Reversible oligospermia in a patient with non-radiographic axial spondyloarthritis due to sulfasalazine treatment – a case report

Rogoznica, Marija; Stazić, Mila; Kehler, Tatjana

Source / Izvornik: **Reumatizam, 2023, 70, 85 - 90**

Journal article, Published version
Rad u časopisu, Objavljena verzija rada (izdavačev PDF)

https://doi.org/10.33004/reumatizam-70-2-5

Permanent link / Trajna poveznica: https://urn.nsk.hr/urn:nbn:hr:184:322608

Reumatizam 2023;70(2):85–90
https://doi.org/10.33004/reumatizam-70-2-5

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

Marija Rogoznica[1], Mila Stazić[1], Tatjana Kehler[1,2]

[1] Special Hospital for Medical Rehabilitation of Heart, Lung and Rheumatism, Thalassotherapia Opatija, Opatija, Croatia / Specijalna bolnica za medicinsku rehabilitaciju bolesti srca, pluća i reumatizma, Thalassotherapia Opatija, Opatija, Hrvatska
[2] Faculty of Medicine, University of Rijeka, Rijeka, Croatia / Medicinski fakultet, Sveučilište u Rijeci, Rijeka, Hrvatska

Corresponding author / Adresa autora za dopisivanje:
Marija Rogoznica, MD / dr. med.
Special Hospital for Medical Rehabilitation of Heart, Lung and Rheumatism Thalassotherapia Opatija / Specijalna bolnica za medicinsku rehabilitaciju bolesti srca, pluća i reumatizma, Thalassotherapia Opatija
Maršala Tita 188
Opatija, Croatia / Opatija, Hrvatska
Mobile phone number / Mob: +385914074404
E-mail / e-pošta: marija.rogoznica@tto.hr

Received / Primljeno: 2nd October 2023 / 2. 10. 2023.
Accepted / Prihvaćeno: 4th December 2023 / 4. 12. 2023.

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.

Acknowledgments: The authors report no acknowledgments.

Funding: For this work authors did not receive any funding.

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

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.

Zahvala: Autori nisu naveli zahvale za ovaj rad.

Financiranje: Autori za ovaj rad nisu primili nikakva sredstva.

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

REFERENCES / LITERATURA

1. Grazio S, Novak S, Laktašić-Žerjavić N, Anić B, Babić-Naglić Đ, Grubišić F i sur. Prijedlog preporuka Hrvatskog reumatološkog društva za liječenje odraslih bolesnika s aksijalnim spondiloartritisom i psorijatičnim artritisom biološkim lijekovima i ciljanim sintetskim molekulama. Reumatizam. 2017;64(2):71–87.
2. Zeidler H, Amor B. The Assessment in Spondyloarthritis International Society (ASAS) classification criteria for peripheral arthritis and for spondyloarthritis in general: the spondyloarthritis concept in progress. Ann Rheum Dis. 2011;70:1–3.
3. Lamot L, Vidović M, Perica M, Tambić Bukovac L, Harjaček M. Genetska podloga različitih oblika spondiloartritisa. Reumatizam. 2014;61(1):23-31.
4. Rudwaleit M, van der Heijde D, Landewé R, Akkoc N, Brandt J, Chou CT et al. The Assessment of SpondyloArthritis International Society classification criteria for peripheral spondyloarthritis and for spondyloarthritis in general. Ann Rheum Dis. 2011;70(1):25-31.
5. Schett G, Lories RJ, D'Agostino MA, Elewaut D, Kirkham B, Soriano ER et al. Enthesitis: from pathophysiology to treatment. Nat Rev Rheumatol. 2017;13(12):731-41.
6. Strand V, Singh JA. Patient burden of axial spondyloarthritis. J Clin Rheumatol. 2017;23(7):383-91.
7. Kameda H, Kobayashi S, Tamura N, Kadono Y, Tada K, Yamamura M et al. Non-radiographic axial spondyloarthritis. Mod Rheumatol. 2021;31(2):277-82.
8. Hay CA, Packham J, Ryan S, Mallen CD, Chatzixenitidis A, Prior JA. Diagnostic delay in axial spondyloarthritis: A systematic review. Clin Rheumatol. 2022;41(7):1939-50.
9. Shin T, Okada H. Infertility in men with inflammatory bowel disease. World J Gastrointest Pharmacol Ther. 2016;7(3):361-9.
10. Semet M, Paci M, Saïas-Magnan J, Metzler-Guillemain C, Boissier R, Lejeune H et al. The impact of drugs on male fertility: a review. Andrology. 2017;5(4):640-63.
11. Tiseo BC, Cocuzza M, Bonfa E, Srougi M, Silva CA. Male fertility potential alteration in rheumatic diseases: a systematic review. Int Braz J Urol. 2016;42(1):11-21.
12. Ramonda R, Foresta C, Ortolan A, Bertoldo A, Oliviero F, Lorenzin M et al. Influence of tumor necrosis factor α inhibitors on testicular function and semen in spondyloarthritis patients. Fertil Steril. 2014;101(2):359-65.
13. Almeida BP, Saad CG, Souza FH, Moraes JC, Nukumizu LA, Viana VS et al. Testicular Sertoli cell function in ankylosing spondylitis. Clin Rheumatol. 2013;32:1075–9.
14. Ozgocmen S, Kocakoc E, Kiris A, Ardicoglu A, Ardicoglu O. Incidence of varicoceles in patients with ankylosing spondylitis evaluated by physical examination and color duplex sonography. Urology. 2002;59(6):919-22.
15. Toovey S, Hudson E, Hendry WF, Levi AJ. Sulphasalazine and male infertility: reversibility and possible mechanism. Gut. 1981; 22(6):445-51.
16. Shin T, Okada H. Infertility in men with inflammatory bowel disease. World J Gastrointest Pharmacol Ther. 2016;7(3):361-9.
17. Riley SA, Lecarpentier J, Mani V, Goodman MJ, Mandal BK, Turnberg LA. Sulphasalazine induced seminal abnormalities in ulcerative colitis: results of mesalazine substitution. Gut. 1987;28:1008–12.
18. Chatzinoff M, Guarino JM, Corson SL, Batzer FR, Friedman LS. Sulfasalazine-induced abnormal sperm penetration assay reversed on changing to 5-aminosalicylic acid enemas. Dig Dis Sci. 1988;33:108–10.
19. Zelissen PM, van Hattum J, Poen H, Scholten P, Gerritse R, te Velde ER. Influence of salazosulphapyridine and 5-aminosalicylic acid on seminal qualities and male sex hormones. Scand J Gastroenterol. 1988;23:1100–4.
20. Micu MC, Micu R, Surd S, Gîrlovanu M, Bolboacă SD, Ostensen M. TNF-α inhibitors do not impair sperm quality in males with ankylosing spondylitis after short-term or long-term treatment. Rheumatology (Oxford). 2014;53(7):1250-5.
21. Boussaid S, Makhlouf Y, Rekik S, Jammali S, Cheour E, Sahli H et al. The effects of autoimmune rheumatic-related diseases on male reproductive health: A systematic review. J Reprod Immunol. 2022;150:103472.