Stevens-Johnson Syndrome After Immunization With Smallpox, Anthrax, and Tetanus Vaccines

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A 19-year-old male military recruit developed erythema multiforme 20 days after receiving a triad of vaccinations: smallpox (vaccinia virus), anthrax, and tetanus. Over the course of a few days, the erythema multiforme evolved into Stevens-Johnson syndrome, associated with widespread bullae, stomatitis, conjunctivitis, and fever. After 7 days of conservative management, the patient's signs and symptoms improved. This case serves as a timely reminder of a severe and potentially life-threatening complication of smallpox vaccination.

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EM = erythema multiforme; SJS = Stevens-Johnson syndrome; TEN = toxic epidermal necrolysis

Smallpox, a highly contagious illness, was declared eradicated in 1980, but recent bioterrorism concerns have renewed interest in smallpox prevention and treatment. Immunization with smallpox vaccine is effective but can produce numerous adverse reactions, ranging in severity from minor to life threatening. We describe a patient in whom Stevens-Johnson syndrome (SJS) developed after immunization with smallpox, anthrax, and tetanus vaccines.

REPORT OF A CASE

A 19-year-old male military reservist who had been immunized recently with smallpox, anthrax, and tetanus vaccines (Figure 1) in preparation for deployment to the Middle East was transferred to the Mayo Clinic in Rochester, Minn, for further evaluation of a rash and systemic symptoms. The patient had no antecedent medical or surgical conditions besides a recurrent allergic contact dermatitis with exposure to nickel, and he was taking no medications. The disease process, which developed 20 days after vaccination, began with lip vesicles (Figure 2) and pruritic papules over the dorsum of the hands. The eruption quickly became widespread, involving the knees and shins followed by dissemination to the extensor surfaces of the arms and to the chest, back, abdomen, and ears.

At the time the patient was transferred to our institution, the papules had become bullae, with confluence over the knees, dorsal aspects of the hands, and elbows (Figures 3 and 4). Macules with vesicular centers and plaques with necrotic centers were present on the extremities. The palms and soles were unaffected. The patient had painful oral ulcers, bilateral conjunctivitis, nasal erosions, myalgias, and fever (temperatures as high as 40°C).

Because of his fever and severely compromised skin integrity at the time of transfer, the patient was placed in contact isolation, broad-spectrum antibiotics were administered, and evaluation for secondary infection was initiated. Contact isolation was also instituted because of the communicable nature of some reactions to smallpox vaccination. He continued to receive valacyclovir until cultures for herpesvirus and varicella-zoster virus from multiple mucocutaneous sites yielded negative results. Findings on investigational in-house polymerase chain reaction studies for vaccinia virus from multiple bullae were also negative. Cutaneous biopsy findings were consistent with erythema multiforme (EM) (Figure 5). With supportive care consisting primarily of intravenous fluids, analgesics, and local skin and mucous membrane care, the patient improved and was discharged on hospital day 7.

DISCUSSION

Smallpox, a highly contagious illness with a 30% mortality rate, is caused by the variola virus, a member of the Poxviridae family.[1] The disease was declared eradicated in 1980,[2] but recent bioterrorism concerns have renewed interest in smallpox prevention and treatment. The only known prophylactic agent and early disease treatment is smallpox vaccine, which consists of administration of live vaccinia virus (another Poxviridae family member) via punctures with a double-tined needle into the deltoid region. Primary vaccination provides 5 to 10 years of immunity in up to 95% of people, secondary vaccination confers an additional 10 to 20 years of protection, and administration within 2 to 3 days of smallpox exposure can prevent or considerably reduce the effects of the disease.[1]

Smallpox vaccine can produce numerous adverse reactions, ranging in severity from minor to life threatening.[3] A

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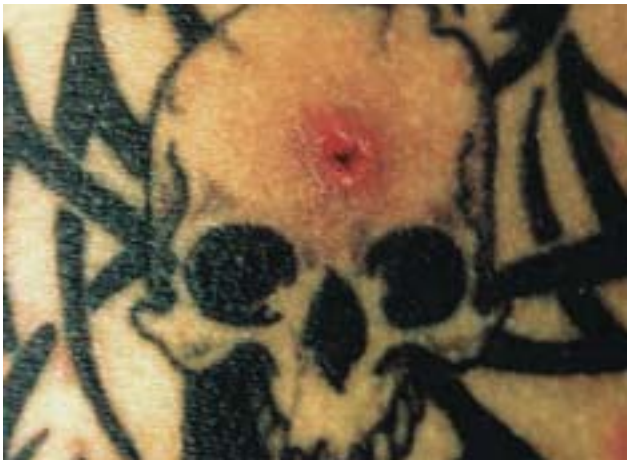

FIGURE 1. Vaccination site, left upper arm.

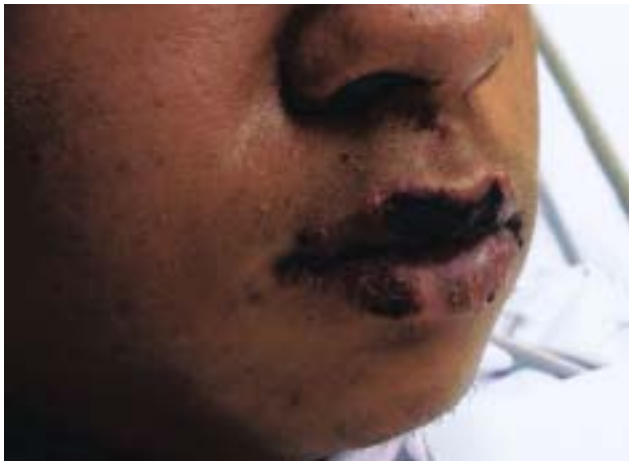

FIGURE 2. Vesicles, bullae, and crusts on patient's lips.

1968 survey of smallpox vaccination–associated complications from 10 states identified 1254 complications per 1 million primary vaccinations and 9 vaccine-related deaths.[4] Severe reactions included generalized vaccinia (self-limited generalized rash), EM, eczema vaccinatum (local or disseminated vaccinia infection), postvaccinial encephalitis, and vaccinia necrosum (progressive vaccinia).[4] The rates of these complications (number of events per million vaccinations) in primary vaccinations across all ages were 242, 165, 39, 12, and 2, respectively.[4] The rates with revaccination were much lower at 9, 9, 5, 5, and 7 events per million vaccinations, respectively. Those at greatest risk for serious complications include patients who are immunocompromised, pregnant, or younger than 4 years and, in the case of eczema vaccinatum, those with a history of eczema or atopic dermatitis.

We describe an extreme manifestation of EM in a young man 20 days after immunization with smallpox, anthrax, and tetanus vaccines. We believe that the cutaneous and systemic signs and symptoms in this patient represented SJS due to smallpox vaccination. His previous tolerance to tetanus vaccine and (to the best of our knowledge) the lack of cases of SJS after anthrax vaccination[5,6] make vaccinia virus the most likely source. The patient was taking no medications at disease onset, and no infection was identified. Although his history of allergic contact dermatitis with exposure to nickel placed him at increased risk for eczema vaccinatum, this cause was excluded by negative results of polymerase chain reaction testing and cultures from skin biopsy specimens.

The entities under the broad category of EM include EM minor and EM major, SJS, SJS-toxic epidermal necrolysis

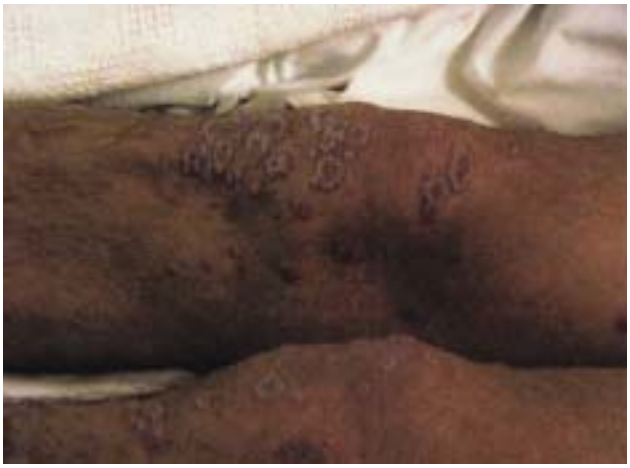

FIGURE 3. Coalescent annular bullae with pustular evolution and surrounding erythema, vesicles, and macules with central vesiculation.

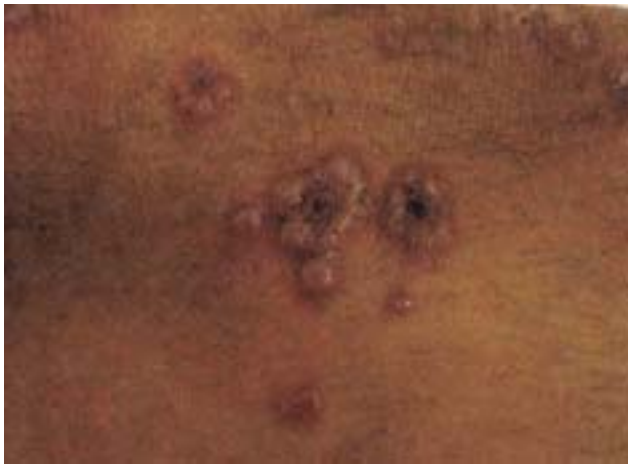

FIGURE 4. Annular bullae with central necrosis and surrounding erythema and vesicles.

(TEN) overlap, and TEN.[7] Criteria used to subcategorize these disease entities include cause, skin lesion morphology, body surface area detachment, distribution, and extent of mucosal involvement (Table 1). The characteristic target lesions of EM are acute, self-limited, rounded inflammatory skin reactions with well-defined borders, erythematous or purpuric central disks, raised edematous intermediate rings, and erythematous outer rings. Stevens-Johnson syndrome and TEN, which are most frequently associated with drug/metabolite exposure, are serious conditions because of their widespread mucocutaneous involvement that can cause difficulty with alimentation, photophobia, painful micturition, synechia formation, excessive percutaneous fluid and electrolyte losses, and bacterial superinfection. Typically with SJS and TEN, a prodrome of influenza-like symptoms precedes the mucocutaneous reaction by 1 to 3 days,[8] and the illness manifests from 1 to 3 weeks after introduction of the causative agent.[9] This time sequence fits well with our patient's history, as he noted the beginning of his reaction 20 days after vaccination.

The management of EM major, SJS, and TEN requires a multidisciplinary approach, the extent of which depends on the amount of skin integrity compromise. Aggressive fluid and electrolyte replacement, pain control, nutritional supplementation, and avoidance of bacterial superinfection with use of topical solutions and dressing changes are treatment mainstays. Surgical débridement of necrotic tissue, whirlpool therapy, artificial tears, and topical ophthalmic agents may be helpful adjuncts. Intravenous immunoglobulin, cyclophosphamide, cyclosporine, and corticosteroids are of unproven value.[10-13]

Erythema multiforme and SJS are well-documented complications of smallpox vaccination. A national survey of the complications of smallpox vaccination in 1968 identified 48 cases of EM among 572 patients with adverse reactions.[14] Nine of the 48 patients were described as having SJS-type bullous EM. The authors cautioned that the national surveillance data were biased toward the most severe complications, especially postvaccinial encephalitis, vaccinia necrosum, and eczema vaccinatum, and that relatively less severe reactions may have been underrepresented by a factor of 10 or more.[14] A sister study concentrating on smallpox vaccine complications in 10 states in 1968 captured these less severe reactions, with EM accounting for 13% of all complications of primary vaccination.[4] The rate of EM associated with smallpox vaccination was 165 cases per 1 million vaccinations, much greater than the rates reported for eczema vaccinatum, postvaccinial encephalitis, and vaccinia necrosum. In a study of 938 adverse reactions to smallpox vaccinations in Australia between 1960 and 1976, 87 cases of EM (9.3% of all complications) were reported.[15] Given this body of experience, cautions about EM, bullous EM, and SJS are prominent in current governmental training materials[16] and in the

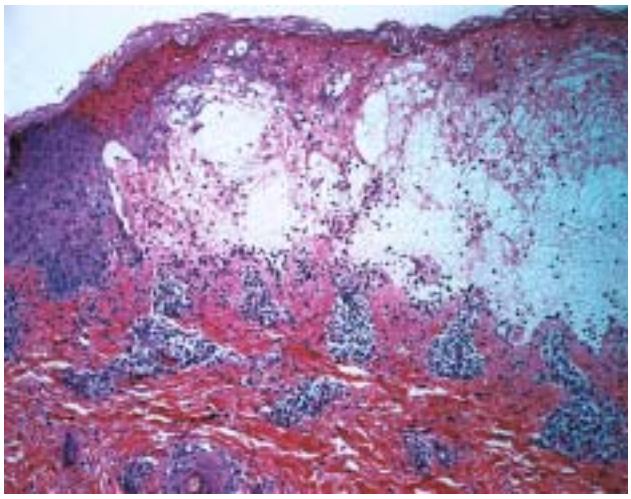

FIGURE 5. Cutaneous biopsy specimen shows full-thickness necrosis with vacuolar interface and perivascular dermatitis (hematoxylin-eosin, original magnification ×10).

TABLE 1. **Classification of the Erythema Multiforme Spectrum***

Diagnosis	Cause	Lesion morphology	Body surface area detachment	Distribution	Mucosal sites
EM minor	Typically herpes simplex or *Mycoplasma pneumoniae*	Typical targets	Usually none	Localized, symmetrical to hands, feet, and palms	0-1
EM major	Typically herpes simplex or *M pneumoniae*	Typical targets and raised atypical targets	<10%	Localized, symmetrical to hands, feet, and palms	2
SJS	Drugs/metabolites, immunologic, or combination	Macules, blisters, and flat atypical targets	≤10%	Widespread	At least 2
SJS-TEN overlap	Drugs/metabolites, immunologic, or combination	Macules, blisters, and flat atypical targets	10%-30%	Widespread	At least 2
TEN with spots	Drugs/metabolites, immunologic, or combination	Macules, blisters, and flat atypical targets	≥30%	Widespread	At least 2
TEN without spots	Drugs/metabolites, immunologic, or combination	Ill-defined erythema	≥10%	Widespread	At least 2

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algorithm developed by the Centers for Disease Control and Prevention for assessment of cutaneous smallpox vaccine reactions.[17]

Although most of the data on EM in the setting of smallpox vaccination date from the 1960s and 1970s, a recent study designed to evaluate the dilution of the smallpox vaccine reported that 2 immunized patients developed EM.[18] A review of the US military's experience with 450,293 smallpox vaccinations administered between December 13, 2002, and May 28, 2003, revealed the range of reactions to smallpox vaccine.[19] The most common symptoms were minor and included local itching (60%), muscle ache (21%), malaise (20%), and headache (18%). "Noteworthy adverse effects" included 36 cases of mild generalized vaccinia, 37 cases of acute myopericarditis, and 1 case each of EM major and postvaccinial encephalitis; no eczema vaccinatum, progressive vaccinia, or deaths were noted.[19] Most adverse events occurred at rates below historical rates. We presume that the single reported case of EM represents the patient described herein.

In summary, our patient developed a severe variant of EM (SJS) after vaccination with smallpox, anthrax, and tetanus vaccines. Based on his past immunization history (previous tolerance of tetanus vaccine) and the rarity of severe skin eruptions reported after anthrax vaccination, it is likely that the inciting agent was smallpox vaccine. This case illustrates that bullae occurring in a patient who has recently received smallpox vaccination may be an EM reaction rather than a rare vaccinia or drug reaction.

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