Late Onset of Organizing Pneumonia Following SARS-CoV-2 Infection: A Case Report of Successful Management and Review Literature

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ABSTRACT: A late consequence of COVID-19, organizing pneumonia is characterized by significant imaging and pathological abnormalities. The goals of this study are to better understand these abnormalities. The use of corticoid continues to be the recommended course of treatment for COVID-19. On the other hand, it is not clear whether or not corticoid has the same impact on organizing pneumonia after COVID-19. A 53-year-old male patient was identified with organized pneumonia following COVID-19 infection. He was diagnosed after experiencing severe respiratory symptoms several days with no improvement. We initiated a high dose of corticoid based on imaging and pathological findings and observed a significant response. In addition, we looked into the research that has been done concerning the diagnosis and treatment of this peculiar ailment. Patients who have been diagnosed with pneumonia after COVID 19 are required to undergo a reevaluation that includes a chest CT scan, and some of these patients may be candidates for an early lung biopsy. The most effective and convincing therapy for COVID-19-induced organizing pneumonia is corticoid treatment at a dose equivalent to 0.5 mg/kg/day of prednisone.

KEYWORDS: COVID-19, organizing pneumonia, corticoid

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Introduction

Lung damage in individuals with early-stage SARS-CoV-2 infection has been thoroughly characterized, including ground glass opacity with or without consolidation.[1] In contrast, the chronic phase, or so-called post-COVID syndrome, is poorly understood, generating diagnostic and therapeutic difficulties. Recently, post-COVID organizing pneumonia has been noted more frequently, both in individual patients and case series, with lung lesions comprising ground glass opacity and widespread reticular interstitial pattern.[2-4] Organizing pneumonia is described pathologically as intraalveolar accumulation of fibroblasts and connective matrix accompanied by interstitial inflammation.[5] Virus remains one of the most common causes of this condition, alongside idiopathy.

Corticosteroids continue to dominate the treatment of organizing pneumonia.[5,6] Nonetheless, it remains uncertain whether organizing pneumonia following SARS-CoV-2 infection possesses important early-detection characteristics and whether corticoid has any effect on this. We report the successful management of a case of organizing pneumonia caused by COVID-19. In addition, we review the literature concerning this condition.

Case Report

This case involves a male patient, age 53, who presented with fever and dry cough. He has a history of intermediate-risk SARS-CoV-2 infection, which was negative 13 days prior to admission. This time, he experienced 2 days of persistent fever that responded to treatment, as well as a severe dry cough. The worsening of the symptoms led to hospitalization. At the emergency department, his heart rate was 120 beats per minute, he had normal blood pressure of 110/80 mmHg, a little higher temperature of 37.9°C, and no notable abnormal findings. White blood cell count (WBC) was elevated: 11.46 G/L with 83.7% neutrophils; high sensitive C reactive protein (hs-CRP) was 41.95 mg/L (<5 mg/L), ferrtitin was 529.37 ng/mL (20-250 ng/mL), interleukin-6 was 35.1 pg/mL (<7 pg/mL), and pro-calcitonin was 0.09 ng/mL (< 0.5 ng/mL). The SARS-CoV-2 PCR test was negative. Chest X-ray showed peripheral consolidation lesions of the right side (Figure 1). Several consolidation patches and some ground glass opacities were primarily observed in the right upper and lower lobes on the chest CT image (Figure 2). At the time, the patient underwent bronchoscopy, which revealed many epithelial bleeding patches in both lungs. We did not send a sample for histology. The first sputum real time PCR (RT-PCR) identified *Methicillin-Resistant Staphylococcus epidermidis*, *Enterococcus faecalis*, and *Fusobacterium nucleatum*; the second sputum RT-PCR, conducted 4 days later, identified *Klebsiella pneumoniae*, *Acinetobacter baumannii*, and *Escherichia coli*. Other culture samples, including sputum and bronchus fluid, were negative for AFB. Since all the sputum samples sent for culture came back negative, we

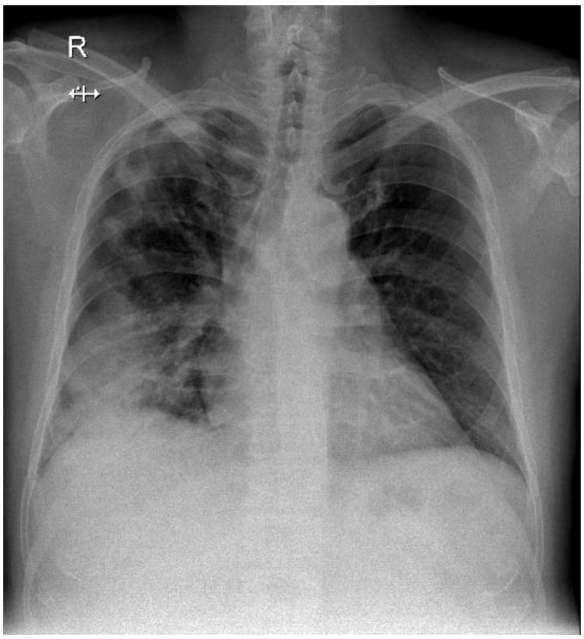

Figure 1. Chest X-ray at the time of admission. Peripheral consolidation lesions noted of the right lung.

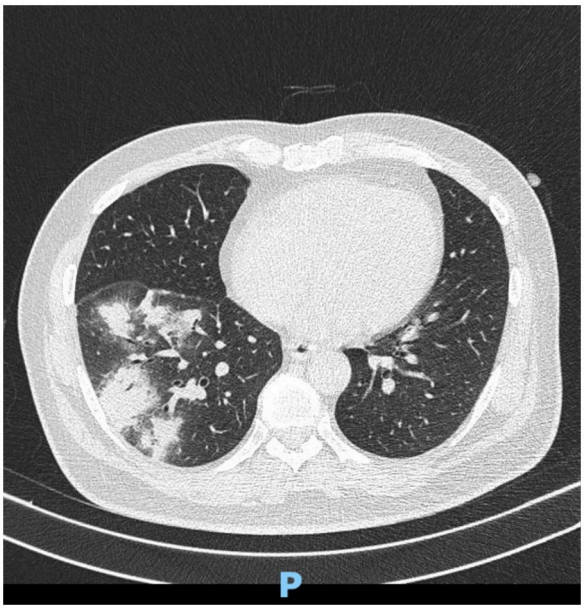

Figure 2. Chest CT-scan at the time of admission. Several consolidation patches and some ground grass opacities were primarily observed in the right upper and lower lobes, more severe than 5-day prior CT-scan.

could not collect antibigram for these antigens. Besides, all the samples sent for culture and RT-PCR came back negative for fungus. In spite of this, we chose to start antifungal medication due to a significant likelihood of infection. He was subsequently administered empirical meropenem and linezolide, an antifungal medication containing caspofungin, combined with 10 mg of rivaroxaban every day.

After 8 days, he still had pyrexia (with a maximum fever of 38.3°C), his sputum had turned yellow, and he experienced severe pain when coughing. On physical examination,

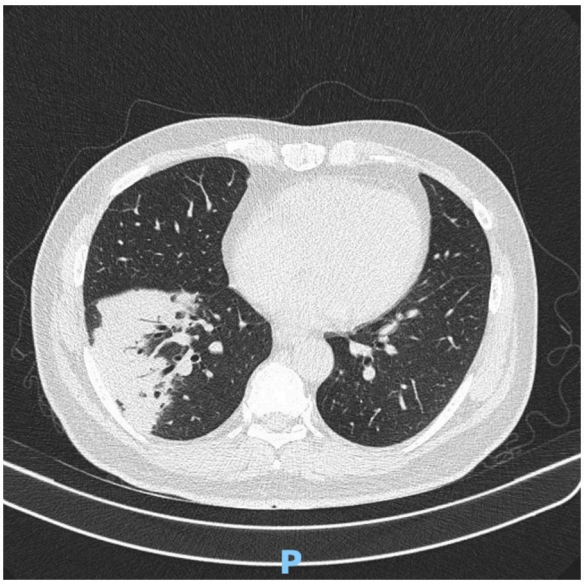

Figure 3. Chest CT-scan obtained 14 days after admission. Significant consolidation lesions in the right upper and lower lobes compared to the most recent images, which were more severe than 14-day prior CT-scan.

harsh crackles and diminished bilateral lung sounds were detected. C reactive protein (CRP) was 68.2 mg/L, ferritin was 638.28 ng/mL, D-dimer was 954 ng/mL, and IL-6 was 26.21 pg/mL, indicating a continuous inflammatory reaction. At this time, the patient was diagnosed with pneumonia caused by a bacterial/invasive fungal infection that responded poorly to an empirical antibiotic. We added ertapenem to the present regimen and continued the double carbapenem, linezolide, and caspofungin for 7 days. The chest CT conducted 7 days later revealed more significant consolidation lesions in the right upper and lower lobes compared to the most recent images. (Figure 3).

After consultation, we agreed at this time to do a second bronchoscopy and a right lower bronchial biopsy. Multiple degrees of alveolar damage, a thick intraalveolar septum, fluid accumulation in bronchial sacs, and fungal hyphae branching at 45° angles were identified in the analyses. Alveolar gaps were entirely obliterated and infiltrated by lymphoid and plasma cells. In addition, there was multilayer pneumocyte hyperplasia (Figure 4). All of the symptoms were consistent with the diagnosis of organizing pneumonia following SARS-CoV-2 infection with fungal infection. Immunohistochemistry study revealed CK7 (+) in lung cells, TTF-1 (+) in lung cells, CD34 (+) in vascular cells, and GMS (Grocott) (+) on fungal hyphae; consistent with organized pneumonia subsequent to SARS-CoV-2 infection. After getting the results, we decided to discontinue all previous antibiotics and commence treatment with methylprednisolon at 1 mg/kg/day and voriconazole at 800 mg/day. The patient felt better after 1 day, with no fever and minimal coughing. With WBC of 6.45 G/L and CRP of 12.8 mg/L, inflammation reaction also dropped dramatically. Chest X-ray obtained 3 days after corticoid initiation showed consolidation lesion of the right lung, which meant significantly reducing (Figure 5).

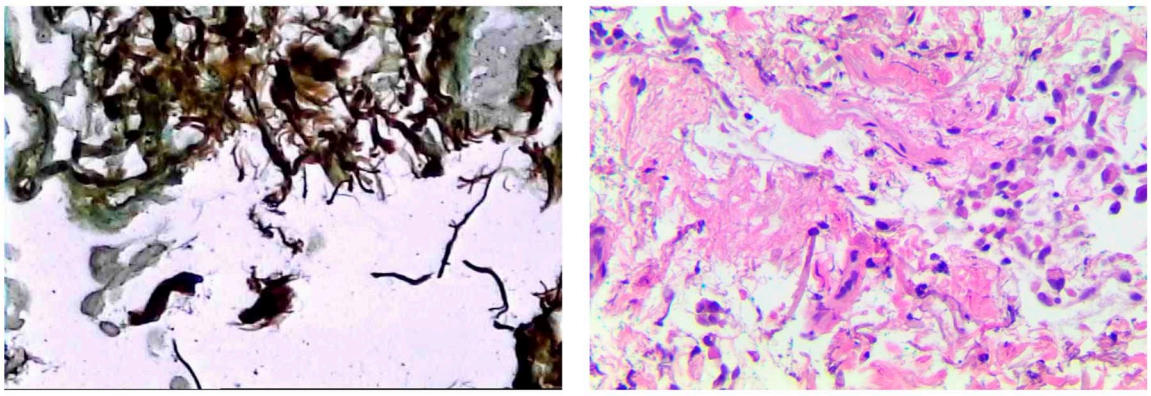

Figure 4. Right lower bronchial biopsy result 17 days after admission. Multiple degrees of alveolar damage, a thick intraalveolar septum, fluid accumulation in bronchial sacs, and fungal hyphae branching at 45° angles were identified in the analyses. Alveolar gaps were entirely obliterated and infiltrated by lymphoid and plasma cells. Immunohistochemistry study revealed CK7 (+) in lung cells, TTF-1 (+) in lung cells, CD34 (+) in vascular cells, and GMS (Grocott) (+) on fungal hyphae; consistent with organized pneumonia subsequent to SARS-CoV-2 infection.

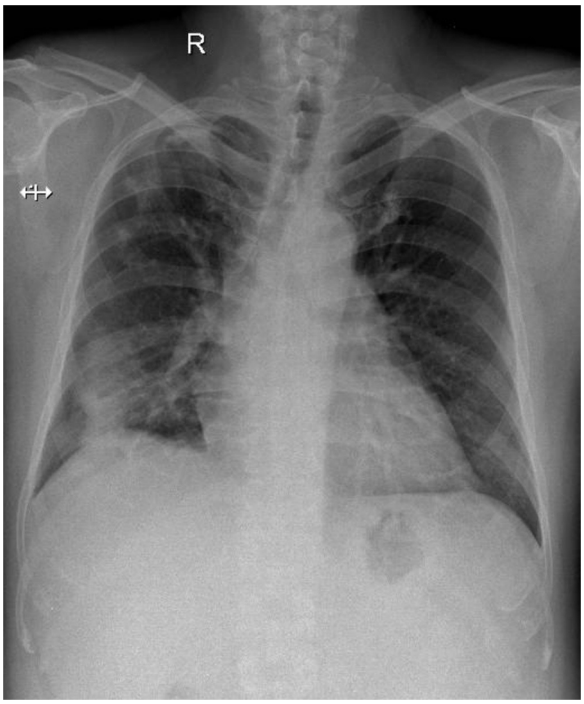

Figure 5. Chest X-ray obtained 3 days after corticoid initiation.

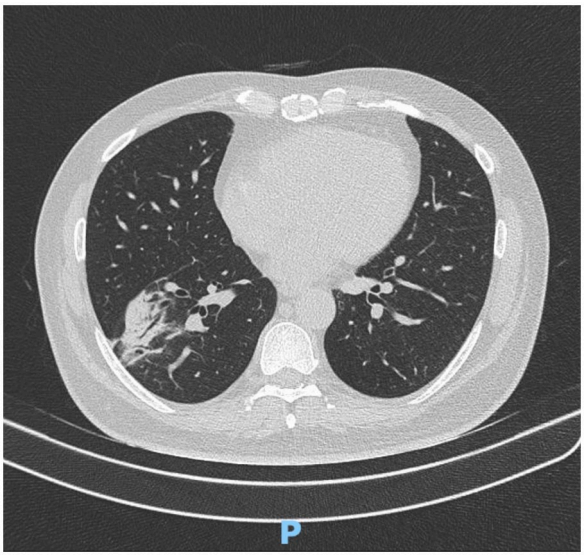

Figure 6. Chest CT-scan obtained 12 days after cortioid re-initiation. Fibrosis and mildly extended of right upper bronchial lobe. Consolidation lesions were reduced remarkable compared to 19-day prior CT-scan.

The patient was successfully discharged after 3 additional days of methylprednisolone therapy. His reaction to corticoid and voriconazole medication, as well as rivaroxaban 10 mg/day, was deemed satisfactory, and he was afterward monitored. Obtaining a chest CT-scan 12 days after corticoid re-initiation and a chest X-ray 1 month following discharge likewise revealed excellent improvement (Figures 6 and 7, respectively).

An informed written consent was obtained from the patient for publication of this case report.

Discussion

A 53-year-old male patient was diagnosed with organizing pneumonia after exposure to COVID-19 and was successfully treated. This case serves as a cautionary tale for clinicians to recognize the phenomenon earlier, initiate the appropriate therapy at the appropriate time, and prevent subsequent consequences from wrong treatments.

Organizing pneumonia is a syndrome beginning with revised lung parenchymal after infury, without particular causes (idiopathic organizing pneumonia), or connected to an agent or systemic disease such as a connective tissue abnormalities (secondary organizing pneumonia).[7] OP is a rare disorder characterized by intraalveolar accumulation of fibroblasts and connective matrix, particularly collagen. First in the chain of events leading to the production of intraalveolar buds is alveolar epithelial damage with pneumocyte necrosis. As a result of alveolar damage, the alveolar lumen is flooded with plasma proteins (permeability edema), including coagulation factors. The equilibrium between coagulation and fibrinolysis is tipped in favor of coagulation (particularly due to decreased fibrinolysis),

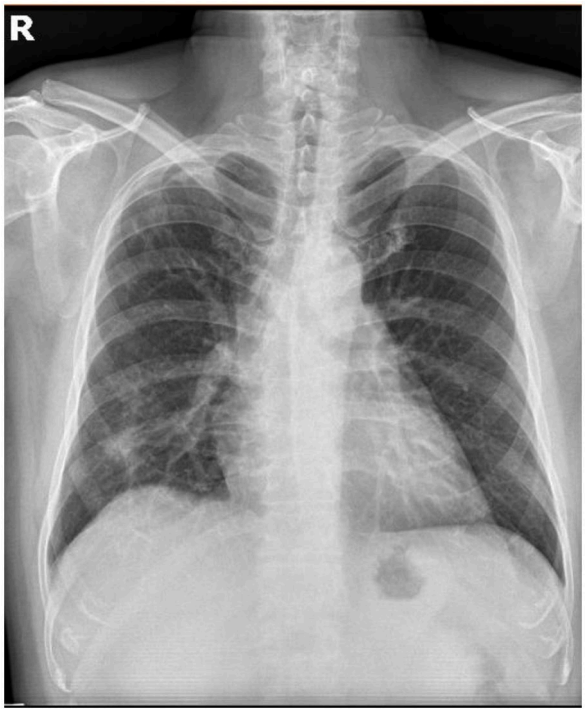

Figure 7. Chest X-ray obtained 1 month after discharge.

resulting in the formation of fibrin deposits that are quickly colonized by migrating inflammatory cells and fibroblasts. Several experimental investigations indicate that the severity of the initial epithelial injury and as-yet-unknown host variables may influence the progression to either OP or widespread alveolar damage. The results of a blood test may suggest a moderate elevation of white blood cell count and CRP, but no substantial elevation of eosinophils. Chest CT-scan frequently reveals increased alveolar opacity, sometimes bilateral and subpleural, occasionally prolonged, ranging from ground glass to consolidation with airbronchogram, with no notable upper or lower lobe allocation. The consolidation area can be as small as 1 to 2 mm or encompass an entire lobe. Other results may be a single peripheral lymph node or tumor-like consolidation masquerading as lung cancer, especially when associated with an elevated metabolic rate detected by PET-CT. Typically, these lesions occur in the higher lobes and are asymptomatic. Several uncommon abnormalities have been recorded, including multiple lymph nodes, cavitary lesions, perilobular or centrilobular pattern, or well-bordered lymph node in the middle of or around the bronchial vascular system, as well as linear subpleural bands. Thoracoscopic biopsy is the standard method for accurately diagnosing organizing pneumonia, and it also assists in ruling out other pseudo-OP diseases. If a transbronchial biopsy was chosen, the sample size is so small that clinicians cannot rule out other pathophysiological disorders; hence, the results of this procedure are only significant when combined with the patient's typical clinical profile and imaging findings. Yet to be established are the sensitivity and specificity of transbronchial biopsies. Core needle biopsy is generally safe and may be appropriate for a subset of individuals suspected of having OP, particularly those with imaging evidence of a consolidation lesion. The videothoracoscopic lung biopsy is still the best way to collect a sufficient sample to diagnose OP and rule out alternative diagnosis. Before beginning corticosteroids, a biopsy and culture of the biopsy sample should be performed. An further viable option to lung biopsies is empirical treatment. It means we must accept the risk of incorrect diagnoses, such as eosinophilic pneumonia, lung lymphoma, and lung cancer.[7]

The COVID-19 pandemic has illuminated how humans respond to natural disasters and what we may do to prevent future occurrences. Current COVID-19 treatment guidelines have supplied us with management options for the acute phase, the preventative phase, and to promote immunization awareness. However, nothing is clearly known on how clinicians should treat post-COVID-19 symptoms. Patients may show symptoms 5 weeks after contracting SARS-CoV-2. The symptoms varied, but weariness and dyspnea predominated.[8] A subset of patients may require long-term oxygen therapy and are at risk of developing chronic respiratory failure. Recently, a number of articles on post-COVID-19 ARDS-related organizing pneumonia have been published (Table 1).[9-13] In a paper from Germany, 12.5% of severe COVID-19 patients were diagnosed with organizing pneumonia. Three weeks after experiencing symptoms, a chest CT scan revealed consolidation and ground glass lesions, an airbronchogram finding, pleural effusion, and thickening, according to a study conducted in China.[14] A case study showed similarities in the presentation and diagnosis of post-COVID-19 organizing pneumonia more recently. All 6 patients in this case series presented with chronic dyspnea and hypoxia, necessitating oxygen therapy. All had a late start of symptoms, the earliest being 14 days, and a negative PCR for SARS-CoV-2 at the time of OP diagnosis.[9] Chest X-rays are useful for suggesting obstructive pulmonary disease (OP), while chest CT scans remain the diagnostic gold standard, with extensive ground glass lesions with bilateral reticular and consolidation lesions.[9] Tran et al[12] also described the case of a 38-year-old male diagnosed with intermediate SARS-CoV-2 infection and treated with corticosteroids for 11 days. After tapering, his dyspnea worsened and his oxygen demand increased. The chest X-ray revealed bilateral infiltration, and the chest CT scan revealed bilateral reticular lesions in both lungs. The diagnosis of OP was made and corticoid was administered again. After 7 additional days, he was successfully discharged after having greatly improved after 2 days.[12] Our patient also experienced fever and dry cough many days after discharge, despite a negative PCR result for SARS-CoV-2. Despite this, the CT scan mostly revealed a consolidation lesion in the right lower lobe, devoid of extensive ground glass or interstitial lesions. Therefore, the patient was not prescribed corticoid until a positive lung biopsy result for organized pneumonia was obtained.

Organizing pneumonia is mostly responsive to glucocorticoids. We are all aware that glucocorticoids (6 mg of

Table 1. Clinical characteristics and outcomes of post-COVID 19 organizing pneumonia case reports.

AUTHORS	NUMBER OF PATIENTS	SEX, AGE	TIME FROM COVID-19 INFECTION TO OP DIAGNOSIS	CLINICAL PRESENTATION	DIGANOSTIC TEST	TREATMENT	OUTCOME
1. Tran et al[12]	1	Male, 38	27 d	Worsening dyspnea	Chest CT-scan	Oral dexamethasone 16 mg/d for 9 d	Complete symptoms resolution
2. Ng et al[15]	2	Female, 58	60 d	Worsening exertional dyspnea	Chest CT-scan	IV MPS 500 mg/d for 3 d; then IV Dexamethasone 6 mg/d for 10 d; discharged with oral prednisolone 0.5 mg/kg/d for 4 wk, then tapered for 2 mo	- Resolution of dyspnea and on thorax CT - Spirometry and gas transfer factors were normal
		Male, 81	70 d	Worsening cough and right-sided pleuritic chest pain	Transbronchial lung biopsy with histopathological examination	0.5 mg/kg/d prednisolone for 4 wk, 20 mg/d for 4 wk, followed by 10 mg/d for 2 wk and tapered over 3 mo	Resolution of both symptoms and radiographic consolidation
3. Alsulami et al[9]	6	Male, 71	22 d	Fever, worsening dyspnea, cough	Chest CT-scan	Prednisone 0.5 mg/kg/d for 4 wk	Significant respiratory improvement, more exercise tolerance
		Male, 54	26 d	Ongoing hypoxia, worsening exertion dyspnea	Chest CT-scan	Prednisone 0.5 mg/kg/d	Significant clinical improvement, remission on chest CT
		Male, 57	40 d	Ongoing hypoxia, persistently tachypneic	Chest CT-scan	Prednisone 0.5 mg/kg/d	Significant clinical and chest CT-scan improvement
		Female, 56	16 d	Persistent dyspnea and hypoxia	Chest CT-scan	Prolonged dexamethasone 10 mg orally	Resolution of respiratory symptoms and hypoxia
		Male, 49	25 d	Persistent hypoxia and opacities on chest X-ray	Chest CT-scan	Prolonged dexamethasone 10 mg orally	Significant respiratory improvement after 1 mo and complete CT-scan resolution after 2 mo
		Female, 83	31 d	Persistent dyspnea and oxygen requirement	Chest CT-scan	Prednisone 0.5 mg/kg/d for 3 wk, then tapered off	Significant clinical improvement
4. Funk et al[16]	1	Male, 49	35 d	Persisting dyspnea, impaired pulmonary function, radiological abnormalites	Lung histology by fluoroscopy-guided transbronchial biopsy	Without treatment	Improved spontaneously
5. Kanaoka et al[11]	2	Male, 56	29 d	Persistent oxygen requirement	Bronchoalveolar lavage and transbronchial lung biopsy	Oral prednisone 1 mg/kg/d for 7 d, then 0.5 mg/kg/d for 42 d, then tapered off	Remarkable respiratory condition and CT-scan consolidations improvement
		Female, 84	45 d	Persistent dyspnea	Microscopic examination of the transbronchial lung biopsy	Oral prenisolone 1 mg/kg/d for 7 d, then 0.5 mg/kg/d for 28 d, then tapered off	Remarkable CT-scan and pulmonary lung function improvement

dexamethasone, once daily for 10 days) are recommended by WHO for patients with severe and serious COVID-19.[17,18] After COVID-19, corticosteroids can attenuate ARDS-induced organizing pneumonia.[17] There is currently no evidence that antibiotics are beneficial against the development of chronic pulmonary fibrosis.[13] The same is applicable for anti-inflammatory and anti-fibrosis medicines. In the past, high-dose corticoid has proven to be an effective drug for organizing pneumonia following H1N1, H7N9, and MERS (infection with the Middle East respiratory syndrome coronavirus), with rapid clinical and radiological recovery.[19-21] Corticoid continues to be the first-line treatment for idiopathic organizing pneumonia[7,22] and post-COVID syndrome[9,12,13,15,23] independent of corticoid dose used in the past.[10]

There are insufficient studies and data to make a firm recommendation regarding post-COVID 19 organizing pneumonia. Clinicians should remember this phenomenon in patients with newly emerging respiratory symptoms in the post-COVID 19 interval or immediately after ending corticosteroid medication. In addition, the most important tool for evaluation and diagnosis is a chest CT scan with unique presentations such as extensive interstitial lesions or progressive consolidation lesions; or a lung biopsy in exceptional situations when conventional treatment is ineffective. Presently, corticoid at a dose equivalent to 0.5 mg/kg/day of prednisone is the most effective and convincing therapy for COVID-19-induced organizing pneumonia.

Conclusion

Since 3 years ago, COVID-19 has posed a new and formidable threat to global health. A chest CT scan reveals many interstitial lesions in the lungs of a patient who has been infected with COVID-19. One of these is the corticoid-sensitive organizing pneumonia. Patients with post-COVID 19 pneumonia must be re-evaluated with a chest CT scan, and some may be candidates for a lung biopsy for early detection.

Author Contributions

(i) Conception and design: DTL, VHV, DHN, DTV, KDN, BQT.
(ii) Administrative support: VHV, DHN, QDDP.
(iii) Provision of study materials or patients: DTL, QDDP, BQT.
(iv) Collection and assembly: VHV, KDN.
(v) Data analysis and interpretation: VHV, KDN.
(vi) Manuscript writing: All authors.
(viii) Final approval of manuscript: All authors.

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