

Necrotising encephalitis in a French bulldog

A 20-month-old, female French bulldog was presented with a three-month history of generalised seizures and progressive ataxia with occasional falling over on either side. Neurological examination revealed signs, suggesting a multifocal intracranial lesion. Magnetic resonance imaging of the brain revealed two connected lesions on the left side of the caudal brainstem and a further lesion in the cerebrum. The dog was euthanased, and histopathological examination revealed lesions which closely resembled those of necrotising encephalitis in Yorkshire terriers. This is the first case describing this type of necrotising encephalitis in a French bulldog.

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INTRODUCTION

Breed-specific necrotising encephalitides are inflammatory disorders of unknown aetiology, thus far described in the Maltese terrier, Yorkshire terrier and pug (Ducoté and others 1999, Lotti and others 1999, Kuwamura and others 2002). In addition, some reports mention the occurrence of the disease in other breeds, including the Chihuahua, papillion and shih-tzu; but no detailed case reports has been published in these breeds.

Two distinct disease entities are recognised and are distinguished by histopathology. Necrotising encephalitis, described in the Yorkshire terrier, is mostly localised in the deep white matter of the forebrain and in the brainstem, whereas the encephalitis described in the pug affects both the grey and the white matter of the cerebrum, with intense meningitis but rarely any significant lesions in the brainstem. Both differ from granulomatous meningoencephalitis (GME), which is primarily associated with blood vessels. To the authors' knowledge, the present report describes the first case of the Yorkshire-terrier-type necrotising encephalitis in a French bulldog.

CASE HISTORY

A 20-month-old, spayed, female French bulldog was presented with a three-month history of ataxia. The owner had had the

dog for one year, and the only previous known medical condition was an episode of otitis externa six months before presentation. The dog had not travelled abroad, and there was no history of trauma or exposure to toxins.

The owner noticed a progressive wobbling gait for several months, with the dog occasionally falling over on either side. For one week before presentation, the dog vomited or regurgitated most of his meals, suffered two generalised seizures and was dyspnoeic. The referring veterinarian additionally noted a slight head tilt to the left. Thoracic radiographs after oral application of barium sulphate revealed the presence of mega-oesophagus and signs consistent with aspiration pneumonia. The dog was treated with 12.5 mg/kg amoxicillin/clavulanic acid (Synulox; Pfizer) orally twice a day for two days before presentation. She was subsequently referred to the neurology unit at the small animal clinic, with the suspicion of an intracranial lesion, mega-oesophagus and aspiration pneumonia, and because the vestibular signs had deteriorated.

Physical examination findings included moderate lethargy, generalised muscle atrophy, moderate dyspnoea and tachypnoea, increased respiratory sounds with ventral crackles, a dull and scaly coat and mildly enlarged mandibular lymph nodes. Cerumen and crusts were seen within the right external ear canal, but the tympanic membrane appeared entire.

Neurological examination revealed a slightly reduced mental state, a wide-based stance and generalised ataxia. There was a moderate head tilt to the left, facial paralysis and ventral strabismus on the left. The knuckling reaction was delayed in the hindlimbs, and the extensor postural thrust was reduced on the left side.

A complete blood count and serum biochemistry panel revealed mild leucopenia ($4.520 \times 10^9/l$; reference interval 6 to $12 \times 10^9/l$), with a mild neutropenia ($2.4 \times 10^9/l$; reference interval 3.0 to $11.5 \times 10^9/l$), mildly increased albumin (41.4 g/l; reference interval 29.7 to 40.0 g/l), mildly decreased urea (2.9 mmol/l; reference interval 3.45 to 11.11 mmol/l)

and mildly increased alanine aminotransferase (277 iu; reference interval 24 to 124 iu), gamma glutamyltransferase (16 iu; reference interval 1 to 7 iu) and glutamate dehydrogenase (230 iu; reference interval 2 to 10 iu). The acetylcholine receptor antibody titre (0.3 nmol/l; reference <0.5 nmol/l), serum total thyroxine (23.2 nmol/l; reference interval 16.7 to 47.7 nmol/l) and canine thyroid stimulating hormone (0.03 ng/l; reference interval 0.03 to 0.32 ng/l) were all within the reference intervals.

Based on the history and results of laboratory examinations, a multifocal intracranial lesion was suspected. Differential diagnoses included an infectious, inflammatory or neoplastic central nervous system disease. Vascular disease was considered unlikely because of the progressive nature of the clinical signs. The dog was hospitalised, a gastrostomy tube was placed, treatment was initiated with intravenous fluids (4 ml/kg/hour of lactated Ringer's solution), 2 mg/kg pyridostigmin (Mestinon; ICN Pharma) orally every eight hours, 20 mg/kg amoxicillin/clavulanic acid (Synulox; Pfizer) intravenously every eight hours and enteral nutrition (Nergycare; Orsco) was given through the gastrostomy tube. Further diagnostic work-up requiring general anaesthesia was deferred because of the dyspnoea and poor general condition of the dog.

On the fifth day of treatment, dyspnoea and abnormal respiratory sounds were no longer evident, and the dog was anaesthetised for a cerebrospinal fluid (CSF) tap and magnetic resonance imaging (MRI) (open 0.3 T MRI unit, Hitachi Airis II; Hitachi Medical Systems) of the brain was performed. Examination of the CSF revealed a negative Pandy test, an albumin concentration at the upper reference limit (30 mg/dl; reference \leq 30 mg/dl) and a moderate pleocytosis (26 cells/ μ l; reference limit 0 to 5 cells/ μ l), consisting of 95 per cent lymphocytes and 5 per cent monocytes. Sequences taken at MRI included a fast-spin echo T2 in sagittal and transverse orientation, a CSF-suppressing fluid-attenuated inversion recovery (FLAIR) in dorsal plane, and a transverse FE3D (field echo) T1-weighted and a dorsal plane T1-weighted high-resolution FE3D multi-planar reconstruction. The T1-weighted sequences were repeated after the intravenous injection of Omniscan

(Gadolinium EDTA; GE-Healthcare) in a dosage of 0.15 mmol/kg bodyweight.

Findings included a left lateral ventricle that was nearly two-thirds larger than the right side and asymmetry of the cerebrum and the mid-brain. A round, FLAIR- and T2-hyperintense lesion 5 mm in diameter was apparent in the rostradorsal white matter of the left ventricle. In addition, two confluent lesions were present on the left side of the caudal brainstem. These displayed a high-intensity fluid signal in T2, a bright signal in FLAIR, with slightly less signal intensity in the centre, and low signal intensity in the T1-weighted sequences. Both the lesions were sharply delineated; the rostral lesion was triangular shaped in the transverse plane (Fig 1). There was moderate contrast enhancement of the forebrain lesion, whereas the brainstem lesions showed no contrast enhancement. The floor of the fourth ventricle in this area was deformed and the ventral part of the right bulla filled with fluid isointense material. Differentials for the lesions included disseminated encephalitis, most likely necrotising encephalitis because of the size and destructive nature of the lesion and, less likely, GME, infectious encephalitis, multiple infarctions or multifocal neoplasia.

Given the unfavourable prognosis, the dog was euthanased with the owner's consent. At necropsy, a moderate megaesophagus was confirmed, but there was no obvious signs of pneumonia.

The right bulla contained viscous, granular material. Macroscopic examination of the brain confirmed the lesions seen on MRI. On histological examination of the medulla and cerebral white matter, notably in the corona radiata, the lesions were inflammatory, with central necrosis, astrogliosis and diffuse invasion of macrophages, lymphocytes and plasma cells. These foci of tissue destruction were surrounded by a wall of intense cellular proliferation, consisting of astrocytes, microglial cells and mononuclear cells. In the periphery of the destructive lesions, large perivascular, mononuclear infiltrates were evident. A similar lesion was found in the centrum semiovale on the right side. Several similar but smaller inflammatory lesions were found in different areas of the brain. The distribution and appearance of the lesions very closely resembled the histological presentation of necrotising encephalitis in Yorkshire terriers.

DISCUSSION

Common to the breed-specific encephalitides thus far described in dogs are their usually chronic and progressive course, severe tissue destruction, intense inflammatory reactions and coexistence of active and burnt-out, often cystic, lesions. The latter consist in complete loss of the original tissue, with glial scar formation and occasional minor residual inflammation

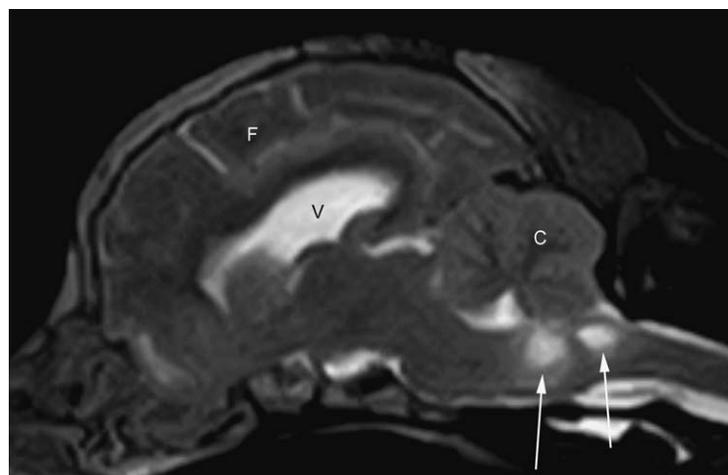


FIG 1. Slightly left parasagittal T2-weighted magnetic resonance image. There are two sharply delineated hyperintense lesions (arrows) in the brainstem. The signal intensity is isointense to cerebrospinal fluid (compared with the ventricles). V Left lateral ventricle, F Forebrain, C Cerebellum

(Tipold and others 1993, Jull and others 1997, Kuwamura and others 2002). Two disparate disease entities appear to be seen in different breeds of dogs, with cerebrocortical and subcortical white matter lesions seen in pugs and Maltese terriers and brainstem/subcortical white matter lesions seen in Yorkshire terriers (Tipold and others 1993, Kuwamura and others 2002). While the perivascular inflammatory infiltrate in both conditions usually has a granulomatous component, there is no other resemblance to GME. The latter consists of accumulation of epithelioid cells, eventually leading to a space-occupying lesion, which is primarily associated with the blood vessels and not accompanied by primary parenchymal damage (Suzuki and others 2003). The lesions in Yorkshire terrier encephalitis are highly characteristic and unique, with a necrotic centre surrounded by a wall of intense cellular infiltration and proliferation (Fig 3) (Tipold and others 1993, Sawashima and others 1996). The neurohistopathological findings in the present case were concordant with this type of encephalitis, hitherto only described in the Yorkshire terrier. The present report is, to the authors' knowledge, therefore the first case of this type of necrotising encephalitis described in a French bulldog.

Based on the MRI findings, differential diagnoses also included GME. However, GME lesions are usually located in the white matter of the cerebral hemispheres, brainstem and spinal cord. Moreover, the MRI findings were consistent with the highly characteristic histological architecture of the lesions, with an area of central necrosis surrounded by a wall of intense inflammation (Fig 2). The multifocal distribution of the lesions together with the cavitory non-enhancing appearance in the brain stem (Fig 3) are highly suggestive of necrotising encephalitis (Sawashima and others 1996, Lotti and others 1999). The type of encephalitis observed in pug and Maltese terriers is far less likely because the lesions were mainly distributed in the brainstem (Kobayashi and others 1994, Kuwamura and others 2002).

Retrospectively, in this case, a diagnosis of Yorkshire-terrier-type necrotising encephalitis could have been made with some confidence by MRI alone. This is

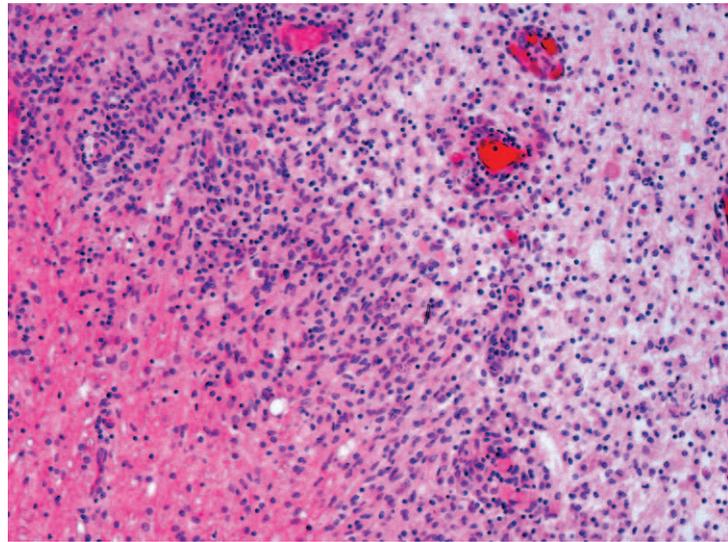


FIG 2. Section at the edge of the brainstem lesion. Complete destruction of original nervous tissue with invasion of macrophages and astroglial proliferation is evident on the right towards the centre of the lesion. This area is bordered by a wall of extremely intense cellular proliferation and invasion of astrocytes, histiocytes and mononuclear inflammatory cells. H&E. $\times 250$

important because MRI may allow more reliable antemortem diagnosis of this disease, which would be important for any future studies into therapy of this disease. In particular, it is our clinical impression that Yorkshire-terrier-type necrotising encephalitis may be more responsive to immunosuppressive doses of glucocorticoids than pug dog encephalitis, and the ability to obtain an antemortem diagnosis is vital in order to design a study to test this hypothesis. In the present case,

destruction of the brainstem was considerable at the time of diagnosis and resulted in autonomic dysfunction with megaesophagus. Treatment was therefore not attempted. While the Yorkshire-terrier-type necrotising encephalitis has been suspected in other dog breeds, this is the first complete report on necrotising encephalitis in a breed other than the Yorkshire terrier. It can be expected that this disease will be recognised in other small dog breeds in the future.

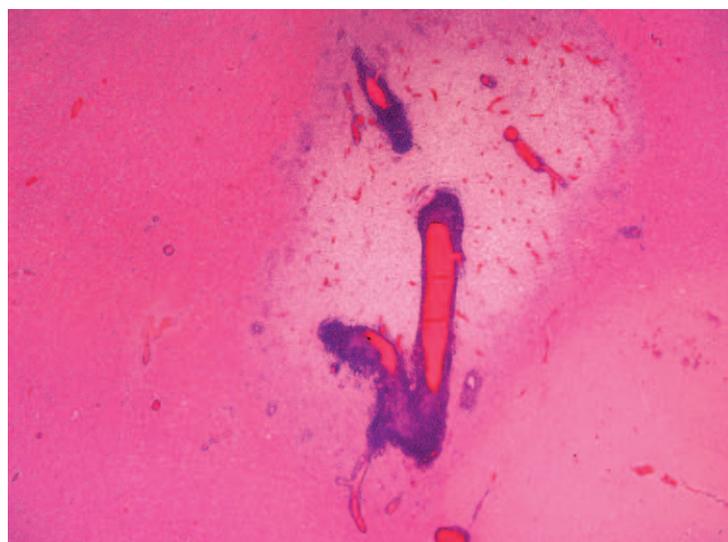


FIG 3. Lesion in the cerebral white matter. A lytic centre surrounded by a wall of dense cellular proliferation with large perivascular cuffs is evident. H&E. $\times 25$

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