СРПСКИ АРХИВ
ЗА ЦЕЛОКУПНО ЛЕКАРСТВО
SERBIAN ARCHIVES
OF MEDICINE

Address: 1 Kraljice Natalije Street, Belgrade 11000, Serbia
☏ +381 11 4092 776, Fax: +381 11 3348 653
E-mail: office@srpskiarhiv.rs, Web address: www.srpskiarhiv.rs

Paper Accepted* **ISSN Online 2406-0895**

Case Report / Приказ болесника

Tanja Janković, Aleksandra Savić♣, Jelena Zvekić-Svorcan, Aleksandra Glavčić, Ksenija Bošković

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

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

University of Novi Sad, Faculty of Medicine, Novi Sad, Serbia;
Special Hospital for Rheumatic Diseases, Novi Sad, Serbia

Received: December 4, 2022
Revised: January 28, 2023
Accepted: January 29, 2023
Online First: February 6, 2023
DOI: https://doi.org/10.2298/SARH221204016J

♣**Correspondence to:**
Aleksandra SAVIĆ
Special Hospital for Rheumatic Diseases, Futoška 68, 21112 Novi Sad, Serbia
E mail: **aleksandra_savic@uns.ac.rs**

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

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

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 on 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 CT 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 a risk of a severe COVID-19, a caution may be required when applying immunosuppressive therapy in patients with rheumatic diseases.

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

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 је примљена на болничко лечење у децембру 2020. Резултати лабораторијских анализа су показали присуство анемије, леукоцитозе, тромбоцитозе и изразито повишених вредности *C*-реактивног протеина, прокалцитонина, *D*-димера и трансаминаза. Компјутеризована томографија грудног коша је указао на постојање промена карактеристичних за ковид 19 пнеумонију 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, се јавила 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 презентације ковида 19.

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

INTRODUCTION

Acute appendicitis is the most common intra-abdominal condition in children that requires surgical intervention. It is considered to occur in approximately 4–8% of pediatric population, with the pick incidence in the second decade of life, while it is extremely rare

(incidence less than 0.5%) during the first year of life [1–4]. Appendicitis can be classified as complicated (appendicitis with generalized peritonitis or appendicitis abscess) or as an uncomplicated disease [5].

The role of appendix in human body is still a subject of debates. It is believed that appendix is an important part of the immune system as a "safe-house" for beneficial microbiota, and therefore is important for recolonizing the bowel after gastrointestinal infections balancing between pathogenic and commensal bacteria [1, 6]. There is also evidence that mesenchymal cells of appendix can be a source for restauration of damages in intestinal tract during a lifetime. It can be used for performing vesicostomy (Mitrofanoff procedure) or appendicostomy for anterograde enemas (Malone procedure), and in recent studies, decellularized appendix was used in a preclinical model for bladder augmentation [7].

Although operative management is a "gold standard" in treating acute appendicitis, conservative (non-operative) management for carefully selected children has been described as efficient alternative [8]. Operative approach can be open (classical) or laparoscopic.

Evidence of conservative treatment of acute appendicitis have been found in a mummy from Byzantine era. However, significant improvement has occurred with implementation of antibiotics in 20th century [9]. This management can be applied if there are no sure indications for surgery, such as the presence of peritonitis or signs of perforation. At first, these studies were conducted only in adults, but recently a larger number of studies include pediatric patients as well [8, 10, 11].

There were debates about need for interval appendectomy after successful conservative management. Recently published studies claim that considering low risk of occult appendiceal neoplasm in young individuals, interval appendectomy is recommended in patients older than 30 and with complicated forms of appendicitis [12]. Considering potential risks related to surgery and/or anesthesia as well as potential benefits of appendix preservation, it is important to analyze safety and efficiency of conservative management of acute uncomplicated appendicitis in children.

METHODS

This study included 76 children treated between January 2015 and December 2016 at the Institute for Child and Youth Health Care of Vojvodina under the diagnosis of acute uncomplicated appendicitis. Respondents were divided into two groups: conservatively treated

and operatively treated. The study was performed as a retrospective descriptive study. In the conservatively treated group were children who had clinical, radiological, and/or laboratory signs of acute appendicitis, but were not operated on during their initial hospitalization according to the clinical monitoring of the patient. Patients with similar signs and symptoms who were selected by the attending surgeon for operative treatment were in the other group.

The diagnosis was made based on the patient's history, physical examination, laboratory tests, and ultrasound findings. The ultrasound examination results were categorized depending on the findings on the appendix and surrounding structures. A negative finding was labeled as U0, unspecified as U1, a positive finding limited to the appendix as U2, while a positive finding on the appendix associated with signs of inflammation of the surrounding adipose tissue and/or the presence of free fluid in the abdomen was labeled as U3.

Children who were operated underwent either laparoscopic or open appendectomy. After hospital admission, per oral intake was paused and parenteral rehydration was initiated. 30–60 minutes preoperatively antibiotic therapy was administered and surgery was performed under general anesthesia. Each removed appendix was sent for histopathological verification. 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 mutual 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 rheumatoid arthritis and concomitant rituximab therapy.

CASE REPORT

A 58-year-old female patient was diagnosed with seropositive rheumatoid arthritis 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 a rituximab. In May 2010, the patient received the first course of rituximab consisted of two infusions with 1000 mg of the drug administered 2 weeks apart with premedication. She 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 a fever, dry cough, nausea and low 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 a 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 a 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 2 doses 12 hours apart. Hypoxemia was corrected with conventional oxygen therapy using an oxygen mask. After 4 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 recommended three week interval between shots and was given a booster dose on 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 lead to a clinical and laboratory improvement in 2 months. On the last rheumatologist visit, the patient had 2 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 Special hospital for rheumatic diseases Novi Sad 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, rheumatologist faced concern regarding an increased risk of more severe forms of the 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 gender 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 those 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 observational, multicenter, French cohort study on a sample of 694 included 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]. On the contrary, a team of the researchers from Boston compared 52 patients with RD and coronavirus disease to 104 participants without RD who were as well 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. 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 [15]. 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. found that the incidence and severity of COVID-19 were consistent with the general population [16]. In a study conducted by Gianfrancesco et al., a multivariable-adjusted models showed that patients using glucocorticosteroids in dose more than 10 mg daily had higher odds of hospitalisation.

In contrast, use of csDMARD as monotherapy or in combination with b/tsDMARS did not lead to the higher hospitalisation rate. Interestingly, patients treated with tumour necrosis factor inhibitors (TNFi), had a reduced risk of hospitalisation [17]. On the other hand, Raiker et al. showed that rituximab and interleukin-6 users were more susceptible to hospitalisation compared to TNFi users. Additionally, patients using JAK inhibitors or abatacept did not have and increased risk of hospitalization compared to TNFi users [18]. 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]. Accumulating data suggest that anti-CD20 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 usage and 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 rheumatic diseases. 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.

REFERENCES

1. Wang Y, Zhang L, Sang L, Ye F, Ruan S, Zhong B, et al. Kinetics of viral load and antibody response in relation to COVID-19 severity. J Clin Invest. 2020;130(10):5235-44. doi: 10.1172/JCI138759. PMID: 32634129
2. Hou X, Wang G, Fan W, Chen X, Mo C, Wang Y, et al. T-cell receptor repertoires as potential diagnostic markers for patients with COVID-19. Int J Infect Dis. 2021;113:308-17. doi: 10.1016/j.ijid.2021.10.033. PMID: 34688948
3. Stašević-Karličić I, Đorđević V, Dutina A, Stašević M , Janjić V , Ignjatović-Ristić D, et al. The impact of COVID-19 pandemic on suicide attempts in the Republic of Serbia. Srp Arh Celok Lek. 2021;149(7-8):455-60. DOI: https://doi.org/10.2298/SARH210506053S.
4. Zhang Q, Meng Y, Wang K, Zhang X, Chen W, Sheng J, et al. Inflammation and Antiviral Immune Response Associated With Severe Progression of COVID-19. Front Immunol. 2021;12:631226. doi: 10.3389/fimmu.2021.631226.
5. Guagnano MT, D'Angelo C, Caniglia D, Di Giovanni P, Celletti E, Sabatini E, et al. Improvement of Inflammation and Pain after Three Months' Exclusion Diet in Rheumatoid Arthritis Patients. Nutrients. 2021;13(10):3535. doi: 10.3390/nu13103535. PMID: 34684536
6. Dernoncourt A, Schmidt J, Duhaut P, Liabeuf S, Gras-Champel V, Masmoudi K, et al. COVID-19 in DMARD-treated patients with inflammatory rheumatic diseases: Insights from an analysis of the World Health Organization pharmacovigilance database. Fundam Clin Pharmacol. 2022;36(1):199-209. doi: 10.1111/fcp.12695.
7. Ozen G, Pedro S, England BR, Mehta B, Wolfe F, Michaud K. Risk of Serious Infection in Patients With Rheumatoid Arthritis Treated With Biologic Versus Nonbiologic Disease-Modifying Antirheumatic Drugs. ACR Open Rheumatol. 2019 ;1(7):424-32. doi: 10.1002/acr2.11064. PMID: 31777822.
8. Wang F, Ma Y, Xu S, Liu H, Chen Y, Yang H, et al. Prevalence and risk of COVID-19 in patients with rheumatic diseases: a systematic review and meta-analysis. Clin Rheumatol. 2022;41(7):2213-23. doi: 10.1007/s10067-022-06087-1. PMID: 35352217.
9. Booth A, Reed AB, Ponzo S, Yassaee A, Aral M, Plans D, et al. Population risk factors for severe disease and mortality in COVID-19: A global systematic review and meta-analysis. PLoS One. 2021;16(3):e0247461. doi: 10.1371/journal.pone.0247461. PMID: 33661992.
10. Akiyama S, Hamdeh S, Micic D, Sakuraba A. Prevalence and clinical outcomes of COVID-19 in patients with autoimmune diseases: a systematic review and meta-analysis. Ann Rheum Dis. 2021;80(3):384-91.
11. Landewé RB, Machado PM, Kroon F, Bijlsma HW, Burmester GR, Carmona L, et al. EULAR provisional recommendations for the management of rheumatic and musculoskeletal diseases in the context of SARS-CoV-2. Ann Rheum Dis. 2020 ;79(7):851-8.
12. Mikuls TR, Johnson SR, Fraenkel L, Arasaratnam RJ, Baden LR, Bermas BL, et al. American College of Rheumatology Guidance for the Management of Rheumatic Disease in Adult Patients During the COVID-19 Pandemic: Version 3. Arthritis Rheumatol. 2021;73(2):e1-e12. doi: 10.1002/art.41596. PMID: 33277981.
13. FAI2R /SFR/SNFMI/SOFREMIP/CRI/IMIDIATE consortium and contributors. Severity of COVID-19 and survival in patients with rheumatic and inflammatory diseases: data from the French RMD COVID-19 cohort of 694 patients. Ann Rheum Dis. 2021;80(4):527-38.
14. D'Silva KM, Serling-Boyd N, Wallwork R, Hsu T, Fu X, Gravallese EM, et al. Clinical characteristics and outcomes of patients with coronavirus disease 2019 (COVID-19) and rheumatic disease: a comparative cohort study from a US 'hot spot'. Ann Rheum Dis. 2020;79(9):1156-62.
15. Ye C, Cai S, Shen G, Guan H, Zhou L, Hu Y, et al. Clinical features of rheumatic patients infected with COVID-19 in Wuhan, China. Ann Rheum Dis. 2020;79(8):1007-13.
16. Favalli EG, Monti S, Ingegnoli F, Balduzzi S, Caporali R, Montecucco C. Incidence of COVID-19 in Patients With Rheumatic Diseases Treated With Targeted Immunosuppressive Drugs: What Can We Learn From Observational Data? Arthritis Rheumatol. 2020;72(10):1600-6. doi: 10.1002/art.41388. PMID: 32506699.
17. Gianfrancesco M, Hyrich KL, Al-Adely S, Carmona L, Danila MI, Gossec L, et al. Characteristics associated with hospitalisation for COVID-19 in people with rheumatic disease: data from the COVID-19 Global Rheumatology Alliance physician-reported registry. Ann Rheum Dis. 2020;79(7):859-66.
18. Raiker R, DeYoung C, Pakhchanian H, Ahmed S, Kavadichanda C, Gupta L, et al. Outcomes of COVID-19 in patients with rheumatoid arthritis: A multicenter research network study in the United States. Semin Arthritis Rheum. 2021;51(5):1057-66.
19. Levavi H, Lancman G, Gabrilove J. Impact of rituximab on COVID-19 outcomes. Ann Hematol. 2021;100(11):2805-12.
20. Alhowaish TS, Alhamadh MS, Alhabeeb AY, Aldosari SF, Masuadi E, Alrashid A. Outcomes of COVID-19 in Inflammatory Rheumatic Diseases: A Retrospective Cohort Study. Cureus. 2022;14(6):e26343. doi: 10.7759/cureus.26343. PMID: 35903564.
21. Strangfeld A, Schäfer M, Gianfrancesco MA, Lawson-Tovey S, Liew JW, Ljung L, et al. Factors associated with COVID-19-related death in people with rheumatic diseases: results from the COVID-19 Global Rheumatology Alliance physician-reported registry. Ann Rheum Dis. 2021;80(7):930-42.

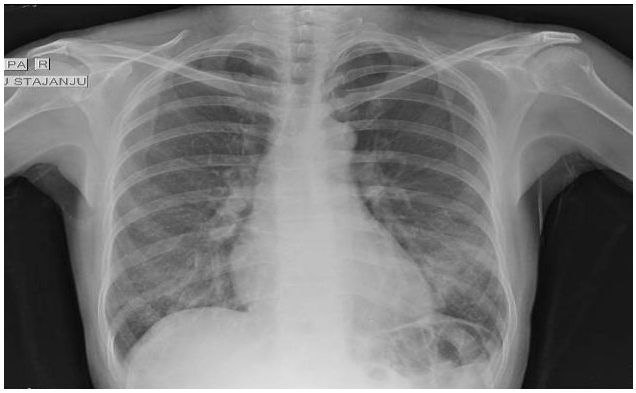

Figure 1. Chest X ray showing signs of a bilateral pneumonia

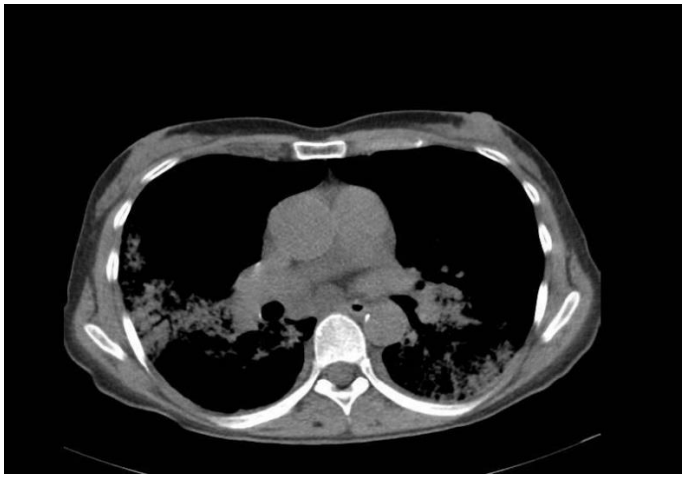

Figure 2. CT scan of lungs showing features of COVID-19 pneumonia

