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CASE REPORT / ПРИКАЗ БОЛЕСНИКА

Therapeutic dilemmas in the management of a patient with long-term rheumatoid arthritis and severe clinical presentation of SARS-CoV-2 infection

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SUMMARY

Introduction The objective of this case report is to present a clinical course of SARS-CoV-2 infection in a patient with long-term rheumatoid arthritis and concomitant rituximab therapy.

Case outline A 58-year-old female patient was diagnosed with seropositive rheumatoid arthritis at the age of 35. She was primarily prescribed chloroquine and glucocorticoid, afterwards methotrexate and biological agent – etanercept. Because of a secondary loss of response, etanercept was switched to rituximab. She had 13 cycles of rituximab and the last was given in June 2020. In December 2020, she was hospitalized due to bilateral pneumonia and respiratory insufficiency. The results of the laboratory analysis revealed anemia, leukocytosis, thrombocytosis, and markedly elevated C-reactive protein, procalcitonin, D-dimer, transaminases. The findings of the chest computed tomography scan were consistent with COVID-19 pneumonia features with accompanying bilateral pleural effusion. The patient was treated with antibiotics, corticosteroids, tocilizumab, hepatoprotective, gastroprotective, oxygen therapy, and parenteral anticoagulant. Three months after recovering from pneumonia, she developed arthritis flare, hence a JAK inhibitor, baricitinib, was started. Low disease activity was achieved with baricitinib monotherapy.

Conclusion Due to risk of severe COVID-19, caution may be required when applying immunosuppressive therapy in patients with rheumatic diseases.

Keywords: inflammatory diseases; rheumatoid arthritis; immunosuppressive drug; COVID-19

INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the causative agent of novel coronavirus disease 2019 (COVID-19), whose complete genome sequence was identified in January 2020, after a cluster of pneumonia of unknown etiology appeared in China in December 2019 [1]. This viral disease spread across the globe, leading to the one of the largest outbreaks in recent years which resulted in COVID-19 being a major public health burden [2]. The clinical presentation of SARS-CoV-2 infection varies from asymptomatic to severe and critical illness with multiorgan involvement [3]. Growing evidence suggests that a key role in the pathogenesis and determining the severity of COVID-19 is played by the immune system of the infected host [4]. Rheumatoid arthritis (RA) is a chronic systemic autoimmune disease with joint inflammation as a hallmark [5]. Considering the aberrant immunological pathways, COVID-19 and RA have some shared pathological features, most importantly cytokine imbalance. Due to similarities between RA and COVID-19 pathogenesis, medical professionals have questioned whether biological disease-modifying antirheumatic drugs (bDMARD) would be effective for the treatment of COVID-19. On the other hand, awareness of this group of medication being a specific risk factor for poor outcomes has drawn a lot of attention [6].

The objective of this case report is to present a clinical course of SARS-CoV-2 infection in a patient with long-term RA and concomitant rituximab therapy.

CASE REPORT

A 58-year-old female patient was diagnosed with seropositive RA at the age of 35. She was primarily treated with chloroquine and low-dose glucocorticoid. After three years of treatment, chloroquine was discontinued due to ocular side effect and methotrexate was prescribed. The weekly dose of methotrexate was gradually escalated to the maximum tolerated dose of 12.5 mg. Periodically, in phases of arthritis flare, short-term glucocorticoid was added. The treatment target was not achieved with a conventional synthetic DMARD (csDMARD), thus a bDMARD, etanercept 50 mg/mL subcutaneously once a week was initiated in combination with 12.5 mg of methotrexate and 5 mg of prednisone in 2009. Because of secondary loss of response, etanercept was switched to rituximab. In May 2010, the patient received the first course of rituximab consisting of two infusions with 1000 mg of the drug administered two weeks apart with premedication. She

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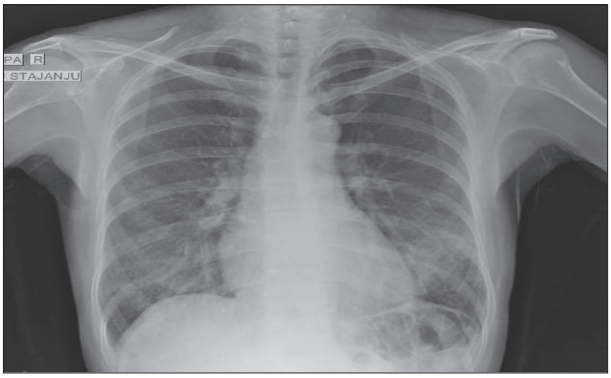

Figure 1. Chest X-ray showing signs of a bilateral pneumonia

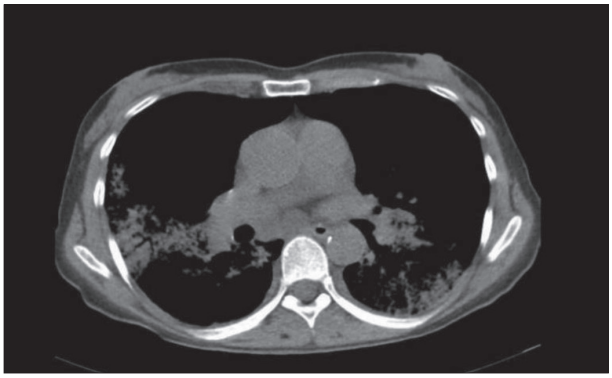

Figure 2. Computed tomography scan of the lungs showing features of COVID-19 pneumonia

had a total of 13 cycles, with the last intravenous infusion given on June 2020. The low disease activity was achieved and no adverse events regarding this biological agent occurred. Her medical history was positive for osteoporosis. In December 2020, six months after the last course, the patient developed fever, dry cough, nausea, and lower back pain, thus a nasopharyngeal swab sample was collected for the SARS-CoV-2 PCR test, which came back positive. The results of the laboratory analysis on admission to the hospital revealed mild anemia [red blood cells (RBC) = 3.7×10^{12}/L; hemoglobin (Hg) = 110 g/L), white blood cells (WBC), platelet count and the chemistry panel were within the reference range, while the C-reactive protein (CRP = 47.6 mg/L) as well as D-dimer were elevated (D-dimer = 1098 ng/mL)]. Initial radiographic work-up showed signs of a bilateral pneumonia in the lower lobes (Figure 1). Due to prolonged fever and the progression of respiratory symptoms, a chest computerized tomography (CT) was performed. The findings of the CT scan were consistent with COVID-19 pneumonia features and it detected multifocal bilateral ground-glass opacities of predominantly peripheral and peribronchial distribution, accompanied by thickening of the interlobular septa and linear opacities. Additionally, a bilateral pleural effusion with an anteroposterior diameter of up to 15 mm on the right and up to 10 mm on the left was seen (Figure 2). Echocardiographic evaluation registered a small amount of pericardial effusion as well as separation of the pericardial layers up to 3–4 mm. Repeated laboratory testing showed persistence of mild anemia (RBC = 3.4×10^{12}/L; Hb = 100 g/L), leukocytosis (WBC = 18.29×10^{9}/L) and thrombocytosis (PLT = 663×10^{9}/L), and markedly elevated inflammatory markers, CRP (203.4 mg/L) and procalcitonin (1.52 ng/mL), D-dimer (5818 ng/mL), transaminases (ALT = 347 U/L; AST = 246 U/L) and gamma-glutamyl transferase (GGT = 574 U/L). The patient was treated with broad-spectrum antibiotics, corticosteroids, hepatoprotective, gastroprotective therapy, and low-molecular-weight heparin. Due to increase in CRP concentration, high levels of interleukin-6 (154 pg/ml) and extensive pneumonic changes on chest X-ray, she received tocilizumab 400 mg in two doses 12 hours apart. Hypoxemia was corrected with conventional oxygen therapy using an oxygen mask. After four weeks of hospitalization, she was discharged home in a good general condition. She was regularly monitored by a pulmonologist, and in May 2021, a complete regression of pneumonic changes was confirmed by radiological evaluation. The patient was vaccinated with two doses of mRNA (Pfizer-BioNTech) vaccine against COVID-19 in the recommended three-week interval between the shots and was given a booster dose in December 2021. Three months after recovering from pneumonia, an exacerbation of arthritis developed, hence Janus kinase (JAK) inhibitor, baricitinib, was started in September 2021. Glucocorticoid therapy was used for the management of RA from January to September 2021. Monotherapy with JAK inhibitor has led to a clinical and laboratory improvement in two months. On the last rheumatologist visit, the patient had two tender joints without swelling, and the measured disease index was suggestive of low disease activity (Disease Activity Score 28 (CRP) = 2.9).

The paper was approved by the Ethics Board of the Novi Sad Special Hospital for Rheumatic Diseases and written consent to publish all shown material was obtained from the patient.

DISCUSSION

We report a patient with long-term inflammatory rheumatic disease (RD) treated with B-cell-depleting therapy, who presented with severe COVID-19 pneumonia. Regarding the case of our patient, a generalized conclusion cannot be drawn, but there is a reasonable possibility that the administration of rituximab affected SARS-CoV-2 infection outcome.

Patients with RA are more susceptible to infections due to the complex interactions of underlying immunological dysregulation, the use of immunosuppressive drugs and comorbidities [7]. With SARS-CoV-2 being spread globally, rheumatologists faced concern regarding an increased risk of more severe forms of COVID-19 and fatal outcome in this vulnerable group [8]. Risk factors associated with a poor prognosis in the general population are the older age, male sex and multiple comorbidities (obesity, hypertension, diabetes mellitus, chronic lung disease, chronic kidney disease, cardiovascular diseases, active cancer) [9]. None of the previously mentioned predisposing factors

was present in our patient. Numerous studies have been conducted with the aim of determining predictors of the severity of COVID-19 infection along with the hospitalization and mortality rate in patients with RDs, but the results differ among each other. In one of the first comprehensive meta-analysis authors reported a higher prevalence in the group of patients with autoimmune diseases, but the severity of the infection was similar to comparators population. The interpretation of a higher prevalence should be questioned because patients with these disorders seek medical help earlier and are tested more frequently [10]. The European and American guidelines pointed out that the patients with rheumatic and musculoskeletal diseases (RMD) are not at higher risk of acquiring the SARS-CoV-2, nor when they become infected have a more severe disease course than individuals without RMD [11, 12]. The findings of an observational multicenter French cohort study on a sample of 694 participants were consistent with the conclusions stated in the previously cited guidelines. Patients with RMD compared with the general population share the same risk factors for a severe clinical presentation of COVID-19 [13]. In contrast, a team of the researchers from Boston compared 52 patients with RD and coronavirus disease to 104 participants without RD who were also infected with SARS-CoV-2 and concluded that after being matched by age, body mass index, smoking and comorbidities, these two groups differed concerning the therapeutic management. In other words, the proportion of individuals with RD treated in intensive care units was significantly higher – namely, this group had three times higher odds of requiring mechanical ventilation [14]. Ye et al. [15] conducted a study aiming to investigate the clinical characteristics and outcomes of COVID-19 infection in 21 patients with different RDs who were collected from a sample of 2326 hospitalized patients. They demonstrated that the duration of hospitalization and death rate were similar between rheumatic and non-rheumatic group, but patients with RDs were more likely to develop respiratory failure. Although these studies have several limitations, most importantly a small sample size and collider bias, they raised some concerns regarding risk factors for poor outcomes that are specific to RDs such as a disease modifying therapy. In terms of treatment, growing evidence suggests that patients using DMARD do not have an increased risk of severe COVID-19 outcomes. An Italian survey addressed whether the patients with RDs treated with biologic/targeted synthetic DMARD (b/tsDMARDs) are predisposed for a more severe clinical course when infected with SARS-CoV-2. Favalli et al. [16] found that the incidence and severity of COVID-19 were consistent with the general population. In a study conducted by Gianfrancesco et al. [17], a multivariable-adjusted models showed that patients using glucocorticosteroids in a dose greater than 10 mg daily had higher odds of hospitalization. In contrast, the use of csDMARD as monotherapy or in combination with b/tsDMARS did not lead to the higher hospitalization rate. Interestingly, patients treated with tumor necrosis factor inhibitors (TNFi) had a reduced risk of hospitalization. On the other hand, Raiker et al. [18] showed that rituximab and interleukin-6 users were more susceptible to hospitalization compared to TNFi users. Additionally, patients using JAK inhibitors or abatacept did not have and increased risk of hospitalization compared to TNFi users. Rituximab is a monoclonal antibody that binds to the CD-20 antigen on B-lymphocytes causing B-cell depletion, impaired opsonization, and reduction in antibody production [19]. Accumulated data suggest that anti-CD-20 therapy is associated with poor COVID-19 prognosis, which could be explained by a drug-induced defect in the antiviral humoral response [20]. It is essential to clarify the association between rituximab use and the risk of severe COVID-19 outcome. One should define whether rituximab has a negative effect on the coronavirus disease or whether a severity is a consequence of the confounding factors impact [21].

Through this clinical case, the authors wanted to highlight that in the context of the COVID-19 pandemic and numerous following doubts, caution may be required when applying immunosuppressive therapy in patients with RDs. Additional studies may potentially provide a better insight into individual risk stratification and determine specific factors leading to a severe COVID-19 in the RA population.

Conflict of interest: None declared.

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Терапијске дилеме у лечењу болесника са дугогодишњим реуматоидним артритисом и тешком клиничком сликом инфекције *SARS-CoV-2*

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САЖЕТАК

Увод Циљ овог рада је да се представи клинички ток инфекције *SARS-CoV*-2 код болеснице са дугогодишњим реуматоидним артритисом и ритуксимабом у терапији.

Приказ болесника Болесници, старој 58 година, дијагноза серопозитивног реуматоидног артритиса постављена је у 35. години живота. Иницијално су за лечење прописани хлороквин и глукокортикоид, потом метотрексат и биолошки лек етанерцепт. Због развоја секундарне неефикасности, етанерцепт је замењен ритуксимабом. Укупно је примила 13 циклуса ритуксимаба, а последњи је дат јуна 2020. Због билатералне пнеумоније и респираторне инсуфицијенције примљена је на болничко лечење у децембру 2020. Резултати лабораторијских анализа су показали анемију, леукоцитозу, тромбоцитозу и изразито повишене вредности *C*-реактивног протеина, прокалцитонина, *D*-димера и трансаминаза. Компјутеризована томографија грудног коша је указала на постојање промена карактеристичних за пнеумонију изазвану ковидом 19 са пратећим билатералним плеуралним изливом. Лечење је спроведено антибиотицима, кортикостероидима, тоцилизумабом, хепатопротективном, гастропротективном, кисеоничном терапијом и парентералним антикоагулансом. Три месеца по опоравку од прележане пнеумоније јавила се акутизација артритиса; стога је у терапију уведен инхибитор Јанусове киназе, барицитиниб. Ниска активност болести је постигнута применом монотерапије барицитинибом.

Закључак Потребан је опрез приликом примене имуносупресивне терапије код болесника са реуматским обољењима због ризика за развој тешке клиничке слике ковида 19.

Кључне речи: инфламаторне болести; реуматоидни артритис; имуносупресивни лек; ковид 19