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Morbilliform rashes as an unusual manifestation of vaccine-induced immune thrombotic thrombocytopenia

Vaccine-induced immune thrombotic thrombocytopenia (VITT) has been reported in individuals who received the ChAdOx1 CoV-19 vaccine. Herein, we report a VITT case with an unusual presentation of bilateral maculopapular rash on the thighs.

A 47-year-old male with no prior medical history, received the ChAdOx1 CoV-19 vaccine eight days before this admission. Two days after receiving the vaccine, fever accompanied by general muscle soreness and headache developed. Faint erythematous maculopapular rashes, resembling morbilliform eruption, developed over the lower extremities one day before admission. Physical examination revealed prominent erythematous maculopapular rashes affecting the bilateral thighs, which was blanchable and non-itching (Fig. 1A and B). Investigations revealed leukopenia 2490/μL (normal range 3900–10600/μL), thrombocytopenia 67 $\times$ 10^3/μL (normal range 150–400 $\times$ 10^3/μL), high D-dimer 3.97 mg/l (normal range <0.55 mg/l), alanine aminotransferase 145 U/L (normal range 10–50 U/L), aspartate aminotransferase 92 U/L (normal range 8–38 U/L), c-reactive protein (CRP) 4.9 mg/dL (normal range <0.3 mg/dL) and ferritin 4003 ng/ml (normal range 21.81–274.66 ng/ml). Prothrombin time, activated partial thromboplastin time, fibrinogen, electrolytes, albumin, lactate and renal function were normal.

A brain computed tomography and cerebral sinus venogram showed a patent cerebral venous system and no other abnormalities. Multi-detector computed tomography showed no pulmonary embolism or deep vein thrombosis. Rheumatologic evaluation showed positive antinuclear antibody (titer 1:320, homogeneous pattern) and rheumatoid factor 617.9 IU/mL (normal range <14 IU/ml). Anti-double-stranded DNA, anti-Scl-70, anti-SSA, anti-SSB, anti-Sm, anti-RNP antibodies, anti-cardiolipin IgM and IgG, and lupus anticoagulant tests were negative. Serum complement 3 and complement 4 levels were normal. The enzyme-linked immunosorbent assay of anti-heparin platelet factor 4 (PF4) antibodies was positive with an optical density value of 0.663; (the cutoff value for a negative result is $\leq$ 0.4). Based on the evidence of thrombocytopenia, high D-dimer, and the presence of anti-PF4 antibodies, VITT was diagnosed. He received oral prednisolone 15 mg per day. Subsequently, the platelet count increased to near normal, and the morbilliform rashes subsided (Fig. 1C). There was no previous data of rheumatic factor, and rheumatoid factor followed up three months later declined from 617.9 IU/mL to 113.2 IU/mL.

The mechanism underlying VITT resembles heparin-induced thrombocytopenia (HIT). Negatively charged components of the vaccine interact with the positively charged protein PF4, and lead to the formation of large multimolecular immune complexes and platelet activation.[1] Isolated thrombocytopenia (without evident thrombosis) and hemorrhage have been reported in patients with VITT.[2] In a previous report on HIT, only one-third to one-half of cases are complicated by thrombosis.[3] We hypothesize that there may be some mild variants of VITT, and thrombocytopenia may be present before thrombosis. In our patient, based on the evidence of thrombocytopenia, high D-dimer, and the presence of anti-PF4 antibodies, VITT was diagnosed despite the lack of evident thrombus on imaging studies.

Adjuvant-induced autoimmunity and autoinflammatory syndrome might be responsible for fever, morbilliform eruption, and elevated liver enzymes in this patient. Since high titers of antinuclear antibody and rheumatoid factor, as well as high levels of inflammatory markers, e.g., C-reactive protein and ferritin, were present in our patient. All of his symptoms improved after systemic corticosteroid treatment.

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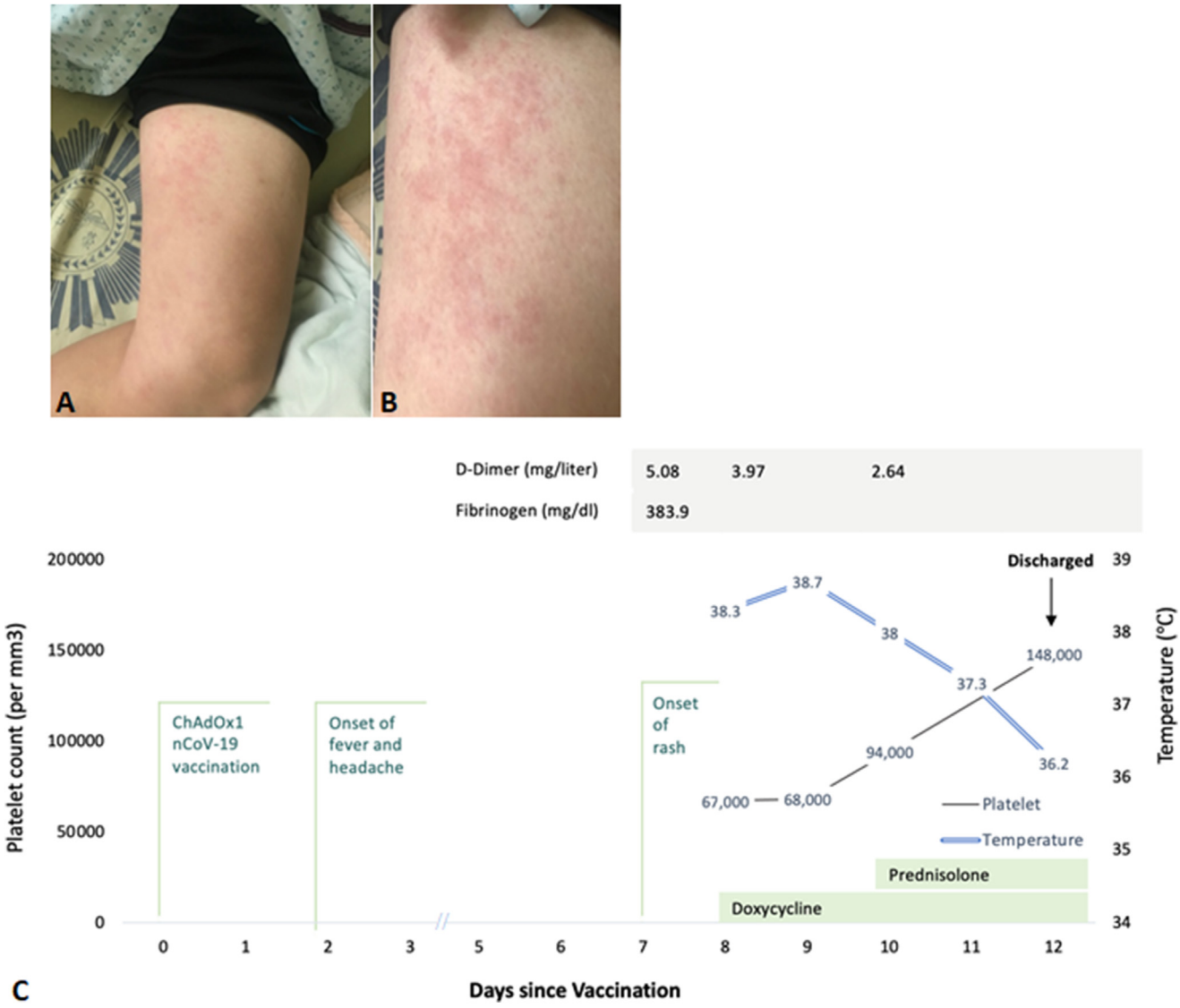

Figure 1 **(A)** Prominent erythematous maculopapular rashes affecting bilateral thighs. **(B)** Close-up figure of the erythematous maculopapular rashes affecting bilateral thighs. **(C)** The clinical course of the patient.

A previous study has observed that morbilliform rashes developed in Coronavirus disease 2019 (COVID-19) patients.[4] They postulated that the viral infection might induce immune-mediated vasodilation or micro thrombosis due to coagulopathy, leading to morbilliform rashes in COVID-19 patients. The immune reaction to the viral-vector COVID-19 vaccine may partially mimic that of COVID-19 infection. Accordingly, we hypothesize that morbilliform eruption in this patient is related to a combination of the above mechanisms.

In conclusion, this is the first case demonstrating concomitant morbilliform rashes in VITT. Although the relationship between morbilliform rashes and VITT remains unclear, the presence of morbilliform rashes implicates a more complex immune dysregulation after vaccination, and warrants comprehensive immunologic investigations.

The patient provided informed consent to publish this case. Yang WT, Liu PY and Lai KL all contributed to direct care of the patient. Yang WT wrote the original draft with review and editing made by Liu PY and Lai KL. We declare no competing interests.

Declaration of competing interest

The authors have no conflicts of interest relevant to this article.

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Wan-Ting Yang
Po-Yu Liu
Division of Infection, Department of Internal Medicine, Taichung Veterans General Hospital, Taichung, Taiwan

Kuo-Lung Lai*
Division of Allergy, Immunology and Rheumatology, Department of Internal Medicine, Taichung Veterans General Hospital, Taichung, Taiwan

*Corresponding author. Division of Allergy, Immunology and Rheumatology, Department of Internal Medicine, Taichung Veterans General Hospital, 1650 Taiwan Boulevard Sect. 4, Taichung 40705, Taiwan. Fax: +886 4 23559016.
E-mail address: kllaichiayi@yahoo.com.tw (K.-L. Lai)

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