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Case Report

Clinical features of newly diagnosed systemic lupus erythematosus after SARS-CoV-2 vaccination

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ABSTRACT

Systemic lupus erythematosus (SLE) is an autoimmune disease that causes damage to multiple organs. Various factors, including vaccination, have been associated with SLE development. Vaccination for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) began in 2020, and there are a few reports on the exacerbation of SLE after SARS-CoV-2 vaccination. The influence of SARS-CoV-2 vaccination on SLE development remains unclear. We present the case of a 53-year-old man who developed peritonitis and was subsequently diagnosed with SLE on Day 9 after receiving a third dose of the messenger ribonucleic acid-1273 SARS-CoV-2 vaccine. This case and previous reports have shown that patients who developed SLE after SARS-CoV-2 vaccination are more likely to develop it within 2 weeks of vaccination, especially when they have a higher rate of immunological abnormalities or a family history of autoimmune diseases. Furthermore, these features suggest that type I interferon is involved in the pathogenesis of SLE after SARS-CoV-2 vaccination.

KEYWORDS: Systemic lupus erythematosus; SARS-CoV-2; vaccination; interferon type I; COVID-19

Introduction

Systemic lupus erythematosus (SLE) is an autoimmune disease that causes damage to multiple organs. In addition to genetic factors, environmental factors such as smoking, ultraviolet light exposure, and viral infections are associated with the development of SLE [1]. A meta-analysis found a 1.5-fold relative risk of developing SLE following vaccination [2], and the authors considered vaccination as a risk factor for developing autoimmune diseases like SLE and rheumatoid arthritis. Vaccination for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) began in 2020, and there are a few reports on the exacerbation of SLE after SARS-CoV-2 vaccination. The influence of SARS-CoV-2 vaccination on SLE development remains unclear. In this report, we present the case of a 53-year-old man who developed peritonitis and was subsequently diagnosed with SLE after receiving a third dose of the SARS-CoV-2 vaccine. Based on our case and previous literature, we discuss the clinical features and pathogenesis of SLE following SARS-CoV-2 vaccination.

Case presentation

A 53-year-old man was admitted to our hospital with fever and abdominal pain. He received the third dose of the messenger ribonucleic acid (mRNA)-1273 SARS-CoV-2 vaccine (Moderna, Inc., Cambridge, MA, USA) 9 days before admission. Twenty-two years prior, at the age of 31 years, he presented with lymphadenopathy, Raynaud's phenomenon, and fever. The subsequent blood tests were positive for antinuclear antibody (ANA, 1:80) and anti-U1-ribonucleoprotein (RNP) antibody at our hospital. He was diagnosed with mixed connective tissue disease and was prescribed daily treatment of 2 mg of prednisolone (PSL). He had complained of arthritis 12 and 9 years ago. Antidouble-stranded (anti-ds) deoxyribonucleic acid (DNA) antibody and anti-Sjögren's-syndrome-related antigen A (anti-SS-A) antibody were measured multiple times in our hospital over the 9-year course of the patient, with the most recent measurement occurring 2 years ago; they were consistently negative. His medical history included fatty liver disease and hyperuricaemia. There was no family history of autoimmune diseases. He previously received his first and second doses of the BT162b2 SARS-CoV-2 vaccine (BioNTech/Pfizer, Mainz, Germany/New York, NY, USA) 8 and 9 months prior, respectively.

On admission, his body temperature was 37.7°C although the blood pressure, heart rate, and oxygen saturation levels were normal. Physical examination revealed a swollen left submandibular lymph node, tenderness in the left lower abdomen, and tapping pain but no rebound tenderness. No skin rash, arthritis, or muscular symptoms were observed. The laboratory findings are shown in Table 1. A complete blood count showed a white blood cell count of 4800/μl, mild lymphocytopaenia at 800/μl, a haemoglobin level of 11.3 g/dl, and a platelet count of 181,000/μl. The direct Coombs test was positive, but the haptoglobin level was normal and haemolytic anaemia was ruled out. The C-reactive

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Table 1. Laboratory findings on admission.

White blood cell count	4800/μl	Direct Coombs test	Positive
Neutrophils	3300/μl	C-reactive protein	10.65 mg/dl
Lymphocytes	800/μl	IgG	2024 mg/dl
Haemoglobin	11.3 g/dl	IgA	529 mg/dl
Platelet count	181,000/μl	IgM	57 mg/dl
AST	56 U/l	C3	128 mg/dl
ALT	35 U/l	C4	13 mg/dl
LDH	190 U/l	CH50	63.7 U/ml
Total bilirubin	0.5 mg/dl	Anti-ds DNA antibody	91 IU/ml (0–12)
Gamma-GTP	72 U/l	Anti-Smith antibody	<1.0 U/l (0–9.9)
Total protein	7.4 g/dl	Anti-U1-RNP antibody	45.2 U/ml (0–9.9)
Albumin	3.1 g/dl	Anti-SS-A antibody	10.1 U/ml (0–9.9)
Creatine kinase	434 U/l	Anti-SS-B antibody	<1.0 U/ml (0–9.9)
Aldolase	5.4 IU/l	Anti-β2 glycoprotein1 IgG	76.2 U/ml (0–20)
Creatinine	0.96 mg/dl	Lupus anticoagulant	1.4 (0–1.2)
Haptoglobin	314 mg/dl		

AST: aspartate aminotransferase; ALT: alanine aminotransferase; LDH: lactate dehydrogenase; GTP: glutamyl transpeptidase; IgA: immunoglobulin A; IgM: immunoglobulin M; C3: complement 3; C4: complement 4; CH50: 50% haemolytic complement activity.

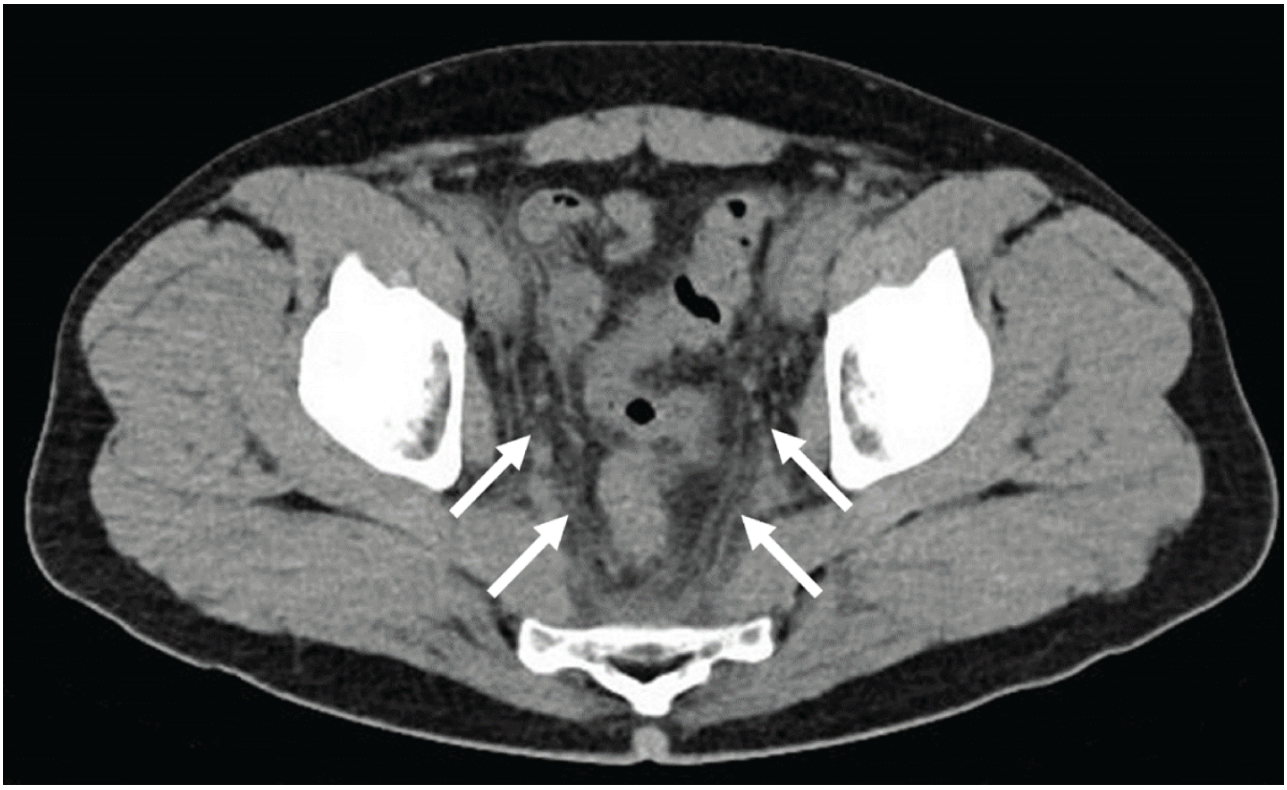

Figure 1. A plain abdominal computed tomography scan shows opacity in the pelvic fat tissue and peritoneal thickening (arrows) without free air, bowel oedema, or ascites.

protein level was elevated at 10.65 mg/dl, whereas the blood urea nitrogen and creatinine levels were normal. Urinalysis revealed no haematuria, significant proteinuria (0.17 g/day), or casts. Computed tomography revealed an enlarged left submandibular lymph node, opacity of the pelvic fat tissue, and peritoneal thickening (Figure 1). No pleural effusion, pericardial effusion, or ascites were found. No free air was present, and peritonitis with perforation of the intestinal tract was ruled out. No oedema of the intestinal tract was associated with enterocolitis on contrast-enhanced computed tomography, and serositis was considered to be a possible cause.

Based on these results, the patient was diagnosed with peritonitis. Considering bacterial infection, intravenous levofloxacin (500 mg/day) was administered. On Day 3 after admission, anti-ds DNA antibody (91 IU/ml), anti-U1-RNP antibody (45.2 U/ml), anti-SS-A antibody (10.1 U/ml), anti-β2 glycoprotein 1 immunoglobulin G (IgG) (76.2 U/ml), and lupus anticoagulant (1.4) were detected. Furthermore, the aforementioned antibodies, excluding anti-U1-RNP antibody, were newly detected. Tests for anti-Smith antibody, anti-Sjögren's syndrome B antibody, myeloperoxidase antineutrophil antibody, and proteinase 3 antineutrophil cytoplasmic antibody were negative. Complement components C3

(128 mg/dl), C4 (13 mg/dl), and CH50 (63.7 U/ml) levels were normal. Based on the findings of arthritis, fever, lymphocytopaenia, thrombocytopaenia, positive anti-ds DNA antibody, ANA, antiphospholipid antibody, and direct Coombs test without haemolytic anaemia, he was diagnosed with SLE after meeting the classification criteria defined by the 1997 American College of Rheumatology [3], 2012 Systemic Lupus International Collaborating Clinics [4], and 2019 American College of Rheumatology/European League Against Rheumatism [5] guidelines. Blood cultures on admission were negative, and the patient had a poor response to antibiotics. Levofloxacin was discontinued on Day 7 after admission. Therefore, we concluded that the patient had non-infectious peritonitis. Fever, abdominal pain, and C-reactive protein levels gradually improved, and no other organ was observed to be damaged. The patient continued to take PSL (2 mg/day) and was discharged on Day 12 after admission. The patient developed lymphadenitis 10 days after discharge, and hydroxychloroquine was initiated. However, four flares of lymphadenitis occurred within 5 months after discharge. One of these flares was accompanied by peritonitis, which was confirmed by a computed tomography scan, and anti-ds DNA antibody was 102 IU/ml at that time. Peritonitis and lymphadenitis resolved with a temporary increase in the daily dose of PSL up to 10 mg. Anti-ds-DNA antibody (27 IU/ml), anti-β2 glycoprotein 1 IgG (46.5 U/ml), and lupus anticoagulant (1.5) remained positive 8 months after discharge.

Search strategy

Literature listed in the MEDLINE/PubMed database from inception to August 2022 was searched using the keywords 'systemic lupus erythematosus' and 'SARS-CoV-2' or 'vaccination', yielding 305 and 224 papers, respectively. A total of 12 reports on SLE that developed after SARS-CoV-2 vaccination were identified [6–17].

Results

Patients who developed SLE after SARS-CoV-2 vaccination received BT162b2 or mRNA-1273, which are classified as mRNA vaccines, or AZD1222 (AstraZeneca/University of Oxford, Cambridge/Oxford, UK), which is classified as a viral vector vaccine. mRNA vaccines contain ribonucleic acid (RNA), and viral vector vaccines contain DNA as components. Table 2 summarises the age, sex, number of vaccine doses before the onset of SLE, time from vaccination to onset, medical history of autoimmune disease, family history, and autoantibody positivity before vaccination in 13 patients who developed SLE after SARS-CoV-2 vaccination, including the present case. The mean age was 38.2 ± 15.4 years, with a male-to-female ratio of 4:9. SLE developed after the first dose in five cases, the second dose in seven cases, and the third dose in only the present case. In 12 of the 13 patients, SLE developed within 2 weeks of SARS-CoV-2 vaccination. In addition to systemic autoimmune diseases such as Sjögren's syndrome and SLE, organ-specific autoimmune diseases such as type 1 diabetes mellitus, hypothyroidism, and primary biliary cholangitis were found in six cases. In addition, four cases were positive for autoantibodies such as ANA, anti-ds-DNA antibody, anti-U1-RNP antibody, and anti-SS-A antibody prior to vaccination, with two cases having a family history of autoimmune diseases. In summary, the number of cases who developed SLE after vaccination with a history of immunological abnormalities such as positivity for autoantibodies, a history of autoimmune diseases, or a family history of autoimmune diseases was as high as 61.5% (8/13 cases).

Table 3 summarises the symptoms, organ damage, and treatment of patients who developed SLE after SARS-CoV-2 vaccination. Skin symptoms included erythema, papules, purpura, and alopecia, with a frequency of 69.2% (9/13). Joint symptoms were present in 46.2% (6/13) of the patients. Haematological abnormalities ranged from monocytopaenia to pancytopaenia in 69.2% (9/13) of the patients. Lymphadenitis and nephritis were observed in 30.8% (4/13) of the patients. To the best of our knowledge, the present case is the first reported case of peritonitis.

Discussion

These results have shown that patients who developed SLE after the SARS-CoV-2 vaccination are more likely to develop it within 2 weeks of vaccination, especially when they have a higher rate of immunological abnormalities or a family history of autoimmune diseases, and frequently have cutaneous and joint symptoms. Here, we discuss these clinical characteristics and the pathogenesis of SLE after SARS-CoV-2 vaccination, including reports from previous publications.

First, patients who developed SLE after SARS-CoV-2 vaccination were found to be more likely to develop the disease within 2 weeks after vaccination. Genes induced by type I interferons (IFNs) have been reported to be overexpressed between 24 hours and 2 weeks after SARS-CoV-2 vaccination [18]; this period is consistent with the period after SARS-CoV-2 vaccination until the onset of SLE. Type I IFN are mainly produced by plasmacytoid dendritic cells via stimulation of Toll-like receptor 7/8, which recognises single-stranded RNA, and Toll-like receptor 9; these, in turn, recognise DNA [19]. Additionally, they promote the differentiation and maturation of antigen-presenting cells [20] and induce B-cell activation and antibody production [21]. It has been reported that patients with hepatitis C and malignant tumours treated with type I IFN develop SLE-like symptoms with ANA [22, 23]. In patients with active SLE, excessive expression of genes induced by type I IFN in peripheral blood mononuclear cells, i.e. the IFN signature, is correlated with disease activity [24]. Accordingly, type I IFN is thought to be involved in the pathogenesis of SLE, and we hypothesised that its production as a result of vaccination may lead to the development of SLE.

Second, 61.5% of the patients who developed SLE after SARS-CoV-2 vaccination had immunological abnormalities; this indicates that patients with some immunological abnormalities were more likely to develop SLE after SARS-CoV-2 vaccination. In general, reactions to vaccines are usually transient, including fever, local reactions, and pain [25]. However, it has been reported that vaccines may modify the pathogenesis of SLE in patients with underlying immunological abnormalities. For example, 75% of the cases with a history of immunological abnormalities developed SLE after human papilloma virus vaccination [26]. The hepatitis B virus vaccine has also been reported to increase titres of serum IgG, ANA, and anti-ds-DNA antibodies in a mouse model of SLE

Table 2. Characteristics of patients with new onset of SLE after SARS-CoV-2 vaccination.

Cases	Age, years	Sex	Dose of vaccination	Time of onset	PMH[a]	FH	Autoantibody before vaccination
[6]	54	M	Second	2 weeks	SjS	None	nd
[7]	27	F	Second	2 weeks	T1DM	SLE	nd
[8]	22	F	First	1 week	None	None	nd
[9]	42	F	First	2 weeks	None	None	nd
[10]	24	M	First	2 days	None	None	nd
[11]	23	F	First	1 week	None	None	nd
[12]	22	F	Second	10 days	None	HD	nd
[13]	60	F	Second	6 weeks	None	None	ANA
[14]	53	F	Second	2 weeks	VKH and hypothyroidism	None	nd
[15]	30	F	Second	10 days	PBC	None	Anti-ds DNA antibody
[16]	62	F	First	10 days	SCLE	None	ANA and anti-SS-A antibody
[17]	24	M	Second	2 weeks	None	None	nd
Our case	53	M	Third	9 days	MCTD	None	Anti-U1-RNP antibody

[a]Limited to immune-related diseases.
PMH: past medical history; FH: family history; nd: no description; SjS: Sjögren syndrome; T1DM: type 1 diabetes mellitus; VKH: Vogt–Koyanagi–Harada disease; PBC: primary biliary cholangitis; SCLE: subacute cutaneous lupus erythematosus; HD: Hashimoto's disease; MCTD: mixed connective tissue disease.

Table 3. Symptoms and treatment of patients with new onset of SLE after SARS-CoV-2 vaccination.

Case	Skin	Arthritis	Lymphadenitis	Haematological disorder	Serositis	Nephritis	Treatment
[6]	+	-	+	+	-	+	PSL + MMF
[7]	+	+	-	-	nd	+	PSL + MMF
[8]	+	-	-	+	nd	-	PSL + HCQ + AZA
[9]	nd	+	nd	-	+	-	PSL + HCQ + SSZ
[10]	+	+	nd	-	nd	-	HCQ + NSAIDs
[11]	+	nd	nd	+	nd	+	PSL + MMF + HCQ
[12]	+	+	+	+	-	-	PSL + MMF + HCQ
[13]	nd	nd	nd	+	nd	+	PSL + IVCY + HCQ
[14]	+	-	-	+	nd	-	PSL
[15]	+	nd	nd	+	nd	nd	PSL
[16]	+	+	nd	+	-	nd	PSL
[17]	-	+	+	+	-	-	PSL + MTX
Our case	-	-	+	+	+	-	PSL

nd: no description; MMF: mycophenolate mofetil; HCQ: hydroxychloroquine; AZA: azathioprine; SSZ: sulfasalazine; NSAID: non-steroidal anti-inflammatory drugs; IVCY: intravenous cyclophosphamide; MTX: methotrexate; +: positive for the symptom; -: negative for the symptom.

[27, 28]. In this case, the patient tested negative for anti-ds-DNA antibody multiple times over 9 years before testing positive after the third dose of the SARS-CoV-2 vaccine. The IFN signature has been suggested to be associated with not only SLE but also other autoimmune diseases such as Sjögren's syndrome and dermatomyositis [29]. Furthermore, anti-SS-A, anti-ds-DNA, and anti-U1-RNP antibodies have been reported to be associated with type I IFN activity in patients with SLE [30]. This patient was positive for anti-U1-RNP antibodies before developing SLE, suggesting that he was prone to high type I IFN activity. Therefore, patients with immunological abnormalities might potentially be predisposed to easier activation of the IFN signature. Consequently, the SARS-CoV-2 vaccine might trigger the onset of SLE in such patients.

Third, skin and joint symptoms were particularly common in patients who developed SLE after SARS-CoV-2 vaccination. Arthralgia and myalgia were reported to occur frequently in 85.1–90% of the patients with SLE relapse after SARS-CoV-2 vaccination, and an exacerbation of skin symptoms was reported to occur in 18.5–57% of patients [31, 32]. Recently, it was suggested that the activation of T helper 1 (Th1) cells and monocytes in patients with SLE may contribute to the pathogenesis of cutaneous and musculoskeletal symptoms, respectively [33]. Stimulation of Toll-like receptor 7/8 by the SARS-CoV-2 vaccine leads to decreased interleukin (IL)-4 and IL-5 and increased IL-12 and IFN-γ levels, which act on monocytes and dendritic cells to enhance IL-27 production, leading to predominant differentiation into Th1 cells in the Th1/Th2 balance [34–36]. Furthermore, anifrolumab, a type I IFN receptor antibody, significantly improved cutaneous and joint symptoms in patients with SLE symptoms [37], indicating that type I IFN is involved in these symptoms. Therefore, in addition to the involvement of type I IFN, another contributing factor for the high frequency of skin rash and musculoskeletal symptoms in patients who developed SLE after SARS-CoV-2 vaccination may be the tendency of the vaccine to activate monocytes and Th1 cells although these symptoms were not observed in the present case.

Finally, it was concluded that the peritonitis in this case was most likely caused by SLE rather than the SARS-CoV-2 vaccine itself. Initially, it was difficult to determine whether the peritonitis was caused by the SARS-CoV-2 vaccine or SLE based on the course of hospitalisation, as the peritonitis, which developed after SARS-CoV-2 vaccination, resolved spontaneously. Actually, two cases in which peritonitis developed after 1–2 days following SARS-CoV-2 vaccination have been reported, one of which resolved spontaneously [38, 39]. On the other hand, peritonitis can occur as a manifestation of SLE. In this case, the disease remained stable until

a third dose of vaccination, and the anti-ds DNA antibody, which had been negative until 2 years ago, became newly positive and remained positive in the subsequent course with other antibodies such as anti-β2 glycoprotein 1 IgG and lupus anticoagulant. Furthermore, after discharge, the patient had recurrent peritonitis and lymphadenitis, which improved with a temporary increase in the dosage of PSL and concomitant use of hydroxychloroquine. It is notable that all cases of SLE including the present case developed after SARS-CoV-2 vaccination, except one in which SLE developed after a longer time interval, specifically 7–14 days. Therefore, the peritonitis in this case was most likely caused by SLE rather than the vaccine itself. As in this case, the symptoms, such as fever, arthralgia, and serositis, are common to both SLE and adverse vaccination reactions and are sometimes difficult to differentiate. Therefore, when a patient exhibits symptoms that cannot be explained by adverse reactions to vaccination, SLE should be suspected, and a screening test should be performed.

A patient was diagnosed with SLE and peritonitis 9 days after SARS-CoV-2 vaccination, in addition to testing positive for anti-ds-DNA antibodies and antiphospholipid antibodies. This case and previous reports have shown that patients who developed SLE after SARS-CoV-2 vaccination are more likely to develop it within 2 weeks of vaccination, especially when they have a higher rate of immunological abnormalities or a family history of autoimmune diseases, and frequently have cutaneous and joint symptoms. In patients with these features after SARS-CoV-2 vaccination, SLE should be considered a differential diagnosis. Furthermore, these features suggest that type I IFN is involved in the pathogenesis of SLE after SARS-CoV-2 vaccination. Reports of SLE development after SARS-CoV-2 vaccination are limited, and its aetiology needs to be investigated in the future.

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Conflict of interest

None declared.

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Ethics approval and consent to participate

This study was approved by the ethics committee of our institution [approved number 34-309(11462)]. Written informed consent for publication was obtained from the patient.

Data availability

The datasets generated during and/or analysed during the current study are available from the corresponding author upon reasonable request.

Author contributions

All authors contributed to the conception and article design, work drafting, and critical revision of the intellectual content. Additionally, the authors decided on the final version to be published and are responsible for all aspects of the work.

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