Progressive Vaccinia Treated with Ribavirin and Vaccinia Immune Globulin

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A 67-year-old man with metastatic melanoma and chronic lymphocytic leukemia was inadvertently given a vaccinia melanoma oncolysate vaccination. He developed progressive vaccinia at the site of inoculation. The lesion started to heal only when he was treated with ribavirin. Vaccinia immune globulin was administered and appeared to help control the initial lesion and limit the development of satellite lesions.

Vaccinia virus is a member of the Poxviridae and has been used as a vaccine against smallpox. Little is known about the origin of vaccinia virus because it was used before there was sufficient technology to characterize it or standardize its use. It is thought to have arisen from cowpox virus but was probably altered by person-to-person passage in the 19th century. It now has no natural host but can infect and replicate in several species including humans.

The site of primary vaccination with vaccinia virus is over the deltoid region of the upper arm; a bifurcate needle that has been dipped into the vaccine is used. The needle is held perpendicular to the skin and pressed in and out five times. The primary vaccination should result in modified swelling and tenderness at the site of vaccination, some regional lymphadenopathy, and mild fever. The resulting pustular lesion may be 4 cm but usually does not exceed 2 cm. The resultant protection against smallpox, which has not been well characterized, is probably due to both cellular and humoral immunity. Complications following vaccination have been well described [1].

Case Report

A 67-year-old man with metastatic melanoma and chronic lymphocytic leukemia was inadvertently given a vaccinia melanoma oncolysate vaccination. The vaccinia melanoma oncolysate vaccine is prepared from the lysate of the melanoma cell line MM220 infected with vaccinia produced by the Commonwealth Serum Laboratories (Melbourne). This vaccine is an experimental treatment with the aim of stimulating production of antibodies to melanoma as immunotherapy for metastatic melanoma [2].

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Fourteen days later, he presented with a weeping erythematous lesion on the right upper arm at the site of vaccination. Cellulitis was diagnosed, and treatment with oral floxacillin (1 g daily; a penicillinase-resistant penicillin with strong antistaphylococcal activity) was commenced. Two days later, 16 days after vaccination, he returned with a fever (temperature, 39°C), nausea, and an increase in the size of the right upper arm lesion. He was admitted to the hospital, and therapy with intravenous floxacillin (2 g daily) was started; however, he remained unwell. He was treated with intravenous immunoglobulin (200 mg/kg; Intragam, Commonwealth Serum Laboratories).

Physical examination at hospital admission revealed tachycardia, flush, and fever (temperature to 39°C) as well as an 11 × 18-cm lesion on his right upper arm that was weeping in areas and partially necrotic (figure 1). There was associated marked erythema and induration extending over the right shoulder and down the right flank as well as across the chest to the left shoulder. Progressive vaccinia was diagnosed. He also had lesions of metastatic melanoma on his forehead. There were no other skin lesions and no significant lymphadenopathy or hepatosplenomegaly. Laboratory studies disclosed the following values: hemoglobin, 101 g/L (normal, 120–180 g/L); WBCs, 9.6×10^9/L (normal, $4.5–11.0 \times 10^9$/L); neutrophils, 3.9×10^9/L (normal, $1.8–8.0 \times 10^9$/L); and lymphocytes, 5.6×10^9/L (normal, $1.0–4.5 \times 10^9$/L). He remained febrile over the ensuing 2 days, and the lesion on his upper arm continued to enlarge and become necrotic.

Because his lesion was progressing 22 days after the vaccination and there had been no response to a 1-week course of floxacillin therapy, treatment with intravenous ribavirin (400 mg every 8 hours for 5 days [3]) was started. Floxacillin therapy was continued. Two days after ribavirin therapy was started, his fever resolved, and there was no further increase in the size of the lesion. However, new satellite lesions were noted on his left ankle, right wrist, and forehead (figure 2),and he had bilateral tender anterior cervical lymphadenopathy. The satellite lesions resulted from hematogenous spread of vaccinia virus and, because of their timing, occurred before the commencement of ribavirin therapy. The Centers for Disease Control and

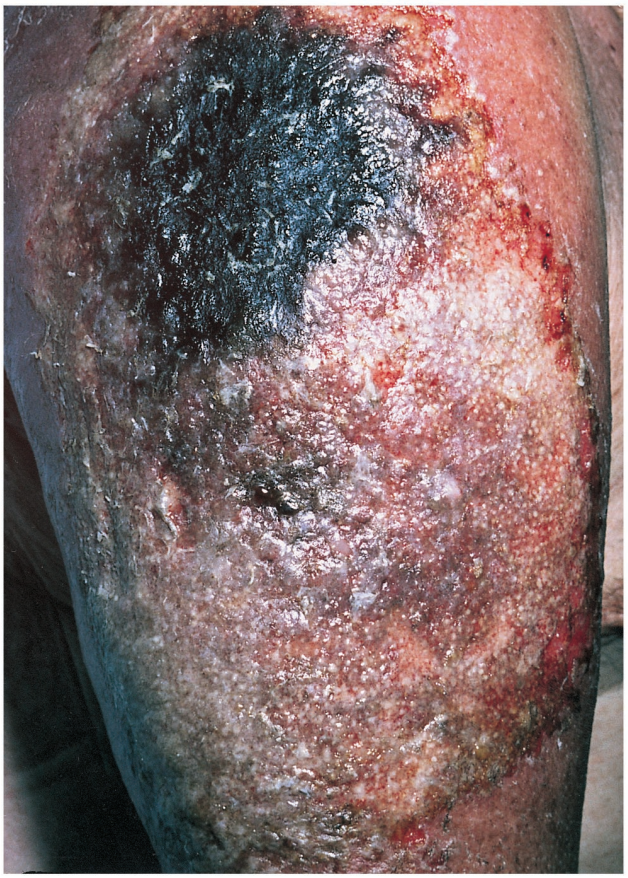

Figure 1

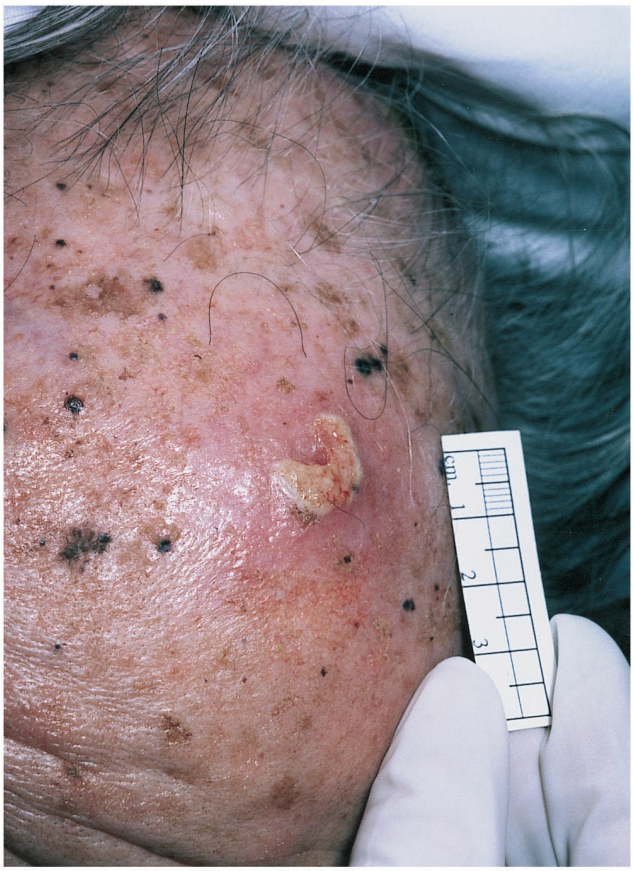

Figure 2

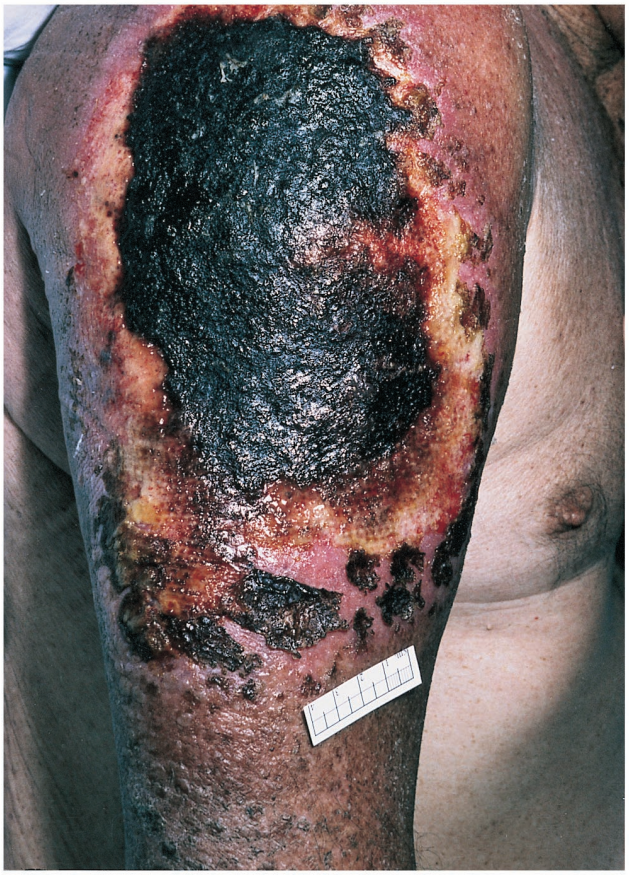

Figure 3

Figure 1. A large 11 × 18-cm vaccinia lesion on the upper arm of a man with metastatic melanoma and chronic lymphocytic leukemia who received a vaccinia melanoma oncolysate vaccination; there is an area of partial necrosis, and the lesion is surrounded by erythema and induration.

Figure 2. Formation of a satellite vaccinia lesion on the forehead of the patient in figure 1 that measured 1 × 1.5 cm. There is a small area of surrounding erythema but no induration. The small black lesions on the forehead are metastatic melanoma.

Figure 3. The same upper arm vaccinia lesion in figure 1 after 5 days of therapy with ribavirin. The lesion is well demarcated and necrotic. There is still an area of surrounding erythema and induration.

Prevention were contacted 22 days after vaccination to obtain vaccinia immune globulin.

Twenty five days after the initial vaccination, he was given an initial dose of 0.25 mL of vaccinia immune globulin/kg intramuscularly. (A small initial dose was chosen to conserve the scarce resource because his condition was clinically stable. Immunoglobulin has a long half-life [3–4 weeks], and a second dose was planned if his condition deteriorated.) His condition continued to improve, and he remained afebrile; no new lesions occurred, and his right upper arm lesion was now fully necrotic and demarcating. He was discharged 2 days later; his medication was oral floxacillin (1 g daily).

At a 2-week follow-up, he was well and afebrile. There were two new small vaccinia lesions on his back; one had healed spontaneously, and one was 0.5 cm in diameter (much smaller than the initial satellite lesions). His right upper arm lesion was now well demarcated (figure 3). The satellite lesions on his wrist and leg had healed, and the scalp lesion was crusted and healing; his cervical lymphadenopathy was now nontender and decreased in size. Floxacillin therapy was stopped.

Three days later, he again presented unwell and febrile. Culture of a specimen from the lesion yielded *Serratia marcescens,* and surgical debridement of the arm lesion was performed. Therapy with intravenous floxacillin, metronidazole, and gentamicin was started. Six days after skin grafting, he had a cerebrovascular event associated with cerebral metastasis of his melanoma. He was discharged home to the care of his family and died of metastatic melanoma 6 weeks later. No postmortem examination was performed.

Discussion

This case illustrates a well-described complication following inoculation of vaccinia virus—progressive vaccinia (vaccinia necrosum or vaccinia gangrenosa). Smallpox vaccine is a highly efficacious vaccine that led to the global eradication of smallpox, with the World Health Organization certifying that the world was free of naturally occurring smallpox in 1980 [4]. As a result of this achievement, very few reports about the management of the complications of vaccinia virus infection have been published after 1980. Progressive vaccinia has been described in patients with immune disorders and represents the failure of the host's immune system to limit viral replication to the immediate area of inoculation of the virus [1]. Individuals with agammaglobulinemia or decreased cell-mediated immunity as a result of congenital immunodeficiency, leukemia, lymphoma, or the use of immunosuppressive drugs are at risk of progressive vaccinia.

The relative roles of humoral and cell-mediated immunity in controlling the replication of vaccinia virus have not been clearly defined. It is probable that humoral immunity controls initial infection, because it has been observed that it is difficult to immunize young infants of vaccinia virus–immune mothers [5]. The level of protection against vaccinia virus in these infants was related to the titer of vaccinia virus–specific immunoglobulin that the infants had acquired transplacentally before birth. On the other hand, cell-mediated immunity is probably critical for localization of the virus to the site of initial inoculation and eradication of the infection from the host [6, 7].

In patients with progressive vaccinia, the lesion at the site of inoculation fails to heal, becomes necrotic, and gradually spreads locally. Then, new satellite lesions appear elsewhere on the body and also undergo local progressive spread and necrosis. If untreated, the condition is invariably fatal [8]. However, previously published studies have demonstrated that treatment with vaccinia immune globulin [9] and methisazone [10] has resulted in survival.

Methiazone (*N*-methylisatin-β-thiosemicarbazone) is an antiviral agent that inhibits protein synthesis. It is no longer produced by Burroughs Wellcome (Research Triangle Park, NC) and is not available. In vitro, methisazone inhibited vaccinia virus–infected cells from synthesizing a ''late'' structural viral protein, thus resulting in failure of viral assembly [11]. Ribavirin (1β-D-ribofuranosyl-1*H*-1,2,4-triazole-3-carboxamide) is an antiviral agent with in vitro activity against a wide range of RNA and DNA viruses, including vaccinia virus [12]. We treated our patient with 20 mg of ribavirin/kg daily in three divided doses for 5 days, and clinical improvement was noted within 48 hours of commencing ribavirin therapy (falling temperature and no further increase in the size of the right upper arm lesion that had started to become necrotic with evident demarcation from normal skin). However, at this stage, new lesions were noted, and he was treated with vaccinia immune globulin to control the hematogenous spread of infection and the development of satellite lesions.

The role of vaccinia immune globulin in the management of progressive vaccinia is controversial. Previous investigators have suggested that vaccinia immune globulin has little or no effect on the replication of vaccinia virus at the site of inoculation and has no clinical effect on the resolution of the primary lesion [11]. In a report by Douglas et al. [13], vaccinia immune globulin had no effect on the primary lesion but did help in controlling the appearance of satellite lesions. Currently, immunoglobulin preparations used for the management of hepatitis B virus, varicella-zoster virus, and measles virus infections have little effect on the established disease but are used as postexposure prophylaxis to prevent infection or limit viremia and ameliorate disease. We used vaccinia immune globulin to control the occurrence of satellite lesions; the number and size of new lesions both decreased after therapy.

For our patient, ribavirin appeared to have an effect on the course of the primary lesion; this effect was shown by resolution of fever and cessation of the spread of the lesion within 48 hours of administration (the lesion had been continuing to spread for the previous 22 days). Furthermore, vaccinia immune globulin did limit the number and size of new vaccinia lesions, which subsequently formed after ribavirin therapy was discontinued. These lesions are thought to occur because of

hematogenous spread of the virus, and it is possible that this spread occurred before initiation of ribavirin therapy. It is usual for new lesions to continue to spread until the patient dies, often 2 to 5 months after initial inoculation [8].

Progressive vaccinia can be prevented by close adherence to the guidelines for the use of vaccinia virus vaccine, particularly by not administering it to patients with impaired cellular immunity. In this case, we attribute a clinical effect to the administration of ribavirin and consider that it has an effect on the replication of vaccinia virus in vivo. We also regard vaccinia immune globulin as an important adjunct therapy because it limited the number and size of new lesions. We believe that the combined treatment of this patient with both ribavirin and vaccinia immune globulin contributed to the favorable outcome of his progressive vaccinia. Vaccinia virus is currently used as a viral vector to carry foreign genetic information into humans [14]. Whether vaccinia virus–cytokine constructs will provide protection against the complications of vaccinia virus infection in humans has yet to be demonstrated [15, 16].

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References

1. Neff JM. Vaccinia virus (cowpox). In: Mandell GL, Bennett JE, Dolin R, eds. Mandell, Douglas and Bennett's principles and practice of infectious diseases. 4th ed. New York: Churchill Livingstone, **1995**: 1325–27.
2. Hersey P, Edwards A, Coates A, Shaw H, McCarthy W, Milton G. Evidence that treatment with vaccinia melanoma cell lysates (VMCL) may improve survival of patients with stage II melanoma. Treatment of Stage II melanoma with viral lysates. Cancer Immunol Immunother **1987**;25: 257–65.
3. Chang T-W, Heel RC. Ribavirin and inosiplex: a review of their present status in viral diseases. Drugs **1981**;22:111–28.
4. WHO. Declaration of global eradication of smallpox. Wkly Epidemiol Rec **1980**;55:145–52.
5. Kempe CH. Studies on smallpox and complications of smallpox vaccination. Pediatrics **1960**;26:176–89.
6. Blanden RV. Mechanisms of recovery from a generalized viral infection: mousepox. I. The effects of anti-thymocyte serum. J Exp Med **1970**; 132:1035–54.
7. Blanden RV. Mechanisms of recovery from a generalized viral infection: mousepox. II. Passive transfer of recovery mechanisms with immune lymphoid cells. J Exp Med **1971**;133:1074–89.
8. Fenner F, Henderson DA, Arita I, Jezek Z, Ladnyi ID. Smallpox and its eradication. Geneva: World Health Organization. **1988**:296–311.
9. Feteky FR Jr, Malawista SE, Young DL. Vaccinia gangrenosa in chronic lymphatic leukemia: report of a case with recovery following the use of vaccinia immune globulin. Arch Intern Med **1962**;109:205–8.
10. Bauer D. Clinical experience with the antiviral drug Marboran (1-methylisatin 3-thiosemicarbazone). Ann NY Acad Sci **1965**;130:110–7.
11. Brainerd H, Hanna L, Jawetz E. Methisazone in progressive vaccinia. N Engl J Med **1967**;276:620–2.
12. Kucers A, Bennett N McK. Ribavirin. In: Kucers A, Bennett N McK, Kemp RJ, eds. The use of antibiotics. A comprehensive review with clinical emphasis. 4th ed. Philadelphia: JB Lippincott, **1987**:1607–12.
13. Douglas RG Jr, Lynch EC, Spira M. Treatment of progressive vaccinia. Use of methisazone, vaccinia immune serum globulin, and surgical debridement. Arch Intern Med **1972**;129:980–3.
14. Moss B. Vaccinia virus: a tool for research and vaccine development. Science **1991**;252:1662–7.
15. Ramshaw IA, Andrew ME, Phillips SM, Boyle DB, Coupar BEH. Recovery of immunodeficient mice from vaccinia virus/IL-2 recombinant infection [letter]. Nature **1987**;329:545–6.
16. Ramsay AJ, Ruby J, Ramshaw IA. A case for cytokines as effector molecules in the resolution of virus infection. Immunol Today **1993**;14: 155–7.