Reumatizam 2021;68(2):86–95
https://doi.org/10.33004/reumatizam-68-2-3

CASE REPORT PRIKAZ BOLESNIKA

INDOLENT EXTRANODAL B-NHL CD20 POSITIVE MALT LYMPHOMA IN A PATIENT WITH PRIMARY SJÖGREN'S SYNDROME WITH A GOOD RESPONSE TO RITUXIMAB TREATMENT

INDOLENTNI EKSTRANODALNI B-NHL CD20 POZITIVNI LIMFOM TIPA MALT U BOLESNICE S PRIMARNIM SJÖGRENOVIM SINDROMOM UZ DOBAR ODGOVOR NA LIJEČENJE RITUKSIMABOM

Nadica Laktašić Žerjavić[1], Mislav Pap[1], Iva Žagar[1], Kristina Kovač Durmiš[1], Porin Perić[1]

[1] Department of Rheumatology and Rehabilitation, School of Medicine, University of Zagreb, University Hospital Centre Zagreb / Klinika za reumatske bolesti i rehabilitaciju, Medicinski fakultet, Sveučilište u Zagrebu, Klinički bolnički centar Zagreb

Corresponding author / Adresa autora za dopisivanje:
Professor Nadica Laktašić Žerjavić, MD, PhD
Department of Rheumatology and Rehabilitation / Klinika za reumatske bolesti i rehabilitaciju
School of Medicine, University of Zagreb / Medicinski fakultet, Sveučilište u Zagrebu
University Hospital Centre Zagreb / Klinički bolnički centar Zagreb
Kišpatićeva 12, 10000 Zagreb
Croatia / Hrvatska
Tel.: +385 1 2388171
E-mail / e-pošta: nadica_laktasic@yahoo.com

Received / Primljeno: 29th October 2021 / 29. 10. 2021.
Accepted / Prihvaćeno: 3rd December 2021 / 3. 12. 2021.

Abstract

Sjögren's syndrome (SS) is a chronic autoimmune disease in which chronic lymphocytic infiltration leads to progressive destruction of the exocrine glands and consequently causes the dry syndrome. The most commonly affected are the lacrimal and salivary glands. Less often, SS presents with the symptoms of exocrine glands of other localisation, arthritis, myositis, vasculitis involving the skin and the nervous system, interstitial lung disease, and kidney disease. The most serious complication is the development of lymphoproliferative disease, primarily non-Hodgkin's lymphoma (NHL). We present the case of a patient who developed indolent extranodal B-NHL CD20-positive MALT-type lymphoma after 23 years of primary SS duration, with a good response to rituximab treatment.

Keywords: Sjögren's Syndrome, Lymphoproliferative Disorders, B-Cell Marginal Zone Lymphoma, Rituximab

Sažetak

Sjögrenov sindrom (SS) kronična je autoimuna bolest u kojoj limfocitna infiltracija dovodi do progresivnog oštećenja egzokrinih žlijezda i sljedstvenoga suhog sindroma. Najčešće zahvaća suzne i slinovne žlijezde, a manje često se javljaju simptomi egzokrinih žlijezda druge lokalizacije, artritis, miozitis, vaskulitis sa zahvaćanjem kože i živčanog sustava, intersticijska bolest pluća i bubrežna bolest. Najteža komplikacija je razvoj limfoproliferativne bolesti, u prvom redu ne-Hodgkinovog limfoma (NHL-a). U radu prikazujemo bolesnicu koja je nakon 23 godine trajanja primarnog SS-a razvila indolentni ekstranodalni B-NHL CD20 pozitivni limfom tipa MALT uz dobar odgovor na liječenje rituksimabom.

Ključne riječi: Sjögrenov sindom, limfoproliferativne bolesti, B-stanični limfom marginalne zone, rituksimab

INTRODUCTION

Sjögren's syndrome (SS) is a chronic autoimmune disease in which chronic lymphocytic infiltration leads to the destruction of the exocrine glands, thus causing the dry syndrome. SS may be classified into primary

UVOD

Sjögrenov sindrom (SS) kronična je autoimuna bolest u kojoj limfocitna infiltracija dovodi do oštećenja egzokrinih žlijezda uzrokujući suhi sindrom. SS se dijeli na primarni (pSS) koji nije udružen s drugim

(pSS), which is not associated with other diseases, and secondary (sSS), which occurs in association with other autoimmune diseases such as systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), polymyositis (PM), granulomatosis with polyangiitis (GPA) or progressive systemic sclerosis (PSS) (1). The prevalence of SS ranges from 0.1 to 4.8%, the incidence is nine times higher in women, and it commonly occurs in middle-aged patients (2).

The occurrence of the disease is associated with the HLA-B8 and HLA-DR3 genes and with viral infections (cytomegalovirus and Epstein-Barr virus). SS should be suspected with the occurrence of symptoms of dry eyes and mouth, and the diagnosis is confirmed by objective evidence of reduced secretion of tears and saliva with the presence of autoantibodies (antinuclear antibodies [ANA], anti-SSA/Ro and anti-SSB/La antigens are present in up to 70% of patients, and the rheumatoid factor [RF] may be positive as well), but the diagnosis can also be made when there is an absence of the typical autoantibodies. Sometimes, to confirm the diagnosis, it is necessary to perform minor salivary gland biopsy (most often in the area of the lower lip mucosa) in order to confirm the diagnosis with a typical histopathology finding of lymphocytic infiltration with the formation of lymphocytic foci. It is important to note that dry eyes and mouth can be caused by numerous diseases, conditions, or medications, so before making a diagnosis of pSS, it is necessary to rule out the aforementioned diseases or conditions and take a medical history. There is a clearly defined set of tests that can be used to objectify the reduction of tear or saliva secretion (3–5).

The typical clinical presentation of the disease includes symptoms of dry eyes and dry mouth. Decreased function of the glands in the nose, pharynx and larynx can cause a feeling of dryness in the nose, cough, and hoarseness, while decreased function of the glands in the vagina causes dyspareunia (1). Dryness of the respiratory mucosa can also be the cause of recurrent infections. Since pSS is a systemic disease, extraglandular symptoms also occur in a large number of patients. The most common symptoms include chronic fatigue, Raynaud's syndrome, skin changes such as erythema multiforme (target-shaped lesions or oedematous papules on the edges, i.e., acral), subacute cutaneous lupus erythematosus (papulosquamous lesions with annular lesions in places exposed to the sun, excluding the face) and cutaneous vasculitis (palpable purpura, maculopapular rash or urticaria) (6).

Joints and muscles can also be affected in the form of arthralgia with morning stiffness, joint swelling, and muscle weakness as a result of synovitis and myositis. Involvement of the central and peripheral nervous system is manifested by peripheral polyneuropathy, cra-

bolestima i sekundarni (sSS) koji se javlja uz druge autoimune bolesti poput sistemskog eritemskog lupusa (SLE), reumatoidnog artritisa (RA), polimiozitisa (PM), granulomatoze s poliangitisom (GPA) ili progresivne sistemske skleroze (PSS) (1). Prevalencija SS-a iznosi od 0,1 do 4,8%, pojavnost je devet puta veća u žena, a većinom se pojavljuje u srednjoj životnoj dobi (2).

Pojavnost bolesti povezuje se uz gene HLA-B8 i HLA-DR3 te uz virusne infekcije (citomegalovirus i Epstein-Barrov virus). Na SS treba posumnjati pri simptomima suhoće očiju i usta, a dijagnoza se potvrđuje objektivnim dokazom smanjene sekrecije suza i sline uz prisutnost autoantitijela (antinuklearna antitijela [ANA], antitijela protiv antigena SSA/Ro i SSB/La prisutna su u do 70% bolesnika, može biti pozitivan i reumatoidni faktor [RF]), no dijagnoza se može postaviti i kada su tipična autoantitijela odsutna. Ponekad je za potvrdu dijagnoze potrebno učiniti i biopsiju male slinovne žlijezde (najčešće u području sluznice donje usnice) kako bi se dijagnoza potvrdila tipičnim patohistološkim nalazom (PHD) limfocitne infiltracije uz formiranje limfocitnih fokusa. Važno je napomenuti da suhoća očiju i usta može biti uzrokovana brojnim bolestima, stanjima ili lijekovima pa je prije postavljanja dijagnoze pSS-a potrebno isključiti navedene bolesti ili stanja i uzeti anamnezu o uzimanju lijekova. Jasno je definiran sklop testova kojima se može objektivizirati smanjenje proizvodnje suza ili sline (3–5).

Tipična klinička prezentacija bolesti uključuje simptome suhih očiju i suhih usta. Smanjena funkcija žlijezda u nosu, ždrijelu i grkljanu može uzrokovati osjećaj suhoće nosa, kašalj, promuklost, dok smanjena funkcija žlijezda u rodnici uzrokuje dispareuniju (1). Suhoća respiratorne sluznice može biti i uzrokom ponavljajućih infekcija. Budući da je pSS sistemska bolest, u velikog broja bolesnika javljaju se i ekstraglandularni simptomi. Među njima su najčešći kronični umor, Raynaudov sindrom, kožne promjene poput multiformnog eritema (lezije oblika mete ili edematozne papule na okrajinama, tj. akralno), subakutnoga kožnog eritematoznog lupusa (papulo-skvamozne lezije s prstenastim lezijama na mjestima izloženim suncu, isključujući lice) i vaskulitičnih kožnih promjena (palpabilna purpura, makulopapulozni osip ili urtikarija) (6).

Također mogu biti zahvaćeni zglobovi i mišići u vidu artralgija s jutarnjom zakočenošću, otekline zglobova i mišićne slabosti posljedično sinovitisu i miozitisu. Zahvaćanje središnjeg i perifernog živčanog sustava očituje se perifernom polineuropatijom, neuropatijom kranijskih živaca, vaskulitisom perifernih živaca, cerebralnim vaskulitisom, transverzalnim mijelitisom ili limfocitnim meningitisom. Zahvaćenost pluća uključuje široki spektar manifestacija, od kašlja do intersticijske bolesti pluća. Zahvaćenost bubrega može se očitovati proteinurijom, leukociturijom, hematurijom,

Table 1. ACR/EULAR Classification Criteria for Primary Sjögren's Syndrome (pSS)
Tablica 1. ACR/EULAR klasifikacijski kriteriji za primarni Sjögrenov sindrom (pSS)

Classification criteria for pSS applies to any individual who meets the inclusion criteria, does not have any of the conditions listed as exclusion criteria, and has a score of ≥4 when the weights from the five criteria items in the table are summed. / Klasifikacija pSS-a primjenjuje se na svakog pojedinca koji ispunjava kriterije uključivanja, nema niti jedan isključni kriterij i ima ocjenu ≥4 kada se zbroje težinske vrijednosti iz pet kriterija prikazanih u tablici.	
Criterion / Kriterij	Weights / Težinski bodovi
Labial salivary gland biopsy finding of focal lymphocytic sialadenitis with a focus score of ≥1 foci/4 mm* / Nalaz biopsije labijalnih žlijezda slinovnica s fokalnim limfocitnim sijaloadenitisom uz ≥ 1 limfocitni fokus u 4 mm² tkiva*	3
Anti-SSA/Ro antibody positivity / Pozitivna anti-SSA/Ro protutijela	3
Objective assessment of dry eyes using Ocular staining score** ≥ 5 or van Bijsterveld score*** ≥ 4 on at least one eye / Objektivna procjena suhoće očiju pomoću „Ocular staining score"** ≥5 ili pomoću „van Bijsterfeld score"*** ≥4 zadovoljena barem na jednom oku	1
Schirmer ≤ 5 mm / 5 min on at least one eye / Schirmerov test ≤ 5 mm/5 min na barem na jednom oku	1
Unstimulated whole saliva flow rate**** ≤ 0.1 ml/min / Nestimulirano lučenje sline**** ≤ 0,1 ml/min	1

Adapted from: Shiboski CH, Shiboski SC, Seror R, Criswell LA, Labetoulle M, Lietman TM et al. 2016 ACR-EULAR Classification Criteria for primary Sjögren's Syndrome: A Consensus and Data-Driven Methodology Involving Three International Patient Cohorts. Arthritis Rheumatol Hoboken NJ. 2017;69(1):35–45. (9) / Prilagođeno prema: Shiboski CH, Shiboski SC, Seror R, Criswell LA, Labetoulle M, Lietman TM i sur. 2016 ACR-EULAR Classification Criteria for primary Sjögren's Syndrome: A Consensus and Data-Driven Methodology Involving Three International Patient Cohorts. Arthritis Rheumatol Hoboken NJ. 2017;69(1):35–45. (9)

* *Numerical assessment of lymphocyte infiltration (focus score) refers to the number of focal aggregations of lymphocytes in 4 mm² of tissue (aggregation ≥50 lymphocytes is considered as the focus), and biopsy should be done according to the protocol of the study conducted by Daniels et al. which was published in 2011 (12). / Numerička procjena limfocitne infiltracije (engl. focus score) odnosi se na broj fokalnih agregacija limfocita u 4 mm² tkiva (agregacija ≥50 limfocita smatra se fokusom), a biopsiju treba učiniti prema protokolu studije Danielsa i suradnika iz 2011. godine (12).*

** *The Ocular Staining Score based on the method described by Whitcher et al., which was published in 2010 (3). / Ocular staining score prema protokolu Whitchera i suradnika iz 2010. godine (3).*

*** *Van Bijsterveld score, based on the van Bijsterveld protocol, which was published in 1969 (4). / Van Bijsterfeld score prema protokolu istoimenog autora iz 1969. godine (4).*

**** *The unstimulated salivary flow rate should be assessed based on the method described by Navazesh and Kumar, which was published in 2008 (5). / Nestimulirano lučenje sline prema protokolu Navazesha i Kumara iz 2008. (5).*

Sensitivity and specificity of the criteria is 96% (95% CI 92% to 98%) and 95% (95% CI 92% to 97%), respectively, thus they are appropriate for use as criteria for enrolment in clinical trials. / Senzitivnost i specifičnost kriterija iznosi 96% (95% CI 92% do 98%) i 95% (95% CI 92% do 97%), kako slijedi, a pogodni su za uključivanje ispitanika u klinička istraživanja.

nial neuropathy, vasculitis of peripheral nerves, cerebral vasculitis, transverse myelitis, or lymphocytic meningitis. Pulmonary involvement includes a wide spectrum of manifestations, from cough to interstitial lung disease. Renal involvement can be manifested by proteinuria, leukocyturia, haematuria, interstitial nephritis, renal tubular acidosis, and glomerulonephritis. Haematological manifestations of the disease include autoimmune anaemia, neutropenia, lymphopenia, and thrombocytopenia, followed by hypergammaglobulinemia and hypogammaglobulinemia, reduced complement production and cryoglobulinemia (7,8).

By using a methodology in accordance with the new SS classification criteria adopted by the umbrella organisations for rheumatology of the United States of America and the European Union (2017 ACR/EULAR classification criteria), a unique set of consensus classification criteria was developed based on data for pSS, which proved to be useful in evaluation and are suitable as entry criteria for clinical trials (Table 1) (9). In order to apply the above classification criteria to an individual patient, it is necessary to first meet the inclu-

intersticijskim nefritisom, renalnom tubularnom acidozom i glomerulonefritisom. Od hematoloških očitovanja bolesti moguće su autoimuna anemija, neutropenija, limfopenija i trombocitopenija, zatim hipergamaglobulinemija i hipogamaglobulinemija, smanjena produkcija komplementa i krioglobulinemija (7,8).

Koristeći metodologiju u skladu s novim kriterijima klasifikacije SS-a donesenim od krovnih reumatoloških organizacija Sjedinjenih Američkih Država i Europske unije (klasifikacijski kriteriji ACR/EULAR iz 2017. godine), razvijen je jedinstveni skup konsenzusnih klasifikacijskih kriterija na temelju podataka za pSS, koji su se dobro pokazali u validaciji i koji su prikladni kao ulazni kriteriji za klinička ispitivanja (tablica 1) (9). Za primjenu navedenih klasifikacijskih kriterija u individualnog bolesnika potrebno je prvo zadovoljiti kriterije uključivanja i isključivanja koje prikazuje tablica 2. Ulazni kriterij za primjenu klasifikacijskih kriterija jest postojanje simptoma suhog oka ili simptoma suhih usta ili pozitivne barem jedne domene u indeksu aktivnosti bolesti ESSDAI (10), uz odsutnost isključujućih kriterija (tablica 2) (9).

Table 2. The exclusion and inclusion criteria for identification of patients applicable for ACR/EULAR Classification Criteria for Primary Sjögren's Syndrome

Tablica 2. Kriteriji uključivanja i isključivanja bolesnika pri primjeni ACR/EULAR klasifikacijskih kriterija za primarni Sjögrenov sindrom

Inclusion criteria are applicable to any patient with at least one symptom of ocular or oral dryness, defined as a positive response to at least one of the following 5 questions or in whom there is suspicion of Sjögren's syndrome (SS) from the EULAR SS Disease Activity Index questionnaire (at least one domain with a positive item at ESSDAI). / **Kriteriji uključivanja** označju prisutnost barem jednog simptoma suhoće očiju ili usta, tj. pozitivan odgovor na barem jedno od 5 pitanja niže navedenih u tablici ili postojanje sumnje na Sjögrenov sindrom (SS) prema EULAR upitniku za procjenu aktivnosti bolesti SS (pozitivna barem jedna domena upitnika ESSDAI).
1. Have you had daily, persistent, troublesome dry eyes for more than 3 months? / Jeste li imali svakodnevne, uporne, poteškoće vezane uz suhoću očiju dulje od 3 mjeseca?
2. Do you have a recurrent sensation of sand or gravel in the eyes? / Imate li ponavljajući osjećaj pijeska ili šljunka u očima?
3. Do you use tear substitutes more than three times a day? / Koristite li umjetne suze više od tri puta dnevno?
4. Have you had a daily feeling of dry mouth for more than 3 months? / Jeste li imali svakodnevni osjećaj suhih usta dulje od 3 mjeseca?
5. Do you frequently drink liquids to aid in swallowing dry food? / Pijete li često tekućinu kako biste lakše progutali suhu hranu?
Exclusion criteria: prior diagnosis of any of the following conditions would exclude diagnosis of SS / **Kriterij isključivanja:** poznata dijanoza bolesti ili stanja niže navedenih u tablici isključuje dijagnozu SS-a
1. History of head and neck radiation treatment / Anamneza liječenja zračenjem glave i vrata
2. Active Hepatitis C infection (with positive PCR) / Aktivna infekcija hepatitisom C (potvrđena PCR testom)
3. Acquired immunodeficiency syndrome / AIDS
4. Sarcoidosis / Sarkoidoza
5. Amyloidosis / Amiloidoza
6. Graft-versus-host disease / Bolest odbacivanja presatka
7. IgG4-related disease / Bolest povezana s IgG4

Adapted from: Shiboski CH, Shiboski SC, Seror R, Criswell LA, Labetoulle M, Lietman TM et al. 2016 ACR-EULAR Classification Criteria for primary Sjögren's Syndrome: A Consensus and Data-Driven Methodology Involving Three International Patient Cohorts. Arthritis Rheumatol Hoboken NJ. 2017;69(1):35–45. (9) / Prilagođeno prema: Shiboski CH, Shiboski SC, Seror R, Criswell LA, Labetoulle M, Lietman TM i sur. 2016 ACR-EULAR Classification Criteria for primary Sjögren's Syndrome: A Consensus and Data-Driven Methodology Involving Three International Patient Cohorts. Arthritis Rheumatol Hoboken NJ. 2017;69(1):35–45. (9)

sion and exclusion criteria shown in Table 2. The entry criterion for the application of the classification criteria is the occurrence of symptoms such as dry eyes and dry mouth or at least one domain with a positive item at the EULAR Sjögren's syndrome (SS) disease activity index (ESSDAI) (10), with the absence of the exclusion criteria (Table 2) (9).

Indeks aktivnosti bolesti ESSDAI razvijen je za bolesnike s pSS-om. Riječ je o indeksu koji mjeri sustavnu aktivnost bolesti, a koji je generiran 2009. godine. Njegova je primjena prvenstveno u kliničkim istraživanjima. Uključuje 12 domena, tj. organskih sustava (*kožni* – vaskulitis; *respiratorni* – intersticijska bolest pluća; *bubrežni* – renalna tubularna acidoza, glomerulonefritis; *zglobni* – artralgije, sinovitis; *mišićni* – miozitis; *periferni živčani sustav* – aksonalna motorna i/ili senzorna neuropatija i/ili polineuropatija, upalna demijelinizirajuća polineuropatija, gangliopatija, vaskulitis sa slikom multiplog mononeuritisa; *središnji živčani sustav* – neuropatija kranijskih živaca, sindrom sličan multiploj sklerozi, vaskulitis sa slikom tranzitorne ishemijske atake ili cerebrovaskularnog inzulta ili transverzalnog mijelitisa, limfocitni meningitis; *žljezdani* – uvećanje suznih ili slinovnih žlijezda; *hematološki* – autoimune citopenije; *konstitucijski* – vrućica; noćno znojenje; nevoljni gubitak na tjelesnoj težini; limfadenopatski – limfadenopatija ili limfom; *biološki* – hipokomplementemija, hipergamaglobulinemija, hipogamaglobulinemija, krioglobulinemija), a svaka domena podijeljena je na tri do četiri razine aktivnosti (10).

Liječenje u prvom redu uključuje simptomatsko liječenje suhoće sluznica. Kod bolesnika koji imaju aktivnu bolest barem jednog organa ili organskog sustava (posebice kod ekstraglandularnih prezentacija bolesti) potrebno je primijeniti sistemsku imunosupresivnu i/ili imunomodulacijsku terapiju, koja uključuje glukokortikoide, antimalarike, klasične imunosupresive, intravenozne imunoglobuline i biološke lijekove (u prvom redu rituksimab). Primjena antimalarika (klorokina/hidroksiklorokina) ima pozitivan učinak na opće simptome i artritis te veličinu slinovnih žlijezda (11).

PRIKAZ BOLESNICE

Autoimuna bolest započela je 1997. godine (u dobi od 30 godina) recidivirajućim simetričnim artritisom šaka praćenim ubrzanom sedimentacijom eritrocita (SE). Bolesnica je do 2004. godine povremeno liječena malom dozom prednizolona (do 10 mg dnevno) i nesteroidnim antireumaticima. Dijagnoza pSS-a postavljena je 2008. godine na osnovi simetričnoga neerozivnog artritisa malih zglobova šaka (slika 1), umjereno ubrzane SE, subjektivnog i objektivnog nalaza suhoće očiju i usta, tipičnog PHD nalaza male slinovne žlijezde (fokalni limfocitni infiltrati), pozitivnog ANF-a (točkasta indirektna imunoflorescencija) i RF-a uz negativan nalaz anti-dsDNA, Sm, SSA/Ro, SSA/La, a u kasnijim kontrolama i negativnog nalaza anti-CCP-a. Tada su ultrazvučnim pregledom utvrđene tipične difuzne promjene slinovnica (heterogena ehostruktura, hipoehogena područja, linearni hiperehogeni odjeci uz brojne cistične formacije i kalcifikacije). Od 2008. godine u nalazima se bilježi višekratna odsutnost hi-

The ESSDAI disease activity index was developed for patients with pSS. It is an index that measures the systemic activity of the disease, and which was generated in 2009. It is primarily applied in clinical research. It includes 12 domains, i.e. organ systems (*cutaneous* – vasculitis; *respiratory* – interstitial lung disease; *renal* – renal tubular acidosis, glomerulonephritis; *articular* – arthralgias, synovitis; *muscular* – myositis; *peripheral nervous system (PNS)* – axonal motor and/or sensory neuropathy and/ or polyneuropathy, inflammatory demyelinating polyneuropathy, gangliopathy, vasculitis with a pattern of mononeuritis multiplex; *central nervous system (CNS)* – neuropathy of the cranial nerves, a syndrome similar to multiple sclerosis, vasculitis with a pattern of transient ischemic attack or cerebrovascular insult or transverse myelitis, lymphocytic meningitis; *glandular* – enlargement of lacrimal or salivary glands; *haematological* – autoimmune cytopenias; *constitutional* – fever; night sweats; unintentional weight loss; *lymphadenopathic* – lymphadenopathy or lymphoma; *biological* – hypocomplementemia, hypergammaglobulinemia, hypogammaglobulinemia, cryoglobulinemia), and each domain is divided into three to four levels of activity (10).

The first-line treatment includes the symptomatic treatment of dry mucous membranes. In patients who have an active disease of at least one organ or organ system (especially with extraglandular presentations of the disease), it is necessary to apply systemic immunosuppressive and/or immunomodulating therapy, which includes glucocorticoids, antimalarials, classical immunosuppressants, intravenous immunoglobulins and biological drugs (primarily rituximab). The use of antimalarials (chloroquine/hydroxychloroquine) has a positive effect on general symptoms and arthritis and the size of the salivary glands (11).

CASE REPORT

The autoimmune disease started in 1997 (when the patient was 30 years old) with recurrent symmetric arthritis of the hands followed by accelerated erythrocyte sedimentation rate (ESR). Until 2004, the patient was occasionally treated with a small dose of prednisolone (up to 10 mg per day) and non-steroidal anti-inflammatory drugs (NSAIDs). The diagnosis of pSS was established in 2008 on the basis of symmetric non-erosive arthritis of the small joints of the hands (Figure 1), moderately accelerated ESR, subjective and objective findings of dry eyes and mouth, standard histopathological findings of a small salivary gland (focal lymphocytic infiltrates), positive ANF (dotted staining pattern in indirect immunofluorescence) and RF with a negative anti-dsDNA, Sm, SSA/Ro and SSA/La result, and, at later follow-ups, a negative anti-CCP result. Then, typical diffuse changes of the salivary glands

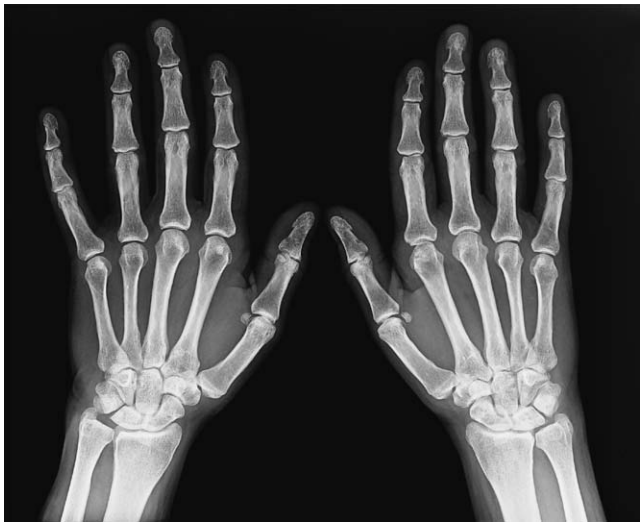

Figure 1. Symmetric non-erosive arthritis of the small joints of the hands on a plain radiograph
Slika 1. Simetrični neerozivni artritis malih zglobova šaka na standardnom radiogramu šaka

pergamaglobulinemije i citopenije. Bolesnica je od 2008. godine kontinuirano liječena antimalarikom (klorokin), a od 2008. do 2016. godine i prednizolonom u dnevnoj dozi do 10 mg, kada se lijek postupno ukida radi razvoja intolerancije glukoze, a bez posljedične aktivacije artritisa. Od prosinca 2013. godine prati se klinički, ultrazvučno i citološki bezbolna nodozna oteklina desne parotide uz odsustvo B-simptoma, limfadenopatije i splenomegalije (slika 2A). Nodozna oteklina desne parotide u početku je shvaćena kao limfni čvor unutar žlijezde. U listopadu 2017. godine prvi put citološki nalaz ukazuje na mogući razvoj NHL-a tipa MALT (ekstranodalni B-stanični limfom marginalne zone podrijetlom limfatičnog tkiva sluznice). Krajem 2020. godine nastupa nagli porast čvora desne parotide. Početkom 2021. godine po hematologu je potvrđena dijagnoza indolentnoga ekstranodalnog B-staničnog NHL-a, CD20 pozitivnog, tipa MALT, bez zahvaćanja limfnih čvorova i koštane srži i bez splenomegalije (utvrđen stadij II AE desne parotide; II – lokalizacija samo s jedne strane dijafragme, A – odsutnost B-simptoma u vidu vrućice i gubitka na tjelesnoj težini te noćnih znojenja, E – ekstranodalno podrijetlo, tj. iz tkiva izvan limfnog sustava). Bolesnica je u travnju 2021. godine primila prvi ciklus rituksimaba s dobrim učinkom u kombinaciji s bendamustinom. Klinički i ultrazvučno nastupilo je smanjenje desne parotidne žlijezde za 30% već tri tjedna nakon početka liječenja uz poboljšanje salivacije (slika 2B).

RASPRAVA

Dosadašnja istraživanja opisala su povećani rizik od razvoja limfoma u bolesnika sa SS-om u odnosu na opću populaciju, a također i u odnosu na bolesnike s

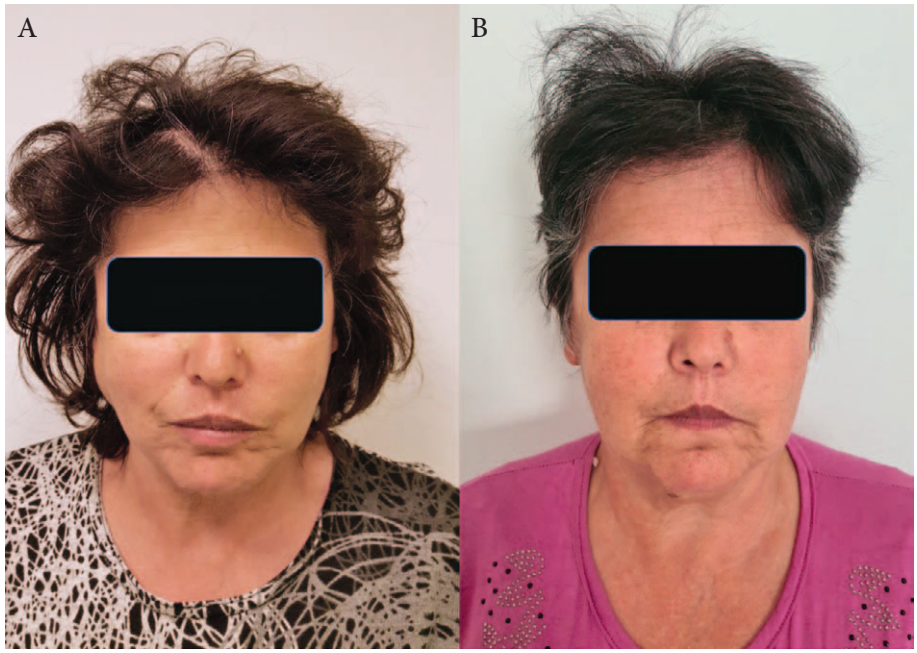

Figure 2. Nodular swelling of the right parotid gland before (A) and after (B) rituximab treatment
Slika 2. Nodozna oteklina desne parotidne žlijezde prije (A) i poslije (B) liječenja rituksimabom

were observed through an ultrasound (heterogeneous echogenicity, hypoechoic areas, linear hyperechoic masses with numerous cystic formations and calcifications). Since 2008, the findings have shown repeated absence of hypergammaglobulinemia and cytopenia. Since 2008, the patient has been continuously treated with an antimalarial (chloroquine), and from 2008 to 2016 with prednisolone at a daily dose of up to 10 mg. Then, the drug was gradually discontinued due to the development of glucose intolerance, without the consequent activation of arthritis. Since December 2013, the follow-up of the painless nodular swelling of the right parotid gland, with the absence of B-symptoms, lymphadenopathy, and splenomegaly, was carried out through clinical, ultrasound and cytological findings (Figure 2A). The nodular swelling of the right parotid gland was initially understood as a lymph node within the gland. In October 2017, for the first time, a cytological finding indicated the possible development of NHL of the MALT type (extranodal B-cell marginal zone lymphoma arising in the lymphatic tissue of the mucous membrane). At the end of 2020, there was a rapid growth in the right parotid node. At the beginning of 2021, the haematologist confirmed the diagnosis of indolent extranodal B-cell NHL of the CD20 positive MALT lymphoma, without the involvement of the lymph nodes and bone marrow and without splenomegaly (stage II AE of the right parotid gland; II – localisation only on one side of the diaphragm, A – absence of B-symptoms in the form of fever, weight loss and night sweats, E – extranodal origin, i.e. from tissues outside the lymphatic system). In April 2021, the

drugim autoimunim bolestima (12–15). Najčešći oblik limfoma u bolesnika sa SS-om jest B-stanični NHL niskog do srednjeg stupnja malignosti, histološki podijeljen na limfom marginalne zone koji obuhvaća limfoidne tumore povezane sa sluznicom, takozvani MALT limfom (engl. *mucosa associated lymphoid tissue*) i nodalni B-stanični limfom marginalne zone (NMZL; engl. *nodal marginal zone lymphoma*). Mogući drugi oblici NHL-a u bolesnika sa SS-om jesu difuzni B-velikostanični limfom (DLBCL; engl. *diffuse large B-cell lymphoma*) koji pripada u skupinu visokog stupnja malignosti. Rjeđe se mogu razviti leukemije, Waldenstromova makroglobulinemija i multipli mijelom (16–22). MALT i NMZL smatraju se limfomima niskog do srednjeg stupnja malignosti.

Ne-Hodgkinovi limfomi koji kompliciraju tijek pSS-a karakterizirani su bezbolnim oteklinama žlijezda slinovnica (najčešće parotida), indolentnim tijekom, normalnim razinama laktat dehidrogenaze (LDH) i beta2 mikroglobulina, dobrim općim stanjem, odsutnošću B-simptoma, a zahvaćenost koštane srži je rijetka. U pristupu takvim bolesnicima i odabiru modaliteta liječenja koristi se klasifikacija Lugano (23) koja je trenutno najnovija klasifikacija proširenosti primarnih nodalnih limfoma i dopunjuje dosadašnje klasifikacije naglašavajući važnost PET/CT-a s FDG-om (PET, engl. *positron emission tomography*; CT, engl. *computed tomography*; FDG, engl. *fluorodeoxyglucose*), za određivanje proširenosti bolesti (tablica 3).

Važnost klasifikacije osim odabira modaliteta liječenja jest i u individualnom pristupu i praćenju bolesnika jer je poznato da se u desetak posto bolesnika limfo-

patient received the first cycle of rituximab which yielded good results in combination with bendamustine. The clinical and ultrasound findings revealed a reduction of the right parotid gland by 30%, as early as three weeks after the start of treatment, with an improvement in salivation (Figure 2B).

DISCUSSION

Previous research has described an increased risk of developing lymphoma in patients with SS compared to the general population, and also compared to patients with other autoimmune diseases (12–15). The most common form of lymphoma in patients with SS is B-cell NHL of low to intermediate grade of malignancy, which is histologically divided into marginal zone lymphoma that includes lymphoid tumours associated with the mucosa, the so-called MALT lymphoma (mucosa-associated lymphoid tissue) and nodal B-cell marginal zone lymphoma (NMZL). Possible other forms of NHL in patients with SS include diffuse large B-cell lymphoma (DLBCL) which belongs to high-grade malignancy group. Leukemias, Waldenstrom macroglobulinemia and multiple myeloma usually develop less frequently (16–22). MALT and NMZL are considered low- to intermediate-grade lymphomas.

Non-Hodgkin's lymphomas that complicate the course of pSS are characterised by painless swelling of the salivary glands (most often the parotid gland), indolent disease course, normal levels of lactate dehydrogenase (LDH) and beta-2 microglobulin (B2M), good general condition and absence of B-symptoms, while bone marrow involvement rarely occurs as a characteristic of this disease. In the approach to such patients and the selection of treatment modality, the Lugano classification (23) is used, which is currently the most recent classification of the extent of spread of primary nodal lymphomas which serves as an addition to the previous classifications by emphasising the importance of (FDG) PET/CT (positron emission tomography (PET), computed tomography (CT), fluorodeoxyglucose (FDG)), in order to determine the extent of spread of the disease (Table 3).

The importance of classification, in addition to the choice of treatment modality, is also in the individual approach to each patient and patient follow-up, because it is known that in ten percent of patients, low-grade lymphomas can transform into high-grade lymphomas, mostly in the case of diffuse large B-cell lymphoma (DLBCL), which we know originates from the same clone as low-grade lymphomas (22–24).

As a result of new insights about the potential malignant transformation in pSS, which, after RA, is the second most frequent systemic autoimmune disease, predictive risk factors for the development of lymphoma in patients with SS have been identified over time,

Table 3. The Lugano classification for primary nodal lymphomas

Tablica 3. Klasifikacija Lugano za primarne nodalne limfome

Stage / Stadij	Involvement Proširenost	Extranodal (E) Ekstranodalno (E)
I	One node or a group of adjacent nodes / Jedan limfni čvor ili grupa susjednih čvorova	Single extranodal lesions without nodal involvement / Pojedinačne ekstranodalne lezije bez uključenosti limfnih čvorova
II	Two or more nodal groups on the same side of the diaphragm / Dvije ili više grupa čvorova na istoj strani dijafragme	Stage I or II by nodal extent with limited contiguous extranodal involvement / Stadij I ili II po nodalnoj proširenosti s ograničenom kontinuiranom proširenosti ekstranodalno
II bulky / glomazni	As stage II with single large tumour mass (bulky); ≥10 cm in diameter or >1/3 transthoracic diameter on CT / Kao stadij II bolesti, no prisutna je pojedinačna velika tumorska masa (engl. *bulky*); ≥10 cm u promjeru ili >1/3 transtorakalng dijametra na CT-u	Not applicable / Nije primjenjivo
III	Nodes on both sides of the diaphragm; nodes above the diaphragm with spleen involvement / Čvorovi s obje strane dijafragme; čvorovi iznad dijafragme sa zahvaćanjem slezene	Not applicable / Nije primjenjivo
IV	Additional noncontiguous extralymphatic involvement / Dodatna nekontinuirana ekstralimfatička proširenost bolesti	Not applicable / Nije primjenjivo

Adapted from: Cheson BD, Fisher RI, Barrington SF, Cavalli F, Schwartz LH, Zucca E et al. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. J Clin Oncol. 2014;32(27):3062. (23) / Prilagođeno prema: Cheson BD, Fisher RI, Barrington SF, Cavalli F, Schwartz LH, Zucca E i sur. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. J Clin Oncol. 2014;32 (27):3062. (23)

mi niskog stupnja mogu transformirati u limfom visokog stupnja, uglavnom u tip DLBCL, a za koji znamo da proizlazi iz istog klona kao i limfomi niskog stupnja (22–24).

which can be classified into clinical and laboratory factors (24,25). Clinical predictive factors include persistent parotid swelling, splenomegaly, lymphadenopathy, palpable purpura, and peripheral neuropathy. Laboratory risk factors include lymphopenia (especially CD4-positive T lymphocytes), cryoglobulinemia, the presence of monoclonal protein in serum and urine, and reduced values of the complement C4. Histopathological predictive factors in the salivary gland biopsy include the presence of structures similar to germinal centres (GC) and a high focus score (23,24). In addition to that, high disease activity with the ESSDAI index was shown to be a predictor of lymphoma development (10).

Although the cause of pSS is not known, various research studies that were conducted so far have revealed a lot about its etiopathogenesis, which explains the increased frequency of the development of lymphoproliferative diseases in these patients.

Reactive lymphocytic infiltration and changes in epithelial cells in SS can cause lymphoepithelial lesions, i.e., lymphoepithelial sialadenitis (LESA), which is a histological feature of the disease, and which has a high risk of transformation into lymphoproliferative diseases (26,27). This process is generally long-lasting and is made up of various histopathological mechanisms. Chronic inflammation, enhanced activation of T and B lymphocytes, secretion of cytokines, oncogenes and chromosomal anomalies can cause the transition from B-polyclonal proliferation to monoclonal proliferation and the development of lymphoma. The prevailing opinion is that the driving role in the transformation of SS into NHL is played by a chronic inflammatory process in which exogenous and endogenous antigens stimulate the swelling of lymphocytes and cause changes in the epithelial cells of the salivary glands, which increases the risk of malignant transformation (2,26–28).

Since the salivary glands are the target organ of pSS, epithelial cells play an active role in the pathogenesis of this disease. They express costimulatory molecules and can present autoantigen to immune cells, and also participate in B-cell activation by secreting B-cell activating factor (BAFF, also known as tumour necrosis factor ligand superfamily member 13B), and after stimulation with viruses or interferon alpha (IFN-α). BAFF levels in plasma and salivary glands have been shown to be significantly elevated in patients with pSS, which is associated with greater disease activity, but also with a greater risk of developing B-cell lymphoma (29–33). Surface RF-expressing B-cells are frequently detected in salivary glands in pSS, suggesting that clonal expansion may result from antigenic selection of RF-expressing B-cells (25). This continuous stimulation of B-cells is the main driver of lymphoproliferation. The identifi-

Posljedično spoznajama o potencijalnoj malignoj transformaciji u sklopu pSS-a koji je, nakon RA, druga po učestalosti sistemska autoimuna bolest, s vremenom su identificirani prediktivni rizični čimbenici razvoja limfoma u bolesnika sa SS-om, koje možemo podijeliti na kliničke i laboratorijske (24,25). U kliničke prediktivne čimbenike ubrajaju se trajno povećanje parotida, splenomegalija, limfadenopatija, palpabilna purpura i periferna neuropatija. Laboratorijski čimbenici rizika jesu limfopenija (posebice CD4-pozitivnih limfocita T), krioglobulinemija, prisutnost monoklonskog proteina u serumu i urinu te snižene vrijednosti C4 komponente komplementa. U PHD prediktivne čimbenike u bioptatu slinovne žlijezde ubraja se prisutnost struktura sličnih germinativnim centrima (GC) i veći broj limfocitnih fokusa (engl. *high focus score*) (23,24). Također, pokazalo se da je visoka aktivnost bolesti s indeksom ESSDAI prediktor razvoja limfoma (10).

Iako nije poznat uzrok pSS-a, dosadašnjim istraživanjima mnogo se saznalo o njegovoj etiopatogenezi, koja nam objašnjava povećanu učestalost razvoja limfoproliferativnih bolesti u tih bolesnika.

Reaktivna limfocitna infiltracija i promjene na epitelnim stanicama u SS-u mogu uzrokovati limfoepitelijalno oštećenje, odnosno limfoepitelijalni sijaloadenitis (LESA), što je histološko obilježje bolesti i koji ima visok rizik za transformaciju u limfoproliferativne bolesti (26,27). Taj proces u pravilu je dugotrajan i čine ga različiti patohistološki mehanizmi. Kronična upala, pojačana aktivacija limfocita T i B, lučenje citokina, onkogeni i kromosomske anomalije mogu uzrokovati prijelaz iz B-poliklonske proliferacije u monoklonsku proliferaciju i razvoj limfoma. Prevladavajući je stav da pokretačku ulogu u transformaciji SS-a u NHL ima kronični upalni proces u kojem egzogeni i endogeni antigeni potiču bujanje limfocita i uzrokuju promjene na epitelnim stanicama žlijezda slinovnica, što povećava rizik maligne transformacije (2,26–28).

Budući da su žlijezde slinovnice ciljni organ pSS-a, epitelne stanice imaju aktivnu ulogu u patogenezi ove bolesti. One izražavaju kostimulacijske molekule i mogu prezentirati autoantigen imunološkim stanicama, a također sudjeluju u aktivaciji B-stanica izlučivanjem faktora aktivacije B-stanica (BAFF, engl. *B-cell activating factor B*, također poznat kao član superobitelji TNF liganda 13B), a nakon stimulacije virusima ili interferonom alfa (IFNα). Pokazalo se da su razine BAFF-a u plazmi i žlijezdama slinovnicama značajno povišene u bolesnika s pSS-om, što je povezano s većom aktivnošću bolesti, ali i s većim rizikom od razvoja limfoma B-stanica (29–33). B-stanice koje eksprimiraju površinski RF često se otkrivaju u žlijezdama slinovnicama kod pSS-a, što sugerira da bi klonska ekspanzija mogla proizaći iz antigenske selekcije B-sta-

cation of multiple steps that support B-cell activation has led to the development of promising targeted therapies that will hopefully lead to the development of an effective therapeutic strategy for pSS.

CONCLUSION

In this paper, we presented the case of a patient with long-term pSS who later developed indolent extranodal B-NHL CD20 positive MALT lymphoma with a good response to treatment with rituximab in combination with bendamustine. The development of malignant lymphoma from benign lymphocytic infiltration, or lymphoepithelial sialadenitis in patients with pSS is usually a long-term process, which is also the case with the patient in this case report. MALT lymphoma is the most common histological type, has a good prognosis and is most often treated with rituximab in combination with an alkylating agent. The development of NHL in patients with SS is considered one of the most serious complications of the disease. The aforementioned is important in the clinical follow-up of patients for the purpose of early diagnosis and timely and adequate treatment, given that lymphoproliferative disorders are the main cause of mortality in SS. Considering the above, it is important to determine the set of clinical, laboratory and imaging tests and their frequency in patient follow-up. For example, in patients with permanently enlarged parotid glands, cutaneous changes and neuropathy, it is necessary to perform a clinical examination and ultrasound every six months in order to detect the possible signs of lymphadenopathy and splenomegaly, closely monitor the lymphocyte values in the laboratory markers, determine the presence of monoclonal protein in serum and urine, cryoglobulin, LDH and beta-2 microglobulin values, and, if necessary, perform a cytological puncture and biopsy of the salivary gland or lymph node with the aim of early detection of the development of lymphoma. Also, it is necessary to continue research in order to get a better understanding of the pathogenetic mechanisms of the disease itself and its lymphoproliferation in order to find targeted therapeutic options and develop an effective therapeutic strategy for pSS.

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

nica koje eksprimiraju RF (25). Ova kontinuirana stimulacija B-stanica glavni je pokretač limfoproliferacije. Identifikacija višestrukih koraka koji podržavaju aktivaciju B-stanica dovela je do razvoja obećavajućih ciljanih terapija koje će, nadamo se, dovesti do razvoja učinkovite terapijske strategije za pSS.

ZAKLJUČAK

U ovom smo radu prikazali bolesnicu s dugogodišnjim pSS-om i kasnije razvijenim indolentnim ekstranodalnim B-NHL CD20 pozitivnim limfomom tipa MALT uz dobar odgovor na liječenje rituksimabom u kombinaciji s bendamustinom. Razvoj malignog limfoma iz benigne limfocitne infiltracije, odnosno limfoepitelijalnog sijaloadenitisa u bolesnika s pSS-om u pravilu je dugotrajan proces, što je slučaj i u prikazane bolesnice. MALT limfom je najčešći histološki tip, ima dobru životnu prognozu i najčešće se liječi rituksimabom u kombinaciji s alkilirajućim lijekom. Razvoj NHL-a u bolesnika sa SS-om smatra se jednom od najtežih komplikacija bolesti. Navedeno je važno u kliničkom praćenju bolesnika radi rane dijagnoze i pravovremenog i adekvatnog liječenja s obzirom na to da su limfoproliferativne bolesti glavni uzrok mortaliteta u SS-u. S obzirom na navedeno, važno je odrediti set kliničkih, laboratorijskih i slikovnih pretraga i njihovu učestalost u praćenju bolesnika. Primjerice u bolesnika s trajno uvećanim parotidama, kožnim promjenama i neuropatijom potrebno je svakih šest mjeseci kliničkim pregledom i ultrazvučno tražiti limfadenopatiju i splenomegaliju, laboratorijski pratiti vrijednosti limfocita, utvrditi prisutnost monoklonskog proteina u serumu i urinu, krioglobuline, vrijednosti LDH i beta2 mikroglobulina te po potrebi učiniti citološku punkciju i biopsiju slinovne žlijezde ili limfnog čvora s ciljem ranog otkrivanja razvoja limfoma. Također, potrebno je nastaviti s istraživanjima u svrhu boljeg razumijevanja patogenetskih mehanizama same bolesti i njezine limfoproliferacije u cilju pronalaska ciljanih terapijskih opcija te razvoja učinkovite terapijske strategije za pSS.

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

REFERENCES / LITERATURA

1. Firenstein GS, Budd RC, Gabriel SE, McInnes IB, O'Dell JR. Kelley and Firestein's Textbook of Rheumatology. 10th ed. Philadelphia: Elsevier; 2016.
2. Tincani A, Andreoli L, Cavazzana I, Doria A, Favero M, Fenini M-G et al. Novel aspects of Sjögren's syndrome in 2012. BMC Med. 2013;11:93.
3. Whitcher JP, Shiboski CH, Shiboski SC, Heidenreich AM, Kitagawa K, Zhang S et al. A simplified quantitative method for assessing keratoconjunctivitis sicca from the Sjögren's Syndrome International Registry. Am J Ophthalmol. 2010;149(3):405–15.
4. Bijsterveld OP van. Diagnostic tests in the Sicca Syndrome. Arch Ophthalmol. 1969;82(1):10–4.
5. Navazesh M. Methods for collecting saliva. Ann N Y Acad Sci. 1993;694(1):72–7.
6. Laktašić Žerjavić N, Anić B, Ćurković B, Babić-Naglić Đ, Nola M, Lončarić D. Leukocitoklastični vaskulitis u primarnom Sjögrenovom sindromu: prikaz bolesnika [Leukocytoclastic vasculitis in primary Sjögren syndrome]. Liječ Vjesn. 2007;129:134–7.
7. Seror R, Ravaud P, Bowman SJ, Baron G, Tzioufas A, Theander E et al. EULAR Sjogren's syndrome disease activity index: development of a consensus systemic disease activity index for primary Sjogren's syndrome. Ann Rheum Dis. 2010;69:1103–9.
8. Ramos-Casals M, Tzioufas A G, Font J. Primary Sjögren's syndrome: new clinical and therapeutic concepts. Ann Rheum Dis. 2005;64:347–54.
9. Shiboski CH, Shiboski SC, Seror R, Criswell LA, Labetoulle M, Lietman TM et al. 2016 ACR-EULAR Classification criteria for primary Sjögren's Syndrome: a consensus and data-driven methodology involving three international patient cohorts. Arthritis Rheumatol Hoboken NJ. 2017;69(1):35–45.
10. Seror R, Bowman SJ, Brito-Zeron P, Theander E, Bootsma H, Tzioufas A et al. EULAR Sjögren's syndrome disease activity index (ESSDAI): a user guide. RMD Open. 2015;1:e000022.
11. Mitrović J. Management of systemic manifestations in Sjögren syndrome [Liječenje sistemskih manifestacija Sjögrenovog sindroma]. Reumatizam 2021;68(Supl 1/Suppl 1):15–9.
12. Daniels TE, Cox D, Shiboski CH, Schiødt M, Wu A, Lanfrachi H et al. Associations between salivary gland histopathologic diagnoses and phenotypic 25 features of Sjögren's syndrome among 1,726 registry participants. Arthritis Rheum. 2011;63(7):2021–30.
13. Zintzaras E, Voulgarelis M, Moutsopoulos HM. The risk of lymphoma development in autoimmune diseases: A meta-analysis. Arch. Intern. Med. 2005;165: 2337–44.
14. Liang Y, Yang Z, Qin B, Zhong R. Primary Sjögren's syndrome and malignancy rsk: a systematic review and meta-analysis. Ann Rheum Dis. 2014;73(6):1151–6.
15. Lazarus MN, Robinson D, Mak V, Møller H, Isenberg DA. Incidence of cancer in a cohort of patients with primary Sjogren's syndrome. Rheumatology (Oxford). 2006;45(8):1012–5.
16. Papageorgiou A, Ziogas DC, Mavragani CP, Zintzaras E, Tzioufas AG, Moutsopoulos HM et al. Predicting the outcome of Sjogren's syndrome-associated non-hodgkin's lymphoma patients. PLoS ONE. 2015;10: e0116189.
17. Ekström Smedby K, Vajdic CM, Falster M, Engels EA, Martinez-Maza O, Turner J et al. Autoimmune disorders and risk of non-Hodgkin lymphoma subtypes: A pooled analysis within the InterLymph Consortium. Blood. 2008;111:4029–38.
18. Theander E, Henriksson G, Ljungberg O, Mandl T, Manthorpe R, Jacobsson LTH. Lymphoma and other malignancies in primary Sjögren's syndrome: a cohort study on cancer incidence and lymphoma predictors. Ann Rheum Dis. 2006;65:796–803.
19. Ioannidis JP, Vassiliou VA, Moutsopoulos HM. Long-term risk of mortality and lymphoproliferative disease and predictive classifcation of primary Sjögren's syndrome. Arthritis Rheum. 2002;46:741–7.
20. Voulgarelis M, Dafni UG, Isenberg DA, Moutsopoulos HM. Malignant lymphoma in primary Sjögren's syndrome: a multicenter, retrospective, clinical study by the European Concerted Action on Sjögren's Syndrome. Arthritis Rheum. 1999;42(8):1765–72.
21. Royer B, Cazals-Hatem D, Sibilia J, Agbalika F, Cayuela JM, Soussi T et al. Lymphomas in patients with Sjogren's syndrome are marginal zone B-cell neoplasms, arise in diverse extranodal and nodal sites, and are not associated with viruses. Blood. 1997;90(2):766–75.
22. Voulgarelis M, Ziakas PD, Papageorgiou A, Baimpa E, Tzioufas AG, Moutsopoulos HM. Prognosis and outcome of non-Hodgkin lymphoma in primary Sjögren syndrome. Medicine (Baltimore). 2012;91(1):1–9.
23. Cheson BD, Fisher RI, Barrington SF, Cavalli F, Schwartz LH, Zucca E et al. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. J Clin Oncol. 2014;32(27):3059–68.
24. Nocturne G, Mariette X. Sjögren Syndrome-associated lymphomas: an update on pathogenesis and management. Br J Haematol. 2015;168:317–27.
25. Stergiou IE, Poulaki A, Voulgarelis M. Pathogenetic Mechanisms Implicated in Sjögren's Syndrome Lymphomagenesis: A Review of the Literature. J Clin Med. 2020;9:3794.
26. Cornec D, Devauchelle-Pensec V, Tobón GJ, Pers JO, Jousse-Joulin S, Saraux A. B cells in Sjögren's syndrome: from pathophysiology to diagnosis and treatment. J Autoimmun. 2012;39(3):161–7.
27. Youinou P1, Devauchelle-Pensec V, Pers JO. Significance of B cells and B cell clonality in Sjögren's syndrome. Arthritis Rheum. 2010;62(9):2605–10.
28. Dong L, Chen Y, Masaki Y, Okazaki T, Umehara H. Possible mechanisms of lymphoma development in Sjögren's syndrome. Curr Immunol Rev. 2013;9(1):13–22.
29. Novak AJ, Grote DM, Stenson M, Ziesmer SC, Witzig TE, Habermann TM et al. Expression of BLyS and its receptors in B-cell non-Hodgkin lymphoma: correlation with disease activity and patient outcome. Blood. 2004;104:2247–53.
30. Gottenberg JE, Seror R, Miceli-Richard C, Benessiano J, Devauchelle-Pensec V, Dieude P et al. Serum levels of beta2-microglobulin and free light chains of immunoglobulins are associated with systemic disease activity in primary Sjögren's syndrome. Data at enrollment in the prospective ASSESS cohort. PLoS ONE 2013;8:e59868.
31. Quartuccio L, Salvin S, Fabris M, Maset M, Pontarini E, Isola M et al. BLyS upregulation in Sjogren's syndrome associated with lymphoproliferative disorders, higher ESSDAI score and B-cell clonal expansion in the salivary glands. Rheumatology (Oxf). 2013;52:276–81.
32. Milas Ahić J. Pathophysiology of Sjögren's syndrome [Patofiziologija Sjögrenovog sindroma]. Reumatizam 2021;68(Supl 1/Suppl 1):15–9.
33. Nocturne, G, Mariette X. B cells in the pathogenesis of primary Sjögren syndrome. Nat Rev Rheumatol. 2018;14(3);133–45.