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CORRESPONDENCE

# Angioedema-like eyelid edema following the second NVX-CoV2373 COVID-19 vaccination

NVX-CoV2373 (Novavax) is a protein-based vaccine targeting severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and composed of recombinant full-length, stabilized prefusion spike protein homotrimers that form approximately 30-nm nanoparticles based on hydrophobic interaction with a central polysorbate-80 micelle.[1] A two-dose regimen of the NVX-CoV2373 administered to adult participants conferred 89.7% protection against SARS-CoV-2 infection,[2] and studies evaluating its efficacy against Omicron variant are ongoing.[3] Herein, we report a case displaying angioedema-like eyelid edema after NVX-CoV2373 coronavirus disease 2019 (COVID-19) vaccination.

A 43-year-old woman noticed a pruritic edematous eruption of the left ear on day +2 after the second NVX-CoV2373 vaccination (all date numbers refer to the second dose). Treatment with oral fexofenadine hydrochloride, introduced on day +5, was insufficient to suppress the skin lesions, and swelling of eyelids appeared on day +6 (Figure 1A). The patient was referred to our department on day +7. There was no family history of skin diseases and her medical history was unremarkable except for 2-year history of fibromyalgia and migraine, which were treated with celecoxib, duloxetine, lomerizine hydrochloride, and Japanese herbal medicines. Physical examination revealed swelling of eyelids with erythema extending to the forehead, a circumscribed erythema on the chin, and an edematous erythema on the right ear (Figure 1B,C), whereas the eruption on the left ear subsided and the vaccination site on the left arm was unaffected. Similarly, there was no swelling of the axillary lymph nodes at the injection site. Laboratory findings showed a normal white blood cell count of 4810/μL, 74.9% neutrophils, 1.0% eosinophils, and slightly increased levels of serum C-reactive protein (CRP) at 0.17 mg/dL and plasma D-dimer at 1.4 μg/mL, whereas serum antinuclear antibody, immunoglobulin E, and complement levels, such as complement 3 (C3), C4 and total complement hemolytic activity (CH50), were within normal ranges. The patient's general condition was otherwise stable without fever and dyspnea. The patient was treated with oral prednisolone 15 mg/day. One week later, the skin lesions almost resolved (Figure 1D) and serum CRP and plasma D-dimer levels normalized. The prednisolone was tapered off on day +13 without any signs of recurrence.

These clinical and laboratory features resembled angioedema, which demonstrated elevated levels of CRP and D-dimer in some

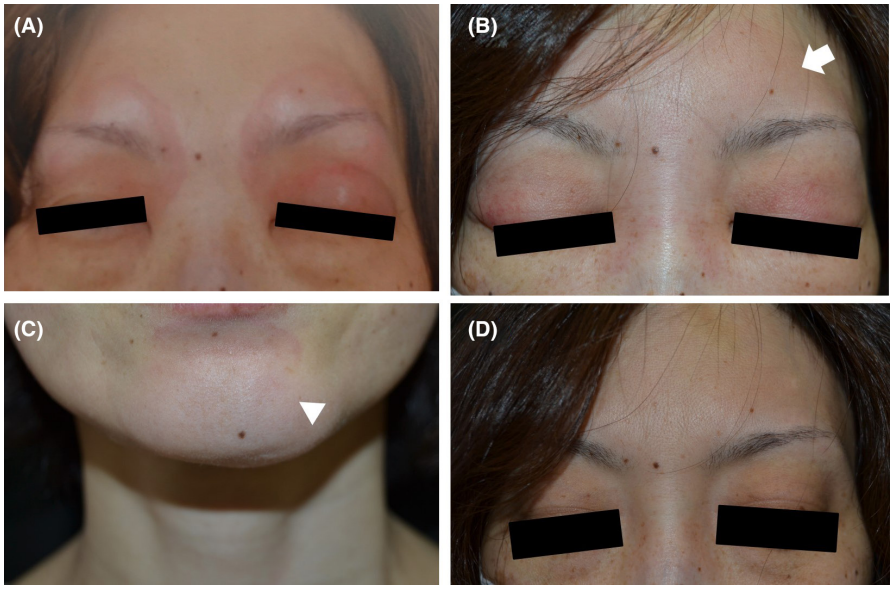


FIGURE 1 Well-demarcated erythema around eyelids accompanied by prominent periorbital edema in the left eye on day +6 (A). Edematous erythema on the forehead (an arrow), glabella, eyelids, and chin (an arrow head) on day +7 (B, C). Complete resolution of facial edema and erythema following short-term prednisolone treatment on day +14 (D). (A) was provided by the patient and consent was given by the patient for publication of these images. All date numbers refer to the second dose of NVX-CoV2373.

cases.[4] NVX-CoV2373 is considered safe and the incidence of serious adverse events in the clinical trials was similar to the placebo group.[2] On the other hand, recent studies of Novavax clinical trials revealed several cases of myocarditis or pericarditis, one case of angioedema, and one case of Guillain-Barré syndrome.[5] NVX-CoV2373 contains polysorbate-80, a high antigenic non-ionic detergent that is cross-reactive with polyethylene glycol (macrogol).[6] These detergents are commonly included in various daily products. Therefore, there is a possibility that our case was sensitized to polysorbate-80 either from the first NVX-CoV2373 vaccination, or from unintentional exposures to polysorbate-80, or polyethylene glycol in daily life. Since cutaneous adverse reactions related to NVX-CoV2373 are not characterized, a detailed description of each individual case is important.

## CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

## ETHICS STATEMENT

Approval of the research protocol: No human participant was involved in this study.
Informed Consent: Informed consent was obtained from the patient.
Registry and the Registration No.: Not applicable.
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