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Necrotizing Meningoencephalitis in Atypical Dog Breeds: A Case Series and Literature Review

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Background: Canine necrotizing meningoencephalitis (NME) is a fatal, noninfectious inflammatory disease of unknown etiology. NME has been reported only in a small number of dog breeds, which has led to the presumption that it is a breed-restricted disorder.

Hypothesis/Objectives: Our objective was to describe histopathologically confirmed NME in dog breeds in which the condition has not been reported previously and to provide preliminary evidence that NME affects a wider spectrum of dog breeds than previously reported.

Animals: Four dogs with NME.

Methods: Archives from 3 institutions and from 1 author's (BS) collection were reviewed to identify histopathologically confirmed cases of NME in breeds in which the disease has not been reported previously. Age, sex, breed, survival from onset of clinical signs, and histopathologic findings were evaluated.

Results: Necrotizing meningoencephalitis was identified in 4 small dog breeds (Papillon, Shih Tzu, Coton de Tulear, and Brussels Griffon). Median age at clinical evaluation was 2.5 years. Histopathologic abnormalities included 2 or more of the following: lymphoplasmacytic or histiocytic meningoencephalitis or encephalitis, moderate-to-severe cerebrocortical necrosis, variable involvement of other anatomic locations within the brain (cerebellum, brainstem), and absence of detectable infectious agents.

Conclusions and Clinical Importance: Until now, NME has only been described in 5 small dog breeds. We document an additional 4 small breeds previously not shown to develop NME. Our cases further illustrate that NME is not a breed-restricted disorder and should be considered in the differential diagnosis for dogs with signalment and clinical signs consistent with inflammatory brain disease.

Key words: Autoimmune; Dog; Inflammatory; Intracranial; Seizures.

Necrotizing meningoencephalitis (NME) is typically described as a rapidly progressive, fatal inflammatory brain disorder affecting young Pugs and a limited group of other toy breed dogs for which the complete etiopathogenesis has yet to be elucidated.[1] Although we have postulated that NME has a multifactorial etiopathogenesis,[2] rigorous molecular investigations have yet to identify a consistent infectious agent that contributes to disease development. Recent genome-wide association studies have demonstrated risk loci and certain canine leukocyte antigen alleles that are associated with the development of NME, specifically in Pug dogs.[2,3] These data support an immune-mediated or autoimmune component to the disease pathogenesis in the Pug and likely other toy breeds.

Abbreviations:

CDV	canine distemper virus
CNS	central nervous system
CSF	cerebrospinal fluid
MRI	magnetic resonance imaging
NLE	necrotizing leukoencephalitis
NME	necrotizing meningoencephalitis

Necrotizing meningoencephalitis has been identified worldwide in small, purebred dogs including the Pug,[1,3–11] Yorkshire Terrier,[1,12] Maltese,[13] Chihuahua,[14] and Pekingese.[15] Necrotizing encephalitis also has been identified in a West Highland White Terrier, but no meningeal component was identified, which may indicate a slightly different or alternate disease process.[16] As in the Pug, genetic and environmental factors have been speculated to play a role in disease development for other small breed dogs.[1–3,7] Characteristic histopathologic features of NME include non-suppurative inflammation of the meninges and brain with extension into the subcortical white matter (corona radiata), deep cortical white matter (internal capsule, thalamus), and mild-to-severe cerebrocortical necrosis with or without cavitation.[1,5] The purpose of this retrospective, multi-institutional study was to identify dogs with histopathologically confirmed NME that have not been previously reported as affected breeds.

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We hypothesized that NME is not a breed-restricted disorder.

Materials and Methods

Histology databases from 3 institutions (Cornell University, Texas A&M University, University of California-Davis) and the personal files of 1 of the authors (BS), reflecting cases referred to Cornell University, were reviewed to identify dogs with NME. Cases were eligible for inclusion in this study if NME was initially confirmed by histopathology by participating investigators, microscopic slides of brain were available for review, and the affected dog was a breed not previously reported with NME based on a PubMed search (accessed March 30, 2011). All identified cases had microscopic slides reviewed independently by 3 pathologists (BP, BS, SS) to confirm the diagnosis of NME. Dogs were excluded if central nervous system (CNS) infection was demonstrated or suspected based on histology or if further review of available records suggested that infection was likely based on microbiological, molecular, or serological testing.

For those cases included in this report, age, sex, breed, survival from onset of clinical signs (in days), and features of cerebrospinal fluid (CSF) examination were recorded if available. Necropsy data, histopathology reports, and available microscopic slides were examined to determine lesion topography and describe salient histopathologic features.

Four dogs that were evaluated by referral centers between 1993 and 2010 were included in this report. CSF was not obtained from 2 dogs, and limited clinical information was available in some of the cases.

Clinical Case Reports

Dog 1

Clinical Features. A 4-year-old intact male Papillon was evaluated for a 24-hour history of cluster seizure activity that was followed by status epilepticus of 4 hours' duration. The dog had a 5-day history of lethargy and reluctance to walk. The dog had been otherwise healthy, was currently on vaccinations for rabies virus, canine distemper virus (CDV), and canine parvovirus, and has received regular heartworm prevention. Complete blood count and serum biochemical profile results were normal. Magnetic resonance imaging was performed and identified a mass effect in the right cerebral hemisphere causing compression of the right lateral ventricle and leftward displacement of the falx cerebri. The vermis of the cerebellum was herniated through the foramen magnum. There was an ill-defined lesion of the right frontal, temporal, parietal, and pyriform lobes that had high signal intensity on T2-weighted (T2W) images (Fig 1A) and fluid-attenuated inversion recovery (T2 FLAIR) images and was iso- or hypointense to normal gray matter on T1-weighted (T1W) images (Fig 1B). The lesion partially followed the white matter of the internal capsule and corona radiata, but it also included portions of gray matter in each hemisphere. No evidence of hemorrhage was present on gradient echo – T2* images. After IV administration of gadopentate dimeglumine, there was mild, heterogeneous enhancement of brain parenchyma throughout the lesion as well as in the adjacent leptomeninges (Fig 1C). The dog died 24 hours later and necropsy was performed.

Gross and Histopathologic Examination. No extracranial abnormalities were noted on gross examination. The intact brain had a poorly demarcated mass lesion in the right parietal lobe, and cerebellar herniation through the foramen magnum was confirmed. On gross transverse sections, the right parietal lobe was uniformly enlarged with loss of distinction between gray and white matter (Fig 2A). Mild hydrocephalus affecting both lateral ventricles also was noted. Microscopically, blood vessels in the meninges, gray matter, and white matter were cuffed by a large number of lymphocytes and plasma cells, with fewer macrophage and occasional neutrophils (Fig 2B). Neuronal necrosis and depletion, marked gliosis, and areas of mild cavitation with gitter cell accumulation also were present throughout the cerebrum (Fig 2C). No infectious agents or viral inclusions were identified. The hippocampus and thalamus had moderate neuronal necrosis

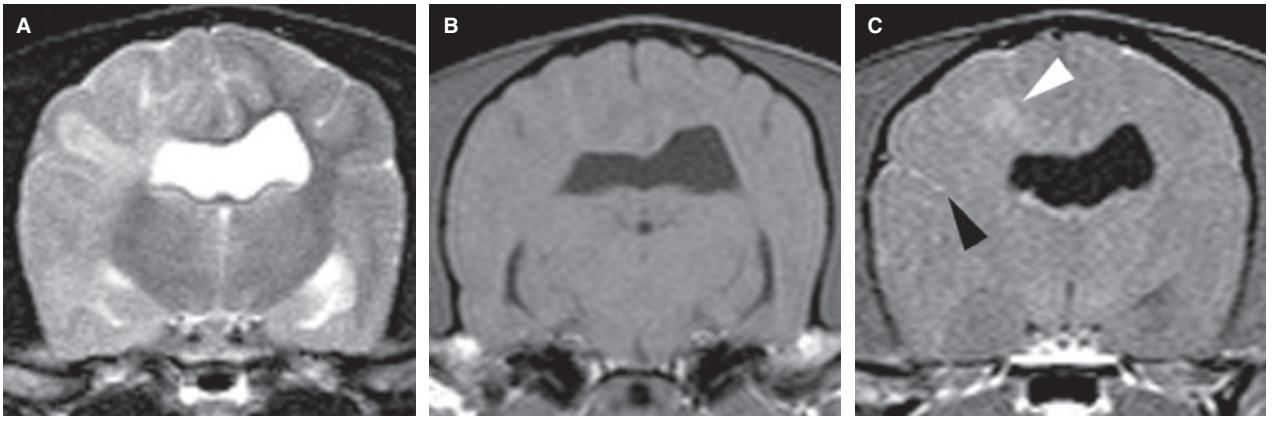

Fig 1. (A–C) Magnetic resonance images of the brain of a 4-year-old Papillon dog with cluster seizures. The patient's right is to the left of each image. Transverse images at the level of the thalamus include T2W **(A)**, precontrast T1W **(B)**, and postcontrast T1W **(C)** images. There is a mass effect in the right cerebral hemisphere compressing the right lateral ventricle. The ill-defined lesion in the right cerebral hemisphere, which is hyperintense on T2W **(A)** and iso- or hypointense on precontrast T1W **(B)**. After contrast administration **(C)**, there is mild contrast enhancement of the cerebral parenchyma (white arrowhead) and leptomeninges (black arrowhead).

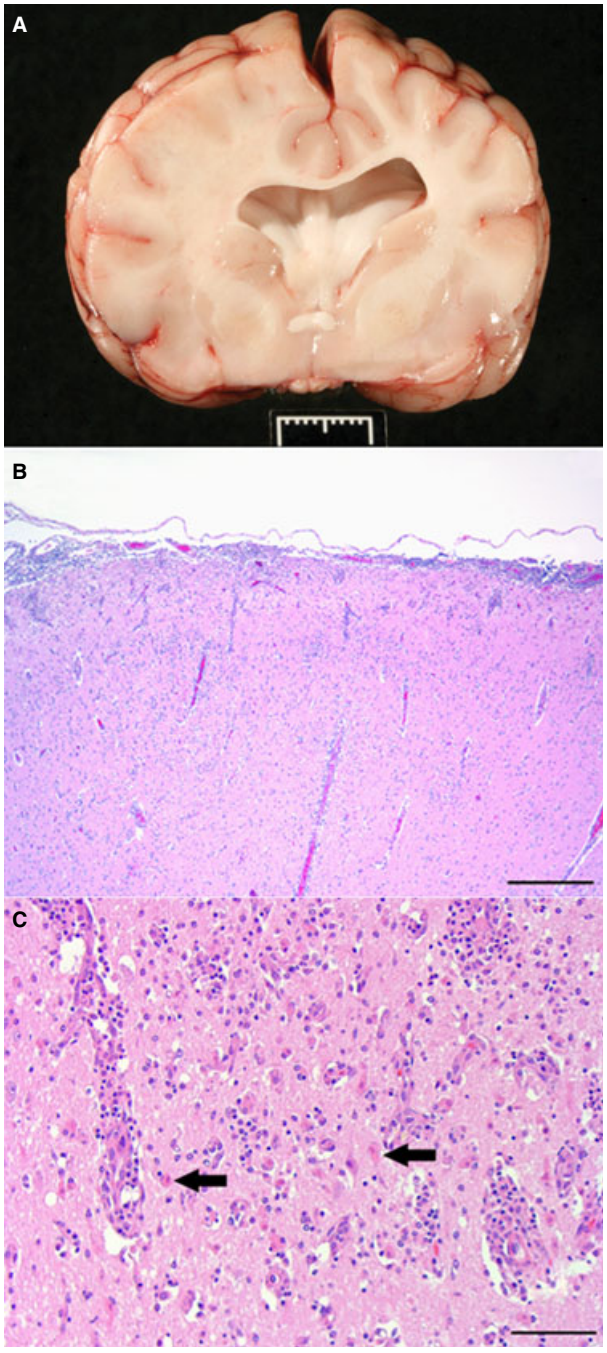

Fig 2. **(A–C)** Gross appearance of the brain of Dog 1 **(A)**. The right parietal lobe is swollen with expansion of the white matter and loss of distinction between the gray matter and white matter. Mild hydrocephalus of the lateral ventricles is evident. Marker = 1 cm. Histologic section of the cerebral cortex from Dog 1 **(B)**. The meninges contain an inflammatory infiltrate composed predominantly of lymphocytes and plasma cells. Inflammatory cells also surround cortical blood vessels and extend into the cortical parenchyma. Bar = 400 μm. Higher magnification of a histologic section of the cerebral cortex from Dog 1 **(C)**. Blood vessels are cuffed by lymphocytes, plasma cells, and macrophages. The parenchyma has increased cellularity composed of a mixture of inflammatory cells and glial cells. Numerous necrotic neurons are evident (arrows). Bar = 80 μm.

and minimal inflammation. The cerebellum and brainstem were within normal limits.

Dog 2

Clinical Features. A 2-year-old castrated male Shih Tzu was examined for a 2-week history of progressive pelvic limb ataxia, hyporexia, vomiting, falling, abnormal mentation, and behavioral changes. Laboratory evaluation by the referring veterinarian was within normal limits. The dog deteriorated despite supportive care and was euthanized.

Gross and Histopathologic Examination. No intra- or extracranial abnormalities were noted on gross examination. On histopathologic examination, moderate-to-severe bilateral necrotizing and nonsuppurative meningoencephalitis with multifocal neuronal necrosis was noted in the cerebral cortex (occipital lobes), basal nuclei, and thalamus. Lymphoplasmacytic and histiocytic inflammation was present and was most severe in the leptomeninges and outer cerebral cortex. Mild multifocal areas of perivascular lymphocytic infiltration also were noted in the cerebellum. Overall, the cerebral lesions were bilateral but not symmetric and were most severe in the rostral forebrain. The caudal brainstem was not affected. Immunohistochemical testing of the brain for CDV antigen was negative.

Dog 3

Clinical Features. An adult (age unknown) castrated male Coton de Tulear was presented for multiple episodes of abnormal mentation, generalized tremors, and circling to the right during the preceding 9-month period. The dog had a 6-week history of progressive obtundation and a behavior change with aggression and seizures. Complete blood count, serum biochemical profile, thoracic radiographs, and abdominal ultrasound examination all were within normal limits. A cisternal CSF sample was analyzed and had a total nucleated cell count (TNCC) of 108 cells/μL (reference range, 0–5 cells/μL),[2] 1 RBC/μL, and a microprotein concentration of 41 mg/dL (reference range, <30 mg/dL).[2] The dog continued to deteriorate, was euthanized, and submitted for necropsy.

Gross and Histopathologic Examination. No gross lesions were detected on external examination, but on transverse sections, there were asymmetrically distributed areas in both left and right cerebral hemispheres with loss of anatomic distinction in both cortex and underlying white matter. The involved parenchyma had a tan discoloration and semisoft texture. Microscopically, there was a focal nonsuppurative meningoencephalitis confined to the cerebral hemispheres with complete sparing of the midbrain and cerebellum. There was a characteristic multifocal but segmental meningitis with an underlying intense nonsuppurative polioencephalitis and necrotizing leukoencephalitis (NLE). In the latter were large numbers of CD-18-immunoreactive macrophages and some perivascular

lymphocytic cuffing. An unusual finding was the bilateral involvement of the optic nerves with extension into the optic radiations.

Dog 4

Clinical Features. A 1.5-year-old intact female Brussels Griffon was evaluated for a 2-day history of lethargy and reluctance to walk. On MRI there was marked T2W hyperintensity involving the white matter of the left frontal lobe. There was marked left-sided mass effect and midline shift with compression of the left lateral ventricle and slight dilatation of the right ventricle (Fig 3). On post-contrast T1W images there were uniform meningeal contrast enhancement, but heterogenous enhancement of the parenchyma (Fig 3). A cisternal CSF sample was analyzed on the day of admission and had a TNCC of 122/μL (reference range 0–5/μL) and a CSF protein concentration of 804 mg/dL (reference range, <30 mg/dL). The nucleated cells were primarily small mature lymphocytes. The dog was treated with dexamethasone IV (0.2 mg/kg/day) for 5 days. When no clinical response was noted, CSF analysis was repeated and was observed to be more inflammatory than the previous sample (TNCC of 2,190/μL and protein concentration of 438 mg/dL). The predominant cell types were mature lymphocytes and macrophages. Seven days after presentation, the dog developed seizures and euthanasia was elected.

Gross and Histopathologic Examination. Gross lesions were found in the left frontal cortex consisting of thickened cortical gyri with some softening and yellow-to-white discoloration of the underlying cortex (Fig 4). Similar but more extensive bilateral necrotic areas were seen on transverse sections, largely confined to the frontal lobe. Mild-to-moderate asymmetric ventricular dilatation was noted affecting the lateral ventricles. Intense asymmetric nonsuppurative meningoencephalitis was confined to the cerebral hemispheres and decreased in severity caudally to end in the midbrain. The main features were an intense T and B cell (immunoreactive to CD3 and CD79a antibodies, respectively) lymphocytic segmental meningitis and multifocal polioencephalitis with massive leukoencephalitis with extensive necrosis and gitter cell and macrophage infiltration and prominent neovascularization (Figs 5 and 6).

Discussion

Necrotizing meningoencephalitis was first reported in California Pug dogs in the United States in 1989, and subsequently in 5 additional small dog breeds.[4] Accordingly, NME has been suggested to be a relatively breed-specific inflammatory brain disease affecting a select group of small, young purebred dogs.[1,5,8,13–16] In this case series, we demonstrated NME in 4 small dog breeds that have not been reported previously (Papillon, Shih Tzu, Coton de Tulear, and Brussels Griffon). There is mention of NME in a Shih Tzu in the discussion of 1 report, but necropsy findings were not described.[13]

In this case series, the ages of the dogs at the time of clinical evaluation ranged from 1.5 to 4 years with a median of 2.5 years of age. Our findings are consistent with the age ranges previously reported for other dog breeds with NME. The reported mean age at the onset of clinical signs of NME in Pugs is approximately 2.5 years.[8]

Seizure activity was observed in 3/4 dogs reported in this series. Seizure activity is the most commonly reported neurological sign in dogs with NME,[5,11] whereas brainstem signs (along with seizure activity) are more commonly described in dogs with NLE.[17–21] In 2 of 4 dogs, clinical signs reflecting a caudal brainstem component to a multifocal neuroanatomical localization (eg, ataxia and nausea) were observed. Infratentorial signs in these dogs resulted either from minor histopathologic NME lesions or from presumed caudal transtentorial herniation of prosencephalic structures. Interestingly, dog 2 also had evidence of inflammation without necrosis in the cerebellum, which has been described in 24/60 Pugs with NME.[8]

The 4 dogs, presented in this case series exhibited histopathologic lesions with topographic distributions consistent with NME as classically described in Pug

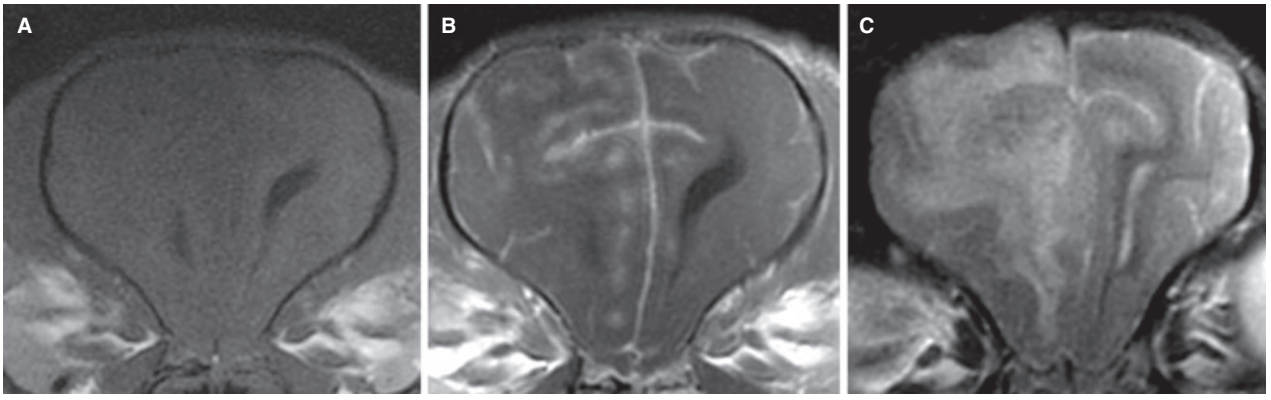

Fig 3. (A–C) MRI images from Dog 4. A. Precontrast T1-weighted **(A)**, postcontrast T1-weighted **(B)**, and T2-weighted **(C)** transverse images. Note the marked meningeal and heterogenous parenchymal contrast enhancement as well as marked mass effect. In image **C**, note the marked hyperintensity of the gray and white matter.

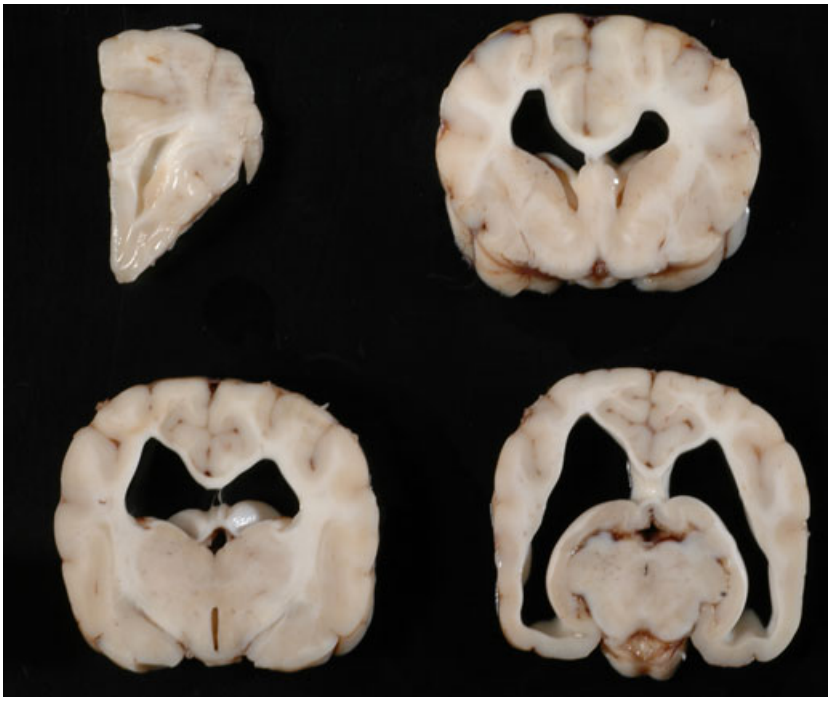

Fig 4. Transverse gross sections of brain from Dog 4. Note the severity of the lesions in the white and gray matter in the frontal lobe and decreasing lesions caudally in the cerebral hemispheres.

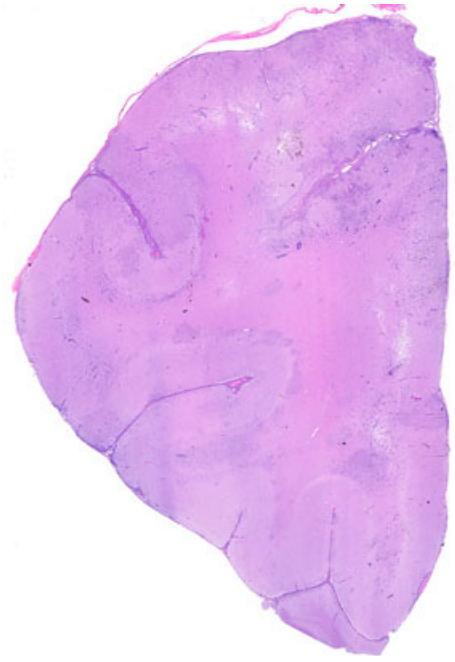

Fig 5. Transverse section through the frontal lobe from Dog 4 illustrating segmental but severe meningitis. Hematoxylin-eosin stain, 1× magnification.

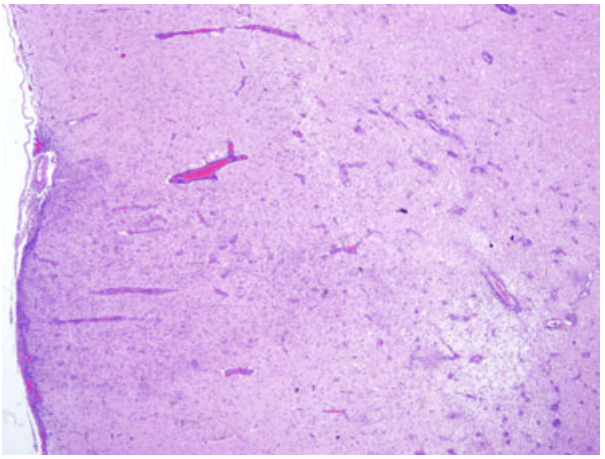

Fig 6. Micrograph of frontal lobe of Dog 4 with marked mononuclear meningitis and underlying polioencephalitis and necrotizing leukoencephalitis. Hematoxylin-eosin stain, 40× magnification.

and Maltese dogs.[4,13] Histopathologic findings, as reported previously, included nonsuppurative (lymphoplasmacytic and histiocytic) inflammation and bilateral, asymmetric cerebral necrosis.[1,9] Lesion topography included extensive leptomeningeal inflammation typically with extension into the neocortex and subcortical white matter, which leads to the loss of the normal distinction between gray and white matter borders in the cerebral hemispheres, extensive astrogliosis, and severe cortical necrosis with variable neuronal loss.[9] Recent reports have demonstrated substantial overlap in the variables by which NME and NLE are currently defined, namely CNS lesion distribution (neuropathology) and breed association.[1,12–14,16,20] The variable degree of necrosis and lesion topography between NME and NLE may simply reflect minor genotypic

differences within and among breeds.[1,14] For example, Pugs and Chihuahuas (which are prototypical "NME breeds"[4,14]) have been reported with histopathologic lesions more characteristic of NLE,[1] whereas NME has been reported in a Yorkshire Terrier, classically described as the classic "NLE breed."[1]

Although strong familial inheritance was reported recently in Pugs with NME, a simple Mendelian inheritance pattern could not be demonstrated.[3] In addition, genome-wide association studies have further supported a genetic basis for NME in Pugs. Although a causative mutation has not been identified, an association between mutations in a region of canine leukocyte antigen class II (which encodes for the antigen presentation complex) and the development of NME has been identified.[2] Whether mutations in the canine leukocyte antigen, other proteins involved in antigen recognition, or modifying genes are present in all breeds with NME is currently unknown. Of the breeds reported with NME, the only ones with any documented evidence of overlap in breed development are the Brussels Griffon and Pug, and possibly a loose relationship between the Shih Tzu and Pekingese.[22] The diagnostic role of genetic testing and any potential impact of the genetic profile on treatment are presently unknown.

Although the pattern of inflammation in NME is fairly distinctive, other diseases must be considered. There is substantial overlap in the patterns produced by CNS inflammatory diseases. Infectious diseases, especially viral infections, can produce lesions very similar to those that occur in NME.[21,22] Viral testing was not done in all of these cases, so infection by a known or novel virus cannot be completely excluded.

Most investigators still consider NME to be a relatively breed-specific inflammatory disorder. The purpose of this study was to describe a series of cases of atypical dog breeds with NME. NME should be included in the differential diagnosis of dogs with acute or chronic, progressive intracranial disease, especially those with seizures that have suspected inflammatory changes in the leptomeninges, cerebral cortex, and subcortical white matter of unknown cause.

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Conflict of Interest Declaration: Authors disclose no conflict of interest.

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