



Cutaneous reactions to vaccinations

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Abstract Vaccinations are important for infectious disease prevention; however, there are adverse effects of vaccines, many of which are cutaneous. Some of these reactions are due to nonspecific inflammation and irritation at the injection site, whereas other reactions are directly related to the live attenuated virus. Rarely, vaccinations have been associated with generalized hypersensitivity reactions, such as erythema multiforme, Stevens-Johnson syndrome, urticaria, acute generalized exanthematous pustulosis, and drug hypersensitivity syndrome. The onset of certain inflammatory dermatologic conditions, such as lichen planus, granuloma annulare, and pemphigoid, were reported to occur shortly after vaccine administration. Allergic contact dermatitis can develop at the injection site, typically due to adjuvant ingredients in the vaccine, such as thimerosal and aluminum.

Vaccinations are important to promote development of both individual and herd immunity. Although most vaccinations are considered relatively safe, there may be adverse effects associated with any vaccine. Cutaneous manifestations make up a large portion of the types of reactions associated with vaccines. There are many different reasons for the development of a cutaneous reaction to a vaccination. Some are directly related to the injection of a live attenuated virus, such as varicella or vaccinia (for immunity to smallpox), whereas others cause more nonspecific erythema and swelling at the injection site, as a result of local inflammation or irritation. Vaccinations have also been associated in rare reports with generalized hypersensitivity reactions, such as erythema multiforme, Stevens-Johnson syndrome, urticaria, acute generalized exanthematous pustulosis, and drug hypersensitivity syndrome. There have been case reports associating the administration of a vaccine with the new onset of a dermatologic condition, such as lichen planus, granuloma annulare, and Sweet syndrome. Finally, allergic contact dermatitis can develop at the injection site, typically due to adjuvant ingredients in the vaccine, such as thimerosal and aluminum.

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Local site reactions

After administration of injectable vaccines, the most common reaction is a local nonspecific injection site reaction with erythema, swelling, and tenderness (Figure 1). Clinical

manifestations usually resolve within a few days to weeks. Supportive treatment with cool compresses and acetaminophen is usually sufficient to reduce symptoms such as pruritus or pain until the cutaneous reaction clears. These findings occasionally may be accompanied by generalized malaise or fever. These symptoms may occur with any vaccine and are not specifically related to any of the vaccine components.¹

Infrequently, patients may experience local injection site reactions that are specific to particular vaccines, as reviewed below.

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Fig. 1 Localized injection site reaction characterized by erythema and edema.

Nicolau syndrome (aka embolia cutis medicamentosa)

Nicolau syndrome is a local site reaction that can occur following any intramuscular drug injection, including many of the intramuscular vaccines, such as influenza, diphtheria-tetanus-pertussis, diphtheria and tetanus, and hexavalent vaccine (diphtheria, tetanus, pertussis, polio, *Haemophilus influenzae*, and hepatitis B).² It is characterized by an acute onset of painful swelling, followed by livedoid erythema, circumscribed hemorrhagic patches, and ultimately necrosis of the cutaneous and soft tissues. These lesions may resolve with scarring but usually cause no long-term functional impairment. The pathogenesis of this condition is not completely understood but is thought to be due to vasospasm secondary to needle prick, embolization of the injected material, or pressure from the injected material around the vessel.² Early intervention to prevent necrosis is important. Improved local blood flow may be accomplished with the use of pentoxifylline, heparin, or hyperbaric oxygen. Local inflammation may be reduced with intralesional corticosteroids, being careful to withdraw before injection to avoid intravascular injection.³ Systemic antimicrobials may also be administered to prevent secondary infection.²

Hepatitis B vaccine

In addition to erythema, edema, and tenderness at the injection site, patients receiving the hepatitis B vaccine have been found to develop nodules and granulomas at the injection site.⁴ These lesions are less common; however, they usually persist longer than the nonspecific findings of edema, erythema, and tenderness.

Smallpox vaccine

The vaccine against smallpox, developed by Edward Jenner in 1798, was the first of its kind. Jenner had succeeded in demonstrating that immunity to cowpox was protective

against smallpox. The smallpox vaccine is still in use today and is made from the virus causing cowpox, known as vaccinia virus. It does not contain the smallpox virus and cannot cause smallpox; however, it is a live virus vaccine with its own set of complications. Smallpox vaccination is not a routine component of the current vaccination schedule. Given recent concern about the smallpox virus being used for biologic warfare, vaccination of military personnel and other “first responders” has been performed since 2001. Increased research efforts have recently been undertaken in an effort to increase the safety of the vaccine, should there be a need for widespread use in the future.

After smallpox vaccine inoculation, erythema develops with a central eschar. In rare cases, a cutaneous reaction related to the introduction of the vaccinia virus via immunization may expand beyond the injection site. These reactions include progressive vaccinia, eczema vaccinatum, and generalized vaccinia. Progressive vaccinia is a rare complication seen in immunocompromised individuals in which the initial injection site fails to heal within 14 days. The nonhealing injection site develops an ulcer with central necrosis and eschar formation. Similar satellite lesions then appear at distant sites. Systemic symptoms usually occur late in the course of the illness. The degree and type of immunodeficiency determines the likelihood of developing progressive vaccinia and the severity of the illness. Progressive vaccinia may be fatal due to overwhelming viremia or secondary septicemia.⁵

Eczema vaccinatum is characterized by an acute onset of disseminated painful vesicles and pustules in a patient with a history of atopic dermatitis (Figure 2).⁶ Positive viral cultures or direct observation of infected cells by direct immunofluorescence solidifies the diagnosis. Pathologic examination typically reveals balloon degeneration of keratinocytes with the presence of multinucleated epithelial cells. Fatality from this reaction ranges from 5-40%. Current guidelines exclude anyone with a personal history of atopic dermatitis from receiving the smallpox vaccine. In addition, vaccinated individuals should not be in contact with anyone with a history of atopic dermatitis until the injection site is completely healed. There have been cases of eczema vaccinatum developing in household contacts of vaccinated individuals.⁷ Given that such a large percentage of the United States population has atopic dermatitis, this issue will likely be very complicated if widespread smallpox vaccination is necessary in the future. Newer vaccines for smallpox are under development that will not contain live inoculates and, therefore, will not be a potential cause of eczema vaccinatum.

Generalized vaccinia is a clinical diagnosis based on the development of a vesicular, pustular, and/or papular eruption in an otherwise healthy individual at sites distant from the vaccination site.⁸ These lesions are thought to be due to hematologic spread of the virus. Recent diagnostic criteria require that smallpox virus be confirmed in these lesions by viral culture, immunohistochemistry, or polymerase chain reaction.

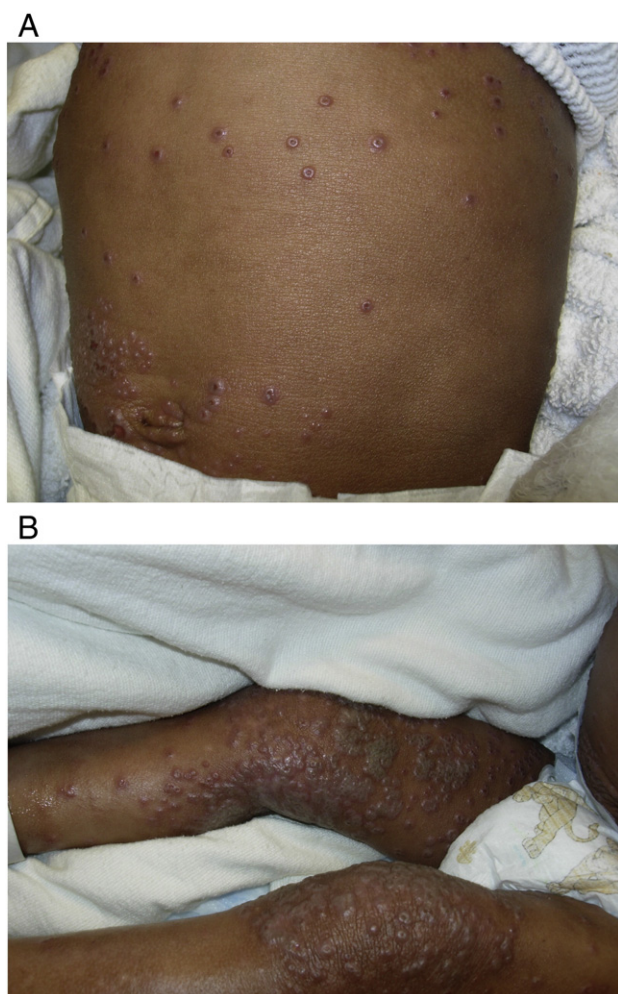


Fig. 2 Eczema vaccinatum affecting the (A) trunk and (B) lower extremities after exposure to an individual who received the smallpox vaccine.

Varicella vaccine

Varicella vaccination in the United States is accomplished with the administration of a milder strain of varicella, termed the Oka strain. Despite the reduced pathogenicity of the strain, more than half of the cutaneous reactions associated with varicella vaccination are described as widespread vesicles on an erythematous base, mimicking a naturally occurring varicella (chickenpox) infection. The vesicular lesions appear about 8 days after vaccination and resolve spontaneously without significant sequelae. Smaller subsets, about 8%, of patients with cutaneous reactions after varicella vaccination develop vesicles isolated to the injection site only.⁹

Generalized hypersensitivity reactions to vaccines

Erythema multiforme (EM) is an acute, usually self-limited, immune-mediated reaction characterized by target-

like lesions. The palms and soles, among other body sites, are often involved. Involvement of the mucous membranes is less common and generally not as severe as in other reaction patterns. EM most often occurs secondary to an infectious trigger, with herpes simplex virus type 1 (HSV-1) being the most common trigger in childhood.¹⁰ It is often difficult in the setting of a live vaccine and associated viremia to know whether the vaccine precipitated HSV and consequent EM or whether the vaccine was the cause of EM, directly. There have been cases of EM associated with vaccinations, as described later. Stevens-Johnson syndrome is a more severe blistering reaction typically due to drugs, though it too has been rarely associated with vaccinations. Other drug reaction patterns, such as morbilliform eruptions, acute generalized exanthematous pustulosis, urticaria, and angioedema, have also occurred after vaccination.¹¹

Human papilloma virus vaccine

EM has been reported in association with human papilloma virus vaccination in an otherwise healthy individual.¹² The patient did not have any recent infections or cold sores and was not on any medications. The human papilloma virus vaccine has also been associated with urticarial and morbilliform eruptions in addition to angioedema.¹² Both bivalent and quadrivalent vaccines have been implicated.¹²

Measles-mumps-rubella vaccine

The measles-mumps-rubella (MMR) vaccine has been associated with EM and in one case report was associated with Stevens-Johnson syndrome.¹³ In this report, the patient developed Stevens-Johnson syndrome 4 days after vaccination; however, the evidence linking this reaction to the vaccination is weakened by the additional history that the patient had six similar but milder episodes of Stevens-Johnson syndrome in the following 7 years, after upper respiratory infections or HSV infection. There have also been multiple reports of the development of urticarial lesions, some with accompanying angioedema, after MMR vaccination. Most of these reactions occur within a few minutes to 15 days after vaccination and are self-limited.

Smallpox vaccine

One group administered smallpox vaccine to 680 individuals between 18 and 32 years of age and followed the patients for 56 days after vaccination. There was one reported case of EM within this study population.⁸ EM has also been rarely reported after the following vaccinations: hepatitis B, meningococcal, pneumococcal, varicella, influenza, diphtheria-pertussis-tetanus, and *Haemophilus influenzae* vaccines.¹⁴

Specific dermatologic conditions

There have been many reports of dermatologic conditions such as lichen planus, granuloma annulare, folliculitis, and bullous pemphigoid being triggered by a recent vaccination. In the majority of these case reports, it is unclear if the vaccination was truly causal to the development of the cutaneous condition or if the timing was simply coincidental.

Diphtheria-pertussis-tetanus vaccine

There is one case report of an individual who developed anti-laminin-332 antibody-induced cicatricial pemphigoid 2 days after administration of diphtheria-pertussis-tetanus vaccine.¹⁵ The authors propose that perhaps this immunologic phenomenon was the result of structural mimicry between domains of the toxoid molecule and a subunit of laminin-332.

There have been several reports of bullous pemphigoid arising after vaccination with diphtheria-pertussis-tetanus.¹⁵ Granuloma annulare and Gianotti-Crosti syndrome (papular acrodermatitis of childhood), have also been reported after vaccination with diphtheria-pertussis-tetanus (DPT).^{16–18} These types of reactions are not a contraindication for further vaccination.

Hepatitis B vaccine

There are several reports of lichenoid or lichen planus–like eruptions after hepatitis B vaccination.^{4,16,19} No other vaccines have been associated with a lichenoid reaction, despite this being a fairly common pattern for drug reactions.¹⁹ The described lichenoid eruption can occur a few days to 3 months after any of the three recommended doses of hepatitis B vaccine. The first report of lichen planus after hepatitis B vaccination was described in 1990.¹⁹ Lichen planus after vaccination occurs irrespective of the brand of hepatitis B vaccine. Either linear or generalized lichen planus can occur.^{20,21}

Isolated cases of erythema nodosum and cutaneous lupus erythematosus have been reported after hepatitis B vaccine.⁴ There has been a single case reported of granuloma annulare developing after hepatitis B vaccination.¹⁶ In this case, a cell-mediated and/or humoral immune response induced by hepatitis B vaccination is the postulated mechanism. Gianotti-Crosti syndrome has been reported developing 3 weeks after hepatitis B vaccination.²²

Influenza vaccine

In addition to bullous pemphigoid and Gianotti-Crosti syndrome, which have been associated with many types of vaccines, Sweet syndrome has also been reported after vaccination against influenza.²³ The patient developed pseudovesicular lesions around the injection site 12 hours

after influenza vaccination. These lesions spread to the extremities and were accompanied by fever and influenza-like symptoms.²⁴ Rarely, influenza vaccination has been associated with induction of autoimmune diseases such as systemic lupus erythematosus, giant cell arteritis, Churg-Strauss syndrome, cutaneous leukocytoclastic vasculitis, Henoch-Schönlein purpura, Guillain-Barré syndrome, and microscopic polyangitis.^{25,26}

Measles-mumps-rubella vaccine

Bullous pemphigoid has been reported after MMR vaccination. Additionally, a 2-year-old girl developed Henoch-Schönlein purpura 3 days after MMR vaccination.¹³ Gianotti-Crosti syndrome has also been reported after MMR vaccination.¹⁸

Smallpox vaccine

Post-vaccinia, nonviral sterile folliculitis has been reported after smallpox vaccination.²⁷ The folliculitis is usually benign and resolves spontaneously within 7 days. Histopathologic study indicates a neutrophilic or lymphohistocytic infiltrate around hair follicles without evidence of viral infection. One hypothesis regarding the pathogenesis of this reaction is that the folliculitis is secondary to vaccinia protein deposition within the pilosebaceous units.²⁸ It can be difficult to clinically distinguish folliculitis from generalized vaccinia after smallpox vaccination. Two clues to distinguish these conditions are folliculitis lesions develop in different stages, unlike generalized vaccinia. Additionally, the folliculitis lesions do not scar after healing. Smallpox vaccination has also been temporally associated with bullous pemphigoid in one report.¹⁵

Allergic reactions

Aluminum

Since 1930, aluminum salt has been used as an adjuvant for the diphtheria-tetanus-acellular pertussis (DTaP) vaccine. Adjuvants are pharmacologic or immunologic agents that enhance the vaccine recipient's immune response to the supplied antigen, thus minimizing the amount of injected foreign material. Adjuvants have been reported to cause type IV mediated immune response and allergic contact dermatitis. In the DTaP vaccine, the aluminum salt is used to precipitate diphtheria toxoid, which in turn increases levels of antibody response.²⁹ Aluminum salt is also present in the hepatitis B vaccine booster. A patient with pruritic subcutaneous nodules at the DTaP vaccination injection site was found to have a positive patch test to aluminum hydroxide, indicating an

allergic reaction to aluminum as the probable culprit for the subcutaneous nodules (Figure 3).³⁰

Thimerosal

Thimerosal is an ethyl mercury derivative used as a preservative to prevent bacterial contamination of multidose vaccine vials after they have been opened.

In 1999, the FDA determined that infants receiving multiple thimerosal-containing vaccines might be exposed to more than the recommended mercury levels; however, there has been no evidence of harm as a result of mercury exposure from vaccinations. Thimerosal is a relatively common cause of allergic contact reactions in general. Patch testing panels for allergic contact sensitivity often reveal a positive reaction to thimerosal, though it is rarely thought to be clinically relevant.¹ There have been reports of allergic hypersensitivity reactions secondary to thimerosal contained in vaccines.³¹ Sensitization to thimerosal is usually lifelong but is not considered a contraindication to vaccination. Since 2001, no pediatric vaccines contain thimerosal, except for multidose vials of inactivated influenza vaccine.

Conclusions

Vaccinations play an important role in infectious disease prevention for society as a whole; however, there are many cutaneous reactions to vaccines that should be recognized. These reactions may be directly related to the vaccine or the adjuvant or may be due to nonspecific inflammation at the injection site. Given the role of vaccines in stimulating an immune response, many inflammatory skin conditions also may be triggered after vaccination, though these reactions are exceedingly rare given the number of vaccinations administered. It is important to identify these reactions and manage them appropriately while continuing to educate the public on the critical importance of vaccinations.



Fig. 3 Contact dermatitis to aluminum at injection site after vaccination.

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