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Granulomatous manifestations associated with COVID19 infection: Is there a link between these two diseases?

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Dear Editor,

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a novel coronavirus responsible of the COVID19 disease pandemic. The S protein of the virus binds to the host cells via the angiotensin-converting enzyme II (ACE II) allowing fusion with the cell membrane and releasing of viral RNA [1,2], thus making ACE II the crucial element in the cellular entry of SARS-CoV-2. ACE II is a transmembrane carboxypeptidase abundantly expressed in the epithelium of the lower (alveolar) and upper (corneal) airways, which can explain the efficient transmission of SARS-CoV-2 in humans. ACE II physiological role is to cleave angiotensin II (Ang II) into angiotensin [1–7] which possesses antagonist roles. ACE II is found among other locations in the lower respiratory system, which leads to an inflammatory response in the lower lung airways. Infection causes an exacerbated inflammatory response, which can dramatically activate pro-inflammatory cytokines such as Interleukin (IL)-6, IL-10, interferon-gamma (IFN-gamma), and Tumor Necrosis Factor (TNF)- alpha [3–7] and promotes a cytokine storm that is thought to be central in the disease progression to acute respiratory distress syndrome and multi-organ failure. Different severe abnormal inflammatory and autoimmune responses induced by SARS-CoV-2 infection have been described [8–10], but the mechanisms by which SARS-CoV-2 triggers those manifestations are still unknown: interestingly, growing evidence suggest that ACE or angiotensin II receptor I (ATR1) inhibition could slow-down or stop the progression of autoimmune diseases, suggesting a role of this particular ACE/ ATR1 system in enhancing autoimmune reactions [11–13]. Moreover, ACE is known to be upregulated in macrophages located inside granulomatous tissue found in many diseases such as sarcoidosis and plays a crucial role in the granuloma formation but also in the regulation of production of TNF-alfa. In another hand, recent finding report that CD8+ mucosal activated invariant T (MAIT) cells might play a role in COVID-19 severity [14]. Interestingly, these same cells might play a role in the pathogenesis of granulomatous diseases such as sarcoidosis [15]. Here, we present three cases of granulomatous manifestations resembling sarcoidosis following the onset of SARS-CoV-2 infection that might illustrate a link between ACE, MAIT cells and SARS-CoV2 and immune-mediated diseases. Better understanding of the pathogenesis of these manifestations might lead to new therapeutic targets.

The first patient was a 32-year-old woman presented with initial possible COVID19 diagnosed on March the 28th. After an initial improvement until mid-April, the apparition of tachycardia lead to the realization of a chest CT that showed multiple lymph nodes of the mediastinum and bilateral hilum associated with interstitial elements and splenomegaly. Clinical examination found erythema nodosum lesions of the legs and inflammatory arthralgia. The whole picture was in favor of Löfgren syndrome with pulmonary grade 2 sarcoidosis. The second patient was a 51-year-old woman, with a familial history of sarcoidosis. Which presented with SARS-CoV-2 pneumonia in April 2020, followed a week later by the onset of painful latero-cervical lymphadenopathies. In May, patient consulted because of the increasing size of the lymph nodes and apparition of new ones. A lymph node biopsy was performed and showed sarcoidosis non-caseating granulomas. A PET-CT was performed and showed multiple supra and infra-diaphragmatic hypermetabolic lymph nodes suggestive of sarcoidosis. The last patient was a 32-year-old woman that developed symptoms compatible with possible COVID19 infection followed the next month with isolated erythema nodosum lesions of the legs, with no evidence for an alternative cause other than post-infectious. Although real-time RT-PCR testing was not directly performed during the infection because of the absence of hospitalization of patients and the confinement politics in France at that moment, all patients presented with typical signs of infection and a positive ELISA SARS-CoV-2 IgG testing one month after probable infection.

COVID-19 is known to be responsible of uncontrolled dramatic release of pro-inflammatory cytokines [3–5]. Progression to pneumonia resembling acute inflammatory interstitial lung disease is documented by radiological findings and usually occurs 1–2 weeks after the beginning of the symptoms, and is believed to be triggered by the uncontrolled immune response [16]. Interesting, all the reported manifestations started very early, one to two weeks after the onset of the infection, suggesting a resembling mechanism.

Recent data suggests that binding of SARS-CoV-2 to its receptor ACE II leads to downregulation a of the expression of ACE II, which in turn results in excessive production of Ang II [17,18]. Ang II plays an important role in the orchestration of the innate immune response with the help of its angiotensin II receptor I (ATR1) receptor which is the

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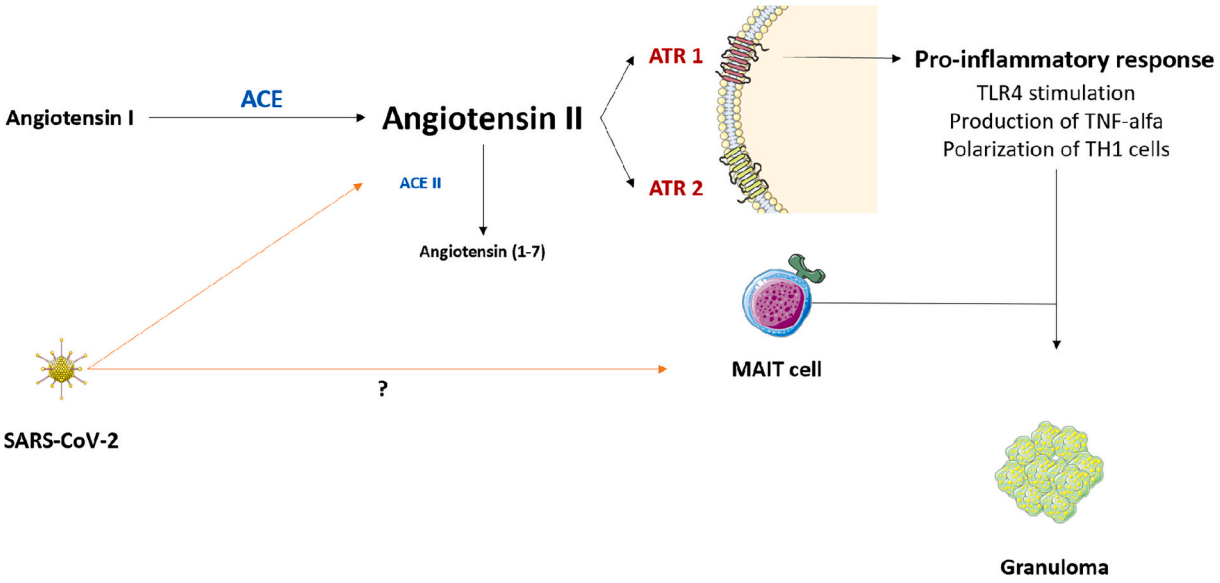

Fig. 1. Suggested model of pathogeny showing links between SARS-CoV-2 and sarcoidosis mechanisms.
SARS-CoV-2 binds to its receptor ACE II, leading to downregulation a of the expression of ACE II, which in turn results in excessive production of Angiotensin II. This might lead to an excess of stimulation of ATR1 in innate immune cells, leading to a pro-inflammatory response that favors TH1 polarization. Among with MAIT cells activation, this pro-inflammatory environment could lead to granuloma formation.

receptor more highly expressed in the immune system cells [19,20]: activation of Toll-like receptor 4 (TLR4), enhancement of diapedesis, enhanced production of reactive oxygen species, potentializing of neutrophil functions and enhancement the expression of TNF-alfa and polarization and potentializing of T helper 1 (Th1) function [11,21–24]. Pathogenesis of sarcoidosis, an idiopathic granulomatous multisystem disease, involves an initial trigger that induces a highly Th1 polarization of T CD4+ lymphocytes which is responsible of the elaboration of IFN-gamma, IL-2 and TNF-alfa [25]. The secretion of these cytokines promotes macrophage activation and accumulation resulting in the constitution of granulomas. Different putative antigens have been found, and some infectious agents are believed to be implicated as possible etiologic agents, such as *Mycobacterium tuberculosis* and *Cutibacterium acnes* [26,27]. ACE is known to be upregulated in macrophages located inside granulomas of granulomatous diseases such as sarcoidosis and plays a crucial role in the granuloma formation, as suggested by shrinking of granulomas after ACE inhibition as seen in *Schistosoma mansoni* infection [28], but also in the regulation of production of TNF-alfa [21,22]. Moreover, TLR4 stimulation of alveolar macrophages might play a role in in the high cytokine levels detected in patients with sarcoidosis, leading among others, to the increased transcription of TNF-alfa. TLR4 activation can be up-regulated by ACE via ATR1 [21,22,29].

Mucosal-associated invariant T (MAIT) cells are a subgroup of innate T cells that express an invariant TCR alfa-chain and are restricted to the non-polymorphic major histocompatibility complex class 1b molecule MR1 [30–32]. Without any clonal expansion, MAIT cells exert innate effector functions after activation of MR1 by exogenous stimuli by different pathogens including *Mycobacterium tuberculosis* and *Cutibacterium acnes*, suggesting a potential role of these cells in the pathogenesis of sarcoidosis. These cells have been found to infiltrate inflamed sites and to be strongly activated in lungs of patients with sarcoidosis [15], and the proportion of MAIT cells in peripheral blood is lower but more activated in patients with sarcoidosis than in healthy controls. Interestingly, a recent study reported a role of MAIT cells in COVID-19 pathogeny and severity, and a similar profile of activation and proportions of cells to what is observed in patients with sarcoidosis. This suggests a role of MAIT cells in exacerbating or self-sustaining inflammation in the lungs of patients with COVID19. Moreover, MAIT cells displayed significantly heightened activation in patients with severe disease, with normalization of their levels in the convalescent phase of the disease [15,33].

The occurrence of granulomatous disease after SARS-CoV-2 infection raises questions, as many actors in the pathogenesis of both diseases seem to be linked. One could hypothesize that as SARS-CoV-2 uses ACE II as a receptor to infect the host cells causing a downregulation of ACE II and an accumulation of Ang II, ACE expression could be upregulated to maintain system homeostasis. In a pro-Th1 environment and in the presence of recruited and activated MAIT cells, both ACE upregulation and/or Ang II accumulation could therefore stimulate granuloma formation and lead to granulomatous responses (see Fig. 1). Interestingly, none of the 3 patients presented with severe or life-threatening COVID19. This could suggest that recruitment of MAIT cells to other sites than lung might protect from severe or life-threatening COVID19, and that this cells play a crucial role in the onset of severe disease as suggested by other authors [33,34]. Thus, these non-severe granulomatous manifestations could be the consequence of an effective response against COVID19.

Altogether, these case reports suggest that SARS-CoV-2 might trigger granulomatous manifestations via the renin-angiotensin system and innate immune response. Targeting of the renin-angiotensin system or MAIT cells (eg with inhibitory MR1 ligands) could be interesting in both COVID19 and sarcoidosis.

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Philippe Mertz[a,*], Juliette Jeannel[a], Aurélien Guffroy[b], Sylvain Lescuyer[a], Anne Sophie Korganow[b], Murielle Rondeau-Lutz[a], Jean Christophe Weber[a]

[a] *Internal Medicine department, Strasbourg University Hospital, Strasbourg, France*

[b] *Clinical Immunology department, National Reference Center for Rare Autoimmune Diseases (RESO), ERN RITA, Strasbourg University Hospital, Strasbourg, France*

[*] Corresponding author at: Service de Médecine interne, Nouvel Hôpital Civil, 1 quai Louis Pasteur, 67000 Strasbourg Cedex, France.
E-mail address: philippe.mertz@chru-strasbourg.fr (P. Mertz).