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CASE SERIES

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Sarcoidosis following COVID infection: A case series

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Abstract

Here we describe three cases of sarcoidosis which were diagnosed following COVID infection. Treating clinicians should consider post-COVID-19 sarcoidosis in their differential, as it represents a potentially treatable cause of persistent symptomatology.

KEYWORDS
COVID-19, sarcoidosis

INTRODUCTION

During the early stages of the COVID-19 pandemic, the potential for a large spike in respiratory disease secondary to severe infection was considered. Although there is now some evidence that a significant proportion of patients have residual lung abnormalities,[1] the prevalence of other conditions has not been described. Here we present three cases of sarcoidosis following COVID-19 infection.

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Case 1

A 64-year-old male never-smoker with no significant past medical history reported new onset cough, breathlessness, fever, myalgia and fatigue in March 2020 but did not require hospital admission. Subsequent antibody testing was positive for COVID-19. Due to persistent breathlessness on exertion, myalgia and fatigue, he presented to the post-COVID clinic 5 months later where a chest x-ray showed bibasal shadowing not seen on x-ray the previous year. A repeat COVID swab was negative. High-resolution CT (HRCT) imaging showed diffuse ground glass opacification and consolidation, worse at the right base. Note was also made of prominent mediastinal lymph nodes. Lung function demonstrated an FVC of 92% predicted and TLCO 71% predicted.

Due to worsening breathlessness, a VQ Spect was performed 5 months later to rule out thromboembolism. No clots were seen, but parenchymal changes persisted prompting follow-up computed tomography (CT) imaging 9 months later. On this repeat test, progression of right basal ground glass changes was observed, alongside new changes in the left base, with evidence of interlobular septal thickening, fissural beading and nodularity. Mediastinal lymphadenopathy also persisted (Figure 1). Findings of this repeat CT scan, along with persistent symptoms of breathlessness prompted further investigations. ACE level was 54 U/L (NR 13–64). Bronchoalveolar lavage showed significant lymphocytosis (76%) and no infection. Lung biopsy was performed due to the atypical nature and extent of the changes and showed non-necrotising granulomatous inflammation (Figure 2a). A multidisciplinary diagnosis of alveolar sarcoidosis post-COVID infection was reached.

Due to persistent symptoms and a histologically confirmed sarcoidosis diagnosis, prednisolone was commenced at 30 mg daily, reducing by 5 mg per month to 10 mg. This was associated with a significant improvement in respiratory symptoms and a reduction in opacification on x-ray imaging

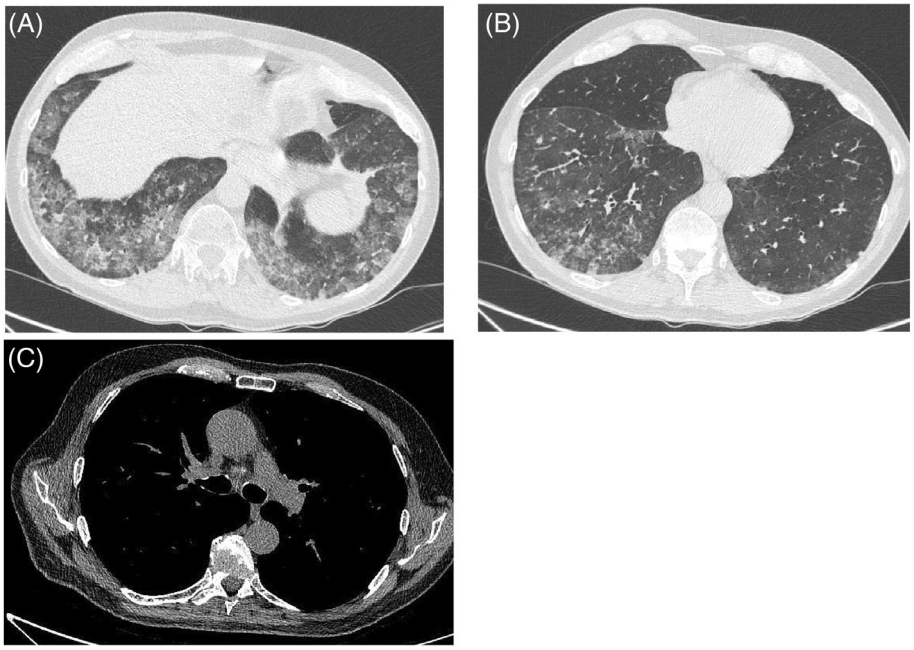

FIGURE 1 Computed tomography imaging of (A, B) lung bases showing ground glass change, septal thickening, beading and nodularity, and (C) persistent lymphadenopathy.

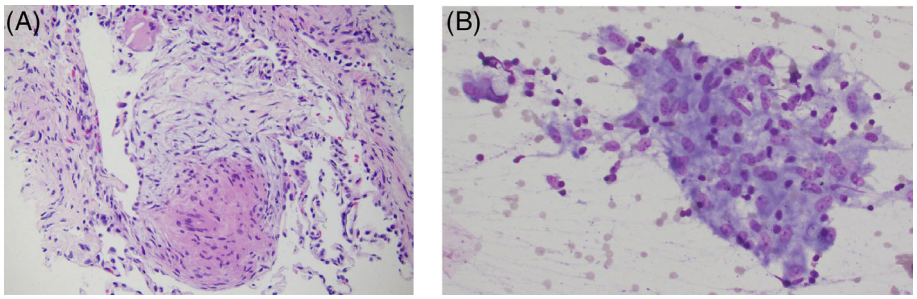

FIGURE 2 (A) lung biopsy from patient 1 showing non-necrotising granulomatous inflammation. (B) Aspirate from station 11R from patient 2 under EBUS demonstrating non-necrotising granulomatous inflammation.

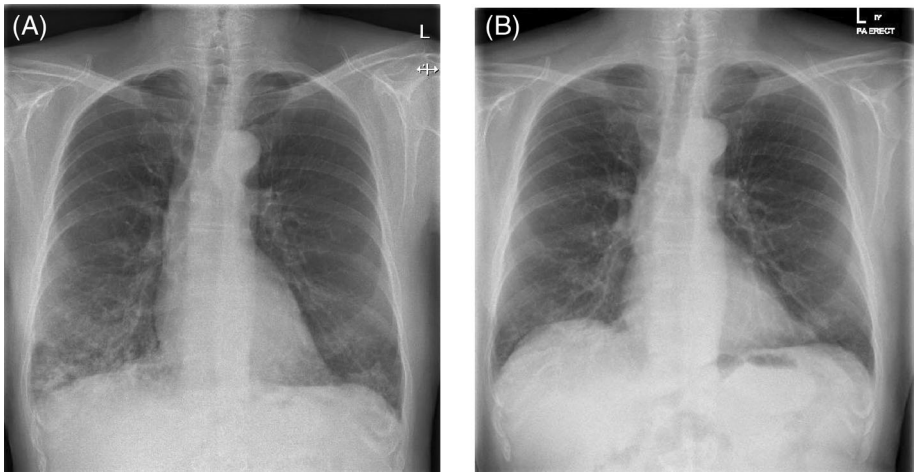

FIGURE 3 Chest x-rays taken in (A) June 2022 and (B) September 2022 showing improvement in bibasal interstitial shadowing.

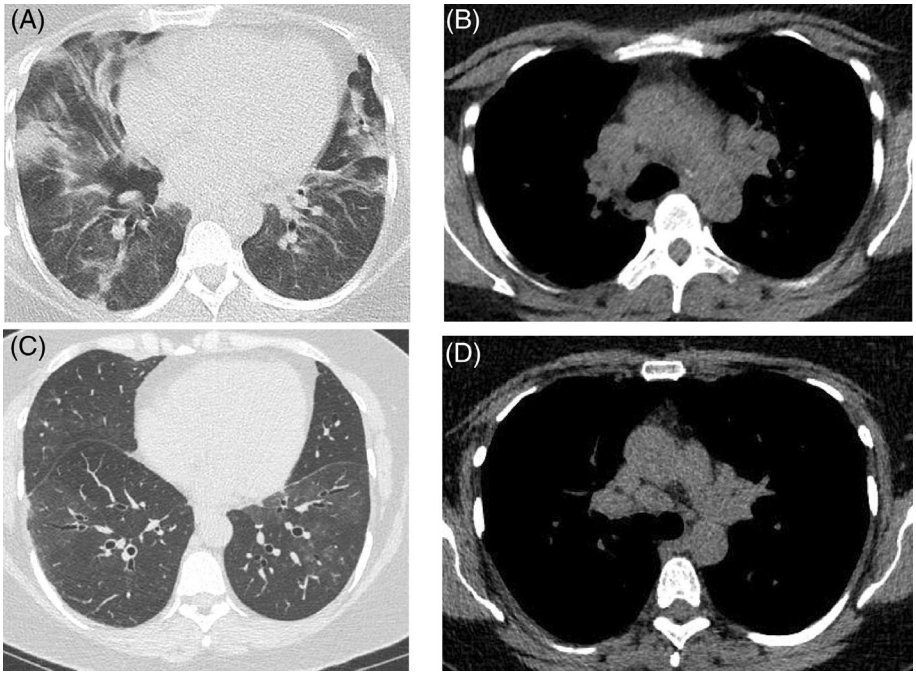

FIGURE 4 Computed tomography images taken (A) during the hospital admission of Case 2 showing diffuse ground glass change and consolidation consistent with COVID-19 pneumonitis and (B) enlarged lymph nodes. Repeat imaging after admission shows (C) improving ground glass change but (D) persistent lymphadenopathy.

(Figure 3). Repeat lung function showed an FVC of 110% and TLCO 89%. He remains under close monitoring with plans to reduce prednisolone further if tolerated.

Case 2

A 53-year-old female developed coryzal symptoms in December 2020. The SARS-CoV-2 virus was detected on polymerase chain reaction (PCR) testing. After 12 days of symptoms, she developed fevers, progressive breathlessness and cough. She required a seven-day hospital admission during which she received oral dexamethasone and oxygen therapy delivered via nasal cannulae. HRCT Imaging showed diffuse ground-glass change and patchy consolidation consistent with severe COVID-19 pneumonitis (Figure 4a). Enlarged hilar lymph nodes (Figure 4b) measuring up to 13 mm were thought to be reactive. Erythrocyte sedimentation rate (ESR) was mildly raised at 56 mm/h. Two weeks following discharge from hospital, she developed worsening breathlessness and a productive cough for which she was given oral antibiotics in the community for a presumed bacterial infection. Her past medical history included antiphospholipid syndrome and rheumatoid arthritis, for which she took methotrexate having previously required treatment with rituximab. A CT thorax was performed 6 months after hospital admission due to persistent right lower lobe consolidation on x-ray. Despite negative COVID swabs and significant improvement in symptoms, some multifocal ground glass opacification persisted (Figure 4c), and mediastinal and hilar lymph nodes remained conspicuous (Figure 4d). ESR had risen further to 89 mm/h. Bronchoalveolar lavage showed lymphocytosis of 42% with a negative microbiological screen. Fine needle aspirate performed under endobronchial ultrasound demonstrated non-necrotising granulomas in keeping with sarcoidosis (Figure 2b). Although FVC and gas transfer were reduced (75% and 50%, respectively), immunosuppressive treatment was not started given the significant improvement in symptoms. Plans were made to repeat lung function at follow-up, although this has been delayed due to missed appointments.

Case 3

A 43-year-old male with a history of type 2 diabetes underwent asymptomatic COVID-19 PCR testing in December 2021 and had a positive result on several occasions despite being fully vaccinated. Four months later, he developed breathlessness, mucus production, upper respiratory tract symptoms and fatigue. A papular rash was also noted on his shins. Despite a normal ACE level (58 U/L), an abnormal chest x-ray was followed by an HRCT scan which showed bilateral hilar, mediastinal and supraclavicular lymphadenopathy as well as diffuse fissural micronodularity consistent with stage 2 sarcoidosis (Figure 5). The diagnosis was confirmed after a lymph node biopsy showed granulomatous inflammation and negative acid-fast bacillus. He was referred to specialist care. Though the absence of pre-morbid imaging limits aetiological inference in this case, the short interval between

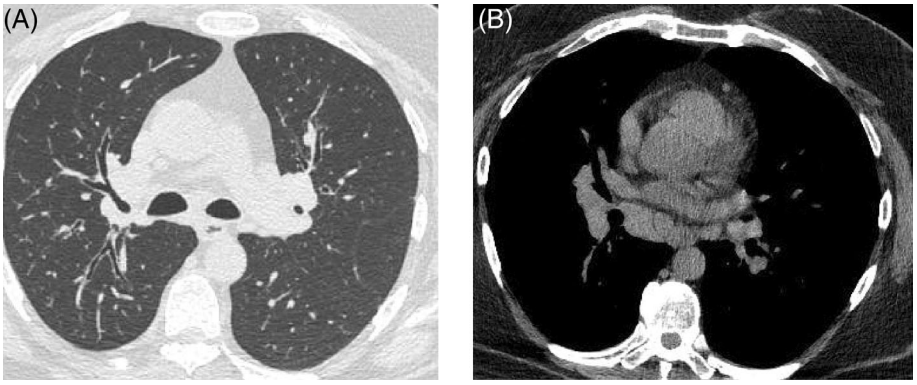

FIGURE 5 Computed tomography images of Patient 3 showing (A) nodularity and (B) hilar lymphadenopathy.

this patient's COVID-19 infection and his symptomatic presentation with sarcoidosis may suggest potential causality.

DISCUSSION

Sarcoidosis is a multisystem inflammatory disease, histologically characterized by the presence of non-necrotising granulomas, consisting of epithelioid cells and lymphocytes.

Though the aetiology of sarcoidosis is unclear, immune cross-reaction to an infectious agent has been postulated in genetically susceptible people.[2,3] Sarcoid-like reactions are also observed in association with inflammatory processes such as malignancy, following occupational exposures, and as adverse reactions to immunotherapy drugs.[4,5] Here we describe three cases that support the theory of COVID-19 infection as a potential trigger for sarcoidosis. While the absence of pre-morbid thoracic imaging for Cases 2 and 3 is a limitation, as subclinical sarcoidosis may have predated COVID infection in these cases, the relatively acute onset of new symptoms after COVID infection is notable. Since the onset of the COVID-19 pandemic, several cases of sarcoid-like reactions following infection with SARS-CoV-2 have been described.[6–10]

Two case reports detail cutaneous sarcoid-like reaction following PCR-confirmed infection with SARS-CoV-2.[6,7] Both cases involved middle-aged caucasian women and occurred 2–4 weeks after infection with SARS-CoV-2. Pathology demonstrated granulomatous panniculitis, consistent with sarcoid-like reaction. In both cases, spontaneous improvement was seen within 1 month of presentation. This post-infectious emergence of sarcoid-like inflammation prompted Behbahani to postulate that it may represent a SARS-CoV-2 convalescence phenomenon.[6]

Similarly, Mihalov and colleagues report a case of Lofgren syndrome occurring in a 30-year-old caucasian male 3 weeks after presumed SARS-CoV-2 infection (presumed based upon clinical history of fatigue and nasal congestion, and a positive SARS-CoV-2 IgM and IgG at the time of presentation 3 weeks later), with skin biopsy confirming the presence of non-necrotising granulomata.[8] Mertz et al reported three cases of presumed SARS-CoV-2 infection presenting with sarcoid-like symptoms approximately 1 month post-infection, varying from biopsy-confirmed non-necrotising granulomas demonstrated on cervical lymph node FNA in a patient with a family history of sarcoidosis, to a clinical diagnosis of isolated erythema nodosum with no other explanation.[9]

Capaccione et al report a case of pulmonary sarcoidosis in a middle-aged Caucasian male developing 5 months post discharge following a prolonged ICU stay with COVID-19.[10] Though typical post-COVID radiographic findings are characterized by fibrotic changes, ground glass opacicties and organizing pneumonia, PET CT imaging prompted by this patient's ongoing respiratory symptoms showed extensive bilateral intense FDG uptake in mediastinal and hilar lymph nodes, as well as diffuse low-level uptake in the lung bases suggestive of persistent inflammation. Overall, radiological findings were suggestive of sarcoidosis, and subsequent core lung biopsy and endobronchial ultrasound-guided FNA of mediastinal lymph nodes yielded sarcoid-like granulomas. The patient was commenced on steroid therapy to treat his ongoing respiratory symptoms.

A recent review from Zhao et al has postulated several possible explanations for the observation of sarcoid-like reaction in association with SARS-CoV-2 infection.[11] First, the classical renin-angiotensin system (RAS) (consisting of angiotensin converting enzyme (ACE), angiotensin II, and angiotensin II type 1 receptor (aT1R)) is negatively regulated by ACE2. SARS-CoV has been shown to reduce pulmonary expression of ACE2[12] with the consequent hyperactivity of the RAS system postulated to contribute to the inflammatory response and cytokine storm seen in COVID-19 lung disease.[11] Sarcoidosis is also associated with elevated circulating ACE levels.[13] However, it is unclear whether increased ACE levels stimulated by human coronaviruses could potentially induce granuloma formation to explain the sarcoid-like reactions observed in these patients. Of note, serum ACE level was within normal limits in the two patients for whom it was checked in the cases presented in this manuscript.

Similarities in immune features of sarcoidosis and SARS-CoV-2 may potentially be indicative of a common pathophysiology that could explain their co-existence. For

example, the 'cytokine storm' seen in severe COVID-19 pulmonary disease is characterized by elevated serum levels of a host of inflammatory cytokines, many of which are also upregulated in sarcoid lungs.[11] However, the majority of post-COVID-19 sarcoid-like reactions reported have occurred in patients with mild disease. An alternative theory may centre upon cell death pathways. Autophagy, a programmed form of cell death that allows highly controlled breakdown of cellular structures and plays an important role in immune responses, is known to be defective in sarcoidosis.[14] Interestingly, increased levels of angiotensin II associated with coronavirus infection may cause negative regulation of autophagy, possibly aiding the virus in hijacking this intracellular system to facilitate its own replication.[15]

Though the pathophysiology of post-COVID-19 sarcoidosis remains unclear, increasing case reports in the literature are highlighting this as a clinical phenomenon. Given the high number of patients who continue to experience symptoms following SARS-CoV-2 infection, further investigation of this entity is warranted. Treating clinicians should consider post-COVID-19 sarcoidosis in their differential, as it represents a potentially treatable cause of persistent symptomatology.

AUTHOR CONTRIBUTIONS

David Smith compiled the case reports and collated the CT images. Laura Gleeson wrote the discussion. Clare Ross, Jamilah Meghji and Melissa Wickremasinghe were involved in conception of the project and provided supervision. Mufaddal Moonim and Patrizia Viola provided input on histology and interpretation of data. All were involved in revising the report critically and final approval.

CONFLICT OF INTEREST STATEMENT

None declared.

DATA AVAILABILITY STATEMENT

Data available on request from the authors.

ETHICS STATEMENT

The authors declare that appropriate written informed consent was obtained for the publication of this manuscript and accompanying images.

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