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CASE REPORT

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Sarcoidosis in a young adult: A rare sequelae of COVID-19 infection

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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.

Abstract

Severe Acute Respiratory Syndrome Coronavirus- 2 (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 rare sequelae of COVID-19. 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. 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. 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
autoimmune disease, case report, post-COVID fibrosis, sarcoidosis, SARS-COV-2

1 | INTRODUCTION

Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) is a virus with a positive sense single-stranded RNA genome 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] The median age at diagnosis for men is 45 years and that of the female is 54 years which is nearly a decade later than that of men.[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.

2 | 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 5 days. Notably, he exhibited no shortness of breath, chest pain, or other respiratory distress. Initial examinations showed normal vital signs except for a slightly elevated temperature (99.6 F). Given 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 after 3 days of onset of his symptoms. 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 after 1 month of positive COVID-19 infection. Baseline investigations done in the outpatient clinic were unremarkable, but a chest x-ray revealed bilateral interstitial infiltrates (Figure 1). In addition, subsequent RT-PCR testing for SARS-CoV-2 showed negative results.

Both invasive diagnostic methods and a computed tomography (CT) scan facility were unavailable to the center. A preliminary diagnosis of post-COVID fibrosis was made based on the findings of the chest X-ray and he was prescribed Rotacap Budesonide 200 mcg twice daily via Rotahaler and Rotacap Salbutamol 200 mcg via Rotahaler as needed. Despite those medications, his symptoms persisted leading him to seek specialized care at a tertiary hospital 3 months after his initial presentation. 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. A physical examination was performed and no abnormalities were detected on abdominal examination, cardiac examination, and central nervous system examination. Additionally, on respiratory examination, bilateral vesicular breath sounds were heard over both lung fields and there were no added sounds. At presentation, there were no joint symptoms, eye symptoms, skin abnormalities, or cardiac symptoms. Furthermore, there were no palpable lymph nodes and the spleen was not enlarged.

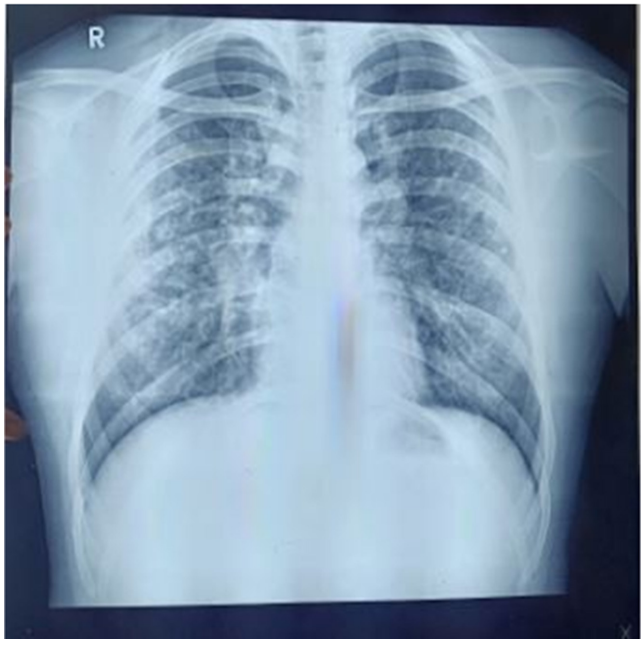

FIGURE 1 Chest x-ray posterior–anterior view showing bilateral interstitial infiltrates.

3 | METHODS (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 (both plain and contrast) 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 (Figure 2). However, no obvious dilatation of bronchi and cavitary lesion was seen. Post-contrast study shows mild enhancement at the region of nodules and consolidation (Figure 3). Mediastinal and bilateral hilar lymphadenopathy were also reported (Figure 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, Diffusing Capacity of the Lungs for Carbon monoxide(DLCO) of 71% predicted, and Peak Expiratory Flow(PEF) of 428 L/min (Table 1). A repeat RT-PCR for SARS-CoV-2 performed yielded a negative result.

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. The biopsy from other sites like skin, eye, and joints was not performed as there was no extra-pulmonary involvement in our case. 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. (Figure 5) Biochemical laboratory results indicated normal values for complete blood count, liver and kidney function, electrolytes, and calcium levels. Based on the findings mentioned above, a diagnosis of pulmonary sarcoidosis was made. Treatment was continued with an increased dose of Rotacap Budesonide (400 mcg twice daily from the previous 200 mcg) via Rotahaler and Rotacap Salbutamol 200 mcg via Rotahaler as needed. The treatment with oral steroids was reserved for potential worsening symptoms at that time.

4 | OUTCOME AND FOLLOW-UP

A follow-up after 2 months showed improvement in cough and shortness of breath, and the previous medication regimen was maintained. However, after 2 weeks of follow-up, 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 1 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 every 3 months.

5 | 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 acnes*, 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.[11–13] 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.[14–16]

The diagnosis of pulmonary sarcoidosis is done by imaging and bronchoscopic biopsy. High-resolution computed tomography (HRCT) peculiarly shows bilateral hilar adenopathy, peribronchial-vascular thickening, and perilymphatic infiltrative lesions.[17] Biopsy and histopathology are typically postponed in asymptomatic or

FIGURE 2 Transverse section of Multi-Detector Computed Tomography (MDCT) of the chest revealing discrete and confluent nodular opacities in the bilateral parahilar region involving peribronchovascular and subpleural location along with ground glass opacities in right upper and middle lobes.

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.[20] Refractory sarcoidosis is treated with infliximab.

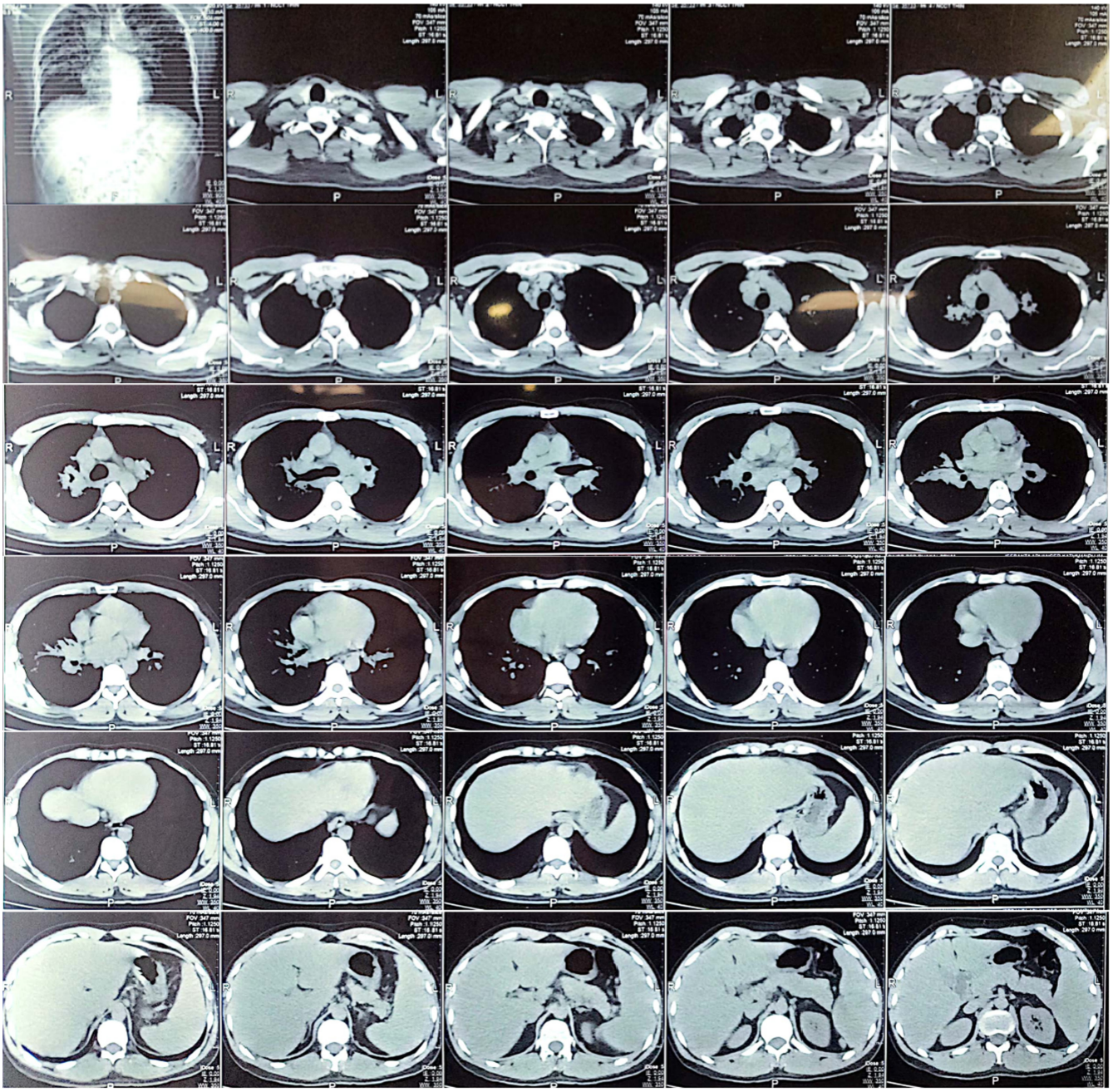

FIGURE 3 Transverse section of contrast-enhanced Computed Tomography (CT) of the chest revealing mild enhancement at the region of the nodule and consolidation.

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.[14,22] This entails examining for extrapulmonary manifestations such as joint, ocular, dermatological, and cardiac involvement, along with maintaining consistent follow-up with the patients.[9,19] 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.[22] 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.

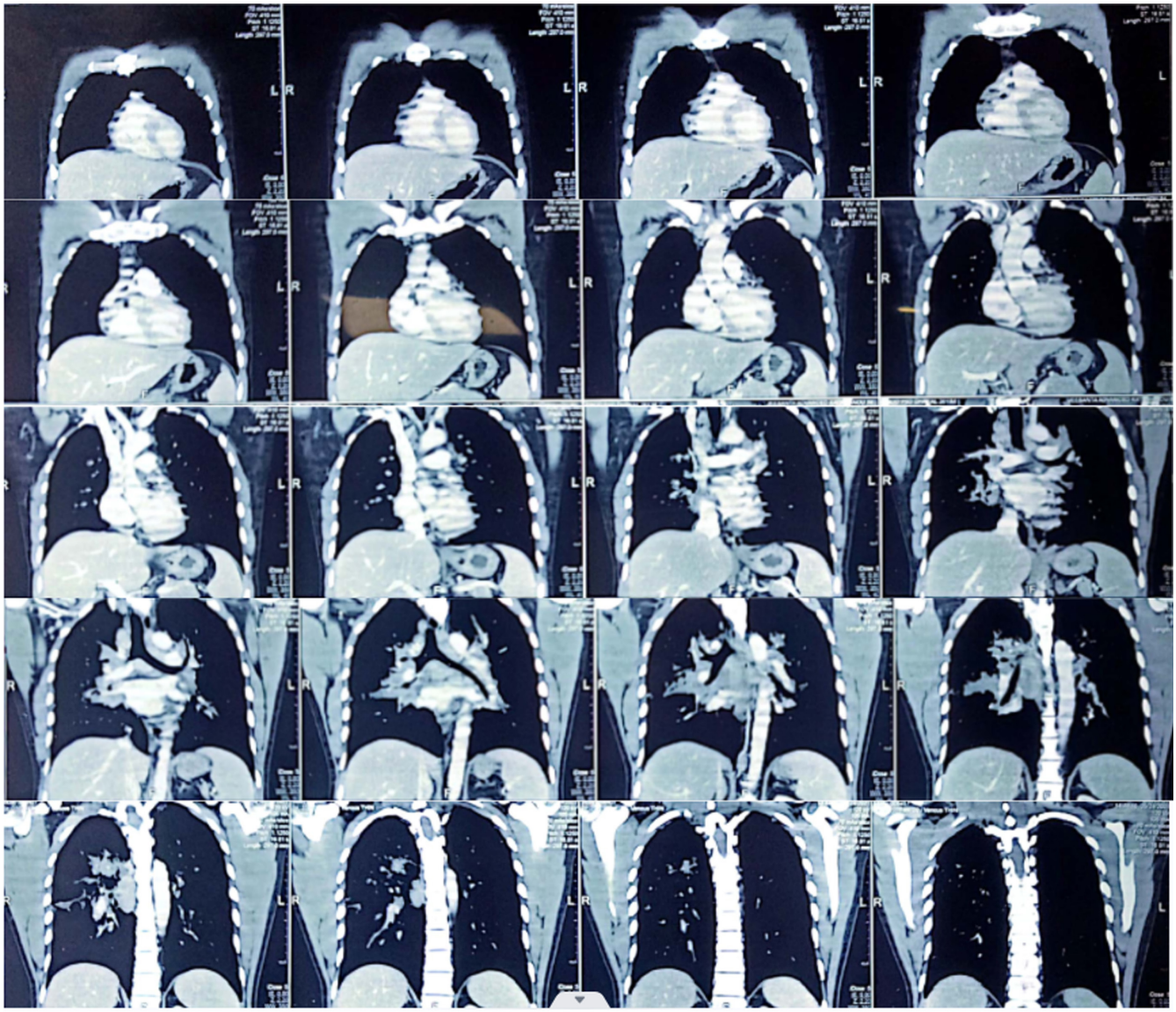

FIGURE 4 Longitudinal section of Computed Tomography (CT) of the chest revealing discrete opacities in the bilateral perihilar region suggestive of hilar lymphadenopathy.

TABLE 1 Showing the result of Pulmonary Function Test (PFT).

Parameters	Predicted	Lower limits of normal (LLN)	Result	% Predicted
FVC (L)	3.91	3.13	3.87	99
FEV1 (L)	3.33	2.67	3.07	92
FEV1/FVC (%)	82.0	72.8	79.4	97
DLCO (mL/min/mmHg)	31.9	25.0	22.7	71
PEF (L/min)	480	370	428	89

6 | 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.

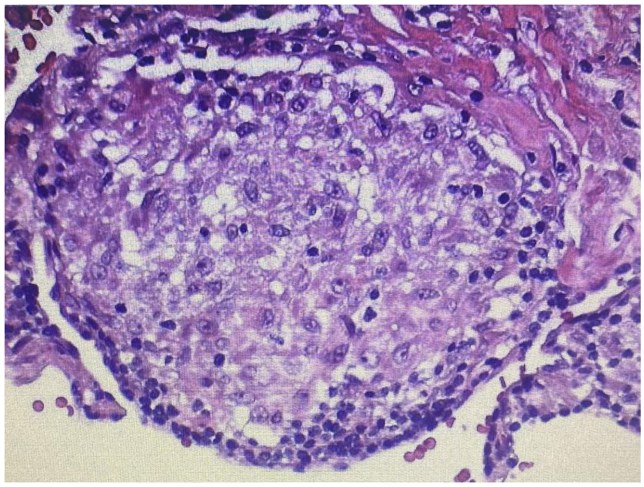

FIGURE 5 Histology showing granuloma with epithelioid histiocytes accompanied by peripheral rim of lymphocytes.

AUTHOR CONTRIBUTIONS

Deepak Subedi: Conceptualization; data curation; investigation; methodology; resources; supervision; writing – original draft; writing – review and editing. **Binod Raj Parajuli:** Data curation; investigation; methodology; project administration; resources; writing – original draft. **Neha Bista:** Conceptualization; data curation; investigation; resources; supervision; writing – original draft; writing – review and editing. **Somee Rauniyar:** Investigation; resources; supervision; writing – review and editing. **Anish Banstola:** Investigation; resources; writing – review and editing. **Ashish Sharma:** Investigation; writing – review and editing. **Monika Gurung:** Writing – review and editing.

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CONFLICT OF INTEREST STATEMENT

The authors report no conflicts of interest.

DATA AVAILABILITY STATEMENT

Data sharing not applicable-no new data generated, or the article describes entirely theoretical research.

CONSENT

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

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