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Clarithromycin in Post COVID-19 Organizing pneumonia

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To the Editor,

An increasing number of patients are reporting with symptoms secondary to post COVID-19 pulmonary sequelae. Radiological findings in these patients include fibrotic lung disease, interstitial lung abnormalities, ground glass opacities, and organizing pneumonia (OP). Therapeutic options in these patients include steroids and anti-fibrotics. The majority of these patients have received steroid therapy for COVID-19 pneumonia, and may continue to receive it for post COVID-19 pulmonary sequelae, subjecting themselves to steroid related adverse effects. Cryptogenic organizing pneumonia (COP) responds well to steroid therapy. Alternatively, macrolide therapy has been successful in the treatment of both cryptogenic and secondary forms of OP. Compared to steroid therapy, macrolide therapy in COP is well tolerated and associated with fewer adverse events. We report two patients who were diagnosed with post COVID-19 OP who were treated successfully with clarithromycin for three months. We believe that clarithromycin offers a potential therapeutic option in post COVID-19 organizing pneumonia.

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Our first patient was a seventy-year-old female who presented with non productive cough and exertional dyspnea of two weeks duration. Two weeks ago, she was discharged after being hospitalized for twelve days for COVID-19 pneumonia with hypoxemia, and was treated with oxygen therapy, once daily subcutaneous low molecular weight heparin (LMWH), intravenous methylprednisolone and remdesivir. On discharge, since she continued to remain hypoxemic, she was advised to continue oral dexamethasone 6 milligram (mg) per oral (PO) (tapering doses) along with home oxygen with recommended flow of two liters per minute, with which, she maintained a peripheral saturation of 94%, for another ten days post discharge. She had no other past medical history. Clinical examination revealed a respiratory rate of 18 per minute with peripheral saturation of 95% with room air, and she had discontinued home oxygen two days ago. She had bilateral inspiratory crepitations on chest auscultation. Computed tomography (CT) of chest presently revealed bilateral peripheral interlobar septal thickening with ground glass opacities in both upper and lower lobes, along with lower lobe predominant peribronchovascular and subpleural coalescing consolidation and areas of peripheral perilobular pattern of thickening surrounding an area of normal attenuation with a solid nodule within its center, suggestive of the target sign (Figure 1). Overall, the radiology was suggestive of organizing pneumonia (OP). She was initiated on oral clarithromycin PO 500 mg twice daily for three months. She was reviewed monthly, during which her symptoms were reported to have

resolved by a month, and did not have any side effects to the medicine. After completing three months of therapy, repeat CT of chest was performed, which showed subtle peripheral interstitial and ground glass opacities, with remarkable clearance of the earlier consolidatory changes (Figure 1). Spirometry at this time was normal.

Our second patient was a sixty-seven-year old male, with past history of long standing diabetes mellitus, systemic hypertension, and hypothyroidism, who presented with exertional dyspnea of over one month duration. He was diagnosed with COVID-19 pneumonia over six weeks ago, following two days of fever and immediately self-quarantined himself at home. However, two weeks later, he developed dyspnea, and was hospitalized after being found to be hypoxemic. A CT scan of chest performed at this time (third week of illness) revealed bilateral peripheral ground glass opacities with interlobar septal thickening. He required supplementary oxygen, and was initiated on intravenous methylprednisolone along with once daily LMWH. He was discharged, after a hospital stay of twelve days, on a two week course of tapering doses of oral prednisolone, and was advised to continue home oxygen at a flow rate of two liters per minute to maintain a saturation of 94%. Two weeks later (sixth week of illness), he no longer required supplementary oxygen, but continued to have dyspnea. Clinical examination revealed a respiratory rate of 20 per minute with peripheral saturation of 94% with room air, and he had discontinued home oxygen five days ago. He had bilateral inspiratory crepitations on chest auscultation. CT thorax scan was repeated which revealed peribronchovascular and peripheral interlobar septal thickening, ground glass opacities, traction bronchiectasis, and perilobular pattern of interstitial thickening with central clearance in right lower lobe, overall suggestive of organizing pneumonia (Figure 1). He was initiated on oral clarithromycin PO 500 mg twice daily for three months. He was reviewed monthly, during which his symptoms gradually resolved, and he did not develop any side effects to the medicine. After completing three months of therapy, repeat CT of chest was performed, which showed interstitial abnormalities, reduction in ground glass opacities, and a thinned out remnant of the target sign, with resolu-

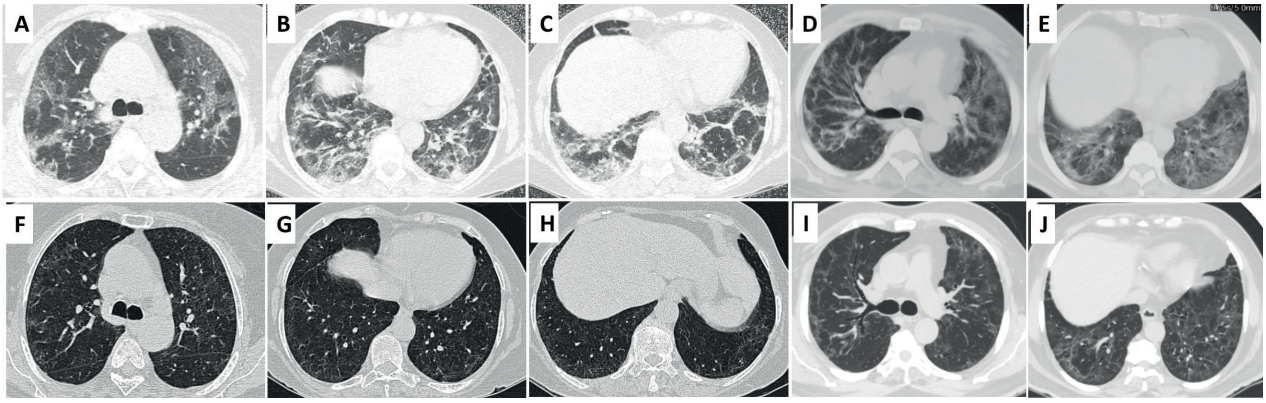

Figure 1. CT scan of chest of our first patient at presentation (A, B and C) (fifth week after onset of COVID-19 pneumonia), and after three months of oral clarithromycin therapy (F, G and H). A, B and C - CT scan of chest at level of carina (A), and apex (B) and distal right hemidiaphragm (C) show interlobar septal thickening with ground glass opacities in peripheral distribution (A), peribronchovascular thickening (B and C), peripheral coalescing consolidation right lower lobe (C) and perilobular pattern of thickening surrounding an area of normal attenuation with a solid nodule within its center (left lower lobe) (C), suggestive of the target sign, overall favouring organizing pneumonia. CT scan of chest at similar levels (F, G and H) show subtle interstitial and ground glass abnormalities, with resolution of the earlier changes. CT scan of chest of our second patient at presentation (D and E) (sixth week after onset of COVID-19 pneumonia), and after three months of oral clarithromycin therapy (I and J). D and E - CT scan of chest at level of carina (D) and right hemidiaphragm (E) show peribronchovascular thickening and peripheral interlobar septal thickening (D), ground glass opacities seen in left upper (D) and lower (E) lobes, traction bronchiectasis in left lower lobe (E), and perilobular pattern of interstitial thickening with central clearance in right lower lobe (E) suggestive of organizing pneumonia. CT scan of chest at similar levels (I and J) shows interstitial abnormalities with reduction in ground glass opacities (I), and a thinned out remnant of the target sign seen in right lower lobe (J), with resolution of the peribronchovascular thickening and reduction in traction bronchiectasis.

tion of peribronchovascular thickening and reduction in traction bronchiectasis (Figure 1).

Organizing pneumonia is a distinct entity characterized pathologically by the development of fibroplastic polypoidal aggregation of organizing inflammatory exudate within alveoli and smaller bronchioles, with preservation of normal lung architecture. When etiology is unknown, it is referred to as cryptogenic organizing pneumonia (COP). The secondary forms occur due to various insults, both infective and non-infective. Patients may often present subacutely with symptoms, such as fever, cough, and dyspnea, or may occasionally be asymptomatic (1-4). CT of chest may show peribronchovascular or peripheral lobar or multilobar consolidation, sometimes with areas of central ground glass opacities surrounded by peripheral consolidation, referred to as the reverse halo sign (1,4-6). In recent times, OP has been increasingly reported following COVID-19 infection with SARS-CoV-2 virus, with the recognition of a myriad of radiological signs such as the reverse halo sign, perilobular pattern, and the target sign (5-7). These signs have good positive predictive value for OP, and do not necessitate lung biopsy for pathological confirmation in an appropriate clinical context, but requires workup for secondary causes of OP to conclusively diagnose cryptogenic OP (1,4,8,9). Though corticosteroid is the mainstay of treatment in crytogenic forms of OP (COP). , several authors have over the last two decades reported resolution of COP with macrolide therapy, either azithromycin, or more commonly clarithromycin, with duration of therapy ranging between three and twelve months (2-4,10). Macrolide is believed to work in these patients due to its anti-inflammatory effect, which has been documented by the decrease in inflammatory cytokines in bronchoalveolar lavage and serum accompanying treatment with clarithromycin in patients with COP (4,11). Compared to corticosteroid, therapy with macrolide was accompanied by lesser adverse events, and was better tolerated. Complete remission rates with macrolide, however, are less than with prednisolone (3). Interestingly, unlike in patients treated with corticosteroids, on long term follow up, relapse was less commonly reported in patients who have responded to macrolide therapy. In patients who failed to show radiological response to macrolide or relapsed after stopping macrolide, subsequent treatment with corticosteroid therapy often was accompanied by remission (2,3).

The role of clarithromycin in secondary forms of OP has also been documented in literature. OP occurring in the background of HIV infection, post lung transplantation, rheumatoid arthritis and radiotherapy has been reported to respond to clarithromycin therapy. However, the etiology was likely crytogenic in the first as extensive infective workup was negative, and prednisolone was administered together with clarithromycin in the latter two (12-15). Combining clarithromycin with prednisolone was attempted in the last group with the aim of reducing total cumulative prednisolone dose, and was non inferior to prednisolone alone in terms of remissions and relapse in this group of patients (15).

The role of macrolide in management of COVID-19 has not been promising (16). Earlier during the pandemic, azithromycin when administered along with hydroxycholoroquine failed to show any clinical benefit in patients with moderate COVID-19 disease (17). Subsequent studies have failed to show any benefit of azithromycin alone, in reducing symptoms or hospitalization in patients with moderate COVID-19 disease (18,19). With the SARS-CoV-2 pandemic running over two years, physicians worldwide are facing an increasing number of patients reporting with respiratory symptoms secondary to post COVID-19 pulmonary sequelae. A number of therapeutic options have been attempted in these patients, including oral corticosteroid and antifibrotics such as nintedanib (20,21). However, there is no published literature on clarithromycin or azithromycin use in OP secondary to COVID-19.

In both our patients, the radiological pattern of OP recognized shortly after COVID-19 was consistent with earlier published literature, and hence we did not investigate for other alternative infectious or autoimmune causes for OP. Both patients had already received systemic corticosteroid therapy during active COVID-19 infection, and both were instructed to continue tapering doses of corticosteroid therapy post discharge as well, receiving in total, close to between three and four weeks of corticosteroid therapy. This short duration of therapy however, may not have been

adequate to result in radiological response in OP, if any, and so cannot be deemed a failure. However, both patients were successfully weaned off supplementary oxygen during this phase and became eligible for macrolide therapy as per prior patient selection in earlier published literature (3). Also, we were weary of the potential side effects of prolonged corticosteroid therapy, especially regarding development of post COVID-19 secondary bacterial and fungal infections in these patients, who have just recently survived a turbulent COVID-19 infection and are still recovering from it. Reviewing earlier published literature on the success of clarithromycin in both cryptogenic and secondary forms of OP, we believed that clarithromycin was a good alternative in these patients. With clarithromycin, the repeat imaging has shown good radiological resolution in both patients. It may be argued, that the radiological changes may have resolved even without any intervention, and macrolide therapy may not be necessary in such patients. However, we believe our case series raises an interesting avenue for further research on the role of macrolide therapy in post COVID-19 OP, in the form of randomized control trials, to identify if macrolide therapy has a role in these patients, and if so, the duration required for effective therapy, as well as relapse rates, on follow up. This is specially important, as with the gradual return to normalcy of clinical outpatient services, we will be seeing a large influx of post COVID-19 patients, with a significant subset of them having OP.

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