Case Based Review

Pneumonia Complicated by SARS-CoV-2 Infection in Three Patients with Ankylosing Spondylitis Who are on Anti-TNF Therapy: Case-Based Review

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Abstract

The mortality rate for the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic is increasing worldwide with each passing day. The risk factors for mortality include advanced age and comorbidities. It is still uncertain whether biological agents pose a risk for the progression of SARS-CoV-2. Although there are studies suggesting the use of biological agents in the literature, there are also studies suggesting the discontinuation of biological agents during SARS-CoV-2. In this study, we aimed to determine whether anti-tumor necrosis factor (anti-TNF-α agents) therapy, which is one of the biological agents commonly used in rheumatology clinics, has an effect on the clinical course of SARS-CoV-2 infection, and to review the literature. We searched the MEDLINE/PubMed and SCOPUS databases until the date of August 15, 2020, using the following keywords: SARS-CoV-2 and anti-TNF-α agents. We reviewed abstracts and retrieved the relevant articles. We reported the clinical manifestation and disease course of SARS-CoV-2 pneumonia in three patients with ankylosing spondylitis who were receiving anti-TNF-α agents. All patients in our case series had a mild course similar to the most cases reported in the literature.

Key Words: *Ankylosing spondylitis, anti-tumor necrosis factor, coronavirus disease 2019, severe acute respiratory syndrome coronavirus 2*

Introduction

The novel severe acute respiratory syndrome coronavirus (SARS-CoV-2) pandemic has rapidly spread globally.[1] According to the World Health Organization (WHO), this disease is believed to have emerged in the Wuhan province of China, and this highly contagious respiratory virus has spread all over the world. According to the latest mid-August data of the WHO, it was reported that 20,439,814 cases were infected with SARS-CoV-2 worldwide, and of whom, 744,385 died of the virus. Of the patients infected with SARS-CoV-2, 80% experience a mild form of the disease, while 20% require hospitalization according to the data from China. Moreover, in reference to the same data, the mortality rate was found to be in the range of 1%–4%.[2] The risk factors for mortality include advanced age, immunodeficiency, and comorbidities.[1] Hence, rheumatologists should be aware of these risk factors for severe SARS-CoV-2 as these are also likely to be operational in their patients with rheumatic diseases. Moreover, SARS-CoV-2 may mimic a rheumatic disease due to arthralgia and myalgia, which may be seen due to SARS-CoV-2 infection. Therefore, it is important that the rheumatologists should closely follow the SARS-CoV-2 pandemic and know the clinical characteristics of the disease and treatment.

In the literature, risk factors for mortality caused by SARS-CoV-2 in the general population had been determined.[1,3] Gianfrancesco stated that as in the general population, people with rheumatic diseases who were older and/or had comorbidities (hypertension, lung disease, diabetes, cardiovascular disease, and chronic renal insufficiency) had higher odds of SARS-CoV-2-related hospitalization. However, the effect of using a biological agent or immunosuppressive drugs for concomitant rheumatic disease on the clinical course of SARS-CoV-2 is

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controversial. Feldman *et al*. stated that biologic agents protected from the progression of SARS-CoV-2 infection.[4] In a case-based review, the authors recommended that patients using glucocorticoids and disease-modifying antirheumatic drugs should not discontinue their medication even if they were infected with SARS-CoV-2.[5] However, in another case report, it was recommended to discontinue the immunosuppressant in a rheumatoid arthritis patient infected with SARS-COV-2, in order not to affect the clinical course.[6] However, there is a limited number of studies regarding the effect of anti-tumor necrosis factor agents (anti-TNF-α) agents on the clinical course of SARS-CoV-2[3,7-18] [Table 1].

Herein, we reported three cases of SARS-COV-2 pneumonia in patients with ankylosing spondylitis (AS) who were receiving anti-TNF agents.

Case Reports

Case-1

A 32-year-old male patient suffering from malaise, arthralgia, loss of appetite, headache, sore throat, dry cough, and dysgeusia persisting for about 5 days was admitted to another center twice. However, since he did not respond to the treatments provided and his complaints increased, he presented to the emergency department of our university. The patient with no comorbidity other than AS was on infliximab (400 mg/6 weeks) for about 8 years. The last infliximab infusion was administered 3 weeks ago. The patient denied any smoking or alcohol consumption habits. The examination of the patient with insignificant family history revealed that his body temperature was 36.7°, heart rate was 86/min, and arterial blood pressure (BP) was 126/72 mmHg. On his physical examination, no pharyngeal infection was identified, and the auscultation of lung sounds was normal. The laboratory studies of the patient showed elevated levels of lactate dehydrogenase, ferritin, and C-reactive protein (CRP) [Table 2]. On the identification of suspicious infiltrative areas on the PA chest X-ray, thoracic computed tomography (CT) was performed. Focal areas of ground-glass density were noted as a result of the tomographic examination [Figure 1]. Since the patient's CT was consistent with viral pneumonia, he was isolated with the pre-diagnosis of SARS-CoV-2. Blood culture and tests for Streptococcus pneumoniae, Mycoplasma pneumonia, Legionella pneumophila, Mycobacterium tuberculosis, and human immunodeficiency virus (HIV) were all negative. However, SARS-COV-2 was confirmed by polymerase chain reaction (PCR) using a Power Chek 2019-nCoV real-time PCR kit (Kogene Biotech Co. Ltd., Seoul, Korea). The patient was initiated on hydroxychloroquine (200 mg tb 2 × 1/day) for 5 days, and azithromycin (250 mg tb 1 × 1/day) and oseltamivir (75 mg tb 1 × 1/day) for 4 days. However, infliximab was discontinued. In the second week of the isolation, the patient's dry cough and constitutional

Table 1: Case reports demonstrating the relationship between SARS-CoV-2 infection and anti-tumor necrosis factor agent in the literature

Reference	Total (*n*)	Diagnosis	Anti-TNF	Outpatient only, *n* (%)	Hospitalized, *n* (%)	ICU, *n* (%)	Ventilator, *n* (%)	Death, *n* (%)
Gianfrancesco *et al*.[3]	107	RA, Vasculitis, SLE, PSA, AS	Not reported	76 (71)	36 (31)	NR	NR	0 (0)
Monti *et al*.[7]	2	RA	Etanercept	0 (0)	2 (100)	0 (0)	0 (0)	0 (0)
Duret *et al*.[8]	1	AS	Etanercept	0 (0)	1 (100)	0 (0)	0 (0)	0 (0)
Tursi *et al*.[9]	1	Crohn	Adalimumab	0 (0)	1 (100)	0 (0)	0 (0)	0 (0)
Dolinger *et al*.[10]	1	Crohn	Infliximab	0 (0)	1 (100)	0 (0)	0 (0)	0 (0)
Abdullah *et al*.[11]	1	UC	Infliximab	1 (100)	0 (0)	0 (0)	0 (0)	0 (0)
Conti *et al*.[12]	1	Psoriasis	Adalimumab	1 (100)	0 (0)	0 (0)	0 (0)	0 (0)
Megna *et al*.[13]	38	Psoriasis	Adalimumab, etanercept, certolizumab and golimumab	38 (100)	0 (0)	0 (0)	0 (0)	0 (0)
Brito *et al*.[14]	1	Behcet	Infliximab	1 (100)	0 (0)	0 (0)	0 (0)	0 (0)
Brito *et al*.[14]	1	RA	Infliximab	1 (100)	0 (0)	0 (0)	0 (0)	0 (0)
Brito *et al*.[14]	1	AS	Infliximab	1 (100)	0 (0)	0 (0)	0 (0)	0 (0)
Bezzio *et al*.[15]	1	UC	Infliximab	0 (0)	1 (100)	0 (0)	0 (0)	0 (0)
Brenner *et al*.[16]	176	IBD	Not reported	150 (85)	25 (14)	3 (2)	1 (1)	1 (1)
Haberman *et al*.[17]	38	Psoriasis PSA, RA Crohn, UC	Not reported	35 (92)	3 (8)	0 (0)	0 (0)	0 (0)
Dursun *et al*.[18]	2	Behcet	Infliximab adalimumab	2 (100)	0 (0)	0 (0)	0 (0)	0 (0)
Present study	3	AS	Adalimumab, golimumab, infliximab	3 (100)	0 (0)	0 (0)	0 (0)	0 (0)

RA: Rheumatoidarthritis, AS: Ankylosing spondylitis, IBD: Inflammatory bowel disease, UC: Ulcerative colitis, NR: Not reported, ICU: Intense care unit, PSA: Psoriatic arthritis, TNF: Tumor necrosis factor, SLE: Systemic lupus erythematosus

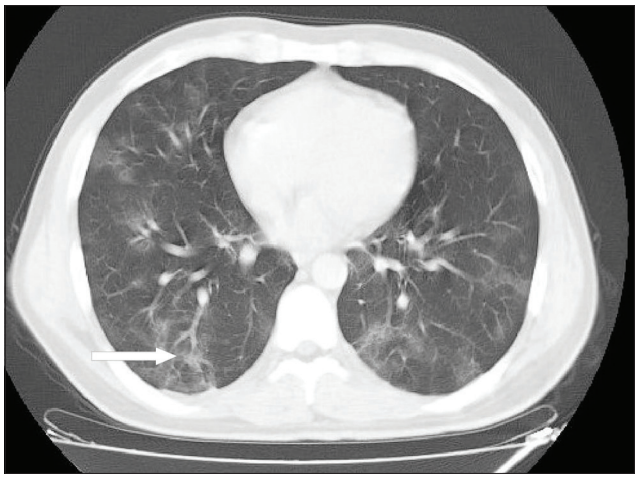

Figure 1: Thoracic tomography of the first case

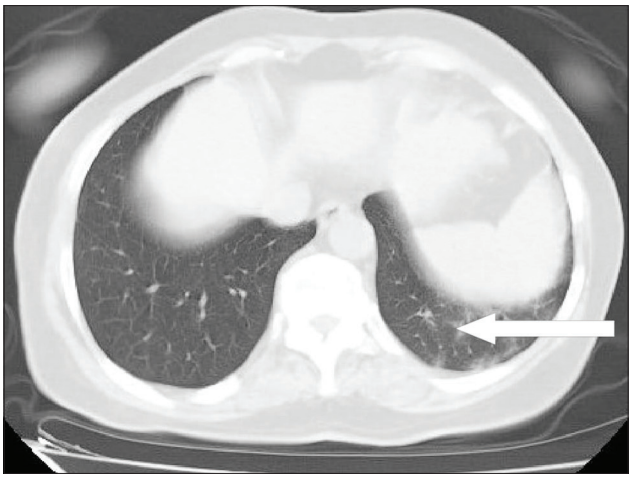

Figure 2: Thoracic tomography of the second case

symptoms regressed. The follow-up CT of the patient which was ordered at the end of the isolation showed a regression in the areas of ground-glass density. Twenty-four days after the admission, real-time PCR could not detect the nucleic acid of SARS-CoV-2, and the patient was discharged without any complications. He was recommended to be isolated at home. The patient was regularly called by phone, and information was received about his disease course. Two weeks after his discharge from the hospital, he was re-initiated on infliximab treatment as his rheumatic complaints increased. The patient regularly attending outpatient follow-ups has a stable course.

Case-2

A 62-year-old female patient presented to the emergency department of the university with the complaints of cough, diffuse muscle pain, and malaise for about 4 days. Due to the history of close contact with a patient infected with SARS-CoV-2, she was immediately isolated. The patient had no comorbidity other than AS and was on adalimumab therapy (40 mg per two weeks) for approximately 13 years. The last adalimumab was administered 2 weeks ago. The examination of the patient whose son was also diagnosed with AS revealed that her body temperature was 37.1°, heart rate was 77/min, and BP was 123/69 mmHg. On her physical examination, no pharyngeal infection was observed and the auscultation of lung sounds was normal. The laboratory studies of the patient showed elevated levels of CRP, and serum immunoglobulin G [Table 2]. Thoracic CT was ordered with the pre-diagnosis of viral pneumonia on the patient's risk of contact and supporting tests. The CT revealed findings consistent with viral pneumonia [Figure 2]. The result of the PCR test ordered with the pre-diagnosis of SARS-CoV-2 was positive. The patient was initiated on hydroxychloroquine (200 mg tb 2 × 1/day) for 5 days, oseltamivir (75 mg/day) and azithromycin (250 mg/day) for four days. Adalimumab was discontinued. Two weeks after isolation, real-time PCR could not detect the nucleic acid of SARS-CoV-2. The patient with regressed complaints was discharged and recommended to be isolated at home. Ten days after her discharge from the hospital, she was re-initiated on adalimumab treatment. The patient regularly attending outpatient follow-ups has a stable course.

Case 3

A 35-year-old female patient was admitted to the emergency department for malaise and cough persisting for about 4 days. Since the patient had a history of close contact with a patient infected with SARS-CoV-2, she was hospitalized and isolated. The patient had no comorbidity other than AS and was on golimumab therapy (50 mg/month) for approximately 5 years. The last golimumab was administered 2 weeks before admission to the emergency department. The examination of the patient revealed that her body temperature was 37.1°, heart rate was 77/min, and BP was 135/72 mmHg. The cardiovascular, pulmonary, and abdominal examinations were normal on her systemic examination. The initial laboratory tests revealed that the complete blood count and CRP level were within the normal range [Table 2]. The posteroanterior chest X-ray ordered with the pre-diagnosis of the virus showed no infiltration areas, while the thoracic CT examination revealed peripheral areas of ground-glass density [Figure 3]. Blood culture and tests for *Streptococcus pneumoniae, Mycoplasma pneumonia, Chlamydia pneumoniae, Legionella pneumophila, Mycobacterium tuberculosis*, and HIV were all negative. She was treated with hydroxychloroquine (200 mg tb 2 × 1/day) for 5 days, oseltamivir (75 mg per day) and azithromycin (250 mg per day) for 5 days. The patient was recommended not to use golimumab. The PCR test result of the swab sample taken from the patient was positive for the virus. After the antiviral treatment, her symptoms gradually improved. Fifteen days after the admission, PCR could not detect the nucleic acid of SARS-CoV-2, and the patient was discharged without any complications. Five days after her discharge,

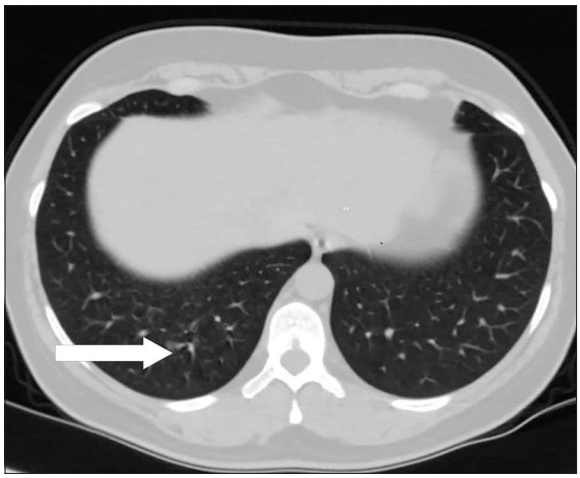

Figure 3: Thoracic tomography of the third case

she was re-initiated on golimumab treatment. The patient regularly attending outpatient follow-ups has a stable course.

Search strategy

We searched MEDLINE/PubMed and SCOPUS databases until the date of August 15, 2020 using the following keywords: SARS-CoV-2 and anti-TNF-α agents. We reviewed abstracts and retrieved the relevant articles. English case reports, case series, and reviews reporting the effects of the anti-TNF agent on the clinical course of SARS-CoV-2 were included. Moreover, all the literature cited these articles were also searched. However, non-English articles and those with unavailable full text were excluded.

Discussion

The severity of COVID-19 varies immensely, ranging from asymptomatic to acute respiratory distress syndrome.[1] The mortality is low, and in healthy individuals, the COVID-19 only shows mild symptoms and recovers without requiring any special treatment.[2] Approximately 19% of patients develop severe pneumonia, with a mortality rate of 2%. Elderly patients with pre-existing comorbid conditions such as cardiovascular diseases, diabetes mellitus, are at high risk.[1] However, the severity of SARS-CoV-2 in AS patients receiving immunosuppressants remains unclear. In this case series, we reviewed the clinical courses of three patients with the diagnosis of AS infected with SARS-CoV-2. These three patients with no comorbidity who were on anti-TNF-α agents had a mild form of the infection.

Studies have reported that anti-TNF-α agents may lead upregulation of ACE 2 receptors, which are responsible for virus penetration into the cell.[19] Therefore, it has been assumed that the use of TNF inhibitors can be effective in reducing both SARS infection and the resulting organ damage caused by SARS infection. In a recent case report, it was stated that anti-TNF-α agents did not affect the progression of SARS-COV-2 in a patient with AS.[8] Moreover, the clinical course of SARS-COV-2 has been observed to be milder in patients using anti-TNF-α agents with the diagnosis of inflammatory bowel disease (IBD) who are infected with SARS-COV-2.[16] In fact, according to a review from Italy, 15% of 198 IBD patients using anti-TNF-α agents were hospitalized for SARS-COV-2. While only 3% of these patients required intensive care/intubation, it was observed that 67% of IBD patients using oral/parenteral steroids required intensive care/intubation.[20] In the study by Gianfrancesco *et al*., it was reported that the use of anti-TNF-α agents did not increase hospitalization rate after SARS-CoV-2 infection.[3] The same study found that the use of high doses of steroids significantly increased mortality and hospitalization rate. Another case report reported that the clinical course of SARS-CoV-2 was mild in a patient with Crohn's disease despite using adalimumab.[9] Moreover, infliximab has been shown to be effective in the treatment of Cytokine storm syndrome (CSS) due to SARS-CoV-2 infection in a patient with Crohn's disease.[10] Despite using anti-TNF agents, the clinical courses of the patients in our study were mild. In addition, the patients remained stable, although their anti-TNF agents were discontinued for a short time in the pandemic and then re-initiated.

Advanced age is considered a risk factor for mortality.[1] In the literature, there is a case report indicating that the clinical course of SARS-CoV-2 was mild despite using anti-TNF agents at an advanced age.[7] In this study, it was seen that an elderly patient using anti-TNF-α agent had a mild clinical course of SARS-CoV-2 despite the lung infiltration. This indicates that Anti-TNF agents can be protective against SARS-CoV-2 infections. The reason for this has been explained by different physiopathologies in the literature. Studies showed that the serum levels of TNF, interleukin (IL)-1, IL-6, interferon-gamma, and adhesion molecules increased after SARS-CoV-2 infection.[21] However, the release of other cytokines had been shown to be TNF-dependent. Therefore, blocking of TNF could reduce lung inflammation, cellularity, exudation, and inflammatory mediators that may occur after SARS-CoV-2 infection. Another study showed that TNF aggravated lymphopenia through TNF/TNF receptor 1, leading to T-cell dysfunction. This hypothesis showed an important and positive contribution of anti-TNF agents to immunomodulatory interventions. These reinforce the hypothesis that anti-TNF agents can be used to treat the infection. However, there is a need for large epidemiological studies to clarify the relationship between SARS-COV-2 and anti-TNF agents.

Although the use of biological agents in the CSS syndrome, which may occur due to the virus, is recommended in the literature, there are a limited number of studies on recommendations for patients who do not have an infection but have an indication for the use of anti-TNF-alpha agents. In a recent study conducted in Italy, the patients were recommended not to discontinue their biological

Table 2: Laboratory results of the cases

	Results		
	Case 1	**Case 2**	**Case 3**
Blood cell count			
WBC	4970 (K/µL)	6460 (K/µL)	5460 (K/µL)
RBC	450 (×10D^4/µL)	531 (×10D^4/µL)	471 (×10D^4/µL)
HgB	13.1 (g/dL)	15.7 (g/dL)	12.7 (g/dL)
PLT	365 (×10^4/µL)	348 (×10^4/µL)	342 (×10^4/µL)
Biochemistry			
Albumin	40.6 (g/dl)	29.9 (g/dl)	44.7 (g/dl)
LDH	230 (U/L)	139 (U/L)	132 (U/L)
AST	20 (U/L)	12 (U/L)	21 (U/L)
ALT	30 (U/L)	23 (U/L)	27 (U/L)
GGT	15 (U/L)	14 (U/L)	15 (U/L)
ALP	42 (U/L)	53 (U/L)	86 (U/L)
BUN	14 (U/L)	16 (U/L)	27 (U/L)
Creatinine	0.88 (mg/dL)	0.64 (mg/dL)	0.79 (mg/dL)
CK	38 (U/L)	43 (U/L)	48 (U/L)
Ferritin	411.8 (ng/mL)	411.5 (ng/mL)	12.8 (ng/mL)
IgG (turbidimetric)	8 (g/L)	17 (g/L)	9 (g/L)
Troponin-T	3.00 (ng/L)	0.66 (ng/L)	5.00 (ng/L)
CK-MB	2.01 (ug/L)	3.08 (ug/L)	2.5 (ug/L)
D-dimer	132 (ng/mL)	152 (ng/mL)	131 (ng/mL)
Immunology			
CRP	15.7 (mg/dl)	16.7 (mg/dl)	5 (mg/dl)
ESR	42 (mm/s)	53 (mm/s)	32 (mm/s)
ELİSA			
HbsAg	Negative	Negative	Negative
Anti- HBs Ag	Positive	Positive	Positive
Anti- HBc IgG	Negative	Negative	Negative
Anti-HIV	Negative	Negative	Negative
Anti-HCV	Negative	Negative	Negative
Serology			
Brucella agglutination test (rose bengal)	Negative	Negative	Negative
Brucella tube agglutination test	Negative	Negative	Negative
Urinalysis			
Leukocyte	Negative	Negative	Negative
HgB	Negative	Negative	Negative
Occult blood	Negative	Negative	Negative

WBC: White blood cell, RBC: Red blood cell, HgB: Hemoglobin, PLT: Platelet, LDH: Lactate dehydrogenase, AST: Aspartate transaminase, ALT: Alanine transaminase, GGT: y-glutamyltransferase, ALP: Alkaline phosphatase, BUN: Blood urea nitrogen, CK: Creatine kinase, IgG: Immunoglobulin, CRP: C-Reactive protein, ESR: Erythrocyte sedimentation rate, HIV: Human immunodeficiency virus, HCV: Hepatitis C Virus

therapies.[7] However, there are also studies approaching with suspicion toward this as there are insufficient data on whether the use of anti-TNF-alpha agents increases the risk of infection or whether it causes morbidity. Therefore, the small sample size and limited data in our case series constitute the major limitation of our study.

As a part of the AS management, our patients were receiving anti-TNF-α agents. However, this therapy has been associated with an increased risk of tuberculosis, septic arthritis, and osteomyelitis. However, to date, the effects of anti-TNF-α agents on SARS-CoV-2 remain uncertain. Hence, we suggest the discontinuation of anti-TNF agents for a short time in SARS-CoV-2 cases, as recommended for previous viral infection.[4]

In conclusion, we reported the clinical manifestation and clinical course of SARS-CoV-2 pneumonia in three patients with AS who were receiving anti-TNF-α agents. Patients had a mild form of infection, possibly due to the blocking of TNF and TNF-dependent mediators secondary to the use of anti-TNF agents. Especially in cases of T-cell dysfunction, the immunomodulatory properties of these agents should also be considered.

However, there is a need for large-scale studies to verify this.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient (s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published, and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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