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Case Report

# Clinical Application of Inhaled Ciclesonide and Enoxaparin for COVID-19 Pneumonia

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SUMMARY

The novel coronavirus disease 2019 (COVID-19) pandemic is a threat to global public health. The disease is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and characterized by high transmission, high mortality, lack of effective treatment, and prolonged hospitalization. Currently, there is no clear management strategy for COVID-19 infection. Some clinical evidence suggests that the use of inhaled ciclesonide and enoxaparin subcutaneous injection maybe helpful for disease treatment. In this article, we report the successful treatment of a 65-year-old male with COVID-19 pneumonia with Inhaled corticosteroid and enoxaparin subcutaneously, which also shortened the course of the disease without significant complications.



## 1. Introduction

According to data from the Taiwan Centers for Disease Control (CDC) at March, 2021, more than 120 million people globally have been infected with the novel coronavirus disease 2019 (COVID-19), and the death toll more than 2 million.[1] The transmission rate (R0) of the SARS-CoV-2 is high, even exceeding that of the influenza virus and severe acute respiratory syndrome coronavirus (SARS-CoV).[2] COVID-19 has a prolonged clinical course because of the lack of effective management with regards to treatment. The median time from diagnosis to first negative conversion has been reported to be 17 days in asymptomatic patients and 19.5 days in symptomatic patients.[3] The global COVID-19 pandemic has placed a huge burden on medical systems worldwide.

In this article, we described a case of COVID-19 pneumonia with oxygen supply. Inhaled ciclesonide was prescribed for its inhibitory effect on SARS-CoV-2 virus replication in the early stage of disease, and subcutaneous enoxaparin was used for thromboprophylaxis due to desaturation. We treated him successfully and shorten the time from diagnosis to first negative conversion in 7 days.

## 2. Case report

A 65-year-old male had stayed in the United States with his family for 5 months before returning to Taiwan on July 20, 2020. He had no fever nor other respiratory symptoms on his arrival in Taiwan, and he was instructed to home isolate according to the policy of the Taiwan CDC.

He noted a problem with his sense of taste on July 24, 2020 (2 days before hospitalization), accompanied with poor appetite, nasal congestion, runny nose, and fatigue. He then contacted the local health bureau and was referred to our hospital emergency department for initial evaluation on July 26 (hospital day 1).

The patient's past medical history included coronary artery disease post percutaneous transluminal coronary angioplasty with stent placement, hypertension, and benign prostatic hyperplasia. He received medical treatment except anticoagulants. In the emergency department, his vital signs were as follows: temperature, 37.4 °C; pulse, 96 beats/min; respiratory rate, 18 breaths/min; blood pressure, 197/104 mmHg; and oxygen saturation under room air, 98%. The results of laboratory test of patient were as follows: white blood cell count, 7000 cells/μL; neutrocytes, 5327 cells/μL; lymphocytes, 847 cells/μL; neutrophil-lymphocyte ratio (NLR), 6.3; C-reactive protein, 2.44 mg/dL; and lactate dehydrogenase (LDH), 195 IU/L. A chest X-ray (CXR) revealed hazy infiltration in both lower lung fields, suspect hypoventilation related (Figure 1). A nasopharyngeal swab was collected for SARS-CoV-2 real-time reverse transcription-polymerase

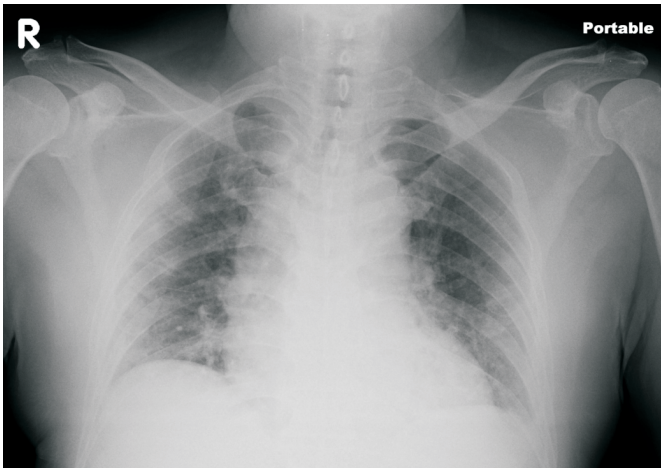


**Figure 1.** CXR on hospital day 1 showed hazy infiltration in both lower lung fields, suspect hypoventilation related. CXR: chest X-ray.

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chain reaction (rRT-PCR) at the emergency room, and he was admitted to an isolation ward for observation on the same day (July 26, hospital day 1). A positive SARS-CoV-2 test result was confirmed the next day (hospital day 2).

After admission, several therapeutic options were discussed with the patient. He declined the use of hydroxychloroquine because of one side effect. Therefore, supportive treatment was given. The patient felt dizziness with desaturation (pulse oximetry 94% under room air) at hospital day 2, then intermittent oxygen supply (nasal cannula at 2 L/min) was given to keep oxygen saturation greater than 94%. And inhaled ciclesonide (160 mcg/dose) 3 puff q8H was given for 2 weeks since hospital day 2.

Desaturation episode was noted again at midnight of hospital day 3, (pulse oximetry 88% under room air), which recovered to 98% with the use of a nasal cannula at 2 L/min. D-dimer level was checked at day 3 and showed elevated (744 ng/mL). Enoxaparin 30 mg Q12H subcutaneously was prescribed for 1 week due to concerns of a pulmonary embolism cause by COVID-19 infection. Chest computed tomography (CT) was performed on the same day, which showed discrete ground glass opacity (GGO) with reticulation involving the subpleural regions of both lungs, predominantly in the upper and middle lung, compatible with a typical presentation of COVID-19 pneumonia (Figure 2a).

His symptoms improved after treatment, and his abnormal taste began to recover. There was no recurrence of desaturation. He was able to breath well without oxygen supply from hospital day 4. A subsequent rRT-PCR assay became negative on hospital day 7 (nasopharyngeal swab and oropharyngeal swab), hospital day 9 (nasopharyngeal swab and oropharyngeal swab) and hospital day 10 (oropharyngeal swab and sputum). Due to administrative regulation policy, the patient was discharged on hospital day 16. Following chest CT at four days after discharge showed bilateral improvements in GGO (Figure 2b).

## 3. Discussion

We reported a patient with confirmed COVID-19 pneumonia, he recovered without significant complication and was discharged from the hospital in the short time after inhaled ciclesonide and enoxaparin using.

Based on previous experience in treating severe acute respiratory syndrome coronavirus (SARS) and middle east respiratory syndrome (MERS), a variety of antiviral medications have been tried, but none has achieved a satisfactory response. Lopinavir/ritonavir treatment could not significantly reduce mortality in clinical trials, and it was accompanied by a higher rate of side effects.[4] Remdesivir has been shown to shorten the clinical course in some patients, but not mortality.[5] Tocilizumab, an anti-IL-6 receptor antibody, has shown promise in observational studies, however randomized clinical trials are still needed to confirm its efficacy.[6] Medications that inhibit virus replication and immune modulation such as hydroxychloroquine +/- azithromycin have been widely used, however most large-scale studies have shown that such treatment does not significantly reduce mortality, and in some cases increases the risk of arrhythmia.[7] Currently, only dexamethasone at a dose of 6 mg once daily for up to 10 days has been shown to reduce 28-day mortality in patients with COVID-19 who are receiving respiratory support.[8]

SARS-CoV-2 induces excessive and prolonged proinflammatory cytokine/chemokine responses in some patients, known as a "cytokine storm". Cytokines may induce acute respiratory distress syndrome (ARDS) or multiple-organ dysfunction, which leads to a high mortality rate.[9] Corticosteroids have anti-inflammatory function and are widely used to treat severe inflammation caused by viral infections (including SARS-CoV-2, SARS-CoV, middle east respiratory syndrome coronavirus (MERS-CoV) and influenza virus), however systemic treatment with corticosteroids is not recommended for patients with severe pneumonia caused by viruses such as MERS-CoV and SARS-CoV, as steroids suppress the innate immune system resulting in increased viral replication.[10] Unlike SARS-CoV, viral shedding in SARS-CoV-2 peaks before symptoms appear,[11] a stage at which the disease may be dominated by immunopathological elements, with active viral replication playing a secondary role.[8] Besides anti-inflammation, some steroid compounds block coronavirus replication. Eight steroid compounds were tested in Vero cell cultures of SARS-CoV-2 and MERS-CoV, and ciclesonide was presumed to interact with viral nonstructural protein 15 (NSP15) to suppress viral replication of SARS-CoV-2 without significant complications.[10] Several case reports from Japan have suggested that inhaled ciclesonide could ameliorate fever and oxygenation in COVID-19 patients.[12,13] The treatment of inhaled ciclesonide was also suggested in Japan's guideline.[14] Currently a phase III trial[15] is ongoing for this application.

The other characteristic of COVID-19 are hypercoagulability with both microangiopathy and local thrombus formation. Viral infection induces systemic inflammation and cytokine production then stimulate procoagulant reaction.[16] In a review article, the overall incidence and mortality rate of COVID-19 patients developing pulmonary embolism was 15.3% and 45.1%.[17] Other researcher suggested that thromboprophylaxis should be started in all patients with sus-

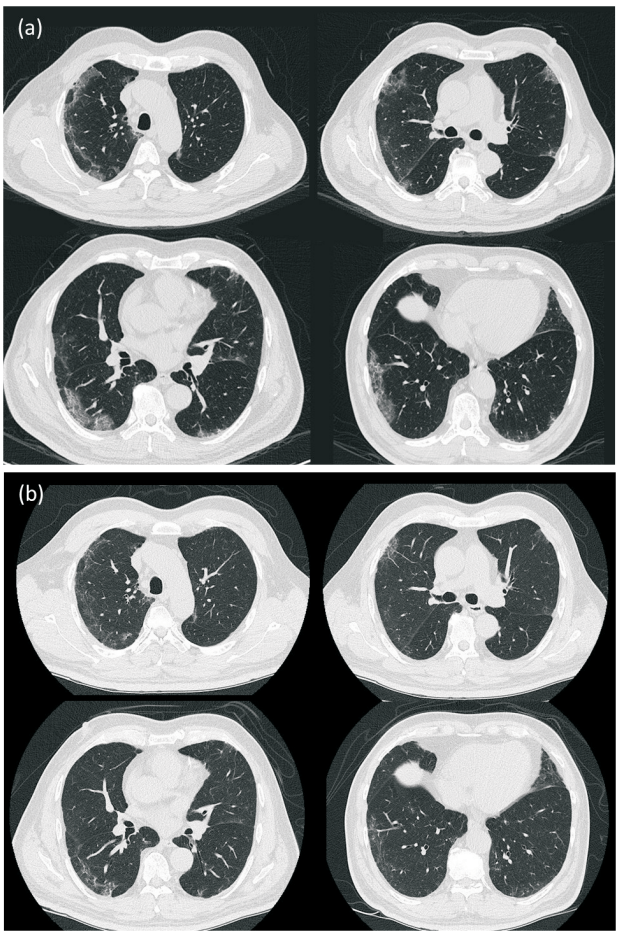


**Figure 2.** (a) Chest CT on hospital day 3 showed bilateral subpleural GGO involving predominantly the upper and middle lung. (b) Chest CT four days after discharge showed bilateral improvements in GGO. CT: computed tomography; GGO: ground glass opacity.

pected or confirmed COVID-19 admitted to the hospital, especially those with multiple risk factors for venous thromboembolism. The prophylactic dose of enoxaparin vary from 40 mg every day to 40 mg every 12 hours.[18] Besides thromboprophylaxis, enoxaparin may had potential effect in prevention of SARS CoV-2 infection by decreasing virus cell entry and hence viral load.[19] In our patient, his symptoms and hypoxemia improved after ciclesonide and enoxaparin treatment, and the rRT-PCR result was negative on hospital day 7 after treatment, which is shorter than that reported for patients receiving other treatments.[2] We believed this combination deserve further investigation.

In conclusion, the early use of inhaled ciclesonide and enoxaparin may relieve symptoms and shorten the clinical course in symptomatic COVID-19 patients. Further studies are needed to validate its clinical efficacy.

## Declaration

The authors have no affiliation with or involvement in any organization or entity with any financial interest.

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