CASE REPORT

Acute Fibrinous Organizing Pneumonia in a COVID-19 Patient: A Case Report

Pailin Ratanawatkul MD[1], Joshua J. Solomon MD[2], Nipon Chaisuriya MD[3], Sasithorn Watcharadetwittaya MD[3], Panaya Tumsatan MD[4], Arunnit Boonrod MD[4], Wipa Reechaipichitkul MD[1], Apichart So-Ngern MD[5], Worawat Chumpangern MD[1], Itthiphat Arunsurat MD[1], Pawornwan Mahawarakorn MD[1], Phitphiboon Deawtrakulchai MD[6], Piroon Mootsikapun MD[7], Songsak Kaitchoosakun MD[8], Chakthip Suttinarakorn MD[9], Napat Yodpinij MD[10], Jeffrey J. Swigris DO, MS[2]

[1] Division of Pulmonary and Critical Care Medicine, Department of Medicine, Faculty of Medicine, Khon Kaen University, Khon Kaen, Thailand

[2] Interstitial Lung Disease Program, National Jewish Health, Denver, CO, USA

[3] Department of Pathology, Faculty of Medicine, Khon Kaen University, Khon Kaen, Thailand

[4] Department of Radiology, Faculty of Medicine, Khon Kaen University, Khon Kaen, Thailand

[5] Division of Sleep Medicine, Department of Medicine, Faculty of Medicine, Khon Kaen University, Khon Kaen, Thailand

[6] Division of Critical Care Medicine, Department of Medicine, Faculty of Medicine, Khon Kaen University, Khon Kaen, Thailand

[7] Division of Infectious and Tropical Medicine, Department of Medicine, Faculty of Medicine, Khon Kaen University, Khon Kaen, Thailand

[8] Division of Cardiology, Department of Medicine, Faculty of Medicine, Khon Kaen University, Khon Kaen, Thailand

[9] Department of Anesthesiology, Faculty of Medicine, Khon Kaen University, Khon Kaen, Thailand

[10] Division of Cardiovascular and Thoracic Surgery, Department of Surgery, Faculty of Medicine, Khon Kaen University, Khon Kaen, Thailand

Background: Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has varied clinical and radiographic manifestations. Severe initial viral infection, cytokine release, opportunistic infection and post-viral inflammation may all contribute to progressive symptoms and severe lung injury. Acute fibrinous and organizing pneumonitis (AFOP), a rare pattern of acute lung injury characterized by intra-alveolar fibrin ball, has so far been reported associated with infections, connective tissue diseases, drugs and toxins, hematologic malignancy, altered immune status and inhalation injury.

Case Report: The authors report a case of 26-year-old man with severe COVID-19 pneumonia that clinical and radiographic imaging worsened after episode of cytokine storm. The diagnosis of AFOP was confirmed by transbronchial biopsy, and the patient was successfully treated with high-dose corticosteroids.

Conclusion: AFOP can be found in severe COVID-19 patients especially when clinical deterioration occurs later in disease course. Clinical suspicion is needed for prompt diagnosis and treatment. High-dose corticosteroid is an effective medication.

Keywords: SARS-CoV-2; COVID-19; Acute fibrinous organizing pneumonia; Respiratory failure; Viral pneumonia; Case report; Acute lung injury

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Pandemic COVID-19 can result in a spectrum of illness ranging from asymptomatic infection to severe pneumonia with acute respiratory distress syndrome (ARDS) – which develops in 15 to 30% of patients – and death[1,2]. The acute phase of lung injury is usually caused by viral pneumonia. The next stage is believed to be caused by cytokine storm evidenced by increased levels of inflammatory biomarkers, such as C-reactive protein (CRP), ferritin, interleukin-6 (IL-6), interleukin-1 (IL-1), and D-dimer[3,4]. There are several treatment modalities used to treat cytokine release syndrome such as glucocorticoids, IL-6 pathway inhibitors (tocilizumab), a Janus kinase inhibitor (baricitinib), and IL-1 pathway inhibitors (anakinra)[5-21]. Despite treatment with these agents, some patients will deteriorate, and a subset will develop lung fibrosis.

From a postmortem study on patients with COVID-related ARDS, diffuse alveolar damage (DAD) was the predominant pulmonary pathology, reported to occur

Correspondence to:

Ratanawatkul P.

Division of Pulmonary and Critical Care Medicine, Department of Medicine, Faculty of Medicine, Khon Kaen University, 123 Moo 16, Mittraphap Road, Nai-Muang, Muang, Khon Kaen 40002, Thailand.

Phone: +66-85-5534517

Email: pailin@kku.ac.th

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in 88% of patients; pulmonary microthrombi reportedly occurred in 57% and organizing pneumonia (OP) was found in up to 52% of these patients[22]. COVID-19-associated pulmonary aspergillosis (CAPA) was found around 19% of ICU patients[23].

Acute fibrinous organizing pneumonia (AFOP) is a nonspecific injury pattern, initially described in 2002 by Beasley, characterized by the presence of fibrin deposition in the form of fibrin "balls" within the alveolar spaces[24]. AFOP has been reported in postmortem studies in patients with COVID-19[25,26]. The authors report a case of severe COVID-19 pneumonia found to have AFOP on transbronchial lung biopsy.

Case Report

A 26-year-old, lifelong nonsmoking male, with no past medical history and unvaccinated for COVID-19 vaccine, presented with fever, dry cough, sore throat, myalgia, and fatigue. On admission in April 2021 (one week after disease onset), his oxygen saturation on room air was 99%, his body temperature was 40.5 degree Celsius, and his respiratory rate was 18/min. His chest x-ray showed patchy opacification in the right lower lobe (Figure 1A). Nasal swab real-time polymerase chain reaction (RT-PCR) was positive for SARS-CoV-2. The RT-PCR cycle threshold (Ct) values of SARS-CoV-2 viral load on ORF 1ab gene was 17.2 and on N gene was 13.8. CRP was 5.6 mg/L. Favipiravir, lopinavir/ritonavir, ceftriaxone, azithromycin and dexamethasone 6 milligram IV once daily were initiated. Awake prone positioning was also implemented. His oxygenation worsened, and his chest x-ray developed bilateral opacities (Figure 1B) with persistent fever. High-flow nasal cannula was initiated. On the seventh day in ICU, the CRP increased to 81.4 mg/L and the white blood cell count rose from 4,000/uL to 16,870/uL. The RT-PCR Ct values on ORF 1ab gene was 27.2 and on N gene was 25.3. Tocilizumab 8 mg/kg single dose was given, and he became afebrile the next day. Oxygenation and chest x-ray slowly improved (Figure 1C). The CRP dropped over time from 36.6 to 2.1 mg/L. On the fourteenth day in ICU, his oxygenation and radiographic opacities worsened (Figure 1D). High-resolution chest computed tomography (HRCT) demonstrated multiple peripheral ground-glass and consolidative opacities. There were also some areas of central ground-glass opacity surrounded by consolidation (the reversed halo sign or "atoll" sign (Figure 2A)). Bronchoalveolar lavage (BAL) analysis showed 699 cells/cubic millimeter of white blood cells with 83% lymphocytes, 10% macrophages and 4% eosinophils. Transbronchial biopsy showed intra-alveolar fibrin ball formation, focal interstitial thickening, focal myxoid change and lymphoplasmacytic cell infiltration in interstitial areas with focal pneumocyte reactive hyperplasia and proliferation without evidence of hyaline membrane formation. No obvious organizing pneumonia, granulomatous reaction, microvascular fibrin thrombi formation or specific viral

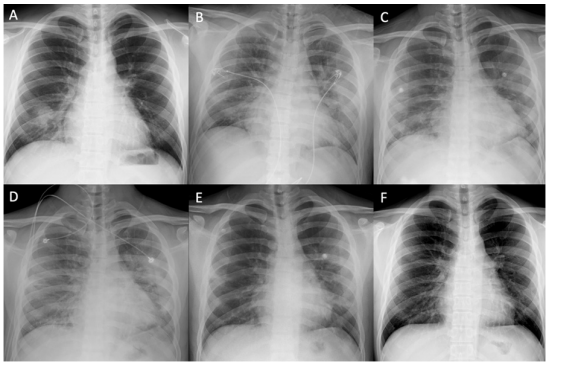

Figure 1. (A) Chest x-ray on admission, day 1, demonstrated patchy alveolar infiltration in the right lower lobe. (B) Day 7, progression to bilateral peripheral consolidation predominated more on left sided. (C) Day 10, infiltration improved after tocilizumab. (D) Day 14, infiltration once again progressed to bilateral peripheral consolidation. (E) Day 18, two days after pulse methylprednisolone, infiltration improved. (F) Chest X-ray on 2 weeks follow-up was much improved. Only minimal peripheral ground glass was observed.

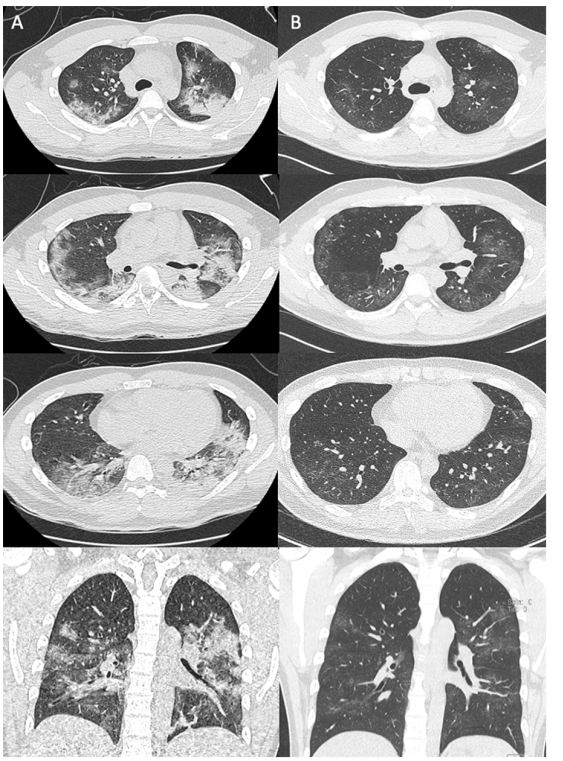

Figure 2. (A) HRCT on day 14 after admission demonstrated multifocal peripheral ground-glass opacities and consolidation in bilateral lungs with reversed halo sign or "atoll" sign. (B) HRCT at 2 weeks follow-up after pulse methylprednisolone revealed significant improvement of multifocal consolidation. Only minimal ground-glass opacity remained.

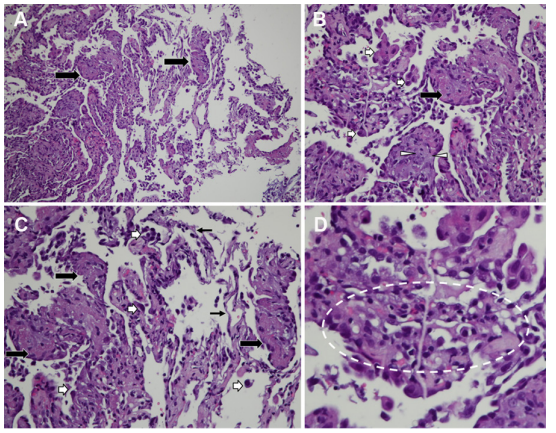

Figure 3. (A) Histopathology (H&E stain) from transbronchial lung biopsy reveals focal interstitial thickening and intra-alveolar fibrin ball formation (thick black arrow); 100X magnification. (B) The section reveals focal pneumocytes reactive hyperplasia and proliferation (short white arrow), intra-alveolar fibrin ball (thick black arrow) and focal myxoid change of interstitium (white arrow head); 400X magnification. (C) The section reveals focal pneumocytes with reactive hyperplasia and proliferation (short white arrow) and intra-alveolar fibrin ball (thick black arrow). Some alveolar interstitial areas have normal thickness (thin black arrow) compare with affected interstitial thickening area at right side of the figure; 400X magnification. (D) Close-up of affected interstitial area reveals occasional lymphoplasmacytic cells infiltration.

inclusion were observed (Figure 3). BAL microbiological work-up was negative. The diagnosis of AFOP associated with COVID-19 was made. The patient was treated with pulse methylprednisolone at 1,000 mg daily for three days. The patient had no adverse effect from the treatment. His clinical status and radiographs improved (Figure 1E). The patient weaned off of high-flow nasal cannula to room air within three days. Chest x-ray and HRCT at 2 weeks follow-up were significantly improved (Figure 1F, 2B).

The present study was approved by Center for Ethics in Human Research, Khon Kaen (HE641310).

Discussion and Conclusion

Some patients with COVID-19 pneumonia face clinical and radiographic deterioration during the later courses of disease[22,27-30]. Understanding the histologic patterns of lung injury might help physicians initiate appropriate and timely treatment. Although a DAD pattern, typically associated with acute lung injury or ARDS, has been found to occur in postmortem studies of patients with COVID-19 pneumonia, OP and AFOP have also been reported to occur[22,25,26,29,31].

AFOP is a histopathologic diagnosis characterized by fibrin “balls” within the alveolar spaces, mild to moderate acute and/or chronic interstitial inflammation, type 2 pneumocyte hyperplasia and alveolar septal expansion with myxoid connective tissue. Interstitial changes are primarily confined to areas adjacent to intra-alveolar fibrin, while the intervening lung shows only minimal changes. Eosinophils are inconspicuous or absent. Extensive bronchopneumonia and/or abscess formation and granulomatous inflammation should be absent[24]. It is postulated that AFOP is a transitional clinical spectrum between DAD and OP. The main features that differentiate AFOP from DAD are that there are no classic hyaline membranes detected in AFOP, and the distribution of DAD is more diffuse whereas AFOP is usually patchy. AFOP might also have features of OP, which is characterized by patchy plugs of granulation tissue in alveolar space and/or terminal bronchioles, but the “plugs” of OP are typically far less extensive than the fibrin “balls” of AFOP. The interstitial abnormality in OP is also far less extensive than in AFOP. No architectural distortion or extensive fibrosis is observed in OP. Typically, OP progresses more slowly than AFOP[32-34].

Radiographic findings in AFOP are non-specific. Bilateral basilar infiltration, diffuse patchy ground glass opacity, focal patchy consolidation resembling atypical pneumonia or bilateral reticulonodular opacities have been previously reported[24,35]. In our case, the authors observed multiple peripheral ground-glass opacities combined with consolidation and some areas of central ground-glass opacity surrounded by consolidation (defined as the reversed halo sign or "atoll" sign were observed). These radiographic signs are more suggestive of OP than AFOP; however, the OP was not observed on histopathology in our case. Therefore, AFOP might represent a histologic pattern that can occur within the clinical spectrum between DAD and OP or might reflect a tissue sampling error.

AFOP can be either idiopathic or secondary to any of a variety of conditions including infections, connective tissue diseases, drugs and toxins, hematologic malignancy, altered immune status and inhalation injury. Two different patterns of disease progression in AFOP are reported: 1) an acute fulminant course, leading to respiratory failure with rapid progression to death and 2) a subacute course with recovery[24]. AFOP and OP usually have a good response to corticosteroid therapy[35]. Fulminant AFOP may have contributed to the high mortality rate of COVID-19 patients prior to the recent adoption of corticosteroid treatment recommendation[30]. Several studies and a meta-analysis showed benefits of corticosteroid therapy in severe and critically ill COVID-19 patients[15-18]. The benefit was also observed in patients in whom treatment was initiated more than 7 days after symptom onset[15,36].

AFOP should be considered in critically ill patients with COVID-19, especially when clinical deterioration occurs later in the disease course[22,25,28,30]. Infection should be ruled out. Bronchoalveolar lavage that reveals lymphocyte predominance is not specific for – but compatible with – AFOP[37]. Transbronchial lung biopsy (TBLB) might not be possible due to clinical condition of some patients. Like OP, AFOP can be patchy and missed

by TBLB; and, like OP, AFOP may be non-specific injury pattern at the periphery of the process driving the injury (e.g., vasculitis, malignancy)[24,35,37]. Prompt treatment with high dose corticosteroids may help to prevent intubation and clinical progression to death[30,38]. There are no definite corticosteroid dosage recommendations in COVID-19 AFOP[38]. In the present study, the authors used one gram of pulse methylprednisolone per day for three days, a dose the authors typically use to treat severe OP and exacerbations of interstitial lung disease[39,40].

In conclusion, AFOP can be found in severe COVID-19 patients especially when clinical deterioration occurs later in disease course. Corticosteroid is an effective medication that has demonstrated significant survival benefit in severe COVID-19 and is strongly recommended by the WHO in severe and critical COVID-19. One possible mechanism of this corticosteroid benefit may be the treatment of underlying AFOP and OP. The right timing and dosage of corticosteroids still needs to be investigated.

What is already known on this topic?

Progressive symptoms and severe lung injury in COVID-19 pneumonia patients may caused by severe initial viral infection, cytokine release, opportunistic infection and post-viral inflammation.

What this study adds?

A case of rare pattern of acute lung injury characterized by intra-alveolar fibrin ball called acute fibrinous and organizing pneumonitis (AFOP) was reported. High-dose corticosteroid is an effective medication to treat AFOP associated with COVID-19.

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Conflicts of interest

The authors declare no conflict of interest.

References

1. Attaway AH, Scheraga RG, Bhimraj A, Biehl M, Hatipoğlu U. Severe covid-19 pneumonia: pathogenesis and clinical management. BMJ 2021;372:n436.
2. Gautret P, Million M, Jarrot PA, Camoin-Jau L, Colson P, Fenollar F, et al. Natural history of COVID-19 and therapeutic options. Expert Rev Clin Immunol 2020;16:1159-84.
3. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020;395:497-506.
4. Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ. COVID-19: consider cytokine storm syndromes and immunosuppression. Lancet 2020;395:1033-4.
5. Marconi VC, Ramanan AV, de Bono S, Kartman CE, Krishnan V, Liao R, et al. Efficacy and safety of baricitinib in patients with COVID-19 infection: Results from the randomised, double-blind, placebo-controlled, parallel-group COV-BARRIER phase 3 trial. medRxiv 2021:2021.04.30.21255934.
6. Ely EW, Ramanan AV, Kartman CE, de Bono S, Liao R, Piruzeli MLB, et al. Efficacy and safety of baricitinib plus standard of care for the treatment of critically ill hospitalised adults with COVID-19 on invasive mechanical ventilation or extracorporeal membrane oxygenation: an exploratory, randomised, placebo-controlled trial. Lancet Respir Med 2022;10:327-36.
7. Stebbing J, Sánchez Nievas G, Falcone M, Youhanna S, Richardson P, Ottaviani S, et al. JAK inhibition reduces SARS-CoV-2 liver infectivity and modulates inflammatory responses to reduce morbidity and mortality. Sci Adv 2021;7:eabe4724.
8. Kalil AC, Patterson TF, Mehta AK, Tomashek KM, Wolfe CR, Ghazaryan V, et al. Baricitinib plus remdesivir for hospitalized adults with Covid-19. N Engl J Med 2021;384:795-807.
9. Ghosn L, Chaimani A, Evrenoglou T, Davidson M, Graña C, Schmucker C, et al. Interleukin-6 blocking agents for treating COVID-19: a living systematic review. Cochrane Database Syst Rev 2021;3:CD013881.
10. Shankar-Hari M, Vale CL, Godolphin PJ, Fisher D, Higgins JPT, Spiga F, et al. Association between administration of IL-6 antagonists and mortality among patients hospitalized for COVID-19: A meta-analysis. JAMA 2021;326:499-518.
11. Gordon AC, Mouncey PR, Al-Beidh F, Rowan KM, Nichol AD, Arabi YM, et al. Interleukin-6 receptor antagonists in critically ill patients with Covid-19. N Engl J Med 2021;384:1491-502.
12. RECOVERY Collaborative Group. Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. Lancet 2021;397:1637-45.
13. Stone JH, Frigault MJ, Serling-Boyd NJ, Fernandes AD, Harvey L, Foulkes AS, et al. Efficacy of tocilizumab in patients hospitalized with Covid-19. N Engl J Med 2020;383:2333-44.
14. Mariette X, Hermine O, Tharaux PL, Resche-Rigon M, Steg PG, Porcher R, et al. Effectiveness of tocilizumab in patients hospitalized with COVID-19: A follow-up of the CORIMUNO-TOCI-1 randomized clinical trial. JAMA Intern Med 2021;181:1241-3.
15. Horby P, Lim WS, Emberson JR, Mafham M, Bell JL, Linsell L, et al. Dexamethasone in hospitalized patients with Covid-19. N Engl J Med 2021;384:693-704.
16. Sterne JAC, Murthy S, Diaz JV, Slutsky AS, Villar J, Angus DC, et al. Association between administration of

systemic corticosteroids and mortality among critically ill patients with COVID-19: A meta-analysis. JAMA 2020;324:1330-41.
17. Wagner C, Griesel M, Mikolajewska A, Mueller A, Nothacker M, Kley K, et al. Systemic corticosteroids for the treatment of COVID-19. Cochrane Database Syst Rev 2021;8:CD014963.
18. Munch MW, Myatra SN, Vijayaraghavan BKT, Saseedharan S, Benfield T, Wahlin RR, et al. Effect of 12 mg vs 6 mg of dexamethasone on the number of days alive without life support in adults with COVID-19 and severe hypoxemia: The Covid Steroid 2 randomized trial. JAMA 2021;326:1807-17.
19. CORIMUNO-19 Collaborative Group. Effect of anakinra versus usual care in adults in hospital with COVID-19 and mild-to-moderate pneumonia (CORIMUNO-ANA-1): a randomised controlled trial. Lancet Respir Med 2021;9:295-304.
20. Kyriazopoulou E, Poulakou G, Milionis H, Metallidis S, Adamis G, Tsiakos K, et al. Early treatment of COVID-19 with anakinra guided by soluble urokinase plasminogen receptor plasma levels: a double-blind, randomized controlled phase 3 trial. Nat Med 2021;27:1752-60.
21. Siemieniuk RA, Bartoszko JJ, Zeraatkar D, Kum E, Qasim A, Martinez JPD, et al. Drug treatments for covid-19: living systematic review and network meta-analysis. BMJ 2020;370:m2980.
22. Hariri LP, North CM, Shih AR, Israel RA, Maley JH, Villalba JA, et al. Lung histopathology in coronavirus disease 2019 as compared with severe acute respiratory sydrome and H1N1 influenza: A systematic review. Chest 2021;159:73-84.
23. van Arkel ALE, Rijpstra TA, Belderbos HNA, van Wijngaarden P, Verweij PE, Bentvelsen RG. COVID-19-associated pulmonary aspergillosis. Am J Respir Crit Care Med 2020;202:132-5.
24. Beasley MB, Franks TJ, Galvin JR, Gochuico B, Travis WD. Acute fibrinous and organizing pneumonia: a histological pattern of lung injury and possible variant of diffuse alveolar damage. Arch Pathol Lab Med 2002;126:1064-70.
25. Copin MC, Parmentier E, Duburcq T, Poissy J, Mathieu D. Time to consider histologic pattern of lung injury to treat critically ill patients with COVID-19 infection. Intensive Care Med 2020;46:1124-6.
26. Borczuk AC, Salvatore SP, Seshan SV, Patel SS, Bussel JB, Mostyka M, et al. COVID-19 pulmonary pathology: a multi-institutional autopsy cohort from Italy and New York City. Mod Pathol 2020;33:2156-68.
27. Gogali A, Kyriakopoulos C, Kostikas K. Corticosteroids in COVID-19: one size does not fit all. Eur Respir J 2021;57:2100224.
28. Flikweert AW, Grootenboers M, Yick DCY, du Mée AWF, van der Meer NJM, Rettig TCD, et al. Late histopathologic characteristics of critically ill COVID-19 patients: Different phenotypes without evidence of invasive aspergillosis, a case series. J Crit Care 2020;59:149-55.
29. Bieksiene K, Zaveckiene J, Malakauskas K, Vaguliene N, Zemaitis M, Miliauskas S. Post COVID-19 organizing pneumonia: The right time to interfere. Medicina (Kaunas) 2021;57:283.
30. Kory P, Kanne JP. SARS-CoV-2 organising pneumonia: 'Has there been a widespread failure to identify and treat this prevalent condition in COVID-19?'. BMJ Open Respir Res 2020;7:e000724.
31. Polak SB, Van Gool IC, Cohen D, von der Thüsen JH, van Paassen J. A systematic review of pathological findings in COVID-19: a pathophysiological timeline and possible mechanisms of disease progression. Mod Pathol 2020;33:2128-38.
32. Katzenstein AL, Bloor CM, Leibow AA. Diffuse alveolar damage--the role of oxygen, shock, and related factors. A review. Am J Pathol 1976;85:209-28.
33. Epler GR. Bronchiolitis obliterans organizing pneumonia, 25 years: a variety of causes, but what are the treatment options? Expert Rev Respir Med 2011;5:353-61.
34. Epler GR, Colby TV, McLoud TC, Carrington CB, Gaensler EA. Bronchiolitis obliterans organizing pneumonia. N Engl J Med 1985;312:152-8.
35. Kim JY, Doo KW, Jang HJ. Acute fibrinous and organizing pneumonia: Imaging features, pathologic correlation, and brief literature review. Radiol Case Rep 2018;13:867-70.
36. Bahl A, Johnson S, Chen NW. Timing of corticosteroids impacts mortality in hospitalized COVID-19 patients. Intern Emerg Med 2021;16:1593-603.
37. Onishi Y, Kawamura T, Higashino T, Mimura R, Tsukamoto H, Sasaki S. Clinical features of acute fibrinous and organizing pneumonia: An early histologic pattern of various acute inflammatory lung diseases. PLoS One 2021;16:e0249300.
38. Yao M, Tang T, Lin X, Jiang S. Mechanism of glucocorticoid for treating severe COVID-19 patients. Am J Pharmacol 2020;3:1028.
39. Bradley B, Branley HM, Egan JJ, Greaves MS, Hansell DM, Harrison NK, et al. Interstitial lung disease guideline: the British Thoracic Society in collaboration with the Thoracic Society of Australia and New Zealand and the Irish Thoracic Society. Thorax 2008;63 Suppl 5:v1-58.
40. Park IN, Kim DS, Shim TS, Lim CM, Lee SD, Koh Y, et al. Acute exacerbation of interstitial pneumonia other than idiopathic pulmonary fibrosis. Chest 2007;132:214-20.