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# Simian Varicella Virus in Pigtailed Macaques (*Macaca nemestrina*): Clinical, Pathologic, and Virologic Features

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**Simian varicella virus (SVV; *Cercopithecine herpesvirus 9*) is a naturally occurring herpesvirus of nonhuman primates. Here we present the clinical, pathologic, and virologic findings from 2 cases of SVV in adult female pigtailed macaques (*Macaca nemestrina*). The initial case presented with hyperthermia and a diffuse inguinal rash which spread centripetally, progressing to vesiculoulcerative dermatitis of the trunk, face, and extremities. At 96 h after presentation, the animal was anorexic and lethargic and had oral and glossal ulcerations. Euthanasia was elected in light of the macaque's failure to respond to clinical treatment. Seven days after the first case was identified, a second macaque presented with a vesicular rash and was euthanized. Gross necropsy lesions for both cases included vesicular, ulcerative dermatitis with mucocutaneous extension and hepatic necrosis; the initial case also demonstrated necrohemorrhagic gastroenterocolitis and multifocal splenic necrosis. Histology confirmed herpetic viral infection with abundant intranuclear inclusion bodies. Immunofluorescence assays detected antibodies specific for SVV. PCR assays of vesicular fluid, tissue, and blood confirmed SVV and excluded varicella–zoster virus (*Human herpesvirus 3*). Serology for *Macacine herpesvirus 1* (formerly *Cercopithecine herpesvirus 1*), poxvirus (monkeypox), and rubella was negative. Banked serum samples confirmed SVV exposure and seroconversion. Investigation into the epidemiology of the seroconversion demonstrated a SVV colony prevalence of 20%. The described cases occurred in animals with reconstituted immune systems (after total-body irradiation) and demonstrate the clinical effects of infection with an endemic infectious agent in animals with a questionable immune status.**

**Abbreviations:** IFA, immunofluorescence assay; SVV, simian varicella virus; TBI, total body irradiation; WaNPRC, Washington National Primate Research Center; VZV, varicella–zoster virus; McHv1, *Macacine herpesvuris* 1; SRV-2, Simian retrovirus 2 (type D).

Simian varicella virus (SVV; *Cercopithecine herpesvirus 9*) is a naturally occurring herpesvirus of Old World primates responsible for sporadic epizootics in biomedical research facilities.[2] Signs of infection include fever, vesicular skin lesions, hemorrhagic ulceration throughout the gastrointestinal tract, and multifocal hemorrhagic necrosis of the liver, spleen, lymph nodes, and endocrine organs.[6,7,8] Other names for SVV include Delta herpesvirus, Liverpool vervet virus, patas herpesvirus, and Medical Lake macaque virus.[16, 20-23] Like many other herpesviruses, SVV establishes persistent lifelong infections, with viral DNA detectable in neural ganglia.[12] Infection with SVV does not necessarily lead to lifelong latency, and periodic reactivation of SVV may occur.[3] SVV is genetically and antigenically similar to *Human herpesvirus 3*,[2] commonly known as varicela–zoster virus (VZV), the etiologic agent of chickenpox and shingles in humans. SVV in macaques and VZV in man present with similar clinical signs; SVV has been proposed as an animal model of VZV disease in man.[24] Rarely, VZV may occur in higher primates (Gorilla).[18] The 2 viruses must be distinguished from one another through molecular techniques.[1,410, 11] Both viral infections are usually mild and self-limiting in immunocompetent hosts,[4,8] reactivation and viral shedding may occur during times of stress or immunosupression.[80,21,22]

A recent review of SVV in Old World Monkeys[8] focused on SVV as a disease of nonhuman primates. This case report expands on the 2 most recent cases of SVV mentioned in that review.[8] The animals described were housed in accordance with the regulations of the Animal Welfare Act and the recommendations of the *Guide for the Care and Use of Laboratory Animals*[11] at the Washington National Primate Research Center (WaNPRC) facility in Seattle. The Institutional Animal Care and Use Committee of the University of Washington approved all aspects of the study to which the animals were assigned. The 2 clinical cases described in this report originated at the WaNPR–Seattle facility; contact animals described originated at the WaNPR–Tulane facility. When animals are relocated between the 2 facilities, they are processed through a domestic quarantine consisting of isolation for 30 d, during which time 3 tuberculin skin tests, 2 physical examinations, and 1 complete blood count and serological panel are performed. The WaNPRC–Tulane facility houses a breeding colony founded by animals relocated to Louisiana from the WaNPRC–Medical Lake facility in 1996.

## Case Report

In the fall of 2005, 2 adult female pigtailed macaques (*Macaca nemestrina*) developed clinical signs consistent with acute viral

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infection. Both animals were born and raised at the WaNPRC–Seattle facility. Both had received total-body irradiation (TBI) and had been reconstituted with autologous cells prior to presentation (11 and 15 mo, respectively). Neither animal was experimentally manipulated after reconstitution, and both were considered to be immunologically normal at the time of presentation. Both animals were housed in the same holding room, along with several other animals that had received TBI. Thirty days prior to presentation, animals exiting domestic quarantine were moved into the animal room. The animals exiting quarantine originated at the WaNPRC–Tulane facility.

**Case 1.** A 2.8-y-old female pig-tailed macaque presented to the clinical staff for an inguinal rash. The animal had received TBI 11 mo prior to presentation and had not been experimentally manipulated after reconstitution. At cageside physical exam, the animal was bright, alert, and responsive, with mild inguinal dermal hyperemia. The next day, the animal was sedated for examination and found to be hyperthermic (39.4 °C). Dermal hyperemia had progressed to an epidermal and mucosal (cheek pouch) vesicular rash extending from the inguinal region, to the ventrum and axilla bilaterally (centripetal spread). An epidermal vesicle was scraped; a smear of vesicular fluid and tissue was submitted for cytology. Histologic evaluation of the smear demonstrated suppurative inflammation; keratinocytes did not contain viral inclusions. Blood (Table 1) was submitted for serology (Laboratory Animal Diagnostic Services, BioReliance, Rockville, MD). Serology was negative for rubella and monkeypox by immunofluorescence assays (IFA) and for *Macacine herpesvirus 1* (McHV1; formerly *Cercopithecine herpesvirus 1*)[2] by ELISA. Treatment consisted of nonsteroidal antiinflammatory drugs, antibiotics, an antiviral agent (acyclovir; 100 mg/kg PO twice daily), and subcutaneous fluids. The animal was moved into isolation; the original housing room was quarantined. Despite aggressive medical management, the clinical condition remained unchanged for the subsequent 48 h. Antihistamines, additional antibiotics, and nutritional support were added to the treatment plan. Over the following 24 h, the animal became anorexic and lethargic; at 96 h after presentation, euthanasia was elected.

Gross necropsy demonstrated a myriad of raised, individual to coalescing vesicular (ulcerated and hemorrhagic) lesions of varying chronicity. Vesicles were present on all parts of the body except the palmar and plantar surfaces and ischial callosities (Figure 1 A through C). Vesicles contained straw-colored fluid; fur surrounding ruptured vesicles was matted and wet. At the mucocutaneous junction, vesicles were flat, ulcerative, opaque white plaques (Figure 1 B). Plaques covered the cheek pouches, sides and bottom of the tongue, oral pharynx, and epiglottis. Ulcerations and erosions were present within the oral cavity, esophagus, stomach, and small and large intestines. The lumen of the small intestines contained frank clotted blood. Multifocal petechial to ecchymotic hemorrhages were present within the epicardium, hepatic and splenic capsules, and adrenal cortex. The liver contained multiple pale spherical (diameter, 0.5 to 1 mm) foci (necrosis). The spleen was moderately enlarged and contained multiple pale foci (diameter, 0.5 to 1 mm) of subcapsular necrosis. On cut surface, lymphoid hyperplasia was evident. Lymph nodes were hemorrhagic and enlarged. All tissues examined were diffusely edematous. Gross lesions were consistent with a disseminated epitheliotropic viral infection. Generalized hemorrhage and edema was consistent with primary or secondary vascular injury, including such sequelae as disseminated intravascular coagulation.

Histopathologically, the integrity of the epidermis was disrupted by multiple vesicles, pustules, and ulcerations (Figure 1 D through F). Suprabasilar keratinocytes were multifocally degenerative, swollen, and often disassociated from one another, forming pustules that contained proteinaceous fluid, cellular debris, free erythrocytes, neutrophils, lymphocytes, and plasma cells. Keratinocytes, both free within vesicles and attached to the intact epidermis, occasionally contained eosinophilic to amphophilic intranuclear inclusion bodies, consistent with herpesviral infection (Figure 1 G). The dermis and musculature demonstrated mild to moderate reactive fibrosis and neovascularization. Adenexa were involved; glandular and hair follicle epithelium occasionally contained eosinophilic intranuclear herpetic inclusion bodies (Figure 1 H). Throughout the gastrointestinal tract, the epithelium was multifocally ulcerated; underlying tissues were necrotic and inflamed. Tissues adjacent to regions of necrosis often contained free erythrocytes (hemorrhage). The spleen contained abundant lymphoid follicles, confirming gross lymphoid hyperplasia. Hepatic and splenic parenchyma contained multifocal regions of cellular necrosis and hemorrhage, which correlated with gross regions of petechial hemorrhage. Cells at the borders of necrotic foci were degenerate and swollen, occasionally containing eosinophilic intranuclear herpetic inclusion bodies (Figure 1 I). Histopathologic lesions were consistent with an epitheliotropic herpetic viral infection, leading to secondary hemorrhage and edema (vascular leakage possibly related to a systemic immune response).

At necropsy, serology was repeated and remained negative for mumps, rubella, monkeypox, and McHV1. Serum collected at necropsy was assayed for measles virus (Morbillivirus; Paramyxovirus) and was negative (Table 1). Seroconversion to SVV positivity was demonstrated by IFA. For confirmation of virus, skin and pustular fluid were submitted to a molecular diagnostic testing company for animal samples (Zoologix, Chatsworth, CA). Buffy coat, skin, and pustular fluid samples were positive by ultrasensitive qualitative detection with nested PCR assays. Qualitative detection of VZV by PCR was negative. Lentiviral assays were performed to rule out immunosupression beyond the TBI procedure. Real-time RNA PCR assays were performed by using SIV–simian-human immunodeficiency virus and HIV2 EHO/287 primers; both were negative. A whole-virus ELISA for SIV was similarly negative. In addition, a Western blot reactive against the gag, pol, and env proteins of SIV and HIV2 (ZeptoMetrix, Buffalo, NY) was negative. All lentiviral assays were performed by the Virology Core at the WaNPRC. Simian retrovirus 2 (type D) (SRV-2) is part of biannual colony screening at the WaNPRC. One month prior to clinical disease, both cases 1 and 2 were negative for SRV-2 by ELISA, Western immunoblot, and PCR.

**Case 2.** A 4.5-y-old female pig-tailed macaque presented to the clinical staff with diffuse mild dermal hyperemia of the inguinal region 96 h after Case 1 was euthanized. Similar to Case 1, this animal had received TBI (15 mo prior) and had not been experimentally manipulated after reconstitution. The animal was sedated and shaved; physical exam demonstrated a diffuse, mild, vesicular dermatitis with mucocutaneous (buccal and glossal) ulcerations. Because of the poor response to treatment demonstrated by Case 1, euthanasia was elected. Gross necropsy demonstrated raised, individual to coalescing vesicular (ulcerated and hemorrhagic) lesions primarily within the inguinal region, with

**Table 1.** Virology data for clinical cases and the presumed index case

| | Sampling point | SVV (IFA) | McHV1 (IFA) | Rubella (IFA) | Measles (ELISA) | Monkeypox (IFA) | SVV (PCR)[a] | VZV (PCR)[a] |
|---|---|---|---|---|---|---|---|---|
| Case 1 | At presentation | negative | negative | negative | not done | negative | not done | not done |
| | At necropsy | positive | negative | negative | negative | negative | positive | negative |
| | Banked sample 1 | negative | not done | not done | not done | not done | not done | not done |
| | Banked sample 2 | negative | not done | not done | not done | not done | not done | not done |
| | Banked sample 3 | negative | not done | not done | not done | not done | not done | not done |
| Case 2 | At necropsy | equivocal | negative | negative | negative | negative | positive | negative |
| | Banked sample 1 | negative | not done | not done | not done | not done | not done | not done |
| | Banked sample 2 | equivocal | not done | not done | not done | not done | not done | not done |
| | Banked sample 3 | equivocal | not done | not done | not done | not done | not done | not done |
| Presumed index case | Presentation | positive | not done | not done | not done | not done | not done | not done |
| | Banked sample 1 | positive | not done | not done | not done | not done | not done | not done |
| | Banked sample 2 | positive | not done | not done | not done | not done | not done | not done |
| | Banked sample 3 | negative | not done | not done | not done | not done | not done | not done |

McHV1, *Macacine herpesvirus 1*
[a]SVV (*Cercopithecine herpesvirus 9*) and VZV (*Human herpesvirus 3*), are antigenically and phylogenetically related herpesviruses, that are distinguished molecularly by using PCR.

extension to the abdomen, neck, and face. Within the oral cavity, scattered plaques and ulcers were present along the mucocutaneous margins, tongue, soft, and hard palate. Petechial hemorrhages were present within the oralpharynx, liver, and kidneys. Lymph nodes were diffusely enlarged. Because this macaque was euthanized early in the progression of clinical disease, lesions were mild; the gastrointestinal tract was spared. Histopathologically, significant lesions were limited to the skin and liver. Gross epidermal vesicles corresponded to mild, subacute, lymphohistiocytic ulcerative and necrotizing vesicular dermatitis. The liver contained multiple foci of coagulative necrosis. Inclusion bodies were rare in both tissues. Serum obtained at necropsy demonstrated equivocal antibodies for SVV by IFA. Blood and buffy coat cells were positive for SVV by PCR and negative for VZV.

**Epidemiology.** Cases 1 and 2 had both been housed in the same room for longer than 6 mo before presentation. The occupants of this housing room were constant from 120 to 30 d prior to presentation and consisted primarily of animals that had received TBI. Serum samples were collected from resident animals within this room at the time of presentation of case 2. Samples were screened serologically for SVV and were confirmed to be seronegative. Thirty days prior to presentation of case 1, macaques from the WaNPRC Tulane facility were moved into the animal housing room after being processed through domestic quarantine. Serum from the new arrivals was screened for SVV. With the exception of 1 animal, all were seronegative. The seropositive macaque, a presumptive source or 'index case,' was antibody-positive by IFA; blood from this animal was negative for SVV and VZV by PCR. The 2 clinical cases and the presumptive index case were further tested by nested PCR specific for VZV. Samples from all 3 animals were negative, excluding the possibility of reverse zoonosis. PCR data were confirmed independently by 2 laboratories (Table 1). All remaining animals that had received TBI were isolated and placed on oral acyclovir at a prophylactic dose of 50 mg/kg given twice daily.

The movements of all animals cohoused (in domestic quarantine) with the presumed index case were traced to 4 separate housing rooms. Remaining quarantine cohort animals and secondary contact animals were placed in quarantine again; samples from animals in each of the 4 rooms were evaluated by IFA. Another 8 macaques (of 18 tested) from these rooms were found to be antibody-positive for SVV, and results for an additional animal were equivocal (Table 2).

Banked serum was assayed for SVV antibodies. Samples from the index case demonstrated seroconversion while housed at the WaNPR–Tulane facility during the year before arrival at the WaNPRC; seropositivity was maintained for a period of 18 mo. A selected colony survey was performed and included as a control population a 'stable' WaNPRC–Seattle facility animal housing room that had a closed animal population into which new animals did not enter. Because 3 (of 15) macaques from the stable housing room were seropositive, banked serum samples from the clinical cases and secondary contact animals were screened. Three banked samples from Case 1 were seronegative. The most recent banked sample from Case 2 was seronegative; 2 previous samples were equivocal by IFA. Banked samples from the secondary-contact seropositive animals were available for 7 of the 8 animals; 5 of the 7 samples were positive prior to exposure to the presumptive index case, demonstrating a background prevalence of SVV in the colony and bringing into question the concept of an index case. A further colony survey involving representative stable WaNPRC housing rooms demonstrated an overall colony prevalence of 20% SVV seropositivity within pigtailed macaques. We therefore conclude that SVV is endemic in the WaNPRC colonies both in Seattle and at the Tulane facility. This finding is logical given that SVV was known to exist within the WaNPRC Medical Lake

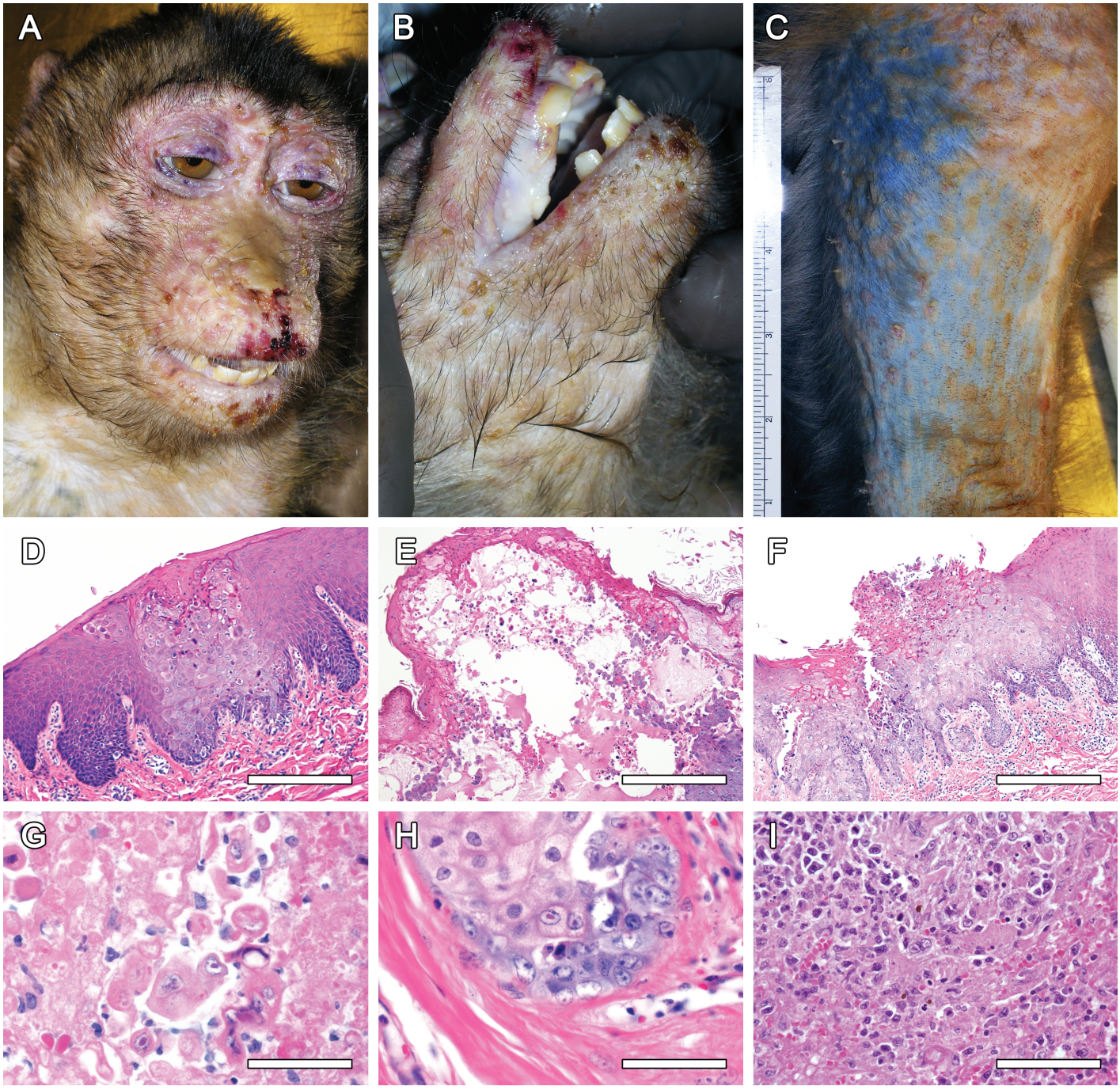


**Figure 1.** Gross and histopathologic images from case 1. (A) Simian varicella vesicular skin rash covering the face: mandibular–maxillary epidermis, mucocutaneous junction, and gingival involvement. Multiple vesicles are ruptured and hemorrhagic; vesicular exudate is multifocally crusted on the epidermis. (B) Simian varicella vesicular rash: mucocutaneous and gingival ulceration. (C) Simian varicella vesicular skin rash covering the abdomen and thorax (animal orientation: lateral with head at the top of image, legs at the bottom). Raised, multifocal to confluent vesicles ruptured upon shaving of the abdomen; vesicular exudate is multifocally crusted on the epidermis. (D) Vesicular dermatitis: early lesion with overlying epithelium intact. Bar, 50 µm. (E) Vesicular dermatitis: intact vesicle raising the epidermis. Vesicle contains necrotic keratinocytes, erythrocytes, and mononuclear inflammatory cells. Bar, 50 µm. (F) Vesicular dermatitis, ruptured vesicle with epidermal ulceration, keratinocytic degeneration and necrosis, and pyogranulomatous inflammation. Bar, 50 µm. (G) Necrotic and degenerative keratinocytes; abundant herpetic amphophilic to eosinophilic intranuclear inclusion bodies with paranuclear clearing. Bar, 250 µm. (H) Dermal adenexa with glandular epithelial degeneration and occasional herpetic inclusions. Bar, 250 µm. (I) Necrohemorrhagic hepatitis with disassociation of hepatic chords and occasional to rare herpetic inclusions. Bar, 100 µm.

**Table 2.** Serology from SVV colony survey by IFA

| | No. of animals tested | SVV-seropositive animals | |
|---|---|---|---|
| Stable housing room[a] | 15 | 3 | |
| Quarantine cohort | 10 | 1[b] | |
| Secondary-contact animals | 18 | 8 | |
| | | No. of preexposure samples available for testing[c] | No. of animals seropositive before exposure to index case |
| | | 7 | 5 |

[a]No animal movement for 18 mo (control population)
[b]Presumed index case
[c]Serology of samples from seropositive secondary-contact animals obtained and banked before their exposure to the presumed index case

colony as Medical Lake macaque virus;[23] the Medical Lake colony was relocated to the Seattle and Tulane facilities in 1996.

## Discussion

On presentation, both clinical cases were assessed for possible etiologies; viral causes were determined to be the most likely based on clinical presentation and progression. The differential diagnosis of exanthematous disease in a nonhuman primate includes SVV, morbillivirus (measles), McHV1, and SIV. Measles causes an erythematous maculopapular abdominal rash that may extend to the inner thighs and perhaps white necrotic foci with a hyperemic rim (Koplik spots) on the oral mucosa.[13] Bronchointersitial pneumonia with syncytial giant cells accompanies the dermal lesions. The classic SVV rash can be differentiated clinically because it is centripetal in spread and vesicular in nature. In addition, pneumonia is not a common sequela to SVV infection. The animals presented in these cases were not vaccinated for measles. Measles serology should be analyzed in the context of vaccination, a common practice at some primate centers. With vaccination, a positive titer would indicate protection from disease in immunocompetent animals.

The etiologic agents of vesicular disease in nonhuman primates include the alphaherpesviruses SVV and McHV1. McHV1 can cause vesicular and ulcerative lesions, most commonly confined to the oral and genital mucosa. In immunocompromised animals, viral infection can disseminate to most visceral organs and cause necroulcerative lesions throughout the gastrointestinal tract. A positive titer to McHV1 would have complicated diagnosis in these cases. Similar to SVV, McHV1 can become latent; infection may produce a positive titer in the absence of overt clinical disease. Human herpesvirus 3 is the human counterpart to McHV1 and must be considered a potential reverse zoonosis. Similarly, rubella (German measles) is a potential reverse zoonosis which presents in humans with a centripetal vesicular rash. Monkeypox can cause epidermal lesions in nonhuman primates; however, cutaneous lesions are raised and proliferative in nature with characteristic eosinophilic intracytoplasmic viral inclusions.[14] Given the clinical presentation, SVV was the most likely cause of disease; serology confirmed the diagnosis (Table 1).

At the onset of serologic investigation, cases 1 and 2 were thought to represent a new introduction of SVV into the WaNPR–Seattle facility. The first round of serology demonstrated that a single seropositive animal entered a room containing seronegative animals, many of which had previously undergone TBI. The seropositive animal was presumed to be responsible for viral shedding, exposure, and clinical disease in cases 1 and 2; therefore, it was thought of as an index case. It was not possible to demonstrate active viral shedding in this animal by PCR, but this difficulty is not surprising; with intermittently shedding latent viruses, only animals with clinical signs will be PCR-positive. Carriers of SVV are best detected through antibody assays.

A second round of serology was performed to include animals with contact to the presumptive index case while in quarantine and thereafter (Table 2). Greater than 50% of these secondary contact animals were SVV-seropositive. Until serology from banked samples was examined, seropositivity was attributed solely to exposure to the presumptive index case. Further investigation demonstrated that as many as 20% of all colony animals were seropositive, both in Seattle and at the Tulane facility. This finding negated the need for SVV quarantine but demonstrated the acute need for knowledge of viral status before experimental alterations of the immune system. Based on this outbreak, an inhouse ELISA has been developed to screen animals for SVV before TBI. Previous reports have documented SVV recrudescence after gamma radiation[13] in macaques; however, affected animals were not fully reconstituted at the onset of clinical disease. In the cases presented here, animals were presumed to be immunologically normal.

SVV and VZV are highly contagious viruses in nonhuman primates and humans, respectively. In immunocompetent animals, SVV demonstrates a high incidence of asymptomatic or mild disease with seroconversion. Why severe disease develops in a small proportion of affected animals is unknown, but SVV has been documented to produce symptomatic disease in cases of immunosupression.[5,15,19] Immune incompetence may have contributed to clinical disease in the 2 cases described. In addition, the stress of animal introductions into an established housing room may have precipitated viral shedding in a seropositive animal; exposure of animals that had received TBI to viral shedding precipitated clinical disease. Our initial view that these animals were immunologically competent after bone marrow reconstitution was based on normal blood profiles (complete blood count and serologic panels) and the length of time after TBI during which the animals were clinically healthy. However, assessment of cellular immunity was limited to cell count and assumed function based on lack of clinical disease. As demonstrated serologically, the humoral immune system in TBI-treated animals is capable of mounting a selective antibody response. In humans, TBI can result in severe and prolonged immunosupression, with alterations in both cellular and humoral immune responses for more than 1 y.[17]. The disparity between host and donor human leukocyte antigen is the leading cause affecting immune reconstitution.[17] If TBI-treated macaques are similarly immunoincompetent after

irradiation, they may have increased susceptibility to reactivation of latent viruses and systemic disease. Evaluation of lymphocyte and CD subsets after TBI may be useful in clinical determination of immunocompetence.

In humans, herpesviruses (particularly VZV) are important pathogens in TBI and chemotherapy patients.[15,19] The high incidence of symptomatic recurrent herpesvirus infections after TBI is associated with decreased CD4 cells and therefore reduced inhibition of viral reactivation.[15] Long-term prophylactic therapy with antivirals is common practice in humans[19] and might be considered for TBI-treated macaques. Acyclovir, when given for prophylaxis (50 mg/kg PO twice daily), is administered at half of the treatment dosage (100 mg/kg PO twice daily). Such prophylaxis may protect animals of unknown immune status from potential exposure to SVV. Prophylaxis is an important consideration in animal rooms that continually receive new animals because risk is related to both the viral status of incoming animals and the stress of animal introductions, which may precipitate shedding in seropositive animals. Quarantine and isolation procedures, as well as prophylactic acyclovir treatment for TBI-treated animals, contained the spread of SVV disease in the presented outbreak.

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## References

1. **Clarke P, Matlock WL, Beer T, Gilden DH.** 1996. A simian varicella virus (SVV) homolog to varicella-zoster virus gene 21 is expressed in monkey ganglia latently infected with SVV. J Virol **70:**5711–5715.
2. **Davidson AJ, Eberle R, Ehlers B, Hayward GS, McGeoch DJ, Minson AC, Pellett PE, Roizman B, Studdert MJ, Thiry E.** 2009. The order *Herpesvirales*. Arch Virol **154:**171–177.
3. **Dueland AN.** 1996. Latency and reactivation of varicella–zoster virus infections. Scand J Infect Dis Suppl **100:**46–50.
4. **Fletcher TM 3rd, Gray WL.** 1992. Simian varicella virus: characterization of virion and infected-cell polypeptides and the antigenic cross-reactivity with varicella–zoster virus. J Gen Virol **73:**1209–1215.
5. **Gilden DH, Cohrs RJ, Mahalingam R.** 2003. Clinical and molecular pathogenesis of varicella virus infection. Viral Immunol **16:**243–258.
6. **Gray WL.** 2003. Pathogenesis of simian varicella virus. J Med Virol **70 Suppl 1:**S4–S8.
7. **Gray WL.** 2004. Simian varicella: a model for human varicella–zoster virus infections. Rev Med Virol **14:**363–381.
8. **Gray WL.** 2008. Simian varicella in Old World monkeys. Comp Med **58:**22–30.
9. **Gray WL, Oakes JE.** 1984. Simian varicella virus DNA shares homology with human varicella–zoster virus DNA. Virology **136:**241–246.
10. **Gray WL, Williams RJ, Soike KF.** 1998. Rapid diagnosis of simian varicella using the polymerase chain reaction. Lab Anim Sci **48:**45–49.
11. **Institute for Laboratory Animal Research.** 1996. Guide for the care and use of laboratory animals. Washington (DC): National Academies Press.
12. **Kennedy PG, Grinfeld E, Traina-Dorge V, Gilden DH, Mahalingam R.** 2004. Neuronal localization of simian varicella virus DNA in ganglia of naturally infected African green monkeys. Virus Genes **28:**273–276.
13. **Kolappaswamy K, Mahalingam R, Traina-Dorge V, Shipley ST, Gilden DH, Kleinschmidt-Demasters BK, McLeod CG Jr, Hungerford LL, DeTolla LJ.** 2007. Disseminated simian varicella virus infection in an irradiated rhesus macaque (*Macaca mulatta*). J Virol **81:**411–415.
14. **Lewis A.** 2007. Diseases of nonhuman primates. Presented at the CL Davis Foundation Gross Morbid Anatomy of Disease of Animals, Silver Springs, MD. [Cited 07 Jul 2009]. Available at http://www.cldavis.org/cgi-bin/download.cgi?pid=87.
15. **Maeda Y, Teshima T, Yamada M, Harada M.** 2000. Reactivation of human herpesviruses after allogenic peripheral blood stem cell transplantation and bone marrow transplantation. Leuk Lymphoma **39:**229–239.
16. **Mahalingam R, Traina-Dorge V, Wellish M, Smith J, Gilden DH.** 2002. Naturally acquired simian varicella virus infection in African green monkeys. J Virol **76:**8548–8550.
17. **Maury S, Mary JY, Rabian C, Schwarzinger M, Toubert A, Scieux C, Carmagnat M, Esperou H, Ribaud P, Devergie A, Guardiola P, Vexiau P, Charron D, Gluckman E, Socié G.** 2001. Prolonged immune deficiency following allogenic stem cell transplantation: risk factors and complications in adult patients. Br J Haematol **115:**630–641.
18. **Myers MG, Kramer LW, Stanberry LR.** 1987. Varicella in a gorilla. J Med Virol **23:**317–322.
19. **Peritz DC, Duncan C, Kurek K, Perez-Atayde AR, Lehmann LE.** 2008. Visceral varicella–zoster virus (VZV) after allogenic hematopoietic stem cell transplant (HSCT) in pediatric patients with chronic graft-versus-host disease (cGVHD). J Pediatr Hematol Oncol **30:**931–934.
20. **Roberts ED, Baskin GB, Soike K, Gibson SV.** 1984. Pathologic changes of experimental simian varicella (Delta herpesvirus) infection in African green monkeys (*Cercopithecus aethiops*). Am J Vet Res **45:**523–530.
21. **Schoeb TR, Eberle R, Black DH, Parker RF, Cartner SC.** 2008. Diagnostic exercise: papulovesicular dermatitis in rhesus macaques (*Macaca mulatta*). Vet Pathol **45:**592–594.
22. **Treuting PM, Johnson-Delaney C, Birkebak TA.** 1998. Diagnostic exercise: vesicular epidermal rash, mucosal ulcerations, and hepatic necrosis in a cynomolgus monkey (*Macaca fascicularis*). Lab Anim Sci **48:**384–386.
23. **Wenner HA, Abel D, Barrick S, Seshumurty P.** 1977. Clinical and pathogenetic studies of Medical Lake macaque virus infections in cynomolgus monkeys (simian varicella). J Infect Dis **135:**611–622.
24. **White TM, Gilden DH, Mahalingam R.** 2001. An animal model of varicella virus infection. Brain Pathol **11:**475–479.