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CASE-BASED REVIEW PREGLEDNI RAD TEMELJEN NA PRIKAZU BOLESNIKA

LYMPHOCYTIC INTERSTITIAL PNEUMONITIS AND CRYOGLOBULINEMIA AS CLUES TOWARDS THE DIAGNOSIS OF SJÖGREN'S SYNDROME

LIMFOCITNI INTERTICIJSKI PNEUMONITIS I KRIOGLOBULINEMIJA KAO POMOĆ U DIJAGNOZI SJÖGRENOVOG SINDROMA

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Abstract

Introduction: Cryoglobulinemia is associated with extraglandular features in patients with Sjögren's syndrome, while lymphocyte interstitial pneumonitis (LIP) is a type of interstitial lung disease relatively specific for this syndrome. *Case presentation:* A 61-year-old male was admitted for further workup of suspected pneumonia, presenting with a history of persistent cough and fever as well as a finding of a unilateral infiltrate on his chest X-ray. His chest CT was consistent with LIP. Due to decreased serum C3 and C4 levels and the presence of cryoglobulinemia type 3, he underwent further workup that finally confirmed the diagnosis of Sjögren's syndrome and LIP as its extraglandular feature. In addition to appropriate antibiotic treatment of his acute respiratory infection, he was initially treated with hydroxychloroquine and prednisone with improvement in symptoms and normalization of his erythrocyte sedimentation rate as well as complement levels. However, due to a slight aggravation of his dyspnea and decline in C3 and C4 levels in the further course, azathioprine was added with a beneficial therapeutic and glucocorticoid-sparing effect. *Conclusion:* Although cryoglobulinemia does not seem to be a direct cause of LIP, it may serve as a clue towards recognizing extraglandular features of undiagnosed Sjögren's syndrome.

Keywords: Sjögren's syndrome, lymphocytic interstitial pneumonitis, cryoglobulinemia, diagnosis

Sažetak

Uvod: Krioglobulinemija je povezana s ekstraglandularnim manifestacijama u bolesnika sa Sjögrenovim sindromom. Limfocitni intersticijski pneumonitis (LIP) vrsta je intersticijske bolesti pluća koja je relativno specifična za ovaj sindrom. *Prikaz slučaja:* Muškarac u dobi od 61 godine primljen je radi dodatne obrade zbog sumnje na pneumoniju, s anamnezom perzistentnog produktivnog kašlja i febriliteta kao i jednostranog infiltrata pluća opisanoga na konvencionalnom radiogramu. CT pluća pokazao je manifestacije LIP-a. Zbog sniženih koncentracija C3 i C4 u serumu kao i

prisutnosti krioglobulinemije tipa 3, provedena je daljnja obrada kojom je konačno potvrđena dijagnoza Sjögrenovog sindroma i LIP-a kao njegove izvanžlijezdane manifestacije. Uz primjerenu antibiotsku terapiju za akutnu respiratornu infekciju, inicijalno je liječen hidroksiklorokinom i prednizonom što je dovelo do oporavka simptoma i normalizacije brzine sedimentacije eritrocita te vrijednosti komplementa. Usprkos tome, zbog blažeg pogoršanja simptoma i sniženja razina C3 i C4 u daljnjem tijeku liječenja uveden je azatioprin, s posljedičnim povoljnim terapijskim učinkom koji je omogućio i sniženje doze glukokortikoida. *Zaključak:* Iako se čini da krioglobulinemija nije izravni uzrok LIP-a, može poslužiti kao pomoć u prepoznavanju ekstraglandularnih manifestacija do tada nedijagnosticiranog Sjögrenovog sindroma.

Ključne riječi: Sjögrenov sindrom, limfocitni intersticijski pneumonitis, krioglobulinemija, dijagnoza

INTRODUCTION

Sjögren's syndrome is a systemic autoimmune disease that generally affects the exocrine glands, primarily salivary and lacrimal, resulting in oral and ocular dryness. One-third of patients present with extraglandular manifestations. (1) One of the typical lung manifestations is lymphocytic interstitial pneumonitis (LIP), a rare form of interstitial lung disease characterized by cellular expansion and infiltration of the lung interstitium with reactive B and T lymphocytes, plasma cells, and histiocytes. (2, 3)

Cryoglobulins are immunoglobulins that precipitate *in vitro* at temperatures below the core body temperature (37 °C) and dissolve when reheated. (4) Cryoglobulinemia may be associated with cryoglobulinemic vasculitis, however, cryoglobulinemia without clinically apparent vasculitis seems to be even more common. It has been documented in various systemic autoimmune diseases, most frequently in patients with primary Sjögren's syndrome, where cryoglobulinemia also has prognostic implications. (5)

We present the case of a patient diagnosed with LIP in which the presence of cryoglobulinemia and decreased serum complement levels served as clues towards the diagnosis of Sjögren's syndrome.

CASE REPORT

A 61-year-old male patient with no history of smoking initially presented to the emergency room with dry cough, dyspnea on exertion, fever lasting for two weeks, as well as diaphoresis.

His past medical history revealed an episode of sunlight "allergy" in his youth as well as a spontaneous ablation of his left retina, without a clear provoking cause. Over the preceding decades, he experienced a few episodes of thrombophlebitis of the varicose veins in his legs.

Over the course of two weeks prior to admission, he suffered from non-spiking fevers up to 39 ^{0}C. He also reported symptoms of dyspnea on exertion as well as occasional productive cough with white sputum. No improvement was observed despite a three-day course of azithromycin. A chest X-ray in the outpatient family

UVOD

Sjögrenov sindrom sistemska je autoimuna bolest koja općenito zahvaća egzokrine žlijezde, prvenstveno slinovnice i suzne žlijezde, što dovodi do suhoće usne šupljine i očiju. Jedna trećina bolesnika ima simptome povezane s ekstraglandularnim manifestacijama. (1) Jedna od tipičnih plućnih manifestacija je limfocitni intersticijski pneumonitis (LIP), rijedak oblik intersticijske bolesti pluća u kojoj se javljaju karakteristike poput ekspanzije stanica i infiltracije plućnog intersticija s reaktivnim limfocitima B i T, plazma-stanicama i histiocitima. (2, 3)

Krioglobulini su imunoglobulini koji se talože in vitro, na temperaturama nižima od normalne tjelesne temperature (37 °C) i otapaju se ponovnim zagrijavanjem. (4) Krioglobulinemija može biti povezana s krioglobulinemijskim vaskulitisom, no čini se da je krioglobulinemija bez klinički vidljivih znakova vaskulitisa još učestalija. Dokumentirana je u različitim sistemskim autoimunim bolestima, najčešće u bolesnika s primarnim Sjögrenovim sindromom, u sklopu kojega krioglobulinemija ima i prognostičke implikacije. (5)

U nastavku predstavljamo slučaj bolesnika s limfocitnim intersticijskim pneumonitisom (LIP) kod kojeg su prisutnost krioglobulinemije i snižene razine komplementa u serumu poslužile kao pomoć za postavljanje dijagnoze Sjögrenovog sindroma.

PRIKAZ SLUČAJA

61-godišnji muškarac bez povijesti pušenja prvi put je došao u hitnu službu sa simptomima koji su uključivali suhi kašalj, dispneju pri naporu, vrućicu koja je trajala dva tjedna, kao i preznojavanje.

U njegovoj povijesti bolesti bila je navedena epizoda „alergije" na Sunčevu svjetlost koja se dogodila u mladosti te spontana ablacija mrežnice lijevog oka bez jasnog uzroka. Tijekom prijašnjih desetljeća bolesnik je doživio nekoliko epizoda tromboflebitisa proširenih vena u nogama.

U razdoblju tijekom dva tjedna prije prijema u bolnicu imao je simptome vrućice do 39 ^{0}C. Također je prijavio dispneju pri naporu, kao i povremeni produk-

Table 1. Laboratory workup at first hospital admission
Tablica 1. Laboratorijska obrada prilikom prvog prijma u bolnicu

Laboratory finding / Laboratorijski nalaz	Value (NR) / Vrijednost (NR)
Erythrocyte sedimentation rate / Sedimentacije eritrocita (mm/h)	90 (3-23)
C-reactive protein / C-reaktivni protein (mg/L)	57 (0-5)
Hb (g/L)	122 (128-175)
MCV (fL)	80.0 (83.0-97.2)
WBC / Leukociti (x10e9/L)	3.8 (3.4-9.7)
Lymphocytes / Limfociti (x10e9/L)	1.26 (1.19-3.35)
Neutrophils / Neutrofili (x10e9/L)	2.09 (2.06-6.49)
PLT / Trombociti (x10e9/L)	225 (158-424)
Ferritin / Feritin (ug/L)	423.1 (30.0-400.0)
Fe/UIBC (umol/L / umol/L)	6/36 (11-32/25-54)
C3 (g/L)	0.86 (0.90-1.80)
C4 (g/L)	0.07 (NR 0.10-0.40)
RF (IU/ml)	39.2 (NR 0-14)
Cryoglobulins / Krioglobulini	Type / Tip III
Cryoprecipitate / Krioprecipitat (mg/L)	132 (0-60)

NR – normal range / normalni raspon; RF – rheumatoid factor / reumatoidni faktor; WBC – white blood count / leukociti; PLT - platelets / trombociti ; MCV – mean corpuscular volume / prosječni obujam eritrocita; C3 – complement component C3 / C3 komponenta komplementa; C4 – complement component C4 / C4 komponenta komplementa.

medicine setting revealed a suspected left-sided perichilar infiltrate.

Given that the symptoms did not improve, he was admitted for further inpatient workup due to suspected pneumonia. His physical findings revealed minimal bilateral lung crackles. He complained of shortness of breath on minimal exertion. Physical examination revealed a small palpable, soft, mobile and painless lymph node (1 cm in diameter) in the left axilla, as well as a mild systolic heart murmur over the mitral valve. There was no enlargement of the salivary glands. His abdomen and extremities were unremarkable, as were his musculoskeletal and skin examination results.

Laboratory workup revealed increased acute phase reactants, mild anemia of chronic disease, slight leukopenia and decreased C3 and C4 complement levels. His serum protein electrophoresis revealed polyclonal hypergammaglobulinemia (21.2 g/L) predominantly due to increased IgG (24.16 g/L, NR 7-16) and IgA (4.39 g/L, NR 0.7-4). Interestingly, the presence of type III cryoglobulinemia was detected. (Table 1)

His chest computed tomography (CT) revealed bilateral thin-walled cystic lesions, interlobular septal thickening and several nodular consolidations with

tivni kašalj s bijelim iskašljajem. Nije primijećeno poboljšanje unatoč trodnevnoj terapiji azitromicinom. Radiogram pluća napravljen u domu zdravlja pokazao je sumnju na postojanje lijevostranog plućnog infiltrata.

S obzirom na to da se simptomi nisu popravili, bolesnik je primljen na daljnju bolničku obradu zbog sumnje na upalu pluća. U fizikalnom pregledu isticale su se bilateralne krepitacije nad plućima. Žalio se na nedostatak zraka pri minimalnom naporu. U statusu je dodatno uočen je mali palpabilan, mekan, pokretljiv i bezbolan limfni čvor (promjera 1 cm) u lijevoj aksili, te blagi sistolički šum na srcu nad mitralnom valvulom.

Nisu uočeni znakovi povećanja žlijezda slinovnica. Bolesnikov abdomen i ekstremiteti bili su bez osobitosti, a nikakve promjene nisu otkrivene ni tijekom pregleda mišićno-koštanog sustava i kože.

Laboratorijska obrada otkrila je povišene vrijednosti reaktanata akutne faze, blagu anemiju kronične bolesti, blagu leukopeniju i snižene razine komplementa C3 i C4. Elektroforeza serumskih proteina otkrila je poliklonsku hipergamaglobulinemiju (21,2 g/L) uglavnom zbog povišenih IgG (24,16 g/L, NR 7-16) i IgA (4,39 g/L, NR 0,7-4) imunoglobulina. Za istaknuti je da je otkrivena i prisutnost krioglobulinemije tipa III. (Tablica 1)

Kompjuterizirana tomografija (CT) toraksa otkrila je bilateralne cistične lezije tankih stijenki, zadebljanje interlobularnog septuma i nekoliko nodularnih konsolidata sa zamućenjima tipa zrnatog stakla, što odgovara kliničkoj slici limfocitnog intersticijskog pneumonitisa (LIP). Nisu otkriveni povećani limfni čvorovi. (Slika 1)

Rezultati serološkog testiranja na HIV, Epstein-Barrov virus, citomegalovirus, kao i hepatitis B i hepatitis C bili su negativni. Hemokulture su također bile negativne, dok je iskašljaj bio pozitivan na bakterije *Pseudomonas monteilii, Streptococcus (viridans)* i *Candida albicans* (105 CFU/ml).

Naknadnom nadopunom anamneze otkriven je subjektivan osjećaj suhoće usne šupljine kod bolesnika, ali ne i suhoće očiju. Bolesnik se također prisjetio epizoda spontanog bolnog povećavanja parotidnih žlijezda tijekom prethodnih desetljeća, kao i činjenice da je u više navrata tijekom prethodnih godina u njegovim laboratorijskim nalazima bilo navedeno neobjašnjivo povećanje sedimentacije eritrocita, kao i blago smanjen broj leukocita. Nije imao drugih znakova ili simptoma bolesti vezivnog tkiva. Do prijema u bolnicu nije primao kroničnu terapiju. Držao se bezglutenske prehrane jer mu je sin bolovao od celijakije.

Daljnjom obradom otkriveno je smanjeno vrijeme pucanja suznog filma (4/5 sekundi) i pozitivan Schirmerov test (3/5 mm). Mjerenje protoka sline otkrilo je smanjenu proizvodnju sline (0,0 ml / 5 minuta; 0,5 ml / 15 minuta).

ground-glass opacities, corresponding to lymphocytic interstitial pneumonitis (LIP). No enlarged lymph nodes were revealed. (Figure 1)

Viral antibody tests for HIV, Epstein-Barr virus, cytomegalovirus, as well as hepatitis B and C came out negative. Blood cultures came out negative as well, while his sputum tested positive (10^5 CFU/ml) for *Pseudomonas monteilii*, *Streptococcus species (viridans)* and *Candida albicans*.

Updated medical history revealed subjective mouth dryness, which was present for several years, but the patient reported no symptoms of ocular dryness. He also recalled episodes of spontaneous painful enlargement of each of his parotid glands over the preceding decades, as well as the fact that, on several occasions over the preceding years, his laboratory findings revealed an unexplained increase in his erythrocyte sedimentation rates as well as slightly decreased white blood cell counts. He had no other signs or symptoms of connective tissue disease. Up until admission, he received no chronic therapy. He followed a gluten-free diet because his son suffered from coeliac disease.

Further workup revealed a decreased tear break-up time (4/5 seconds), and a positive Schirmer's test (3/5 mm). A salivary flow test revealed a decreased saliva production (0.0 ml/5 minutes; 0.5 ml/15 minutes).

He was started on moxifloxacin, leading to a decline in his fever and CRP levels. In addition to a 10-day course of moxifloxacin, he was also treated with fluconazole over the course of 10 days. He was scheduled for elective pulmonary workup 14 days after completing his antibiotic treatment.

Lung function tests came out unremarkable including his forced expiratory volume (FEV1) of 108%, forced vital capacity (FVC) of 110%, FEV1/FVC of 0.77. His CO diffusing capacity (DLCO) was 69% and his transfer coefficient (KCO) was 70%. Bronchoalveolar lavage (BAL) revealed a CD4/CD8 ratio of 2.2, while cytology revealed a lymphocytic type of BAL with a slightly elevated neutrophil count (numerous lymphocytes (21.5%), alveolar macrophages (72.5%) and neutrophils (6%)). The angiotensin-converting enzyme level in the serum was unremarkable and his bronchoalveolar fluid tested negative for *Pneumocystis jirovecii*. Given the diagnosis of LIP, he was started on prednisone at a dose of 30 mg qd.

Two weeks after, at the patient's follow-up visit at the Division of Rheumatology, the patient's antinuclear antibodies came out positive (indirect immunofluorescence titer of 1:6400), with a positive Luminex test for dsDNA (807 IU/L, NR 0-40), histone (180 IU/L, NR 0-40), SS-A 52 (158 IU/L, NR 0-40), SS-A 60 (122 IU/L, NR 0-40), SS-B (64 IU/L, NR 0-40), U1-RNP (51 IU/L, 0-40) and ribosomal (77 IU/L, NR 0-40) antibodies. Anti-leukocyte antibodies also came out posi-

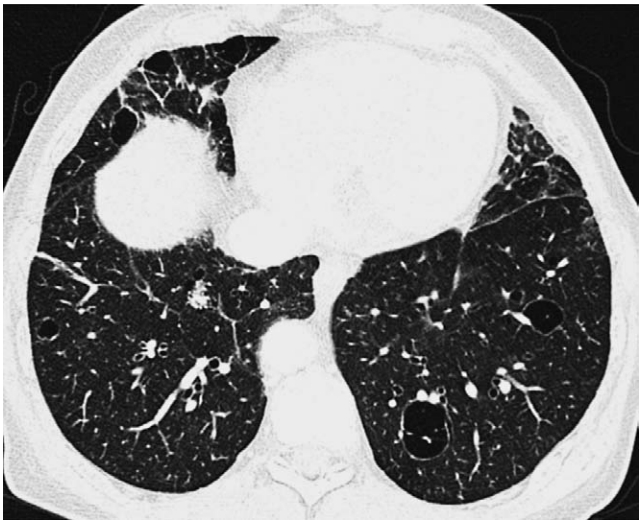

Figure 1. Chest CT in a patient with Sjögren's syndrome revealing cysts consistent with lymphocyte interstitial pneumonitis

Slika 1. CT toraksa u bolesnika sa Sjögrenovim sindromom pokazuje ciste sukladne dijagnozi limfocitnog intersticijskog pneumonitisa

Započeto je liječenje moksifloksacinom, što je dovelo do povlačenja vrućice i razine C-reaktivnog proteina (CRP). Uz 10-dnevnu terapiju moksifloksacinom, bolesnik je 10 dana primao i terapiju flukonazolom. Imao je zakazan termin za elektivnu pulmološku obradu 14 dana nakon završetka terapije antibioticima.

Testovi plućne funkcije bili su bez osobitosti, uključujući forsirani ekspiratorni volumen u prvoj sekundi (FEV1) od 108 %, forsirani vitalni kapacitet (FVC) od 110 %, FEV1/FVC 0,77. Bolesnikov difuzijski kapacitet pluća za ugljični monoksid (DLCO) iznosio je 69 %, a njegov transfer koeficijent (KCO) iznosio je 70 %. U bronhoalveolarnom lavatu (BAL) utvrđen je omjer CD4/CD8 od 2,2, dok je citološkim pregledom utvrđen limfocitni tip BAL-a s blago povišenim brojem neutrofila (brojni limfociti (21,5 %), alveolarni makrofagi (72,5 %) i neutrofili (6 %)). Razina angiotenzin-konvertirajućeg enzima u serumu bila je bez osobitosti, a bolesnikova bronhoalveolarna tekućina bila je negativna na bakteriju *Pneumocystis jirovecii*. S obzirom na dijagnozu LIP-a, počeo je uzimati terapiju prednizonom od 30 mg dnevno.

Dva tjedna nakon, na kontrolnom reumatološkom pregledu, bolesnikova antinuklearna protutijela pristigla su pozitivna (titar indirektne imunofluorescencije 1:6400), s pozitivnim Luminex testom na dsDNA antitijela (807 IU/L, NR 0-40), histonska (180 IU/L, NR 0-40), SS-A 52 (158 IU/L, NR 0-40), SS-A 60 (122 IU/L, NR 0-40), SS-B (64 IU/L, NR 0-40), U1-RNP (51 IU/L, 0-40) i anti-ribosomska (77 IU/L, NR 0-40) antitijela. Anti-leukocitna antitijela su također bila pozitivna. Anti-fosfolipidna antitijela bila su

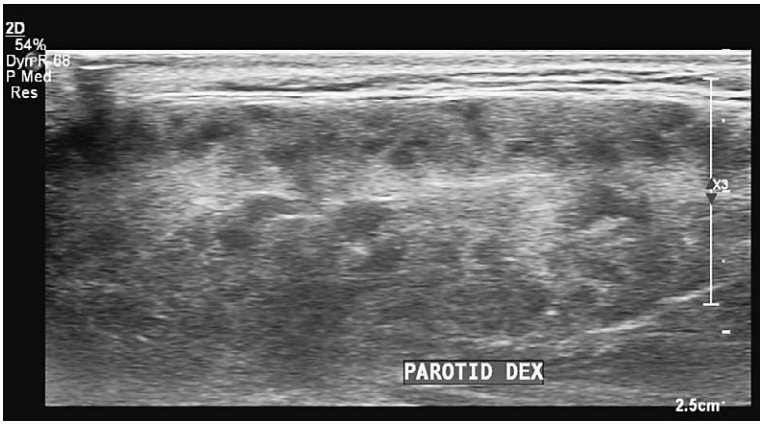

Figure 2. Parotid gland ultrasound revealing hypoechogenic focal changes as well as hyperechogenic areas consistent with the diagnosis of Sjögren's syndrome.

Slika 2. Ultrazvuk parotidnih žlijezda pokazuje hipoehogene fokalne promjene te hiperehogena područja sukladna dijagnozi Sjögrenovog sindroma.

tive. Anti-phospholipid antibodies came out negative, while IgG4 antibodies were unremarkable. The biopsy of the lower-lip minor salivary glands revealed several lymphocytic foci. The patient was finally diagnosed with Sjögren's syndrome with LIP as the presenting symptom.

Three months thereafter, the patient was feeling well on prednisone at a dose of 15 mg qd, and he reported less episodes of dyspnea on exertion – he was able to hike and to be physically active. His ESR was 16 mm/h, CRP was undetectably low, whilst his gamma globulin level was 15.6 g/L. Hydroxychloroquine was introduced at a dose of 200 mg qd. He was feeling well for the next several months, allowing a prednisone taper to a dose of 10 mg qd. However, at a follow-up visit one year following his first admission, he complained again of increased dyspnea and diaphoresis. His salivary ultrasound revealed a diffuse heterogeneous pattern with hypoechogenic foci and fibrotic areas. (Figure 2) His ESR and CRP levels were unremarkable, however his previously normal complement levels became slightly decreased again, with C3 values of 0.7 g/L and C4 values of 0.09 g/L. Once again, his SS-A 52 148 IU/L, SS-A 60 99 IU/L, and SS-B 91 IU/L values were positive, however, dsDNA became only slightly detectable, with a value of 40 IU/L. All of the aforementioned symptoms, in addition to a slight decline in the patient's complement levels, were crucial for the decision to introduce azathioprine at a dose of 2 mg/kg body weight (150 mg daily divided into two doses). This led to the alleviation of his dyspnea with persistently normal levels of ESR and CRP and stabilization of lung function tests over the next months. Two years after his first admission, his lung function tests came out unremarkable: FVC of 101%, FEV1 of 102%, FEV1/FVC of 0.78; DLCO of 88% and KCO of 84%. A follow-up chest CT revealed no changes in the bilateral cysts with a diameter of up to 3 cm. This allowed a further prednisone taper to a dose of 5 mg qd. Over the further follow-up during the course of 4.5 years in total, the patient was stable on the same treatment regimen. His SS-A, SS-B negativna, a IgG4 antitijela bila su bez osobitosti. Biopsija malih žlijezda slinovnica donje usne otkrila je nekoliko limfocitnih žarišta. Bolesniku je konačno dijagnosticiran Sjögrenov sindrom s LIP-om kao glavnim očitovanjem.

Tri mjeseca nakon toga, bolesnik se osjećao dobro uz terapiju prednizonom od 15 mg dnevno, a prijavio je i manju dispneju pri naporu: mogao je planinariti i biti fizički aktivan. Njegova sedimentacija eritrocita (SE) bila je 16 mm/h, CRP je bio nemjerljivo nizak, a razina gama-globulina bila je 15,6 g/L. Uvedena je terapija hidroksiklorokinom u dozi od 200 mg dnevno. Bolesnik se osjećao dobro sljedećih nekoliko mjeseci, što je omogućilo smanjenje doze prednizona na 10 mg dnevno. Međutim, prilikom kontrole godinu dana nakon prvog prijema u bolnicu, ponovno se žalio na pojačanu dispneju i preznojavanje. Ultrazvuk žlijezda slinovnica otkrio je difuzni heterogeni uzorak s hipoehogenim žarištima i područjima fibroze. (Slika 2) Njegove razine SE-a i CRP-a bile su bez osobitosti, no njegove prethodno normalne razine komplementa ponovno su se malo smanjile: C3 je iznosio 0,7 g/L, a C4 je iznosio 0,09 g/L. Bolesnik je opet imao pozitivna SS-A 52 antitijela u vrijednosti od 148 IU/L, SS-A 60 antitijela u vrijednosti od 99 IU/L i SS-B antitijela u vrijednosti od 91 IU/L, no dsDNA je postala tek neznatno detektabilna, u vrijednosti od 40 IU/L. Njegove tegobe i blagi pad razine komplementa doveli su do odluke o uvođenju terapije azatioprinom u dozi od 2 mg/kg tjelesne težine (150 mg dnevno podijeljeno u dvije doze). To je zauzvrat dovelo do ublažavanja dispneje s postojano normalnim razinama SE-a i CRP-a i stabilizacije rezultata testova plućne funkcije tijekom sljedećih nekoliko mjeseci. Testovi plućne funkcije dvije godine nakon prvog prijema u bolnicu bili su bez osobitosti: FVC je bio 101 %, FEV1 je bio 102 %, FEV1/FVC 0,78, DLCO je bio 88 %, a KCO je bio 84 %. Na kontrolnom CT-u toraksa nije bilo promjena na bilateralnim cistama promjera do 3 cm. To je omogućilo daljnje smanjenje terapije prednizonom na dozu od 5 mg dnevno. Tijekom daljnjeg razdoblja praćenja koje je ukupno trajalo 4,5 godi-

and SS-B were persistently positive, while his ds-DNA antibodies became negative.

DISCUSSION

The association between LIP and Sjögren's syndrome was first elaborated in 1973. (6) Although LIP has been described as a feature specific to Sjögren's syndrome, it is not its most common pulmonary manifestation. According to a systematic review of 273 studies on systemic features associated with primary Sjögren's syndrome, pulmonary involvement has been described in 16% of patients: Moreover, 45% of patients had nonspecific interstitial pneumonia (NSIP), making it the most frequent pulmonary feature, whereas 15% of patients exhibited symptoms of LIP. (7)

LIP is usually linked to an underlying systemic disease, mostly Sjögren's syndrome (53.3%). (8) Besides Sjögren's syndrome, it has less frequently been reported in cases of other autoimmune disorders, such as systemic lupus erythematosus (SLE) (8, 9, 10), rheumatoid arthritis (RA) (8, 11), polymyositis (PM) (8), and Hashimoto's disease (11). LIP has also been associated with immunodeficiencies (8) and chronic viral infections, including human immunodeficiency virus (HIV) infection (12) and Epstein-Barr virus (EBV) infection. (9) Despite the fact that the patient initially had anti-dsDNA antibodies, we believe that the patient had primary Sjögren's syndrome rather than SLE (and secondary Sjögren's syndrome), due to the lack of other clinical and laboratory items typically seen in the context of SLE (except for leukopenia). Moreover, LIP seems to be more strongly associated with Sjögren's syndrome than with SLE.

The most common presenting symptoms of LIP include cough and dyspnea on exertion, sometimes with pleuritic chest pain and systemic symptoms such as fever, fatigue, arthralgias, and weight loss. Inspiratory crackles can be heard on auscultation. (8, 13) Pulmonary function tests usually reveal a restrictive pattern with decreased diffusing capacity for carbon monoxide. (13, 14) It can be expected that, in the case of predominantly cystic disease, a normal FVC and FEV1 with a decreased DLCO may be observed, similar to emphysema. HRCT findings associated with LIP include ground-glass opacities, poorly defined centrilobular and subpleural nodules, interlobular septal thickening, and enlargement of the mediastinal lymph nodes. Thin-walled cysts are characteristically seen in patients with LIP associated with Sjögren's syndrome. (15-18) CT findings that may help differentiate LIP from lymphoma include cysts, which are more common in patients with LIP, while large nodules (11 – 30 mm in diameter) and pleural effusions have been more commonly described in patients with lymphoma. (19) Bronchoalveolar lavage (BAL) is non-specific and usually shows in-

ne, bolesnikovo stanje je bilo stabilno uz isti režim terapije. Njegova SS-A i SS-B antitijela bila su stalno pozitivna, dok su njegova ds-DNA antitijela postala negativna.

RASPRAVA

Povezanost između LIP-a i Sjögrenovog sindroma prvi je put utvrđena 1973. (6) Iako je LIP opisan kao manifestacija specifična za Sjögrenov sindrom, to nije njegova najčešća plućna manifestacija. Prema sustavnom pregledu literature koji je uključivao 273 studije o sistemskim manifestacijama povezanim s primarnim Sjögrenovim sindromom, plućna zahvaćenost opisana je u 16 % bolesnika: 45 % bolesnika imalo je nespecifičnu intersticijsku pneumoniju (NSIP), što je čini najčešćom plućnom manifestacijom, dok je 15 % bolesnika imalo LIP. (7)

LIP je obično povezan s osnovnom sistemskom bolešću, uglavnom Sjögrenovim sindromom (53,3 % slučajeva). (8) Osim Sjögrenovog sindroma, LIP se rjeđe prijavljuje u slučajevima drugih autoimunih poremećaja, kao što su sistemski eritemski lupus (SLE) (8, 9, 10), reumatoidni artritis (RA) (8, 11), polimiozitis (PM) (8) i Hashimotov tireoiditis (11). LIP je također povezan s imunodeficijencijama (8) i kroničnim virusnim infekcijama, uključujući infekciju virusom humane imunodeficijencije (HIV) (12) i infekciju Epstein-Barrovim virusom (EBV). (9) Unatoč činjenici da je bolesnik u početku imao anti-ds-DNA antitijela, vjerujemo da je imao primarni Sjögrenov sindrom, a ne SLE (i sekundarni Sjögrenov sindrom), zbog nedostatka drugih kliničkih i laboratorijskih pokazatelja koji su tipično vidljivi u kontekstu SLE-a (osim leukopenije). Štoviše, čini se da je LIP jače povezan sa Sjögrenovim sindromom nego sa SLE-om.

Najčešći simptomi LIP-a uključuju kašalj i dispneju pri naporu, ponekad s pleuritičnom boli u prsima i sustavnim simptomima kao što su vrućica, umor, artralgija i gubitak težine. Auskultacijom pluća mogu se čuti krepitacije. (8, 13) Testovi za ispitivanje plućne funkcije obično otkrivaju restriktivni obrazac sa sniženim difuzijskim kapacitetom pluća za ugljični monoksid (DLCO). (13, 14) Moguće je da se kod pretežno cistične bolesti uoče normalni nalazi FVC i FEV1 sa smanjenim DLCO-om, kao što je slučaj s emfizemom pluća. HRCT nalazi povezani s LIP-om uključuju zamućenja tipa zrnatog stakla, slabo definirane centrilobularne i subpleuralne nodule, zadebljanje interlobularnog septuma i povećanje medijastinalnih limfnih čvorova. Ciste tankih stijenki karakteristične su za bolesnika s LIP-om povezanim sa Sjögrenovim sindromom. (15-18) Nalazi CT-a koji mogu pomoći u razlikovanju LIP-a od limfoma uključuju ciste, koje su češće u bolesnika s LIP-om, dok su veliki noduli (promjera od 11 do 30 mm) i pleuralni izljevi češće opisani

creased white blood cell counts and lymphocytosis with a normal CD4/CD8 ratio. (8) In selected cases, BAL may be used to detect lymphocyte clonality suggestive of lymphoma. In rare cases, surgical lung biopsy may be required to confirm the diagnosis.

Our decision to assess the patient for the presence of cryoglobulinemia despite the absence of overt small vessel vasculitis was driven by the presence of LIP in a patient with decreased complement levels and high suspicion of Sjögren's syndrome, that is, a case in which cryoglobulinemia (with or without vasculitis) has significant prognostic implications. Such a diagnostic approach may be of use, especially in the setting where results of ANA testing may not be promptly available. Cryoglobulinemia has been described in 16 – 47% of patients with Sjögren's syndrome: type 2 has been more commonly associated with Sjögren's syndrome than type 3. (20) Patients with cryoglobulinemia associated with Sjögren's syndrome exhibit higher RF values, lower values of C4 in the serum, as well as Ro (SS-A) antibody positivity more commonly compared to their cryoglobulin-negative counterparts. Extraglandular manifestations are more commonly observed in patients with cryoglobulinemia (in 82% of patients with cryoglobulinemia compared to 47% of patients without cryoglobulinemia). (21) The presence of cryoglobulins at diagnosis of Sjögren's syndrome has been associated with a higher mortality rate (HR=5,09, p=0,001). (22) Moreover, there is a higher risk of developing B-cell lymphoma, usually MALT lymphoma, in patients with Sjögren's syndrome with cryoglobulinemia (HR=2,56). The risk is even higher in patients with cryoglobulinemic vasculitis (HR=7,47). The time to diagnosis of lymphoma is also shorter in patients with cryoglobulinemia. (23, 24)

The exact association of LIP and cryoglobulinemia is not clear. Our search of the Pubmed database, which was conducted on May 30, 2024, revealed only 11 publications, and it involved the search query: "lymphocytic interstitial pneumonia" AND "cryoglobulinemia". Interestingly enough, only one report was noted in the context of Sjögren's syndrome. In their work, Abou Ziki et al. described a 78-year-old patient with LIP, pleural effusions and cryoglobulinemia with vasculitis. (25) The only additional case of LIP and cryoglobulinemic vasculitis was described in the context of HIV infection. (26) It is interesting to note that, despite the fact that hepatitis C virus (HCV) infection is a frequent cause of cryoglobulinemia worldwide, our literature search revealed no description of LIP in an HCV patient.

Although cryoglobulinemic vasculitis can affect the lungs irrespective of the context of Sjögren's syndrome, it is highly unlikely that pulmonary vasculitis will be the sole manifestation of cryoglobulinemic vasculitis in a given patient. Furthermore, LIP has not been de-

u bolesnika s limfomom. (19) Nalaz bronhoalveolarnog lavata (BAL) je nespecifičan i obično pokazuje povećan broj leukocita i limfocitozu s normalnim omjerom CD4/CD8. (8) U određenim slučajevima, BAL se može upotrebljavati za otkrivanje klonalnosti limfocita koja ukazuje na limfom. U rijetkim slučajevima može biti potrebna kirurška biopsija pluća za potvrdu dijagnoze.

Naša odluka da utvrdimo prisutnost krioglobulinemije u bolesnika unatoč odsutnosti vidljivih znakova vaskulitisa malih krvnih žila bila je potaknuta prisutnošću LIP-a u bolesnika sa sniženim razinama komplementa i velikom sumnjom na Sjögrenov sindrom, u sklopu kojega krioglobulinemija (sa ili bez vaskulitisa) ima značajne prognostičke implikacije. Takav dijagnostički pristup može biti iznimno koristan, posebno u slučajevima u kojima rezultati ANA testova možda neće biti odmah dostupni. Krioglobulinemija je opisana u 16 – 47 % slučajeva bolesnika sa Sjögrenovim sindromom: tip 2 je češće povezan sa Sjögrenovim sindromom nego tip 3. (20) Bolesnici s krioglobulinemijom povezanom sa Sjögrenovim sindromom imaju više vrijednosti RF-a, niže vrijednosti C4 u serumu, kao i pozitivna Ro (SS-A) antitijela. Ekstraglandularne manifestacije češće se opažaju u bolesnika s krioglobulinemijom (u 82 % bolesnika s krioglobulinemijom u usporedbi s 47 % bolesnika bez krioglobulinemije). (21) Prisutnost krioglobulina kod dijagnoze Sjögrenovog sindroma povezana je s višom stopom smrtnosti (HR=5,09, p=0,001). (22) Štoviše, postoji veći rizik od razvoja B-staničnog limfoma, obično MALT limfoma, u bolesnika sa Sjögrenovim sindromom s krioglobulinemijom (HR=2,56). Rizik je još veći u bolesnika s krioglobulinemijskim vaskulitisom (HR=7,47). Vrijeme do dijagnoze limfoma također je kraće u bolesnika s krioglobulinemijom. (23, 24)

Točna povezanost između LIP-a i krioglobulinemije još uvijek nije jasna. Pretraživanjem baze podataka Pubmed 30. svibnja 2024. uspjeli smo otkriti samo 11 publikacija za termine u nastavku: „limfocitna intersticijska pneumonija" i „krioglobulinemija". Zanimljivo je da je naveden samo jedan rad u kontekstu Sjögrenovog sindroma. U radu čiji su autori Abou Ziki i sur. opisan je slučaj 78-godišnjeg bolesnika s LIP-om, pleuralnim izljevima i krioglobulinemijom s vaskulitisom. (25) Jedini dodatni slučaj LIP-a i krioglobulinemijskog vaskulitisa opisan je u kontekstu HIV infekcije. (26) Također je zanimljivo da, unatoč činjenici da je infekcija virusom hepatitisa C (HCV) čest uzrok krioglobulinemije u cijelom svijetu, naše pretraživanje literature nije dovelo do opisa LIP-a kod bolesnika s HCV-om.

Iako krioglobulinemijski vaskulitis može zahvatiti pluća bez obzira na kontekst Sjögrenovog sindroma, mala je vjerojatnost da će plućni vaskulitis biti jedina manifestacija krioglobulinemijskog vaskulitisa u odre-

scribed as a feature of cryoglobulinemic vasculitis. Our opinion is that the association of LIP and cryoglobulinemic vasculitis is probably indirect, with cryoglobulinemia serving as a predictor of extraglandular disease including LIP.

Despite the lack of clinical trial data focusing on the treatment of LIP, a relatively comprehensive therapeutic approach to the treatment of ILD in patients with Sjögren's syndrome has been provided within the EULAR recommendations for the treatment of Sjögren's syndrome and the American College of Rheumatology (ACR) guidelines for the treatment of ILD in patients with rheumatic diseases. (27, 28)

In both sets of recommendations, glucocorticoids represent the first line of treatment. In the EULAR recommendations, oral immunosuppressant drugs are positioned as the second line of treatment, with azathioprine being the most frequently used drug. Mycophenolate mofetil (MMF) and cyclosporine A have been mentioned as other options, although some authorities might have a preference towards MMF. Rituximab and cyclophosphamide can be considered as rescue options, yet rituximab may be preferred especially in the context of cryoglobulinemic vasculitis. (27) On the other hand, the recently published ACR guidelines conditionally recommended MMF over the other listed immunosuppressant options for the treatment of ILD in Sjögren's syndrome, which include azathioprine, rituximab and cyclophosphamide. They also included MMF as the first line of treatment, indicating that glucocorticoids may be used as a short-term option along with the immunosuppressive agent. Unlike azathioprine, MMF remains a therapeutic option according to ACR even in cases of progressive ILD despite the failure of the initial immunosuppressant. (28) It should be noted that none of these two recommendations are specific for LIP, although the EULAR recommendations specified that glucocorticoids as the first treatment line may be especially recommended for LIP and organizing pneumonia, and less so for non-specific interstitial pneumonia (NSIP) and usual interstitial pneumonia (UIP). Unlike the EULAR recommendations, the ACR guidelines did not recognize glucocorticoid monotherapy as the first line of treatment. (27,28)

Our decision to start glucocorticoid monotherapy was based on a beneficial treatment effect at disease onset and was backed by the EULAR guidelines. Azathioprine was added for the purpose of disease control and glucocorticoid sparing. The reason for the difference between the preferred immunosuppressive agent between the EULAR and ACR recommendations/guidelines (azathioprine vs. MMF) is not clear, especially given the lack of comparative clinical trials. A possible preference towards MMF in the ACR guide-

đenog bolesnika. Nadalje, LIP nije opisan kao manifestacija krioglobulinemijskog vaskulitisa. Naše je mišljenje da je povezanost LIP-a i krioglobulinemijskog vaskulitisa vjerojatno neizravna, pri čemu krioglobulinemija služi kao prediktor ekstraglandularne manifestacije, uključujući LIP.

Unatoč nedostatku podataka u vezi s kliničkim ispitivanjima usmjerenim na liječenje LIP-a, relativno sveobuhvatan terapijski pristup liječenju intersticijske bolesti pluća (ILD) u bolesnika sa Sjögrenovim sindromom naveden je u okviru EULAR-ovih preporuka za liječenje Sjögrenovog sindroma i smjernica reumatološkog društva *American College of Rheumatology* (ACR) za liječenje ILD-a u bolesnika s reumatskim bolestima. (27, 28)

U oba navedena slučaja glukokortikoidi predstavljaju prvu liniju liječenja. U EULAR-ovim preporukama, oralni imunosupresivi navedeni su kao druga linija liječenja, a najčešće se koristi azatioprin. Mikofenolat mofetil (MMF) i ciklosporin A spomenuti su kao druge mogućnosti, iako neki eksperti daju prednost MMF-u. Rituksimab i ciklofosfamid mogu se smatrati opcijama spašavanja, no rituksimab bi mogao biti bolji izbor, posebno u kontekstu terapije za krioglobulinemijski vaskulitis. (27) S druge strane, nedavno objavljene ACR-ove smjernice uvjetno preporučuju MMF u odnosu na ostale navedene opcije imunosupresiva za liječenje ILD-a u Sjögrenovom sindromu, što uključuje azatioprin, rituksimab i ciklofosfamid. Te smjernice također navode MMF kao prvu liniju liječenja, što ukazuje na to da se glukokortikoidi mogu upotrebljavati kao kratkoročna opcija zajedno s imunosupresivima. Za razliku od azatioprina, prema ACR-u MMF ostaje terapijska opcija čak i u slučajevima progresivne ILD, unatoč neuspješnoj primjeni početnog imunosupresiva. (28) Također je bitno napomenuti da niti jedne od ovih dviju preporuka/smjernica nisu specifične za LIP, iako EULAR-ove preporuke navode da se glukokortikoidi kao prva linija liječenja mogu posebno preporučiti za LIP i organiziranu pneumoniju, no da su manje preporučljive za nespecifičnu intersticijsku pneumoniju (NSIP) i običnu intersticijsku pneumoniju (UIP). Za razliku od EULAR-ovih preporuka, ACR-ove smjernice nisu priznale monoterapiju glukokortikoidima kao prvu liniju liječenja. (27,28)

Naša odluka da počnemo s primjenom monoterapije glukokortikoidima temeljila se na povoljnom učinku liječenja na početku bolesti i imala je uporište u EULAR-ovim preporukama. Azatioprin je uveden u terapiju u svrhu kontrole bolesti i snižavanja doze glukokortikoida. Razlog za razliku između preferiranog imunosupresiva u EULAR-ovim i ACR-ovim preporukama/smjernicama (azatioprin u odnosu na MMF) nije jasan, osobito s obzirom na nedostatak komparativnih kliničkih ispitivanja. Moguća sklonost prema MMF-u u ACR-ovim smjernicama može biti

lines may be due to caution, which was somewhat erroneously raised by the 2012 trial on patients with idiopathic pulmonary fibrosis (IPF) in which the mortality of patients treated with combined glucocorticoids and azathioprine exceeded the mortality of the control group. (29) Extrapolation of the result of this trial to CTD-ILD population is not biologically plausible due to its pathogenetic differences from IPF. Furthermore, in the original IPF trial, it was not possible to identify whether excess mortality was driven by glucocorticoids or azathioprine.

CONCLUSION

Cryoglobulinemia can be perceived as a feature of excessive lymphocyte activation in Sjögren's syndrome, associated with a higher risk of extraglandular disease and lymphoma (30). Except for the general association of cryoglobulinemia and extraglandular disease, LIP and cryoglobulinemia do not seem to be directly causally associated. In patients presenting with a potential extraglandular manifestation of non-recognized Sjögren's syndrome, cryoglobulinemia may serve as a clue that is crucial for disease diagnosis.

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posljedica opreza koji je uvjetovan istraživanjem koje je provedeno 2012. na bolesnicima s idiopatskom plućnom fibrozom (IPF) u kojem je smrtnost bolesnika liječenih kombiniranim glukokortikoidima i azatioprinom premašila smrtnost kontrolne skupine. (29) Ekstrapolacija rezultata ovog ispitivanja s obzirom na populaciju bolesnika s bolesti vezivnog tkiva (CTD) i intersticijske bolesti pluća (ILD) nije biološki prihvatljiva zbog patogenetskih razlika u odnosu na idiopatsku plućnu fibrozu (IPF). Nadalje, u izvornom ispitivanju IPF-a nije bilo moguće utvrditi je li povećana smrtnost uzrokovana glukokortikoidima ili azatioprinom.

ZAKLJUČAK

Krioglobulinemija se može definirati kao manifestacija pretjerane aktivacije limfocita u sklopu Sjögrenovog sindroma, povezana s većim rizikom od ekstraglandularnih manifestacija i limfoma (30). Osim opće povezanosti krioglobulinemije i ekstraglandularnih manifestacija, čini se da LIP i krioglobulinemija nisu izravno uzročno povezane bolesti. U bolesnika s potencijalnom ekstraglandularnom manifestacijom neprepoznatog Sjögrenovog sindroma, krioglobulinemija može poslužiti kao pomoć u postavljanju dijagnoze.

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