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CASE SERIES

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A case series of three patients with histologically proven post COVID-19 organizing pneumonia

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Abstract

Organizing pneumonia, a form of interstitial lung disease, may occur in patients who have recovered from COVID-19. In this article, we report three cases of post COVID-19 organizing pneumonia, proven histologically with transbronchial biopsies showing fibroblastic plugs in the alveolar spaces. Our patients received a range of 86–166 days of continuous corticosteroid therapy and all of them made excellent recovery.

KEYWORDS
COVID-19, organizing, pneumonia

INTRODUCTION

Coronavirus disease 2019 (COVID-19) is caused by severe acute respiratory syndrome coronavirus (SARS-CoV-2) infection. It has resulted in a pandemic since its emergence in Wuhan, China, in December 2019. The severity of the disease ranges from asymptomatic infections to severe pneumonia with respiratory failure and death.[1] Post COVID-19 organizing pneumonia (PCOP) is a rare but serious complication that can occur in some patients who have recovered from COVID-19.[2] PCOP is a form of interstitial lung disease, characterized histologically by fibroblastic plugs of alveolar spaces that may also extend up into the bronchioles, which can lead to scarring and permanent damage to the lungs. In this article, we report three cases of PCOP and discuss its epidemiology, clinical features, diagnosis and treatment.

CASE SERIES

Case one

The patient is a 40-year-old man with a past medical history of poorly controlled type two diabetes mellitus, end stage renal failure requiring hospital haemodialysis, hypertension, obesity and ischaemic heart disease. He was vaccinated with three doses of CoronaVacs prior to COVID-19 infection, with symptom onset on 19/12/2022 (COVID-19 Day 0). On COVID-19 day 1, he presented to the Accident and Emergency Department with fever and dyspnoea, with no desaturation initially. Physical examination of the chest was unremarkable. His chest x-ray (CXR) showed right lower zone consolidation. COVID-19 was confirmed by the detection of SARS-CoV-2 RNA by using real-time reverse-transcription polymerase chain reaction (RT-PCR) in his nasopharyngeal and throat swab specimens. Molnupiravir was initiated along with empirical co-amoxiclav. On COVID-19 day 2, the patient developed type one respiratory failure requiring high flow nasal cannula (HFNC) support with FiO2 of 0.4. CXR was repeated which showed new right middle zone consolidation. His white cell count (WCC) was 13.3×10^9/L and C-reactive protein (CRP) was 275 g/L. Intravenous (IV) dexamethasone 6 mg daily was started, antiviral was changed to remdesevir and antibiotics to piperacillin/tazobactam. On COVID-19 day 7, he appeared to have recovered from acute COVID-19 with CXR showing resolved right sided consolidation and white cell count improved to 9.2×10^9/L. His oxygen was weaned off and he was discharged home.

On COVID-19 day 15, the patient was admitted to the hospital again for dyspnoea, requiring 2 L/min of oxygen (O_2). His CXR showed bilateral consolidation, WCC was 12.7×10^9/L and CRP was 191 g/L. He was treated for

bacterial pneumonia with IV cefoperazone/sulbactam and later IV meropenem with no significant improvement. On COVID-19 day 28, he remained on 2 L/min O_2. His WCC was 8.9 × 10^9/L and CRP was 209 g/L. Computed tomography (CT) of thorax with IV contrast showed diffuse mixed ground glass opacities (GGO), consolidative changes and reversed halo signs in both lungs (Figure 1). Flexible bronchoscopy was performed on COVID-19 day 31, with transbronchial biopsy (TBBx) taken over the right middle lobe and right lower lobe showing an organizing pneumonia (OP) pattern on histological examination. Bronchoalveolar lavage (BAL) at RB4 was negative for *Pneumocystis jirovecii* (PCP) culture, acid-fast bacilli (AFB) culture and bacterial culture. Cytomegalovirus (CMV) by early antigen fluorescent foci (DEAFF) was negative and no malignant cells were identified. The patient, weighted 93 kg, was started on prednisolone 40 mg on COVID-19 day 28, due to high suspicion of PCOP before histology was obtained, and was gradually tapered over 94 days. His O_2 was weaned off soon after initiation of prednisolone. No significant side effects from corticosteroid were reported. CXR at the end of corticosteroid treatment showed resolved bilateral consolidation with normal inflammatory markers. He reported no residual dyspnoea.

Case two

The patient is a 72-year-old man with a past medical history of chronic hepatitis B, asthma, stroke, hyperlipidaemia, hypertension, type two diabetes mellitus and chronic kidney disease. He was vaccinated with three doses of CoronaVacs prior to COVID-19 infection on 22/12/2022 (COVID-19 day 0), diagnosed by rapid antigen test. He was admitted on COVID-19 day 4 for fever and dyspnoea, requiring 2 L/min of O_2 support. CXR showed right lower zone consolidation, WCC was 10.3 × 10^9/L and CRP was 73 g/L. He was treated with IV dexamethasone 6 mg daily for 6 days, co-amoxiclav and remdesevir. On COVID-19 day 11, the patient complained of worsened dyspnoea and required FiO_2 0.5 via a non-rebreathable mask. Chest examination revealed bilateral wheeze and he was treated for infective asthma exacerbation with IV hydrocortisone 100 mg every 8 h for 4 days,

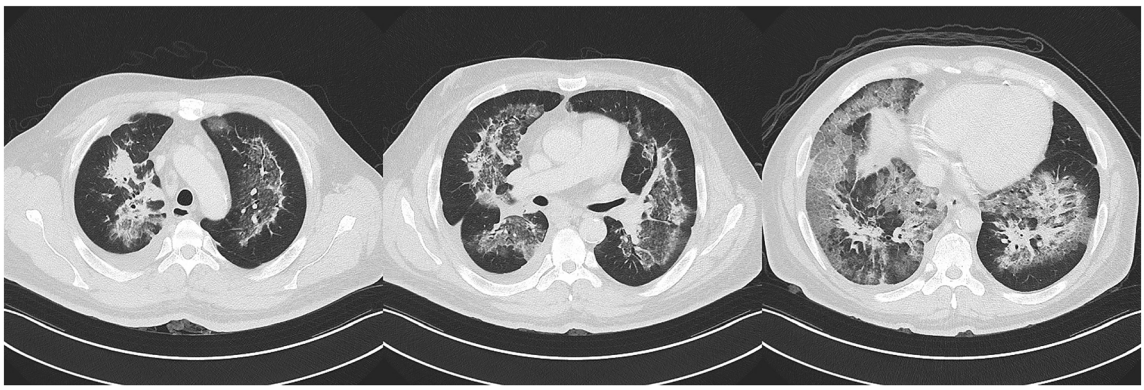

FIGURE 1 Computed tomography thorax of Case 1 showed diffuse mixed ground glass opacities, consolidative changes and reversed halo signs in both lungs.

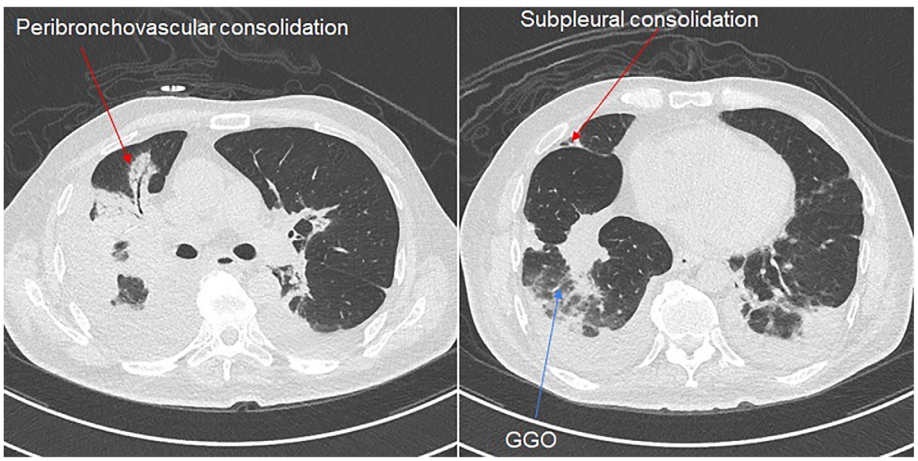

FIGURE 2 High resolution computed tomography thorax of Case 2 on COVID-19 day 28 showed bilateral peribronchovascular and subpleural consolidation with patchy ground glass opacities.

meropenem, salbutamol inhaler and ipratropium inhaler. By COVID-19 day 17, his O_2 requirement remained at 2 L/min and CXR showed increased right middle zone consolidation.

On COVID-19 day 28, the patient still required 2 L/min O_2 and his WCC was 10.3×10^9/L and CRP was 57 g/L. High resolution CT thorax showed bilateral peribronchovascular and subpleural consolidation with patchy GGO (Figure 2). Flexible bronchoscopy was performed on COVID-19 day 39, with TBBx taken over the right upper lobe showing an OP pattern with fibroblastic plugs in alveolar spaces on histological examination (Figure 3). BAL at RB2&3 was negative for PCP culture, AFB culture and bacterial culture, with no malignant cells identified. CMV DEAFF was positive, but no viral inclusion was seen on histological examination of TBBx. The patient, weighed 70 kg, was treated with prednisolone 30 mg daily for PCOP with a tapering dose and his oxygen was shortly weaned off. Including the initial dexamethasone and hydrocortisone treatment, he received 86 days of corticosteroid in total. No significant side effects from corticosteroid were reported. At the end of the treatment course, the patient reported no dyspnoea. His CXR showed bilateral ground glass opacity, likely signifying consolidation absorption.

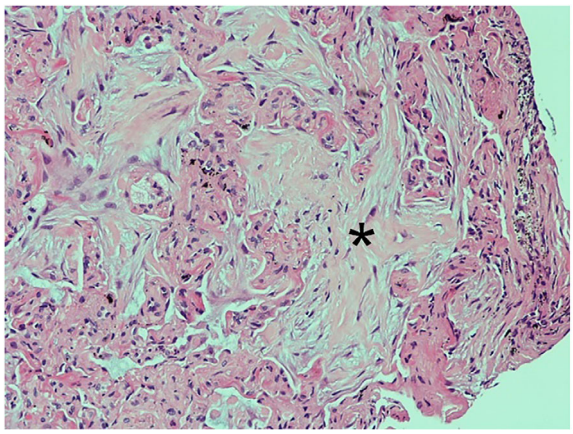

FIGURE 3 A pathology slide of transbronchial biopsy taken over the right upper lobe of Case 2 showed an OP pattern with fibroblastic plugs (asterisk) in the alveolar spaces.

Case three

The patient is a 73-year-old man with a past medical history of hypertension, type two diabetes mellitus, hyperlipidaemia, epilepsy, obesity and metastatic renal cell carcinoma. He was vaccinated with two doses of Comirnaty prior to COVID-19 infection on 24/3/2022 (COVID-19 day 0), diagnosed by rapid antigen test. He was treated in an outpatient clinic with a 5-day course of Molnupiravir since COVID-19 day 2 and appeared to have recovered well. On COVID-19 day 26, he complained of shortness of breath and was admitted to hospital the same day. He was given 2 L/min of oxygen. His WCC was 5.5×10^9/L and CRP was not checked. CT thorax on COVID-19 day 27 showed patchy consolidation involving all lobes and patchy GGO at left lung apex (Figure 4). Flexible bronchoscopy on COVID-19 day 35 with TBBx taken over the right upper lobe confirmed the diagnosis of PCOP. BAL at RB3 was negative for PCP culture, AFB culture and bacterial culture. CMV DEAFF was negative, and no malignant cells were identified. The patient, weighed 92 kg, was started on prednisolone 60 mg daily which was gradually tapered over 166 days. He recovered well with no dyspnoea after the completion of treatment. No significant side effects from corticosteroid were reported. CT thorax after steroid treatment showed resolution of the previously seen multifocal consolidations, which were largely replaced with scattered linear fibrotic changes in both lung fields (Figure 4).

DISCUSSION

Persistent respiratory symptoms post COVID-19 likely have various and often co-existing aetiology, including myopathy and deconditioning, thromboembolism, cardiac injury, ventilator induced lung injury, post-acute respiratory distress

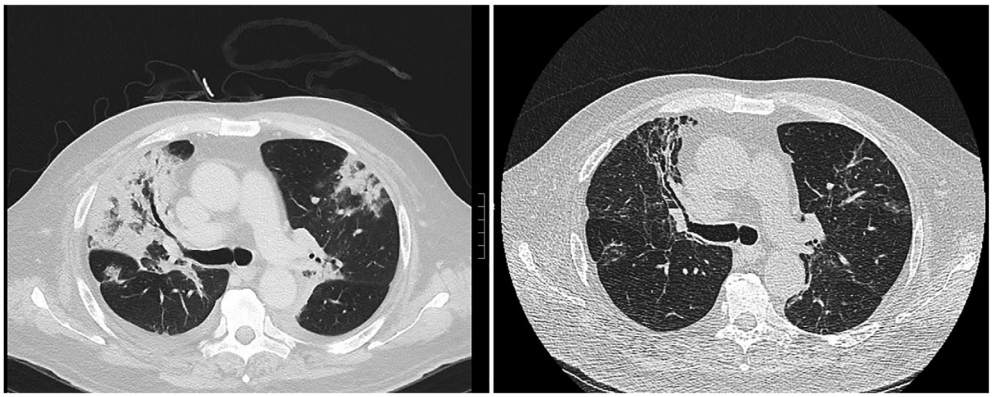

FIGURE 4 Computed tomography thorax of Case 3 before (left) and after (right) receiving 166 days of oral prednisolone as treatment for post COVID-19 organizing pneumonia.

syndrome and PCOP.[3] OP has various etiologies. It can be either cryptogenic, or secondary to infection, drug reaction, radiotherapy, connective tissue disease, inflammatory bowel disease, diffuse alveolar damage, haematological malignancies, post-bone marrow transplant, lung malignancies, pulmonary infarct, and so on.[4] Various viral infections have been reported to cause OP, including influenza, parainfluenza, cytomegalovirus (CMV), adenovirus, human Immunodeficiency Virus, herpes simplex virus, Middle East respiratory syndrome coronavirus and severe acute respiratory syndrome coronavirus.[5]

PCOP typically presents with dyspnoea and dry cough, often with fever and malaise. The epidemiology of PCOP is unknown and data were drawn from small studies only. Bazdyrev et al. reported the probability of having PCOP within 3 months after hospitalization for COVID-19 to be around 5%.[2] Studies have found PCOP to be more prevalent in patients who were hospitalized for severe COVID-19.[6] Its prevalence can be as high as 58% among COVID-19 patients admitted to a respiratory intermediate care unit, who required non-invasive respiratory support with HFNC, continuous positive airway pressure and/or non-invasive ventilation.[7] The quoted prevalence varies due to different definitions of PCOP used in studies, ranging from radiological diagnosis to PCOP with histological proof.

High resolution computed tomography is an important investigation for diagnosing OP.[8] Radiological features of OP include peripheral and peribronchovascular consolidations, bandlike consolidation and reversed halo sign.[9] It is important to remember these features are not specific to OP, and they often overlap with acute COVID-19 radiological features, including subpleural GGO, consolidation and crazy paving pattern.[10] Therefore, we believe performing flexible bronchoscopies for histological verification is important for diagnosing PCOP, and at the same time, ruling out other diagnoses such as fungal pneumonia and CMV pneumonitis. In all three PCOP cases described, we performed 6–8 TBBx for each subject. Histological exam revealed fibroblastic plugs of alveolar spaces (Figure 3), which is characteristic of OP. In our centre, unless contraindicated or refused by the patient, we have been performing flexible bronchoscopy with TBBx on all patients with suspected PCOP.

The mainstay of PCOP treatment is corticosteroid. However, there is no consensus on its optimal duration and dosage. Myall et al. suggested a regimen of 0.5 mg/kg/day prednisolone with a rapid wean over 3 weeks, which increased the transfer factor and forced vital capacity, with significant symptomatic and radiological improvement.[11] Dhooria et al. reported improvement in dyspnoea and radiological features of post-COVID-19 diffuse parenchymal lung abnormalities with prednisolone 10 mg/day for 6 weeks. However, both studies lack a control arm and therefore cannot prove if patients with PCOP could have improved spontaneously without any corticosteroid.[12]

The RECOVERY trial[13] published in the New England Journal of Medicine on 17th July 2020 has transformed the treatment of acute COVID-19 around the world. In patients hospitalized with COVID-19, who received either invasive mechanical ventilation or oxygen alone, the use of dexamethasone resulted in lower 28-day mortality. However, studies cannot prove if treatment with dexamethasone for acute COVID-19 infection can impact the incidence and clinical outcome of PCOP.[14]

In summary, we reported three cases of histologically proven PCOP, an important diagnosis to suspect when patients have persistent dyspnoea after the initial COVID-19 symptoms. Corticosteroid is often prescribed but its optimal dose and duration are unknown. Our patients received a range of 86–166 days of corticosteroid with good radiological and symptom response.

AUTHOR CONTRIBUTIONS

Cheuk Cheung Derek Leung drafted the case series. Yiu Cheong Yeung was involved in the final approval of the version to be published.

CONFLICT OF INTEREST STATEMENT

None declared.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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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