Journal of the Postgraduate Institute of Medicine 2020; 7(1): E171 1-9
http://doi.org/10.4038/jpgim.8353

Case Report

Post-COVID-19 interstitial lung disease - An emerging problem during the current pandemic of SARS-CoV-2 infection

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Key words: SARS-CoV-2, Post-COVID–19, interstitial lung disease, pandemic

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Received: 31 Aug 2021, Accepted revised version: 12 Nov 2021, Published: 22 Mar 2022
Competing Interests: Authors have declared that no competing interests exist

Introduction

Severe acute respiratory syndrome corona virus 2 (SARS-CoV-2) infection was first reported from Wuhan, China, in December 2019 [1]. It has spread all over the world rapidly, during the past one and half years. The World Health Organization (WHO) declared it a pandemic in March 2020. As of 20th September 2021, it had affected two hundred and twenty-nine million three hundred and twenty-nine thousand four hundred and six people and caused four million seven hundred and five thousand eight hundred and ninety deaths, worldwide [2]. Corona virus disease-19 (COVID-19) has a wide spectrum of presentations ranging from mild upper respiratory tract symptoms in the majority to severe pneumonia with adult respiratory distress syndrome (ARDS) [3]. Approximately, 80% of infections are mild, 15% of infections are severe and the remaining 5% are life threatening [4]. As there is a vast population of patients living after COVID-19 infection, the sequelae of the disease will cause a major disease burden in the near future.

One of the most important and debilitating sequelae is post-COVID-19 interstitial lung disease (ILD) [5]. Amongst this, organizing pneumonia (OP) accounts for about 12.5% [6]. There is an important association between acute respiratory distress syndrome and the later development of organizing pneumonia among patients with severe COVID-19 [7]. Early recognition is of utmost importance, to modify the disease course in order to prevent irreversible lung injury and long-term debility.

Case Presentation

A 52-year-old patient with a history of COVID-19 four weeks previously, presented with progressive worsening shortness of breath of two weeks' duration. Shortness of breath was mainly on exertion and had worsened over time, restricting the patient's daily

activities and occupation. There was a persistent cough without sputum production or fever. He denied any chest pain, orthopnoea, frothy urine or reduced urine output. He did not have any past episodes of shortness of breath or significant medical history other than recent COVID-19. He had no history of occupational dust or allergen exposure and had no pets. He was not on any long term drugs. He denied any family history of chronic lung disease. He was a smoker with ten pack years and gave a history of regular alcohol consumption (10 IU/week) for the past twenty years.

Four weeks previously, he had been evaluated for upper respiratory tract symptoms and fever with a positive COVID-19 contact history. A rapid antigen test, performed on a nasopharyngeal aspirate, was positive for SARS-CoV-2. He was managed as a moderate COVID- 19 infection with pneumonia at a COVID-19 treatment centre. As per local guidelines, the patient was treated with supplementary oxygen, dexamethasone, enoxaparin and clarithromycin. He was discharged home after a twelve days stay at the treatment centre. The patient did not have significant breathlessness at the time of discharge.

On admission, the patient was dyspnoeic and tachypnoeic with no fever, calf swelling or tenderness or ankle oedema. Oxygen saturation on air was 80% with a respiratory rate of 30/min and lung auscultation revealed inspiratory crepitations in bilateral mid to lower lung zones with occasional rhonchi. He was haemodynamically stable with a pulse rate of 92 beats/min and a blood pressure of 130/80mmHg with an undisplaced apex.

He was admitted to a high dependency unit and was commenced on high flow nasal oxygen with a saturation target of 92-96%. Regular monitoring of vital signs was commenced. Empirical treatment with intravenous cefotaxime, after obtaining cultures, and a prophylactic dose of enoxaparin was started. Salbutamol metered-dose inhaler was also commenced for symptom relief.

Immediate arterial blood gas analysis revealed evidence of type 1 respiratory failure. His partial pressure of oxygen (pO_2) was 56mmHg, partial pressure of carbon dioxide (pCO_2) was 35mmHg with a pH value of 7.4 and a bicarbonate level of 26mmol/L. Basic blood investigations revealed a normal full blood count and mildly high inflammatory markers, with a C-reactive protein of 10mg/dL and an erythrocyte sedimentation rate of 30mm/1st hour. A SARS-CoV-2 rapid antigen test and reverse-transcriptase polymerase chain reaction (RT- PCR) test for SARS-CoV-2 were negative. COVID-19 IgG and IgM antibody tests were positive, indicative of past COVID-19. His chest X-ray revealed bilateral inflammatory shadows in the mid to lower zones, predominantly involving the left lung with sub pleural bronchiectatic changes (Figure 1).

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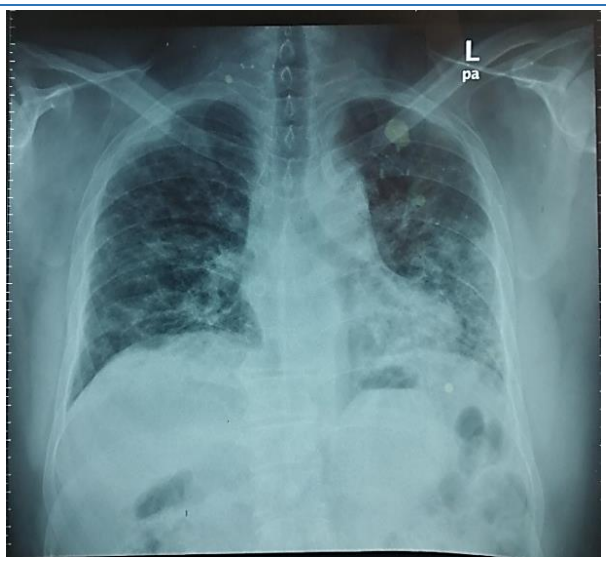

Figure 1: Chest X-ray showing bilateral inflammatory shadows and bronchiectatic changes predominantly in the mid and lower zone

His blood cultures, sputum for acid fast bacilli and sputum bacterial and fungal cultures were all negative for organisms. Nucleic acid amplification test for tuberculosis (Xpert MTB/ RIF) assay was negative. His electrocardiogram (ECG) revealed only a sinus tachycardia. His troponin test was negative. Computed tomography pulmonary angiogram revealed no evidence of pulmonary embolism, even though the D-dimer level was high, with a value of 700ng/mL. His 2-D echocardiogram was also normal, without evidence of pulmonary hypertension. Subsequent high resolution computed tomography (HRCT) revealed bilateral lower lobe and sub-pleural upper lobe consolidation, ground glass shadows with septal thickening and traction bronchiectasis (Figure 2). A diagnosis of post-COVID-19 organizing pneumonia was made based on the HRCT findings.

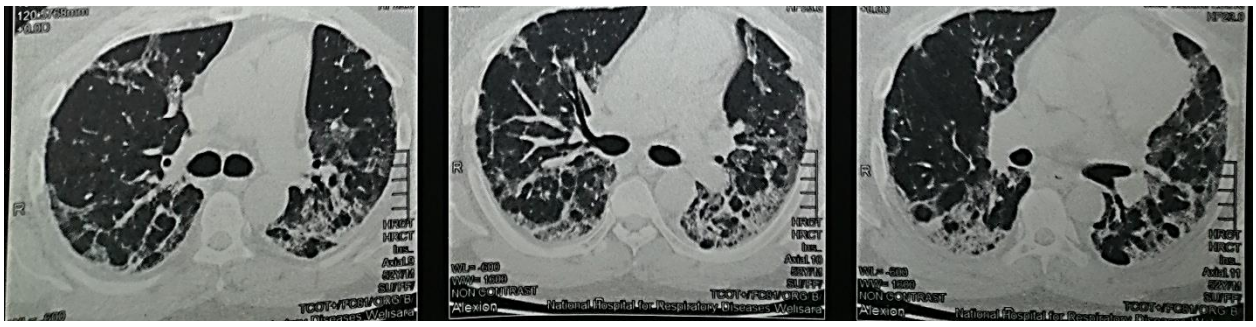

Figure 2: HRCT of chest showing bilateral consolidation and ground glass shadows with septal thickening and traction bronchiectasis.

He was commenced on pulse therapy with intravenous methyl prednisolone 1g daily for 3 days followed by oral high dose prednisolone (1mg/kg dose) with calcium lactate 200mg three times daily and vitamin D 800 IU/day. Chest physiotherapy was also initiated. His oxygen requirements gradually declined and his exercise tolerance, as assessed by the

six-minute walking test, improved. He was discharged home on corticosteroids after 10 days of treatment with a plan to continue high dose prednisolone for 3 months and then tail off. Follow up was arranged at a dedicated clinic for post-COVID-19 patients. A repeat HRCT scan and a bone density scan was planned.

Discussion

ILD is an important and a dreaded sequel of COVID-19. With the increasing numbers of COVID- 19 infections globally, even a minority affected would amount to a significant disease burden. Several studies have shown that persistent inflammatory shadows in radiographs beyond the acute stage of illness, may lead to fibrotic lung disease [7,8]. Similar fibrotic sequelae have been reported previously with Middle East respiratory syndrome-related coronavirus [9].

The predictors of lung fibrosis are increasing age, severity of illness, length of intensive care stay, mechanical ventilation, history of smoking and chronic alcohol consumption [10]. Premorbid illnesses such as hypertension, ischaemic heart disease, diabetes mellitus and obesity are risk factors for severe COVID-19 [11] and may increase the risk of later fibrosis. Initial CT severity score (CT- SS) is also an important predictive factor for progression to post-COVID-19 ILD [12]. Severe infection was also recognized among patients with preexisting ILDs [13]. There is an important association between post-COVID-19 OP type of ILD and a history of severe COVID pneumonia with ARDS [7]. Diffuse alveolar damage is seen in both [7].

The pathogenesis of post-COVID-19 ILD involves both virus related lung injury and a dysregulated host immune response [14]. The spike protein receptor binding domain of SARS- CoV-2 virus uses the angiotensin converting enzyme-2 (ACE- 2) receptor, which is mainly located in type 2 pneumocytes, to gain entry into the lung [15]. The host inflammatory response, with a cytokine storm mounted by viral entry into cells, leads to fibrotic changes. Inflammatory mediators, such as interleukin 6 (IL-6), tumor necrosis factor-α (TNF-α), transforming growth factor-beta (TGF-β) and vascular endothelial growth factor (VEGF) play a vital role in the initiation of the fibrotic cascade. Widespread vascular dysfunction also contributes to progression of fibrosis [16,17]. Diffuse alveolar damage due to dysregulated release of matrix metalloproteinases during the inflammatory phase of ARDS leading to type 2 pneumocyte hyperplasia is also a major contributor to fibro proliferation [15].

A persistent dry cough and worsening or new onset shortness of breath are common presentations in post-COVID-19 ILD [12]. Temporal association with a recent COVID-19 infection, imaging studies and, sometimes, histological examination is utilised to make a diagnosis [7]. A prospective cohort study among 114 patients who recovered from severe COVID-19 revealed that common CT findings after six months of follow up were fibrotic lung changes like honey combing, parenchymal banding and traction bronchiectasis. Others had inflammatory type infiltrates with ground glass shadows and interstitial thickening [18].

Secondary OP is known to occur following viral infections [19]. It has intra-alveolar organized exudates, composed of myofibroblasts and connective tissue, with a varying degree of inflammation as its histological hallmark [20]. Treating the underlying causative condition and systemic corticosteroids are indicated in the management [21]. Post-COVID-19 related OP, as seen in this case, is characterised by a diffuse ground glass appearance, reticular pattern, peripheral consolidation and distorted lung parenchyma [22]. Successful treatment with high dose corticosteroids resulting in oxygen independency/reduced requirement and clinical and radiologic improvement has been reported in these patients, as was seen in our patient [7,23].

Post-COVID-19 ILD, dominated by fibrosis, has currently no fully proven therapy. Various treatment strategies, such as antifibrotics, anti-inflammatory medications and immunomodulators, including biologics, are under evaluation. Prolonged use of systemic corticosteroids may prevent lung remodeling [24]. They should be used after weighing the risk vs benefits of prolonged use. The antifibrotics, pirfenidone and nintedanib, have anti- inflammatory properties as well [25]. Pirfenidone reduces lipopolysaccharide-induced acute lung injury and fibrosis by suppression of the NLRP3 inflammasome activation [26]. So, it may attenuate ARDS induced lung injury. A phase three clinical trial on 250 patients to assess the effectiveness of nintedanib (compared to placebo) for post-COVID-19 lung fibrosis is ongoing [27]. Hepatotoxicity is an important issue with both ~~the~~ agents, especially in the presence of acute COVID-19 transaminitis. Nintedanib is also known to cause an increased bleeding tendency. It may have to be used with caution in the setting of regular anticoagulation as indicated in moderate to severe COVID- 19. Markers to identify patients who are prone to develop fibrosis, who will benefit from the above antifibrotics, should be developed.

Tocilizumab, an interleukin 6 receptor antagonist, is currently approved for use in the treatment of selected severe COVID 19 victims. Both tocilizumab and sarilumab (another IL-6 inhibitor) have been shown to improve mortality in patients with severe COVID-19 [28], especially when used in conjunction with systemic corticosteroids [29]. These immunomodulatory biologic agents reduce the cytokine storm which is the hallmark of severe COVID-19 and subsequent fibrosis. The interleukin-1 receptor antagonist, anakinra, has also been shown to reduce mechanical ventilation rates [30], which is a risk factor for post-COVID- 19 lung fibrosis, in a cohort study. Use of convalescent plasma has also shown promise [31,32]. Mesenchymal cell transplantation has also been studied as a treatment modality [33]. It has multipotent ability and can replace damaged lung epithelium, inhibit fibrogenesis and act as an anti-inflammatory agent. Lung transplantation has also been considered as a treatment strategy in these patients [34]. Lung rehabilitation is beneficial both in the acute and recovery stages. It has been shown to improve lung functions, increase exercise tolerance and improve mental status [35].

As no treatment strategy has a proven benefit in the treatment of post-COVID ILD, steps to minimize the risk of development should be undertaken. Use of lung protective ventilator settings with low tidal volumes and inspiratory pressures is beneficial [36]. General advice, such as the importance of cessation of smoking to reduce lung inflammation and remodeling, is also beneficial [37]. Close follow up of patients at

dedicated clinics is of the utmost importance in order to detect post- COVID-19 sequelae early.

Conclusion

There are an increasing number of COVID- 19 survivors, globally. Therefore, post-COVID-19 sequelae have become important disease entities. Amongst them, post-COVID-19 ILD is a debilitating consequence with no definitive treatment strategies. So preventive measures to minimize lung injury are of utmost importance. The cautious use of corticosteroids, especially in the setting of OP, may be beneficial. Tocilizumab has been shown to be beneficial, especially when used along with systemic corticosteroids. Other treatment modalities including the prolonged use of antivirals and early use of antifibrotic agents needs further evaluation. In resource rich settings, mesenchymal cell transplant and lung transplant may be considered. There is a great need for evidence based treatment strategies for post-COVID- 19 ILD as it will pose a major disease burden in the near future.

Acknowledgements

We are thankful to the house officers, nursing staff and minor staff of Ward 13 of the National Hospital for Respiratory Diseases for the important role played in management of this patient.

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