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Review

Pathological and immunological features of canine necrotising meningoencephalitis and granulomatous meningoencephalitis

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ABSTRACT

Necrotising meningoencephalitis (NME) and granulomatous meningoencephalitis (GME) are idiopathic inflammatory diseases of the canine central nervous system (CNS). Typical NME occurs predominantly in small breeds of dogs, such as Pug, Maltese and Yorkshire terriers. Although there is no specific breed predisposition to GME, toy and terrier breeds appear to be overrepresented. Recent molecular investigations have identified genetic risk factors for NME in Pug, Maltese and other toy breed dogs; however, details of the pathogenesis of this disease remain to be clarified. NME is characterised pathologically by necrotic lesions with mononuclear cell infiltration in the meninges and perivascular spaces. On the basis of the distribution pattern of major necrotic foci, NME can be divided into cortex dominant and white matter dominant types; the latter is designated necrotising leucoencephalitis (NLE). Lesions in GME are characterised by the accumulation of lymphocytes and macrophages with epithelioid morphology, forming granulomas around blood vessels. Some common genetic factors and/or some additional triggers, such as infection or vaccination, may play a role in the pathogenesis of NME, NLE and GME; however, the host immune responses may define the pathological phenotypes. Different cytokine and chemokine responses are seen in NME, NLE and GME, whilst autoantibodies against astrocytes are detected predominantly in NME. This review focuses on the pathological and immunological characteristics of these canine idiopathic inflammatory CNS disorders.

Introduction

Necrotising meningoencephalitis (NME) and granulomatous meningoencephalitis (GME) are idiopathic inflammatory diseases of the central nervous system (CNS) of dogs (Cordy, 1979; Cordy and Holliday, 1989; Talarico and Schatzberg, 2010; Park et al., 2012). The pathogenesis of these CNS diseases is not fully understood; however, aberrant immune responses against CNS tissues have been suspected on the basis of immunohistochemical features in GME (Kipar et al., 1998; Suzuki et al., 2003; Park et al., 2012) and the presence of autoantibodies against CNS tissues in NME (Uchida et al., 1999; Matsuki et al., 2004). Several studies have also attempted to identify infectious agents in NME and GME, but no agents have been associated aetiologically with these diseases (Schatzberg et al., 2005; Barber et al., 2012). This review article examines the clinical, pathological and immunological characteristics of NME and GME.

Clinical features

Necrotising meningoencephalitis

Canine NME occurs predominately in young to middle aged Pug dogs (Kobayashi et al., 1994; Levine et al., 2008; Talarico and Schatzberg, 2010; Park et al., 2012), but also occurs in Maltese terriers (Stalis et al., 1995), Yorkshire terriers (Jull et al., 1997; Kuwamura et al., 2002) and other breeds (Higgins et al., 2008; Spitzbarth et al., 2010). Recent molecular investigations have demonstrated genetic risk factors for NME in Pug dogs (Greer et al., 2009, 2010; Barber et al., 2011; Pedersen et al., 2011; Safra et al., 2011), along with Maltese terriers and other breeds (Schrauwen et al., 2014). NME in Pug dogs has been likened to atypical forms of human multiple sclerosis (MS) associated with a specific human leucocyte antigen class II genotype (Greer et al., 2010). A genome-wide scan of Pug dogs with NME showed that the risk for NME maps to a specific region on canine chromosome 12 encoding the dog leucocyte antigen (DLA) complex (Barber et al., 2012). However, the pathological changes in the human and canine diseases are substantially different; demyelinating changes are often observed in human MS, but are not evident in canine NME.

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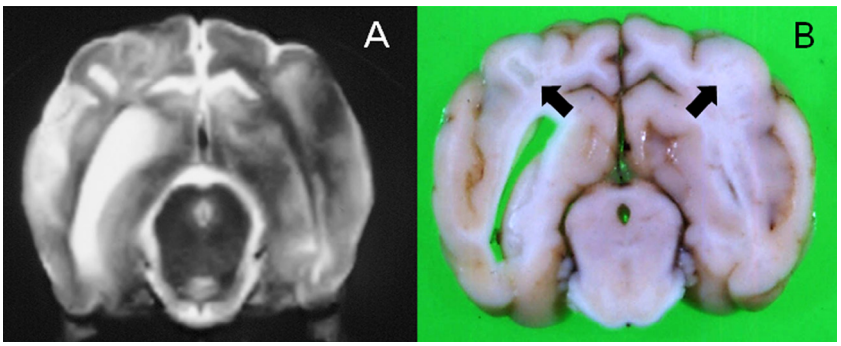

Fig. 1. Pug dog with necrotising meningoencephalitis with a subacute clinical history. (A) Typical MRI with T2 weighted image. Hyperintense lesions are detected diffusely in the cerebral cortex and focally in the deep cortex. (B) Gross lesion of the cerebrum after fixation. Malacic foci were observed in the deep cortex extending to the white matter (arrows).

Necrotising leucoencephalitis

Necrotising encephalitis (NE) in Yorkshire terriers and other breeds is characterised by pronounced asymmetrical malacic changes in the cerebral white matter and thalamus, and thus is also known as necrotising leucoencephalitis (NLE), distinct from typical NME (Talarico and Schatzberg, 2010; Park et al., 2012). Clinical features, including canine breed predispositions and prognosis, are different between NME and NLE, but the pathological features sometimes overlap (Cooper et al., 2014). It remains unclear whether NME and NLE are separate disease entities or share a common pathogenesis.

Granulomatous meningoencephalitis

Canine GME is characterised by idiopathic granulomatous inflammation, with perivascular accumulation of epithelioid macrophages and lymphocytes in the canine CNS (Cordy, 1979; Braund, 1985). The pathogenesis, including genetic risks and causative agents, remains unclear (Muñana and Luttgen, 1998; Granger et al., 2010; Talarico and Schatzberg, 2010). Unlike NME and NLE, GME can affect any canine breed, whilst toy and terrier breeds appear to be overrepresented.

Pathological features

Necrotising meningoencephalitis

The characteristic morphological changes of 'typical' NME are multifocal, asymmetrical necrosis in the deep cerebral cortex, which is detected on antemortem magnetic resonance imaging (MRI) examination (Fig. 1A) or postmortem gross observations of the brain from affected dogs (Fig. 1B). In cases of acute NME found frequently in Pug dogs and characterised by severe generalised seizures, sometimes resulting in sudden death, inflammatory changes are characterised by diffuse leptomeningeal infiltration of mononuclear cells, mainly consisting of lymphocytes (Cordy and Holliday, 1989; Summers et al., 1995; Talarico and Schatzberg, 2010; Park et al., 2012), along with swelling of vascular endothelial cells in the superficial cerebral cortex (Fig. 2A). Necrotic changes are usually absent in acute NME; thus, the differential diagnosis from other non-suppurative meningoencephalitides may be difficult. An antemortem diagnosis of NME is supported by laboratory evidence for absence of infection with infectious agents, such as canine distemper or herpesviruses, along with the presence of autoantibodies against CNS tissues in CSF. Subacute and typical NME is characterised clinically by persistent seizures or depression and the presence of hyperintense lesions in the cerebral cortex on MRI examinations.

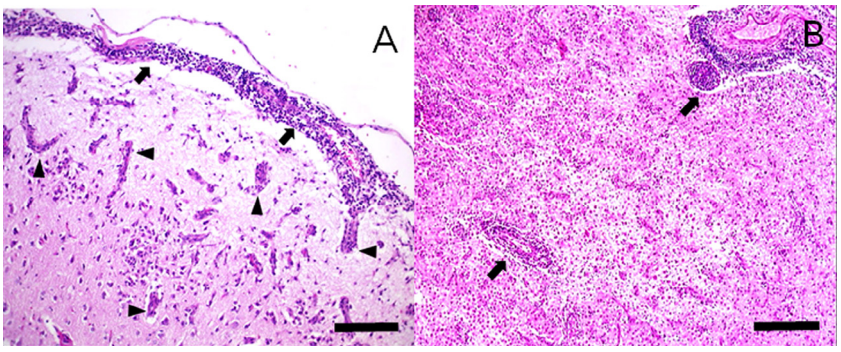

Fig. 2. Histopathological features in the cerebral cortex in Pug dogs with necrotising meningoencephalitis with an acute clinical onset (A) and a subacute clinical onset (B). (A) Diffuse infiltration of mononuclear cells is observed in the leptomeninges (arrows). There are no significant necrotic lesions in the cerebral cortex, whilst mild to moderate swelling of vascular endothelial cells (arrow heads) is found in the superficial area of the cerebral cortex. Haematoxylin and eosin. Bar = 240 μm. (B) Intensive inflammatory changes, including leptomeningeal and perivascular accumulations (arrows) and parenchymal infiltration of mononuclear cells, and diffuse malacic lesions are observed in the cerebral cortex. Haematoxylin and eosin. Bar = 300 μm.