SKIN

BRIEF ARTICLE

Urticaria Following COVID-19 Booster Vaccination: Case Series and Review

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ABSTRACT

Background: Over 610 million doses of the COVID-19 vaccine have been administered since late 2020, and adverse events associated with these vaccinations have been widely reported. Less commonly reported are cutaneous complications associated with COVID-19 vaccination, which are rare but troublesome.
Case Series: We report 7 cases of delayed-onset urticaria following Moderna Covid-19 booster vaccination. Patients ranged from aged 20-46, and no patients had a history of previous urticaria. Average day of onset following the booster vaccination was 10.9, with 6 of the 7 patients experiencing chronic urticaria. No patients experienced anaphylaxis. All patients were managed with oral antihistamines in an outpatient setting.
Discussion: Unlike previously documented reactions following COVID-19 vaccination, we report on widespread and long-lasting dermatographic urticarial eruptions that presented an average of 10.9 days after receipt of the booster vaccination. The pathophysiology underlying these eruptions is difficult to elucidate given the lack of connection to atopy, autoimmune conditions, or systemic illness; however, we propose 3 possible mechanisms involving the prostaglandin pathway, IL-2 upregulation, and ACE2 receptors. Despite the benign nature and outpatient treatment of chronic urticarial eruptions, these eruptions distress patients and impact quality of life. Fortunately, no systemic reactions or respiratory system involvement occurred in any of our patients, and outpatient antihistamine therapy provided adequate symptomatic relief to our patients. Given the delayed reaction time and lack of systemic involvement, there is likely minimal risk in receiving additional COVID-19 booster following post-vaccination urticaria.

INTRODUCTION

Following mass COVID-19 vaccinations, the CDC reported adverse events associated with these vaccinations, ranging from arthralgias to anaphylaxis, and included injection site reactions.[1] Other than the latter complication, skin complications were rare. Seven cases of urticaria and/or

dermatographism following COVID-19 booster vaccination administration are reported here.

CASE SERIES

The presentation of urticaria or dermatographism following the administration of the third dose of Moderna Booster Covid-19 vaccination is reviewed (**Table 1**). Of the 7 patients, 6 experienced urticaria for more than 6 weeks (**Figures 1-3**). No patients reported urticaria or other dermatologic symptoms following the first or second dose of COVID vaccine.

DISCUSSION

Millions of COVID-19 vaccines have been administered since the vaccine release in late 2020. The CDC has openly published vaccine safety data, including delayed, large local reactions occurring within 2 weeks of the 1st and 2nd doses of the COVID-19 vaccine.[1-4] Less commonly characterized are chronic spontaneous urticaria cases primarily appearing over a week after vaccine administration and persisting for months to years. Additionally, affected patients typically have histories of atopy or urticaria.[5,6]

Urticaria present as recurrent wheals of the superficial dermis, often accompanied by angioedema within the dermis.[7] Pruritic, pale pink swellings last for 24 hours maximum and the accompanying angioedema lasts for 2-3 days. Histologically, the upper dermis contains a mild, mixed perivascular and interstitial infiltrate of lymphocytes, eosinophils, basophils, and neutrophils.[7] Acute urticaria last for less than 6 weeks and are idiopathic in less than 50% of cases. Chronic urticaria appear for at least 2 days of the week for greater than 6 weeks.[7] Six of our 7 cases of urticaria were chronic and all demonstrated dermatographism.

Dermatographic urticaria is an inducible urticaria resulting from an exogenous stimulus like stroking the skin which can appear within minutes of pressure administration and last for over 24 hours. The prolonged presence of dermatographism suggests that T-cell mediated immune reactions could be responsible, as was the case in delayed hypersensitivity reactions to the Moderna vaccine.[2] Although this form of urticaria can appear in 5% of the normal population due to an exaggerated physiological response, dermatographism can result in disruption of daily life secondary to intense pruritus that disrupts daily tasks and sleep.

Unlike the previously documented reactions lasting 5 days after Moderna vaccination, our patients' eruptions were widespread and long-lasting. Additionally, none of our patients experienced symptoms following the 1st or 2nd doses of the vaccine.[2] The chronic nature of the dermatographism experienced by 6 of the 7 patients is not easily explained. A shift from the prostaglandin pathway to the leukotriene pathway of arachidonic acid breakdown could be responsible for the dermatographism and chronic urticaria associated with the COVID-19 booster vaccine immune response. Leukotrienes, specifically LTC4, LTB4, and LTE4, are long-lasting inflammatory mediators.[7] Alternatively, the upregulation of inflammatory mediator IL-2, also associated with capillary leak syndrome, could be the result of the COVID-19 booster immune response. Finally, ACE2 receptor may be involved in the chronic dermatographism of our patient population. ACE2 is the known target of the COVID-19 spike protein, and the COVID-19 vaccination triggers spike protein antibody production. Thus, antibody

Table 1. Presentation of urticaria or dermatographism following the administration of the third dose of Moderna Booster Covid-19 vaccination

Age	Gender	Booster Given	Onset, days	Duration, weeks	History of Previous Urticaria	Dermato-graphism	Other Symptoms	Treatment
27	Male	Moderna	13	8	None	+	None	Diphenhydramine, PRN Cetirizine, 10 mg, 2x daily for 4 weeks Hydroxyzine, 25mg, 4x daily for 4 weeks Loratadine, 10 mg, 1x daily Methylprednisolone, 125mg, IM; 80mg, IM
46	Male	Moderna	12	10+	None	+	None	Loratadine, 10 mg, 2x daily Prednisone 20 mg, 6 days, taper dose
37	Male	Moderna	11	8	None	-	None	Fexofenadine 180 mg PRN
29	Female	Moderna	10	12+	None	+	Bruising Angioedema	Cetirizine, 10 mg, 1x daily Diphenhydramine, 25 mg, PRN for 8 weeks Loratadine, 10 mg, 1x daily
27	Male	Moderna	9	7+	None	+	None	Loratadine, 10 mg, 2x daily Fexofenadine, 180 mg, 1x daily
31	Male	Moderna	14	4+	None	+	None	Fexofenadine, 180 mg, 1x daily
20	Female	Moderna Bivalent	7	12+	None	+	None	Cetirizine 20 mg, BID

interacting with the ACE receptor could trigger urticaria, in a manner like the mechanism of drug reaction urticaria results from ACE inhibitor interactions with the ACE receptor.[7]

The treatment of urticaria focuses on blocking H1 histamine receptors to minimize the effects of elevated blood and tissue histamine levels that have been observed in urticaria patients.[8] Treatment with H1-antihistamines, including diphenhydramine, loratadine, and cetirizine, reduced pruritus and erythema in patients with post-vaccination dermatographic urticaria.[9] While 20% of chronic urticaria sufferers report symptoms 20 years after diagnosis, these 7 patients responded to antihistamine therapy with improvement in symptoms.[7]

Four of our 7 patients are USAF aircrew members. Because of their safety critical roles, their condition and treatment require a greater degree of scrutiny by aeromedical providers. These individuals control aircraft directly as pilots or perform mission critical "back of the aircraft" functions. Their ability to safely function in an inherently dangerous, unpredictable environment requires well controlled, stable disease that is not

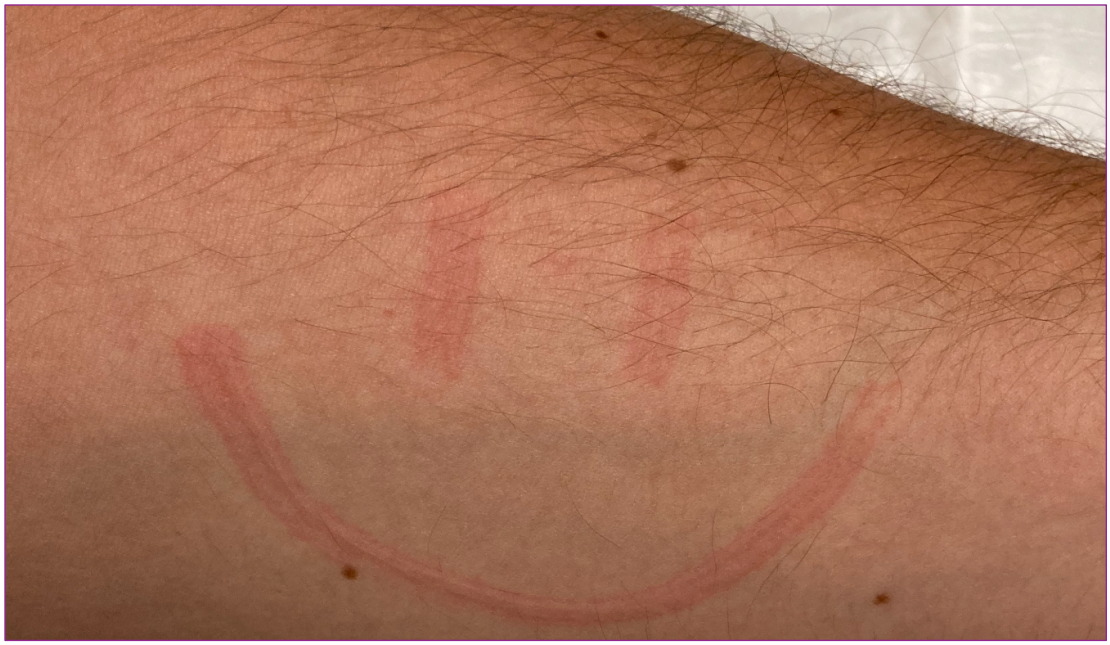

Figure 1. Patient 1 experienced persistent dermatographism (8 weeks) post-Moderna booster dose despite treatment with Loratadine, 10 mg daily.

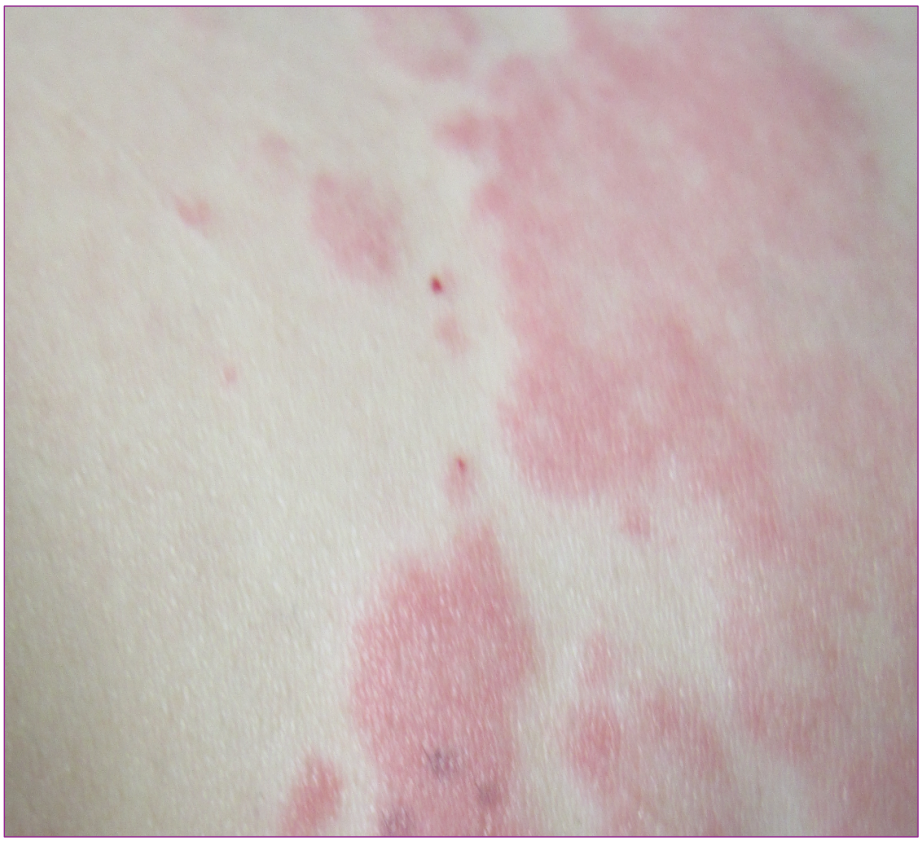

Figure 2. An allergic urticarial reaction followed Moderna COVID-19 vaccination dose 3 in patient 4. Edematous, non-scaly papules and plaques were associated with bruising and persisted for 2 months. A second flare-up occurred 3 months post-vaccination, which was controlled by loratadine 10 mg and cetirizine 10 mg daily.

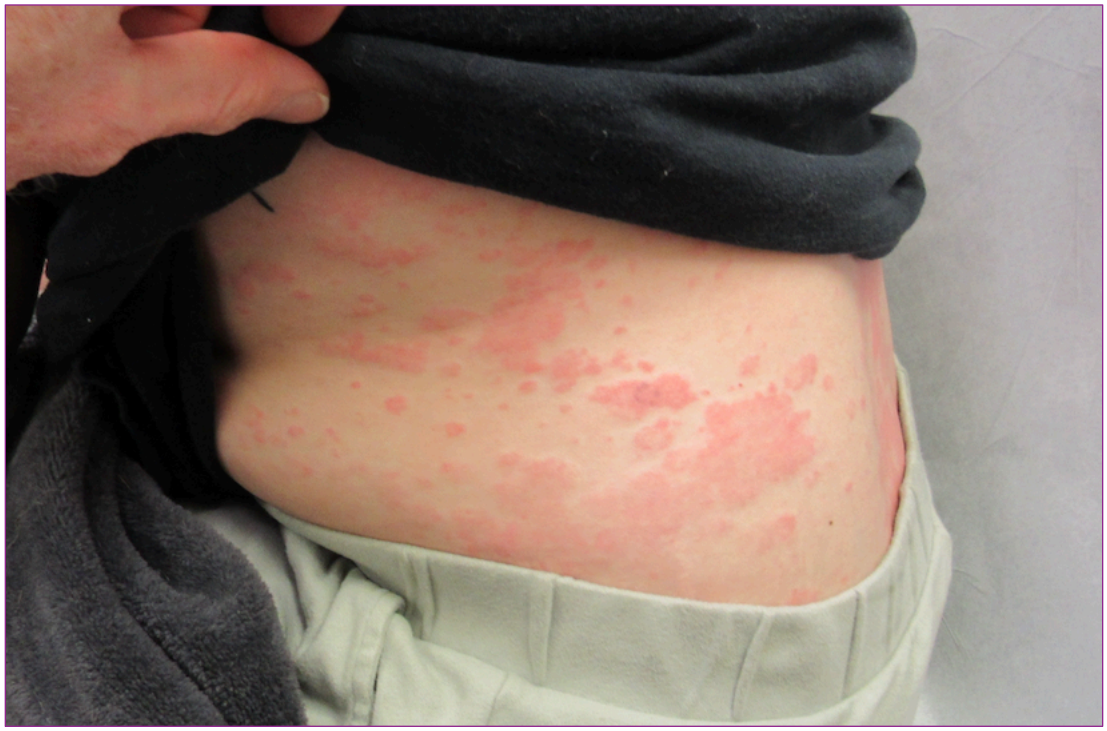

Figure 3. The extent of the urticaria is visualized on the trunk of patient 4.

distracting from primary duties.[10] Dermatographism, while largely benign, could be problematic if there is distracting pruritic urticaria or sedation caused by antihistamine treatment. Control of urticaria in these patients is paramount, but it must be achieved through non-sedating medications. According to the medical standards directory (MSD), derived from the DAFMAN 48-123, chronic urticaria is disqualifying because it presents a distracting condition. Fortunately, with appropriate evaluation and control, the member may receive a waiver to continue safety critical duties with this condition.[11] To receive a waiver, a member with urticaria would require a thorough allergy evaluation; treatment with a non-sedating, aircrew approved medication, i.e. low dose loratadine; and demonstrated control of symptoms without idiosyncratic reaction.[10] An additional caveat is that any urticaria, angioedema, or anaphylaxis deemed "chronic, severe, and not amenable to treatment" requires a retention evaluation for continued military service. Once stable and returned to duty (retained in military service), the member would be returned to flying status with an approved flying waiver to be tracked for continued stability and afforded appropriate follow-on care.

Fortunately, no systemic reactions or respiratory system involvement occurred in any of our patients. Per the CDC's pre-vaccination guidelines, allergic reactions within 4 hours of vaccination administration warrant concern regarding continuation of the vaccine series; however, no contraindication is recommended for reactions occurring outside of this 30-minute period.[12] Given the delayed reaction time and lack of systemic involvement, there is likely minimal risk in receiving additional COVID-19 booster following post-vaccination urticaria.

CONCLUSION

In summary, none of our 7 patients had a history of previous urticaria and the onset of

symptoms suggests they likely suffered from delayed urticaria and/or dermatographism secondary to COVID-19 booster vaccination. All cases were managed with antihistamine therapy and anaphylaxis did not occur. These cases contribute to the knowledge regarding post-COVID-19 vaccination reactions and provide evidence that delayed urticaria and dermatographism following booster vaccination will respond to standard antihistamine treatment, and these reactions are not contraindications to completion of the vaccination series.

Conflict of Interest Disclosures: Robert T. Brodell is a principal investigator for clinical trials (Novartis and Pfizer) the Corevitas psoriasis biologic registry, and owns stock in Veradermic, Inc. He serves on editorial boards of Practice Update Dermatology (Editor-in-Chief); Journal of the American Journal Academy of Dermatology (Associate Editor); Practical Dermatology; Journal of the Mississippi State Medical Society; SKIN: The Journal of Cutaneous Medicine and Archives of Dermatological Research. Ms. Watson, Dr. Badon, Dr. Braswell, and Dr. Sorensen have no conflicts of interest to report.

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