

[CASE REPORT]

Delayed-onset Organizing Pneumonia Emerging after Recovery from Coronavirus Disease 2019: A Report of Three Cases Diagnosed Using Transbronchial Cryobiopsy and a Review of the Literature

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Abstract:

We present three cases with an atypical clinical course of organizing pneumonia (OP) secondary to coronavirus disease 2019 (COVID-19). Three patients were discharged with satisfactory improvement after standard steroid therapy for COVID-19. Shortly after the completion of treatment, the patients experienced a flare-up of symptoms. Imaging results showed new lesions in the lungs. Transbronchial lung cryobiopsy showed histological findings consistent with OP in all cases. Steroids were administered, and a good therapeutic response was observed.

This report is the first to describe pathologically confirmed OP that developed after recovery from COVID-19. Careful follow-up is advisable for patients who have recovered from COVID-19.

Key words: COVID-19, organizing pneumonia, transbronchial cryobiopsy, steroid therapy, case report

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Introduction

Coronavirus disease 2019 (COVID-19), which is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), continues to spread worldwide. As various treatment methods have evolved and vaccination has progressed, the situation surrounding COVID-19 has entered a new phase. However, persistent sequelae after recovery from COVID-19, called long-COVID, have become a serious concern. Moreover, interstitial lung disease (ILD) secondary to COVID-19 leads to long-term loss of the respiratory function, and appropriate interventions need to be implemented, even after acute treatment (1, 2). We previously reported a case of COVID-19 with rapidly progressive organizing pneumonia (OP) (3). OP is now widely recognized as a condition secondary to COVID-19, which may explain the im-

portance of corticosteroid use in treating COVID-19. Based on the findings of studies exemplified by the RECOVERY trial, corticosteroids have been used as standard treatment for COVID-19 (4). However, little is known about the effect of steroid therapy on OP secondary to COVID-19. We herein present three cases of COVID-19 pneumonia in which the patients were treated with steroids and discharged with satisfactory improvement but later developed OP. Notably, all cases were histologically examined using transbronchial lung cryobiopsy (TBLC). To the best of our knowledge, our report of these three cases is the first to describe the development of pathologically confirmed OP after recovery from COVID-19. We also discuss the previous reports on OP secondary to COVID-19.

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Table 1. Laboratory Findings in the Three Cases.

	Case 1		Case 2		Case 3	
	Initial admission	Readmission	Initial admission	Readmission	Initial admission	Readmission
Blood tests	(Day 10)	(Day 33)	(Day 6)	(Day 44)	(Day 14)	(Day 39)
WBC (μL)	5,100	7,300	2,300	6,900	4,900	11,000
Hb (g/dL)	14.6	13.0	13.8	13.6	15.6	14.0
Plt ($\times 10^4/\mu\text{L}$)	18.3	22.0	12.6	24.7	19.6	31.7
LDH (U/L)	395	305	265	310	362	228
CRP (mg/dL)	7.6	6.9	3.3	6.5	1.3	13.2
KL-6 (U/mL)	293	471	337	771	438	455
SP-D (ng/mL)	44.2	182.6	27.9	259.1	74.5	27.8
Bronchoalveolar lavage fluid	(Day 34)		(Day 45)			
Recovery (%)	67		35		NA	
Total cells (/mL BALF)	107.5×10^4		45×10^4		NA	
Macrophages (%)	14.5		20.0		NA	
Lymphocytes (%)	78.5		76.3		NA	
Neutrophils (%)	2.8		0.3		NA	
Eosinophils (%)	3.8		3.3		NA	
Others (%)	0.5		0		NA	
CD4/CD8	2.06		3.93		NA	

WBC: white blood cell, Hb: hemoglobin, Plt: platelet, LDH: lactate dehydrogenase, CRP: C-reactive protein, KL-6: Krebs von den Lungen-6, SP-D: surfactant protein-D, BALF: bronchoalveolar lavage fluid, CD: cluster of differentiation, NA: not applicable

Case Reports

In this report, we describe, in detail, the cases of three patients who fully recovered from COVID-19 and who later presented with OP. The laboratory and imaging findings for each case are summarized in Table 1 and Fig. 1.

Case 1

The patient was a 61-year-old man with a history of hypertension and hyperlipidemia. He developed fever and cough and was found to be polymerase chain reaction (PCR)-positive for SARS-CoV-2 on the second day of illness. He was admitted to hospital due to persistent fever. He developed respiratory failure on day 10. Chest radiography revealed bilateral pneumonia. After ten days of treatment with dexamethasone (6 mg/day), the patient was discharged from the hospital with no deterioration. However, on day 31, the patient reported fever, dyspnea on exertion, and malaise, with new infiltration appearing on chest X-ray. Computed tomography (CT) revealed diffuse ground-glass opacity (GGO) and infiltration, and the patient was readmitted to the hospital. PCR for SARS-CoV-2 was negative. Bronchoalveolar lavage (BAL) on day 34 showed an elevated total cell count and lymphocyte fraction in BAL fluid (BALF); the BALF culture was negative. On day 38, TBLC of the lungs was performed. The results showed diffuse and mild thickening of the alveolar septa, suggestive of a histological non-specific interstitial pneumonia pattern, as well as intra-alveolar lymphocytic infiltration and fibrohistiocytic proliferation (shown in Fig. 2). Intra-alveolar fibrinous exudates

were observed in some areas. These findings were consistent with clinical manifestations of OP. The patient was treated with prednisolone (0.5 mg/kg/day), which resulted in the improvement of symptoms and the disappearance of the abnormal shadows in the lungs. The dose of prednisolone was gradually tapered and discontinued 5 months after the initiation. The patient has not shown any signs of relapse.

Case 2

The patient was a 79-year-old woman with pre-existing diabetes and hypertension who developed fever and anorexia and was diagnosed with COVID-19 based on PCR testing. On the sixth day of illness, she was admitted to hospital because of hypoxemia, and treatment with dexamethasone (6 mg/day) and remdesivir was initiated. Her oxygen demand increased on day 8; thus, the steroid was changed to methylprednisolone (2 mg/kg/day), and a single dose of tocilizumab (8 mg/kg) was administered. Her respiratory status improved soon after, and oxygen support was no longer required on day 13. The dose of methylprednisolone was reduced by half every 3 days and was stopped 15 days after the initiation. The patient's symptoms and radiological findings significantly improved, and she was discharged from the hospital. However, dyspnea and fatigue were reported on day 33, which was 10 days after the completion of steroid therapy. Comparison with X-ray films obtained before discharge revealed a marked worsening and the new emergence of shadows. CT showed GGO and infiltrative shadows in both lungs with traction bronchiectasis. The cycle threshold value of the SARS-CoV-2 saliva PCR test was above 35, indicating no infectivity or activity. TBLC of the lungs was

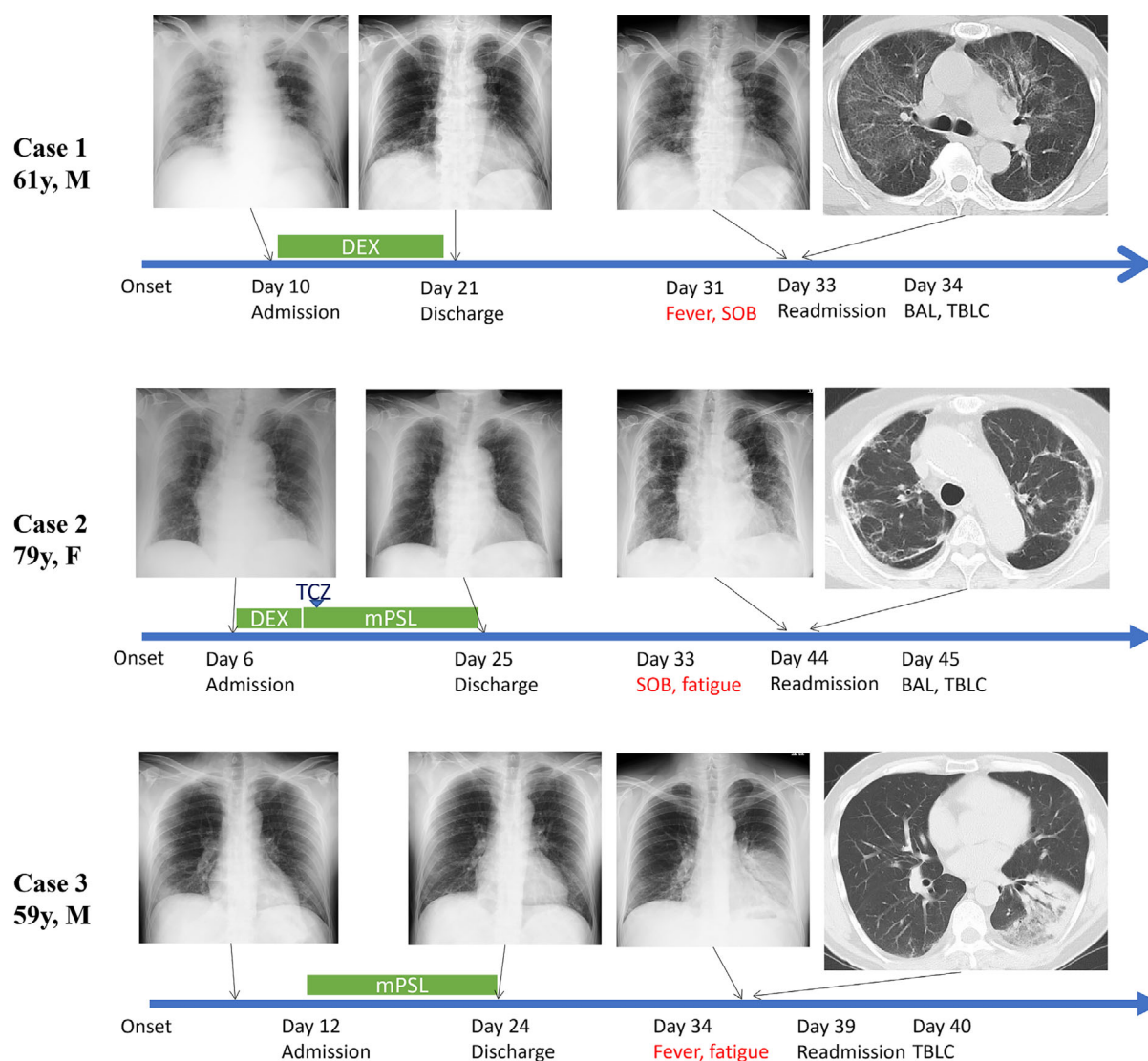


Figure 1. A schematic illustration of the clinical course and imaging findings in each case. BAL: bronchoalveolar lavage, DEX: dexamethasone, mPSL: methylprednisolone, SOB: shortness of breath, TBLC: transbronchial lung cryobiopsy, TCZ: tocilizumab

performed on day 45. It revealed intra-alveolar fibroblastic plugs in the peribronchiolar areas and lymphohistiocytic infiltrate in the adjacent alveolar spaces (shown in Fig. 3). A BAL analysis revealed an elevated total cell number and increased lymphocyte fraction. No pathogens were detected in the BALF. The patient was diagnosed with OP, and treatment with prednisolone (0.5 mg/kg/day) was initiated. The prednisolone dose was gradually tapered due to a favorable response to treatment.

Case 3

The patient was a 59-year-old man with a history of diabetes, in whom a diagnosis of COVID-19 was confirmed. He was admitted to hospital for oxygen administration 12 days after the onset of illness. Methylprednisolone (2 mg/kg/day), remdesivir, and heparin were administered. Since oxygen was no longer required 3 days after the commencement of treatment, the steroid dosage was halved every three days, and the treatment was completed after 13 days (day

24). The patient was discharged, but he developed fatigue and fever 10 days after the end of treatment (day 34). Since the fever persisted, the patient visited our hospital on day 36. At this time point, blood tests revealed an elevated inflammatory response, and both X-ray and CT showed a localized infiltrative shadow in the left lower lobe. Despite the prescription of amoxicillin/clavulanic acid, his condition did not improve, and he was admitted on day 39. Viral RNA was not detected in a saliva sample by PCR. On day 40, we performed TBLC to investigate the infiltrative shadows in the left lower lobe. A histopathological examination revealed prominent airspace obliteration by fibrinous exudate admixed with lymphohistiocytic accumulation. Diffuse and mild thickening of the alveolar septa were also observed, but few neutrophils or eosinophils were seen. Intra-alveolar fibromyxoid plugs were not observed. These findings were interpreted as an early stage of OP (shown in Fig. 4). Given that no significant bacteria were detected in the sputum after bronchoscopy, we started the administration of prednisolone

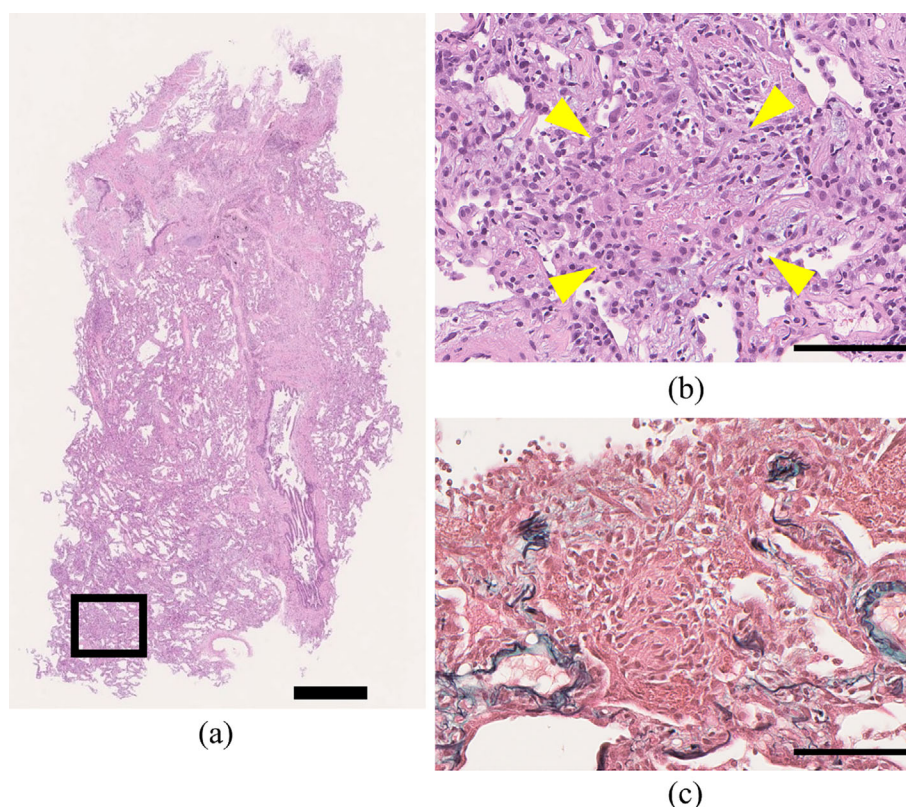


Figure 2. Photomicrograph of a TBLC tissue sample in Case 1. (a) A loupe view showing diffuse obliteration of the alveolar airspace [Hematoxylin and Eosin (H&E) staining, bar=1 mm]. The rectangle represents a view field of (b) and (c). (b) and (c) are high power views showing mild thickening of the alveolar septa, intra-alveolar lymphocytic infiltration, and fibrohistiocytic proliferation [(b) H&E staining; (c) Elastica-Masson staining; original magnification 10 \times , bar=0.1 mm]. TBLC: transbronchial lung cryobiopsy

(0.5 mg/kg/day). Significant improvements in the patient's symptoms and in the infiltrative shadows in the lungs were observed.

Discussion

We describe the clinical course of histologically-confirmed, delayed-onset organizing pneumonia that developed after recovery from COVID-19.

According to reports on the pathological examination of autopsied cases, diffuse alveolar damage (DAD) is frequently seen in severe COVID-19 pneumonia, and the lesions often have coexisting OP (5, 6). However, these manifestations represent the pathogenesis of fatal COVID-19 cases, and it is unclear what the main pathogenesis is in patients who have recovered from COVID-19 and survived. Owing to the accumulation of several valuable case reports, including our previous report, the clinical presentation of OP secondary to COVID-19 has been widely recognized (3, 7-12). Although there is no systematic review of the histopathology or cytology of secondary OP (SOP) caused by COVID-19, these cases were thought to have been mainly immune reactions that triggered fibrin accumulation and granuloma proliferation rather than leakage of

fluid and protein accumulation directly caused by lung injury, as occurs in DAD (13). This pathogenesis of SOP, which is not fatal and which shows a good response to treatment, has also been reported in influenza (14).

In this study, Cases 1 and 2 underwent BAL, and an elevated total cell count and lymphocyte fraction were observed. The addition of detailed histopathological examination by TBLC confirmed the absence of findings of DAD and allowed for a more reliable diagnosis of OP. In Case 3, BAL was not performed, and based on the histological examination of the TBLC tissue sample, the differential diagnosis included acute fibrinous and organizing pneumonia (AFOP) at this time. According to autopsy case studies, AFOP is a rare condition in COVID-19 pneumonia (15), and it has been considered a severe variant of OP in recent studies (16). However, Case 3 showed a satisfactory response to steroid therapy, which finally led to the clinical diagnosis of OP.

We believe that TBLC was the key to allowing a detailed pathological study of all cases. Transbronchial lung biopsy (TBLB), which is often used to diagnose OP, is not sensitive enough and may fail to prove the pathology. On the other hand, TBLC shows significantly greater diagnostic accuracy for ILD than TBLB because of the larger volume of the

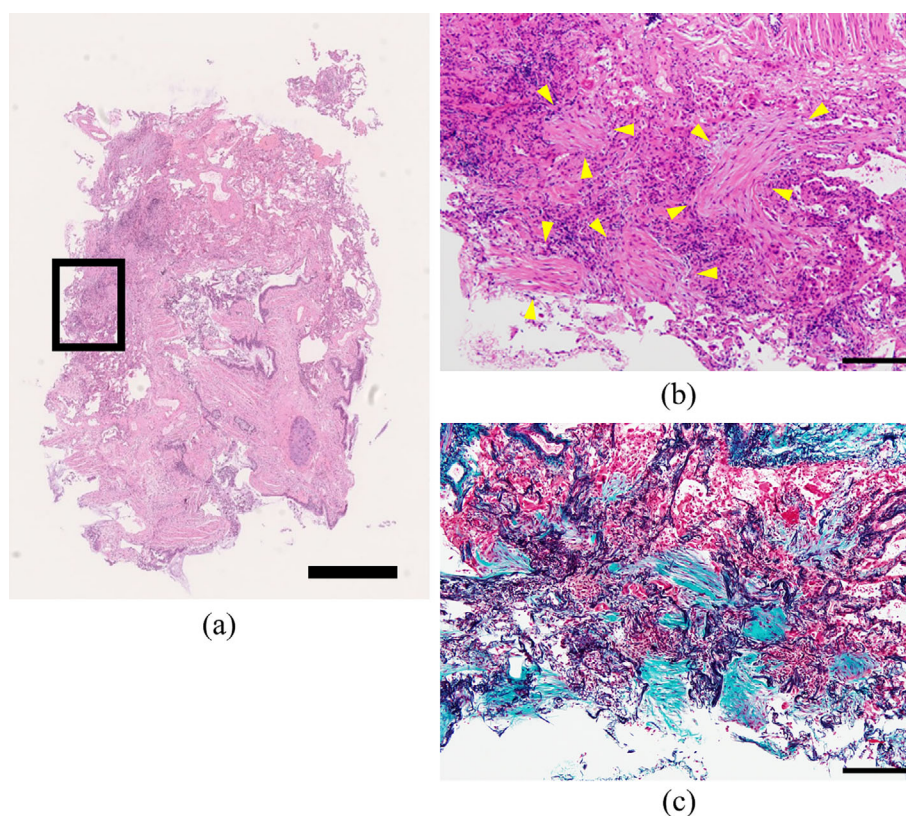


Figure 3. Photomicrograph of a TBLC tissue sample in Case 2. (a) A loupe view showing the peribronchiolar distribution of the lesion [Hematoxylin and Eosin (H&E) staining, bar=1 mm]. Each rectangle represents a view field of (b) and (c). (b) and (c) are high power views showing intra-alveolar fibroblastic plugs and lymphohistiocytic infiltration in the adjacent alveolar spaces [(b) H&E staining; (c) Elastica-Masson staining; original magnification 10 \times , bar=0.2 mm]. TBLC: transbronchial lung cryobiopsy

sample (17). As demonstrated in Figs. 2-4, the tissue fragments were large, which allowed for easier evaluation of the disease distribution. Aggressive TBLC should be considered when conducting biopsies.

In our cases, we did not search for SARS-CoV-2 in the BALF or lung tissue. Thus, we could not determine whether the virus was directly involved in the pathophysiology of organizing pneumonia. Although it has been previously shown that direct lung damage caused by SARS-CoV-2 is transient and does not persist throughout the course of disease progression (18), this is a limitation of the pathological examinations in our cases.

Our cases provided two important insights: i) COVID-19 can cause delayed-onset OP despite adequate recovery after the completion of standard treatment; ii) in view of such cases, careful follow-up is advisable for patients who have made a complete recovery.

All three cases showed sufficient improvement in respiratory status with short-term steroid treatment for COVID-19, and the patients were discharged without the need for oxygen support. However, after discharge, they developed OP, which was diagnosed both clinically and pathologically. Most previous studies have shown that patients with prolonged respiratory symptoms and lung infiltration after se-

vere COVID-19 responded well to steroid therapy (3, 7, 11, 12). However, many of these cases were reported at a time when the efficacy of steroid therapy for COVID-19 had not been demonstrated. With the generalization of the use of systemic steroid therapy as the standard treatment for COVID-19 pneumonia, the clinical course of “classical” OP secondary to COVID-19 is becoming rare.

There have been several case reports of patients who received steroids as the initial treatment for COVID-19 pneumonia; however, they failed to recover and were finally diagnosed with OP. A summary of these cases is presented in Table 2. Kanaoka et al. and Takumida et al. reported the successful diagnosis of OP using BAL and lung biopsy in COVID-19 pneumonia in patients who showed poor improvement after steroid treatment (8, 10). It can be interpreted that the OP that emerged in their cases was a persistent condition that was present from the onset of COVID-19. In contrast, Kostroz-Nosal et al. reported two cases in which short-term steroid therapy for COVID-19 pneumonia resulted in a temporary recovery, but in which the respiratory symptoms flared up over time (9). However, histological evidence was lacking in those cases. To the best of our knowledge, there have been no reports of pathologically confirmed OP that developed after recovery from COVID-19.

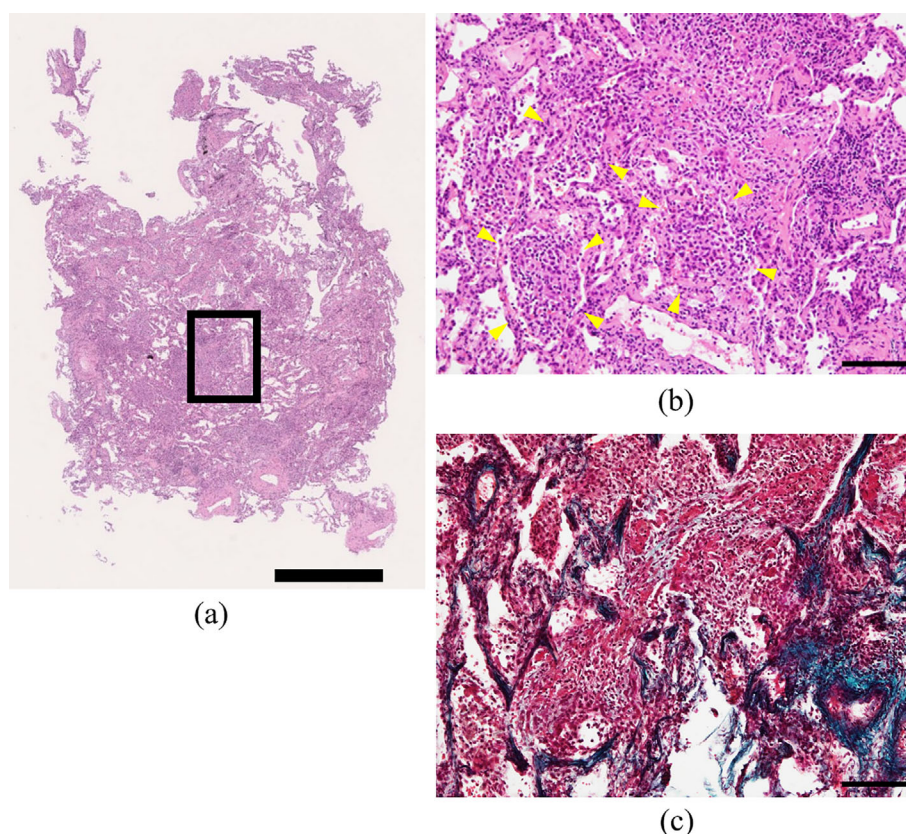


Figure 4. Photomicrograph of a TBLC tissue sample in Case 3. (a) A loupe view showing diffuse obliteration of the alveolar airspace [Hematoxylin and Eosin (H&E) staining, bar=1 mm]. Each rectangle represents a view field of (b) and (c). (b) and (c) are high power views showing prominent airspace obliteration by fibrinous exudate admixed with lymphohistiocytic accumulation [(b) H&E staining; (c) Elastica-Masson staining; original magnification 10 \times , bar=0.2 mm]. TBLC: transbronchial lung cryobiopsy

Two pathologies can be considered in our cases. First, it is possible that the OP seen in our patients was temporarily masked due to the use of steroids and that it became apparent only after the steroid effect wore off. Now that steroids are being administered earlier as standard treatment, some patients who recover from COVID-19 may follow the course of partially treated OP. Chong et al. pointed out that 10 days of dexamethasone in cases of secondary OP might not be sufficient treatment; thus, they advocated longer steroid treatment (7). The cases reported in this study may illustrate their concerns. In addition, although infection with SARS-CoV-2 was undoubtedly the trigger, in these cases there may have been a long interval from viral exposure to the onset of OP. As secondary OP is typically caused by drugs, some time may exist between exposure to the causative agent and the onset of disease (19, 20). Influenza-induced SOP may occur 2-3 weeks after the onset of viral infection (14). In a study of SOP due to various causes, including infectious diseases, the median time from the onset to hospitalization was 1 week, which is significantly shorter than cryptogenic OP (21). In our cases, the manifestation of symptoms in the form of OP occurred 31-34 days after the onset of COVID-19, which seems to be longer than SOP caused by other infections. In cases involving a potentially similar condition,

the development of OP took approximately 30 days or more, although the cases were not described in detail (9). One possibility is that these cases may represent a novel phenotype of COVID-19 that remains unrecognized. Further reports or and the accumulation of further cases will help clarify this.

In conclusion, we reported the cases of three patients who recovered from COVID-19 with systemic steroid treatment but who later presented OP. Now that short-term steroid therapy is administered in the early phases of COVID-19 pneumonia, the number of patients who show a similar clinical course may increase. However, it is difficult to determine whether each case is an OP-associated phenotype. The risk factors predisposing patients with COVID-19 to secondary OP are unclear, and further studies are needed (22). Currently, patients should be treated with standard therapy and followed up appropriately, and imaging and pathologic studies should be carried out when respiratory symptoms flare up.

Written informed consent was obtained from the patients to publish this case report series and any accompanying images.

The authors state that they have no Conflict of Interest (COI).

Table 2. Case Series and Reports Describing Organizing Pneumonia That Has Prolonged or Developed after Completion of Steroid Therapy.

Reference	Age, Sex comorbidity	Clinical course	Radiological findings (days since onset)	BAL (days since onset)	Pathological findings (days since onset)
9	67 M	Received dexamethasone 6 mg/day for 2 weeks for COVID-19 pneumonia. In the following 2 weeks, dyspnea worsened.	CT (date unknown): GGO deterioration compared with the previous CT.	NA	NA
	45 M Hypertension	Received dexamethasone 6 mg/day for 3 weeks. Seven days after discharge, severe dyspnea and exercise intolerance developed.	CT (date unknown): a widespread, bilateral, GGO with consolidations	NA	NA
8	56 M	Dexamethasone and favipiravir were initiated on day 8 after onset. Treatment was completed in 5 days, but his respiratory failure persisted.	CT (day 26): GGOs remained and consolidations in both lobes.	(Day 29): elevated total cell count, 94% macrophages, 5% lymphocytes, 1% neutrophils.	TBLB (day 29): intra-alveolar granulation, interstitial lymphocytes infiltration, and fibroblastic tissue proliferation in the interstitium.
	84 F Hypertension, hypercholesterolemia, and hypothyroidism	On day 10 after onset, dexamethasone and favipiravir were administered for 10 days. Despite treatment, dyspnea and desaturation persisted.	CT (day 43): GGOs and consolidations in both lungs.	(Day 45): elevated total cell count, 93.5% macrophages, 3.5% lymphocytes, 1.5% neutrophils, 1.5% eosinophils.	TBLB (day 45): interstitial and intra-alveolar infiltration of lymphocytes and macrophages as well as fibroblastic connective tissue proliferation.
10	70 M	Methylprednisolone 1 mg/kg/day for 5 days was given for COVID-19 pneumonia on day 11. No improvement in respiratory status and inflammatory response was observed.	CT (day 35): Peripheral non-segmental GGOs and consolidations that worsened since admission.	(Day 40): elevated total cell count, 91% macrophages, 6.0% lymphocytes, CD4/CD8 0.4.	TBLC (day 40): fibrosis was focally embedded in a myxoid matrix, predominantly involving the alveolar spaces and alveolar ducts. In the central part of the fibrosis, the elastic fibers in the alveoli were destroyed. Lymphoplasmacytic infiltration and scattered alveolar macrophages were observed within the airspaces.

BAL: bronchoalveolar lavage, CT: computed tomography, GGO: ground-glass opacity, NA: not applicable, OP: organizing pneumonia, TBLB: transbronchial lung biopsy, TBLC: transbronchial lung cryobiopsy

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