Acta Scientiae Veterinariae, 2023. 51(Suppl 1): 881.

CASE REPORT
Pub. 881

ISSN 1679-9216

Meningoencephalitis of Unknown Origin in Dogs

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ABSTRACT

***Background*:** Meningoencephalitis of unknown origin (MUO) is a critical cause of neurological disorders in dogs, mainly affecting small young individuals. Its symptomatology is varied and depends on the affected neuroanatomic region. The *ante mortem* diagnosis of this condition is uncertain, being achieved by discarding other conditions and often occurring definitively only by performing a necropsy. Thus, this study aims to report 2 cases of meningoencephalitis, one necrotizing and the other granulomatous in dogs.

***Cases*:** *Case 1*. A 3-year-old, Shih Tzu bitch with a body weight of 4 kg, showing proprioceptive ataxia, behavior of walking in circles, and evolving rapidly to non-ambulatory paresis, was treated. The neurological examination showed a posture of decerebrate stiffness and absence of withdrawal reflex and proprioception, suggesting brainstem injury. Laboratory tests showed mild neutrophilia and lymphopenia, while the rapid test for distemper was non-reactive. The cerebrospinal fluid (CSF) analysis showed lymphocytic pleocytosis, and the PCR tests of the CSF, blood, and urine for the detection of infectious diseases were negative, as well as the culture. With no improvement in clinical condition and exams showing a progressive degenerative condition unresponsive to available treatments, the tutor opted for euthanasia of the patient. The subsequently requested necropsy confirmed the diagnosis of granulomatous meningoencephalitis. *Case 2*. This case refers to a 1-year-and-5-month-old male Maltese breed weighing 4.8 kg. This animal presented walking in circles behavior and loss of vision for a week, with signs worsening rapidly. In the neurological evaluation, the patient presented sensitivity in the middle ear, difficulty opening the mouth, hearing deficit in the right ear, blindness in the right eye, a proprioceptive deficit in the right anterior limb, and head pressing. Laboratory tests showed nonregenerative anemia and mild lymphopenia. After 1 day of hospitalization, the patient showed worsening clinical condition, with obstruction, absence of facial and auricular sensitivity, and nasal stimulus. In addition, onset of generalized seizures was observed; therefore, CSF was analyzed, which did not present significant alterations except for detecting reactive lymphocytes. The bacteriological culture of CSF resulted in no bacterial growth. In addition, the same neurological PCR panel performed for the previous patient was negative. After 5 days of intensive care, the patient presented a cardiorespiratory arrest and died. The subsequently requested necropsy confirmed the diagnosis of necrotizing meningoencephalitis.

***Discussion*:** The 2 reported cases confirm that MUO should be considered during the differential diagnoses of patients with neurological alterations. It is known that small-breed dogs are predisposed to these diseases. Laboratory tests and medical imaging are crucial for clinical guidance, helping to discard other neurological pathologies, especially those due to bacterial, fungal, and/or viral agents. However, definitive diagnosis of MUO can only be performed through necropsy and histopathological analysis. For the reported cases, CSF analysis, neurological PCR panel for detecting possible infectious agents, and bacterial culture were essential to rule out other possible causes of meningoencephalitis. Unfortunately, MUO includes progressive neurological disorders causing the patient's death.

Keywords: meninges, necropsy, histopathology, diagnosis.

DOI: 10.22456/1679-9216.126781

Received: 23 November 2022 Accepted: 20 April 2023 Published: 5 June 2023

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INTRODUCTION

Meningoencephalitis of unknown origin (MUO) is a non-infectious inflammation of the brain and meninges showing necrotizing forms of leukoencephalitis and meningoencephalitis, as well as granulomatous meningoencephalitis (GME), which can be diagnosed only by *post mortem* histopathology [3,9]. Although the etiology and pathophysiology of MUO are unknown, genetic predisposition and an exacerbated immune response are considered crucial factors for manifestation of the disease [5].

The *in vivo* diagnosis is presumptive and based on data from anamnesis associated with neurological signs and neuroanatomical location, cerebrospinal fluid (CSF) analysis, medical imaging, and tests for infectious diseases [11]. Hence, the definitive diagnosis can only be made through histopathology [7]. There is no consensus regarding treatment, and the probable immune-mediated origin of the disease leads to the choice of immunosuppressive therapies for its treatment [10].

This study aims to report 2 clinical cases of MUO in canines, diagnosed as GME and necrotizing meningoencephalitis (NME), with an emphasis on describing their clinical and diagnostic characteristics.

CASES

Case 1. This case refers to GME diagnosed in a 3-year-old bitch Shih Tzu breed weighing 4 kg. This dog developed a worsening neurological condition over 2 weeks, starting with proprioceptive ataxia, walking in circles, and rapidly evolving to ambulatory and non-ambulatory paresis. The animal did not show alterations in the general clinical examination except for the neurological condition, with a decerebrate stiffness posture, and absence of withdrawal reflex and proprioception, suggesting brainstem injury. Given this clinical picture, additional tests were requested, and the patient was hospitalized. Support therapy was initiated, administering methadone hydrochloride[1] [Mytedom® - 0.3 mg/kg SC, QID], methylprednisolone sodium succinat[2] [Solu-Medrol® - 2 mg/kg IV, BID], omeprazole sodium[3] [Oprazon® - 1 mg/kg IV, SID], and fluid therapy with 40 mL/kg/h of ringer's lactate[4] solution.

The blood count showed mild neutrophilia (11,745/mm^3; ref: 3,000-11,500), lymphopenia (405/mm^3; ref: 1,000-4,800), and hypersegmented neutrophils. Areas of mineralization in the cervical spine were observed by X-ray imaging of the cervicothoracic region. Therefore, the myelography of this region was also performed, and no changes explaining the clinical picture were observed. After 10 days of hospitalization, the signs evolved, with the patient showing tetraparesis, positional strabismus, myoclonus, hyperkeratosis in paw pads and nasal plane, and hyperthermia. The rapid immunochromatography test for distemper virus antigens[5] (Alere™) was negative. Piracetam[6] [Nootron® - 10 mg/kg VO, SID] and a combination of sulfadoxine and trimethoprim[7] [Borgal® - 15 mg/kg IV, bid] was added to the drug prescription.

The CSF analysis collected from the cisterna magna showed lymphocytic pleocytosis (total nucleated 6 cells/μL, ref: < 5/μL) with 84% of small lymphocytes, 8% of macrophages, and 8% of intact segmented neutrophils. The neurological qualitative real-time PCR panel CSF analysis and whole blood tested negative for *Neospora caninum, Ehrlichia* spp.*, Blastomyces dermatitidis, Histoplasma capsulatum, Babesia* spp., *Cryptococcus* spp.*, Coccidioides* spp., canine distemper virus, and *Toxoplasma gondii.* Urine PCR for the distemper virus was also negative. In addition, culture under aerobic and anaerobic conditions showed no bacterial growth. Subsequently, contrast-enhanced computed tomography of the brain was recommended, but the animal's tutor chose not to perform this exam due to its cost. After 16 days of hospitalization, without improvement of the clinical condition and with exams showing a progressive degenerative condition not responsive to treatment, the tutor opted for euthanasia of the patient, followed by necropsy.

The diagnosis of GME was confirmed after necropsy. Histopathological findings showed microgliosis in the brain and cerebellum, with astrogliosis, satellitosis, neuronophagy, and multifocal phantom neurons associated with multiple foci of perivascular cuffs in the white and gray matter (Figure 1A). In addition, mild multifocal mononuclear meningitis, mild multifocal perineuronal and perivascular edema in the white and gray matter, and mild to moderate multifocal congestion were observed. In the cervical, thoracic, lumbar, and sacral portions of the spinal cord, the same alterations as described for the brain and cerebellum were observed, in addition to mild to moderate multifocal malacia (Figure 1B) associated with mild multifocal hemorrhage and moderate presence of Gitter cells.

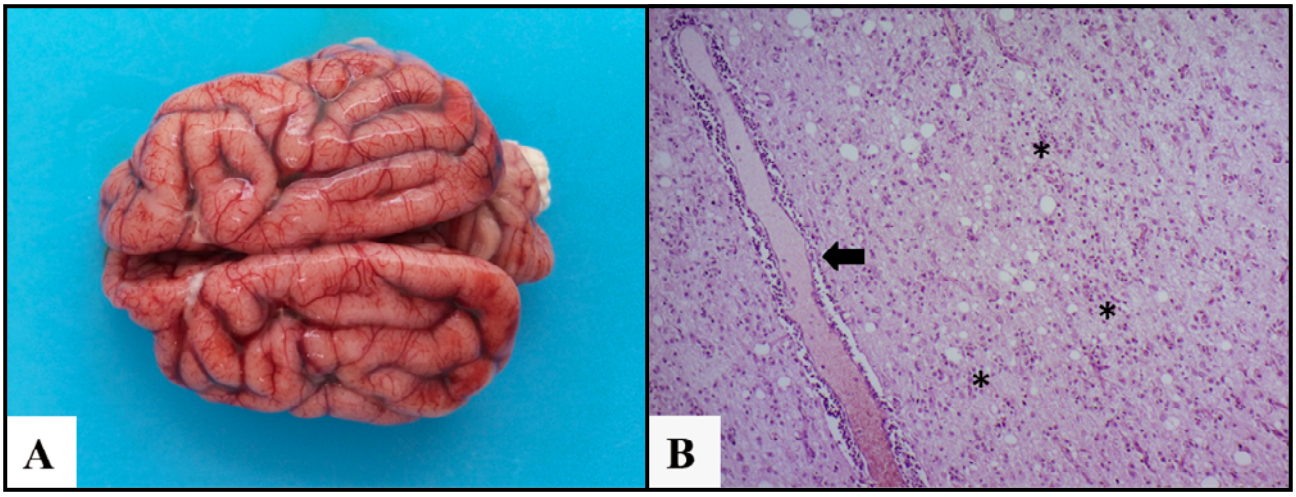

Figure 1. Case 1. Meningoencephalitis of unknown origin in dog. A- Brain microscopy showing areas of cavitation (arrowhead), microgliosis (asterisk), and perivascular cuffs (arrow) in canine diagnosed with granulomatous meningoencephalitis [HE; obj.10x]. B- Spinal cord microscopy showing an area of focally extensive malacia in canine diagnosed with granulomatous meningoencephalitis [HE; obj.5x].

Case 2. This case refers to the diagnosis of NME in a 1-year-and-5-month-old male Maltese breed weighing 4.8 kg. This animal displayed walking in circles behavior and loss of vision lasting a week, with rapidly worsening signs. The tutor also reported a history of recurrent otitis. On neurological examination, the patient presented sensitivity in the middle ear, manifesting pain in response to the palpation of the auditory canal, as well as difficulty in opening the mouth, auditory deficit in the right ear, blindness in the right eye, a proprioceptive deficit in the right anterior limb, and head pressing. Therefore, this patient was referred for hospitalization and complementary examination. Support therapy was initiated, administering 50 mL/kg/h Ringer's lactate solution, omeprazole sodium[3] [Oprazon® - 1 mg/kg IV, SID], a combination of sulfadoxine and trimethoprim7 [Borgal® - 15 mg/kg IV, BID], dipyrone[8] [Febrax® - 25 mg/kg IV, TID], and meloxicam[9] [Meloxinew® - 0.1 mg/kg SC, SID]. In addition, otologic cleaning with ear cleaner[10] [Phisio® Anti-odor, SID] was performed.

The blood count showed mild lymphopenia (776 mm^3). Abdominal ultrasonography and radiographs to evaluate auditory bullae, foramen magnum, and axis odontoid process showed no noteworthy changes. After 1 day of hospitalization, the patient showed a worsening clinical condition, with obfuscate behavior, absence of facial and auricular sensitivity, and nasal stimulus. The animal also started to present generalized seizures, leading to the addition of phenobarbital[11] [Gardenal® - 3 mg/kg IV, BID] to the drug prescription. Thus, CSF collection from the cisterna magna was examined, showing no altered physical, chemical, or cell count, with only the detection of reactive lymphocytes. The bacteriological culture was performed in aerobiosis and anaerobiosis of the CSF without bacterial growth. The bacteriological culture performed in aerobiosis and anaerobiosis showed no bacterial growth in CSF. The same real-time PCR neurological panel performed in samples from the patient of the 1st reported case also showed a negative result for this patient. Contrast-enhanced computed tomography of the brain was also recommended, but as for the 1st related case, the animal's tutor chose not to perform this exam due to its cost.

After 5 days of intensive care, the patient suffered cardiac arrest and died; therefore, a necropsy was requested. Upon macroscopic examination, the brain showed marked hyperemia and areas of congestion (Figure 2A), while the spinal cord showed mild hyperemia. Other organs did not show any noteworthy changes. Under microscopic examination, the brain showed microgliosis, astrogliosis, satellitosis, neuronophagy, multifocal ghost neurons associated with multiple foci of perivascular cuffs (Figure 2B), a predominance of mononuclear cells in white and gray matter, discrete multifocal mononuclear meningitis, mild to moderate multifocal perineuronal and perivascular edema in the white and gray matter, and mild to moderate multifocal congestion and hemorrhage. The cerebellum exhibited mild to moderate multifocal perineuronal and perivascular edema in the white and grey matter, mild multifocal spongiosis in white and grey matter, and mild multifocal congestion. Coincidently, the

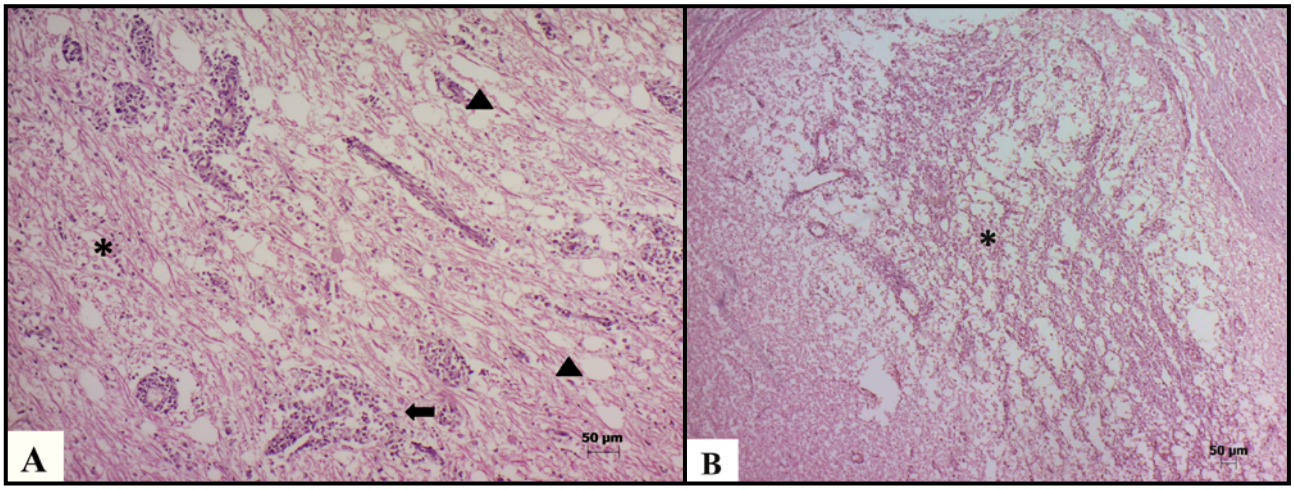

Figura 2. Case 2. Meningoencephalitis of unknown origin in dog. A- Macroscopic aspect of the canine brain diagnosed with necrotizing meningoencephalitis showing marked hyperemia and areas of congestion. B- Brain microscopy showing foci of perivascular cuffs (arrow) and a conspicuous microgliosis (asterisk) [HE; obj.10x].

cervical, thoracic, lumbar, and sacral portions of the spinal cord also presented mild multifocal congestion. Hence, the anatomopathological findings supported the diagnosis of NME.

DISCUSSION

Dogs of the Pug, Yorkshire, and Maltese breeds are predisposed to NME and GEM, with more prevalence in females from 3 to 7 years old [9]. Clinical signs may vary depending on the affected site of the central nervous system (CNS) [2]. The clinical signs of GEM are similar, mainly displaying disorientation, behavioral changes, epileptic seizures, head pressing, and sleepiness. When the spinal cord is involved, the predominant signs are neck pain and tetraparesis or paraparesis [15]. The clinical signs of NME are acute onset of seizures associated with difficulty in walking or incoordination, walking in circles behavior, head pressing, and decubitus prostration with evolution to coma [2]. The epidemiological and clinical aspects of our study findings agree with the literature on GEM and NME for each of the two reported cases [13].

In both patients, the blood counts show a leukogram coincident with a stress condition possibly justified by increased circulating cortisol due to pain or chronicity of the disease [16]. On the other hand, the rapid test for distemper is important in screening patients with neurological alterations. However, molecular biology tests are considered definitive for diagnosis [14]. Regarding non-infectious inflammatory causes, CSF analysis generally reveals a high concentration of proteins. In addition, mononuclear pleocytosis seems to be the most commonly observed alteration in CSF examination, although it may also present extremely variable cytology [5]. In our study, only the patient with GEM had mild pleocytosis, with a predominance of lymphocytes. In contrast, the patient with NME showed no significant alterations, except for the presence of reactive lymphocytes. Despite the lack of visualization of pleocytosis, the occurrence of reactive lymphocytes can be visualized in NME and GEM cases [1]. The presence of fungal and bacterial agents will not always be visualized in cytological analyses of CSF or isolated in cultures, as in the reported cases. However, the genetic material of these agents can be easily detected by PCR. In the cases reported here, the neurological PCR panel was essential for excluding infectious agents as causes of the observed clinical picture [8].

The definitive diagnosis of GEM and NME can only be performed *post mortem*, based on necropsy and histopathology. Upon macroscopic analyses, GEM may present lesions characterized by dark brown foci, which may be accompanied by isolated nodules, while NME usually shows multifocal alterations and asymmetric necrosis in the deep cerebral cortex associated with edema of the vascular endothelium [19]. In both conditions, although alterations can be macroscopically observed in any area of the CNS, the lesions seem to appear predominantly in the brain [6]. The patient diagnosed with GEM did not show macroscopic alterations, while the one diagnosed with NME showed only hyperemia and areas of congestion in the brain. According to the literature, dogs with GEM may not present alterations in the macroscopic evaluation [12].

Therefore, the definitive diagnosis of these patients is reached through a microscopic study. Studies report that hyperemia and petechiae are the main macroscopic neural lesions in acute cases of NME, besides brain edema causing asymmetry [4].

Regarding histological alterations, the lesions caused by GEM and NME are widely distributed throughout the CNS [18]. Specifically, perivascular cuffs are often observed in GEM, and diffuse necrosis is not found [19]. On the other hand, the main lesions in NME include the perivascular cuffs of lymphocytes and macrophages, extensive areas of necrosis, and reactive microglia and astrogliosis proliferation [17]. In addition, patients with GEM and NME may present neuronophagia and signs of intense neuronal distress represented by observation of phantom neurons [20], which are features consistent with the microscopic findings of the 2 patients analyzed.

The treatment of MUO is based on corticosteroid therapy [9]. The use of associated immunosuppressants is controversial, and cytosine arabinoside is the most commonly used drug [10]. According to a previous study [7], the survival time of patients treated only with corticosteroids ranges from one to 1,215 days, while for patients using immunosuppressive therapy associated with corticosteroids, survival reached 26 to 2,469 days [10]. In the reported cases, both patients were unresponsive to corticosteroid therapy, and there was no time to initiate treatment with cytosine arabinoside.

The definitive diagnosis of MUO was reached through necropsy. However, CSF analysis and a neurological panel with exams of biological material for possible infectious agents associated with bacterial culture were essential to rule out other possible causes of meningoencephalitis. Unfortunately, MUO includes progressive neurological disorders that rapidly progress to the patient's death.

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Declaration of interest. The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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