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EDITORIAL UVODNIK

ON REGARD AT THE END OF THE TERM OF EDITOR-IN-CHIEF OF JOURNAL *REUMATIZAM*, 2014–2023

OSVRT NA KRAJU MANDATA GLAVNOG UREDNIKA ČASOPISA *REUMATIZAM* 2014. – 2023.

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Dear readers and esteemed colleagues,

At the end of the two consecutive terms of being the editor-in-chief of our *Rheumatism* journal, let me take this opportunity to briefly recall the history of this official professional journal of the Croatian Society for Rheumatology of the Croatian Medical Association, with a special focus on the work that we have done over the past 10 years.

Rheumatism is a journal which was first published in 1954 and it has a prominent role in Croatian medicine and beyond. This journal holds a tradition of 70 years of uninterrupted publication, which is something that very few Croatian professional journals, but also rheumatology journals in general, can boast about. In addition to that, *Rheumatism* is the seventeenth rheumatology journal in the world. The journal was founded by Primarius Drago Čop, MD, at the time of commemoration of the 80th anniversary of the establishment of the Croatian Medical Association and its journal named *Liječnički vjesnik* (in English: *The Medical Journal*). Prim. Čop, the first editor-in-chief of *Rheumatism* (1954–1963), founded this journal so that it would represent an informative and educational reading for physicians who encounter rheumatic patients in clinical practice, and also for it to arouse interest in rheumatic diseases. The journal was first intended for postgraduate training of family medicine physicians. When it comes to different columns in the journal that were

Poštovani čitatelji, kolegice i kolege,

na kraju dva uzastopna mandata glavnog i odgovornog urednika našeg i vašeg *Reumatizma* prigoda je da se ukratko podsjetimo na povijest ovoga službenog stručnog časopisa Hrvatskoga reumatološkog društva HLZ-a, s posebnim osvrtom na posljednjih deset godina.

Reumatizam je časopis koji zauzima istaknuto mjesto u hrvatskoj medicini, pa i šire. Počeo je izlaziti 1954. godine. S tradicijom od sedamdeset godina neprekinutog izlaženja može se pohvaliti vrlo malo ne samo hrvatskih stručnih časopisa, nego i reumatoloških časopisa uopće, a *Reumatizam* je sedamnaesti reumatološki časopis na svijetu. Časopis je utemeljio prim. dr. Drago Čop u vrijeme kada se obilježavala 80. obljetnica osnutka Hrvatskoga liječničkoga zbora i njegova glasila *Liječnički vjesnik*. Dr. Čop je kao prvi urednik (1954. – 1963.) časopis ustanovio s idejom da prvenstveno bude informativan i edukativan za liječnike koji se u kliničkoj praksi susreću s reumatološkim bolesnicima, da se uopće pobudi interes za reumatske bolesti, a isprva je bio namijenjen poslijediplomskom usavršavanju liječnika obiteljske medicine. Od rubrika koje su bile različite i pojavljivale su se ovisno o raspoloživosti zanimljivog materijala, s razlogom su se osobito njegovale one *Ekscerpti* i *Referati iz časopisa*. U doba kada hrvatska reumatološka literatura gotovo nije postojala u časopisu su 1954. – 1955. bili objavljeni važni prilozi

published depending on the availability of the interesting material, some of them, which sparked the readers' interest for a reason, were *Ekscerpti* (in English: *Excerpts*) and *Referati iz časopisa* (in English: *Papers from Journals*). From 1954 until 1955, at the time when literature related to Croatian rheumatology was scarce and almost inexistent, the important supplements *Osnovi praktične reumatologije* (in English: *Introduction to Practical Rheumatology*) and *Reumatološki vademecum* (in English: *Rheumatological Vade Mecum*) were published, with the latter also representing the then official European guidelines for the diagnosis and treatment of rheumatic diseases. From 1961 until 1963, the journal was called *Praxis medica —Reumatizam*. It is worth noting that, in accordance with the basic ideas of the journal, in all issues of the first year and in the first issue of the second year, a translation of the well-known prestigious text *Primer on the Rheumatic Diseases* of the American College of Rheumatology was published.

Prim. Čop occasionally commissioned the world's leading rheumatologists to write an article for the *Rheumatism* journal, and from the very beginning almost every published article had a summary written in one of the world languages. After the tragic death of Prim. Čop, the role of the editor-in-chief was given to Prof. Theodor Dürrigl, MD, PhD, who was previously the secretary of the journal. Prof. Dürrigl served as the editor-in-chief of the *Rheumatism* journal for 27 years (from 1963 until 1990). In his desire to make the journal more interesting and with plenty of educational material, Prof. Dürrigl introduced some new columns, and, after obtaining permission from the other respective journals, he introduced exams for the purpose of examining the knowledge of physicians, reports from intersectional meetings and encouraged the publication of a collection of papers in non-standard issues, and many other things. The progress of the overall profession and particularly the new scientific knowledge are responsible for the gradual improvement in the quality of the journal. The other experts who took over the role of the editor-in-chief from Prof. Dürrigl were Prof. Ivo Jajić, MD, PhD (1991–1998) and Prim. Goran Ivanišević, MSc (1999–2013). The journal managed to stay on track and maintain its continuity of publication, with two issues being published annually, and with number 2 becoming the congress issue related to the start of the organization of the Annual Congresses of the Croatian Society for Rheumatology (since 1999). In 2008, Prim. Ivanišević published the bibliography called *Reumatizam, Bibliografija 1954.–2008.*, which contained articles from all 55 years of the journal's existence, from the first issue published in 1954 until the second issue published in 2008. In addition to the standard issues, all of the non-standard issues of the journal were included in this bibliography as well.

Osnovi praktične reumatologije i *Reumatološki vademecum,* a potonji su bile tadašnje službene europske smjernice za dijagnostiku i liječenje reumatskih bolesti. Od 1961. do 1963. godine časopis je nosio naziv *Praxis medica – Reumatizam*. Zanimljivost je da je, u skladu s osnovnim idejama časopisa, u svim brojevima prvoga i u prvom broju drugoga godišta tiskan prijevod poznatog teksta *Primera on the rheumatic diseases* Američkoga reumatološkog društva. Čop je povremeno angažirao vodeće svjetske reumatologe da napišu članak za *Reumatizam*, a od početka je gotovo svaki objavljeni članak imao i sažetak na nekom od svjetskih jezika. Nakon tragične smrti dr. Čopa, uredništvo je preuzeo dotadašnji tajnik časopisa, prof. dr. sc. Theodor Dürrigl, koji je njegov urednik bio čak 27 godina (1963. – 1990.). U želji da časopis bude što atraktivniji i edukativniji, prof. Dürrigl je uveo neke nove rubrike, a s dopuštenjem odgovarajućih časopisa pokrenuo je testove za provjeru znanja liječnika, referate s intersekcijskih sastanaka, objavljivani su *zbornici* u izvanrednim brojevima itd. Napredak struke i osobito nove znanstvene spoznaje dovele su do postupnog podizanja kvalitete časopisa. Sljedeći glavni urednici bili su prof. dr. sc. Ivo Jajić (1991. – 1998.) i prim. mr. sc. Goran Ivanišević (1999. – 2013.). Časopis je zadržao kontinuitet izlaženja te su izlazila dva broja godišnje, od kojih je broj 2 postao kongresni broj, a vezano za početak organiziranja hrvatskih godišnjih reumatoloških kongresa (od 1999. godine). Godine 2008. prim. Ivanišević je objavio publikaciju *Reumatizam: Bibliografija 1954. – 2008.*, u kojem su navedeni članci svih 55 godišta časopisa, od 1. broja 1954. godine do 2. broja 2008. godine, a osim redovitih brojeva uvršteni su i svi izvanredni brojevi časopisa.

Preuzimanjem dužnosti glavnog urednika želja mi je bila unaprijediti časopis u svakom pogledu. S ciljem motiviranja kolega reumatologa za upućivanjem rukopisa u *Reumatizam*, kao i njihovog recenziranja, odlučio sam značajno povećati broj članova uredničkoga odbora. S članovima uredničkoga odbora dogovoreno je da se obavežu redovito objavljivati određeni broj članaka kao prva tri autora ili kao zadnji autor / autor za dopisivanje, što je u praksi većim dijelom ispunjeno. Proširenje broja članova uredničkoga odbora odnosi se i na poziv eminentnim inozemnim stručnjacima koji su tijekom 2017. i 2018. godine svi prihvatili moj poziv: Xenofon Baraliakos (Njemačka), Laszlo Czirjak (Mađarska), Iztok Holc (Slovenija), Marco Matucci Cerinic (Italija), Mevludin Mekić (Bosna i Hercegovina), Denis Poddubnyy (Njemačka), Zoltan Szekanecz (Mađarska) i Ladislav Šenolt (Republika Češka). Osim toga, uredništvu su se pridružili Armen Yuri Gasparyan kao savjetnik za znanost, inače glavni urednik jednog od najpoznatijih svjetskih časopisa *Rheumato-*

By taking over the role of the editor-in-chief, my desire was to improve the journal in every aspect. In order to motivate my fellow rheumatologists to submit their manuscripts for them to be selected for the *Rheumatism* journal, as well as to review these manuscripts, I decided to significantly increase the number of members in the editorial board. The members of the editorial bord have agreed to regularly publish a certain number of articles as the first three authors or as the last author / corresponding author, and this type of approach was adhered to in practice for the most part. The act of increasing the number of the editorial board members also refers to the invitation that was sent to eminent foreign experts who have accepted my invitation during 2017 and 2018: Xenofon Baraliakos (Germany), Laszlo Czirjak (Hungary), Iztok Holc (Slovenia), Marco Matucci Cerinic (Italy), Mevludin Mekić (Bosnia and Herzegovina), Denis Poddubnyy (Germany), Zoltan Szekanecz (Hungary) and Ladislav Šenolt (Czech Republic). In addition to that, Armen Yuri Gasparyan, the editor-in-chief of one of the world's most prominent journals, *Rheumatology International*, and Olena Zimba, an expert in the field of editorial work for internationally recognized journals, have joined our editorial board as a scientific advisor and editor in the field of Education and Social Media.

The instructions to the authors and the editorial work rules have been adjusted in accordance with the *Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals* of the International Committee of Medical Journal Editors (ICMJE) and ethical standards according to the requirements of COPE (Committee on Publication Ethics) and CSE (Council of Science Editors). The necessary documents were filled out by the author when submitting their work. In addition to that, we have also obtained a DOI (Digital Object Identifier), a standard unique number that is assigned to each article for the purpose of its identification, and we have also met all other administrative requirements for journal indexing in one of the world's databases. We have to mention one of the most important achievements: the new official website of the journal, where you can find all the articles from 2004 to the present day, which were also published on *Hrčak*, the central portal of Croatian scientific and professional journals. You can access the articles completely free of charge, one is the so-called *platinum open access*. The journal also underwent visual changes in terms of creating the thematic link of the cover to rheumatology, and it experienced modernization in the area of graphic design.

During my term as the editor-in-chief, I have actively encouraged all the colleagues to submit manuscripts in order for them to be selected for the Rheumatism journal. Moreover, after every Annual Congress of the

logy International, i Olena Zimba, iskusna u uredničkim poslovima međunarodno priznatih časopisa, na mjestu urednice za edukaciju i socijalne medije.

Upute autorima i pravila rada uredništva prilagođena su prema preporukama za izvještavanje, uređivanje i objavu znanstvenih radova u medicinskim časopisima (*Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals*) Međunarodnog odbora urednika medicinskih časopisa (engl. *International Committee of Medical Journal Editors* – ICMJE) i etičkim standardima prema zahtjevima organizacija COPE (engl. *Committee on Publication Ethics*) te CSE (engl. *Council of Science Editors*). Dopunjeni su dokumenti koji se zahtijevaju od autora prilikom upućivanja rada. Također, pribavili smo DOI (engl. *Digital Object Identifier*), standardni jedinstveni broj koji se dodjeljuje svakom članku za njegovu identifikaciju, a ostvarili smo i sve ostale administrativne zahtjeve za indeksiranje časopisa u nekoj od svjetskih baza. Jedno od važnih postignuća jest nova mrežna stranica časopisa na kojoj se mogu naći svi članci od 2004. do danas, koji su postavljeni i na *Hrčak*, portal hrvatskih znanstvenih časopisa. Dakle, pristup člancima je potpuno besplatan, tzv. platinum otvoreni pristup. Časopis je doživio i vizualne promjene u smislu tematske poveznice naslovnice s reumatologijom te modernizaciju grafičkog dizajna.

Tijekom svog mandata glavnog urednika aktivno sam poticao sve kolege da upućuju rukopise u časopis, uključujući i to da sam nakon svakog godišnjega reumatološkog kongresa pisanim putem pozivao autore da daju svoj stručni prilog za časopis. U tom desetogodišnjem razdoblju uspjeli smo objavljivati dva redovita broja godišnje uz kongresni suplement, uključujući i onaj povodom Srednjoeuropskoga reumatološkog kongresa održanog u Zagrebu, 2018. godine. Od svojevrsnog panoramskog prikaza novosti iz struke i aktivnosti stručnog društva, *Reumatizam* sam nastojao usmjeriti prema objavi što kvalitetnijih stručnih radova, dok sam smatrao da je, sukladno novim trendovima i tehnologijama, prikladnije da se primjerice obavijesti o stručnim skupovima i drugim sličnim aktivnostima prezentiraju na mrežnoj stranici Društva, u časopisima drugačijeg profila namijenjenog široj čitalačkoj publici i na društvenim mrežama. Uveo sam pravilo da svi rukopisi upućeni u časopis, osim naručenih preglednih radova, moraju proći „slijepu" recenziju dvaju stručnjaka, za koje smo, u cilju što veće kvalitete, dogovorno odredili da bi trebali biti barem doktori znanosti ili primarijusi. Sve navedeno rezultiralo je postupnim poboljšanjem kvalitete radova objavljenih u *Reumatizmu*, čije se razine ne bi posramili ni ugledniji časopisi. Od 2019. časopis izlazi dvojezično, na hrvatskom i na engleskom jeziku, s paralelnim prikazom unutar poje-

Croatian Society for Rheumatology, I invited the authors in writing to provide their expert contribution to the journal. In that ten-year period, we managed to publish two regular issues annually, along with a congress supplement, including one issue that was published to commemorate the occasion of the Central European Congress of Rheumatology which was held in Zagreb in 2018. From a panoramic type of display of news from the profession and the activities of the professional society, I made an effort to direct the path of *Rheumatism* towards the publication of professional papers of the highest quality. I believed that it is more appropriate, considering the new trends and technologies, to present the information about professional meetings and other similar activities on the official website of the Society, in journals of different profiles intended for a wider readership and on social media platforms. I made it as a rule for all manuscripts submitted for the purpose of being selected for the journal, except for the commissioned review papers, to be blindly reviewed by two experts who were holders of PhD or who were given the title of Primarius. This was done for the purpose of achieving the highest possible quality. Furthermore, this resulted in a gradual improvement in the quality of the papers published in the *Rheumatism* journal, and the overall quality of the journal was catapulted to a level that other reputable journals strive for. Since 2019, the journal has been published in a bilingual manner, in Croatian and in English, with bilingual presentation within individual articles. In 2020, we have established a journal award for the best paper published in the *Rheumatism* journal in the previous year, which is selected by the members of the editorial board as another incentive for the publication of papers in the journal.

Throughout this whole period, the support of Prof. Branimir Anić, MD, PhD, the president of the Croatian Society for Rheumatology, who simultaneously served as the editor-in-chief of the *Liječnički vjesnik* journal, was extremely important to us. The *Liječnički vjesnik* journal provided supplements for the *Rheumatism* journal, thus enabling it to continue the steady path of its publication and it also proved to be helpful in our endeavours to obtain a license for the purpose of meeting certain administrative requirements. Continuous funding of the journal by the Croatian Society for Rheumatology was a prerequisite for the engagement of permanent external associates: a proofreader for the Croatian language, a proofreader and translator for the English language, and a graphic designer.

In the last ten-year period, *Rheumatism* was omitted from the Medline database, so the last issues published in that database were those from 2016. With this happening, the *Rheumatism* journal, which was a part of that database since its very beginning in 1954, experi-

dinog članka. Od 2020. godine ustanovili smo nagradu časopisa za najbolji rad objavljen u *Reumatizmu* u prethodnoj godini, koji biraju članovi Uredničkog odbora, kao još jedan poticaj za objavu radova u časopisu.

U cijelom ovom razdoblju izuzetno nam je važna bila podrška prof. dr. sc. Branimira Anića, predsjednika Hrvatskoga reumatološkog društva, istodobno glavnog urednika *Liječničkog vjesnika*, s kojim se časopisom *Reumatizam* nadopunjavao i pomagao, uključujući i dobivanje licencije za pojedine administrativne zahtjeve. Stabilno financiranje časopisa od strane Hrvatskoga reumatološkog društva bilo je preduvjet angažmana stalnih vanjskih suradnika: lektora za hrvatski jezik, lektora i prevoditelja za engleski jezik i grafičkog urednika.

U posljednjem desetogodišnjem razdoblju dogodilo se da je *Reumatizam* izostavljen iz *Medlinea* tako da su zadnji brojevi koji su objavljeni u toj bazi bili oni iz 2016. godine. Time je *Reumatizam*, koji je u toj bazi bio od samog svoga početka, 1954. godine, podijelio sudbinu brojnih drugih svjetskih časopisa kao posljedicu pooštravanja kriterija za navedenu bazu časopisa. Prethodno navedenim unaprjeđenjima, koja su započela i prije ovog događaja, *Reumatizam* je zadovoljio glavne formalne uvjete za uvođenje časopisa u tu ili neku drugu bazu časopisa, npr. *Scopus*. Ono što nam još nedostaje jest striktna ažurnost redovitog izlaženja časopisa kao ključnog uvjeta indeksacije u nekoj svjetski priznatoj bazi časopisa. Taj se redoviti ritam izlaženja časopisa može uspostaviti samo većim priljevom kvalitetnih rukopisa i većom ažurnošću recenzenata, dok je istovremeno „bazen" za oboje u našim uvjetima relativno malen. Stoga smo u prethodnom razdoblju razmišljali o proširenju baze potencijalnih autora kao i recenzenata na takav način da se uključe i reumatološka društva susjednih zemalja, npr. Slovenije, ali sve je ostalo na razini ideje. Također, razmišljalo se i o potpunom prelasku na engleski jezik, čime bi se povećao interes potencijalnih autora izvan Hrvatske te poboljšala mogućnost provjere plagijarizma, za što se, s obzirom na inače relativno mali priljev radova i jer sam prilikom tog prijedloga bio pri kraju drugog mandata urednika, ipak u konačnici nisam odlučio. Sve su to izazovi za novoga glavnog urednika koji će, nadam se, na njih uspješno odgovoriti.

Na kraju, uz pogled na povijesni razvoj i zahvalnost prema prethodnim glavnim i odgovornim urednicima, ovom prigodom prvenstveno želim zahvaliti svim autorima i recenzentima te suradnicima u sklopu uredništva časopisa u svom desetogodišnjem mandatu glavnog urednika, kao i volonterkama Marijani Bregni i Draženki Kontek. Zajedničkim smo angažmanom u izazovnim vremenima, uključujući pandemiju COVID-19, uspjeli održati časopis i poboljšati njegovu

enced the same fate of numerous other world journals, as a result of the stricter selection criteria of the aforementioned journal database. With the previously mentioned improvements that were introduced to the *Rheumatism* journal, which were in the initial stage of implementation prior to this happening, *Rheumatism* has managed to meet the main formal conditions for its introduction into this or some other database, such as Scopus, for example. The part that we are lacking in is the strict up-to-dateness in relation to the regular publication of the journal, which is a key requirement for indexing in some world-recognized journal databases. This regular rhythm of journal publication can only be established through a greater influx of quality manuscripts and greater promptness of reviewers. The issue is that the pool for both of these is relatively small in our case. Therefore, in the previous period, we have thought about expanding the base of potential authors as well as reviewers in such a way as to include the rheumatology societies of our neighbouring countries, for example, Slovenia, in our base of authors. Unfortunately, this still remains as an idea that has not been put into practice. In addition to that, we thought about completely switching to English language, which would increase the interest of potential authors beyond Croatia, and improve the possibility of plagiarism checks. However, considering the relatively small influx of papers and the fact that I was nearing the end of my second term as the editor-in-chief of the *Rheumatism* journal at the time when that proposal was made, I opted not to make a decision on this matter. These are all challenges that will be tackled by the new editor-in-chief, and I hope that they will manage to find a solution for all of the ongoing issues.

Finally, as we are taking a look-back at the historical development of this journal and expressing our gratitude to the previous editors-in-chief, I would like to take this opportunity to thank all of the authors and reviewers, as well as the collaborators within the journal's editorial board who I have had the pleasure of cooperating with during my ten-year term as the editor-in-chief of the *Rheumatism* journal. I would also like to express my gratitude to our volunteers, Marijana Bregni and Draženka Kontek. We have managed to keep this journal going and improve its quality through our joint efforts in challenging times, especially during the COVID-19 pandemic. I strongly believe that *Rheumatism* will continue to be recognized as a renowned rheumatology journal, and that its quality and visibility will prosper even further over time.

Warmest regards and best wishes to you all!

kvalitetu. Vjerujem da će *Reumatizam* i dalje biti prepoznat kao vrijedan reumatološki časopis, uz daljnje podizanje njegove kvalitete i vidljivosti.

Srdačan pozdrav i svako dobro!

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PROFESSIONAL PAPER STRUČNI RAD

LUNG DISEASES IN RHEUMATOID ARTHRITIS – EXPERIENCES OF A TERTIARY CENTRE

BOLESTI PLUĆA U REUMATOIDNOM ARTRITISU – ISKUSTVA TERCIJARNOG CENTRA

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Abstract

Introduction. Rheumatoid arthritis (RA) is a systemic autoimmune disease, and its most common extra-articular manifestation is involvement of the lung parenchyma and pleura. The most common pleuropulmonary manifestation of RA is interstitial lung disease (ILD). The aim of this study was to show the frequency and characteristics of pleuropulmonary manifestations in patients with RA who were treated at the University Hospital Centre Split. *Subjects and methods.* Patients treated with biological and targeted synthetic disease-modifying antirheumatic drugs (DMARDs) who were diagnosed with RA according to the 2010 EULAR/ACR classification criteria were included in the study. Data from the archive of medical records were analysed using the method of descriptive statistics. *Results.* A total of 188 patients with RA were analysed. There were 18 (9.6%) patients with pleuropulmonary manifestations of RA. The average age was 66.5 (range: 48–85), and 13 of these patients were women (72.2%). 6 patients were smokers (33.3%). 12 patients were diagnosed with seropositive RA (66.6%), and four of these patients were smokers (33.3%). Patients with seropositive RA and associated pleuropulmonary manifestations had the shortest disease duration (<10 years), and there were five of them (83.3%), with four of them being smokers (66.6%). Nodular lung disease was found in 12 patients (66.6%), and 9 of these patients had seropositive RA (75%). Bronchiectasis was found in 8 patients (44.4%) and pleural thickening in three patients (16,6%). ILD was radiologically diagnosed in 10 patients (55.5%), and 7 of them had seropositive RA (70%). The pattern of usual interstitial pneumonia (UIP) was present in 8 patients (80%), while the pattern of non-specific interstitial pneumonia (NSIP) was found in two patients (20%). *Conclusion.* Patients with seropositive RA have a higher risk of developing nodular lung disease and ILD than patients with seronegative RA. The most common radiologically determined pattern of ILD was UIP, which coincides with data available from the literature.

Key words: arthritis, rheumatoid, lung diseases, interstitial

Sažetak

Uvod. Reumatoidni artritis (RA) je sustavna autoimuna bolest čija je najčešća izvanzglobna manifestacija zahvaćanje plućnog parenhima i pleure. Najčešća pleuropulmonalna manifestacija RA je intersticijska bolest pluća (engl. interstitial lung disease, skr. ILD). Cilj istraživanja bio je prikazati učestalost i obilježja pleuropulmonalnih očitovanja u bolesnika s reumatoidnim artritisom liječenih u Kliničkom bolničkom centru Split. *Ispitanici i metode.* U istraživanje

su uključeni bolesnici na biološkoj i ciljanoj sintetskoj terapiji antireumaticima koji mijenjaju tijek bolesti (engl. disease-modifying antirheumatic drugs, skr. DMARDs) s dijagnozom RA prema EULAR/ACR klasifikacijskim kriterijima iz 2010. godine. Analizirani su podatci iz arhive medicinske dokumentacije metodom deskriptivne statistike. *Rezultati.* Ukupno je analizirano 188 bolesnika s RA-om. Broj bolesnika s pleuropulmonalnim očitovanjima RA bio je 18 (9,6%). Prosječna životna dob bila je 66,5 godina (raspon: 48 – 85), od toga je 13 bilo žena (72,2%). Među oboljelima, šest ispitanika bili su pušači (33,3%), od čega ih je četiri ženskoga spola (66,6%). U dvanaest bolesnika dijagnosticiran je seropozitivni RA (66,6%), od kojih je četvero bilo pušača (33,3%). Bolesnici sa seropozitivnim RA-om i pridruženim pleuropulmonalnim očitovanjima imali su najkraće trajanje bolesti (<10 godina), a bilo ih je petero (83,3%), od čega je četvero bilo pušača (66,6%). Nodularna bolest pluća bila je utvrđena u dvanaest bolesnika (66,6%), a devet ih je imalo seropozitivni RA (75%). Bronhiektazije su nađene u osam bolesnika (44,4%) te zadebljanje pleure u tri bolesnika (16,6%). U deset bolesnika (55,5%) radiološki je utvrđena ILD, od čega ih je sedam imalo seropozitivni RA (70%). Uzorak uobičajene intersticijske pneumonije (UIP) bio je zastupljen u osam bolesnika (80%), dok je uzorak nespecifične intersticijske pneumonije (NSIP) utvrđen u dva bolesnika (20%). *Zaključak.* U bolesnika sa seropozitivnim RA-om utvrđena je veća prevalencija nodularne te intersticijske bolesti pluća, nego u seronegativnih bolesnika. Najčešći radiološki utvrđen uzorak ILD-a bio je UIP, što se poklapa s podatcima dostupnim iz literature.

Ključne riječi: artritis, reumatoidni, plućne bolesti, intersticijske

INTRODUCTION

Rheumatoid arthritis (RA) is a systemic autoimmune disease whose prevalence is slightly less than 1% in developed countries (1). The most common extra-articular manifestation of RA is involvement of the lung parenchyma and pleura, primarily interstitial lung disease (ILD), with an estimated prevalence between 1.8% and 67% (2). In most patients, lung disease occurs within the period of nine years since RA diagnosis, although respiratory symptoms may precede the occurrence of joint disease in 2.3% to 10% of patients (3,4). Pleuropulmonary diseases in patients with RA include parenchymal lung diseases such as ILD and nodular lung disease, followed by airway diseases such as bronchiolitis, bronchiectasis, and chronic small airways obstruction, and pleural diseases such as pleurisy, pleural effusion, and pleural thickening. Chronic infections of the respiratory system can also be the cause of lung disease, particularly bronchiectasis. The impact of immunomodulators that increase the risk of developing infections, but can have a direct toxic effect on the lung parenchyma, is also important (4,5). Lung diseases present with symptoms such as exertion intolerance, chest pains and cough, but they can also be asymptomatic. Since pleuropulmonary diseases are responsible for 10–20% of mortality cases in patients with RA, clinical, functional and radiological monitoring is necessary in order to identify patients with progressive lung disease in the earliest possible stage (6,7). Factors that increase mortality include old age, male gender, history of smoking, low values of pulmonary function tests, pattern of usual interstitial pneumonia (UIP) shown on high-resolution computed tomography (HRCT), presence of emphysema, and acute exacerbation of ILD (8). Methotrexate (MTX) treatment is recommended as a first-line treatment for RA, as it effectively reduces disease activity, morbidity,

UVOD

Reumatoidni artritis (RA) je sustavna autoimuna bolest čija je prevalencija nešto manja od 1% u razvijenim zemljama (1). Najčešće izvanzglobno očitovanje RA jest zahvaćanje plućnog parenhima i pleure, ponajprije intersticijska bolest pluća (engl. interstitial lung disease, skr. ILD), s procijenjenom prevalencijom između 1,8% i 67% (2). U većine bolesnika bolest pluća javlja se unutar devet godina od postavljanja dijagnoze RA, iako respiratorni simptomi mogu prethoditi zglobnoj bolesti u 2,3% do 10% bolesnika (3,4). Pleuropulmonalni poremećaji u bolesnika s RA-om obuhvaćaju bolesti plućnog parenhima koje uključuju ILD te nodularnu bolest pluća, zatim bolesti dišnih putova koji uključuju bronhiolitis, bronhiektazije i kroničnu opstrukciju malih dišnih putova te bolesti pleure koje uključuju pleuritis, pleuralni izljev i zadebljanje pleure. Kronične infekcije dišnog sustava također mogu biti uzrok bolesti pluća, osobito bronhiektazija. Važan je i utjecaj imunomodulacijskih lijekova koji povećavaju rizik za razvoj infekcija, ali mogu imati izravni toksični učinak na plućni parenhim (4,5). Bolesti pluća prezentiraju se intolerancijom napora, bolovima u prsima te kašljem, međutim mogu biti i asimptomatske. Budući da su pleuropulmonalni poremećaji odgovorni za 10 – 20% smrtnosti u bolesnika s RA-om, neophodno je kliničko, funkcijsko i radiološko praćenje kako bismo što ranije prepoznali bolesnike s progresivnom bolešću pluća (6,7). Čimbenici koji povećavaju mortalitet uključuju stariju dob bolesnika, muški spol, anamnezu pušenja, snižene vrijednosti testova plućne funkcije, uzorak uobičajene intersticijske pneumonije (UIP) na kompjuteriziranoj tomografiji visoke rezolucije (engl. skr. HRCT), prisutnost emfizema te akutnu egzacerbaciju ILD-a (8). Liječenje metotreksatom (engl. skr. MTX) preporučuje se kao prva linija liječenja RA, budući da učinkovito smanjuje aktivnost bolesti, mor-

mortality, and the occurrence of RA-related ILD (RA-ILD) (9,10).

The aim of our study was to present the clinical features of patients with pleuropulmonary manifestations as part of RA, in a sample of patients treated with biologics or targeted synthetic disease-modifying antirheumatic drugs (DMARDs).

SUBJECTS AND METHODS

This retrospective observational study was conducted during the course of 2022 on patients with RA, who were treated with biologics and targeted synthetic DMARDs, at the Division of Rheumatology, Allergy and Clinical Immunology of the University Hospital Centre Split. Data taken from the medical records archived at the outpatient clinic, inpatient unit and day-care hospital of the Division were used in the study. Moreover, the study included patients older than 18 years of age who met the 2010 EULAR/ACR classification criteria for RA, which was the inclusion criterion for the participation in the study. The exclusion criteria included the presence of another inflammatory rheumatic disease other than RA and known lung disease, the occurrence of which is not dependent on the presence of RA. Lung involvement was based on the findings of the high-resolution CT (HRCT) of the chest. Age and gender of the subjects, presence of rheumatoid factor (RF) and antibodies to anti-cyclic citrullinated peptide (anti-CCP), disease duration, history of smoking, pleuropulmonary manifestations and therapy were analysed.

Methods of descriptive statistics were used in the analysis of the results.

RESULTS

A total of 188 patients with RA who were treated with biologics and targeted synthetic DMARDs were included in the study. There were 18 (9.6%) patients with pleuropulmonary manifestations of RA, whose average age was 66.5 (range: 48–85), and 13 of these patients were women (72.2%). 6 patients were smokers (33.3%) and four of them were women (66.6%). 12 patients were diagnosed with seropositive RA (66.6%), and four of these patients were smokers (33.3%). According to disease duration, we divided the subjects into three groups (<10 years, 10–20 years, >20 years), with 6 patients in each group (33.3%). Patients with seropositive RA and associated pleuropulmonary manifestations had the shortest disease duration (<10 years), and there were five of them (83.3%), with four of them being smokers (66.6%). Nodular lung disease was found in 12 patients (66.6%), and 9 of these patients had seropositive RA (75%). Bronchiectasis was found in 8 patients (44.4%) and pleural thickening in three

biditet, mortalitet te pojavu ILD-a povezanog s RA-om (RA-ILD) (9,10).

Cilj našeg istraživanja bio je prikazati klinička obilježja bolesnika s pleuropulmonalnim očitovanjima u sklopu RA, u uzorku bolesnika liječenih biološkim ili ciljanim sintetskim antireumaticima koji mijenjaju tijek bolesti (engl. skr. DMARDs).

ISPITANICI I METODE

U ovo retrospektivno opservacijsko istraživanje uključeni su bolesnici s RA-om, koji su liječeni biološkom terapijom i ciljanim sintetskim DMARDs-ima, u Zavodu za reumatologiju, kliničku imunologiju i alergologiju Kliničkoga bolničkog centra Split tijekom 2022. godine. Korišteni su podatci iz medicinske dokumentacije u ambulanti, stacionaru i dnevnoj bolnici Zavoda. U istraživanje su uključeni bolesnici stariji od 18 godina koji su zadovoljavali klasifikacijske kriterije EULAR/ACR iz 2010. godine za RA, što je bio uključni kriterij. Isključni kriteriji bili su prisutnost druge upalne reumatske bolesti osim RA te poznata bolest pluća neovisno o RA-u. Zahvaćenost pluća temeljila se na rezultatima HRCT-a prsišta. Analizirani su dob i spol ispitanika, prisutnost reumatoidnog faktora (RF) i antitijela na ciklički citrulirani peptid (anti-CCP), trajanje bolesti, povijest pušenja, pleuropulmonalna očitovanja i terapija.

U analizi rezultata korištene su metode deskriptivne statistike.

REZULTATI

Ukupno je uključeno 188 bolesnika s RA-om koji su liječeni biološkim i ciljanim sintetskim DMARDs-ima. Broj bolesnika s pleuropulmonalnim očitovanjima u sklopu RA bio je 18 (9,6%), a njihova prosječna životna dob bila je 66,5 godina (raspon: 48 – 85 godina), od čega je bilo 13 žena (72,2%). Među oboljelima, šest ispitanika su bili pušači (33,3%), od čega ih je četiri žene (66,6%). U dvanaest bolesnika dijagnosticiran je seropozitivni RA (66,6%), od kojih je četvero bilo pušača (33,3%). Prema trajanju bolesti, ispitanike smo podijelili u tri skupine (<10 godina, 10 – 20 godina, >20 godina) te smo dobili po šest bolesnika u svakoj skupini (33,3%). Bolesnici sa seropozitivnim RA-om i pridruženim pleuropulmonalnim očitovanjima imali su najkraće trajanje bolesti (<10 godina), a njih je bilo petero (83,3%), od čega je četvero bilo pušača (66,6%). Nodularna bolest pluća bila je zastupljena u dvanaest bolesnika (66,6%), od čega je njih devet imalo seropozitivni RA (75%). Bronhiektazije su nađene u osam bolesnika (44,4%) a zadebljanje pleure u tri bolesnika (16,6%). U deset bolesnika (55,5%) radiološki je utvrđena ILD, od čega ih je sedam imalo seropozitivni RA (70%). Uzorak uobičajene intersticijske pneumonije (UIP) bio je zastupljen u osam bolesnika (80%), dok je

Table 1 Pulmonary diseases in patients with rheumatoid arthritis
Tablica 1. Pleuropulmonalna očitovanja u bolesnika s reumatoidnim artritisom

	Year of birth / Godina rođenja	Gender/Spol	Disease duration in years / Trajanje bolesti u godinama	RF / anti-CCP	ILD /IBP	Nodular lung disease / Nodularna bolest pluća	Bronchiectasis / Bronhiektazije	Pleural thickening / Zadebljanje pleure	Smoking / Pušenje
1	1954.	Man/Muškarac		–	–	+	+	+	+
2	1964.	Woman/Žena		+	+	–	+	–	+
3	1959.	Woman/Žena	<10	+	+	+	–	+	–
4	1963.	Woman/Žena		+	+	+	–	–	+
5	1959.	Man/Muškarac		+	–	–	+	–	+
6	1953.	Man/Muškarac		+	–	+	–	–	–
7	1967.	Woman/Žena		+	–	+	–	–	–
8	1954.	Woman/Žena		+	–	+	–	–	–
9	1974.	Woman/Žena	10–20	–	+	–	–	–	–
10	1957.	Woman/Žena		+	+	+	+	–	–
11	1949.	Woman/Žena		–	+	–	+	–	–
12	1959.	Woman/Žena		–	+	–	+	–	+
13	1951.	Man/Muškarac		–	–	+	–	–	–
14	1957.	Woman/Žena		+	+	+	+	–	–
15	1937.	Woman/Žena	>30	+	+	+	–	–	+
16	1948.	Woman/Žena		+	–	+	–	+	–
17	1952.	Woman/Žena		+	+	–	+	–	–
18	1953.	Man/Muškarac		–	–	+	–	–	–

Legend / Legenda: RF – Rheumatoid factor / reumatoidni faktor, anti-CCP – Anti-Cyclic Citrullinated Peptide Antibody / antitijela na ciklički citrulirani peptid, ILD/IBP – interstitial lung disease / intersticijska bolest pluća

patients (16,6%). ILD was radiologically diagnosed in 10 patients (55.5%), and 7 of them had seropositive RA (70%). The pattern of usual interstitial pneumonia (UIP) was present in 8 patients (80%), while the pattern of non-specific interstitial pneumonia (NSIP) was found in two patients (20%) (Table 1). 8 patients (44.4%) were treated with rituximab, while four patients were treated with TNF-α and IL-6 inhibitors (22.2% in both cases), and two patients were treated with Janus kinase (JAK) inhibitors (11.1%). 10 patients (55.5%) were treated with concomitant therapy with methotrexate (MTX).

DISCUSSION

Pleuropulmonary diseases occur in 30–40% of patients with RA and are the second main cause of mortality, right after cardiovascular diseases (11). There are several factors associated with the development of lung disease in RA. It has been confirmed that lung disorders are associated with the male gender, seropositive RA, smoking and mucin-5B (MUC-5B) gene mutation. The MUC-5B polymorphism leads to inefficient removal of inhaled particles and pathogens in the re-

uzorak nespecifične intersticijske pneumonije (NSIP) utvrđen u dva bolesnika (20%) (tablica 1). Broj bolesnika liječenih rituksimabom bio je osam (44,4%), dok je po četvero bolesnika liječeno TNFα i IL-6 inhibitorima (oboje po 22,2%), a dvoje bolesnika inhibitorima Janus kinaze (JAK) (11,1%). Na konkomitantnoj terapiji s MTX-om bilo je deset bolesnika (55,5%).

RASPRAVA

Pleuropulmonalni poremećaji javljaju se u 30 – 40% bolesnika s RA-om i drugi su glavni uzrok smrtnosti, odmah iza kardiovaskularnih bolesti (11). Postoji više čimbenika povezanih s nastankom bolesti pluća u RA. Potvrđena je povezanost plućnih poremećaja s muškim spolom, seropozitivnim RA-om, pušenjem te mutacijom gena za mucin 5B (MUC5B). Polimorfizam MUC5B dovodi do neučinkovitog uklanjanja inhaliranih čestica i patogena u sluznici dišnog sustava, povećavajući rizik za nastanak RA-ILD-a (3,4,12,13). Najčešći uzorci na HRCT-u toraksa u bolesnika s RA-ILD-om su uobičajena intersticijska pneumonija (UIP), nespecifična intersticijska pneumonija (NSIP), limfocitna intersticijska pneumonija (LIP), organizirana pneumonija (OP),

spiratory mucosa, thus increasing the risk of RA-ILD development (3,4,12,13). The most common patterns found on chest HRCT in patients with RA-ILD are usual interstitial pneumonia (UIP), nonspecific interstitial pneumonia (NSIP), lymphocytic interstitial pneumonia (LIP), organizing pneumonia (OP), acute interstitial pneumonia (AIP), and desquamative interstitial pneumonia (DIP) (6).

In our study, the proportion of patients with pleuropulmonary disorders in RA was 9.6%, with an average age of 66.5, which is in accordance with data from the literature. The subjects were predominantly female (72.2%), while in some studies, male predominance was established (3–5,7).

Smoking was present in 6 patients (33.3%), which is slightly less than in the researched literature, where smokers comprised more than 50% of subjects, especially with RA-ILD pattern found on chest HRCT (3, 4). In our study, the majority of smokers were female (66.6%), while in the multicentre study conducted by Kelly et al., a larger proportion of smokers were male (3). The RA-ILD pattern found on chest HRCT was present in all subjects who used tobacco products, in contrast to the aforementioned study conducted by Kelly and colleagues, which did not establish that smoking is a risk factor for the development of RA-ILD in women (3). The mentioned deviation may be a consequence of the smaller number of subjects in our study. It is believed that smoking induces the formation of enzymes that promote the modification of peptides in the lung parenchyma, that is, the conversion of arginine into citrulline, which binds to human leukocyte antigen II (HLA II) on antigen-presenting cells (the so-called "common epitope" HLA-DRB1). This type of a more immunogenic, citrullinated peptide is presented to T lymphocytes and leads to the formation of anti-CCP antibodies, activation of cytokines and growth factors (vascular endothelial growth factor — VEGF, platelet-derived growth factor — PDGF) that contribute to fibroblast proliferation (5,11,13,14).

Patients with RA have elevated values of circulating RF and anti-CCP antibodies, which can be present in the serum several years before the clinical onset of the disease. Both antibodies may be associated with the development of lung disease in RA, especially anti-CCP which is primarily associated with the development of RA-ILD (5,13). In our study, 12 patients were diagnosed with seropositive RA (66.6%), which is in accordance with data from the literature (3, 4). However, we found that in the case of 5 patients (83.3%) with seropositive RA there was a significantly shorter period until the diagnosis of lung disease (<10 years) and that four of them were smokers (66.6%). This data shows that seropositivity and smoking lead to an earlier onset of pulmonary manifestations in patients with RA.

akutna intersticijska pneumonija (AIP) i deskvamativna intersticijska pneumonija (DIP) (6).

U našem istraživanju, udio bolesnika s pleuropulmonalnim poremećajima u RA-u bio je 9,6%, s prosječnom dobi 66,5 godina, što je u skladu s podatcima iz literature. Prevladavale su osobe ženskog spola (72,2%), dok je u nekim istraživanjima utvrđena predominacija muškog spola (3–5,7).

Pušenje je bilo zastupljeno u šest bolesnika (33,3%), što je nešto manje nego u pretraženoj literaturi, gdje su pušači obuhvaćali više od 50% ispitanika, osobito s uzorkom RA-ILD-a na HRCT-u toraksa (3,4). U našem istraživanju većina pušača bile su osobe ženskog spola (66,6%), dok je u multicentričnom istraživanju Kellyja i suradnika veći udio pušača bio muškoga spola (3). Uzorak RA-ILD-a na HRCT-u toraksa bio je zastupljen u svih ispitanica koje su koristile duhanske proizvode, za razliku od navedenog istraživanja Kellyja i suradnika koje nije utvrdilo da je pušenje rizični čimbenik za razvoj RA-ILD-a u žena (3). Spomenuto odstupanje moguće je posljedica manjeg broja ispitanika u našem istraživanju. Smatra se da pušenje inducira nastanak enzima koji potiču modifikaciju peptida u plućnom parenhimu, odnosno konverziju arginina u citrulin koji se veže za humani leukocitni antigen II (HLA II) na antigen-predočnim stanicama (tzv. „zajednički epitop" HLA-DRB1). Takav imunogeničniji, citrulirani peptid predočuje se T-limfocitima te dovodi do stvaranja anti-CCP antitijela, aktivacije citokina i čimbenika rasta (čimbenik rasta vaskularnog endotela – VEGF, čimbenik rasta podrijetlom iz trombocita – PDGF) koji pridonose proliferaciji fibroblasta (5,11,13,14).

Bolesnici s RA-om imaju povišene vrijednosti cirkulirajućih antitijela RF i anti-CCP, koja mogu biti prisutna u serumu i nekoliko godina prije kliničke pojave bolesti. Oba antitijela mogu biti povezana s nastankom bolesti pluća u RA, osobito anti-CCP koji je povezan ponajprije s razvojem RA-ILD-a (5,13). U našem istraživanju, u dvanaest bolesnika dijagnosticiran je seropozitivni RA (66,6%), što je u skladu s podatcima iz literature (3,4). Ipak, utvrdili smo da je pet bolesnika (83,3%) sa seropozitivnim RA-om imalo značajno kraće vrijeme do postavljanja dijagnoze bolesti pluća (<10 godina) te da ih je četvero bilo pušača (66,6%). Ovaj podatak pokazuje da seropozitivitet i pušenje dovode do ranije pojave plućnih očitovanja u bolesnika s RA-om.

U našem istraživanju najzastupljenija bolest plućnog parenhima bila je nodularna bolest pluća u dvanaest bolesnika (66,6%), što je nešto više nego u dostupnoj literaturi u kojoj je prevalencija iznosila između 1% i 32% (4,15–17). Ovo odstupanje u našim rezultatima može biti povezano s manjim brojem ispitanika. Druga po zastupljenosti bila je RA-ILD u deset ispitanika (55,5%), od kojih ih je sedam (70%) imalo seropozitivni RA. Prema dostupnoj literaturi, vjerojatnost da će bole-

In our study, the most common disease of the lung parenchyma was nodular lung disease, which was found in 12 patients (66.6%), which is slightly more than in the available literature, where the prevalence was between 1% and 32% (4,15–17). This deviation in our results may be related to a smaller number of subjects in our study. The second most common disease of the lung parenchyma was RA-ILD, which was found in 10 subjects (55.5%), and 7 of them (70%) had seropositive RA. According to the available literature, the probability that patients with RA will develop ILD is nine times higher than in the general population, and the prevalence of RA-ILD in other studies was as high as 67% (2,4–6,15–17). In our study, the most common RA-ILD pattern found on chest HRCT was the UIP pattern (80%), which is slightly higher than in the available studies, which could be a consequence of late diagnosis of pulmonary manifestations (4,15,17). Bronchiectasis was the most common manifestation of respiratory diseases and was present in 8 patients (44.4%), four of whom were smokers (50%). In other studies, the prevalence of bronchiectasis was somewhat lower and was up to 30% (5,15–17). More frequent bronchiectasis are probably caused by smoking and chronic inflammation. The most common manifestation of pleural involvement was pleural thickening, which was present in 3 subjects (16.6%). All subjects with involvement of the pleura also had nodular lung disease. In other studies, a slightly lower frequency of involvement of the pleura was demonstrated, approximately between 3 and 5%, and this primarily includes pleural effusions (5,15–17). It should be noted that it was difficult to make an estimation of prevalence due to the great heterogeneity among studies and the imaging methods used for the purpose of making a diagnosis. Given that malignant diseases can present with symptoms that are similar to those of nodular lung disease, the importance of multidisciplinary collaboration with pulmonologists should be highlighted.

In patients with RA, it is important to immediately evaluate the presence of pulmonary manifestations, the severity of the disease, and identify patients with progressive disease through further monitoring. Factors suggestive of progressive disease are worsening symptoms, low values of pulmonary function tests (PFTs), and/or radiological progression. It is recommended to perform pulmonary function tests in all patients who are newly diagnosed with RA. In asymptomatic patients, pulmonary function tests should be performed once a year, and in the case of RA-ILD confirmed through HRCT, they should be repeated every 6 months (18). Disease severity and progression are two major factors to consider when deciding on immunomodulatory treatment in patients with RA-ILD. Among other things, it is necessary to consider other

snici s RA-om razviti ILD devet je puta veća u odnosu na opću populaciju te je prevalencija RA-ILD-a u drugim istraživanjima iznosila i do 67% (2,4–6,15–17). U našem istraživanju najzastupljeniji uzorak RA-ILD-a na HRCT-u toraksa bio je uzorak UIP-a (80%), što je nešto više nego u dostupnim istraživanjima, što bi moglo biti posljedica kasnijeg dijagnosticiranja plućnih promjena (4,6,15,17). Bronhiektazije su bile najčešća očitovanja bolesti dišnih putova te su bile zastupljene u osam bolesnika (44,4%), a njih četvero je bilo pušača (50%). U drugim istraživanjima prevalencija bronhiektazija bila je nešto manja te je iznosila do 30% (5,15–17). U podlozi učestalijih bronhiektazija vjerojatno su pušenje i kronična upala. Najčešća manifestacija zahvaćenosti plućne ovojnice bilo je zadebljanje pleure, što je bilo prisutno u tri ispitanika (16,6%). Svi su ispitanici sa zahvaćenom pleurom imali i nodularnu bolest pluća. U drugim istraživanjima dokazana je nešto manja učestalost zahvaćanja pleure, otprilike između 3% i 5%, i to ponajprije pleuralni izljevi (5,15–17). Potrebno je napomenuti da je procjena prevalencije bila otežana zbog velike heterogenosti među studijama i slikovnih metoda korištenih za postavljanje dijagnoze. Budući da se i maligne bolesti mogu prezentirati slično nodularnoj bolesti pluća, valja istaknuti važnost multidisciplinarne suradnje sa specijalistima pulmologije.

U bolesnika s RA-om važno je odmah u početku procijeniti prisutnost plućnih manifestacija i težinu bolesti te daljnjim praćenjem prepoznati bolesnike s progresivnom bolešću. Čimbenici koji upućuju na progresivnu bolest jesu pogoršanje simptoma, smanjenje testova plućne funkcije (PFT) i/ili radiološka progresija. Preporučljivo je obaviti testove plućne funkcije u svih novodijagnosticiranih bolesnika s RA-om. U asimptomatskih bolesnika testovi plućne funkcije trebali bi se kontrolirati jednom godišnje, a u slučaju HRCT-om utvrđene RA-ILD potrebno ih je ponavljati svakih šest mjeseci (18). Ozbiljnost i progresija bolesti dva su glavna čimbenika koja treba uzeti u obzir pri odlučivanju o imunomodulacijskom liječenju u bolesnika s RA-ILD-om. Među ostalim, potrebno je razmotriti i druge čimbenike, poput dobi i komorbiditeta kao i želje bolesnika kod donošenja terapijskih odluka (15,18). U našem istraživanju deset bolesnika bilo je na konkomitantnom liječenju metotreksatom (55,5%). Juge i suradnici su također u svom istraživanju naveli slične podatke koji su uključivali između 55,3% i 66,7% ispitanika liječenih metotreksatom te su dokazali smanjenu pojavnost RA-ILD-a u tih bolesnika (10). Osim konvencionalne terapije, osam ispitanika u našem istraživanju liječeno je rituksimabom (44,4%), po četvero je liječeno inhibitorima TNF-α i IL-6 (oboje po 22,2%) te dvoje ispitanika inhibitorima JAK (11,1%). U kohortnoj studiji provedenoj u Ujedinjenom Kraljevstvu rituksimab je pokazao zadovoljavajući sigurnosni profil u bolesni-

factors, such as age and comorbidities, as well as the patient's wishes when it comes to making decisions regarding treatment (15,18). In our study, 10 patients received concomitant treatment with methotrexate (55.5%). In their study, Juge et al also reported similar data, which included between 55.3% and 66.7% of subjects treated with methotrexate, and they proved a reduced incidence of RA-ILD in these patients (10). In addition to conventional therapy, 8 subjects in our study were treated with rituximab (44.4%), four of them were treated with TNF-α and IL-6 inhibitors (22.2% in both cases) and two subjects were treated with JAK inhibitors (11.1%). In a UK cohort study, rituximab showed a satisfactory safety profile in patients with RA-ILD, with stable or improved lung function over a 10-year follow-up period, which is similar to the results of a smaller study conducted by Fui et al (19,20). A study conducted by Detorakis et al. which included 82 subjects with RA, showed an effective and favourable safety profile of TNF-α inhibitors in these patients. Therefore, no new ILDs or exacerbations of already existing ILDs were found in the studied population (21). Treatment with tocilizumab has also shown a potential role in the stabilization of lung disease (6,22). In a retrospective cohort study conducted by Baker et al. RA patients treated with a JAK inhibitor had the lowest incidence of ILD compared to patients treated with biologics (23). Therefore, JAK inhibitors are introduced as the drug of choice in patients with ILD as part of RA.

CONCLUSION

In our sample of patients with RA who were treated with biologics or targeted synthetic DMARDs, a higher prevalence of nodular and interstitial lung diseases was found in seropositive patients than in seronegative patients. Therefore, it is necessary to conduct more intensive clinical, functional and radiological monitoring of patients with seropositive RA, especially smokers, in order to prevent the progression of lung disease. The most common radiological pattern of RA-ILD was usual interstitial pneumonia (UIP).

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ka s RA-ILD-om, uz stabilnu ili poboljšanu plućnu funkciju tijekom desetogodišnjeg razdoblja praćenja, slično kao i istraživanje Fui i suradnika s manjim brojem ispitanika (19,20). Istraživanje Detorakisa i suradnika koje je uključivalo 82 ispitanika s RA-om pokazalo je učinkovit i povoljan sigurnosni profil inhibitora TNF-α u ovih bolesnika. Dakle, nisu utvrđene novonastale ILD ili egzacerbacija već postojećih ILD-a u ispitivanoj populaciji (21). Liječenje tocilizumabom također je pokazalo potencijalnu ulogu u stabilizaciji plućne bolesti (6,22). U retrospektivnom kohortnom istraživanju Bakera i suradnika bolesnici s RA-om liječeni inhibitorom JAK imali su najmanju incidenciju ILD-a u usporedbi s bolesnicima liječenim biološkom terapijom (23). Stoga se inhibitori JAK nameću kao lijek izbora u bolesnika s ILD-om u sklopu RA.

ZAKLJUČAK

U našem uzorku bolesnika s RA-om liječenih biološkim ili ciljanim sintetskim DMARDs-ima, u seropozitivnih bolesnika utvrđena je veća prevalencija nodularne te intersticijske bolesti pluća nego u seronegativnih bolesnika. Stoga je bolesnike sa seropozitivnim RA-om, posebice pušače, neophodno intenzivnije klinički, funkcijski i radiološki nadzirati radi sprječavanja progresije bolesti pluća. Najčešći radiološki uzorak RA-ILD-a bio je UIP.

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CASE REPORT PRIKAZ BOLESNIKA

MASSIVE STROKE IN A YOUNG MALE PATIENT AS A MANIFESTATION OF TAKAYASU'S ARTERITIS

MASIVNI MOŽDANI UDAR U MLADOG BOLESNIKA KAO MANIFESTACIJA TAKAYASUOVOG ARTERITISA

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Abstract

Takayasu's arteritis (TA) is a less common type of large vessel vasculitis associated with inflammation of the wall of the aorta and its major branches. Patients with Takayasu's arteritis are at risk of developing neurological complications, such as cerebrovascular ischemic events. In this paper, we present a case of a male in his mid-fifties with no prior medical history, who abruptly developed right-sided hemiplegia and motor aphasia. Brain and neck angiography revealed an infarction in the territory of the left middle cerebral artery, along with a substantial occlusion of the left common carotid artery and left subclavian artery. The patient was diagnosed with Takayasu's arteritis. The occurrence of stroke in young patients should include, among the differential diagnoses, rheumatological diseases such as Takayasu's arteritis. A prompt diagnosis can lead to early treatment and reduced complications.

Keywords: Takayasu's arteritis, young-onset stroke, large vessel vasculitis, pulseless disease

Sažetak

Takayasuov arteritis (TA) rjeđi je tip vaskulitisa velikih krvnih žila povezan s upalom stijenke aorte i njezinih glavnih ogranaka. Bolesnici s Takayasuovim arteritisom izloženi su riziku od neuroloških komplikacija, poput cerebrovaskularnih ishemijskih događaja. U ovom radu predstavljamo slučaj muškarca u srednjim pedesetim godinama bez prethodne povijesti bolesti, koji je naglo razvio desnu hemiplegiju i motoričku afaziju. Angiografija mozga i vrata otkrila je infarkt u području lijeve srednje mozgovne arterije, zajedno sa značajnom okluzijom lijeve zajedničke karotidne arterije i lijeve potključne arterije. Bolesniku je dijagnosticiran Takayasuov arteritis. U slučaju moždanog udara u bolesnika mlađe dobi među diferencijalne dijagnoze treba uključiti i reumatološke bolesti kao što je Takayasuov arteritis. Brza dijagnoza može dovesti do ranog liječenja i manjeg broja komplikacija.

Ključne riječi: Takayasuov arteritis, moždani udar u mlađoj dobi, vaskulitis velikih krvnih žila, bolest bez pulsa

INTRODUCTION

Takayasu's arteritis (TA) is an infrequently occurring form of large vessel vasculitis linked to inflammation in the walls of the aorta and its primary branches, resulting in a reduction in blood flow and subsequent affectation (1). This leads to a pulseless disease with claudication, compromised peripheral pulses, and frequent ischemia (2).

UVOD

Takayasuov arteritis (TA) oblik je vaskulitisa velikih krvnih žila koji se rijetko javlja i povezan je s upalom stijenki aorte i njezinih primarnih ogranaka, što dovodi do smanjenja protoka krvi i posljedičnog oštećenja (1). To dovodi do bolesti bez pulsa s klaudikacijom, kompromitiranim perifernim pulsom i čestom ishemijom (2).

TA is rare, with some studies reporting an incidence of 1 patient per 1 million inhabitants and tends to be more common in women, with the onset of symptoms typically occurring between the ages of 15 and 25 (3).

Neurological involvement can occur in half of the patients, and strokes are a common complication of Takayasu's arteritis (4). In this paper, we describe the case of a male patient suffering from Takayasu's arteritis, who had a severe ischemic stroke as a manifestation.

CASE REPORT

In this paper, we present a case of a male in his mid-fifties with a history of generalized myalgias and arthralgias, accompanied by headaches and cervical pain that had worsened over the previous month. Due to the abrupt development of right-sided hemiplegia and motor aphasia, he was admitted to our hospital. No other systemic symptoms accompanied the patient's presentation.

During the physical examination, his vital signs revealed a normal heart and respiratory rate, with no need for oxygen support. However, it was unusual that the blood pressure in his right arm was recorded as 72/55 mmHg. The patient was non-verbal but responsive when it came to simple commands, and he exhibited right hemiplegia. Brain computed tomography (CT) showed the absence of hemorrhaging and mass effect. The patient was treated within a 4-hour timeframe from the onset of the stroke with alteplase, and there were no complications, but there was also no improvement in his neurological status.

Brain and neck angiography revealed an infarction in the territory of the left middle cerebral artery, along with a substantial occlusion of the left common carotid artery and the left subclavian artery, with extensive collaterals of the vertebral arteries and basilar artery. No signs of aortic dissection were observed. (Figure 1).

Brain magnetic resonance imaging (MRI) showed a left hemispheric stroke in the left middle cerebral artery (MCA), involving the temporal region, without any hemorrhagic transformation. (Figure 2).

This pattern was highly suggestive of Takayasu's arteritis. In a focused physical examination, the patient exhibited a wide pulse deficit and a difference in blood pressure of >10 mmHg between the two arms.

Laboratory tests revealed a normal hemogram with no electrolyte abnormalities. However, the erythrocyte sedimentation rate (ESR) was elevated at 40 mm/hour (normal range: 0–15 mm/hr). The rheumatological profile showed negative results for anti-nuclear antibodies (ANA), including extractable nuclear antigens (ENA) and double-stranded DNA (dsDNA). Additionally, vasculitis studies indicated negative results for anti-neutrophil cytoplasmic antibodies (ANCA).

With the findings of a pulseless disease, elevated erythrocyte sedimentation rate (ESR), and arterial

Takayasuov arteritis (TA) rijetka je bolest, a neka istraživanja pokazuju incidenciju od jednog bolesnika na milijun stanovnika. Bolest je češća u žena, sa simptomima koji se obično javljaju u dobi između 15 i 25 godina (3).

Neurološka zahvaćenost može se javiti u polovice bolesnika, a moždani udari česta su komplikacija Takayasuovog arteritisa (4). U ovom radu opisujemo slučaj bolesnika s Takayasuovim arteritisom koji je kao manifestaciju imao teški ishemijski moždani udar.

PRIKAZ BOLESNIKA

U ovom radu predstavljamo slučaj muškarca u srednjim pedesetim godinama s poviješću bolesti generaliziranih mialgija i artralgija, popraćenih glavoboljama i cervikalnim bolovima koji su se pogoršali tijekom prethodnog mjeseca. Zbog naglog razvoja hemiplegije na desnoj strani tijela i motoričke afazije, bolesnik je primljen u našu bolnicu. U kliničkoj slici bolesnika nisu bili prisutni drugi sustavni simptomi.

Tijekom fizikalnog pregleda, njegovi vitalni znakovi otkrili su normalan broj otkucaja srca i normalno disanje, bez potrebe za potpornom terapijom kisikom. Međutim, zanimljivo je da je njegov krvni tlak zabilježen kao 72/55 mmHg u desnoj ruci. Bolesnik je imao neverbalnu komunikaciju, ali je reagirao na jednostavne naredbe, a pokazivao je znakove hemiplegije na desnoj strani tijela. Kompjuterizirana tomografija mozga (CT) nije pokazala krvarenje ili masovni učinak. Liječen je alteplazom unutar vremenskog razdoblja od četiri sata od početka moždanog udara i u tom razdoblju nije došlo do komplikacija, ali nije došlo ni do poboljšanja bolesnikova neurološkog statusa.

Angiografijom mozga i vrata otkriven je infarkt u području lijeve srednje mozgovne arterije, zajedno sa značajnom okluzijom lijeve zajedničke karotidne arterije i lijeve potključne arterije, s opsežnim kolateralama vertebralnih arterija i bazilarne arterije. Nije bilo znakova disekcije aorte. (slika 1)

Magnetska rezonancija mozga (MR) pokazala je infarkt lijeve hemisfere u lijevoj srednjoj mozgovnoj arteriji (engl. *middle cerebral artery*, MCA), zahvaćajući temporalnu regiju, bez hemoragijske transformacije. (slika 2)

Ovaj je obrazac ukazivao na Takayasuov arteritis. Na fokusiranom fizikalnom pregledu, bolesnik je pokazao izražen deficit pulsa, a zabilježena je i razlika u krvnom tlaku od > 10 mmHg između dviju ruku.

Laboratorijske pretrage pokazale su urednu krvnu sliku (hemogram) bez poremećaja ravnoteže elektrolita. Međutim, sedimentacija eritrocita (SE) bila je povišena na 40 mm/h (normalni raspon: 0 – 15 mm/h). Reumatološki profil pokazao je negativne rezultate za antinuklearna antitijela (ANA), uključujući ekstrakti-

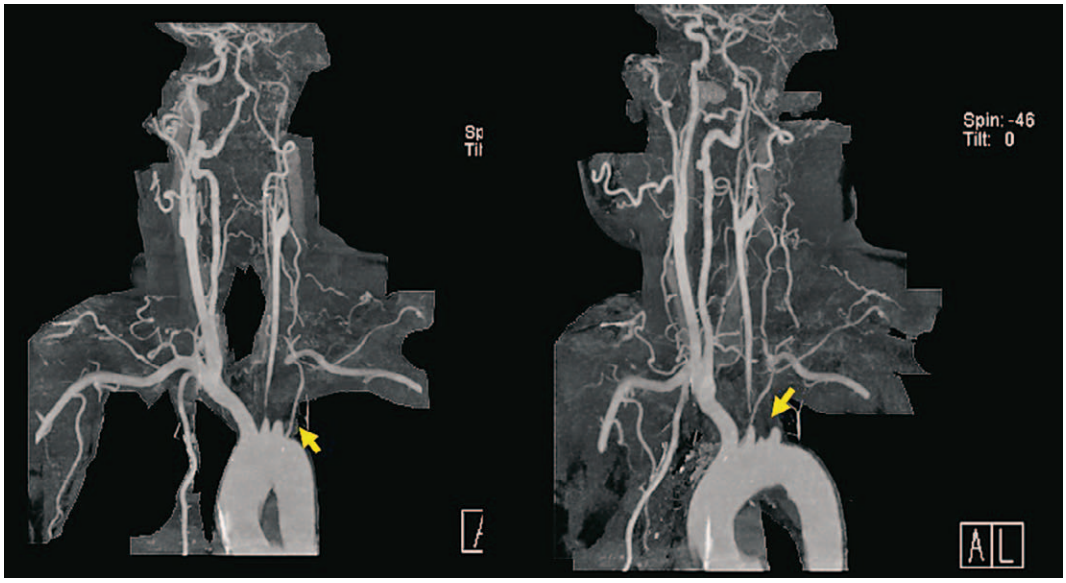

FIGURE 1. *Neck and brain CT angiogram.* Stenosis involving the origin of the left common carotid artery and left subclavian artery, with extensive collaterals of the vertebral arteries and basilar artery
SLIKA 1. CT angiografija vrata i mozga. Stenoza koja zahvaća ishodište lijeve zajedničke karotidne arterije i lijeve potključne arterije, s opsežnim kolateralama vertebralnih arterija i bazilarne arterije

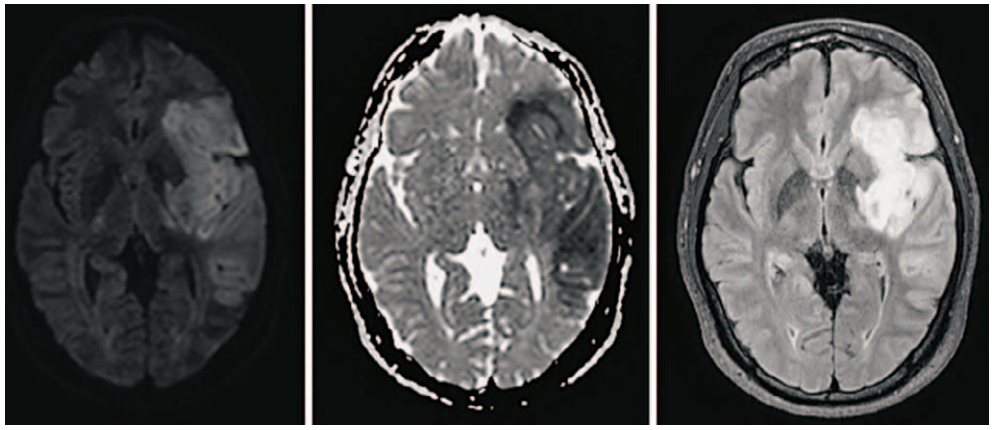

FIGURE 2. *Brain magnetic resonance image (MRI).* Evolving infarct involving the area of the middle cerebral artery (MCA)
SLIKA 2. Magnetska rezonancija mozga (MR). Razvoj infarkta koji zahvaća područje srednje mozgovne arterije (MCA)

compromise observed on a CT angiogram, the patient was diagnosed with Takayasu's arteritis. Treatment was initiated with high-dose steroids and cyclophosphamide (5), due to the unavailability of biologic therapies targeting TNF-alpha and IL-6 at the hospital. At the patient's follow-up at the Department of Rheumatology, the therapeutic plan was adjusted, with the introduction of tocilizumab into therapy. Two months later, the patient demonstrated partial recovery of movement but continued to experience aphasia. Currently, he is undergoing an intense rehabilitation program.

DISCUSSION

Takayasu's arteritis presents as a pulseless disease and it was first described in 1908 by Mikito Takayasu as *"a case of peculiar changes in the central retinal ves-*

bilne nuklearne antigene (ENA) i dvolančanu DNA (dsDNA). Osim toga, ispitivanja vaskulitisa pokazala su negativne rezultate za antineutrofilna citoplazmatska antitijela (ANCA).

Uz nalaz bolesti bez pulsa, povišenu sedimentaciju eritrocita (SE) i kompromitirani arterijski dotok uočen na CT angiografiji, bolesniku je dijagnosticiran Takayasuov arteritis. Liječenje je započeto visokim dozama steroida i ciklofosfamida (5), zbog nedostupnosti bioloških terapija usmjerenih na TNF-alfa i IL-6 u bolničkoj ustanovi. U praćenju na Zavodu za reumatologiju terapijski plan je prilagođen te je u liječenje uveden tocilizumab. Dva mjeseca kasnije bolesnik je pokazao djelomični oporavak opsega pokreta, ali je i dalje imao afaziju. Trenutno je uključen u intenzivan rehabilitacijski program.

sels." In this condition, the pulse is altered due to inflammation of the wall of the aorta and its major branches (6). The etiology of Takayasu's arteritis is still idiopathic (7).

The clinical manifestations of Takayasu's arteritis (TA) can vary widely, ranging from asymptomatic to severe neurological complications. There are also differences in presentation between younger and older patients (those over 40 years of age), with diagnosis often being delayed in the latter group (1). Therefore, it is important to investigate the signs of generalized inflammation syndrome in patients with TA who present with symptoms such as fever, night sweats, malaise, anorexia, weight loss, and diffuse myalgias, as this condition can often be misdiagnosed as an infection (7). In the case of our patient, frequent cervical pain and headaches were associated symptoms.

It is important to emphasize the triphasic pattern of the disease, as patients often present during the prepulse inflammatory phase with non-specific systemic symptoms (fever, arthralgia, and weight loss). Due to this, they are initially diagnosed with a prolonged viral syndrome (8). However, in the case of our patient, systemic symptoms were not considered until neurological complications developed.

Approximately 50% of patients suffering from Takayasu's arteritis can experience neurological symptoms, with visual symptoms being the most prevalent. The neurological presentation is so forgotten that there are Neurorheumatology books in which there is no description of it.(9) Strokes can affect 10% of the patients. The presentation of embolic disease in Takayasu's arteritis has been associated with stenotic or occlusive lesions in the aorta and its branches. Additionally, it is linked to subsequent hypertension or eventual cerebral hypoperfusion (4).

Our patient experienced a manifestation of the disease with a massive ischemic stroke. According to the criteria outlined by the American College of Rheumatology in 1990, he met five of them, which led to the suspicion of the diagnosis of Takayasu's arteritis. This was not the sole factor leading to the diagnosis; considering the radiological characteristics, other potential causes of medium vessel vasculitis were taken into account. In the differential diagnosis of cranial artery involvement, distinguishing between Takayasu's arteritis and giant cell arteritis (GCA), it's crucial to note that GCA primarily does not impact intracranial (i.e., cerebral) arteries (10).

Standard treatment with high-dose steroids and cyclophosphamide as additional immunomodulators was initiated (11). However, corticosteroids need to be withdrawn as soon as possible to avoid side effects, and it is preferable to consider new biological therapies, es-

RASPRAVA

Takayasuov arteritis predstavlja se kao bolest bez pulsa, a prvi ga je put 1908. opisao Mikito Takayasu kao „slučaj čudnih promjena u središnjim retinalnim žilama". U ovom stanju puls je promijenjen zbog upale stijenke aorte i njezinih glavnih ogranaka (6). Etiologija Takayasuovog arteritisa još uvijek je idiopatska, to jest, nepoznata (7).

Kliničke manifestacije Takayasuovog arteritisa (TA) mogu uvelike varirati, u rasponu od asimptomatskih do teških neuroloških komplikacija. Također postoje razlike u kliničkoj slici mlađih i starijih bolesnika (onih iznad 40 godina), pri čemu se dijagnoza često kasnije postavlja u potonjoj skupini (1). Stoga je važno ispitati sindrom generalizirane upale u bolesnika s TA koji imaju simptome kao što su vrućica, noćno znojenje, malaksalost, anoreksija, gubitak tjelesne težine i difuzna mijalgija, jer se ovo stanje često može pogrešno dijagnosticirati kao infekcija (7). U slučaju našeg bolesnika česta cervikalna bol i glavobolja bili su pridruženi simptomi.

Važno je naglasiti trofazni obrazac bolesti, budući da se bolesnici često javljaju tijekom prestimulus intervala upalne faze s nespecifičnim sustavnim simptomima (vrućica, artralgija i gubitak težine). Zbog toga se bolesnicima u početku dijagnosticira sindrom produžene virusne infekcije (8). Međutim, u slučaju našeg bolesnika, sustavni simptomi nisu uzeti u obzir sve dok se nisu razvile neurološke komplikacije.

Otprilike 50% bolesnika s Takayasuovim arteritisom može doživjeti neurološke simptome, pri čemu su vizualni simptomi najčešći. Neurološki simptomi bolesti toliko su zaboravljeni da njihov opis ne postoji ni u nekim knjigama o neuroreumatologiji (9). Moždani udar može se dogoditi kod 10% bolesnika. Simboli embolije kod Takayasuovog arteritisa povezani su sa stenoznim ili okluzivnim lezijama u aorti i njezinim ograncima. Uz to, povezani su s naknadnom hipertenzijom ili eventualnom cerebralnom hipoperfuzijom (4).

Naš je bolesnik doživio manifestaciju bolesti u obliku masivnoga ishemijskog moždanog udara. Prema kriterijima koje je 1990. postavila organizacija *American College of Rheumatology* bolesnik je zadovoljavao njih pet, što je dovelo do sumnje na dijagnozu Takayasuovog arteritisa. Ovo nije bio jedini čimbenik koji je doveo do dijagnoze. S obzirom na radiološke značajke, uzeti su u obzir i drugi mogući uzroci vaskulitisa srednjih krvnih žila. U diferencijalnoj dijagnozi zahvaćenosti kranijalnih arterija, u razlikovanju Takayasuovog arteritisa i arteritisa divovskih stanica (engl. *Giant Cell Arteritis*, GCA), ključno je napomenuti da GCA prvenstveno ne utječe na intrakranijalne (tj. cerebralne) arterije (10).

Započeto je standardno liječenje s visokim dozama steroida i ciklofosfamidom kao dodatnim imunomo-

pecially tocilizumab, an IL-6 inhibitor, in order to improve the course of the disease (12).

CONCLUSSION

Nowadays, the physical exam has been relegated to a secondary role, but there are certain diseases where an exhaustive physical examination could easily lead to an early clinical diagnosis. In this report, we emphasize the severity of Takayasu's arteritis in a young male patient, a condition that could have a different course if diagnosed during the pre-pulse inflammatory phase.

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dulatorima (11). No, kortikosteroide je potrebno što prije ukinuti kako bi se izbjegle nuspojave, a poželjno je razmotriti nove biološke terapije, posebice tocilizumab i inhibitor IL-6 kako bi se poboljšao tijek bolesti (12).

ZAKLJUČAK

U današnje vrijeme fizikalnom pregledu pripisuje se manja, to jest, sekundarna uloga, ali postoje određene bolesti kod kojih detaljan fizikalni pregled može lako dovesti do rane kliničke dijagnoze. U ovom izvješću naglašavamo težinu Takayasuovog arteritisa kod mladog bolesnika, bolesti koja bi mogla imati drugačiji tijek ako se dijagnosticira tijekom prestimulus intervala upalne faze.

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CASE REPORT PRIKAZ BOLESNIKA

FIRST DESCRIPTION OF A FEMALE PATIENT WITH ADVANCED ANKYLOSING SPONDYLITIS AND POLYMYALGIA RHEUMATICA — A CASE REPORT

PRVI OPIS KOEGZISTENCIJE UZNAPREDOVALOG ANKILOZANTNOG SPONDILITISA I REUMATSKE POLIMIALGIJE KOD ŽENE – PRIKAZ BOLESNICE

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Abstract

This is the first case report regarding the co-existence of advanced ankylosing spondylitis (AS) and polymyalgia rheumatica (PMR) in a female patient. So far, it was described in a case series report but exclusively in male patients. A 63-year-old female patient was diagnosed with PMR in 2015, according to EULAR/ACR provisional classification criteria. Glucocorticoid (GC) therapy was successful for all of the symptoms except for the long-lasting pain in the spine. In 2018, additional diagnostic tests were performed. HLA typing showed the presence of HLA-B*27, radiographs of sacroiliac joints showed grade III bilateral sacroiliitis and MRI described bilateral chronic sacroiliitis with partial ankylosis and subchondral sclerosis of the joints. AS was diagnosed in accordance with the modified New York criteria. Non-steroidal anti-inflammatory (NSAIDs) drugs were used with only small benefits and were discontinued in 2021 due to gastrointestinal complications (development of subileus). In 2021, an MRI of thoracic spine showed signs of anterior spondylitis at the Th5/Th6 level (Romanus lesion) and chronic Romanus lesion at the Th8/Th9 level. Adalimumab was introduced in October of 2021 and reduced symptoms by 60% after four months of treatment, significantly reduced abdominal pain and improved the overall quality of life. Adalimumab had no effect on PMR, but methotrexate and GK were effective in the treatment of PMR.

Keywords: ankylosing spondylitis, polymyalgia rheumatica, adalimumab, sacroiliitis

Sažetak

Ovo je prvi prikaz koegzistencije uznapredovaloga ankilozantnog spondilitisa (AS) i reumatske polimialgije (PMR) u osobe ženskog spola. Do sada je koegzistencija ovih dviju bolesti opisana samo u bolesnika muškog spola. Bolesnica u dobi od 63 godine liječena je od 2015. godine od strane specijalista infektologa pod dijagnozom reumatske polimijalgije (dijagnosticirana prema klasifikacijskim kriterijima EULAR/ACR). Primijenjena glukokortikoidna (GK)

terapija imala je odličan učinak na bol i zakočenost u mišićima. Kako bolesnica cijelo vrijeme ima i perzistentnu bol duž kralježnice koja se ne smanjuje na primijenjenu terapiju, 2018. godine upućena je reumatologu i u daljnju dijagnostičku obradu. HLA tipizacija pokazala je prisutnost HLA-B*27 alela, radiogram sakroilijakalnih (SI) zglobova prisutnost bilateralnog sakroileitisa trećeg stupnja, a MR SI zglobova bilateralni sakroileitis s parcijalnom ankilozom i subhondralnom sklerozom zglobnih površina. AS je dijagnosticiran prema modificiranim Njujorškim kriterijima. Nesteroidni protuupalni lijekovi (NSAID-ovi), korišteni u početku u punim protuupalnim dozama, polučili su samo blago poboljšanje. Ukinuti su 2021. godine zbog gastrointestinalnih tegoba (razvoj subileusa). Godine 2021. na MR-u torakalne kralježnice opisan je anteriorni spondilitis u razini Th5/Th6 (Romanusova lezija) i kronična Romanusova lezija na razini Th8/Th9. U listopadu 2021. godine započeto je liječenje adalimumabom. Nakon četiri mjeseca bolovi u kralježnici i aktivnost bolesti smanjeni su za oko polovicu, bolesnica više nije imala gastrointestinalnih tegoba, a kvaliteta života joj je poboljšana. Pri pokušaju smanjivanja doze glukokortikoida pojačali su se simptomi reumatske polimialgije na koje adalimumab nema učinak. Dobar učinak na reumatsku polimialgiju ostvaren je kombinacijom metotreksata i glukokortikoida.

Ključne riječi: ankilozantni spondlitis, reumatska polimilagija, adalimumab, sakroileitis

INTRODUCTION

Ankylosing spondylitis (AS) is a part of spondyloarthritis (SpA), a group of chronic inflammatory arthropathies. SpA affects mainly the spine and sacroiliac (SI) joints (axial form of SpA), but also peripheral joints and entheses (peripheral form of SpA) and some extra-articular sites. Ninety-five percent of the white AS population is HLA-B*27 positive. The estimated worldwide prevalence of AS is between 0.01 and 0.2% [1]. AS is more common in men, with male to female ratio being 2–3:1 [2]. In women, the disease has a later onset, the time period from the onset of symptoms to the diagnosis is longer, and the disease is more often associated with fibromyalgia (FM) [3]. As the disease progresses, irreversible structural changes in the spine and joints occur, which lead to deterioration of the functional status and quality of life in these patients. Although these changes are more pronounced in male patients, it is also known that women who initially have high disease activity measured by the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) have a more severe form of the disease and a worse treatment outcome [4]. With the introduction of magnetic resonance imaging (MRI), it became possible to diagnose the disease at an early stage, before the occurrence of irreversible changes in the spine and joints. Non-steroidal anti-inflammatory drugs (NSAIDs) are used to treat the axial form of the disease. In case of their ineffectiveness or intolerance, biological therapy is used for treatment, i.e. tumour necrosis factor alpha (TNF-α) inhibitors, interleukin 17 inhibitors and Janus kinase (JAK) inhibitors. TNF-α inhibitors, especially adalimumab, have been used for the longest time, therefore the experience with the use of this drugs is the greatest.

This case report presents the case of a 63-year-old female who was diagnosed with advanced HLA-B*27 positive AS and polymyalgia rheumatica (PMR). This is the first described case of the co-existence of these

UVOD

Ankilozantni spondilitis (AS) dio je spondiloartritisa (SpA), skupine kroničnih upalnih artropatija. SpA zahvaća uglavnom kralježnicu i sakroilijakalne (SI) zglobove (aksijalni oblik SpA), ali također i periferne zglobove i enteze (periferni oblik SpA) i neka izvanzglobna mjesta. Devedeset pet posto populacije bijelaca s AS-om pozitivno je na HLA-B*27. Procijenjena prevalencija AS-a u svijetu je između 0,01% i 0,02% [1]. AS se češće javlja u muškaraca nego žena, u omjeru 2 – 3:1 [2]. Kod žena bolest počinje kasnije, razdoblje od pojave simptoma do dijagnoze je dulje, a bolest je češće povezana s fibromialgijom (FM) [3]. Kako bolest napreduje dolazi do ireverzibilnih strukturnih promjena u kralježnici i zglobovima, što dovodi do pogoršanja funkcionalnog statusa i kvalitete života ovih bolesnika. Iako su ove promjene izraženije kod muških bolesnika, također je poznato da žene koje u početku imaju visoku aktivnost bolesti mjerenu indeksom aktivnosti bolesti za AS (engl. *Bath Ankylosing Spondylitis Disease Activity Index,* BASDAI) imaju teži oblik bolesti i lošiji ishod liječenja [4]. Uvođenjem magnetske rezonancije (MR) postalo je moguće dijagnosticirati bolest u ranom stadiju, prije nego što nastupe ireverzibilne promjene na kralježnici i zglobovima. Nesteroidni protuupalni lijekovi (NSAID-ovi) upotrebljavaju se za liječenje aksijalnog oblika bolesti. U slučaju njihove neučinkovitosti ili intolerancije na te lijekove, u liječenju se upotrebljava biološka terapija, tj. inhibitori faktora tumorske nekroze alfa (TNF-α), inhibitori interleukina 17 i inhibitori Janus kinaze (JAK). Inhibitori TNF-α, posebice adalimumab, upotrebljavaju se najdulje, stoga je i iskustvo s primjenom ovih lijekova najveće.

U radu prikazujemo slučaj 63-godišnje bolesnice kojoj je dijagnosticiran uznapredovali ankilozantni spondilitis (AS) s pozitivnim HLA-B*27 i reumatska polimialgija (PMR). Ovo je prvi opisani slučaj koegzistencije ovih dviju bolesti kod ženske osobe. Do sada je to

two diseases in a female person. So far, it was described in the case report in which the authors express the opinion that shoulder pain is probably part of the clinical features of spodyloarthritis [5]. But, in the case series report, the authors express the opinion that shoulder pain is part of the clinical features of PMR [6]. They believe that in these five patients there is a coexistence of two diseases. In both articles, only male patients were presented. Also, case reports have been published in which patients with late-onset spondyloarthritis were described and their symptoms resembled those of polymyalgia rheumatica [7,8].

In the following part, we will present the course of the patient's illness and the therapeutic dilemmas that arose during the treatment period. This case report will end with a discussion based on the effects of adalimumab in these two diseases.

CASE REPORT

The first examination of the patient was in 2018 at the Physical Medicine and Rehabilitation with Rheumatology Division, University Hospital of Split. No one in the patient's family suffers from rheumatic diseases, psoriasis or inflammatory bowel disease (IBD). The patient previously suffered from a duodenal ulcer, and she is now being treated for arterial hypertension and her blood count shows an increased number of eosinophils. Over the last ten years, the patient has been experiencing chronic back pain. The back pain was predominantly mechanical in nature. At the beginning of 2015, the diagnosis of spondyloarthritis was ruled out by a rheumatologist but only on the basis of clinical examination. The patient is allergic to diclofenac. Since the end of 2015, the patient was treated for PMR with glucocorticoids (GK) and several NSAIDs as recommended by an infectious disease specialist and a rheumatologist. The reason why the patient was referred to an infectious disease specialist was due to elevated acute phase reactants. PMR was diagnosed in accordance with 2012 EULAR/ACR provisional classification criteria [9]. The patient presented with pain and stiffness of the cervical spine and shoulder girdle muscles, with a slight weakness of the pelvic girdle muscles. Laboratory findings showed elevated acute phase reactants (ESR 46 mm/h, CRP 32 mg/L). The patient had a quick and satisfactory clinical response to a medium dose of GK therapy with a decrease in inflammatory markers. Due to long-lasting pain in the entire spine and limited mobility of the lumbar spine (Schober's test 3,5 cm), additional diagnostic tests were performed in 2018. Laboratory findings showed elevated acute phase reactants again, HLA typing showed the presence of HLA-B*27 antigen, radiographs of SI joints showed loss of joint space and bilateral partial ankylosis (grade III bilateral sacroiliitis according to the New

opisano u prikazu slučaja u kojem autori iznose mišljenje da je bol u ramenu vjerojatno dio kliničke slike spodiloartritisa [5]. No, u prikazu serije slučajeva, autori izražavaju mišljenje da je bol u ramenu dio kliničke slike reumatske polimialgije (PMR) [6]. Smatraju da kod ovih pet bolesnika postoji koegzistencija dviju bolesti. U oba članka prikazani su samo muški bolesnici. Također, objavljeni su prikazi slučajeva u kojima su opisani bolesnici s kasnim početkom spondiloartritisa čiji su simptomi nalikovali onima kod reumatske polimijalgije [7,8].

U nastavku ćemo prikazati tijek bolesti bolesnika i terapijske dileme koje su se javljale tijekom razdoblja liječenja. Ovaj prikaz slučaja završit će raspravom o učincima adalimumaba u ove dvije bolesti.

PRIKAZ BOLESNICE

Prvi pregled bolesnice bio je 2018. u Zavodu za fizikalnu medicinu i rehabilitaciju s reumatologijom KBC-a Split. Nitko u obitelji bolesnice ne boluje od reumatskih bolesti, psorijaze ili upalne bolesti crijeva (engl. *inflammatory bowel disease*, IBD). Bolesnica je ranije bolovala od čira na dvanaesniku, sada se liječi od arterijske hipertenzije, a krvna slika joj pokazuje povećan broj eozinofila. Posljednjih deset godina ima kronične bolove u kralježnici. Bolovi u kralježnici bili su pretežno mehaničke prirode. Početkom 2015. godine reumatolog je odbacio dijagnozu spondiloartritisa, ali samo na temelju kliničkog pregleda. Alergična je na diklofenak. Od kraja 2015. liječena je od PMR-a glukokortikoidima (GK) i raznim NSAID-ovima prema preporuci infektologa i reumatologa. Razlog zbog kojega je bolesnica upućena infektologu bili su visoki reaktanti akutne faze. Reumatska polimialgija (PMR) dijagnosticirana je pomoću privremenih kriterija klasifikacije EULAR/ACR iz 2012. [9]. Bolesnica je imala bolove i ukočenost mišića vratne kralježnice i ramenog obruča uz blagu slabost mišića zdjeličnog obruča. Laboratorijski nalazi pokazali su povišene reaktante akutne faze (sedimentacija eritrocita [SE] 46 mm/h, C-reaktivni protein [CRP] 32 mg/L). Imala je brz i dobar klinički odgovor na srednju dozu terapije glukokortikoidima (GK) sa smanjenjem upalnih markera. Zbog dugotrajne boli u cijeloj kralježnici i ograničene pokretljivosti lumbalnog dijela kralježnice (Schober test 3,5 cm) učinjene su dodatne dijagnostičke pretrage tijekom 2018. godine. Laboratorijski nalazi opet su pokazali povišene reaktante akutne faze, HLA tipizacija pokazala je prisutnost HLA-B*27 antigena, radiografije sakroilijakalnih (SI) zglobova pokazale su gubitak zglobnog prostora i bilateralnu parcijalnu ankilozu (III. stupanj bilateralnog sakroileitisa prema Njujorškim kriterijima [NY]: slika 1). Nalaz magnetske rezonancije (MR) opisan je kao bilateralni kronični sakroileitis s parcijalnom ankilozom srednjih dijelova sa subhondralnom

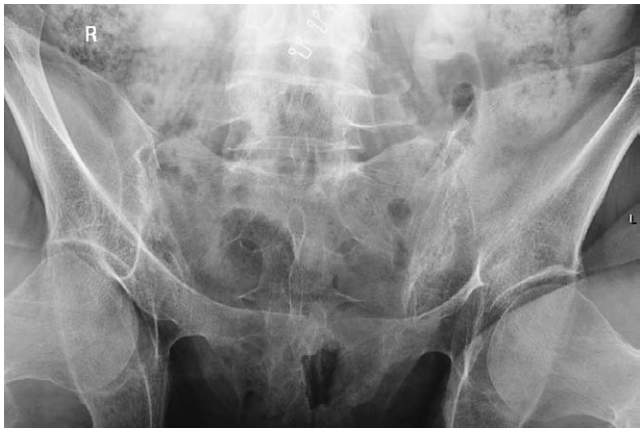

Figure 1. Anteroposterior radiograph oblique view of sacroiliac joints showing partial ankylosis of both SI joints defined as grade III sacroiliitis by the New York criteria

Slika 1. Rendgenska snimka sakroilijakalnih zglobova po Barshonyju pokazuje parcijalnu ankilozu obaju sakroilijakalnih zglobova koja odgovara trećem stupnju upale prema Njujorškim kriterijima

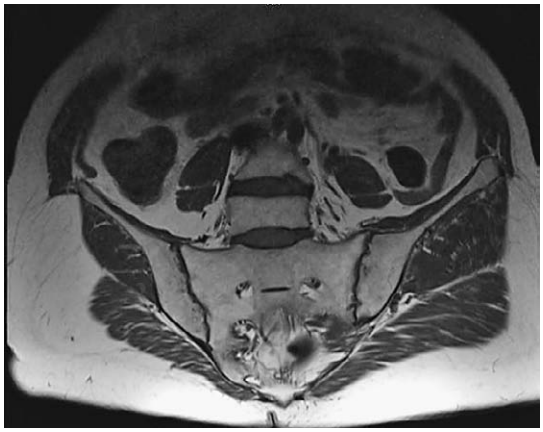

Figure 2. MRI of sacroiliac joints – coronal T1 weighted image illustrates narrowing of joint space with partial ankylosis and periarticular fat metaplasia

Slika 2. MR sakroilijakalnih zglobova po protokolu za spondiloartritise – koronalna T1 snimka opisuje suženje zglobnih prostora s parcijalnom ankilozom i periartikularnom masnom metaplazijom

York criteria – Figure 1). An MRI revealed signs of bilateral chronic sacroiliitis with partial ankylosis of the middle parts with subchondral sclerosis of the cranial and caudal parts of the joints (Figure 2). Linear subchondral bone marrow oedema was detected in the caudal part of the right SI joint. Only small effusion was detected in both joints. Fibromyalgia (FM), which is diagnosed primarily based on the symptoms, medical history and physical exam, was excluded. AS was diagnosed in accordance with the modified New York criteria (1994) and NSAIDs in full anti-inflammatory doses along with GK and proton pump inhibitors were introduced into the treatment with a moderate effect.

Due to constantly elevated acute phase reactants and persistent back pain, in 2019, bone scintigraphy was also performed. Apart from already known diagnoses, no other cause of the mentioned complaints was found in the case of this patient. Despite medication and regular physical therapy, spinal pain, especially in the cervicothoracic and thoracolumbar areas, was constantly present. This pain prevented the patient from performing work and carrying out daily activities. Therefore, the patient requested a change of workplace first and, following that, she took an early retirement.

In August 2020, the patient developed sudden abdominal pain. MSCT of the abdomen was performed and due to the suspicion that the patient had developed obstructive ileus, she was treated operatively at the Department for Abdominal Surgery. No cause of ileus was found during the operation. An appendectomy was performed, and the tissue of the appendix was found to be normal according to the pathohistological findings. The patient was diagnosed with subileus of unknown cause. At that time, the patient was being treated for AS and PMR with the combination of meloxicam and

sklerozom kranijalnih i kaudalnih dijelova zglobova (slika 2). Linearni edem subhondralne kosti uočen je u kaudalnom dijelu desnog SI zgloba. Primijećen je samo mali izljev u oba zgloba. Fibromialgija (FM), koja se dijagnosticira prvenstveno na temelju simptoma, povijesti bolesti i fizikalnog pregleda, bila je isključena. Ankilozantni spondilitis (AS) dijagnosticiran je u skladu s modificiranim Njujorškim kriterijima (mNY) (1994.) te su u liječenje uvedeni NSAID-ovi u punim protuupalnim dozama uz GK i inhibitore protonske pumpe s umjerenim učinkom.

Zbog konstantno povišenih reaktanata akutne faze i stalnih bolova u kralježnici, 2019. godine učinjena je i scintigrafija kostiju. Osim već poznatih dijagnoza, kod bolesnice nije pronađen nijedan drugi uzrok navedenih tegoba. Unatoč lijekovima i redovitoj fizikalnoj terapiji, bolovi u kralježnici, osobito u cervikotorakalnom i torakolumbalnom području, bili su stalno prisutni. Bolovi su je ograničavali u obavljanju poslova i svakodnevnim aktivnostima. Stoga je prvo tražila promjenu radnog mjesta, a potom otišla u prijevremenu mirovinu.

U kolovozu 2020. počela je osjećati iznenadne bolove u trbuhu. Učinjen je MSCT abdomena, a zbog sumnje da je bolesnica razvila opstruktivni ileus, operativno je zbrinuta u Zavodu za abdominalnu kirurgiju. Tijekom operacije nije pronađen uzrok ileusa. Učinjena je apendektomija, a tkivo slijepog crijeva je prema patohistološkom nalazu normalno. Bolesnici je dijagnosticiran subileus nepoznatog uzroka. U to vrijeme bila je liječena meloksikamom i metilprednizolonom u dozi od 6 mg zbog ankilozantnog spondilitisa (AS) i reumatske polimialgije (PMR). Kada je MSCT abdomena kasnije analiziran od strane tima reumatologa i radiologa, uočene su promjene koje potvrđuju AS na sakroilijakalnim zglobovima (slika 3).

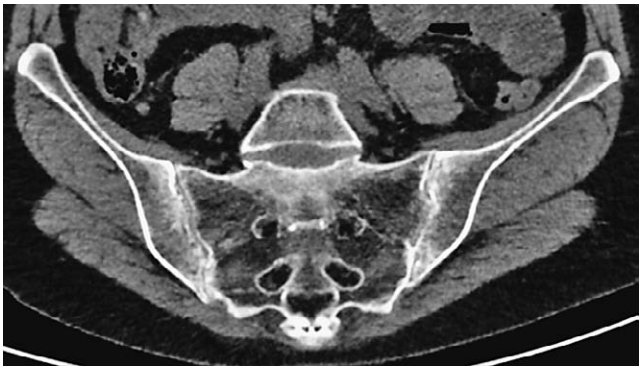

Figure 3. Abdominal CT – coronal MPR image showing bilateral grade III sacroilitiis with joint space narrowing, sclerosis and both sacral and iliac bone erosions

Slika 3. MSCT abdomena u koronalnom MPR prikazu opisuje, kao usputni nalaz, obostrani sakroileitis trećeg stupnja sa suženjem zglobnog prostora, sklerozacijom zglobnih površina te erozijama na ilijakalnoj i sakralnoj strani zgloba

methylprednisolone in a dose of 6 mg. When the MSCT of the abdomen was later analysed by a team of rheumatologists and radiologists, changes that confirmed the diagnosis of AS were observed on sacroiliac joints (Figure 3).

In September 2020, the patient developed abdominal pain once again due to subileus. The finding of MSCT of the abdomen was very similar to the previous one, the calprotectin level was 648 µg/g (normal values are <50 µg/g) and small bowel follow-through findings were normal. The patient continued to take meloxicam and methylprednisolone as this combination of drugs is the most effective for the symptoms of AS and PMR.

In October 2020, she was hospitalized once again and treated for the same reasons, but this time the calprotectin values were significantly lower (68 µg/g). Antibodies for celiac disease and MR enterography were also performed, and all findings were normal. The patient was then referred to another hospital where a capsule endoscopy was performed. During this procedure, the capsule endoscopy camera was retained in her small intestine. The patient underwent surgery and 7.5 cm of her small intestine was removed. Pathohistological findings were described as normal.

In April 2021, after the patient underwent gastroscopy, colonoscopy and small bowel follow-through, she was treated by a gastroenterologist due to sideropenic anemia. NSAIDs and GK were excluded from therapy by a gastroenterologist and the patient was advised to use only paracetamol. The patient was also recommended to undergo an MR enteroclysis and a colonoscopy with biopsy.

In August 2021, additional exacerbation of inflammatory back pain was observed. The pain level was 9/10 according to the Visual Analogue Scale (VAS), and the acute phase reactants were elevated (ESR 33 mm/h, CRP 28.5 mg/L). The patient was referred for

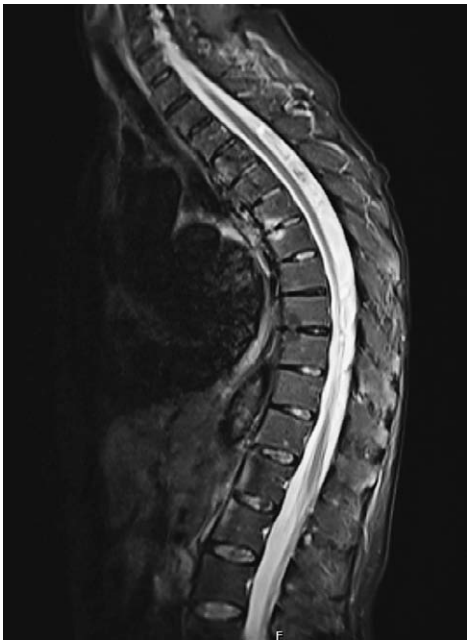

Figure 4. MRI of thoracic spine on T2 STIR sagittal sections. Anterior spondylitis of Th5/Th6 level (Romanus lesion), and chronic lesion at the Th8/Th9 level (chronic Romanus lesion)

Slika 4. MR torakalne kralježnice na sagitalnom presjeku T2. Anteriorni spondilitis nivoa Th5/Th6 (Romanusova lezija) te kronična Romanusova lezija na nivou Th8/Th9

U rujnu 2020. ponovno je počela osjećati bolove u trbuhu zbog subileusa. Nalaz MSCT-a abdomena bio je vrlo sličan prethodnom, razina kalprotektina bila je 648 µg/g (normalne vrijednosti su < 50 µg/g), a pasaža tankog crijeva uredna. Nastavlja uzimati meloksikam i metilprednizolon jer je ova kombinacija lijekova najučinkovitija za simptome ankilozantnog spondilitisa (AS) i reumatske polimialgije (PMR).

U listopadu 2020. ponovno je hospitalizirana i liječena iz istih razloga, ali ovoga puta vrijednosti kalprotektina bile su znatno niže (68 µg/g). Učinjen je i test antitijela na celijakiju te MR enterografija, svi nalazi bili su uredni. Bolesnica se zatim upućuje u drugu bolnicu u kojoj je obavljena kapsulna endoskopija. Tijekom ovog postupka, kapsulna endoskopska kamera zadržana je u tankom crijevu bolesnice. Bolesnica je operirana te joj je odstranjeno 7,5 cm tankog crijeva. Patohistološki nalaz opisan je kao uredan.

U travnju 2021., nakon gastroskopije, kolonoskopije i pasaže tankog crijeva, liječena je kod gastroenterologa zbog sideropenične anemije. Gastroenterolog je iz terapije isključio nesteroidne protuupalne lijekove (NSAID) i glukokortikoide (GK) te joj je savjetovao da uzima samo paracetamol. Bolesnici je također preporučeno da učini MR enteroklizu i kolonoskopiju s biopsijom.

U kolovozu 2021. primijećeno je dodatno pogoršanje upalne boli u leđima. Razina boli bila je 9/10 prema vizualno-analognoj ljestvici (engl. *Visual Analogue*

an MRI of the thoraco-lumbar spine according to the spondyloarthritis protocol. The findings of the MRI of the thoracic spine showed the presence of anterior spondylitis at the Th5/Th6 level (Romanus lesion), and chronic lesion in the front ends of the vertebral bodies at the Th8/Th9 level (chronic Romanus lesion) as seen in Figure 4. The patient also underwent an MR enteroclysis and a colonoscopy with biopsy in September 2021. MR enteroclysis showed a 3 cm long narrowing of the preterminal ileum. Synovitis of the right hip joint and sacroiliitis of the right SI (subchondral oedema of the sacrum) joint were also observed as incidental findings. The pathohistological findings of the biopsy of the terminal ileum showed a normal histological architecture with mononuclear and secondary follicles of medium density in the lamina propria.

In the meantime, the patient started taking methylprednisolone again (on her own accord) in a dose of 4 mg due to the exacerbation of the PMR symptoms.

Due to high disease activity of AS measured by the BASDAI questionnaire (9.6), severe pain measured by VAS (9/10) and morning stiffness lasting longer than two hours, our rheumatology team decided to start the treatment of AS with adalimumab.

We decided to introduce adalimumab into the therapy because of its proven effectiveness in the treatment of AS, as well as in the treatment of inflammatory bowel disease. Laboratory findings showed increased inflammatory markers and the anaemia of chronic disease again.

Treatment with adalimumab began in October 2021. The patient received 40 mg of the drug subcutaneously every 2 weeks. After the third dose of the drug, the patient already felt better. The pain and stiffness were significantly less intense and shorter in duration, but the mobility of the lumbar part of the spine remained the same. The Schober's mobility index was 3.5 cm, same as before the introduction of adalimumab into treatment. Since the patient felt better, she decided to stop taking methylprednisolone. Very quickly, her pain and stiffness in the shoulder girdle muscles got worse and there was an increase in the inflammatory markers. Methylprednisolone in a dose of 6 mg was reintroduced to therapy. Additionally, we introduced methotrexate (MTX) in a dose of 10 mg once a week as a GK-sparing agent but also with the aim of reducing the immunogenicity of adalimumab. GK and MTX significantly reduced the symptoms of PMR.

We evaluated the effectiveness of adalimumab treatment of AS in February 2022, four months after the introduction of the drug. Disease activity and pain level were lower (BASDAI 5.2; VAS 4/10) and morning stiffness was shorter than before, lasting up to one hour.

Abdominal pains no longer occured. Reactants of the acute phase were lower (ESR 16 mm/h, CRP 21.0

Scale, VAS), a reaktanti akutne faze bili su povišeni (sedimentacija eritrocita [SE] 33 mm/h, C-reaktivni protein [CRP] 28,5 mg/L). Bolesnica je upućena na MR torakolumbalne kralježnice prema protokolu za spondiloartritis. Nalazi magnetske rezonancije (MR) torakalne kralješnice pokazali su prisutnost prednjeg spondilitisa na razini Th5/Th6 (Romanus lezija), te kronične lezije u prednjim krajevima tijela kralješaka na razini Th8/Th9 (kronična Romanus lezija) što je vidljivo na slici 4. Bolesnica je također podvrgnuta MR enteroklizi i kolonoskopiji s biopsijom u rujnu 2021. godine. MR enterokliza pokazala je suženje preterminalnog ileuma u dužini od 3 cm. Sinovitis desnog zgloba kuka i sakroileitis desnog SI (edem subhondralne krstačne kosti) zgloba također su opisani kao slučajni nalazi. Patohistološki nalaz biopsije terminalnog ileuma pokazao je normalnu histološku arhitekturu s mononuklearima srednje gustoće i sekundarnim folikulima u lamini propriji.

U međuvremenu je bolesnica vlastitom odlukom ponovno počela uzimati metilprednizolon u dozi od 4 mg zbog pogoršanja simptoma reumatske polimialgije (PMR).

Zbog visoke aktivnosti bolesti ankilozantnog spondilitisa (AS) mjerene indeksom aktivnosti bolesti za AS (engl. *Bath Ankylosing Spondylitis Disease Activity Index*, BASDAI) (9,6), jake boli mjerene vizualno-analognom ljestvicom (VAS) (9/10) i jutarnje ukočenosti koja traje dulje od dva sata, naš reumatološki tim odlučio je započeti liječenje ankilozantnog spondilitisa (AS) adalimumabom.

Adalimumab smo odlučili uvesti u terapiju zbog njegove dokazane učinkovitosti u liječenju AS-a, kao i u liječenju upalnih bolesti crijeva. Laboratorijski nalazi opet su pokazali povišene upalne markere i anemiju kroničnih bolesti.

Liječenje adalimumabom počelo je u listopadu 2021. godine. Bolesnica je dobivala 40 mg lijeka supkutano svaka dva tjedna. Nakon treće doze lijeka već se osjećala bolje. Bolovi i ukočenost bili su znatno manjeg intenziteta i trajanja, ali je pokretljivost lumbalnog dijela kralježnice ostala ista. Schoberov indeks pokretljivosti bio je 3,5 cm, kao i prije uvođenja adalimumaba. Budući da se osjećala bolje, odlučila je prestati uzimati metilprednizolon. Vrlo brzo pogoršali su se bolovi i ukočenost mišića ramenog obruča i došlo je do porasta upalnih markera. U terapiju je vraćen metilprednizolon u dozi od 6 mg. Dodatno, uveli smo metotreksat (MTX) u dozi od 10 mg jednom tjedno kao sredstvo koje štedi glukokortikoide (GK), ali i s ciljem smanjenja imunogenosti adalimumaba. Glukokortikoidi (GK) i metotreksat (MTX) značajno su smanjili simptome reumatske polimialgije (PMR).

Učinkovitost liječenja ankilozantnog spondilitisa (AS) adalimumabom procijenili smo u veljači 2022., če-

mg/L), and anaemia of chronic disease was no longer found.

DISCUSSION

In the discussion, we will try to answer these three questions:

1. Is it reasonable to treat a 60-year-old patient with an advanced form of AS and partial ankylosis of the SI joints with a biologic drug?
2. Was adalimumab the best choice for the treatment of this patient?
3. Why didn't we observe a drastically positive effect of adalimumab in the treatment of AS like it was observed in some other diseases?

Answers to these questions are as follows.

Ad 1. We believe that it was reasonable to introduce adalimumab into the treatment despite the partial ankylosis of the SI joints, considering that acute lesions of the thoracic spine are still visible on MRI findings and that this patient still experiences pronounced inflammatory back pain. A good treatment effect and good safety profile of adalimumab is found even in patients with advanced AS and complete spinal ankylosis who still complain of stiffness and inflammatory back pain. Such results were described both on the national level and internationally [10, 11].

Ad 2. Adalimumab has a proven effectiveness in the treatment of both AS and inflammatory bowel disease. Although this patient, despite experiencing abdominal pain and occasionally increased levels of calprotectin in her stool (the patient was then treated with meloxicam), did not have a diagnosis of inflammatory bowel disease, gastrointestinal complaints decreased and the patient was not treated in the hospital again after the introduction of adalimumab into therapy. On the other hand, TNF-α inhibitors have no effect in the treatment of PMR [12]. Some studies showed that the IL-6 inhibitor, tocilizumab, can be effective in the treatment of resistant PMR [13] but tocilizumab has no effect in the treatment of AS. Therefore, we believe that adalimumab, combined with GK and MTX in the treatment of PMR, is the best choice for the treatment of AS in the case of this patient.

Ad 3. Although significant improvement was achieved with the introduction of adalimumab into therapy, this patient still experiences morning stiffness of the spine that lasts for about an hour and disease activity with a BASDAI score above 5. The moderate effect of adalimumab can be explained by a high initial index of disease activity (BASDAI 9.6), as previously described in literature [4].

CONCLUSION

This is the first described case of advanced AS and PMR in a female patient. NSAIDs did not have a satis-

tiri mjeseca nakon uvođenja lijeka. Aktivnost bolesti i razina boli bili su niži (BASDAI 5,2; VAS 4/10), a jutarnja ukočenost bila je kraća i trajala je do sat vremena.

Više se ne javljaju bolovi u abdomenu. Reaktanti akutne faze su niži (sedimentacija eritrocita [SE] 16 mm/h, C-reaktivni protein [CRP] 21,0 mg/L), nema više anemije kronične bolesti.

RASPRAVA

U raspravi ćemo pokušati odgovoriti na ova tri pitanja:

1. Je li razumno bolesnicu od 60 godina s uznapredovalim oblikom ankilozantnog spondilitisa (AS) i djelomičnom ankilozom sakroilijalnih (SI) zglobova liječiti biološkim lijekom?
2. Je li adalimumab bio najbolji izbor za liječenje ove bolesnice?
3. Zašto nije vidljiv drastično dobar učinak adalimumaba u liječenju ankilozantnog spondilitisa (AS) kao kod nekih drugih bolesti?

Odgovori na ova pitanja navedeni su u nastavku.

Odg. 1. Smatramo da je bilo razumno uvesti adalimumab u liječenje unatoč djelomičnoj ankilozi sakroilijakalnih (SI) zglobova, s obzirom na to da su akutne lezije torakalne kralježnice i dalje vidljive na nalazima MR-a te da ova bolesnica još uvijek ima izraženu upalnu bol u kralježnici. Dobar učinak liječenja i dobar sigurnosni profil adalimumaba utvrđen je čak i kod bolesnika s uznapredovalim AS-om i potpunom spinalnom ankilozom koji se i dalje žale na ukočenost i upalnu bol u kralježnici. Takvi rezultati opisani su i na nacionalnoj razini i u inozemstvu [10, 11].

Odg. 2. Adalimumab je dokazano učinkovit u liječenju AS-a i upalne bolesti crijeva. Iako ova bolesnica, unatoč bolovima u trbuhu i povremeno povišenim razinama kalprotektina u stolici (bolesnica je tada liječena meloksikamom), nije imala dokazanu upalnu bolest crijeva, gastrointestinalne tegobe su se smanjile, a bolesnica nije niti jednom bolnički liječena nakon uvođenja adalimumaba. S druge strane, inhibitori TNF-α nemaju učinka u liječenju reumatske polimialgije (PMR) [12]. Neka su istraživanja pokazala da inhibitor IL-6, tocilizumab može biti učinkovit u liječenju rezistentne reumatske polimialgije (PMR) [13], ali tocilizumab nema učinka u liječenju ankilozantnog spondilitisa (AS). Stoga smatramo da je adalimumab, u kombinaciji s glukokortikoidima (GK) i metotreksatom (MTX) u liječenju reumatske polimialgije (PMR), najbolji izbor za liječenje ankilozantnog spondilitisa (AS) u slučaju ove bolesnice.

Odg. 3. Iako smo postigli značajno poboljšanje u liječenju adalimumabom, ova bolesnica još uvijek ima jutarnju ukočenost kralježnice koja traje oko sat vremena i aktivnost bolesti s BASDAI indeksom iznad 5. Umjereni učinak adalimumaba može se objasniti viso-

factory effect on the treatment of AS in our patient. After only four months of treatment, adalimumab reduced pain measured through VAS pain scoring and disease activity measured through BASDAI by about half. Also, according to the patient's own opinion, it significantly reduced abdominal pain and improved her overall quality of life. As expected, adalimumab had no effect on PMR, but MTX and GK were effective in the treatment of PMR.

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kim početnim indeksom aktivnosti bolesti (BASDAI 9,6), kako je prethodno opisano u literaturi [4].

ZAKLJUČAK

Ovo je prvi opisani slučaj uznapredovaloga ankilozantnog spondilitisa (AS) i reumatske polimialgije (PMR) kod osobe ženskog spola. Nesteroidni protuupalni lijekovi (NSAID) nisu imali zadovoljavajući učinak na liječenje ankilozantnog spondilitisa (AS) u slučaju naše bolesnice. Nakon samo četiri mjeseca liječenja, adalimumab je otprilike upola smanjio rezultate intenziteta boli mjerene vizualno-analognom ljestvicom (VAS) i aktivnost bolesti mjerenu BASDAI indeksom. Bolesnica je, prema vlastitom mišljenju, primijetila i značajno manju bol u abdomenu i bolju kvalitetu života. Očekivano, adalimumab nije imao učinak na reumatsku polimialgiju (PMR), ali metotreksat (MTX) i glukokortikoidi (GK) su bili učinkoviti u njezinom liječenju.

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CASE REPORT PRIKAZ BOLESNIKA

REVERSIBLE OLIGOSPERMIA IN A PATIENT WITH NON-RADIOGRAPHIC AXIAL SPONDYLOARTHRITIS DUE TO SULFASALAZINE TREATMENT – A CASE REPORT

REVERZIBILNA OLIGOSPERMIJA U BOLESNIKA S NERADIOGRAFSKIM AKSIJALNIM SPONDILOARTRITISOM USLIJED LIJEČENJA SULFASALAZINOM – PRIKAZ BOLESNIKA

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Abstract

Axial spondyloarthritis (axSpA) is an inflammatory rheumatic disease, which belongs to the group of spondyloarthritis, and predominantly affects the axial skeleton. Research shows that sulfasalazine (SSZ) can cause changes in the semen analysis (spermiogram).

The patient, born in 1984, was referred to a rheumatologist due to back pain that had lasted for three years. During the clinical examination, there was pain in the left sacroiliac joint (SIJ) as well as sternocostal entheses and restricted movements in the right hip. Further diagnostic processing determined the presence of the Human Leukocyte Antigen (HLA) B27. Magnetic resonance imaging confirmed the existence of chronic changes in the left SIJ, degenerative changes in the right hip with areas of bone marrow edema, a smaller amount of effusion and synovial thickening. A diagnosis of non-radiographic axSpA was made. SSZ was introduced along with non-steroidal anti-rheumatic drug (NSAID) therapy. Five months after sulfasalazine (SSZ) was introduced into therapy, drug-induced infertility was suspected. A spermiogram was performed, and, following that, oligoasthenozoospermia was confirmed: reduced absolute sperm count (9.95 — reference interval (ref.int.) > 39 million/ milliliter [ml]), reduced sperm concentration (2.94 — ref. int. > 15 million/ml), reduced sperm motility percentage (17 — ref. int. > 40%), reduced percentage of progressively motile sperm (17 — ref. int. > 32%) and immotile sperm result: 83/ml. SSZ was discontinued, which resulted in an improvement in all of the semen parameter findings.

The causes of infertility in men are multifactorial, they are related to the underlying disease, drug therapy and other urological, endocrinological and genetic causes. Most studies on the effects of sulfasalazine (SSZ) on fertility were conducted on patients suffering from inflammatory bowel diseases. The mechanism of toxicity of sulfasalazine (SSZ) on infertility is unknown. The assumption is that the active metabolite, sulfapyridine, leads to oxidative stress with consequent effects on semen quality. Routine monitoring of sexual function and family planning is necessary.

Keywords: male infertility, spondyloarthritis, sulfasalazine

Sažetak

Aksijalni spondiloartritis (axSpA) je upalna reumatska bolest, pripada skupini spondiloartritisa, a zahvaća dominantno aksijalni skelet. Poznato je iz istraživanja da sulfasalazin (SSZ) može uzrokovati promjene u spermiogramu.

Bolesnik (rođen 1984.) javlja se reumatologu radi križobolje s trajanjem od tri godine. U kliničkom pregledu nalazimo bolan lijevi sakroilijakalni zglob (SIZ) kao i sternokostalne enteze te blokirane kretnje u desnom kuku. Daljnjom dijagnostičkom obradom utvrđen je HLA B27 (engl. *Human Leukocyte Antigen*). Magnetskom rezonancijom verificirane su kronične promjene lijevoga SIZ-a te osteodegenerativne promjene desnog kuka uz zone koštanog edema te manju količinu izljeva i zadebljanje sinovijalne membrane. Postavljena je dijagnoza neradiografskog axSpA. Uz terapiju nesteroidnim antireumaticima (NSAR) uveden je SSZ. Pet mjeseci od početka liječenja SSZ-om javila se sumnja na neplodnost uzrokovana lijekom. Učinjen je spermiogram, verificirana je oligoastenozoospermija: smanjen apsolutni broj spermija (9,95 – referetni interval [ref. int.] > 39 milijuna/mililitru [ml]), smanjena koncentracija (2,94 – ref. int. >15 milijuna/ml), smanjen postotak pokretljivosti (17 – ref. int. >40%), smanjen postotak progresivno pokretljivih spermija (17 – ref. int. >32%) te nalaz nepokretnih spermija 83/ml. Ukinut je SSZ, na što dolazi do poboljšanja nalaza svih parametara spermiograma.

Multifaktorijalni su uzroci neplodnosti u muškaraca, povezani su s osnovnom bolešću, terapijom te drugim uzrocima, urološkim, endokrinološkim i genetskim. Većina istraživanja o učincima SSZ-a na plodnost provedena je u bolesnika s upalnim bolestima crijeva. Toksičan mehanizam na neplodnost je nepoznat; aktivan metabolit, sulfapiridin dovodi do oksidativnog stresa s posljedičnim djelovanjem na spermije. Nužno je rutinsko praćenje spolne funkcije i planiranje obitelji.

Ključne riječi: muška neplodnost, spondiloartritis, sulfasalazin

INTRODUCTION

Spondyloarthritis (SpA) is a heterogeneous group of chronic inflammatory rheumatic diseases. These diseases are characterized by various articular and extra-articular manifestations. According to the dominant involvement, we divide them into two groups: axial and peripheral SpA (1). Axial SpA (axSpA) primarily affects the spine and sacroiliac (SI) joints. According to the new classification of the European Alliance of Associations for Rheumatology (EULAR) axSpA is divided into non-radiographic form (nr-axSpA) and radiographic (r-axSpA) form with diagnostic delay, and the latter was previously called ankylosing spondylitis (AS) (2). A strong link between the tissue histocompatibility gene HLA B27 and the etiology of SpA is well-known (3). According to the classification criteria of the Assessment of SpondyloArthritis international Society (ASAS) HLA B27 is included as one of the significant characteristics of this group of diseases (4). There is a hypothesis that enthesitis is a precursor of pathophysiological events in SpA (5). The functional deficit of patients with SpA represents a burden not only for the patient but also for society as a whole (6).

The characteristic pathophysiological changes of axSpA are sacroiliitis and spondylitis, which cause inflammatory back pain, stiffness and fatigue, and are most often manifested in the third decade of life (7). In addition to the axial skeleton, root and peripheral joints, tendons (especially the Achilles tendon) and entheses can be affected. According to data obtained through research conducted in Great Britain in 2017, the incidence of axSpA is 8 per 100,000, and the prevalence is 15.8 per 10,000 (8). Making the diagnosis of axSpA is a challenging task, which leads to delays in diagnosis and timely treatment.

UVOD

Spondiloartritisi (SpA) su heterogena skupina kroničnih upalnih reumatskih bolesti. Obilježavaju ih različite zglobne i izvanzglobne manifestacije. Sukladno dominantnom zahvaćanju dijelimo ih u dvije skupine: aksijalne i periferne SpA (1). Aksijalni SpA (axSpA) primarno zahvaća kralježnicu i SIZ. Prema novoj klasifikaciji Europske lige protiv reumatizma (engl. *European Alliance of Associations for Rheumatology* – EULAR) axSpA se dijeli na neradiografski oblik (nr-axSpA) i kasni, radiografski (r-axSpA), a potonji je prethodno poznat pod nazivom ankilozantni spondilitis (AS) (2). Poznata je snažna poveznica gena tkivne histokompatibilnosti HLA B27 s etipatogenezom SpA (3). Prema klasifikacijskim kriterijima po međunarodnoj organizaciji ASAS (engl. *Assessment of SpondyloArthritis international Society*), HLA B27 je uključen kao jedna od značajnih karakteristika ove skupine bolesti (4). Postoji hipoteza da je entezitis preteča patofizioloških zbivanja u SpA (5). Funkcionalni deficit bolesnika oboljelih od SpA predstavlja teret ne samo za bolesnika, nego i za društvo u cjelini (6).

Karakteristične patofiziološke promjene axSpA su sakroiliitis i spondilitis koji uzrokuju upalnu križobolju, ukočenost i umor, te se najčešće manifestiraju u trećem desetljeću života (7). Uz aksijalni skelet mogu biti zahvaćeni korijenski i periferni zglobovi, tetive, posebno Ahilova tetiva, kao i enteze. Prema podatcima iz Velike Britanije iz 2017., incidencija axSpA je 8 na 100.000, a prevalencija 15,8 na 10.000 ljudi (8). Postavljanje dijagnoze axSpA je izazovno, time dolazi do kašnjenja u dijagnosticiranju i pravodobnom liječenju.

Tijekom liječenja koriste se nesteroidni antireumatici (NSAR), glukokortikoidi, konvencionalni sintetski lijekovi koji modificiraju tijek bolesti (engl. *disease mo-*

Nonsteroidal antirheumatic drugs (NSAIDs), glucocorticoids, conventional synthetic drugs that modify the course of the disease (disease-modifying antirheumatic drugs, DMARDs) and biologic and targeted synthetic DMARDs are used during treatment (1). Certain drugs that we use in the treatment of patients with SpA can cause changes in the semen analysis (spermiogram). It is a known fact that sulfasalazine (SSZ) can lead to reversible changes in semen parameters (9, 10). Long-term use of acetylsalicylic acid and, very rarely, NSAIDs, can have a reversible effect on semen quality (10).

Chronic inflammation due to axSpA can cause infertility in patients. It can have an effect on the libido and erectile function and lead to reduced testicular function (11,12). A strong link was found between the underlying disease and semen quality (11).

CASE REPORT

A patient, who was born in 1984, came to the rheumatologist appointment presenting with symptoms of back pain, groin pain and chest pain. The symptoms are of an inflammatory nature, with a duration of over 3 years. The patient did not previously suffer from severe pain, he did not undergo surgery, and did not have children. There is no history of inflammatory rheumatic disease, psoriasis or infertility in the family. During the clinical examination, a slight trunk inclination was observed with an antalgic gait in the right leg. During palpation, there was pain in the left sacroiliac (SI) joint and after bending over the flexion arch of the lumbar spine was not formed. There was pain in the sternocostal entheses during palpation. Right hip movement was restricted and painful. The patient was referred for diagnostic treatment under suspicion of axSpA. HLA typing was done, according to the usual A, B and DR locus protocol. The patient had a positive HLA-B27 test. Serological findings for other rheumatic diseases (rheumatoid factor (RF), antinuclear antibodies (ANA)) were negative. Magnetic resonance imaging (MRI) was performed according to the protocol for SpA and, following that, chronic changes in the left sacroiliac joint and osteodegenerative changes in the right hip were confirmed along with areas of bone marrow edema of the femoral head and a reactively smaller amount of free fluid and synovial thickening. A diagnosis of HLA B27 positive nr-axSpA was made. NSAID therapy was initially introduced in an anti-inflammatory dose, but there was no significant therapeutic effect. Due to the symptomatology in the right hip area and the MR findings, the patient was referred to an orthopedist who recommended hip arthroscopy. Given that the clinical features also included involvement of peripheral joints, sulfasalazine (SSZ) was introduced into therapy with a gradual increase to a daily

*difying antirheumatic drug*s - DMARD) te biološki i ciljani sintetski DMARDi (1). Pojedini lijekovi koje koristimo u liječenju bolesnika sa SpA mogu uzrokovati promjene u spermiogramu. Poznato je da SSZ može dovesti do reverzibilne promjene u parametrima sperme (9, 10). Dugotrajna upotreba acetilsalicilne kiseline i, vrlo rijetko, NSAR mogu reverzibilno utjecati na kvalitetu sperme (10).

Kronična upala uslijed axSpA može uzrokovati neplodnost bolesnika. Utječe na libido i erektilnu funkciju i dovodi do smanjena tesktikularne funkcije (11,12). Nađena je snažna poveznica između osnovne bolesti i kvalitete sperme (11).

PRIKAZ BOLESNIKA

Bolesnik, rođen 1984. godine, javlja se reumatologu radi križobolje, bolova u preponama i prsištu. Simptomi su upalnog karaktera, s trajanjem više od tri godine. Ranije nije teže bolovao, nije bio podvrgnut operativnim zahvatima, nije imao djece. U obitelji nema upalne reumatske bolesti, psorijaze ni neplodnosti. Kod kliničkog pregleda uočava se blaga inklinacija trupa uz antalgičan hod na desnu nogu. Prilikom palpacije nalazi se bolan lijevi sakroilijakalni zglob (SIZ), po izvođenju pretklona ne formira fleksijski luk lumbalne kralježnice. Na palpaciju su bolne sternokostalne enteze. Kretnje u desnom kuku blokirane su uz bol. Upućen je na dijagnostičku obradu pod sumnjom na axSpA. Učinjena je HLA tipizacija, po uobičajenom protokolu A, B i DR lokus. Pristiže pozitivan nalaz za HLA B27. Serološki nalazi za druge reumatske bolesti (reuma faktor – RF, antinuklearna protutijela – ANA) bili su negativni. Učinjena je magnetska rezonancija (MR), po protokolu za SpA, te su verificirane kronične promjene lijevog SIZ-a te osteodegenerativne promjene desnog kuka, uz zone koštanog edema glave femura te reaktivno manja količina slobodne tekućine i zadebljanje sinovijalne membrane. Postavljena je dijagnoza HLA B27 pozitivnog nr-axSpA. Inicijalno je uvedena terapija NSAR u protuupalnoj dozi, no na to nije došlo do značajnijeg terapijskog učinka. Poradi simptomatologije u području desnog kuka te nalaza MR-a, bolesnik je upućen na pregled ortopeda koji je indicirao artroskopiju kuka. Budući da je u kliničkoj slici postojala i zahvaćenost perifernih zglobova, u terapiju je uveden SSZ s postupnim povećanjem do dnevne doze od 2 g. Planirana je biološka terapija pa je u tom smislu učinjena dodatna predterapijska dijagnostička obrada. Pet mjeseci nakon početka liječenja SSZ-om javila se sumnja na neplodnost uzrokovana lijekom. Prije uvođenja temeljne terapije spermiogram nije rutinski učinjen kao ni endokrinološka obrada. Dijagnostička obrada neplodnosti po protokolu uključila je spermiogram, hormonsko testiranje (spolni hormoni, tiroidni stimulirajući hormon – TSH) i ultrazvuk (UZV) testi-

dose of 2 g. Biological therapy was planned, so additional pre-therapeutic diagnostic processing was performed. Five months after sulfasalazine (SSZ) was introduced into therapy, drug-induced infertility was suspected. Semen analysis (spermiogram) and endocrinological examination were not routinely performed before the basic therapy was introduced. According to the protocol, the diagnostic treatment of infertility included a semen analysis (spermiogram), hormone testing (sex hormones, thyroid stimulating hormone, TSH) and testicular ultrasound. The semen analysis findings showed signs of oligoasthenozoospermia with the following characteristics: reduced absolute sperm count (9.95 — ref. int. > 39 million/ml), reduced sperm concentration (2.94 — ref. int. > 15 million/ml), reduced sperm motility percentage (17 — ref.int. > 40%), reduced percentage of progressively motile sperm (17 — ref.int. > 32%) and immotile sperm result: 83/ml. No abnormalities were found in other findings. It is a known fact that sulfasalazine (SSZ) can cause reversible oligospermia, so the aforementioned drug was discontinued, and therapy was continued with NSAIDs. At the control semen analysis (spermiogram), which was performed three months after the discontinuation of sulfasalazine (SSZ), all of the semen parameter findings were completely normal. In the further course of treatment, certolizumab pegol was introduced into therapy, but it was discontinued at the first evaluation control due to primary ineffectiveness. The patient stopped coming for check-ups, so the further course of the disease is unknown.

DISCUSSION

The causes of infertility in men suffering from SpA are multifactorial. They are related to the underlying disease, drug therapy and other urological, endocrinological and genetic causes. Chronic systemic inflammation can have an effect on the libido and erectile function (11). Research shows that patients suffering from AS have reduced sperm motility, elevated values of luteinizing and follicle-stimulating hormone, and decreased serum testosterone levels compared to healthy individuals (11). Long-term AS leads to impairment of the patient's sexual activity both due to reduced sexual desire and functional deficit due to the ongoing disease (11). According to a study conducted by Almeida BP et al., varicoceles are frequent in patients with AS and they occur in as many as 40% of patients (13). Their clinical significance should be assessed and then treated accordingly (14).

Most studies on the effects of sulfasalazine (SSZ) on fertility were conducted on patients suffering from inflammatory bowel diseases (15, 16). The mechanism of toxicity of sulfasalazine (SSZ) on infertility is unknown (10, 15). The assumption is that the active metabolite,

sa. Nalaz spermiograma je pokazao oligoastenozoospermiju sa sljedećim obilježjima: smanjen apsolutni broj spermija (9,95 – ref. int. >39 milijuna/ml), smanjena koncentracija spermija (2,94 – ref.int. >15 milijuna/ml), smanjen postotak pokretljivosti spermija (17 – ref. int. >40%), smanjen postotak progresivno pokretljivih spermija (17 – ref. int. >32%) te nalaz nepokretnih spermija 83/ml. Ostali nalazi su bili uredni. Kako je poznato da SSZ može uzrokovati reverzibilnu oligospermiju, navedeni lijek je ukinut i nastavljena je primjena NSAR-a. Na kontrolnom spermiogramu, koji je učinjen nakon tri mjeseca od ukidanja SSZ-a, dolazi do potpune normalizacije nalaza svih parametara sperme. U daljnjem tijeku liječenja uveden je certolizumab pegol, no isti je ukinut na prvoj evaluacijskoj kontroli zbog pojave primarne neučinkovitosti. Bolesnik je prestao dolaziti na kontrole te je nepoznat daljnji tijek bolesti.

RASPRAVA

Multifaktorijalni su uzroci neplodnosti u muškaraca koji boluju od SpA. Povezani su s osnovnom bolešću, medikamentoznom terapijom te drugim uzrocima, urološkim, endokrinološkim i genetskim. Kronična sistemska upala djeluje na libido i erektilnu funkciju (11). Istraživanja pokazuju da bolesnici koji boluju od aAS-a imaju reduciran motilitet spermija, povišene vrijednosti luteinizirajućeg i folikulostimulirajućeg hormona te sniženu razinu serumskog testosterona usporedno sa zdravim kontrolama (11). Dugotrajni AS dovodi do narušavanja spolne aktivnosti bolesnika kako zbog smanjene spolne želje tako i zbog funkcionalnog deficita uslijed bolesti (11). Varikokele su učestale u bolesnika s AS-om, prema istraživanju Almeide i suradnika javljaju se čak u 40% bolesnika (13). Njihova klinička značajnost treba biti ocijenjena te se potom liječe na odgovarajući način (14).

Većina istraživanja o učincima SSZ-a na plodnost provedena je u bolesnika koji boluju od upalnih bolesti crijeva (15, 16). Toksičan mehanizam SSZ-a na neplodnost je nepoznat (10, 15). Pretpostavka je da aktivan metabolit, sulfapiridin, dovodi do oksidativnog stresa s posljedičnim djelovanjem na kvalitetu sperme (10, 15). Upotreba SSZ-a dulje od dva mjeseca dovodi do reverzibilnih promjena u parametrima sperme (10, 16). Istraživanja su dokazala poboljšanje parametara sperme i fertilnosti ako se SSZ zamijeni drugim derivatom salicilata, bez sulfapiridina, kao što je mesalazin (17, 18, 19).

Dugotrajna upotreba acetilsalicilne kiseline, vrlo rijetko i NSAR-a, može reverzibilno utjecati na kvalitetu sperme i dovesti do smanjenja broja, promjene motiliteta, vitalnosti i morfologije spermija (10). Toksični učinci lijekova ovisni su o dozi (10). Istraživanja pokazuju da liječenje inhibitorima tumor-nefrotizirajućeg

sulfapyridine, leads to oxidative stress with consequent effects on semen quality (10, 15). The use of sulfasalazine (SSZ) in the period longer than 2 months leads to reversible changes in semen parameters (10, 16). Research shows that improvement in semen parameters and fertility is achievable if sulfasalazine (SSZ) is changed to another salicylate derivative, without sulfapyridine, such as mesalazine (17, 18, 19).

Long-term use of acetylsalicylic acid, and, very rarely NSAIDs, can reversibly affect the semen quality and lead to a decrease in the sperm count and change in sperm motility, vitality and morphology(10). The toxic effects of drugs depend on their dosage (10). Research shows that treatment with inhibitors of tumor nephrotic factor alpha (anti-TNFα) leads to a decrease in the activity of the underlying disease and consequently to an improvement in semen parameters (20). The safety of short-term and long-term use of anti-TNFα in testicular function has also been proven (11,20).

CONCLUSION

In this paper we present the case of a patient suffering from nr-axSpA, who was treated with sulfasalazine (SSZ) and developed drug-induced reversible oligospermia. When treating patients with SpA in fertile age, it is important to routinely monitor sexual function and implement the process of family planning (21). The possible effect of sulfasalazine (SSZ) on semen parameters should also be kept in mind. If there is information or suspicion about infertility, it is necessary to do an evaluation of sex hormones, a semen analysis (spermiogram) and testicular ultrasound (11). Improvement of reproductive health is achieved by treating the underlying disease, in addition to comprehensive patient counseling and a multidisciplinary approach.

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faktora alfa (anti-TNFα) dovodi do smanjenja aktivnosti osnovne bolesti, a time i do poboljšanja spermalnih parametara (20). Također je dokazana sigurnost kratkotrajne i dugotrajne upotrebe anti-TNFα u testikularnoj funkciji (11,20).

ZAKLJUČAK

U ovom radu prikazan je bolesnik s nr-axSpA, liječen SSZ-om, koji je razvio reverzibilnu oligospermiju uzrokovanu lijekom. Prilikom liječenja bolesnika sa SpA u fertilnoj dobi važno je praćenje seksualne funkcije i rutinsko planiranje obitelji (21). Treba imati na umu podatak o mogućem učinku SSZ-a na parametre sperme. Ako postoji podatak ili sumnja o neplodnosti nužno je učiniti evaluaciju spolnih hormona, spermiogram i ultrazvuk testisa (11). Poboljšanje reproduktivnog zdravlja postiže se liječenjem osnovne bolesti, sveobuhvatnim savjetovanjem bolesnika i multidisciplinarnim pristupom.

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REVIEW PAPER PREGLEDNI RAD

ANTIPHOSPHOLIPID SYNDROME AND PREGNANCY

ANTIFOSFOLIPIDNI SINDROM I TRUDNOĆA

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Abstract

Antiphospholipid syndrome (APS) is a chronic autoimmune disease characterized by the presence of antiphospholipid autoantibodies, such as anticardiolipin antibodies (aCL), antiβ2 glycoprotein 1 antibodies (aβ2GP1), and circulating lupus anticoagulant (LA).

The clinical festures include recurrent thrombosis of the arteries, veins, and microvasculature, which are the main features of vascular APS (vAPS), and/or obstetric complications that are part of obstetric APS (oAPS).

Obstetric complications have a direct effect on maternal and fetal morbidity, causing recurrent pregnancy miscarriages, fetal death, and signs of placental insufficiency that include preeclampsia, intrauterine growth restriction, and HELLP *(Hemolysis, Elevated Liver enzymes, and Low Platelets)* syndrome.

In APS, thrombosis is the most prominent feature of the disease. In oAPS, the main pathological findings include impaired spiral artery remodeling, decidua inflammation with neutrophil infiltration, local tumor necrosis factor (TNF) -α production, deposition of complement split products, and placental infarction, which suggest a state of thrombo-inflammation. Antiphospholipid antibodies have both a direct embryotoxic and an effect on the placenta, causing a pro-inflammatory state, disrupting trophoblast development and implantation, and impaired spiral artery remodeling.

Standard oAPS therapy includes low-molecular-weight heparin and low-dose aspirin.

Approximately 20–30% of oAPS patients do not benefit from standard treatment, and additional therapeutic options are necessary in those refractory cases, which may include small doses of prednisolone, hydroxychloroquine, plasmapheresis, immunoglobulins, TNF-α inhibitors, statins, and eculizumab.

Keywords: antiphospholipid syndrome, obstetric antiphospholipid syndrome, antiphospholipid antibodies, thrombosis, inflammation, pregnancy morbidity

Sažetak

Antifosfolipidni sindrom (APS) je kronična autoimunosna bolest karakterizirana prisutnošću antifosfolipidnih protutijela kao što su lupus antikoagulans (LA), antikardiolipinska protutijela (aCl) i anti-β2 glikoprotein I protutijela (aβ2GPI). Klinička slika može varirati od pojave tromboze vena, arterija i mikrožilja koja je klinička slika tzv. vaskularnog APS-a (vAPS) i/ili *opstetričkih* komplikacija koje su obilježje opstetričkog APS-a (oAPS).

Najčešća su komplikacija oAPS-a višestruki pobačaji, fetalna smrt te prijevremeni porod zbog insuficijencije posteljice koja uzrokuje zastoj u fetalnom rastu, preeklampsiju ili HELLP-sindrom (hemoliza, povišeni jetreni enzimi i niski trombociti; engl. *hemolysis, elevated liver transaminase enzymes, low platelet counts*).

U vAPS-u je tromboza vodeće kliničko obilježje bolesti, dok u oAPS-u vodeća patološka obilježja uključuju nepotpuno remodeliranje spiralnih arterija, upalu decidue uz infiltraciju neutrofila, lokalnu sintezu *čimbenika tumorske nekroze alfa* (engl. *tumor necrosis factor* [TNF] -α), odlaganje komponenti komplementa i infarkte posteljice koji upućuju na stanje tromboinflamacije.

Antifosfolipidna protutijela imaju izravan embriotoksični učinak djelujući i na embrij i na posteljicu, aktivirajući proupalno stanje i uzrokujući prekid normalnog razvoja trofoblasta te posljedično dovode do nemogućnosti implantacije i nepotpunog remodeliranja spiralnih arterija. Standardna terapija u oAPS-u uključuje niskomolekularni heparin i niske doze acetilsalicilne kiseline. U 20 – 30% slučajeva bolesnice s oAPS-om imat će *opstetričke* komplikacije unatoč standardnoj terapiji. U tim refraktornim slučajevima dodatna terapija je potrebna, a može uključivati male doze prednizolona, hidroksiklorokin, plazmaferezu, imunoglobuline, TNF-α inhibitore, statine i ekulizumab.

Ključne riječi: antifosfolipidni sindrom, opstetrički antifosfolipidni sindrom, antifosfolipidna protutijela, tromboza, upala, patologija trudnoće

INTRODUCTION

Antiphospholipid syndrome (APS) is a chronic autoimmune disease with main clinical features that include recurrent thrombosis of the arteries, veins, microvasculature, or/and obstetric complications. The main characteristics of the disease are the presence of antiphospholipid autoantibodies (aPL): anticardiolipin antibodies (aCL) directed against membrane anion phospholipids, antiβ2 glycoprotein 1 antibody *(aβ2GPI)* directed against β2 glycoprotein I (a cardiolipin binding factor), and circulating lupus anticoagulant (LA) (1).

The estimated incidence of the disease is around 2 cases per 100,000, and prevalence is around 45 per 100,000. The prevalence of aPL with obstetric complications is 6–9%, and with vascular complications it is 9–10% (2).

The prevalence of aPL in seemingly healthy individuals is around 5% and it is more likely to be found in elderly patients (3).

Traditionally, APS is subcategorized into 1.) Primary (PAPS), in which no associated systemic autoimmune disease exists, 2.) Secondary (SAPS), which is accompanied by systemic autoimmune disease, such as systemic lupus erythematosus (SLE), and 3.) Catastrophic APS (CAPS) in which thrombosis affects multiple organs in a short period of time (4).

DIAGNOSIS

For the diagnosis of APS to be established, a clinical criterion, such as venous, arterial, or microvasculature thrombosis and/or obstetric complications, in combination with persistently circulating aPL, must be present (5).

The Sapporo criteria were established in 1998 and updated in 2006 as the Sydney criteria. Patients were classified as having APS if they had a clinical event (vascular thrombosis and/or pregnancy morbidity) along with laboratory criteria that were defined as at least double positive aPL (LA, aCL IgG/IgM in medium to high titer, or aβ2GPI IgG/IgM higher than the 99th percentile), and they were tested 12 weeks apart (6).

UVOD

Antifosfolipidni sindrom (engl. *antiphospholipid syndrome*, APS) kronična je autoimuna bolest čija klinička slika najčešće uključuje rekurentnu arterijsku i vensku trombozu, mikrovaskulature i/ili opstetričke komplikacije. Glavne su karakteristike bolesti prisutnost antifosfolipidnih autoantitijela (aPL): antikardiolipinska antitijela (aCL) usmjerena protiv membranskih anionskih fosfolipida, antiβ2 glikoprotein 1 antitijela (aβ2GPI) usmjerena protiv β2 glikoproteina I (faktor vezanja kardiolipina) i cirkulirajući lupus antikoagulans (LA)(1).

Procijenjena incidencija bolesti je oko 2:100.000 u općoj populaciji, a prevalencija je oko 45:100.000 u općoj populaciji. Prevalencija aPL-a s opstetričkom komplikacijom je 6 – 9%, a s vaskularnom 9 – 10% (2).

Prevalencija aPL-a u naizgled zdravih osoba jest oko 5% i vjerojatnije je da će biti prisutna u starijih bolesnika (3).

Što se tiče tradicionalne podjele, APS je bolest koja je podijeljena u tri potkategorije: 1.) primarni APS (engl. *primary antiphospholipid syndrome*, PAPS) u kojem ne postoji pridružena sistemska autoimuna bolest; 2.) sekundarni APS (engl. *secondary antiphospholipid syndrome*, SAPS) u kojem se javlja sistemska autoimuna bolest, poput sistemskoga eritemskog lupusa (SLE) i 3.) katastrofični APS (engl. *catastrophic antiphospholipid syndrom*e, CAPS) u kojem tromboza zahvaća više organa u kratkom razdoblju (4).

DIJAGNOZA

Da bi se postavila dijagnoza APS-a mora postojati klinički kriterij poput venske, arterijske ili mikrovaskularne tromboze i/ili opstetričkih komplikacija, u kombinaciji s trajno cirkulirajućim aPL-om (5).

Kriteriji Sapporo klasifikacije uspostavljeni su 1998. i ažurirani 2006. i to pod nazivom Sydneyevi kriteriji. Bolesnice su klasificirane kao one koje imaju APS ako su doživjele klinički događaj (vaskularna tromboza i/ili morbiditet u trudnoći) zajedno s laboratorijskim kriterijima koji su definirani kao najmanje dva puta pozitivni aPL (LA, aCL IgG/IgM u srednjem do visokom titru ili aβ2GPI IgG/IgM viši od 99. percentila), s tim da su ta testiranja provedena u razmaku od 12 tjedana (6).

For the diagnosis of obstetric APS, the clinical criteria defining pregnancy morbidity included a) one or more unexplained deaths of a morphologically normal fetus at/beyond the 10th week of gestation; b) one or more premature births at/before the 34th week of gestation due to severe preeclampsia (PEC)/eclampsia, or severe placental insufficiency; (PI) c) three or more unexplained consecutive spontaneous abortions before the 10th week of gestation (other possible reasons such as chromosomopathy, hormonal or anatomy abnormalities were excluded) (6).

The 2023 ACR/EULAR APS criteria require an entry criterion of at least one positive aPL test within three years of identification of clinical criterion, followed by additive weighted criteria (1–7 points each) divided into six clinical domains (macrovascular venous thromboembolism, macrovascular arterial thrombosis, microvascular, obstetric, cardiac valve, and hematologic) and two laboratory domains (lupus anticoagulant functional coagulation assays, and solid-phase enzyme-linked immunosorbent assays for IgG/IgM aCL and aβ2GPI. For the established diagnosis, at least 3 points in the laboratory domain and 3 points in the clinical domain are needed (7).

When defining pregnancy morbidity, the following clinical criteria are included: a) three or more consecutive pre-fetal (<10th week) and/or early fetal (10w 0d – 15w 6d) deaths, which is weighted as 1 point, b) fetal death (16w 0d – 33w 6d) in the absence of PEC or PI with severe features — 1 point; c) PEC or PI with severe features (<34w 0d) with/without fetal death — 3 points; d) PEC and PI with severe features (<34w 0d) with/without fetal death — weighted the most as 4 points (7).

OBSTETRIC ANTIPHOSPHOLIPID SYNDROME

Obstetric complications are one of the significant manifestations of APS that have a direct effect on maternal and fetal morbidity, causing recurrent pregnancy miscarriages, fetal death, and signs of placental insufficiency, such as preeclampsia, intrauterine growth restriction, and HELLP *(Hemolysis, Elevated Liver enzymes, and Low Platelets)* syndrome (8).

PATHOPHYSIOLOGY OF OBSTETRIC ANTIPHOSPHOLIPID SYNDROME

Thrombosis, the most prominent feature of vascular APS (vAPS), was once thought to be the primary mechanism in the pathophysiology of obstetric APS.

Pathological examinations of the placentas in patients with APS have revealed changes beyond just thrombosis. These changes include impaired spiral artery remodeling, inflammation of the decidua with neutrophil infil-

Za dijagnozu opstetričkog APS-a, klinički kriteriji koji definiraju morbiditet u trudnoći uključivali su a) jednu ili više neobjašnjivih smrti morfološki normalnog fetusa u/nakon desetog tjedna gestacije; b) jedan ili više prijevremenih poroda u/prije 34. tjedna gestacije zbog teške preeklampsije (engl. *preeclampsia*, PEC) / eklampsije ili teške insuficijencije posteljice (engl. *placental insufficiency*, PI); c) tri ili više neobjašnjivih uzastopnih spontanih pobačaja prije desetog tjedna gestacije (drugi mogući razlozi kao što su kromosomopatija, osim hormonalnih ili anatomskih abnormalnosti) (6).

Klasifikacijski kriteriji za APS reumatoloških društava *American College of Rheumatology/European League Against Rheumatism* (ACR/EULAR) iz 2023. zahtijevaju kao ulazni kriterij najmanje jedan pozitivan aPL test unutar tri godine od identifikacije kliničkog kriterija, nakon čega slijede aditivni ponderirani kriteriji (1 – 7 bodova svaki) podijeljeni u šest kliničkih domena (makrovaskularna venska tromboembolija, makrovaskularna arterijska tromboza, mikrovaskularna i opstetrička domena, domena srčanih zalistaka i hematološka domena) i dvije laboratorijske domene (lupus antikoagulans test funkcionalne koagulacije i enzimski povezani imunosorbentni test u čvrstom stanju (engl. *Enzyme-Linked Immunosorbent Assay*, ELISA) za IgG/IgM aCL i aβ2GPI. Za postavljenu dijagnozu potrebna su najmanje tri boda u laboratorijskoj domeni i tri boda u kliničkoj domeni (7).

Pri definiranju morbiditeta u trudnoći uključeni su sljedeći klinički kriteriji: a) tri ili više uzastopnih predfetalnih (< 10 tjedana) i/ili ranih fetalnih (10 tjedana 0 dana – 15 tjedana 6 dana) smrti, što se ponderira 1 bodom, b) fetalna smrt (16 tjedana 0 dana – 33 tjedna 6 dana) bez prisutnosti PEC-a ili PI-a s teškim značajkama: 1 bod; c) PEC ili PI s teškim značajkama (< 34 tjedana 0 dana) s fetalnom smrti ili bez nje: 3 boda; d) PEC i PI s teškim značajkama (< 34 tjedna 0 dana) s fetalnom smrti ili bez nje: ponderirani najviše kao 4 boda (7).

OPSTETRIČKI ANTIFOSFOLIPIDNI SINDROM

Opstetričke komplikacije imaju izravan učinak na morbiditet majke i fetusa, uzrokujući ponavljajuće pobačaje u trudnoći, fetalnu smrt i znakove insuficijencije posteljice, preeklampsije, zastoja rasta fetusa (engl. *intrauterine growth restriction*, IUGR) i HELLP sindrom (hemoliza, povišeni jetreni enzimi i niski trombociti, engl. *Hemolysis, Elevated Liver enzymes, and Low Platelets*) (8).

PATOFIZIOLOGIJA OPSTETRIČKOGA ANTIFOSFOLIPIDNOG SINDROMA

Tromboza, koja je najistaknutija značajka vaskularnog APS-a (vAPS), nekoć se smatrala primarnim mehanizmom u patofiziologiji opstetričkog APS-a.

tration, local production of tumor necrosis factor (TNF)-α, deposition of complement split product, and placental infarction. All these findings suggest that thrombo-inflammation is the primary cause of the condition. (9,10).

Additionally, it is important to note that not all patients with oAPS will develop vAPS, and vice versa. This understanding has helped distinguish vAPS from oAPS as a distinct pathophysiological mechanism.

In 2017. *Taraborelli et al.* performed a multicentric, retrospective study that included 115 women diagnosed with primary APS. During the 18-year follow-up period, 19% (6/31) of patients with a history of pregnancy morbidity but without a prior history of thrombosis developed thrombosis during the follow-up period, and 12% of patients (6/49) with a history of thrombosis developed an obstetrical adverse outcome during the follow-up period (11).

A retrospective multicentric study conducted in Israel revealed that among primary APS patients, 21.2% of patients with oAPS developed arterial thrombosis and 6% of them developed venous thrombosis during the 15-year follow-up period (12).

To facilitate understanding of the pathophysiology of oAPS, it is important to comprehend placental development during a normal pregnancy.

A fertilized egg rapidly undergoes multiple mitotic cleaves and reaches the uterine cavity. There, it is differentiated into blastomere, and then morula until the blastocyst stage is reached.

Blastocystis comprises the inner cell mass (ICM)-embryonic stem cells, and cells surrounding and protecting ICM- trophectoderm cells. From the trophectoderm, cytotrophoblast arises (13). One part of the cytotrophoblast is developed in syncytiotrophoblast by fusing and growing towards the placenta primed for implantation through decidualization. Syncytiotrophoblast has multiple roles: the role of connecting to the uterus by covering the surface of the villi, secreting hormones like progesterone, leptin, lactogen, and human chorionic gonadotropin which are essential to maintain early pregnancy, forming intervillous space by secreting protease in the decidua. One part of the cytotrophoblast is differentiated in extravillous trophoblasts that invade the uterine spiral arteries and remodel them into non-vasoactive large-bore conduits (14). This process is essential for future fetal development because impaired spiral artery remodeling is one of the main culprits in the pathology of placental insufficiency, leading to preeclampsia and fetal growth restriction (15).

In oAPS, antiphospholipid antibodies have a major role in the pathophysiology of the disease. *In vitro* studies have demonstrated that they directly affect the proliferation and growth of trophoblasts and lead to the loss of trophoblast-endothelium interactions. There is a reduced invasion of extravillous trophoblast

Patološkim ispitivanjima posteljica u bolesnica s APS-om otkrivene su i druge promjene osim same tromboze. Te promjene uključuju poremećeno remodeliranje spiralne arterije, upalu decidue s neutrofilnom infiltracijom, lokalnu produkciju faktora nekroze tumora (TNF)-α, taloženje produkta cijepanja komplementa i infarkt posteljice. Svi ovi nalazi upućuju na to da je tromboupala primarni uzrok ove bolesti. (9,10)

Osim toga, bitno je napomenuti da neće sve bolesnice s opstetričkim APS-om (oAPS) razviti i vaskularni (vAPS), i obrnuto. Time se vAPS mogao razlikovati od oAPS-a i to kao zasebni patofiziološki mehanizam.

Godine 2017. Taborelli i suradnici proveli su multicentričnu retrospektivnu studiju u kojoj je sudjelovalo 115 žena s dijagnozom primarnog APS-a. Tijekom 18-godišnjeg razdoblja praćenja, 19% (6/31) bolesnica s poviješću morbiditeta u trudnoći, ali bez prethodne anamneze tromboze, razvilo je trombozu tijekom razdoblja praćenja, a u 12% bolesnica (6/49) s prethodnom anamnezom tromboze došlo je do razvoja opstetrički nepovoljnog ishoda tijekom razdoblja praćenja (11).

Retrospektivna multicentrična studija koja je provedena u Izraelu otkrila je da je među bolesnicama s primarnim APS-om 21,2% bolesnica s oAPS-om razvilo arterijsku, a 6% vensku trombozu tijekom 15-godišnjeg razdoblja praćenja (12).

Kako bi se olakšalo razumijevanje patofiziologije oAPS-a, bitno je shvatiti razvoj posteljice tijekom normalne trudnoće.

Oplođeno jajašce brzo prolazi kroz višestruke mitotičke diobe i dospijeva u maternicnu šupljinu. Ondje se diferencira u blastomeru, zatim morulu i dostiže stadij blastociste.

Blastocista sadrži unutarnju staničnu masu (engl. *inner cell mass*, ICM), embrijske matične stanice i stanice koje okružuju staničnu masu i štite unutarnju staničnu masu, stanice trofektoderma. Iz trofektoderma razvija se citotrofoblast (13). Jedan dio citotrofoblasta razvija se u sinciciotrofoblastu spajanjem i rastom prema posteljici pripremljenoj za implantaciju kroz proces decidualizacije. Sinciciotrofoblast ima više uloga: ulogu povezivanja s maternicom pokrivanjem površine resica, ulogu lučenja hormona poput progesterona, leptina, laktogena i humanoga korionskog gonadotropina koji su bitni za održavanje rane trudnoće te ulogu stvaranja interviloznog prostora lučenjem proteaze u decidui. Jedan dio citotrofoblasta diferenciran je u ekstravilozne trofoblaste koji napadaju spiralne arterije maternice i preoblikuju ih u nevazoaktivne kanale velikog promjera (14). Taj je proces neophodan za budući razvoj fetusa jer je poremećeno remodeliranje spiralne arterije jedan od glavnih krivaca u patologiji insuficijencije posteljice, što dovodi do preeklampsije i zastoja rasta fetusa (15).

with impaired spiral artery remodeling. aPL antibodies also trigger the production of pro-inflammatory cytokines (interleukin (IL)-1, IL-7, IL-8) that attract monocytes and neutrophils, leading to macrophage activation and release of neutrophil extracellular traps (NETosis), which results in inflammation around trophoblast and apoptosis. Additionally, they activate macrophages and complement deposition, thus promoting inflammation around trophoblasts and apoptosis. Complement activation leads to local TNF-α production and secretion, adding to a vicious inflammation circuit. (14,16,17)

Animal models and in vitro research showed the direct embryotoxic activity of aPL. Antibodies taken from women with APS directly affect the growth and viability of animal embryos. (18, 19)

In 2013, Gardiner and the authors conducted research that included around 190 women with APS with vascular and obstetric manifestations. Interestingly, over 50% of women with oAPS, but no known thrombosis had low-titre aCL and/or aβ_2GPI in the absence of LA. The researchers suggested that low-titer aCL and aβ_2GPI should be included in the criteria for the diagnosis of oAPS (20). One possible explanation is that decidual cells and cytotrophoblast usually exhibit high basal levels of β2GPI and represent easily accessible targets for aβ2GPI. This might also explain why a second hit, such as trauma, surgery, infection, primary autoimmune disease or another proinflammatory stimulus needed for developing thrombosis in vAPS is not required to develop oAPS (21).

The different effects of aPL in vAPS and oAPS leading to divergent pathophysiological mechanisms were also confirmed by two in vitro studies. In the first study, aPLs from vAPS and oAPS were observed to activate the monocyte signaling pathway. aPL against β2GPI from vAPS patients were the only ones to induce thrombin factor (TF) production by monocytes, while antibodies from the patient with obstetric manifestations failed to do this. In the second study, purified IgG from patients with obstetric APS, but not the one from non-obstetric APS, inhibited trophoblast invasion (10,22,23).

Clinical manifestations:

1.) Early miscarriages (>10th week of gestation)

Early miscarriages are the most common clinical finding in aPL-positive patients with pregnancy morbidity and were included in the 2006 revised Sapporo classification criteria (6).

According to the 2023 ACR/EULAR classification criteria, it is no longer sufficient to have three or more early miscarriages to fulfill the clinical domain of APS diagnosis. Nonetheless, the authors emphasize that they still remain a part of the high-priority research agenda to guide the future update of the 2023 ACR/EULAR APS classification criteria (7).

U oAPS-u antifosfolipidna antitijela imaju glavnu ulogu u patofiziologiji bolesti. Istraživanja *in vitro* pokazala su da antifosfolipidna antitijela izravno utječu na proliferaciju i rast trofoblasta i dovode do gubitka međudjelovanja trofoblasta i endotela. Postoji smanjena invazija ekstraviloznog trofoblasta s poremećenim remodeliranjem spiralne arterije. Antitijela aPL također pokreću proizvodnju proupalnih citokina (interleukin [IL]-1, IL-7, IL-8) koji privlače monocite i neutrofile, što dovodi do aktivacije makrofaga i oslobađanja izvanstaničnih zamki neutrofila (NEToza), što rezultira upalom oko trofoblasta odnosno apoptozom. Uz to, ta antitijela aktiviraju makrofage i taloženje komplementa, potičući upalu oko trofoblasta i apoptozu. Aktivacija komplementa dovodi do lokalne proizvodnje i izlučivanja TNF-α, što dalje pospješuje začarani krug upale. (14,16,17)

Životinjski modeli i istraživanja *in vitro* pokazali su izravnu embriotoksičnu aktivnost aPL-a, a protutijela uzeta od žena s APS-om izravno utječu na rast i održivost životinjskih embrija. (18, 19)

Godine 2013. Gardiner i suradnici proveli su istraživanje u kojem je sudjelovalo oko 190 žena s APS-om s vaskularnim i opstetričkim manifestacijama. Zanimljiva je činjenica da je više od 50% žena s oAPS-om, ali bez poznate dijagnoze tromboze imalo nizak titar aCL i/ili aβ2GPI u odsutnosti LA. Istraživači su predložili da se aCL i aβ2GPI s niskim titrom uključe u kriterije za dijagnozu oAPS-a (20). Jedno od mogućih objašnjenja jest to da decidualne stanice i citotrofoblast obično pokazuju visoke bazalne razine β2GPI i predstavljaju lako dostupne mete za aβ2GPI. Time se također može objasniti zašto drugi udar, kao što je trauma, operacija, infekcija, primarna autoimuna bolest ili drugi proupalni podražaj koji je potreban za razvoj tromboze u vAPS-u nije potreban za razvoj oAPS-a (21).

Različiti učinci aPL-a u vAPS-u i oAPS-u koji dovode do različitih patofizioloških mehanizama također su potvrđeni u dva istraživanja *in vitro*. U prvom istraživanju primijećeno je da aPLs iz vAPS-a i oAPS-a aktiviraju signalni put monocita. aPL protiv β2GPI u bolesnica s vAPS-om jedini su inducirali proizvodnju faktora trombina (TF) od strane monocita, dok antitijela bolesnica s opstetričkim manifestacijama nisu uspjela u tome. U drugom istraživanju pročišćeni IgG iz bolesnica s opstetričkim, ali ne i neopstetričkim APS-om, inhibirao je invaziju trofoblasta (10, 22, 23).

Kliničke manifestacije:

1.) Rani pobačaji (> 10. tjedan trudnoće)

Rani pobačaji najčešći su klinički nalaz u aPL-pozitivnih bolesnica s morbiditetom u trudnoći i uključeni su u revidirane Sapporo kriterije klasifikacije iz 2006. godine (6).

Prema kriterijima klasifikacije ACR/EULAR iz 2023. više nije dovoljno imati tri ili više ranih pobačaja da bi se

Carvera et al. published a multicentric observational study that included 1000 APS patients (820 women). During the 10-year follow-up period, 127 (15.5%) women got pregnant. The most common obstetric complication was early pregnancy loss (16.5% of pregnancies) (24).

Alijotas-Reig et al. analyzed obstetric outcomes in 1000 patients with oAPS using the European Registry of oAPS. They found that the most prevalent manifestations were miscarriages in 38.6% of the pregnancies (25).

In another study that included 183 patients with oAPS during a 10-year follow-up, recurrent early abortions were found in 58.6% of patients (26).

2.) Stillbirth *(loss of a baby at or after 20 weeks of pregnancy)*

When assessing maternal sera in 582 stillbirth deliveries, elevated levels of aCL and aβ2GPI were associated with a threefold increased odd of stillbirth (27).

A retrospective French study that included 65 women with APS and intrauterine fetal death (IUFD), found that IUFD was the first APS clinical manifestation in 74% of women (28).

3.) Preeclampsia and fetal growth restriction

When assessing the European Registry on Obstetric Antiphospholipid Syndrome (EUROAPS), PE was found to be present in 18.1% and fetal growth restriction in 16.1% of cases (25).

The prevalence of aPL is twice as high in pregnant women who develop PE compared to those who have healthy pregnancies. (29).

In a prospective case-control study that compared the frequency of aPL positivity in women who delivered their baby in the period before the 36th week due to PE or placental insufficiency and women with normal pregnancies, it was found that aPL was present in 11.5% of women with PE or placental insufficiency, which was significantly higher compared to 1.4% of women with uncomplicated pregnancies (30).

Carvera et al. found that intrauterine growth restriction (26.3% of live births) and prematurity (48.2%) were the most frequent fetal morbidities.

The observational study of patients with pregnancy loss showed that patients with oAPS who were treated with low-molecular-weight heparin (LMWH) plus low-dose aspirin (LDA) had a lower rate of pregnancy losses but a higher rate of PE than the others, and the study confirmed the greater risk of PE in the oAPS group. (31).

THROMBOTIC EVENTS IN PATIENTS WITH OBSTETRIC ANTIPHOSPHOLIPID SYNDROME

Pregnancy itself carries a risk of thrombotic events; for example, the risk of venous thromboembolism is

ispunili kriteriji za kliničku domenu dijagnoze APS-a. Bez obzira na to, autori naglašavaju da oni ostaju dio visokoprioritetnog istraživačkog programa za usmjeravanje budućeg ažuriranja kriterija klasifikacije ACR/EULAR za APS iz 2023. godine (7).

Carvera i suradnici objavili su multicentrično opservacijsko istraživanje u kojem je sudjelovalo 1.000 bolesnica s APS-om (820 žena). Tijekom desetogodišnjeg razdoblja praćenja zatrudnjelo je 127 (15,5%) žena. Najčešća opstetrička komplikacija bio je rani gubitak trudnoće (16,5% trudnoća) (24).

Alijotas-Reig i suradnici analizirali su opstetričke ishode u 1.000 bolesnica s oAPS-om koristeći se registrom *European Registry on oAPS* (EUROAPS). Otkrili su da su najčešće manifestacije spontani pobačaji u 38,6% trudnoća (25).

U drugom istraživanju, u kojem su sudjelovale 183 bolesnice s oAPS-om tijekom desetogodišnjeg razdoblja praćenja, ponovljeni rani pobačaji dogodili su se kod 58,6% bolesnica (26).

2.) Mrtvorođenče (gubitak djeteta u 20. tjednu trudnoće ili kasnije)

Pri procjeni majčinih seruma kod 582 poroda mrtvorođene djece, povišene razine aCL i aβ2GPI bile su povezane s trostruko većim izgledima za mrtvorođenče (27).

Retrospektivna francuska studija u kojoj je sudjelovalo 65 žena s APS-om i intrauterinom smrti ploda (engl. *intrauterine fetal death*, IUFD), otkrila je da se IUFD javlja kao prva klinička manifestacija APS-a u 74% žena (28).

3.) Preeklampsija i zastoj rasta fetusa

Pri procjeni registra *European Registry on Obstetric Antiphospholipid Syndrome* (EUROAPS), utvrđeno je da je preeklampsija (PE) prisutna u 18,1% slučajeva, a zastoj rasta fetusa u 16,1% slučajeva (25).

Prevalencija aPL-a dvostruko je veća u trudnica koje razviju preeklampsiju (PE) u usporedbi s onima koje imaju zdrave trudnoće (29).

U prospektivnom istraživanju parova u kojem se uspoređivala učestalost pozitivnog aPL-a u žena koje su rodile prije 36 tjedana trudnoće zbog preeklampsije (PE) ili insuficijencije posteljice i žena s normalnom trudnoćom, otkriveno je da je aPL bio prisutan u 11,5% žena s preeklampsijom (PE) ili insuficijencijom posteljice, što je bilo značajno više u usporedbi s 1,4% žena koje su imale trudnoću bez komplikacija (30).

Carvera i suradnici otkrili su da su intrauterini zastoj rasta (26,3% živorođene djece) i prematuritet (48,2%) najčešći fetalni morbiditeti.

Opservacijsko istraživanje bolesnica s prekidom trudnoće pokazalo je da su bolesnice s oAPS-om koje su liječene heparinom niske molekularne mase (engl. *low-molecular-weight heparin*, LMWH) i niskom dozom aspirina (engl. *low-dose aspirin*, LDA) imale nižu stopu prekida trudnoće, ali veću stopu preeklampsije (PE) od

five times higher in a pregnant woman than in a non-pregnant woman of similar age (32).

A retrospective study on 200 APS patients divided into four groups based on previous medical history (obstetric, thrombotic, non-criteria antiphospholipid syndrome, and aPL carriers) showed that 2.5% of patients experienced thrombotic events during pregnancy and puerperium. Most cases were reported in the thrombotic group with prior thrombotic events. Unfortunately, in 85% of these cases, the thrombotic event occurred despite the use of adequate antithrombotic therapy (33).

RISK FACTORS FOR ADVERSE OUTCOMES IN PREGNANCY

Various studies were conducted in search of risk factors for the adverse outcomes in oAPS and found, for example, SLE or hypocomplementaemia to be an additional risk factor (33, 34).

The 2021 meta-analysis, that included 27 eligible records, identified previous thrombosis, double and triple aPL positivity, and lupus anticoagulant positivity as the most important predictors of adverse pregnancy outcomes in APS (35).

These findings should be utilized routinely in preconception counseling and pregnancy follow-up to guide individualized risk assessment for adverse pregnancy outcomes.

MANAGEMENT OF OBSTETRIC ANTIPHOSPHOLIPID SYNDROME

1.) Standard therapy: low-molecular-weight heparin and low-dose aspirin

Anticoagulant therapy plays an essential role in the treatment of APS. In patients with thrombotic APS, vitamin K antagonists (VKAs), such as warfarin, should be included in therapy. Due to warfarin teratogenicity, especially in the first trimester, in pregnant patients with prior thrombosis, warfarin should be discontinued (36).

There is a rising interest in using direct oral anticoagulants (DOACs) in APS patients with vascular manifestations of the disease. Current guidelines recommend that warfarin should be the first-choice treatment in APS, especially in patients with triple aPL positivity and with previous arterial thrombosis due to increased rates of recurrent thrombosis treated with DOAC compared with VKAs (37). Although DOACs may be effective in single/double aPL-positive patients with an exclusively venous thrombotic event, there is no adequate data for the use of DOACs in pregnancy. Limited real-world data and animal studies raised concern for embryo-fetal safety, with a higher rate of miscarriages and possible fetal anomalies, so the current guidelines recommend against DOAC use throughout pregnancy (38).

ostalih, a istraživanjem se potvrdio i veći rizik za preeklampsiju (PE) u skupini bolesnica s oAPS-om (31).

TROMBOTSKI DOGAĐAJI U BOLESNICA S OPSTETRIČKIM ANTIFOSFOLIPIDNIM SINDROMOM

Sama trudnoća podrazumijeva rizik od trombotskih događaja. Primjerice, rizik od venske tromboembolije pet je puta veći u trudnice nego u žene iste dobi koja nije trudna (32).

Retrospektivno istraživanje provedeno na 200 bolesnica s APS-om koje su bile podijeljene u četiri skupine na temelju prethodne povijesti bolesti (opstetrički, trombotski, nekriterijski antifosfolipidni sindrom i nositelji aPL-a) pokazalo je da je 2,5% bolesnica doživjelo trombotske događaje tijekom trudnoće i razdoblja puerperija. Većina slučajeva prijavljena je u trombotskoj skupini s prethodnim trombotskim događajima. Nažalost, u 85% bolesnica došlo je do trombotskog događaja unatoč primjeni antitrombotske terapije u to vrijeme (33).

ČIMBENICI RIZIKA ZA NEPOVOLJNE ISHODE TRUDNOĆE

Provedena su različita istraživanja u potrazi za čimbenicima rizika za nepovoljne ishode kod oAPS-a i utvrđeno je da su, na primjer, sistemski eritemski lupus (SLE) ili hipokomplementemija dodatni čimbenici rizika (33, 34).

U metaanalizi provedenoj 2021. godine, koja je uključivala 27 prihvatljivih nalaza, pronađeni su prethodna tromboza, dvostruka i trostruka pozitivnost na aPL te pozitivnost na lupus antikoagulans, koji su najvažniji prediktori nepovoljnih ishoda trudnoće u APS-u (35).

Ovi se nalazi trebaju rutinski upotrebljavati u savjetovanju prije začeća i praćenju trudnoće kako bi se na pravilan način upravljalo individualiziranom procjenom rizika za nepovoljne ishode trudnoće.

UPRAVLJANJE OPSTETRIČKIM ANTIFOSFOLIPIDNIM SINDROMOM

1.) Standardna terapija: niskomolekularni heparin i niska doza aspirina

Antikoagulantna terapija ima bitnu ulogu u liječenju APS-a. U bolesnica s trombotičnim APS-om u terapiju treba uključiti antagoniste vitamina K (VKA), poput varfarina. Zbog teratogenosti varfarina, osobito u prvom tromjesečju, u trudnica s prethodnom trombozom potrebno je prekinuti primjenu varfarina (36).

Postoji sve veći interes za primjenu direktnih oralnih antikoagulansa (*engl.* direct oral anticoagulants, DOAC) u bolesnica s APS-om s vaskularnim manifestacijama bolesti. Trenutačne smjernice preporučuju da varfarin bude prvi izbor u liječenju APS-a, osobito u bolesnica s trostrukom aPL pozitivnošću i prethodnom arterijskom trombozom zbog povećanih stopa rekurentne

In pregnant patients with prior thrombosis, therapeutic doses of LMWH and LDA are recommended in therapy. For pregnant patients with purely obstetric morbidity and no prior thrombosis, prophylactic dose LMWH and LDA until six weeks postpartum is recommended (36).

Since early recurrent miscarriages are one of the prominent features of oAPS, it is necessary to emphasize the importance of starting the treatment promptly.

In patients with recurrent miscarriages, a prophylactic dose of LMWH should be included since the positive pregnancy test and LDA at least one month before starting attempts for a new pregnancy. For the patients who are in the process of assisted reproductive technique (ART), a prophylactic dose of LMWH should be included since estrogens are started in the substituted cycle or 14 days before the transfer, combined with LDA, at least one month before starting ART (10).

2.) Management of refractory oAPS

Approximately 20–30% of oAPS patients do not benefit from standard treatment (LMWH+LDA), and additional therapeutic options are necessary in those refractory cases (39).

In pregnant patients who receive prophylactic doses of LMWH but still experience recurrent fetal loss, therapeutic doses of LMWH can be administered to prevent adverse events.

Other therapeutic options include small doses of prednisolone, hydroxychloroquine, plasmapheresis, immunoglobulins, tumor necrosis factor (TNF)-α inhibitors, e.g., certolizumab-pegol, statins (pravastatin), and eculizumab, with promising results (36,39–48).

CONCLUSION

Pregnant women with APS must have frequent follow-up visits with both gynecologists and rheumatologists. During these visits, detailed check-ups should be performed, and risk factors for pregnancy morbidity should be screened for. A better understanding of the pathophysiology of the disease will enable the use of new therapeutic options, which can help improve outcomes in oAPS for both the mother and the child.

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tromboze liječenih DOAC-ima u usporedbi s antagonistima vitamina K (VKA) (37). Iako DOAC-i mogu biti učinkoviti u jednostruko/dvostruko aPL-pozitivnih bolesnica s isključivo venskim trombotičnim događajem, nema odgovarajućih podataka za primjenu DOAC-a u trudnoći. Ograničeni podatci iz stvarnog svijeta i studije provedene na životinjama izazvale su zabrinutost za sigurnost embrija i fetusa, s većom stopom pobačaja i mogućih fetalnih anomalija, tako da trenutne smjernice preporučuju da se DOAC-i ne primjenjuju tijekom cijele trudnoće (38).

U trudnica s prethodnom trombozom u terapiji se preporučuju terapijske doze niskomolekularnog heparina (LMWH) i niska doza aspirina (LDA). Za trudnice s opstetričkim morbiditetom i bez prethodne tromboze preporučuje se profilaktička doza niskomolekularnog heparina (LMWH) i niska doza aspirina (LDA) do šest tjedana nakon poroda (36).

Budući da su rani ponovljeni pobačaji jedno od istaknutih obilježja oAPS-a, potrebno je naglasiti važnost pravovremenog početka liječenja.

U bolesnica s ponavljajućim pobačajima potrebno je u liječenju primijeniti profilaktičku dozu LMWH-a od pozitivnog testa na trudnoću i LDA najmanje mjesec dana prije početka pokušaja nove trudnoće. U bolesnica koje su u postupku potpomognute oplodnje (engl. *assisted reproductive technique*, ART) treba primijeniti profilaktičku dozu LMWH-a budući da se s estrogenima počinje u supstituiranom ciklusu ili 14 dana prije transfera, u kombinaciji s LDA, najmanje mjesec dana prije početka postupka potpomognute oplodnje (ART). (10)

2.) Upravljanje refraktornim oAPS-om

Otprilike 20 – 30% bolesnica s oAPS-om nema koristi od standardnog liječenja (LMWH + LDA), a dodatne terapijske opcije potrebne su u tim refraktornim slučajevima (39).

U trudnica koje primaju profilaktičke doze niskomolekularnog heparina (LMWH), ali još uvijek doživljavaju ponovljeni gubitak fetusa, mogu se primijeniti terapijske doze niskomolekularnog heparina (LMWH) kako bi se spriječili nepovoljni događaji.

Druge terapijske opcije uključuju male doze prednizolona, hidroksiklorokina, plazmafereze, imunoglobulina, inhibitora faktora nekroze tumora (TNF)-α, npr. certolizumab pegola, statina (pravastatina) i ekulizumaba te nude obećavajuće rezultate (36, 39–48).

ZAKLJUČAK

Trudnice s dijagnozom APS-a moraju često pohoditi kontrolne preglede i kod ginekologa i kod reumatologa. Tijekom tih pregleda potrebno je obaviti detaljne preglede i ispitati čimbenike rizika za morbiditet u trudnoći. Bolje razumijevanje patofiziologije bolesti omogućit će primjenu novih terapijskih mogućnosti koje mogu biti korisne u poboljšanju ishoda oAPS-a i za majku i za dijete.

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