



Coronavirus Disease 19 (COVID-19) complicated with pneumonia in a patient with rheumatoid arthritis receiving conventional disease-modifying antirheumatic drugs

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Received: 26 March 2020 / Accepted: 7 April 2020 / Published online: 20 April 2020
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Abstract

In December 2019, numerous coronavirus disease 2019 (COVID-19) cases were reported in Wuhan, China, which has since spread throughout the world. However, its impact on rheumatoid arthritis (RA) patients is unknown. Herein, we report a case of COVID-19 pneumonia in a 61-year-old female RA patient who was receiving conventional disease-modifying antirheumatic drugs (cDMARDs). The patient presented with a 4-day history of myalgia and febrile sensation. COVID-19 was confirmed by real-time polymerase chain reaction (PCR). Chest X-ray showed increased opacity on the right lower lung area, and C-reactive protein level was slightly elevated. The patient was treated with antiviral agents (lopinavir/ritonavir), and treatment with cDMARDs was discontinued except hydroxychloroquine. Her symptoms and laboratory results gradually improved. Three weeks later, real-time PCR for COVID-19 showed negative conversion, and the patient was discharged without any complications.

Keywords Coronavirus · COVID-19 · Pneumonia · Rheumatoid arthritis · Disease-modifying antirheumatic drugs

Introduction

Since December 2019, several cases of coronavirus disease 2019 (COVID-19) have been reported in Wuhan, the capital city of Hubei province, and the disease has spread to many countries worldwide, thus declared a global public health emergency [1]. Individuals with COVID-19 showed varied

symptoms, such as fever, cough, nausea/vomiting, or rarely diarrhea. The clinical severity of COVID-19 ranges from asymptomatic to acute respiratory distress syndrome and multiple organ dysfunction requiring mechanical ventilation and admission to the intensive care unit (ICU) [2].

Rheumatoid arthritis (RA) is a risk factor of serious infections, contributing to the high overall morbidity and mortality in RA patients compared to the general population [3]. The higher susceptibility of RA patients to infections could be explained by several endogenous and exogenous risk factors, including (1) the dysregulation of the immune system by the disease itself, (2) presence of immunocompromising comorbidities, and/or (3) immunosuppressive medications such as disease-modifying antirheumatic drugs (DMARDs) [3].

However, there have been few reports on COVID-19 in RA patients. Herein, we report a case of COVID-19 pneumonia in an RA patient who was receiving conventional DMARDs (cDMARDs) treatment.

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Case report

A 61-year-old woman visited our hospital complaining of myalgia and febrile sensation for 4 days. Eight days before her visit to our hospital, she had contact with her daughter, who was confirmed to be COVID-19-positive 2 days before that hospital visit. The patient was diagnosed with RA at a local clinic 3 years ago, and disease remission was achieved after treatment with leflunomide (20 mg per day), hydroxychloroquine (200 mg per day), methylprednisolone (2 mg per day), meloxicam (7.5 mg per day), famotidine

(20 mg per day), and folic acid (1 mg per day). The patient denied any smoking and alcohol drinking habits.

On admission, the patient had no respiratory symptoms, and her vital signs were as follows: blood pressure, 169/79 mmHg; heart rate, 80 beats/min; body temperature, 37.6 °C; and respiratory rate, 20 breaths/min. On physical examination, no pharyngeal injection and clear lung sounds were observed. The initial laboratory tests revealed that the complete blood count, liver function markers, and C-reactive protein level were within the normal range [Table 1, hospital day (HD) 1]. A chest X-ray also showed no abnormal findings (Fig. 1a). Blood culture and tests for *Streptococcus*

Table 1 Laboratory results of the patient at different days of hospitalization

Variables	HD 1	HD 3	HD 10	HD 17	HD 24
White blood cell (/mm ³)	4020	4670	6080	6270	6070
Segment neutrophil, %	58.5	75.1	68.5	67.7	72.1
Lymphocyte, %	29.2	13.2	18.8	21.2	17.5
Monocyte, %	10.6	9.9	9.8	7.6	6.6
Eosinophil, %	1.3	1.4	2.4	3.1	3.4
Hemoglobin (g/dL)	12.1	11.8	10.7	11.3	10.5
Platelet (/mm ³)	291,000	272,000	412,000	360,000	353,000
Total bilirubin (mg/dL)	0.3	0.7	0.2	0.3	0.4
AST (IU/L)	31	15	28	20	27
ALT (IU/L)	22	13	32	20	25
Alkaline phosphatase (IU/L)	80	71	88	84	88
Total protein (g/dL)	7.2	6.6	6.5	7.1	6.4
Albumin (g/dL)	4.2	4.1	4.0	4.2	4.0
BUN (mg/dL)	7.9	14.8	11.8	9.8	12.3
Creatinine (mg/dL)	0.58	0.64	0.57	0.56	0.47
Uric acid (mg/dL)	1.9	3.8	2.0	2.1	2.3
Glucose (mg/dL)	87	141	89	105	137
Sodium (mmol/L)	140	138	141	142	143
Potassium (mmol/L)	3.9	3.9	4.0	4.1	3.5
Chloride (mmol/L)	104	97	105	105	106
C-reactive protein (mg/dL)	0.40	1.11	0.42	0.1	0.24
Pro-calcitonin, ng/mL	0.04	–	0.04	0.03	0.04

HD hospital day, AST aspartate aminotransferase, ALT alanine aminotransferase, BUN blood urea nitrogen

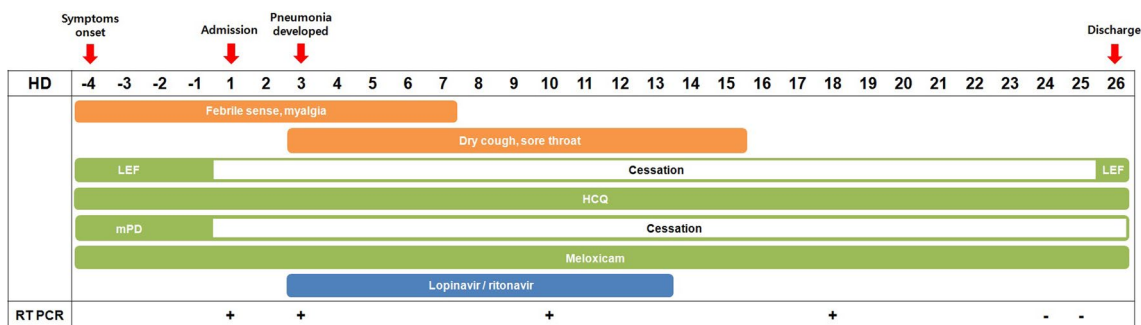


Fig. 1 Clinical course and treatment according to the day of hospitalization. HD hospital day, LEF leflunomide, HCQ hydroxychloroquine, mPD methylprednisolone, RT PCR real-time polymerase chain reaction

pneumoniae, *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, *Legionella pneumophila*, *Mycobacterium tuberculosis*, and human immunodeficiency virus (HIV) were all negative. However, COVID-19 was confirmed by polymerase chain reaction (PCR) using PowerChek 2019-nCoV Real-time PCR kit (KogeneBiotech Co. Ltd., Seoul, Korea).

Three days after admission, the patient developed a dry cough, scanty sputum, and sore throat without any severe respiratory symptoms, such as shortness of breath or chest pain. The C-reactive protein levels were slightly elevated (Table 1, HD 3), and chest X-ray showed the haziness on the right lower lung area (Fig. 1b), suggesting the development of COVID-19 pneumonia.

The patient was treated with lopinavir/ritonavir for 10 days; 2 tablets (lopinavir 200 mg/ritonavir 50 mg) were given twice per day (Fig. 2). Of the RA medications, leflunomide and methylprednisolone were discontinued; however, the patient continued receiving hydroxychloroquine, meloxicam, and famotidine. After the antiviral treatment, her symptoms gradually improved, and 10 days after admission, her C-reactive protein levels returned to normal (Table 1, HD 10). Twenty-four days after admission, real-time PCR could not detect the nucleic acid of SARS-CoV-2, and the patient was discharged without any complications.

Search strategy

Following the published guideline on narrative biomedical reviews [4], we screened MEDLINE/PubMed and SCOPUS databases up to March 2020, by using the following keywords: COVID-19, RA, immunosuppressant, and DMARDs. We reviewed abstracts and retrieved the relevant articles. Original articles, case reports, case series, and reviews reporting on COVID-19 and RA published in English were included.

Discussion

COVID-19 caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was first reported in Wuhan, China, in December 2019 and has spread rapidly worldwide, resulting in the 2019–2020 coronavirus pandemic. The severity of COVID-19 varies immensely, ranging from asymptomatic to acute respiratory distress syndrome [2]. Most COVID-19 cases involve patients aged 30–80 years. The mortality in healthy individuals is low, and the COVID-19 patients only show mild symptoms and recover without any special treatment [5]. Approximately 19% of patients develop severe pneumonia, with a fatality rate of 2%. Elderly patients with preexisting comorbid conditions such as cardiovascular diseases, diabetes, chronic respiratory diseases, or cancer, are at high risk [5]. However, the severity of COVID-19 in RA patients receiving immunosuppressants remains unclear.

Previous studies reported that RA is associated with the increased risk of respiratory infection and its complication, including viral diseases such as influenza [6, 7]. This finding might be due to the immunologic dysfunction of circulating T cells in RA patients, rendering patients' immune system unable to respond to the infectious agent. The impaired thymic function and increased turnover of peripheral T cells, which causes dysregulation in peripheral T cell homeostasis, could also contribute to the higher susceptibility of RA to infections [8]. Moreover, RA patients are frequently treated with immunosuppressive medications, such as steroid or DMARDs. The administration of such immunosuppressive agents and subsequent inhibition of T cell activation and granulocyte function could also contribute to the higher frequency of infections observed in RA patients [9].

The development of COVID-19 treatment in RA patients is clinically challenging, as the immunosuppressive agents

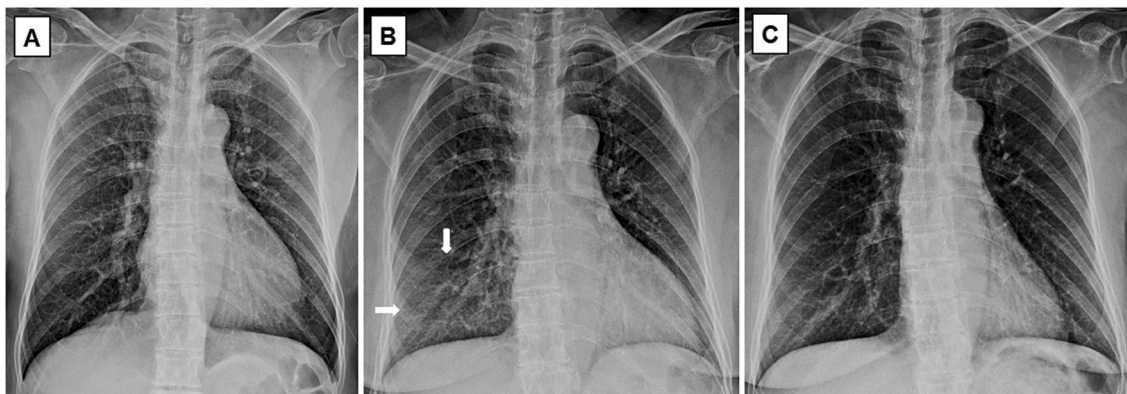


Fig. 2 Chest X-ray imaging findings. **a** No abnormal findings were observed at hospitalization day 1. **b** Haziness was observed on the right lower lung area at hospitalization day 3. **c** Resorption of haziness on right lower lung area was observed at hospitalization day 10

could aggravate COVID-19 infection. For patients admitted to hospitals with severe infections, temporary discontinuation of most DMARDs is recommended to allow RA patients to develop protective immunity and eliminate the pathogens [10]. On the other hand, pausing the administration of DMARDs might provoke an inflammatory exacerbation of RA, which usually is managed by increased doses of immunosuppressive medications. The effect of steroid use in COVID-19 is still unknown. Steroid might worsen the infections by reducing the immune system, but the inflammatory cascade of pneumonia could be blocked by the administration of systemic steroid treatment [11]. Previous reports demonstrated that the steroid treatment was related with higher mortality of patients with a viral infection such as influenza pneumonia [12] and that steroid use was associated with delayed coronavirus RNA clearance of both Middle East respiratory syndrome (MERS) [13] and Severe Acute Respiratory Syndrome (SARS) [14]. In the presented cases, while we discontinued leflunomide and steroids to minimize the severity of COVID-19, we continued the administration of hydroxychloroquine due to its possible antiviral effects [15], as well as its antirheumatic effects.

Nevertheless, 3 days after admission, the symptoms of the patient worsened, and the patient developed pneumonia. After the administration of lopinavir/ritonavir, the clinical symptoms and inflammatory markers were improved within 1 week. Several case reports showed that the combination of the protease inhibitors lopinavir and ritonavir, which are widely used in individuals infected with HIV, exhibited a therapeutic effect in patients with COVID-19 [16–18]. Therefore, close monitoring is required in RA patients with COVID-19 to ensure the early detection of disease progression, even in initially asymptomatic cases. Moreover, lopinavir/ritonavir could be prescribed to RA patients with early-stage COVID-19 pneumonia.

As a part of the RA management, our patient was receiving cDMARDs, but not biologic DMARDs (bDMARDs) or targeted synthetic DMARDs (tsDMARDs). Similar to cDMARDs, bDMARDs and tsDMARDs have also been associated with an increased risk of infection. Antitumor necrosis factor therapy has been associated with an increased risk of tuberculosis and severe infections of bones, joints, soft tissue, and respiratory tract [9]. Abatacept, rituximab, and tocilizumab have been associated with pneumonia and pyogenic bacterial infections, while tofacitinib with herpes zoster infection [9]. Meanwhile, selective cytokine blockade (anakinra or tocilizumab) and Janus kinase (JAK) inhibition might be beneficial in improving mortality in severe COVID-19 cases with cytokine storm syndrome [19]. However, to date, the effects of bDMARDs or tsDMARDs on COVID-19 remain uncertain. Therefore, while more evidence regarding the risk of COVID-19 infection in RA patients, we suggest the discontinuation of bDMARDs and

tsDMARDs in COVID-19 cases, as has been recommended for previous viral outbreaks [20].

In conclusion, we reported the clinical manifestation and disease course of COVID-19 pneumonia in an RA patient who was receiving cDMARDs. After the discontinuation of cDMARDs (except hydroxychloroquine) and with the administration of antiviral agents, COVID-19 pneumonia was improved, providing a reference case for the management of such patients. More clinical data are needed to further optimize the treatment regimen for COVID-19 in RA patients receiving immunosuppressive drugs.

Acknowledgements We would like to thank Editage (<https://www.editage.co.kr>) for English language editing.

Author contributions JS, SK: data collection, writing and original draft. SWC, KWS: methodology and investigation. SL, MWS: review and editing. DHL: supervision, writing, review and editing. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Funding None.

Compliance with ethical standards

Conflict of interest No potential conflict of interest relevant to this article was reported.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from a patient included in the study.

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