

Chronic spontaneous urticaria after COVID-19 primary vaccine series and boosters



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INTRODUCTION

A range of cutaneous reactions has been reported in response to SARS-CoV-2 vaccination. Of the reported findings, the most common ones include mild, self-limiting injection site reactions and a morphologic spectrum of vaccine-related eruptions of papules and plaques.^{1,2} Chronic spontaneous urticaria (CSU), also known as chronic idiopathic urticaria, is an inflammatory reaction classified by the appearance of waxing and waning pruritic, erythematous wheals for >6 weeks. Prior reports of urticaria after SARS-CoV-2 vaccination have focused on either acute urticaria or exacerbation of previously diagnosed CSU.³⁻⁵ Here, we describe 3 cases of new-onset CSU: 1 after the Pfizer BNT126b2 vaccine and 2 after the Moderna messenger RNA-1273 (mRNA-1273) booster vaccine.

Case 1

The patient is a 68-year-old woman who first experienced a mild pruritic eruption a few days after the initial dose of the Pfizer BNT126b2 vaccine. These evanescent pruritic papules resolved shortly before her second dose. Four days after her second dose, she experienced similar but more widespread pruritic eruption consisting of wheals on her upper portion of the body. These lesions progressed over 2 weeks to large urticarial plaques over her upper and lower portion of the extremities, chest, and abdomen. The reaction responded favorably to a 6-day taper of prednisone at a starting dose of 60 mg from an outside provider on day 18 but rebounded

Abbreviations used:

CSU: chronic spontaneous urticaria
 mRNA: messenger RNA

when therapy was discontinued. The pruritus improved slightly with loratadine, cetirizine, and famotidine. At the time of presentation, 7 weeks after the second dose, urticaria persisted, and the patient was having difficulty sleeping (Fig 1).

The dermatopathology report from a punch biopsy indicated interstitial and perivascular inflammatory infiltrate in the dermis with abundant eosinophils consistent with urticaria. Laboratory data revealed elevated immunoglobulin E levels (288 IU/mL; reference value, 0-100 IU/mL) and a positive SARS-CoV-2 spike antibody test result. Complete blood cell count, liver function panel, and basic metabolic panel data were all within reference ranges.

The timing of onset after vaccination, and the dose-response (starting after first dose, exacerbated by second dose) are suggestive of COVID-19 vaccination-induced CSU. The patient was continued on H₁ and H₂ blockers. Omalizumab was added at 150 mg subcutaneously for 4 weeks. This dosage resulted in partial response. The dose was subsequently increased to 300 mg with complete clearance. The patient elected to continue omalizumab 300 mg injections monthly along with daily 180 mg fexofenadine. On this medication regimen of 300 mg omalizumab subcutaneously

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Fig 1. Case 1 at presentation 7 weeks after administration of the second dose of the Pfizer BNT126b2 vaccine. The circle indicates the site of the skin biopsy.

once monthly and a daily dose of 180 mg fexofenadine, she received the booster vaccination 8 months after her second dose of the Pfizer BNT126b2 vaccine and did not experience any flare in her symptoms. She intends to receive any recommended booster doses in the future.

Case 2

The patient is a 24-year-old woman who first experienced mild pruritus without rash following the initial dose of the Moderna COVID-19 mRNA-1273 vaccine. The pruritus without rash did not fully resolve between the vaccine doses, intensified after the second dose, then persisted until her booster vaccination. Ten months later, the patient received a booster of the Moderna COVID-19 mRNA-1273 vaccine. Twelve days after the booster, she developed her first urticarial eruption. Migratory, pruritic wheals with surrounding erythema and significant dermatographism (Fig 2) appeared on the face, upper and lower extremities, chest, back, and abdomen. The patient had no significant medical history, had no history of atopy or urticaria, and was on no medications at the time of presentation.

The patient's urticaria significantly improved with separate trials of diphenhydramine and cetirizine; however, the patient discontinued both due to side effects. Within 48 hours of discontinuation, a rebound rash appeared. The patient subsequently began 180 mg fexofenadine twice daily and 1000 IU vitamin D once daily, which controlled her



Fig 2. Case 2 demonstrating dermatographism 3 weeks after administration of the Moderna mRNA-1273 booster dose.

symptoms. She was prescribed 20 mg famotidine twice daily in the event of a breakthrough pruritus, which did not occur while on fexofenadine and vitamin D therapy.

Laboratory data revealed a positive screening for antinuclear antibodies (titer, 1:320; reference value, <1:80); a repeat test result was negative (titer <1:80). Complete blood cell count, liver function panel, basic metabolic panel, inflammatory markers (including C-reactive protein) and erythrocyte sedimentation rate, tryptase levels, and thyroid-stimulating hormone levels were within reference ranges.

Symptom time course and dose-response, with increased severity after each successive vaccination, is concerning for CSU induced by the COVID-19 booster vaccine. The patient has had urticaria for >6 weeks. Symptoms are managed with regularly scheduled antihistamine therapy; however, rebound urticaria recurs within 24 to 28 hours of discontinuing medications. The patient will continue the course of treatment with fexofenadine for an additional

4 weeks before any further medication discontinuation trials.

Case 3

The patient is a 31-year-old man with no significant medical history who presented with urticaria and pruritic papules following his Moderna mRNA-1273 booster vaccination. He received both initial Moderna mRNA-1273 vaccinations in early 2021, experiencing transient systemic symptoms, including headache, chills, and fever, but no cutaneous reaction. Eleven days after the Moderna mRNA-1273 booster dose, severely pruritic papules appeared on his head, extending over the neck and both arms over the next few days. The pruritus was most significant at night. He also reported migratory, intermittent wheals that appeared spontaneously but could be provoked with showering or increased pressure to the skin. On day 15 after the booster vaccination, his palms became severely pruritic, erythematous, and painful. Laboratory evaluation revealed a positive SARS-CoV-2 spike antibody test result.

The reaction initially responded favorably to a 2-week course of oral steroids and cetirizine, however dermatographism persisted and caused significant discomfort. Antihistamine therapy was adjusted to fexofenadine 180 mg and famotidine 20 mg daily, with cetirizine 10 mg in the evening. This combination resulted in a minimal side effect profile and provided adequate symptom relief. At 12 weeks after the initial eruption, the patient remained on combination antihistamine therapy, and his urticarial and dermatographic reaction had improved significantly with minimal to no interference in daily activities or sleep.

DISCUSSION

CSU is a clinical diagnosis of recurrent urticaria lasting for >6 weeks, on average 3 to 5 years in adults, with an unknown etiology. CSU is present in 0.1% of the population and has significant impact on patient quality of life. The exact etiology of CSU remains largely unclear but involves repeated activation of the dermal mast cell and subsequent release of vasoactive chemical mediators.⁶ Despite a variety of proposed triggers, the treatment mainstay is elimination of any known triggers and use of second generation H₁ antihistamines. The goal of treatment is symptom control and patient comfort. Therefore, antihistamine therapy may be tailored to patient tolerance.⁷ If symptoms persist, the use of the immunoglobulin E-targeting monoclonal antibody omalizumab may be added and has shown significant success in controlling persistent pruritic symptoms.⁸

CSU has been reported in response to various well-established vaccinations, including live, subunit, and toxoid vaccinations, with a mean onset of 8.4 days reported for a small cohort.⁹ CSU in response to the SARS-CoV-2 primary vaccination series has been previously described in 2 reports to date.^{3,4} In the few reported cases, common demographic variables include female sex, middle age, and Caucasian race.^{3,4,10} It is worth noting that these findings may be skewed toward those with access to vaccination.

CSU has not yet been studied extensively for booster doses, as we present here in cases 2 and 3. Omalizumab therapy in a patient with reactions to the initial vaccine series to prevent reactions due to the booster doses (case 1) is also novel. All patients were able to receive their booster vaccine doses. With the introduction of mRNA-based COVID-19 booster vaccinations, the incidence of CSU in those receiving booster doses is not yet established. Patients have created support groups and discussion boards on the topic, including a Facebook group of 4500+ members titled “Chronic Spontaneous Urticaria After COVID-19 Support Group,” suggesting a need to address patient concerns in this area and provide appropriate counseling.

Improper classification of CSU as a vaccine allergy can prove detrimental to achieving both personal protection and herd immunity. It is important to recognize CSU as a separate entity from anaphylaxis (defined as a combination of respiratory compromise, reduced blood pressure, swelling of tongue/throat, or hives within 4 hours of exposure) following vaccination and does not preclude completion of vaccination series.

In summary, we describe 3 rare presentations of CSU: one developing after administration of the Pfizer BNT126b2 vaccine that responded favorably to omalizumab without recurrence after a booster dose while on omalizumab therapy, and the second and third developing after administration of the Moderna mRNA-1273 booster vaccine that both responded to combination antihistamine therapy. For patients who experience vaccine-associated CSU, counseling on treatment options and the importance of completion of their vaccination series is important.

Conflicts of interest

Dr Freeman is a member of the American Academy of Dermatology (AAD) COVID-19 Ad Hoc Task Force and is an author of *COVID-19 Dermatology* for UpToDate. Authors Strahan and Ali have no conflicts of interest to declare.

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