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Refractory chronic spontaneous urticaria after heterologous COVID-19 booster vaccination

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Abstract

Chronic spontaneous urticaria (CSU) involves recurrent, pruritic wheals lasting more than 6 weeks in response to various etiologies, including unknown causality. Though most cutaneous reactions to the COVID-19 vaccine series are self-limited and of short duration, more complex presentations including chronic spontaneous urticaria have been described. To the best of our knowledge, this is the first report of chronic spontaneous urticaria following heterologous mRNA COVID-19 booster vaccination that includes vaccination with both forms of the mRNA vaccine. Our patient received Pfizer-BioNTech for the primary series and Moderna for the booster. After failing several therapies, our patient's urticaria was refractory even to omalizumab. The source for chronic spontaneous urticaria development in our patient may be related to the unique humoral response elicited by receipt of a different mRNA vaccine manufacturer.

Keywords: COVID-19, mRNA vaccine, omalizumab, urticaria

Introduction

Chronic spontaneous urticaria (CSU) is defined as recurrent pruritic wheals with or without angioedema, with at least twice weekly episodes and duration beyond 6 weeks [1]. Initial management of CSU involves avoidance of aggravating factors and H1 receptor antihistamine (cetirizine, fexofenadine) pharmacotherapy. Second-line therapies have no proven effectiveness except for omalizumab, an anti-IgE monoclonal antibody [1]. Systemic immunosuppressants such as cyclosporine have been used with variable success [1,2].

In the last few years, COVID-19-related morbidities and mortalities have dominated medical discourse. COVID-19 vaccination has garnered particular attention as its adoption becomes widespread. Consequently, recent research efforts aim to understand both the protective benefits and the potential adverse effects of this evolving vaccine series.

A broad range of cutaneous reactions have been reported in relation to SARS-CoV-2 mRNA vaccination, including urticarial eruptions that meet the criteria for CSU [3-5]. We report a case of chronic spontaneous urticaria after heterologous mRNA COVID-19 booster vaccination, in which a Moderna booster supplemented a primary Pfizer series. The patient's symptoms were refractory to first- and second-line management.

Case Synopsis

A 55-year-old man presented with new-onset angioedema and urticarial lesions involving his back, chest, abdomen, buttocks, and extremities, which developed four days after receiving the booster

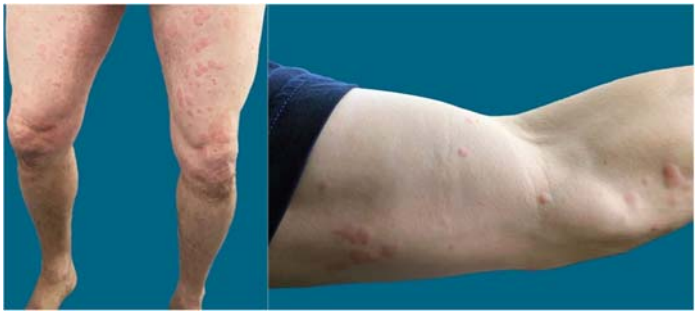

Figure 1. *Bilateral lower extremities with diffuse, contiguous wheals, and left upper extremity with scattered, edematous wheals.*

Moderna mRNA 1273 vaccine (**Figure 1**). One year prior, he completed both doses of the Pfizer BNT162b2 vaccine series without complication. Four months prior, he had tested positive for COVID-19 infection with mild clinical course not requiring hospitalization.

The patient was healthy overall with a history of treated pulmonary tuberculosis 28 years prior and self-reported Raynaud phenomenon. He had no history of urticaria or angioedema and no known allergies. He had no recent infection, medication or food changes, outdoor exposures, or changes in personal products. The patient denied personal history of thyroid disease, rheumatoid arthritis, type I diabetes, or mixed connective tissue disorder. However, the patient's mother does have hypothyroidism, Sjögren syndrome, and interstitial lung disease. Complete blood count with differential, complete metabolic panel, erythrocyte sedimentation rate, and C-reactive protein were all within normal range. Autoimmune work-up was additionally unremarkable.

The patient was diagnosed with CSU after suffering daily widespread urticaria and recurrent angioedema. Punch biopsy of a wheal lesion revealed mild inflammatory perivascular dermatitis with neutrophilic predominance and rare eosinophils and lymphocytes (**Figure 2**). His symptoms were refractory to H1 (cetirizine and fexofenadine) and H2 (famotidine) antihistamine therapy. He also received several short courses of high dose oral prednisone (up to 60mg daily) which provided temporary relief. However, his symptoms rebounded upon tapering. After two consecutive 75mg doses of omalizumab therapy, he experienced a two-month period of relief. Unfortunately, his urticaria recurred despite continued omalizumab treatments. Currently, he is receiving monthly omalizumab injections and takes levocetirizine 5mg daily with variable relief of symptoms.

Case Discussion

The presentation of CSU reflects a persistent inflammatory response to an elusive stimulus. The pathogenesis is not well understood but likely involves prolonged dermal mast cell release of histamine following exposure to a provoking factor. This is believed to occur at least in part through IgG autoantibodies binding to the high affinity IgE receptor or by directly degranulating mast cells, which then release inflammatory cytokines [1]. Drugs, foods, infection, inhalants, and autoimmune diseases can be underlying triggers of CSU. This condition typically lasts 1-5 years or longer, with a significant negative impact on quality of life [1,6].

The management of CSU arising to vaccine is the same as the conventional therapeutic ladder. After failing combination antihistamine and systemic corticosteroid therapy, our patient achieved some relief with omalizumab injections. By suppressing levels of IgE and function of the high affinity receptor for the Fc region of IgE, omalizumab has become an effective agent for allergic rhinitis, asthma, and

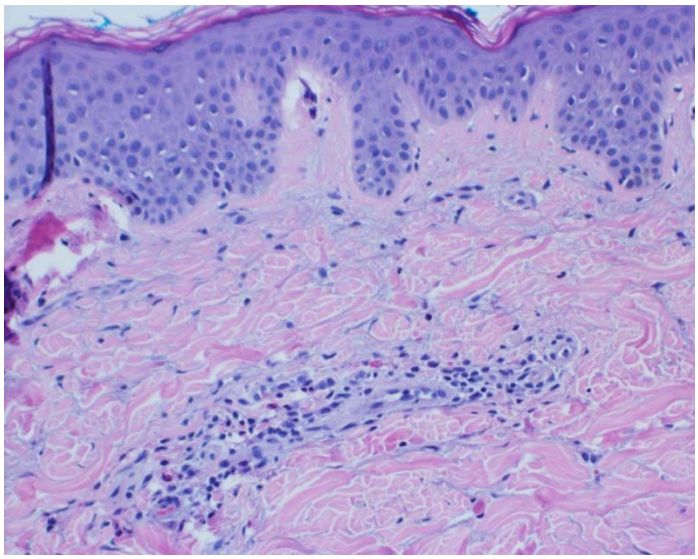

Figure 2. *Mild inflammatory perivascular dermatitis with neutrophilic predominance and rare eosinophils, consistent with urticaria. H&E, 100×.*

allergen-mediated skin reactions [7]. A multicenter, randomized double-blind study found omalizumab administered as three doses of 150mg or 300mg at 4-week intervals significantly reduced symptoms as compared with placebo in patients with symptomatic CSU despite the use of H1 antihistamines [2]. Though our patient achieved only temporary resolution, omalizumab has proven a useful therapy for CSU resistant to standard management.

A variety of cutaneous adverse events have been associated with COVID-19 immunization. SARS-CoV-2 mRNA vaccination promotes type IV hypersensitivity reactions by inducing effector CD4 T cell secretion of cytokines (IFNγ, TNF, IL2) and CD8 T cell IFNγ and IL2 production [8]. The most common presentation has been large local reactions at the injection site that usually appear the day after receiving the first vaccine dose and resolve within a week [3]. Other reported dermatologic findings include morbilliform eruption, erythromelalgia, dermal hypersensitivity, flare of existing dermatological diseases, pernio/chilblains, pityriasis rosea, erythema multiforme, filler reaction, sweet syndrome, lichen planus, bullous and papulovesicular eruptions, and vasculitis [3,4]. Following local injection site reaction, urticaria and angioedema are fairly common COVID-19 vaccine-related cutaneous eruptions, with frequency of 0.9% and 0.5% respectively. Of note, the mean duration of urticaria following vaccination was 22 hours [4].

Reports of CSU have followed mRNA (Moderna mRNA-1273, BNT162b2), viral vector (AstraZeneca/Oxford ChAdOx1-S/nCoV-19), and inactivated viral (Sinovac-Coronovac) vaccine types (**Table 1**), [5,9-19]. However, new-onset CSU following heterologous mRNA vaccination has yet to be evaluated specifically. Brooks et al. presented a patient who was advised to receive an mRNA booster after developing CSU with the first dose of AstraZeneca/Oxford ChAdOx1-S [11]. This patient experienced a similar urticarial rash one hour after receiving the booster, but it completely resolved with five days of bilastine 20mg daily [11].

Interestingly, there is mixed consensus regarding the effects of COVID-19 vaccination on previously well-controlled CSU. Vaccination has caused exacerbation, with some cases resolving in less than a day [16,20] and others requiring management beyond the patient's standard therapy [9,12]. On the other hand, some reports note no significant change in CSU course after vaccination [14,19]. In their cohort of 91 patients, Purayil et al. found most patients (70.3%) with chronic urticaria did not experience worsening of symptoms after vaccination [14]. One study followed 90 participants with CSU for 28 days following the first or second dose of the Pfizer vaccine and found only 14 out of 90 (15.5%) experienced recurring urticaria [21]. Although the literature is conflicting, COVID-19 vaccination nonetheless has incited not only new-onset CSU, but worsening urticaria in patients with previously controlled CSU.

Recent literature has also described CSU affected by COVID-19 illness. A recent pediatric study found that of 26 patients with inactive CSU, COVID-19 illness elicited relapse in four (19.2%), and worsening of prior symptoms in one (3.8%), [22]. Another report estimated roughly one-third of patients with CSU, especially those with moderate-to-severe disease, experience some degree of exacerbation with COVID-19 infection [23]. However, just as with vaccination, there is inconsistency in CSU worsening with COVID-19 infection. A pediatric cohort of 101 patients with CSU found no relapse of disease after the first or second dose of the Pfizer vaccine [24]. Regardless, some understanding of inflammation pathogenesis may help make sense of CSU recurring with COVID-19 disease and immunization. SARS-CoV-2 virus and vaccine may increase pro-inflammatory cytokines, which could directly promote mast cell degranulation and initiate the cascade of reactions to produce a CSU exacerbation [25].

The unique element of this case is the history of heterologous vaccination, which entailed utilizing a different mRNA vaccine for the booster than for the primary series. The patient received Pfizer for his primary series and then developed CSU following the Moderna booster. One study tested serum of 73 patients at a median of 19 days following the second primary vaccine dose (28 received Moderna and 45 received Pfizer); results showed robust humoral

responses induced by both vaccines but two distinct antibody profiles. Moderna recipients demonstrated augmented responses in receptor binding domain-specific IgA1 and IgG2, N-terminal domain-specific IgA1, FcγR2A and FcγR2B binding when compared to Pfizer recipients [26]. A recent study found that, in two cohorts of 80 and 752 individuals with CSU after COVID vaccination, the relative risk of developing CSU after the Moderna booster compared to Pfizer booster was 20.8 (95% CI, 6.5-66.0) and 16.1 (10.8-24.0) respectively [5]. Also, for both cohorts, the booster dose of the Moderna vaccine was by far the most reported with new-onset CSU (90% and 81% respectively), [5]. Previously, studies of the Moderna vaccine showed greater amounts of mRNA and more associations with immunogenic and allergic responses when compared to the Pfizer vaccine [27, 28]. Given the distinct antibody response and immunogenicity of the Moderna and Pfizer vaccines, it is logically consistent that our patient did not experience urticaria after his two primary Pfizer shots, but only after his Moderna booster.

Conclusion

Although most cutaneous reactions to the COVID-19 vaccine series are benign, allergen-driven responses that self-resolve, our case presents a persistent and complex immunologic eruption that was refractory even to monoclonal antibody therapy. Given the widespread public adoption of COVID-19 vaccines and the recommendations of regular booster doses, it is crucial that the medical community remain attentive and curious regarding the immunological sequelae of the mRNA vaccines.

Potential conflicts of interest

The authors declare no conflicts of interest.

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Table 1. *Review of chronic spontaneous urticaria with COVID-19 vaccination.*

Publication	Study design	Notable findings	Implicated vaccine type
Alflen 2021 [9]	Case Series	2 patients with previously well-controlled CSU relapsed: one became resistant to prior omalizumab regimen and all other pharmacotherapies	Moderna mRNA-1273 primary series; first dose Moderna mRNA-1273 primary series; second dose
Thomas 2021 [10]	Case Report	Previously healthy 20-year-old with new-onset CSU	BNT162b2 mRNA primary series; second dose
Brooks 2022 [11]	Case Report	60-year-old with new onset CSU 5 days following AstraZeneca vaccination. Remission with rupatadine 20mg and multiple prednisone tapers. Received Pfizer booster and developed similar rash 1 hour later, resolved after five days of bilastine 20mg daily	AstraZeneca/Oxford ChAdOx1-S; first dose
Magen 2022 [12]	Case-control	27 patients with relapsed CSU and 39 patients with new-onset CSU; had more allergic comorbidities compared to healthy controls and patients with CSU not related to vaccination (P<0.001)	BNT162b2 mRNA primary series
Suan 2022 [13]	Case Report	39-year-old with new onset CSU, eventually controlled with regular cetirizine use. Failed multiple steroid tapers and high dose H1 and H2 antihistamines	AstraZeneca/Oxford ChAdOx1-S; second dose
Purayil 2022 [14]	Cross-sectional	91 patients with chronic urticaria received COVID-19 vaccine; most (70.3%) did not experience worsening in urticaria after vaccination. 62.6% reported immediate side effect, of which 16.4% had exacerbation of urticaria	mRNA COVID vaccines
Strahan 2022 [15]	Case Series	New-onset CSU in 3 patients; 1 resolved with omalizumab, 2 (following Moderna booster) resolved with combination antihistamines	BNT162b2 mRNA primary series; second dose Moderna mRNA-1273 booster; first dose Moderna mRNA-1273 booster; second dose
de Montjoye 2022 [16]	Case Series	8 patients developed CSU; 3 of which had flares following second doses and 1 following third dose	BNT162b2 mRNA primary series; first dose Moderna mRNA-1273 primary series; first dose AstraZeneca ChAdOx1 nCoV-19; second dose AstraZeneca ChAdOx1 nCoV-19; first dose
Pescosolido 2022 [17]	Cross-sectional	32 patients developed CSU at median 10 days following vaccine; 30 (94%) followed booster dose, which was Moderna mRNA-1273 in 29	BNT162b2 mRNA primary series; second dose BNT162b2 mRNA booster

		Basophil activation (BAT) was tested in 7 patients; all were negative, suggesting unlikely autoimmune reaction	Moderna mRNA-1273 primary series; second dose Moderna mRNA-1273 booster
Ben-Fredj 2022 [18]	Case Series	10 patients with new onset CSU, resolved at median 2 months despite antihistamine therapy	BNT162b2 mRNA Moderna mRNA-1273 AstraZeneca/Oxford ChAdOx1 S Sinovac-CoronaVac
Kanokrungsee 2022 [19]	Prospective cohort	28 patients with CSU, no significant flaring at weeks 1 and 2 following vaccination; no significant difference from baseline at week 3	mRNA COVID vaccination
Duperrex 2023 [5]	Retrospective cohort	2 Swiss cohorts of patients with new-onset CSU following mRNA COVID vaccination: N=80 and N=782; 90% and 81% followed Moderna booster dose respectively. Relative risk of CSU following Moderna booster compared to Pfizer booster was 20.8 (95% CI, 6.5-66.0) and 16.1 (10.8-24.0) respectively	BNT162b2 mRNA Primary series (first or second dose) BNT162b2 mRNA booster Moderna mRNA-1273 primary series (first or second dose) Moderna mRNA-1273 booster

CSU, chronic spontaneous urticaria.