

Adverse Events Following Smallpox Vaccination With ACAM2000 in a Military Population

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Background: Generalized vaccinia and benign exanthems are 2 adverse events that have been associated with the smallpox vaccination. Accurate incidence and prevalence rates of each are not readily available, but these events are thought to be uncommon. To our knowledge, this is the first case series to provide clinical as well as pathologic descriptions of multiple papulovesicular eruptions occurring after receiving the second-generation smallpox vaccine, ACAM2000 (Acambis, Canton, Massachusetts), among a vaccinia-naïve military population. In addition, we report the first confirmed case, to our knowledge, of generalized vaccinia following administration of the ACAM2000 vaccine.

Observations: All patients received primary smallpox immunization as well as 1 to 3 concurrent or near-concurrent (within the preceding 21 days) immunizations for typhoid, anthrax, hepatitis B, and/or seasonal influenza. One patient presented with a flulike prodrome and diffuse vesicopustules covering the face, neck, chest, back, and upper and lower extremities. Vaccinia

polymerase chain reaction confirmed generalized vaccinia. The remaining 7 patients presented with unusual, painful, and pruritic papulovesicular eruptions occurring on the extensor surfaces of their upper and lower extremities without systemic symptoms. Histologic findings revealed 2 general patterns, including a dermal hypersensitivity reaction with lymphocytic vasculitis and a vesicular spongiotic dermatitis with eosinophils.

Conclusions: We present the first confirmed case of generalized vaccinia following immunization with the second-generation smallpox vaccine ACAM2000. In addition, we describe 7 cases of benign, acral, papulovesicular eruptions thought to be associated with ACAM2000 administration. Further research is needed to discern the pathogenesis of these benign eruptions as well as their incidence and prevalence and that of generalized vaccinia with ACAM2000.

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OWING TO THE ONGOING threat of bioterrorism, limited vaccine supply availability, and unfavorable production methods for the older smallpox vaccine, Dryvax (Wyeth Pharmaceutical Inc, Philadelphia, Pennsylvania), a new smallpox vaccine, was developed. ACAM2000 (Acambis, Canton, Massachusetts), the successor of Dryvax, was developed via a clone from the Dryvax vaccine that was plaque purified and amplified in cell culture.¹ After clinical trials, the US Food and Drug Administration approved ACAM2000 in August 2007 for people at high risk for smallpox exposure, and the US military completely transitioned to using the new vaccine by February 2008.^{2,3} It was found to be similar in safety and efficacy to Dryvax, based on non-clinical and clinical trials.⁴ Serious adverse events (SAEs) were observed in less than 1% of the 2983 patients vaccinated during clinical trials. Reported SAEs included myocarditis, pericarditis, atrial fibrillation, atypical chest pain, coronary artery disease,

pregnancy, and seizure. No other SAEs historically associated with the smallpox vaccine were observed, including generalized vaccinia (GV), ocular vaccinia, postvaccinia encephalitis, progressive vaccinia, erythema multiforme, or eczema vaccinatum.

Generalized vaccinia and benign cutaneous eruptions are known adverse events following immunization with the old smallpox vaccine, Dryvax. The incidence of GV is unknown; however, it is thought to be a rare adverse event that has often been overreported owing to lack of adherence to the guidelines required for diagnosis.^{5,6} Lesions typically occur within a week of vaccination and evolve from vesicles to pustules to scars.⁵ Typically, cases are self-limited and resolve without specific intervention and the use of vaccinia immune globulin is not indicated.

Clinical descriptions of the varied cutaneous morphologic reactions from previous cases noted following the use of Dryvax include exanthematous, urticarial, morbilliform, vesicular, pustular, and Stevens Johnson–like syndrome.⁵⁻⁸ Re-

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ports from the 1960s note that most benign eruptions tend to occur 4 to 10 days after vaccination.^{9,10} However, more recent reports describe eruptions occurring as late as 12 to 19 days following vaccination.^{8,11,12} The clearance time for these benign eruptions varies widely in the literature. Early data suggested resolution within 2 to 4 days^{11,13}; however, subsequent studies report a delay of 10 to 20 days.^{11,12} No specific treatment is required, although antihistamines, nonsteroidal anti-inflammatory drugs (NSAIDs), and topical or oral steroids have been reported to provide some degree of symptomatic relief. Vaccinia immune globulin is not recommended as treatment for these cutaneous reactions.⁶

METHODS

We reviewed 8 cases of cutaneous reactions that occurred following smallpox vaccination with ACAM2000 that took place from July 2008 through July 2009. During that time, more than 150 000 members of the US military were vaccinated (data from T. Vactor, June 17, 2009, contained in an e-mail forwarded from M. Hartshorn, MSHP, CMPE, on June 18, 2009). Patients were identified through multiple sources within Wilford Hall Medical Center, Lackland Air Force Base, Texas, to include the Vaccine Healthcare Center (2 cases), emergency department (2 cases), and pathology department (1 case). Additional cases throughout the military were identified using the Army Medical Department teledermatology system (3 cases). A dermatologist (C.M.H.) was involved in the immediate care (either directly or via the teledermatology system) of all patients. Clinical photographs were taken of all but 1 patient, and at least 1 punch or shave biopsy specimen was obtained from each patient. Laboratory studies were neither standardized nor consistent among patients; however, studies included the following: vaccinia polymerase chain reaction (PCR), viral culture, bacterial culture, IgG/IgM assays for Varicella zoster virus (VZV), and IgG assays for herpes simplex virus (HSV) 1 and 2. All specimens were examined by the same dermatopathologist with hematoxylin-eosin staining, while a few were additionally analyzed with Giemsa, Fite method, and Tzanck stains. Immunohistochemical analysis for various substrates, including C3, C5b-9, fibrinogen, IgG, IgM, IgA, HSV, and VZV were also performed in select cases.

REPORT OF A CASE

GENERALIZED VACCINIA

A 34-year-old man who was negative for the human immunodeficiency virus with an otherwise benign medical history received his initial anthrax, typhoid, and hepatitis B immunizations along with the seasonal influenza immunization on April 23, 2009, and subsequently received his primary smallpox vaccination with ACAM2000 per the manufacturers' instructions 6 days later on April 29, 2009. On postvaccination day (PVD) 11, the patient developed headache, dizziness, shortness of breath, decreased appetite, and fatigue and subsequently presented to the medical clinic the following day (PVD 12) with similar symptoms. He was diagnosed as having pharyngitis and given a prescription for azithromycin, guaifenesin, nasal saline solution, and loratadine. That evening the patient presented to the emergency department with pain, swelling, ery-

thema of his right knee, and the development of a small erythematous-based pustule in his right axilla and left groin. He was diagnosed as having cellulitis of his right knee and was prescribed trimethoprim-sulfamethoxazole and clindamycin. The following day (PVD 13) the patient was seen in clinic for follow-up and noted to have a heart rate of 110 beats per minute, a temperature of 101.7°F, and was experiencing pain at a level of 7 on a 10-point scale. Findings from a skin examination were documented as unchanged. Subsequently, the patient was sent home with acetaminophen for treatment of his fever.

The following day (PVD 14) the patient was seen in the emergency department with subsequent development of generalized pustules on his scalp, trunk, and upper and lower extremities. He was then started on intravenous clindamycin and vancomycin and transferred to the intensive care unit (ICU) (on PVD 15) for further monitoring and treatment of GV and cellulitis. At that time, the dermatology consultant noted that all lesions were in a similar morphologic state (J. Schwartz, D.O., oral communication [telephone], July 9, 2009). Laboratory evaluation revealed a nonspecific elevation in inflammatory markers (erythrocyte sedimentation rate, C-reactive protein) and pancytopenia that was attributed to viral bone marrow suppression. The following day (PVD 16, ICU day 2) the patient was noted to have the interval development of a vesicle on his left ulnar, distal upper extremity and subsequent resolution of the right knee erythema, induration, warmth, and tenderness.

Laboratory studies, including blood and a wound cultures from a representative distal lesion, were negative for bacterial growth. A viral culture from a representative distal lesion yielded a nonspecified virus that was negative on direct fluorescent antibody testing for the following: adenovirus, influenza virus, parainfluenza virus, respiratory syncytial virus, HSV, VZV, and cytomegalovirus. Initial vaccinia PCR testing at Brook Army Medical Center confirmed the presence of vaccinia virus, which was later confirmed by the Pox Virus Branch at the Centers for Disease Control and Prevention. A punch biopsy specimen from a vesicle on the right wrist revealed superficial epidermal necrosis with a mixed pustular/vesicular spongiotic dermatitis, including scattered neutrophils and eosinophils (**Figure 1**).

Owing to the patient's overall clinical improvement, he was discharged to his home on (PVD 16) with a 2-week prescription of clindamycin for continued treatment of his right lower extremity cellulitis. He was given strict contact precautions and scheduled to follow up with the consulting infectious disease physician as an outpatient.

On PVD 28 the patient was seen in outpatient follow-up by the department of infectious disease and was noted to have complete resolution of his right lower extremity cellulitis and vesiculopustular eruption, with the exception of the smallpox immunization site, which was described as ulcerated with crusting. On PVD 44, the patient was further evaluated by outpatient hematology and oncology departments owing to ongoing pancytopenia. At that time, it was noted that his pancytopenia was resolving and likely secondary to GV and that he would not require reevaluation by hematology unless his complete blood cell counts did not return to normal within

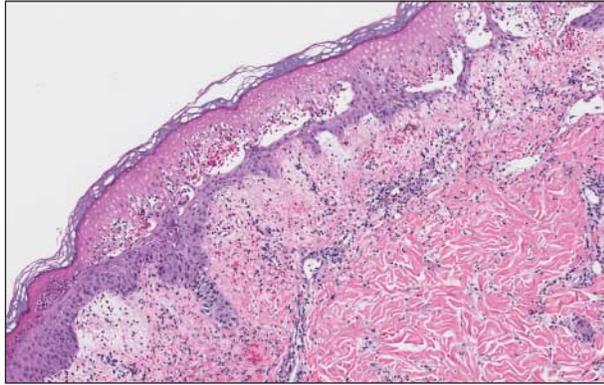


Figure 1. A punch biopsy specimen from a vesicle on the right wrist of a patient with generalized vaccinia. Hematoxylin-eosin staining and examination at original magnification $\times 10$ revealed superficial epidermal necrosis with a mixed pustular/vesicular spongiotic dermatitis, including scattered neutrophils and eosinophils.

4 to 6 months. The patient is currently deployed to a remote location with follow-up immunologic and hematologic evaluations planned on his return.

REPRESENTATIVE CASE OF A PAINFUL AND PRURITIC PAPULOVESICULAR ERUPTION

A 22-year-old Asian American woman with a medical history of human papilloma virus cervicitis but who was otherwise presumed to be previously healthy received her primary smallpox vaccination with ACAM2000 (Acambis) per the manufacturer's instructions along with anthrax (series 3) on July 29, 2008. On PVD 16, the patient developed a skin eruption that was described on August 18, 2008 (PVD 20), as the following: 15 to 20 vesicles, 1 to 4 mm in size, over both knee extensors, and 30 to 40 vesicles on palmar and dorsal surfaces of the hands, especially on the fingers, 15 to 20 vesicles along right arm and over the elbow extensor, and 7 to 10 vesicles on the dorsolateral surfaces of each foot, sparing the soles. The patient also had a few lesions on her lips, ear, and scalp. A 10×6 -mm erosion with crust was noted on the left lateral proximal arm at the site of the smallpox vaccination. The lesions were described as painful and pruritic. The patient further denied any systemic symptoms or fevers. On PVD 20, a punch biopsy specimen of a vesicle on the right forearm showed a vesicular/spongiotic dermatitis with eosinophils (**Figure 2A**). Further diagnostics included negative viral and bacterial cultures as well as a negative vaccinia PCR and negative direct immunofluorescent studies for VZV and HSV. The patient was initially treated with diphenhydramine, acetaminophen-oxycodone, ibuprofen, and a 7-day course of valacyclovir hydrochloride and flucaninonide topical cream, 0.05%. On PVD 23 the patient did not have any new lesions; however, she had worsening erythema at the vesicle bases (**Figure 3**) and was started on a 4-day burst of prednisone, 60 mg/d. After completing the burst (PVD 27), the patient's lesions were shrinking, drying up, and healing, and she further denied pruritus or pain (**Figure 4**). Despite continued resolution of her lesions (**Figure 5**), she experienced a recurrence of her symptoms and noted the eruption of 2 new vesicles on PVD 34 that subsequently resolved following a 3-week steroid taper.

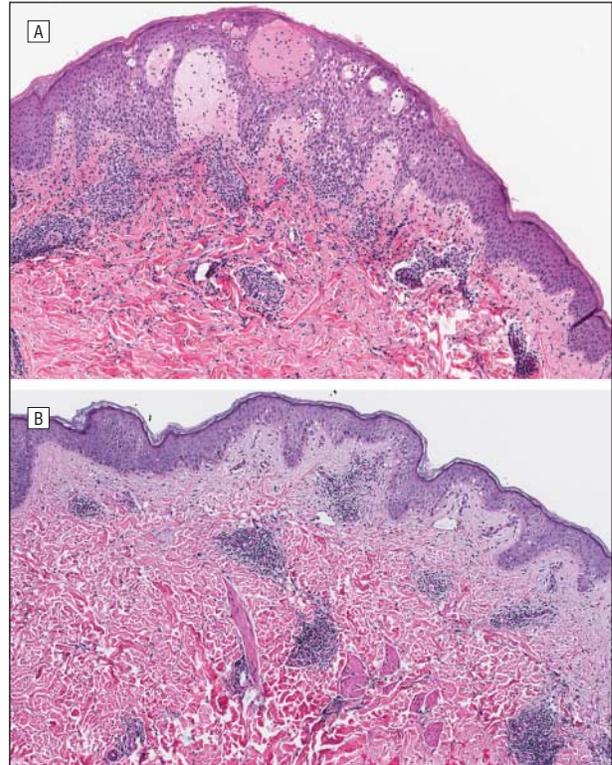


Figure 2. Punch biopsy specimens from patients with a papulovesicular eruption. Hematoxylin-eosin staining and examination at original magnification $\times 10$ revealed stereotypical histologic findings. A, Vesicular/spongiotic dermatitis with eosinophils; B, dermal hypersensitivity reaction with lymphocytic vasculitis (capillaritis).

RESULTS

All patients were young adults on active duty in the military and primary vaccinees who received ACAM2000 (per the manufacturer's guidelines). In addition, all of the patients received either concurrent or near-concurrent (within the preceding 21 days) vaccinations of a combination of typhoid, anthrax, hepatitis B virus, and influenza. Specifically, all of the patients received the anthrax immunization either concurrently or within 21 days prior to receiving the smallpox immunization. Five of the 8 patients received the typhoid vaccination either concurrently or within 21 days prior to receiving the smallpox immunization. Two patients received hepatitis B virus vaccinations either concurrently or within 6 days of receiving the smallpox immunization, and 1 patient received the influenza vaccination 6 days prior to receiving the smallpox immunization. None of the patients reported any acute illnesses prior to immunization. A few patients had preexisting medical conditions, including hypertension and depression. None of the patients reported any contact with sick persons or previous adverse events following prior immunizations.

Of the more than 150 000 military members who received the ACAM2000 smallpox vaccine between July 2008 and July 2009, we observed 8 cases of adverse cutaneous eruptions following immunization. One case revealed a patient who presented with flulike symptoms and on PVD 11 subsequently developed a diffuse rapidly progressing vesiculopustular eruption. The patient had a brief, unevent-



Figure 3. A 22-year-old woman with a painful and pruritic papulovesicular eruption involving her hands and knees. Hands and knees (A) and close-up of left hand (B) on postvaccination day (PVD) 23 showed increasing perivesicular erythema following 3 days (PVDs 20-23) of fluocinonide topical cream, 0.05%.



Figure 4. Left hand of same patient in Figure 3 on postvaccination day (PVD) 27 following a 4-day (PVDs 24-27) treatment course with prednisone, 60 mg/d, revealing regressing papules and macules with decreased erythema.

ful hospitalization, and the eruption subsequently cleared within 14 days. Vaccinia PCR of a swab from a distant biopsy site confirmed the diagnosis of GV, and the biopsy specimen revealed a mixed pattern of spongiotic dermatitis with neutrophils and eosinophils.

The remaining 7 cases revealed patients who developed dramatic, pruritic, and painful papulovesicular/bullous eruptions that were located predominantly over the extensor surfaces of the upper and lower extremities without any systemic symptoms. The eruptions occurred on PVDs 10 to 18 and resolved within 14 to 71 days. As stated in the "Methods" section, diagnostic tests were not con-

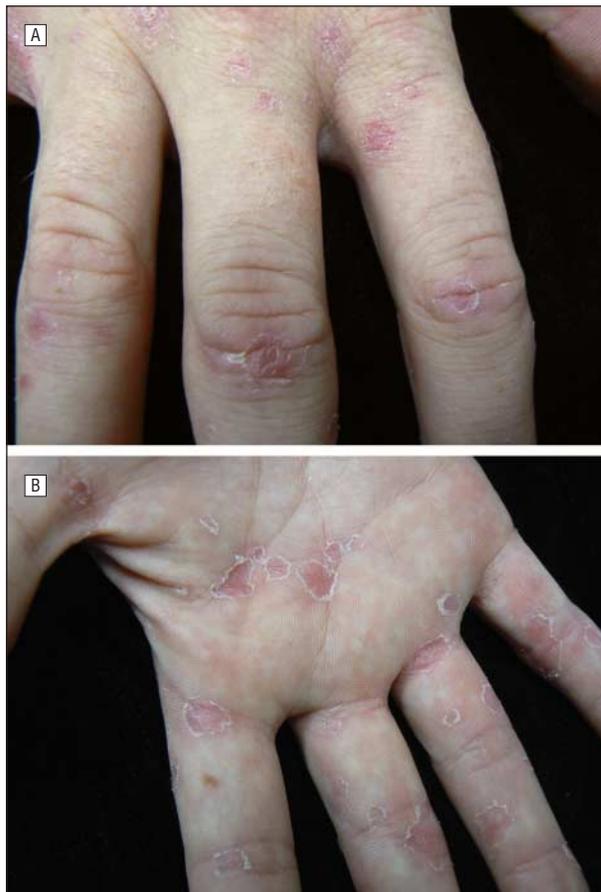


Figure 5. A resolving painful and pruritic papulovesicular eruption involving the hands of the patient from Figure 3. A, Dorsal view of the right hand on postvaccination day 35 showed continued healing as lesions flattened into erythematous macules with circumferential scale. B, Palm of the right hand.

sistently obtained; however, all patients did undergo at least 1 biopsy, and photographs were taken of all of the patients. Biopsy findings revealed 2 nonspecific patterns, including 4 cases of epidermal vesicle formation and spongiosis with superficial dermal eosinophils (Figure 2A) and 3 cases of a dermal hypersensitivity reaction with lymphocytic vasculitis (capillaritis) (Figure 2B). All patients required some form of pharmacotherapy for symptomatic relief to include oral and topical steroids, antihistamines, NSAIDs, and antibiotics. Specifically, 6 patients required oral steroid tapers using prednisone (range, 5 days to 3 weeks), and 2 patients experienced relapses of their eruptions when they completed and/or stopped their steroid tapers and subsequently required prolonged treatment. No patients received vaccinia immune globulin. **Table 1** provides a summary of individual patient clinical and pathologic data as well as vaccinia PCR result when available.

COMMENT

We describe 2 uncommon adverse events following immunization with ACAM2000, a case of GV, believed to be the first confirmed case in 6 years and the first among patients receiving ACAM2000, and 6 cases of an acral, vesiculopustular dermatosis. Currently, there is a lack of data in the literature to accurately calculate incidence and preva-

Table 1. Demographic, Clinical, Pathologic, and Vaccinia Polymerase Chain Reaction (PCR) Data of Patients Experiencing Papulovesicular Eruptions After Smallpox Vaccination With ACAM2000^a

Patient No./Sex/Age, y	Interval Between Inoculation and Eruption, d	Length of Eruption Until Clearance, d	Gross Morphologic Findings	Histologic Characteristics	Vaccinia PCR
1/F/22 ^b	16	44	Papulovesicles on hands, elbows, knees, feet	Vesicles with a spongiotic dermatitis and eosinophils	Nonreactive
2/F/32	17	71	Vesicobullous on hands, elbows, knees, feet	Vesicles with a spongiotic dermatitis and eosinophils	Nonreactive
3/M/22	18	21	Papules on hands	Spongiotic dermatitis and eosinophils	NA
4/M/25	10	53	Plaques on shoulder, elbow	Dermal hypersensitivity reaction with lymphocytic vasculitis (capillaritis)	Nonreactive
5/M/22	15	32	Papules on hands, elbow	Dermal hypersensitivity reaction with lymphocytic vasculitis (capillaritis)	Nonreactive
6/M/19	16	15	Papules, plaques on hands, elbows, knees	Vesicles with a spongiotic dermatitis and eosinophils	NA
7/M/26	13	11	Papules on hands, elbow	Lymphocytic vasculitis with spongiotic dermatitis (capillaritis vs dermal hypersensitivity)	Nonreactive
8/M/34 ^c	11	14	Vesicopustules on scalp, axilla, trunk, arms, legs	Mixed pattern with predominantly pustule/vesicle formation and spongiotic dermatitis with neutrophils and eosinophils	Positive

Abbreviation: NA, not applicable.

^aAcambis, Canton, Massachusetts.

^bPatient is currently deployed to a military location and not available for follow-up.

^cPatient with generalized vaccinia.

Table 2. Comparison of Generalized Vaccinia (GV) and the Benign Papulovesicular Eruptions Observed in This Case Series^a

Diagnosis	Etiology	Time of Onset	Clinical Manifestations	Laboratory Finding	Treatment	Contributing Factors
GV	Vaccinia viremia	Typically within 7 d of vaccination	Vesicles and/or pustules at 4 sites separate from the vaccination	Confirmation of vaccinia virus in the blood or lesions other than the vaccination site	Supportive therapy, consider vaccinia immune globulin for extensive disease	Immunodeficiency
Acral, papulovesicular eruption	Unknown	10-18 d postvaccination	Erythematous papules and vesicles located over acral extensor surfaces	Nonspecific	Supportive therapy, consider oral glucocorticoid taper if GV is unlikely	Unknown; however, concurrent immunization may be contributory

^aSee Fulginiti et al⁵ and Beigel et al.¹⁴

lence statistics for such uncommon events; however, postlicensure trials will hopefully help elucidate these figures. A causal relationship cannot be definitively proven; however, we feel that the cases presented herein are due in part, if not wholly, to the smallpox vaccination the patients received. Although covaccination with anthrax, typhoid, hepatitis B, and influenza may have played a contributory role, we believe these reactions are more likely related to the smallpox vaccine because similar yet less dramatic cutaneous reactions have been previously reported with Dryvax immunization. While these reactions could be due to one of the other coadministered vaccines such as anthrax, the anthrax vaccine, alone or in combination with other vaccines, is not known to produce this type of adverse reaction.

Benign cutaneous eruptions following vaccination with ACAM2000 were poorly defined during clinical trials, but benign rashes following smallpox vaccination are not uncommon and have been previously described elsewhere. Studies from the 1960s most commonly discuss rare cases of generalized maculopapular rashes that occur around

PVD 7.^{9,10} More recently, controlled studies using different formulations and dosages of early-generation smallpox vaccines have been conducted. Greenberg et al¹² described multiple benign and self-limited eruptions, including urticaria, exanthems, and folliculitis, that occurred during PVDs 6 to 9 and resolved within 4 to 20 days. Bessinger et al¹¹ described similar findings in which cases of urticaria, exanthems, and erythema multiforme-like reactions occurred at roughly the same interval between PVDs 7 to 11 that were clinically distinct from the acral papulovesicular lesions seen in this series. Findings from their biopsy specimens revealed similar nonspecific inflammatory changes consisting of some degree of epidermal spongiosis and a dermal perivascular lymphocytic infiltrate with scattered eosinophils. Frey et al⁸ also described similar findings of erythematous rashes and erythema multiforme as well as cases of localized and generalized vesicular eruptions. **Table 2** provides a brief comparison of GV and the acral papulovesicular eruptions described herein.

While the etiology of these acral papulovesicular eruptions remain unclear, several previously proposed hypotheses for benign skin reactions include an allergic reaction to the vaccine's "vehicle," a hypersensitivity reaction, and a mild form of GV. We propose an additional etiologic hypothesis similar to the mechanism of HSV-associated erythema multiforme, in which viral proteins have been identified within biopsy specimens of typical skin lesions.¹⁵ Although previous attempts to culture these eruptions have been unsuccessful, we are currently pursuing further work attempting to identify vaccinia protein deposits within these eruptions by testing the biopsy specimens with immunohistochemical antibodies against various vaccinia proteins.

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