Review Article

Immune-Mediated Central Nervous System Disease—Current Knowledge and Recommendations

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A B S T R A C T

Immune-mediated inflammation is responsible for about 25% of central nervous system disease in dogs. The disease can affect all ages and breeds, but young to middle-aged small breed dogs are over-represented for most forms. Diagnosis consists of advanced imaging (MRI), cerebrospinal fluid analysis, and infectious disease testing, but biopsy is required for definitive diagnosis and classification of the disease into one of the many subtypes. Treatment consists of immunosuppressive medication with the goal being to control and/or improve clinical signs. Current literature shows that prognosis is variable.

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Introduction

Immune-mediated inflammation of the central nervous system is reported to account for up to 25% of central nervous system (CNS) disease in dogs.[1] Definitive diagnosis of immune-mediated inflammatory disease of the CNS requires histopathologic diagnosis. Therefore, antemortem diagnosis can be challenging, and typically involves a combination of tests such as screening for systemic and metastatic diseases, magnetic resonance imaging (MRI), cerebrospinal fluid (CSF) analysis, and testing for various infectious diseases that can cause CNS inflammation. Once a presumptive diagnosis has been made, the patient is often placed under the umbrella diagnosis of meningoencephalitis of unknown etiology (MUE), which accounts for the various subtypes of noninfectious inflammatory CNS disorders. Following biopsy or postmortem examination, patients can be further classified. Histopathologically described subtypes include granulomatous meningoencephalitis (GME), necrotizing leukoencephalitis (NLE), and necrotizing meningoencephalitis (NME). Steroid responsive meningitis arteritis (SRMA) and eosinophilic meningoencephalitis (EME) are more easily characterized antemortem, and are also suspected to be immune-mediated in origin. Inflammatory disease of the CNS can affect the meninges (meningitis), the brain (encephalitis), the spinal cord (myelitis), or a combination. For the purpose of this review, the term MUE will be employed for all general discussions on immune-mediated CNS inflammation.

Terminology aside, this group of CNS diseases is increasingly being recognized in companion animal medicine. A thorough review of our current knowledge on this disease and the existing diagnostic and treatment options is warranted.

Demographics of Disease

MUE has been shown to affect both males and females, but females tend to be over-represented in a number of studies.[1−4] Additionally, female dogs have been reported to be affected by various forms of MUE at a significantly younger age than males.[5]

Dogs of all ages can be affected by MUE, but the necrotizing diseases tend to affect younger dogs than GME. In 2010, Granger et al

provided a thorough review of the existing literature on immune-mediated CNS inflammatory diseases in order to better characterize the clinical picture of these diseases. Dogs with a histopathologic diagnosis of GME tended to be older than dogs with the necrotizing forms (4-8 years vs. <4 years, respectively).[3] In a retrospective study comparing the imaging findings of neoplastic, vascular, and inflammatory CNS diseases, the median age for patients with inflammatory disease was 5 years, compared with 9 years for neoplasia, and 11 years for vascular disease.[6]

Small and toy breed dogs are considered to be predisposed to most forms of MUE, although certain breeds are more predisposed to various subtypes. NME has only been reported in a handful of breeds, including Pug dogs, Papillon, Shih Tzu, Coton de Tulear, Brussels Griffon, Yorkshire Terrier, Maltese, Chihuahua, Pekingese,[7] and recently in 1 larger breed, a Staffordshire Terrier mix.[8] NLE has been previously known as "Yorkie encephalitis," but has been described in other breeds including the French Bulldog.[9] GME has been reported in many different breeds, and should be considered as a differential in any patient that presents for CNS disease, regardless of age and breed. In one study that included 42 dogs with histopathologically confirmed GME, 19 (45%) of dogs were >10 kg. Eosinophilic meningoencephalitis is an uncommon variety of immune-mediated or idiopathic inflammatory CNS disease, which is more common in young, male, large breed dogs.[10] SRMA is also more common in young large breed dogs, and will be discussed in more detail later (Table 1).[11]

Pathogenesis—What We Know

A predominantly T-cell-mediated autoimmune pathogenesis has been suggested for idiopathic meningoencephalidities; however, the trigger of this autoimmune response has yet to be determined.[12,13] Given the prevalence of young to middle-aged small and toy breed dogs affected with GME and the identified breed predispositions for NME and NLE, some degree of genetic or familial predisposition has been assumed. However, there are likely environmental factors in play as well, although they remain undetermined.[14]

NME has been extensively studied in Pug dogs in the hopes of better understanding the pathogenesis. One study recruited any Pug dog that was presented for intracranial disease and had a necropsy performed regardless of etiology. In this study, 60 of 74 Pugs had a necropsy diagnosis of NME. The demographics of the 60 Pugs with

Table 1
Summary of Relevant Clinical and Diagnostic Differences Between the Subtypes of MUE.

	Breeds	Neurolocalization	MRI	Histopathology
GME	Reported in many different breeds, including large breeds	Can affect the cerebrum, cerebellum, brainstem, or spinal cord. There are 3 forms: ocular, focal, and disseminated.	Variable—typically hyperintense on T2 and variably contrast enhancing	Mixed lymphoid population, perivascular cuffing
NME	Small breeds: pugs predominate, also reported in papillon, Shih Tzu, Coton de Tulear, Brussels Griffon, Yorkshire Terrier, Maltese, Chihuahua, Pekingnese, and one large breed mix	Cerebrum, seizures are common	Loss of gray matter/white matter distinction in the cerebrum	Inflammation and necrosis affecting the gray matter/white matter junction in the prosencephalon
NLE	Most commonly reported in Yorkshire terrier and French bulldogs	Cerebrum and brainstem	Asymmetrical multifocal lesions within the subcortical white matter of the prosencephalon	Inflammation and necrosis predominantly affecting the white matter

GME, granulomatous meningoencephalitis; NME, necrotizing meningoencephalitis; NLE, necrotizing leukoencephalitis.

NME compared with the 14 Pugs without revealed that the body weight of Pugs with NME was significantly lower than Pugs with other diseases. Females were over-represented in the NME group. When evaluating season, temperature, and geographic locations as possible environmental factors, no significant correlation was found.[4]

Genomic analysis has identified 2 disease-associated loci in Pug dogs with NME, and later Maltese dogs with NME.[15,16] Serum glial fibrillary acid protein (GFAP), which is an astrocyte-specific protein, has been shown to be significantly more elevated in Pugs with NME than other breeds with NME, dogs with other CNS diseases, dogs with non-CNS diseases, and healthy control dogs. The concentrations of both GFAP and anti-GFAP antibodies have also been measured in the CSF. CSF anti-GFAP IgG was significantly higher in dogs with NME than dogs with other inflammatory diseases, noninflammatory CNS diseases, and healthy controls. NME dogs also had higher levels of GFAP than dogs with noninflammatory CNS disease and healthy dogs. There was no significant difference between NME and other CNS inflammatory diseases. Healthy Pugs had a higher concentration of GFAP than other healthy dogs and 2 had concentrations similar to the Pugs with NME. These results highlight the need to further investigate the role of GFAP and astrocyte stability in the pathogenesis of NME, particularly in Pug dogs.[17,18]

Viral disease is a common cause of cause of encephalitis and/or meningitis in people. As such, there have been a few investigations regarding a possible infectious etiology for MUE. Viral diseases implicated in human meningoencephalitis include herpesviruses, cytomegalovirus, Epstein-Barr, influenza A, human parvovirus B19, adenoviruses, and others. One study performed polymerase chain reaction (PCR) for herpesvirus, adenovirus, and canine parvovirus on the brains of 7 dogs with histologically confirmed GME and 15 with NME/NLE, and no viral nucleic acids were found in any sample.[14] Another study performed PCR on brains of GME and NME cases for adenovirus, bunyavirus, coronavirus, enterovirus, flavivirus, herpesvirus, paramyxovirus, and parechovirus, and no viral nucleic acids were detected. The same study also found *Mycoplasma* species via PCR in 1 dog with GME, 5 with NME, and 1 control. *Mycoplasma* was also cultured in 4 dogs with GME, 4 with NME, and 2 controls. Due to lack of statistical significance, a conclusion regarding the role of *Mycoplasma* spp. in the etiopathogenesis of the encephalidities could not be determined; however, it seems to warrant further investigation.[19]

The fecal microbiome has also been investigated as a possible environmental risk factor in the development of immune-mediated encephalitis. So far, *Prevotellaceae* has been shown to be significantly less abundant in the gut microbiota of dogs with meningoencephalitis of unknown origin compared with normal dogs.[20] While it is too early to draw conclusions regarding case management from this single study, it encourages further research regarding environmental factors that might contribute to this disease.

Clinical Presentation

A variety of neurologic exam abnormalities have been reported in association with MUE. Typically, the abnormalities found on exam reflect the neurolocalization, and given the multifocal nature of these diseases, quite a variety of signs can be present. SRMA tends to have a more specific clinical presentation, which is detailed below. In Granger's review of 457 cases, necrotizing diseases were more likely to have forebrain signs, including seizures, MUE cases (no histopathologic diagnosis) were more likely to be multifocal, and GME cases had an equal distribution of neurolocalizations, including spinal cord only.[3] There are 3 reported forms of GME: focal, disseminated, and ocular.[1]

In a retrospective of 60 pugs with histopathologically confirmed NME, all 60 Pugs had seizures. Of those, 24 of 60 had involvement of the cerebellum and 23 of 60 had brainstem involvement in addition to the cerebrum.[4]

MUE can also affect the spinal cord alone, and it accounts for about 6% of myelopathic disorders in dogs. In a retrospective of 21 dogs with myelopathic inflammatory disease only, 13 (62%) had a focal neurolocalization, most commonly T3-L3, and 71% had pain on spinal palpation. Unfortunately, it is difficulty to differentiate dogs with focal meningomyelitis from other causes of myelopathy, such as intervertebral disc disease (IVDD), with exam alone. Meningomyelitis can have varied presentations including acute or chronic duration with varying degrees of paresis and urinary/fecal incontinence, although no dogs were plegic on presentation in this particular study. A variety of both large and small breed dogs were represented in this study as well, with ages ranging from 10 months to 10 years, so this should be considered as a differential for all dogs presenting with focal or multifocal myelopathic signs.[21]

Diagnostics

After completion of a thorough physical and neurologic exam, the following diagnostics should be considered in a patient suspected of having immune-mediated CNS inflammatory disease.

Bloodwork

Complete blood count (CBC), serum chemistry, urinalysis, and when appropriate, evaluation of baseline cortisol, thyroid hormone concentration, and/or creatine phosphokinase (CPK) should be performed with the intent of identifying metabolic or systemic diseases that can explain the presenting neurologic signs. With the exception
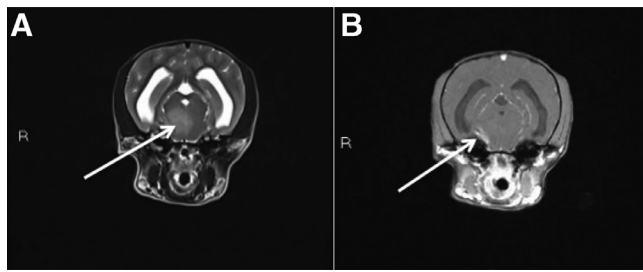
Fig. 1. T2W (A) and T1W postcontrast (B) images a the level of the midbrain. There is a patchy T2W hyperintensity within neural parenchyma (arrows), predominantly on the right side, with very a very mild area of contrast enhancement on the right lateral aspect of the midbrain. This patient was diagnosed with leukoencephalomalacia on histopathology.

of SRMA, immune-mediated neurologic diseases are rarely reflected on routine bloodwork.[22]

Imaging

Radiography is not diagnostic for inflammatory CNS diseases, but spinal radiographs may be considered to screen for fracture/luxation, discospondylitis, osseous neoplasia, or signs suggestive of IVDD in patients with myelopathic signs. At the authors' institution, thoracic and abdominal imaging is often recommended to screen for metastatic disease, particularly in older patients.

Ultimately, advanced, three-dimensional imaging is recommended for evaluation of the CNS. MRI is the gold standard for diagnosing MUE antemortem. While computed tomography (CT) may have some utility at identifying lesions, particularly when the lesions are contrast enhancing, the lack of soft tissue detail and the difficulty evaluating the caudal fossa due to beam hardening artifact, makes differentiating inflammatory lesions from other pathology even more challenging.[2] However, CT can be considered in situations where MRI is not available or desired. CT findings in 3 Yorkshire Terriers with histopathologically confirmed NLE have been described and include areas of multifocal decreased opacity without contrast enhancement throughout the cerebrum.[23]

The MRI appearance of GME is quite variable and has been described extensively in the literature. The following descriptions have been reported for dogs with histologically confirmed GME: hyperintensity on T2W and FLAIR images, variable intensity on T1W precontrast images (hypo, iso, or mixed intensity), and variable contrast enhancement (none, moderate, heavy, and ring enhancement). Lesions are commonly described as infiltrative with irregular margins. Additionally, lesions can be associated with mass effect and obstructive hydrocephalus. One dog in this study had a normal MRI.[24]
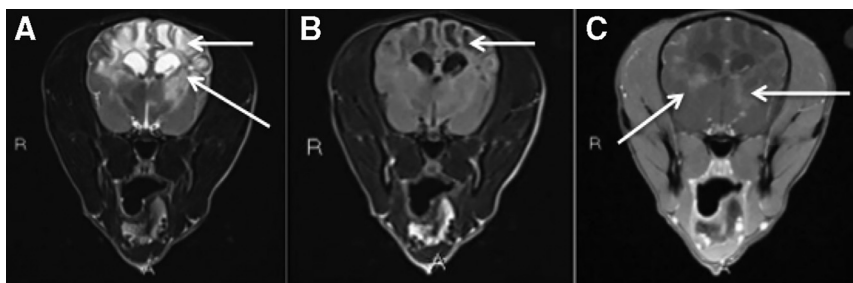
NME and NLE are histopathologically characterized based on the types of tissue that they tend to affect, and these changes can sometimes be appreciated on MRI. For example, characteristic MRI lesions in NME include asymmetric multifocal lesions affecting the gray matter and white matter with loss of the demarcation between the two. These lesions occur most commonly in the prosencephalon and have variable degree and characterization of contrast enhancement. In one study, Pugs with NME were more likely to have a midline shift on MRI than Chihuahuas with NME.[25] In NLE, reported characteristics include asymmetrical multifocal lesions within the subcortical white matter of the prosencephalon with variable contrast enhancement, but meningeal enhancement is uncommon (Figs 1 and 2). In either disorder, there can be areas of T1W hypointensity, consistent with cystic or necrotic areas.[2,26] It is also of note that most reported imaging findings in regard to NLE are in Yorkshire Terriers, the breed in which this version of encephalitis was first described. However, NLE has also been reported in French Bulldogs, which seem to have less severe lesions than Yorkshire terriers.[25]

Regardless of the etiology, contrast enhancement is variable in inflammatory diseases and its presence may not provide additional information about the character of the lesion. Contrast enhancement occurs due to various pathologic mechanisms, such as increased blood supply to a lesion and/or break down of the blood brain barrier. One study compared the MRI findings with the histopathologic changes observed in 55 cases with various CNS diseases including neoplasia, inflammatory, and ischemic disease. This study found vascular proliferation, dilation, and leakage in areas both with and without enhancement and that some necrotic areas were homogeneously contrast enhancing on MRI. Other areas that exhibited ring enhancement on MRI were not correlated to areas of central cavitation and necrosis, as expected. These findings are important, because it is tempting to interpret areas suggestive of necrosis, such as ring enhancing areas, with concern for the more aggressive forms of encephalitis, which may not be the case.[27] A case series involving 2 Yorkshire terriers with NLE found that areas with more contrast enhancement correlated with an increased amount of lymphohistiocytic inflammation. These areas tended to be isointense on T1. Hypointense areas on T1 tended to have minimal or no contrast enhancement.[27] Contrast enhancement is not likely to provide prognostic information based on these reports.

Finally, it has been reported in one study that 6 of 25 (24%) dogs with inflammatory CSF had a normal MRI. Therefore, CSF analysis is warranted even in cases that are suspected to have inflammatory disease but have normal MRIs.[28]

It can be challenging to differentiate inflammatory diseases from other CNS diseases, such as neoplasia and ischemic disease. When compared with vascular and neoplastic diseases, meningeal enhancement, irregular lesion shape, and multifocal location were significantly more likely to be seen in inflammatory disease. Defined lesion

Fig. 2. T2W (A), T2 FLAIR (B), and T1 postcontrast (C) MR images at the level of the thalamus in a 4-year-old FS Yorkshire Terrier with suspected necrotizing leukoencephalitis. There is significant T2W hyperintensity within the cerebrocortical white matter and extending into the thalamus (arrows). On FLAIR images, this area appears iso- to hypointense (arrow). This is concerning for the presence of free fluid in the place of the cortical tissue, rather than infiltration within the cortical tissue. On T1W images, these areas are also hypo- to isointense, with diffuse, patchy, mild contrast enhancement (arrows). This patient was euthanized due to the progression of signs despite multiple immunosuppressive medications, but necropsy was not performed.

margins, extra-axial origin, and FLAIR mixed intensity were found to be independent predictors of neoplasia compared with vascular and inflammatory diseases combined. Supratentorial location alone and the presence of only 1 lesion were significantly less likely to be associated with inflammatory disease.[6]

Short tau inversion recovery (STIR) hyperintensity in the paraspinal musculature, particularly the longus colli, has been reported in 20 dogs with cervical inflammatory myelitis. This study showed that STIR hyperintensities in the cervical epaxial musculature had a sensitivity and specificity of 78% and 92%, respectively, for predicting inflammatory CSF.[29]

CSF Analysis

CSF analysis is used concurrently with MRI to help identify inflammatory diseases. When evaluating the CSF, the number, types, and differential count of white blood cells is recorded, as well as the red blood cell count and the protein concentration. Conventionally, CSF is considered abnormal if the white blood cell count is >5 cells/mm^3 and if the protein concentration is >25 mg/dL (cisternal), and >40 mg/dL (lumbar).[30]

The CSF white blood cell count can have variable elevations or can be normal in patients with any variety of the encephalidities, with or without concurrent protein elevations. The term for elevated CSF protein in the face of a normal cell count is albuminocytologic dissociation, and is a nonspecific finding seen in a variety of degenerative, compressive, neoplastic, and inflammatory CNS diseases.[30] In most MUE cases, the predominant cell types are lymphocytes, monocytes, or both. Less commonly, a neutrophilic or eosinophilic pleocytosis is seen.[3] A predominance of these cell types should raise suspicion for infectious etiologies, which are discussed later. A neutrophilic pleocytosis should be interpreted cautiously in the event of blood contamination of the CSF sample.[30]

Infectious Disease Testing

Infectious disease testing should be considered for all patients presenting with neurologic disease, regardless of whether a neurodiagnostic with MRI and CSF is performed. While infectious causes of meningitis/encephalitis are less common in dogs than other species, therapy for immune-mediated disease requires immunosuppression, which can be fatal in the case of an infectious etiology. Several infectious agents can affect the CNS of dogs. Protozoal diseases include *Toxoplasma gondii* and *Neospora caninum*. Viral diseases include rabies and canine distemper virus. Tick borne diseases include *Ehrlichia canis* and *Anaplasma phagocytophilum*. Fungal diseases should also be considered, depending on the individual organisms endemic to the patient's home state or locations of recent travel (i.e., blastomycosis in the southeast and Mississippi and Ohio river valleys, cryptococcus, and coccidiomycosis in the southwestern United States).[30]

Histopathology

Given the variable appearance on MRI and wide range of CSF findings, there is no definitive antemortem diagnostic, apart from biopsy, that can classify inflammatory disorders into various subtypes. Histopathology is ultimately required for a definitive diagnosis. Histopathologically, GME consists of a mixed lymphoid population of inflammatory cells that prefer the perivascular spaces of the white matter (Fig 4). NME and NLE are distinguished histologically by the areas they affect. NME affects both the gray matter and white matter, and often the areas of demarcation between them are obscured, which can be appreciated on both histopathology and MRI. NLE, on the other hand, is characterized by its preference for white matter, as its name suggests. NLE lesions can also involve the brainstem (Fig 3).[2]

One study evaluated the safety and efficacy of freehand, minimally invasive biopsy of forebrain inflammatory lesions using MRI for measurements and surgical planning. Seventeen dogs had biopsies performed. There were lesions observed in samples from all 17 patients, and the biopsy was sufficient to diagnosis "encephalitis" in 16 of 17 cases. A total of 14 of 17 (82%) cases were able to have a specific histologic subtype confirmed (6 GME, 2 NME, 5 NLE, and 1 CDV). One dog developed seizures after the biopsy and died 2 days later due to aspiration. Otherwise, there were no deaths associated with the biopsy. Five of 17 dogs were neurologically worse after the biopsy
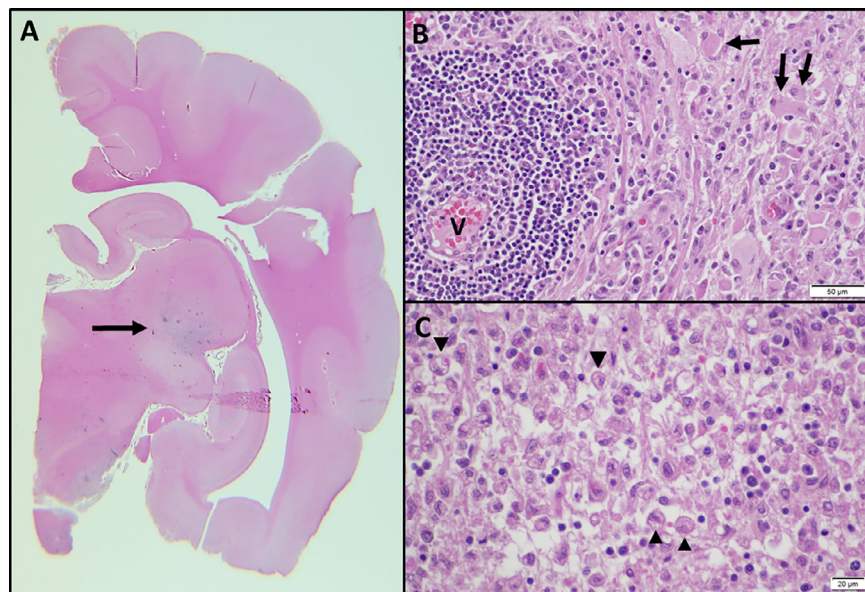

Fig. 3. Representative histomicrographs of the dog in Fig. 1 with necrotizing leukoencephalomalacia (NLE). (A) The most prominent lesions are located within the periventricular white matter at the level of the hippocampus and thalamus. Hematoxylin and eosin. Subgross. (B) Prominent perivascular cuffs (V) comprise predominantly lymphocytes with fewer plasma cells and macrophages. The adjacent neuropil is markedly hypercellular attributed to infiltration by mononuclear cells and astrocytosis (gemistocytic astrocytes, arrows). H&E. 20× magnification. (C) Necrotizing regions are characterized by neuropil rarefaction, dissolution, and replacement by foamy macrophages (gitter cells, arrowheads) and fewer mononuclear inflammatory cells. H&E. 40× magnification.
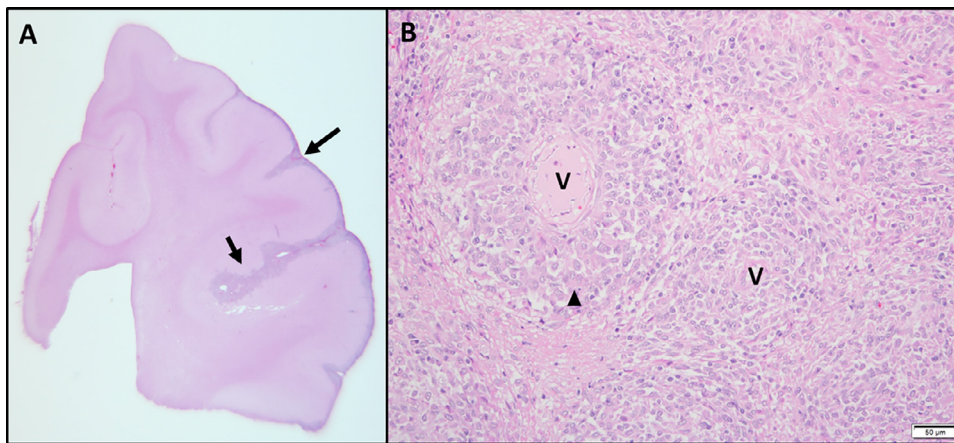
Fig. 4. Representative histomicrographs of a dog with granulomatous meningoencephalitis (GME). (A) Inflammatory lesions are focused within and expanding the leptomeninges of the cerebral cortex (arrow). Hematoxylin and eosin. Subgross. (B) The inflammation is prominent angiocentric (V) comprising predominantly macrophages with very few lymphocytes, plasma cells, and rare multinucleated giant cells (arrowhead). H&E. 20× magnification.

(29% morbidity), 1 was improved, and 11 were the same. Twelve dogs had an MRI performed after the biopsy, and mild, clinically insignificant changes were seen in 6 including epidural/subdural hematoma (1), pneumocephalus in lateral ventricles (2), and the epidural/subdural space (1), and gas in biopsy trajectory (3). It is important to note that all of these cases involved forebrain lesions, and biopsy of cases without parenchymal changes or cases with only brainstem/cerebellum lesions would likely be impractical.[31]

Other CNS Inflammatory Diseases

Steroid Responsive Meningitis Arteritis

While considered to be an autoimmune inflammatory CNS disease, SRMA has several unique characteristics that are worthy of mention. Unlike the other diseases discussed thus far, SRMA is reported to occur more commonly in large breed dogs, is accompanied by systemic signs (fever and leukocytosis), and generally responds more favorably to steroid therapy with a higher chance of achieving remission. Hence, its recognition in clinical practice based on characteristic signalment, presentation, and results of minimum database screening may justify treatment without referral.

SRMA was initially described in beagles, and was known by the colloquial term "Beagle Pain Syndrome." It has since been recognized in a number of breeds, with a predisposition in certain breeds including Bernese Mountain dogs, Boxers, and beagles. It occurs more commonly in younger dogs.[11,32,33] A familial predisposition has also been described in Nova Scotia Duck Tolling Retrievers.[34]

Clinical signs of SRMA include fever, cervical hyperesthesia, lethargy, and sometimes neurologic deficits, such as ataxia, tetraparesis, and proprioceptive deficits.[11]

Preliminary diagnostics should include a complete CBC, serum chemistry, and in some cases cervical radiographs.[33] On CBC, leukocytosis (inflammatory leukogram ± left shift) is common. Hypoalbuminemia may be seen on CBC, likely due to its role as a negative acute phase protein. Infectious disease testing should be considered as described above.[11,32,35] Cervical radiographs would be expected to be unremarkable in SRMA, but are often warranted to rule out other diseases that cause neck pain, such as discospondylitis and vertebral fracture/luxation.

It is important to note that SRMA is truly a systemic disease. As a result of the arteritis, other body systems may exhibit evidence of inflammation. One retrospective study evaluated the prevalence of dogs with concurrent immune-mediated polyarthritis and SRMA. In 11 patients diagnosed with idiopathic immune-mediated polyarthritis, 5 had a CSF analysis performed due to concurrent spinal pain had inflammatory CSF from the cisterna magna. All of these patients were young, male dogs (4 dogs were ≤ 1 year and 1 dog was 3 years).[36]

Several biomarkers have been evaluated in the diagnosis and monitoring of SRMA. C-reactive protein (CRP), serum amyloid A, alpha-1 acid glycoprotein and haptoglobin have been reported as potential serum biomarkers of SRMA. The same study found CSF biomarkers to be less reliable. Additionally, CRP and serum amyloid A were shown to be valuable markers of relapse.[35] Another study evaluated the CSF D-dimer, blood D-dimer, CSF CRP, and blood CRP concentrations at the time of diagnosis and after 6 weeks of treatment in 8 dogs. In this study, the CSF D-dimer concentrations were unreadable at 6 weeks and the other parameters were significantly lower than at diagnosis.[37] IgA has been considered a promising biomarker in the identification and monitoring of SRMA for many years. In 2012, this was re-evaluated and confirmed in a large study of 525 paired canine CSF and serum samples of patients with various CNS and systemic diseases. Significant differences in CSF IgA concentrations were detected when compared with all other disease groups aside from other CNS inflammatory diseases. However, serum IgA concentrations in the SRMA patients were significantly higher than all other categories. The CSF IgA values remained elevated throughout the course of disease (diagnosis, treatment, and relapse), but were highest at diagnosis and relapse. The sensitivity and specificity of diagnosing SRMA by measuring IgA concentration in paired CSF and serum samples are 91% and 78%, respectively.[33]

Treatment of SRMA involves immunosuppressive doses of glucocorticoids followed by a taper to the lowest effective dose. In one study of 20 dogs treated with glucocorticoids alone, 12 dogs were tapered off of their medication without relapse (60% remission rate). In a second study of 20 dogs, only 4 suffered a relapse during their taper (75% remission rate).[11,32] Mycophenolate has been reported as a possible adjunctive therapy in patients that experience relapse that is refractory to increased prednisone.[38]

Eosinophilic Meningitis/Meningoencephalitis

Eosinophils rarely occur in the CNS; however, they can be increased (eosinophilic pleocytosis) in certain disease states. Reported criterion for diagnosis of eosinophilic meningitis in people is a pleocytosis with >10% eosinophils in the CSF. Reported causes of CNS eosinophilia in veterinary species besides dogs are primarily parasitic in nature, including aberrant *Dirofilaria immitis*, *Cuterebra*, *Toxolasma gondii* infection, etc. It has also been reported in acute lead

toxicity in calves and salt toxicity in swine. However, eosinophilia of any cause is uncommon. Eosinophilic CNS disorders have also been uncommonly reported to be associated with various infectious in dogs (*Cryptococcus*, *Neospora caninum*, and *Prototheca*). It has also been reported as an uncommon "idiopathic" disorder."[39] Idiopathic EME has been reported more commonly in large breed dogs, which differs from many other variations of the immune-mediated encephalidities.[10]

In one report, only 25% (4/16) dogs with EME died. Treatment in this study ranged from no treatment (2 dogs) to various doses of prednisone (.33-1 mg/kg q12).[39] In another study of 11 dogs, similar results were found: 10 of 11 survived to discharge and 75% of dogs with available follow-up were doing well.[10]

Greyhound Nonsuppurative Meningoencephalitis

Greyhound nonsuppurative meningoencephalitis occurs most commonly in young greyhounds (<1 year of age), and may affect multiple dogs in a litter. Similar to other inflammatory diseases, the clinical course is typically progressive and reflective of the neurolocalization. Presenting signs and neurologic exam findings have been reported to include behavior change, anorexia, lethargy, circling, and proprioceptive deficits. MRI findings reported in a case series of 4 greyhounds with MRI and histopathologic confirmation revealed heterogenous, multifocal T2W hyperintensity without significant contrast enhancement aside from mild meningeal enhancement around the olfactory bulb in 1 case. The key findings which differentiate the greyhound version from other forms of MUE are the classic locations of both MRI and histopathologic changes, namely, a preference for cerebrocortical GM (especially in the frontal and olfactory lobes) and involvement of the caudate nuclei. Histopathologically, gliosis, gemistocytosis, and perivascular cuffing have been described in these locations. In these 4 cases, cerebral white matter was involved, as well as cerebellar white matter in 3 dogs. Lymphoplasmacytic meningeal infiltration was also described. Antemortem CSF analysis was performed in 3 of 4 the dogs, and a mild mononuclear/lymphocytic pleocytosis was found in all dogs with protein concentrations ranging from 22.8 to 30 mg/dL (ref <25 mg/dL).[40]

Treatment Recommendations

There is no consensus at this time on the best treatment options for MUE. Immunosuppressive therapy, typically with glucocorticoids, is the mainstay of treatment, but it is well known that higher dose of glucocorticoids long term can be associated with severe adverse effects. Additionally, some dogs do not respond to glucocorticoids alone. Therefore, multimodal immunosuppressive therapy is often pursued. The ultimate goals of therapy are to achieve and maintain clinical remission at the lowest doses of medications possible.

The following treatment options have been reported either alone or in combination with glucocorticoids. While some of these studies state survival rates associated with certain treatment protocols, it is impossible to compare treatment options across studies. Some studies require a histopathologic diagnosis, which inherently selects for cases that do poorly. Additionally, there are different treatment protocols, dosages, monitoring standards, etc. at each institution. In 2010, Granger et al performed a thorough review of the literature with the intent of developing criteria to be used across all institutions to enroll suitable candidates for a prospective study on treatment options. We look forward to future prognostic information that might be derived in such a study.[3] In the meantime, the available treatment options are listed in Table 2, along with reported doses and adverse events.

Radiation therapy is a reported treatment option for MUE, but reports are limited. In one retrospective of 42 dogs with histopathologically confirmed GME, the reported survival time in dogs that received radiation therapy were significantly longer than dogs that did not.[1]

Prognosis

Many studies have addressed prognostic factors, with various findings.

Prognostic Factors Associated With Clinical Presentation

In one study of 42 dogs with histologically confirmed GME, the median survival time (MST) for dogs with focal signs was 114 days (3-1215) and the MST of dogs with multifocal disease was 8 days (range 1-274).[1] The MST for dogs with presumed spinal only MUE was 669 days, with 48% of cases ultimately dying or being euthanized due to progression of their disease.[21] In one study, older age at diagnosis was associated with shorter survival time.[41]

Prognostic Factors Associated With Imaging Findings

MRI characteristics do not seem to provide much insight into expected survival time or response to therapy. In one retrospective imaging case series in Pug dogs with NME, there was not a significant correlation between the lesion burden seen on MRI and survival time.[42] Another study evaluating the association between midline shift on MRI and survival time also found that the degree and presence of a midline shift did not correlate with a shorter survival time.[41]

Prognostic Factors Associated With CSF Analysis

Multiple studies have found that the CSF total nucleated cell count does not correlate with prognosis[1,43,44]; however, one study did show that a higher total nucleated cell count (TNCC) was associated with a worse prognosis.[41]

Prognostic Factors Associated With Response to Therapy

In one study, dogs with both GME and NE that survived the initial 3-4 months of treatment were likely to survive at least 9 months.[5] In another study of 2 groups of 10 dogs each, the responses to different immunosuppressive drug combinations (prednisone + cytarabine vs. prednisone + vincristine + cyclophosphamide) were evaluated. In this study, only 1 dog that survived the first month failed to survive at least 12 months.[45] Another study evaluating the success of treatment with prednisone and azathioprine in 40 dogs with MUE found that there was a significant increase in MST for dogs that had a complete vs. partial response to therapy as well as for dogs that did not relapse compared with those that did.[46]

In a retrospective study evaluating the likelihood of patients with MUE surviving to 7 days, the following factors were found to be associated with poor prognosis: decreased mentation at presentation, seizures, and increased percentage of neutrophils in CSF. Patients with any one of these factors had an increased risk of death within 1 week. In that study, 30 of 116 dogs (26%) died within the first 7 days of diagnosis, despite initiation of appropriate immunosuppressive therapy.[47]

Finally, in a retrospective study including 60 dogs with histopathologically confirmed NME, the MST was 93 days with dogs that received treatment having an MST of 101 days compared with 7.4 days without treatment. The only treatment that was found to have a positive association with survival was treatment with an anticonvulsant. As with all studies that require histopathologic diagnosis as inclusion criteria, these results must be interpreted cautiously, as this may inadvertently select for more severe cases.[4]

Table 2
Treatments for Immune-Mediated Diseases.

Drug	Mechanism of action	Dose	Adverse effects	Citation
Azathioprine	Purine analog that inhibits DNA synthesis	2 mg/kg PO q24 × 2 wk, then q48h	Bone marrow suppression (all cell lines), GI upset, poor hair growth, pancreatitis, liver toxicity	[46]
Cyclosporine	Block transcription of cytokines in activated T-cells	10 mg/kg PO SID × 6 wk, then 5 mg/kg PO SID if improved	Vomiting and/or diarrhea (usually transient)	[49]
		3 mg/kg PO BID	1 dog with GI bleeding and pruritis, 3 dogs with transient vomiting/diarrhea	[50]
Cytarabine	Anti-metabolite drug (synthetic nucleoside analog), incorporates into DNA and prevents replication	One time dose with long-term prednisone therapy: 100 mg/m² as CRI over 24 h	Myelosuppression and GI upset (not specific to these studies)	[45]
			Temporary lethargy, dysphagia or limb tremors—infrequently reported; alopecia, dermatitis, hindlimb weakness	[43]
		50 mg/m² SQ q12 × 2 d, repeated every 3 wk for 4 mo, then duration between treatments extended	Infiltrative lung disease	[51]
Leflunomide	Inhibits B and T cell proliferation by inhibiting pyrimidine synthesis	1.5-4 mg/kg PO q24	Decreased appetite, lethargy, mild anemia, blood in vomit and/or stool	[2,52]
			8/92 dogs experienced adverse events possibly attributable to leflunomide: diarrhea, lethargy, unexplained hemorrhage. Clinically insignificant thrombocytopenia in 2 dogs (resolved with dose decrease) and mild liver enzyme elevations 1 dog (resolved with dose decrease)	[48]none of the dogs in this retrospective were being treated for CNS disease
Lomustine	Alkylating agent, suppress B, and T cell proliferation	44-88 mg/m2 PO q6 weeks	Bone marrow suppression (leukopenia-7 d after admin, anemia less common, thrombocytopenia is cumulative); liver toxicity; GI toxicity	[5]
Mycophenolate	Inhibit inosine 5′-monophos, phate dehydrogenase, which prevents B and T cell proliferation by inhibiting purine synthesis	9.2-10.6 mg/kg PO or IV q12	2/25 cases—1 vomiting and 1 with decreased appetite	[53]
Procarbazine	Cell cycle nonspecific methylation of DNA, also produces toxic free radicals	25-50 mg/m2 PO q24	Myelosuppression, hemorrhagic enteritis	[44]
Vincristine with cyclophosphamide and prednisone	Vincristine: Anti-microtubule agent, causing metaphase arrest in the M phase of the cell cycle	Vincristine: .5 mg/m2 IV q7d × 8 wk, then q14d	Vincristine: GI toxicity, bone marrow suppression,± peripheral neurotoxicity	[45]The authors concluded that given the high incidence of adverse effects in the 10 dogs receiving the COP protocol, this protocol is not acceptable
	Cyclophos-phamide: alkylating agent[54]	Cyclophos-phamide: 50 mg/m2 PO q48h × 8 wk, then q48h every other week; Prednisolone 40 mg/m2 PO q24 × 7 d, then 20 mg/m2 q48 × 7 wk, then q48 every other week.	Cyclophos-phamide: Hemorrhagic cystitis, bone marrow suppression[54]	

Conclusion

The meningoencephalidities can prove challenging to diagnose and manage in both general and specialty practice alike. Referral for MRI, CSF analysis, and brain biopsy (when indicated) is ideal, but not always practical. When diagnosis of MUE is suspected and referral is declined, diagnostic recommendations include a systemic workup to rule out metabolic or metastatic disease and infectious disease testing. The patient's signalment and neurolocalization are instrumental in prioritizing the differential list. In young to middle-aged small and toy breed dogs (especially Pug dogs, Maltese, and Yorkshire Terriers) with progressive neurologic signs who have an unremarkable systemic workup and negative infectious disease tests, MUE should be strongly considered. Treatment with steroids (1-2 mg/kg per day) should be initiated once a reasonable attempt has been made to exclude infectious diseases. Response to treatment is variable, and prognosis is guarded for most forms of MUE. There is great need for additional prospective studies evaluating response to different immunosuppressive treatment options as well as improved techniques for determining prognostic criteria antemortem.

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