Post COVID-19 organizing pneumonia treated with mycophenolate mofetil

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INTRODUCTION

The spread of SARS-CoV-2 coronavirus has resulted in the COVID-19 pandemic. The clinical course of the disease is highly variable ranging from asymptomatic infection to multi-organ failure. Pulmonary disease (COVID-19 pneumonia) is the commonest manifestation leading to hospitalization. The post-acute COVID-19 pneumonia phase is generally favourable with variable rates of progressive recovery. Nevertheless, a subset of patients continues to have significant clinico-physiologic deficits with persistent inflammatory interstitial lung disease (ILD) changes resembling an organizing pneumonia (OP) pattern on radiology. Decades of cumulative experience have established corticosteroids as a highly effective and successful therapy for OP but rarely cases of steroid-resistant OP or fibrosing variant of OP have been encountered, with positive outcomes reported using mycophenolate mofetil (MMF, Mycofit®).

The following case reports describe post COVID-19 OP patients pre-vaccination era with clinically inadequate response to corticosteroids but who improved after the addition of mycophenolate Mofetil (MMF). Case 1: A gentleman was diagnosed with post COVID-19 OP but had suboptimal clinico-physiologic-radiologic response and steroid toxicity during outpatient reviews. MMF was initiated resulting in marked clinical response and quick weaning from corticosteroids. Case 2: A gentleman with post COVID-19 OP relapsed during tapering of steroids. Clarithromycin and MMF were added to his regimen, which improved his clinico-physiologic parameters and allowed corticosteroid tapering. Unfortunately, he developed MMF-related colitis needing therapy cessation. Currently, no studies have reported on MMF utilization in difficult post COVID-19 OP patients. Nevertheless, we believe, similar as in non-COVID OPs, MMF or other immunomodulators, potentially have a role in treating difficult or steroid-resistant OPs.
remained oxygen-dependent on nasal prong 3 L/min. High resolution computed tomography (HRCT) of his lungs were performed and revealed severe post-infectious OP. Therefore, we decided to start Clarithromycin as a form of immunomodulator to aid in his recovery. But the trial of Clarithromycin was aborted due to QTc interval

**FIGURE 1** Physiologic objective evaluation using 6-minute-walk-test, FVC and DLCO shows a gradual improvement & stabilization during the course of treatment

**FIGURE 2** Serial CT imaging during the course of treatment shows marked improvement in terms of reduction of areas of interlobular septal thickening and ground glass opacities in bilateral lungs
prolongation. This given the fact that patient was also diagnosed to have post-viral dilated cardiomyopathy with an ejection fraction of 35%. He was prescribed high dose oral prednisolone 50 mg OD (0.75 mg/kg/od) and was finally discharged after 28 days without needing oxygen therapy.

Nonetheless, he continued to have suboptimal clinico-physiologic-radiologic response despite remaining on high dose prednisolone (40 mg OD). His steroid toxicity (facial puffiness, rapid weight gain and myopathy) quickly became apparent during outpatient reviews. He complained of worsening dyspnea with a desaturation of 88% therefore was admitted in-patient for a CT Pulmonary Angiogram to rule out the possibility of pulmonary embolism. The repeated CTPA after prolonged treatment of steroids showed residual fibrosing OP thus MMF was initiated. MMF was initiated at 500 mg twice daily (BD) to assess tolerability then was increased to 1 g BD after 2 weeks. Patient experienced mild side effects from MMF which was mild colicky abdominal pain but that quickly subsided after a week. With the initiation of MMF, he showed marked clinical response and was quickly weaned from corticosteroids. During his follow ups, his overall clinic-physiologic-radiologic response was promising throughout his treatment with MMF as evidenced in Figures 1 and 2. The total duration of MMF treatment was 6 months. Patient continues to thrive during follow ups and has returned to his normal duty as a navy officer.

Patient 2

Our second patient is a 56-year-old gentleman who is an ex-smoker with co-morbidities of type 2 diabetes mellitus, hypertension, and dyslipidemia. As for our patient 1, he also had not been vaccinated. He was diagnosed to have acute SARS-CoV-2 infection (Category 4)—highest oxygen requirement was nasal prong 3 L/min. He was given a course of Dexamethasone and oral Favipiravir during his

**FIGURE 3** Physiologic objective evaluation using 6-minute-walk-test, FVC and DLCO shows a gradual improvement & stabilization despite cessation of therapy due to colitis

**FIGURE 4** Serial CT imaging showing fibrotic progression despite on a protracted course of corticosteroids
course of infection. Patient was discharged home after 15 days with tapering oral prednisolone.

During his steroid tapering he was readmitted for hypoxemic respiratory failure. His sputum and blood microbiological workup for secondary bacterial infections were all negative. The repeated HRCT showed fibrotic progression of the previously seen OP pattern (Figure 4). He was then diagnosed with relapse OP therefore Clarithromycin & MMF were added to his regimen. The dose given for Clarithromycin was 250 mg BD whilst MMF was initiated at 500 mg BD then increased to 1gm BD after 2 weeks. We were able to witness improvements in his clinico-physiologic parameters and this allowed further corticosteroid tapering. Unfortunately, he developed severe episodes of diarrhoea with blood-streak stools after 10 weeks of MMF. He was admitted for hydration and colonoscopy performed showed no abnormalities necessitating cessation of both Clarithromycin and MMF. We also ruled out Clostridium Difficile infection since he had been on Clarithromycin. Nevertheless, despite stopping MMF, our patient continued to improve as evident in Figure 3. He also remains clinically stable despite further corticosteroid tapering. Low-dose prednisolone was eventually completed and stopped at week 40 since presentation and our patient remains well during his follow-ups.

DISCUSSION

A rising number of post-COVID-19 persistent inflammatory ILDs like fibrotic interstitial lung disease or progressive pulmonary fibrosis are emerging. An observational study conducted by Han et al illustrated the natural course post-COVID-19 during a 6-month follow up, found 35% of them have fibrotic-like changes on chest CT; 27% had remnants of ground-glass opacities or interstitial thickening, and only 38% had complete radiological recovery. The study was also able to identify the risk factors associated with lung fibrotic changes, that is, age over 50 years, heart rate >100 beats per min at admission, hospital stay of 17 days or more, ARDS and non-invasive ventilation.

An OP-like pattern is the commonest appearance radiologically although there is a paucity in the number of studies proving it to be histological OP. Given the burden of the pandemic, invasive procedures are not routinely performed, thus histological evidence was not pursued in both our cases. We decided to treat it as post-infectious OP based on radiological evidence.

We also acknowledge the natural history of this entity is not yet clear and there is every possibility that the patients could have spontaneously improved. Rapid and complete recovery with corticosteroids was to be expected in secondary OP when the primary insult has been rectified. Nevertheless, treatment was justified on the grounds that the patients were very symptomatic and had evidence of respiratory failure. Corticosteroid response was less than expected for a typical case of OP and steroid-toxicities were progressively building up. There is no evidence-base or proven regimen for such a clinical scenario; in other words, steroid-resistant OP or fibrosing variant of OP is unchartered territory.

MMF was chosen in view of its increasing use as a steroid sparing agent for interstitial lung disease and in our centre as we have extensive experience with it. The active component is mycophenolic acid (MPA); MPA reduces T cells proliferation by interrupting the synthesis phase of cell division. It also suppresses the formation of adhesion molecules in endothelial cells, resulting in reduced recruitment of lymphocytes to the site of inflammation leading to less cytokine production. MMF was an effective agent in terms of aiding both patients in resolving their respiratory failure. However, the exact mechanism of its benefit in OP is unknown.

MMF appears to have benefitted both our patients based on the trajectory of response. However, this is not a placebo-controlled setting, and we will be the first to acknowledge and implore for more clinical trials and registries in the near future to enhance our understanding and treatment of post-COVID-19 persistent inflammatory ILDs. More histological-based studies are also needed to complement the radiological appearances of post-COVID-19 lung sequelae. Nevertheless, we hope by sharing these case series, we are able to highlight the possibility of using steroid-sparing or alternative immunosuppressants (e.g. MMF) for the treatment of post-COVID-19 persistent inflammatory ILDs with an OP pattern.

AUTHOR CONTRIBUTIONS

Hui Xin Tan conceptualized the design of the work. Together Hui Xin Tan, Chee Kin Wong, Weng Fai Yik & Yoke Fong Lam contributed towards acquisition, analysis, interpretation of the results and drafting of the manuscript. Kumaresh Raj Lachmanan revised critically important content and supervised the study. Hui Xin Tan wrote the original draft and all other co-authors worked together to revise it.

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CONFLICT OF INTEREST

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 written informed consent was obtained from patients for the publication of this manuscript and accompanying images.

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