MILITARY MEDICINE, 171, 8:788, 2006

Delay of Chemotherapy to Prevent Progressive Vaccinia

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Objective: The goal was to discuss the potential risk of progressive vaccinia in the setting of smallpox vaccination with immunosuppression and to present strategies to avoid progressive vaccinia. Methods: A case report and literature review are presented. Results: A 21-year-old, male, military member received smallpox vaccination and was coincidentally diagnosed as having osteosarcoma ~2 weeks later. His recent vaccination was recognized, and chemotherapy was subsequently delayed until separation of the scab at the vaccination site. The patient received neoadjuvant chemotherapy and fared well, without any evidence of progressive vaccinia or other smallpox vaccine complications. Conclusions: Smallpox vaccine should be withheld from immunocompromised patients because of the risk of progressive vaccinia. Conversely, immunosuppressive therapies should be delayed for recently vaccinated patients. There are no controlled trials in this area, but withholding immunosuppressive therapy until separation of the scab is a rational approach. This patient was exposed to chemotherapy after scab separation and did not develop progressive vaccinia.

Introduction

Progressive vaccinia occurs when a primary smallpox vaccination site fails to resolve in a vaccinated person. The vaccinial infection spreads from the vaccination site and can lead to local necrosis, metastatic lesions, bacterial superinfections, and sometimes death. Immunocompromised persons are at risk for progressive vaccinia in the setting of smallpox vaccination. There are many historical case reports of progressive vaccinia among immunosuppressed patients, many of whom had hematologic malignancies or primary immunodeficiencies.

The United States discontinued routine smallpox vaccination in 1972, and military members received the vaccine until 1990.[1,2] After the terrorist attacks of September 11, 2001, there was concern that undisclosed stockpiles of smallpox could be used as a biologic weapon; therefore, a targeted smallpox vaccination program was restarted in January 2003.[3] Given the increased use of immunosuppressive therapies for a variety of malignant, rheumatic, and allergic conditions, compared with 30 years ago, as well as the advent of human immunodeficiency virus/acquired immunodeficiency syndrome, prevention of progressive vaccinia is a concern in the new vaccination program. Fortunately, no cases of progressive vaccinia have been reported since the beginning of the new program.[3] We present a case that illustrates the appropriate delay of immunosuppressive therapy to avoid progressive vaccinia.

Case Report

A 21-year-old male member of the Army National Guard was called to active duty and received routine smallpox vaccination on January 30, 2003. For 2 to 3 months before vaccination, he had noted pain in the distal right thigh, with some recent swelling. After vaccination, the patient presented to medical attention for evaluation of this pain, and radiographs were consistent with a tumor of the distal right femur. The patient was referred to Wilford Hall Medical Center, and biopsy revealed osteosarcoma. During the patient's initial oncology consultation on February 14, 2003, the recent smallpox vaccination was recognized. Because of concern that severe immunosuppression from chemotherapy could cause progressive vaccinia, chemotherapy was delayed until separation of the scab at the vaccination site (which represents the end of the normal smallpox vaccination response). The scab separated on approximately February 27, 2003 (4 weeks after vaccination), and high-dose neoadjuvant chemotherapy, including methotrexate, doxorubicin, cisplatin, and ifosfamide, was begun on March 5, 2003. The patient eventually underwent limb-sparing surgery, which showed complete necrosis of the tumor. He tolerated chemotherapy well and never experienced progressive vaccinia or other smallpox vaccine complications.

Literature Review

A recent review of progressive vaccinia identified 56 cases of progressive vaccinia reported in the English-language medical literature from 1893 to 1997.[4] Seventeen of those cases involved adults with hematologic malignancies who were receiving chemotherapy, steroid therapy, or both; 8 of those 17 patients died. The adult patients with malignancies who developed progressive vaccinia were the most relevant to our patient's situation.[5-19] Study of the original articles that presented the 17 cases revealed two cases involving adults with leukemia who developed progressive vaccinia that were not included in the review article; both patients received smallpox vaccine as a treatment for herpes simplex virus infection (a long-discredited practice). These two cases were referenced in a table in an article reviewing this practice.[15] One patient eventually died as a result of sepsis.[20] The other patient's case bore some similarity to our situation, in that the patient received smallpox vaccine before she was coincidentally diagnosed with a malignancy (leukemia). That patient

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Presented at the 60th Annual Meeting of the American Academy of Allergy, Asthma, and Immunology, March 23, 2004, San Francisco, CA; the 2004 Military Allergy Program (18th Annual Harold S. Nelson Allergy/Immunology Symposium), 60th Annual Meeting of the American Academy of Allergy, Asthma, and Immunology, March 18, 2004, San Francisco, CA; and the 46th Annual Meeting of the Society of Air Force Physicians, March 9, 2004, San Antonio, TX.

The views expressed in this article are those of the authors and do not represent the official policy or position of the U.S. government.

This manuscript was received for review in October 2004. The revised manuscript was accepted for publication in April 2005.

developed progressive vaccinia, was treated with corticotropin, antibiotics, and "blood transfusion from a recently vaccinated donor," and survived.[21] There are no known case reports of progressive vaccinia in the setting of chemotherapy for a solid tumor.

Also relevant to our inquiry are cases of patients with concurrent immunosuppression and recent smallpox vaccination who did not develop progressive vaccinia. Ten service members who received smallpox vaccination before it was known that they were human immunodeficiency virus positive have been identified.[2,22] None of those patients developed progressive vaccinia. Another case involved a service member who was severely burned 5 days after smallpox vaccination and who received prophylactic vaccinia immunoglobulin (VIG) therapy after that event.[2] The patient did not develop progressive vaccinia but did develop some new vesicles that were negative for vaccinia in polymerase chain reaction assays and cultures. Another service member was burned after his primary vaccination site had scabbed over.[2] That person was not treated with VIG and did not develop progressive vaccinia or any new vesicles.

Discussion

The risk of progressive vaccinia presents in two ways, namely, administration of smallpox vaccine to a patient who is an inappropriate candidate because of immunosuppression or initiation of immunosuppression for a recently vaccinated patient. There is a thorough screening mechanism in place to prevent the former scenario and, to date, there have been no cases of progressive vaccinia in the new smallpox vaccination program.[3] However, physicians must guard against the latter scenario and must consider whether a patient might have recently received the smallpox vaccine before immunosuppressive therapy is initiated in our military population.

There is only anecdotal evidence available to guide physicians regarding when it is safe to administer immunosuppressive therapy in the setting of recent smallpox vaccination, including the case of the service member who was burned after his vaccination site scabbed over and our case, in which chemotherapy was withheld until separation of the scab. Neither of these patients developed progressive vaccinia. Given this evidence, it is reasonable to wait until scab separation, which usually occurs 2 to 3 weeks after vaccination, before giving immunosuppressive therapy. It is known that vaccinia virus is recoverable from the vaccination site during the normal vaccination response, from vaccination through formation of the Jennerian pustule to scab separation.[1] However, if there is a delay in scab separation, it is not known whether culture or polymerase chain reaction testing can provide guidance regarding whether it is safe to administer immunosuppressive therapy.

If progressive vaccinia occurs, then physicians should discontinue immunosuppressive therapies if possible. There are two treatments currently available for progressive vaccinia (as well as other serious smallpox vaccine complications), VIG and cidofovir. VIG is the recommended initial treatment for progressive vaccinia. Cidofovir carries a serious risk of renal failure and is recommended only if VIG supplies are exhausted, if the patient fails to exhibit improvement with VIG, or if the patient is near death.[23] Both agents are available through investigational new drug protocols. For release of either agent, civilians should contact the Centers for Disease Control and Prevention and military physicians should contact the U.S. Army Medical Research Institute of Infectious Diseases.[23] Our patient did not require emergency chemotherapy but, if other patients have an indication for emergency immunosuppressive therapy, then VIG can be released through a compassionate-use protocol from either of the sources cited. Ultimately, physicians must consider the risks of delaying therapy against the perceived risk of progressive vaccinia.

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