Pathology in Practice

In cooperation with

Figure 1—Photograph of the tongue and gingival surfaces of a 2.75-year-old sexually intact male rhesus macaque (*Macaca mulatta*) that developed swelling of the lips and tongue 4 days after receiving immunosuppressive drugs for research purposes. Notice the focal to coalescing white lesions, some of which are ulcerated.

History

A 2.75-year-old 3.3-kg (7.26-lb) sexually intact male rhesus macaque (*Macaca mulatta*) was evaluated because of mild swelling of the lips and tongue. The monkey had been born at the Yerkes National Primate Research Center field station in Lawrenceville, Ga, and was group housed in a large compound (indoor and outdoor access); it had no notable history except for trauma. It was transferred to Yerkes National Primate Research Center main center in Atlanta for assignment to a renal transplant research protocol approved by the Emory University Institutional Animal Care and Use Committee and was moved to single housing on the basis of study requirements. Prior to surgery, the monkey received busulfan, a potent cytotoxic drug that causes profound myelosuppression; following surgery, it was treated with mycophenolate mofetil, an immunosuppressant used extensively in transplant medicine. On day 4 after surgery, mild swelling of the monkey's lips and tongue was observed.

This report was submitted by Melissa A. Dugan, AB, DVM; Cindy Courtney, DVM, DACVP; and Elizabeth W. Howerth, DVM, PhD, DACVP; from the Department of Pathology, College of Veterinary Medicine, University of Georgia, Athens, GA 30602 (Dugan, Howerth): and Yerkes National Primate Research Center, 954 Gatewood Rd, Atlanta, GA 30329 (Courtney).

Supported by YNPRC NIH base grant 2P51RR000165-51.

Address correspondence to Dr. Howerth (howerth@uga.edu).

Clinical and Gross Findings

Diagnostic procedures included a CBC, which revealed leukocytosis (total WBC count, 16,800 WBCs/µL [reference range, 4,200 to 8,100 WBCs/µL]; differential assessment revealed neutrophils, 92%; band neutrophils, 2%; lymphocytes, 4%; and monocytes, 2%). On the gingiva and the tongue, there were multifocal to coalescing smooth white plaques (0.5 to 1.0 cm in diameter) with irregular margins. Some of these plaques progressed to lingual or gingival ulcers that were covered by fibrinopurulent exudate (**Figure 1**). Numerous raised white-yellow plaques were visible on the hard palate, rostral half of the tongue, buccal surfaces, and the commissures of the mouth. There were 2 small raised papules on the chin. A buccal biopsy specimen was collected and submitted for histologic evaluation.

Formulate differential diagnoses from the history, clinical findings, and Figure 1—then turn the page →

Histopathologic Findings

Histologic evaluation of the 3-mm-diameter punch biopsy specimen revealed severe ulceration of the squamous epithelium and inflammation of the buccal mucosa. Epithelial cells at the ulcer margins were in various stages of necrosis. Eosinophilic intranuclear inclusion bodies and multinucleated syncytial cells were present in squamous epithelium and submucosa (**Figure 2**). In the underlying submucosa, areas of necrosis and marked infiltration by degenerating neutrophils, lymphocytes, and macrophages were present.

Morphologic Diagnosis and Case Summary

Morphologic diagnosis: severe acute multifocal to coalescing vesicular and ulcerative gingivitis and stomatitis with syncytia and intranuclear inclusion bodies consistent with B virus (Macacine herpesvirus 1 [MHV-1]) infection.

Case summary: B virus infection in a rhesus macaque.

Comments

Because of the high probability of B virus infection in the monkey of this report, treatment with an antiviral agent (acyclovir administered IV) was initiated. Scrapings of the monkey's buccal mucosal surfaces were obtained for viral isolation, which yielded MHV-1. Analysis of a serum sample obtained from the monkey revealed that the titer of anti–MHV-1 antibodies was > 5,000. Despite antiviral treatment, the oral lesions worsened. The monkey's general condition continued to worsen with development of dehydration and signs of depression. The monkey was euthanized because of the severity of the lesions and the failure to respond to antiviral treatment.

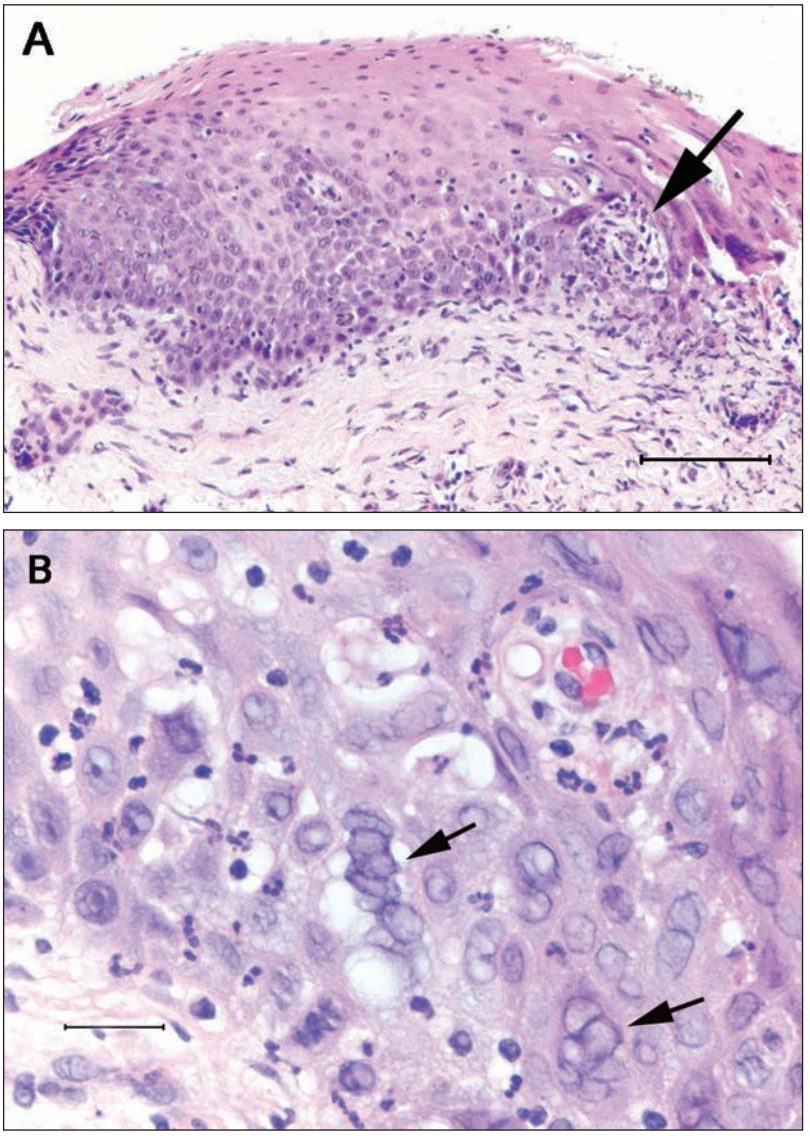

Figure 2—Photomicrographs of a section of a buccal biopsy specimen obtained from the monkey in Figure 1. A—The mucosal epithelium adjacent to an ulcer has evidence of acute inflammation and vesiculation (arrow). H&E stain; bar = 100 µm. B—Higher magnification image of the same tissue section. Notice the eosinophilic intranuclear inclusion bodies in the syncytial cells (arrows) surrounding necrotic debris associated with the ulcerative lesions seen in the mouth. H&E stain; bar = 25 µm.

In the case described in this report, other diseases that were ruled out included simian varicella virus (SVV) infection and rubella.[1] Simian varicella virus can cause similar oral ulcers but only affect the epithelium as revealed via histologic examination of samples of a lesion. In monkeys with measles, oral ulcers may be present, but other clinical signs, such as a diffuse rash, rhinitis, or conjunctivitis, often develop.

Macaques are considered the natural host of MHV-1, also known as B virus or herpes B virus. Clinical disease in the host species is typically mild with development of vesicular to ulcerative lesions on the genitalia, tongue, buccal surfaces, and lips that resolve within 14 days.[2,3] Other clinical signs develop less frequently and may include elevation in body temperature, mucopurulent nasal discharge, keratoconjunctivitis, and secondary infections.[2] On rare occasions, systemic infections that affect various organs, including the lungs, liver, spleen, adrenal glands, and bone marrow, can develop in macaques, with fatal consequences.[2,4] Histologic evaluation of skin or oral cavity tissue samples often reveals intranuclear inclusion bodies in epithelial and syncytial cells and hemorrhagic necrosis.[2,4] The monkey of the present report was part of an organ transplant research project and had received immunosuppressive drugs. The induced immunosuppression most likely contributed to disease progression and the monkey's failure to respond to antiviral treatment.

Macaques are typically infected with MHV-1 at an early age, often at sexual maturity, by close physical contact in group housing situations.[5] Few to no clinical

signs develop as a result. After this initial infection, B virus migrates to the sensory ganglia associated with the inoculation site, where it remains latent throughout the life of the animal, and the virus has been isolated from both trigeminal and genital ganglia of monkeys.[6–9] One study[8] isolated virus from the genital ganglia more often than from the trigeminal ganglia, suggesting that the major mode of transmission between macaques is venereal, not oral as previously thought. Regardless of where the virus remains latent, it is secreted in both oral and genital secretions, and a lesion does not always have to be present for secretion to occur.[5,8] The latent virus may also recrudesce during periods of stress or when the infected monkey becomes immunocompromised,[5,7] which was most likely the case in the macaque of this report. Because of latency of infection, macaques can intermittently shed virus in oral and genital secretions with no apparent clinical signs.[3,8,9] This latent infection and intermittent shedding have important implications for all laboratory personnel working with macaques. Infection with B virus has been implicated in several human deaths and is associated with a high case fatality rate in untreated individuals.[3,10–12] Humans can acquire the infection through contact with oral or genital secretions or tissue samples from infected monkeys, fomites, and needlesticks and, rarely, via human-to-human contact.[11,12] Typical herpetic lesions develop at the inoculation site early but rapidly progress to an acute ascending myelitis that ultimately causes respiratory paralysis and death of affected humans.[10] Treatment options are available for humans that become infected, but early intervention is essential to adequately treat and prevent advanced disease and death. Among laboratory personnel, any direct contact of exposed mucous membranes or damaged skin with body fluids or tissues from macaques should be immediately reported to a supervisor as well as a health-care professional.[11] All monkeys in the *Macaca* genus should be considered B virus positive by anyone handling them, and proper training in handling and exposure procedures should always be enforced.[11,12]

References

1. Exotic and laboratory animals. In: Kahn CM, ed. *The Merck veterinary manual*. 9th ed. Whitehouse Station, NJ: Merck & Co, 2005;1549–1555.
2. Keeble SA. B virus infection in monkeys. *Ann N Y Acad Sci* 1960;85:960–969.
3. Elmore D, Eberle R. Monkey B virus (cercopithecine herpesvirus 1). *Comp Med* 2008;58:11–21.
4. Carlson CS, O'Sullivan MG, Jayo MJ, et al. Fatal disseminated cercopithecine herpesvirus 1 (herpes B) infection in cynomolgus monkeys (*Macaca fascicularis*). *Vet Pathol* 1997;34:405–414.
5. Zwartouw HT, MacArthur JA, Boulter EA, et al. Transmission of B virus infection between monkeys especially in relation to breeding colonies. *Lab Anim* 1984;18:125–130.
6. Boulter EA. The isolation of monkey B virus (herpesvirus simiae) from the trigeminal ganglia of a healthy seropositive rhesus monkey. *J Biol Stand* 1975;3:279–280.
7. Oya C, Ochiai Y, Taniuchi Y, et al. Prevalence of herpes B virus genome in the trigeminal ganglia of seropositive cynomolgus macaques. *Lab Anim* 2008;42:99–103.
8. Zwartouw HT, Boulter EA. Excretion of B virus in monkeys and evidence of genital infection. *Lab Anim* 1984;18:65–70.
9. Vizoso AD. Recovery of herpes simiae (B virus) from both primary and latent infections in rhesus monkeys. *Br J Exp Pathol* 1975;56:485–488.
10. Sabin AB, Wright AM. Acute ascending myelitis following a monkey bite, with isolation of a virus capable of reproducing the disease. *J Exp Med* 1934;59:115–136.
11. Cohen JI, Davenport DS, Stewart JA, et al. Recommendations for prevention of and therapy for exposure to B virus (cercopithecine herpesvirus 1). *Clin Infect Dis* 2002;35:1191–1203.
12. CDC. B virus (herpes B, monkey B virus, herpesvirus simiae and herpesvirus B) resources and publications. Available at: www.cdc.gov/herpesbvirus/resources-pubs.html. Accessed Sep 20, 2011.