Severe chronic cough relating to post-COVID-19 interstitial lung disease: a case report

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ABSTRACT

Cough is a common symptom occurring in patients with acute coronavirus disease 2019 (COVID-19) infection as well as during the post-COVID-19 period. The post-COVID-19 cough can improve over time and the incidence of sustained post-COVID-19 chronic cough is low. Approaching post-COVID-19 cough is challenging to clinicians including pulmonologists and allergists due to a diverse set of etiologies and the lack of published guidance on effective treatments. A 60-year-old male ex-smoker presented to the outpatient long COVID-19 clinic because of a prolonged cough for 4 months after a severe COVID-19 infection. His cough was so violent that he had suffered a spontaneous pneumothorax on 2 occasions. In addition, he also complained of exertional breathlessness. Due to concerns over ongoing systemic inflammation from COVID-19 or thromboembolism, a serum C-reactive protein and d-dimer were checked and were normal. Chest computed tomography (CT) images revealed diffuse ground glass opacities combined with scattered emphysema in the bilateral upper lobes and several small bullae located close to the pleura. His diagnosis was post-COVID-19 interstitial lung disease (ILD) and he was treated with methylprednisolone 32 mg/day. After 2 weeks of treatment, he showed improvement with near cessation of cough and a significant decline in dyspnea. The follow-up chest CT also showed improvement in the ground glass opacities. Severe chronic cough could be a manifestation of post-COVID-19 ILD. This case demonstrates the use of systemic corticosteroid to improve both post-COVID-19 ILD and its associated chronic cough.

Keywords: Corticosteroid; Chronic cough; Long COVID-19; Pulmonary sequelae

INTRODUCTION

The outbreak of coronavirus disease 2019 (COVID-19) pandemic, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), started with a case report in Wuhan, China and afterwards extended worldwide. Its influence was measured not only by the burden of acute communicable disease but also by the persistent physical and psychological sequelae during the convalescence stage. The post-acute sequelae, with a prevalence...
estimated at 10%-20% [1], has been referred to in the literature as post-COVID-19 syndrome, persistent COVID-19, post-acute COVID-19 sequelae, COVID-19 long-hauler, ongoing COVID-19, etc. In this manuscript we will use the term “long COVID-19” which includes both “ongoing COVID-19” (patients with symptoms lasting from 4 to 12 weeks after acute SARS-CoV-2 infection) and “post-COVID-19 syndrome” (patients with symptoms lasting more than 12 weeks). Risk factors of long COVID-19 include older age, female sex, Black and Asian racial group, minority race, underlying comorbidities, and the severity of acute SARS-CoV-2 infection [2, 3]. A study looking at predictors of long COVID-19 at the time of acute COVID-19 infection identified specific risk factors such as diabetes mellitus, the presence of SARS-CoV-2 RNAemia, Epstein-Barr virus viremia, and specific autoantibodies (anti-interferon-α and 5 antinuclear antibodies: Ro/SS-A, La/SS-B, U1-snRNP, Jo-1, and P1) [4]. Long COVID-19 can affect multiple facets of quality of life such as the performance of daily activities and the ability to work.

Cough is one of the most common symptoms in post-COVID-19 patients and is seen not only during a severe episode of acute COVID-19 infection (a brief report of 384 hospitalized patients showing the rate of persistent cough 34% [5]) as well as in mild infection with a reported incidence of 29%-43% [6]. The frequency of cough varies depending on the stage of infection (a study reported a rate of cough of 2.5% in patients one-year after COVID-19 infection [7]). This supports the widely held belief that post-COVID-19 cough can improve gradually and the rate of long-term post-COVID-19 chronic cough is low [8]. Patients with post-COVID-19 cough should be evaluated carefully for a possible etiology. Post-COVID-19 cough can be a symptom of an underlying condition not related to SARS-CoV-2 and these should be excluded before concluding an association with COVID-19 infection. There have been no reported effective treatments for post-COVID-19 chronic cough. We report a post-COVID-19 patient with severe chronic cough successfully treated with systemic corticosteroids.

**CASE REPORT**

A 60-year-old male patient presented to our outpatient long COVID-19 clinic because of prolonged cough after SARS-CoV-2 infection lasting for more than 4 months. He had not received COVID-19 vaccination and his past medical history was unremarkable with exception of a 20 pack-year smoking history and being tobacco-free for the last 10 years. His history of SARS-CoV-2 infection started with fever, progressed to breathlessness and eventually he was hospitalized and treated with oxygen via high flow nasal cannula (HFNC). Initial testing for SARS-CoV-2 was positive but turned negative after 3 weeks from symptom onset. He remained in the hospital for 2 months due to difficulty weaning him off oxygen therapy. After discharge, he had an ongoing dry cough accompanied with exertional breathlessness (modified Medical Research Council [mMRC] score 2). He coughed so frequently during the day that it affected his daily activities and quality of sleep, no alleviating factors recorded. His cough was so violent that he had suffered a spontaneous pneumothorax on 2 occasions separated by a month and both requiring admission for the insertion of a chest tube. In both instances, he described a harsh bout of cough followed by chest pain on the side of the pneumothorax. Fig. 1 showed the chest computed tomography (CT) images at the time of the first pneumothorax. For this current visit, he added complaining of lumbar pain. His vital signs included a pulse 90 beats/min, blood pressure 130/80 mmHg, respiratory rate 22/min, and peripheral oxygen saturation (SpO2) 95%-96% on ambient air. Physical examination was normal with body mass index 23.3 kg/m2. Fig. 2 illustrates the outline of disease progression.
The laboratory tests showed the cell blood count with white blood cell 9.73 G/L, lymphocytes 27.7%, red blood cell 4.53 T/L, hemoglobin 143 g/L, and platelet 291 G/L; serum glucose 121 mg/dL; glycosylated hemoglobin 5.7%; aspartate aminotransferase 22 U/L; alanine aminotransferase 16 U/L; serum creatinine 0.69 mg/dL; serum lactate dehydrogenase 231.69 U/L; serum C-reactive protein (CRP) 5.8 mg/L; d-dimer 486 ng/mL; serum cortisol 203.35 mmol/L. His electrocardiogram revealed regular sinus rhythm at 88 beats/min and echocardiogram was normal with an ejection fraction of 68%. Chest x-ray (CXR) revealed no lung parenchymal abnormality able to be detected.

Due to the history of severe cough promoting pneumothorax, we performed chest CT without contrast material to evaluate for the presence of bullae in the lung parenchymal (Fig. 3). Based on the CT findings, his diagnosis was post-COVID-19 interstitial lung disease (ILD) and treatment initiated and included methylprednisolone 32 mg/day, tramadol hydrochloride/paracetamol 37.5 mg/325 mg, calci-D, and zinc. After 2 weeks of treatment, he showed improvement with near cessation of cough and significant decline in dyspnea (mMRC
score 1, no breathlessness with 2-km walking while wearing a mask). He continued the above treatment during 4 weeks and the follow-up chest CT (Fig. 4) showed improvement in the ground glass opacities. The dose of methylprednisolone was reduced until to stop completely.

**Fig. 3.** Chest computed tomography images after severe acute respiratory syndrome coronavirus 2 infection about 5 months revealed diffuse ground glass opacities combined with scattered emphysema at the bilateral upper lobes, several small bullae located closely the parietal pleura.

**Fig. 4.** Chest computed tomography images after one month of treatment with methylprednisolone showed reduction in the ground glass abnormalities but the emphysema was unchanged.
and he was followed up at the outpatient clinic afterwards. Spirometry was not conducted due to the concern for recurrent spontaneous pneumothorax. The diffusing capacity for carbon monoxide (DLCO) revealed a mild reduction (65.3% of predicted value).

Written informed consent was obtained from participant for publication of the details of their medical case and any accompanying images.

DISCUSSION

Long COVID-19 may involve multiple organ systems such as the lungs, heart, liver, kidney, brain, thyroid gland, skin, hematologic system, etc. with a variety of symptoms. Though its pathogenesis is still poorly understood, several hypotheses suggest that the long COVID-19 could be associated with the persistence of SARS-CoV-2 components in human body, the immune dysregulation occurring after acute SARS-CoV-2 infection, the change in the human microbiome associated with COVID-19, disorder of cellular functions, or a combination of these factors [9]. It is common among patients with severely acute COVID-19 infection requiring hospital admission but is also seen in those with mild acute COVID-19 infection with or without COVID-19 vaccination. Therefore, the approach to a long COVID-19 patient involves a comprehensive medical history, thorough physical examination, and details of the progression of acute COVID-19 infection. Routine tests (include cell blood count, fasting glucose, liver enzymes, kidney function, serum electrolytes, serum CRP, d-dimer, electrocardiogram, and CXR) are essential for post-COVID-19 patients [10]. For our case, the normal levels of serum CRP and d-dimer diminished the concern of hyperinflammation and hyper-coagulation due to COVID-19 infection.

Though CXR is recommended as a routine test to evaluate post-COVID-19 patients at the long COVID-19 outpatient clinic [10], it is less sensitive than high-resolution CT of chest in detecting pulmonary abnormalities in acute COVID-19 patients [11]. Recent evidence has suggested the utility of lung ultrasound to assess for interstitial pulmonary complications in post-COVID-19 patients [12]. Our patient presented with prominent diffuse ground glass opacities and emphysema which could be difficult to detect on CXR and would require characterization with a high-resolution CT of the chest. A personalized approach is necessary to select the most appropriate radiological modality (CXR, high-resolution CT, or lung ultrasound).

Consensus guidelines on the management of chronic cough after COVID-19 infection has been recently published by the World Allergy Organization and Allergic Rhinitis and its Impacts on Asthma [13]. Identifying possible etiologies of chronic cough such as upper airway cough syndrome, cough-variant asthma, nonasthmatic eosinophilic bronchitis, and Gastroesophageal Reflux Disease are still the initial steps in its management [8]. SARS-CoV-2 infection can trigger cough in patients with a pre-existing underlying cause of cough, increase the inflammatory cytokines such as interleukin (IL)-6, IL-8 similar to post viral cough, or can be related directly to persistent interstitial inflammation of lung. In our experience, post-COVID-19 chronic cough in patients with a normal CXR often relate to upper airway cough syndrome or cough-variant asthma. Management of these possible etiologies of chronic cough should follow current recommendations. To treat chronic cough relating to post-COVID-19 pulmonary abnormality, the use of systemic corticosteroids showed efficacy in our case and could be associated with the treatment of underlying interstitial abnormalities.
The presence of post-COVID-19 pulmonary abnormality on chest CT is variable and is more commonly seen in severe acute SARS-CoV-2 infection [14, 15]. The patterns are diverse and include ground glass opacities, consolidation, linear or curvilinear band, reticular opacity, traction bronchiectasis, emphysema, and/or cysts. The pathogenesis of prolonged pulmonary complications after COVID-19 infection is not understood clearly and may be a consequence of lung injury or acute respiratory distress syndrome during the acute infection, a complication of mechanical ventilation, a result of the inflammatory process triggered or directly injured by virus, or associated with the oxidative stress from high oxygen concentrations during the acute illness [15]. For some patients, the presence of post-COVID-19 pulmonary abnormalities could be an exacerbation of pre-existing ILD. Factors that predict post-COVID-19 pulmonary complication include older age, severity of acute lung injury, high inflammatory markers at the time of acute illness, low lymphocyte, and a prolonged hospital stay [15]. Our patient was 60 years old and received long-term treatment with HFNC and was hospitalized more than 2 months which put him at risk develop post-COVID-19 pulmonary complications.

Optimal management of post-COVID-19 pulmonary disease is still unknown and several questions require further investigation. Published case series of post-COVID-19 organizing pneumonia showed a good response to treatment with systemic corticosteroids and a recent observational study also came the same conclusion [16, 17]. In spite of these successes early with corticosteroids, a prospective study with 1-year follow up reported a high rate of spontaneous remission of abnormality on chest CT without treatment [14] which is consistent with our experience in caring for post-COVID-19 patients. Therefore, management should be individualized for each patient considering possible etiologies of their pulmonary abnormalities such as superinfection, pulmonary tuberculosis, pulmonary fungal infection, and post-COVID-19 ILD. In addition, the clinician should consider the clinical progression of both the disease itself and the pulmonary abnormality, and the balance between benefits and risks of using systemic corticosteroids. Our case demonstrated long-term cough accompanied by dyspnea which worsened and chest CT with diffuse ground glass opacities suggesting that the use of systemic corticosteroids may be effective. The efficacy and appropriate use of antifibrotics or inhaled corticosteroids is not yet known.

A follow-up strategy for post-COVID-19 patients is important to evaluate the response to treatment and/or to document disease progression. Both pulmonary function tests (spirometry and DLCO) and chest images (chest CT 3 to 6 months after initiation of therapy) are essential to follow the progression of post-COVID-19 patients [10, 18, 19]. Rehabilitation should also be considered in their management. Further recommendations both in the acute management and the long-term follow-up of these patients will be seen in the near future pending ongoing studies.

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