Comparative Medicine
Copyright 2011
by the American Association for Laboratory Animal Science

Vol 61, No 6
December 2011
Pages 538–545

Case Report

Facial Paralysis and Lymphocytic Facial Neuritis in a Rhesus Macaque (*Macaca mulatta*) Positive for Simian Retrovirus Type D2

Anna L Hampton,[1,2,*] Lesley A Colby,[1] and Ingrid L Bergin[1]

Simian retrovirus type D (SRVD) is a naturally occurring betaretrovirus in nonhuman primates of the genus *Macaca*. Infection can lead to a variety of clinical, hematologic, and histopathologic abnormalities. We report an unusual clinical presentation of facial paralysis and histologic lymphocytic neuritis in an SRVD type 2 (SRVD2)-infected rhesus macaque (*Macaca mulatta*) with a catheter-associated vena caval thrombus, anemia, thrombocytopenia, and multisystemic lymphoid hyperplasia. At initial presentation, a right atrial mass was detected by echocardiography. The macaque was clinically asymptomatic but had persistent anemia, thrombocytopenia, hyperglobulinemia, and later neutropenia. It was seropositive for SRV and PCR-positive for SRVD 2. Approximately 1 mo after initial presentation, the macaque developed right facial paralysis and was euthanized. Histologic lesions included lymphoplasmacytic aggregates affecting multiple organs, consistent with SRV-related lymphoid hyperplasia. The right facial nerve showed lymphoplasmacytic inflammation. The nerve itself was negative immunohistochemically for SRV antigen, but antigen was present infrequently in pericapillary lymphoid cells within the facial nerve and abundantly within lymphoid aggregates in the adjacent parotid salivary gland, bone marrow, and soft tissue. Known neurotropic viruses could not be identified. Given the widespread inflammation in this macaque, particularly in the area surrounding the facial nerve, lymphocytic neuritis and facial paralysis likely were an indirect effect of SRV infection due to local extension of SRV-related inflammation in the surrounding tissue.

Abbreviation: SRVD2, simian retrovirus type D2.

Simian retrovirus type D (SRVD) is a single stranded-RNA virus in the family Retroviridae.[18] SRV is isolated only from Asian monkeys of the genus *Macaca*.[18,21] Currently, at least 5 different SRVD subtypes have been identified in 4 different macaque species (*Macaca mulatta*, *M. nemestrina*, *M. fascicularis*, and *M. nigra*) in United States primate centers, and none of these subtypes show species-specificity.[36] SRVD has cellular tropism for both lymphoid and nonlymphoid tissues, leading to disseminated infection with a wide variety of clinical signs.[18,21,26,30] Asymptomatic carriers can occur, or nonspecific clinical signs including diarrhea, weight loss, splenomegaly, or generalized lymphadenopathy can be present.[17,20,22,23] More severe clinical signs include immunosuppression[11,20,26] and rare neoplastic diseases (cutaneous fibrosarcoma and retroperitoneal fibromatosis).[27] Clinical pathologic findings include anemia, neutropenia, lymphopenia, and thrombocytopenia.[11,18,20,22,23,38] Although lymphoma has been reported in cynomolgus macaques (*M. fascicularis*),[18,33] neurologic signs have not previously been reported associated with SRV infection of rhesus macaques.[25]

Received: 27 Jan 2011. Revision requested: 03 Mar 2011. Accepted: 22 Jul 2011.
[1]Unit for Laboratory Animal Medicine, University of Michigan Medical School, Ann Arbor, Michigan; [2]Laboratory Animal Resources Unit, College of Veterinary Medicine, North Carolina State, Raleigh, North Carolina.
[*]Corresponding author. Email: Anna.L.Hampton@gmail.com

Case Report

The macaque used in this study was on an IACUC-approved protocol. The macaque was individually housed for research purposes, in accordance with the regulations of the Animal Welfare Act,[1] Animal Welfare Regulations,[2] and Public Health Service Policy on Humane Care and Use of Laboratory Animals[31] in accordance with the *Guide for the Care and Use of Laboratory Animals*.[13] Our animal research facility has had continuous AAALAC accreditation since December 1971.

An 11-y-old male rhesus macaque (*Macaca mulatta*) underwent echocardiography to verify the location of a chronic right jugular catheter that was placed in October 2008. During the echocardiogram a 1×1.5-cm^2 mass originating from the right atrial wall was detected (day 0). Physical examination, including auscultation under sedation, was within normal limits. The macaque had been at our facility for 6 y, was part of a semistatic rhesus macaque research colony for a multiyear drug evaluation study, and had no history of clinical abnormalities.

Hematologic abnormalities on day 7 (Table 1) consisted of a moderate nonregenerative, normocytic, normochromic anemia, and thrombocytopenia. Moderate anisocytosis and agglutination were present. The MCHC was elevated, suggesting hemolysis, but specific evidence of immune-mediated hemolysis (spherocytes) or other red cell destruction (poikilocytosis) was absent.

Table 1. Hematologic abnormalities

	Reference range[a]	Day 7	Day 22	Day 35	Day 42
WBC (×10³/μL)	5–21.0	7.52	7.88	5.76	7.8
Neutrophils (×10³/μL)	0.7–12.7	1.41	1.68	0.61↓	0.54↓
Lymphocytes (×10³/μL)	1.7–17.4	5.67	5.56	4.02	6.12
Platelets (×10³/μL)	259–734	97↓	84↓	82↓	146↓
RBC (×10⁶/μL)	4.6–7.3	2.89↓	2.28↓	3.14↓	2.24↓
Hematocrit (%)	30.3–47.3	21.2↓	18.4↓	24.5↓	19.9↓
MCV (fL)	69.5–83.4	73.4	80.5	77.9	89.0↑
MCHC (g/dL)	27.1–33.0	43.9↑[b]	45.7↑[b]	38.4↑[b]	46.2↑[b]
Reticulocyte (%)	0.5%–2.0%	0.78↓	0.09↓	2.64	nd
Reticulocyte (x10⁹/L)	35.0–87.5	22.5↓	20.5↓	81.6	nd
RBC abnormalities	—	Anisocytosis, moderate agglutination	Anisocytosis	Anisocytosis	Anisocytosis

nd, not done
[a]From the Animal Diagnostic Laboratory (University of Michigan Ann Arbor, MI)
[b]Elevated MCHC is due to hemolysis

Serum biochemical analysis demonstrated a moderate hyperglobulinemia (7.1 g/dL; reference range, 3.1 to 3.2 g/dL). The remainder of the chemistry panel was within normal limits. Aerobic and anaerobic peripheral blood cultures (Diagnostic Center for Population and Animal Health, Michigan State University, Lansing, MI) were negative for bacterial growth. Postechocardiogram daily monitoring of behavior, appetite, thirst, and clinical appearance showed a bright, alert, and responsive animal with no clinical abnormalities. Differential diagnoses at this stage included vegetative endocarditis, thromboembolic disease, and a neoplastic process with anemia of chronic disease. Because of the absence of clinical signs, no treatment was initiated, and daily monitoring was implemented. During a recheck examination under sedation on day 22, a grade III–VI left systolic heart murmur was ausculted.

Repeat CBC (Table 1) and serum biochemistry profiles were similar to the previous results (anemia, thrombocytopenia, and hyperglobulinemia), the macaque was normotensive, and urinalysis was unremarkable. Blood smear cytology (Antech Diagnostics, Oak Brook, IL) demonstrated moderate numbers of lymphocytes with increased cytoplasm and azurophilic granules, some of which had multilobulated nuclei (interpreted as reactive lymphocytes). Blood was submitted for viral serology (VRL Laboratories, San Antonio, TX). Serology was positive for SRV group-specific antibody and measles (rubeola) and negative for *Macacine herpesvirus 1* (formally *Cercopithecine herpesvirus 1*),[6] SIV, and simian T-cell leukemia virus by indirect ELISA. The measles titer was attributed to previous vaccination. The macaque continued to be clinically normal. Repeated blood work on day 35 showed persistence of hyperglobulinemia, anemia, and thrombocytopenia with the development of a neutropenia (Table 1). A bone marrow aspirate was planned; however, 3 d prior to the procedure (day 37), the monkey developed right facial paralysis.

On cageside examination, the monkey was bright, alert, responsive, and actively eating. The right cheek and lip were flaccid and did not move during mastication, and the right eye showed no menace response. Facial nerve paralysis ('Bell palsy') and thromboembolism-induced transient ischemic attack (TIA, stroke) were added to the differential diagnostic list. The monkey showed no clinical improvement over 4 d of monitoring and supportive care.

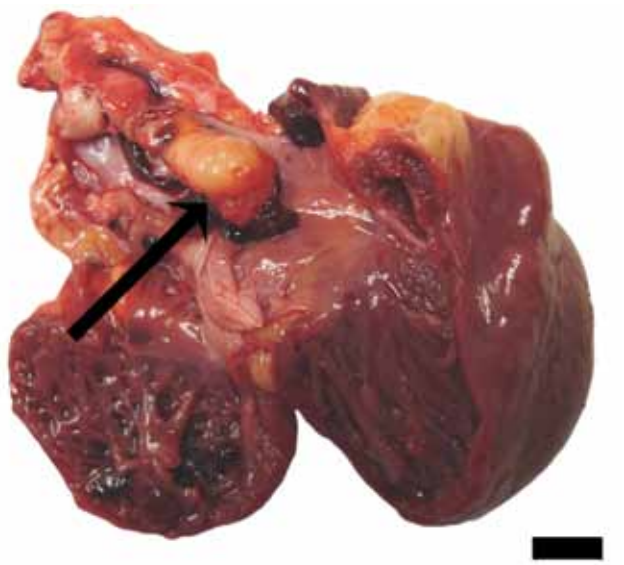

Figure 1. Gross necropsy image of the catheter-associated caval thrombus (arrow) extending into the right atrium. Scale bar, 1 cm.

With this clinical development, the persistent hematologic abnormalities, and history of a right atrial heart mass, the macaque was euthanized on day 42 owing to a poor prognosis for return to experimental function.

Gross necropsy revealed a large (length, 3.5 cm; width, 1 cm) thrombus in the distal superior vena cava. Approximately 1 cm protruded into the right atrium, consistent with the location of the right atrial mass visualized on echocardiogram (Figure 1). Additional gross findings included prominent splenic white pulp consistent with lymphoid hyperplasia. The remaining tissues were grossly normal. Tissues collected at necropsy were immersion-fixed in 10% neutral buffered formalin and routinely processed to hematoxylin-and-eosin–stained sections. Histopathologically, the vena cava contained a partially occlusive, well-organized thrombus with focal recanalization, smooth muscle hypertrophy, and fibrosis. In addition, there was pronounced, multifocal, lymphoplasmacytic inflammation affecting the kidney (Figure 2 A),

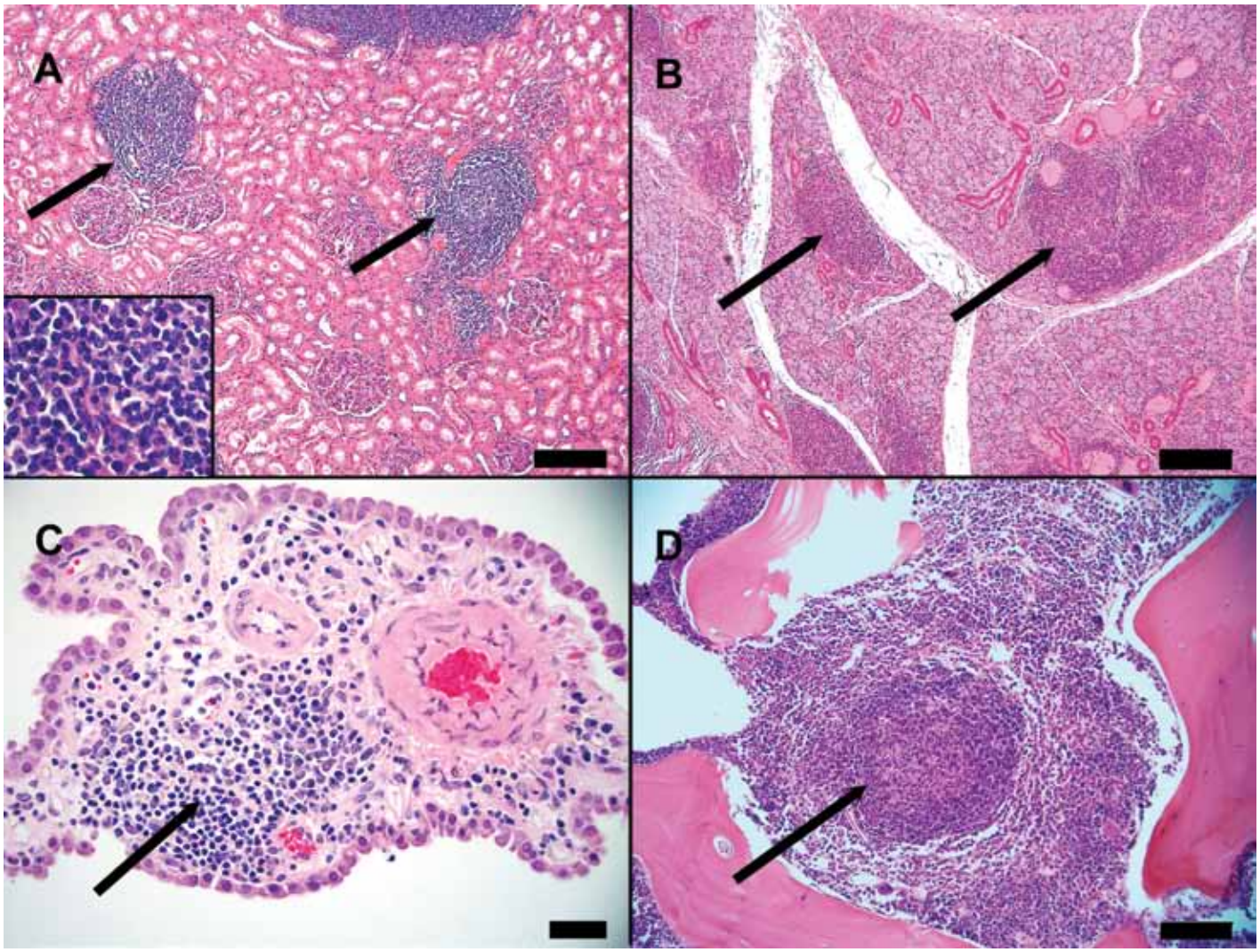

Figure 2. Multifocal, lymphoplasmacytic and lymphofollicular inflammation affecting the (A) kidney, (B) salivary gland, (C) choroid plexus, and (D) bone marrow. Lower magnification photos illustrate multifocal distribution of lesions. Inset in panel A shows the lymphoplasmacytic character of the inflammation, which was similar in all affected tissues. Similar aggregates were seen in the liver, spleen, pancreas, lung, heart, and facial nerve also. Hematoxylin and eosin stain. Bars: 100 µm (A, B); 20 µm (C); 50 µm (D).

liver, spleen, salivary gland (Figure 2 B), pancreas, choroid plexus (Figure 2 C), lung, heart, and bone marrow (Figure 2 D). In most areas, these foci were highly organized and consisted of discrete foci of mature lymphocytes surrounded by plasma cells (Figure 2). Larger stellate shaped cells resembling follicular dendritic cells were present centrally in some aggregates, particularly within bone marrow. Acid-fast stains of bone marrow were negative for mycobacterial organisms. In lymph nodes and spleen, lymphoid areas were large but contained central lymphoid depletion. The right facial nerve contained foci of predominantly lymphoplasmacytic inflammation (Figure 3). This right-sided lymphoplasmacytic neuritis corresponded to the clinical observation of right facial paralysis. Vascular or other lesions were not seen in the brain.

Additional diagnostics at necropsy (day 42) included a repeat CBC, which indicated persistence of the anemia, neutropenia, and thrombocytopenia (Table 1). There were increased reticulocytes compared with previous time points and slightly elevated MCV, but overall erythroid regeneration remained minimal. A postmortem bone marrow aspirate from the proximal femur showed normal maturation and progression of the myeloid and erythroid lineage with slightly increased myeloid cells and slightly increased megakaryocytes, demonstrating a slight hyperplasia of these cell lines. Erythroid hyperplasia was not evident, but a mild erythroid response could have been masked by the myeloid hyperplasia. In addition, the bone marrow aspirate contained increased lymphocytes and plasma cells. A range of lymphocytes from small to large were present, and monotypia or other distinct features of neoplasia were absent. This bone marrow picture was consistent with the lymphoplasmacytic hyperplasia seen histologically. Whole blood was PCR-positive for SRVD type 2 (VRL Laboratories, San Antonio, TX). In addition, a culture (Diagnostic Center for Population and Animal Health, Michigan State University) of the right jugular catheter tip was negative for aerobic bacterial growth. Morphologic diagnoses based on these necropsy and ancillary findings were chronic vena caval thromboem-

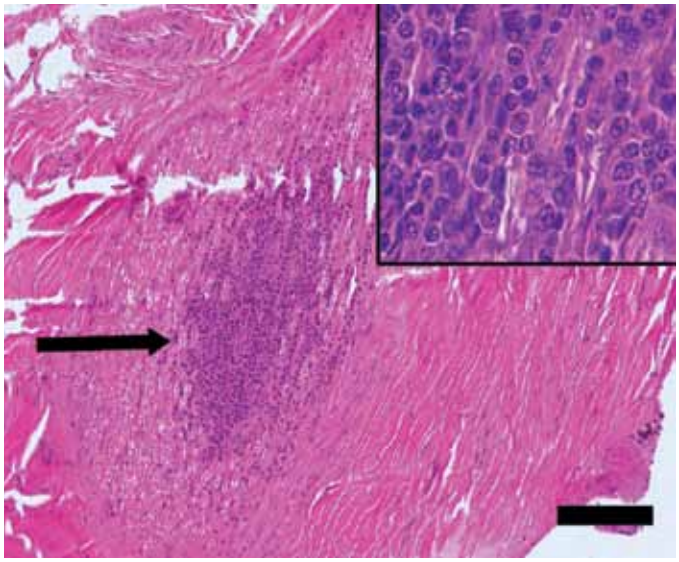

Figure 3. Section through salivary gland and right facial nerve within the masseter muscle adjacent to the right ear. There is a focal region of cellular infiltration in the facial nerve (arrow). Higher magnification (inset) reveals lymphoplasmacytic inflammation. Hematoxylin and eosin stain. Bar: 100 µm; 10 µm (inset).

bolism; multifocal–multisystemic lymphoid hyperplasia with lymphoid neuritis; and poorly regenerative anemia, thrombocytopenia, and neutropenia.

To define the cell populations in the lymphoid aggregates and rule out a monoclonal lymphocyte population (lymphoma),[41,42] immunohistochemistry was performed on formalin-fixed, paraffin-embedded, decalcified tissue sections of bone marrow. Antibodies against CD3 (rabbit polyclonal, catalog no. A0452, Dako, Carpinteria, CA), CD79a (mouse monoclonal, catalog no. AM414-5M, Biogenex, Freemont, CA), and CD21 (Rabbit monoclonal, catalog no. ab75985, Abcam, Cambridge, MA) were used to identify T cells, B cells, and follicular dendritic cells, respectively. Immunohistochemistry against the antiapoptotic protein Bcl2 (mouse monoclonal, catalog no. M0887, Dako) was performed also. For immunohistochemistry, unstained sections underwent heat-mediated antigen retrieval in citrate buffer (20 to 30 min, 95 °C) in a pressure cooker. Sections were cooled to room temperature and blocked with hydrogen peroxide and an appropriate blocking reagent (Power Block, catalog no. HK083, Biogenex). The primary antibodies were applied at appropriate dilutions (1:200 for CD3; as supplied [prediluted] for CD79a; 1:200 for CD21) for 1 h at room temperature. Chromogenic detection was performed by using a commercial kit (SuperSensitive Detection Kit, Biogenex) with diaminobenzidine, as the chromagen. Negative controls used naive serum in place of the primary antibody. Immunohistochemically, the bone marrow aggregates had a well-organized structure, with B cells situated at the periphery and scattered positive cells in the center (Figure 4 A), mature T cells loosely distributed (Figure 4 B), and strong central CD21 staining for follicular dendritic cells (Figure 4 C). This pattern was consistent with lymphoid follicular formation. There was often a peripheral rim of plasma cells. Centrally the lymphoid aggregates were negative for Bcl2, a pattern most consistent with a reactive process compared with a neoplastic one. Reticulin staining was performed on spleen and bone marrow by standard histochemistry techniques to identify increased collagen staining in centrally depleted follicular aggregates. This organization was most consistent with reactive lymphoid hyperplasia as compared with a neoplastic process.[41]

Because lymphoid hyperplasia and cytopenias have previously been associated with SRV infections,[11,21,25] immunohistochemical detection of SRVD was undertaken to determine whether SRV was colocalized with the inflammatory foci. This staining was performed at the Pathogen Detection Laboratory (California National Primate Research Center, Davis, CA) by using rabbit polyclonal antibody against the viral protein gp20. In sections through the temporal bone and soft tissue adjacent to the right ear, SRV antigen was detected within lymphocytes and nucleated cells of other lineages within the bone marrow. Megakaryocytes and mature erythrocytes were negative (Figure 4 D). SRV antigen was detected similarly within lymphoid aggregates in the parotid salivary gland adjacent to the right ear (data not shown). SRV antigen was not detected within the facial nerve itself, although a few individual macrophages and lymphocytes adjacent to capillaries within the nerve had cytoplasmic labeling (Figure 5 A). Because the section chosen for immunohistochemistry did not have as much inflammation as did the initial histology slide, the histology slide was destained and used for SRV immunohistochemistry. This assessment was negative for SRV even within the facial nerve inflammatory foci, but labeling in adjacent bone marrow aggregates was decreased also, likely due to destaining. A destained section of the inflamed choroid plexus had scattered individual plasma cells positive for SRV (Figure 5 B).

To rule out other viral candidates likely to have neural tropism, PCR for *Macacine herpesvirus 1* was performed on formalin-fixed, trigeminal ganglia (Zoologix, Chatsworth, CA), PCR for lymphocryptovirus was performed on formalin-fixed spleen (Zoologix), and PCR for macaque cytomegalovirus was performed on formalin-fixed tissue that contained salivary gland and facial nerve (Zoologix). All PCR tests were negative. Finally, immunohistochemistry for cytomegalovirus (catalog no. CM118A, Biocare, Concord, CA) was performed as described earlier, by using heat-induced antigen retrieval on formalin-fixed, paraffin-embedded, decalcified tissue sections that included salivary gland, facial nerve, and bone marrow. This test was negative also.

Discussion

This case involved facial neuritis as an unusual clinical presentation in a rhesus macaque that also had cytologic manifestations of SRV viremia (anemia, thrombocytopenia) and a catheter-associated caval thrombus. Cytopenias and lymphoid hyperplasia, manifesting as lymphofollicular aggregates in multiple tissues, are well described in SRV-infected macaques.[11,21,25] Thromboembolic disease is a known complication of chronic catheterization and has been associated with endothelial and immune changes in SIV infection but is not described with respect to SRV. Facial neuritis has not been reported in association with SRVD2, to our knowledge. We believe that this clinical sign was most likely a local extension of SRV-induced inflammation to the facial nerve, rather than a direct neurotropic effect of SRV. Although individually positive inflammatory cells were seen in the choroid plexus and around capillaries within the facial nerve, we were unable to demonstrate SRVD2 directly within neural tissue. However, in surrounding tissues (bone marrow of the temporal bone, parotid salivary gland), SRV antigen was strongly detectable by

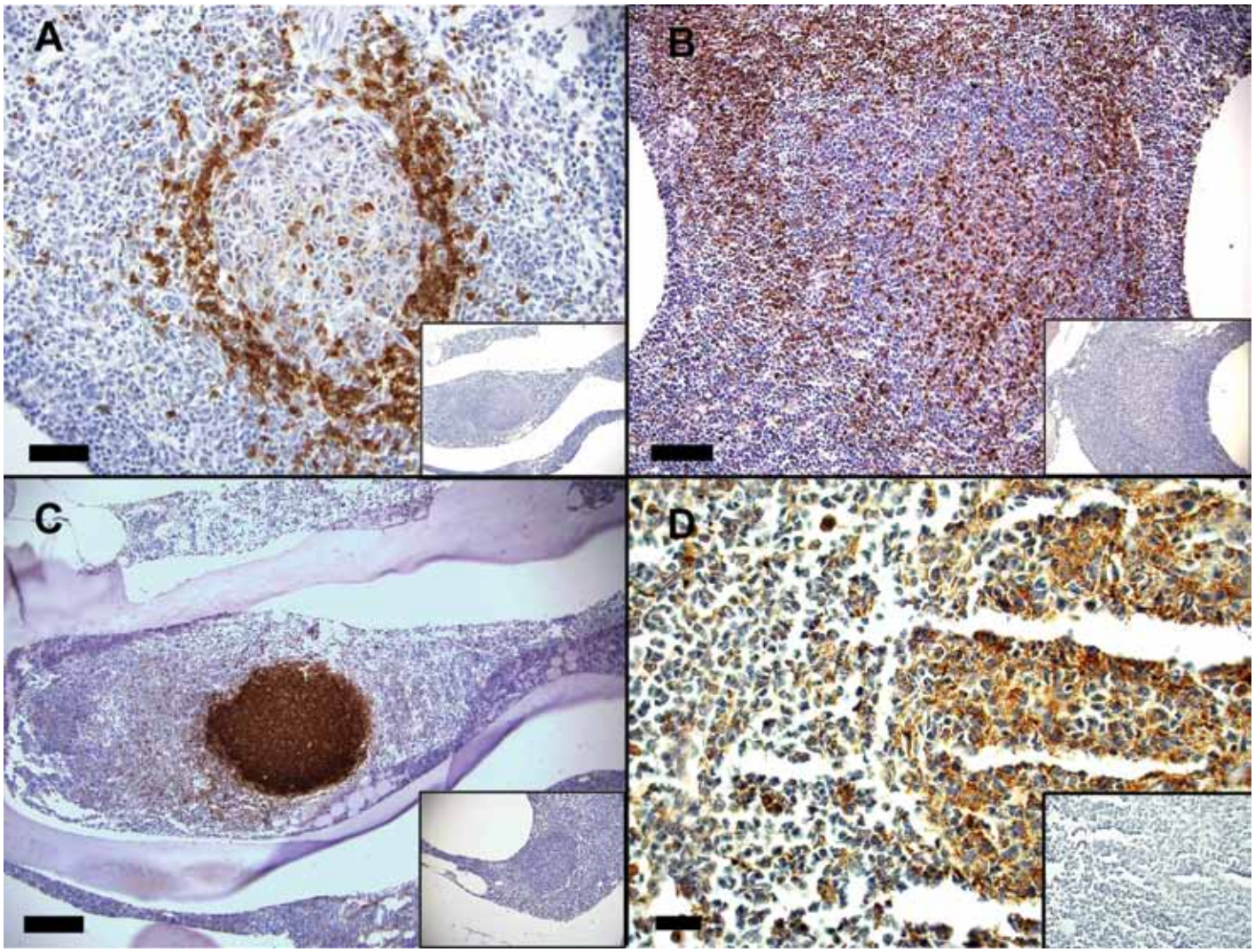

Figure 4. Immunohistochemical analysis of bone marrow inflammatory aggregates. (A) B cells (CD79a). (B) T cells (CD3). (C) Follicular dendritic cells (CD21). (D) SRVD antigen. Samples in panels A through C are not serial sections but are from the same section of sternum. Slide D shows bone marrow from the right temporal bone. Brown cytoplasmic precipitate indicates positively labeled cells. The aggregates had a distinct organizational pattern, with B cells situated at the periphery and scattered positive cells in the center (A), T cells loosely distributed centrally and peripherally (B), and well-defined central labeling for follicular dendritic cells (C). Lymphocytes and nucleated cells of other lineages within the bone marrow are positive for SRVD, whereas megakaryocytes and mature erythrocytes are negative. Negative controls are pictured in insets. Diaminobenzidine chromagen with hematoxylin nuclear counterstaining. Bar: 20 µm (A), 100 µm (B, C) 10 µm (D).

immunohistochemistry within and around lymphoplasmacytic aggregates. Evidence of direct neurotropism (neuronal loss, glial nodules) as seen in SIV-related encephalitis was not present.[16]

Lymphoma was considered as a differential diagnosis, in light of the large multisystemic lymphoid aggregates. SRV has infrequently been associated with intracranial lymphomas in cynomolgus macaques (*Macaca fascicularis*)[33] although lymphoma is not a typical sequelae of infection in rhesus macaques, and neuritis has not been described.[25,26] In the current case, although reactive lymphocytes were present in peripheral blood early in the disease course, a monotypic lymphoid population was not detected in blood or tissue. In addition, the lymphoid tissue infiltrates were polyclonal and highly organized, with moderately elevated central reticulin staining, lack of Bcl2 staining, high numbers of CD21-positive follicular dendritic cells, accompanying T cells, and a peripheral rim of B and plasma cells. This appearance has been used to distinguish reactive from neoplastic lymphocytic aggregates in human bone marrow.[41] We also considered whether the macaque had a T-cell–rich, B-cell lymphoma. A subtype of T-cell–rich B-cell lymphomas termed 'lymphomatoid granulomatosis' has been described in connection with Epstein–Barr infections in humans[14] and can affect the CNS. In our case, however, the macaque was negative for lymphocryptovirus (Epstein–Barr-like gammaherpesvirus) by PCR.[39]

The multisystemic distribution of lymphoid follicles in the current case was consistent with previous findings in SRV, which include involvement of kidney, pancreas, salivary gland, bone marrow, brain including the choroid plexus, reproductive organs, peripheral nerves (in *Macaca fascicularis*), retina, skeletal muscle, urinary bladder, and thymus.[11,12,33] The presence of lymphoid

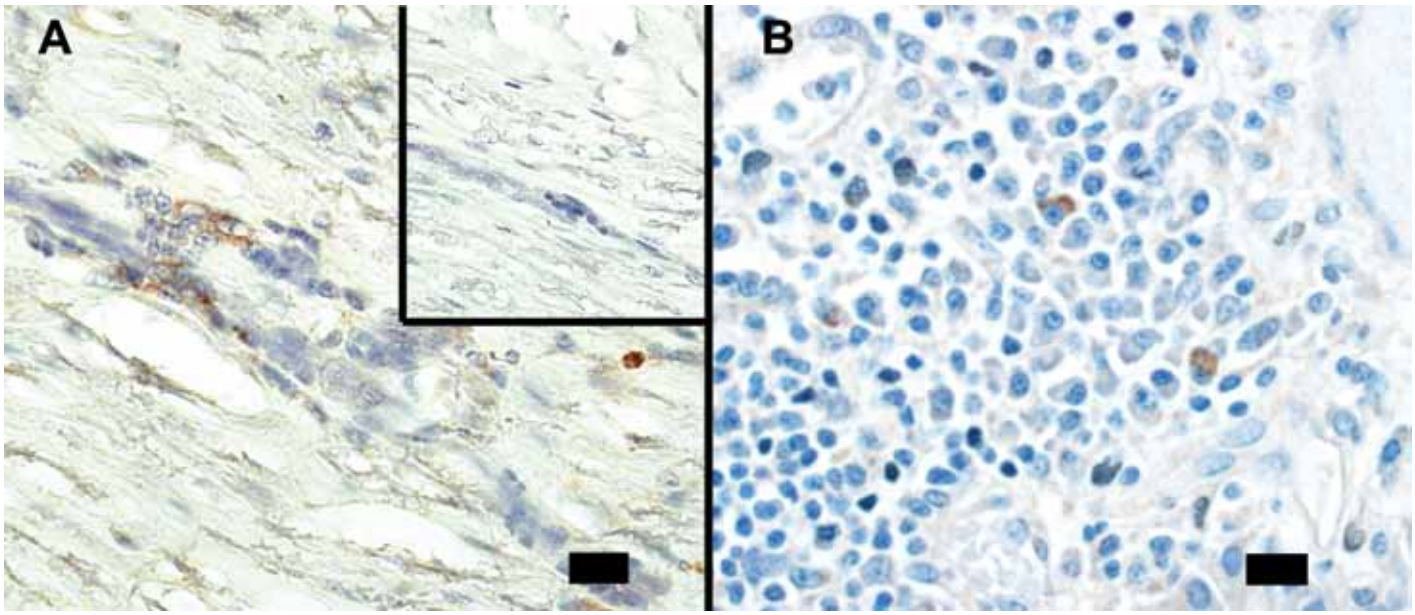

Figure 5. Immunohistochemical analysis for SRVD within the (A) facial nerve and (B) choroid plexus. The majority of the facial nerve was negative for SRVD antigen, but there were rare, individually positive inflammatory cells (lymphocytes and macrophages) along small capillaries in the nerve (A). Inset is the negative control. Rare individual plasma cells within the inflammatory aggregates in the choroid plexus had positive cytoplasmic labeling (B). Diaminobenzidine chromagen with hematoxylin nuclear counterstaining. Bar, 20 µm.

hyperplasia would seem to be counterintuitive in an immunosuppressive virus. However, an interesting aspect of SRVD infection in macaques is that serum antibodies, although not often curative, are neutralizing and protective against SRV-associated disease. Therefore, as in the initial presentation in our macaque, seropositive animals are typically nonviremic carriers, whereas animals that are actively viremic are often seronegative.[4] The onset of active disease often coincides with a decrease in viral titer, decreased lymphocytes, and eventually lymphopenia.[4,11,28] At the time of necropsy, our macaque appeared somewhere between these 2 disease stages. Although lymphoid hyperplasia certainly was present, there was central depletion of white pulp within the spleen, suggesting that the macaque was progressing to a lymphopenic state. Unlike SIV, SRV is polytropic and infects many cell types.[26,29,30] In the present case, erythroid elements, platelets, and (to a lesser degree) neutrophils were decreased, again suggesting that the macaque was heading toward viremia and active disease.

The conditions under which SRVD is reactivated are defined only incompletely.[20] It is interesting that our macaque originally presented with a right atrial thrombus. Atrial thrombi have been associated with SIV infection[39] but not, to our knowledge, with SRV infection. In the current case, it is difficult to evaluate direct relationships between SRV infection and thrombus formation, because this macaque had a history of chronic catheterization, which is itself a risk factor for thrombus formation. Nevertheless, systemic illness and experimental manipulation are reported risk factors for reactivation of SRVD latent infection,[19,21] and the development of thromboembolic disease in our case may be related temporally to symptomatic SRV infection.

The current case was also unusual in that the SRV strain was identified as type 2. Although SRVD type 1 is recognized as the most prevalent type in rhesus macaques,[19,21] only SRVD type 2 has been isolated from rhesus macaques in the colony described here. The prevalence of SRVD infections among laboratory macaques in the United States varies and can range from 0% to over 50% in captive populations; these numbers have been declining in recent years due to culling of affected animals.[20,26] The overall prevalence of SRVD2 in the colony of chronically catheterized monkeys discussed here is unknown. On a case-by-case basis, macaques in this facility that are PCR-positive for SRVD2 have included both seropositive and seronegative animals.

The mechanism of SRV-associated anemia and granulocytopenia is not known. One suggestion is direct viral inhibition of granulocyte progenitor cell differentiation.[44] Anemia and neutropenia were identified in the current case and are among the most common cytopenias described in SRVD infection.[11,18,21-23,38] In our case, although the MCHC was elevated, suggesting hemolysis, other factors (principally the lack of spherocytes and the lack of a regenerative erythroid response) were not consistent with immune-mediated hemolytic anemia. This pattern seems more consistent with decreased erythroid production than destruction.

Reports of spontaneous facial paralysis in nonhuman primates are rare to nonexistent. Peripheral neuropathies described in nonhuman primates include genetic disorders,[3] neural tumors,[24] nutritional deficiencies,[32] and poisoning.[8] Unilateral hemiparesis, mydriasis, and ptosis were present in a SRV-positive cynomologus macaque (*Macaca fascicularis*) with intracranial lymphoma.[33] In humans, facial paralysis is classified into acute and chronic presentations, with multiple etiologies in both categories. Differential diagnoses for acute presentations include polyneuritis, idiopathic palsy, tuberculosis, herpes zoster oticus, autoimmune disease, Lyme disease, HIV, trauma, otitis media, sinusitis, sarcoidosis, and diabetes mellitus.[5,9,34,35,37] Some causes are a direct result of nerve-directed damage, whereas others are due to local extension of an inflammatory process. Idiopathic paralysis (Bell palsy) and Herpes zoster infection are the most common underlying diagnoses.[35] In addition, herpes simplex 1 has been implicated; however, there is controversy surrounding this diagnosis.[10,15]

Extensive evaluation for concurrent neurotropic viruses was undertaken in the current case. *Macacine herpesvirus 1* (an alphaherpesvirus), lymphocryptovirus (an Epstein–Barr-like gammaherpesvirus), and cytomegalovirus (a betaherpesvirus) could not be detected by PCR or immunohistochemistry (for cytomegalovirus). The characteristic viral inclusions of cytomegalovirus were not detected, despite heavy salivary gland inflammation. Cranial nerve involvement (optic and trigeminal nerve) has been reported in macaques infected with SIV.[16] Our macaque was seronegative for SIV and has no history of experimental or other exposure to this agent. Acute facial paralysis has not been linked to SIV or SRVD infection in macaques but has occurred in humans infected with HIV,[9,34,37] a lentivirus in the Retroviridae family. Whether this paralysis is a direct or indirect effect is unclear.

In conclusion, the current case describes an unusual presentation of facial paralysis with histologically evident lymphocytic neuritis in an SRVD2-infected rhesus macaque. Given the rarity of this clinical presentation (as evidenced by the absence of similar reports in the SRV literature) and lack of direct evidence of SRV in neural tissue, the facial paralysis in our macaque most likely was due to local extension of inflammation rather than a direct neurotropic effect. The time course and prognosis for return of facial function in facial paralysis in humans is variable based on initial severity and the particular cause.[35,37,40,43] In humans with idiopathic paralysis (Bell palsy), 71% achieved complete remission between 3 wk and 5 mo; however, in patients with herpes zoster oticus, only 21% and 31% showed complete remission without or with treatment, respectively.[7,35] The time course to resolution or possible progression of facial paralysis in the current case is unknown. In addition, the SRV-associated cytopenias seen here are unlikely to show clinical remission, and the prognosis for return to experimental function after clinical manifestation of SRV infection is poor.

Acknowledgments

We thank Ann Rosenthal, Jessica White, and Amanda Carpenter (Pathogen Detection Laboratory, UC Davis) for SRV immunohistochemistry; Dr Lauren B Smith (University of Michigan Department of Pathology) for facilitating Bcl2 immunostaining; and Paula Arrowsmith (Unit for Laboratory Animal Medicine Pathology Cores for Animal Research) for histology, special stains, and immune cell immunohistochemistry.

References

1. **Animal Welfare Act as Amended**. 2007. 7 USC §2131–2156.
2. **Animal Welfare Regulations**. 2008. 9 CFR §3.129.
3. **Baskin GB, Ratterree M, Davison BB, Falkenstein KP, Clarke MR, England JD, Vanier MT, Luzi P, Rafi MA, Wenger DA.** 1998. Genetic galactocerebrosidase deficiency (globoid cell leukodystrophy, Krabbe disease) in rhesus monkeys (*Macaca mulatta*). Lab Anim Sci **48:**476–482.
4. **Brody BA, Hunter E, Kluge JD, Lasarow R, Gardner M, Marx PA.** 1992. Protection of macaques against infection with simian type D retrovirus (SRV1) by immunization with recombinant vaccinia virus expressing the envelope glycoproteins of either SRV1 or Mason–Pfizer monkey virus (SRV3). J Virol **66:**3950–3954.
5. **Christen HJ.** 1996. Lyme neuroborreliosis in children. Ann Med **28:**235–240.
6. **Davison 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.
7. **Dickins JR, Smith JT, Graham SS.** 1988. Herpes zoster oticus: treatment with intravenous acyclovir. Laryngoscope **98:**776–779.
8. **Fedigan L, Joiner GN, Russell LH, Bush DE, Gleiser CA, Johnston TD.** 1975. A spontaneous neuropathy of free-ranging Japanese macaques. Lab Anim Sci **25:**232–237.
9. **Gallego Perez-Larraya J, Riverol M.** 2009. Facial diplegia and vestibular neuritis secondary to HIV seroconversion syndrome. Can J Neurol Sci **36:**527–528.
10. **Gilbert SC.** 2002. Bell's palsy and herpesviruses. Herpes **9:**70–73.
11. **Guzman RE, Kerlin RL, Zimmerman TE.** 1999. Histologic lesions in cynomolgus monkeys (*Macaca fascicularis*) naturally infected with simian retrovirus type D: comparison of seropositive, virus-positive, and uninfected animals. Toxicol Pathol **27:**672–677.
12. **Heyes MP, Gravell M, London WT, Eckhaus M, Vickers JH, Yergey JA, April M, Blackmore D, Markey SP.** 1990. Sustained increases in cerebrospinal fluid quinolinic acid concentrations in rhesus macaques (*Macaca mulatta*) naturally infected with simian retrovirus type D. Brain Res **531:**148–158.
13. **Institute of Laboratory Animal Resources.** 1996. Guide for the care and use of laboratory animals. Washington (DC): National Academies Press.
14. **Katzenstein AL, Doxtader E, Narendra S.** 2010. Lymphomatoid granulomatosis: insights gained over 4 decades. Am J Surg Pathol **34:**e35–e48.
15. **Kennedy PG.** 2010. Herpes simplex virus type 1 and Bell's palsy—a current assessment of the controversy. J Neurovirol **16:**1–5.
16. **Laast VA, Pardo CA, Tarwater PM, Queen SE, Reinhart TA, Ghosh M, Adams RJ, Zink MC, Mankowski JL.** 2007. Pathogenesis of simian immunodeficiency virus-induced alterations in macaque trigeminal ganglia. J Neuropathol Exp Neurol **66:**26–34.
17. **Lackner AA, Moore PF, Marx PA, Munn RJ, Gardner MB, Lowenstine LJ.** 1990. Immunohistochemical localization of type D retrovirus serotype 1 in the digestive tract of rhesus monkeys with simian AIDS. J Med Primatol **19:**339–349.
18. **Lerche N.** 2005. Common viral infections of laboratory primates, p 75–89 In: Wolfe-Coote S, editor. The handbook of experimental animals: the laboratory primate. Boston (MA): Academic Press.
19. **Lerche NW.** 2010. Simian retroviruses: infection and disease—implications for immunotoxicology research in primates. J Immunotoxicol **7:**93–101.
20. **Lerche NW, Marx PA, Osborn KG, Maul DH, Lowenstine LJ, Bleviss ML, Moody P, Henrickson RV, Gardner MB.** 1987. Natural history of endemic type D retrovirus infection and acquired immune deficiency syndrome in group-housed rhesus monkeys. J Natl Cancer Inst **79:**847–854.
21. **Lerche NW, Osborn KG.** 2003. Simian retrovirus infections: potential confounding variables in primate toxicology studies. Toxicol Pathol **31 Suppl:**103–110.
22. **Lerche NW, Osborn KG, Marx PA, Prahalada S, Maul DH, Lowenstine LJ, Munn RJ, Bryant ML, Henrickson RV, Arthur LO, Gilden RV, Barker CS, Hunter E, Gardner MB.** 1986. Inapparent carriers of simian acquired immune deficiency syndrome type D retrovirus and disease transmission with saliva. J Natl Cancer Inst **77:**489–496.
23. **Letvin NL, Daniel MD, Sehgal PK, Chalifoux LV, King NW, Hunt RD, Aldrich WR, Holley K, Schmidt DK, Desrosiers RC.** 1984. Experimental infection of rhesus monkeys with type D retrovirus. J Virol **52:**683–686.
24. **Long PH, Schulman FY, Koestner A, Fix AS, Campbell MK, Cameron KN.** 1998. Primitive neuroectodermal tumor in a 2-month-old black and white Colobus monkey. Vet Pathol **35:**64–67.
25. **Lowenstine LJ.** 2003. A primer of primate pathology: lesions and nonlesions. Toxicol Pathol **31 Suppl:**92–102.
26. **Mansfield K, King N.** 1998. Viral diseases, p 1–57. In: Bennett BT, Abee CR, Henrickson R, editors. Nonhuman primates in biomedical research: diseases. San Diego (CA): Academic Press.
27. **Marx PA, Lowenstine LJ.** 1987. Mesenchymal neoplasms associated with type D retroviruses in macaques. Cancer Surv **6:**101–115.
28. **Maul DH, Lerche NW, Osborn KG, Marx PA, Zaiss C, Spinner A, Kluge JD, MacKenzie MR, Lowenstine LJ, Bryant ML, Blakeslee JR, Henrickson RV, Gardner MB.** 1986. Pathogenesis of simian

AIDS in rhesus macaques inoculated with the SRV1 strain of type D retrovirus. Am J Vet Res **47:**863–868.

29. **Maul DH, Zaiss CP, MacKenzie MR, Shiigi SM, Marx PA, Gardner MB.** 1988. Simian retrovirus D serogroup 1 has a broad cellular tropism for lymphoid and nonlymphoid cells. J Virol **62:**1768–1773.
30. **Moazed TC, Thouless ME.** 1993. Viral persistence of simian type D retrovirus (SRV2/W) in naturally infected pigtailed macaques (*Macaca nemestrina*). J Med Primatol **22:**382–389.
31. **Office of Laboratory Animal Welfare**. 2002. Public health service policy on humane care and use of laboratory animals. Bethesda (MD): National Institutes of Health.
32. **Oxnard CE, Smith WT, Torres I.** 1970. Vitamin B12 deficiency in captive monkeys and its effect on the nervous system and the blood. Lab Anim **4:**1–12.
33. **Paramastri YA, Wallace JM, Salleng KJ, Wilkinson LM, Malarkey DE, Cline JM.** 2002. Intracranial lymphomas in simian-retrovirus-positive *Macaca fascicularis*. Vet Pathol **39:**399–402.
34. **Parry GJ.** 1988. Peripheral neuropathies associated with human immunodeficiency virus infection. Ann Neurol **23 Suppl:**S49–S53.
35. **Peitersen E.** 2002. Bell's palsy: the spontaneous course of 2500 peripheral facial nerve palsies of different etiologies. Acta Otolaryngol Suppl (549):4–30.
36. **Philipp-Staheli J, Marquardt T, Thouless ME, Bruce AG, Grant RF, Tsai CC, Rose TM.** 2006. Genetic variability of the envelope gene of type D simian retrovirus 2 (SRV2) subtypes associated with SAIDS-related retroperitoneal fibromatosis in different macaque species. Virol J **3:**11.
37. **Schot LJ, Devriese PP, Hadderingh RJ, Portegies P, Enting RH.** 1994. Facial palsy and human immunodeficiency virus infection. Eur Arch Otorhinolaryngol **Dec:**S498–S500.
38. **Schroder MA, Fisk SK, Lerche NW.** 2000. Eradication of simian retrovirus type D from a colony of cynomolgus, rhesus, and stumptailed macaques by using serial testing and removal. Contemp Top Lab Anim Sci **39:**16–23.
39. **Shannon RP.** 2001. SIV cardiomyopathy in nonhuman primates. Trends Cardiovasc Med **11:**242–246.
40. **Sugita T, Murakami S, Yanagihara N, Fujiwara Y, Hirata Y, Kurata T.** 1995. Facial nerve paralysis induced by herpes simplex virus in mice: an animal model of acute and transient facial paralysis. Ann Otol Rhinol Laryngol **104:**574–581.
41. **Thiele J, Zirbes TK, Kvasnicka HM, Fischer R.** 1999. Focal lymphoid aggregates (nodules) in bone marrow biopsies: differentiation between benign hyperplasia and malignant lymphoma—a practical guideline. J Clin Pathol **52:**294–300.
42. **Utz GL, Swerdlow SH.** 1993. Distinction of follicular hyperplasia from follicular lymphoma in B5-fixed tissues: comparison of MT2 and bcl2 antibodies. Hum Pathol **24:**1155–1158.
43. **Wakisaka H, Hato N, Honda N, Takahashi H, Kisaki H, Murakami S, Gyo K, Mominoki K, Kobayashi N, Matsuda S.** 2002. Demyelination associated with HSV1-induced facial paralysis. Exp Neurol **178:**68–79.
44. **Yoshioka S**. 2000. Effects of simian type D retrovirus serotype 1 (SRV) on in vitro differentiation of bone marrow-derived progenitor cells of the rhesus macaque (*Mucaca mulatta*). [MS thesis]. Davis (CA): University of California, Davis.