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Department of Dermatology

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Title Page:

A Case Series of Cutaneous COVID-19 Vaccine Reactions at Loma Linda University

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Manuscript

Introduction

To date, the United States' Food and Drug Administration (FDA) has issued emergency use authorization (EUA) for three vaccines for the prevention of coronavirus disease 2019 (COVID-2019): Pfizer-BioNTech's COVID-19 vaccine, Moderna's COVID-19 vaccine, and Janssen's COVID-19 vaccine.^{1,2}

The vast majority of COVID-19 vaccinations administered at Loma Linda University Medical Center were Pfizer and Moderna- novel messenger RNA vaccines. The EUA for the Pfizer vaccine was issued based on a randomized, controlled trial demonstrating a less than 1.2% rate of local side effects rated grade three or higher including redness, swelling, and pain.³ The EUA for the Moderna vaccine was based on a randomized, controlled trial that demonstrated less than 7.4% of vaccine recipients experienced a grade three or higher local reaction.⁴

In October 2020, Wibawa explored ethical issues inherent in rapid vaccine development including the fact that messenger RNA vaccines have the possibility of inducing a strong type I interferon response contributing to inflammation and autoimmune conditions.⁵

Studies fully elucidating the cutaneous side effects related to the vaccination effort are ongoing. Shimabukuro reported 175 possible cases with 21 confirmed cases of anaphylaxis often with concomitant, diffuse erythematous rash or generalized urticaria after vaccination.⁶ Castells and Phillips suggest that the Pfizer messenger RNA vaccine may have higher rates of anaphylaxis when compared to Moderna vaccination while another study found relatively equivalent rates of

anaphylaxis with individuals vaccinated for COVID-19- seven cases with the Pfizer vaccine and nine cases with the Moderna vaccine.^{7,8} A now well-documented cutaneous manifestation of COVID-19 vaccination is a delayed local reaction that occurs within a median of eight days of vaccine administration that presents with an erythematous, edematous plaque. This reaction was noted by both Wei et al. and Blumenthal et al. whose group theorized that this reaction is a delayed-type or T-cell-mediated hypersensitivity.^{9,10}

McMahon et al.'s recent publication based on data collected from an international registry outlined delayed large local reactions, local injection site reactions, urticarial eruptions, and morbilliform eruptions as the most common vaccination reactions.¹¹ The case series that follows outlines unique vaccine reactions that have been observed at the Loma Linda University Department of Dermatology.

Case 1: Urticaria and Angioedema

The patient is a 68-year-old female with a history of stable multiple sclerosis, not on therapy, who presented with angioedema and urticarial rash post COVID-19 vaccine. After her first dose of the Moderna vaccine, the patient experienced an urticarial rash distributed on the trunk and upper and lower extremities (Figure 1) followed by angioedema of the lips and other soft tissues of the face within 48 hours. The angioedema was short-lived, persisting for several hours before resolving with a patient-initiated one-time dose of oral Benadryl. The urticarial rash persisted for three days and resolved with, again, patient-initiated baking soda baths. The patient did not have a COVID-19 infection prior to vaccine administration. Additionally, she had no prior history of

skin disease, cutaneous reaction after other vaccines, nor known allergies to injectable medications.

The patient was advised against obtaining the second dose of her two dose Moderna vaccine regimen due risk of airway obstruction with fatal asphyxiation and/or systemic circulatory symptoms.

Case 2: Urticarial Vasculitis

An 86-year-old female with no relevant past medical history, including autoimmune conditions, presented with rash involving her face, trunk, and extremities after receiving her Pfizer vaccination regimen. Approximately five days after her second Pfizer vaccine dose, she experienced an urticarial rash on her face, trunk, and extremities that coalesced into purpuric, reticulated patches (Figure 2). The rash was intensely pruritic without other symptoms. Review of systems was otherwise negative including for arthralgias. The patient had no history of dermatologic conditions, nor any skin reactions following other vaccinations or injectable medication administration. She denied prior COVID-19 infection.

Laboratories demonstrated a CBC and CMP within acceptable limits. C1q, C2, C3, C4, C5, and C1 esterase inhibitor were within normal limits. Hepatitis B and hepatitis C serologies were negative. A skin biopsy was performed, revealing superficial perivascular inflammation with rare eosinophils and leukocytoclastic debris, raising suspicion for prior vascular injury. The patient was diagnosed with resolving urticarial vasculitis likely secondary to the COVID-19 vaccine.

The patient was treated with oral prednisone 40 mg for five days, topical triamcinolone ointment, oral fexofenadine, and oral diphenhydramine as needed for itch. She reported progressive improvement with resolution within two weeks of treatment initiation.

Case Report 3: Chilblains-like Dermal Hypersensitivity Reaction

The patient is a 48-year-old female with a remote history of allergic contact dermatitis to fragrances and positive ANA without rheumatologic disease manifestations, who presented with multiple subtle chilblains-like papules overlying the joint spaces of the hands and feet (Figure 3).

The rash started 10 days after the patient received the first dose of her Moderna vaccination regimen. The rash was associated with mild pruritus and tenderness to palpation. The patient had attempted oral diphenhydramine without relief but topical hydrocortisone improved the rash's pruritus.

A biopsy was performed at her initial dermatology evaluation that demonstrated a psoriatic and spongiotic dermatitis with superficial and deep perivascular lymphocyte-predominant inflammation as well as numerous perivascular and interstitial eosinophils. There was no evidence of vasculitis. The pathology findings supported a diagnosis of a dermal hypersensitivity reaction.

The rash resolved by post-vaccination day 23 without additional treatment. She was advised to proceed with the second Moderna vaccine dose. She received the second dose of the Moderna vaccine without side effects or adverse reactions.

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116 Case 4: Morbilliform Eruption

117 The patient is a 33-year-old female who presented to our dermatology clinic with a morbilliform
118 eruption. The patient received her first dose of the Moderna vaccine and the second dose four
119 weeks later. One day after the second dose, she developed a morbilliform rash consisting of
120 erythematous, edematous papules coalescing into plaques on her trunk with eventual spread to
121 her extremities and face (Figure 4). She endorsed pruritus and burning at the rash sites. The
122 patient had no history of prior COVID-19 infection, other dermatologic conditions, and no prior
123 allergic reactions to injectable medications or vaccinations.

124

125 The patient's primary care physician started the patient on a seven day prednisone taper (which
126 she had finished two weeks prior to her appointment), cetirizine daily, and famotidine daily. A
127 punch biopsy showed a spongiotic/psoriasiform dermatitis with superficial perivascular
128 lymphocyte predominant infiltrate and numerous eosinophils without active vasculitis. Since the
129 patient had started no new medications in the months leading up to the vaccine and the fact that
130 the prescriptions for famotidine and cetirizine were initiated after the rash had occurred, the
131 patient was diagnosed with a morbilliform vaccine reaction. The patient was instructed to use
132 topical triamcinolone ointment as well as oral fexofenadine and hydroxyzine as needed for
133 pruritus. Her rash resolved within two weeks of her clinic visit.

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136 Case 5: Eczematous Dermatitis

The patient is a 37-year-old male with no past medical history who presented with an eczematous dermatitis shortly after receiving the COVID-19 vaccine. The patient noticed faint pink, scaly plaques on his eyelids and arms within seven days of the first dose of his Pfizer vaccination. The patient noticed a similar, more dramatic rash after the second dose of his Pfizer vaccination regimen (Figure 5). The symptoms associated with the rash included burning and stinging. He had used triamcinolone ointment several days prior to his evaluation. The patient had no history of rashes including atopic dermatitis, denied prior COVID-19 infection, and denied reaction to previous vaccinations.

A four millimeter punch biopsy demonstrated a psoriasiform/spongiotic dermatitis with superficial perivascular inflammation and dermal mucin. While not entirely specific, a subacute to chronic dermal hypersensitivity reaction producing a nummular dermatitis was made. Tacrolimus ointment was prescribed for his eyelids, and fluocinonide ointment for his forearms. The patient noted complete resolution within two to three weeks.

Conclusion

Cutaneous manifestations of COVID-19 vaccination are variable. All of the vaccine reactions tended to resolution with two reactions treated with a short course of oral corticosteroids. Only one patient who experienced a reaction after the first dose of the vaccine was advised to forgo completing the vaccine course due to concerns regarding inciting recurrent angioedema or anaphylaxis.

It is interesting to note that female patients were involved in four of the five cases and four of the five individuals had no history of dermatologic conditions. This aligns well with McMahon et al.'s report on 414 cutaneous reactions to COVID-19 vaccination reported to the international registry between December 2020 and February 2021 finding that 90% of vaccination reactions were noted in female patients and 84% of vaccination reactions occurred in individuals with no dermatologic history. In contrast, Asian Americans were involved in three of the five cases and our patients' ages ranged from 33 to 86 (average 54.4 years) whereas Asian Americans represented 11% of cutaneous reactions and vaccine reactions were noted in individuals ranging from 36 to 60 years of age (average 44 years) in McMahon et al.'s study.⁹

As previously mentioned, messenger RNA vaccines have important risks including the possibility of strong type I interferon responses that could result in inflammation and autoimmune conditions. This could potentially explain the reactions observed after vaccination. An alternative explanation could be allergenic components in the vaccine. Both the Pfizer and Moderna vaccines are composed of messenger RNA and lipids as well as salts, sugars, and buffers as shown in the table below (Table 1).^{12,13}

2[(polyethylene glycol)-2000]-N,N-ditetradecylacetamide and polyethylene glycol 2000 dimyristoyl glycerol are incorporated as the polyethylene glycol (PEG) products of the polymer-lipid nanoparticle of the Pfizer vaccine and Moderna vaccine, respectively. Topical exposure to products containing a PEG vehicle have been associated with immediate urticarial and delayed eczematous eruptions.¹⁴⁻¹⁷ Paoletti et al. highlighted the PEG products in the Pfizer and Moderna vaccines as the most likely culprit ingredient resulting in anaphylactic reactions.¹⁸

Both vaccines also have an aminolipid component of the lipid nanoparticle that aids messenger RNA compaction and delivery. The aminolipid (4-hydroxybutyl)azanediylbis(hexane-6,1-diyl)bis(2-hexyldecanoate), also known as ALC-0315, is found in the Pfizer vaccine and SM-102, a proprietary compound, is found in the Moderna vaccine.¹⁹ While little is published about the allergenic potential of these compounds, a study on ALC-0315 clearance in rat models demonstrated that maximal concentrations were obtained three hours after intravenous injection and concentrations dropped 75% over the course of two weeks.²⁰ It is notable that the cutaneous reactions to COVID-19 vaccinations all tended to resolution over a similar timeframe.

Finally, the Moderna vaccine contains tromethamine and tromethamine hydrochloride, amino containing compounds used as buffers. There are reports of eyelid contact allergic eczema in response to topical ketorolac tromethamine ophthalmic drops as well as anaphylaxis in response to ketorolac tromethamine injection in a patient without non-steroidal anti-inflammatory intolerance.^{21,22}

Patch testing or skin prick testing could be performed on this group of patients in an attempt to determine if an allergenic component plays a role in cutaneous reactions to COVID-19 vaccination and potentially confirm the ingredient inciting those reactions.

Figure Legends

Figure 1: Faintly erythematous, edematous grouped wheals on the volar wrist.

Figure 2. Purpuric macules coalescing into reticulated patches on the bilateral thighs.

Figure 3: Subtle chilblains-like erythematous-to-blue dermal papules overlying the joint spaces of the hands.

Figure 4. Erythematous, edematous papules scattered across the abdomen.

Figure 5. Pink annular plaques with fine overlying scale on the right forearm.

Tables

Pfizer Vaccine Ingredients	Moderna Vaccine Ingredients
mRNA	mRNA
(4-hydroxybutyl)azanediylbis(hexane-6,1-diyl)bis(2-hexyldecanoate)	SM-102
2[(polyethylene glycol)-2000]-N,N-ditetradecylacetamide	Polyethylene glycol 2000 dimyristoyl glycerol
1,2-distearoyl-sn-glycero-3-phosphocholine	1,2-distearoyl-sn-glycero-3-phosphocholine
Cholesterol	Cholesterol
Potassium chloride	Tromethamine
Monobasic potassium phosphate	Tromethamine hydrochloride
Sodium chloride	Acetic acid
Dibasic sodium phosphate dihydrate	Sodium acetate
Sucrose	Sucrose

Table 1. The ingredients of the Pfizer and Moderna COVID-19 vaccines.

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