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**Title:** Medical Intelligence: Disseminated Vaccinia In A Military Recruit With Human Immunodeficiency Virus (HIV) Disease.

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LIVE-VIRUS vaccines have been well recognized as a cause of severe complications when inadvertently administered to recipients with impaired immunologic function<sup>1</sup>. The acquired immunodeficiency syndrome (AIDS) has been recognized as a severe immunodeficiency state caused by infection with a retrovirus, human immunodeficiency virus (HIV)<sup>2</sup>. HIV infection and disease include a wide spectrum of clinical presentations, such as asymptomatic infections, chronic generalized lymphadenopathy, and frank T-cell deficiency (AIDS-related complex and AIDS)<sup>3</sup>. Although the natural history of HIV infection has only been partly defined, it is clear that patients with AIDS represent only a minority of the total number of T-cell-deficient patients with HIV disease.

Originally, some patients were identified as having AIDS because they had chronic mucocutaneous herpes simplex infections<sup>4</sup>. In addition, patients with AIDS or AIDS-related complex are predisposed to severe and progressive disease due to other cutaneous viral infections (including infections with poxviruses). Depletion of stores of immunologically active, Ia-positive Langerhans' cells could explain this observation<sup>5</sup>. Recently, we reported a case of chronic, progressive molluscum contagiosum (a poxvirus infection) in a patient with HIV disease<sup>6</sup>. Here we describe a patient with HIV infection and subclinical T-cell deficiency in whom AIDS and disseminated vaccinia developed during basic training; both diseases appeared after the patient had received a series of immunizations upon entering military service. This case illustrates that primary smallpox immunization of persons with subclinical HIV disease poses a risk of vaccine-induced disease, and that multiple immunizations may accelerate the progression of HIV disease. In addition, the case raises concern about the ultimate safety of vaccinia-based vaccine in developing countries where HIV infection is increasing. In an attempt to minimize the occurrence of this complication, U.S. military forces currently require screening for HIV antibody before immunization is performed.

### Case Report

A 19-year-old black man from the mid-southwestern United States began basic training at a military base in April 1984. He had been healthy throughout high school, taking part in competitive

athletics without difficulty. In February 1984 the results of a complete physical examination including a complete blood count (6200 white cells with 24 percent lymphocytes) were reported to be within normal limits. The patient received multiple immunizations (including the following vaccines -- adenoviruses 4 and 7, measles, rubella, bivalent influenza, trivalent poliomyelitis, tetravalent meningococcus, tetanus, and diphtheria) within the first three days of basic training, followed by a primary smallpox vaccination at the end of the first week (May 8). He participated fully in basic training until 2 1/2 weeks after the smallpox vaccination, when fever, headache, neck stiffness, and night sweats developed. Cerebral spinal fluid analysis showed 12 white cells per milliliter (100 percent mononuclear cells), a glucose concentration of 26 mg per deciliter (1.4 mmol per liter), a protein level of 37 mg per deciliter, and a cryptococcal antigen titer of 1:128; a culture was positive for *Cryptococcus neoformans*. On May 30 the patient was transferred to Walter Reed Army Medical Center for treatment of cryptococcal meningitis and further evaluation.

In addition to cryptococcal meningitis, generalized lymphadenopathy (bilateral axillary and femoral nodes 2 to 3 cm in diameter), oral candidiasis, leukopenia (3800 cells per cubic millimeter), lymphopenia (610 cells per cubic millimeter), and severe depletion of T helper (Leu-3+) cells (<25 cells per cubic millimeter) were present. Cutaneous anergy occurred upon skin testing with mumps, trichophyton, candida, and tetanus antigens. HIV was isolated from phytohemagglutinin-stimulated peripheral-blood mononuclear cells, and serum antibody to multiple viral structural proteins (p64, p55, p53, gp41, p31, p24, and p17) was detected by Western blot techniques (according to methods previously described<sup>7,8</sup>).

Interviews with the patient and family members, conducted by trained investigators, failed to reveal evidence of homosexual activity or intravenous drug use. The patient did admit to multiple heterosexual contacts, including some with prostitutes over the previous five years. He had no history of prior smallpox vaccination or any clinical evidence of a scar consistent with such vaccination. Four weeks after vaccination, while the patient was hospitalized for treatment of meningitis, an ulcer 3 by 4 cm developed at the vaccination site and a satellite ulcerated lesion 0.25 by 0.50 cm developed nearby. Over 48 to 72 hours (June 7 through 9), 80 to 100 pustular lesions appeared on the buttocks and the posterior aspects of the legs, rapidly progressing to ulceration (Fig. 1A). A skin biopsy revealed acanthosis with ballooning degeneration of the keratinocytes of the lower half of the epidermis. Paranuclear oval hyalinized intracytoplasmic inclusion bodies (Guarnieri's bodies) of vaccinia were clearly demonstrated in cells in various stages of ballooning degeneration (Fig. 2). Vaccinia was cultured in chorioallantoic membrane inoculated with material obtained during skin biopsy of the disseminated lesion and from scrapings of both the vaccination site and the disseminated lesions (Fig. 3). The patient was treated with vaccinia immune globulin, 50 ml given intramuscularly weekly for 12 weeks. The ulcers gradually epithelialized and were completely healed by mid-August (Fig. 1B).

\*Figure 1. Vaccinia Lesions on the Proximal Lower Extremities.

Panel A shows the lesions during the first week of disseminated disease (day 5).

Panel B shows extensive scarring of the resolving lesions after nine weeks of passive immunotherapy\*.

\*\*FIGURE OMITTED\*\*

\*Figure 2. Paranuclear Oval Hyalinized Intracytoplasmic Inclusion Bodies (Guarnieri's Bodies) of Vaccinia in Cells in Various Stages of Ballooning Degeneration (Hematoxylin-Eosin, x 68)\*.

\*\*FIGURE OMITTED\*\*

\*Figure 3. Electron Micrograph of Vaccinia in Egg Culture of Inoculum Obtained from the Skin-Biopsy Site (x 48,125) \*.

\*\*FIGURE OMITTED\*\*

Over the next three months, the oral candidiasis and cutaneous anergy spontaneously resolved in association with a gradual but persistent increase in the total T-helper-cell population (to 300 cells per milliliter). However, subsequently gradual depletion of these cells occurred and was associated with persistent clinical evidence of T-cell dysfunction (cutaneous anergy and chronic oral candidiasis) complicated by a progressive neurologic syndrome. Anticryptococcal therapy with amphotericin was continued up to the patient's death, in December 1985. An autopsy was not performed.

### Discussion

We have identified a complication of smallpox vaccination in a patient with HIV infection; however, the simultaneous appearance of these two diseases should not be surprising. When smallpox vaccination was in general use, the risk of complications due to vaccination was known to be increased among persons whose immunologic response was impaired because of a neoplasm or treatment with corticosteroids or antimetabolic drugs<sup>9</sup>.

It is important to note that the patient in this report appeared to be healthy when he entered military service and underwent immunization during basic training. It is probable that he had severe quantitative T-cell deficiency at the time of recruitment; however, the disease was subclinical. T-cell activation has been shown to enhance T-helper-cell permissiveness for HIV replication in vitro (Shearer GM: personal communication). It has been demonstrated that HIV-induced death of T helper cells is dependent on expression of the interleukin-2 gene<sup>10</sup>. Of particular concern is the possibility that multiple immunizations (which would result in T-cell activation and increased interleukin-2 production) accelerated HIV-induced T-helper-cell death and thereby accelerated the development of AIDS in the patient. Although the role of multiple immunizations in accelerating the progression of clinical T-cell deficiency remains speculative, one should recall that AIDS not associated with Kaposi's sarcoma and not associated with receipt of blood products is extremely rare among American men of this patient's age.

Although not observed in this patient, complications from other live vaccines (such as those for polio, measles, mumps, rubella, and the BCG vaccine) may occur in some patients with HIV-induced T-cell deficiency, particularly those undergoing primary immunization. The Advisory Committee on Immunization Practices (U.S. Public Health Service) has recently stated that live vaccines are not recommended for use in persons with clinically apparent HIV-associated immunodeficiency<sup>11</sup>. Although the Committee acknowledges the concern about the potential role of immunization-induced deterioration, it believes that the potential benefits of immunization of infected children by means of killed vaccines outweigh this theoretical adverse event<sup>11</sup>.

The patient described in this report had not been vaccinated against smallpox before he entered military service. The rates of complications of smallpox vaccination are approximately 10 times greater among persons undergoing primary smallpox vaccination than among those undergoing revaccination<sup>12,13</sup>. Routine smallpox vaccination during childhood was discontinued in the United States in the early 1970s<sup>14</sup>. As more men and women born after 1970 enter military service, the percentage of those undergoing primary vaccination will continue to increase, probably increasing the rate of complications. In the 1990s the majority of recruits will never have been vaccinated against smallpox. If, as the present case suggests, HIV infection predisposes to an

increased risk of severe complications of smallpox vaccination, and if the prevalence of HIV infection continues to increase in the general population, then the rate of complications from smallpox vaccination among military vaccine recipients will increase independently of the increase in the proportion of all persons undergoing primary vaccination.

The medical indications for vaccinating any general population against smallpox no longer exist. However, the vaccine continues to be given to certain military populations worldwide because of strategic defensive military and antiterrorist considerations. U.S. military services have recently evaluated medical options for minimizing complications of vaccinia vaccination. At present, the vaccine is given only to recruits in basic training. Prevacination screening and exclusion of recruits with evidence of HIV infection should reduce the occurrence of such complications among those with HIV-induced immunodeficiency. This is currently the policy adopted for the U.S. military.

Extensive research is being conducted on recombinant live-virus vaccines in which vaccinia is used as a biologic carrier<sup>15</sup>. Recently, several groups have developed candidate recombinant HIV vaccines<sup>16,17</sup>. Our case report raises provocative questions concerning the ultimate safety of such vaccines. It is thought that vaccinia-based vaccines might be most useful in developing countries, in that several immunizations could be combined into a single procedure. Given the reported high prevalence of seropositivity for HIV in some parts of Africa, the use of such vaccinia-based recombinant vaccines might be associated with high rates of complications among recipients infected with HIV. It is particularly noteworthy that although unusual serotypes of adenoviruses (such as adenoviruses 34 and 35) have rarely been demonstrated to cause end-organ damage in recipients of renal transplants and patients with AIDS, the common respiratory adenovirus serotypes have not<sup>18</sup>. Live adenovirus vaccine (serotypes 4 and 7) has been extensively used by the U.S. military to prevent upper respiratory tract infection in recruits, without complications. In the light of this information, it would seem prudent to consider the use of the serotypes of common respiratory adenoviruses (such as type 4, 7, or 21) as potential carrier viruses, instead of vaccinia.

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