Pneumonia rebound after stopping steroid in a patient with COVID-19: A case report

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Abstract
Patients with severe coronavirus disease 2019 (COVID-19) can develop a systemic inflammatory response that can lead to lung injury and multisystem organ dysfunction. The current treatment guideline recommends the use of corticosteroids in patients who require supplemental oxygen or are mechanically ventilated. This study reports a patient with severe COVID-19 pneumonia. Initially, the patient was treated with dexamethasone for 10 days and remdesivir for 5 days. There was clinical improvement following the treatments. However, on day 15, the patient experienced rebound pneumonia and clinical deterioration. His clinical condition improved until dexamethasone was re-administered. This case demonstrates the rebound phenomenon after the steroid was discontinued. The duration and timing of steroids are crucial to reduce the risk of prolonged systemic inflammation and rebound pneumonia.

KEYWORDS
corticosteroid, COVID-19, pneumonia, rebound

INTRODUCTION
Coronavirus disease 2019 (COVID-19) is a disease that can cause systemic hyperinflammation. Therefore, immunomodulatory agents that inhibit an excessive inflammatory response, such as corticosteroids, play a key role in treating patients with severe COVID-19.1 The current guideline recommends using 6 mg dexamethasone for up to 10 days to treat COVID-19 in hospitalized patients who require oxygen.2 However, a rebound phenomenon has been reported after treating patients with COVID-19 with standard corticosteroids.3 Here, we report a patient with COVID-19 who was recovering following steroid treatment but experienced rebound pneumonia after the steroid was discontinued.

CASE REPORT
A 78-year-old male presented to our institution with fever and myalgia for 1 day. He subsequently tested positive for COVID-19. He desaturated to 91% under room air requiring supplemental oxygen. Chest x-ray (CXR) showed bilateral lower lung ground-glass opacity (Figure 1; CXR day 1). He was given intravenous dexamethasone (6 mg from days 1 to 10), remdesivir (from days 4 to 8) and empirical antibiotics (ceftriaxone from days 1 to 5 and levofloxacin from days 2 to 12). Clinical symptoms and saturation level improvement were noted following treatment. However, his symptoms worsened at day 15, where CXR revealed progressed bilateral consolidation (Figure 1; CXR day 15). Laboratory examination showed that his C-reactive protein level was increasing again and that his reverse transcription-polymerase chain reaction cycle threshold (Ct) value was 19.75 (Figure 1). The procalcitonin level was in the normal range. His clinical condition deteriorated, even though he was administered broad-spectrum antibiotics (teicoplanin from days 15 to 21 and cefoperazone/sulbactam from days 12 to 21). Therefore, we re-administered 6 mg dexamethasone from days 15 to 30. This improved his supplemental oxygen requirement, radiological findings (Figure 1; days 19 and 25) and...
laboratory examination results (Table 1), and he showed symptomatic improvement following the treatment. He was discharged on day 30 with tapering to a low dose of corticosteroid (10 mg oral prednisolone for 3 weeks).

**FIGURE 1** Clinical course. The patient received empirical antibiotics and 6 mg dexamethasone between days 1 and 10 of hospitalization because of pneumonia with desaturation. CXR on day 5 remained stationary, and his clinical symptoms gradually improved. Dexamethasone was discontinued after 10 days of treatment. On day 15, his clinical symptoms deteriorated, and the CXR revealed worsening bilateral peripheral infiltrates. After re-administration of systemic corticosteroid therapy on days 15–30, the CXR images, CRP levels and PCR Ct value displayed immediate improvement. CRP, C-reactive protein; Ct, cycle threshold; CXR, chest x-ray; PCR, polymerase chain reaction; SpO₂, oxygen saturation.
DISCUSSION

In this study, we reported that a 78-year-old male with severe COVID-19 pneumonia experienced rebound pneumonia after being treated with a standard course of corticosteroid. The hypoxia, inflammatory markers and radiographic findings improved after dexamethasone was re-administered. This implies that the duration of steroid treatment may not be sufficient to reduce prolonged systemic inflammation and prevent rebound pneumonia in some patients.

The causes of rebound pneumonia are not well understood. However, delayed viral clearance caused by prolonged cytokine release syndrome is a possible mechanism. To et al.\textsuperscript{5} reported that seroconversion occurs between 4 and 40 days following symptom onset. This prolonged humoral and cytokine response is considered to be related to delayed interferon (IFN) release compared to other typical viral infections (COVID-19 3 weeks vs. other viruses 1–2 weeks).\textsuperscript{6} Channappanavar et al.\textsuperscript{7} demonstrated that when mice with severe acute respiratory syndrome coronavirus (SARS-CoV) were administered IFN early in the disease course, there was no immunopathology, while administration later resulted in elevated lung cytokine levels, vascular leakage and impaired virus-specific T-cell responses. As T-cell response is required for SARS-CoV clearance, delayed IFN signalling promotes the accumulation of pathogenic inflammation and delayed viral clearance. Similarly, in SARS-CoV-2, a delayed peak IFN level is also observed, and both viruses may share similar pathogenesis of delayed cytokine release syndrome and viral clearance.

Secondary organizing pneumonia (OP) is considered to be another cause of rebound pneumonia. Previous studies have reported a correlation between secondary OP and highly contagious viruses infections such as SARS, Middle East respiratory syndrome and influenza A. It is possible that, as has been described with other viruses, secondary OP in the setting of COVID-19 represents a dysregulated immune response after initial infection. Chong et al.'s review\textsuperscript{8} included three case series that described secondary OP diagnosis among hospitalized COVID-19 patients with histopathological confirmation. According to the study,

\begin{table}[h]
\centering
\caption{Laboratory data during hospitalization}
\begin{tabular}{lccccc}
\hline
 & Day 1 & Day 7 & Day 12 & Day 16 & Day 23 \\
\hline
\textbf{Complete blood count} & & & & & \\
White blood cell count (per $\mu l$) & 8700 & 8900 & 14,800 & 10,100 & 8300 \\
Neutrophil (%) & 92.3 & 86.9 & 94.5 & 91.3 & 83.5 \\
Lymphocyte (%) & 5.5 & 7.1 & 2.6 & 4.9 & 8.8 \\
Monocyte (%) & 2.1 & 5.9 & 2.7 & 3.7 & 6.2 \\
Eosinophil (%) & 0 & 0 & 0.1 & 0 & 1.4 \\
Red blood cell count (per $\mu l$) & $458 \times 10^4$ & $465 \times 10^4$ & $496 \times 10^4$ & $396 \times 10^4$ & $455 \times 10^4$ \\
Haemoglobin (g/dl) & 14.8 & 15 & 15.9 & 12.8 & 14.6 \\
Haematocrit (%) & 41.7 & 43.8 & 45.4 & 36.6 & 43.2 \\
Platelets count (per $\mu l$) & $158 \times 10^3$ & $234 \times 10^3$ & $238 \times 10^3$ & $217 \times 10^3$ & $350 \times 10^3$ \\
\hline
\textbf{Coagulation system} & & & & & \\
D-dimer (mg/L FEU) & 0.34 & 4.38 & 2.5 & 2.23 & 917 \\
PT (s) & 10.1 & & & & \\
APTT (s) & 32.4 & & & & \\
\hline
\textbf{Blood chemistry} & & & & & \\
C-reactive protein (mg/L) & 47.16 & 19.99 & 33.1 & 37.21 & 2.74 \\
Ferritin (ng/ml) & 632 & 1133 & & & 917 \\
Procalcitonin (ng/ml) & 0.07 & & & & 0.16 \\
Urea nitrogen (mg/ml) & 31.6 & 34.4 & & & 33.4 \\
Creatinine (mg/ml) & 1.47 & 1.1 & 1.05 & 0.89 & \\
Sodium (mEq/ml) & 131 & 140 & 140 & & \\
Potassium (mEq/ml) & 4.7 & 4.8 & 4.6 & & \\
Aspartate aminotransferase (U/L) & 21 & 34 & & & \\
Alanine aminotransferase (U/L) & 18 & 41 & & & \\
Lactate dehydrogenase (U/L) & 197 & 339 & 265 & & \\
Alkaline phosphatase (U/L) & 61 & 60 & & & \\
Albumin (g/dl) & 3.32 & 2.96 & & & \\
\hline
\end{tabular}
\end{table}

Abbreviations: APTT, activated partial thromboplastin time; FEU, fibrinogen equivalent units; PT, prothrombin time.
Histopathological findings of OP were found in 27%–44% of cases after 2 weeks of hospitalization, which helps explain the favourable response to immunosuppressive therapy of corticosteroids. A high clinical suspicion should exist for secondary OP when clinical deterioration occurs in people with COVID-19 when radiological findings are compatible, especially in patients with recent cessation of corticosteroid therapy. Secondary OP can be highly suspected in this patient. However, no lung histopathology or chest computed tomography has been conducted to confirm OP. Therefore, the broad term of rebound pneumonia is used.

Concerns exist that the recommended dose of 6 mg dexamethasone daily for 10 days is insufficient to achieve complete remission or prevent relapse. Imai et al. reported that patients with rebound pneumonia (about 8% of patients) tend to receive corticosteroids for a shorter time and suggested that steroids be administered for a sufficient period to reduce prolonged systemic inflammation.

A prolonged period of corticosteroids treatment beyond the recommended 10-day course may further suppress an inflammatory burst in patients with COVID-19, thus achieving complete remission and preventing the development of rebound pneumonia. However, the benefit–risk of prolonged corticosteroid treatment should be carefully evaluated. The optimal duration and dose of steroids for rebound pneumonia cannot be determined due to limited data. A large and well-designed study should be conducted that explores this issue.

Our study demonstrated the clinical characteristics of rebound pneumonia in a patient with severe COVID-19 treated with standard corticosteroids. The re-administration of steroids is crucial in patients with the rebound phenomenon to reduce prolonged systemic inflammation and improve their clinical condition.

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CONFLICT OF INTEREST
None declared.

AUTHOR CONTRIBUTION
Po-Hao Chen prepared the first draft of this paper under the supervision of Chung-Chieh Yu. Chung-Chieh Yu, Chun-Yuan Cheng and Li-Fu Li contributed to the revision of the manuscript and final approval of the version to be published.

ETHICS STATEMENT
The authors declare that appropriate written informed consent was obtained for the publication of this manuscript and accompanying images.

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REFERENCES
1. Horby P, Lim WS, Emberson JR, Mathem M, Bell JL, Linsell L, et al. Dexamethasone in hospitalized patients with Covid-19. N Engl J Med. 2021;384:693–704.
2. COVID-19 Treatment Guidelines Panel Coronavirus disease 2019 (COVID-19) treatment guidelines. National Institutes of Health. [cited 2021 Aug 31]. Available from: https://www.covid19treatmentguidelines.nih.gov/.
3. Imai R, Ro S, Tomishima Y, Nishimura N. Steroid resistance and rebound phenomena in patients with COVID-19. Respir Investig. 2021;59:608–13.
4. Moore JB, June CH. Cytokine release syndrome in severe COVID-19. Science. 2020;368:473–4.
5. To KK, Tsang OT, Leung WS, Tam AR, Wu TC, Lung DC, et al. Temporal profiles of viral load in posterior oropharyngeal saliva samples and serum antibody responses during infection by SARS-CoV-2: an observational cohort study. Lancet Infect Dis. 2020;20:565–74.
6. Chau AS, Weber AG, Maria NI, Narain S, Liu A, Hajizadeh N, et al. The longitudinal immune response to coronavirus disease 2019: chasing the cytokine storm. Arthritis Rheumatol. 2021;73:23–35.
7. Channappanavar R, Fehr AR, Vijay R, Mack M, Zhao J, Meyerholz DK, et al. Dysregulated type I interferon and inflammatory monocyte-macrophage responses cause lethal pneumonia in SARS-CoV-infected mice. Cell Host Microbe. 2016;19:181–93.
8. Chong WH, Saha BK, Chopra A. Does COVID-19 pneumonia signify secondary organizing pneumonia?: a narrative review comparing the similarities between these two distinct entities. Heart Lung. 2021;50:667–74.

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