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Acute Progress of Necrotizing Meningoencephalitis in a Dog; Serial Clinical Observation, Magnetic Resonance Imaging, and Histopathological Findings

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Abstract : A 13-month-old intact female poodle dog presented with an acute history of circling and seizure episodes. On the basis of the results of neurologic examination combined with magnetic resonance imaging and cerebrospinal fluid analysis (CSF), meningoencephalitis of unknown etiology (MUE) was suspected. Therapy with mycophenolate mofetil plus prednisolone was initiated, following which the clinical signs showed improvement for only one month before gradually worsening again. Acute progression of the clinical disease was observed, and the patient was euthanized 91 days after initial presentation. This case was definitively diagnosed as necrotizing meningoencephalitis (NME) according to the results of post-mortem histopathological examination. This report describes the clinical findings, serial magnetic resonance imaging (MRI) characteristics, and histopathological changes in a case of acute NME.

Key words **:** dog, magnetic resonance imaging (MRI), mycophenolate mofetil (MMF), necrotizing meningoencephalitis (NME).

Introduction

Granulomatous meningoencephalitis (GME) and necrotizing encephalitis (NE) are common inflammatory diseases of the canine central nervous system (CNS) (4,20). These are thought to be autoimmune disorders directed against the CNS (13,15,18,20,22). NE includes two pathologically distinct diseases referred to as necrotizing meningoencephalitis (NME) and necrotizing leukoencephalitis (NLE). The diseases have similar characteristic features such as multiple cavitary, necrotic, nonsuppurative inflammatory lesions in the gray and white matter of the brain (20). NME is typically described as a rapidly progressive, fatal disorder affecting most commonly the Pug, Maltese, and Yorkshire Terrier breeds. A limited number of other breeds are also affected (2,20,21). The disease course of NME cases can be differentiated into acute and chronic forms: the acute group shows overt signs for 2 weeks or less while the chronic group is affected for several months (3,4). To date, glucocorticoids and other immunosuppressive drugs are the mainstays of treatment in dogs with NME (4,7-9). However, the response to treatment is variable and the prognosis for NME remains poor to grave (4,7,9).

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Case

A 13-month-old intact female poodle dog presented with an acute history of circling and seizure episodes. On conducting physical and neurological examinations, left-sided facial twitching and wide-based circling to the right side were identified. The other responses including postural reactions, cranial nerve reflexes, and spinal reflexes were within normal limits. The results of complete blood counts, serum chemistry profiles, and radiographs were not remarkable. On the basis of the results of neurological examination, the lesion was localized to the forebrain. The dog had not been vaccinated, and there was no history of trauma or toxin exposure.

To identify the intracranial lesion(s), we performed a brain MRI scan using a 0.2-T scanner (E-scan; ESAOTE, Genova, Italy), and CSF analysis. T1- and T2-weighted images as well as post contrast T1-weighted images were obtained. On MRI images, it was possible to identify multiple, ill-defined lesions in the cerebrum (Fig 1). These lesions appeared hyperintense on T2-weighted images (Fig 1A, 1C) and iso- to hypointense on T1-weighted images (Figs 1B, 1D). Examination of the CSF revealed an increased nucleated cell count of 26 cells/μl (reference range, < 5 cells/μl) and a protein concentration of 100 mg/dl (reference range, < 25 mg/dl). Cytological examination of CSF revealed a mononuclear cell pleocytosis. To rule out distemper infection, canine distemper

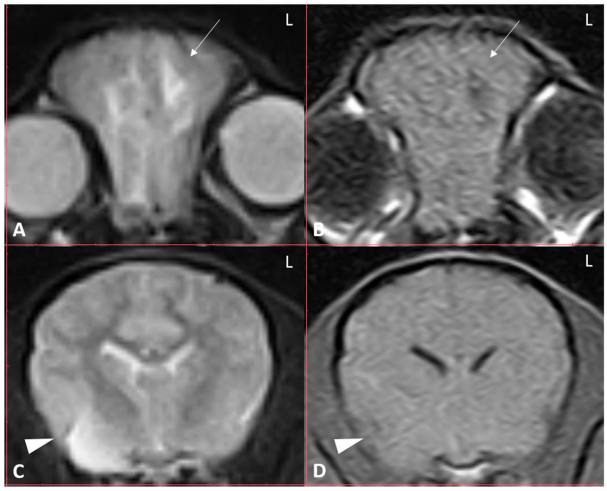

Fig 1. MRI findings at initial presentation. A, C: Transverse T2-weighted images. B, D: Transverse T1-weighted images. On T2-weighted images, multifocal ill-defined, hyperintense lesions are noted in the frontal lobe (arrow) and temporal lobe (arrowhead). The same lesions produced iso- to hypointense signals on T1-weighted images.

virus detection by RT-PCR was performed, which revealed negative results. We tentatively diagnosed the patient with meningoencephalitis of unknown etiology (MUE).

Treatment with prednisolone (Solondo, Yuhan Pharma, Korea; 1 mg/kg, PO, q 12 hr), mycophenolate mofetil (MMF) (Cellcept®, Roche, USA; 20 mg/kg, PO, q 12 hr), and phenobarbital (Phenobarbital, Hana Pharm, Korea; 2 mg/kg, PO, q 12 hr) was initiated and the clinical signs gradually improved. One month after the initiation of treatment, prednisolone was tapered to 0.5 mg/kg, PO, q 12 hr; the MMF dosage was not changed. However, the seizures and circling behavior recurred and the prednisolone dosage was again increased to 1 mg/kg, PO, q 12 hr. The seizure activity reduced within a few days; however, there was no improvement in the circling behavior. Abrupt right-sided falling was temporarily identified.

Approximately 2 months after initial presentation, status epilepticus, tetraparesis, and torticollis to the right were identified. Phenobarbital (2 mg/kg, IV) and diazepam (2 mg/kg, IV) were administered to control the seizure activity. The seizures gradually resolved after administering the medications; the tetraparesis and torticollis did not show response to treatment. Cytosine arabinoside (Cytosar-U®, Pfizer pharm, Korea; 50 mg/m^2, SC, q 12 hr for 48 hr) was added to the treatment regimen. The neurological signs did not improve and the clinical status did not change. Status epilepticus recurred and the patient was euthanized at the owner's request 91 days after initial presentation.

A brain MRI was repeated prior to euthanasia, which revealed diffuse lesions in the cerebrum (Fig 2). There were marked hyperintense signals on T2-weighted images involving the gray and white matter of the frontal, temporal, and parietal lobes. These were most obvious on the right side of

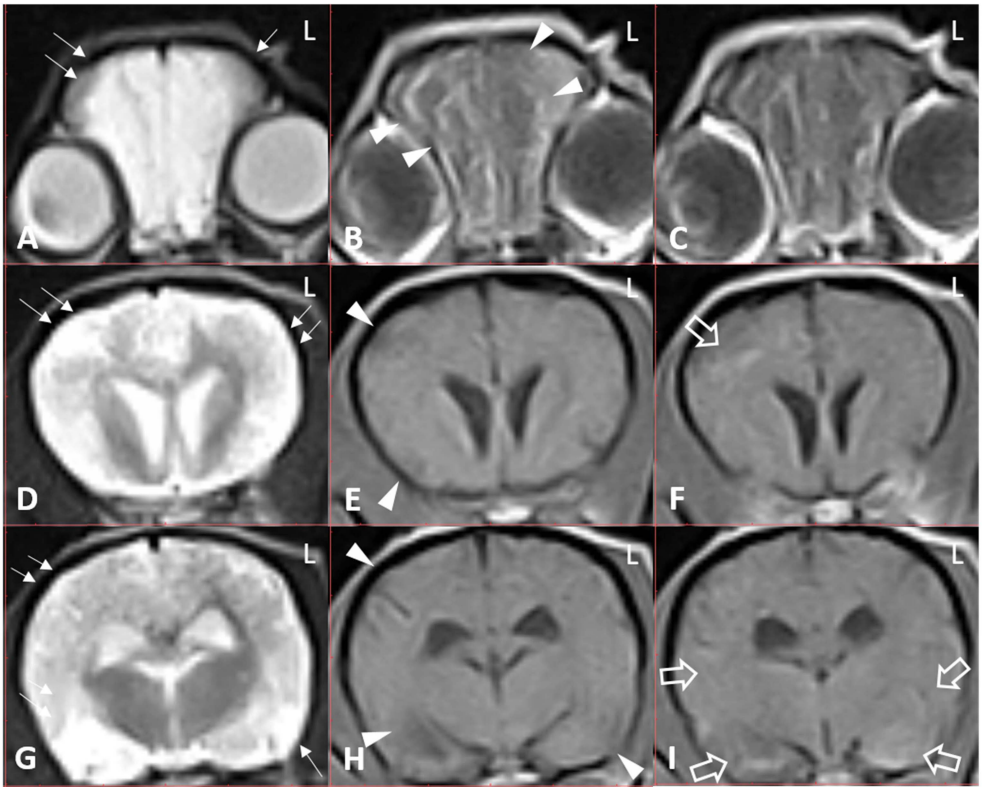

Fig 2. MRI findings at 91 days after initial presentation. A, D, G: Transverse T2-weighted images. B, E, H: Transverse T1-weighted images. C, F, I: Transverse post contrast T1-weighted images. Markedly hyperintense diffuse lesions (arrows) were seen on T2-weighted images, and these lesions showed loss of demarcation between the gray and white matter. The lesions produced hypointense signals (arrowheads) on T1-weighted images and were irregularly enhanced (empty arrows) following administration of contrast medium.

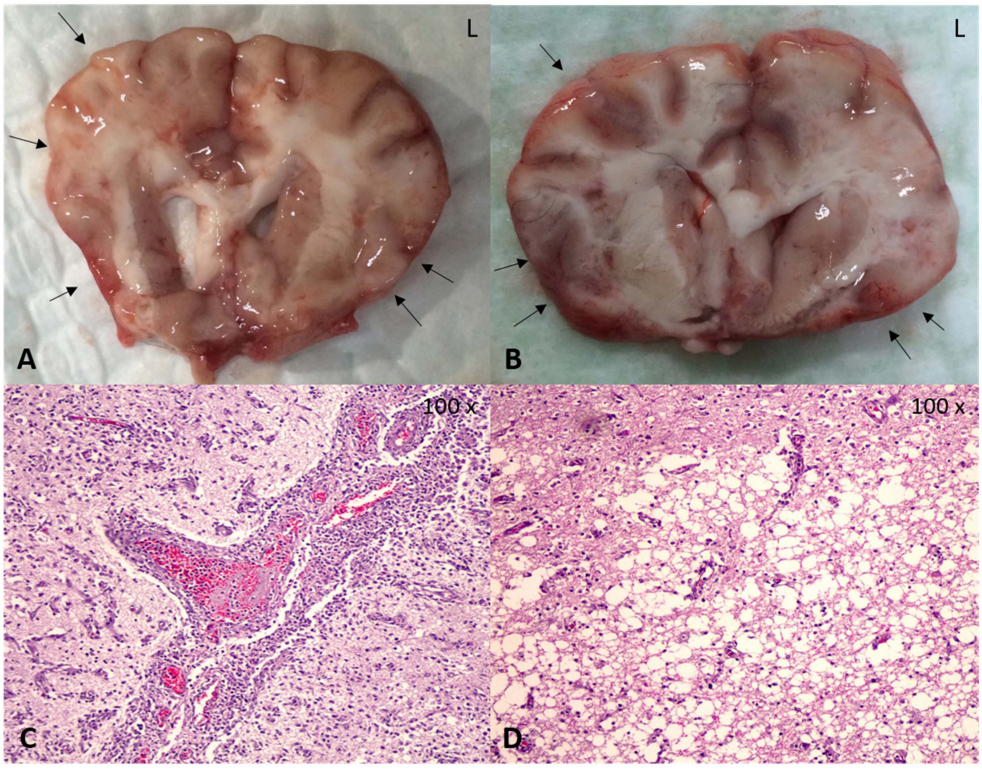

Fig 3. Necropsy (A and B) and histopathological findings (hematoxylin and eosin staining; C and D). Multifocal necrotic, inflammatory lesions with edematous changes are seen in a transverse section of the brain (arrows). The histopathological results indicate extensive infiltration of the cerebral perivascular area by inflammatory cells (C) and marked liquefactive necrosis of the cerebral parenchymal cells with edematous changes (D).

the cerebrum. Loss of demarcation between the gray and white matter was noted in the lesions. The lesions also displayed hypointense signaling on T1-weighted images and were irregularly enhanced after administration of contrast medium. The sizes of the parenchymal lesions were larger than they had been in the initial scan. Moreover, the lesions were more hyperintense in T2-weighted images than in the initial MRI scans.

Necropsy revealed multifocal necrotic, inflammatory lesions with edematous changes involving both the gray and white matter of the cerebrum and the overlying meninges (Figs 3A and 3B). Histopathological findings indicated extensive infiltration of inflammatory cells into the cerebral perivascular area (Fig 3C) and marked liquefactive necrosis of cerebral parenchymal cells with edematous changes (Fig 3D).

This case was definitively diagnosed as an acute form of NME according to the clinical course and the results of the histopathological examination.

Discussion

The antemortem diagnosis of autoimmune CNS diseases is challenging, and a presumptive diagnosis is usually achieved via MRI. According to previous reports (4,20), in NME cases, MRI revealed diffuse, asymmetric cerebral lesions. The lesions were irregularly hyperintense on T2-weighted images, iso- to hypointense on T1-weighted images, and affected both the gray and white matter resulting in loss of demarcation. Moreover, in acute NME cases, edematous changes are more prominent than they are in the chronic form of NME (8). In the present case, the initial MRI images demonstrated multiple, ill-defined lesions with edematous changes on T1-weighted and T2-weighted images (Fig 1). Three months after the initial presentation, a second MRI scan revealed larger cerebral lesions with more edematous changes (Fig 2). These MRI findings indicated that NME progressed rapidly in this case. Treatment was not effective in stopping or delaying the progression of acute NME.

GME and NE are thought to be immune-mediated disorders directed against the CNS, and aggressive immunosuppression is the current mainstay of treatment for these diseases (9,13,15,18,20,22). Immunosuppressive glucocorticoid therapy has long been the standard treatment protocol (4). Cytosine arabinoside, azathioprine, lomustine, procarbazine, leflunomide, and cyclosporine have also been used in the treatment of these diseases (1,8-11,14,20,24). The prognosis for GME and NE depends on the aggressiveness of the disease and on the treatment protocol followed (7,8,11). As with GME, survival data on histopathologically confirmed cases of NE is scarce and there is limited information on the efficacy of treatment (6,9,16). According to a previous study, the mean survival time of histopathologically confirmed NE cases receiving combination therapy with prednisolone and other immunosuppressive drugs (n = 21) was 403 days compared to 50 days in the prednisolone only group (n = 42) (6-9,11,12,23). Furthermore, acute type autoimmune CNS inflammation progresses rapidly and results in a high mortality rate even in the early stages of the disease (8). However, one

previous case study described the successful long-term management of the acute form of NME with cyclosporine plus prednisolone therapy (the patient survived for 1096 days with treatment) (8).

Recently, some reports have suggested that MMF is an effective therapeutic option for MUE in dogs (1,24). Therapy with MMF in dogs with MUE is comparable to treatment with other published immunosuppressive protocols (24). In addition, administration of MMF appears to be relatively safe and enables reduction of the prednisolone dose when the drugs are used in combination (1,5,24). However, studies evaluating the beneficial effects of MMF in histopathologically confirmed cases of MUE are limited (24). The present case had an acute form of NME that was not well controlled with MMF plus prednisolone. This patient's survival time was relatively short as compared to the times that were previously reported for cases with the acute form of NME (6,8,11). In this case, we also administered cytosine arabinoside, but this did not result in an improvement in clinical signs or survival time.

We surmised that autoimmune disorders of the CNS do not always respond to combination immunosuppressive therapy. The immunosuppressive drugs do not always stop or delay progression of the disease. The present case was affected by an acute form of NME and the disease progressed rapidly despite the institution of immunosuppressive therapy. Generally, acute NME cases are less likely to respond to treatment. According to previous studies (6,19), the initial few months (three to four months) of therapy seem to be the most critical in cases of MUE. If MUE cases are successfully managed for the first few months, then the patients are likely to survive for at least nine months (6,19). We prescribed MMF and prednisolone to this patient initially, but the survival time was relatively shorter than that reported in previous studies (6-9, 11,12,23). This patient showed a good response to treatment with prednisolone and MMF for one month. However, the clinical signs gradually worsened and the patient was euthanized approximately three months after commencement of treatment. We suspect that our treatment protocol was not adequate to stop or even delay progression of the disease. More aggressive immunosuppression might have been required in this acute NME case. The focus should be on improvement of clinical signs during the first month of therapy. In the present case, if additional immunosuppressive drugs such as cyclosporine or azathioprine were added, or if the doses of prednisolone and phenobarbital were increased during that initial month, then the survival time might have been extended.

Although data on pharmacokinetics and measurement of plasma MMF levels following oral administration of the medication in dogs are somewhat limited, we did not measure the plasma MMF concentration and could not identify the exact therapeutic concentration after therapy. As MMF is being increasingly used in dogs, additional pharmacological studies evaluating its use in dogs with autoimmune diseases are warranted to establish effective and safe treatment protocols.

In conclusion, this report describes the clinical findings, serial MRI characteristics, histopathological changes, and management of an acute form of NME with MMF.

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