

# Herpes Zoster After Tocilizumab Therapy in COVID-19 Survivor: A Case Report

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## ABSTRACT

The COVID-19 pandemic has become a concern for the world community. However, despite abundant attempts taking place, there is currently no definitive therapy for COVID-19 yet. The clinical approaches recently adopted are the provision of antiviral therapy and immunomodulators. One of the immunomodulators that are currently being researched is tocilizumab, an IL-6 receptor antagonist monoclonal antibody. Many case studies and retrospective observational studies have shown that there is a chance that tocilizumab could diminish death rates in COVID-19 patients with severe or critical symptoms. Along with the growing use of tocilizumab in the COVID-19 cases that are emergent in nature, the occurrence of unpredictable adverse effects of the drugs have also been raising. This case report describes a COVID-19 confirmed patient with severe symptoms who was given tocilizumab in addition to standard therapy. The patient developed Herpes Zoster infection which was suspected to be related to the adverse effects of using tocilizumab, which is known for its likelihood to increase the risk of new infections and also probably reactivate latent infections. Tocilizumab use seems to be effective in combating cytokine storm associated with severe COVID-19 infection. The possibility of serious adverse effects in the utilization of tocilizumab, though rare, cannot be excluded. The presence of a latent or chronic infection that can undergo reactivation should be a consideration for appropriate screening or prophylaxis before administering tocilizumab.

**Keywords:** COVID-19, Tocilizumab, Herpes Zoster, adverse drug effects, cytokine storm.

## INTRODUCTION

The COVID-19 pandemic has become a concern for the world community. In handling it, various therapeutic modalities are used both for emergency reasons and research purposes. Tocilizumab, a monoclonal antibody against the IL-6 receptor from the immunoglobulin G1k group, is one of the immunomodulators that has been used for a long time in the therapy of Rheumatoid Arthritis. It is known that IL-6 levels increase sharply in COVID-19 patients with critical symptoms, even up to ten times higher,

triggering a cytokine storm.<sup>1</sup> Tocilizumab can bind to both membrane-bound IL-6 receptor (mIL-6R) and soluble IL-6 receptor (sIL-6R).<sup>2</sup> The potential benefits of Tocilizumab in suppressing cytokine storms that occur in COVID-19 patients make it an option that is starting to get a lot of attention.<sup>3</sup>

This case report presents a patient with severe pneumonia caused by SARS-CoV-2. During hospitalization, the patient was given Tocilizumab (Actemra) to alleviate symptoms associated with cytokine storm. The patient later

developed a skin rash due to reactivation of the herpes zoster virus which was suspected to be a side effect that occurred after using Tocilizumab.

### CASE ILLUSTRATION

A 43-year-old woman presented to the emergency room on July 12, 2020 with a complaint of severe shortness of breath that started three days prior. Approximately seven days before being admitted to the hospital, the patient developed a fever accompanied by dry cough, malaise, and decreased appetite but denied any abdominal pain. There are no complaints of headache, sore throat, diarrhea, or skin rash. Any history of contact with confirmed or suspected cases of COVID-19 was denied. Patient also disproved any travel history prior to symptoms.

On initial examination, rapid shallow breathing was found at a rate of 34 breaths per minute. On auscultation, there were crackles found in both lung fields and the oxygen saturation was 84% on ambient air. Other physical examinations were within normal limits. Blood tests showed lymphopenia (lymphocyte count was 14.4% of total leucocytes), an increase in the value of D-dimer ( $> 4 \mu\text{g/mL}$ ) and ferritin (1493.55 ng/mL). SARS-COV-2 Antibody Rapid Test was also conducted using immunochromatography methods which showed reactive results to both IgG and IgM. IL-6 examination was not carried out due to limitations in health facilities. The patient had a history of poorly controlled type-2 diabetes mellitus with HbA1c at 10%. The presence of other comorbidities was refuted.

A Thoracic Computed Tomography scan (CT Scan) at admission provided images of multiple consolidation and multifocal ground glass opacities extending to the periphery, which correspond to the features commonly found in COVID-19 infection in severe classification (**Figure 1**). RT-PCR examinations were carried out using the Kit for 2019 Novel Coronavirus RNA with the RT-PCR ABI 7500 method. Samples for the RT-PCR examination were obtained from naso-oropharyngeal swabs and the result came out as positive. The patient was thus a COVID-19-confirmed case and was then being treated in the isolation room.

Based on the clinical presentations, laboratory, and radiological examination results, the patient showed manifestations of severe pneumonia. In accordance with the guidelines for handling COVID-19 that were in effect at the time, at the beginning of treatment, the patient was given a standardized supportive therapy which consisted of empirical antibiotics therapy, high-dose vitamin C, glucocorticoids, anticoagulants, and lopinavir-ritonavir as antiviral.<sup>4,5</sup>

On the eighth and ninth day of treatment, the patient manifested trend towards worsening of the respiratory distress with her oxygen saturation being below 90% despite oxygen supplementation with CPAP (continuous positive airway pressure) device. Settings of the CPAP device were by itself under clinical judgment from our fellow anesthetist. On the tenth day, based on the deteriorating clinical presentations which suggested a cytokine storm might be going on, tocilizumab therapy was initiated. Tocilizumab was given twice with the first dose of 400 mg, followed by the second dose of 200 mg given 12 hours after the first dose. At the time of the administration of the tocilizumab, no significant adverse reaction was observed.

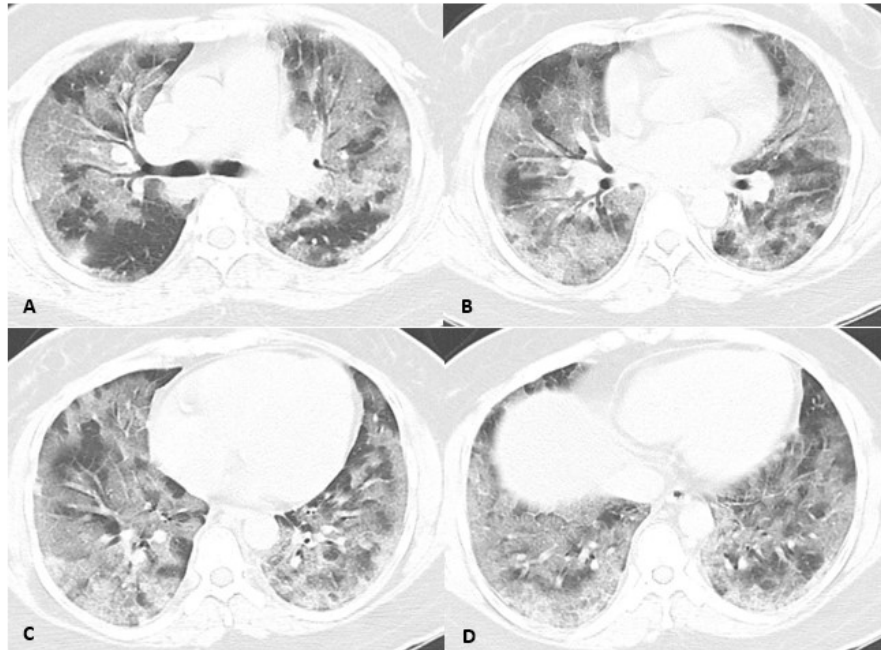
Improvements were apparent during the next few days. Shortness of breath and the oxygen requirement gradually decreased and the patient no longer needed any oxygen supplementation in one week after receiving tocilizumab. The extent of pneumonia also showed coherent reduction on the follow-up chest x-ray performed three days later. The follow-up CT scan conducted one month afterwards also showed satisfactory result (**Figure 2**). Inflammation markers also showed improvement, with the ferritin value of 842.9 ng/mL and the D-dimer value declined to 1.54  $\mu\text{g/mL}$  in ten days after tocilizumab administration. Follow-up SARS-COV-2 RT-PCR with negative results were obtained after 25 days of hospitalization.

However, on the eleventh day after tocilizumab administration, a sensation of prickling pain was felt at the area around the right upper torso. The pain was then followed by the appearance of a reddish rash with multiple clusters of papules and vesicles (**Figure 3**). The erythematous rash began to appear on the

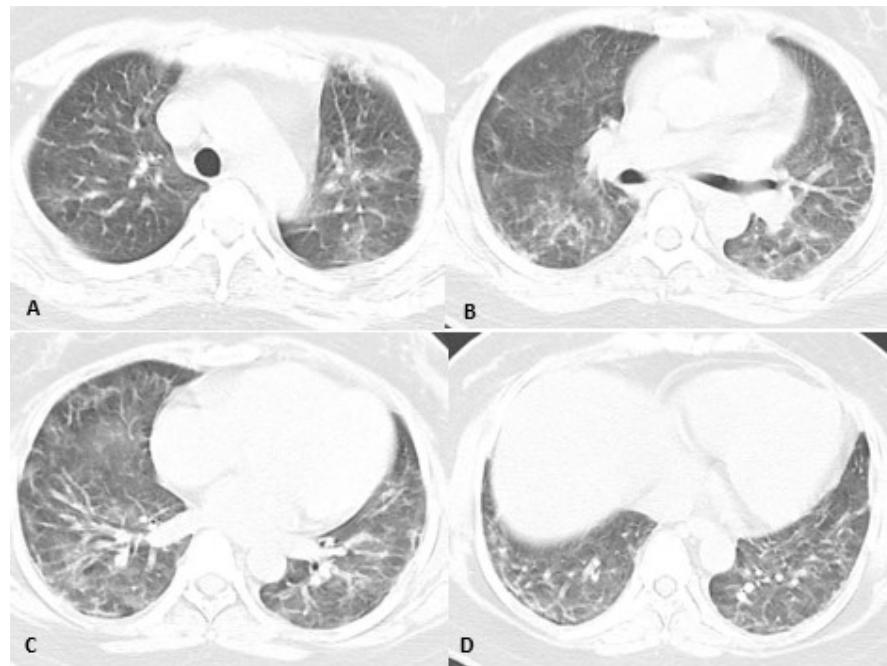
fourth day since the complaints of pain emerged, multiplied and expanded, spreading to the back within ten days. The patient denied having experienced such complaints before.

The clinical appearance clearly indicated a herpes zoster infection. The patient was then treated with acyclovir, gabapentin, gentamicin

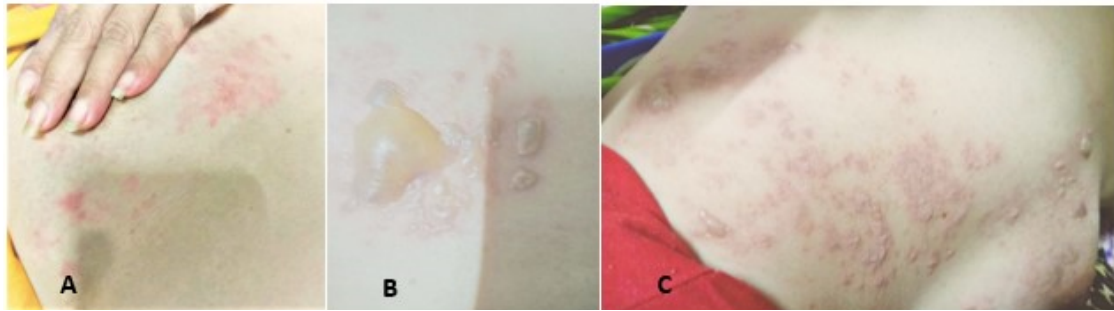
ointment applied on ruptured vesicles, and salicylic powder for intact vesicles. After the initiation of therapy, no new papules or vesicles emerged, leaving erosions, crusts, and hyperpigmented macules (**Figure 4**). However, the pain persisted even after the patient had been given combination of analgesic therapy (gabapentin and NSAIDs).



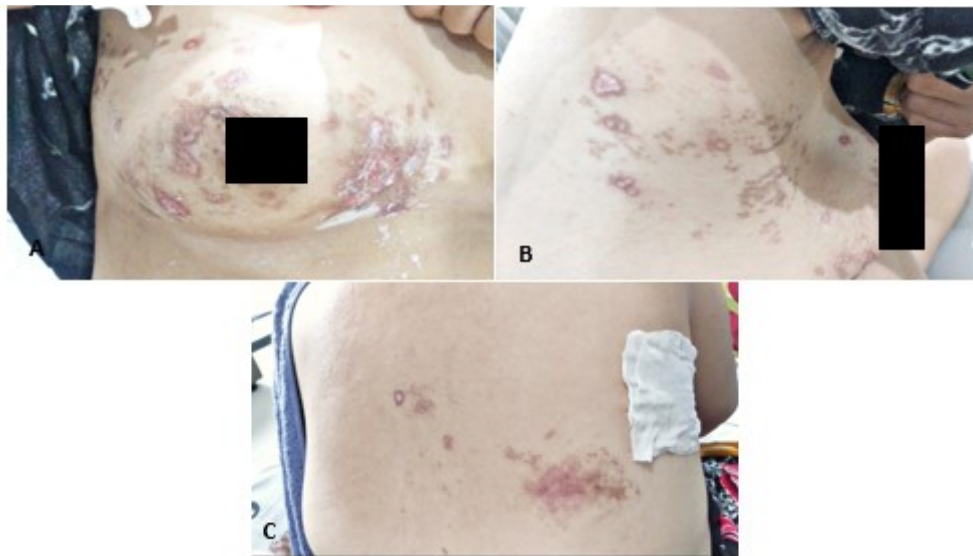
**Figure 1.** (A-D) Multifocal ground glass opacities and extensive consolidation was found on thoracic computed tomography scan examination on the first day of admission.



**Figure 2.** (A-D) A follow-up CT scan conducted one month apart showed a satisfactory reduction of ground glass opacities and consolidation, accompanied by increasing linear opacities indicating the process of lung fibrosis.



**Figure 3.** Multiple papules and vesicles initially appeared on the area around the right breast (A) on the fourth day since the first complaint of pain, followed by bullae which appeared (B) on the seventh day, and spread to the back (C) on the tenth day.



**Figure 4.** (A-C) The appearance of the lesions on day 20 showed that the rash subsided after therapy

## DISCUSSION

As is the case with SARS and MERS-CoV infection, COVID-19 caused by SARS-CoV-2 has also been proven to increase levels of inflammatory cytokines. This cluster of inflammatory messengers which includes IL-6, IL-2, IL-7, IL-10, G-CSF, IFN- $\gamma$ , macrophage inflammatory protein 1 $\alpha$ , and TNF- $\alpha$  could indicate the occurrence of a cytokine storm.<sup>6-7</sup> IL-6 plays a role in T cell activation and proliferation, B cell differentiation, and regulation of acute phase response and hormonal activity.<sup>6</sup> Levels of IL-6 increased sharply in COVID-19 patients with critical symptoms, even up to ten times higher.<sup>1,7-8</sup>

Tocilizumab (TCZ) is an anti-inflammatory therapy that has a potential to suppress cytokine storms triggered by MAS (macrophage-activating syndrome) and has shown benefit in

the management of COVID-19 in several case studies<sup>9-12</sup> and recent systematic reviews.<sup>13-14</sup> Majority of clinical experiences support the use of TCZ in COVID-19 because the TCZ group is associated with significant reduction in mortality rate compared to that of standard therapy group, despite some of the studies being retrospective observational studies.

Tocilizumab is a monoclonal recombinant antibody against IL-6 receptors from the immunoglobulin G1k group which binds well to membrane-bound IL-6 receptors (mIL-6R) and soluble IL-6 receptors (sIL-6R). On top of that, TCZ is even said of having the capability to shift IL-6 that has been sitting on its receptor.<sup>2</sup> TCZ effectively ameliorates severe clinical symptoms in critically-ill COVID-19 patients and averts the unstoppable series of vicious cycle in a cytokine storm. Thus, TCZ can be used

as a therapeutic strategy in severe and critical COVID-19 infections, if given immediately at a severe stage.<sup>10,12,15</sup>

Serum IL-6 value was not assessed in the presented case due to laboratory limitations in health care facility. However, judging from the rapid clinical deterioration and respiratory distress, clinicians made the decision to administer TCZ in two doses. TCZ was approved for use in Japan for the first time in 2005 as a therapy for Castleman's disease, a lymphoproliferative disease that involves the expansion of the plasma cell count which is a very rare condition.<sup>16</sup> Other indications include the treatment of rheumatoid arthritis, juvenile idiopathic arthritis, giant-cell arteritis, and cytokines release syndrome induced by chimeric antigen receptor (CAR) T-cell therapy.<sup>17</sup> Its usefulness is also being studied in other conditions such as Crohn's disease, SLE, Takayasu arteritis, polymyalgia rheumatica, and refractory adult-onset Still disease.<sup>2</sup>

The main consideration for using TCZ is its immunosuppressive effect, which is a gratifying solution when given at the appropriate time to combat an excessive immune response. However, TCZ use is often linked with the risks of infection and its negative effect on lipid profile is well known. The most commonly reported adverse effects of TCZ use are infections, particularly upper respiratory tract infections, nasopharyngitis, cellulitis, herpes, and pneumonia. Gastrointestinal disorders such as nausea, abdominal pain, oral mucosal ulcers, and gastritis are also common adverse effects. Transient neutropenia is also a common adverse effect but it is less common.<sup>16,18-19</sup>

The occurrence of serious adverse effects with TCZ use was 3.8% in a study where TCZ was administered every 4 weeks for 24 weeks as indicated by rheumatoid arthritis. The most common side effect is infection (34.4%), with 4.1% of which is skin infection. The occurrence of herpes infection, although not commonly found, can occur in TCZ users.<sup>17,19-20</sup>

A study in Italy analyzed the use of Tocilizumab in COVID-19 patients with severe symptoms and found that Tocilizumab showed a reduced risk of mechanical ventilation or death. The side effects seen in the study were

mostly infection (13%), with one subject (<1%) experiencing severe reactions 12 days after subcutaneous administration of Tocilizumab, with severe liver failure due to reactivation of HSV-1, resulting in death. These patients received high doses of glucocorticoids after administration of TCZ.<sup>21</sup> Because the possibility of severe to life-threatening reactions exist, many clinicians have emphasized the importance of screening for possible reactivation of latent infections especially when glucocorticoids are used.

In other studies, no side effects of moderate or severe magnitude were observed on using Tocilizumab in COVID-19 patients with severe symptoms. However, the patients included in this particular study were only followed-up for 14 days post administration.<sup>11</sup> Many patients who experienced side effects of infection did not show fever, and the increase in CRP was insignificant or even absent due to IL-6 inhibition and suppression of the inflammatory response.<sup>19</sup> Reactivation of tuberculosis is also a challenge, especially in developing countries where the burden of tuberculosis infection is still high.<sup>15</sup> A prophylactic strategy is probably needed to diminish the risk of reactivation of infection in people with tuberculosis or who are Hepatitis B carriers.<sup>23-24</sup>

Although TCZ is only used in the acute phase of COVID-19 cases, unlike the long term of TCZ use for other indications, adverse effects remain a matter of concern. As has been described in this case report, the patient received TCZ at a dose of 8 mg/kg of body weight intravenously in two divided doses and the adverse effect appeared ten days later even though previous history of herpes zoster was denied.

In general, Tocilizumab is well tolerated, and most adverse effects are usually mild or moderate, temporary in nature, and does not lead to discontinuation of therapy.<sup>16,18-19</sup>

## CONCLUSION

Tocilizumab use seems to be effective in mitigating cytokine storm associated with severe COVID-19 infection. It can be concluded that the possibility of serious adverse effects, though rare, cannot be excluded. The presence of a latent or chronic infection that can undergo reactivation

should be a consideration for appropriate screening or prophylaxis before administering TCZ. COVID-19 patients with severe and critical symptoms are by themselves more susceptible to infection. The ideal goals of therapy are always to save lives, prevent life-threatening inflammation, and minimize possible adverse effects.

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