Sarcoidosis in a Young Adult: A Rare Sequelae of COVID-19 Infection

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ABSTRACT

Introduction

SARS-CoV-2, a positive-sense single-stranded RNA virus, causes COVID-19 and has been linked to autoimmune disorders. Sarcoidosis is a multi-system disease that is frequently triggered by infections. It is characterized by non-necrotizing granulomas in multiple organs. We present a case of sarcoidosis as a rare sequelae of COVID-19.

Case Presentation

A 26-year-old man presented with mild COVID-19 symptoms, followed by prolonged fever and cough despite initial therapy, prompting a provisional diagnosis of post-COVID fibrosis. A subsequent assessment at a tertiary hospital revealed dyspnea, weight loss, and abnormal chest imaging, all of which were consistent with pulmonary sarcoidosis with pulmonary tuberculosis as a differential diagnosis. A biopsy taken during bronchoscopy confirmed pulmonary sarcoidosis and treatment with inhalation steroids resulted in symptom relief, which was followed by remission with oral steroid therapy.

Case Discussion

Sarcoidosis is a systemic disease of unknown etiology, characterized by non-necrotizing granulomas in multiple organs. It may be triggered by infections and involves an abnormal immune response. COVID-19 can potentially initiate sarcoidosis, with both sharing common immune mechanisms. Diagnosis involves imaging and biopsy, and treatment typically includes glucocorticoids and regular monitoring.

Conclusion

This case report emphasizes the potential link between COVID-19 and autoimmune conditions like sarcoidosis, highlighting the need for a comprehensive diagnostic approach and long-term observation to distinguish between sarcoidosis and post-COVID fibrosis.

KEYWORDS

Sarcoidosis, SARS-COV-2, autoimmune disease, post-COVID fibrosis, case report

Key Clinical Message

This case illustrates sarcoidosis as a potential complication of COVID-19, highlighting the need for a comprehensive diagnostic approach, including histopathology and prolonged monitoring, to distinguish it from post-COVID fibrosis. Further research is crucial to elucidate these associations and understand their underlying mechanisms.

INTRODUCTION

Severe Acute Respiratory Syndrome Coronavirus- 2 (SARS-CoV-2) is a virus with a positive sense single-stranded RNA genome that is responsible for causing coronavirus disease 2019 (COVID-19) infection.[1] COVID-19 has been linked to the emergence of autoimmune diseases.[2, 3] SARS-CoV-2 infection increases the risk of various autoimmune conditions, like rheumatoid arthritis, lupus, psoriasis, and type 1 diabetes.[4]Sarcoidosis is a multi-system disease of unknown etiology, but viral, bacterial, and fungal infections may serve as one of the most crucial triggers in the emergence of immune system impairment resulting in autoimmunity.[5] It is characterized by the infiltration of various organs by non-necrotizing granulomas.[6]Sarcoidosis generally occurs between the ages of 25 and 40.[7] Its incidence is estimated to range from 2.3 to 11 cases per 100,000 individuals annually.[8] During presentations, around 30% to 53% of patients diagnosed with sarcoidosis commonly experience respiratory symptoms like cough, difficulty breathing, and chest discomfort. Other organs involved include joints (6-35%), eyes (10-15%), isolated skin conditions (30%), and cardiac (3%-39%).[7, 9] We present a case of sarcoidosis as a rare sequelae of COVID-19.

CASE HISTORY AND EXAMINATION

We present the case of a 26-year-old male who experienced mild symptoms including low-grade fever, sore throat, dry cough, and myalgia persisting for five days. Notably, he did not exhibit any signs of shortness of breath, chest pain, or other respiratory distress. Initial examinations showed normal vital signs except for a slightly elevated temperature (99.6 F). Due to the emergence of the first surge of COVID-19 in Nepal during that period and considering his presenting symptoms, he was advised to undergo Reverse Transcription-Polymerase Chain Reaction (RT-PCR) testing for SARS-Cov-2 which came positive on January 10, 2021. He was advised to self-isolate at home and receive supportive care. However, his fever and cough persisted despite the treatment, prompting him to visit an outpatient clinic on February 11, 2021. Baseline investigations were unremarkable, but a chest x-ray revealed bilateral interstitial infiltrates (Fig-1). Subsequent RT-PCR testing for SARS-CoV-2 showed negative results. A provisional diagnosis of post-COVID fibrosis was made, and he was prescribed budesonide and a rotacap inhaler. Despite those medications, his symptoms persisted and he sought specialized care at a tertiary hospital on May 24, 2021. The patient presented to a pulmonologist in a tertiary center with a history of low-grade fever on and off (5 episodes in 3 months), malaise, and non-productive cough. He also reported exertional dyspnea and weight loss of 5 kilograms in the last 3 months. Physical examination findings were normal. There were no palpable lymph nodes and the spleen was not enlarged.

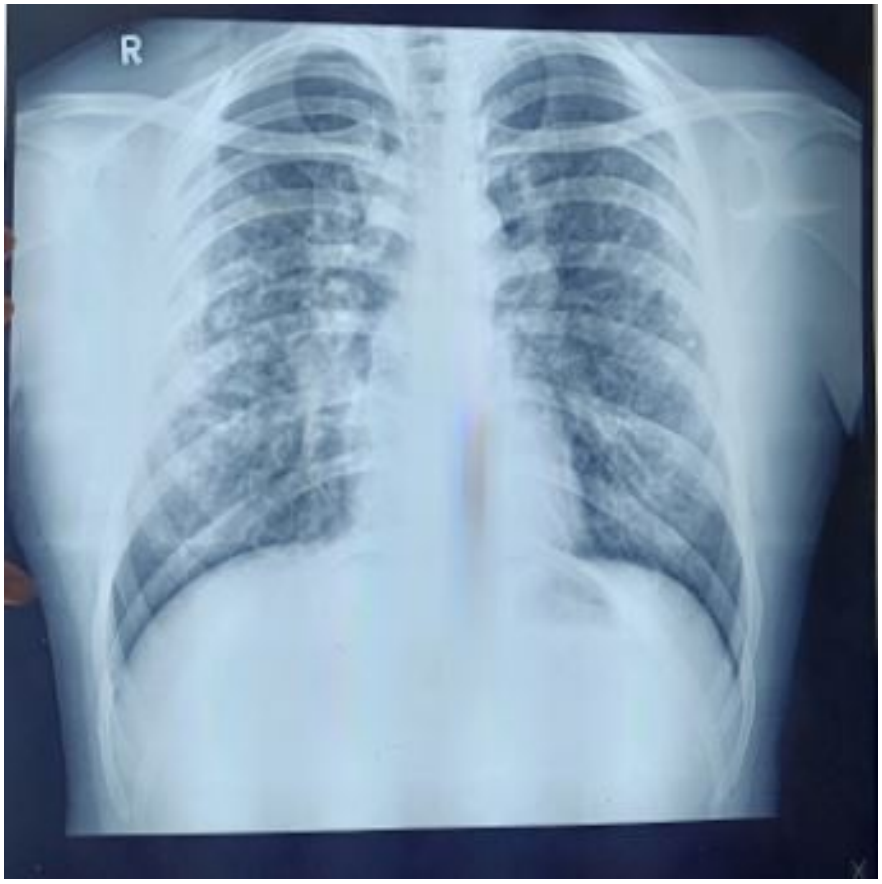

Fig -1: Chest X-ray posterior-anterior view showing bilateral interstitial infiltrates

DIFFERENTIAL DIAGNOSIS, INVESTIGATIONS AND TREATMENT

Based on the patient's symptoms and examination findings, pulmonary tuberculosis was among the potential differential diagnoses explored. Following the initial assessment, the patient underwent Multi-Detector Computed Tomography (MDCT) of the chest which revealed discrete and confluent nodular opacities in the bilateral para hilar region involving peri bronchovascular & subpleural location and involving all lobes. Additionally, there were ground glass opacities with areas of crazy paving and consolidation in the right upper and middle lobes. Mediastinal and bilateral hilar lymphadenopathy were also reported (Fig-2, Fig-3 and Fig-4). Furthermore, a Pulmonary Function Test (PFT) showed a Forced expiratory volume in the first second (FEV1) of 92% predicted, Forced vital capacity (FVC) of 99% predicted, and Diffusing Capacity of the Lungs for Carbon monoxide(DLCO) of 71% predicted. A repeat RT-PCR for SARS-CoV-2 on May 24, 2021, was negative.

With the suspicion of pulmonary sarcoidosis based on the above findings, a bronchoscopic guided transbronchial needle aspiration was performed on the subcarinal and right hilar lymph nodes. Tuberculosis was ruled out through Gene Xpert Mycobacterium tuberculosis /rifampicin resistance (MTB/RIF) testing and tuberculosis culture from bronchoalveolar lavage (BAL) obtained during bronchoscopy. The histopathological findings from the biopsy during bronchoscopy revealed well-formed non-necrotizing granulomas characterized by epithelioid histiocytes accompanied by lymphocytes. Biochemical laboratory results indicated normal values for complete blood count, liver and kidney function, electrolytes, and calcium levels. Based on the above-mentioned findings, a diagnosis of pulmonary sarcoidosis was made. Treatment was continued with Rotacap Budesonide 400 mcg twice daily via Rotahaler and Rotacap Salbutamol via Rotahaler as needed.

OUTCOME AND FOLLOW-UP

A follow-up on July 30, 2021, showed improvement in cough and shortness of breath, and the previous medication regimen was maintained. However, on August 15, 2021, the patient reported an increased cough over the past week. Initially, oral prednisolone at a dose of 40 mg daily was started. The steroid dose was then gradually tapered to 30 mg over the course of one month and then maintained at this dose. Three months after starting oral steroids, the patient's non-productive cough resolved. Following this improvement, the steroid was gradually tapered and discontinued. At present the patient is asymptomatic and not under any medications. He is on regular follow-up at three-month intervals.

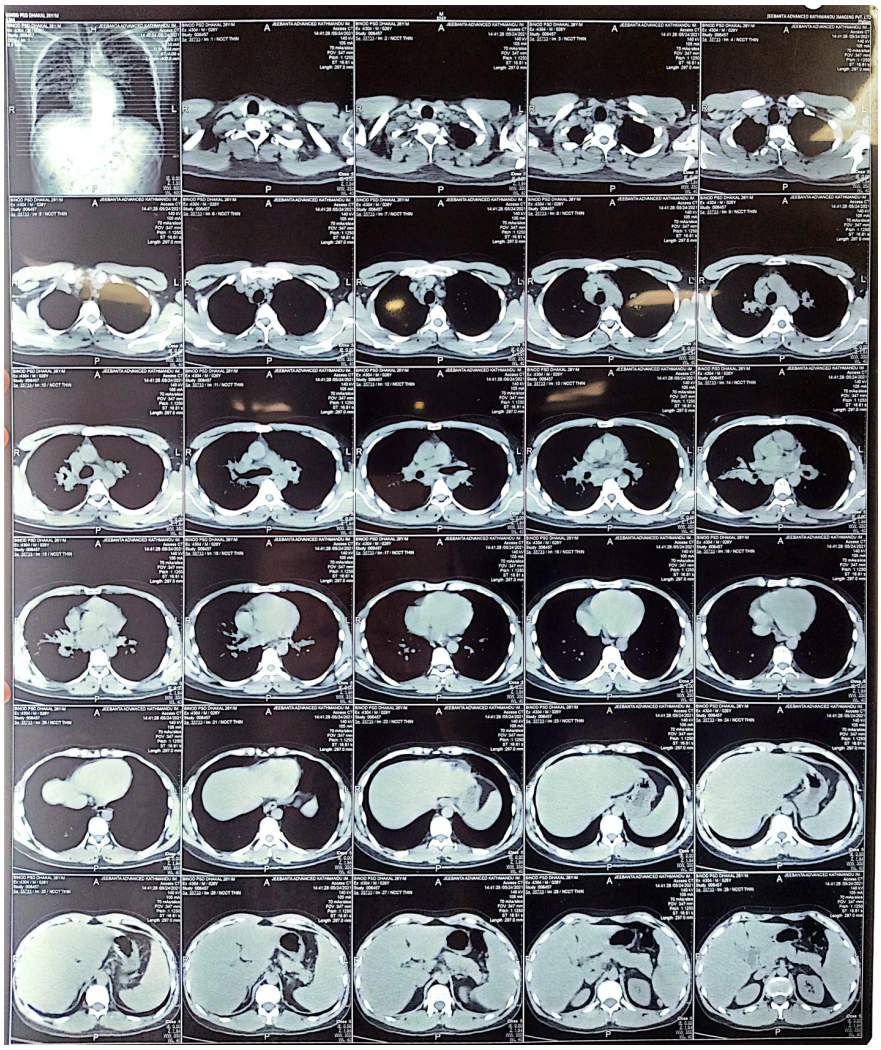

Fig-2:Transverse section of non-contrast Computed Tomography(CT) of the chest revealing discrete and confluent nodular opacities in the bilateral parahilar region involving peribronchovascular and subpleural location and involving all lobes

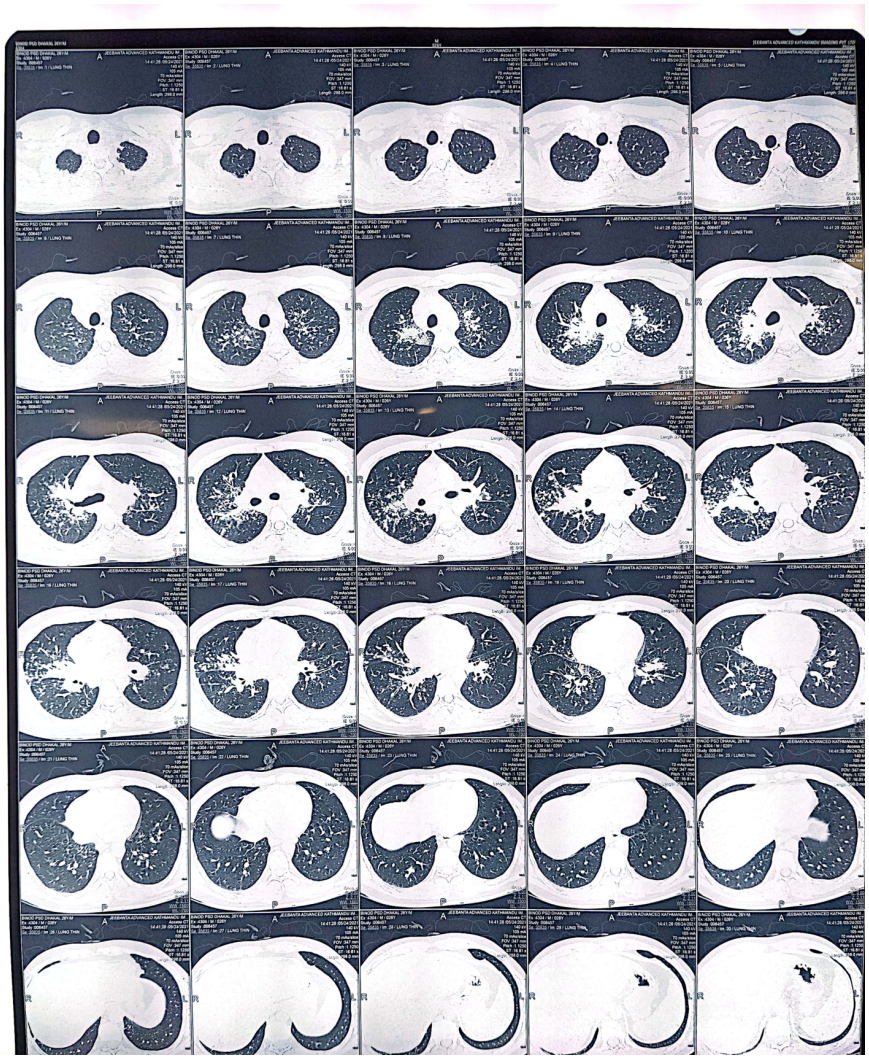

Fig-3: Transverse section of contrast Computed Tomography (CT)of the chest revealing mild enhancement at the region of the nodule and consolidation

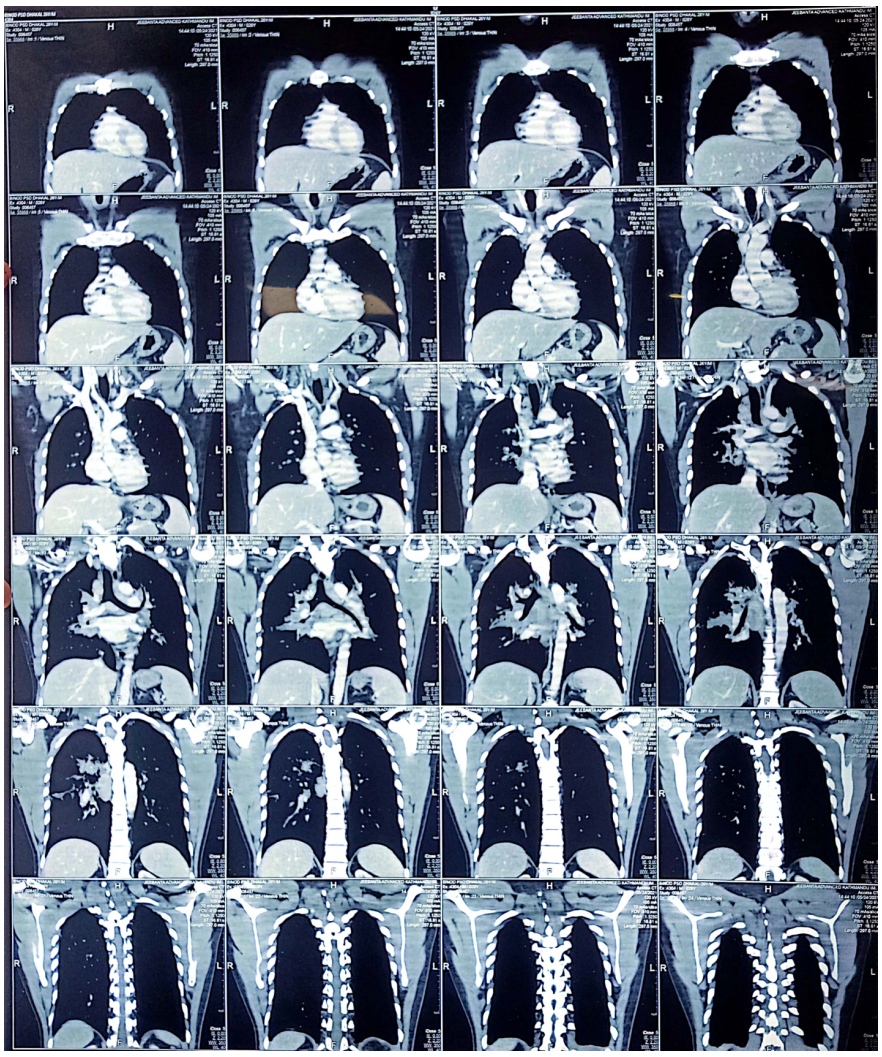

Fig-4: Longitudinal section of Computed Tomography(CT) of the chest revealing discrete and confluent nodular opacities in the bilateral perihilar region

DISCUSSION

Sarcoidosis is a systemic disease of unknown etiology characterized by the presence of non-necrotizing granulomas in various organs. While the exact cause of sarcoidosis remains unclear, the formation of granulomas is believed to involve genetic predisposition and environmental factors.[6] An abnormal immune response targeting specific antigens likely triggers an inflammatory process aimed at eliminating these antigens. Various infections like*Mycobacterium* spp, *Cutibacterium acne* s, and Herpes can potentially initiate sarcoidosis by disturbing immune cells such as antigen-presenting cells, alveolar macrophages, and T-cells.[10]

SAR-Cov-2 virus uses its S protein to attach to Angiotensin-converting enzyme II(ACEII) receptors on host cells, leading to fusion and the release of RNA, triggering a potent inflammatory response via cytokines like Interleukin-6 (IL-6) and Interferon-gamma (IFN-γ), causing a "cytokine storm." This cytokine dysregulation is common to the pathophysiology of both COVID-19 and sarcoidosis. According to the literature, COVID-19 infection can cause new-onset sarcoidosis, indicating a potential role of COVID-19 in autoimmune dysregulation.[11, 12, 13] This association between COVID-19 and diseases like sarcoidosis is highlighted by the discovery of increased T helper 17.1 (Th17.1) cells in the bronchoalveolar lavage of sarcoidosis patients,

indicating a shared immune mechanism.[14,15,16]

The diagnosis of pulmonary sarcoidosis is done by imaging and bronchoscopic biopsy. HRCT peculiarly shows bilateral hilar adenopathy, peribronchial-vascular thickening, and perilymphatic infiltrative lesions.[17] Biopsy and histopathology are typically postponed in asymptomatic or minimally symptomatic patients. However, distinguishing between COVID-19 and sarcoidosis based on clinical and imaging features can be difficult due to significant overlap. Therefore, for symptomatic patients, obtaining a histopathological diagnosis of sarcoidosis is crucial to initiate early treatment. [18]Thus, it is diagnosed by confirming non-caseating granulomatous inflammation through histology, alongside consistent clinical and radiographic findings, after ruling out other possible causes of granulomas.[19, 20]

The majority of patients have self-limiting, non-progressive diseases, thus they do not require treatment. Patients with asymptomatic disease and coincidental findings of bilateral hilar lymphadenopathy may be managed with surveillance alone.[14] Indications for starting treatment in sarcoidosis include poor performance status due to exhaustion, weight loss, arthralgia, and shortness of breath.[21] For individuals requiring therapy, the primary choice for treatment is glucocorticoids. Methotrexate, azathioprine, leflunomide, Tumor Necrosis Factor alpha (TNF-α) inhibitors, and mycophenolate may be used as steroid-sparing alternatives.[22] Refractory sarcoidosis is treated with infliximab.

Our patient presented with bilateral hilar lymphadenopathy and had granulomatous formation confirmed on histology. The other causes of granulomas, such as tuberculosis were excluded with Gene Xpert, and culture from both BAL and lymph node aspiration. Based on his symptoms and new radiographic findings, he was diagnosed with sarcoidosis as a later complication of COVID-19. Routine clinical monitoring is of paramount importance to confirm the diagnosis and to differentiate it from transient symptoms due to the host's immune response to COVID-19.[14, 23] This entails examining extrapulmonary manifestations such as joint, ocular, dermatological, and cardiac involvement, along with maintaining consistent follow-up with the patients.[19, 9] Patients on prednisone who are symptomatic are often evaluated in 4 to 8-week intervals while those who are asymptomatic are seen at 3–4 month intervals.[23]Our patient was symptomatic and followed up every 8 weeks. He improved with oral corticosteroids which were gradually tapered off and later discontinued. Now the patient is doing fine without any medication and is on regular follow-up at three-month intervals.

CONCLUSION

This case report emphasizes that sarcoidosis like many autoimmune conditions arises due to immune system dysfunction following COVID-19 infection. However, distinguishing between post-COVID fibrosis and sarcoidosis after COVID-19 infection requires a multimodal diagnostic approach involving histopathology, along with long-term observation. Further research and extended follow-up are necessary to clarify these associations and understand the underlying mechanisms comprehensively.

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None.

CONFLICT OF INTEREST

The authors report no conflicts of interest.

DATA AVAILABILITY STATEMENT

No data were used.

CONSENT STATEMENT

Written informed consent was obtained from the patient to publish this report in accordance with the journal's patient consent policy.

REFERENCES

1. Yüce M, Filiztekin E, Özkaya KG. COVID-19 diagnosis -A review of current methods. *Biosens Bioelectron* . 2021;172:112752. doi:10.1016/j.bios.2020.112752

2. Tang KT, Hsu BC, Chen DY. Autoimmune and Rheumatic Manifestations Associated With COVID-19 in Adults: An Updated Systematic Review.*Front Immunol* . 2021;12:645013. Published 2021 Mar 12. doi:10.3389/fimmu.2021.645013

3. Saad MA, Alfishawy M, Nassar M, Mohamed M, Esene IN, Elbendary A. COVID-19 and Autoimmune Diseases: A Systematic Review of Reported Cases.*Curr Rheumatol Rev* . 2021;17(2):193-204. doi:10.2174/1573397116666201029155856

4. Chang, R, Chen, TY-T, Wang, S-I, Hung, Y-M, Chen, H-Y, and Wei, C-CJ. Risk of autoimmune diseases in patients with COVID-19: a retrospective cohort study. *EClinicalMedicine* . (2023) 56:101783. doi: 10.1016/j.eclinm.2022.101783

5. Sundaresan B, Shirafkan F, Ripperger K, Rattay K. The Role of Viral Infections in the Onset of Autoimmune Diseases. *Viruses* . 2023;15(3):782. Published 2023 Mar 18. doi:10.3390/v15030782

6. Sakthivel P, Bruder D. Mechanism of granuloma formation in sarcoidosis. *Curr Opin Hematol* . 2017;24(1):59-65. doi:10.1097/MOH.0000000000000301

7. Hunninghake G., Costabel U. Statement on Sarcoidosis. Am. J. Respir. Crit. Care Med. 1999;160:20. doi: 10.1034/j.1399-3003.1999.14d02.x.

8. Arkema EV, Cozier YC. Epidemiology of sarcoidosis: current findings and future directions. *Ther Adv Chronic Dis* . 2018;9(11):227-240. Published 2018 Aug 24. doi:10.1177/2040622318790197

9. Sève P, Pacheco Y, Durupt F, et al. Sarcoidosis: A Clinical Overview from Symptoms to Diagnosis. *Cells* . 2021;10(4):766. Published 2021 Mar 31. doi:10.3390/cells10040766

10. Saidha S, Sotirchos ES, Eckstein C. Etiology of sarcoidosis: does infection play a role?. *Yale J Biol Med* . 2012;85(1):133-141.

11. Mihalov P, KrajVcoviVcovaE, KaVcerova H, Sabaka P. Lofgren syndrome in close temporal association with mild COVID-19 - case report.IDCases. 2021;26:e01291.

12 Vij O, Dey M, Morrison K, Kouranloo K. Incidence, management and prognosis of new-onset sarcoidosis post COVID-19 infection.*Sarcoidosis Vasc Diffuse Lung Dis* . 2024;41(1):e2024004. Published 2024 Mar 26.

13 Smith DJF, Meghji J, Moonim M, et al. Sarcoidosis following COVID infection: A case series. *Respirol Case Rep* . 2023;11(11):e01231. Published 2023 Oct 13. doi:10.1002/rcr2.1231

14. Capaccione KM, McGroder C, Garcia CK, Fedyna S, Saqi A, Salvatore MM. COVID-19-induced pulmonary sarcoid: A case report and review of the literature. *Clin Imaging* . 2022;83:152-158. doi:10.1016/j.clinimag.2021.12.021

15. Mertz P, Jeannel J, Guffroy A, et al. Granulomatous manifestations associated with COVID-19 infection: Is there a link between these two diseases?. *Autoimmun Rev* . 2021;20(6):102824. doi:10.1016/j.autrev.2021.102824

16. Ni W, Yang X, Yang D, et al. Role of angiotensin-converting enzyme 2 (ACE2) in COVID-19. *Crit Care* . 2020;24(1):422. Published 2020 Jul 13. doi:10.1186/s13054-020-03120-0

17. Honda O, Johkoh T, Ichikado K, et al. Comparison of high-resolution CT findings of sarcoidosis, lymphoma, and lymphangitic carcinoma: is there any difference of involved interstitium?. *J Comput Assist*

Tomogr . 1999;23(3):374-379. doi:10.1097/00004728-199905000-00010

18. Koontz CH. Lung biopsy in sarcoidosis. *Chest* . 1978;74(2):120-121. doi:10.1378/chest.74.2.120

19.Hunninghake GW, Costabel U, Ando M, et al. ATS/ERS/WASOG statement on sarcoidosis. American Thoracic Society/European Respiratory Society/World Association of Sarcoidosis and other Granulomatous Disorders. *Sarcoidosis Vasc Diffuse Lung Dis* . 1999;16(2):149-173.

20. Crouser ED, Maier LA, Wilson KC, et al. Diagnosis and Detection of Sarcoidosis. An Official American Thoracic Society Clinical Practice Guideline. *Am J Respir Crit Care Med* . 2020;201(8):e26-e51. doi:10.1164/rccm.202002-0251ST

21. Saketkoo LA, Jensen K, Nikoletou D, et al. Sarcoidosis Illuminations on Living During COVID-19: Patient Experiences of Diagnosis, Management, and Survival Before and During the Pandemic. *J Patient Exp* . 2022;9:23743735221075556. Published 2022 Mar 24. doi:10.1177/23743735221075556

22. Crouser ED, Maier LA, Wilson KC, et al. Diagnosis and Detection of Sarcoidosis. An Official American Thoracic Society Clinical Practice Guideline. *Am J Respir Crit Care Med* . 2020;201(8):e26-e51. doi:10.1164/rccm.202002-0251ST

23. Clinical manifestations and diagnosis of pulmonary sarcoidosis - Uptodate Free. pro.uptodatefree.ir. Accessed May 23, 2024. https://pro.uptodatefree.ir/Show/4353