Separate Worlds Set to Collide: Smallpox, Vaccinia Virus Vaccination, and Human Immunodeficiency Virus and Acquired Immunodeficiency Syndrome

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Concerns about the possible release of smallpox by bioterrorists has led to policies that recommend smallpox vaccination of some health care providers, and, in the near future, the vaccine may become available to the general population on a voluntary basis. Both smallpox virus (variola virus) and the smallpox vaccine (vaccinia virus) will have a significant impact on people infected with human immunodeficiency virus (HIV). Given that populations with acquired immunodeficiency syndrome and populations with immunosuppressed conditions due to solid organ and bone marrow transplantation were not present in the days when smallpox was prevalent, we will speculate on how smallpox might present in immunodeficient patients, and we will review the adverse events expected from the smallpox vaccine in hosts with HIV infection.

The threat that bioterrorism will reintroduce smallpox into the population has forced the medical community to address several difficult issues that, in an ideal world, would be confined to the history books. The last known case of smallpox in the United States occurred in 1949. By the 1960s, the risks associated with vaccination were being studied, and, when the risks outweighed the benefits, routine civilian vaccination in the United States was ended in 1972 [1–3]. The last naturally occurring case of smallpox occurred in 1977 in Africa. After intense worldwide surveillance, the disease was declared eradicated in 1980. Now, because of concerns about smallpox bioterrorism, military personnel and health care workers are again being immunized, and the vaccine may soon be available to the population at large [4]. Both smallpox virus and the smallpox vaccine will have an enormous impact on people infected with HIV. Because populations with AIDS were not present in the days when smallpox was prevalent, we will speculate on how smallpox might present in patients with defective cellular immunity, and we will also review the expected toxicities of the vaccinia virus vaccine in hosts with HIV infection.

**SMALLPOX**

Because smallpox was eradicated before the emergence of the HIV epidemic, speculation guides our analysis of a world in which these 2 diseases coexist. Despite medical advances, a smallpox epidemic would be dreadful and especially devastating to those with immunodeficiencies. Studies of poxvirus infection in animal models [5] and the known complications associated with vaccinia virus vaccination in immunocompromised hosts [6–9] support the conclusion that smallpox infection will have grave consequences in hosts with defective immune systems. When smallpox was endemic, 3 main manifestations of variola major were characterized according to the nature and evolution of the rash as ordinary, flat, and hemorrhagic smallpox. The latter 2 types were nearly universally fatal. We know from the epidemiology of transmission of these various types that host factors, rather than viral factors, played an important role in whether a patient would present with ordinary smallpox or with one of the more deadly forms. That is, people who developed smallpox after contact with someone with flat or hemorrhagic rashes would more likely develop ordinary smallpox. This suggests that host factors, such as immune function, played an important role in how smallpox manifested [10]. A complete
understanding of cellular immune mechanisms came too late to fully examine whether cellular defects were responsible for the development of the universally fatal forms of smallpox. Data on how smallpox presented in pregnant women might provide hints on how smallpox might manifest in immunocompromised patients. This hypothesis is based on the controversial theory that pregnancy represents an altered immune state that occurs to prevent fetal allograft rejection [11].

Ordinary smallpox. The most common form of smallpox associated with variola major was ordinary smallpox. This form was subcategorized into confluent, semiconfluent, and discrete varieties. The confluent variety was the most severe and lethal form of variola major, and the discrete variety was the mildest form [10]. Mortality among unvaccinated individuals was >50%, and mortality among those vaccinated at various intervals before contracting the disease was as low as 1%–10% [12].

Flat smallpox. An uncommon form, flat smallpox accounted for ~7% of cases in a large Indian series of 3500 unvaccinated patients [10]. Seventy-two percent of these cases occurred in children and there was a high incidence in pregnant women. This form of the disease was rarely found in individuals who had successfully been vaccinated [10]. The disease was characterized by a confluent macular rash, a slow maturation of focal skin lesions, an absence of frank pustule development, and a severe exanthem (figure 1). Between 7 and 8 days after the onset of disease, patients would begin to slough mucus membranes and have a severely ill appearance, with pulmonary edema, pneumonia, and internal bleeding. Extensive respiratory involvement made flat smallpox extremely contagious. The outcome was typically death [10]. It was known by the 1960s that cellular immune mechanisms were involved in localizing the virus in discreet lesions [13]; hence, there was speculation that flat smallpox, in which no distinct lesions formed, was due to infection in a susceptible host with a deficient cellular immune response [10].

Hemorrhagic smallpox. Even less common than flat smallpox, hemorrhagic smallpox occurred in ~3% of cases. Hemorrhagic smallpox was an overwhelming infection, and patients had viremia and disseminated intravascular coagulation until death [14]. This was quite unlike the disease symptoms of ordinary smallpox, in which viremia was seen only in the preeruptive and early eruptive stages [15]. Hemorrhagic smallpox was subcategorized into early type and late type varieties.

Early type hemorrhagic smallpox involved widespread bleeding and could have been mistaken for a viral hemorrhagic fever, meningococccemia, or acute leukemia. Patients had bleeding into the skin, subconjunctiva, and gums and from every orifice, and they typically died before developing focal rash (figure 2B). Two-thirds of patients with early smallpox were women, with pregnant women particularly susceptible [10].

Late type hemorrhagic smallpox was characterized by hemorrhaging into the skin, the mucous membranes, and the bases of developing skin lesions, which were flat or confluent in appearance (figure 2B). Late type hemorrhagic smallpox occurred mostly in adults and was seen in both unvaccinated and previously vaccinated individuals [10]. In contrast to early type hemorrhagic smallpox, with its high prevalence among females and its markedly high incidence during pregnancy, there was an equal prevalence of late type hemorrhagic smallpox among men and women. However, there was a slightly increased prevalence among pregnant women (6% of cases in pregnant women vs. 2% of cases in nonpregnant women in a large Indian series) [10].

Although it is certainly possible that other factors were responsible for the greater incidence of fatal smallpox manifestations in pregnant women, if pregnancy represents an altered immune state, the indication is that immunocompromised individuals would more likely present with flat and hemorrhagic smallpox. Smallpox hit populations with such brutal force that the detection of manifestations in hosts with subtle alterations in immune function was not easy because smallpox killed both healthy and immunocompromised individuals. Thus, it is hard to guess the CD4 cell count at which HIV-infected patients would be at the greatest risk of developing the highly lethal
Because the vaccine is a live virus, it resulted in complications, especially in immunocompromised individuals. There is every reason to think that the risks associated with widespread vaccinia virus inoculation in today’s population will lead to more complications than occurred during prior smallpox vaccination campaigns [16]. In contrast to the above discussion of smallpox, we have developed an increased understanding of how this vaccine produces toxicities and results in frank disease in those with depressed cellular immunity.

**Progressive vaccinia (PV).** PV, also known as vaccinia gangrenosum or vaccinia necrosum, is the complication associated with vaccination campaigns that puts the immunocompromised host at greatest risk if inoculation occurs. It is classically considered to be the most serious adverse manifestation in immunodeficient hosts [6–9]. PV most often occurred in children with inborn cell-mediated immune defects or in individuals with acquired defects secondary to hematological malignancies and chemotherapy. However, it was also seen in individuals with debilitation from advanced age or cardiac disease [1, 15]. In PV’s most aggressive form, vaccinia virus replicates unchecked, leading to progression of the primary lesion (figure 3), viremia, and secondary lesions of the skin and other forms of smallpox. However, because HIV-infected patients with high CD4 cell counts and those with immune reconstitution resulting from HAART have been shown to reverse the immune disregulation [11], smallpox presentation in such individuals may be similar to that in non–HIV-infected individuals. It is important to note that, similar to the historical cases of these fatal forms of smallpox, it would be expected that disease in patients with smallpox and advanced AIDS would be extremely contagious. These assumptions on the impact that smallpox would have on immunocompromised hosts and society have important implications for the need to develop effective smallpox vaccines that can be safely administered to immunocompromised populations and to develop effective treatments for smallpox.

**SMALLPOX VACCINATION WITH VACCINIA VIRUS**

Vaccinia virus, a virus closely related to variola virus, was used in the vaccine that helped lead to the eradication of smallpox.

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**Figure 2.** Examples of hemorrhagic smallpox. A, Early type hemorrhagic smallpox in an unvaccinated 60-year-old woman; she died on the fourth day of illness. B, Late type hemorrhagic smallpox in a young woman, with bleeding in the base of pustules and development of a general hemorrhagic diathesis late in disease [10]; reprinted with permission.

**Figure 3.** Progressive vaccinia in a 64-year-old immunocompromised man after receipt of a smallpox vaccination (Public Health Image Library, ID# 1995, Centers for Disease Control and Prevention).
organs [7]. Patients may appear deceptively healthy, despite progression of the ulceration and metastatic lesions [17]. PV with dissemination occurred in the most severely immunocompromised individuals with profound defects in both cellular and humoral immunity [6]. Progression of the primary lesion without dissemination occurred in patients who were immunocompromised to a lesser degree [7]. Before the introduction of vaccinia immunoglobulin (VIG) therapy, PV resulted universally in death within weeks and months after the onset of disease [15]. Those who succumbed despite having received VIG therapy typically had extreme defects in cellular immunity, such as thymic aplasia and an inability to halt progression of primary and metastatic lesions [6]. If widespread vaccination without careful screening occurs, we would expect to see cases of PV. In contrast with a normal vaccination take which heals over 2 weeks, if the inoculation site has not begun healing after 15 days, one should consider PV as a diagnosis, along with the differential diagnosis of superimposed bacterial and fungal infections [3].

The stage of HIV infection at which vaccinia virus becomes an opportunistic pathogen is not known specifically, although we can make inferences on the basis of limited clinical experience. Like other opportunistic infections associated with HIV infection, we would expect individuals with CD4 cell counts of <200 cells/mm³ to have the highest risk of complications. We know from a published report of progressive vaccinia in a military recruit subsequently diagnosed with AIDS that the disease presentation in patients with AIDS is similar to that in others with cellular immunodeficiencies [18]. In 1984, a recruit received a smallpox vaccine along with a large number of other vaccines. Two-and-a-half weeks later, he developed cryptococcal meningitis and a 3–4 cm ulcer at his vaccination site with satellite lesions. Then, 2–3 days later, he developed 80–100 pustules, which turned into ulcerations on his buttocks and legs. Specimens of ulcerations were cultured and yielded vaccinia virus. His CD4 cell count was determined to be <25 cells/mm³. He was treated with VIG for 12 weeks, and the ulcers gradually healed, resolved, and did not recur. He had overall clinical improvement, and his CD4 cell count increased to 300 cells/mm³. One important caveat is that the infectious inoculum was unknown in the patients who died. Although it was likely a small amount of vaccinia virus that had escaped inactivation, it could have been a dose much higher than the dose administered during routine scarification.

Given these examples, we can speculate that vaccinia is unlikely to become progressive in the HIV-infected individual with a high CD4 cell count and a virus load that is well controlled with HAART. Given the experience treating the HIV-positive military recruits mentioned above, vaccinia is also unlikely to become progressive in HIV-infected persons who lack symptoms. Indeed, other live vaccinations are being given to those with well-controlled HIV infection [22]. A live chickenpox vaccine has been safely given to HIV-infected patients with CD4 cell counts of >400 cells/mm³ [23], and this vaccine has also been safely administered to children with hematological malignancies. Patients with AIDS will be at significant risk for complications associated with vaccinia virus vaccination. At the moment, there does not appear to be an urgent need to intentionally expose any HIV-infected people to vaccinia virus. However, if a smallpox threat becomes imminent, the individual with well-controlled HIV infection may tolerate and respond to the vaccine. Vaccinia...
virus does not exist in a latent form or in a reservoir in the body. Therefore, a successfully vaccinated HIV-infected patient will not be at risk for the emergence of progressive vaccinia later in life if immune function wanes.

**Eczema vaccinatum (EV).** EV can be a serious or fatal complication of smallpox vaccination in a person with eczema or atopic dermatitis [3]. EV that occurred after accidental exposure of an eczematous individual to a vaccinated individual was usually considered to be more severe than when acquired by vaccinees themselves [1]. The disease is characterized by a vaccinia eruption on parts of the body that either currently or previously had eczema lesions. Of note, the eczema need not be in an active state, and the resulting eruption can spread to healthy skin. Patients with EV developed high temperatures and generalized adenopathy. Deaths occurred in infants with large areas of skin affected. Experts estimated that 1% of eczematous patients accidentally vaccinated would go on to develop EV [24]. Data from the 1960s estimate a rate of EV of ∼8–24 cases per million primary vaccinees [1, 2, 25]. Estimates of eczema or atopic dermatitis in HIV-infected individuals are variable (i.e., 30%–80%) [26, 27]. Although the more common seborrheic dermatitis likely does not pose a risk for EV, one imagines that other skin conditions that are seen commonly in those with CD4 cell counts of <200 cells/mm³ may lead to excoriations and open wounds that put patients at risk for vaccinia via contact inoculation. EV acquired accidentally via exposure to a vaccinated family contact or health care provider could result in progressive vaccinia in a patient with AIDS who has both skin disease and deficient cellular immunity.

**Accidental infection.** Accidental infection involved auto-infection or spread of vaccinia virus to another unvaccinated individual. US surveys during the 1960s noted a lower incidence of simple contact vaccinia than that of EV [1, 2, 25], but accidental spread was likely underreported. The incidence of potentially serious contact vaccinia today is difficult to predict. The incidence in a world in which adults are the primary vaccinees and the majority of people are naive to vaccinia virus would be quite different than when vaccination was widespread. In the 1980s, military recruits were typically being vaccinated at the beginning of basic training, but several cases of contact vaccinia occurred when soldiers took leave after being vaccinated. Some cases led to severe infection in unvaccinated adult contacts [28]. In the past, if the person who acquired contact vaccinia did not have eczema, typically a mild infection resulted, mainly among children [25]. There are known cases of primary vaccinated health care workers who have transmitted vaccinia to patients [25, 29]. Before the use of VIG therapy, such nosocomial infection had been fatal in ∼10% of cases [29]. Thus, accidental infection in a patient with a contraindication to vaccination (e.g., eczema, undiagnosed HIV infection, and poorly controlled HIV disease) should lead to prophylactic VIG administration. To prevent accidental spread to others in the health care setting, it is recommended that the vaccine site be covered with gauze and a non- or semipermeable dressing [30]. This has been shown to prevent environmental contamination and person-to-person transmission of the vaccine [31]. However, such occlusive dressings will increase the risk of bacterial superinfection at the vaccine site [32].

**TREATMENTS FOR SMALLPOX AND VACCINATION COMPLICATIONS**

In the past, because no treatment for smallpox existed, the chief intervention against an outbreak was postexposure vaccination of those exposed to an active case. This modified the course of disease or aborted it [33]. An HIV-infected patient with a high CD4 cell count who has had direct contact with smallpox should be vaccinated. The situation is more problematic if patients with AIDS come in contact with patients with smallpox. In the past, when smallpox exposure occurred, patients with contraindications to vaccination (e.g., skin conditions) were vaccinated. In patients with AIDS, it is unclear if vaccination would simply expose the patient to the risks of the vaccine without any potential benefit. In the 1960s, it was shown that administration of VIG early during the variola incubation period further decreased the incidence and severity of smallpox [15]. No trials were performed with variola-specific immunoglobulin, although, if ever available, this might be a more effective therapy. Although not part of the official Centers for Disease Control and Prevention (Atlanta, GA) recommendations [32], a potential option for HIV-infected patients at high risk for complications associated with vaccination who need to be vaccinated may be prophylactic VIG therapy prior to vaccination. This was a strategy that was successfully used in patients with eczema [34]. No medications are currently available that have been shown to be effective for treating smallpox. Drugs in the thiosemicarbazone class, such as methisazone (not currently available in the United States), were not shown to be effective for treating smallpox, although methisazone was potentially effective for preventing disease when administered to exposed contacts within 1–2 days [35]. The antiviral cidofovir has in vitro activity against a wide range of orthopoxviruses, including variola virus. It has shown promise for treating cowpox infection in an in vivo murine model, although it did not prevent death in immunocompromised mice [36].

The primary treatment for vaccinia virus vaccine complications would be VIG. Although VIG was never tested in randomized clinical trials, it is believed to be effective, and it decreased the mortality among patients with PV [37]. VIG is also used in the treatment of generalized or contact vaccinia in...
patients who appear toxic or in contacts with a contraindication to vaccination who acquire vaccinia. The thiosemicarbazones, again, may be useful for treating PV [17]. Cidofovir may have promise for treating vaccinia virus infection [36]. Developing a safer vaccine, the obvious solution to the problem of vaccinia virus vaccine toxicity, is difficult, given that the effectiveness of a modified vaccine against smallpox is unknown and, in current circumstances, cannot be tested [38]. In the past, a modified vaccine was given to individuals with vaccine contraindications, such as eczema, as a prelude to a full-strength vaccine and was an effective strategy for decreasing vaccine-related complications [24]. There are studies underway of a highly attenuated vaccinia virus that should be safe to administer to individuals with immunodeficiencies [39] but whose efficacy against smallpox is unknown.

CONCLUSION

The mortality among immunodeficient patients due to smallpox would undoubtedly be high. Disease in these patients would more likely present as flat or hemorrhagic smallpox. These types are more difficult to recognize and are more contagious than ordinary smallpox and have resulted in a large number of fatal outcomes. These factors have important implications in terms of rapidly diagnosing smallpox, limiting the spread of smallpox, and aggressively instituting immune and antiviral therapy for these patients in hopes of improving survival. In preparing for the potential threat of smallpox, vaccinia virus vaccination and its complications are becoming a reality again in the United States. Because of complications associated with the vaccine, HIV-infected people should not be vaccinated before an outbreak occurs. In the event of an outbreak, we believe that the measurement of an individual’s CD4 cell count will be important for stratifying the risk of the vaccine. Anyone who has been directly exposed to smallpox should be vaccinated, and individuals with low CD4 cell counts should receive concurrent VIG therapy. In the outbreak setting, for which public health officials are recommending widespread vaccination, individuals with CD4 cell counts of >300 cells/mm³ should be vaccinated. Such individuals, who also have a well-constituted immune system and a low virus load, will likely be at no significantly increased risk for complications, compared with non–HIV-infected individuals. For those with low CD4 cell counts, the decision whether or not to vaccinate must be made within the context and circumstances of the smallpox outbreak. Vaccination may only expose these patients to risk; however, with concomitant VIG and anti-HIV therapy, this risk may be lessened. In addition, to prevent HIV-infected patients from exposure to cases of smallpox, hospitals should ensure that patients with smallpox are segregated from wards that house patients with immunodeficiencies.

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References