Veterinary Record
casereports

TITLE OF CASE

Intracerebral haemorrhage in a dog with steroid responsive meningitis-arteritis.

SUMMARY

A 1 year 6 months old female neutered Boxer dog was presented with a four-day history of pyrexia, lethargy and neck pain. An intracerebral haemorrhage and a mediastinal mass were identified. Cerebrospinal fluid analysis revealed severe neutrophilic pleocytosis and steroid responsive meningitis-arteritis was suspected. A significant improvement was observed with immunosuppressive steroid therapy and subsequent imaging revealed a reduction in size of the intracerebral haemorrhage and disappearance of the mediastinal mass. Steroid responsive meningitis-arteritis is a systemic disease with potential involvement of multiple organs. Intracerebral haemorrhage can occur secondary to steroid responsive meningitis-arteritis and can have a successful outcome.

BACKGROUND

Steroid responsive meningitis-arteritis (SRMA) is the most frequently diagnosed inflammatory central nervous system disease of dogs (Fluehmann and others 2006) and is characterized by suppurative leptomeningitis and spinal arteritis (Harcourt 1978, Tipold and others 1995).

It is a systemic disease with potential involvement of multiple organs (Navarro-Cubas and others 2011, Tipold and others 1995, Snyder and others 1995), but the clinical and pathological manifestation of SRMA is predominantly neurological (Harcourt 1978, Tipold and others 1995, Tipold and Jaggy 1994, Lowrie and others 2009). Intraparenchymal central nervous system lesions secondary to SRMA are uncommon (Snyder and others 1995, Wrzosek and others 2009, Hughes and others 2015); and to the authors' knowledge, an intracerebral haemorrhage secondary to SRMA has not been previously reported.

CASE PRESENTATION

A 1 year 6 months old female neutered Boxer dog was referred to the Neurology and Neurosurgery Service of Glasgow Small Animal Hospital with a four-day history of pyrexia, lethargy and neck pain. Treatment with tramadol, amoxicillin-clavulanic, and meloxicam was initiated by the referring veterinarian at onset of clinical signs with no significant improvement. Similar clinical signs occurred five months prior to presentation but resolved with a similar treatment.

On physical examination the dog was lethargic and the neurological examination revealed a stiff gait and low head carriage. Severe discomfort was elicited on palpation of the thoracic vertebral column and flexion of the neck. During the examination, an episode of proprioceptive ataxia affecting all limbs, followed by collapse without loss consciousness that lasted approximately fifteen seconds was observed. The rest of the neurological examination was normal. Based on history, signalment and the multifocal pain a lesion affecting the cervical and thoracic vertebral column was suspected. Additionally, to explain the episode of proprioceptive ataxia an intracranial lesion was considered.

INVESTIGATIONS

Haematology, serum biochemistry, prothrombin and activated partial thromboplastin times, serial blood pressure measurements and echocardiography were within normal limits. Fibrinogen was increased (965mg/dl; reference range, 150-400). *Toxoplasma gondii* and *Neospora caninum* serum titres were negative. A faecal sample obtained for Baermann test was also negative. C-reactive protein and urinalysis were not performed.

Magnetic resonance imaging (MRI) of the brain and neck was performed using a 1.5-Tesla unit (Siemens Magnetom Essenza; Frimley). Turbo spin echo T1-weighted (T1W), fluid-attenuation inversion recovery (FLAIR), turbo spin echo T2-weighted (T2W) and T2* images of the head were acquired in the transverse plane. Sagittal and dorsal T2W images of the head and neck and sagittal T1W images of the head and neck were also obtained. Post-contrast T1W images of the head were acquired in the sagittal and transverse planes; and postcontrast T1W images of the neck were acquired in the sagittal plane after intravenous administration of gadolinium (0.1mmol/kg; Gadovist, Bayer plc). MRI revealed an intra-axial oval-shape well-defined mass (3cm x 2cm x 1cm) located within the left olfactory bulb and frontal lobe causing mild mass effect with right-sided midline shift. The mass lesion was heterogeneously hyperintense on T2W and FLAIR images compared to grey matter, with a hyperintense periphery and isointense core on T1W images, and no contrast enhancement. The hyperintense periphery had a signal void on T2* images and the centre was hypointense in some areas and had a signal void in others. Surrounding the main lesion there was an ill-defined hyperintense T2W and FLAIR, and T1W isointense area consistent with perilesional oedema. There was marked contrast enhancement of the leptomeninges surrounding the cerebrum (Fig. 1) and the cervical spinal cord (Fig. 2). There was also contrast enhancement of the longus colli muscles at the level of C3-C4 (Fig. 2).

An oval-shaped well-defined mass (9cm x 3cm) located dorsally within the cranial mediastinum that displaced ventrally the trachea and the oesophagus was also identified. The mass had a T2W hypointense capsule and a T2W homogenously hyperintense and T1W isointense centre with a thin contrast medium-enhanced peripheral rim (Fig. 2).

A Computed Tomography (CT) of the thorax and an ultrasound of the mediastinal mass (via a thoracic inlet window) and the abdomen were also performed. The abdominal ultrasound was normal. Ultrasonographically, the mass in the mediastinum (5.9cm x 4.4cm) was heterogeneous and was associated with multiple irregular anechoic areas, consistent with cystic, necrotic and/or hemorrhagic regions. Blood flow was not detected with colour flow Doppler and there were no reactive changes in the surrounding tissue. On CT the mass was well defined, slightly heterogeneous and had a soft tissue density. A fine needle aspirate could not be safely performed due to the relative position of the mass and the major blood vessels.

A sample of cerebrospinal fluid (CSF) was collected from the cerebellomedullary cistern (c) and the lumbar region (l). Both samples revealed neutrophilic leucocytosis, (c-960 nucleated cells/µl and l-1360 nucleated cells/µl [reference range: <5]; consisting of 78-80% neutrophils, 10-14% lymphocytes and 2-6% macrophages, respectively), presence of red blood cells (c-24000/µl and l-3340/µl [reference range: 0]) and increased total protein (c-136mg/dl and l-638.2mg/dl [reference range: <25 and <45 respectively]). The neutrophils were not degenerated and no microorganisms were observed. The presence of blood was likely the result of iatrogenic contamination. When applying protein concentration and leukocyte count correction formulas (1mg/dl or one white blood cell down every 1000 or 500 red blood cells respectively) values remain increased (c-112mg/dl and l-634.2mg/dl; c-912 nucleated cells/µl and l-1353 nucleated cells/µl).

DIFFERENTIAL DIAGNOSIS

The main differential diagnosis taking into consideration the patient's signalment, clinical signs, CSF analysis results and the MRI findings was a severe manifestation of SRMA with multiple

haemorrhages. Other differential diagnoses, such as infectious meningoencephalomyelitis were not fully excluded but were considered less likely.

TREATMENT

Treatment with 20mg/kg of oral metronidazole (Metrobactin, Dechra) every 12 hours for 7 days and 25mg/kg of oral amoxicillin-clavulanic acid (Clavaseptin, Vetoquinol) every 12 hours for 7 days was initiated while waiting for CSF analysis results. During hospitalization and to control the severe pain, 0.3mg/kg of intravenous methadone (Comfortan, Dechra) every 4 hours for 2 days and 0.02mg/kg intravenous buprenorphine (Vetergesic, Ceva Animal Health Ltd) every 6 hours for 1 day after discontinuing treatment with methadone were administered. Immunosuppressive doses of oral prednisolone (Prednidale, Dechra) at 2mg/kg every 12 hours and 1mg/kg of oral omeprazole (Losec mups, AstraZeneca) every 24 hours for 7 days were initiated when the CSF analysis results were obtained. The dose of prednisolone was gradually decreased over a six months period as previously described (Lowrie and others 2009).

OUTCOME AND FOLLOW-UP

A significant improvement was observed and the dog was discharged five days after admission.

The dog was re-examined two and eight weeks after diagnosis. Neurological examinations during both rechecks were normal and the owners reported a significant improvement. An ultrasound of the thoracic mass was performed at the first re-examination and revealed that the mass had reduced in size (1.5cm x 3.6cm) and appeared more homogeneous. Follow-up MRI at the second recheck revealed the mediastinal mass had disappeared and the olfactory bulb/frontal lobe mass had significantly reduced in size (1cm x 0.5cm). The mass was homogenously hypointense on T2W, FLAIR and T1W images with a signal void on T2* and no contrast enhancement (Fig. 3).

The owners were contacted by phone 13 months after diagnosis. The dog had been normal for 10 months and then had another episode of neck pain and pyrexia that resolved with another course of prednisolone using the same protocol (Lowrie and others 2009).

DISCUSSION

The aetiology is obscure, but SRMA is an immune-mediated disease. The lack of identifiable infectious organisms, response to treatment with steroids, high concentrations of immunoglobulin A (IgA) in the serum and CSF and increased interleukin 6 (IL-6) and transforming growth factor *beta* 1 (TGF-ß$_1$) in CSF support this statement (Maiolini and others 2012, Rose and Harcourt-Brown 2013, Biedermann and others 2016, Maiolini and others 2013). IL-6 and TGF-ß$_1$ cause CD4 progenitors to differentiate towards a T helper (Th 17) and a recent study demonstrated that Th17 cells induce the autoimmune response in SRMA and are involved in the development of the severe neutrophilic pleocytosis and disruption of the blood brain barrier (Maiolini and others 2013, Freundt-Revilla and others 2017).

Although the clinical and pathological manifestation of SRMA is predominantly neurological (Harcourt 1978, Tipold and others 1995, Tipold and Jaggy 1994, Lowrie and others 2009), SRMA is a systemic disease with potential involvement of multiple organs (Tipold and others 1995, Navarro-Cubas and others 2011, Snyder and others 1995). Small to medium-sized muscular arteries of the heart, cranial mediastinum and cervical spinal cord are consistently involved and vasculitis occurs occasionally in other organs (Snyder and others 1995). The extracranial mass in this dog was possibly a hematoma located in the cranial mediastinum that disappeared following immunosuppression with steroids, supporting its possible relationship with SRMA.

The mass was mainly located within the left olfactory lobe and may explain why no cranial nerve

or proprioceptive deficits were identified. The cause of the transient proprioceptive ataxia followed by collapse without loss consciousness is unknown, but the authors hypothesise it could be explained by quick changes in intracranial pressure secondary to the intracerebral haemorrhage.

Intraparenchymal central nervous system lesions are uncommon with SRMA, but can occur. Massive extension of suppurative inflammation to the ventricles and the forebrain was reported in a boxer (Wrzosek and others 2009) and haemorrhage in the central canal of the cervical spinal cord with mild inflammatory infiltrate that occasionally extended into the superficial spinal cord parenchyma was reported in a coonhound (Hughes and others 2015). Furthermore, some dogs with SRMA have proprioceptive deficits and/or gait abnormalities identified on clinical examination (Tipold and Jaggy 1994). This could be due to spinal cord compression by enlarged vessels or tissue ischaemia secondary to vasculitis (Moore and Cupps 1983). Vacuolization of the white matter spinal tracts underlying the severely affected leptomeninges has been previously identified histopathologically in two cases (Snyder and others 1995).

Dogs with non-traumatic intracranial haemorrhage are frequently diagnosed with concurrent medical conditions (Lowrie and others 2012). The presence of these conditions does not necessarily mean they were the cause of the haemorrhage, but a relationship is suspected in some cases. To the authors' knowledge, this is the first report of intracerebral haemorrhage in a dog with SRMA. Despite being unspecific, measuring C-reactive protein could have provided further support of our presumptive diagnosis (Bathen-Noethen and others 2008).

Focal suppurative inflammation with vascular changes and secondary haemorrhages has been previously identified on histopathology in the epidural outer layers of the dura matter and the epineurium of the spinal nerve roots of dogs with SRMA (Tipold and others 1995). The meningeal haemorrhages can occasionally be extensive and affect the cerebrum, cerebellum and spinal cord (Hughes and others 2015). Thrombosis and dissolution of arterial wall integrity leads to haemorrhage and necrosis (Snyder and others 1995). This pathophysiological mechanism could have led to the formation of the intracerebral haemorrhage in our dog.

The MRI signal for intracerebral haemorrhage is well documented and its appearance varies based on location, size, duration and source (due to alterations in blood haemoglobin) (Weingarten and others 1991, Zimmerman and others 1988, Taber and others 1996). The signal of the cerebral lesion during the first MRI varied between the centre and its periphery and this could represent different stages of clot formation. The signal of the lesion during the second MRI was compatible with a chronic haemorrhage (>14 days) (Weingarten and others 1991). The signal void observed on T2* sequences is not specific for haemorrhage and can be seen with mineralization, gas, fibrous tissue and iron deposits (Mulkern 2002). These were all considered less likely in this dog. Mild changes in cervical muscles were also identified; however, this can occur with inflammatory spinal cord disease (Eminaga and others 2013). The absence of an identifiable coagulopathy and other medical conditions suggested the cerebral haemorrhage possibly occurred secondary to the SRMA.

The main limitation of this case report is the absence of histopathological confirmation. There is no definitive ante-mortem diagnostic test for SRMA and current diagnosis is based on clinical signs, laboratory findings and exclusion of other diseases (Lowrie and others 2012). Signalment, clinical signs (excluding the episode of collapse), CSF analysis results and response to treatment in our dog were characteristic of SRMA (Tipold and Jaggy 1994, Rose and Harcourt-Brown 2013, Rose and others 2014, Cizinauskas and others 2000, Tipold and Schatzberg 2010). The clinical response to treatment with steroids, the absorption of the intracerebral haemorrhage and the mediastinal mass and the lack of more clinically significant haemorrhages during the follow-up period, support the possible relationship of the intracerebral haemorrhage and the mediastinal mass with SRMA.

LEARNING POINTS/TAKE HOME MESSAGES

- SRMA is a systemic disease with potential involvement of multiple organs.
- Intracerebral haemorrhage can occur secondary to SRMA.
- Outcome of cases with SRMA and secondary haemorrhages can be good.

REFERENCES

Bathen-Noethen A., Carlson R., Menzel D., Mischke R., Tipold A (2008) Concentrations of acute-phase proteins in dogs with steroid-responsive meningitis-arteritis. Journal of Veterinary Internal Medicine 22, 1149-1156

Biedermann E., Tipold A., Flegel T. (2016) Relapses in dogs with steroid-responsive meningitis-arteritis. Journal of Small Animal Practice 57**,** 91-95

Cizinauskas S., Jaggy A., Tipold A. (2000) Long-term treatment of dogs with steroid-responsive meningitis-arteritis clinical, laboratory and therapeutic results. Journal of Small Animal Practice. 41, 295-301

Eminaga S., Cherubini GB., Villiers E., Targett M., Caine A. (2013) STIR muscle hyperintensity in the cervical muscles associated with inflammatory spinal cord disease of unknown origin. Journal of Small Animal Practice 54, 137-142

Fluehmann G., Doherr M. G., Jaggy A. (2006) Canine neurological diseases in a referral hospital population between 1989 and 2000 in Switzerland. Journal of Small Animal Practice 47**,** 582-587

Freundt-Revilla J., Maiolini A., Carlson R., Beyerbach M., Rentmeister K., Flegel T., Fischer A., Tipold A. (2017) Th17-skewed immune response and cluster of differentiation 40 ligand expression in canine steroid-responsive meningitis-arteritis, a large animal model for neutrophilic meningitis. Journal of Neuroinflammation 14, 20

Harcourt R. (1978) Polyarteritis in a colony of beagles. Veterinary Record 102**,** 519-522

Hughes K. L., Stieger-Vanegas S. M, Valentine B. A. (2015) Hemorrhage in the central canal of the cervical spinal cord in a coonhound diagnosed with canine juvenile polyarteritis (steroid responsive meningitis-arteritis). The Canadian Veterinary Journal 56, 567-570

Lowrie M., De Risio L., Dennis R., Llabres-Diaz F., Garosi L. (2012) Concurrent medical conditions and long-term outcome in dogs with nontraumatic intracranial hemorrhage. Veterinary Radiology and Ultrasound 53**,** 381-388

Lowrie M., Penderis J., McLaughlin M., Eckersall P. D., Anderson T. J. (2009) Steroid responsive meningitis arteritis- a prospective study of potential disease markers, prednisolone treatment and long term outcome in 20 dogs. Journal of Veterinary Internal Medicine 23, 862-870

Maiolini A., Carlson R., Schwartz M., Gandini G., Tipold A. (2012) Determination of immunoglobulin A concentrations in the serum and cerebrospinal fluid of dogs: an estimation of its diagnostic value in canine steroid-responsive-meningitis-arteritis. Veterinary Journal 191**,** 219-24

Maiolini A., Otten M., Hewicker-Trautwein M., Carlson R., Tipold A. (2013) Interleukin-6, vascular endothelial growth factor and transforming growth factor beta 1 in canine steroid

responsive meningitis-arteritis 9, 23

More P. M., Cupps T. T., (1983) Neurological complications of vasculitis. Annals of Neurology 14, 155-167

Mulkern R. V. (2002) Fast imaging techniques. In: Atlas SW (ed): Magnetic resonance imaging of the brain and spine., Philadelphia, Lippincott Williams & Wilkins. p.178

Navarro-Cubas J., Bell R., Wotton P.R., Gutierrez-Quintana R., Mclauchlan G. (2011) Steroid-responsive meningitis-arteritis with spontaneous echocardiographic contrast and elevated cardiac troponin I in a dog. Veterinary Record 169**,** 527

Rose J. H., Harcourt-Brown T. R. (2013) Screening diagnostics to identify triggers in 21 cases of steroid-responsive meningitis-arteritis. Journal of Small Animal Practice 54**,** 575-578

Rose J. H., Kwiatkowska M., Henderson E. R., Granger N., Murray J. K., Harcourt-Brown T. R. (2014) The impact of demographic, social, and environmental factors on the development of steroid-responsive meningitis-arteritis (SRMA) in the United Kingdom. Journal of Veterinary Internal Medicine 28**,** 1199-1202

Snyder P. W., Kazacos E. A., Scott-Moncrieff J. C., Hogenesch H., Carlton W. W., Glickman L. T., Felsburg P. J. (1995) Pathologic features of naturally occurring juvenil polyarteritis in beagle dogs. Veterinary Pathology. 32, 337-345

Taber K. H., Hayman L. A., Herrick R. C., Kirkpatrick J. B. (1996) Importance of clot structure in gradientl echo magnetic resonance imaging of hematoma. Journal of Magnetic Resonance Imaging 6, 878-883

Tipold A., Schatzberg S. J. (2010) An update on steroid-responsive meningitis-arteritis. Journal of Small Animal Practice 51**,** 150-4

Tipold A., Vandevelde M., Zurbriggen A. (1995) Neuroimmunological studies in steroid-responsive meningitis-arteritis in dogs. Research in Veterinary Science 58, 103-108

Tipold A., Jaggy A. (1994) Steroid-responsive meningitis-arteritis in dogs- Long-term study of 32 cases. Journal of Small Animal Practice 35, 311-316

Weingarten K., Zimmerman R., Deo-Narine V., Markisz J., Cahill P., Deck M. (1991) MR imaging of acute intracranial hemorrhage: findings on sequential spin-echo and gradient-echo images in a dog model. American Journal of Neuroradiolog, 12**,** 457-467

Wrzosek M., Konar M., Vandevelde M., Oevermann A. (2009) Cerebral extension of steroid-responsive meningitis arteritis in a boxer. Journal of Small Animal Practice 50**,** 35-37

Zimmerman R. D., Heier L. A., Snow R. B., Liu D. P., Kelly A. B., Deck M. D. (1988) Acute intracranial hemorrhage: intensity changes on sequential MR scans at 0.5 T. American Journal of Roentgenology 150**,** 651-661

FIGURE/VIDEO CAPTIONS

Figure legends:

Figure 1
Transverse magnetic resonance images at the level of the olfactory lobes illustrating the suspected haemorrhage (arrow). The haemorrhage was heterogeneously hyperintense on T2W (A) and had a hypointense center and peripheral a signal void on T2* images (B). On T1W images the haemorrhage had a hyperintense periphery and isointense core (C) with no contrast enhancement (D).

Figure 2
Sagittal magnetic resonance images of the neck illustrating the oval-shaped well-defined mass located dorsally within the cranial mediastinum (large arrow) and the contrast enhancement of the cervical meninges (small arrow). The mass had a T2W hypointense capsule (A) and a T2W (A) homogenously hyperintense and T1W (B) isointense center with a peripheral thin ring of contrast uptake (C).

Figure 3:
Transverse magnetic resonance images at the level of the olfactory lobes illustrating reduction in size of the intracranial haemorrhage (arrow). The mass was homogenously hypointense on T2W (A), with a signal void on T2* (B), homogenously hypointense on T1W images (C) and with no contrast enhancement (D).

OWNER'S PERSPECTIVE *Optional*

None

Copyright Statement

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