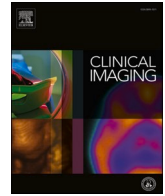




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## Cardiothoracic Imaging

## Can infections trigger sarcoidosis?

Temi Lampejo<sup>a,\*</sup>, Naman Bhatt<sup>b</sup><sup>a</sup> Department of Infection Sciences, King's College Hospital, London, UK<sup>b</sup> Department of Radiology, Northwick Park Hospital, London, UK

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## To the Editor,

We read with interest the article by Capaccione et al. on coronavirus disease 2019 (COVID-19)-induced pulmonary sarcoidosis.<sup>1</sup> As this is a single case report of COVID-19-induced pulmonary sarcoidosis on a background of over 300 million severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections worldwide to date,<sup>2</sup> one must be cautious in attributing the development of sarcoidosis to their SARS-CoV-2 infection in patients with prior SARS-CoV-2 infection. Sarcoidosis poses a diagnostic challenge given the overlapping clinico-radiological features with lymphoma, tuberculosis and certain autoimmune diseases.<sup>2</sup> Therefore, it is often a diagnosis of exclusion taking into consideration clinical (although often asymptomatic), biochemical (e.g., elevated serum angiotensin-converting enzyme levels [ACE] and hypercalcaemia), radiological (such as bilateral hilar lymphadenopathy and pulmonary infiltrates) and histological findings (e.g., well-formed noncaseating granulomas), most if not all of which were present in the case by Capaccione and colleagues, thus strongly supporting the diagnosis. Although the authors report the first case of pulmonary sarcoidosis following COVID-19 (occurring one year after being critically unwell with COVID-19), prior to this in September 2020, Behbahani et al. reported a case of a “sarcoid-like reaction” occurring two weeks after a hospital admission with COVID-19.<sup>3</sup> The sarcoid-like features in this patient were erythema nodosum and skin biopsy findings of well-formed noncaseating granulomas in subcutaneous tissue suggestive of sarcoidosis. Unlike the case reported by Capaccione et al. however, serum ACE levels and chest imaging were normal (although these findings do not rule out sarcoidosis). In May 2021, Polat Ekinici et al. reported a similar cutaneous/subcutaneous, biopsy-confirmed sarcoid-reaction with no radiological evidence of pulmonary sarcoid in a patient

1 month after the onset of her COVID-19 illness.<sup>4</sup>

We do agree that the mechanism postulated by Capaccione et al. by which COVID-19 could potentially trigger sarcoidosis (an inflammatory condition characterised by increased inflammatory cytokine release) through COVID-19 induced cytokine-mediated immune stimulation, is plausible given the now widely recognised cytokine storm that occurs with COVID-19,<sup>5</sup> which has led to widespread use of anti-cytokine monoclonal agents (such as the interleukin-6 receptor monoclonal antibody drug tocilizumab) in the treatment of COVID-19.<sup>6</sup> It is also supported by the fact that there are data to support the triggering of sarcoidosis by other infections, the most extensively studied of which are *Mycobacterium tuberculosis* and *Propionibacterium acnes*, which in animal (murine) studies have both been shown to stimulate the development of granulomas with corresponding increases in the concentrations of inflammatory cytokine-producing immune cells within the affected tissues/organs.<sup>7</sup> However, there are a lack of studies demonstrating the direct effects of infectious pathogens on the development of granulomas in humans. There are case reports/series' of sarcoidosis with biopsy-confirmed hepatic sarcoid involvement in patients with hepatitis C virus infection<sup>8,9</sup> and in one patient with hepatitis B<sup>10</sup> virus infection, thus supporting a role for viral infections as direct triggers for sarcoidosis.

A meta-analysis which investigated whether there is any association between infectious agents and sarcoidosis not only found a strong etiological link of sarcoidosis with mycobacteria and *Propionibacterium acnes* but also with *Borrelia*, human herpes virus-8, *Rickettsia helvetica*, *Chlamydia pneumoniae*, Epstein-barr virus and HIV.<sup>11</sup> However, this study was performed prior to the declaration of the COVID-19 pandemic, therefore data specifically relating to any potential association between SARS-CoV-2 infection and sarcoidosis are lacking. Given

\* Corresponding author at: Department of Infection Sciences, King's College Hospital, Denmark Hill, London SE5 9RS, UK.

E-mail address: [temi.lampejo@nhs.net](mailto:temi.lampejo@nhs.net) (T. Lampejo).

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that sarcoidosis is frequently asymptomatic and the fact that most individuals with SARS-CoV-2 infection during this ongoing pandemic do not undergo post-infection imaging (given that only a minority are admitted to hospital), there may be additional cases of COVID-19-associated sarcoidosis that remain undiagnosed or that are yet to develop. If sarcoidosis with pulmonary involvement potentially triggered by SARS-CoV-2 infection can occur relatively shortly after their infection, identification of sarcoid features on chest imaging may be made more challenging by the fact that sarcoidosis and COVID-19 can have similar radiological features in certain cases, partly dependent on the radiological stage of sarcoidosis.<sup>12</sup> The cases by Capaccione et al., Behbahani et al. and Polat Ekinci et al. however, will widen awareness of COVID-19 associated sarcoid disease thus helping to increase clinical and radiological vigilance and lead to greater consideration amongst physicians and radiologists of this potential association. It may also give the impetus for further scientific and clinical studies of this largely unrecognised potential complication of COVID-19.

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### Declaration of competing interest

None of the authors have any competing interests to declare.

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