Persistent unilateral diaphragmatic paralysis in the course of Coronavirus Disease 2019 pneumonia: a case report

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Abstract

Coronavirus Disease 2019 infections can cause a wide range of symptoms, particularly in the respiratory system. Diaphragmatic paralysis is a rare condition that is poorly documented in the literature. We present the case of a 38-year-old Caucasian male adult who developed unilateral diaphragmatic paralysis during the course of the disease. The patient presented to the Emergency Department with fever, cough, and dyspnea: at admission, he was immediately fitted with a high flow nasal cannula. When his condition worsened eight days later, he was admitted to the Intensive Care Unit and a tracheostomy was performed. A CT scan of the chest revealed significant left diaphragm elevation. On the 48th day, the patient gradually improved and was discharged. The paralysis of the diaphragm persisted three months later in the follow-up examination. This case illustrates a possible neuromuscular virus invasion that may have an impact on the patient's health after discharge.

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection presents with a varied range of manifestations from mild flu-like symptomatology to severe respiratory failure [1]. However multiple organs can be influenced during the acute or late phase of the disease, occasionally leading to persisting and challenging aftereffects as well as increasing mortality and morbidity [2]. Diaphragmatic paralysis is one of the three main diaphragmatic dysfunctions (including eventration and weakness) and can seriously affect the respiratory function causing hypoventilation and long-lasting dyspnea [3]. Chest ultrasound, computed tomography (CT)-scan and X-ray are helpful tools to diagnose and evaluate the malfunction of the diaphragm [4]. Among the great variety of complications attributed to SARS-CoV-2 infections, a lesser studied neuromuscular one is the paralysis of diaphragm. In the existing bibliography, there are scarce evidence relating the virus with malfunction of the diaphragm muscle, and most of them are published in a case report form. Here we report a case of unilateral diaphragm paralysis in a middle-aged male patient.

Case Report

We report the case of 38-year-old Caucasian male with a medical history significant for hypothyroidism on medication (levothyroxine 100 μg q.d) and a body mass index of 37.7 kg/m^2 who presented in our emergency department with fever, worsening dyspnea, cough and low oxygen saturation levels. Reverse

transcription polymerase chain reaction (RT-PCR) for SARS-CoV-2 was positive six days earlier. Vital signs on initial presentation were SpO_2: 80% (pO_2:39.7 mmHg) while breathing room air, body temperature: 38.4°C, blood pressure (BP):140/80 mmHg, heart rate (HR):89 beats/min. Pulmonary auscultation revealed crackles on inferior posterior lung fields, physical examination was otherwise unremarkable. Laboratory analysis showed: white blood cells (WBC): 4.17 x 10^3 /µL (lymphocytes 14.8%), hemoglobin (Hb):16.7 g/dl, platelets (PLT): 92 x 10^3 /µL, C-reactive protein (CRP):5.73 mg/L, D-dimers: 1.81 mg/dL, creatine phosphokinase (CPK) 11,869 IU/L lactate dehydrogenase (LDH):1098 IU/L, serum alanine transaminase (ALT) of 102 U/L, aspartate transaminase (AST) of 204 U/L, procalcitonin (PCT): 0.28 ng/mL. X-ray of the chest demonstrated bilateral infiltrates (Figure 1a).

The patient was admitted in the Coronavirus Disease 2019 (COVID-19) ward, receiving 100% oxygen via high flow nasal cannula (HFNC) and was initially administered remdesivir, methylprednisolone, moxifloxacin and enoxaparin while two days

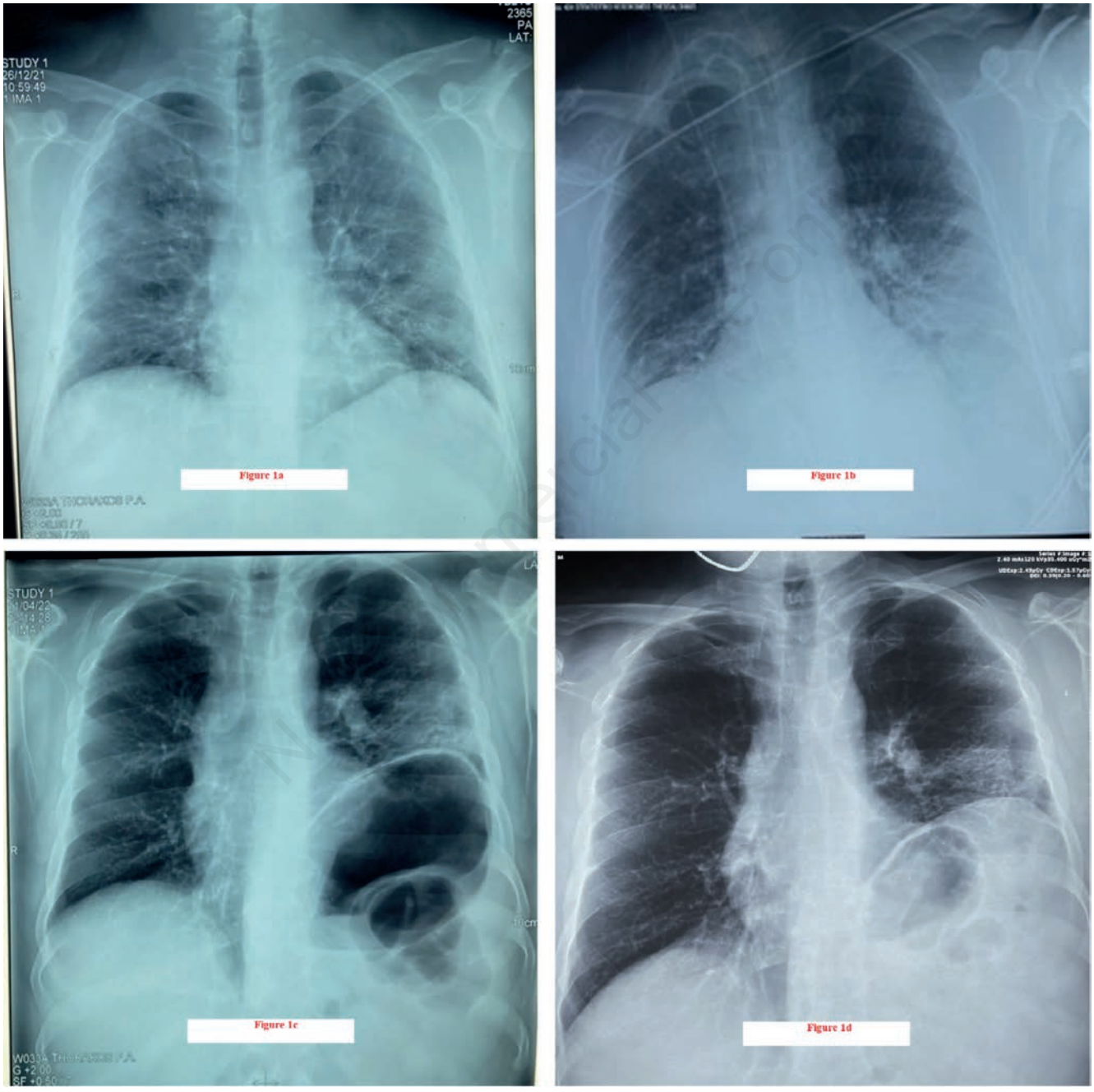

Figure 1. a) Chest X-ray on admission showing presence of parenchymal infiltrations in the lower segments of the left lung, with normal hemidiaphragms position. b) Chest X-Ray performed immediately after the tracheostomy procedure showing presence of worsening parenchymal infiltrations in the lung's lower segments bilaterally, with normal hemidiaphragms position. c) Chest X-ray on three months after hospital discharge, showing significant elevation of the left hemidiaphragm as well as air filled dilatation of the left colic flexure's loops. d) Chest X-ray on nine months after hospital discharge showing persistently elevated left diaphragm.

later subcutaneous interleukin-1 inhibitor (anakinra) was added to his medication.

Despite both antiviral and anti-inflammatory treatment, the patient was persistently febrile and presented worsening clinical features of dyspnea and PaO_2. He was eventually admitted in the Intensive Care Unit (ICU), intubated on mechanical ventilation on day nine of hospitalization, due to severe respiratory failure.

The patient was tracheostomized without complications on day 17 of hospitalization (day eight in the ICU) and the chest X-ray performed immediately after the tracheostomy procedure is shown in Figure 1b. A chest CT scan was conducted demonstrating left diaphragm elevation as well as bilateral ground glass opacities (GGO), more prominent in the superior lobes, bilateral pulmonary consolidations and infiltrates with air bronchogram in inferior lobes and fibrotic bunds in the right inferior lobe (Figure 2) .His ICU admission was also remarkable for positive blood culture with Acinetobacter, positive percutaneous dilational tracheostomy's culture and positive pharyngeal culture for Klebsiella, treated with a targeted antibiotic regimen.

Weaning from mechanical ventilation was gradually achieved during the next days, until day 35 of hospitalization, when he was discharged from the ICU to the pulmonology ward, with satisfactory gas exchange on oxygen therapy FiO_2: 35-40% *via* tracheostomy. Tracheostomy was discontinued during the patient stay in the pulmonary ward without complications and he therefore received oxygen via nasal cannula 2-3 lpm. During his ICU stay as well as during his stay in the pulmonary ward, the patient developed delirium with optical hallucinations, and he performed daily physiotherapy sessions. On the 48th day from admission, the patient was discharged from hospital into a rehabilitation facility for respiratory and movement physiotherapy.

Subsequent follow-up examination was performed three months later, including spirometry, new chest CT and dynamic digital radiography. The severe restrictive pattern in spirometry [forced vital capacity (FVC): 4.65 L (49%), forced expiratory volume in one second (FEV_1): 2.56 L (55%), FEV_1/FVC: 75%, peak expiratory flow (PEF): 6.65 L/s, was consistent with the minimal movement of the left hemidiaphragm during full inhalation and full exhalation in fluoroscopy. Chest CT findings are shown in Figure 3. The patient walked 560 m during 6-minute walking test (6MWT) with a mean SpO_2 of 88.9% during the test.

On examination nine months after the COVID-19 pneumonia hospitalization, the patient reported dyspnea only on heavy excretion while having returned to heavy duty daily tasks. He walked 800 m on 6MWT without desaturation whereas his spirometry values were remarkably improved, namely FVC: + 1.64 L (72%), FEV_1: 3,67 (79%), FEV_1/FVC: 87% and PEF: 9.46 (94%). Despite the improved spirometry results, left diaphragm appears persistently elevated in the chest X-ray, without mobility during respiration in fluoroscopy (Figure 1d).

Discussion

SARS-CoV-2 is the virus responsible for the current pandemic causing COVID-19 and reaching, as of 29 July 2022, 572,239,451 confirmed infections worldwide [5]. COVID-19 is manifested with a wide spectrum of symptoms including asymptomatic disease, flu-like symptoms with fever, cough and fatigue and severely impacted cases with dyspnoea, acute respiratory distress syndrome (ARDS) and multi-organ failure requiring hospitalization [1]. Nervous system complications are also associated with acute phase or late sequalae of COVID-19. Central and peripheral neural systems are both affected with varied outcomes and peripheral neuropathies are amongst the entities which have been reported [6].

Phrenic nerve (PN) innervates the diaphragm, the major muscle for respiration. Phrenic palsy disrupts optimal ventilation which is achieved when diaphragm functions efficiently. Multiple causes are associated with diaphragmatic paralysis, involving the central nervous system (CNS), the PN, the neuromuscular conjunction or the muscle itself and etiologically can be ascribed to infections, vascular complications, inflammation, and

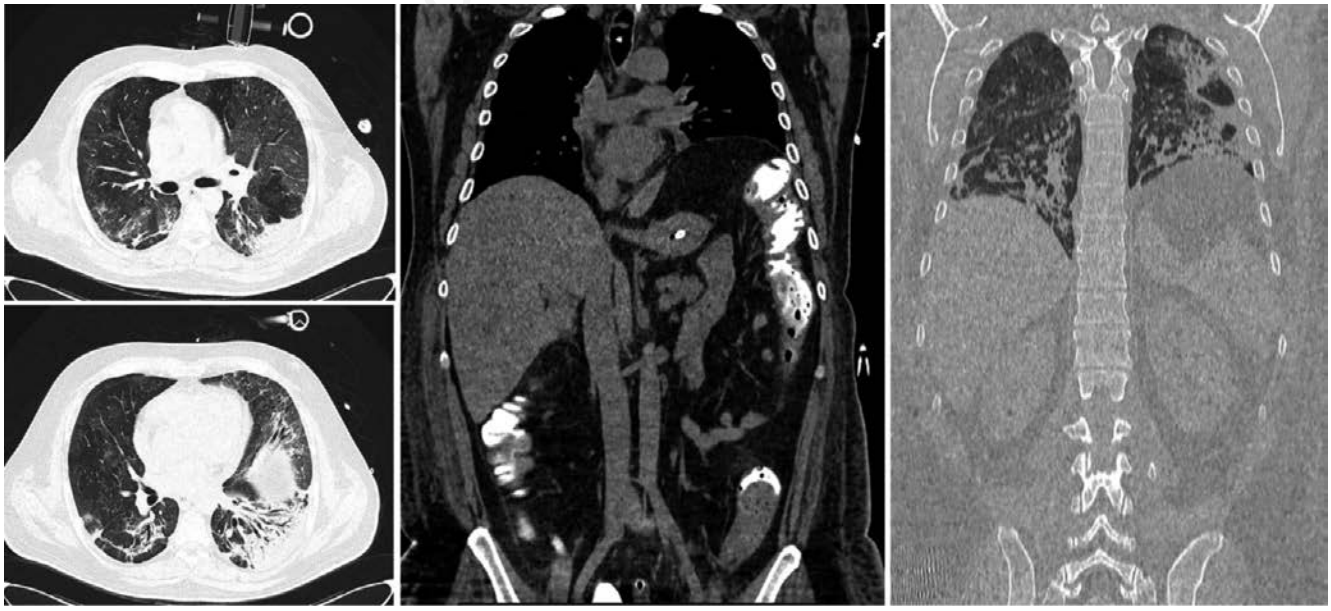

Figure 2. Chest CT scan during hospitalization showing areas of consolidation in the left lower lobe, traction bronchiectasis and fibrous subpleural bands in both lungs and left hemidiaphragm elevation.

iatrogenic/traumatic procedures. Iatrogenic procedures involved in diaphragm paralysis include anesthetic blockages, obstetric procedures, chiropractic manipulations of the neck, radiotherapy thoracic surgeries, steroid myopathy, mechanical ventilation, percutaneous punctures of veins (subclavian and internal jugular) and placement of intercostal drainages [3].

Mechanical ventilation associated diaphragm dysfunction is increasingly recognized as a cause of difficulty in weaning as well as a major predictor of mortality in ICU patients [3,7]. There are two main factors contributing towards diaphragm weakness and atrophy in these patients: ventilator and infection, the former being linked to reversible diaphragm dysfunction in animal studies [7]. In our case, left hemidiaphragm lost mobility somewhen during the patient stay in the ICU (Figure 1 a-c), most probably due to sepsis and high inflammatory burden in the course of COVID-19 disease. Interestingly, diaphragm hemiparesis persists nine months after initial COVID-19 infection and was the main cause for patient impairment during the post COVID-19 rehabilitation. Our report is one of the limited cases to delineate the case of unilateral diaphragmatic paralysis occurring in a patient during ICU admission for severe COVID-19 pneumonia.

In our case report mechanical ventilation with protected airway pressure was administered through out ICU admission and complicated invasive thoracic and neck procedures did not occur. A subcohort of 23 patients with varied degree of post COVID-19 lung affection and unilateral diaphragm paralysis is presented by Abdeldayem *et al*. In this cohort only one had persistent diaphragm complication [8]. Dandawate *et al.* report the case of a 56-year-old obese woman with obstructive sleep apnea, hospitalized with COVID-19 with oxygen supplementation (not requiring mechanical ventilation) who demonstrated persistent dyspnea due to right hemidiaphragm paralysis. The patient showed gradual resolution of paralysis and dyspnea 11 months later [9]. A 54-year-old male with identical comorbidities going through mechanical ventilation with prolonged ICU stay and experiencing right hemidiaphragm palsy is descripted. Surgical plication was conducted to alleviated dyspnea at nine months [10]. Similarly, a 58-year-old woman with obesity and prominent orthopnea was diagnosed with phrenic paralysis at one and half months past the acute phase of COVID-19 [11]. Shahid et al .report one case of left diaphragm paralysis in an 80-year-old male with COVID-19 pneumonia [12] and another case is descripted in a post COVID-19 cohort [13].

SARS-CoV-2 has the potential to inflict the neuromuscular system via multiple ways. Research has shown that angiotensin-converting enzyme 2 (ACE-2), a probable virus entering location, is expressed in the cell-membrane of both neural and diaphragm

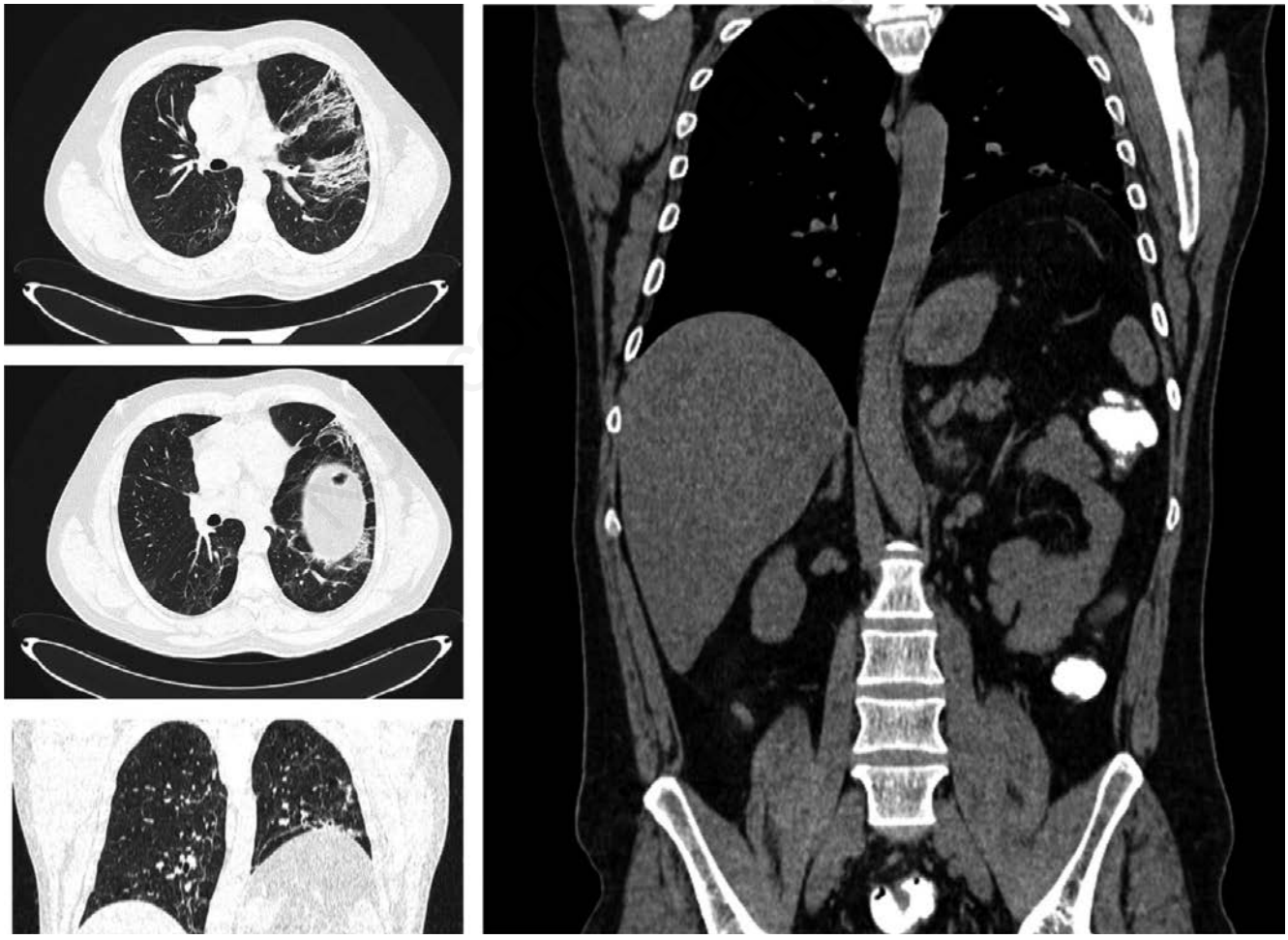

Figure 3. Chest CT scan on three months after hospital discharge (corresponding to chest X-ray shown in Figure 1c), showing remission of lung consolidations, presence of traction bronchiectasis and linear atelectasis in the lingula, left upper and lower lobes and significant left hemidiaphragm elevation.

muscle tissue [14,15]. Possible entry point to nervous system is through the olfactory system and another through efferent transport of the virus from peripheral nerve endings in the skin and mucosa to nerve cells. Neuromuscular complications induced by SARS-CoV-2 may also be mediated *via* severe cytokine production which leads to tissue inflammation [15]. The above mechanisms give a possible explanation of the pathogenesis behind diaphragmatic paralysis. Abdeldayem *et al*. studied 1527 patients with COVID-19 pneumonia and 1.5% of them presented with hemidiaphragm paralysis [8]. Extrapolation of these results to the general SARS-CoV-2 positive population (symptomatic and asymptomatic) is not possible as this cohort involved only symptomatic patients with respiratory compromise, and it was a cross-section study lacking CT/X-ray follow-up of the patients without diaphragm decompensation. However unilateral diaphragmatic paralysis may occur during later phases of COVID-19 and may provide explanation for the long-lasting dyspnea in some patients, even the ones who were asymptomatic during the acute phase.

Despite radiologically persistent in our case, unilateral diaphragmatic paralysis resolves spontaneously in almost half the patients during observation period [3]. Furthermore, our patient shows improved exercise tolerance in 6MWT as well as improved spirometry findings in the follow-up visit. In cases of symptomatic patients with a higher respiratory impairment non-invasive ventilation or surgical diaphragm plication can be a therapeutic option, whereas phrenic pacemaker is indicated for bilateral diaphragm paralysis cases [3]. More research is required to elucidate the true incidence, pathophysiology, pathogenesis, and treatment of diaphragmatic paralysis in SARS-CoV-2 patients.

Conclusions

Diaphragmatic paralysis can be another feature of COVID-19 with elusive pathogenesis. Chest CT/X-ray and spirometry may lead to diagnosis and should be conducted to patients with respiratory symptoms during acute or later phases of COVID-19. Follow up and specific treatment plans are lacking.

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