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## New onset of sarcoidosis after COVID-19 infection

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Sarcoidosis is an uncommon granulomatous disease with potentially multi-organ involvement.<sup>1</sup> Besides pulmonary involvement, cutaneous manifestations constitute the second most frequent complications of sarcoidosis. Its cause is unknown. The disease is thought to occur in genetically predisposed individuals exposed to a triggering factor, such as bacterial and viral infections, and chemicals.<sup>2</sup> The SARS-CoV-2 infection (COVID-19) causes a variety of severe potentially devastating complications. In addition, COVID-19 has been shown to alter immune tolerance, which may result in either inflammatory or autoimmune systemic disorders or affect their evolution.<sup>3</sup> We here report a striking case of disseminated cutaneous sarcoidosis with pulmonary involvement occurring during COVID-19 infection. A 31-year-old male presented with a 6-month-history of a recurrent and widespread erythematous lesions, which developed on his back, legs and arms. The first cutaneous lesions appeared some weeks after the patient was tested positive for COVID-19 by real-time reverse-transcriptase-polymerase chain reaction (rRT-PCR) during a screening procedure, while the patient was in perfect general condition and asymptomatic. The cutaneous lesions spontaneously resolved after a few weeks. After a second positive COVID-19 test around 6 months later, the patient reported similar but much more widespread, itchy and extensive skin lesions. He developed disseminated, erythematous papules and plaques on the back and legs. (**Fig 1**). The thoracic CT scan showed mediastinal lymphadenopathies consistent with sarcoidosis. Furthermore, an elevated ACE concentration (145 U/L; normal: 20 – 64 U/L) was detected. The remaining investigations, including bronchoscopy and ocular examination were unremarkable. Laboratory tests, including full blood count, electrolytes, liver and renal tests were within normal range. Treatment with oral prednisolone 40 mg daily was started, which resulted in regression of the cutaneous lesions.

Histological [haematoxylin & eosin] studies of a skin punch biopsy specimen showed compact non-caseating epithelioid cell granulomas with a discrete inflammatory reaction composed predominantly of lymphocytes. (**Fig 2**).

Immunohistochemical analysis using the avidin-biotin complex-alkaline phosphatase method was performed using the following primary antibodies: CD1a (clone MTB1; Leica Biosystems, Germany), CD4 (clone 4B12; DakoCytomation, Denmark), CD8 (clone 4B11; Leica Biosystems), CD11c (clone 5D11; Novocastra, Switzerland), CD32 (clone EPR6657; Abcam, USA), CD68 (clone PG-M1, DakoCytomation),

CD163 (clone EDHU-1; Serotec MCA, UK), neutrophil elastase (clone NP57; DakoCytomation, Denmark), Mx1 (polyclonal rabbit antibody, GenTex, USA), BDCA-2 (clone AC144; Dendritics) and HLA-DR (clone TAL.1B5; DakoCytomation, Denmark), while irrelevant immunoglobulin G subclass-matched antibodies were used as negative control. As shown in **Fig 2**, the inflammatory infiltrate found around the granulomas predominantly consisted of CD4<sup>+</sup> T cells and, less abundantly of CD8<sup>+</sup> T cells. Dendritic cell (DC) and macrophage subsets were variably distributed. Langerhans cells (CD1a<sup>+</sup>) were mainly seen in the epidermis and occasionally around the granulomas. Together with the activation marker (HLA-DR), a strong infiltration of myeloid DCs (CD11c<sup>+</sup>) and M1-like (CD68<sup>+</sup>, CD32<sup>+</sup>) macrophages was detected within the granulomas. In contrast, there was an increased number of M2-like macrophages (CD163<sup>+</sup>) around the granulomas. Only a few plasmacytoid DCs (BDCA-2<sup>+</sup>) and neutrophils were detected in the infiltrate. Focal expression of MX1 as surrogate marker of type I interferon was detected within the granulomas and in the cell infiltrate.

The exact pathophysiologic mechanisms underlying sarcoidosis remains unclear. It has been claimed that induction of granuloma formation result from exposure to one or several still elusive, putative microbial antigen(s).<sup>2,4</sup> COVID-19 might have served as an antigenic trigger in our patient with further aggravation of the cutaneous lesions after each infection episode. Similarly, a case of sarcoidal granulomas mimicking scar sarcoidosis in a patient diagnosed with COVID-19 infection has been reported.<sup>4</sup> Furthermore, a new-onset, biopsy confirmed sarcoid-like reaction in the setting of COVID-19 pneumonia has been also describe elsewhere.<sup>5</sup>

In cutaneous sarcoidosis, various cells of the innate and adaptive immunity, including cutaneous DCs, macrophages and CD4<sup>+</sup> lymphocytes, are involved in the induction and evolution of granuloma formation. Thereby, the adaptive immune system participates in disease development by activation of CD4<sup>+</sup> T helper 1 cells and their cytokines, i.e. IFN- $\gamma$ .<sup>4</sup> Furthermore, TNF $\alpha$ , which is mainly produced by myeloid DCs and M1-like macrophages, plays a crucial role in the maintenance of granuloma formation. CD4<sup>+</sup> T cells as well as myeloid DCs and M1-like macrophages were also abundantly found around and within the granulomas in our case. Cytokines like IFN- $\gamma$  and TNF- $\alpha$  have also been reported to be involved in the COVID-19-related cytokine storm.<sup>4,6</sup> Furthermore, type-I IFNs are considered to play an essential role in the first-line antiviral defense in COVID-19,<sup>4,7</sup> interestingly, focal expression of MX1

(surrogate marker of type I interferon (IFN) was also detected in the granulomas in our case, suggesting that such factors may contribute to occurrence of cutaneous sarcoidosis in susceptible patients.

Although in our patient we cannot exclude that the development of cutaneous sarcoidosis is coincidental, the close temporal relation between the two episodes of COVID-19 infection and sarcoidosis in absence of other triggers and further aggravation of the cutaneous lesions after each COVID-19 infection episode strongly suggests a casual association. With the increasing number of people with COVID-19 infection, dermatologists should maintain an index of suspicion for these potential complications.



## Ethics Statement

The patients in this manuscript have given oral and written informed consent to publication of the case detail.

## Conflict of Interest Statement

None

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**Figure-Legend**

**Figure-1:** Clinical image

Widespread, itchy, erythematous papules and plaques on the back and legs

**Figure-2:** Histopathological analysis of the skin lesions with additional immunohistochemical stainings. Original magnification H&E x 40; IHC x 200



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