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Chronic Spontaneous Urticaria after COVID-19 primary vaccine series and boosters

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1 **Introduction:**

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

11 Case 1:

12 The patient is a 68-year-old female who first experienced a mild pruritic eruption a few
13 days after the initial dose of Pfizer BNT126b2 vaccine. These evanescent pruritic papules
14 resolved shortly prior to 2nd dose. Four days after her 2nd dose, she experienced similar but
15 more widespread pruritic eruption consisting of wheals of the upper body. These
16 lesions progressed over 2 weeks to large urticarial plaques over her upper and lower
17 extremities, chest, and abdomen. The reaction responded favorably to a six-day taper of
18 prednisone at a starting dose of 60mg from an outside provider on day 18 but rebounded when
19 discontinued. The pruritus improved slightly with loratadine, cetirizine and famotidine. At
20 the time of presentation, seven weeks after the second dose, urticaria persisted and the patient
21 was having difficulty sleeping.

22 Dermatopathology report from a punch biopsy indicated interstitial and perivascular
23 inflammatory infiltrate in dermis with abundant eosinophils consistent with urticaria. Laboratory
24 data revealed elevated IgE levels (288 IU/mL, reference value 0-100 IU/mL) and positive SARS-
25 CoV-2 spike antibody. Complete blood count, liver function panel and basic metabolic panel
26 were all within reference ranges.

27 Timing of onset after vaccination, and the dose-response (starting after first dose, exacerbated by
28 second dose) are suggestive of COVID-19 vaccination induced chronic spontaneous urticaria.
29 The patient was continued on H₁ and H₂ blockers. Omalizumab was added at 150mg SQ for 4
30 weeks. This dosage resulted in partial response. The dose was subsequently increased to 300mg
31 with complete clearance. The patient elected to continue omalizumab 300mg injections monthly
32 along with daily 180mg fexofenadine. On this medication regimen of 300mg omalizumab SQ
33 once monthly and daily 180mg fexofenadine, she received the booster vaccination eight months

- 34 after her 2nd dose of Pfizer BNT126b2 vaccine and did not experience a flare in her symptoms.
- 35 She intends to receive any recommended booster doses in the future.

Case 2:

The patient is a 24-year-old female 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 vaccine doses, intensified after the second dose, then persisted until 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 appeared on the face, upper and lower extremities, chest, back, and abdomen. The patient had no significant medical history, had no prior history of atopy or urticaria, and was on no medications at 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, rebound rash appeared. The patient subsequently began 180mg fexofenadine twice daily and 1,000 IU Vitamin D once daily which controlled symptoms. She was prescribed 20mg famotidine twice daily in the event of breakthrough pruritus, which did not occur while on fexofenadine and Vitamin D therapy.

Laboratory data revealed positive screening antinuclear antibodies (ANA) (titer 1:320, reference value < 1:80). Repeat ANA was negative (titer <1:80). Complete blood count, liver function panel, basic metabolic panel, inflammatory markers including c-reactive protein and erythrocyte sedimentation rate, tryptase levels, and TSH were within reference ranges.

Symptom time course and dose-response, with increased severity after each successive vaccination, is concerning for chronic spontaneous urticaria induced by the COVID-19 booster vaccine. The patient has had urticaria for >6 weeks. Symptoms are managed with regularly

59 scheduled antihistamine therapy but rebound urticaria recurs within 24-28 hours of discontinuing
60 medications. The patient will continue course of treatment with fexofenadine for an additional 4
61 weeks before any further medication discontinuation trials.

Case 3:

The patient is a 31-year-old male with no significant past medical history who presented with urticaria and pruritic papules post 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, which extended over the neck and bilateral 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 post- booster vaccination, his palms became severely pruritic erythematous and painful. Laboratory evaluation revealed a positive SARS-CoV-2 spike antibody.

The reaction initially responded favorably to a 2-week course of oral steroids and cetirizine, but dermatographism persisted and caused significant discomfort. Antihistamine therapy was adjusted to fexofenadine 180mg and famotidine 20mg daily with cetirizine 10mg in the evening. This combination resulted in a minimal side effect profile and provided adequate symptom relief. At twelve weeks post 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:

Chronic spontaneous urticaria (CSU) is a clinical diagnosis of recurrent urticaria lasting for greater than six weeks, on average 3-5 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, treatment mainstay is elimination of any known triggers and use of second generation H1 anti-histamines. 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 IgE-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 in a small cohort.⁹ CSU in response to the SARS-CoV2 primary vaccination series has been previously described in two 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 towards those with access to vaccination.

CSU has not yet been studied extensively for booster doses, as we present here in Cases 2 and 3. Management with omalizumab in patient with reactions to the initial vaccine series as prevention for reactions from the booster (Case 1) is also novel. All cases 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 boosters is not yet established. Patients have created support groups and discussion boards on the topic, for example a Facebook group

of 4,500+ 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 three unique presentations of chronic spontaneous urticaria: one after Pfizer BNT126b2 vaccine that responded favorably to omalizumab without recurrence after booster while on omalizumab therapy, and the second and third after Moderna mRNA-1273 booster vaccine that both responded to combination antihistamine therapy. For patients who experience vaccine-associated chronic spontaneous urticaria, counseling on treatment options and the importance of completion of their vaccination series is paramount.

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145 **Figure Legend**

146 Figure 1: Case 1 at presentation 7 weeks after 2nd dose of Pfizer BNT126b2 vaccine. Circle

147 indicating site of skin biopsy.

148 Figure 2: Case 2 demonstrating dermatographism 3 weeks after Moderna mRNA-1273 booster.



