Long-Term Immunosuppressive Therapy with Cyclosporine plus Prednisolone for Necrotizing Meningoencephalitis in a Pekingese Dog

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ABSTRACT. A 4-year-old intact female Pekingese dog was presented with ataxia and seizure episodes. Based on magnetic resonance imaging and cerebrospinal fluid analysis results, meningoencephalitis of unknown etiology was suspected. The present case survived for 1,096 days under cyclosporine plus prednisolone therapy and was definitively diagnosed with necrotizing meningoencephalitis. This report describes the clinical findings, serial magnetic resonance imaging characteristics and pathologic features of a necrotizing meningoencephalitis and long-term survival after cyclosporine with prednisolone therapy.

KEY WORDS: canine, cyclosporine, necrotizing meningoencephalitis (NME).


Necrotizing meningoencephalitis (NME) is an idiopathic noninfectious inflammatory disorder of the brain in dogs and has been reported in various breeds, including the Pekingese, Yorkshire terrier, Maltese, Chihuahua, Pug and Shih tzu [2, 5, 7, 8, 12–14]. While there is little information about the pathogenesis of NME, several previous reports [9, 10, 12] have described the presence of autoantibodies against glial fibrillary acidic protein in the cerebrospinal fluid (CSF) of affected dogs, indicating an autoimmune pathophysiology of NME. Thus, NME is suggested to be an idiopathic autoimmune CNS disease like granulomatous meningoencephalitis (GME). Beneficial but limited effects of various immunosuppressive drugs in autoimmune CNS inflammatory diseases have been reported previously [1, 2, 4, 6, 7, 16].

This report describes the clinical findings, serial magnetic resonance imaging (MRI) characteristics, histopathologic changes, and long-term management with cyclosporine in an NME case.

A 4-year-old intact female Pekingese dog with a body weight of 3.9 kg was presented with a 1-week history of ataxia and seizure episodes. Neurological signs were observed suddenly and worsened gradually. On neurological examination, postural reactions of 4 limbs were reduced, and other reflexes, including cranial nerve and spinal reflexes, revealed no remarkable findings. The results of a fundus examination and other ophthalmologic examinations were normal. The results of complete blood count, serum chemistry profiling, and radiography were not remarkable. On the basis of a neurological examination, the clinical signs were deemed to be likely due to an intracranial lesion.

We then performed a brain MRI scan using a 0.2-T scanner (E-scan®, ESAOTE, Genova, Italy). T1- and T2-weighted images, and postcontrast T1-weighted images were obtained. Analysis of the images revealed multifocal lesions in the cerebrum (Fig. 1). Multiple, ill-defined hyperintense lesions were noted in the white matter area on both sides (left and right) of the frontal, parietal and temporal lobes including the cortical portion on T2-weighted images (Fig. 1B, 1D and 1F). These lesions appeared isointense or hypointense on T1-weighted images (Fig. 1A, 1C and 1E) and were not enhanced after a contrast study. Results of CSF analysis indicated an increased nucleated cell count of 25 cells/µl (reference range, 0–5 cells/µl) and a protein concentration of 45 mg/dl (reference range, <25 mg/dl).

Cytologic examination of the CSF revealed a population of monocytoid cells and small lymphocytes (Fig. 2A). To rule out infectious causes, canine distemper virus detection by RT-PCR and toxoplasma antigen detection by ELISA, as well as bacterial and fungal cultures, were performed. All tests on the CSF gave negative results. On the basis of all above-mentioned examinations, we tentatively diagnosed this case as meningoencephalitis of unknown etiology (MUE).

Management with prednisolone (Prednisolone, Korea Pharma, Korea; 1 mg/kg, PO, q 12 hr) and cyclosporine microemulsion (CYPOL-N®, Chong Kun Dang Pharma, Korea; 6 mg/kg, PO, q 24 hr) was initiated, and clinical signs improved gradually. The cyclosporine dosage was not tapered, and the initial dosage was maintained until death. One month after initiation of treatment, prednisolone was tapered to 0.75 mg/kg, PO, q 12 hr. The neurological signs did not reoccur after the first steroid tapering, and the pred-
nisolone dosage was tapered again to 0.5 mg/kg, PO, q 12 hr (one week after the first tapering). Two weeks after the second tapering, the prednisolone dosage was tapered again to 0.3 mg/kg, PO, q 12 hr. We maintained the prednisolone dosage (0.3 mg/kg, PO, q 12 hr) for 3 weeks and then stopped prednisolone administration. Four weeks after sole cyclosporine therapy, mild ataxia reoccurred and prednisolone was administered again (0.3 mg/kg, PO, q 12 hr). The signs of mild ataxia improved a few days after readministration of prednisolone. The combination of prednisolone (0.3 mg/kg, PO, q 12 hr) and cyclosporine was continued for a few months and controlled the symptoms well. However, mild ataxia and cluster seizure reoccurred because the client arbitrarily stopped giving the medicine for a few weeks. Then, we prescribed a higher dose of prednisolone (0.5 mg/kg, PO, q 12 hr) with cyclosporine and phenobarbital (3 mg/kg, PO, q 12 hr). Clinical signs improved gradually after medication, and we stopped giving phenobarbital 2 weeks later. Therapy with prednisolone (0.25 mg/kg, PO, q 12 hr) and cyclosporine was continued and controlled symptoms well. About two years after initiation of treatment, we stopped prednisolone administration and continued therapy with cyclosporine only. Isolated seizures were occasionally observed, but the total frequency of seizure episodes was not more than 5 times during therapy with cyclosporine only.

About 1 year after initiation of treatment, CSF analysis was performed to check the progress, and normal results were obtained. We could not perform an MRI check again because of the client’s refusal.

Every few months, we regularly rechecked the patient status at our hospital. The patient’s condition was well controlled for 1,096 days (about 36 months) under cyclosporine with prednisolone therapy, but the patient was ultimately euthanized because of worsening neurological dysfunction thereafter, which included cluster seizure and ataxia. About 1,090 days after initial diagnosis, the patient was rehospitalized because of relapse and worsening the neurological signs. We administered prednisolone (1 mg/kg, PO, q 12 hr) with cyclosporine and phenobarbital (3 mg/kg, PO, q 12 hr) again, but the patient did not respond to medication. Finally, the client offered to donate the patient and wanted it to be euthanized.

One day before euthanasia, we performed a brain MRI follow-up study using a 3.0-T research scanner (Impedance Imaging Research Center, Kyung-Hee University, Korea). Transverse T1- and T2-weighted images and postcontrast T1-weighted images were obtained. Multifocal lesions with very hyperintense signals were found on T2-weighted images. These lesions showed very hypointense signals on
T1-weighted images and were not enhanced after a contrast study (Fig. 3). Most lesions were located in the cerebral cortex and corresponded to the initial MRI scan results. However, the volumes of the parenchymal lesions were larger and the ventricles were more enlarged than in the initial scanning. Moreover, hypointense lesions on T1-weighted images were more definite than in the initial MRI scans. The results of CSF analysis indicated an increased nucleated cell count of 15 cells/µl (reference range, 0–5 cells/µl) and a protein concentration of 40 mg/dl (reference range, <25 mg/dl). Cytologic examination of the CSF revealed monocytoid pleocytosis (Fig. 2B).

Necropsy findings showed multifocal necrotic lesions in the cerebral cortex, which was consistent with the MRI findings (Fig. 4A and 4B). The results of histopathologic examination revealed severe necrotic lesions in the cerebral cortex (Fig. 4C and 4D). Severe neuronal necrosis and vacuolation were also identified in the cerebral cortex.

This case was definitively diagnosed as NME according to the results of histopathologic examinations. Recent reports [7, 9, 10, 12] have suggested that GME and NME are autoimmune CNS diseases, and that reducing the immune reaction is the best management option for patients. Generally, prednisolone is widely used in treating various canine neurological diseases, including GME and NME [1, 5–7, 16]. Prednisolone could reduce inflammatory and immune reactions during the initial stages of GME and NME [7]. Although some GME or NME cases showed relatively long survival times with prednisolone therapy [8], most GME and NME cases expired within a few weeks under a single therapy of prednisolone [5, 7, 16]. Furthermore, long-term management with prednisolone is difficult because of the drug’s side effects, for example, hepatotoxicity, iatrogenic hyperadrenocorticism, gastrointestinal ulceration, polyuria-polydipsia, polyphagia and lethargy. According to previous reports [1, 2, 4, 6, 7, 16], cytosine arabinoside plus prednisolone, procarbazine plus prednisolone or cyclosporine plus prednisolone therapy for MUE could prolong survival compared with prednisolone therapy alone. Moreover, combination therapies could decrease the required prednisolone dosage, which consequently could reduce the side effects of the drug.

In human medicine, cyclosporine is an immunosuppressant drug used for organ transplant patients to decrease the risk of organ rejection [1, 2, 7]. In veterinary medicine, cyclosporine has been widely used for dermatologic diseases and other systemic immune-mediated diseases [1, 2, 7]. Recently, some reports have suggested that cyclosporine is an effective therapeutic option for CNS inflammation in dogs [1, 2, 6, 7]. However, studies on the beneficial effects of cyclosporine in histopathologically confirmed cases are limited [7]. One previous report [7] has demonstrated the beneficial effects of cyclosporine in histopathologically confirmed NME cases. In that report, the mean survival time of 4 dogs under cyclosporine plus prednisolone therapy was 305.7 ± 94.7 days (410, 210, 243 and 360 days, respectively), and the mean survival time of 3 dogs under prednisolone therapy alone was 58.3 ± 30.5 days (25, 65 and 85 days, respectively). The dog in the present case survived for 1,096 days under cyclosporine plus prednisolone therapy, and the disease was histopathologically confirmed as NME.

Although clinical signs depend on the location of lesions, most GME or NME cases showed various neurological signs, such as seizure, ataxia, circling, blindness and lethargy [1–8, 11, 14, 16]. Partial or complete remission of clinical signs might be achieved after an immunosuppressive drug therapy [1, 2, 4, 6, 7, 16]. The present case had a history of ataxia and seizure when referred to our hospital.
After cyclosporine plus prednisolone therapy, the clinical signs were completely resolved (complete remission) for the initial few months and relatively well controlled for 3 years under cyclosporine with prednisolone therapy.

NME cases could differentiate to acute and chronic forms [5]. Acute form NME cases showed fast clinical sign progression within few days after onset, and chronic form NME cases showed slow clinical sign progression within a few weeks to months after onset [5]. In our experience, the prognosis of chronic form NME cases was better than for acute form NME cases. The present case had acute form NME (seven day history of clinical sign progression after onset) that was relatively well controlled and survived 1,096 days under cyclosporine with prednisolone therapy.

CNS inflammatory diseases can be tentatively diagnosed using computed tomography or MRI. According to a previous report [15], MRI shows edematous changes such as hypointense signals on T1-weighted images and hyperintense signals on T2-weighted images in acute forms of NME cases. In chronic NME cases, necrosis and cystic changes, such as very hypointense signals on T1-weighted images and very hyperintense signals on T2-weighted images, are usually observed. In the present case, the initial MRI findings demonstrated multifocal hypointense lesions on T1-weighted images and hyperintense lesions on T2-weighted images in the cerebral cortex, as well as mild edematous changes (Fig. 1). Three years after the initial diagnosis, a second MRI found more progressed necrotic and cystic changes compared with the initial MRI (Fig. 3).

Severely hypointense lesions were found on T1-weighted images, and severely hyperintense lesions were found on T2-weighted images (Fig. 3). These MRI findings indicated that immune suppression with cyclosporine could not stop the progress of NME. However, we suspected that cyclosporine with prednisolone therapy could improve inflammatory and edematous changes initially and then decrease the speed of disease progression in NME cases. We also supposed that long-term cyclosporine with prednisolone therapy might change an acute form NME case to a chronic form NME case. In our experience, some chronic form NME cases were asymptomatic even though brain lesions had progressed. Thus, this could be the reason for the relatively long-term survival and mild clinical sign progression in the present acute form NME case under cyclosporine with prednisolone therapy.

Thus, cyclosporine with prednisolone therapy might be one of the best treatment options for increasing patient survival in NME cases.

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