Reumatizam 2021;68(2):103–108
https://doi.org/10.33004/reumatizam-68-2-5

CASE REPORT PRIKAZ BOLESNIKA

THERAPEUTIC APPROACH TO A PATIENT WITH ANTISYNTHETASE SYNDROME – A CASE REPORT

TERAPIJSKI PRISTUP BOLESNIKU S ANTISINTETAZNIM SINDROMOM – PRIKAZ BOLESNIKA

Dora Uršić[1,2], Ivana Kovačević[1], Željka Kardum[1,2], Kristina Kovačević Stranski[1], Ana Marija Masle[1,2], Ana Kovač[1], Mirna Lucić[1], Višnja Prus[1,2], Jasminka Milas Ahić[1,2]

[1] Division of Rheumatology, Clinical Immunology and Allergology, Department of Internal Medicine, University Hospital Centre Osijek, Croatia / Zavod za reumatologiju, kliničku imunologiju i alergologiju, Klinika za unutarnje bolesti, Klinički bolnički centar Osijek, Hrvatska
[2] Faculty of Medicine Osijek, Josip Juraj Strossmayer University of Osijek, Osijek, Croatia / Medicinski fakultet Sveučilišta Josipa Jurja Strossmayera u Osijeku, Osijek, Hrvatska

Corresponding author / Adresa autora za dopisivanje:
Dora Uršić, MD, PhD
Division of Rheumatology, Clinical Immunology and Allergology / Zavod za reumatologiju, kliničku imunologiju i alergologiju
Department of Internal Medicine / Klinika za unutarnje bolesti
University Hospital Centre Osijek / Klinički bolnički centar Osijek
Huttlerova 4, 31000 Osijek
Croatia / Hrvatska
E-mail / e-pošta: dora.cvitkusic@gmail.com

Received / Primljeno: 4th October 2021 / 4. 10. 2021.
Accepted / Prihvaćeno: 17th November 2021 / 17. 11. 2021.

Abstract

Introduction: Antisynthetase syndrome (ASS) is a rare autoimmune systemic disease characterised by myositis, arthritis, Raynaud's syndrome, mechanic's hands, and interstitial lung disease. *Materials and methods:* We present the case of a 50-year-old patient with predominant signs of polymyositis, pulmonary interstitium involvement and positive anti-Jo1 antibodies with suspected antisynthetase syndrome. *Results:* He was treated with glucocorticoids and following that the treatment was continued with an additional immunosuppressive therapy drug, azathioprine, which was discontinued due to a liver lesion. The treatment was then continued with cyclophosphamide. In the later course of the disease, radiological regression of pulmonary changes was monitored, and mycophenolate mofetil was introduced as a maintenance therapy. *Conclusion:* If left unrecognised, ASS can lead to the development of irreversible pulmonary fibrosis. However, timely application of immunosuppressive therapy can improve the quality of life and the prognosis of patients with ASS.

Key words: antisynthetase syndrome, anti-Jo1 antibody, interstitial lung disease

Sažetak

Uvod: Antisintetazni sindrom (ASS) je rijetka autoimunosna sustavna bolest koju karakteriziraju miozitis, artritis, Raynaudov sindrom, mehaničarske ruke i intersticijska bolest pluća. *Materijali i metode:* Prikazujemo 50-godišnjeg bolesnika sa znacima polimiozitisa i zahvaćanja plućnog intersticija uz pozitivna anti-Jo1 protutijela kod kojega je postavljena sumnja na antisintetazni sindrom. *Rezultati:* Liječen je glukokortikoidima, a potom je kao dodatna imunosupresivna terapija uveden azatioprin koji je isključen zbog jetrene lezije, a liječenje je nastavljeno ciklofosfamidom. U kasnijem tijeku bolesti pratila se radiološka regresija plućnih promjena te se kao terapija održavanja uvede mikofenolat mofetil. *Zaključak:* Ako ostane neprepoznat ASS dovodi do razvoja ireverzibilne plućne fibroze, međutim pravovremenom primjenom imunosupresivne terapije može se poboljšati kvaliteta života i prognoza bolesnika s ASS-om.

Ključne riječi: antisintetazni sindrom, anti-Jo1 protutijela, intersticijska bolest pluća

INTRODUCTION

Antisynthetase syndrome (ASS) belongs to a group of systemic autoimmune disorders characterised by antibodies against aminoacyl-tRNA synthetase (1). It accounts for 30% of all inflammatory myopathies (2). The most common antisynthetase antibodies are those against histidyl (anti-Jo1). Other aminoacyl-tRNA synthetase antibodies, found in 1%–5% of cases, include anti-PL7, anti-PL12, anti-OJ, anti-EJ, anti-KS, anti-ZO, and anti-tyrosyl antibodies (2, 3, 4, 5, 6). Standard clinical features of ASS include myositis, arthritis, Raynaud's syndrome, mechanic's hands, and interstitial lung disease (ILD) (2). ILD occurs in approximately 70% of patients with ASS and most significantly affects the outcome and prognosis of patients with ASS (2, 7). The treatment of ASS is a demanding process, and it is based on the results of small retrospective studies (8, 9).

CASE REPORT

Our patient was a 50-year-old man with a one-month case history of polymyalgia, polyarthralgia, pain in the inguinal region, and weight loss. He was treated at the Department of Urology under the diagnosis of left-sided epididymitis and nephrolithiasis. During the patient's hospital stay, the diagnosis of bilateral interstitial lung infiltration was confirmed through radiologic testing. Due to the suspected autoimmune disease, further diagnostic processing and treatment were continued at the Division of Rheumatology, Clinical Immunology and Allergology. The leading symptoms included polymyalgia, upper and lower limb muscle weakness, fever, sudden extreme fatigue, and general weakness. A physical examination revealed that the patient had poor grip strength and difficulty standing up from a squatting position (positive Gowers' sign), without signs of limb muscular hypotrophy. The patient's body mass index was 22.5 kg/m², and his anamnesis included information about a 5 kg weight loss in the past month.

The results at diagnosis were the following: leukocyte count 17.1 x 10^9/L (3.4–9.7 x 10^9/L), erythrocyte sedimentation rate (ESR) 91 mm/3.6 ks (2–13 mm/3.6 ks), C-reactive protein (CRP) 198.7 mg/L (0–5 mg/L), lactate dehydrogenase (LDH) 150 U/L (< 241), aspartate aminotransferase (AST) 44 U/L (< 38), alanine aminotransferase (ALT) 130 U/L (< 48), ferritin 2580.3 µg/L (30 – 300 ug/L), with normal values of creatine kinase (CK) and myoglobin (Mb). Immunologic testing showed high values of rheumatoid factor (RF) 2350 IU/ml (< 15) with positive antibodies to histidyl (anti-Jo1) 85 AU/ml (< 30). Hepatomegaly was detected through an abdominal ultrasound, while serological testing results for HBV, HCV, HIV, CMV and EBV were negative. Radiograph (X-ray) of the thoracic or-

UVOD

Antisintetazni sindrom (ASS) pripada skupini sustavnih autoimunosnih poremećaja koji su karakterizirani protutijelima na aminoacil-tRNA sintetazu (1). Čini 30% svih upalnih miopatija (2). Najčešća antisintetazna protutijela su ona na histidil (anti-Jo1). Ostala protutijela na aminoacil-tRNA sintetazu koja su nađena u 1–5% slučajeva uključuju anti-PL7, anti-PL12, ati-OJ, anti-EJ, anti-KS, anti-ZO i anti-tirozil protutijela (2, 3, 4, 5, 6). Klasična slika ASS-a uključuje miozitis, artritis, Raynaudov sindrom, mehaničarske ruke i intersticijsku bolest pluća (IBP) (2). IBP se pojavljuje u oko 70% bolesnika s ASS-om te najznačajnije utječe na ishod i prognozu bolesnika s ASS-om (2, 7). Liječenje ASS-a je zahtjevno te se temelji na rezultatima malih retrospektivnih studija (8, 9).

PRIKAZ BOLESNIKA

Naš bolesnik je bio 50-godišnji muškarac s jednomjesečnom anamnezom polimialgija, poliartralgija, bolova u ingvinalnoj regiji te gubitka na tjelesnoj masi. Liječen je na Odjelu za urologiju pod dijagnozom lijevostranog epididimitisa i nefrolitijaze. Tijekom boravka radiološki je verificirana bilateralna intersticijska infiltracija pluća. Zbog sumnje na autoimunosnu bolest daljnja dijagnostička obrada i liječenje su nastavljeni na Zavodu za reumatologiju, kliničku imunologiju i alergologiju. Vodeći simptomi bili su polimialgija, slabost muskulature gornjih i donjih ekstremiteta, febrilitet, brzo umaranje i opća slabost. Fizikalnim pregledom otkriveni su oslabljena snaga stiska šaka te poteškoće prilikom ustajanja iz čučnja (pozitivan Gowersov znak), a bez znakova hipotrofije muskulature ekstremiteta. Indeks tjelesne mase bolesnika je bio 22,5 kg/m², uz anamnestički podatak o gubitku od 5 kg na tjelesnoj masi u proteklom mjesecu.

Nalazi kod postavljanja dijagnoze bili su: leukociti 17,1 x 10^9/L (3,4 – 9,7 x 10^9/L), sedimentacija eritrocita (SE) 91 mm/3,6 KS (2 – 13 mm/3,6 KS), C-reaktivni protein (CRP) 198,7 mg/L (0 – 5 mg/L), laktat dehidrogenaza (LDH) 150 U/L (< 241), aspartat aminotransferaza (AST) 44 U/L (< 38), alanin aminotransferaza (ALT) 130 U/L (< 48), feritin 2580,3 ug/L (30 – 300 ug/L), uz normalne vrijednosti kreatin kinaze (CK) i mioglobina (Mgb). Imunološka obrada pokazala je visoke vrijednosti reumatoidnog faktora (RF) 2350 IU/ml (< 15) uz pozitivna protutijela na histidil (anti-Jo1) 85 AU/ml (< 30). Na ultrazvuku abdomena opisana je hepatomegalija, dok je serologija na HBV, HCV, HIV, CMV i EBV bila negativna. Radiogram (RTG) torakalnih organa pokazao je intersticijski crtež retikulonodularnog tipa (slika 1), dok je difuzijski kapacitet za CO (skr. DLCO) bio značajno snižen po tipu restriktivnih promjena za 43%. Nalaz visokorazlučivog

gans showed a reticulonodular interstitial pattern (Figure 1), while the diffusing capacity for carbon monoxide (DLCO) was significantly reduced by 43% according to the type of restrictive changes. The findings of the high-resolution computed tomography (HRCT) indicated diffuse changes according to the ground-glass opacity type with reticulation and traction bronchiectasis (Figure 2). Bronchoscopy findings were in the normal range. Electromyoneurography (EMNG) showed a high percentage of low-voltage polyphasic action potentials.

On the basis of clinical and laboratory markers, along with EMNG of the muscles, poliomyositis with ILD was detected, and due to the presence of anti-Jo1 antibodies, ASS was diagnosed. The patient was treated with methylprednisolone at a dose of 1 mg/kg in addition to antibiotic therapy. The applied therapy resulted in the improvement in the clinical status of the patient and a gradual normalisation of laboratory markers. The entire process was monitored closely. As an additional immunosuppressive therapy, azathioprine was introduced at a dose of 100 mg per day. Glucocorticoid treatment was continued on an outpatient basis with a gradual dose reduction.

After three months, azathioprine was discontinued due to the development of a liver lesion, and treatment was continued with cyclophosphamide administered intravenously at a dose of 15 mg/kg (1000 mg) during the course of 6 treatment cycles. The control HRCT scan of the thorax revealed the regressive dynamics of changes according to the type of ground-glass opacity. In the later course of the disease, symptoms of Raynaud's syndrome appeared in the patient, immunological findings have revealed an anti-Jo1 antibody result of 47 AU/ml, unremarkable inflammatory markers, and mycophenolate mofetil administered intravenously was introduced as maintenance therapy, at a dose of 1000 mg per day. Regular outpatient follow-up of the clinical status, laboratory markers and radiological changes was resumed. The clinical status of the patient is stable, but with mild limitations in carrying out difficult physical activities.

DISCUSSION

Antisynthetase syndrome (ASS) was first described as a separate entity in 1990, in patients suffering from polymyositis and ILD, who had antibodies directed against aminoacyl t-RNA synthetase (10). The estimated prevalence of the disease is 1.5 per 100,000 population. The disease more commonly occurs in women (2–3:1) (5). The diagnosis is made on the basis of two major criteria (interstitial lung disease, polymyositis, or dermatomyositis) and one major and two minor criteria (arthritis, Raynaud's syndrome, and mechanic's hands) (11). Myositis occurs in approximately 90% of

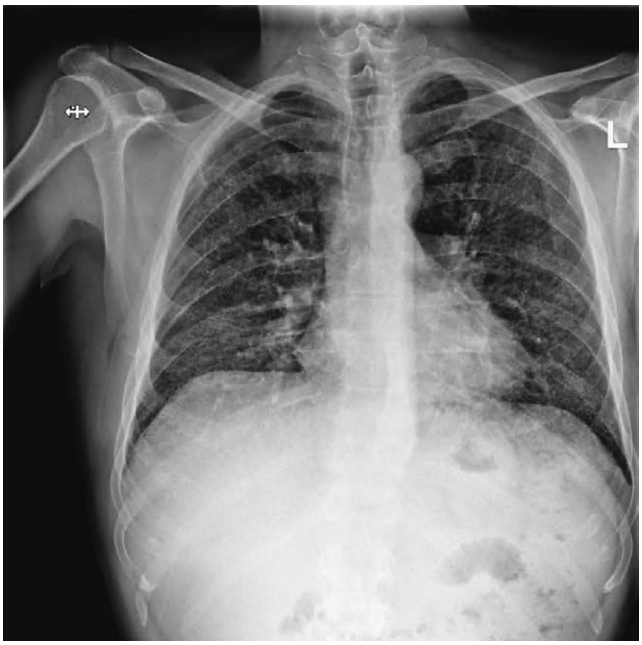

Figure 1. Radiography of the heart / lungs – interstitial pattern of the reticulonodular type
Slika 1. Radiogram srca/pluća – intersticijski crtež retikulonodularnog tipa

CT-a toraksa (skr. HRCT) upućivao je na difuzne promjene po tipu mliječnog stakla uz retikulacijske i trakcijske bronhiektazije (slika 2). Nalaz bronhoskopije je bio uredan. Elektromioneurografija (EMNG) je pokazala visok postotak niskonaponskih polifaznih akcijskih potencijala.

Na temelju kliničkih i laboratorijskih parametara uz EMNG mišića detektiran je poliomiozitis uz IBP, a uz prisutna anti-Jo1 protutijela postavljena je dijagnoza ASS-a. Bolesnik je liječen metilprednizolonom u dozi od 1 mg/kg uz antibiotsku terapiju. Na primijenjenu terapiju pratilo se poboljšanje kliničkog stanja uz postupnu normalizaciju laboratorijskih parametara. Kao dodatna imunosupresivna terapija uveden je azatioprin u dozi od 100 mg na dan. Liječenje glukokortikoidima je nastavljeno ambulantno uz postupno snižavanje doze.

Nakon tri mjeseca azatioprin je isključen zbog razvoja jetrene lezije, a liječenje je nastavljeno intravenskom primjenom ciklofosfamida u dozi od 15 mg/kg (1000 mg) kroz 6 ciklusa. Na kontrolnom HRCT-u toraksa bila je vidljiva regresivna dinamika promjena po tipu mliječnog stakla. U kasnijem tijeku bolesti kod bolesnika su se pojavili simptomi Raynaudovog sindroma, u imunološkim nalazima anti-Jo1 47 AU/ml, mirni upalni parametri, te se kao terapija održavanja uvede mikofenolat mofetil i.v. u dozi od 1000 mg na dan. Nastavljeno je redovito ambulantno praćenje kliničkog stanja, laboratorijskih parametara i radioloških promjena. Bolesnik je stabilnoga kliničkog stanja, ali uz blažu ograničenost u obavljanju težih fizičkih aktivnosti.

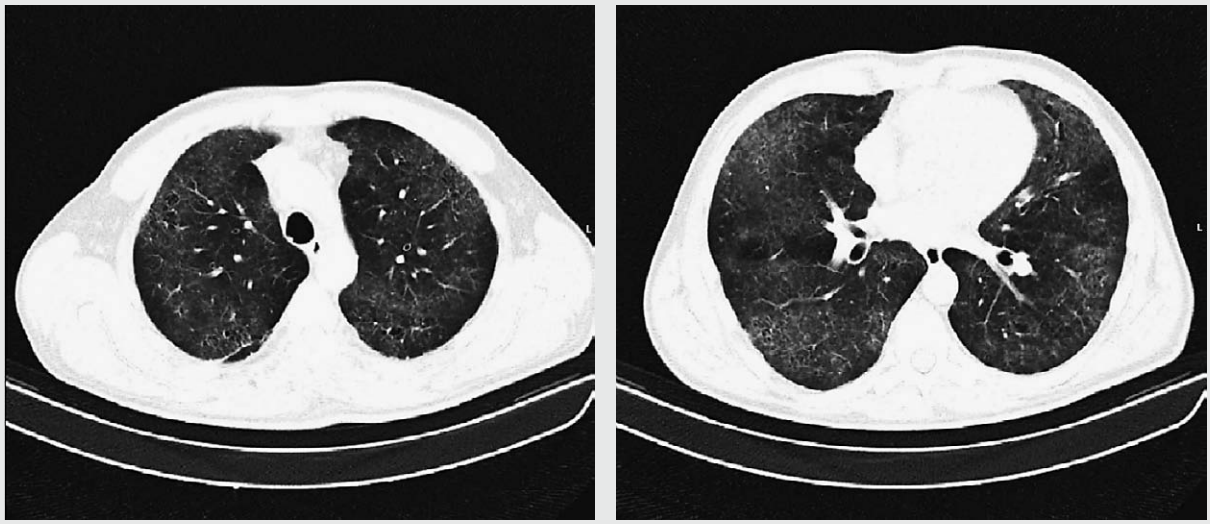

Figure 2. High-resolution computed tomography (HRCT) of the chest – axial section: interstitial lung disease
Slika 2. Kompjuterska tomografija visoke razlučivosti toraksa – horizontalni presjek: intersticijska bolest pluća

patients. The values of muscle enzymes are usually 5–50 times higher than the normal upper limit. However, CK values may be in the normal range due to significant loss of muscle mass (12). In the case of our patient, the CK values were within the reference interval, while the EMNG showed a myopathic pattern. Therefore, it is important to highlight the fact that normal CK values do not exclude the diagnosis of polymyositis. Arthritis occurs in 50% of patients with ASS, most often at the very onset of the disease. Its characteristics include symmetric polyarthritis of the small joints of the hands and feet and is usually non-erosive. Therefore, ASS should be considered primarily in the differential diagnosis of rheumatoid arthritis (12).

ILD occurs in approximately 70% of patients, it is usually described as non-specific interstitial pneumonia (NSIP) and is the main cause of morbidity. In patients with ASS and ILD, the course of the disease can be complicated by the development of pulmonary hypertension (6). Pulmonary function tests indicate restrictive changes, while CD8 T lymphocytes predominate in the bronchoalveolar lavage (BAL) findings (13). In the case of our patient, the presence of CD8 T lymphocytes was confirmed in BAL findings. Clinical features should take precedence over laboratory markers in establishing the diagnosis of ASS. If anti-Jo1 antibodies are negative, and there is a clinical suspicion of ASS, diagnostic tests for other antibodies associated with ASS should be performed (14).

In the case of our patient, antinuclear antibodies were negative. In a cohort study conducted by Noguchi et al., which included 51 patients with ASS, the presence of ANA antibodies was confirmed in only 12% of subjects (15).

RASPRAVA

Antisintetazni sindrom (ASS) je kao zaseban entitet opisan 1990. godine u bolesnika koji su bolovali od polimiozitisa i IBP-a, a imali su antitijela usmjerena na aminoacil t-RNA sintetazu (10). Procijenjena prevalencija je 1,5 na 100.000 stanovnika. Bolest se češće javlja u žena (2–3:1) (5). Dijagnoza se postavlja na temelju dvaju velikih kriterija (intersticijska bolest pluća, polimiozitis ili dermatomiozitis) te jednog velikog i dvaju malih kriterija (artritis, Raynaudov sindrom i „mehaničarske“ ruke) (11). Miozitis se javlja u 90% bolesnika. Vrijednosti mišićnih enzima uobičajeno su povišene i do 5–50 puta iznad gornje granice. Međutim, vrijednosti CK mogu biti uredne uslijed značajnog gubitka mišićne mase (12). Kod našeg bolesnika vrijednosti CK su bile unutar referentnog intervala, dok je na EMNG-u dokazan miopatski uzorak. Stoga, važno je naglasiti da uredne vrijednosti CK ne isključuju dijagnozu polimiozitisa. Artritis se javlja u 50% bolesnika s ASS-om, najčešće u samom početku bolesti. Karakterizan je simetričnim poliartritisom malih zglobova šaka i stopala te je najčešće neerozivan. Stoga, ASS treba razmotriti u diferencijalnoj dijagnozi prvenstveno reumatoidnog artritisa (12).

IBP se javlja u oko 70% bolesnika, uobičajeno se opisuje kao nespecifična interisticijska pneumonija (NSIP) te je glavni uzrok morbiditeta. Kod bolesnika s ASS-om i IBP-om tijek bolesti se može komplicirati razvojem plućne hipertenzije (6). Testovi plućne funkcije ukazuju na restriktivne promjene, dok u nalazu bronhoalveolarnog lavata (BAL) prevladavaju CD8 T limfociti (13). Kod našeg bolesnika potvrđen je nalaz CD8 T limfocita u BAL-u. Klinička obilježja trebaju imati prednost nad laboratorijskim parametrima u po-

There is still no standardised treatment for ASS with ILD. The first-line therapy includes the use of glucocorticoids. The second-line therapy consists of drugs that reduce the need for glucocorticoids, such as azathioprine, methotrexate, cyclophosphamide, and mycophenolate mofetil (16). Multiple randomised trials have confirmed the better effectiveness of the combination of prednisone and azathioprine compared to prednisone monotherapy (5). In ASS with significant pulmonary involvement that does not respond to the use of glucocorticoids and azathioprine, the use of cyclophosphamide administered intravenously should be considered (5, 17). In the case of our patient, the first-line therapy included the use of glucocorticoids, and azathioprine was introduced as a drug that reduces the need for glucocorticoids. However, due to the development of a liver lesion as a consequence of azathioprine use, and due to the extent of pulmonary involvement, we decided to use cyclophosphamide administered intravenously. In a study conducted by Qureshi et al., the case of a patient with ASS and ILD of the NSIP type was presented. The applied cyclophosphamide therapy resulted in the improvement in the clinical status and the laboratory markers of the patient. The entire process was monitored closely. (18). In a study conducted by Kumar et al., a significant improvement was described in the case of a patient with ASS and ILD of the NSIP type who was using cyclophosphamide during the course of seven treatment cycles (19). A similar case report was published in a study conducted by Cleetus et al. A patient from their study initially presented with respiratory problems, there were no signs of myositis, a HRCT chest scan confirmed that this was a case of ILD according to the type of NSIP pattern. However, immunological findings revealed a positive anti-PL12 antibody result (20). ASS patients who are anti-Jo1 negative have a worse survival rate than the patients who are anti Jo-1 positive (13). In a study conducted by Brulhart et al., a case of a 57-year-old patient with ASS was presented, who initially responded well to the use of methotrexate and prednisone, but three months later the patient had a relapse and rituximab was administered with a good response (21). Langlois et al. published the results of an observational study that included 62 patients with ASS and ILD. Out of the total number of patients, 34 of them were treated with cyclophosphamide administered in cycles, while 28 of them received rituximab. The results showed an equal efficacy on pulmonary progression-free survival at six months of follow-up. However, rituximab was associated with a significantly better outcome at two years of follow-up (22). In the case of our patient, mycophenolate mofetil was chosen for maintenance therapy as a drug that reduces the need for glucocorticoids, but also because of the results of studies that showed a lower incidence of disease restavljanju dijagnoze ASS-a. Ukoliko su anti-Jo1 protutijela negativna, a postoji klinička sumnja na ASS, trebalo bi učiniti dijagnostičke testove na ostala antitijela povezana s ASS-om (14).

Kod našeg bolesnika antinuklearna protutijela su bila negativna. Noguchi i sur. u kohortnoj studiji koja je uključivala 51 bolesnika sa ASS-om potvrdili su prisutnost ANA protutijela u samo 12% ispitanika (15).

Liječenje ASS-a uz IBP i dalje nije standardizirano. Prva linija liječenja uključuje primjenu glukokortikoida. Drugu liniju liječenja čine lijekovi koji omogućuju smanjivanje potrebe za glukokortikoidima poput azatioprina, metotreksata, ciklofosfamida te mikofenolat mofetila (16). Multiple randomizirane studije potvrdile su bolju učinkovitost primjene kombinacije prednizona i azatioprina u odnosu na monoterapiju prednizonom (5). Kod ASS-a sa značajnim zahvaćanjem pluća koji ne odgovara na primjenu glukokortikoida i azatioprina treba razmotriti primjenu intravenoznog ciklofosfamida (5, 17). Kod našeg bolesnika prva su linija liječenja bili glukokortikoidi, a azatioprin je uveden kao lijek koji smanjuje potrebu za glukokortikodima. Međutim, radi razvoja jetrene lezije na primjenu azatioprina i opsega plućnog zahvaćanja odlučili smo se za primjenu intravenoznog ciklofosfamida. Qureshi i sur. su prikazali bolesnika s ASS-om i IBP-om po tipu NSIP kod kojega se na primjenu ciklofosfamida pratilo značajno kliničko i laboratorijsko poboljšanje (18). Kumar i sur. su također opisali značajno poboljšanje kod bolesnika s ASS-om i IBP-om po tipu NSIP koji je primao ciklofosfamid kroz sedam ciklusa (19). Sličan prikaz bolesnika objavili su Cleetus i sur. Njihov bolesnik se inicijalno javio zbog respiratornih tegoba, nije bilo znakova miozitisa, HRCT toraksa je potvrdio IBP po tipu NSIP uzorka, međutim u imunološkim nalazima pristigao je pozitivan anti-PL12 (20). Bolesnici s ASS-om koji su anti-Jo1 negativni imaju lošije preživljenje od onih bolesnika koji su anti Jo-1 pozitivni (13). Brulhart i sur. su prikazali 57-godišnjeg bolesnika s ASS-om koji je inicijalno dobro odgovorio na primjenu metotreksata i prednizona, međutim tri mjeseca kasnije pratio se relaps bolesti te je primijenjen rituksimab s dobrim odgovorom (21). Langlois i sur. su objavili rezultate opservacijske studije koja je uključivala 62 bolesnika s ASS-om i IBP-om, od kojih su 34 bolesnika liječena ciklusima ciklofosfamida, dok je 28 bolesnika primalo rituksimab. Rezultati su pokazali jednaku učinkovitost na preživljenje bez plućne progresije nakon šest mjeseci praćenja, međutim rituksimab je bio povezan sa značajno boljim ishodom nakon dvije godine praćenja (22). Kod našeg bolesnika mikofenolat mofetil je odabran za terapiju održavanja kao lijek koji omogućava smanjivanje potrebe za glukokortikoidima, ali i zbog rezultata studija koje su pokazale manju

lapse with the use of mycophenolate mofetil compared to prednisone monotherapy (23).

In conclusion, antisynthetase syndrome is a rare autoimmune systemic disease that, if left unrecognised, can lead to the development of irreversible pulmonary fibrosis as the main cause of poor prognosis and mortality. The timely application of immunosuppressive therapy can improve the quality of life and prognosis of these patients.

pojavnost relapsa bolesti uz mikofenolat mofetil u odnosu na monoterapiju prednizonom (23).

Zaključno, antisintetazni sindrom je rijetka autoimunosna sustavna bolest koja, ukoliko ostane neprepoznata, dovodi do razvoja ireverzibilne plućne fibroze kao glavnog uzroka loše prognoze i smrtnog ishoda. Pravovremenom primjenom imunosupresivne terapije može se poboljšati kvaliteta života i prognoza tih bolesnika.

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

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

REFERENCES / LITERATURA

1. Targoff IN. Autoantibodies and their significance in myositis. Curr Rheumatolog Rep. 2008;10(4):333–40.
2. Katzap E, Barilla-LaBarca ML, Marder G. Antisynthetase syndrome. Curr Rheumatolog Rep. 2011;13(3):175–81.
3. Cojocaru M, Cojocaru IM, Chicos B. New Insights into Antisynthetase syndrome. Maedica (Buchar). 2016;11(2):130–5.
4. Imbert-Masseau A, Hamidou M, Agard C, Grolleau JY, Cherin P. Antisynthetase syndrome. Joint Bone Spine. 2003;70:161.
5. Solomon J, Swigris JJ, Brown KK. Myositis-related interstitial lung disease and antisynthetase syndrome. J Bras Pneumol. 2011;37(1):100–9.
6. Nishikai M, Reichlin M. Heterogeneity of precipitating antibodies in polymyositis and dermatomyositis. Characterization of the Jo-1 antibody system. Arthritis Rheum. 1980;23(8):881–8.
7. Sem M, Molberg O, Lund MB, Gran JT. Rituximab treatment of the anti-synthetase syndrome: a retrospective case series. Rheumatology (Oxford). 2009;48(8):968–71.
8. Yamasaki Y, Yamada H, Yamasaki M, Ohkubo M, Azuma K, Matsuoka S et al. Intravenous cyclophosphamide therapy for progressive interstitial pneumonia in patients with polymyositis/dermatomyositis. Rheumatology. 2007;46:124–30.
9. Mira-Avendano IC, Parambil JG, Yadav R, Arrossi V, Xu M, Chapman JT et al. A retrospective review of clinical features and treatment outcomes in steroid-resistant interstitial lung disease from polymyositis/dermatomyositis. Respir Med. 2013;107:890–6.
10. Novak S. Antisintetaza sindrom. Reumatizam. 2012:59(2):53–7.
11. Witt LJ, Curran JJ, Strek ME. The Diagnosis and Treatment of Antisynthetase Syndrome. Clin Pulm Med. 2016;23(5):218–26.
12. Bartoloni E, Gonzalez-Gay MA, Scire C, Castaneda S, Gerli R, Lopez-Longo FJ et al. Clinical follow-up predictors of disease pattern change in anti-Jo1 positive anti-synthetase syndrome: results from a multicenter, international and retrospective study. Autoimmune Rev. 2017;16:253–7.
13. Aggarwal R, Cassidy E, Fertig N, Koontz DC, Lucas M, Ascherman DP et al. Patients with non-Jo-1 anti-tRNA-synthetase autoantibodies have worse survival than Jo-1 positive patients. Ann Rheum Dis. 2014;73:227–32.
14. Mahler M, Miller FW, Fritzler MJ. Idiopathic inflammatory myopathies and the anti-synthetase syndrome: a comprehensive review. Autoimmun Rev. 2014;13:367–71.
15. Noguchi E, Uruha A, Suzuki S, Hamanaka K, Ohnuki Y, Tsugawa J et al. Skeletal Muscle Involvement in Antisynthetase Syndrome. JAMA Neurol. 2017;74(8):992–9.
16. Devi HG, Pasha MM, Padmaja MS, Halappa S. Antisynthetase Syndrome: A Rare Cause for ILD. J Clin Diagn Res. 2016;10(3):8–9.
17. Gonzalez-Gay MA, Montecucco C, Selva-O'Callaghan A, Trallero-Araguas E, Molberg O, Andersson H et al. Timing of onset affects arthritis presentation pattern in antisynthetase syndrome. Clin Exp Rheumatol. 2018;36:44–9.
18. Qureshi MA, Hoey E, Fletcher T, Ahmed Z. Antisynthetase syndrome: a case report. Quant Imaging Med Surg. 2016;6(2):207–9.
19. Kumar N, Basetii B, Ramachandran R, Radhan P, Sai VPM. Antisynthetase syndrome and its association with interstitial lung disease – a clinical and radiological review. Int J Med Case Reports. 2020;3(3):8–13.
20. Cleetus M, Emmanuel D, Venkitakrishnan R, Augustine J, Ramachandran D. Anti-PL-12 Associated Antisynthetase Syndrome-A Less Recognized Clinical Entity. Int J Respir Pulm Med. 2020;7:146.
21. Brulhart L, Waldburger JM, Gabay C. Rituximab in the treatment of antisynthetase syndrome. Ann Rheum Dis. 2006;65(7):974–5.
22. Langlois V, Gillibert A, Uzunhan Y, Chabi ML, Hachulla E, Landon-Cardinal O et al. Rituximab and Cyclophosphamide in Antisynthetase Syndrome-related Interstitial Lung Disease: An Observational Retrospective Study. J Rheumatol. 2020 Nov 1;47(11):1678–86.
23. Marco JL, Collins BF. Clinical manifestations and treatment of antisynthetase syndrome. Best Pract Res Clin Rheumatol. 2020;10:101503.