

Supraclavicular Lymphadenopathy Secondary to Smallpox Vaccination

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An airman scheduled for deployment presents with a mass highly associated with malignancy. Might it be an adverse reaction to his recent smallpox vaccination?

Enlarged lymph nodes (> 0.5 cm if supraclavicular or scalene; > 1 cm if located in any other region¹) can be an incidental finding or the presenting sign or symptom of an illness. Palpable supraclavicular lymph nodes are a particularly ominous sign because they are associated with malignancy in 50% to 85% of all cases.²⁻⁵ The supraclavicular nodes are known to drain the lungs, retroperitoneal space, gastrointestinal tract, breasts, testes, and ovaries. In addition to malignancy, they can signal such infectious processes as tuberculosis, sarcoidosis, and toxoplasmosis. At least 1 case of supraclavicular lymphadenopathy after vaccination with the human papilloma virus (HPV) has been reported,⁶ and anecdotally, it is known to occur as an adverse effect of the live smallpox vaccine, which is administered routinely to active duty military members prior to deployment.

Here we report the case of a patient who developed reactive supraclavicular lymphadenopathy secondary to inoculation with the live smallpox vaccine. An extensive medical literature review,

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including a search of the CDC's Vaccine Adverse Event Reporting System (VAERS),⁷ suggests that lymphadenopathy in this particular region has never before been reported as a reaction to the live smallpox vaccine. This case highlights the importance of reporting all potential adverse vaccination reactions to the VAERS (<http://vaers.hhs.gov/esub/index>), considering recent vaccination of any kind as a potential cause of supraclavicular lymphadenopathy, and—in the case of the live smallpox vaccination—using the time of eschar separation as the starting point for the 4-week observation period so as to prevent unnecessary lymph node biopsies and delayed deployment of military personnel.

INITIAL EXAM

A 20-year-old active duty airman presented to our primary care clinic because a painless mass had appeared just above his left clavicle, although he was unsure as to when it had developed. He reported no weakness, fatigue, night sweats, sore throat, or cough, but had a sore left shoulder due to a smallpox vaccine he had received 11 days prior in preparation for his deployment to the Middle East in 3 months. He had no history of tobacco use, no significant per-

sonal medical history, and no family history of cancer, including leukemia or lymphoma.

Physical examination revealed the nontender, single, left-sided supraclavicular lymph node to be approximately 1 cm in diameter, rubbery in consistency, and mobile. All other palpable lymph node groups, the spleen, and the testes were normal. A 5-mm eschar was visible on the patient's left deltoid region. Surrounding erythema measured 10 cm in diameter, consistent with a large, local reaction (Figure 1). The patient's physical examination was otherwise unremarkable. His vital signs were normal, as were results of his chest x-ray and laboratory studies (complete blood count, metabolic panel, liver function tests, thyroid stimulating hormone test, and HIV enzyme immunoassay).

A discussion with staff at a major military treatment facility's Vaccine Healthcare Centers Network suggested that lymphadenopathy in reaction to smallpox vaccination was not uncommon and typically resolved within 4 weeks of inoculation. Given the patient's recent smallpox vaccination and the large, local reaction at the inoculation site, he was given a provisional diagnosis of acute supraclavicular lymphadenitis secondary to smallpox vaccination.

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CASE IN POINT

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TREATMENT COURSE

Because the condition was expected to resolve without treatment, initial management was limited to observation over the following 4 weeks, patient counseling on the possible causes of the condition, and a review of inoculation site care (including the importance of avoiding contact with the eschar and thorough hand washing after bandage changes to prevent the accidental transmission of live virus to other body sites or people). The patient was allowed to continue with the predeployment process.

At his 4-week follow-up visit, the patient remained asymptomatic. The large, local reaction at the inoculation site had resolved, but the eschar had not yet separated and the supraclavicular lymph node was unchanged. At this point, the predeployment process was halted and the patient was referred to general surgery at a large military medical center for possible lymph node biopsy.

After conducting a thorough examination, the surgeon determined that the patient's lymphadenopathy was likely due to his smallpox vaccination and recommended that he undergo another 4 weeks of observation. At the next follow-up visit, 3 weeks later, the patient's eschar had separated, his lymphadenopathy had subsided completely (Figure 2), and he was allowed to deploy. We submitted an online report to the VAERS.

ABOUT THE CONDITION

Although the medical literature suggests that supraclavicular lymphadenopathy is malignant in at least half of biopsied cases,²⁻⁵ published studies typically focus on unexplained cases.^{2,5} According to the prescribing information for live smallpox vaccine, lymphadenopathy occurs as an adverse effect of inoculation in 8% of vaccine-naïve patients and 6% of



Figure 1. A 5-mm eschar on the left deltoid region and a visible 1-cm left-sided supraclavicular lymph node on a patient 2 weeks after he received a live smallpox vaccine.



Figure 2. At follow-up, 3 weeks later, the supraclavicular lymph node is no longer visible and the eschar has separated.

previously vaccinated patients.⁸ Localized lymphadenopathy is associated with many commonly used vaccines, including those for hepatitis A and B, herpes zoster, varicella zoster, measles-mumps-rubella, tetanus-diphtheria-pertussis, and anthrax,⁹⁻¹⁴ although it is unclear how frequently it occurs in the supraclavicular region.

The live vaccinia virus induces an immune reaction upon inoculation into the superficial layers of the skin.¹⁵ Intense erythema around the vaccination site is common.^{8,15} Other adverse events frequently associated with the live smallpox vaccine are nausea, diarrhea, injection site pain, fatigue, malaise, myalgia, and headache.⁸ Less frequent, boxed warnings include myocarditis, pericarditis, encephalitis, Stevens-Johnson syndrome, and eczema vaccinatum. Since live virus can be transmitted to close contacts of the vaccinee, both are at equal risk for such adverse events.⁸

In the case presented here, because the enlarged node was on the same side as the patient's smallpox vaccination site and was not known to be present prior to his inoculation, vaccination was the most plausible cause of lymphadenopathy. The initial decision to limit management of the condition to patient counseling and observation was based on the algorithm devised by Robert Ferrer for evaluating a patient with lymphadenopathy.¹⁶ With a suggestive cause of the lymphadenopathy and a reassuring clinical picture, Ferrer deems 3 to 4 weeks of observation an appropriate course of action.

The smallpox vaccination differs from most intramuscular vaccines in that it is administered with a bifurcated needle that is dipped into a multidose vial and then used to puncture a 5-mm area of skin 15 times. A sizable pustule forms, fol-

lowed by a thick brown or black eschar, which does not separate for approximately 3 weeks after the inoculation.¹⁵ Active viral particles are found in the eschar and at the healing site after eschar separation. Patients should take precautions against exposure until the site is well healed, at least 30 days after immunization.¹⁷ Reactions, however, may persist beyond that point, as is demonstrated by the fact that this patient's lymphadenopathy failed to subside within 4 weeks of vaccination.

When the history or physical examination of a patient with un-

pathologist to review, thereby reducing the risk of false-positive cancer diagnoses.

IN SUMMARY

Palpable supraclavicular lymph nodes are always a concern, given their association with advanced malignancy. If a patient has received a live smallpox vaccination, the pustule, eschar, and healing scar are obvious indications of a recent inflammatory reaction. When a similar reaction follows HPV vaccination,⁶ however, the immunologic stimulus is not so apparent. To determine a cause in such

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explained supraclavicular lymphadenopathy reveals a risk of malignancy, or when the condition fails to resolve in a recently vaccinated patient after an appropriate observation period, a biopsy is indicated.¹⁶ Because our patient's impending deployment required definitive diagnosis, we referred him for biopsy after only 4 weeks of observation (5 weeks and 4 days after inoculation), despite the fact that the eschar had failed to separate.

Fine needle aspiration has been shown to be an excellent tool for determining the cause of unexplained lymphadenopathy,^{2,4} with a diagnostic accuracy of 96%² and considerably less morbidity than excisional lymph node biopsy. In patients with a probable viral illness, however, an excisional biopsy may be preferable because reactive lymph nodes may mimic lymphoma,¹⁶ and excisional biopsies provide more tissue for the

cases, it is necessary to include immunizations as part of a thorough patient history. If a vaccination is thought to be the cause of supraclavicular lymph node enlargement in an otherwise healthy patient, careful observation and follow-up to document resolution is essential. In addition, a report should be filed with the VAERS. To prevent unnecessary biopsies and, in the case of military patients, canceled or delayed deployments, clinicians should be aware that supraclavicular lymphadenopathy is a potential adverse effect of live smallpox and other vaccines. ●

Author disclosures

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