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CASE REPORT PRIKAZ BOLESNIKA

# ADULT-ONSET STILL'S DISEASE IN AN ELDERLY PATIENT – CASE REPORT

## STILLOVA BOLEST ODRASLIH KOD BOLESNIKA STARIJE ŽIVOTNE DOBI – PRIKAZ BOLESNIKA

**Indira Melezović[1], Samir Mehmedagić[1], Lejla Granulo[2], Mevludin Mekić[1], Emela Čvorak[1]**

[1] Clinical Center of the University of Sarajevo, Bolnička 25, Sarajevo / Klinički Centar Univerziteta u Sarajevu, Bolnička br. 25, Sarajevo
[2] Public Institution Health Center of the Sarajevo Canton, Vrazova 11, Sarajevo / Javna ustanova Dom zdravlja Kantona Sarajevo, Vrazova 11, Sarajevo

**Corresponding author / Adresa autora za dopisivanje:**
**Indira Melezović, MD / Indira Melezović, dr. med.**
Clinical Center of the University of Sarajevo / Klinički Centar Univerziteta u Sarajevu
Bolnička 25, 71000 Sarajevo
Bosnia and Herzegovina / Bosna i Hercegovina
E-mail / e-pošta: indira_melezovic@yahoo.com

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### Abstract

*Introduction:* Adult-onset Still's disease (AOSD) is a rare systemic inflammatory disorder characterized by a triad of symptoms: fever, transient maculopapular rash, arthralgia or arthritis. Symptoms of the disease usually appear before the age of sixteen, and if they do, then that is the case of systemic juvenile idiopathic arthritis. The appearance of clinical symptoms in adulthood usually occurs by the age of 46. Rare cases of disease occurrence in patients over sixty years of age are described in the literature. *Case report:* We present the case of a 73-year-old patient with numerous comorbidities who was admitted to our inpatient ward due to a protracted febrile condition accompanied by rash and arthralgia. After excluding infection and malignancy, we have finally diagnosed the patient with AOSD. *Conclusion:* Despite the fact that AOSD is typically diagnosed in young adulthood, the diagnosis of this condition is possible even in the elderly, after exclusion of other more common differential diagnoses.

**Keywords:** adult-onset Still's disease, fever of unknown origin, the elderly

### Sažetak

*Uvod:* Stillova bolest odrasle dobi (engl. AOSD – *adult onset Still's disease*) rijedak je sistemski upalni poremećaj karakteriziran trijasom simptoma: povišenom tjelesnom temperaturom, prolaznim makulopapuloznim osipom te artralgijama ili artritisom. Obično se simptomi bolesti javljaju prije šesnaeste godine života i tada govorimo o sistemskom juvenilnom idiopatskom artritisu. Pojava kliničkih simptoma u odrasloj dobi obično se javlja do 46. godine života. U literaturi su opisani rijetki slučajevi pojave bolesti kod bolesnika starijih od šezdeset godina. *Prikaz slučaja:* U ovom radu predstavljamo slučaj 73-godišnjeg bolesnika s brojnim komorbiditetima koji je hospitaliziran zbog protrahiranoga febrilnog stanja praćenog osipom i artralgijama. Isključenjem infekcije i maligne bolesti u konačnici smo postavili dijagnozu Stillove bolesti starije životne dobi. *Zaključak:* Iako se Stillova bolest odrasle dobi najčeće razvija u mlađih odraslih, dijagnoza ovog stanja dolazi u obzir i u bolesnika starije životne dobi nakon isključenja mogućih diferencijalnih dijagnoza.

**Ključne riječi:** Stillova bolest odrasle dobi, vrućica nepoznatog uzroka, starija životna dob

## INTRODUCTION

Adult-onset Still's disease (AOSD) is a rare systemic inflammatory disorder characterized by a triad of symptoms: a febrile state that includes daily tempera-

## UVOD

Stillova bolest odrasle dobi (engl. AOSD – *adult-onset Still's disease*) rijedak je sistemski upalni poremećaj karakteriziran trijasom simptoma: febrilnim stanjem

ture spikes that can reach up to 40°C, a characteristic transient maculopapular rash that most often appears during temperature spikes and predominantly occurs on the trunk and extremities, as well as arthralgias or arthritis, most often in the knees, ankles, wrists, and shoulders. (1)

Adult-onset Still's disease and systemic juvenile idiopathic arthritis (sJIA) are terms used for similar clinical conditions that have different ages of onset, meaning that the first symptoms of the disease appear at different ages. If the disease occurs before the age of sixteen, that is considered to be the case of systemic juvenile arthritis. In other cases, the commonly used term is adult-onset Still's disease. (2)

In patients with adult-onset Still's disease, two age ranges have been observed in which the first symptoms of the disease most often appear: between 15 and 25 years of age and between 35 and 46 years of age. The incidence of the disease is estimated to be between 0.16 and 0.4 cases per 100,000 people. No male or female predominance of the disease has been determined. (3) The occurrence of Still's disease after the age of 60 is extremely rare and is then referred to as elderly-onset Still's disease (EOSD). (4)

The disease pathogenesis remains unknown, but it is believed that genetic predisposition, autoinflammatory cascade reaction due to an inadequate innate immune response, and infectious agents as triggers for the development of the disease are the key factors. Genetic background and environmental triggers such as PAMP (pathogen-associated molecular pattern) and DAMP (damage-associated molecular pattern) are the starting points of inflammation in AOSD. They promote macrophage stimulation and activate NLPR3 inflammasomes. Following that, NLRP3 inflammasomes facilitate the activation of caspase-1, which leads to the proteolytic cleavage of pro-interleukin-1 beta (pro-IL-1β) and pro-interleukin 18 (pro-IL-18) into their bioactive and mature forms, which further generate a burst of cytokine storm with interleukin 6 (IL-6), interleukin 8 (IL-8) and tumour necrosis factor alpha (TNF-α) involvement. Neutrophils are also extensively activated in AOSD and release more neutrophil extracellular traps (NETs), which can further stimulate NLRP3 activation. (5)

Numerous microorganisms have been reported as triggers for adult-onset Still's disease, including rubella virus, Epstein-Barr virus, cytomegalovirus, parvovirus B19, hepatitis viruses, and the following bacteria: *Mycoplasma pneumoniae, Yersinia enterocolitica, Chlamydia pneumoniae, Campylobacter jejuni,* and *Borrelia burgdorferi*. (6,7,8)

In addition to the classic triad of symptoms, sore throat, myalgia, splenomegaly, hepatomegaly, liver disease, pleural and pericardial effusion, and lymphade-

koje uključuje svakodnevnu pojavu temperature koja može dosezati i visoke vrijednosti preko 40°C, karakterističnim prolaznim makulopapuloznim osipom koji se najčešće pojavljuje pri skokovima temperature i predominantno se javlja u području trupa i ekstremiteta, kao i artralgijama ili artritisom najčešće koljena, skočnih, ručnih i ramenih zglobova. (1)

Stillova bolest odrasle dobi i sistemski juvenilni idiopatski artritis (sJIA) termini su koji se koriste za slična klinička stanja koja se razlikuju po godinama pojave prvih simptoma bolesti. Ako se bolest javi prije šesnaeste godine života riječ je o sistemskom juvenilnom artritisu. U ostalim slučajevima govorimo o Stillovoj bolesti odrasle dobi. (2)

U bolesnika sa Stillovom bolešću odrasle dobi primijećena su dva životna razdoblja u kojima se prvi simptomi bolesti najčešće pojavljuju: između 15. i 25. te između 35. i 46. godine života. Incidencija bolesti se procjenjuje između 0,16 i 0,4 slučajeva na 100.000 ljudi. Nije utvrđena predominacija u obolijevanju između muškaraca i žena. (3) Pojava Stillove bolesti nakon 60. godine života iznimno je rijetka i tada govorimo o Stillovoj bolesti starije životne dobi (engl. EOSD – *elderly-onset Still's disease*). (4)

Patogeneza bolesti je nepoznata, ali se smatra da su genetska predispozicija, autoinflamatorna kaskadna reakcija uslijed neadekvatnoga urođenog imunog odgovora te infektivni agensi kao okidači za razvoj bolesti ključni čimbenici. Genetska pozadina i okidači iz okoline poput PAMP-a (engl. *pathogen associated molecular pattern*) i DAMP-a (engl. *damage associated molecular pattern*) početne su točke upale u AOSD-u. Oni potiču stimulaciju makrofaga i aktiviraju NLPR3 inflamasome. Zatim NLRP3 inflamasomi olakšavaju aktivaciju kaspaze-1, što dovodi do proteolitičkog cijepanja prointerleukina 1 beta (pro-IL-1β) i prointerleukina 18 (pro-IL-18) u njegove bioaktivne i zrele oblike, koji dalje generiraju eksploziju citokinske oluje s interleukinom 6 (IL-6), interleukinom 8 (IL-8) i čimbenikom tumorske nekroze alfa (TNF-α, engl. *tumor necrosis factor alpha*). Neutrofili se također ekstenzivno aktiviraju u AOSD-u i otpuštaju više neutrofilnih ekstracelularnih zamki (NET, engl. *neutrophill extracellular traps*), što može dodatno stimulirati aktivaciju NLRP3. (5)

Brojni mikroorganizmi se dovode u vezu kao okidači Stillove bolesti odrasle dobi uključujući virus rubelle, Epstein-Barrov virus, citomegalovirus, parvovirus B19, viruse hepatitisa te bakterije *Mycoplasma pneumoniae*, *Yersinia enterocolitica*, *Chlamydia pneumoniae*, *Campylobacter jejuni* i *Borrelia burgdorferi*. (6,7,8)

Pored klasičnog trijasa simptoma individualno, ovisno o slučaju, mogu se pojavljivati i grlobolja, mijalgija, splenomegalija, hepatomegalija, disfunkcija jetre, pleuralni i perikardijalni izljev te limfadenopatija. U labo-

nopathy may also occur individually, depending on the case. Laboratory findings typically include leukocytosis with a predominance of neutrophils, increased C-reactive protein levels and erythrocyte sedimentation rate, and elevated ferritin levels. Affection of the liver commonly includes increased aspartate aminotransferase and alanine aminotransferase levels. (1)

Disease complications can occur due to the development of cytokine storm and macrophage activation syndrome (MAS) with multiorgan failure, which is a life-threatening condition. (9)

Establishing a diagnosis of AOSD is challenging because it is necessary to exclude other clinical entities such as infections, neoplastic and paraneoplastic syndromes, and other autoimmune and anti-inflammatory diseases. The diagnosis is most often made on the basis of Yamaguchi's or Fautrel's criteria. Both lists of criteria showed high specificity and sensitivity, with the fact that, unlike Fautrel's criteria, Yamaguchi's criteria also contain the exclusion criteria. (10)

Initial treatment of AOSD depends on the severity of clinical symptoms. In mild forms of the disease, nonsteroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen or indomethacin are recommended over glucocorticoids. (11) If there is no patient response to NSAIDs or if the clinical symptoms of adult-onset Still's disease are moderate to severe, the introduction of a biologic is recommended. If a biologic is not available, glucocorticoids are introduced into the therapy in doses of 20–60 mg per day, orally. The use of parenteral glucocorticoids is recommended depending on the clinical features according to the preference of the attending physician. If the development of macrophage activation syndrome (MAS) is suspected, it is recommended that these patients be treated with anakinra and pulse glucocorticoid therapy (1000 mg of methylprednisolone, intravenously) for one to three days. In maintenance therapy, disease-modifying antirheumatic drugs (DMARDs), such as methotrexate and leflunomide, can be introduced. Among other biologics, canakinumab, rilonacept, tocilizumab and infliximab are also used in the treatment of AOSD. (12,13,14)

## CASE REPORT

A 73-year-old patient was admitted to the Department of Rheumatology due to a prolonged febrile state with a body temperature of up to 40°C, accompanied by a maculopapular rash on the trunk (Figure 1) and swelling and pain in the joints. The patient had a history of coronary artery disease with a triple bypass graft, which was preceded by a myocardial infarction. The patient also had a history of hypertension, diabetes, and stage 2 kidney disease. He was previously hospitalized at another hospital where he was treated with broad-spectrum antibiotics and non-steroidal anti-inflammatory

ratorijskim nalazima tipična je pojava leukocitoze s predominacijom neutrofila, porast C-reaktivnog proteina i sedimentacije eritrocita te povišene vrijednosti feritina. Disfunkciju jetre prate i porast aspartat-aminotransferaze i alanin-aminotransferaze. (1)

Bolest se može komplicirati razvojem citokinske oluje i sindroma aktivacije makrofaga (MAS) s multiorganskim zatajenjem, što predstavlja životno ugrožavajuće stanje. (9)

Postavljanje dijagnoze AOSD-a je izazovno jer je neophodno isključiti ostale kliničke entitete kao što su infekcije, neoplastični i paraneoplastični procesi te druge autoimunosne i aniinflamatorne bolesti. Dijagnoza se najčešće postavlja na osnovi Yamaguchijevih ili Fautrelovih kriterija. Obje liste kriterija pokazale su visoku specifičnost i senzitivnost, s tim da za razliku od Fautrelovih kriterija Yamaguchijevi kriteriji sadrže i kriterije isključenja. (10)

Incijalno liječenje AOSD-a ovisi o težini kliničkih simptoma. U blagim oblicima preporučuje se dati prednost nesteroidnim protuupalnim lijekovima (NSAIL) kakvi su ibuprofen ili indometacin u odnosu na primjenu glukokortikoidne terapije. (11) Ako bolesnici ne odgovore na NSAIL ili ako je riječ o umjernoj i ozbiljnoj težini kliničkih simptoma novonastale Stillove bolesti odraslih, preporučuje se uvođenje biološkog lijeka. Ako biološki lijek nije dostupan u terapiju se uvode glukokortikoidi u dozama od 20 – 60 mg dnevno *per os*. Primjena glukokortikoida parenteralno je preporučena ovisno o kliničkoj slici prema procjenama nadležnog liječnika. Ako se sumnja na razvoj sindroma aktivacije makrofaga (MAS) preporučuje se da se ti bolesnici liječe anakinrom te pulsnim dozama glukokortikoida (1000 mg metilprednizolona intravenskom primjenom) jedan do tri dana. U terapiji održavanja mogu se uvesti lijekovi koji modificiraju tijek bolesti (DMARD, engl. *disease-modifying antirheumatic drugs*) kakvi su metotreksat i leflunomid. Od ostalih bioloških lijekova svoju primjenu u tretiranju AOSD-a imaju i kanakinumab, rilonacept, tocilizumab i infliksimab. (12,13,14)

## PRIKAZ SLUČAJA

Bolesnik u dobi od 73 godine primljen na odjel reumatologije zbog protrahiranog febrilnog stanja s tjelesnom temperaturom koja se kretala do 40°C, praćenog makulopapuoznim osipom trupa (slika 1) te oteklinom i bolovima zglobova. Od ranije je koronarni bolesnik s ugrađenom trostrukom premosnicom čemu je prethodio infarkt miokarda. Isto tako, u anamnezi je poznato da je bolesnik hipertoničar, dijabetičar te da boluje od renalne insuficijencije drugog stupnja. Prethodno je hospitaliziran u drugoj bolničkoj ustanovi gdje je liječen antibioticima širokog spektra i nesteroidnim protuupalnim lijekovima bez poboljšanja te biva upućen u

drugs (NSAIDs), but his condition did not improve and was referred to our institution. In the patient's family history, it is stated that he had not previously experienced similar joint problems. He states that there is a positive family history of autoimmune diseases. His sister died of complications of systemic lupus erythematosus at a young age. His brother suffers from ankylosing spondylitis. On admission, the patient was almost motionless, with swelling and pain in all metacarpophalangeal and proximal interphalangeal joints, as well as pain and swelling in the ankle joints. Laboratory findings show signs of leukocytosis, with a white blood cell count of 27.10 x 10^9 leukocytes/L (reference range of 4 – 10 x 10^9 leukocytes/L) with a predominance of neutrophil granulocytes of 96.2% in the differential blood count, elevated fibrinogen values of 6.2 g/L (reference range of 1.8 – 3.5 g/L), elevated ferritin values of 3880 ng/mL (reference range of 17.9 – 464 ng/nL), slightly elevated values of the D-dimer, nitrogenous substances and transaminases and elevated C-reactive protein values of 117.9 mg/L (0.0 – 5.0 mg/L). Given the patient's age, we first treated the patient's condition as an infectious syndrome and, in consultation with an infectious disease specialist, we initiated empirical dual-antibiotic therapy. The patient continued to have fever with progression of the clinical features. Blood cultures were taken at the fever spikes; however, the results of several blood cultures were sterile. In the control laboratory findings, there were still signs of persistent leukocytosis with a predominance of neutrophilic granulocytes, anaemia, elevated transaminases, elevated ferritin values of up to 15750 ng/mL (reference range of 17.9 – 464 ng/nL), without a drop in C-reactive protein values. Bone marrow biopsy was performed, which showed signs of reactive bone marrow hyperplasia. Urine cultures were sterile. Physiological microflora was isolated from the throat and nasal swabs. Given the laboratory findings and the progression of the clinical features, a working diagnosis of Still's disease with the life-threatening development of macrophage activation syndrome was made. Methylprednisolone in moderately high doses (alternately 60 and 80 mg) was included in therapy and administered intravenously along with other forms of supportive therapy. Three days after initiating glucocorticoid therapy, the patient became afebrile and the joint swelling subsided.

Ultrasound of peripheral lymph nodes confirmed the finding of reactive lymphadenopathy. Immunological findings showed a negative rheumatoid factor result, anti-citrullinated protein antibodies and antistreptolysin antibodies (ASO), negative double-stranded DNA antibodies (anti-dsDNA), low titre positive antinuclear antibodies with a negative ENA-8 test.

Tumour markers were negative. Abdominal ultrasound showed signs of splenomegaly. X-ray of the

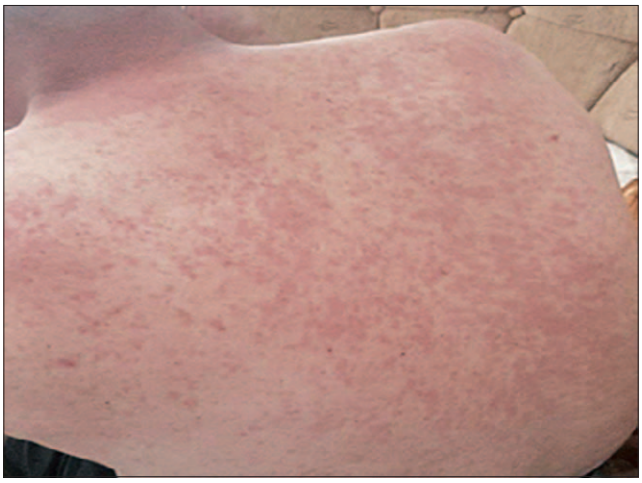

Figure 1. Salmon-pink maculopapular rash on the patient's back

*Slika 1. Makulopapulozni osip (engl. salmon-pink maculopapular rash) na leđima bolesnika*

našu ustanovu. Bolesnik anamnestički navodi da ranije nije imao sličnih tegoba sa zglobovima. Navodi pozitivnu obiteljsku anamnezu na autoimunosne bolesti. Sestra je umrla od komplikacija sistemskog lupusa u mlađoj životnoj dobi. Brat ima ankilozantni spondilitis. Prilikom prijma bolesnik je gotovo nepokretan, s oteklinom i bolnošću svih metakarpofalangealnih i proksimalih interfalangealnih zglobova, te bolnošću i otokom skočnih zglobova. U laboratorijskim nalazima bilježi se leukocitoza, L 27,10 x 10^9/L (ref. 4 – 10 x 10^9/L) s predominacijom neutrofilnih granulocita od 96,2% u diferencijalnoj krvnoj slici, povišene vrijednosti fibrinogena 6,2 g/L (ref. 1,8 – 3,5 g/L), povišene vrijednosti feritina 3880 ng/mL (ref. 17,9 – 464 ng/nL), blago povišene vrijednosti D-dimera, dušičnih supstancija i transaminaza te povišenim C-reaktivnim proteinom 117,9 mg/L (0,0 – 5,0 mg/L). Bolesnikovo stanje s obzirom na životnu dob najprije shvaćamo kao infektivni sindrom te u konzultaciji s infektologom uključujemo empirijsku dvojnu antibiotsku terapiju. Bolesnik je u daljnjem tijeku i dalje febrilan s progresijom kliničke slike. Uzete su hemokulture u vrškovima febriliteta, međutim nalazi više hemokultura pristigli su sterilni. U kontrolnim laboratorijskim nalazima i dalje je perzistentna leukocitoza s predominacijom neutrofilnih granulocita, anemija, porast transaminaza, porast feritina na 15750 ng/mL (ref. 17,9 – 464 ng/nL), bez pada vrijednosti C-reaktivnog proteina. Učinjena je biopsija koštane srži kojom je opisana reaktivna hiperplazija koštane srži. Urinokulture pristižu sterilne. Iz brisa ždrijela i nosa izolirana je fiziološka mikroflora. S obzirom na pristigle laboratorijske nalaze i progresiju kliničke slike postavljena je radna dijagnoza Stillove bolesti uz prijeteći razvoj sindroma aktivacije makrofaga. U terapiju je uključen intravenski metilprednizolon u umjereno visokim dozama (naizmjenič-

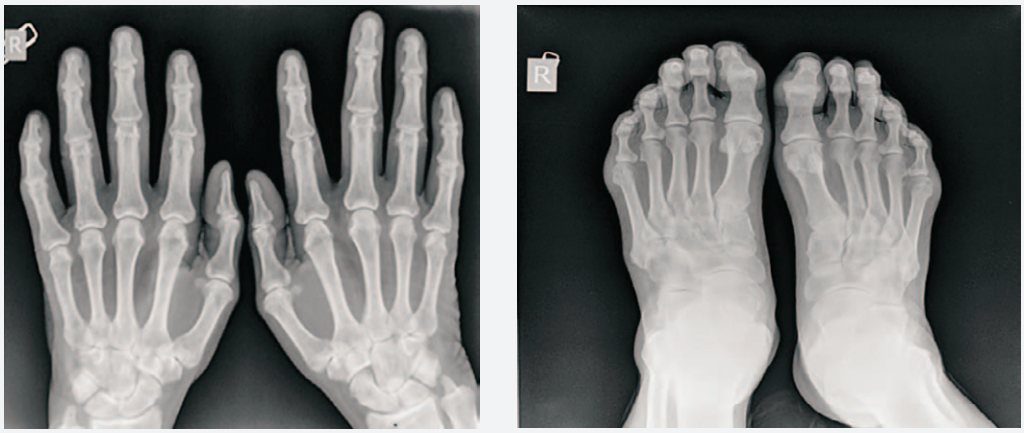

Figure 2: X-ray of the hands and feet: no clear signs of erosive changes
*Slika 2: RTG šaka i stopala – bez jasnih erozivnih promjena*

hands and feet did not show any erosive changes (Figure 2). Considering all laboratory findings and the patient's clinical features, the diagnosis of adult-onset Still's disease was made using Yamaguchi's criteria. The patient was treated with moderately high doses of glucocorticoids administered parenterally for three weeks with the use of antimalarials, and after the administration of the aforementioned therapy the clinical features and laboratory parameters improved. When the patient was discharged from hospital, his laboratory findings showed a white blood cell count of 8.10 x 10^9 leukocytes/L (reference range of 4 – 10 x 10^9 leukocytes/L), with persistent anaemia, slightly elevated transaminase values, and a drop in CRP levels to 29.3 mg/L (reference range of 0.0 – 5.0 mg/L). At the follow-up examination after one month, the patient did not report any subjective complaints, during the physical examination there were no signs of swollen joints, and in the laboratory findings the inflammatory parameters were unremarkable, as were the liver enzyme levels. Given the presence of kidney disease, we decided not to include methotrexate in the therapy, but we have opted for the inclusion of leflunomide in a dose of 20 mg/day.

After receiving the prescribed therapy for three months, the patient showed no signs of disease relapse at the follow-up examination.

## DISCUSSION

The occurrence of Still's disease in elderly patients is extremely rare. Due to this, it was challenging to make an initial diagnosis of the disease. In this case, the patient had a classic triad of symptoms including fever, transient maculopapular rash, and arthralgias. However, given that these are symptoms that may individually be of limited specificity, and which occur more often as part of certain infectious syndromes, and given 60 i 80 mg) uz ostalu suportivnu terapiju. Tri dana po uključenju glukokortikoidne terapije bolesnik je postao afebrilan te se povukla oteklina zglobova.

Ultrazvukom perifernih limfnih čvorova verificirana je limfadenopatija reaktivnog tipa. U imunološkim nalazima reumatoidni faktor, anticitrulinska protutijela i antistreptolizinska antitijela (ASTO) pristižu negativni, protutijela na dvostruku uzvojnicu DNA (anti-dsDNA) su negativna, antinuklearana antitijela su u niskom titru pozitivna uz negativan ENA-8 profil.

Tumorski markeri pristižu negativni. Ultrazvuk abdomena pokaže splenomegaliju. RTG šaka i stopala nije dokazao erozivne promjene (slika 2). S obzirom na sve realizirane laboratorijske nalaze te kliničku sliku bolesnika koristeći Yamaguchijeve kriterije postavljena je dijagnoza Stillove bolesti odrasle dobi. Bolesnik je tijekom tri tjedna liječen umjereno visokim dozama glukokortikoida parenteralno uz primjenu antimalarika, nakon čega nastupa poboljšanje kliničke slike i laboratorijskih parametara. U laboratorijskim nalazima prilikom otpusta L 8,10 x 10^9/L (ref. 4 – 10 x 10^9/L), uz i dalje perzistiranje anemijskog sindroma, blago povišene vrijednosti transaminaza te pad CRP-a na 29,3 mg/L (ref. 0,0 – 5,0 mg/L). Na kontrolnom pregledu za mjesec dana bolesnik je subjektivno bez tegoba, a u fizikalnom nalazu bez otečenih zglobova, a u laboratorijskim nalazima upalni parametri su mirni, kao i nalazi jetrenih enzima. S obzirom na prisutnu renalnu insuficijenciju ne odlučujemo se za uključivanje metotreksata u terapiju, već smo uključili leflunomid u dozi od 20 mg dnevno.

Na ordiniranu terapiju na kontrolom pregledu nakon tri mjeseca bolesnik je bez znakova relapsa bolesti.

## RASPRAVA

Pojava Stillove bolesti kod bolesnika starije životne dobi iznimno je rijetka. Shodno tomu bilo je izazovno

en the patient's age, the disease was treated as an infectious syndrome for the first two days. Suspicion of elderly-onset Still's disease (EOSD) was based on the persistence of the clinical features, with leukocytosis, further elevation of ferritin values, and elevated values of C-reactive protein.

In the literature review of 25 presented cases with a diagnosis of EOSD, the age at which symptoms first appeared was 76.6 ± 4.9 years of age, which corresponds to the age of the patient in our case report. (4)

In a 10-year retrospective study conducted by Sheng Li et al., patients diagnosed with EOSD had similar symptoms of fever and arthralgia compared to patients diagnosed with Still's disease at a young age. Fewer patients with EOSD reported sore throat as their initial symptom, and they also reported having less pronounced skin rash. (15)

The acute phase of patients with Still's disease is most often accompanied by leukocytosis with a predominance of neutrophil granulocytes. Before the inclusion of glucocorticoids in the therapy, the patient underwent a bone marrow biopsy to rule out the existence of a hematopoietic neoplasm. It is important to note that hemophagocytic activity was not verified during the bone marrow biopsy. Hypercellular bone marrow of the reactive type was verified in about two-thirds (63.6%) of patients in a Korean study conducted on 40 patients diagnosed with Still's disease. (16)

Elevated ferritin levels are present in as many as 90% of patients with AOSD. Ferritin levels are not only a good indicator of the disease, presence but also play an important role in the disease pathogenesis, and are a predictor of further development of macrophage activation syndrome according to a study conducted by Jia et al. (17)

Suda et al. compared the clinical symptoms and laboratory findings of 25 patients with EOSD described individually in the literature with those of patients with AOSD and no significant difference was found between the two groups, other than the fact that elderly patients more often developed disseminated intravascular coagulation (DIC) as a disease complication and had a more frequent tendency to develop opportunistic infections (OIs). (4)

In addition to the classic triad of symptoms, our patient had splenomegaly (verified through an ultrasound scan) lymphadenopathy, liver disease with elevated transaminases, and pleural effusion (verified through an X-ray). All of these findings, in addition to the negative tumour markers and negative immunological findings, except for the low titre positive antinuclear antibodies, which can also be found in healthy older populations, resulted in the final diagnosis of EOSD based on the Yamaguchi's criteria.

inicijalno postaviti dijagnozu same bolesti. U našem slučaju bolesnik je imao klasični trijas simptoma uključujući povišenu tjelesnu temperaturu, tranzitorni makulopapulozni osip i artralgije. Međutim, s obzirom na to da je riječ o simptomima koji ipak pojedinačno mogu biti ograničene specifičnosti, a koji se pojavljuju češće u sklopu pojedinih infektivnih sindroma, kao i na životnu dob bolesnika, prva dva dana je liječen kao infektivni sindrom. Sumnja na EOSD temeljena je na perzistiranju kliničke slike, uz leukocitozu, daljnji porast vrijednosti feritina i visoke vrijednosti C-reaktivnog proteina.

U pregledu literature 25 prikazanih slučajeva s postavljenom dijagnozom EOSD-a, životna dob u kojoj su se simptomi prvi put javili bila je 76,6 ± 4,9 godine života, što bi odgovaralo životnoj dobi bolesnika iz našeg prikaza slučaja. (4)

U desetogodišnjoj retrospektivnoj studiji koju su proveli Sheng Li i suradnici bolesnici kojima je postavljena dijagnoza EOSD-a podjednako su imali zastupljene simptome u vidu povišene tjelesne temperature i artralgije u usporedbi s bolesnicima kojima je dijagnoza Stillove bolesti postavljena u mlađoj životnoj dobi, s tim da je manji broj bolesnika s EOSD-om kao incijalni simptom navodio prisutnost grlobolje te su imali manje izražen kožni osip. (15)

Akutna faza bolesnika sa Stillovom bolešću najčešće je praćena leukocitozom s predominacijom neutrofilnih granulocita. Bolesniku je prije uključivanja glukokortikoida u terapiju učinjena biopsija koštane srži kako bi se isključilo postojanje neoplazme hematopoetskog sustava. Napominjemo da u bioptatu koštane srži nije dokazana hemofagocitna aktivnost. Hipercelularna koštana srž reaktivnog tipa verificirana je u oko dvije trećine (63,6%) bolesnika u korejskom istraživanju provedenome na 40 bolesnika sa Stillovom bolešću. (16)

Povišene vrijednosti feritina prisutne su kod čak 90% bolesnika s AOSD-om. Vrijednosti feritina ne samo da su dobar pokazatelj postojanja bolesti, nego imaju i značajnu ulogu u patogenezi bolesti i prediktor su daljnjeg razvoja sindroma aktivacije makrofaga prema studiji koju su proveli Jia i suradnici. (17)

Suda i suradnici usporedili su kliničke simptome i laboratorijske nalaze 25 bolesnika s EOSD-om opisanih pojedinačno u literaturi s onim u bolesnika s AOSD-om i nije nađena bitnija razlika između dviju skupina, osim što su bolesnici starije životne dobi češće razvijali diseminiranu intravaskularnu koagulaciju kao komplikaciju i pokazivali češću tendenciju razvoja oportunističih infekcija. (4)

Pored klasičnog trijasa simptoma naš bolesnik je imao ultrazvučno verificiranu splenomegaliju, limfadenopatiju, hepatalnu disfunkciju uz porast jetrenih transaminaza te radiografski verificiranu pleuralnu efuziju. Svi ti nalazi uz negativne tumorske markere te

Although the presence of another autoimmune disease is the exclusive criterion for diagnosing Still's disease according to Yamaguchi's criteria, we found a case report in the literature of an elderly patient who, in addition to a previous diagnosis of systemic lupus erythematosus, was also diagnosed with EOSD. (18)

The therapy protocol we applied in our case was conditioned by the unavailability of drugs such as anakinra and the presence of comorbidities in the patient including coronary artery disease, diabetes mellitus and kidney disease. Given the serious clinical features and the lack of adequate response to NSAIDs, we decided to include methylprednisolone administered parenterally in moderately high doses.

In the absence of other therapeutic options, the combination of leflunomide and hydroxychloroquine may be used in the treatment of patients with AOSD. (19)

In a study conducted by Sheng Li et al, patients with EOSD had an equally good response to initial glucocorticoid therapy as patients with AOSD. The frequency of relapses and disease complications in patients with EOSD was similar to that in patients with AOSD. A higher mortality rate was observed in patients with EOSD even though they had more moderate disease activity compared to patients with AOSD. (15)

## CONCLUSION

Establishing the diagnosis of Still's disease in adulthood is challenging in elderly patients because it is an extremely rare condition. Early symptom recognition and differential diagnostic inclusion of this diagnosis is important in order to initiate treatment in a timely manner and prevent complications of the disease such as the development of macrophage activation syndrome. Although the clinical symptoms and the course of the disease in elderly patients do not differ from those in younger patients according to the available literature, the treatment of these patients is often further complicated by the presence of other comorbidities.

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negativne imunološke nalaze izuzev pozitivnih antinuklearnih antitijela u niskom titru, koja se mogu naći i kod zdrave populacije starije životne dobi, rezultirali su postavljanjem konačne dijagnoze EOSD-a na osnovi Yamaguchijevih kriterija.

Iako je po Yamaguchijevim kriterijima prisutnost druge autoimunosne bolesti isključni kriterij za postavljanje dijagnoze Stillove bolesti, u literaturi smo pronašli opisan slučaj bolesnice starije životne dobi kojoj je pored ranije dijagnoze sistemskoga eritemskog lupusa postavljenja i dijagnoza EOSD-a. (18)

Terapijski protokol koji smo primijenili u našem slučaju bio je uvjetovan nedostupnošću lijekova kao što je anakinra i prisutnošću komorbiditeta kod bolesnika uključujući koronarnu bolest, dijabetes melitus i renalnu insuficijenciju. S obzirom na to da je bila riječ o ozbiljnoj kliničkoj slici kao i na to da nije postignut adekvatan odgovor na NSAR, odlučili smo se za uključivanje parenteralnog metilprednizolona u umjereno visokim dozama.

U odsutnosti drugih terapijskih opcija, kombinacija leflonomida i hidroksiklorokina može se primjeniti u tretiranju bolesnika s AOSD-om. (19)

U studiji koju su proveli Sheng Li i suradnici, bolesnici s EOSD-om imali su podjednako dobar odgovor na incijalnu terapiju glukokortikoidima kao i bolesnici s AOSD-om. Učestalost relapsa i komplikacija kod bolesnika s EOSD-om bila je slična onoj kao kod bolesnika s AOSD-om. Viša stopa mortaliteta uočena je kod bolesnika s EOSD-om iako su oni imali umjereniju aktivnost bolesti u odnosu na bolesnike s AOSD-om. (15)

## ZAKLJUČAK

Postavljanje dijagnoze Stillove bolesti odrasle dobi izazovno je kod starijih bolesnika jer je riječ o izuzetno rijetkom stanju. Rano prepoznavanje simptoma i diferencijalno dijagnostičko uključivanje ove dijagnoze važno je kako bi se pravovremeno započelo s liječenjem i spriječile komplikacije bolesti u smislu razvoja sindroma aktivacije makrofaga. Iako se klinički simptomi i sam tijek bolesti u bolesnika starije životne dobi po dostupnoj literaturi ne razlikuju od onih kod mlađih, liječenje ovih bolesnika najčešće dodatno otežava postojanje drugih komorbiditeta.

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