteristics, including reduced hilar signal and rounded morphology. This finding prompted bone marrow biopsy. Histopathological and immunohistochemical analysis of the bone marrow was normal, without evidence of malignant lymphoid infiltration. Together with normal CT staging and absence of systemic symptoms, these findings supported the diagnosis of localized cutaneous disease (T1–T2 stage according to the ISCL/EORTC staging system).

Based on the diagnosis of PCMZL associated with pSS, a multidisciplinary team consisting of dermatologists, rheumatologists, and hematologists established the therapeutic strategy. Considering the indolent disease

Tabela 2. Imunohistohemijski parametri**Table 2. Immunohistochemical parameters**

IHH Marker/IHH Marker	Rezultat/Result	Klinički značaj/Clinical significance
CD20	+	Pan-B ćelijski marker; potvrđuje B-ćelijsko poreklo limfoma Pan-B cell marker; confirms B-cell lymphoma origin
CD79a	+	B-ćelijski koreceptor; dodatna potvrda B-ćelijskog fenotipa B-cell coreceptor; additional confirmation of B-cell phenotype
Bcl-2	+	Anti-apoptotski protein; tipičan za MZL, negativan u reaktivnim centrima Anti-apoptotic protein; typical for MZL, negative in reactive centers
CD43	+/-	Aberantna ekspresija; karakteristična za MZL/CLL fenotip Aberrant expression; characteristic for MZL/CLL phenotype
CD5	-	Negativan; isključuje CLL/mantle cell limfom Negative; excludes CLL/mantle cell lymphoma
CD10	-	Negativan; isključuje folikularni limfom Negative; excludes follicular lymphoma
Bcl-6	-	Negativan; isključuje folikularni i DLBCL GCB tip Negative; excludes follicular and DLBCL GCB type
MUM1/IRF4	-	Negativan; dodatna distinkcija od plazmablastičnog limfoma Negative; additional distinction from plasmablastic lymphoma
Ki-67	~5%	Niska proliferativna aktivnost; potvrđuje indolentni tok Low proliferative activity; confirms indolent course

nignih CT karakteristika (stabilne, bez rasta, morfološki benigne). Ostali parenhimalni, medijastinalni i abdominalni CT nalaz bez patoloških promena. Ehsonografski nalaz abdomena je bio uredan.

Tokom hospitalizacije rađen je i EHO vrata, aksila i prepona gde su u vratu desno uočeni hipoehogeni limfni čvorovi (LN) veličine oko 23 x 9 mm sa dominantno patološkim ehsonografskim karakteristikama (smanjeni hilusni signal, okruglast oblik). Ovaj nalaz je doprinelo odluci o biopsiji koštane srži. Histopatološki i imunohistohemijski nalaz koštane srži je bio uredan – bez infiltracije koštane srži malignim limfoidnim infiltratom. Ovaj nalaz, zajedno sa urednim CT evaluacijom stadijuma bolesti i bez prisustva sistemskih simptoma, ukazuje na lokalizovanu kožnu bolest (stadijum T1-T2 prema ISCL/EORTC stejdžing sistemu).

Na osnovu postavljene dijagnoze PCMZL u sklopu pSS, multidisciplinarni tim u sastavu dermatologa, reumatologa i hematologa je usaglasio terapijski pristup. S obzirom na sporoprogresivni tok bolesti, lokalizovanu kožnu zahvaćenost bez sistemske diseminacije i odsustvo simptoma, donesena je odluka o watch

course, localized skin involvement without systemic dissemination, and absence of symptoms, a “watch-and-wait” approach was adopted while continuing existing therapy. Resochin (chloroquine sulfate) 250 mg once daily was maintained by the rheumatologist. The patient was included in a regular multidisciplinary follow-up protocol.

Discussion

The association between primary Sjögren's syndrome (pSS) and Non-Hodgkin lymphoma (NHL) represents one of the best-documented examples of transformation from chronic autoimmune disease into malignant lymphoproliferative disorder [3,13,25]. According to meta-analyses and large cohort studies, the risk of NHL in patients with pSS is 6 to 44 times higher than in the general population, with a cumulative risk of 9.8% within 15 years after diagnosis [11,13,23]. This association becomes even more significant when compared to other systemic autoimmune diseases, as the lymphoma risk in pSS

and wait strategiji uz nastavak dosadašnje terapije. Nastavljena je terapija Resochin-om® (hlorokin-sulfat) 250 mg 1 x 1 dnevno koju je propisao reumatolog. Pacijentkinja je uključena u redovni multidisciplinarni protokol praćenja.

Diskusija

Veza između pSS i NHL jedan je od najdokumentovanih primera transformacije hronične autoimune bolesti u maligno limfoproliferativno oboljenje [5,8]. Prema podacima iz metaanaliza i velikih kohortnih studija, rizik od NHL kod pSS pacijenata je 6–do 44 puta veći nego u opštoj populaciji, sa kumulativnim rizikom od 9,8% u roku od 15 godina od dijagnoze [3–5]. Ova cifra posebno dobija na značaju kada se stavi u kontekst ostalih sistemskih autoimunih bolesti – rizik je značajno viši nego kod reumatoidnog artritisa ili sistemskog lupusa eritematosus [4,5].

Dominantni histološki tip limfoma koji nastaje u sklopu pSS jeste limfom marginalne zone, u oko 65% slučajeva u ekstranodalnoj MALT lokalizaciji [6,8]. Pacijentkinja u prikazanom slučaju nosi više prediktivnih obeležja – snižen C4, pozitivan RF i visoko pozitivna ANA antitela – što retrogradno objašnjava biološku osnovu razvoja limfoma i naglašava potrebu za aktivnim nadzorom ove podgrupe bolesnika [4,5]. Klinička medicina je kroz decenije identifikovala niz kliničkih i laboratorijskih pokazatelja koji izdvajaju bolesnike sa pSS kod kojih je rizik za razvoj limfoma naročito izražen. Među najznačajnije faktore ubrajaju se prisustvo parotidne bolesti, pozitivnost reumatoidnog faktora, nizak nivo C4 komplementa, mešovita krioglobulinemija tipa II, limfopenija i povišen ESSDAI skor [3,5]. Pacijentkinja u prikazanom slučaju ispoljava više ovih karakteristika – snižen C4, pozitivan RF i visoko pozitivna ANA antitela – što retrogradno objašnjava biološku osnovu razvoja limfoma i naglašava potrebu za pažljivim i kontinuiranim praćenjem ove podgrupe bolesnika [3,5].

U srži procesa stoji hronična autoantigen-ska stimulacija B-limfocita. U pSS, autoreaktivni B-limfociti pod stalnim su antigenim pritiskom, što vodi njihovoj neadekvatno regulisanoj proliferaciji [2,7]. Signalizacija putem B-ćelijskog receptora (BCR) centralni je motor ove stimulacije koji održava B-ćelijsku aktivnost i sprečava fiziološku eliminaciju potencijalno opasnih klonova [7]. Paralelno, struktur-

is considerably higher than in rheumatoid arthritis or systemic lupus erythematosus [3,12].

The predominant histological subtype of lymphoma associated with pSS is marginal zone lymphoma (MZL), occurring in approximately 65% of cases in extranodal MALT locations [5,13,34]. The patient presented in this case exhibited several predictive markers, including reduced C4 complement levels, positive rheumatoid factor, and strongly positive ANA antibodies, retrospectively explaining the biological basis for lymphoma development and emphasizing the need for active surveillance in this subgroup of patients [23,29].

Over the decades, clinical medicine has identified numerous clinical and laboratory predictors associated with increased lymphoma risk in pSS patients. The most important factors include parotid gland involvement, positive rheumatoid factor, low C4 complement levels, type II mixed cryoglobulinemia, lymphopenia, and elevated ESSDAI scores [23,26,27,29]. The patient in the present case demonstrated several of these characteristics, further supporting the biological background of lymphoma development and highlighting the importance of careful and continuous monitoring in this subgroup [23,29].

At the core of this process lies chronic autoantigenic stimulation of B lymphocytes. In pSS, autoreactive B lymphocytes are exposed to persistent antigenic stimulation, leading to dysregulated proliferation [6,19]. B-cell receptor (BCR) signaling represents the central driver of this stimulation, maintaining B-cell activation and preventing physiological elimination of potentially dangerous clones [6]. Simultaneously, structural alterations in the TNFAIP3 gene encoding the A20 protein – a negative regulator of the NF-κB signaling pathway – have been associated with the development of MALT lymphoma in pSS [5,13]. BAFF is another key cytokine involved in both pSS pathogenesis and lymphomagenesis through activation of the NF-κB pathway and prolonged B-cell survival [5,19].

An additional contribution to lymphomagenesis arises from newly formed lymphoid structures within exocrine glands, which provide a favorable microenvironment for somatic hypermutation and accumulation of oncogenic mutations that may trigger lymphoma development [4,5]. Recent studies have also highlighted the importance of epigenetic alterations and the potential role of the microbiome and viral

ne promene gena TNFAIP3 koji kodira protein A20-negativni regulator NF- κ B signalnog puta – povezane su sa razvojem MALT limfoma kod pSS [6]. BAFF predstavlja ključni citokin u pSS patogenezi i limfogenezi, kroz aktivaciju NF- κ B puta i produženi životni vek B-limfocita [2,6].

Poseban doprinos limfogenezi dolazi od novonastalih limfnih struktura unutar egzokri-nih žlezda – one obezbeđuju specifično okru-ženje povoljno za somatsku hipermutaciju i akumulaciju onkogenih mutacija koje mogu biti okidač za nastanak limfoma [5,6]. Najno-viji radovi ukazuju na značaj epigenetskih pro-mena i potencijalnu ulogu mikrobioma i viru-snih agenasa u aktivaciji proinflamatornih i proonkogenih signalnih puteva [2,6].

Prema SZO klasifikaciji pete edicije (2022) i Međunarodnoj konsenzus klasifikaciji (ICC, 2022), primarni kutani B-ćelijski limfomi pode-ljeni su na tri osnovna entiteta: PCFCL, PCMZL i PCDLBCL-LT [9,10]. PCMZL čini oko 7–9% svih primarnih kutanih limfoma, a petogodišnje preživljavanje > 95% svrstava ga među pro-gnostički najbenignije limfome [11,12].

Diferencijalna dijagnoza PCMZL zahteva sistematičan pristup, jer niz entiteta može opo-našati njegovo histološko lice. Na prvom mestu u razmatranju stoje pseudolimfomi, primarni kutani folikularni limfom (PCFCL), sekundarna kutana zahvaćenost sistemskog MZL, kutani vaskulitis i različite inflamatorne dermatoze čine spektar koji mora biti razmatran i isključen [11–13]. U pojedinim evropskim regionima *Borrelia burgdorferi* prepoznata je kao mogući etiološ-ki faktor u nastanku PCMZL [12,15]. Kod naše pacijentkinje ova mogućnost je nedvosmisleno otklonjena negativnim serološkim testovima.

Prikazani slučaj jasno pokazuje dijagno-stičke izazove PCMZL u kontekstu aktivnog pSS [12,13]. Inicijalni histopatološki nalaz bio je nespecifičan i protumačen kao autosenzi-bilizacija u okviru pSS – što nije neuobičajen nalaz u ranim fazama PCMZL [13]. Odluka o rebiopsiji, praćena proširenim imunohistohemij-skim panelom, bila je ključna tačka preokreta i konačno je razrešila dijagnostičku dilemu [13]. Optimalan model zbrinjavanja ovih bole-snika podrazumeva ravnoopravno učešće der-matologa, reumatologa i hematologa [12,14].

Nakon potvrde dijagnoze PCMZL, kom-pletna klinička i laboratorijska evaluacija bo-lesti neophodna je kako bi se isključila sistem-ska diseminacija bolesti [8,14]. U prikazanom slučaju, bolest je klasifikovana kao lokalizova-

agents in activating pro-inflammatory and pro-oncogenic signaling pathways [2,17].

According to the WHO 5th edition clas-sification (2022) and the International Consensus Classification (ICC, 2022), primary cutaneous B-cell lymphomas are divided into three major entities: primary cutaneous folli-cle center lymphoma (PCFCL), primary cuta-neous marginal zone lymphoma (PCMZL), and primary cutaneous diffuse large B-cell lymphoma, leg type (PCDLBCL-LT) [7,11]. PC-MZL accounts for approximately 7–9% of all primary cutaneous lymphomas, and with a 5-year survival rate exceeding 95%, it is con-sidered one of the most prognostically favo-rable lymphomas [14,15,17].

The differential diagnosis of PCMZL re-quires a systematic approach, as numerous entities may mimic its histological appearance. Pseudolymphomas, primary cutaneous follicle center lymphoma (PCFCL), secondary cutane-ous involvement by systemic MZL, cutaneous vasculitis, and various inflammatory derma-toses must all be considered and excluded [15,17,18]. In certain European regions, *Borrelia burgdorferi* has been recognized as a potential etiological factor in PCMZL development [17]. In our patient, this possibility was unequivocally excluded by negative serological testing.

The presented case clearly illustrates the diagnostic challenges of PCMZL in the context of active pSS [17,18]. The initial histopathologi-cal findings were nonspecific and interpreted as autosensitization associated with pSS, which is not uncommon in early PCMZL stages [18]. The decision to perform a re-biopsy accompa-nied by an expanded immunohistochemical panel represented the key turning point that ul-timately resolved the diagnostic dilemma [18]. Optimal management of such patients requires equal participation of dermatologists, rheuma-tologists, and hematologists [10,17].

Following confirmation of PCMZL diagno-sis, comprehensive clinical and laboratory evaluation is mandatory to exclude systemic disease dissemination [10,13]. In the presented case, the disease was classified as localized cutaneous lymphoma stage T2N0M0 accord-ing to the ISCL/EORTC TNM staging system [10]. Therapeutic strategies for PCMZL are not uniform and must be individualized according to lesion number and distribution [13,15,17]. In localized disease, radiotherapy at doses of ap-proximately 24 Gy or surgical excision are con-

ni kutani oblik u stadijumu T2N0M0 prema ISCL/EORTC TNM sistemu [14]. Terapijska strategija u PCMZL nije uniformna – individualizuje se prema broju i rasprostranjenosti lezija [8,11,12]. Kod lokalizovane bolesti, terapija izbora je radioterapija u dozama od 24 Gy ili hirurška ekscizija [8,12]. Kod asimptomatskih bolesnika sa stabilnom bolešću opravdana je watch and wait strategija [13].

Kutani relapsi su deo prirodnog toka PCMZL i javljaju se učestalo, ali – što je klinički važno – ne utiču značajno na ukupno preživljavanje, što ovaj limfom čini jednim od retkih malignih bolesti gde relaps sam po sebi ne mora biti alarm [11]. Na poseban aspekt terapijskog razmišljanja u kontekstu pSS ukazuju antimalarici: hlorokin i hidroksihlorokin poseduju dobro dokumentovana imunomodulatorna svojstva i što je posebno relevantno za ovu populaciju bolesnika, potencijalni antilimfomski efekat posredovan inhibicijom TLR signalnog puta – što ih čini biološki privlačnom opcijom u terapijskom arsenalu [2,6].

Kod serološki pozitivnih pacijenata (*B. burgdorferi*), terapija antibioticima (doksiciklin, penicilin) može indukovati regresiju PCMZL, pri čemu stopa odgovora varira između studija i zavisi od *Borrelia* statusa i primenjenog antibiotskog režima [15].

U literaturi postoje podaci o potencijalnom imunomodulatornom dejstvu antimalarika i u kontekstu MALT limfoma udruženih sa autoimunim bolestima, što ovaj terapijski izbor čini racionalnim. Definitivna terapijska odluka (radioterapija, rituksimab, lokalna ekscizija) rezervisana je za slučaj progresije bolesti ili pojave novih lezija.

Zaključak

Prikazani slučaj ilustruje retku ali klinički značajnu vezu između dugogodišnjeg primarnog Sjogrenovog sindroma i razvoja primarnog kutanog B-čelijskog limfoma marginalne zone. Imajući u vidu sporonapredujući karakter PCMZL, odličnu prognozu i mogućnost watch and wait strategije kod asimptomatskih bolesnika sa lokalizovanom bolešću, rana i tačna dijagnoza je od presudnog značaja za izbegavanje prekomerne terapije i osiguranje adekvatnog praćenja. Kontinuirani nadzor, rano prepoznavanje relapsa i pravovremena intervencija čine osnovu uspešnog zbrinjavanja ovog retkog, ali savladivog onkološkog

sidered treatments of choice [13,17]. In asymptomatic patients with stable disease, a “watch-and-wait” strategy is justified [13].

Cutaneous relapses are part of the natural history of PCMZL and occur frequently; however, importantly, they do not significantly affect overall survival, making PCMZL one of the rare malignancies in which relapse itself does not necessarily represent an alarming prognostic event [14].

Antimalarial agents deserve special consideration in the context of pSS-associated PCMZL. Chloroquine and hydroxychloroquine possess well-documented immunomodulatory properties and, particularly relevant for this patient population, potential anti-lymphoma effects mediated through inhibition of Toll-like receptor (TLR) signaling pathways, making them biologically attractive therapeutic options [5,19].

In serologically positive patients for *Borrelia burgdorferi*, antibiotic therapy (doxycycline or penicillin) may induce PCMZL regression, although response rates vary among studies depending on *Borrelia* status and antibiotic regimen [21,22].

The literature also reports potential immunomodulatory effects of antimalarial drugs in MALT lymphomas associated with autoimmune diseases, further supporting the rationale for this therapeutic approach. Definitive therapeutic interventions, including radiotherapy, rituximab, or local excision, remain reserved for disease progression or development of new lesions.

Conclusion

The presented case illustrates a rare but clinically significant association between long-standing primary Sjögren's syndrome and the development of primary cutaneous marginal zone B-cell lymphoma. Considering the indolent nature of PCMZL, its excellent prognosis, and the possibility of a “watch-and-wait” strategy in asymptomatic patients with localized disease, early and accurate diagnosis is crucial in order to avoid overtreatment and ensure appropriate follow-up.

Continuous monitoring, early recognition of relapse, and timely intervention represent the foundation of successful management of this rare but manageable oncological entity. This specific case contributes significantly to the growing body of scientific literature regarding lymphomas arising in the setting of

entiteta. Ovaj specifičan slučaj pruža značajan doprinos sve većem broju naučnih radova o limfomima koji se razvijaju u sklopu pSS. On dodatno naglašava veliku potrebu za jasnim protokolima praćenja bolesnika sa pSS, redovnim skriningom na limfome, kako bi se ove maligne bolesti otkrile u što ranijoj fazi, kao i pravovremena intervencija, koja predstavlja temelj za uspešno lečenje ovog retkog, ali izlečivog onkološkog oboljenja.

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