Cardiothoracic Imaging

COVID-19-induced pulmonary sarcoid: A case report and review of the literature

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ABSTRACT

Background: The COVID-19 pandemic has resulted in dramatic loss of life worldwide, but as the large number of acutely ill patients subsides, the emerging group of "COVID-19 long-haulers" present a clinical challenge. Studies have shown that many of these patients suffer long-term pulmonary disease related to residual fibrosis. Prior studies have shown that while many patients have non-specific findings of fibrotic-like changes, others develop specific patterns of interstitial lung disease.
Case report: Here, we present the first case of a patient developing pulmonary sarcoidosis one year after critical illness from COVID-19. He developed numerous non-necrotizing and well-formed granulomas in mediastinal lymph nodes and pulmonary nodules, compatible radiographically and pathologically with sarcoid.
Conclusions: While the pathophysiology of sarcoid is incompletely understood, inflammation is mediated through the dysregulation of a number of different cytokines (IFNγ, IL-2, IL-12, IL-17, IL-22). This case provides valuable clues for better understanding of the shared pathophysiology of cytokine dysregulation seen in COVID-19 and other interstitial lung diseases such as sarcoidosis.

1. Introduction

The COVID-19 pandemic has been an unparalleled event in modern healthcare resulting in an unprecedent number of acutely ill individuals during the height of the pandemic.[1,2] Although the acute phase of the pandemic has subsided in the United States in large part due to vaccination[3] and immunity in individuals who have recovered from the disease,[4] a subset of patients with lasting symptoms has emerged, colloquially known as "COVID-19 long-haulers".[5] These patients continue to have a variety of symptoms which may or may not relate to their presentation of acute COVID-19 and are challenging to manage from a clinical perspective.

While the acute phase of COVID-19 has been extensively characterized at the clinical and pathophysiological level,[6] the long-term effects of COVID-19 are less well understood. Long-term COVID-19 syndrome is defined as COVID-19 complications persisting beyond 4 weeks of symptom onset.[7] Major long-term sequala often include but are not limited to respiratory and neurologic symptoms.[8–10] A study by Carfi,

et al. evaluated symptoms of patients who had recovered from COVID-19 but had long-term sequelae. Of the 143 patients that they evaluated, 72.7% had interstitial pneumonia and 44.1% reported a worsened quality of life in the post-COVID-19 period.[11] In a meta-analysis of post COVID-19 complications, dyspnea was a symptom of long COVID-19 in nearly all cohorts studied, with an overall pooled prevalence of 0.32.[10,11]

The pathophysiology of prolonged pulmonary disease in patients with post-acute COVID-19 stems from inflammation within the pulmonary parenchyma and microvasculature during the acute phase resulting in damage to the pulmonary endothelium and interstitium, leading to tissue remodeling and collagen deposition.[12,13] While diffuse alveolar damage and microthrombi are the most common findings pathologically, other less common findings include vascular congestion and hemangiomatosis-like change.[14,15] These processes in the acute phase may ultimately mediate progression to fibrotic lung disease.

Radiographic features of long COVID-19 mirror those seen pathologically. Two Chinese cohorts that followed previously hospitalized
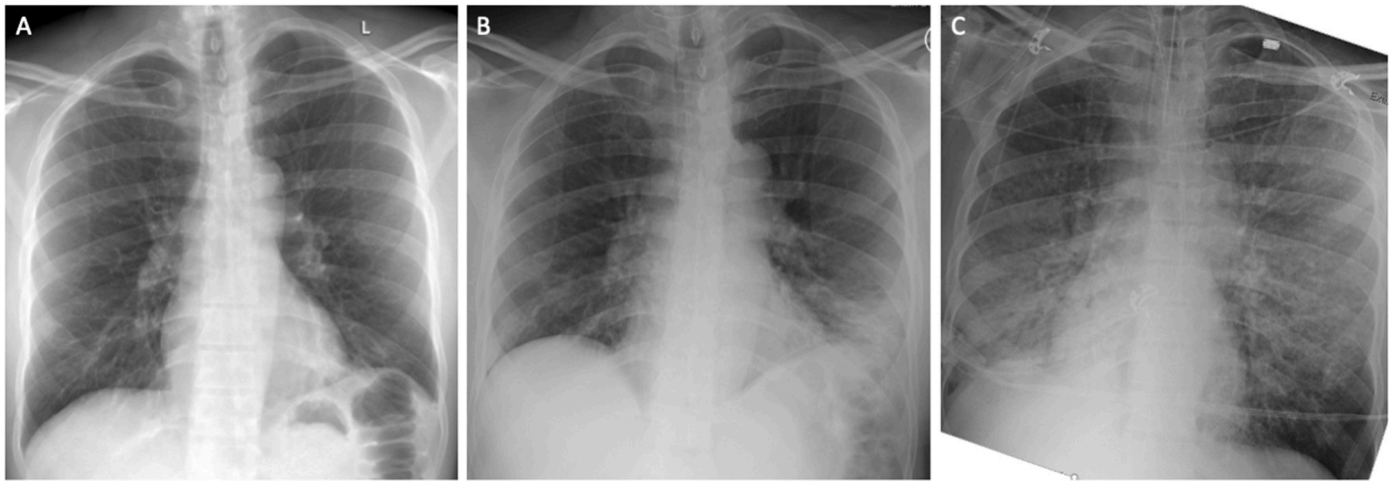

Fig. 1. (A) Prior radiograph from 2016 for comparison. (B) Initial chest radiograph for COVID-19-related admission demonstrated mild lower lobe predominant airspace opacities suggestive of COVID-19 infection, (C) which progressed over the first 12 days of the patient's hospital admission.
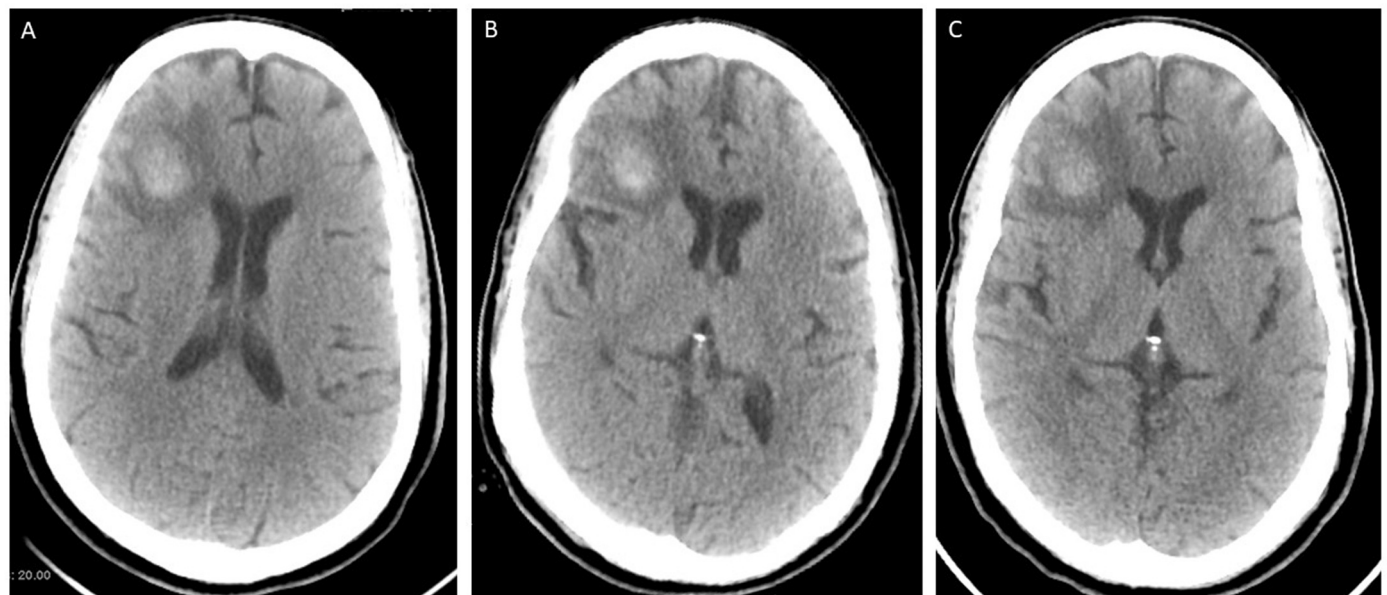

Fig. 2. Right frontal lobe intracranial hemorrhage on (A) initial imaging and follow-up imaging at (B) 24 and (C) 48 h demonstrates slowly progressive evolution with a decreasing component of acute blood products.

COVID-19 patients to 6-months demonstrated that ground glass opacities, consolidations, and irregular lines were the most common residual CT findings, and Han et al. found that 35% of patients also had fibrotic-like changes.[16,17] Another study reported that in patients hospitalized with SARS-CoV-2 pneumonitis who had residual symptoms at 6 weeks, 18% (59/325) had persistent parenchymal abnormalities on CT scan, the majority of which were described as organizing pneumonia.[18]

While fibrotic changes, ground glass opacities and organizing pneumonia account for the majority of abnormal cases, studies have shown that post-COVID-19 pulmonary disease can present in less common patterns, including probable UIP/UIP and NSIP. Two case reports have described a post-COVID-19 patient presenting with a sarcoid-like reaction with primary dermatologic manifestations confirmed on biopsy.[19,20] Here, we present the first case to date of a post-COVID-19 patient who went on to develop pulmonary sarcoid. This case may shed light on the underlying pathophysiology of long COVID-19 and its interaction with the immune system.

2. Case description

The patient is a 61-year-old male never smoker with a history of prostate cancer and chronic kidney disease who presented to the emergency room with 9 days of fever, cough, and dyspnea. He had no family history of pulmonary fibrosis, pulmonary sarcoid, COPD, or any other lung disease. Prior to admission, he reportedly was not taking any medications regularly. In the emergency room, he was febrile but did not require supplemental oxygen. Labs demonstrated lymphopenia, a mild transaminitis and markedly elevated ferritin, ESR and CRP and he subsequently tested positive for SARS-CoV-2. Initial chest radiograph obtained in the emergency room demonstrated mild lower lobe predominant airspace opacities, suggestive of viral infection; a prior study from 2016 is shown for comparison (Fig. 1A, B). He was admitted for supportive management and treated with hydroxychloroquine and azithromycin. On hospital day 8, his clinical status deteriorated and his oxygen requirement rapidly increased, necessitating urgent intubation. Initial PaO2:FiO2 was <100, which improved with deep sedation and
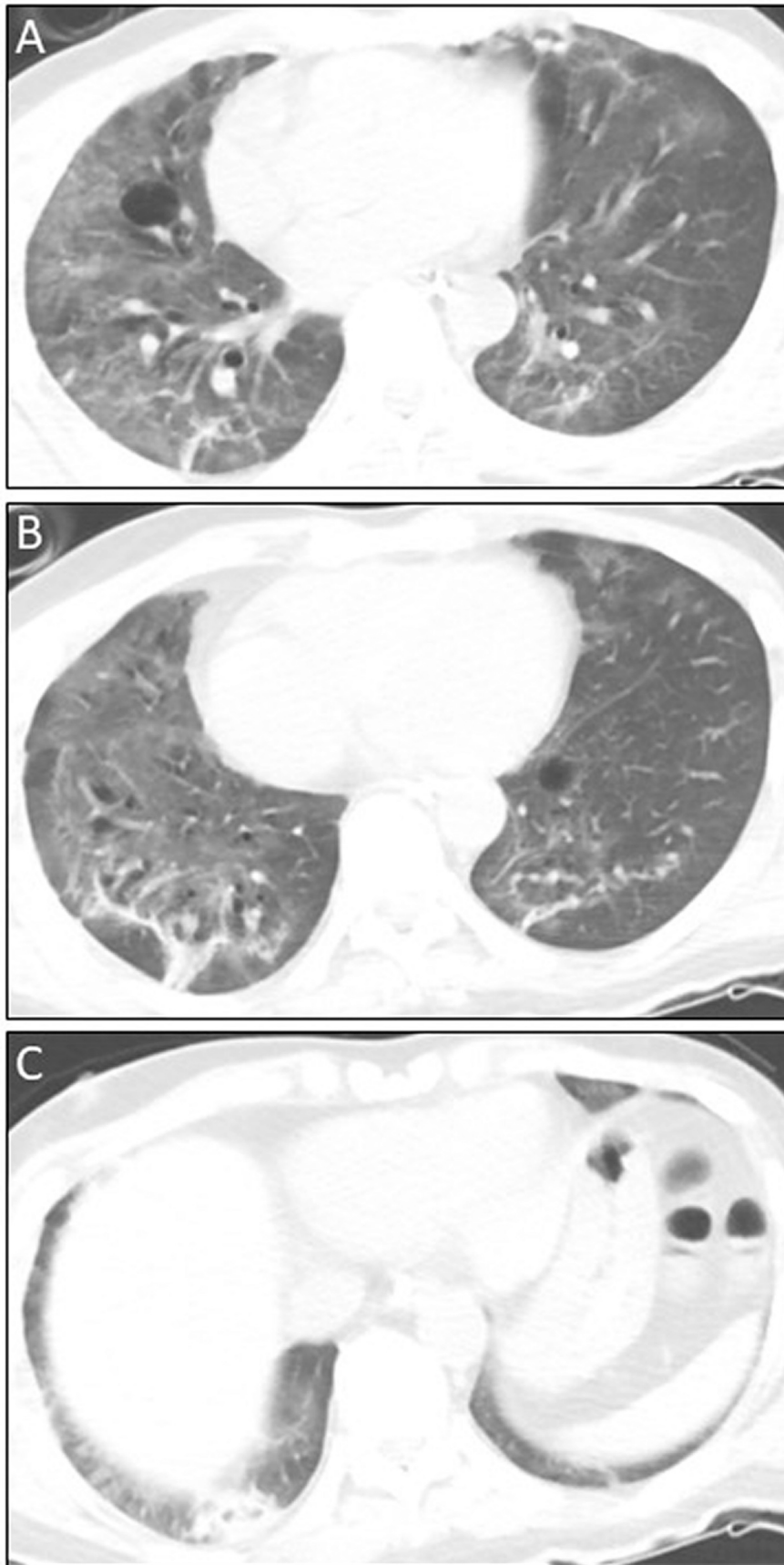
Fig. 3. Serial axial CT images of the chest from CT of the abdomen and pelvis demonstrated prominent peripheral reticulations, traction bronchiectasis, and ground glass opacities, in excess of what is typically seen in the post-COVID-19 setting.
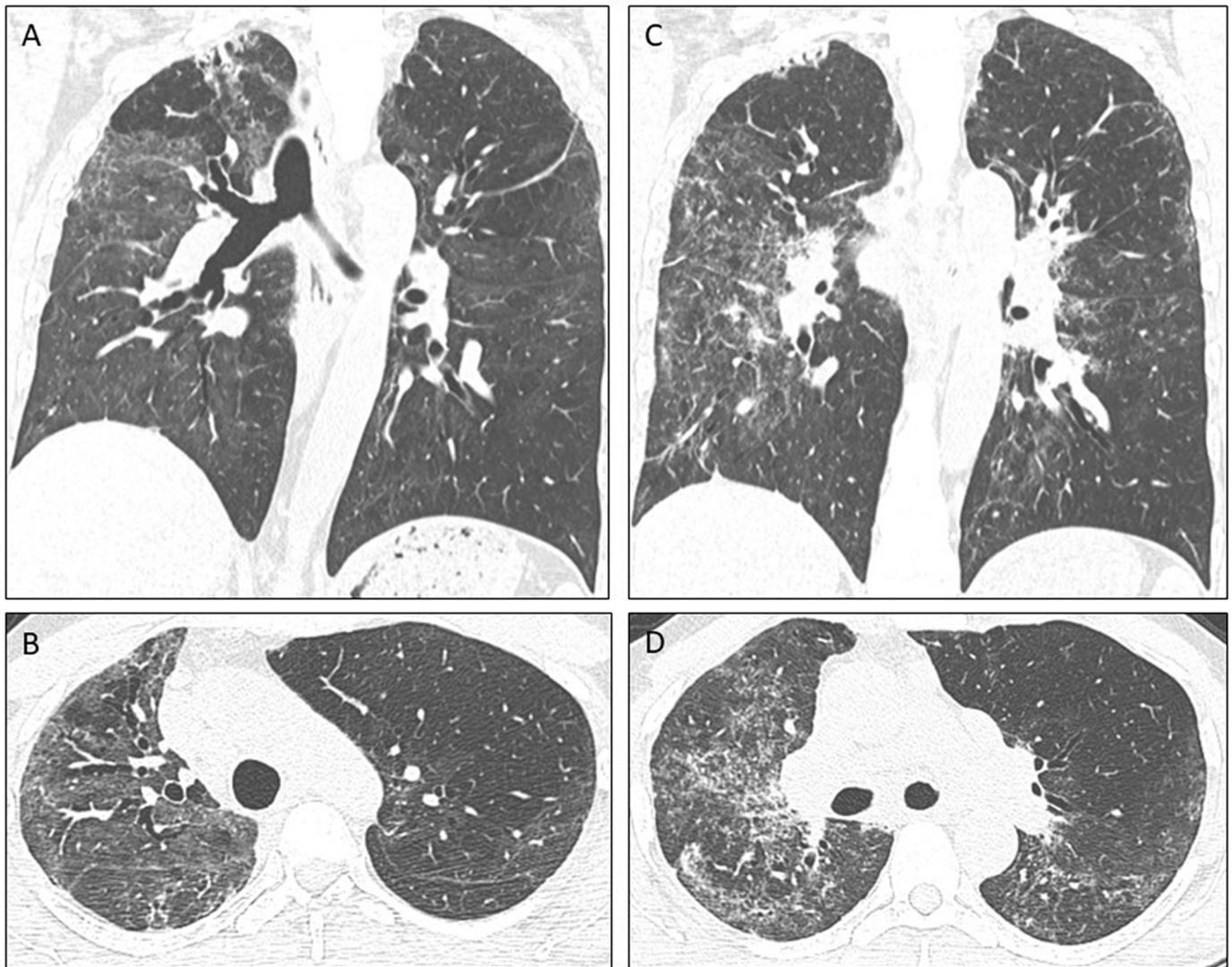
Fig. 4. Progression of pulmonary parenchymal disease at 5-months (A, B) and 14-months (C, D) post admission demonstrated progression from diffuse lower lobe predominant ground glass opacities to mosaic attenuation (A, B), followed by the development of innumerable pulmonary nodules and diffuse reticulation (C, D). Radiographically these findings are compatible with pulmonary sarcoid.

paralysis. A chest radiograph on hospital day 12 demonstrated lower lobe predominant interstitial and alveolar airspace opacities characteristic of COVID-19 infection (Fig. 1C). His ICU course was complicated by renal failure requiring continuous renal replacement therapy, polymicrobial bacteremia and acute right frontal intracranial hemorrhage (Fig. 2A, B, C).

The patient underwent tracheostomy after 3 weeks and was ultimately weaned from ventilatory support and decannulated approximately two months after initial presentation. He was discharged to physical therapy to address general deconditioning as well as focal deficits resulting from his ICH. The patient continued to follow with pulmonology for persistent respiratory symptoms post-COVID-19. Lungs were partially imaged on a CT of the abdomen and pelvis obtained 2-months post discharge, demonstrating peripheral reticulations, traction bronchiectasis, and ground glass opacities (Fig. 3A, B, C), more prominent than typical post COVID-19 findings.

Pulmonary follow-up at 5 months demonstrated a forced vital capacity (FVC) and diffusing capacity for monoxide (DLCO) of 61 and 38% of predicted values respectively based on demographics and height. These values improved at the 14-month visit, but the patient did report ongoing fatigue and a 5–10 pound weight loss. Dedicated chest imaging at 5-months and 14-months post admission demonstrated continued

evolution of pulmonary changes with innumerable pulmonary nodules, diffuse reticulation (Fig. 4A-D), and extensive mediastinal and hilar adenopathy (Fig. 5A, B). Given the patient's prior history of prostate cancer, the development of pulmonary nodules and mediastinal adenopathy (Fig. 5A, B) raised concern for metastatic malignancy. PET-CT was ordered and demonstrated extensive bilateral high level FDG-avidity of mediastinal and hilar lymph nodes (Fig. 5C, D). Additionally, FDG-PET demonstrated diffuse low-level uptake in the lung bases, compatible with pulmonary inflammation which may be seen in the setting of infection and/or active interstitial lung disease.

Radiographic findings were suggestive of pulmonary sarcoid. Given the concern for malignancy, the patient underwent biopsy of a PET-avid right lower lung nodule. Core biopsies of the lung demonstrated numerous non-necrotizing and well-formed sarcoid-like granulomas in a background of mild chronic inflammation and focal organizing pneumonia; cultures for fungi, norcardia, actinomyces, and acid-fast bacilli were negative. (Fig. 6A, B). Lab work obtained several days prior to biopsy subsequently resulted and was significant for an elevated ACE of 207 U/L (reference range 9–67 U/L), elevated ESR of 25 mm/h (reference range 1–15 mm/h) and hypercalcemia of 10.6 mg/dL, (reference range 8.8–10.3 mg/dL). These findings also supported a diagnosis of sarcoid. Lab work was also significant for a PSA measuring 80.86 ng/mL
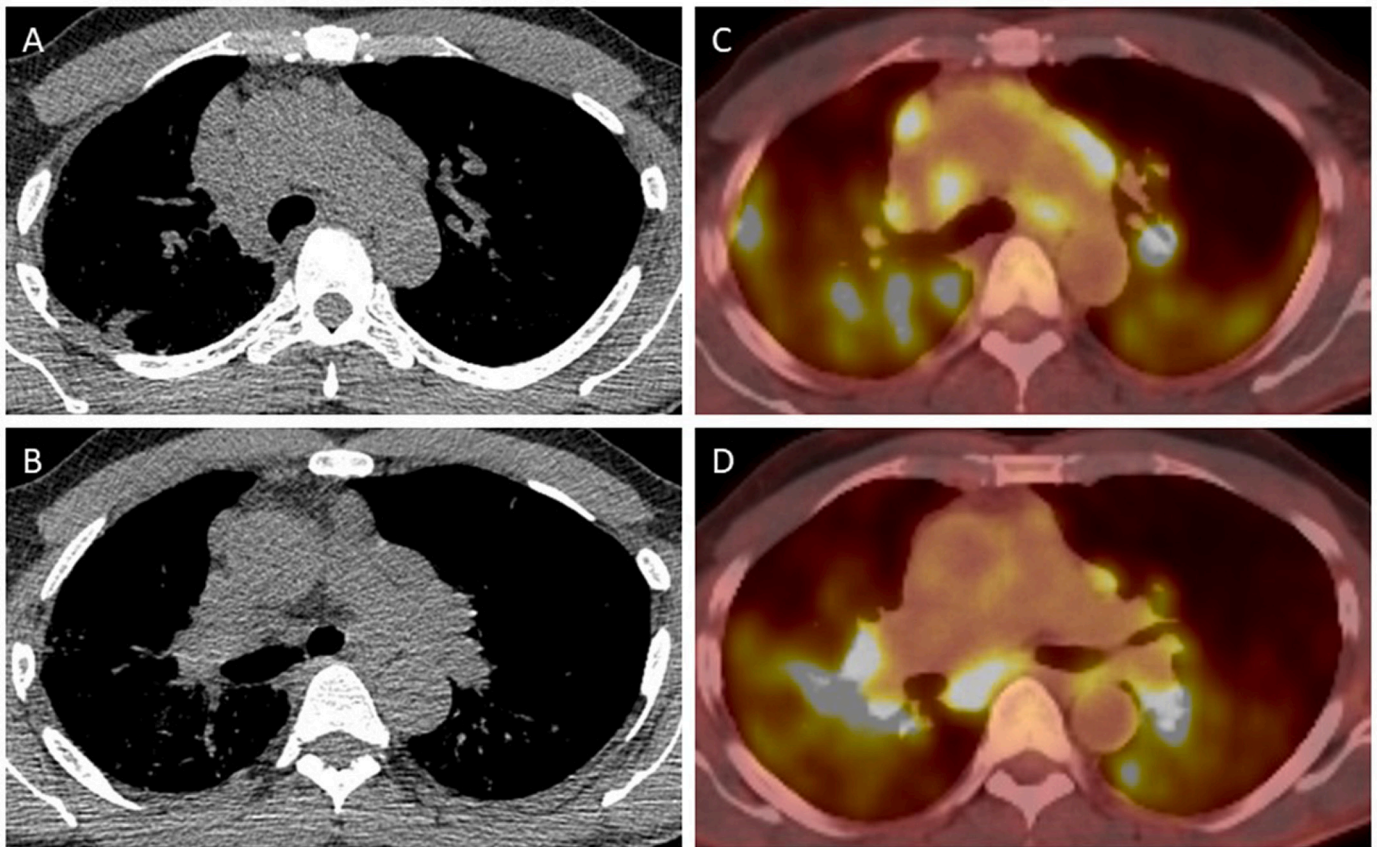
Fig. 5. Extensive mediastinal and hilar adenopathy on CT at 14 months post infection was best seen on abdomen windows (A, B) and prompted FDG-PET-CT which exhibited high FDG avidity in mediastinal and hilar nodes (C, D). The study was also significant for low level FDG uptake in the lung bases suggestive of infection and/or inflammation.
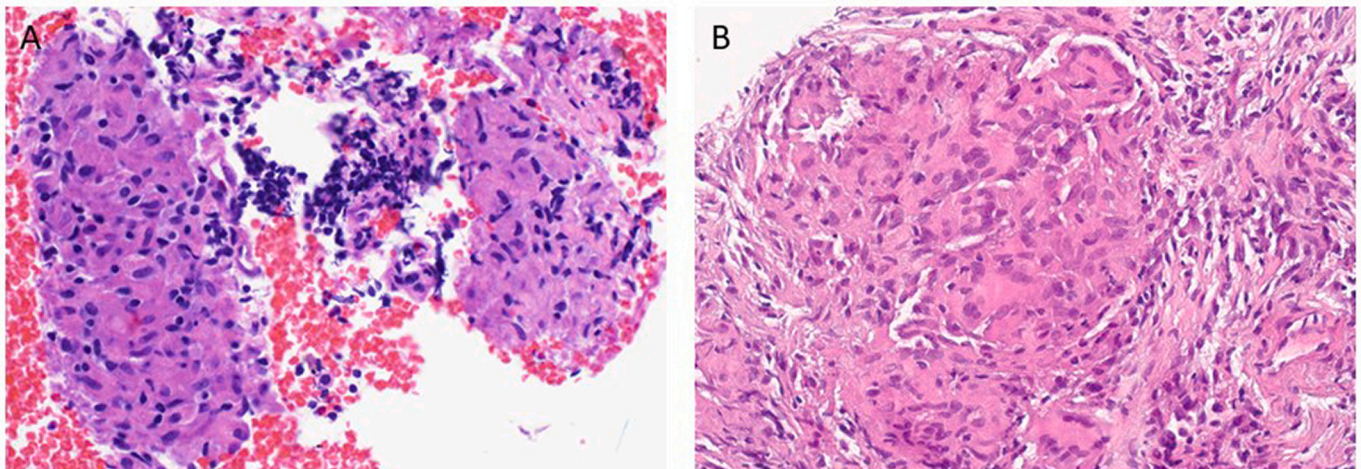

Fig. 6. Endobronchial ultrasound guided fine needle aspiration of a lymph node (A) and core biopsy of the lung with non-necrotizing and well-formed granu-lomas (B).

(reference range 0.00–4.00 ng/mL). Given the possibility of concurrent metastatic prostate cancer and after multidisciplinary discussion of the case, the decision was made to repeat biopsy with endobronchial ul-trasound guided fine needle aspiration of a right paratracheal, sub-carinal and hilar lymph nodes. All of these demonstrated granulomas morphologically similar to those seen in the pulmonary nodule. No malignant cells were identified, flow cytometry showed no

immunophenotypic evidence of a B-cell lymphoma, and aspirate AFB and fungal cultures were negative.

Given these findings, the patient has been diagnosed with pulmonary sarcoid and continues to follow with pulmonology for treatment and monitoring of his disease. CT imaging of the chest, abdomen, and pelvis obtained two months after this diagnosis did not demonstrate any extrapulmonary involvement. The patient was started on 20 mg oral

prednisone daily for treatment which was subsequently tapered to 10 mg daily.

3. Discussion

Sarcoidosis is a multisystem disorder that affects the pulmonary system in the majority of cases.[21,22] Despite extensive clinical and pathologic characterization, the pathophysiology of sarcoid remains obscure.[23] While a family history of sarcoid is associated with a higher risk of disease, our patient has no family history of sarcoid. However, in light of the changes in the T-cell populations as well as levels of TH17-related cytokines, interleukin (IL) -17 and interleukin-22, groups have postulated that sarcoid is a fundamentally immune-mediated response to an antigen which may be environmental or infectious.[23,24] Research has demonstrated a high percentage of Th17.1 cells in lung lavage from patients with sarcoid compared to control patients, and that about 60% of these cells produced only IFN-γ.[25] In another study by the same group, they went on to show that the IFN-γ-producing Th17.1 cells are the dominant phenotype with the lungs of sarcoid patients.[26,27]

Given the patient's COVID-19, perturbation of the immune system is a likely a causative agent in his development of sarcoid given that there were no clinical or radiographic symptoms or signs of sarcoidosis prior to COVID-19 infection. A robust study of 1953 COVID-19 patients admitted to the hospital during the pandemic characterized cytokine levels in comparison to healthy donors and found elevated levels of IL-6, IL-8, TNF-a, and IL-1B.[28] While this study did not directly address IL-17 and IL-22, it supports COVID-19 induced activation of the immune response often referred to as the "cytokine storm". A case report in Lancet Respiratory Medicine described an increase in the number of Th17 cells and increased concentration of highly proinflammatory CCR6+ Th17 in CD4 T cells in a 50-year-old who died of COVID-19.[29] A subsequent study implicated IL-17 in the pathogenies of the COVID-19 cytokine storm and suggested that targeting this pathway might be an effective treatment strategy.[30] These shared mechanisms may help to explain how SARS-CoV-2 infection may predispose to pulmonary sarcoidosis.[31]

The patient's history of prostate cancer may be a confounding factor in attributing the development of sarcoid to a post-COVID-19 effect. Todd and Garnick reported the case of a 78-year old man with a history of sarcoid who went on to develop prostate cancer and hypercalcemia.[32] Mulpuru, et al. reported a case in which a 45-year-old African American man with a known history of sarcoidosis went on to develop elevated PSA. Biopsy demonstrated noncaseating epithelioid granulomas with multinucleated giant cells, and elevated PSA was ultimately attributed to prostate inflammation in the setting of sarcoid of the prostate.[33] These cases underscore the overlapping features of sarcoid and prostate cancer, however the chronicity of our patient's development of pulmonary sarcoid in the immediate post-COVID-19 period suggest that the cytokine storm and subsequent changes to the pulmonary microenvironment were the proximate cause of the patient's new-onset sarcoid.

Given the large number of COVID-19 infections since the onset of the pandemic and the significant number of patients who went on to develop long-term pulmonary complications,[16] caring for "long-haulers" will likely be a significant component of pulmonary medicine practice for years to come. COVID-19 pathophysiology, particularly the mediators of pulmonary inflammation and cytokine storm, has already been extensively characterized and additional studies are currently underway[34–36] Here we present the first case to date of a patient who went on to develop sarcoid in the post-COVID-19 setting. Understanding the pulmonary pathophysiology, immune response, and progression to interstitial lung disease in COVID-19 infection will illuminate the pathophysiology of other pulmonary diseases and provide novel treatment targets.

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