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Simian Varicella in Old World Monkeys

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Simian varicella virus (SVV) causes a natural erythematous disease in Old World monkeys and is responsible for simian varicella epizootics that occur sporadically in facilities housing nonhuman primates. This review summarizes the biology of SVV and simian varicella as a veterinary disease of nonhuman primates. SVV is closely related to varicella–zoster virus, the causative agent of human varicella and herpes zoster. Clinical signs of simian varicella include fever, vesicular skin rash, and hepatitis. Simian varicella may range from a mild infection to a severe and life-threatening disease, and epizootics may have high morbidity and mortality rates. SVV establishes a lifelong latent infection in neural ganglia of animals in which the primary disease resolves, and the virus may reactivate later in life to cause a secondary disease corresponding to herpes zoster. Prompt diagnosis is important for control and prevention of epizootics. Antiviral treatment for simian varicella may be effective if administered early in the course of infection.

Abbreviations: FEAU, 1-(2´-deoxy-2´-flouro-β-D-arabinofuranosyl)-5-iodouracil; IE, immediate early; ORF, open reading frame; PBL, peripheral blood lymphocyte; SVV, simian varicella virus; VZV, varicella–zoster virus

Simian varicella is a natural erythematous disease of Old World primates (Superfamily Cercopithecoidea, Subfamily Cercopithecinae), involving particularly patas (*Erythrocebus patas*), African green or vervet (*Chlorocebus aethiops*), and various species of macaque (*Macaca* spp.) monkeys. Epizootics of simian varicella occur sporadically in facilities housing nonhuman primates. These outbreaks are sometimes associated with high morbidity and mortality and the loss of valuable research animals. Simian varicella virus (SVV; *Cercopithecine herpesvirus 9*), a primate herpesvirus, is the etiologic agent of the disease. SVV is antigenically and genetically related to varicella–zoster virus (VZV; *Human herpesvirus 3*), the cause of human varicella (chickenpox) and herpes zoster (shingles). The clinical similarities between simian and human varicella and the relatedness of SVV and VZV, indicate that SVV infection of nonhuman primates is a useful model for study of varicella pathogenesis and development of antiviral therapies. A previous comprehensive review emphasized simian varicella as an experimental model for VZV infections.[22] This review focuses on simian varicella as a veterinary disease of nonhuman primates. Simian varicella outbreaks and their epidemiology are considered, and the etiologic agent, clinical manifestations, pathogenesis, diagnosis, treatment, and control of the disease are discussed.

Simian Varicella Epizootics and Epidemiology

Simian varicella outbreaks have occurred over the past several decades in primate facilities worldwide (Table 1). In 1967 an outbreak of a varicella-like disease occurred at a medical school in England.[11] Five newly acquired African vervet monkeys from Nairobi were introduced into a colony of 12 vervet monkeys that had been housed together for over 1 y. Two of the 5 newly acquired monkeys and 7 of the existing monkeys developed simian varicella, characterized by fever, vesicular skin rash, visceral dissemination, and high morbidity. Five of the 9 infected monkeys (56%) died within 48 h of the appearance of the rash. The remaining animals were euthanized to terminate the epizootic.

A year later, a varicella-like disease occurred in a group of 47 African patas monkeys at a commercial laboratory in England.[57] The affected monkeys had recently been imported from Nigeria and Chad and were quarantined in a single room. Eight of the monkeys died within 5 to 8 wk of arrival with symptoms resembling the earlier varicella outbreak in vervet monkeys. The epizootic spread to an adjacent room housing 48 patas monkeys, resulting in 12 deaths and euthanasia of 7 additional monkeys exhibiting vesicular skin rash. Further spread of the disease was prevented by euthanasia of the remaining animals.

A primate research center in Louisiana experienced similar outbreaks of simian varicella in patas monkeys in 1968 and again in 1974.[3,68] The epizootics were associated with severe disease and approximately 50% mortality. Newly imported monkeys were not associated with these outbreaks. The monkeys involved in the 1974 occurrence had been housed together for at least 6 mo, suggesting that the epizootic was initiated by reactivation of a latent virus.

A series of simian varicella outbreaks involving macaque monkeys occurred between 1969 to 1971 at a field station of a primate research center in Washington.[7] The disease involved primarily pigtailed macaques (*Macaca nemestrina*), although a few Japanese macaques (*M. fuscata*) and cynomolgus (*M. fasicularis*) monkeys also developed clinical symptoms. The severity of disease and the mortality rate (1.9%) were lower than those in previously reported epizootics. The disease likely was introduced into the colony by newly acquired monkeys from Southeast Asia.

Major simian varicella outbreaks occurred during the 1980s in primate facilities in Maryland (1981), North Carolina (1983), and Virginia (1984).[73] The 1981 epizootic involved a total of 101 patas monkeys and started in a room housing male monkeys, with an outbreak involving 100% morbidity and 44% mortality.[19,71] Fourteen days later, the disease spread to an adjoining room housing

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Table 1. Simian varicella outbreaks and clinical isolates

Year	Location	Monkey species	No. of clinical infections	No. of deaths	SVV isolate
1966	Liverpool, UK	*Chlorocebus aethiops*	9	5	Liverpool vervet virus (LVV)
1967	Glaxo Labs, UK	*Erythrocebus patas*	27	20	Patas herpesvirus (PHV)
1968	Delta Primate Center, USA	*Erythrocebus patas*	24	12	Delta herpesvirus (DHV1)
1969	Washington Primate Center, USA	*Macaca nemestrina*	20	9	Medical Lake Macaque virus (MLMV)
1970	Washington Primate Center, USA	*Macaca fasicularis*	50	4	Medical Lake Macaque virus (MLMV)
1974	Delta Primate Center, USA	*Erythrocebus patas*	24	14	Delta herpesvirus (DHV2)
1981	Litton Labs, USA	*Erythrocebus patas*	101	44	Litton herpesvirus
1983	Bowman Gray University, USA	*Chlorocebus aethiops*	9	5	Bowman Gray herpesvirus
1984	Hazelton Labs, USA	*Chlorocebus aethiops*	NR	8	Hazelton herpesvirus (HAZV)
		Macaca fasicularis	NR	5	
		Macaca mulatta	NR	2	
1989	Tsukuba Primate Center, Japan	*Macaca fasicularis*	111	46[a]	Tsukuba herpesvirus

NR, not reported.
[a]Figure includes 31 infected monkeys with severe disease that were euthanized to terminate the outbreak.

female monkeys, with a mortality rate of 12%. The 1983 outbreak in North Carolina was somewhat less contagious, with only 9 cases of acute disease and 5 deaths among the 49 African green monkeys that were exposed to the infection.[48] More than 400 animals were at risk during the 1984 epizootic, but early initiation of antiviral treatment helped control the outbreak, and fatalities were limited to 8 vervet monkeys, 5 cynomolgus monkeys, and 2 rhesus monkeys (*M. mulatta*).[73]

In Japan, an outbreak in 1989 involved 111 clinical cases of simian varicella in cynomolgus monkeys.[82] Despite early control measures and antiviral intervention, 46 monkeys died, including 31 animals with severe clinical signs that were euthanized to prevent further spread of the disease.

In addition to these reported major epizootics, smaller outbreaks and individual cases of simian varicella have occurred sporadically in primate facilities, including a report of varicella-like disease involving 2 African green monkeys at a New Orleans, LA, zoo.[46,59,68,83] Most recently, cases of fatal simian varicella have been reported in monkeys 3 to 15 mo after experimental total-body irradiation.[40,46]

Simian varicella appears to be an uncommon natural infection of Old World monkeys in the wild, on the basis of an epidemiologic analysis of sera collected from monkeys in Southeast Asia.[7] The incidence of SVV antibodies in newly captured wild pigtailed and cynomolgus macaque monkeys in Malaysia was only 0.8%. However, the frequency of animals exposed to SVV increased dramatically with length of captivity in the holding facility, such that SVV antibodies were detected in 4% of monkeys held for less than 1 mo but in more than 40% of monkeys held for more than 3 mo.

Varicella-like disease has also been described in hominoid apes, including chimpanzees (*Pan troglodytes*), gorillas (*Gorilla gorilla*), and orangutans (*Pongo pygmaeus*).[39,45,56,58,61] The herpesviruses responsible for most of these outbreaks were not characterized. However, in 1 case of varicella infection in a zoo gorilla, the causative agent was confirmed to be VZV, not SVV, by restriction endonuclease analysis of viral DNA.[61]

SVV-related disease in humans has not been reported, possibly because of species specificity of SVV for nonhuman primates but perhaps also because prior exposure to VZV as chickenpox may confer immunity against subsequent SVV infection. However, researchers and veterinary staff working with infectious virus or handling SVV-infected monkeys or tissues should take protective measures to safeguard against possible infection.

SVV Infectious Agent

In several of the simian varicella epizootics, a viral agent with typical herpesvirus morphology was isolated from tissues of infected monkeys. The viral isolates initially were given names related to the monkey species involved or the location of the epizootic (Table 1) and were classified as distinct viruses. However, restriction endonuclease analysis of viral DNAs derived from epidemiologically distinct isolates confirmed that all of the isolates are closely related and are classified as members of the *Cercopithecine herpesvirus 9* species within the *Varicellovirus* genus of alphaherpesviruses.[26]

Simian cell cultures, usually African green monkey kidney (Vero, BSC1, CV1) cells, are used to grow infectious SVV in vitro.[70] The cytopathic effect of infected monolayers includes swollen, rounded, multinucleated cells that eventually detach (Figure 1A). Viral nucleocapsids within the cell nucleus are evident on electron microscopy (Figure 1B). SVV, like VZV, is highly cell-associated in cell culture due to the sensitivity of the virus to cellular lysosomal enzymes. Degraded viral particles occur within cytoplasmic vacuoles, and extracellular viral particles include a mixture of intact and degraded virions. Therefore, a relatively low titer of infectious virus (10^2 to 10^4 PFU/ml) is released from infected cells into the media. Serial passage of virus in cell culture generally is conducted by means of transfer of infected cells rather than with cell-free virus. In addition, virus stocks are cryopreserved at –70 °C or in liquid nitrogen as infected cells.

SVV virions are 170 to 200 nm in diameter and include a viral envelope surrounding an icosahedral nucleocapsid that includes the viral double-stranded DNA genome. The virions are composed of at least 30 protein species, which range in size from 16 kDa to greater than 200 kDa and include at least 6 glycoprotein species (46 to 115 kDa).[17] The SVV virion proteins share extensive antigenic crossreactivity with corresponding VZV polypeptides.

The SVV and VZV genomes are similar in size, structure, and genetic content, sharing 70% to 75% DNA homology.[27,33,34,65] The DNA sequence of the entire SVV genome has been determined.[35]

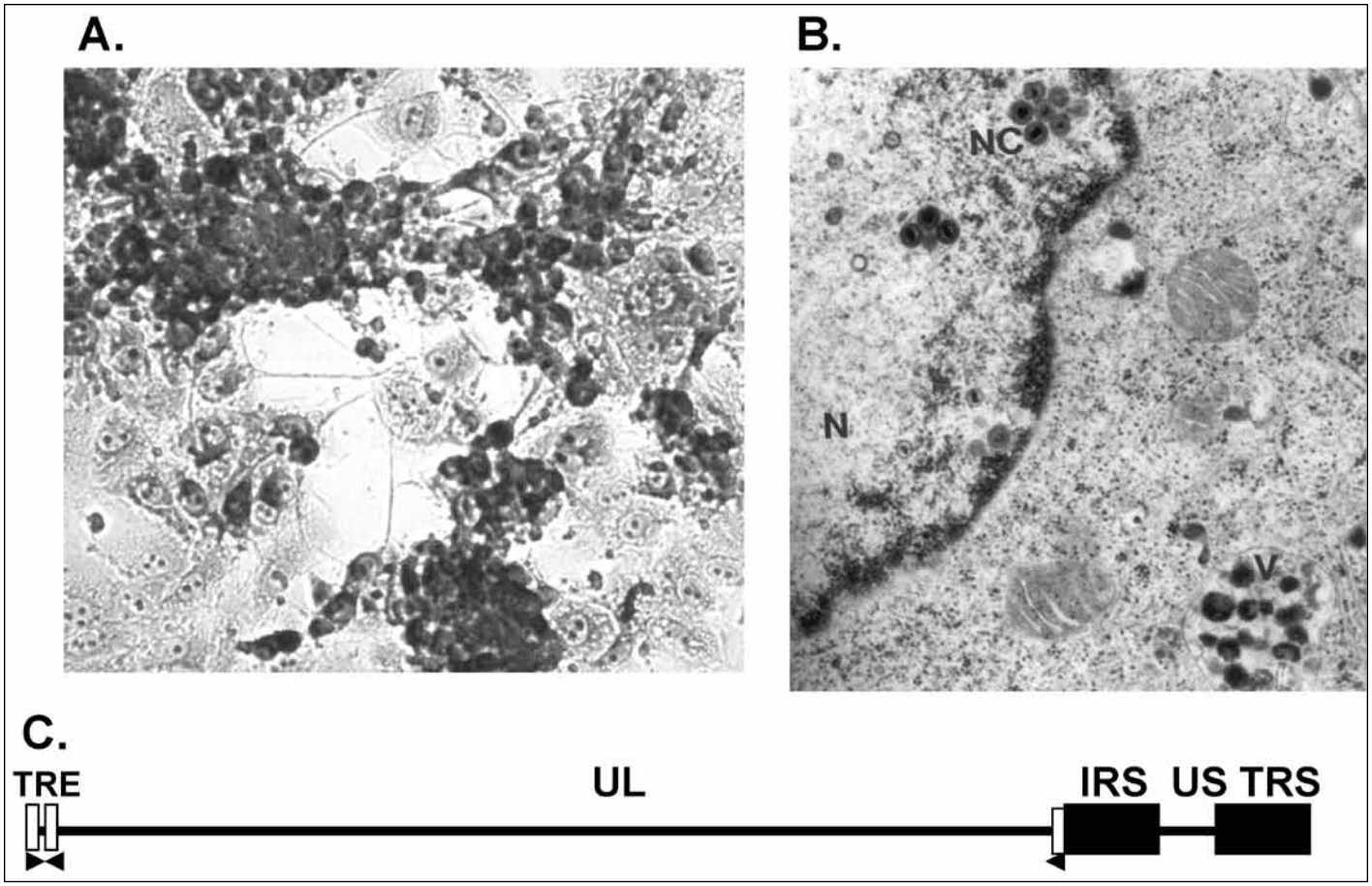

Figure 1. SVV-infected Vero cells and the SVV genome. (A) Light microscopy of SVV cytopathic effect in a Vero cell monolayer (magnification, ×20). (B) Electron microscopy of a SVV-infected Vero cell. Note the SVV nucleocapsids (NC) within the cell nucleus (N) and degraded virions within cell vacuoles (V). Reprinted with kind permission by Springer Science and Business Media.[62] (C) The 124.7-kb SVV genome includes a long (L) component with a unique long region (UL) bracketed by 64-bp repeat sequences (open rectangles) and a short (S) component composed of a unique short (US) sequence bracketed by 7.5-kb internal and terminal inverted repeats (IRS and TRS, respectively). The invertable terminal repeat element (TRE) at the left end of the genome is indicated.

SVV DNA is 124,785 bp in size, 99 bp shorter than VZV DNA, and its guanosine-plus-cytosine content is 40.4%, compared with 46.0% for VZV DNA. The viral genome includes a 104.1-kb unique long component, which is bracketed by 64-bp inverted-repeat sequences, and a short component that comprises a 4.9-kb unique short region bracketed by 7.6-kb inverted-repeat sequences (Figure 1C). SVV DNA includes 4 tandem direct repeat sequences denoted as R1, R2, R3, and R4, and 3 of these (R2, R3, and R4) correspond to reiterations in similar locations within the VZV genome.[35] These direct repeat elements can vary in number and length so that SVV genomes of various SVV isolates may vary slightly in size. Whether these repeats have a function in viral replication is unknown.

A total of 69 distinct SVV open reading frames (ORFs) have been identified, including 3 that are duplicated within the inverted repeats of the short component. Each of the SVV ORFs shares extensive homology to a corresponding VZV gene. Some differences do exist between the leftward termini of the SVV and VZV genomes.[55] SVV encodes an 882-bp ORF A, which is absent in VZV and is a truncated homolog of ORF 4; ORF4 is present in both SVV and VZV and encodes a viral transactivator protein. The function of the ORF A is unknown, but it is nonessential for SVV replication in cell culture.[23] SVV lacks a homolog of the VZV ORF 2, which encodes a membrane phosphoprotein of unknown function that is not required for replication in vitro.[69] Finally, the SVV left end includes a 665-bp invertable terminal element that is also present in other varicelloviruses (*Equid herpesviruses 1* and *4* and pseudorabies virus [*Suid herpesvirus 1*]) but is absent in VZV DNA.[50]

Investigation of SVV gene function during lytic infection is inhibited by the inability to obtain high-titer infectious virus stocks or to induce synchronous infections in cell culture. However, SVV gene expression, like that of VZV and other alphaherpesviruses, is considered to be coordinately regulated into immediate early (IE), early, and late phases. The ORF62 product (IE62) is a strong transactivator that stimulates the expression of SVV IE, early, and late genes. The SVV ORF4 and ORF61 proteins are modest viral transactivators, as indicated by in vitro transfection assays.[25] Several SVV early genes, which are involved in viral DNA replication, have been identified and characterized, including the viral dUTPase (ORF8), ribonucleotide reductase (ORF19), viral thymidine kinase (ORF 36), and uracil DNA glycosylase (ORF59).[4,67] SVV glycoproteins, encoded by putative viral late or delayed early genes, have also been characterized, including SVV

gB (ORF31), gC (ORF14), gE (ORF68), gH (ORF37), and gL (ORF 60).[5,25,31,66] Viral genes across the SVV genome are expressed during lytic infection.[28]

Studies on the role of SVV genes in viral replication and pathogenesis are facilitated by the ability to generate gene-specific viral mutants. A SVV cosmid-based recombination system for generating mutations in the SVV genome has been developed.[30] SVV DNA fragments (30 to 45 kb in size), which collectively include the entire SVV genome, were cloned into cosmid vectors. Transfection of Vero cells with 4 overlapping SVV cosmids (A, B, C, and D) generates infectious SVV clones within 10 d. Infectious SVV clones generated in this manner replicate as efficiently does as wild-type SVV.[30] The RecA-assisted restriction endonuclease cleavage procedure has been used to insert site-specific mutations and foreign genes into individual cosmids for generation of SVV gene mutants and recombinant viruses, respectively.[16] To date, mutants lacking SVV gC, ORF61, ribonucleotide reductase, uracil DNA glycosylase, and dUTPase have been constructed. [23-25] Each of these SVV mutants replicates efficiently in cell culture, indicating that the mutated genes are nonessential for in vitro replication. In addition, SVV recombinant viruses expressing the SIV gag and env antigens have also been constructed.[64]

Simian Varicella Transmission, Clinical Signs, and Pathology

Inhalation of aerosolized infectious droplets is the most likely mode of simian varicella transmission, but direct contact transmission via infected skin lesions is also possible.[48,89] Intratracheal inoculation of African green (vervet) monkeys with SVV-infected Vero cells is commonly used for experimental SVV infection because it provides a method to deliver a controlled SVV dose in a manner that simulates the respiratory route of infection.[21,36] Alternatively, a natural method of experimental infection sometimes is used and involves exposure of susceptible animals to monkeys infected by intratracheal inoculation.[53] After experimental infection, SVV replicates in the respiratory epithelium of the lungs, invades the bloodstream, and establishes a viremia, which disseminates the virus throughout the body (Figure 2). After their coculture with Vero cells, infectious SVV in peripheral blood lymphocytes (PBLs) is detected as early as day 3 after infection. SVV DNA can be detected in circulating T cells and B cells, but not monocytes, on day 10 after infection, suggesting that these infected lymphocytes disseminate SVV during viremia.[87] The viremia is transient, because PBLs harboring infectious virus generally are not detected after day 11 postinfection, corresponding to onset of humoral and possibly cellular immune responses to SVV.[29]

The incubation period for simian varicella is 7 to 14 d, corresponding to the 10- to 15-d incubation period for human chickenpox (Figure 2). The first sign of clinical disease is a vesicular skin rash, which often first appears in the inguinal area around days 8 to 10 after infection, followed by a generalized erythematous rash with lesions on the face, thorax, and abdomen but not on the palms, soles of the feet, or ischial callosites (Figure 3A).[36] The lips and oral cavity, including the tongue and gingiva, also may exhibit lesions. Crops of skin lesions ranging from macules to papules to vesicles (2 to 4 mm in size) appear over the next several days, reaching a maximum around days 11 to 13 after infection and diminishing between days 14 to 18 after infection, as the skin lesions progress to crusted scabs. Monkeys with acute

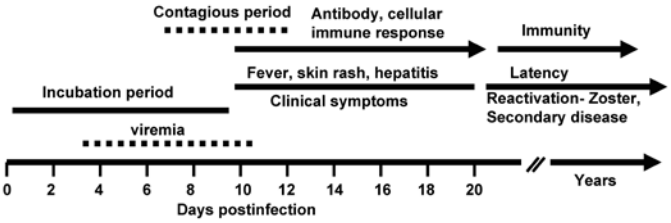

Figure 2. Pathogenesis and clinical course of simian varicella.

simian varicella exhibit other symptoms, including mild fever, lethargy, loss of appetite, and a mild hepatitis that can be detected on day 10 postinfection by elevated serum aminotransaminase enzyme levels. A transient elevated PBL cell count is detected in some infected monkeys.

Clinical simian varicella may range from a mild infection to a severe and life-threatening disease. In some cases, the disease may be overlooked unless the animals are examined carefully, because animal hair may hide a mild rash. In contrast, a severe hemorrhagic skin rash is a poor prognostic sign that is associated with pneumonia, hepatitis, and an incidence of high mortality (Figure 3B). Asymptomatic primary infection is also possible, as indicated by detection of antiSVV antibodies in monkeys with no history of clinical varicella.[85] Severity of disease has not been correlated with specific monkey species, housing conditions, or environmental factors.

Gross and histopathologic changes are evident in the skin, lung, liver, spleen, and other tissues of acutely infected animals and may vary depending on the severity of infection.[12,32,36] Skin vesicles result from ballooning degeneration of the epidermis and include multinucleated syncytial giant cells. Vesicle fluids contain infectious virus which may serve as a source for spread of infection. The lungs and liver may grossly have a mottled appearance due to hemorrhage, especially in severely infected monkeys. Pulmonary pathology may range from mild edema to extensive congestion and hemorrhage with alveolar wall necrosis and thickening, and fibrin formation. The liver may exhibit multifocal necrosis and cytoplasmic vacuolation.[32] Viral intranuclear inclusions are evident in infected alveolar cells and hepatocytes. SVV infection may be widespread with histopathology and inflammation apparent in other tissues including the esophagus, kidney, adrenals, and gastrointestinal epithelium.[12] SVV antigens and viral DNA and RNA are readily detected in tissues of acutely infected monkeys.[21,36]

Although simian varicella can be fatal, animals otherwise resolve the acute disease without residual complications or sequelae within 21 d after infection, as humoral and cellular immune responses effectively clear the infection. Animals that survive the primary infection develop immunity against subsequent simian varicella derived from exogenous SVV infection.[29] However, the animals remain latently infected and may experience endogenous reactivation disease despite being SVV seropositive.

SVV Latency and Reactivation

SVV, like other neurotropic herpesviruses, establishes in neural ganglia a latent infection, as defined by persistence of the viral genome in ganglionic cells but in the absence of infectious virus in the ganglia or other tissues.[60] SVV latency initially was demonstrated through detection of viral DNA in neural ganglia but

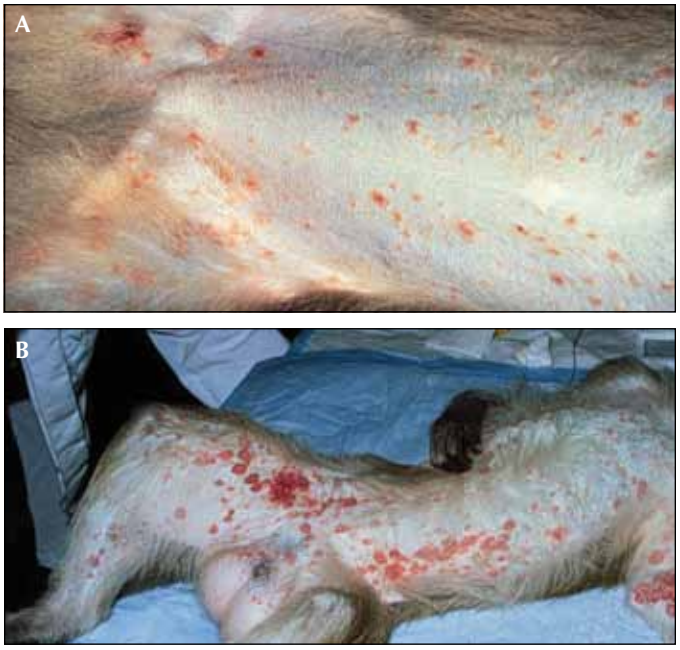

Figure 3. Simian varicella skin rash. (A) Typical skin vesicles observed in a monkey with uncomplicated simian varicella.[73] Reprinted with permission from Blackwell Publishing. (B) Hemorrhagic skin rash in a monkey with severe varicella. Photograph provided by the Washington National Primate Research Center.

not brain, lung, or liver tissues of experimentally infected monkeys that had resolved the acute disease.[49,51] Viral DNA along the neuraxis was present in trigeminal, cervical, thoracic, and lumbar ganglia collected from monkeys at 5 mo to 4 y after the initial SVV infection. SVV DNA localizes predominantly within ganglionic neurons, as demonstrated by in situ PCR analysis and in situ hybridization.[44]

Recent studies using sensitive DNA detection methods, including nested PCR and real-time PCR, have indicated that SVV DNA may persist in ganglia as well as other tissues of experimentally infected monkeys after intratracheal inoculation. SVV DNA was detected in low copy number in liver and lung tissues of experimentally infected monkeys for as long as 12 mo postinfection and in CD4+ and CD8+ T cells derived from peripheral blood for nearly 2 y after infection.[87,88] The finding regarding T cells indicates that SVV can establish a low-level persistent or latent infection in lymphocytes. VZV DNA has also been detected in the PBLs of VZV-seropositive persons at various times after resolution of chickenpox.[20,84] In naturally infected monkeys, SVV DNA is detected in latently infected ganglia, but not in PBLs or liver or lung tissues.[53] However, these studies are consistent and indicate viral latency in light of the inability to detect infectious virus in the ganglia or other tissues of monkeys in which acute disease resolved.

The route and timing through which SVV establishes latent infection is not clear. SVV infection of the skin may enable the virus to invade nerve endings, thus facilitating transaxonal transport to neural ganglia. Alternatively, SVV may gain access to the ganglia early in infection during viremia, as supported by the following findings:[54] (1) by day 6 after infection, before the onset of rash, SVV DNA can be detected in ganglia of experimentally infected monkeys; (2) SVV DNA can be present in ganglia of monkeys that do not develop skin rash; and (3) intravenous SVV inoculation induces in a higher incidence of SVV DNA-positive ganglia than does infection by intratracheal inoculation.

Analysis of SVV gene expression during latent infection may provide clues regarding the molecular basis of viral latency and reactivation. SVV DNA and IE, early, and late gene transcripts, but not viral proteins, were detected for as long as 12 mo after infection in ganglia, liver, and lung tissues of monkeys that were experimentally infected by intratracheal inoculation.[88] The results indicate that SVV nucleic acids persist in various tissues of monkeys after intratracheal inoculation. In contrast, gene expression restricted to neural ganglia was demonstrated in monkeys that were infected with SVV by intratracheal inoculation and then given booster immunizations.[63] A SVV latency-associated transcript, which is antisense to the SVV ORF61 transactivator gene (homologous to ICP0 of herpes simplex virus type 1), was detected consistently in neural ganglia derived from these monkeys nearly 4 mo after the initial infection. The SVV latency-associated transcript corresponds to similar transcripts antisense to ICP0 homologs that are detected in ganglia of animals latently infected with other neurotropic alphaherpesviruses, including herpes simplex virus type 1, *Equid herpesvirus 1* and *4*, pseudorabies virus, and *Bovine herpesvirus 1*.[6,8,9,13,43] SVV transcripts mapping to ORF 21 have also been detected in monkey ganglia months after intratracheal inoculation, although less consistently.[10,63] Most recently, in situ PCR detected SVV DNA exclusively in neural ganglia, but in situ hybridization failed to reveal SVV gene 63 and gene 21 transcripts as long as 2 y after intratracheal inoculation of monkeys.[38] Further studies are needed to define SVV latency and to elucidate SVV gene expression during latency after natural and experimental infection.

SVV reactivation from latency can result in secondary infection and disease, just as VZV reactivation causes herpes zoster. During reactivation, an undefined molecular stimulus induces viral gene expression of the latent viral genome within the neural ganglia. The resulting production of infectious virus may cause reactivation disease and spread of infectious virus to other susceptible animals. That stimulation of endogenous viral DNA is associated with secondary disease is supported by the finding that SVV DNAs derived from viral isolates collected from primary and secondary bouts of simian varicella in the same monkey have identical DNA fingerprint patterns.[26]

Due to the sporadic incidence of reactivation and the lack of a reliable experimental approach to induce reactivation in latently infected monkeys, relatively little is known concerning the clinical manifestations and pathogenesis of SVV reactivation disease. However, a recent study indicates that immunosuppression or environmental stress might be used to experimentally induce SVV reactivation in latently infected animals.[52] Viral reactivation may induce the usual signs of simian varicella, including a generalized vesicular skin rash that sometimes does not follow the unilateral segmental, dermatomal distribution that typically occurs with herpes zoster in humans.[81] Asymptomatic reactivation without skin rash also can occur.[46,52] In any case, viral reactivation may lead to transmission of infectious virus and disease to susceptible monkeys and provides a source for epizootics in monkey populations.

The factors associated with inducing SVV reactivation are not understood. SVV outbreaks are often correlated with transporting monkeys from one room or facility to another or to the addition

of new animals into a group, suggesting that social or environmental stress is linked to reactivation.[11,57,73] Immunosuppression has been associated with SVV reactivation disease in irradiated pigtailed and rhesus macaque monkeys.[40,46] However, in other instances, reactivation and secondary disease appear to occur spontaneously with no obvious cause.

Diagnosis of Simian Varicella

Because of the highly contagious nature of simian varicella, immediate diagnosis is critical in order to initiate control measures that may prevent an epizootic. In addition, it is important to differentiate simian varicella from other primate diseases that may cause vesicular skin lesions, especially herpes B virus (*Cercopithecine herpesvirus 1*) infection of macaque monkeys, which, if transmitted to animal caretakers or laboratory personnel, can cause life-threatening illness.

Diagnosis by isolation and growth of the infectious agent is optimal for confirming the etiology of a simian varicella outbreak. Propagation in Vero cell monolayers can be used to recover SVV from clinical specimens derived from infected monkeys. Virus isolation from peripheral blood of animals with clinical disease may be difficult, given that viremia is transient and generally limited to the period comprising a few days before and a few days after the onset of skin rash. Infectious virus can be derived from skin vesicles by aspiration of lesion fluid or application of a cotton swab and direct inoculation of Vero cell cultures. SVV can be collected from other infected tissues, including lung, liver, and spleen, if the samples are collected immediately after euthanasia or death from disease.[41,85,86] Cytopathic effect in cell culture, including the presence of rounded, ballooned, and multinucleated cells with intranuclear inclusions, is indicative of herpesvirus infection, but additional diagnostic means are necessary to confirm SVV infection. Likewise, electron microscopy revealing viral particles with herpesvirus morphology within infected Vero cells is consistent with, but not diagnostic for, SVV infection. Detection of SVV antigens by immunofluorescence using SVV-specific antisera is a useful method to confirm SVV infection in cell culture. Alternatively, detection of SVV DNA by PCR or DNA hybridization using SVV-specific DNA probes can be performed to confirm SVV infection.[37] A disadvantage of viral diagnosis by cell culture is that 5 to 14 d may be required to propagate and identify the virus, depending on the viral load in the inoculum. Therefore, cell culture is most valuable as a means to confirm a diagnosis, rather than as an approach for prompt diagnosis.

A rapid approach for laboratory diagnosis of acute simian varicella or reactivation disease involves detection of SVV antigens or nucleic acid directly in clinical specimens, especially easily accessible skin rash specimens. Immunohistochemistry reveals SVV antigens in the skin, lung, liver, spleen, and neural ganglia of acutely infected monkeys by using SVV-specific antisera, which is generated in rabbits after infection with SVV virions.[32] Specific SVV glycoproteins can be detected in tissues by using antisera generated by the immunization of rabbits with SVV gE, gH, and gL peptides.[5,31]

PCR detection of SVV DNA in clinical samples offers a rapid, specific, and sensitive method for diagnosis of simian varicella.[37] Within a few hours after collection of a skin biopsy, simian varicella can be confirmed by SVV DNA detection by using ORF31 (gB), ORF68 (gE), and ORF 63 primer sets. Southern blot and in situ hybridization offer alternative, but more labor-intensive, approaches to identify SVV DNA in infected tissues.[36,44]

Serologic detection of SVV antibodies provides an additional diagnostic means to confirm simian varicella and to evaluate the clinical course of the disease. ELISA and immunoblot assays permit detection of SVV IgM and IgG antibodies in infected monkeys.[1,2,42] SVV-specific IgM antibodies, indicative of primary infection, are detected as early as day 5 after infection, reach a peak titer around day 12, and are not usually detected after day 43. SVV IgG antibodies are detected by day 10 after infection, reach a peak titer around day 17, and remain relatively high for at least 90 d. Perhaps the most reliable method to detect SVV antibodies is the viral serum neutralization assay, in which the ability of SVV antibodies in diluted monkey serum to neutralize cell-free SVV and reduce plaques on Vero cell monolayers is determined.[64] A 4-fold rise in serum neutralization antibody titers between acute disease (days 10 through 14 after infection) and the early convalescent stage (days 21 through 28) provides evidence for SVV infection. SVV neutralizing antibodies are detected for more than 4 mo after infection. Relatively little is known concerning the long-term persistence of SVV antibodies in infected monkeys, but latently infected monkeys likely remain SVV-seropositive.[29]

Treatment, Control, and Prevention of Simian Varicella

Antiviral agents have been used to control simian varicella outbreaks, with varying degrees of success at reducing morbidity and mortality and minimizing economic and research losses.[73] Infected patas monkeys involved in the 1981 epizootic were treated with a variety of antiviral agents, including intravenous acyclovir, interferon α, and transfer factor and intramuscular phosphonoacetic acid, with marginal effectiveness.[19] Intramuscular phosphonoacetic acid (200 mg/kg) was effective in reducing mortality during the 1983 simian varicella epizootic, although dermal toxicity was a complication.[48,73] The nucleoside analog 1-(2´-deoxy-2´-flouro-β-D-arabinofuranosyl)-5-iodouracil (FEAU; 15 mg/kg PO) was effective in controlling spread of disease during the 1984 outbreak.[73] During the 1989 outbreak in Japan, treatment of macaque monkeys early in infection with 1-β-D-arabinofuranosyl-E-(2-bromovinyl) uracil (10 mg/kg IM) reduced the mortality rate from 68% in untreated monkeys to 4%.[82]

Acyclovir, a nucleoside analog frequently used to treat VZV and herpes simplex virus infections, has been evaluated in experimentally infected monkeys. An initial study indicated that acyclovir administered IV at 20 or 45 mg/kg daily was only slightly effective against simian varicella in SVV-infected patas and African green monkeys.[77] However, a higher acyclovir dose (100 mg/kg IM or IV daily for 10 d) inhibited viremia, skin rash, and hepatitis when delivered beginning 48 h after SVV intratracheal inoculation of African green monkeys; occasional hepatic toxicity was noted with IV, but not IM, dosage.[78] SVV is 10-fold more resistant to acyclovir than is VZV and 30-fold more than HSV-1, when assayed in Vero cell culture.[18,67] Therefore, a higher acyclovir dose is required to treat simian varicella in monkeys than generally is needed to treat human HSV and VZV infections.

The antiviral efficacy and pharmacokinetics of several other antiviral agents have been evaluated in monkeys by using the simian varicella model.[14,47,72-76,79] Some of these drugs have demonstrated greater therapeutic effectiveness against experimental SVV infection than does acyclovir. For example, FEAU administered

IV or PO at doses as low as 1 mg/kg daily for 10 d prevented skin rash and markedly reduced viremia in African green monkeys infected 48 h earlier by intratracheal inoculation.[75] Combination treatment with FEAU and human recombinant interferon β was even more effective.[75] Delivery of 1-β-D-arabinofuranosyl-E-(2-bromovinyl) uracil at 0.1 mg/kg PO for 10 d also prevented skin rash and inhibited viremia in infected monkeys.[72]

In addition to initiation of antiviral therapy, measures to control SVV epizootics in primate facilities have included quarantine or euthanasia (or both) of infected animals to prevent further spread of the disease.[11,22,57,73,82]

Because of the sporadic nature of simian varicella, there has not been a demand for a SVV vaccine. However, given the success of the live, attenuated VZV vaccine, a simian varicella vaccine is feasible. Studies are ongoing to develop and test a safe and effective attenuated SVV vaccine created by deleting potential virulence factors, such as the viral glycoprotein C.[24] Alternatively, the VZVOka vaccine might be useful to prevent simian varicella, in light of evidence that VZV infection effectively immunizes patas monkeys against subsequent challenge with SVV.[15] In addition, immunization of vervet monkeys with VZV glycoproteins was partially protective against simian varicella.[80] An effective simian varicella vaccine could be useful to protect populations of Old World monkeys that include both animals latently infected with SVV and susceptible seronegative monkeys.

Another approach for minimizing simian varicella outbreaks is to identify SVV latently infected animals within Old World monkey populations by detection of SVV-seropositive animals by using ELISA and serum neutralization assays to determine SVV antibody titers. Elimination or quarantine of latently infected animals and close observation of these animals during transport and other times of stress, including irradiation and immunosuppression, may avoid viral reactivation and spread of infectious virus to susceptible monkeys. However, little is known currently concerning the incidence of SVV latently infected monkeys in facilities housing Old World monkeys.

Summary

The number of reported simian varicella epizootics has decreased since the major outbreaks that occurred in the 1960s, 1970s, and 1980s (Table 1). Greater awareness of the disease, improvements in animal care that reduce social and environmental stress, and other operating procedures that minimize virus transmission are likely responsible for this decrease in outbreaks. In addition, more is now known about simian varicella and approaches to its diagnosis, treatment, and control. However, as long as latently infected monkeys reside with susceptible animals, the potential exists for simian varicella epizootics, which can result in loss of valuable animals and research data.

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