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Letter to the Editor

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Letter to the Editor (Case report)

A flare of systemic sclerosis potentially triggered by anti-SARS-CoV-2 mRNA vaccination

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Key message

- SSc flare is possibly triggered by anti-SARS-CoV-2 vaccination.

Dear Editor, The effects of the anti-severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) mRNA vaccine on rheumatic disease activity, including SSc, are unclear. Here we present the case of an SSc patient with disease relapse after anti-SARS-CoV-2 mRNA vaccination.

A 46-year-old Japanese man was referred to our hospital in 2017 after developing Raynaud's symptoms on his fingers, taut facial skin and heartburn. Significant skin sclerosis had spread from his fingers to his entire body. Although the patient did not have digital ulceration, pigmentation over his trunk was observed. His modified Rodnan's skin score (mRSS) was 36/51 points. Respiratory symptoms such as cough and shortness of breath were absent, but chest CT showed interstitial pneumonia in both lungs (Fig. 1A). Forced vital capacity (FVC) was 4.13 l (predicted value 4.2 l) and remained stable. His anti-topoisomerase I antibody titre was ≥850.0 U/ml (normal <10.0 U/ml). Based on these findings, he was diagnosed with SSc.

Combination therapy with oral prednisolone (PSL) 30 mg/day and monthly intravenous cyclophosphamide (IVCY) was started. His skin symptoms gradually improved and the lung lesions did not progress (Fig. 1B). PSL was gradually tapered to 2 mg/day and after six courses the IVCY was changed to tacrolimus. The mRSS improved to 4/51 points and in June 2021 his condition had stabilized following PSL (2 mg) and tacrolimus therapy.

In August 2021 he was vaccinated twice with the anti-SARS-CoV-2 mRNA vaccine (Pfizer-BioNTech) at an interval of 3 weeks. Two weeks after the first vaccination he had difficulty bending his fingers and upper limbs and felt that his facial skin was taut. After the second vaccination, the skin symptoms worsened and dyspnoea on effort appeared. His mRSS at the time he visited our outpatient clinic, 1 month after the second injection, was 16/51 points. His KL-6 increased to 502 U/ml from 292 U/ml (normal range 105.3–401.2) and chest CT showed ground glass opacities in the lower lobe pleura bilaterally (Fig. 1C). His FVC had decreased to 3.35 l. A treatment regimen of four weekly rituximab infusions (375 mg/m2) was started. The symptoms improved over 2 months, including dyspnoea on effort and difficulty bending the fingers. The mRSS also improved to 10/51 points.

The SARS-CoV-2 pandemic has led to the active promotion of the anti-SARS-CoV-2 mRNA vaccination worldwide. Although systemic symptoms, such as fever, chills, myalgia, arthralgia, headache and malaise, are commonly reported in vaccinated individuals, rigorous investigation of the effects of the vaccines on rheumatic disease activity, including SSc, have failed to identify any impact. The anti-SARS-CoV-2 vaccine is considered safe for patients with rheumatic disease.

Machado et al. [1] studied 4604 patients with inflammatory rheumatic and musculoskeletal diseases (RMDs), including 62 scleroderma patients, vaccinated with the anti-SARS-CoV-2 vaccine and reported a flare rate of 4.4% and an occasionally severe flare rate of 0.6%. Connolly et al. [2] studied 1377 patients with RMDs, including 14 with scleroderma, who received the anti-SARS-CoV-2 vaccine. While there were no cases of severe flare, 11% of patients had a flare requiring treatment. Post-vaccine RMD relapse was more common in patients with a prior SARS-CoV-2 diagnosis or flare within the 6 months before vaccination. Our patient had stable disease activity for >2 years and no history of SARS-CoV-2 infection. A small number of cases of rheumatic disease, both new-onset and relapse, have been reported after anti-SARS-CoV-2 vaccination [3]. Cole et al. [4] reported a case of new-onset scleroderma in a patient vaccinated with the ChAdOx1 nCOV-19 vaccine. They hypothesized that a recombinant adenovirus vector encoding the SARS-CoV-2 spike protein antigen triggered an immune response that led to the development of scleroderma.

Regarding mRNA vaccination, a patient with discoid lupus developed overlap syndrome comprising scleroderma and myositis after vaccination [5]. It has been reported that myocarditis

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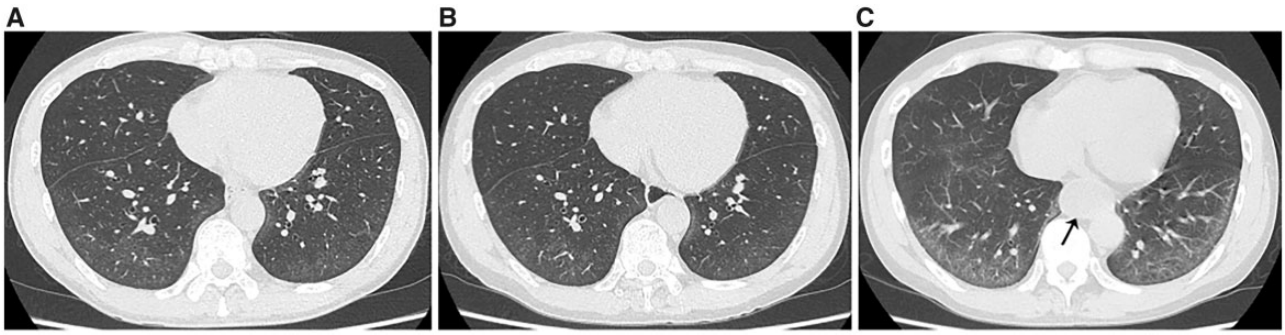

Figure 1. (**A**) Chest CT obtained at the onset of SSc shows faint ground glass shadows on both sides of the lung bottom. **(B)** After six courses of IVCY, no remarkable change was observed. **(C)** After vaccination, there was an exacerbation of ground glass shadows in the lower lung bilaterally and marked dilation of the oesophagus (arrow)

may occur, although rarely, after two doses of SARS-CoV-2 mRNA vaccine, especially in young males. The mRNA vaccine is composed of mRNA encapsulated in lipid nanoparticles (LNPs), and the LNPs are thought to cause myocarditis directly or indirectly by triggering an immune response [6]. Moreover, SARS-CoV-2 mRNA vaccination is thought to elicit CD4+ and CD8+ T cell responses and elevate cytokine levels [7]. The exacerbation of skin and lung lesions after vaccination in our patient suggests that the resultant immune responses triggered the SSc flare. The efficacy of rituximab in SSc has been recently demonstrated and is consistent with the improvement of scleroderma [8]. In our patient, scleroderma progressed rapidly after vaccination but gradually improved after rituximab administration. Thus rituximab is also effective against scleroderma induced by anti-SARS-CoV-2 mRNA vaccination.

This is the first report of SSc exacerbation following anti-SARS-CoV-2 mRNA vaccination. While RMD patients should be vaccinated, given their higher rates of SARS-CoV-2 infection, SARS-CoV-2-related mortality and the rarity of relapse, SSc patients should be monitored for worsening symptoms after the vaccine [9].

Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

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