

Acral Papulovesicular Eruption in a Soldier Following Smallpox Vaccination

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PRACTICE POINTS

- There are several potential cutaneous adverse reactions associated with smallpox vaccination, ranging from benign self-limited hypersensitivity reactions to life-threatening eczema vaccinatum and progressive vaccinia.
- Acral papulovesicular eruption is a distinct presentation that has been described in the US Military following vaccination with the second-generation live smallpox vaccine (ACAM2000).

Smallpox vaccination is associated with several potential cutaneous adverse reactions, ranging from benign self-limited hypersensitivity reactions to life-threatening eczema vaccinatum and progressive vaccinia. Acral papulovesicular eruption is a distinct presentation that has been described in US Military service members following vaccination with the second-generation smallpox vaccine (ACAM2000, Sanofi Pasteur Biologics Co). We describe a case of this unique cutaneous eruption and review previously described cutaneous adverse events associated with smallpox vaccination.

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Following the attacks of September 11, 2001, heightened concerns over bioterrorism and the potential use of smallpox as a biological weapon made smallpox vaccination a critical component of military readiness. Therefore, the US Military resumed its smallpox vaccination program in 2002 using the first-generation smallpox vaccine (Dryvax, Wyeth Pharmaceuticals), a live vaccinia

virus vaccine created in the late 19th century. This vaccine was developed by pooling vaccinia strains from the skin of infected cows¹ and had previously been used during the worldwide vaccination campaign in the 1970s. Dryvax was associated with various cardiac and cutaneous complications, from benign hypersensitivity reactions to life-threatening eczema vaccinatum and progressive vaccinia.

Due to concerns that the remaining supply of Dryvax was insufficient to vaccinate the US population in the case of a bioterrorism attack, investigators developed the second-generation smallpox vaccine (ACAM2000, Sanofi Pasteur Biologics Co) using advances in vaccine technology.² ACAM2000 is a plaque-purified isolate of vaccinia virus propagated in cell culture, thereby reducing contaminants and lot-to-lot variation.¹ Clinical trials demonstrated comparable immunogenicity and frequency of adverse events compared with Dryvax,² and ACAM2000 replaced Dryvax in 2008. However, these trials focused on serious adverse events, such as cardiac complications and postvaccinal encephalitis, with less specific characterization and description of cutaneous eruptions.³

Since 2008, there have been few reports of cutaneous adverse reactions following vaccination with ACAM2000. Beachkofsky et al⁴ described 7 cases of papulovesicular eruptions and 1 case of generalized vaccinia. Freeman and Lenz⁵ described 4 cases of papulovesicular eruptions, and there has been 1 case of progressive vaccinia reported in a soldier with newly diagnosed acute myelogenous leukemia.⁶ Kramer⁷ described a patient with multiple vesiculopustular lesions secondary to autoinoculation. The distinct pruritic acral papulovesicular eruptions following ACAM2000 vaccination have occurred in healthy military service members at different locations since the

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introduction of ACAM2000. We describe an additional case of this unique cutaneous eruption, followed by a review of previously described cutaneous adverse events associated with smallpox vaccination.

Case Report

A 21-year-old female soldier who was otherwise healthy presented to the dermatology clinic with a pruritic papular eruption involving the upper and lower extremities of 1 week's duration. The lesions first appeared 8 days after she received the ACAM2000 vaccine. She received no other concurrent vaccines, had no history of atopic dermatitis, and had no systemic symptoms. Physical examination revealed numerous erythematous indurated papules involving the dorsolateral hands and fingers, as well as the extensor surfaces of the elbows, knees, and thighs (Figures 1 and 2). Based on the clinical presentation, the differential diagnosis included lichen planus, verruca plana, dyshidrotic eczema, and smallpox vaccine reaction. Erythema multiforme was considered; however, the absence of palmoplantar involvement and typical targetoid lesions made this diagnosis less likely.

Biopsies of lesions on the arm and thigh were performed. Histologic findings revealed interface and spongiotic dermatitis with scattered necrotic keratinocytes and extravasated erythrocytes (Figure 3). There was no evidence of viral cytopathic effects. Similar clinical and histologic findings have been reported in the literature as acral papulovesicular eruptions following smallpox vaccination or papular spongiotic dermatitis of smallpox vaccination.⁸ The presence of eosinophils was not conspicuous in the current case and was only a notable finding in 1 of 2 cases previously described by Gaertner et al.⁸ This may simply be due to an idiosyncratic drug reaction. Furthermore, in the cases described by Beachkofsky et al,⁴ there were essentially 2 histologic groups. The first group demonstrated a dermal hypersensitivity-type reaction, and the second group demonstrated a lymphocytic capillaritis.



FIGURE 1. Multiple discrete, erythematous, indurated papules on the dorsal and lateral sides of the fingers.

Based on these findings, the patient was diagnosed with an acral papulovesicular eruption following smallpox vaccination. Of note, the patient's presentation was not consistent with other described smallpox vaccine reactions, which included eczema vaccinatum, autoinoculation, generalized vaccinia, and progressive vaccinia. The patient was treated supportively with triamcinolone acetonide cream 0.1%, cool compresses, and oral diphenhydramine as needed for pruritus. The lesions notably improved within the first week of treatment.



FIGURE 2. Papular eruption on the extensor surface of the knee.

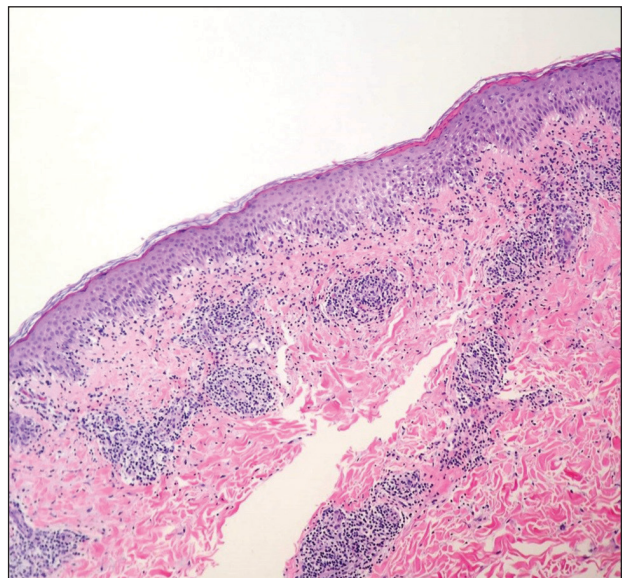


FIGURE 3. Interface and spongiotic dermatitis with scattered necrotic keratinocytes and extravasated erythrocytes (H&E, original magnification $\times 40$).

Comment

Reported cases of acral papulovesicular eruption⁴⁻⁶ demonstrated an onset of cutaneous symptoms an average of 14 days following vaccination (range, 8–18 days postvaccination). Lesions were benign and self-limited in all cases, with resolution within an average of 25 days (range, 7–71 days). All patients were active-duty military adults with a mean age of 24 years. Supportive treatment varied from topical steroids and oral antihistamines to tapering oral prednisone doses. Of note, all previously reported cases of this reaction occurred in patients who also had received other concurrent or near-concurrent vaccines, including anthrax, hepatitis B, influenza, and typhoid. Our patient represents a unique case of a papulovesicular eruption following smallpox vaccination with no history of concurrent vaccines.

Since the 1970s, smallpox vaccination has been associated with numerous cutaneous reactions, most of which have been reported with the first-generation Dryvax. Minor local reactions occurred in approximately 2% to 6% of vaccinees in clinical trials.⁹ These reactions included local edema involving the upper arm, satellite lesions within 2.5 cm of the vaccination site, local lymphadenopathy, intense inflammation or viral cellulitis surrounding the inoculation site, and viral lymphangitis tracking to axillary lymph nodes. In clinical trials, these reactions were self-limited and required only symptomatic treatment.⁹

Autoinoculation is another cutaneous reaction that can occur because Dryvax and ACAM2000 both contain live-attenuated replicating vaccinia virus. Accidental implantation may occur when the high titers of virus present at the vaccine site are subsequently transferred to other sites, especially abnormal mucosa or skin, resulting in an additional primary inoculation site.¹⁰

Eczema vaccinatum is a potentially life-threatening reaction that may occur in patients with disruptive skin disorders, such as atopic dermatitis. These patients are at risk for massive confluent vaccinia infection of the skin.¹⁰ In patients with atopic dermatitis, the virus rapidly disseminates due to both skin barrier dysfunction and impaired immunomodulation, resulting in large confluent skin lesions and the potential for viremia, septic shock, and death.^{10,11} Mortality from eczema vaccinatum may be reduced by administration of vaccinia immune globulin.¹⁰

The vaccinia virus also may spread hematogenously in healthy individuals,¹⁰ resulting in a benign reaction called generalized vaccinia. These patients develop pustules on areas of the skin other than the vaccination site. Although typically benign and self-limited, Beachkofsky et al⁴ described a case of generalized vaccinia in a healthy 34-year-old man resulting in a rapidly progressive vesiculopustular eruption with associated fever and pancytopenia. The patient made a complete recovery over the course of the following month.⁴

Alternatively, progressive vaccinia is a severe complication of smallpox vaccination seen in patients with

impaired cell-mediated immunity. It also is known as vaccinia gangrenosum or vaccinia necrosum. These patients develop expanding ulcers due to exaggerated viral replication and cell-to-cell spread of the vaccinia virus.^{10,11} Hematogenous spread may result in viral implantation at distant sites of the body. This disease slowly progresses over weeks to months, and it often is resistant to treatment and fatal in patients with severe T-cell deficiency.¹⁰

Acral papulovesicular eruption is a distinct cutaneous adverse event following smallpox vaccination. Although further research is needed to discern the pathogenesis of this reaction, it is benign and self-limited, and patients have fully recovered with supportive care. In addition, a modified vaccinia Ankara vaccine (Bavarian Nordic) was approved by the US Food and Drug Administration in 2019.^{12,13} It is a nonreplicating attenuated viral vaccine that had fewer adverse events compared to ACAM2000 in clinical trials.¹³ To date, papulovesicular eruptions have not been reported following vaccination with the modified vaccinia Ankara vaccine; however, continued monitoring will help to further characterize any cutaneous reactions to this newer vaccine.

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