A case of cutaneous sarcoidosis with pulmonary involvement after SARS-CoV-2 mRNA vaccination

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INTRODUCTION

The mRNA-1273 (Moderna) vaccine against COVID-19 is a mRNA-based vaccine that encodes the prefusion stabilized spike protein of the SARS-CoV-2.[1] It has a favorable safety profile; however, several cutaneous reactions have been reported, such as injection site reactions, urticaria, and macular rash after vaccination.[1] Recently, one case of Löfgren's syndrome, an acute manifestation of sarcoidosis consisting of the symptom triad of bilateral hilar lymphadenopathy, erythema nodosum, and ankle periarthritis, was reported after vaccination, although no histologic diagnosis was pursued.[2] Several cases of sarcoidosis have been described after COVID-19 infection, but only a limited number of cases have been reported following vaccination.[3] Herein, we report a case of cutaneous sarcoidosis with pulmonary involvement following mRNA-1273 vaccination.

Abbreviations used:

DISRs:	drug-induced sarcoidosis-like reactions
IFN:	interferon
Th1:	T helper 1
TNF:	tumor necrosis factor

CASE REPORT

A 54-year-old woman presented with erythematous papules and plaques on the left elbow, both hands, and right lower leg for 3 months (Fig 1). An initial skin lesion was detected in the right knee, which subsequently spread to other sites, accompanied by mild tenderness. She had also experienced a mild cough persisting for 2 months, but had not reported dyspnea or other systemic symptoms, such as fever or myalgia. Two days before the onset of the first lesion, she received a second dose of the mRNA-1273 vaccine; however, no cutaneous reaction was observed at the first dose of the same vaccine. She had no medical or contact history of COVID-19 infection or allergic diseases.

A punch biopsy performed on the right knee lesion revealed dense, non-necrotizing granulomatous infiltrates in the dermis and discrete granulomas, which are characteristic findings of sarcoidosis (Fig 2). Laboratory test results, including angiotensin-converting enzyme levels, were within the normal range. Chest radiography performed to screen for pulmonary involvement revealed bilateral hilar lymphadenopathy, in contrast to the normal findings observed in images from 2 years ago. Furthermore, transbronchial lung biopsy revealed the presence of non-necrotizing epithelioid cell granulomas (Fig 3). Stains for acid-fast bacteria and fungi (Gomori methamine silver) were negative.

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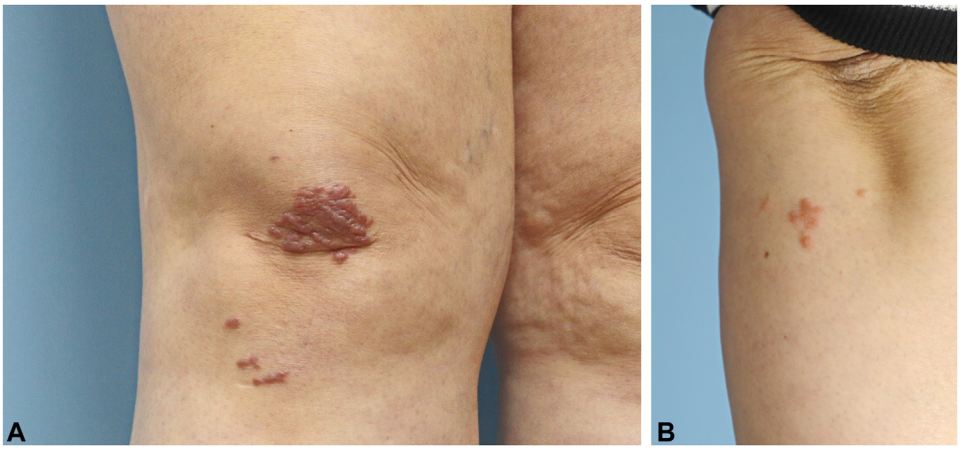

Fig 1. A 54-year-old woman presented with multiple erythematous papules, plaques on (**A**) the right knee, and (**B**) the left elbow. The lesion on the right knee presented first and progressively spread to the other sites.

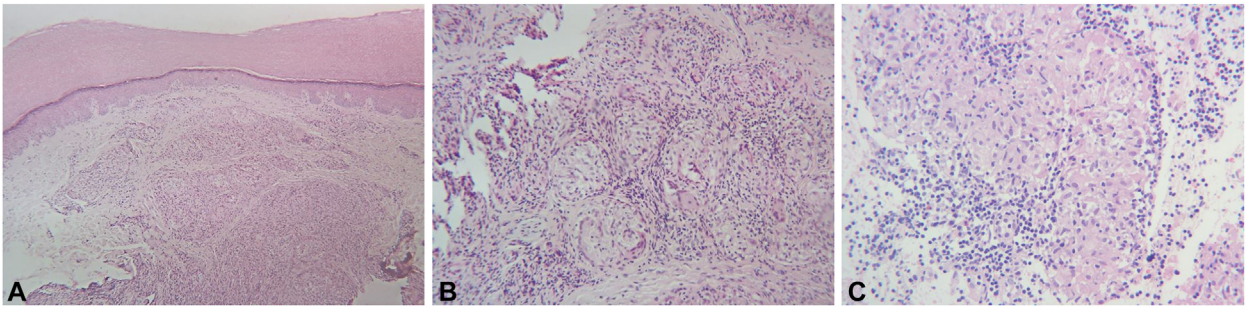

Fig 2. A, At low magnification, well-formed, non-necrotizing granulomas are observed in the dermis (H&E, ×40). **B,** Granulomas comprise epithelioid histiocytes and multinucleated giant cells with peripheral fibrosis (H&E, ×100). **C,** Non-necrotizing granulomatous inflammation is observed in lung biopsy. (H&E, ×200).

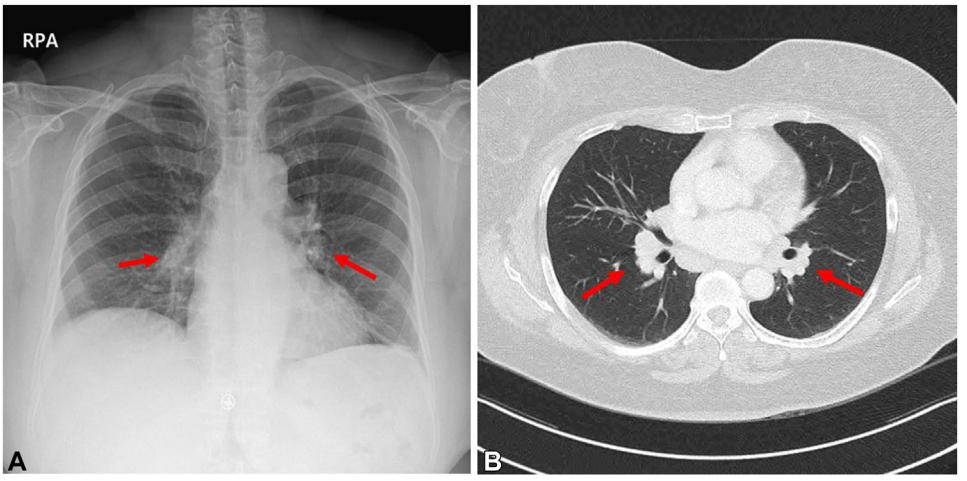

Fig 3. A, Chest X-ray revealing bilateral enlargement of the hila, indicating lymphadenopathy (*arrows*). **B,** Chest computed tomography showing parenchymal infiltrates associated with hilar enlargement (*arrows*).

The patient was diagnosed with systemic sarcoidosis and treated with systemic and topical corticosteroids, along with hydroxychloroquine. After 3 months, both the skin lesions and hilar lymphadenopathy had improved. With a good response, the therapy was discontinued, and there was no relapse.

Table I. Reported cases of sarcoidosis after COVID-19 vaccination

Case	Author (year)	Sex/age	Clinical manifestation	Vaccine	Interval between vaccination	Dose	ACE level	Treatment
1	Bauckneht et al (2021)[3]	M/44	Axillary and mediastinal lymphadenopathy	BNT162b2 (Pfizer)	Few days	2nd	N/A	N/A
2	Rademacher et al (2021)[2]	F/21	Erythema nodosum Periarthritis Bilateral hilar lymphadenopathy (Löfgren's syndrome)	mRNA-1273 (Moderna)	1 month	1st	Normal	Systemic steroid Ibuprofen
3	Rademacher et al (2021)[2]	M/27	Erythema nodosum Periarthritis Bilateral hilar lymphadenopathy (Löfgren's syndrome)	ChAdOx1 (AstraZeneca)	3 days	2nd	Normal	Systemic steroid Oral anticoagulation
4	Santiago et al (2021)[7]	M/32	Mediastinal lymphadenopathy Multiple nodules on lung Bilateral anterior uveitis	mRNA vaccine (unspecified)	10 days	2nd	N/A	Systemic steroid Azathioprine
5	Numakura et al (2022)[6]	M/61	Uveitis Bilateral hilar lymphadenopahty	BNT162b2 (Pfizer)	1 day	1st	Elevated	Subcapsular steroid
6	Carolin et al (2023)[8]	M/41	Sharply defined swelling of the tattoo Mediastinal lymphadenopathy	BNT162b2 (Pfizer)	10 days	2nd	Elevated	Hydroxychloroquine
7	Tchernev et al (2023)[9]	F/59	Erythematous papules Pericarditis, supraventricular tachycardia, hepatitis, iritis/iridocyclitis, pulmonary fibrosis/bihilar lymphadenopathy, arthritis	ChAdOx1 (AstraZeneca)	Few days	2nd	N/A	Systemic steroid Methotrexate Hydroxychloroquine Topical calcineurin inhibitor
8	Our case (2023)	F/54	Erythematous plaques Bilateral hilar lymphadenopathy	mRNA-1273 (Moderna)	2 days	2nd	Normal	Systemic and topical steroid

ACE, Angiotensin converting enzyme; *N/A*, not available.

DISCUSSION

Sarcoidosis is an idiopathic granulomatous disease characterized by dense epithelioid, non-necrotizing granulomas in various organs, such as the lungs, skin, eye, heart, joints, and kidneys. Cutaneous lesions are present in various morphologies, including papules, nodules, plaques, and infiltrating scars. Although the pathogenesis of sarcoidosis is unclear, it is generally accepted that it is caused by abnormal cell-mediated immune responses upon exposure to specific environmental factors.[4]

This case showed the typical clinical manifestation of cutaneous sarcoidosis with pulmonary involvement, and the causal relationship between SARS-CoV-2 mRNA vaccination and the onset of cutaneous sarcoidosis may be considered "possible" according to the Naranjo's adverse drug reaction probability scale. The severity was classified as level 3 according to Hartwig's Severity Assessment scale, indicating a "moderate" level of severity. However, when evaluating the preventability of adverse drug reaction, it was determined to be "not preventable" based on the Schumock and Thorton scale. Several drugs could induce a systemic granulomatous syndrome clinically indistinguishable from sarcoidosis, known as drug-induced sarcoidosis-like reactions (DISRs). DISRs typically occur in temporal relationship with drug administration and can improve or resolve if the drug is discontinued.[5] Although the clinical history and course of the disease strongly supported a diagnosis of sarcoidosis, it remains challenging to definitively exclude DISRs in this case.

To our knowledge, this is the first case of typical cutaneous sarcoidosis after COVID-19 vaccination that was confirmed using biopsy[2,3,6-9] (Table I). In a previous report of Löfgren's syndrome, skin lesions presented as erythema nodosum rather than cutaneous sarcoidosis, although a biopsy was not performed.[2] The occurrence of cutaneous sarcoidosis due to vaccination, such as Bacillus Calmette-Guérin and influenza virus vaccines, has also been reported.[10]

Although the pathogenesis of sarcoidosis following vaccination remains unclear, vaccination likely induces sustained antiviral memory T-cell responses in both CD4+ and CD8+ subsets. Considering that activated CD4+ T helper 1 (Th1) cells and interferon (IFN)-γ are crucial for inflammation and subsequent granuloma formation in sarcoidosis, Th1-type inflammation characteristic of vaccination might trigger sarcoidosis in genetically susceptible populations. Some cases of new-onset cutaneous sarcoidosis followed by COVID-19 infection have been reported, which might result from a similar basis considering increased IFN-γ and tumor necrosis factor (TNF)-α in COVID-19 infection-related cytokine storm.[6-8]

Sarcoidosis-related skin lesions do not usually require treatment unless they are cosmetically serious or accompanied by systemic involvement. Topical or intralesional corticosteroids are usually sufficient to treat localized cutaneous sarcoidosis. Systemic glucocorticoids and disease-modifying antirheumatic drugs are recommended in cases of systemic involvement.[9] According to previous reports, improvement in sarcoidosis following COVID-19 vaccination has been achieved in most patients after treatment.[6,7]

Although coincidental development cannot be completely ruled out, a close temporal relationship between vaccination and the occurrence of skin lesions could indicate an association between COVID-19 vaccine and sarcoidosis.

Conflicts of interest

None disclosed.

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