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CASE REPORT PRIKAZ BOLESNIKA

TUBERCULOSIS SPONDYLODISCITIS IN A PATIENT WITH PSORIATIC ARTHRITIS ON TARGETED SYNTHETIC DISEASE-MODIFYING ANTIRHEUMATIC DRUGS – CASE REPORT

TUBERKULOZNI SPONDILODISCITIS U BOLESNIKA S PSORIJATIČNIM ARTRITISOM LIJEČENOG CILJANIM SINTETSKIM ANTIREUMATSKIM LIJEKOVIMA KOJI MODIFICIRAJU BOLEST – PRIKAZ BOLESNIKA

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Abstract

Tuberculosis (TB) has been recognised as an important opportunistic infection that occurs in patients with inflammatory rheumatic diseases. The results of global registries show that the risk of reactivation of latent TB or the development of new TB infection increases in patients treated with tumour necrosis factor inhibitors (TNFis). However, the results of randomised clinical studies and few data from everyday practice show that targeted synthetic disease-modifying anti-rheumatic drugs (tsDMARDs) such as apremilast and janus kinase inhibitors (JAKi), have a lower risk of TB activation compared to TNFis.

In this article, we shall present a male patient in whose case skin psoriasis preceded the development of articular involvement, and the definite diagnosis of psoriatic arthritis (PsA). He was treated with conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs) methotrexate and sulfasalazine, and, following that, with tsDMARDs apremilast and tofacitinib, with previously obtained negative results of hepatitis markers and QuantiFERON-TB Gold (QFT) test for latent tuberculosis. Considering the intense pain in the lumbosacral segment of the spine along with the occurrence of fever and alteration of serological inflammatory laboratory markers, the diagnostic evaluation was performed in order to determine the presence of TB spondylodiscitis L5-S1 with epidural abscess and abscess in the right psoas muscle. Specific therapy was discontinued, and, following that, surgical abscess drainage, and microdiscectomy and vertebrosynthesis of the L5-S1 lumbosacral joint were performed. In addition to that, the anti-TB therapy was induced for a total duration of 12 months.

In conclusion, this is the first case report in literature which discusses the case of tuberculous spondylodiscitis in patients with PsA treated with tofacitinib. The patient had been treated with apremilast for 3 months a year earlier, but the connection between the use of the aforementioned drug and the development of extrapulmonary tuberculosis was not established. Results from national registries need to be collected due to the fact that phase III randomised controlled trials did not register any cases of TB in PsA patients treated with tofacitinib. In the event of symptoms that do not fit into the clinical features of PsA, the possibility of developing pulmonary or extrapulmonary TB manifestations should be considered even though the patient is being treated with tsDMARDs.

Key words: apremilast, psoriatic arthritis, tofacitinib, tuberculosis

Sažetak

Tuberkuloza (TBC) je prepoznata kao važna oportunistička infekcija koja se javlja u bolesnika s upalnim reumatskim bolestima. Rezultati svjetskih registara pokazuju da se rizik od reaktivacije latentne TBC ili nastanka nove TBC-infekcije povećava u bolesnika liječenih inhibitorima faktora tumorske nekroze (TNFi). Dok rezultati randomiziranih kliničkih studija i malobrojni podatci iz svakodnevne prakse pokazuju da ciljani sintetski antireumatski lijekovi koji modificiraju bolest (*eng. targeted synthetic disease-modifying anti-rheumatic drugs*; tsDMARD), kao što su apremilast te inhibitori janus-kinaza (JAK-i), imaju niži rizik za aktivaciju TBC-a u usporedbi s TNFi.

U ovom članku prikazati ćemo bolesnika u kojega je dugi niz godina psorijaza kože prethodila razvoju zglobnih tegoba i postavljanju dijagnoze psorijatičnog artritisa (PsA). Liječen je konvencionalnim sintetskim antireumatskim lijekovima koji modificiraju bolest (*eng. conventional synthetic disease-modifying anti-rheumatic drugs*; csDMARD) metotreksatom i sulfasalazinom, te potom i tsDMARD-ovima apremilastom i tofacitinibom, uz prethodno utvrđene negativne nalaze hepatitis markera i kvantiferonskog testa na latentnu tuberkulozu. S obzirom na intenzivnu bolnost lumbosakralnog segmenta kralježnice uz febrilitet i alteraciju upalnih laboratorijskih parametara, učini se dijagnostička obrada kojom se utvrdi postojanje tuberkuloznog spondilodiscitisa L5-S1, epiduralnog apscesa i apscesa desnog mišića psoasa. Ukine se specifična terapija te se učini kirurška evakuacija apscesa, mikrodiscektomija i vertebrosinteza L5-S1 te započne antituberkulotska terapija u ukupnom trajanju od 12 mjeseci.

Zaključno, ovo je prvi prikaz u literaturi tuberkuloznog spondilodiscitisa u bolesnika sa PsA liječenog tofacitinibom. Pacijent je godinu dana ranije bio liječen apremilastom tri mjeseca, ali ga ne možemo povezati s razvojem ekstrapulmonalne tuberkuloze. Potrebno je prikupiti rezultate iz nacionalnih registara s obzirom na to da randomizirane kontrolirane studije faze III nisu registrirale niti jedan slučaj TBC-a u pacijenata s PsA liječenih tofacitinibom. Kod pojave simptoma koji se ne uklapaju u kliničku sliku PsA, treba razmišljati o mogućnosti razvoja pulmonalne ili ekstrapulmonalne manifestacije tuberkuloze iako se bolesnik liječi tsDMARD-om.

Ključne riječi: apremilast, psorijatični artritis, tofacitinib, tuberkuloza

INTRODUCTION

Patients with autoimmune rheumatic diseases have an increased risk of developing tuberculosis (TB) as an opportunistic infection. Results from global registries show that the risk of reactivation of TB or the development of *de novo* TB is higher in patients treated with tumour necrosis factor inhibitors (TNFis) (1). It is also a well-known fact that in rheumatoid arthritis (RA), long-term use of glucocorticoids and methotrexate represent a slightly increased risk of TB infection (2), while TNFis increase this risk by 4–8 times (3). Over the last few years, new therapeutic options have been introduced for the treatment of inflammatory rheumatic diseases, both for RA and psoriatic arthritis (PsA). The treatment of PsA includes targeted synthetic disease-modifying anti-rheumatic drugs (tsDMARDs), such as apremilast and Janus-kinase inhibitors (JAKi). The results of randomised clinical trials and data from clinical practice show that these drugs have a lower risk of TB activation in patients with PsA compared to TNFis (1). In the following text, we shall present the case of a patient with PsA who developed TB, spondylodiscitis and psoas muscle abscess during treatment with tsDMARDs.

CASE REPORT

A male patient, born in 1952, has been suffering from psoriasis for many years with involvement of the

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Bolesnici s autoimunim reumatskim bolestima imaju povišeni rizik za razvoj tuberkuloze (TBC) kao oportunističke infekcije. Podatci iz svjetskih registara pokazuju da je rizik za reaktivaciju TBC-a ili nastanak TBC-a *de novo* viši u bolesnika koji su liječeni inhibitorima faktora tumorske nekroze (engl. skr. TNFi) (1). Također se zna da kod reumatoidnog artritisa (RA) trajno uzimanje glukokortikoida i metotreksata predstavljaju blago povećan rizik za nastanak TBC infekcije (2) dok TNFi povisuju taj rizik za 4–8 puta (3). Tijekom zadnjih nekoliko godina uvedene su nove terapijske opcije za liječenje upalnih reumatskih bolesti, kako za RA tako i za psorijatični artritis (PsA). U liječenje PsA uključeni su ciljani sintetski antireumatski lijekovi koji modificiraju bolest (*eng. targeted synthetic disease-modifying anti-rheumatic drugs*; tsDMARD-ovi) kao što su apremilast i inhibitori janus-kinaza (engl. skr. JAK-i). Rezultati randomiziranih kliničkih studija i podatci iz kliničke prakse pokazuju da navedeni lijekovi imaju niži rizik za aktivaciju TBC-a u bolesnika s PsA u usporedbi s TNFi (1). U daljnjem tekstu prikazat ćemo bolesnika s PsA koji je razvio TBC spondilodiscitis i apsces mišića psoasa tijekom liječenja tsDMARD-ovima.

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Muškarac, rođen 1952. godine, dugi niz godina boluje od psorijaze uz zahvaćenost vlasišta, kože eksten-

scalp, skin of the extensor surfaces of the knees and nails. The patient was treated with local therapy as recommended by a dermatologist. In 2017, the patient was diagnosed with PsA on the basis of the clinical findings of asymmetric polyarthritis of the small joints in the hands and feet, along with dactylitis of the second toe of the right foot, without any signs of enthesitis. The inflammatory markers are mildly raised, anaemia of chronic disease with uric diathesis is observed. In addition to that, the disease activity score, measured by the Disease Activity Score 28 (ESR) (DAS28/ESR), was 4.31 and measured by the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) it was evaluated as 3.8, which indicates moderate disease activity. In addition to non-steroidal anti-inflammatory drugs (NSAIDs), conventional synthetic disease-modifying anti-rheumatic drug (csDMARDs), methotrexate, was also included in the therapy, at a dose of up to 20 mg once a week. Furthermore, due to the exacerbation of joint symptoms with the occurrence of inflammatory back pain and the raised inflammatory laboratory markers (ESR 61, C-reactive protein (CRP) 12 mg/L), in November 2018 sulfasalazine was introduced in a daily dose of 2 grams. Smaller areas of bone marrow oedema in the ventral and caudal part of the vertebral body of T12 and L1 vertebrae were detected through MRI, while no signs of sacroiliitis were observed on the sacroiliac joints. Therapy with csDMARDs was difficult for the patient to tolerate due to pronounced gastrointestinal complications. In May 2019, exacerbation of the joint disease had occurred, DAS28(CRP) was 4.88, and a diagnostic evaluation was performed before the application of a biological drug or tsDMARDs. The results of markers for hepatitis B and C were negative, as well as the results of the QuantiFERON-TB Gold (QFT) test for latent tuberculosis. Since the patient was not inclined to intravenous and subcutaneous administration of the biological drug, treatment with orally administered tsDMARD apremilast was initiated in August 2019. At the evaluation after three months of treatment, the clinical features continued to show pronounced signs of asymmetric polyarthritis of the small joints in the hands and feet, with enthesitis of the right Achilles tendon, while the DAS28(ESR) score was 3.91. In December 2019, apremilast was replaced, due to the ineffectiveness of the drug, by another tsDMARD, tofacitinib. After its application, remission of the disease activity occurred at the evaluation after three months of treatment (March 2020), with a DAS28(SE) score of 2.62. In August 2020, the patient had a fever up to 38 °C with a negative result of the PCR *Polymerase Chain Reaction*) test for SARS-CoV-2 (*severe acute respiratory syndrome coronavirus 2*), raised inflammatory laboratory markers (ERS 61

zornih strana koljena te noktiju. Liječen je lokalnom terapijom po preporuci dermatologa. Godine 2017. postavljena je dijagnoza PsA temeljem kliničkog nalaza asimetričnog poliartritisa malih zglobova šaka i stopala, uz daktilitis II. prsta desnog stopala, a bez znakova entezitisa. Upalni parametri su blago povišeni, registrira se anemija kronične bolesti uz uričnu dijatezu, a indeks aktivnosti bolesti mjeren indeksom *Disease activity score* 28 (SE) (DAS28/SE) bila je 4,31 te indeksom *The Bath Ankylosing Spondilytis Disease Activity Index* (BASDAI) bila je 3,8, što pokazuje umjereno aktivnu bolest. U terapiju je tada uz nesteroidni antireumatski lijek (skr. NSAR) uključen i konvencionalni sintetski antireumatski lijek koji modificira bolest (engl. *conventional synthetic disease-modifying antirheumatic drugs*; skr. csDMARD) metotreksat u dozi do 20 mg 1 x tjedno, a zbog pogoršanja zglobnih simptoma uz pojavu upalne križobolje te povišenja laboratorijskih upalnih parametara (SE 61, C-reaktivni protein (CRP) 12 mg/L) od studenog 2018. dodaje se sulfasalazin u dnevnoj dozi od 2 grama. Na snimkama magnetske rezonancije utvrđene su manje zone koštanog edema ventrokaudalnog dijela trupa Th12 i L1 kralješka, dok je prikaz sakroilijakalnih zglobova bio bez znakova sakroileitisa. Terapiju csDMARD-ovima bolesnik je teško podnosio zbog izraženih gastričnih tegoba. U svibnju 2019. nastupilo je pogoršanje zglobne bolesti, DAS28(CRP) je bio 4,88 te je učinjena dijagnostička obrada prije primjene biološkog lijeka ili ciljane sintetske molekule. Nalazi markera na hepatitis B i C bili su negativni, kao i nalaz kvantiferonskog testa na latentnu tuberkulozu. Budući da bolesnik nije bio sklon intravenskoj i supkutanoj aplikaciji biološkog lijeka, u kolovozu 2019. započne se liječenje peroralnim tsDMARD-om apremilastom. Na evaluaciji nakon tri mjeseca liječenja i dalje je bila izražena klinička slika asimetričnog poliartritisa malih zglobova šaka i stopala, uz entezitis desne Ahilove tetive, dok je vrijednost DAS28(SE) bila 3,91. U prosincu 2019. apremilast je zbog neučinkovitosti lijeka zamijenjen drugim tsDMARD-om, tofacitinibom. Po njegovoj primjeni nastupila je remisija aktivnosti bolesti na evaluaciji nakon tri mjeseca (ožujak 2020.), uz vrijednost DAS28(SE) 2,62. U kolovozu 2020. bolesnik je postao febrilan do 38°C uz negativan nalaz PCR (*eng. Polymerase Chain Reaction*) testa na SARS-CoV-2 (engl. *severe acute respiratory syndrome coronavirus 2*), povišenih vrijednosti upalnih laboratorijskih parametara (SE 61 mm/h, CRP 72 mg/L), uz jaku križobolju i bolnost u području zdjelice mjerenu vizualnom skalom boli (skr. VAS) 10/10. Iz kliničkog statusa ističe se hod uz pomoć dviju podlakatnih štaka, bolni i ograničeni pokretni lumbosakralnog segmenta kralježnice, a bez radikularne simptomatologije, te palpatorna bolnost sakroilijakalnih zglobova, bez aktivne upale u perifernim zglo-

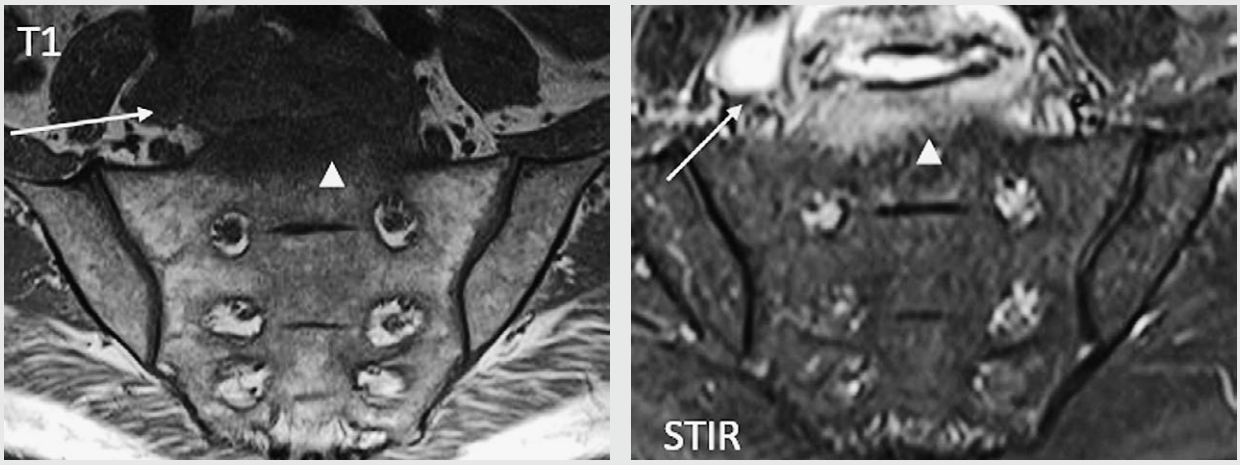

Figure 1. MRI of coronal cross-section of the lumbosacral L5-S1 spine in STIR (*short TI inversion recovery*) and T1 images which show inflammatory changes. Arrowhead: bone oedema – high signal in STIR and low signal in T1; long arrows: epidural abscess – low signal in T1, high signal in STIR.

Slika 1. Koronalni presjek na magnetskoj rezonanciji (MR) lumbosakralnog L5-S1 segmenta kralježnice u STIR (engl. short TI inversion recovery) i T1 slikama u smislu upalnih promjena. Glava strelice: edem kosti – visok signal u STIR, nizak signal u T1. Duge strelice: epiduralni apsces (u T1 je nizak signal, u STIR je visok).

mm/h, CRP 72 mg/L), and severe back pain and pelvic pain measured by the visual analogue scale (VAS) with his pain intensity score evaluated as 10/10. The patient's clinical status indicates that the patient is walking with the help of two forearm crutches, with painful and limited movement of the lumbosacral segment of the spine, without any symptoms of radiculopathy, and the presence of tenderness on palpation in the sacroiliac joints, with no signs of active inflammation in the peripheral joints, with DAS28(CRP) score of 3.9, while the score of disease activity index (BASDAI) of spinal affection was *6.6*. Following that, the drug tofacitinib was discontinued from therapy. In diagnostic evaluation, the radiograph of the thorax organs, thoracic and lumbar segment of the spine, sacroiliac joints and pelvis with hips did not show any significant deviation. On the bone scan (Tc-99), intense remodelling was observed in the area of the lumbosacral transitional vertebrae with a well-vascularised process in the early phase of the imaging, indicating a possible inflammatory component, but the finding was of unknown aetiology. On the magnetic resonance cross-sections, spondylodiscitis at the L5-S1 level, epidural abscess and abscess of the right psoas muscle were confirmed (Figure 1, Figure 2). A positive result of the QuantiFERON-TB Gold (QFT) test for tuberculosis was also obtained. In October 2020, drainage of the epidural abscess as well as microdiscectomy, transpedicular fixation and intercorporeal vertebrosynthesis of the L5-S1 lumbosacral joint were performed. Microbiological analysis of the sample taken intraoperatively revealed a positive finding for Mycobacterium tuberculosis. Furbovima uz DAS28(CRP) 3,9, dok je vrijednost indeksa aktivnosti bolesti afekcije kralješnice BASDAI bila *6,6*. Tada je iz terapije isključen lijek tofacitinib. U dijagnostičkoj obradi radiogram grudnih organa, torako-lumbalnog segmenta kralježnice, sakroilijakalnih zglobova i zdjelice s kukovima nije pokazao značajnije odstupanje. Na scintigramu skeleta (Tc-99) uočena je intenzivna pregradnja u području lumbosakralnog prijelaza kralježnice uz dobro vaskulariziran proces u ranoj fazi snimanja, moguće upalne komponente, no nalaz je bio otvorene etiologije. Na presjecima magnetske rezonancije verificiran je spondilodiscitis u razini L5-S1, epiduralni apsces i apsces desnog mišića psoasa (slika 1, slika 2). Utvrđen je i pozitivan nalaz kvantiferonskog testa na tuberkulozu. U listopadu 2020. operativno je učinjena evakuacija epiduralnog apscesa te mikrodiscektomija, transpedikularna fiksacija i interkorporalna vertebrosinteza L5-S1. Mikrobiološkom analizom intraoperativno uzetog materijala utvrđen je pozitivan nalaz na mikobakterijum tuberkuloze. Daljnjom obradom nije dokazano postojanje plućne tuberkuloze te je postavljena dijagnoza ekstrapulmonalne tuberkuloze s razvojem tuberkuloznog spondilodiscitisa s apscesom desnog mišića psoasa. Započeto je liječenje antituberkulotskom terapijom (rifampicin, etambutol, pirazinamid, izonijazid) u trajanju od dva mjeseca, a potom izonijazid i rifampicin u trajanju do ukupno 12 mjeseci. Provedeno je i preporučeno liječenje hiperbaričnom oksigenoterapijom (50 terapija). U rujnu 2021. bolesnik je dobroga općeg stanja, afebrilan, pokretan pomoću štapa na duže relacije ili bez ortopedskog pomagala na kraće relacije, minimalnog opsega kretnji lumbosakralnog segmenta kralježnice te bolnih više zglo-

ther processing did not prove the occurrence of pulmonary tuberculosis, and extrapulmonary tuberculosis with the development of tuberculous spondylodiscitis with the abscess of the right psoas muscle was diagnosed. Treatment with antituberculosis therapy (rifampicin, ethambutol, pyrazinamide, isoniazid) was initiated and it lasted for two months, followed by the treatment with the use of isoniazid and rifampicin for a total duration of 12 months. Hyperbaric oxygen therapy (50 treatments) was also recommended and carried out. In September 2021, the patient was in a good general condition, afebrile, using a cane for long distances or walking without an orthopaedic aid for short distances, with a minimal range of motion of the lumbosacral segment of the spine, with painful multiple joints (both hips, both knees) and painful and swollen second metacarpophalangeal joints of both hands, and with improved inflammatory laboratory parameters (ESR 62 mm/h, CRP 11 mg/L), with a DAS28(CRP) score of 4.07, and with a BASDAI score of 1.6. The patient was referred for a control computed tomography (CT) of the lumbosacral segment of the spine (on 8 June 2021), which showed an extensive bone destruction of the vertebral body of the L5 vertebra and the superior surface of the S1 vertebra as part of the progression of changes from the previously known spondylodiscitis, while the previously noted soft tissue substrate of the L5/S1 level in the ventral part of the spinal canal and in the prevertebral space is in regression. By performing the follow-up of the patient's clinical status and laboratory markers, we have decided against reintroducing csDMARDs or tsDMARDs for the time being.

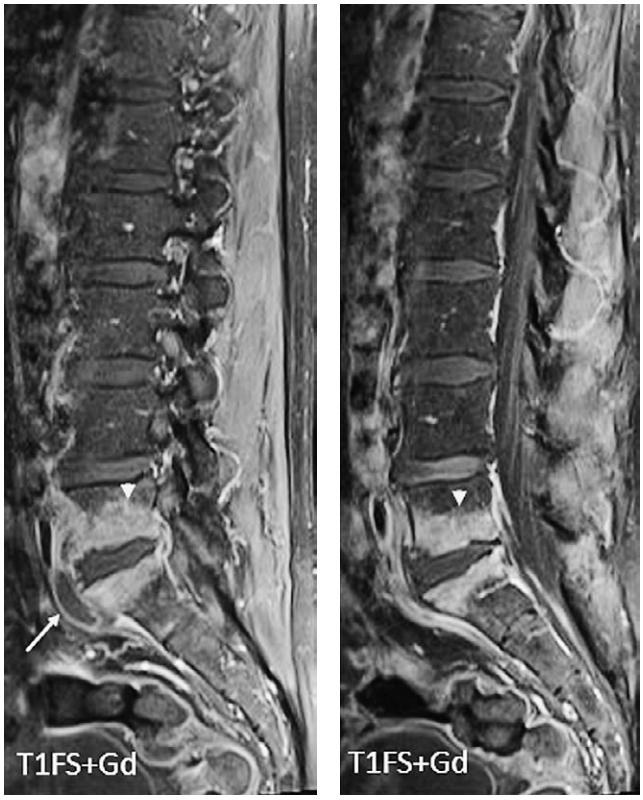

Figure 2. Sagittal T1 fat saturated post contrast cross-sectional MR images of the lumbosacral segment of the spine demonstrate extensive enhancement of L5 and S1 vertebral endplates, enhancement of paravertebral soft tissues and epidural abscess in keeping with spondylodiscitis of the L5/S1 segment. Arrowhead: bone oedema/osteitis – high signal in T1FSGd; long arrow: epidural abscess – low signal in T1, low signal in the centre (necrotic content) and post contrast peripheral enhancement.

Slika 2. Sagitalni postkontrastni presjeci na MR lumbosakralne kralježnice prikazuju širu zonu patološkog povišenja signala u području subdiskalne kosti trupova kralježaka L5 i S1, povišenje signala okolnog mekog tkiva i epiduralni apsces u sklopu spondilodiscitisa segmenta L5/S1. Glava strelice: upalno promijenjena kost – visok signal u T1FSGd. Duga strelica: epiduralni apsces – u T1 je nizak signal, postkontrastno se rubno boji, a centar je niskog signala (nekrotični sadržaj).

DISCUSSION

The results of global registries show that the risk of reactivation of latent TB or the development of new TB infection increases in patients treated with TNFis, especially if these patients reside in countries in which TB is an endemic disease (1,4). In recent years, new drugs were introduced in the treatment of inflammatory rheumatic diseases, tsDMARDs, such as apremilast and JAKi. The results of randomised clinical trials and few data from clinical practice show that these drugs have a lower risk of TB activation compared to TNFis (1.4). Randomised clinical trials that included the follow-up of patients with PsA that were treated with apremilast during one year of follow-up (5,6) and later in a four-year extension of the studies, did not detect the occurrence of a TB infection, and the authors concluded that the long-term risk for opportunistic infection is similar to a one-year period of using apremilast and that it is comparable to a placebo treatment (6,7). In national registries there is no data regarding

bova (oba kuka, oba koljena) i bolnih i otečenih II. metakarpofalangealnih zglobova obje šake, poboljšanih upalnih laboratorijskih parametara (SE 62 mm/h, CRP 11 mg/L), DAS28(CRP) 4,07; BASDAI 1,6. Upućen je na kontrolnu kompjuteriziranu tomografiju (CT) lumbosakralnog segmenta kralježnice (8. 6. 2021.), koja je pokazala opsežniju koštanu destrukciju korpusa kralješka L5 i gornje pokrovne plohe kralješka S1 u sklopu progresije promjena od prethodno poznatog spondilodiscitisa, dok je prethodno notirani mekotkivni supstrat razine L5/S1 u ventralnom dijelu spinalnog kanala te prevertebralno u regresiji. Praćenjem bolesnikova kliničkog statusa i laboratorijskih parametara za sada se nismo odlučili na ponovno uključivanje csDMARD-ova ni tsDMARD-ova.

the detection and recording of latent or active TB in patients during treatment with apremilast (1,6,8). In addition to that, two observational studies that included 202 patients with PsA and their follow-up during 6 months of apremilast administration did not detect or record the occurrence of a TB infection (8,9). Furthermore, tofacitinib is one of the drugs in the JAKi group. Numerous studies have been conducted on its effectiveness and safety in patients with RA, and it was concluded that the risk of developing TB during treatment is the same as with treatment with TNFis. It is also important to note that in half of the patients who developed TB, it was a case of extrapulmonary manifestation (10). However, phase III randomised controlled trials on the efficacy and safety of tofacitinib in patients with PsA did not record a single case of TB (11,12). There is currently no data available from extension studies and from national registers.

In this case report which describes the case of a patient with predominantly peripheral manifestations of PsA with the activation of axial symptoms, the possibility of progression of the underlying inflammatory rheumatic disease, i.e., the development of spondylitis and/or sacroiliitis as part of PsA, should be taken into account. Given the patient's age, which in this case is over 65, the differential diagnosis should consider the development of osteodegenerative changes, i.e., the occurrence of mechanical low back pain in patients with established inflammatory rheumatic disease, and the possibility of oncological disease should also be ruled out in accordance with the patient's age. Due to the presence of general symptoms, i.e., fever and raised inflammatory laboratory markers that are relatively higher than normal values found in the case of reactivation of PsA disease activity, further processing is carried out with the aim of detecting a possible infection. Regardless of the previous negative result of the QuantiFERON-TB Gold (QFT) obtained during the introduction of tsDMARD in therapy, there was enough reasons to suspect the de novo TB infection, and this suspicion was later confirmed by further processing.

Therefore, it is important to note that, in the event of symptoms that do not fit into the clinical features of PsA, the possibility of developing pulmonary or extrapulmonary TB manifestations should be considered even though the patient is being treated with tsDMARDs, in order to apply the appropriate treatment as soon as possible.

CONCLUSION

In this case report, based on the clinical features and diagnostic evaluation, we did not find the connection between the use of apremilast and the development of extrapulmonary TB, so the aforementioned drug could

RASPRAVA

Rezultati svjetskih registara pokazuju da se rizik od reaktivacije latentne TBC ili nastanka nove TBC infekcije povećava u bolesnika liječenih TNFi-ma, pogotovo ako žive u zemljama u kojima je TBC endemska bolest (1,4). Zadnjih godina u liječenje upalnih reumatskih bolesti uključeni su novi lijekovi, tsDMARD kao što su apremilast te JAK-i. Rezultati randomiziranih kliničkih studija i malobrojnih podataka iz svakodnevne prakse pokazuju da navedeni lijekovi imaju niži rizik za aktivaciju TBC-a u usporedbi s TNFi-ma (1,4). Randomizirane kliničke studije koje su pratile bolesnike s PsA na apremilastu tijekom jedne godine praćenja (5,6) te kasnije u četverogodišnjem produžetku studija nisu registrirale TBC infekciju, te su autori zaključili da je dugoročni rizik za oportunističku infekciju sličan jednogodišnjem uzimanju apremilasta te je usporediv s placebom (6,7). Nema podataka glede evidentiranja latentne ili aktivne TBC iz nacionalnih registara u bolesnika tijekom liječenja apremilastom (1,6,8). Također, dvije opservacijske studije koje su uključile 202 bolesnika s PsA i pratile ih tijekom 6 mjeseci primjene apremilasta nisu registrirale TBC infekciju (8,9). Nadalje, tofacitinib je jedan od lijekova skupine JAK-i te su provedene brojne studije o njegovoj učinkovitosti i sigurnosti u bolesnika s RA, sa zaključkom da je rizik od razvoja TBC-a tijekom liječenja jednak kao i kod liječenja TNFi, a važno je napomenuti da je u polovice bolesnika koji su razvili TBC ona bila ekstrapulmonalna manifestacija (10). No, randomizirane kontrolirane studije faze III o učinkovitosti i sigurnosti tofacitiniba u bolesnika s PsA nisu registrirale niti jedan slučaj TBC-a (11,12). Trenutno nema dostupnih podataka iz produžetaka studija i iz nacionalnih registara.

U ovom prikazu bolesnika dominantno periferne manifestacije PsA, kod koje dolazi do aktivacije aksijalne simptomatologije, treba uzeti u obzir u prvom redu mogućnost progresije osnovne upalne reumatske bolesti, odnosno razvoj spondilitisa i/ili sakroileitisa u sklopu PsA. S obzirom na dob bolesnika, koja je u ovom slučaju veća od 65 godina, diferencijalno-dijagnostički valja razmišljati o razvoju osteodegenerativnih promjena, odnosno pojave mehaničke križobolje u bolesnika s etabliranom upalnom reumatskom bolesti, a sukladno dobi valja otkloniti i mogućnost nastanka onkološke bolesti. S obzirom na prisutnost općih simptoma, odnosno visokog febriliteta i povišenja upalnih laboratorijskih parametara koji su razmjerno viših vrijednosti od uobičajenih nego kod reaktivacije aktivnosti bolesti PsA, provede se daljnja obrada s ciljem otkrivanja mogućega infektivnog zbivanja. Bez obzira na prethodno negativan nalaz kvantiferonskog testa kod uključivanja tsDMARD-a postavljena je sumnja na *de novo* TBC infekciju koja se obradom i potvrdi.

Stoga je važno napomenuti da kod pojave simptoma koji se ne uklapaju u kliničku sliku PsA treba razmi-

have been a safer treatment option if its effectiveness had been confirmed, which was not the case with our patient. In patients treated with tsDMARDs, when symptoms do not fit the clinical features of PsA, the possibility of developing pulmonary or extrapulmonary tuberculosis should be considered in order to apply the appropriate treatment as soon as possible. This should be done even though phase III randomised controlled trials did not record a single case of TB, and there are no results from national registers which would confirm this occurrence. Finally, the question arises as to when and which drug to choose for patients after treatment with antituberculosis drugs, and in case of increased activity of the PsA disease.

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šljati o mogućnosti razvoja pulmonalne ili ekstrapulmonalne manifestacije TBC-a iako se bolesnik liječi tsDMARD-om, kako bi se što prije primijenilo odgovarajuće liječenje.

ZAKLJUČAK

Kod prikazanog bolesnika temeljem kliničke slike i dijagnostičke obrade nismo povezali apremilast s razvojem ekstrapulmonalne TBC i navedeni lijek bi mogao biti sigurnija opcija liječenja ako postoji njegova učinkovitost, što kod našeg bolesnika nije bio slučaj. U bolesnika koji se liječe tsDMARD-om svakako bi kod pojave simptoma koji se ne uklapaju u kliničku sliku PsA trebalo razmišljati o mogućnosti razvoja pulmonalne ili ekstrapulmonalne tuberkuloze, iako randomizirane kontrolirane studije faze III nisu registrirale niti jedan slučaj TBC-a, a nema rezultata niti iz nacionalnih registara, kako bi se što prije primijenilo odgovarajuće liječenje. Također se na kraju postavlja pitanje kada i koji lijek izabrati kod bolesnika nakon provedene antituberkulostatske terapije, a u slučaju pojačanja aktivnosti bolesti PsA.

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