OXFORD

QJM: An International Journal of Medicine, 2022, 1–2

https://doi.org/10.1093/qjmed/hcac119
Advance Access Publication Date: 19 May 2022
Commentary

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Elevated serum ACE levels in patients with post-acute COVID-19 syndrome

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Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is causing the current coronavirus disease (COVID-19) pandemic.[1] Over recent months, a plethora of novel research articles has been published, dealing with multiple aspects and manifestations of both the acute disease and its longer-term sequelae. Recovery from coronavirus disease 2019 (COVID-19) can take months in previously hospitalized and non-hospitalized adult patients. Even though most recover fully, several large cohort studies have shown that up to 30% of patients develop persistent symptoms (for >12 weeks after acute COVID-19 infection) such as profound fatigue, dyspnoea, 'brain fog', chest tightness, depression, headache and muscle pain.[2–4] The National Institute for Health Care Excellence guideline for managing the long-term effects of COVID-19 defined the term 'long COVID' or post-acute COVID-19 syndrome (PACS) for patients having signs and symptoms that continue or develop 12 weeks post-acute COVID-19 infection.[5] It is currently unknown how long, PACS lasts or what proportion of patients will recover or have long-term chronic symptoms. For example, lung damage appears to manifest for at least 4 months after acute infection.[6] It is a frustratingly perplexing condition for both the physician and the patient. The pathophysiology is also unknown, and many plausible ideas abound including autoimmune or inflammatory sequelae, or dysautonomia.[7] However, evidence connecting possible causes to outcomes is absent. Severe fatigue, 'brain fog' and/or dyspnoea is present amongst up to 70% of patients with PACS and severely impacts of quality of life and ability to work.[5,8] Pertinently, a major feature of active sarcoidosis is fatigue experienced by up to 80% of those affected. Sarcoidosis-associated fatigue is globally recognized as a severely disabling symptom.[9] Sarcoidosis is associated with an elevated serum angiotensin converting enzyme (ACE) level.[10] Here, we report on a patient with PACS (not hospitalized and did not require supplemental oxygen) causing severe fatigue, 'brain fog' and dyspnoea 5 months after his initial acute COVID-19 infection. The patient underwent several tests including a serum ACE level and a computed tomography (CT) chest (Figure 1 below). The serum ACE was elevated at 121 μ/l—normal 0–65 μ/l. The chest CT scan performed 5 months after the patients' acute COVID infection demonstrated extensive bilateral subpleural peripheral dense consolidation throughout both lungs. The CT chest and patient's symptoms prompted a bronchoscopy including a bronchoalveolar lavage (BAL) and biopsy. The BAL resulted in no significant microbiological growth however the CD4:CD8 ratio was 4:1 and lymphocyte count of 31%, neutrophil count of 2% and eosinophil count 1%. The endobronchial biopsy (see Figure 1A below) demonstrated non-necrotizing granulomas consistent with a sarcoid-like reaction. It was taken from a 64-year-old non-smoking male with no history of sarcoidosis. The patient did not receive corticosteroids. We measured serially serum ACE in 124 patients seen at our PACS outpatient clinic. Patients were seen due to unresolving symptoms such as fatigue, dyspnoea and 'brain fog'. All patients had previously confirmed PCR positive acute COVID-19 acute infection a mean of 4 months previously. Twenty-eight (22.6%) of subjects were found to have an elevated serum ACE level where samples were obtained > 3 months post-acute COVID-19 infection (m = 84.2, SD = 15.9). Ninety-six (77.6%) of subjects had a normal serum ACE level (m = 42.5, SD =13.5). Serum ACE is elevated in ∼40–60% of patients with sarcoidosis. It is only elevated in ∼2–3% or normal healthy people. Of course, there are other conditions that can cause an elevated serum ACE level such as (not limited to) tuberculous, hyperthyroidism, diabetes mellitus, lymphoma and lung cancer, but we have no evidence for these in our population. We postulate that in those patients who developed long COVID syndrome along with an elevated serum ACE level may have developed an aberrant longer-term immune response to COVID infection.

Received: 26 January 2022; **Revised (in revised form):** 21 March 2022

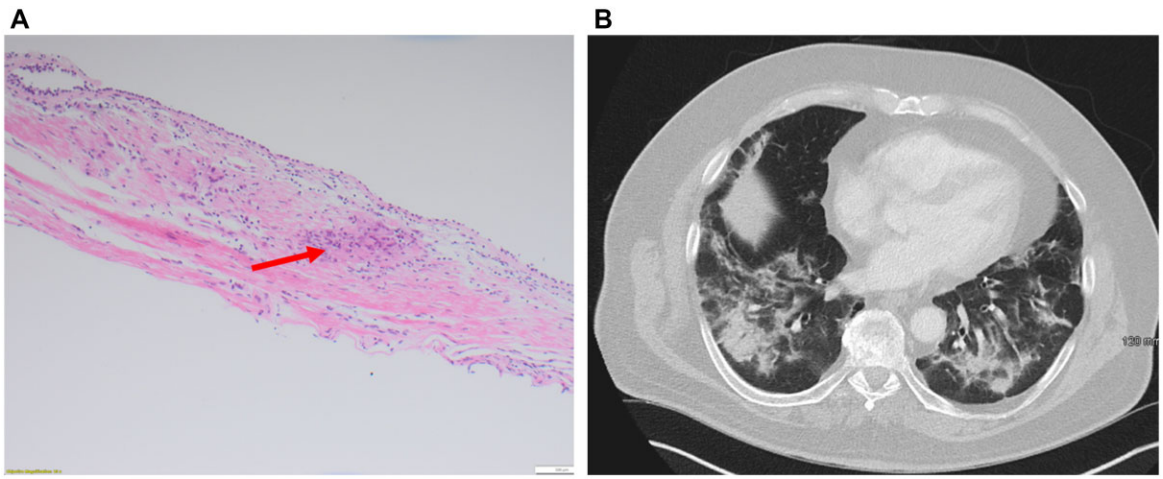

Figure 1. (A) Endobronchial biopsy of the left lower lobe of a patient with PACS 5 months after acute COVID-19 infection demonstrating a non-necrotizing granuloma (red arrow). (B) CT chest. There is extensive bilateral subpleural peripherally located dense consolidation throughout both lungs seen 5 months after acute COVID-19 infection.

The ACE2 receptor has been implicated as the entry point for SARS-CoV-2, and expression of this receptor is inversely related to ACE levels. Increased ACE levels suppress ACE2 expression and vice versa. It has been theorized that COVID-19 infection leads to the downregulation of the ACE2 receptor, thus increasing ACE2 levels. We postulate that, in the case of pulmonary involvement, the ACE-producing non-caseating granulomas in a sarcoid-like immune reaction could act to decrease additional viral induction into cells by further downregulating ACE2 receptor expression. Therefore, sarcoid-like reactions in COVID-19 patients with PACS could be a sign of aberrant convalescence causing some of the symptomatology encountered in PACS clinics. Our patient also had histological evidence of a pulmonary granulomatous reaction 5 months after his acute COVID-19 infection. The prominent symptoms of shortness of breath and fatigue, the CT thorax findings, excess CD4 cells within the airways, associated with non-necrotizing granuloma on bronchial biopsy, suggest a sarcoidosis-like reaction in this patient attending our PACS clinic and leads us to suggest a sub-group of patients attending PACS services may have this phenotype and deserves further consideration. In the context of accelerating recovery—would low dose systemic corticosteroids be of benefit to this sub-group of patients—only a formal real-world clinical trial could answer this question.

Conflict of interest. None declared.

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