

Severe Acute Respiratory Syndrome Coronavirus 2 Vaccines and Cutaneous Adverse Reactions: A Review

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We are entering a new stage of the severe acute respiratory syndrome coronavirus 2 pandemic with the initiation of large-scale vaccination programs globally. In these circumstances, even rare adverse effects of vaccines may be encountered more often, if millions of people are to be vaccinated in a short period. Vaccination has the potential for causing cutaneous adverse effects. Thus, it is paramount that dermatologists worldwide are acquainted with the possible skin reaction patterns to the coming vaccines. Herein, we conduct a review to discuss the most frequent cutaneous adverse effects of vaccines and their management, with a particular focus on the expected adverse reactions for the coming severe acute respiratory syndrome coronavirus 2 vaccines, such as local reactions, as well as immediate- and delayed-type hypersensitivity reactions, including erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrosis, serum sickness-like reactions, and vasculitides. We also discuss the yet unanswered questions on vaccines for which we may soon be asked to provide an expert opinion.

The current severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic has brought to light countless challenges to clinical practice. We are now entering a new phase of this crisis, which might become the largest vaccination movement in human history. Most countries are expecting to vaccinate most citizens within a year, with vaccines that were subject to a fast development phase, at the relative expense of long-term data on safety. Although messenger ribonucleic acid (mRNA) technology for vaccine development has been extensively studied over the last decade, only a year has separated the identification of this novel coronavirus and the approval of a new vaccine by most international drug agencies, which contrasts with the several years to more than a decade of clinical development of other recent vaccines, such as those against human papillomavirus or varicella-zoster viruses. It is thus possible that even relatively rare adverse effects of these vaccines will be seen occasionally,

if hundreds of millions or billions of people are to be vaccinated, as may happen with any other vaccines under the same circumstances.

Vaccination has the potential for causing cutaneous adverse effects. Thus, it is paramount that physicians worldwide are acquainted with the possible skin reaction patterns to vaccines, which might become more frequent in daily practice in the coming months.

Herein, we conduct a short review on the most frequent cutaneous adverse reactions to vaccines and what may be expected from the upcoming SARS-CoV-2 vaccines (summarized in Table 1).

LOCAL REACTIONS

Local reactions are the most frequent adverse reaction to vaccines. Erythema, edema, and tenderness at the administration site are frequent and common to all known vaccines and usually develop within the first few hours after administration and subside after a few days. They represent a nonspecific innate immune response to foreign body injection and are usually mild and easily managed by local ice application and acetaminophen.¹

Local reactions to mRNA vaccines against SARS-CoV-2 have been extensively recognized. One particular reaction to Moderna's vaccine has been popularly dubbed as "COVID arm," which should more appropriately be called "COVID vaccine arm." This reaction, which has been known since the clinical trials leading to approval, represents the development of an erythematous and edematous patch around the administration site, which may develop 5 to 10 days after the injection of the vaccine and resolves spontaneously within days.² This adverse effect has been postulated to represent a

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TABLE 1. Summary of the Most Frequent Reactions to Vaccines, Their Characteristics, and General Management

Reaction	Mechanism	Clinics	Frequency	Management	Notes
Mild local reaction	Nonspecific inflammatory reaction to foreign body	Erythema, swelling, tenderness	Frequent	Local cold dressing; mild analgesics	May occur with any injectable
Foreign body granuloma	Granulomatous reaction to foreign body	Cutaneous/subcutaneous nodules	Uncommon	Tincture of time; intralesional corticosteroids or surgery for severe cases	More frequent in vaccines with aluminum salts
Nicolau syndrome	Vascular collapse/occlusion/embolism?	Severe pain, livedoid changes, hemorrhagic plaque	Rare	Pentoxifylline, low-molecular-weight heparin	May occur with any injectable
Immediate hypersensitivity reaction	IgE-mediated histamine release	Mild: urticaria; moderate: diarrhea, wheezing; severe: angioedema, anaphylaxis	Uncommon to rare	Antihistamines ± corticosteroids; adrenaline in severe cases	Due to PEG derivatives?
SCD	Delayed hypersensitivity reaction	Pruritic eczematous lesions with variable distribution	Uncommon to rare	Topical or systemic corticosteroids	More frequent in vaccines with preservatives such as thimerosal; PEG and polysorbate 80 in mRNA vaccines may be a potential cause
Drug eruptions	Delayed hypersensitivity reaction	Any pattern of usual drug eruptions	Rare	Topical or systemic corticosteroids	
EM	Delayed hypersensitivity reaction, usually as a reaction to viral infections	Targetoid lesions on acral areas; mucous erosions may occur	Uncommon to rare	Supportive; antivirals or systemic corticosteroids may be pondered	Intact viral vaccines and adenovirus-vector vaccines may pose a higher risk
SJS/TEN	Delayed hypersensitivity reaction, usually as a reaction to drugs	Prominent systemic symptoms; erythematous macules with subsequent blistering and epidermal detachment; mucous erosions frequent	Rare	Critical patient approach; consider admission at burn unit; systemic steroids/cyclosporine A/tumor necrosis factor inhibitors could be considered	
Vasculitides	Mostly mediated by antigen-antibody complex deposition	Palpable purpura; in severe cutaneous diseases, livedoid changes or necrosis may be present; may affect other organs	Uncommon to rare	Exclude other organ involvement; rest; consider systemic corticosteroids	
Serum sickness–like reaction	Yet obscure; similar to type III hypersensitivity reaction, but no immunocomplexes are found	Urticaria, fever, arthralgia	Rare	Supportive; antihistamines and systemic steroids may be used	More frequent in children

Frequency is reported semiquantitatively based on the assessed evidence of published cases, as a general reference only, and may have significant publication bias or underreporting of some milder presentations.

EM, erythema multiforme; IgE, immunoglobulin E; PEG, polyethylene glycol; SCD, systemic allergic contact dermatitis; SJS/TEN, Stevens-Johnson syndrome/toxic epidermal necrolysis; SSLR, serum sickness–like reaction.

delayed hypersensitivity reaction, but the mechanism remains to be elucidated.

Uncommonly, foreign body granulomas may develop within days to weeks and may become persistent. Subcutaneous granulomatous nodules are a well-known reaction to vaccines containing aluminum, which is a frequent ingredient in vaccines to boost immune reaction.^{3,4} Proposed vaccine candidates against COVID-19 with aluminum in their composition include the inactivated vaccine CoronaVac (Sinovac).

Often, the reaction ameliorates with time. Intralesional corticosteroids or surgery may be an option in severe cases.³

Rarely, Nicolau syndrome (embolia cutis medicamentosa) may occur. This condition is not exclusive to vaccination but rather a possible complication shared by all injectable treatments. It is characterized by extreme pain after injection, followed by erythema and by a livedoid reticular or hemorrhagic patch, and may result in skin necrosis and ulceration. The pathogenesis of this reaction is yet

obscure but may be related to embolization of the administered drug or vascular collapse because of increased local interstitial hydrostatic pressure. Cold dressings may aggravate this condition by increasing arterial vasoconstriction. Treatment is usually supportive, and oral pentoxifylline and subcutaneous heparin may be helpful.⁵ Proper injection technique is paramount to prevent this avoidable complication.⁶

IMMEDIATE HYPERSENSITIVITY REACTIONS

Immediate (type I) hypersensitivity reactions develop within 4 hours after vaccine administration and are mediated through immunoglobulin E-dependent histamine release. These reactions may range from mild, with urticarial lesions only, to moderate, with wheezing and/or diarrhea, to life-threatening with angioedema and anaphylactic shock. They may develop in response to any vaccine, but severe reactions are rare, with an estimated incidence of approximately 1 case per million administered vaccines.^{7–9} Treatment is supportive, and immediate administration of intravenous antihistamines and hydrocortisone may be considered for nonsevere reactions, whereas anaphylaxis may be addressed with adrenaline injection.¹⁰ Monitoring patients after vaccine administration is important in individuals with a history of hypersensitivity reactions to vaccines. Patients should be referred to an allergy expert for further study after an episode of immediate hypersensitivity reactions to vaccines.¹¹

Polyethylene glycol (PEG) moieties and polysorbate-80 have the potential to cause immediate hypersensitivity reactions,^{12–15} as well as delayed hypersensitivity reactions (see below). Polyethylene glycol moieties, present in both Moderna's and Pfizer's vaccines, have been postulated to be responsible for anaphylactic reactions to these vaccines.^{16–18}

DELAYED HYPERSENSITIVITY REACTIONS

Systemic Contact Dermatitis

Delayed (type IV) hypersensitivity to vaccine constituents often presents as systemic allergic contact dermatitis. Systemic allergic contact dermatitis usually develops after systemic administration (oral, intravenous, intramuscular, subcutaneous, inhalational, transmucosal, or transcutaneous) of a given allergen, to which an individual had become previously sensitized, usually through cutaneous route.¹⁹ The clinical presentation may be diverse, with recurrence of skin lesions on previously affected areas of dermatitis or on areas of previous positive patch test; vesicular hand dermatitis (pompholyx); symmetrical drug-related intertriginous and flexural erythema; or, less frequently, pruritic papules on extensor surfaces of knees and elbows, erythroderma, or even vasculitis-like lesions.¹⁹

Systemic allergic contact dermatitis has been described as a reaction pattern not only to metals, namely, nickel, cobalt, and chrome, but also to a wide range of drugs and other substances, including but not limited to antibiotics, topical anesthetics, aminophylline, and even corticosteroids.^{19–23}

Vaccine constituents have been implicated in systemic allergic contact dermatitis, the most common of which being antibiotics (eg, neomycin²⁴) and preservatives²⁵ (eg, thimerosal,²⁶ formaldehyde,²⁷ propylene glycol,²⁸ sorbic acid²⁹).^{11,30} Mercury derivatives have been ubiquitous in the past, accounting for high rates of sensitization in the general population, but have been recently abandoned for most of their uses. Thimerosal is currently not used in most vaccines in the Western world, but it is still not banned from use according to the World Health Organization recommendations, which refer a positive benefit-risk assessment for its use. Other preservatives and antibiotics remain common, and their use is widespread. Most vaccines in development for COVID-19 have not disclosed their composition publicly, which makes it difficult to ascertain the risk for this type of reaction. Pfizer's vaccine (COMIRNATY) lists 2-[(PEG)-2000]-N,N-ditetradecylacetamide (ALC-0159), a PEG derivative, as an excipient intended to stabilize lipidic particles. Moderna's vaccine also features another PEG derivative, 1,2-dimyristoyl-rac-glycero-3-methoxypolyethylene glycol-2000, for similar purposes. Cases of allergic contact dermatitis to PEG moieties have been described in the literature,^{31,32} but so far, no cases have been reported on COVID-19 vaccine administration. Moderna's vaccine also lists trometamol as an excipient, a substance to which allergic contact dermatitis has been described,^{33,34} thus raising the possibility of systemic contact dermatitis in some patients. AstraZeneca's vaccine lists polysorbate-80 and disodium edetate dihydrate as excipients, both known potential allergens.^{14,35–39}

It is worth mentioning that cases of cross-reactivity between polysorbate-80 and PEG moieties have been described.^{40,41} Most cases of cross-reactivity between these allergens presented as an immediate-type reaction in perioperative context, where PEGylated moieties are ubiquitous (antiseptic gels, bowel preparation solutions, ultrasound gel, lubricants, volume expanders, etc).^{40,41} Considering that reports of both immediate and delayed hypersensitivity reactions are found in the literature and the potential for cross-reactivity, testing for such allergens may be useful should a suspicion of allergy to any of those compounds arise. Prick tests and patch tests may be necessary to accurately assess the full gamut of possible allergic reactions to these substances, according to the suspected pathophysiological mechanism, and may be complementary in selected cases. The dermatologist thus plays a pivotal role in the clinical assessment and diagnostic workup of these cutaneous adverse reactions.

Drug Eruptions

Other patterns of delayed hypersensitivity reactions are those of drug eruptions, which may range from the most frequent disseminated and symmetrical maculopapular exanthem (morbilliform eruption) to less frequent bullous fixed-drug eruptions^{42,43} or even potentially severe reactions, such as drug reaction with eosinophilia and systemic symptom syndrome.⁴⁴ Onset ranges from a few days to weeks after the administration of the vaccine, with re-exposure featuring earlier onset than the first reactions. Most of these adverse effects are non-life-threatening and easily manageable with topical corticosteroids for limited extension disease or systemic corticosteroids for more widespread disease. For more severe cases, hospital

admission and systemic steroids may be warranted. Referral to a dermatologist/allergist who specializes in type IV hypersensitivity reactions should be pursued for additional studies, after the resolution of the episode.¹¹

Erythema Multiforme

Erythema multiforme (EM) is a cutaneous reaction pattern, clinically characterized by erythematous papules (less frequently macules) with a target morphology, primarily affecting acral areas with symmetric distribution, and mucosal erosions in more severe cases. Erythema multiforme is a delayed hypersensitivity reaction most frequently elicited by active herpesvirus infection, but many other viral agents and atypical bacteria have been implicated in their etiopathogenesis (most frequently *Mycoplasma pneumoniae*, parapoxvirus, adenovirus, hepatitis viruses, cytomegalovirus, and HIV).^{45–47} Cases of EM have also been described in COVID-19 patients,^{48–50} and as a reaction pattern to multiple vaccines has been described,⁵¹ particularly in children, although confounding factors make the nexus of causality dubious in most instances.

Although virtually any vaccine may cause EM, virus-based vaccines, either live-attenuated or inactivated SARS-CoV-2 vaccines (eg, CoronaVac, from Sinovac) or vaccines using adenoviruses as vectors (eg, AstraZeneca's AZD122 and CanSino Biologics' Ad5-nCoV), may theoretically pose a higher risk for this adverse reaction.

Should a patient present with EM after vaccination, we recommend other more frequent causes to be excluded. Treatment is usually supportive as the disease is self-limited, but systemic corticosteroids and antivirals have been used in clinical practice in more severe cases, despite the evidence for use being low.^{46,47,52}

Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis

Stevens-Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN) represent a spectrum of conditions, which feature varying degrees of epidermal necrosis and detachment, accompanied by prominent systemic symptoms with significantly associated morbidity and mortality. Clinically, a prodrome of malaise and/or fever predates the onset of rapidly progressing erythematous exanthem with subsequent blistering and epidermal detachment in some areas. Target lesions may be present, but unlike EM, SJS/TEN affects preferentially the torso and face, and mucosal involvement of the mouth, conjunctiva, and/or genitals is very frequent. Epidermal detachment may be elicited through tangential mechanical stress with a finger (Nikolsky sign). Stevens-Johnson syndrome/TEN is a delayed hypersensitivity reaction typically caused by drugs, which promote immune activation with cytotoxic damage of keratinocytes, but infections have infrequently been implicated as etiological agents. These entities have rarely been described after vaccine administration, and the nexus of causality is thus highly dubious.^{51,53–55} Stevens-Johnson syndrome/TEN is, however, a severe condition that requires prompt diagnosis and management. Careful assessment of these patients is advised, and hospital admission is frequently necessary. Electrolyte

imbalance is frequent, and hypocalcemia may be a cause of sudden death in these patients. Epidermal detachment of more than 30% constitutes indication for admission at a burn unit. Treatment is still a matter of discussion, but more severe cases may benefit from systemic corticosteroids, cyclosporine A, and/or antitumor necrosis factor α therapy (eg, etanercept), in addition to skin care and supportive hydration and nutrition, which have been reviewed extensively elsewhere.^{56,57}

VASCULITIDES

Vasculitides are a heterogeneous group of diseases, which share the common feature of endothelial damage secondary to inflammation.

Some vasculitides have been recognized as a reaction pattern to infectious or xenobiotic stimuli. The most frequent form of vasculitis, hypersensitivity (leukocytoclastic) vasculitis, usually presents with palpable purpura of the lower limbs, because of antigen-antibody complex deposition (type III hypersensitivity reaction) in the small vessels under a gravity gradient, but other organ involvement has been acknowledged, most frequently affecting the kidney, intestines, and joints. Several cases of leukocytoclastic vasculitis, Henoch-Schönlein purpura, and even antineutrophil cytoplasmic antibodies-associated small-vessel vasculitis have been described in association with vaccines against viral diseases, namely, influenza and human papillomavirus,^{58–62} but more severe cases of medium-vessel vasculitis, such as Kawasaki disease, have also been reported.^{63,64} These reactions seem to be more frequent in children, adolescents, and young adults, but the relative risk of vaccination to vasculitis development seems to be low.

Incidentally, vasculitis seems to be a feature of COVID-19, as well in some cases.⁶⁵ This raises the question whether the coming vaccines against SARS-CoV-2 may feature vasculitis as possible adverse reactions.

Management of vasculitis should focus on the exclusion of organ involvement other than the skin. Most patients without evidence of other organ lesion in small-vessel vasculitis with palpable purpura only may be discharged under topical or systemic corticosteroids, according to disease extension. Symptomatic measures to alleviate pruritus and rest with elevation of lower limbs should be proposed. Patients with skin necrosis, livedoid changes, or other organ involvement should be promptly referred to specialized hospital care with a multidisciplinary team.^{66,67}

SERUM SICKNESS-LIKE REACTIONS

Serum sickness-like reactions (SSLRs) are so described as they share overlapping clinical manifestations with serum sickness disease (a type III hypersensitivity reaction), but no circulating immunocomplexes are found. This entity is more frequently found in children after administration of certain antibiotics, such as cefaclor, but cases of SSLRs after vaccination have been described.^{68–70} Clinically, an SSLR is characterized by urticarial lesions, arthralgia, and fever days to 3 weeks after relevant exposure. Additional symptoms, such

as generalized lymphadenopathy, nausea, vomiting, glomerulonephritis, and neurological symptoms, may be present in a few cases. Treatment is usually symptomatic with complete resolution after cessation of the offending agent. In more severe cases, systemic corticosteroids may be used, although evidence to support this approach is lacking.⁷¹

OTHER REACTION PATTERNS

There have been reports of lichenoid eruptions,⁷² Sweet syndrome,⁷³ Gianotti-Crosti syndrome,⁷⁴ acute generalized exanthematic pustulosis,⁷⁵ and bullous pemphigoid⁷⁶ after vaccination. However, these cases are rare and make a causative relationship hard to establish.

SPECIAL CONSIDERATIONS AND UNANSWERED QUESTIONS

Vaccines against SARS-CoV-2 are truly groundbreaking and disruptive of the usual process of vaccine development, assessment, and distribution. Although this allows for a fast development and an expedited bench-to-the-patient time, it also raises significant questions.

mRNA vaccines have long been postulated as favorable candidates for large-scale immunization as they feature fast and simple production and promote both humoral and cellular immunity against viral antigens. However, this is the first time that this kind of vaccine will be used in humans. Although the available data for efficacy and safety for these vaccines, which are relatively scarce, point toward general safety, the profile of cutaneous reactions is still unclear.^{77,78} It is known whether these vaccines are strong stimulators of both the innate and adaptive immune responses, with increased production of interferon, the consequence of which to the skin is yet unclear.

So far, most reports of cutaneous adverse reactions to vaccines have been local or type I hypersensitivity reactions, but other adverse reactions may come to light over time.

Viral vector-based vaccines may represent a further risk for cutaneous adverse reactions. Adenoviruses are a recognized precipitant of many cutaneous reaction patterns as described previously. Some voices have also advocated for caution when dealing with adenovirus 5 vectors, as previous research has raised the possibility that these vaccines may put some individuals at increased risk for other viral diseases, namely, HIV.⁷⁹ These authors suggest that Ad5 immune complexes may activate the dendritic cell-T-cell axis, which could potentiate HIV-1 replication in CD4 T cells. Furthermore, Ad5-specific CD4 T cells have been suggested to feature increased susceptibility to HIV infection.⁷⁹

Perhaps one of the most pressing questions for dermatologists and allergists on vaccination would be on the appropriate course of vaccination should a cutaneous adverse reaction occur. Most vaccines currently marketed or at phase III in development require 2 doses, except for Janssen's *Ad26.COV2.S* and CanSino's *Ad5-nCoV*, which require only 1. It is known that reactions at second dose tend to be more frequent and more severe.⁸⁰ Should a patient

develop an adverse skin reaction, these specialists would be called to ascertain whether a second dose should be administered or withheld. On the one hand, withholding the second dose may compromise vaccine efficacy; on the other hand, a second dose may cause more severe reactions. As a rule of thumb, mild local reactions pose no contraindication to second dosage.⁸⁰ Severe reactions should be assessed on a case-by-case basis. As per the current Centers for Disease Control and Prevention guidelines, individuals with a known diagnosis of PEG/polysorbate immediate-type allergy or allergy to any mRNA vaccine should not receive vaccination with another mRNA vaccine against SARS-CoV-2, unless deemed otherwise by an specialized allergist, and only under strict medical observation.⁸⁰ As most immediate hypersensitivity reactions are due to excipients, initiating and completing the approved posological schedule of a different vaccine with distinct composition may become an option, but as of now, there are no formal recommendations on this aspect. For severe adverse skin reactions, such as SJS/TEN or systemic vasculitides, it is our opinion that a rechallenge poses inadmissible risks. One-dose schemes may obviate this dilemma, but that does not mean that they are necessarily safer. Furthermore, these severe adverse reactions are infrequent at most and thus should not dictate public health policies on vaccinal schemes.

Last, physicians will be asked to provide opinion on the vaccination of patients with chronic severe skin diseases and those under immunosuppressant or immunomodulating therapies. To date, there is no evidence to support any course of action, and advice should be provided based on expert consensus and individual characteristics of the patients until data are available.

CONCLUSIONS

Vaccination against SARS-CoV-2 will represent a significant progress toward ending this pandemic crisis. Physicians should be aware that large mass vaccination may lead to a rise in certain reactive dermatosis, which should be promptly identified and appropriately managed. Nevertheless, the individual risk for any such adverse reaction will be probably low and should not be considered a valid argument against vaccination, in most cases. Detailed data on safety from the available clinical trials and long-term surveillance of adverse effects are paramount to identify possible risks, thus allowing for adequate prevention. Nationwide databases to register adverse effects should be encouraged as a primary pharmacovigilance strategy.

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