Canine granulomatous meningoencephalitis: a case report and review of the literature

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Abstract
Canine granulomatous meningoencephalomyelitis (GME) is a subtype of a large group of idiopathic central nervous system diseases with a relatively high incidence (up to 25%) among dogs with central nervous system affection (Tipold, 1995). Neurological presentation of GME can vary from focal to multifocal, or ocular form. Histologically, GME is characterized by focal, disseminated or perivascular mononuclear cells spreading in the white matter and meninges (Coates and Jeffery, 2014). The aim of the current case report is to describe the pathological findings and to discuss the diagnostic features of this disease. Therefore, we should further emphasize the importance of this disease in current veterinary practice.
Key words: *granulomatous meningoencephalomyelitis, dog, histology*

Introduction

Canine granulomatous meningoencephalitis (GME) is an idiopathic inflammatory disease of the central nervous system (CNS) in dogs, which belongs to a category of diseases termed meningoencephalitis of unknown origin (MUO) (Cordy, 1979; Cordy and Holliday, 1989; Talarico and Schatzberg, 2010; Park et al., 2012). This disease was reported worldwide with an incidence of 5% to 25% of the CNS disorders in dogs (Cuddon and Smith-Maxie, 1984). Although firstly reported in 1978 by Braund et al. in 6 dogs, the pathogenesis of this CNS inflammation is poorly understood. Multiple etiologies have been suggested, such as an aberrant response to Canine Distemper Virus (CDV) infection, a modified immune response after vaccination (Braund, 1985), either a T cell-mediated delayed-type hypersensitivity reaction (Kipar et al., 1998; Coates and Jeffery, 2014). The aberrant immune response hypothesis is sustained by the fact that GME responds well to the immunosuppressive treatment (Wong et al., 2010).

Clinically GME occurs commonly in young adults (4 to 8 years of age), usually in small toy-breed dogs. Neurological signs are nonspecific, can have forebrain, brainstem, and spinal cord localization (Granger et al., 2010). Based on the clinical onset and CNS distribution of the lesions, GME is further classified as focal, multifocal (or disseminated) and ocular. Clinical diagnosis can be made based on signalment, clinical signs, neurological examination, magnetic resonance imaging, and CSF analysis results (Amado et al., 2007; Talarico and Schatzberg, 2010; Coates and Jeffry, 2014). A definitive diagnosis is made based on histopathology, the typical GME lesions consisting of CNS perivascular cuffing of mononuclear cells (mainly lymphocytes, macrophages and, occasionally plasma cells), often associated in severe cases with central coagulation necrosis, and lymphohistiocytic meningitis.

The purpose of this study is to describe the pathological findings in a dog diagnosed with GME and to further discuss the main diagnostic features and differential diagnoses.

Materials and methods

Case history

An eight-year-old intact female Bichon Maltese dog with a history of chronic vomiting, weight loss and neurological signs (moderate obtundation), and hypothyroidism was presented for examination to the Pathology Department of the University of Agricultural Sciences and Veterinary Medicine Cluj- Napoca, Romania.

Pathology

A complete post mortem examination was performed. During necropsy, multiple impression smears were realized from the brain and further stained with Diff-Quik for cytological evaluation.

Histopathology

Formalin-fixed sections (10% NBF) of the brain were processed into paraffin blocks using routine histology techniques, sectioned to 4-µm thickness, mounted on histological slides, and finally standardly stained with hematoxylin-eosin (H&E).

Results

Pathological findings

The dog was in good body condition (5, on a 1-9 scale; Laflamme, 1997).

Within the brain, there was a mild internal hydrocephaly and multifocal, poorly defined areas (measuring up to 0.5 cm) of softening and greyish discoloration. At the cranial entrance of the optical nerves a 2 x 1.2 x 1 cm, white-gray, heterogeneous, dense mass was present (Fig. 1) slightly compressing the adjacent neural tissue. Cytologically, the above-described foci contained many lymphocytes admixed with foamy-macrophages and few extracellular cell debris on a lipidic background (Fig. 1)

Additionally to the CNS lesions, a 2 cm follicular cyst was observed on the left ovary, and multiple foci of adrenal-cortical hyperplasia were present bilaterally. On the liver, three small foci (measuring up to 1 cm in diameter) of nodular hyperplasia were observed.

Histologically, the lesions were multifocally distributed within the cerebrum and optic nerve. Affecting mostly the white matter, the poorly defined multifocal areas replaced the neural tissue and were infiltrated by perivascular cuffs of lymphocytes (1-9 layers), admixed with fed macrophages and plasma cells, separated by areas of broad-sheets consisting mainly of foamy-macrophages, occasionally with few plasma cells and multinucleate giant cells. A mild, diffuse leptomeningeal infiltrate consistinf of the above mentioned cells was also present (Fig. 1).

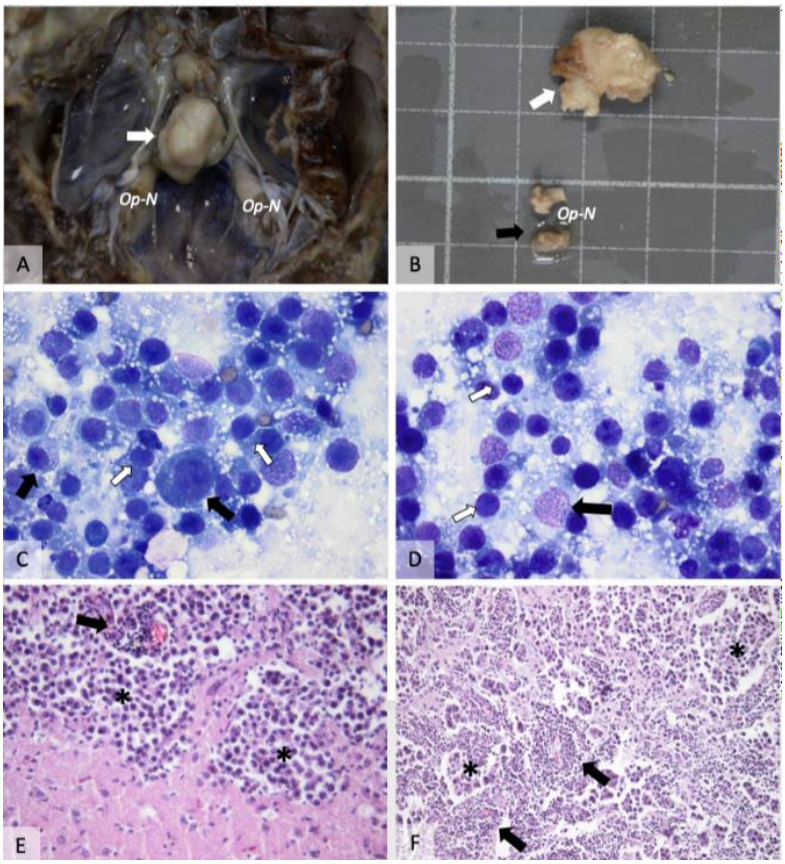

Figure 1. Gross (image A and B), cytological aspect (image C and D) and histopathological (image E and F) features of the GME. Grossly, at the cranial entrance of the optical nerves (Op-N), a 2 x 1.2 x 1 cm, white-gray, dense mass is present (image A, B-white arrow). Citological aspect of the GME (C, D): marked leukocyte infiltration consisting of many lymphocytes (white arrows) admixed with foamy-macrophages (black arrows) and few mainly extracellular cell debris on a lipidic background. Diff-Quik stain, ob x100. Histologically, replacing the neural tissue, the multifocal masses consists of perivascular lymphocytic cuffing (image E and F-black arrows) separated by broad-sheets of foamy-macrophages (asterisks), occasionally admixed with few plasma cells and multinucleated giant cells. H&E, ob x 40 (image E) and ob x 20 (image F).

Discussions

GME is a subtype of the large group of meningoencephalomyelitis of unknown origin (MUO), characterized by acute onset and progressive neurological signs. This group of idiopathic, non-infectious CNS diseases (GME, steroid responsive meningitis-arteritis, eosinophilic meningoencephalitis, necrotizing encephalitis) are the most common causes of meningoencephalitis in countries where distemper virus infection is rare (Cornelis et al., 2019).

GME can affect any small-breed dogs and usually has a poor prognosis. It was reported that dogs with multifocal forms have a shorter survival time compared to dogs with focal form of GME (O'Neill et al., 2005). A recent review shows that 15% of dogs diagnosed with GME die before before receiving treatment. Because most of the reported studies had a small number of dogs

and different treatment protocols, it is difficult to identify reliable prognostic factors (Cornelis et al., 2019).

Generally, the diagnosis of this disease is made based on a combination of signalment, clinical examination, MRI and cerebrospinal fluid (CSF) findings (Amado et al.,2007; Talarico and Schatzberg, 2010; Coates and Jeffry, 2014). Ante-mortem CSF analysis resulted in pleocytosis (>50% monocytes/lymphocytes) is one of the proposed diagnostic criteria, adjoining the signalments (dogs older than 6 months of age), MRI changes with multiple, single or diffuse intra-axial hyperintensities on T2-weighted sequences and elimination of any infectious cause specific to the geographic area (Granger et al., 2010; Cornelis et al., 2019). Ante-mortem histopathological diagnosis can be performed by computed tomography-guided, magnetic resonance imaging-guided stereotactic systems or free-handed techniques biopsies (Koblik et al., 1999; Moissonnier et al., 2000; Flegel et al., 2002; Giraux et al., 2002; Troxel and Vite, 2008; Chen et al., 2012; Thoman et al., 1993). The definitive diagnosis of inflammatory brain disease is based on histopathology.

On gross examination, GME lesions can present mild, occasionally with granulomatous mass formation. Microscopically, the lesions in acute phase necrotizing meningoencephalitis are similar to GME lesions. Perivascular, disseminated or focal infiltrates of mononuclear cells are present in the white matter and meninges. The histological aspect of the lesions in necrotizing meningoencephalitis is consistent with asymmetric extensive necrosis and cavitation with prominent astrogliosis (Coates and Jeffery, 2014).

Our findings are similar to the reported literature (O'Neill et al., 2005; Coates and Jeffery, 2014; Cornelis et al., 2019). Histological diagnosis is not regularly available antemortem, therefore, the clinical diagnosis should be made based on the criteria mentioned above. In dogs with focal or multifocal CNS signs, GME should be more often taken into consideration for the differential diagnosis and its importance should be further underlined in the veterinary practice.

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