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A Naturally Occurring Fatal Case of Herpesvirus papio 2 Pneumonia in an Infant Baboon (*Papio hamadryas anubis*)

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Here we describe the unusual finding of herpesvirus pneumonia in a 7-d-old infant baboon (*Papio hamadryas anubis*). This animal had been separated from its dam the morning of its birth and was being hand-reared for inclusion in a specific-pathogen-free colony. The baboon was presented for anorexia and depression of 2 d duration. Physical examination revealed a slightly decreased body temperature, lethargy, and dyspnea. The baboon was placed on a warm-water blanket and was given amoxicillin–clavulanate orally and fluids subcutaneously. The animal's clinical condition continued to deteriorate despite tube feeding, subcutaneous fluid administration, and antibiotic therapy, and it died 2 d later. Gross necropsy revealed a thin carcass and severe bilateral diffuse pulmonary consolidation. Histopathology of the lung revealed severe diffuse necrotizing pneumonia. Numerous epithelial and endothelial cells contained prominent intranuclear herpetic inclusion bodies. Virus isolated from lung tissue in cell culture was suspected to be *Herpesvirus papio* 2 (HVP2) in light of the viral cytopathic effect. Real-time polymerase chain reaction (PCR) analysis and DNA sequencing of PCR products both confirmed that the virus was HVP2. This case is interesting because the age at onset suggests perinatal transmission at or immediately after birth, and the disease course suggests inoculation of the virus into the respiratory tract.

Abbreviations: ARDS, acute respiratory distress syndrome; CMV, cytomegalovirus; DNA, deoxyribonucleic acid; g, gravity; GFP, green fluorescent protein; HSV, herpes simplex virus; HVP2, *Herpesvirus papio* 2; Ig, immunoglobulin; PCR, polymerase chain reaction; SA8, simian agent 8; STLV, simian T-cell lymphotropic virus; SV40, simian virus 40; SPF, specific pathogen free

Members of the family Herpesviridae are divided into 3 subfamilies, on the basis of their biologic properties: *Alphaherpesvirinae*, *Betaherpesvirinae*, and *Gammaherpesvirinae*.[26] Alphaherpesviruses typically have a variable host range and relatively short reproductive cycle, exhibit rapid spread in culture with efficient destruction of infected cells, and establish latent infections primarily, but not exclusively, in sensory ganglia.[27] Numerous different alphaherpesviruses have been isolated from various primate species. These include *Cercopithecine herpesvirus* 1 (monkey B virus) of macaques, *C. herpesvirus 2* (SA8) of African green monkeys, *Saimirine herpesvirus* 1 (*Herpesvirus saimiri* 1) of squirrel monkeys, *C. herpesvirus 16* (*Herpesvirus papio* 2; HVP2) of baboons, and human herpes simplex virus types 1 and 2 (HSV1 and HSV2).

HVP2 was first isolated from a rectal swab taken from a baboon (*Papio ursinus*) in 1969.[17] At that time the virus was reported as simian agent 8 (SA8) because it was antigenically indistinguishable from the SA8 that had been previously isolated from an African vervet monkey (*Chlorocebus aethiops*) in 1958.[16] Since that time, DNA sequencing has documented that the 2 viruses are indeed distinct.[9] The International Committee on the Taxonomy of Viruses recently recognized the baboon virus as being distinct from the vervet virus, and the baboon virus has been officially designated *Cercopithecine herpesvirus* 16.[6]

The alphaherpesviruses are prevalent in adult animals, and 85% of indoor- and 96% of outdoor-housed baboons at the University of Oklahoma Health Sciences Center (OUHSC) baboon breeding colony are serologically positive for HVP2.[7,22] In baboons, HVP2 usually does not cause serious clinical disease, although vaginal and penile obstruction, neoplasia, and neuritis have been reported.[18] Primary infection involves mucosal surfaces, commonly resulting in oral lesions in sexually immature animals and genital lesions in adults.[8,15,18] Lesions generally begin as an erythematous focus that progresses to a pustule or vesicle. The pustule and vesicle are ruptured easily and subsequently form an ulcer that usually heals with little scarring, although more serious sequelae, including vaginal stenosis, urethral stenosis, sciatic neuritis, and perineal neoplasia, can sometimes occur.[18] After primary infection, the virus establishes lifelong latent infections in sensory ganglia.[11] Latent virus can subsequently be reactivated, with infectious virus being shed in body secretions, including saliva and vaginal secretions.[8,15]

Alphaherpesvirus infections can cause devastating disease in neonates. Two cases of possible HVP2 pneumonia and septicemia in neonatal Gelada baboons (*Theropithecus gelada*) have been described.[20] These animals were found dead within 24 h after birth. In human neonates, HSV can cause disseminated infection (with or without pneumonia) and has a mortality rate of 57% to 85%.[32] Experimentally, intratracheal and intravenous inoculation of neonatal baboons with HVP2 has been shown to cause bronchopneumonia and septicemia respectively, both leading to rapid death.[5] The present case report describes a naturally

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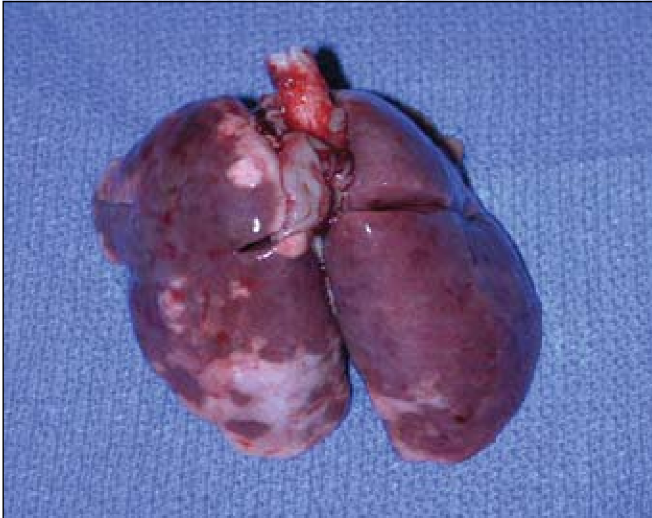

Figure 1. Photograph of the lungs. Observed were large areas of diffuse consolidation and discoloration (purplish color) involving all lung lobes. Upon palpation, the lungs had a firm consistency.

occurring, rapidly progressing, fatal case of pneumonia caused by HVP2 in a neonatal baboon.

Case Report

All procedures were performed in compliance with the *Guide for the Care and Use of Laboratory Animals*.[19] Protocols for maintenance of the baboon colonies were approved by the OUHSC Institutional Animal Care and Use Committee.

A 7-d-old infant baboon (*Papio hamadryas anubis*) born to a healthy 7.5-y-old dam (who had delivered 3 healthy infants from 3 previous pregnancies) was presented for anorexia of 2 days' duration. The animal had been separated from its conventionally housed dam the morning of its birth and was being hand-reared for inclusion in a specific-pathogen-free (SPF) colony. Physical examination revealed a decreased body temperature of 34.8 °C (normal, 37 to 39 °C), lethargy, and dyspnea. Its weight was 770 g (compared with 820 g at birth). Mucous membranes had a grayish-blue tinge, and thoracic auscultation revealed decreased breath sounds. There was no nasal or ocular discharge. Abnormal laboratory test results were a low platelet count of $70 \times 10^3/mm^3$ (normal, 268 to $579 \times 10^3/mm^3$) and a low-normal white blood cell count of $7 \times 10^3/mm^3$ (normal, 7 to $15 \times 10^3/mm^3$). Further blood tests were not done due to difficulty in obtaining sufficient sample. The baboon was placed on a warm-water blanket and was given amoxicillin–clavulanate (20 mg every 12 h) orally and 60 ml warm normal saline subcutaneously. The animal's clinical condition continued to deteriorate despite tube feeding with infant formula, subcutaneous fluid administration, and antibiotic therapy, and the baboon died 2 d later.

Necropsy findings. Gross observation at necropsy revealed a thin carcass and severe bilateral diffuse pulmonary consolidation (Figure 1). No other gross pathology was apparent. Cultures of lung did not reveal bacterial growth, and touch preps of lung were unremarkable. Histopathology of lung revealed severe diffuse necrotizing pneumonia and alveolar damage consistent with acute respiratory distress syndrome (ARDS; Figure 2). Numerous epithelial and endothelial cells contained prominent intranuclear inclusion bodies typical of herpetic infections. Immunohistochemical staining using polyclonal hyperimmune rabbit serum followed by peroxidase-conjugated goat antirabbit immunoglobulin G (Vector Laboratories, Burlingame, CA) as previously described[24] detected the presence of HVP2 viral antigen in sections of lung tissue (Figure 3).

Virus isolation. Lung samples collected at necropsy were frozen at –80 °C. Tissue was later thawed, homogenized, clarified by low-speed centrifugation ($419 \times g$ for 5 min), and the supernatant plated on confluent monolayers of both Vero and DBG3 cells for virus isolation.[4,8] DBG3 cells are a unique cell line that was constructed to fluoresce in response to infection with an alphaherpesvirus.[4] Plaques were observed within 24 h, infected DBG3 cells fluoresced, and the morphology and temporal appearance of cytopathic effect was consistent with HVP2 (Figure 4). A pure viral stock was prepared by 3 rounds of plaque purification on Vero cells for use in genomic analysis.

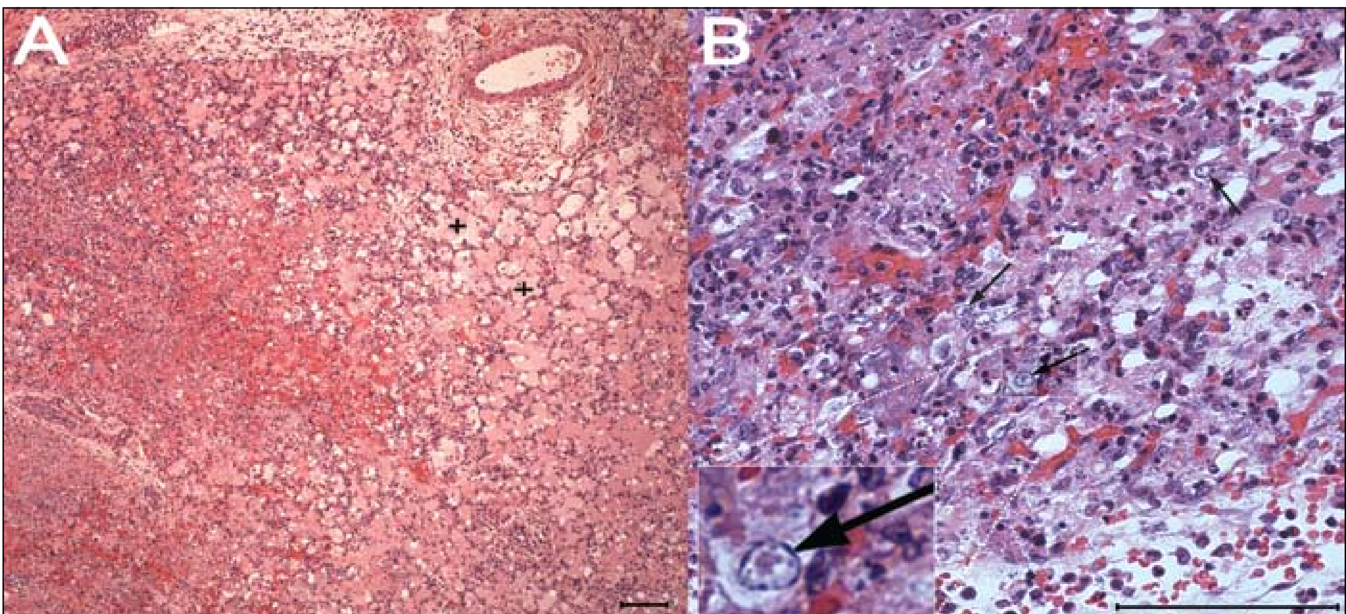

Figure 2. Photomicrographs of lung tissue. Present were severe diffuse necrotizing and hemorrhagic pneumonia. (A) Most alveolar sacs (+) were filled with cellular material, fibrin, edematous fluid, and red blood cells. Many of the alveolar septa were damaged as characterized by the presence of severe acute cellular necrosis. (B) Numerous epithelial and endothelial nuclei contained a prominent viral inclusion body (arrows and inset). Hematoxylin and eosin; bar, 100 µm.

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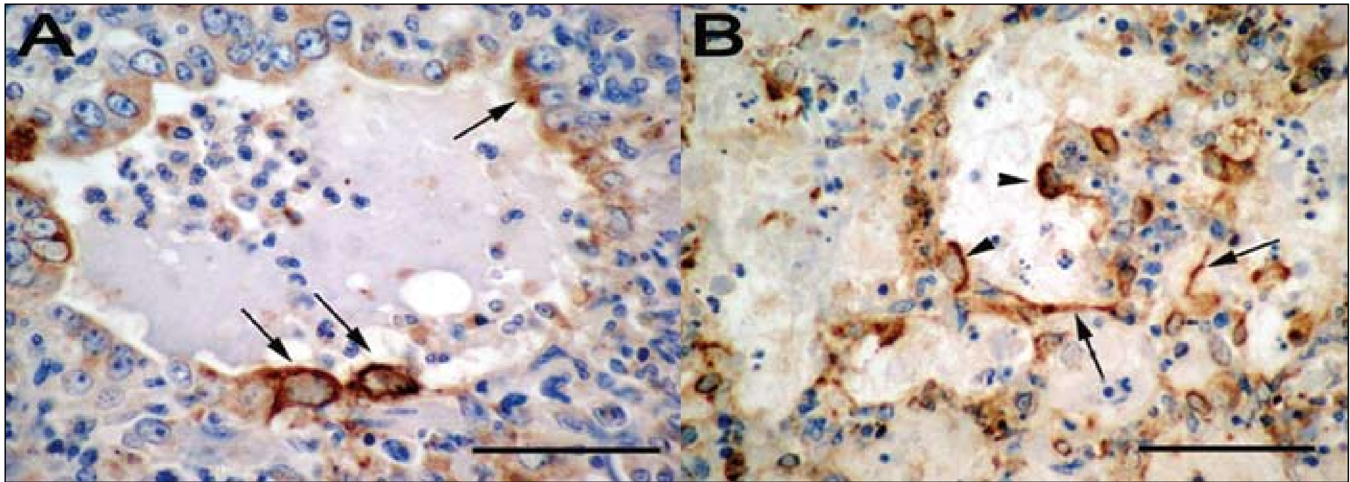

Figure 3. Photomicrographs of lung stained with a polyclonal hyperimmune rabbit serum against HVP2 and Mayer's hematoxylin counterstain. (A) Bronchiolar epithelial cells exhibit strong immunoreactivity (dark brown staining) for herpesviral antigens (arrows). The bronchiolar lumen is flooded with neutrophils and edema fluid. Bar, 65 µm. (B) Viral antigen is detected in alveolar regions (dark brown staining). Viral antigens are present in flattened epithelial cells (arrows) morphologically consistent with type I pneumocytes as wells as more polyhedral cells consistent with type II pneumocytes (arrowheads). Bar, 50 µm.

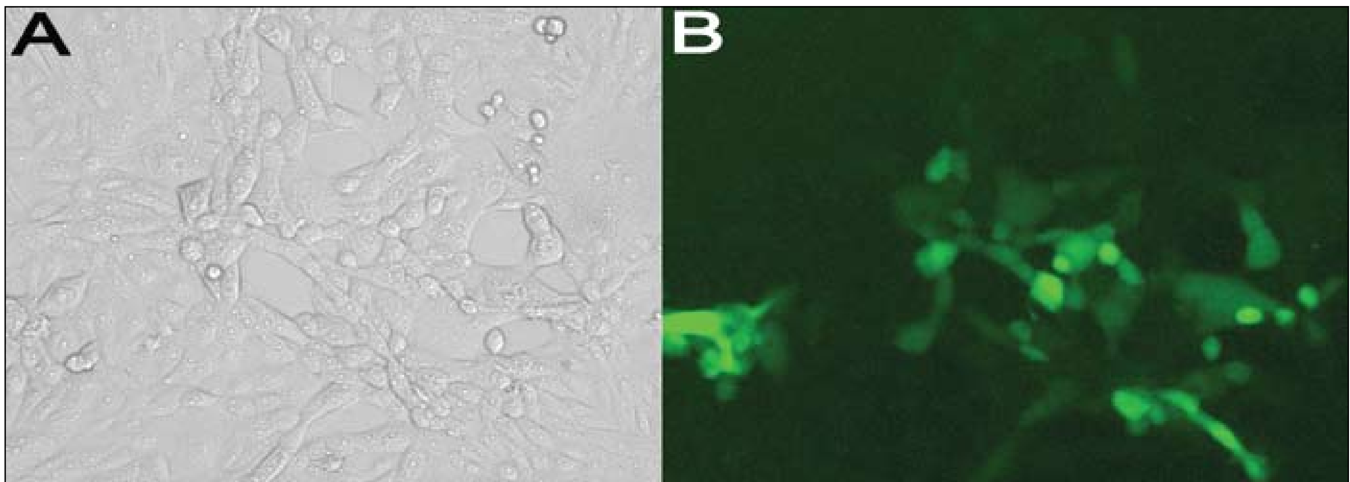

Figure 4. Photographs taken in white light (A) and ultraviolet light (B) of DBG3 cell monolayers 24 h after inoculation with homogenized lung tissue taken at necropsy. Panel A shows a typical herpesvirus plaque in DBG3 cells under white light. Panel B confirms that the cells are infected with a primate herpesvirus, as indicated by the expression of green fluorescent protein (GFP) from the endogenous GFP gene present in the DBG3 cells.

Genomic analysis. To obtain template DNA for quantitative real-time polymerase chain reaction (PCR) analysis, total DNA was extracted from lung tissue by using DNAeasy Tissue Kit (Qiagen, Chatsworth, CA) according to the manufacturer's protocol. The HVP2-specific quantitative real-time PCR assay was specific for a region of the HVP2 UL41 coding sequence that has been shown to be invariant among HVP2 isolates.[25] An 800-bp segment of the HVP2 UL41 coding sequence in the pCR2.1-TOPO plasmid (Invitrogen, Carlsbad, CA) was used as a viral standard in the PCR assay, as described on the Applied Biosystems web site.[1] TaqMan Pre-Designed Assay for 18S rRNA (Applied Biosystems, Foster City, CA) was used as directed by the manufacturer as a cellular standard. Results of the real-time PCR assay demonstrated an average of 149.51 viral genome copies per cell across a range of 5×10^1 to 5×10^3 cells.

A phylogenetically informative 1.1-kb area from the unique short region of the HVP2 genome (US4-6) was amplified by standard PCR for sequencing and phylogenetic analyses as described.[24,29] Briefly, viral DNA was purified from infected cells and standard PCR performed using r*Tth* polymerase (Applied Biosystems) with the primer set KT1 (5' TCC CGA GTT CGG TAC ACG CGA CTG 3') and KT10 (5' CAC GTC GGG GGG GTC CGT CTT CTG CTC C 3'). After a 3-min denaturation at 94 °C, amplification was completed using 35 cycles of 96 °C for 30 s, 68 °C for 30 s, and 72 °C for 2 min, followed by 7 min at 72 °C. Several internal primers were used to sequence the region in both forward and reverse directions. PCR products were purified prior to sequencing by using Wizard PCR Preps (Promega, Madison, WI). Vector NTI Suite 8.0 (InforMax, Frederick, MD) was used to assemble sequence files, and the MEGA program[13] was used for phylogenetic analyses. Distances were calculated using the Tamura–Nei algorithm,[30] and the tree was constructed by the neighbor joining method.[28] The vervet (SA8) and macaque virus (BVrh) sequences were used as outgroups to root the HVP2 tree. HVP2nv and HVP2ap (neurovirulent and apathogenic respectively, when inoculated into mice) isolates always formed separate clades.[24] Separate analyses of the coding and intergenic noncoding sequences gave trees of the same topology. These phylogenetic analyses confirmed the identity of the virus as a neurovirulent subtype of HVP2 (Figure 5).

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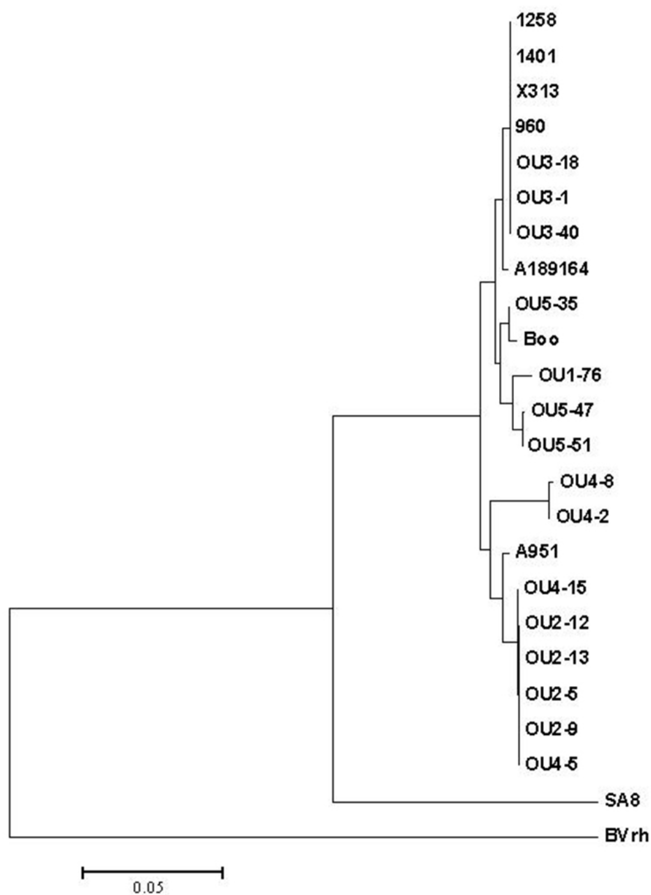

Figure 5. Phylogenetic relationship of the virus isolated from lung tissue (Boo) to other primate herpesviruses on the basis of US4–US6 gene sequences. "Boo" always grouped with the HVP2nv isolates. The bar represents 0.05 replacements per site.

Discussion

Histopathologic findings were consistent with ARDS, a clinical syndrome caused by diffuse alveolar damage (10). Alveoli become collapsed or distended and may contain proteinaceous debris, desquamated cells, and hyaline membranes (Figure 2). ARDS is recognized clinically by the rapid onset of respiratory insufficiency, cyanosis, and severe arterial hypoxemia. Differential diagnoses for a neonatal baboon presenting with ARDS include sepsis, viral pneumonia, *Mycoplasma* pneumonia, gastric aspiration, head trauma, and disseminated intravascular coagulation. The pulmonary inclusion bodies we saw on histopathology were suggestive of a viral infection. HVP2 was diagnosed with immunohistochemical staining, virus isolation, and PCR analysis.

The neonatal baboon described in this case study was being hand-reared for inclusion in an SPF baboon colony. This SPF program is aimed at eliminating all 5 known baboon herpesviruses (including HVP2) as well as 4 retroviruses and simian virus 40 (SV40) from the colony. Baboons, group-housed in large indoor-outdoor corrals, deliver their newborns vaginally. Neonates are removed as soon as possible within 24 h of birth from their dams before being hand-raised in small peer groups in strict isolation from conventional animals. Infants are collected after normal vaginal delivery instead of Caesarean section (C-section), the more common method of obtaining SPF animals. We felt that the postoperative complications associated with multiple C-sections per year as well as the expense of the surgeries outweighed the benefit of the decreased risk of maternal transmittal of viruses associated with C-section. Once collected, animals are housed separately for the first 4 wk and then put into age-matched groups of 3 or 4 animals, rather than by the more traditional methods of single or pair housing when creating SPF animals. Group-raised baboons appear to be much more behaviorally normal,[31] a trait that may contribute to the long-term success of a breeding colony. Baboons are tested by serology and PCR at 1, 2, 4, 6, 9 and 12 mo of age and then semiannually. A positive test result for any of the target viruses results in the immediate removal of the entire cohort from the SPF program.

Because the infants do remain with their dams for several hours after birth, we expected to encounter breaks due to viruses known to be transmitted efficiently to infant baboons during their first year of life.[22] Specifically, we both expected and have experienced breaks due to the betaherpesvirus, baboon cytomegalovirus (BaCMV); and 2 gammaherpesviruses, *Herpesvirus papio* 1 (HVP1) and baboon rhadinovirus. One break due to BaCMV occurred in a 6-mo-old infant. Demonstrated in the results of testing at 2 and 4 mo, this infant exhibited an initial drop in the level of maternal anti-BaCMV IgG levels. However, at the 6-mo time point, anti-BaCMV IgG levels sharply increased (data not shown). Consistent with the efficient transmission of BaCMV in the breeding colony setting,[22] the infection was transmitted rapidly to other infants in the cohort, resulting in loss of the entire group from the SPF program.

Although HVP2 infection of very young baboons does occur, we did not expect to encounter HVP2 infections in infants taken immediately after birth, because this virus is not efficiently transmitted to infants in the breeding colony setting.[22] HVP2 is endemic in baboons, with prevalence gradually reaching approximately 60% of baboons (including the dam of the affected infant) at 3 y of age in the OUHSC colonies[7,22] and continues to increase to near 100% in the adult population. Two cases of fatal pneumonia and septicemia have been described in neonatal Gelada baboons (*Theropithecus gelada*[20]). The etiologic agent in these cases was possibly HVP2, but no confirmation by virus isolation was attempted. In the human medical literature, HSV disease in neonates is rare but well described.[2,12,14,23,32]

HVP2 is biologically, genetically, and antigenically related to HSV1 and HSV2 as well as monkey B virus.[3,21] These viruses all cause similar clinical disease in their natural host species. Clinically apparent primary HSV1 and HSV2 infections usually present as vesicular lesions on oral and genital mucous membranes, respectively, followed by viral latency in sensory neurons and lifelong periodic reactivation and shedding of virus. Neonatal HSV infections are rare, occurring at a rate of 0.13 to 0.5 cases per 1000 births in the United States.[2,12,14,32] However, morbidity and mortality of neonatal HSV infections is high. Transmission usually occurs during labor via shedding of HSV in vaginal secretions (80%), but in rare instances the virus can also be transmitted transplacentally or postnatally.[12] Disease in infants commonly manifests as a localized infection of the eye, mouth, or skin; meningoencephalitis; or disseminated infection. Disseminated infection includes pneumonia with or without involvement of other organs and has a mortality rate of 57% to 85%.[2] Typical human presentation is a 5- to 6-d-old neonate with temperature instability, lethargy, respiratory distress, feeding difficulties, jaundice, cyanosis, bleeding diathesis, shock, and a characteristic rash. Even with supportive therapy, mortality is common. Early identification and treatment with acyclovir has been shown to improve outcome and decrease long-term sequelae.[23]

The route of HVP2 infection in the present case is not known.

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However, the animal's age at onset of clinical signs (5 d) along with the fact that it was being raised in a barrier facility under strict isolation procedures to ensure no contact with other baboons strongly suggests in utero or perinatal transmission from the dam to the infant during or immediately after birth. The infant's dam was known to be serologically positive for HVP2 (as well as BaCMV and HVP1 but negative for SV40 and simian T-cell lymphotropic virus [STLV]). In one study, experimental inoculation of HVP2 into the trachea of newborn baboons (*Papio cynocephalus*) caused bronchopneumonia,[5] as observed in this case of a natural infection. Intravenous inoculation (a model for in utero transmission) caused adrenal necrosis without pulmonary lesions. HSV infections in neonatal humans, often contracted during delivery from intratracheal inoculation with vaginal secretions, can also result in pneumonia.[2] Together, this evidence suggests that the infant we describe acquired HVP2 periparturiently as an oral infection from its dam. Although the dam was known to be seropositive for HVP2, it is unknown whether she was actively shedding virus at the time she gave birth.

Evidence has accumulated that the primate herpesviruses have coevolved with their host species, and infection of monkeys with their own herpesviruses often results in disease very similar to that observed in humans as a result of infection with the homologous human herpesvirus. The neonatal pneumonia in a baboon associated with an alphaherpesvirus infection represents one more instance where a simian herpesvirus causes disease in its natural host that appears very similar to disease seen in humans as a result of infection with a human herpesvirus, in this case HSV-associated neonatal pneumonia.[2] The physiologic similarity of baboons and humans, close parallels in the elements of their immune systems, and the similarities of their natural complement of herpesviruses make baboons an extremely powerful and very promising system in which various aspects of herpesvirus-induced disease can be examined in the context of a natural virus–host relationship that is not possible in humans.

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