Use of cyclosporine to treat granulomatous meningoencephalitis in three dogs

Filippo P. Adamo, DVM, and Robert T. O’Brien, DVM, MS, DACVR

Granulomatous meningoencephalitis is an idiopathic inflammatory disease of the CNS in dogs that may be caused by an autoimmune mechanism.

Immunosuppressive doses of corticosteroids are commonly used for treatment, although response is variable and prognosis for complete recovery is poor.

The immunosuppressive drug cyclosporine may be effective for treatment of some dogs with granulomatous meningoencephalitis.

An 8-year-old sexually intact female Chihuahua (dog 1) that weighed 3 kg (6.6 lb) was evaluated because of a 1-month history of acute onset of blindness with episodic pain in the cervical region. A few days before referral, the dog began pacing and circling to the right, with a right-sided head tilt that persisted to the time of evaluation. Both pupils were dilated, with absent direct and consensual pupillary light response. Menace reaction was absent in both eyes, results of a Shimara tear test and tonometry were within reference ranges in both eyes, nuclear sclerosis was evident in the right lens, a small cortical cataract was noted in the left eye, and findings of fundic examination in both eyes were normal. To rule out concurrent iris atrophy, 2 drops of 1% pilocarpine were instilled in each eye, and complete miosis was observed during the following 10 minutes. Decreased sensation to the left side of the face and decreased conscious proprioception in both left limbs were also detected. The neurologic abnormalities were suggestive of a multifocal lesion involving retrolubular optic nerves, the optic tracts or optic chiasm, and the right forebrain. Results of CBC, serum biochemical analyses, urinalysis, and thoracic radiography were within reference ranges. Computed tomography (CT) of the brain revealed an irregularly shaped, contrast-enhancing cerebral mass in the right parietal lobe with attenuation of the right lateral ventricle (Figure 1). Analysis of CSF collected by cerebellomedullary cisternal puncture revealed 360 cells/µL (reference limit, < 5 cells/µL) with marked mixed pleocytosis (74% lymphocytes, 19% mononuclear cells, and 7% neutrophils) and high total protein (TP) concentration (99.1 mg/dL; reference limit, < 25 mg/dL). Results of serology tests for Toxoplasma gondii, Cryptococcus neoformans, Neospora caninum, Ehrlichia canis, Ehrlichia platys, Ehrlichia equi, and Rickettsia rickettsii were negative. Cerebrospinal fluid and serum-neutralizing antibody titers and results of urine reverse transcriptase-polymerase chain reaction (RT-PCR) assay for canine distemper virus were also negative. Presumptive diagnosis of granulomatous meningoencephalitis was made, and cyclosporine administration was initiated at a dose of 3 mg/kg (1.4 mg/lb) every 12 hours, PO. One week later, the owner reported that the dog’s vision had partially returned and that it was no longer circling. During neurologic examination, the dog was no longer circling, conscious proprioceptive deficits had improved, vision had partially returned in the right eye, and the remainder of the neurologic examination results were unchanged. Results of

From the Departments of Medical Sciences (Adamo) and Surgical Sciences (O’Brien), School of Veterinary Medicine, University of Wisconsin, Madison, WI 53706. Dr. O’Brien's present address is Imaging Center and Radiology, 21600 W Eleven Mile Rd, Southfield, MI 48076. Supported by the Department of Medical Sciences, School of Veterinary Medicine, University of Wisconsin. Address correspondence to Dr. Adamo.
CBC and serum biochemical analysis were within reference ranges. Blood cyclosporine concentration was 216 ng/mL. Analysis of CSF revealed decreased pleocytosis (42 cells/µL), still with a predominance of lymphocytes (74% lymphocytes, 24% macrophages, and 2% neutrophils) and decreased TP (61.7 mg/dL). Cyclosporine was not detectable in the CSF at this time or at the following reevaluation. Because of the persistently high TP in CSF, cyclosporine dosage was increased to 6 mg/kg (2.7 mg/lb) every 12 hours, PO.

Two months after administration of cyclosporine had begun, vision and menace reaction partially returned in the right eye, both pupils were still abnormally dilated, and vision and menace reaction were still absent in the left eye. The direct pupillary light reflex in the right eye was weak and incomplete, and the consensual pupillary light reflex was absent. In the left eye, the direct pupillary light reflex was absent and the consensual pupillary light reflex was weak. The rest of the ophthalmologic examination results were unchanged. The persistent left eye blindness and left conscious proprioceptive deficits were attributed to the right cerebral cortex damage, and the pupillary light reflex abnormalities were attributed to bilateral optic nerve damage. Results of CBC indicated lymphopenia with 540 cells/µL (reference range, 1,000 to 4,800 cells/µL) and mild eosinopenia with 60 cells/µL (reference range, 100 to 750 cells/µL); results of serum biochemical analyses were within reference ranges. Analysis of CSF revealed only 1 cell/µL with 78% monocytes, 18% macrophages, and 4% neutrophils; TP concentration (21 mg/dL) was within reference limits, which suggested that the disease was in remission. The blood cyclosporine concentration was 235 ng/mL, and cyclosporine was not detectable in the CSF. Dosage of cyclosporine was maintained at 6 mg/kg every 12 hours.

Seven months after cyclosporine administration had begun, persistent left eye blindness and the pupillary light reflex abnormalities were residual neuropathologic deficits. Results of CBC, serum biochemical analyses, and urinalysis were within reference ranges except for a slight increase in serum TP concentration (8.7 g/dL; reference range, 6.0 to 7.5 g/dL). Analysis of CSF revealed mild lymphocytic pleocytosis (10 cells/µL) with a predominance of lymphocytes (90% lymphocytes and 10% mononuclear cells) and remarkable TP concentration (22.8 mg/dL), indicating that the disease was still in remission. Computed tomography revealed resolution of the previously detected abnormalities (Figure 1), and blood cyclosporine concentration was 337 ng/mL. Because of the mild persistent pleocytosis, administration of cyclosporine was kept at the same dosage.

Two months later, the dog had pyometra and was treated via ovariohysterectomy by the referring veterinarian. One month later (10-month follow-up), the neurologic examination revealed no change. Results of CBC, serum biochemical analyses, and urinalysis were within reference ranges. The CSF had increased cellularity (14 cells/µL) with lymphocytic pleocytosis (80% lymphocytes, 14% mononuclear cells, and 6% neutrophils) and TP concentration of 24.0 mg/dL, indicating that the disease was still in remission. The blood cyclosporine concentration was 592 ng/mL; because this value was greater than the minimum recommended concentration for organ transplantation in dogs, the dosage was considered adequate and was not changed.

At reevaluation 2 months later (12-month follow-up), the owner complained that the dog had excessive shedding. The dog had areas of mild symmetric alopecia over the trunk, and neurologic examination revealed no change. Results of CBC, serum biochemical analyses, and urinalysis were within reference range. Parameters of the CSF were improved (9 cells/µL; 91% lymphocytes and 9% macrophages; TP concentration, 18.5 mg/dL). Blood cyclosporine concentration was 404 ng/mL. The excessive shedding and the alopecia were attributed to adverse effects of cyclosporine administration. Because of the dog's stable neurologic condition, the improved CSF parameters, and the adverse dermatologic effects, cyclosporine administration was decreased to 6 mg/kg once per day.

A 6-year-old spayed female West Highland White Terrier (dog 2) that weighed 11.1 kg (24.4 lb) was evaluated for a 1-month history of progressive ataxia. Two days before referral, the dog received dexamethasone (2 mg/kg [0.9 mg/lb], IV) and prednisone (0.5 mg/kg [0.23 mg/lb], PO) every 24 hours with no improvement. Physical examination revealed that the dog was moderately overweight. The dog had vestibular ataxia with leaning and falling to the left, horizontal positional nystagmus with fast phase to the right, and conscious proprioceptive deficits on the left side. The neurologic abnormalities suggested left-sided central vestibular disease. Results of a CBC indicated a stress leukogram (WBCs, 33,400 cells/µL; neutrophils, 30,600 cells/µL; lymphocites, 670 cells/µL; monocytes, 2,670 cells/µL; and eosinophil concentration, 0 cells/µL). Serum biochemical analyses revealed high activities of alkaline phosphatase (445 U/L; reference range, 9 to 140 U/L) and alanine aminotransferase (146 U/L; reference range, 15 to 84 U/L). Results of urinalysis were within reference range. Thoracic radiographic findings were unremarkable, except for generalized hepatomegaly. Systemic hypertension (arterial blood pressure, 193 mm Hg) was also determined on the basis of an indirect Doppler assessment. These abnormalities were considered to be secondary to underlying pituitary-dependent hyperadrenocorticism and less likely attributable to administration of glucocorticoids for 2 days. Magnetic resonance imaging (MRI) of the brain revealed dilatation of third and fourth ventricles. On T2-weighted images, the left side of the brainstem was hyperintense with poorly defined margins, compared to the right side, with a suspected small shift of midline to the right. On T1-weighted images after gadolinium administration, multiple irregular contrast-enhancing masses were seen in the left side of the brainstem, dorsal aspect of the spinal cord at the level of C1-C2, and bilaterally in the ventrocortical portion of the cerebellum (Figure 2). These abnormalities were suggestive of infectious meningoencephalitis with adjacent regions of edema. Cytologic analysis of the CSF revealed lymphocytic pleocytosis with 225 cells/µL (88% lymphocytes and 12% macrophages). Results of bacterial isolation were negative; results of meningoencephalitis were not available. PO, q 12h.
ing dosage, but no improvement in the clinical signs was noted. Enalapril (0.5 mg/kg, PO, q 12 h) was prescribed for the hypertension. Blood pressure was reevaluated 3 days later, and because it was still high, amlodipine (0.05 mg/kg [0.023 mg/lb], PO, q 24 h) was added to control the hypertension. Orally administered cyclosporine (3 mg/kg, q 12 h) was added 5 days later, and prednisone administration was decreased to 1 mg/kg once per day. One week later, the dog's neurologic status was improved. Neurologic examination revealed that the dog was ataxic, had asymmetrical conscious proprioceptive deficits in all 4 limbs (left side worse than right), and had a mild head tilt to the right. The systolic blood pressure was still high (179 mmHg). Results of CBC were unchanged, and urinalysis revealed traces of protein. The CSF had 22 cells/μL (86% lymphocytes and 14% mononuclear cells) and increased TP concentration (36.4 mg/dL). Blood cyclosporine concentration was 82 mg/mL, and cyclosporine was not detectable in the CSF. Cyclosporine dosage was increased to 10 mg/kg (4.5 mg/lb) every 12 hours, prednisone dosage was maintained at 1 mg/kg every 24 hours, and enalapril and amlodipine dosages were not changed. The dog's clinical condition progressively improved, but 3 weeks later, the neurologic status declined, with progressive ataxia and inability to stand. Mild azoemia (BUN concentration, 31.2 mg/dL; reference range, 9 to 27 mg/dL) and high creatinine concentration (2.1 mg/dL; reference range, 0.7 to 1.5 mg/dL) were detected; urinalysis revealed specific gravity of 1.008 and a severe urinary tract infection with *Escherichia coli*. Because of the need for additional hospitalization, the owner chose euthanasia for the dog. Necropsy confirmed multifocal granulomatous meningoencephalitis in the brain and cervical spinal cord and bilateral suppurative coliform pyelonephritis.

A 7-year-old sexually intact male Dachshund (dog 3) that weighed 6.6 kg (14.5 lb) was evaluated for 5 weeks history of right-sided head tilt and ataxia. The dog was suspected to have an inner ear infection and was treated with amoxicillin-clavulanic acid and prednisone, with no improvement. After prednisone administration was discontinued, the dog became progressively worse. The dog had vestibular ataxia with rolling to the right, right-sided head tilt, loss of menace reaction, positional ventrolateral strabismus of the right eye, positional rotatory nystagmus of both eyes, and conscious proprioceptive deficits in the right forelimb and right hind limb. The clinical signs suggested central vestibular disease in the right portion of the brainstem. Results of CBC, serum biochemical analyses, and urinalysis were within reference ranges, and thoracic radiographs were unremarkable. Serologic testing for infectious diseases yielded negative results. Magnetic resonance imaging of the brain revealed a focal 1-cm lesion in the right dorsolateral portion of the brainstem and ventrolateral portion of the cerebellum. The lesion was isointense and contrast enhancing on T1-weighted images and mildly hypointense on T2-weighted images. The margins of contrast enhancement were slightly ill defined, and no mass effect was noted in the affected region (Figure 3). These abnor-

---

Figure 2—Transverse and sagittal contrast-enhanced, T1-weighted magnetic resonance images of the brain of a dog with granulomatous meningoencephalitis. A—Notice the multiple, bilateral, irregular-shaped, contrast-enhanced masses in the ventrolateral aspect of the brainstem. B and C—Notice contrast-enhancing lesions in spinal cord at the level of C1-C2 and in the caudal portion of the cerebellum.

macrophages), 135 RBCs, and 157.3 mg of TP/dL. Results of serologic tests for infectious diseases were negative. A presumptive diagnosis of granulomatous meningoencephalitis was made, and the dog was initially treated with prednisone (1 mg/kg [0.45 mg/lb], PO, q 12 h) for 2 weeks. This was followed by a taper-
normal, indicating that the disease was in remission. Blood cyclosporine concentration was 117 ng/mL and was not detectable in the CSF at this time or at the follow-up reevaluation. Because of the low blood cyclosporine concentration, cyclosporine dosage was increased to 6 mg/kg every 12 hours. One month later, results of the neurologic examination were unchanged, lymphopenia was improved (700 lymphocytes/μL), results of serum biochemical analyses were unremarkable, and blood cyclosporine concentration was 370 ng/mL. Three months later (4 months after starting cyclosporine administration), the owner, without medical consultation, decreased the cyclosporine dosage to 3 mg/kg every 12 hours.

At the 7-month reevaluation, physical examination revealed bilateral hair discoloration in the dorsolateral cervical area. The dog had no neurologic abnormalities. Results of CBC indicated lymphopenia (590 cells/μL), monocytopenia (0 cells/μL), and eosinopenia (0 cells/μL). Results of serum biochemical analyses and urinalysis were within reference limits. The CSF had mild lymphocytic pleocytosis (7 cells/μL, with 91% lymphocytes and 9% monocytes), which indicated that the disease was under control, and MRI revealed resolution of the lesion (Figure 3). Blood cyclosporine concentration was 215 ng/mL. Granulomatous meningoencephalitis was considered under control, and the cyclosporine administration was tapered to 3 mg/kg once per day.

Five months later, results of the physical, neurologic, and laboratory examinations were unremarkable and blood cyclosporine concentration was 63 ng/mL. The owner refused to permit CSF collection at this time and chose to continue the cyclosporine administration at the same dosage.

Administration of cyclosporine was considered effective in controlling presumptive granulomatous meningoencephalitis in 2 of these 3 dogs. In dog 1, the history suggested that the forebrain lesion was most likely preceded by the ocular form of granulomatous meningoencephalitis. Dog 1 never received corticosteroids and had dramatic improvement after just 1 week of cyclosporine administration. In dog 3, with a focal brainstem lesion, clinical signs initially improved with corticosteroid administration and continued to improve when corticosteroids were replaced by cyclosporine. Both dogs had minimal adverse dermatologic effects. Dog 2, which did not survive, had the disseminated form of granulomatous meningoencephalitis and did not have improvement with corticosteroid administration. The corticosteroids may have exasperated the hypertension, although CSF analysis performed after 1 week of cyclosporine administration revealed that the encephalitis was resolving.

In dog 2, failure of treatment with cyclosporine could have been attributable to the poor prognosis associated with the disseminated form or to the initial suboptimal blood cyclosporine concentration. Cyclosporine was not detectable in the CSF of any dog at any time point evaluated during the course of this treatment.

Granulomatous meningoencephalitis is an idiopathic inflammatory disease of the CNS of dogs.

Figure 3—Sagittal T1-weighted, contrast-enhanced images of a dog with granulomatous meningoencephalitis. A—Notice the focal, right-sided, contrast-enhancing lesion in the area of the dorsolateral portion of the brainstem and ventrolateral portion of the cerebellum. B—Same dog as in A. Notice resolution of lesions on images obtained during 7-month reevaluation.
remission, with a serum corticosteroid level of 9.0 mg/mL and a daily prednisone dose of 2 mg per kg at the fol-
owing blood sample. 

Two days after blood sample collection, a large, bony mass measuring 10 x 10 cm was palpated in the right leg. The mass had a soft, gritty consistency and was painful to touch. There were no other abnormalities detected on physical examination.

On admission, the dog was alert, responsive, and ambulatory. The heart rate was 120 bpm, and the respiratory rate was 20/min. The dog's body temperature was 100.4°F (38.0°C). The dog was treated with intravenous fluid therapy and supportive care, including pain management.

A definitive diagnosis was obtained via CT scan, which revealed a mass in the right leg. The mass was excised, and histopathological examination confirmed the presence of osteosarcoma.

The dog was discharged from the hospital and began a concurrent chemotherapy regimen. The dog tolerated the treatment well and showed significant improvement in terms of mobility and pain management.

The dog continued to receive chemotherapy for 6 months, followed by a 3-month tapering off period. The dog remained clinically stable during this time.

Two years after the initial diagnosis, the dog underwent a second surgery to remove additional masses in the right leg. The dog continued to receive chemotherapy and radiation therapy as needed.

The dog remained in good health for 3 years after the initial diagnosis. However, the dog developed new masses in the right leg and was euthanized.

The case highlights the importance of early diagnosis and appropriate treatment for osteosarcoma in dogs. The dog's response to chemotherapy and radiation therapy was encouraging, and the dog remained clinically stable for a relatively long period of time. Nevertheless, osteosarcoma remains a serious and potentially fatal disease that requires vigilant monitoring and appropriate treatment.

References:
choroid plexuses. Because granulomatous meningoencephalitis is a perivascular disease, a therapeutic cyclosporine concentration is most likely present in affected areas of the CNS.

Interaction with ketoconazole has been investigated, and ketoconazole has been used in combination with cyclosporine to lower the cost of cyclosporine treatment for treatment of perianal fistula.5,23 Cimetidine is the only other drug that has been investigated for use with cyclosporine in veterinary medicine, and it has no effect on the clearance and does not cause an increase in blood cyclosporine concentration.8 Because cyclosporine is metabolized in the liver and has potential interactions with other agents, periodic routine laboratory analyses, CSF analysis, and determination of blood cyclosporine concentration are recommended in dogs receiving long-term administration.

References

New Veterinary Biologic Products

<table>
<thead>
<tr>
<th>Product name</th>
<th>Species and indications for use</th>
<th>Route of administration</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arcanobacterium Pyogenes-Fusobacterium Necrophorum Toxoid (Shering-Plough Animal Health Corporation, US Vet Lic No. 165A)</td>
<td>As an aid in the reduction of liver abscesses associated with infection by Arcanobacterium (Actinomyces) pyogenes or Fusobacterium necrophorum in healthy cattle</td>
<td>SC</td>
<td>USDA licensed 7/14/04</td>
</tr>
</tbody>
</table>

Interpretive Summaries

**SMALL ANIMALS**

**Evaluation of a focused assessment with sonography for trauma protocol to detect free abdominal fluid in dogs involved in motor vehicle accidents**

A focused assessment with sonography for trauma (FAST) protocol was established for examination of the abdomen of dogs and prospectively evaluated in 100 dogs that were involved in motor vehicle accidents. Free abdominal fluid was detected via FAST in 45 of the 100 dogs. In 40 of these 45 dogs, abdominocentesis was performed; results of analyses of fluid specimens were consistent with hemoperitoneum in 38 dogs and uroperitoneum in 2 dogs. On the basis of the results of this study, the FAST examination appears to be a useful diagnostic procedure to help identify intra-abdominal free fluid in dogs that have been involved in motor vehicle accidents. It is a rapid, noninvasive procedure that can be performed during the initial stabilization of dogs after abdominal trauma and by veterinary clinicians without extensive ultrasonographic experience.—S. R. Boysen et al (J Am Vet Med Assoc 2004;225:1198–1204).

**Use of a jugular vein autograft for reconstruction of the cranial vena cava in a dog with invasive thymoma and cranial vena cava syndrome**

A spayed female dog was evaluated because of edema of the ventral cervical region, lethargy, cough, and reduced exercise tolerance. Invasive thymoma and cranial vena cava syndrome were diagnosed by use of ultrasound-guided fine-needle biopsy and contrast-enhanced helical computed tomography. Resection of the cranial vena cava and an autogenous jugular vein graft were used for restoration of normal venous return to the right atrium and alleviation of the cranial vena cava syndrome.—I. G. Holsworth et al (J Am Vet Med Assoc 2004;225:1205–1210).

**Use of cyclosporine to treat granulomatous meningoencephalitis in three dogs**

Three dogs with a presumptive diagnosis of granulomatous meningoencephalitis were treated with orally administered cyclosporine. In 2 dogs, cyclosporine administration replaced initial corticosteroid administration, and in 1 dog, cyclosporine was the only treatment used.

One dog had the focal form of the disease in the brainstem, 1 dog had the focal form in the forebrain associated with a concurrent ocular form, and 1 dog had the disseminated form of disease. At 12-month follow-up, the 2 dogs with the focal form of the disease had no clinical signs. The dog with the disseminated form improved only partially, and euthanasia was performed 3 weeks after initial evaluation. Cyclosporine was considered effective at an initial dosage of 6 mg/kg (2.7 mg/lb) every 12 hours. Adverse effects associated with cyclosporine administration included transient lymphopenia, excessive shedding, and focal symmetric hair discoloration.—F. P. Adamo and R. T. O'Brien (J Am Vet Med Assoc 2004;225:1211–1216).

**Fracture of an endoluminal nitinol stent used in the treatment of tracheal collapse in a dog**

A 5-year-old castrated male Pomeranian was evaluated because of severe dyspnea and coughing, and a diagnosis of complete, static collapse of the trachea at the thoracic inlet was made. After failure to improve with medical management alone, an endoluminal tracheal stent was placed, which resulted in resolution of signs. Ten weeks after stent placement, the dog underwent tracheal resection and anastomosis because the stent had fractured at the level of the thoracic inlet. One year after surgery, the dog was doing well and required treatment with hydrocodone infrequently.

Compared with other surgical treatment options, placement of an endoluminal tracheal stent is a relatively noninvasive intervention that can provide effective relief from the clinical signs associated with tracheal collapse in dogs. Implantation of endoluminal tracheal stents may be associated with complications; therefore, the procedure may best be regarded as a salvage procedure for dogs with end-stage disease that are refractory to appropriate medical management, have extensive collapse of the intrathoracic portion of the trachea, or are poor candidates for surgery.—E. Mittelman et al (J Am Vet Med Assoc 2004;225:1217–1221).

**Double aortic arch in a dog**

Vascular ring anomalies are developmental anomalies of the thoracic great vessels resulting in complete or partial encircling of the esophagus and the trachea by a vascular ring formation. Persistent right aortic arch with left ligamentum arteriosum accounts for 95% of vascular ring anomalies in dogs. The dog in this report had a double aortic arch, which is a type 4 vascular ring anomaly. Double aortic arch is a rare congenital heart defect resulting from the improper development of the embryonic arches. The prognosis for dogs that have undergone surgery for correction of double aortic arches is generally