J Vet Clin 23(3) : 344-348 (2006)

Journal of Veterinary Clinics
www.ksvc.or.kr

Trial of Mycophenolate Mofetil Treatment on Necrotizing Meningoencephalitis in a Yorkshire Terrier Dog

Hyo-Won Jeon, Chul Park, Dong-In Jung, Byeong-Teck Kang, Ha-Jung Kim, Ju-Won Kim, Chae-Young Lim, Ki-Jin Ko, So-Young Lee, Sue-Kyung Cho, Su-Hyun Gu, Ra-Young Heo, Hyo-Jin Park, Jong-Hyun Yoo*, Byung-Hyun Chung and Hee-Myung Park[1]

Department of veterinary internal medicine, College of veterinary medicine, Konkuk University, #1 Hwayang-dong, Kwangjin-gu, Seoul, South Korea 143-701
**Department of veterinary internal medicine, College of veterinary medicine, Seoul National University, Seoul, Korea*

(Accepted: August 21, 2006)

Abstract : A 5-year-old, male Yorkshire terrier dog was presented with progressive seizure and anorexia. Definitive diagnosis of necrotizing meningoencephalitis (NME) was made based on characteristic clinical features, brain lesion with MRI, and histopathologic examination. The dog was treated with prednisolone for 20 days, firstly. Prednisolone and mycophenolate mofetil (MMF) were then administered for 40 days following the initial therapy. However, the clinical signs were not improved and seizure frequency was increased. This patient survived around 2 months after diagnosis. This case report described the clinical findings, imaging characteristics and pathologic features of NME in a Yorkshire terrier with trial treatment using MMF.

Key words **:** necrotizing meningoencephalitis, seizure, mycophenolate mofetil.

Introduction

Necrotizing meningoencephalitis (NME) is a unique inflammation disorder of brain in small breed dogs. The disease primarily affecting the cerebral hemispheres has been described in Pug, Maltese, and Yorkshire terrier. Even though the cause of this disease is unknown, the brain lesions are quite similar to those of alpha herpes virus meningoencephalitis in people (3). A previous report (11) showed that a certain autoantibody against a canine brain tissue was detected in the cerebrospinal fluid and serum, indicating an autoimmune pathology in NME. In addition, a recent study revealed all tested cases with NME possessed the anti-astrocyte autoantibody (6).

Histopathological finding is characterized by parenchymal necrosis, severe infiltration of mononuclear cells, and glial satellitosis in the cerebrum, especially in the subleptomeningeal area (6). However, according to several previous reports, a different lesion distribution has been described in the Yorkshire terrier breed, such as brain-stem and/or cerebral lesions (1,3,10).

Generally, NME varied in age at presentation between 6 month and 7 year. The onset and progression of clinical signs of neurologic dysfunction may be acute (2 weak or less) or chronic (4~6 month) (3). In particular, Yorkshire terrier with NME has been reported between the age 1 and 10 years.

This case report described the clinical findings, imaging characteristics and pathologic features of NME. In addition, this case was first attempted for treatment of NME in Yorkshire terrier with a chronic progressive worsening of neurologic dysfunction over several months by mycophenolate mofetil (MMF).

Case Report

A 5-year-old, male Yorkshire terrier dog was referred due to seizure and anorexia. All preventive measures (viral vaccination, rabies and heartworm prevention) had been taken. The seizure was first noted six months ago. The recent seizures occurred one week before presentation, which were progressively increasing in frequency and duration.

The patient was evaluated with physical and neurological examination, a complete blood count (CBC), serum biochemistry profiles, intraocular pressure (IOP), electrocardiography (ECG), thoracic and abdominal radiography, magnetic resonance imaging (MRI) and cerebrospinal fluid (CSF) analysis. On physical examination, the most conspicuous findings were regular bradycardia and ocular discharge. Neurologic examination revealed normal findings. Results of CBC showed mild polycythemia ($8.31 \times 10^6/\mu l$; reference range, 5.5 to 8.5 $\times 10^6/\mu l$) and thrombocytosis ($760 \times 10^3/\mu l$; reference range, 200 to $500 \times 10^3/\mu l$). Serum biochemistry profiles revealed hypertriglyceremia (269 mg/dl; reference range, 20 to 155 mg/dl), mildly elevated hepatic enzymes (ALT: 93 mg/dl; reference range, 17 to 78 mg/dl) and hypokalemia (3.2 mmol/L ; reference

[1]Corresponding author.
E-mail : parkhee@konkuk.ac.kr

range, 3.8 to 5.0 mmol/L). IOP was increased bilaterally (OS: average; 32.3 mmHg, OD: average; 32.0 mmHg; reference range, 15 to 25 mmHg). Radiographic findings of the thorax and abdomen showed enlargement of pulmonary vein (PV) and right atrium (RA), splenomegaly, and hepatomegaly. On ECG, bradycardia (60 to 80 bpm), increased R-R intervals, SA block and weak T wave were present. Hypothyroidism was ruled out through the thyroid-stimulating hormone (TSH) stimulation.

Based on these initial examinations, we suspected that the cause of seizure was intracranial disorder.

Thus, we performed a brain magnetic resonance imaging (MRI) scan using 0.2 T unit (E-scan; ESAOTE, Italy). T1- and T2-weighted images and postcontrast T1-weighted images were obtained. Assessment of the images revealed asymmetric lateral ventricle and the midline was shifted to the right. On T1-weighted images, a focal, hypointensed lesion detected in the left frontal lobe. This lesion showed hypersignal intensity on T2-weighted images. There was no enhancement on postcontrast T1-weighted images (Fig 1).

CSF evaluation revealed erythrophagocytosis, monocytic-lymphocytic pleocytosis, especially monocytic predominant and mildly elevated protein concentration (30 mg/dl; reference rage; <25 mg/dl) but bacteria were not noted.

The tentative diagnosis was necrotizing meningoencephalitis (NME) based on history, physical and neurologic examination, MRI findings and CSF analysis. As the (tonic-clonic and cluster seizure) were observed one day after MRI scaning. Phenobarbital sodium (Phenobarbital, Bi-nex, pharm, Seoul, Korea, 4 mg/kg, PO, BID) and prednisolone (Korus prednisolone, koruspharm, Seoul, Korea, 1mg/kg, PO, BID) were initiated for the symptoms. For the prevention of prednisolone side effects, sucralfate (Ulcerlmin, Choongwae Phama, Whaseong, Korea, 250 mg/kg, PO, BID), silymarine (Silymarin®, Sin-il Pharm, seoul, Korea, 50 mg/kg, PO, SID) and biphenyldicarboxylate (Lefotil®, cellart Pharm, Siheung, Korea, 12.5 mg/kg, PO, SID) were added to the regime described earlier.

After initial therapy, seizure frequency was gradually decreased and disappeared.

However, the patient was severely depressed and left eyeball was mildly extruded. After patient was stabilized, prednisolone administration was gradually tapered up to minimal effective dose (up to 0.5 mg/kg, PO, BID) but potassium bromide (KBr, Sigma-aldrich, USA, 40 mg/kg, PO, SID) was added. However, 10 days after the therapy, seizure was relapsed and not controlled well. Therefore, MMF (Cellcept®, Roche Korea Co., Korea, 20 mg/kg, PO, BID) was given additionally. The dog's condition deteriorated after the MMF therapy. Proprioception deficits were worsened and showed abnormal mental status. The patient revealed the painful manifestation as barking and groaning. Furthermore, seizure frequency was increased. Finally, the patient was euthanized two months after initial treatment.

On necropsy findings, the brain showed large defect of left frontal lobe. Gross examination of the sagittal section exhibited loss of structure in left frontal cerebral hemisphere. The left

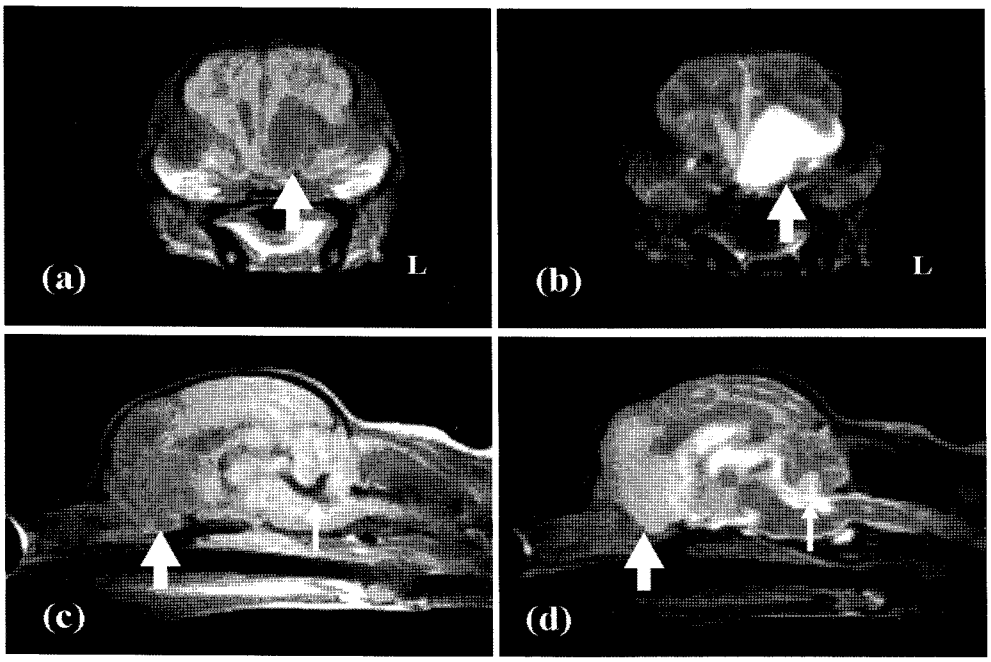

Fig 1. MR images of the present case. (a) Transverse T1-weighted image. A hypo-intense lesion in the left cerebral hemisphere was detected (thick arrow). The midline is shifted to the right. (b) Transverse T2-weighted image at the same level as (a), the lesion is revealed hyperintense. (c) The mid-sagittal T1-weighted image. Hypointensed lesion was observed on frontal lobe (thick arrow) and dilatation of the 4th ventricle was also founded (thin arrow). (d) The mid-sagittal T2-weighted image. The same lesion showed hypersignal intensity (thick arrow)

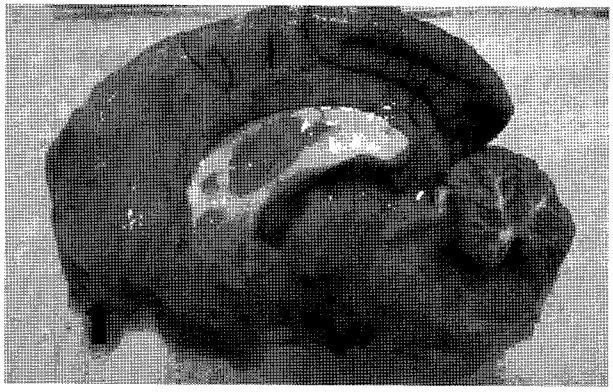

Fig 2. The sagittal section of the brain, slice level at the corresponding to Fig 1C and Fig 1D. The frontal lobe is partially defected and loss of structure. There are extensive malacic lesions in left frontal hemisphere involving corpus callosum. The affected areas are discolored pale (black arrow).

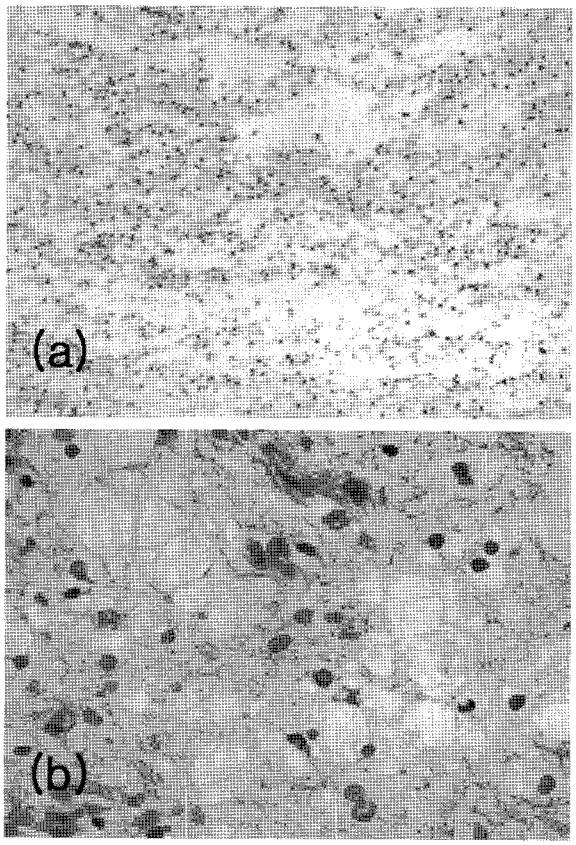

Fig 3. Histopathologic findings in the present case. (a) Neuronal necrosis in this patient, cerebrum (frontal lobe). (Hematoxyllin and eosin, x 100), (b) Cystic cavitation in the white matter of cerebrum. (Hematoxyllin and eosin, x 400).

frontal cerebral hemisphere was soft and poorly defined sulci (Fig 2).

Histologic examination of the left frontal lobe was revealed severe necrotic lesion. Both gray matter and white matter were affected, however inflammation was minimal (Fig 3).

Discussion

CNS inflammatory disease should be ruled out in any patient with neurological deficits. A through history, neurological examination and analysis of CSF are important in the diagnosis of inflammatory disease, since in many patient with CNS inflammatory disease, results of hematology and serum chemistry profiles are nonspecific. MRI is also helpful in the evaluation of many inflammatory brain diseases. However, definitive diagnosis should be based on histopathologic examination (13). Therefore, we performed several examination tests including neurological examination, MRI and CSF analysis for differential diagnosis, and performed necropsy and histopathologic examination for definitive diagnosis.

According to the previous reports (3,4), the most common clinical sign is generalized seizure in NME patients. The chief clinical signs of necrotizing encephalitis in the Yorkshire terrier (NEYT) include circling, head tilt, abnormal gait, visual deficits and altered sensorium, apparently depending on the distribution of the lesions (3,4). In this case, the major clinical sign was seizure, which recently occurred one week before presentation. Although frequency and duration of seizure was increasing, the dog was generally normal during the interictal period. Another prominent clinical sign was bradycardia. Bradycardia and seizure also can be presented in hypothyroidism. Thus, it is necessary to differentiate it. A diagnosis of hypothyroidism is likely if both pre-and post-TSH serum T4 concentrations are below the reference range (< 1.5 μg/dl) (7). Post-TSH stimulation T4 concentration was 5.8 μg/dl in this patient and hypothyroidism could be ruled out.

MRI of the brain in NME patients commonly showed asymmetric ventricular dilation and area of radiolucency in the brain. In one Maltese dog, a contrast-enhancing lesion was identified in the cerebrum, however, in all other dogs of NME in which imaging was performed, contrast-enhancement of brain lesions was lacking (3). In this case, MRI findings of the brain are consistent with those of the previous reports described above. The midline was shifted to the right in this case. A legion on the surface of the left frontal lobe showed hypointensity on T1-weighted image and hyperintensity on T2-weighted image. This lesion was not enhanced on post contrast T1- weighted images. However, MRI of the brain in granulomatous meningoencephalitis (GME) patients showed solitary or multiple circumscribed mass lesion. The lesion of GME did not show hypointensity on T1-weighted image (3). This is a major difference between GME and NME.

The pattern of malacia and destruction of white matter and clinical sign (seizure) were similar to that seen in canine distemper encephalitis (1). Therefore, we performed reverse transcriptase- polymerase chain reaction (RT-PCR) for CDV (canine distemper virus) and CDV infection was negative in serum and CSF.

Increased number of nucleated cells and protein concentrations is commonly present in CSF from animal with inflammatory CNS disease. It may also be present with a variety of CNS disease that result in secondary inflammations (ie, tumors, trauma, vascular disease) (10). Result of CSF analysis in this case revealed erythrophagocytosis, monocytic-lymphocytic pleocytosis, especially monocytic predominant and midly elevated protein concentration. Based on the result of a previous report (12), most of CNS tumor cases demonstrated no remarkable findings on CSF analysis, except elevation of protein concentration. Furthermore, malignant cells or large blast-type cells were not found in this case. Therefore, the possibility of CNS tumor in this case was not likely.

Gross findings of NME include dilation of the lateral ventricle and discoloration, malacia or cavitation in the cerebrum. On the contrary, gross lesions of GME are milder, except for occasional granulomatous mass formation (10).

This case revealed massive defect and loss of structure in left frontal lobe. Histopathologically, when the clinical course in NME was longer, the necrotic changes were more apparent but inflammatory changes were milder (10). Clinically, the dog of this report can be included in the group of dogs chronically affected with NME. Perivascular cuffing and inflammatory cells were not founded, however severe glial and axonal destruction, areas of malacia with eventual cavitation was revealed (Fig 3).

A one neurologist suggested that the MMF showed effective response in the NME patient which was responding poorly to glucocorticoid therapy (3). However, the effects of MMF on NME have not been reported yet.

The actions of MMF are multiple and include selective depletion of both T and B lymphocytes, reduced expression of adhesion molecules, diminished expression of inducible nitric oxide synthase (5). We tried to treat of NME in Yorkshire terrier by MMF because the patient had poor response to prednisolone. Therapy despite the patient was treated with MMF, in this case, nerurologic dysfunction were worsen and finally this patient was euthanized at 40 days after the therapy with MMF.

Survival times in Maltese dogs with NME that are treated with prednisolone were reported median survival of 4 to 6 weeks. Reportedly another Maltese dog had median survival of 3 and 4 days from treatment with Phenobarbital (9). Although one Yorkshire terrier with NME survived for 18 months, the majority of dogs died or were euthanized due to progressive neurologic dysfunction within 6 months of onset of neurologic dysfunction (3). This case survived 2 months after treatment initiation.

References

1. Brian AJ, Joyce IM, William BT, Artur MA. Necrotizing encephalitis in a Yorkshire Terrier. J Am Vet Med Assoc 1997; 211: 1005-1007.
2. Cordy DR, Holiday TA. A necrotizing meningoencephalitis of pug dogs. Vet Pathol 1989; 26: 191-194.
3. Dewey CW. Encephalopathies. In: A Practical Guide of to Canine and Feline neurology, 1st ed. Iowa: Blackwell. 2003: 157, 160-161.
4. Kuwamara M, Adachi T, Yamate J, Kotani T, Ohashi F, Summers BA. Necrotizing encephalitis in the Yorkshire terrier. J Small Anim Pract 2002; 43: 459-463.
5. Luis F. Remission of Severe Relapsing or persistent Lupus Nephritis Using Mycophenolate Mofetil. Archives of medical research 2006; 37: 68-73.
6. Matuski N, Fujiwara K, Tamahara S, Uchida K, Matsunaga S, Nakayama H, Doi K, Ogawa H, Ono K. Prevalence of Autoantibady in Cerebrospinal Fluids form Dogs with Various CNS Disease. J Vet Med Sci 2004; 66: 295-297.
7. Nelson RW, Couto CG. Encephalitis, Myelitis, Meningitis. In: Small animal internal medicine, 3rd ed. St.luis: Mosby. 2003: 1013.
8. Ettinger SJ, Feldman EC. Hypothyroidism. In: Veterinary internal medicine, 6th ed. Philadelphia: Elsevier saunders. 2005: 837.
9. Stalis IH, Chadwick B, Dayrell-Hart B, Summers BA, Van Winke TJ. Necrotizing meningoencephalitis of Maltese dogs. Vet Pathol 1995; 32: 230-235.
10. Susuki M, Uchida K, Morozumi M, Hasegawa T, Yanai T, Nakayama, H Tateyama S. A comparative pathology study on canine necrotizing meningoencephalitis and granulomatous meningoencephalomyelitis. J Vet Med Sci 2003; 65: 1233-1239.
11. Uchida K, Hasegawa T, Ikeda M, Yamaguchi R, Tateyama S. Detection of an autoantibody from Pug dogs with necrotizing encephalitis. Vet pathol 1999; 36: 301-307.
12. Wallace BM. Clinical signs, diagnosis and treatment of specific cancer in Dogs and Cats. In: Cancer in dogs and cats medical and surgical management, 2nd ed. WY: Teton-Newmedia. 2002: 636.
13. Thomas WB. Inflammatory diseases of the central nervous system in dogs. Clinical techniques in small animal practice 1998; 13: 167-178.

요크셔 테리어 견에서 발생한 괴사성 수막뇌염을 Mycophenolate Mofetile로 치료 시도한 증례

전효원 · 박 철 · 정동인 · 강병택 · 김하정 · 김주원 · 임채영 · 고기진 · 조수경 · 구수현 · 허라영 · 박효진 · 유종현* · 정병현 · 박희명[1]

건국대학교 수의과대학 수의내과학교실
서울대학교 수의과대학 수의내과학교실*

요 약 : 5년령의 수컷 요크셔테리어 견이 진행성의 발작과 식욕부진으로 내원하였다. 임상증상, MRI에서의 뇌병변, 조직병리학적 검사로 괴사성 수막뇌염(NME)으로 확진되었다. 이 환견은20일동안 프레드니솔론으로 치료되었다. 그리고 이후 40일 동안은 프레드니솔론과 mycophenolate mofetil (MMF) 혼합하여 치료되었다. 하지만 임상증상은 개선되지 않았고 발작의 빈도도 증가하였다. 이 환견은 진단후 2달 동안 생존하였다. 이번 증례보고는 괴사성 수막뇌염의 임상증상, 영상학적 특성, 조직학적 특성을 묘사하였다. 게다가 괴사성 수막뇌염에 걸린 요크셔테리어 견에서MMF를 이용한 치료를 시도한 최초 보고이다.

주요어 : 괴사성 뇌수막염, 발작, mycophenolate mofetile.