Focal and Generalized Folliculitis Following Smallpox Vaccination Among Vaccinia-Naive Recipients

Thomas R. Talbot, MD, MPH
H. Keipp Bredenberg, MD
Michael Smith, MD
Bonnie J. LaFleur, PhD
Alan Boyd, MD
Kathryn M. Edwards, MD

ADVERSE DERMATOLOGIC REACTIONS after smallpox vaccine administration, including eczema vaccinatum and progressive vaccinia, were well described when smallpox vaccination was routine practice.1 While these reactions were rare, they were associated with significant morbidity and occasional mortality. Other less severe dermatologic reactions to smallpox vaccine also were reported, including generalized vaccinia2 and erythema multiforme.3

During a clinical trial investigating the efficacy and safety of vaccinia immunization in healthy, vaccinia-naive adult volunteers, (ie, those not previously vaccinated) we observed a papulovesicular eruption following vaccination in several volunteers that mirrored generalized vaccinia on initial inspection. While cases were initially identified as generalized rashes, with a heightened awareness to this eruption, cases of focal variants were noted as the trial progressed. To further define the focal eruption to and contrast it with generalized vaccinia, we reviewed the cases in our cohort and outlined the clinical, virologic, and histopathological characteristics of this eruption.

METHODS

Study Participants

After providing written informed consent, healthy, vaccinia-naive adult participants aged 18 years to 32 years were enrolled in a multicenter, double-blind, randomized controlled trial that was investigating the safety and efficacy of 3 dilutions of smallpox vaccine.

Context With the reintroduction of smallpox vaccination, detailed contemporary descriptions of adverse reactions to the vaccine are needed to adequately inform the public and clinicians. During a multicenter, randomized controlled trial investigating the efficacy of various dilutions of smallpox vaccine, we observed the appearance of a papulovesicular eruption (focal and generalized) in study volunteers.

Objective To characterize the papulovesicular eruptions by clinical, virologic, and histopathological characteristics.

Design, Setting, and Participants Prospective case series of papulovesicular eruptions following smallpox vaccination in healthy, vaccinia-naive adult participants compared with noncases conducted from October 2002 to March 2003. Variables potentially related to these eruptions were collected retrospectively through chart review. Eruptions were described based on viral culture, clinical examination, and histopathological evaluation (1 biopsy specimen from 1 case).

Main Outcome Measure Cases of papulovesicular eruptions following vaccination.

Results During the trial, of 148 volunteers (56% women; mean age 23.6 years), 4 participants (2.7%) developed generalized eruptions and 11 (7.4%) noted focal eruptions. Viral cultures of sample lesions were negative for vaccinia. The result of a skin biopsy sample from 1 case of generalized rash revealed suppurative folliculitis without evidence of viral infection. All lesions resolved without scarring. In the cohort, cases and noncases did not show significant differences in terms of sex, in the use of nonsteroidal anti-inflammatory drugs or oral or depo contraceptives, in medication allergies, in the incidence of fever or lymphadenopathy after vaccination, or in the dilution of vaccine received.

Conclusions Folliculitis is a common and benign eruption observed in vaccinia-naive adult volunteers following smallpox vaccination. This eruption may be seen in volunteers receiving the vaccine in the newly instituted vaccination programs and may be met with heightened anxiety, potentially being confused with generalized vaccinia. This description of folliculitis using clinical, virologic, and histopathological findings should allay these concerns and provide additional insight into this eruption.
(Aventis Pasteur Smallpox Vaccine, Swiftwater, Pa). Exclusion criteria for eligibility to participate in this clinical trial and to receive smallpox vaccine are noted in the Box. Approval for the trial was granted by the Vanderbilt University institutional review board.

Vaccination Methods and Follow-up
Eligible participants were randomized to receive 1 of 3 dilutions of the vaccine (undiluted, n=49; 1:5, n=48; and 1:10, n=51 dilutions). Randomization was performed using an Internet-based program with fixed blocks of 6 assignments per block. Vaccine dilutions were performed by the study pharmacist, and vaccine doses were delivered to the study clinic in vials labeled with a dilution group number (G1, G2, or G3). Both volunteers and study personnel were blinded during the course of the study to the specific vaccine dilution associated with each group number.

The frozen vaccine was reconstituted with diluent-containing glycerin, phenol, and sterile water. The vaccine was administered to the deltoid region via scarification by 15 punctures with a bifurcated needle, and the site was covered with occlusive dressings, as described previously. Volunteers were examined every 3 to 5 days for scheduled dressing changes, assessment of response to the vaccine, and evaluation of adverse events. Volunteers were counseled on routine self-assessment for new dermatologic lesions. Baseline dermatologic examinations were performed at initial screening, but subsequent examinations occurred only after volunteer report of a cutaneous eruption. Bandages were changed until the site was deemed well-scabbed by study investigators, usually several weeks after vaccination.

Culture Collection and Methods
Specimens from eruptions were cultured for vaccinia virus using methods described previously. Briefly, specimens were placed into viral transport media and frozen at −70°C for batch processing. After thawing, 0.2 mL of each specimen was inoculated onto BSC-40 cells and incubated at 37°C. Uninfected BSC-40 cells were used as controls. The presence of the distinctive cytopathic effect of vaccinia was assessed every 48 to 72 hours for 10 days. Specimens considered positive for vaccinia were those that developed cytopathic effect, while those without cytopathic effect at 10 days were considered negative for vaccinia. Polymerase chain reaction for vaccinia virus was not available for confirmation of culture data.

Case Ascertainment
Cases were prospectively defined as volunteers who developed a focal or generalized papulovesicular rash distant from the vaccination site during the month following vaccination. Noncases did not develop these findings.

Risk Factor Assessment and Analysis
Variables potentially related to a focal or generalized papulovesicular rash were collected retrospectively for both cases and noncases via chart review and included concurrent medications (oral or depot contraceptives, nonsteroidal anti-inflammatory medications), medication allergies, the presence of fever or lymphadenopathy after vaccination (surrogate markers of systemic and local immune response), and vaccine dilution group number. Continuous variables were compared between cases and noncases using the Fisher exact test; age was compared using the Student t test with unequal variances.

The statistical analysis was performed using STATA version 7.0 (Stata Corp, College Station, Tex).

RESULTS
At the Vanderbilt site, 148 volunteers underwent smallpox vaccination. The mean age of the cohort was 23.6 years; 56% of the group were women. All participants completed follow-up. Four participants (2.7%) developed a generalized papulovesicular reaction following vaccination with onset between 9 and 11 days postvaccination. The eruption was observed on several body sites, including the face, torso, and extremities. The lesions began as follicular erythematous papules that progressed into pustules, which eventually resolved without scarring. Concurrent lesions were at different stages...
of development. All 4 participants were afebrile at the time of the eruption.

In an additional 11 participants (7.4%), focal eruptions that were morphologically similar to the generalized lesions were noted. These eruptions occurred on various body sites away from the primary vaccination site, including the face, neck, back, and extremities. Ten of these cases were afebrile throughout the postvaccination course. One individual developed fever on day 6 post-vaccination, 2 days before rash onset. All rashes resolved without scarring.

**Report of a Case**

A 20-year-old man presented 10 days after vaccination with a 2-day history of “worsening acne” and “ingrown hairs” on his leg. He noted an acneiform rash along his beard line as well as several nontender, nonpruritic papules on his legs. He denied fevers, chills, or other systemic symptoms. He denied use of any new medications except ibuprofen and naproxen taken after vaccination. He was afebrile (98.6°F [37°C]) and did not appear ill. His mucous membranes were without abnormalities. His vaccination site measured 17mm in diameter with 135 mm of surrounding skin showing erythema and associated induration. Dermatologic examination revealed numerous follicular papules, macules, and pustules in different stages of develop-

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**Figure 1. Examples of Acneiform Eruption From Reported Case of Generalized Rash**

A. Lesions along beard line. B. Follicular lesion on left thigh.

**Figure 2. Histopathological Sections of a Skin Biopsy Sample of a Lesion Taken From the Back of Reported Case With Generalized Rash**

A. Within the dermis is an inflammatory infiltrate intimately involving a pilosebaceous structure. Note the sparing of the epidermis and adjacent dermis (original magnification ×40, hematoxylin-eosin stain). B. Enlargement of boxed area from panel A showing inflammatory infiltrate consisting of lymphocytes and neutrophils surrounding a sebaceous gland (original magnification ×100, hematoxylin-eosin stain).
ment on his chest, back, legs, face, and right axilla (FIGURE 1). The result of viral culture of 1 sample lesion was negative for vaccinia. Histopathological findings of a skin biopsy sample taken from a lesion on the back revealed a suppurative folliculitis with a neutrophil-predominant infiltrate involving pilosebaceous structures (FIGURE 2). The result of Gomori-Methenamine silver stain was negative for fungi. Histopathological changes associated with viral infection (Guarnieri inclusion bodies, ballooning keratinocyte degeneration, giant cells, dyskeratotic keratinocytes, ulceration, and dermal edema) were absent. Treatment was given to ameliorate any symptoms (eg, pain, itching), and the eruptions resolved during the next week without scarring.

Culture Analysis

Vaccinia virus was not isolated from any of the 17 lesion samples from 7 of the volunteers available for culture (4 cases with generalized rash and 3 cases with focal rash).

Risk-Factor Analysis

Cases and noncases were not significantly different in terms of their sex, in the use of nonsteroidal anti-inflammatory drug or oral or depo contraceptives, in medication allergies, in vaccine dilution group, and in incidence of fever or lymphadenopathy. Cases were significantly younger than noncases (mean age 22.2 years vs 23.7 years, \(P = .03\)).

**COMMENT**

Serious cutaneous adverse reactions after smallpox vaccination have been described\(^1\) and, while rare, are associated with significant morbidity and some mortality. Vaccinia necrosum, usually seen in patients who have immunodeficiencies, begins as a necrotic lesion that relentlessly progresses to systemic infection and death. Eczema vaccinatum occurs in individuals with eczema (active or quiescent) and may lead to disseminated disease with extensive scarring and, rarely, death. Other less-severe, self-limited cutaneous reactions due to smallpox vaccination also have been described, including an erythematous urticarial reaction in primary vaccinees,\(^7\) mild forms of erythema multiforme,\(^2\) and generalized vaccinia, which appears 6 to 9 days after vaccination and has lesions similar in appearance to those at the vaccination site.\(^2\)

We describe folliculitis following smallpox vaccination, another eruption that should be added to this list of cutaneous complications. While benign in our cohort, this eruption may be initially confused with generalized vaccinia, because of morphological characteristics of the lesions and the generalized distribution in some cases. Folliculitis following smallpox vaccination appears distinct from earlier descriptions of generalized vaccinia. The lesions of folliculitis exhibit neutrophil-predominant follicular inflammation without histopathological evidence of viral infection, develop in different stages (unlike generalized vaccinia), and do not scar after healing (TABLE). Mild forms of generalized vaccinia\(^1,2\) have been previously described and may represent the folliculitis observed in our study, although the vaccine type administered in these cases may have differed from the vaccine used in our study (Aventis Pasteur smallpox vaccine).

In this study, most cases of folliculitis following smallpox vaccination occurred at the time of maximal viral replication and local inflammatory symptoms, suggesting that the pathophysiology of this eruption may be explained by the host response to vaccination and its accompanying inflammatory reaction. Similar eruptions related to drug- and viral exposures have been reported. Acute generalized exantheme supravaccinal, a generalized pustular rash associated with fever and histopathological results showing leukocytosis and supplicative dermal pustules, has been associated with drug and viral-induced T-cell activation and an increase in IL-8 production.\(^14,15\) Our study cohort comprised healthy adults who could be expected to mount a robust immune response to exposed antigens, and the substantial incidence of folliculitis seen in our study may reflect a vigorous immune response to the vaccine. In contrast to the children immunized with vaccinia virus when vaccination was routine practice, the primary vaccinees in the current study are older and may represent slightly different hosts. For example, prepubertal children have lim-

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**Table. Comparison of Classic Generalized Vaccinia and Folliculitis Following Smallpox Vaccination**

<table>
<thead>
<tr>
<th></th>
<th>Generalized Vaccinia(^2,3,8-13)</th>
<th>Folliculitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time of onset</td>
<td>5-10 d after vaccination, usually in primary vaccinees</td>
<td>8-10 d after vaccination</td>
</tr>
<tr>
<td>Location</td>
<td>Anywhere on the body (including palms and soles)</td>
<td>Greater in areas with larger numbers of hair follicles (eg, extremities, face) or sebaceous glands (eg, back)</td>
</tr>
<tr>
<td>Multiphase or monotonous</td>
<td>Monotonous</td>
<td>Multiphase</td>
</tr>
<tr>
<td>Duration</td>
<td>Days and, rarely, months</td>
<td>3-5 d</td>
</tr>
<tr>
<td>Presence of fever and/or chills</td>
<td>Rare</td>
<td>Rare</td>
</tr>
<tr>
<td>Presence of regional lymphadenopathy</td>
<td>Rare</td>
<td>None</td>
</tr>
<tr>
<td>Malaise</td>
<td>Rare</td>
<td>Rare</td>
</tr>
<tr>
<td>Local pruritus</td>
<td>Not reported</td>
<td>Occasional</td>
</tr>
<tr>
<td>Isolation of vaccinia</td>
<td>Yes with severe disease</td>
<td>No</td>
</tr>
<tr>
<td>Histopathological results of lesions</td>
<td>Guarnieri inclusion bodies, keratinocyte degeneration, acanthosis</td>
<td>Suppurative folliculitis</td>
</tr>
<tr>
<td>Progression</td>
<td>Self-limited in immunocompetent hosts; systemic illness in some compromised hosts</td>
<td>Complete resolution</td>
</tr>
<tr>
<td>Residual scarring</td>
<td>With severe disease</td>
<td>None</td>
</tr>
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Focal and Generalized Folliculitis Following Smallpox Vaccination

This high rate of presumed folliculitis following smallpox vaccination has clinical importance, especially in the setting of larger-scale vaccination. Early reports from the current military and civilian vaccination campaigns have separately highlighted individuals who developed a pustular rash approximately 10 days after vaccination that was classified as “generalized vaccinia.” These eruptions also may represent folliculitis following smallpox vaccination. While these individuals received a different formulation of vaccinia (New York City Board of Health strain, Dryvax, Wyeth Laboratories, Marietta, Pa) than that administered in our trial, it was derived from the same strain of vaccinia virus and might be expected to have similar adverse events. In addition, a recent clinical trial investigating the New York City Board of Health strain of smallpox vaccine noted the development of a papular rash that appears very similar to folliculitis following smallpox vaccination.

While folliculitis following vaccination resolved fully in our volunteers, required no specific interventions, and showed no apparent residual sequelae, the concern caused by this eruption on the part of the participants and the clinicians was substantial. The potential for misinformation and concern about skin eruptions following smallpox vaccination are important issues. It is hoped that this report will help educate clinicians, reduce anxiety, and provide reassurance to the medical community.

REFERENCES