

Recurrent, Localized Urticaria and Erythema Multiforme: A Review and Management of Cutaneous Anthrax Vaccine–Related Events

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GOAL

To be able to effectively manage a cutaneous adverse event caused by the anthrax vaccine

OBJECTIVES

Upon completion of this activity, dermatologists and general practitioners should be able to:

1. Describe the anthrax vaccine's dosing schedule and contraindications.
2. Explain the types of anthrax vaccine–related events.
3. Discuss the management of anthrax vaccine–related events.

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The October 2001 domestic anthrax attacks affected 22 people, resulting in 5 fatalities. The added global terrorist threats have created an increasing need for homeland protection, as well as protection of our widely deployed forces battling terrorism. It is now relevant for physicians to be familiar with both clinical anthrax and adverse vaccine-related events associated with the resumption of the anthrax vaccine program.

Dermatologists played a lead role in the initial response to the anthrax attack. We must be the lead providers most familiar with the cutaneous reactions that may be seen with the preventive vaccination. This article reviews the latest recommended evaluation and management of anthrax vaccine adverse events.

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Case Reports

Patient 1—A 36-year-old white male active duty military fighter pilot developed recurrent, localized urticaria after receiving his sixth anthrax vaccination (Figure 1). Results of a skin biopsy showed a superficial perivascular dermatitis with eosinophils consistent with urticaria. The urticaria continues to recur 2½ years after his last vaccination and remains localized to the vaccinated arm.

Patient 2—A 33-year-old black male military member developed erythema multiforme one day after receiving his fifth anthrax vaccination. He had been treated for pharyngitis with a 10-day course of oral penicillin, which had been completed 2 days prior to receiving the vaccination. Target lesions were present on both arms and hands but were more prominent on the arm that received the vaccination (Figure 2). Results of a skin biopsy revealed a superficial perivascular and interface lymphocytic dermatitis, with vacuolar changes along the dermoepidermal junction compatible with erythema multiforme.

Patient 3—A 28-year-old white male military member presented with a pruritic rash that had

developed on his face approximately 12 hours after receiving his fifth anthrax vaccination. The rash had spread to his torso (Figure 3) and lower extremities. Results of a punch biopsy revealed a superficial and deep lymphocytic infiltrate with interface changes and some extravasated red blood cells, findings felt to be consistent with an erythema multiforme reaction (Figure 4). The patient was treated with a 2-week course of prednisone and intramuscular diphenhydramine (Benadryl®), and clearing of symptoms was noted within 10 days.

Comment

The threat of anthrax is deadly and real, as shown by the domestic attacks via the US Postal Service



Figure 1. Recurrent localized urticaria on the arm of patient 1.



Figure 2. Erythema multiforme on the right arm of patient 2.



Figure 3. Erythema multiforme reaction on the torso of patient 3.

in October 2001. In all, there were 11 confirmed cases of inhalation anthrax, resulting in 5 fatalities. In addition, there were 7 confirmed cases and 4 suspected cases of cutaneous anthrax. Twenty of the 22 cases were unquestionably linked to mail contaminated with a single strain of *Bacillus anthracis*.¹ Anthrax is easy and cheap to produce and can be stored for prolonged periods, with spores survivable for decades in ambient conditions.² The spores are resistant to dryness, heat, UV light, gamma radiation, and many disinfectants.³ In addition, anthrax is odorless, colorless, tasteless, and difficult to detect, thus making it a likely choice for future biological attacks. After the first gulf war, Iraq admitted to producing and deploying weaponized anthrax in missiles.⁴ The Sverdlovsk anthrax outbreak in the former Soviet Union occurred after the accidental release of aerosolized anthrax spores from a bioweapons facility and resulted in as many as 250 cases with 100 deaths.² Fortunately, we have a vaccine that has been judged safe and effective by the US Food and Drug Administration (FDA), Centers for Disease Control and Prevention, and National Academy of Sciences. Protecting the health of US military forces who defend our vital interests is a national obligation.⁵ The trade-off for force protection of our military personnel involves

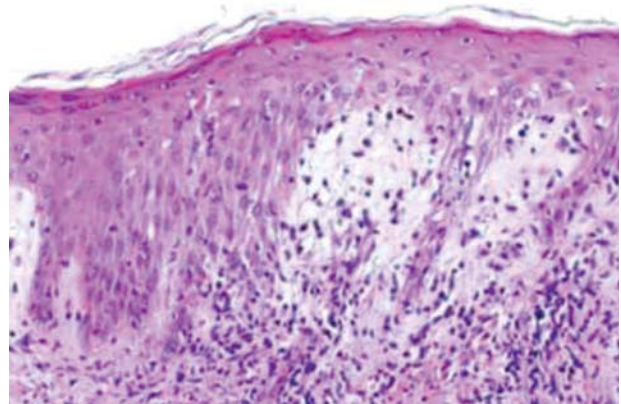


Figure 4. A superficial and deep lymphocytic infiltrate with interface changes and some extravasated red blood cells, findings felt to be consistent with an erythema multiforme reaction (patient 3)(H&E, original magnification $\times 100$). (Photograph courtesy of Col Chris P. Myers, USAMH.)

a small incidence of vaccine-related adverse events (AEs), the most common being local type injection site reactions or skin reactions.

Natural cutaneous anthrax manifests within a few days as a painless, pruritic papule that progresses to a blister and evolves to a painless ulcer, with a black central eschar and surrounding local edema. In contrast, vaccine-related events manifest differently, and the vaccine cannot cause clinical anthrax infections. An algorithm for the evaluation of suspected cutaneous anthrax has been published by the American Academy of Dermatology Ad Hoc Task Force on Bioterrorism.⁶ Additional guidelines for clinical and laboratory diagnoses, specimen handling, and postexposure prophylaxis are available from the US Centers for Disease Control and Prevention.⁷

The vaccine itself is made from a noninfectious, cell-free sterile filtrate of an attenuated, nonencapsulated, nonproteolytic strain of *B anthracis*.⁸ It is considered an inactivated vaccine and is unable to cause infection. The anthrax vaccine has been approved by the FDA since 1970 and is safely administered to veterinarians, laboratory workers, woolen mill workers, and livestock handlers.⁸ In 1997, it was mandated that all US military personnel receive it. Full protection requires a schedule of 6 injections over 18 months (specifically, at 0, 2, and 4 weeks and 6, 12, and 18 months), with an annual booster thereafter. In the event of anthrax exposure, the vaccine also can be offered as post-exposure prophylaxis with 3 doses at 2-week intervals, along with postexposure antibiotics.² Contraindications

to the anthrax vaccine include hypersensitivity reaction to a prior dose or vaccine component, human immunodeficiency virus positivity or immune suppression (active corticosteroid or other immunosuppressive treatment), any active infection or acute illness, pregnancy (confirmed or suspected), and age younger than 18 years or older than 65 years.

Efficacy and Safety

The vaccine's efficacy against aerosolized anthrax was shown in studies on nonhuman primates. Sixty-two (95%) of the 65 primates vaccinated with the anthrax vaccine adsorbed (AVA) survived a lethal aerosol challenge, whereas all 18 unvaccinated controls died.⁸ In actively monitored studies on the safety of AVA, mild local reactions occurred in 3% to 20% of doses, moderate reactions in 1% to 3% of doses, and severe reactions in less than 1% of doses.⁸ Acute systemic reactions were reported in 0.06% of doses and consisted of transient symptoms of fever, chills, nausea, and general body aches.⁸

The current system for reporting AEs is the Vaccine Adverse Event Reporting System (VAERS), and the FDA reviews 100% of these reports. In addition, a US Department of Defense directive requires its military providers to initiate a report for any event following AVA that results in hospitalization, any loss of duty of more than 24 hours, or for suspected vaccine contamination.⁹ Reporting of other reactions suspected because of vaccination is encouraged, especially those that are clinically significant or unusual. The form can be obtained on the Web at <http://www.vaers.org> or via telephone at 800-822-7967. Electronic reporting is available on the Web at <http://secure.vaers.org/VaersDataEntryintro.htm>. The VAERS is a passive surveillance system, and determining causal associations between vaccines and AEs is not always possible.¹⁰ Other concurrent infections or exposures may precipitate a given symptom that may simply coincide with the receipt of a vaccine.¹¹ For example, patient 2 may have had vaccine-associated erythema multiforme but because he had recently completed a course of penicillin, we cannot exclude the possibility of a concurrent antibiotic association.

The Anthrax Vaccine Expert Committee reviewed 602 VAERS reports filed from 1998 through 1999.¹² Nearly one half of reports noted a local injection site AE, 33% of which were noted to be moderate to large. A subcutaneous nodule was cited in 5.3% of reports. Although three fourths of reports noted a "systemic" AE, these covered a broad spectrum, with 34 types cited at a frequency of more than 1%. The most common AEs, in

declining order of incidence, were flulike symptoms, 20.8%; malaise, 13.3%; rash, 14.2%; arthralgia, 12%; headache, 10.1%; with the remainder of AEs all affecting fewer than 10% of patients. Among the reported 45 total "serious or medically important AEs," one report of each of the following was noted: systemic lupus erythematosus, angioedema, anaphylactoid reaction, and toxic epidermal necrolysis. None of these AEs were judged to be causally (defined as likely, certain, or probable) related to the vaccine itself.¹² According to Friedlander et al,⁸ the "FDA continues to view the anthrax vaccine as safe and effective for individuals at risk of exposure to anthrax."

Management of Adverse Events

Adverse reactions after vaccination can be divided into local and systemic.

Cutaneous Reactions—The cutaneous manifestations and the latest recommendations from the Walter Reed National Vaccine healthcare center network⁹ are summarized partially in Tables 1 and 2.

Local reactions involve the injection site or have contiguous spread and are graded based on the measured size of the local redness or swelling (Table 1). Most local anthrax vaccine reactions require no treatment and resolve within 72 hours, though topical or oral steroids and oral antihistamines can be used to help manage symptoms. Unless the local reaction is very large or complicated, the patient can usually proceed with subsequent doses. Although some of these reactions may mimic cellulitis, antibiotic therapy for postvaccination inflammation is not warranted. Allergy consultation is recommended for a large or complicated reaction, especially if this occurs after the second dose. In this instance, the patient may be immune (a hyperresponder) and may not require further series (with the exception of the yearly booster).⁹ When a significant local type reaction has occurred, pretreatment to help prevent future large local reactions is indicated.

Systemic Reactions—These commonly include flulike symptoms, such as fever, anorexia, nausea, arthralgia, myalgia, or malaise. Treatment of mild to moderate systemic events is symptomatic (Table 2). Pretreatment also may be given with the next vaccine in patients who have had these symptoms on prior AVA vaccinations. If symptoms are clinically consistent with serum sickness or are severe and prolonged, the patient may benefit from a short course of oral prednisone. Vaccine-related AEs may warrant temporary delay from the schedule. When resumed, this does not require starting over but rather simply continuing from the last dose.⁹

Table 1.

Localized Reactions After Vaccination⁹

Type	Treatment	Future Doses	Consultation/ Added Comments	Pretreatment
Mild, <5 cm	Reassure patient. Usually requires no treatment	Yes		Consider local steroid/ antihistamine with next vaccination, if itching is present
Moderate, 5–12 cm	Topical steroid/ antihistamine; consider oral steroid if symptoms persist or worsen	Yes		If itching predominates, pretreat with oral anti- histamine 24 h before vaccination and for 2–3 d
Large, >12 cm (simple or complicated*)	May use short course of oral steroid	Yes, temporary exemption may be warranted	Consider allergy consultation, especially if symptoms occur after second vaccination (hyperresponder)	Pretreatment with oral antihistamine; avoid simultaneous vaccinations
Sub- cutaneous nodule	Normally requires no specific therapy; may consider topical steroid, if painful	Yes, but use contra- lateral site (avoid injecting into a nodule)	Painless nodule without redness or heat usually appears within 1–2 d of injection, persisting for weeks before gradually dissipating	

*Classified as complicated if reactions result in periarticular soft tissue swelling, soreness, or stiffness.

Data are from Vaccine Healthcare Centers Network. Available at: www.vhcinfo.org.

For a generalized maculopapular rash or target lesions, a skin biopsy should be performed, especially if the rash is suggestive of early erythema multiforme, Stevens-Johnson syndrome, or toxic epidermal necrolysis. In these cases, temporary exemption from further vaccinations and VAERS reporting are indicated. The possibility exists that additional doses may result in a more serious skin reaction and should be given with caution only after expert evaluation and consideration of the risk:benefit ratio. The dermatologist should provide a clinical histopathologic diagnosis to help the allergist or expert in the vaccination program decide the best course for continuation or exemption from the full anthrax series. These cases may warrant permanent exemption from further vaccination series. No apparent safety data for challenge dosing or desensitization in these potentially life-threatening skin reactions exist. In patient 2 with erythema multiforme, further vaccinations for

anthrax were waived permanently. Similarly, deferral from further anthrax vaccinations was recommended in patient 3.

In those cases of severe urticaria or angioedema, temporary exemption may be granted while requesting allergy consultation. Additional doses should be given with caution only after expert evaluation and consideration of the risk:benefit ratio. Permanent exemption may be required for those with anaphylaxis or sudden onset angioedema. In patient 1 with recurrent localized urticaria, the allergist recommended that a formal skin-prick test to future vaccine lots be performed before he received any further vaccine in the series. Although this local allergic-type reaction may be due to some component of the vaccine, we are unable to define the specific cause at this time. This is a rather unusual manifestation, with recurrence of the urticaria still persisting 2½ years later and restricted only to the vaccinated arm.

Table 2.

Systemic or Generalized Type Reactions*⁹

Type	Treatment	Waivers/ Consultation	VAERS Reporting/ Future Doses
Flulike symptoms, fever, arthralgia, nausea, headache	Acetaminophen or ibuprofen, analgesics, and antiemetics, as needed. Consider serum sickness if symptoms are severe or prolonged		Acetaminophen or ibuprofen 1 h before next vaccination
Generalized maculopapular or target lesions	Consider prednisone 50–60 mg for 5–7 d if severe, but only after specific diagnosis. Skin biopsy indicated. Longer treatment may be indicated if the rash is early EM, SJS, or TEN	Temporary exemption pending routine consultation with specialist	VAERS report encouraged. Additional doses should be given with caution only after expert evaluation and considerations of risk:benefit ratio
Diffuse blistering dermatitis or mucositis, EM, SJS, or TEN	Treat acutely based on specific diagnosis Accurate diagnosis with skin biopsy	Temporary exemption pending immediate dermatology and allergy consultations	Submit VAERS report. There are no safety data for challenge dosing and/or desensitization for these reactions. Likely warrants permanent exemption
Angioedema	If sudden onset, treat as anaphylaxis. If late onset, over 4 h (typically 2–3 wk), treat as serum sickness with corticosteroid and antihistamine for 5–7 d	Temporary exemption pending allergy and dermatology consultation	Submit VAERS report. Review risk:benefit ratio carefully before any further vaccinations, under controlled, desensitization conditions. Permanent exemption may be required
Anaphylaxis or generalized rash with itching and shortness of breath	Potentially life threatening and may require admission to the hospital, treatment with epinephrine, and corticosteroid	Temporary exemption pending consultation with allergist. Permanent exemption may be required	Submit VAERS report. Review risk:benefit ratio carefully with patient. Consult with patient regarding treatment options and further vaccinations, under controlled, desensitization conditions

*VAERS indicates Vaccine Adverse Event Reporting Systems; EM, erythema multiforme; SJS, Stevens-Johnson syndrome; and TEN, toxic epidermal necrolysis.

Data are from Vaccine Healthcare Centers Network. Available at: www.vhcinfo.org.

Conclusion

There are ongoing studies to evaluate whether a reduced number of anthrax vaccinations will provide the same immunity. In addition, other ongoing studies are comparing intramuscular

administration versus the current usual subcutaneous route. Preliminary reports have shown that local reactions are less common in patients who received the vaccine via the intramuscular route than in those who received the vaccine via the

subcutaneous route.¹³ This change in route of administration could reduce the number of adverse cutaneous reactions in the future. For further expert advice or clinical consultations, contact the Walter Reed National Vaccine Healthcare Center via telephone: 202-782-0411; fax: 202-782-4658; or e-mail: askVHC@amedd.army.mil.

Since the domestic anthrax attacks in October 2001 and in the presence of continued worldwide threats to our armed forces, force protection remains a top priority. As dermatologists, we should be familiar with the current anthrax vaccine program and be able to recognize and treat anthrax vaccine-related AEs.

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