



Noninfectious Inflammatory Central Nervous System Diseases in Dogs

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ABSTRACT: Inflammatory diseases of the central nervous system are often challenging to diagnose. Necrotizing meningoencephalitis, necrotizing leukoencephalitis, and granulomatous meningoencephalomyelitis have characteristic locations of lesions on histopathologic examination and, therefore, characteristic findings from advanced imaging. Together with clinical signs and clinicopathologic data, these characteristic imaging findings may aid in establishing an accurate antemortem diagnosis. Prompt diagnosis can lead to initiation of treatment using a combination of immunosuppressive drugs.

The diagnosis of inflammatory disease of the central nervous system (CNS) can be quite challenging. Inflammation can be the consequence of infectious disease or may represent an autoimmune process. Many results of the diagnostic evaluation of patients with inflammatory CNS diseases are not only non-specific but also similar, regardless of the cause of the disease. This can present a significant dilemma to clinicians. Several inflammatory conditions unrelated to infectious diseases have recently been identified in different canine breeds.

Necrotizing meningoencephalitis (NME) has an unknown cause and is recognized by its tendency to cause cavitory necrosis in the neuroparenchyma. Although first described in pugs, NME has affected several other small breeds. A distinct form of NME, known as *necrotizing leukoencephalitis* (NLE), has been described mainly in Yorkshire terriers. Granulomatous meningoencephalomyelitis (GME) is another relatively common noninfectious inflammatory CNS disease in dogs with the same signalment. GME can often be mistaken for NME. This article reviews the clinicopathologic features and treatment options of these inflammatory CNS diseases and briefly describes their imaging characteristics.

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NECROTIZING LEUKOENCEPHALITIS

NLE is a multifocal, necrotizing, nonsuppurative encephalitis that occurs mainly in Yorkshire terriers and has varying degrees of leptomeningeal involvement.¹⁻⁵ NLE has been referred to in the literature as *necrotizing encephalitis* in Yorkshire terriers, but some have suggested that NLE is a more accurate term because the disease has occurred in other breeds and some aspects of it are unique among the types of NME.⁶ The disease was first described in 1993; since then, numerous cases have been reported in the literature.^{1-5,7,8} The mean age of affected dogs is approximately 4.5 years (range: 1 to 10 years of age). NLE seems to have no predilection for gender or intact status. In all but one of the reported cases, lesions associated with the disease were found in the cerebrum and brainstem. The presence of NLE in both of these areas is an important characteristic that distinguishes this disease from other types of NME in which lesions are largely restricted to the cerebrum. The course of this disease is highly variable but is usually chronic and progressive. Patients typically present with clinical signs reflecting a mixture of prosencephalic (cerebrum or thalamus) and brainstem abnormalities dictated by the loca-

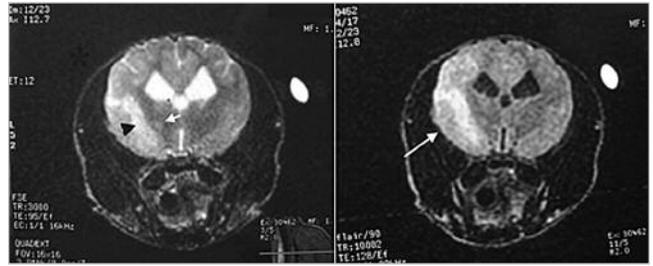


Figure 1. Images of the cerebrum of a Yorkshire terrier at the level of the diencephalon.

On left: T2-weighted transverse MRI. Note the hyperintensity in the white matter of the internal capsule on the left (black arrowhead). There is an additional lesion in the white matter of the thalamus (white arrow).

On right: FLAIR image. Note the hyperintensity of the internal capsule. The lesion in the corona radiata dorsal to the internal capsule is more conspicuous (arrow).

appear hypointense on T1-weighted images, hyperintense on T2-weighted images, and mildly enhanced with administration of intravenous contrast agents.^{3,4} The T1- and T2-weighted image characteristics have an intensity similar to that of CSF; however, with fluid-attenuating

Unlike necrotizing leukoencephalitis or granulomatous meningoencephalomyelitis, lesions and clinical signs of necrotizing meningoencephalitis in pugs, Maltese, and Chihuahuas are confined to the cerebral hemispheres.

tion of the lesions. The clinical signs can include altered mentation, visual deficits, central vestibular signs, proprioceptive placing and hopping deficits, and seizures.

The definitive diagnosis is currently obtained through histopathologic examination; however, a presumptive antemortem diagnosis can be made through a combination of various clinicopathologic data. Cerebrospinal fluid (CSF) analysis is often used in cases of inflammatory CNS disease. The results usually include moderate pleocytosis with a prevalence of mononuclear cells (macrophages, monocytes, lymphocytes, plasma cells) and mild to moderate elevation of the protein concentration.⁴ Magnetic resonance imaging (MRI) has been used in several reports to help assess patients with suspected NLE.^{2-4,8} MRI is one of the primary diagnostics that allows a presumptive antemortem diagnosis. Lesions can be observed on T1-weighted, T2-weighted, and T1-weighted postcontrast image sequences. Affected areas

inversion recovery (FLAIR) sequences, lesions remain hyperintense, likely reflecting a higher protein content within the lesions compared with CSF protein levels (Figure 1). Varying degrees of ventriculomegaly can also be seen.^{2-4,8}

Ultrasonography, plain radiography, and cisternography have all been attempted but have had no more specificity than MRI.¹ In one report,⁸ an elevated level of brain-type isoenzyme of creatinine kinase, along with high-voltage and slow-activity waves on an electroencephalogram, was found in a Yorkshire terrier that was later diagnosed with NLE during a postmortem examination. None of these tests has been used repeatedly in the literature to help diagnose NLE.

On histopathologic examination, lesions predominate in the deep white matter of the cerebrum and thalamus. Typically affected areas of white matter include the centrum semiovale, thalamocortical fibers, internal capsule,

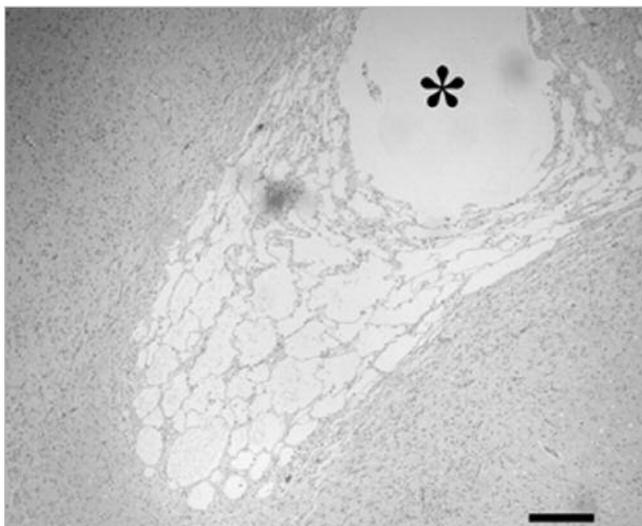


Figure 2. Photomicrograph of a Yorkshire terrier showing necrosis in the white matter of the corona radiata, which has resulted in cavitation (asterisk). (Hematoxylin–eosin, original magnification $\times 40$)

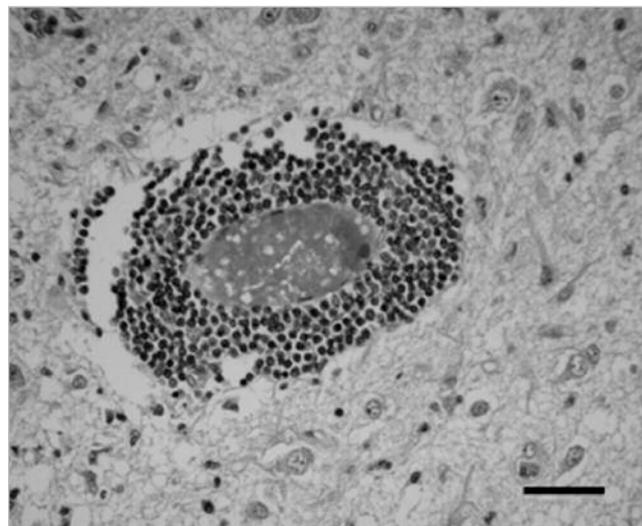


Figure 3. Photomicrograph of a perivascular cuff containing mostly lymphocytes and plasma cells from the dog in Figure 2. (Hematoxylin–eosin, original magnification $\times 100$)

and thalamus. Areas of necrosis often coalesce to form variable-sized areas of cavitation, depending on the severity and duration of the disease (Figure 2). Within the white matter are numerous swollen and necrotic axons, gemistocytes, gitter cells (local macrophages), and reactive microglia and occasional perivascular infiltrates^{2,3} (Figure 3). Leptomeningeal involvement is gen-

disease was called *pug dog encephalitis* for many years because it was thought to be strictly breed specific. It is now thought that this disease is not truly breed specific and should be referred to by the more descriptive term *NME*. This disease occurs in males and females, both intact and neutered. The predominant presenting clinical signs are seizures and altered mentation, which can be

In necrotizing leukoencephalitis, lesions affect the deep white matter of the cerebrum and brainstem.

erally minimal; however, infiltration by a small number of lymphocytes and plasma cells can be observed. Neurons within the gray matter appear to be unaffected despite the surrounding inflammation.^{3,4} These specific differences distinguish this disease from other forms of NME and have prompted the change in nomenclature.

NECROTIZING MENINGOENCEPHALITIS IN PUGS

Almost 25 years ago, the first cases of a uniquely necrotizing, nonsuppurative meningoencephalitis were reported^{9–16} in juvenile to young-adult pugs. The disease was first identified in 1982 in California and Massachusetts but is becoming increasingly recognized throughout the United States and various other countries.^{9,10} This

explained by the disease's predilection for the cerebral hemispheres. Unlike NLE, in NME, cerebellar, brainstem, and spinal cord involvement is rare. If present, the lesions are mild and mainly consist of petechial hemorrhages.^{10,14,15} Affected dogs often present after only a few days of showing clinical disease, whereas other dogs are affected to some degree for several weeks to months before presentation.¹¹ The signs reflect the almost exclusive prosencephalic (cerebrum and/or thalamus) location and can include lethargy, anorexia, blindness with normal pupillary light reflexes, circling, head pressing, and partial or generalized seizures. Cerebellovestibular signs are occasionally observed.^{9,10} Cervical pain and rigidity may accompany any of these signs, depending on the degree of leptomeningeal involvement.¹¹

A unique feature of NME in pugs is the leukocyte differential in the CSF. In a study of dogs with NME confirmed by histopathologic examination, the CSF of 16 of 17 dogs contained an overwhelming predominance of small lymphocytes.¹¹ The mean percentage of lymphocytes in CSF was 90%.¹¹

There are only a few published reports¹² of the detection of NME in pugs by MRI. In one report,¹² lesions were seen in all areas of the cerebrum but were not seen in the brainstem or cerebellum. The lesions appeared hypointense on T1-weighted images, hyperintense on T2-weighted images, and only slightly enhanced after intravenous contrast administration. In our experience, the characteristic appearance of lesions associated with NME, as seen on MRI, correlates with that in the aforementioned report, but the lesions are most often located at the junction between cerebral gray and white matter. As a result, there are multifocal areas with a definitive loss of the sharp demarcation of the gray and white matter of the cerebral cortex (Figure 4).

An autoantibody directed against an astrocytic protein has recently been identified in the serum and CSF of pugs with NME.^{13,17} Although the role of this autoantibody remains unclear, one possible explanation is that NME

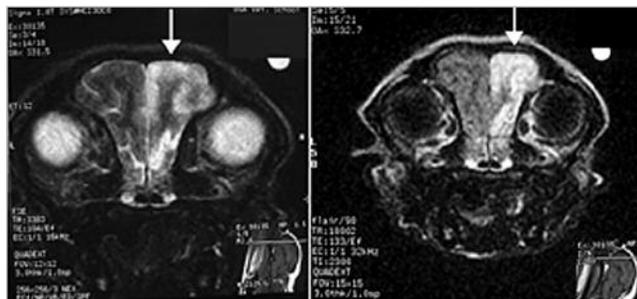


Figure 4. Images of the frontal lobes of a pug with NME. On left: T2-weighted transverse MRI scan. Note the hyperintensity of the cerebral cortex corresponding to the inflammatory infiltrate at the corticomedullary junction of the cerebrum (arrow). On right: FLAIR image at the same level as the image on the left. Note the hyperintensity (arrow).

encephalitis in humans and other animals.^{20,21} It has been suggested that cases of NME are a recurrence of neonatal canine herpesvirus type 1 infection.¹¹ A herpesvirus-like virus was isolated in a previously reported case¹¹ of a pug with NME, but the isolate was not retained for further characterization. To date, an underlying viral cause of NME appears to be unlikely.²² Thorough questioning of the owner or breeder about other

Granulomatous meningoencephalomyelitis lacks the necrosis and microcavitation that occur in necrotizing meningoencephalitis.

may represent a primary autoimmune disease directed against astrocytes. Autoantibodies directed against self-antigens of the nervous system have been identified in various human diseases, including multiple sclerosis and Guillain-Barré syndrome.^{18,19} Alternatively, autoantibodies may develop secondary to damage induced by an independent primary insult. In this scenario, autoantibodies may play only a minor role, if any, in the overall pathogenesis. Although it was once thought that these autoantibodies were specific to cases of NME in pugs, a recent study¹⁷ found the presence of such autoantibodies in the CSF of other breeds with NME confirmed by histopathologic examination and with focal GME. All nine pugs examined had the highest titers (>1:100), but 13 other toy-breed dogs diagnosed with NME had titers ranging from 1:1 to greater than 1:100, with varying titers found in three cases of focal GME.¹⁷

A strong predilection for the cerebral hemispheres and widespread necrosis occur in α -type herpesvirus

animals in the same litter and the health and history of the dam and sire may prove helpful in distinguishing NME from possible active infections.

Concurrent myocardial necrosis has been reported in two cases of NME in pugs.^{14,15} The correlation between acute CNS damage and myocardial necrosis has been well established in humans and experimentally induced in animal models, in which it is thought to be due to catecholamine release by the sympathetic nervous system.^{23,24} This finding has been reported²³ in veterinary patients with acute trauma as well as inflammatory diseases. Experimental use of β -receptor antagonists has proven helpful in preventing myocardial damage in animals with induced intracranial trauma.²⁵ This treatment has not been evaluated in patients with NME.

On histopathologic examination, lesions can be seen in both the cerebral gray and white matter in patients with NME. Disseminated meningitis, choroiditis, and encephalitis occur in varying degrees. Meningeal infil-

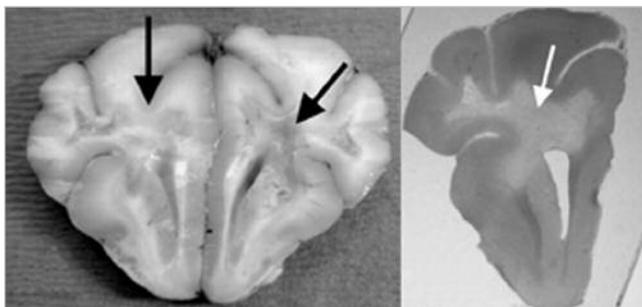


Figure 5. Cerebrum of a Maltese with NLE.

On left: Gross specimen of a Maltese brain at the level of the frontal lobes of the cerebrum. Note the cavitation of the white matter of the corona radiata and the internal capsule (arrows). On right: Subgross photomicrograph of the right cerebrum at the same level as the image on the left showing necrosis of the white matter of the internal capsule and corona radiata (arrow). (Hematoxylin–eosin)

trates consisting of plasma cells, lymphocytes, and occasional histiocytes can be widespread over the entire cerebrum.¹⁵ The areas of the cerebrum with more profound involvement and the cerebral sulci and fissures often contain the strongest infiltrates.¹⁵ There may be areas of malacia, necrosis with liquefaction, and cavitation as in NLE.^{11,15} The inflammatory infiltrate extends from the leptomeninges into the adjacent cerebral cortex, where it spans the gray matter and extends into the underlying white matter. On gross examination, the anatomic junction between the gray and white matter is lost. In cases in which there was a more protracted course of disease, neuronal loss and gemistocyte infiltration can be found.¹¹

NECROTIZING MENINGOENCEPHALITIS IN MALTESE

Maltese can be affected by NME in a manner almost identical to the disease in pugs.^{15,26} In both breeds, NME is nonsuppurative, can affect dogs of any age and sex, and has been reported as a breed-specific disease process. In Maltese, NME was first reported^{26,27} in 1987 but has been found throughout the United States and abroad since then.

This disease has been reported in only a small number of dogs. In Maltese, the presenting clinical signs, onset and progression of the disease course, and histologic abnormalities are almost identical to those in pugs with NME. All Maltese with NME have initially presented with seizures. CSF analysis has revealed an elevated protein concentration with lymphocytic pleocytosis, and

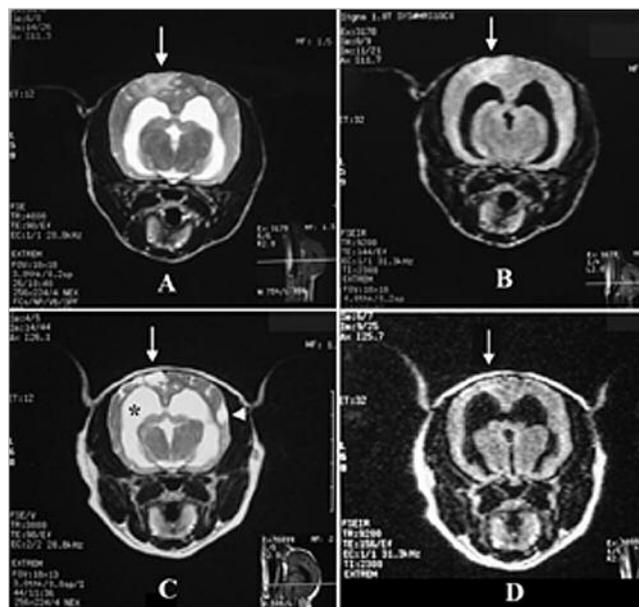


Figure 6. Cerebrum of a Pomeranian with NME.

A: T2-weighted transverse image. Note the hyperintensity of the white matter of the corona radiata in the dorsal cerebrum (arrow). B: Corresponding FLAIR image. Note the hyperintensity of the white matter of the corona radiata in the dorsal cerebrum (arrow). C and D: Corresponding T2-weighted and FLAIR images obtained 6 months after treatment with prednisone and cytosine arabinoside. The previous hyperintensities of the corona radiata are more hyperintense and sharply demarcated, which is consistent with cavitation (arrows), and there is a greater degree of ventriculomegaly secondary to loss of the overlying cerebral cortex (asterisk). Note the decreased thickness of the cerebral cortex 6 months after treatment.

the appearance of Maltese encephalitis on MRI is similar to that of pugs with NME.^{26,27} Given the similarities, it is thought that the pathologic process that occurs in pugs also occurs in Maltese with NME and that these diseases are not necessarily breed specific.^{6,26} We have also seen Maltese terriers with NLE that have lesions similar to those in Yorkshire terriers (Figure 5).

OTHER BREEDS WITH INFLAMMATORY CNS DISEASE

Several isolated case reports involving disease in other breeds have been published. We have found NME in other breeds, including shih tzus, Lhasa apsos, and Chihuahuas. The clinicopathologic, imaging, and histopathologic findings were identical to those in other cases of NME (Figure 6). A single report²⁸ of NME in a Pekingese seems remarkably similar to NME in pugs and Maltese. This patient showed similar clinical signs

and had histopathologic lesions restricted to the same locations as in the other affected breeds. The dog also had a second, likely unrelated lesion that seemed to affect only the right hippocampus. Whether this dog's pathology was a variation of NME or a specific disease exclusively affecting Pekingese is unknown.

There is also a report²⁹ of nonsuppurative meningoencephalitis in 14 greyhounds in Ireland. These dogs were from three different kennels separated by at least 15 miles. The pathology in all the animals was similar and included infiltrative inflammatory lesions in the cerebral hemispheres and the brainstem. There was no evidence of tissue necrosis or microcavitation in any of the greyhounds, thus excluding the condition as a variation of NME. The history, lesion description, and geographic distribution of the cases were highly suggestive of a

exact cause of GME is currently unknown. Bacterial, viral, and fungal cultures of blood and CSF as well as special tissue stains and polymerase chain reaction testing for viral DNA isolation have all failed to identify a causative agent.^{22,31,33,35-37} Although GME is highly variable, there are three basic forms of the disease. In the ocular form, inflammation is initially restricted to the retinal and postretinal portions of the optic nerve.^{10,34} The clinical signs, including acute blindness, mydriasis, papilledema, and retinal hemorrhages, usually reflect this isolated location.^{10,34,38} In focal GME, a single lesion can be located in the cerebrum, brainstem, or, rarely, cerebellum,^{39,40} or several small lesions can coalesce to form a larger, space-occupying mass. These cases often have a relatively longer clinical course than do the other forms of this disease.^{33,41} In disseminated or generalized

Lesion topography and characteristics seen on MRI may aid in antemortem diagnosis of noninfectious inflammatory CNS diseases.

genetic or infectious cause. Despite this, serologic testing for multiple infectious diseases, immunohistochemical staining for protozoal agents, and in situ hybridization to demonstrate canine distemper virus (CDV) mRNA all failed to determine a cause of disease in these animals.²⁹ Although this appears to be a novel condition in greyhounds, additional cases have not been documented since this report from 2002.

More recently, an abstract described NME in five Chihuahuas.³⁰ The clinical course appeared similar to that of NME in other breeds. MRI characteristics showed a loss of distinction of the gray-white matter junction throughout much of the cerebral hemispheres. Cortical hyperintensity on T2-weighted images suggested cavitation. Gross and microscopic findings of the postmortem examination confirmed multifocal, nonsuppurative NME with cystic cavitation.

GRANULOMATOUS MENINGOENCEPHALOMYELITIS

GME is often difficult to distinguish clinically from other forms of encephalitis. This disease was first documented in 1978 but had perhaps been described as early as 1962 using different terminology.^{31,32} Although any canine breed can be affected, the disease most often occurs in young to middle-aged toy breeds, and there is evidence to suggest a predilection for females.^{31,33,34} The

GME, a multifocal lesion location is implied, and patients present with signs that reflect the areas involved. In these cases, onset is acute and progression is rapidly fatal.⁴¹

The term *reticulosis* was previously used to describe GME because it mimics a similar disease in humans.^{32,42} In the strictest sense of the word, reticulosis implies proliferation of the reticuloendothelial cells originating in any tissue. It is thought that the lesions associated with GME are not proliferative in this sense but are merely the result of the migration and maturation of blood-derived monocytes.³⁵ This distinguishing characteristic, along with the classic histologic appearance of GME, is the basis for defining it.³⁵ Primary reticulosis has been reported⁴² in dogs but rarely mentioned in the literature since then. This likely reflects the common opinion that what was previously thought to be reticulosis is, in fact, GME.¹⁰

One of the distinguishing histopathologic differences between GME and NME is that GME lacks the tissue necrosis and secondary cavitation associated with NME and NLE.⁴³ On histologic examination, GME is characterized by widespread inflammatory cell infiltration situated in a whorling pattern around small blood vessels within the neuroparenchyma with secondary malacia and petechial hemorrhages.^{33,35,36,38} On MRI, these lesions appear isointense on T1-weighted image

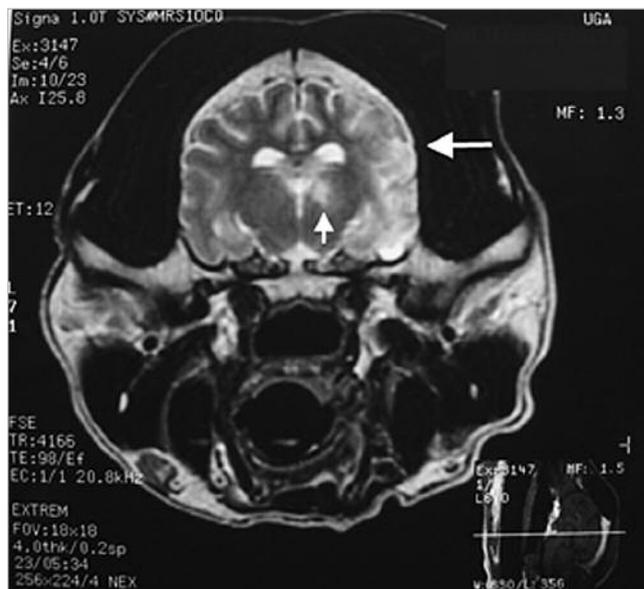


Figure 7. T2-weighted transverse image of the cerebrum of a dog with GME at the level of the diencephalon. The hyperintensity of the cerebral cortex was consistent with focal GME (large arrow) on histologic examination. However, a smaller lesion is also visible within the thalamus (small arrow).

sequences and hyperintense on T2-weighted image sequences and may show meningeal enhancement^{40,44,45} (Figure 7). Multifocal lesions are generally observed and often include lesions in the brainstem. Although GME has a predilection for white matter, it is not associated with distinct topography, as NME and NLE are.

Although the exact cause of GME is unknown, several hypotheses have been presented regarding its pathophysiology. Several reports describe the nature of the inflammatory cells within the lesions associated with disseminated GME. The predominant cell types include CD3-positive T lymphocytes and major histocompatibility complex, class II antigen-positive macrophages.^{17,46} Therefore, it has been suggested that a delayed-type hypersensitivity reaction may underlie the pathogenesis of GME.^{17,46} Some^{33,41} have suggested that the lesions of focal GME show similarities to certain neoplasms, such as B-cell lymphoma. In the study of lymphocytes within the perivascular cuffs, variable degrees of pleomorphism and mitotic index have been noted, thus suggesting a neoplastic behavior.³³ Alternatively, as already mentioned, autoantibodies to astrocytic proteins were found in the CSF of dogs with focal GME that was confirmed on histopathologic examination in addition to cases of NME, suggesting an autoimmune pathogenesis of GME.¹⁷

DIFFERENTIAL DIAGNOSIS

Classically, inflammatory CNS disease results in multifocal neurologic deficits. The differential diagnosis of patients that present with multifocal disease includes inflammatory disease, infectious encephalitis, congenital abnormalities, metabolic derangements, intracranial neoplasia, and exposure to toxins. In general, patients with metabolic and toxic encephalopathies present with symmetric deficits, whereas the remaining multifocal causes result in asymmetric deficits. Infectious causes of encephalitis include rabies virus, herpesvirus, CDV, and, rarely, canine adenovirus type 1 and canine parainfluenzavirus.¹⁰ Of these viruses, CDV is an important diagnostic differential that must be included in suspected cases of NLE because the histopathologic distribution and white matter demyelination of CDV infection are similar to those of NLE.¹ This pattern of demyelination may lead to similar neurologic signs. Dogs affected by CDV may also have extraneural signs, such as hyperkeratosis of the footpads or nose, myoclonus, urinary and fecal incontinence, and cachexia.⁴⁷ Altered mentation and seizures may be caused by hydrocephalus, metabolic derangements (e.g., hypoglycemia, hepatic dysfunction), and many different intracranial neoplasms.

TREATMENT

No large, long-term studies have specifically evaluated treatment options for these necrotizing encephalitides. In one report,¹⁶ a single pug was treated using a combination of anticonvulsants, corticosteroids, antibiotics, and herbal remedies and lived 533 days after initiation of treatment. However, the foundation of treating noninfectious inflammatory CNS disease has been medical therapy using corticosteroids at doses ranging from antiinflammatory (prednisone at 0.5 to 1.0 mg/kg/day) to immunosuppressive (prednisone at 2.0 to 4.0 mg/kg/day). Success and survival time are reportedly highly variable and may largely be a function of clinical severity when the treatment was initiated.

Immunosuppression has also been a basis of treating GME. Several drugs have been used adjunctively with prednisone to treat this disease. In a report³⁴ of a dog with disseminated GME diagnosed by characteristic results of computed tomography and CSF analysis, treatment with immunosuppressive doses of prednisone along with cytosine arabinoside showed promising results. Eight weeks after treatment was initiated, the CSF abnormalities had resolved, and the lesions that

had been detected by computed tomography had resolved, except for minimal changes, which were assumed to be residual scar tissue.³⁴ Cytosine arabinoside, which is used as an antineoplastic agent, disrupts DNA synthesis by inhibiting DNA polymerase during the S-phase of the cell cycle.⁴⁸ Its benefits over corticosteroids include lack of polyuria, polydipsia, and polyphagia. It also avoids potential steroid hepatopathy and does not require daily dosing.³⁴ Although myelosuppression is a rare complication, routine monitoring of hematologic parameters is still required.³⁴

Cyclosporine has also shown promise in treating GME.³⁷ Cyclosporine is a lipophilic polypeptide primarily used to inhibit organ transplant rejection.³⁷ Specifically, the drug inhibits transcription of interleukin-2 and α -interferon.⁴⁹ Blockage of interleukin-2 transcription leads to decreased activation of T lymphocytes.⁴⁹ α -Interferon is a cytokine that provides amplification signals for monocyte and macrophage activation.⁴⁹ Cyclosporine is thought to counteract the

11 dogs had no treatment. While the median survival time (MST) of all dogs was 4.5 months, the treated group had an MST of 15 months, and the untreated group had an MST of 0.62 months. The procarbazine dosage is 25 to 50 mg/m²/day and can be compounded into an elixir for easier dosing.^{50,51} Reduction to every other day may be attempted after the first month of treatment. The use of procarbazine was significantly associated with survival time.

Leflunomide is an experimental immunomodulatory drug that has been used to treat many different immune-mediated disease processes.⁵² It inhibits de novo synthesis of pyrimidine.⁵³ In three dogs with inflammatory or malacic brain lesions, leflunomide was initiated after complete or partial resolution of clinical signs was obtained using glucocorticoids.⁵⁴ All three dogs survived longer than 12 months after leflunomide therapy was begun.

Radiation therapy has been used as adjunctive treatment in cases of focal GME. The rationale for its use is

Treatment of noninfectious inflammatory CNS diseases appears promising using drugs such as cytosine arabinoside, cyclosporine, procarbazine, and leflunomide in addition to corticosteroids.

proposed T cell-mediated, delayed-type hypersensitivity reaction already mentioned. In one study³⁷ using cyclosporine, clinical signs in two of three dogs with a presumptive diagnosis of disseminated GME were controlled after 12 months.

Procarbazine is another antineoplastic that has shown promise in treating GME.⁵⁰ It is a potent alkylating agent that is often used in treating lymphoma in dogs and cats.⁴⁸ It is lipid-soluble and readily crosses the blood-brain barrier.⁵¹ The exact mechanism of cytotoxicity of procarbazine is unknown, but it is thought that the drug mainly damages DNA, RNA, and protein synthesis.⁵⁰ The major adverse effects of procarbazine include myelosuppression, gastrointestinal disturbance, and CNS effects.⁴⁸ The nadir for thrombocytopenia is approximately 4 weeks, making routine hematologic screening a requirement. Nausea, vomiting, diarrhea, and hepatic dysfunction are potential side effects that must be monitored. Neurotoxic effects can include sedation, agitation, loss of tendon reflexes, and myalgia.^{48,51} In a recent study,⁵⁰ 31 dogs with presumed or confirmed GME were examined. Twenty dogs were treated with a combined therapy of prednisone and procarbazine, and

based on the apparent neoplastic qualities of the cells within focal lesions.^{33,41,55} In a study⁴¹ of radiation therapy, six of seven dogs with diagnosed focal GME had an MST of greater than 404 days while receiving a combination of corticosteroids and megavoltage radiation delivered by cobalt-60 teletherapy or a 6-mV linear accelerator. This modality may not prove helpful in cases of disseminated GME. Larger, long-term studies using radiotherapy and various drug combinations are warranted to help determine the optimum treatment protocol for these diseases.

CONCLUSION

Noninfectious inflammatory CNS diseases in small animals are challenging to diagnose and treat. Although these diseases were previously reported to be breed specific, this view has changed as more breeds with the same clinical and histopathologic disease processes have been affected. NME affects many small breeds and is almost exclusively limited to the cerebral hemispheres. NLE almost exclusively affects Yorkshire terriers, causing widespread necrosis in the white matter of the cerebrum, brainstem, and, rarely, cerebellum. GME is

nonnecrotizing and multifocal and affects the same canine breeds.

Use of MRI is integral to diagnosing neurologic disease. MRI has largely supplanted alternative advanced imaging techniques for this purpose. The ability of MRI to differentiate similar soft tissues is superior to that of CT. In addition, areas that are inherently difficult to image using CT, such as the caudal fossa, are easily visualized with MRI. Consequently, MRI is the preferred imaging modality for nervous system disorders.

With a great degree of certainty, MRI can be used to provide an accurate presumptive diagnosis of noninfectious inflammatory encephalitis in pugs, Yorkshire terriers, and Maltese. The MRI characteristics of NME and NLE precisely mirror the topography of the gross and histopathologic lesions seen at necropsy. In pugs with NME, lesions on MRI are generally limited to the cerebral cortex, where there is loss of the demarcation between the gray and white matter, reflecting the inflammation infiltrating from the leptomeninges through the gray matter and into the white matter of the cortex. In contrast, NLE in Yorkshire terriers predominantly affects the deep white matter, of the cerebrum. Lesions on MRI are principally located in white matter areas, such as the centrum semiovale, thalamocortical fibers, internal capsule, and thalamus. Topographically, these lesions exactly parallel the cavitating necrosis observed at necropsy. Knowledge of the characteristic appearance and, most important, the pattern of distribution of noninfectious inflammatory diseases can help establish an accurate antemortem presumptive diagnosis, which can lead to rapid initiation of therapy.

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ARTICLE #3 CE TEST



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1. **The encephalitides that were once thought to be breed specific are considered necrotizing because**
 - a. necrotic debris is often found in the CSF.
 - b. there are markedly necrotic meninges, while the cerebral tissue is only mildly affected.
 - c. massive areas of neuroparenchymal loss are often observed on gross and histologic examination.
 - d. affected tissues may culture necrotizing strains of *Staphylococcus aureus*.
2. **Encephalitis in which breed most closely resembles NME in pugs?**
 - a. Yorkshire terrier
 - b. greyhound
 - c. Alaskan husky
 - d. Maltese
3. **Where would a lesion associated with NME in a pug likely be found via MRI?**
 - a. at the junction of cerebral gray and white matter
 - b. deep in the thalamic white matter
 - c. within the vestibular nuclei located in the medulla
 - d. in the arbor vitae of the cerebellum
4. **NME is best characterized**
 - a. by neutrophilic infiltrates.
 - b. exclusively by inflammation of the meninges and ependyma.
 - c. by areas of necrotic nervous tissue with eventual granuloma formation.
 - d. by areas of necrotic nervous tissue with eventual cavitation.
5. **Widespread necrotic lesions, including in the brainstem, characterize encephalitis in which breed?**
 - a. pug
 - b. Chihuahua
 - c. Yorkshire terrier
 - d. Maltese
6. **The histologic hallmark of GME is**
 - a. the presence of plasma cells.
 - b. perivascular whorls of inflammatory cells.
 - c. large areas of necrosis.
 - d. a high mitotic index and evidence of anaplasia.

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7. Which statement regarding MRI findings in pugs with NME is correct?

- a. The lesions appear hyperintense on T1-weighted images.
- b. The lesions appear hyperintense on T2-weighted images.
- c. The lesions can be greatly enhanced by administration of intravenous contrast.
- d. The lesions appear with a characteristic hyperintense whorling pattern on T1-weighted images.

8. Given the topography of NME lesions in pugs, which is the least likely clinical sign of the disease?

- a. circling
- b. central vestibular disease
- c. seizures
- d. altered mentation

9. Radiation therapy has reportedly prolonged survival in

- a. patients with focal GME.
- b. patients with disseminated GME.
- c. Yorkshire terriers with necrotizing encephalitis.
- d. patients with optic neuritis secondary to ocular GME.

10. Which chemotherapeutic drug has not shown promise in treating GME?

- a. leflunomide
- b. cytosine arabinoside
- c. doxorubicin
- d. cyclosporine