Serum sickness-like reaction following an administration of the first dose of inactivated COVID19 vaccine

Sasipim Chaijaras, MD,[a] Chutima Seree-aphinan, MD,[a] Suthinee Rutnin, MD,[a] Pintip Ngamjanyaporn, MD,[b] and Ploysyne Rattanakaemakorn, MD[a]
Bangkok, Thailand

Key words: CoronaVac; COVID-19 vaccines; serum sickness-like reactions; serum sickness reactions.

INTRODUCTION

Numerous vaccine-related adverse reactions have emerge amidst an emergency rollout of COVID-19 vaccines. The nature and incidence of these reactions vary according to the type of vaccine. An inactivated COVID19 vaccine (CoronaVac) is widely distributed in Thailand and several other countries. It has been considered relatively safe, with the most commonly encountered side effects being injection site reactions, fever, fatigue, diarrhea, and muscle pain.[1] Regarding cutaneous side effects, discoloration at the injection site and pruritus have been reported from vaccine trials.[1] Herein, we present a case of a severe adverse reaction to the inactivated COVID19 vaccine. The patient developed serum sickness-like reactions (SSLRs) 4 days after receiving the first dose of the vaccine, which required a prolonged course of systemic corticosteroid and precluded the patient from receiving further doses of the vaccine. This condition occurs rarely in association with vaccination; previous cases were found only in case reports and small observational studies.[2-4]

CASE REPORT

A 43-year-old previously healthy female patient presented to a dermatology outpatient clinic with pruritic blanchable erythematous macules and patches and excoriated papules and plaques on her trunk and extremities, which resolved with post-inflammatory hyperpigmentation (Fig 1, *A* and *D*).

Abbreviations used:

SS: serum sickness syndrome
SSLR: serum sickness-like reaction

The lesions on the chest and back of the right shoulder exhibited a feature resembling reticulate erythema (Fig 1, *B* and *D*). Four days prior, the patient had received the first dose of an inactivated COVID19 vaccine (CoronaVac; Sinovac, Beijing) without any immediate adverse reaction. The rashes started as a single patch on the chest and became generalized within 9 days; they appeared randomly and did not follow a pattern of centrifugal distribution. The rashes were accompanied by fever (body temperature, 38.1 °C), generalized malaise, severe myalgia and arthralgia, and cervical lymphadenopathy. Before this presentation, the patient had not had any recent history of respiratory tract infection, taken any medication, vaccination, or blood transfusions. Laboratory investigations revealed leukocytosis predominated by neutrophils and elevation of various inflammatory markers, including erythrocyte sedimentation rate (42 mm/hr; normal range, 4-20 mm/hr), C-reactive protein (165.74 mg/L; normal range, 0-5 mg/L), ferritin (3210.2 ng/mL; normal range, 15-150 ng/mL), and lactate dehydrogenase (336 U/L; normal range, 125-220 U/L). Chest x-ray, urinalysis, and serum creatinine level were normal. Serology for hepatitis viruses indicated an inactive carrier state for hepatitis

From the Division of Dermatology[a] and Division of Allergy, Immunology, and Rheumatology[b], Department of Medicine, Faculty of Medicine, Ramathibodi Hospital, Mahidol University, Bangkok.
Funding sources: None.
IRB approval status: Not applicable.
Correspondence to: Ploysyne Rattanakaemakorn, MD, Division of Dermatology, Department of Medicine, Faculty of Medicine, Ramathibodi Hospital, Mahidol University, 270 RamaVI, Ratchathewi, Bangkok 10400, Thailand. E-mail: ploysyne@gmail.com.
JAAD Case Reports 2022;19:21-4.
2352-5126

https://doi.org/10.1016/j.jdcr.2021.11.004

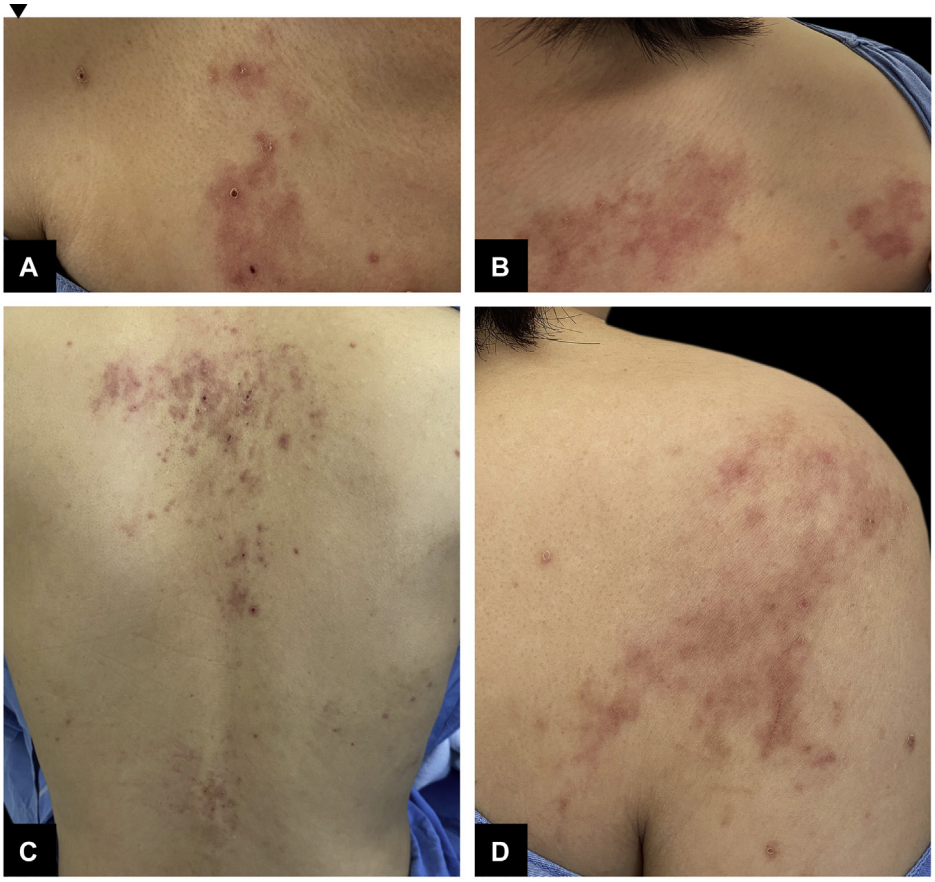

Fig 1. Cutaneous findings. Erythematous patches with excoriation on the trunk and extremities with post-inflammatory hyperpigmentation (**A-D**). Some lesions showed a feature resembling reticulate erythema (**B**, **D**).

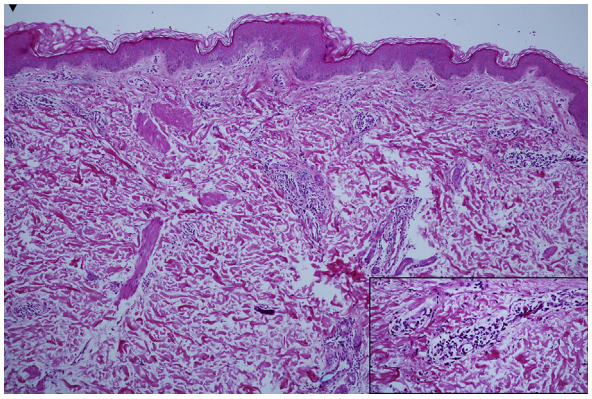

Fig 2. Histopathology of the skin lesion. Superficial perivascular and interstitial inflammatory cell infiltrates. (Hematoxylin-eosin stain; original magnification: ×100.) **Inset**, the inflammatory cell infiltrates were composed of lymphocytes, neutrophils, nuclear dust, and extravasation of erythrocytes. (Hematoxylin-eosin stain; original magnification: ×400.)

B virus infection (viral load, 24 IU/mL with normal liver function tests) and the absence of hepatitis C infection. Hemocultures, nasopharyngeal swabs for SARS-CoV-2 real-time polymerase chain reaction, and tests for antinuclear antibodies and rheumatoid factors were negative. Complement levels, including C3c and C4, were normal. A test for anti-CIC C1q IgG antibodies, which indicate the presence of an abnormal circulating immune-complex, was also negative. Biopsy of the lesional skin demonstrated superficial perivascular and interstitial inflammatory cell infiltrates (Fig 2) composed of lymphocytes, neutrophils, nuclear dust, and extravasation of erythrocytes (Fig 2, *inset*). Fibrinoid necrosis of the blood vessel wall was not observed. Histopathologic differential diagnoses might encompass urticarial vasculitis; nonetheless, the overall clinical presentation, the temporal relationship with the vaccine, together with the normal complement levels, favored the diagnosis of vaccine-related SSLR (Table I).[5-7] The diagnosis prompted the prescription of high-dose oral corticosteroid treatment (prednisolone 1 mg/kg/day), colchicine (1.2 mg/day), antihistamines, and a moderate-potency topical steroid. Given the rapid improvement of the patient's

Table I. Clinical features of serum sickness-like reaction and its main differential diagnoses

	Serum sickness-like reaction[5,6]	Serum sickness syndrome[5,6]	Urticarial vasculitis[7]
Patient characteristics	Children > adults, no sex predilection	No age or sex predilection	adults > children, women > men
Causes	Most common: Medications (cefaclor, penicillins, minocycline, NSAIDs, bupropion, propranolol, sulfonamides, phenytoin) Others: Biologics, vaccines	Most common: Venom or microbial antitoxins Others: Anti-thymocyte globulin, biologics, vaccines	Most common: Idiopathic Others: Medications, infections, autoimmune diseases, myelodysplastic disorders, malignancies
Disease onset after the exposure	5-10 days	1-2 weeks	Variable
Skin manifestations	Pruritic, blanchable, urticarial plaques or morbilliform eruption on the trunk and extremities	Pruritic, blanchable, urticarial plaques, morbilliform eruptions, or palpable purpura on the trunk and extremities; often starting around the drug injection site and becoming most prominent at the lateral side of the junction between the palmoplantar and dorsal aspects of hands and feet	Non-painful or partially blanchable, indurated wheals (0.5-5 cm) with a central dark-red or brown area, lasting for several days and leaving residual hyperpigmentation. True urticarial and angioedema occur in 50% of the patients
Systemic manifestations	Fever, arthralgia, abdominal pain, lymphadenopathy	Common: Fever, malaise, arthralgia, or arthritis Uncommon: Facial or peripheral edema, lymphadenopathy, splenomegaly, glomerulonephritis, gastrointestinal symptoms or intestinal ischemia, uveitis, peripheral neuropathy	Common: fever, arthralgia or arthritis, myalgia Uncommon: glomerulonephritis, chronic obstructive lung disease or pleuritis, gastrointestinal symptoms or intestinal ischemia, ocular inflammation (uveitis, episcleritis, conjunctivitis)*
Circulating immune complexes	No	Yes	Yes
Laboratory findings†	Normal serum complement levels Absence of anti-C1q antibodies	Low serum complement levels Elevated anti-C1q antibodies	Low or normal serum complement levels* Elevated anti-C1q antibodies observed in 50%-100% of the patients
Histopathology	Perivascular and interstitial mixed cell infiltrates; no or scant vasculitis.[8] DIF: negative	Leukocytoclastic vasculitis DIF: Deposits of immunoglobulins and complements within vessel walls	Leukocytoclastic vasculitis DIF: Deposits of immunoglobulins and complements within vessel walls
Clinical courses and prognosis	Self-limiting after the removal of causative agents No long-term sequelae May require NSAIDs, antihistamines, and systemic corticosteroids for symptom control	Spontaneously improve after the withdrawal of causative agents Prognosis depends on the degree of systemic involvement NSAIDs, antihistamines, systemic corticosteroids, and plasmapheresis are warranted in severe cases	Mostly chronic (resolves in only 30%-40% of patients in one year) or recurrent (4-8 weeks per episode) Requires immunosuppressive therapy for disease control

DIF, Direct immunofluorescence; *NSAIDs*, nonsteroidal anti-inflammatory drugs.

*Hypocomplementemic urticarial vasculitis is more common than the normocomplementemic variant; serum complement levels and anti-C1q antibodies are inversely proportionate to the extent and magnitude of systemic involvement. Systemic involvement is rare in the case of normocomplementemic urticarial vasculitis.

†Non-specific elevation inflammatory markers can be observed in patients with serum sickness-like reaction, serum sickness syndrome, and urticarial vasculitis.

condition in less than a week, a 2-week taper was attempted; however, the symptoms recurred with this regimen. Therefore, prednisolone was reintroduced at 15 mg per day with gradual tapering guided by erythrocyte sedimentation rate levels. After 2 months of treatment, inflammatory markers normalized, allowing a slow withdrawal of corticosteroid treatment while continuing others. Because of the prolonged course and severity of the illness, the caring physicians and the patient agreed to cancel further vaccine doses. The reaction was reported to the vaccine adverse event reporting system.

DISCUSSION

Serum sickness syndrome (SS) is an immune-complex mediated hypersensitivity reaction that occurs following vaccination and protein-based medications.[6] By contrast, SSLR, despite its clinical resemblance to SS, currently has an unclear pathogenesis, although current evidence suggests that it is not mediated by abnormal immune-complex formation.[5] This delayed hypersensitivity reaction was first described as a drug-induced reaction and is rarely encountered in adults; it is more frequently found in children with an incidence of approximately 7%.[5] Its clinical manifestations are remarkably similar to those of SS and include fever, malaise, arthritis or arthralgia, and rashes.[5,6] The rashes observed in SSLR are non-specific and may include urticaria, morbilliform eruption, and polycyclic plaques.[5] The histopathology of the rashes usually reveals the features of neutrophilic urticaria without vasculitis.[8,9]

The differential diagnoses of SSLR include SS, normocomplementemic urticarial vasculitis, viral exanthem, Adult Still disease, and Schnitzler syndrome. Among these diagnoses, SS and urticarial vasculitis can be challenging to differentiate from SSLR, as the diagnosis is based on clinical grounds (Table I). Though the extravasation of erythrocytes observed in our case may raise suspicion for urticarial vasculitis, scant perivascular leukocytoclasis has been reported in a previous case of SSLR,[8] and, therefore, is not necessarily indicate the presence of vasculitis. Additionally, joint involvement is mainly found in hypocomplementemic urticarial vasculitis rather than in normocomplementemic urticarial vasculitis.[7] Besides, although not all viral infections are investigated, these diagnoses are unlikely, as they are usually accompanied by other features characteristic of the specific viral infections (eg, transaminitis for viral hepatitis and pharyngitis for Epstein-Barr virus infection).

To date, causes of SSLR reported in adults include antibiotics, psychiatric drugs (mostly bupropion), biologics, and vaccines. Influenza,[4] hepatitis B,[3] and rabies[2] vaccines were reported as causes of SSLRs. Our case adds inactivated COVID19 vaccine to the list of disease triggers, even though previous unreported SSLR cases related to this vaccine may be grouped under an umbrella term of hypersensitivity reactions.[1] Recognition of this condition is crucial since it precludes the patients from receiving further doses of the vaccine, unless there is an absolute necessity that outweighs the risk of re-developing this condition. Successful attempts of desensitization in patients who developed SSLR have been documented in only a few cases.[10]

Regarding disease prognosis, SSLR is self-limited within 1-2 weeks upon removing the causes.[6] However, nonsteroidal anti-inflammatory agents or corticosteroid treatment may be needed for patients with severe disease.

Conflicts of interest

None disclosed.

REFERENCES

1. Zhang Y, Zeng G, Pan H, et al. Safety, tolerability, and immunogenicity of an inactivated SARS-CoV-2 vaccine in healthy adults aged 18-59 years: a randomised, double-blind, placebo-controlled, phase 1/2 clinical trial. *Lancet Infect Dis*. 2021;21(2):181-192. https://doi.org/10.1016/S1473-3099(20)30843-4
2. Dreesen DW, Bernard KW, Parker RA, Deutsch AJ, Brown J. Immune complex-like disease in 23 persons following a booster dose of rabies human diploid cell vaccine. *Vaccine*. 1986;4(1):45-49. https://doi.org/10.1016/0264-410x(86)90096-4
3. Arkachaisri T. Serum sickness and hepatitis B vaccine including review of the literature. *J Med Assoc Thai*. 2002;85(Suppl 2):S607-S612.
4. Apisarnthanarak A, Uyeki TM, Miller ER, Mundy LM. Serum sickness-like reaction associated with inactivated influenza vaccination among Thai health care personnel: risk factors and outcomes. *Clin Infect Dis*. 2009;49(1):e18-e22. https://doi.org/10.1086/599615
5. McNamara K, Hughes OB, Strowd LC. Cutaneous drug eruptions including serum sickness-like reaction, symmetrical drug-related intertriginous and flexural exanthema, and drug-induced lupus. *Clin Dermatol*. 2020;38(6):641-647. https://doi.org/10.1016/j.clindermatol.2020.06.013
6. Peter JG, Lehloenya R, Dlamini S, et al. Severe delayed cutaneous and systemic reactions to drugs: a global perspective on the science and art of current practice. *J Allergy Clin Immunol Pract*. 2017;5(3):547-563. https://doi.org/10.1016/j.jaip.2017.01.025
7. Gu SL, Jorizzo JL. Urticarial vasculitis. *Int J Womens Dermatol*. 2021;7(3):290-297. https://doi.org/10.1016/j.ijwd.2021.01.021
8. Nguyen CV, Miller DD. Serum sickness-like drug reaction: two cases with a neutrophilic urticarial pattern. *J Cutan Pathol*. 2017;44(2):177-182. https://doi.org/10.1111/cup.12863
9. Tolpinrud WL, Bunick CG, King BA. Serum sickness-like reaction: histopathology and case report. *J Am Acad Dermatol*. 2011;65(3):e83-e85. https://doi.org/10.1016/j.jaad.2011.02.037
10. Ali S, Corcea SL, Cristian RM, Bumbacea RS. A rapid desensitization protocol in a case of drotaverine-induced serum sickness-like reaction in a pregnant woman: a case report. *Exp Ther Med*. 2019;18(6):5105-5107. https://doi.org/10.3892/etm.2019.8170