Fatal Herpesvirus Infection in Patas Monkeys and a Black and White Colobus Monkey

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SUMMARY

Fatal herpesvirus infections were diagnosed in 3 patas monkeys and 1 black and white colobus monkey over a 4-week period. Herpesvirus was isolated from 1 patas monkey and from the black and white colobus monkey. Both isolates had growth characteristics similar to *Herpesvirus hominis* and *Herpesvirus simiae*. The isolate from the colobus monkey antigenically appeared to be *H simiae* or *H simiae*-like, whereas the isolate from the patas monkey could not be conclusively identified with the antisera used. All affected animals were housed in close proximity to rhesus monkeys, the carrier host of *H simiae*.

THIRTY-SEVEN herpesviruses have been isolated from human beings and from a variety of nonhuman primates.[1] Some of these viruses do not cause overt disease. Some herpesviruses isolated from man can infect various species of nonhuman primates.[2-4] The only nonhuman primate isolate known to infect human beings is *Herpesvirus simiae* (herpesvirus B, HVB). The herpesviruses that cause neurologic or generalized disease in human beings and nonhuman primates are *H hominis* 1 (HVH1, herpes simplex 1), *H hominis* 2 (HVH2, herpes simplex 2), *H simiae, H tamarinus, H ateles* 1, and *H aotus*. Other herpesviruses that generally cause exanthematous diseases but can be associated with high mortality have been isolated from vervet monkeys *(Cercopithecus aethrops),* patas monkeys *(Erythrocebus patas),* and macaques (*Macaca* sp). In this report, we describe fatal herpesvirus infection in 3 patas monkeys and 1 black and white colobus monkey *(Colobus abyssinicus),* which were referred to the National Zoological Park at the time of the infections from a small zoo without diagnostic capabilities.

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The primates from the referral zoo were maintained in outdoor enclosures in the warm months, and inside during cold weather. The infections developed during November and December 1980, while the primates were housed indoors. The floor plan of the caging system is given (Fig 1). The cages were cleaned after shifting the animals in cage A to an outdoor enclosure, cleaning cage A, then shifting the animals in cage B into cage A and cleaning cage B. This procedure was continued until all animals were shifted 1 cage to the left and all cages were cleaned. The animals were then shifted back to their original cages.

The clinical signs in 2 of the patas monkeys (No. 1 and No. 2) initially consisted of anorexia, depression, and swollen upper eyelids. The signs progressed for approximately 2 weeks until death. The eyelids became ulcerated and covered with a crusted, serous exudate (Fig 2) about 1 week prior to death.

The clinical course was more acute in patas monkey 3 and the black and white colobus monkey, both dying within 2 days of the onset of clinical signs. Both animals were depressed and anorexic, and had swollen upper eyelids. The colobus monkey was vomiting and had diarrhea prior to death. Hemograms and serum chemical panels of the colobus monkey and patas monkey 2 were within expected limits.

Materials and Methods

Patas monkeys 1 and 2 and the colobus monkey were necropsied. Patas monkey 3 was not available for necropsy.

Frozen tissue specimens from the colobus monkey and from patas monkeys 1 and 2 were sent to Southwest Foundation for Research and Education for attempted virus isolation and identification. Serum was also sent there for determination of serum neutralization titers against *H simiae* and *H hominis* 1. Techniques for virus isolation and serum neutralization were as previously described.[5]

All tissue specimens for histologic examination were fixed in buffered 10% formalin, processed in routine

Outside Enclosure	A	B	C	D	E	F
	Baboons	Colobus	Rhesus 2 Heck's Macaque	Patas 4	Rhesus 1	Patas 1,2,3,5*

*Originally in cage F but moved to D prior to first death.

Fig 1—Floor plan of enclosures and monkey locations at the beginning of the herpesvirus outbreak.

manner, and stained with hematoxylin and eosin. Special stains, including Giemsa and periodic acid-Schiff were performed on selected tissues.

Results

Gross Pathologic Findings—Externally, the 2 patas monkeys had vesicular and ulcerated lesions on both eyelids (Fig 2). The colobus monkey had edema involving 1 eyelid. In all 3 animals, there was a general lack of subcutaneous and body fat stores. The colobus monkey and patas monkey 2 had multiple purple-red areas in both lung lobes. The liver of the colobus monkey and of patas monkey 2 had miliary pale foci of necrosis on the surface and within the parenchyma. A few similar foci were in the spleen and adrenal glands. The colobus monkey also had a large gastric ulcer covered by a pseudomembrane and patas monkey 2 had ulcers in the colon.

Histopathologic Findings—There was acute ulcerative dermatitis with intranuclear acidophilic inclusions of the herpetic type in the eyelids of patas monkey 2. All of the animals had acute pneumonia, hemorrhages, and foci of necrosis, the latter cells with intranuclear inclusions. In the liver of the colobus monkey and of patas monkey 2, there were numerous foci of necrosis. Hepatocytes at the periphery of the lesions contained intranuclear inclusions (Fig 3). Necrotic foci containing herpetic inclusions were also evident in the adrenal glands, spleen, and mesenteric lymph nodes. The colobus monkey had evidence of acute encephalitis, with numerous inclusions in neurons in the medulla. Evidence of acute ulcerative gastritis with minimal inflammatory infiltrate and numerous bacterial rods was also found. Intranuclear inclusions were not observed in cells associated with the gastritis.

Viral Culture and Identification—A rapidly growing herpesvirus was isolated from liver, lung, and spleen of the colobus monkey and from eyelid, liver, lung, and spleen of patas monkey 2. No virus was isolated from patas monkey 1. Results of serum neutralization of isolated herpesviruses are given in Table 1.

The only herpesvirus antiserum that neutralized

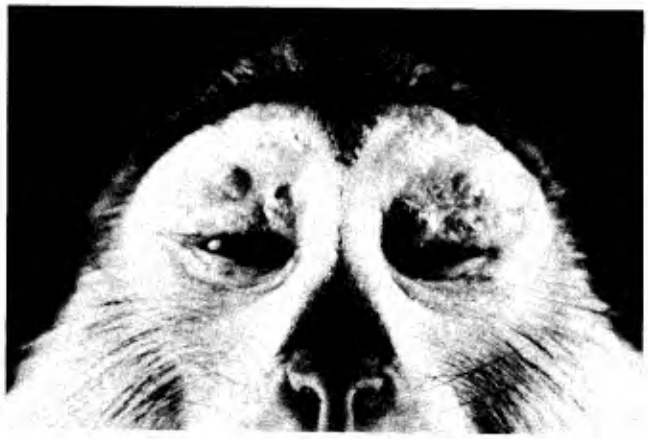

Fig 2—Patas monkey with herpetic vesicular lesions on both eyelids.

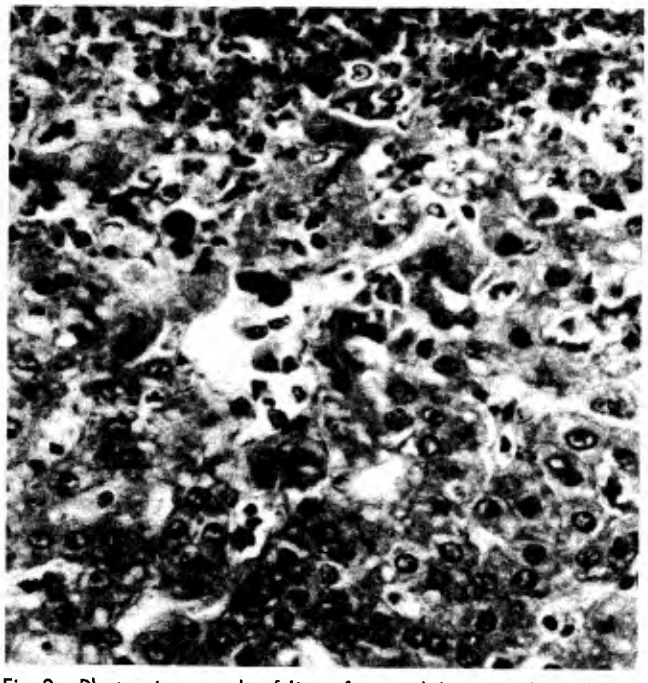

Fig 3—Photomicrograph of liver from colobus monkey, showing necrosis of hepatocytes; many nuclei have herpetic inclusion bodies. H&E stain; ×400.

TABLE 1—Serum-Neutralization Titers of Viral Isolates to Herpesvirus Antisera

	Colobus monkey		Patas monkey 2
	Liver	Lung	eyelid
Antisera			
Herpesvirus simiae (SFRE)	1:640	ND	<1:10
Herpesvirus simiae (NIAID)	<1:5	ND	<1:5
Herpesvirus hominis 1	<1:10	ND	<1:5
Herpesvirus hominis 2	<1:10	ND	ND
SA8	<1:10	ND	<1:5
Herpesvirus tamarinus	<1:10	ND	ND
SMV	<1:10	ND	ND
Sera			
Patas monkey 2	<1:5	<1:6	<1:3-1:3
Colobus monkey	<1:5	ND	ND

ND = no determination.

TABLE 2—Serum-Neutralization Titers of Monkey Sera to Herpesviruses

Monkey	Date	*Herpesvirus simiae*	*Herpesvirus hominis*
Colobus	12-2-80	<1:3	<1:3
Rhesus 1	12-2-80	1:6	1:48
Rhesus 2	12-2-80	1:12	1:48
Patas 5	12-2-80	<1:3	ND
Patas 2	11-17-80	<1:3	<1:3
	12-2-80	1:3	1:24
	12-3-80	1:3	1:24
Patas 4	12-2-80	1:48	≥1:96
Moor macaque	12-2-80	1:6	1:24
Stump-tailed macaque	12-2-80	<1:6	1:24

ND = not determined.

the virus from the colobus monkey at a high titer was antiserum to a HVB produced by Southwest Foundation for Research and Education. A 2nd antiserum to HVB, produced by the National Institute for Allergies and Infectious Disease failed to neutralize the isolated virus. None of the antisera neutralized the herpesvirus from the patas monkey at a high titer. Neither the serum from the colobus monkey nor the serum from patas monkey 2 neutralized either virus.

Virus Titers—Sera for determination of herpesvirus titers were obtained from 2 of the animals that died (colobus monkey and patas monkey 1), from several other primates housed in the same group of cages, and from human beings who were involved with the management and clinical or pathologic workups of these animals. These titers are in Table 2.

The results for rhesus monkey *(Macaca mulatta)* 1, rhesus monkey 2, patas monkey 4, and a Heck's macaque *(Macaca maurus)* were equivocal, and these animals were considered suspect for HVB infection. For the remaining monkeys and the human beings, the results were suggestive of HVH infection rather than HVB infection. However, inasmuch as both acute and convalescent sera were not available, it was impossible to differentiate between HVB and HVH, even though both antigens had been used.[7] It also was not possible to determine whether titers were a result of current or past exposure to the viruses. Even with paired sera, results are sometimes equivocal.[6] Paired sera were available for patas monkey 2, which did have rising neutralization titers to both HVB and HVH.

Discussion

The isolate from the colobus monkey represents either a new host for a known virus or a new virus. The fact that the colobus virus was neutralized at a high titer by 1 HVB antiserum suggests that it is a herpes B or B-like virus. However, failure of the other HVB antiserum to neutralize this virus makes it difficult to classify the virus as a B type. The virus was neutralized at a titer of <1:10 by 8 other herpesvirus antisera tested.

The failure of the virus from the colobus monkey to be neutralized by serum from that monkey is not unexpected inasmuch as the serum was obtained during the acute phase of infection.

The close proximity of the colobus monkey to rhesus monkeys, and the fact that the rhesus monkeys were shifted into the colobus cage, is significant. The rhesus monkey and other macaques are the reservoir hosts for HVB. Although none of the macaques housed in the building was identified as a HVB carrier, rhesus monkeys 1 and 2 as well as the Heck's macaque were serologically suspect for HVB. Also, rhesus monkey 1 was reported by a keeper to have had vesicular oral lesions during the outbreak. A circumstantial case can be made for HVB infection; however, without consistent cultural and serologic evidence, it would be imprudent to call this virus HVB.

A herpesvirus isolated from patas monkeys has been described.[8,9] However, it causes an exanthematous disease that may be accompanied by systemic involvement. This virus more closely antigenically and culturally resembles the herpes varicellazoster group.

The herpesvirus isolated from the patas monkey in this report had growth characteristics similar to HVB and not varicella. This virus was not neutralized at a high titer by any of the herpesvirus antisera used, including the B virus antiserum. Therefore, the possibility of a second type of herpesvirus must be considered. However, considering the temporal and spatial associations for the colobus monkey and the patas monkeys, it seems unlikely that 2 distinct viruses are involved. Although virus was not isolated from patas monkey 1, it has histologic evidence of a herpesvirus infection.

Patas monkey 2 did have rising HVB and HVH titers. A one-way cross neutralization exists between HVB and HVH in which antibodies to HVB neutralize HVH, but not the reverse.[10] Although the rise in titer to HVH was of a greater magnitude than the rise in HVB titer, this does not necessarily indicate HVH infection, as opposed to HVB infection.

The conflicting results of virus neutralization studies and the inconclusive serum titer studies point out the difficulty of differentiating herpesviruses that are closely related antigenically by the methods currently employed,[7] especially when dealing with more exotic primates.

The shifting of animals in the manner described and the mixing of species are not good practices. Although animals were shifted into previously cleaned cages, the cages were not recleaned prior to the animals being shifted back to their original cages. This situation can result in the animals being exposed to the body secretions of another species. Herpesvirus B has been experimentally transmitted via aerosols.[11] The advisability of not mixing various species of nonhuman primates to avoid transmission of herpesviruses from reservoir to aberrant hosts and to avoid other disease problems has been recognized.[12] In this instance, in addition to possible transmission of HVB from macaques to other species, a potential existed for the transmission of Simian hemorrhagic fever virus from patas monkeys, the reservoir hosts, to the macaques, the aberrant hosts.[13]

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