中文題目：接種新冠肺炎疫苗後新發生之全身性紅斑性狼瘡：巧合抑或確有相關－某區域醫院之小型個案系列報告

英文題目：Newly diagnosed systemic lupus erythematosus after SARS-CoV-2 vaccination: coincidental or relevant — a small case series in a regional hospital

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**Introduction:** COVID-19 has overwhelmed the world for 3 years, leading to a tremendous and long impact on global economy and public health. Herd immunity through mass vaccination seems the optimal strategy to end the pandemic. While currently available SARS-CoV-2 vaccines are administered under emergency use authorization, safety concerns still exist, notably regarding intricate interaction with host immunity. Herein we report four cases of new-onset systemic lupus erythematosus (SLE) and one probable case following SARS-CoV-2 vaccination.

**Case presentation:**

Case 1, a 70-year-old female with hypertension noted only for months, developed general anasarca 1 month after 1st dose of SARS-CoV-2 vaccination (Moderna). Edema got alleviated with oral diuretic prescribed by a cardiologist at Hospital A. However, marked exertional dyspnea and headache in addition to recurrent anasarca took place 1 month after 2nd dose of SARS-CoV-2 vaccination (Moderna) 3 months apart. There were no associated shortness of breath, paroxysmal nocturnal dyspnea, and orthopnea. High and fluctuated blood pressure persisted despite antihypertensive agent introduced at Hospital A. She eventually turned to another cardiologist at Hospital B 4 months later and was admitted in view of progressive deterioration of renal function, heavy proteinuria (5949 mg/day), bilateral pleural effusion, pericardial effusion, and pancytopenia. Serial serologic tests showed elevated titres of ANA, anti-dsDNA, anti-Ro/SSA, anti-La/SSB, anti-Sm, anti-RNP, positive Coombs' tests (direct/indirect) with low haptoglobin, and hypocomplementemia. Lupus nephritis was confirmed by renal biopsy at our hospital. Hence the patient has met 2019 American College of Rheumatology (ACR)/ European League against Rheumatism (EULAR) classification criteria (scoring 30), 2012 Systemic Lupus International Collaborating Clinics (SLICC) criteria, and 1997 modified ACR classification criteria for SLE.

Case 2, a 33-year-old female without underlying systemic disease, developed

persistent nausea/vomiting, poor appetite, and progressive abdominal distension for 3 weeks after 1st dose of SARS-CoV-2 vaccination (Medigen). Bilateral pleural effusion, massive ascites with diffuse edematous change of bowels, and heavy proteinuria (5013 mg/day) were found when she was present at our hospital and admitted to the gastroenterologist's service. Serial serologic tests showed elevated titres of ANA, anti-dsDNA, anti-Ro/SSA, anti-La/SSB, anti-Sm, positive direct Coombs' test with normal haptoglobin, and hypocomplementemia. Lupus nephritis was confirmed by renal biopsy. Hence the patient has met 2019 ACR/EULAR classification criteria (scoring 23), 2012 SLICC criteria, and 1997 modified ACR classification criteria for SLE.

Case 3, a 28-year-old female without underlying systemic disease, had received 1st dose (AstraZeneca) and 2nd dose (Moderna) of SARS-CoV-2 vaccination 3 months apart. Pitting swelling over lower back and lower legs ensued shortly after 2nd shot, followed by fever and exertional dyspnea. Proteinuria and pancytopenia with splenomegaly were found when she visited emergency room at Hospital C. Then the patient was referred to the hematologist of our hospital. Pericardial effusion, bilateral pleural effusion, and heavy proteinuria (4256 mg/day) were demonstrated after hospitalization, along with pancytopenia, hemolytic anemia, elevated titres of ANA, anti-dsDNA, and hypocomplementemia. Lupus nephritis was confirmed by renal biopsy. Hence the patient has met 2019 ACR/EULAR classification criteria (scoring 32), 2012 SLICC criteria, and 1997 modified ACR classification criteria for SLE.

Case 4, a 33-year-old female, had got a pruritic coin-sized erythematous macule with scales over right preauricular area 1+ years ago. Dermatitis was told by a local dermatologist, and rash was alleviated with topical corticosteroids. Sparse itching erythematous maculopapules occurred in turn over forehead, neck, and upper limbs under sunlight exposure after 1st dose of SARS-CoV-2 vaccination (AstraZeneca) 1 year ago, usually with spontaneous resolution 1 week later or ameliorated with the local dermatologist's prescription but relapsing. She received 2nd (AstraZeneca) and 3rd (Moderna) doses of SARS-CoV-2 vaccination respectively 2.5 months later and 7 months later, while rash waxed and waned. Nevertheless, the patient still contracted COVID-19 four months ago. She eventually presented at my outpatient clinic with vague discomfort over dorsal sides of bilateral PIP joints, knees, and ankles for 2+ months without obvious erythema and swelling, notably in the morning with reduced handgrip strength, and alleviated with activities 4 hours later. Serial serologic tests

showed elevated titres of ANA, anti-dsDNA, anti-Ro/SSA, anti-Sm, anti-RNP, positive direct Coombs' test, and hypocomplementemia. Hence the patient has met 2019 ACR/EULAR classification criteria (scoring 22), 2012 SLICC criteria, and 1997 modified ACR classification criteria for SLE.

Case 5, a 41-year-old female healthy hepatitis B carrier, developed weakness and numbness of lower limbs without intermittent claudication 2 weeks right after 1st dose (AstraZeneca) of SARS-CoV-2 vaccination. Antiphospholipid syndrome was told when she visited the rheumatologist at Hospital D, and disease-modifying anti-rheumatic therapy was started with hydroxychloroquine 200mg QD to BID. Because of no serologic reduction found in the follow-up tests, the patient came to my clinic 5 months later for second opinion despite clinical remission. Further blood tests showed elevated titres of ANA, anti-dsDNA, anticardiolipin IgM, and lupus anticoagulant, as well as low C3 level. The patient has scored 11 according to 2019 ACR/EULAR classification criteria for SLE in the absence of lupus-related symptoms, and not met 2012 SLICC criteria and 1997 modified ACR classification criteria yet. The serologic derangement persisted 9 months later without clinical flare.

**Discussion:** SLE is the greatest imitator of autoimmune syndromes for its diverse and changeable manifestations, characterized by aberrant immune responses under environmental stimulation and epigenetic changes in the predisposed genetic background. Of note is that dysregulated type I interferon (IFN-I) signaling is vital in SLE, and the extent of dysregulation is associated with disease severity.[1] IFN-Is mediate critical antiviral responses and modulate innate and adaptive immune systems. While IFN-Is and plasmacytoid dendritic cells (pDCs), the most potent producers of IFN-Is, are well-elucidated in SLE pathogenesis, it has recently been demonstrated that IFN-Is and pDCs also play significant roles during COVID-19 infection or vaccination.[2,3] Although vaccination has reduced disease severity and mortality of COVID-19, vaccine-related adverse events such as autoimmune and autoinflammatory diseases have been documented increasingly. Previously proposed mechanisms included molecular mimicry, bystander killing, and adjuvant activation. In SLE, disease flares have been reported more than newly diagnosed events following SARS-CoV-2 vaccination,[4] and there have been 16 cases of new-onset SLE reported in the literature so far. Our cases imply possible relationship between SARS-CoV-2 vaccination and SLE in the genetically susceptible population. Further large well-controlled studies are warranted.

**Conclusion:** Our cases highlight rare but plausible association of newly diagnosed SLE after SARS-CoV-2 vaccination. Further investigation is required to delineate true incidence, since clinical vigilance and early recognition may conduce to a favorable outcome.