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**TITLE OF CASE**

**MRI and Clinical Resolution of a Suspected Intracranial Toxoplasma Granuloma with Medical Treatment in a Domestic Short Hair Cat**

**SUMMARY**

A 2-year-old cat was presented with a left paradoxical vestibular syndrome. MRI of the brain revealed an extra-axial homogeneously contrast enhancing mass in the region of the left caudal cerebellar peduncle. Toxoplasma serology was consistent with active infection and the lesion was suspected to be a toxoplasma granuloma. Following 8 weeks of tapering oral prednisolone and 11 weeks of oral clindamycin treatment, repeat MRI revealed resolution of the lesion. Eighteen months after initial diagnosis the cat remained neurologically normal. Differential diagnoses for a solitary, extra-axial, contrast enhancing mass lesion in the feline brain should include toxoplasma granuloma, which can undergo MRI and clinical resolution with medical treatment.

**BACKGROUND**

*Toxoplasma gondii* is an obligate intracellular protozoal parasite, of which cats are the sole definitive host (Dubey and others 2009). Oocysts are shed in the faeces of infected cats and will subsequently sporulate, becoming infectious to all mammals and birds. After ingestion, sporozoites are released into the gastrointestinal tract, where they can penetrate the mucosa and migrate to a variety of tissues including the liver, kidney, muscle, eye, brain and spinal cord (Dubey and others 2009; Turner 1978). Feline CNS toxoplasmosis typically causes an encephalitis or meningoencephalitis without gross lesions. Histopathological lesions include microscopic pyogranulomas containing intracellular tachyzoites (Dubey and Carpenter 1993; Turner 1978). However, macroscopic granulomas are also recognised (Falzone and others 2008; Pfohl and Dewey 2005). Clindamycin or a trimethoprim-sulphonamide has been prescribed most

frequently for the treatment of clinical toxoplasmosis (Dubey and others 2009; Lappin 2010; Lappin and others 1989). The prognosis is variable, and generally considered to be poorer in cats with hepatic, CNS or pulmonary disease (Dubey and Carpenter 1993; Dubey and others 2009; Lappin 2010; Lappin and others 1989). Cats with neurological deficits as a result of toxoplasmosis may show persistence of those deficits despite therapy (Lappin 2010).

The following case report describes the clinical findings, MRI features, medical treatment and outcome of a cat with a suspected macroscopic toxoplasma granuloma in the caudal cranial fossa. To the authors' knowledge this is the first report of successful medical management of a CNS toxoplasma granuloma.

#### **CASE PRESENTATION**

A 2-year-old, female neutered domestic short hair cat was presented with a six-week history of obtundation. The cat had been obtained from a rescue centre 8 months previously, had outdoor access and was fed a complete feline diet. Two days prior to referral the cat deteriorated with the development of vestibular ataxia, reluctance to ambulate and inappetance. On presentation, the cat was quiet but responsive and the general physical examination was unremarkable. Neurological examination findings were consistent with a left paradoxical vestibular syndrome, and included vestibular ataxia (leaning to the right), a right-sided head tilt, a rotatory positional nystagmus (fast phase to the left) and delayed postural reactions in the left thoracic and pelvic limbs. The anatomical neuro-localisation was the left caudal cerebellar peduncle.

#### **INVESTIGATIONS**

Hematology and biochemistry analysis was within reference intervals, and serological analysis for feline leukemia virus antigen and feline immunodeficiency virus antibodies was negative.

MRI of the brain (Intera 1.5T, Philips Medical Systems, Best, The Netherlands) was performed under general anaesthesia following a routine premedication, induction with propofol and

maintenance with isoflurane in oxygen. Compound sodium lactate was administered throughout the procedure at 5ml/kg/hr. MRI examination included T2-weighted (T2W) (repetition time, [TR] [ms], echo time [TE], [ms] 3333/110) sagittal and transverse images and T2W fluid attenuated inversion recovery (FLAIR) (TR/TE, 3612/80, inversion time [TI] [ms] 2000) transverse images. T1-weighted (T1W) (TR/TE, 515/15) sagittal, transverse and dorsal images were acquired before and after intravenous administration of gadolinium contrast (0.1mmol/kg, Gadobutrol, Gadovist, Bayer, Bayer House, Strawberry Hill, UK). Slice thickness was 1.75mm in the sagittal plane, 2mm in the transverse plane and 1.5mm in the dorsal plane with an inter-slice gap of 0.9mm in all planes.

The MRI showed a roughly spherical (9mm diameter) extra-axial mass in the region of the left caudal cerebellar peduncle (Figure 1). The mass was poorly and irregularly marginated. It was predominantly hyperintense to normal gray matter on T2W and FLAIR sequences, with a mixed intensity potentially consistent with regions of fluid and inflammatory cell accumulation. It was mostly T1W isointense to normal gray matter and had strong, homogenous enhancement following intravenous contrast administration. There was mild dural extension of the contrast enhancement from the border of the lesion (Figure 1E,F). The adjacent cerebellar parenchyma was hyperintense to normal gray matter in T2W sequences, consistent with possible vasogenic edema (Figure 1A,B). The mass was flattening and displacing the left cerebellar hemisphere and caudal brainstem, causing marked herniation of the cerebellar vermis through the foramen magnum (Figure 1A). There was slight subjective dilation of the third ventricle and the mesencephalic aqueduct suggesting partial occlusion by the mass lesion (Figure 1A). Computed tomography of the thorax and abdomen was performed immediately after the MRI using a 16-slice scanner (Mx8000 IDT, Philips Medical Systems. 120 kVp, 140 mAs, and 2.0 mm slice thickness). The CT was unremarkable, with no evidence of metastatic or primary disease.

CSF collection was not performed as the MRI findings were consistent with elevated intracranial pressure, posing increased risk of exacerbation of brain herniation (Falzone and others 2008;

Pfohl and Dewey 2005). To attempt to reduce the intracranial pressure via osmotic diuresis and reduction of the perimass vasogenic oedema intravenous mannitol (0.5g/kg) was administered as a single bolus prior to recovery, as well as intravenous dexamethasone (0.1mg/kg), and the cat made an uneventful recovery from anaesthesia.

#### **DIFFERENTIAL DIAGNOSIS**

The main differential diagnoses for the mass lesion included neoplasia (meningioma, lymphoma) and toxoplasma granuloma. Surgical biopsy was offered at this stage as histopathology would likely have provided a definitive diagnosis, but was declined by the owners. Toxoplasma serology using an immunofluorescent antibody assay revealed an elevated IgG titer of 100 (50-200 = evidence of toxoplasma exposure), and an elevated IgM titer of 40 (>20 = consistent with active infection) (Dubey and others 2009). Thus a toxoplasma granuloma was felt to be the most likely differential diagnosis.

**TREATMENT**

The cat received clindamycin (11mg/kg every 12 hours intravenously for 48 hours, then orally) and prednisolone (1mg/kg once a day orally for one week and then decreased by 25% every 14 days). Prednisolone was used to attempt to control any exacerbation of the CNS inflammation as a result of parasite death. A rapid clinical improvement was noted following initiation of medical treatment and the cat was discharged from the hospital 3 days later at which time it was bright, appetent with a mild right-sided head tilt and mild vestibular ataxia.

**OUTCOME AND FOLLOW-UP**

The cat was presented for re-examination seven weeks following hospital discharge, at which time it was reported to have made a full recovery. Neurological examination was normal. The oral clindamycin was continued, and the prednisolone dose progressively tapered and discontinued after 8 weeks of treatment.

Following 11 weeks of oral clindamycin treatment the cat remained neurologically normal and underwent follow-up MRI (Figure 2). This revealed gross resolution of the previously detected extra-axial mass lesion and the associated cerebellar vermis herniation (Figure 2A, B, C). Repeat Toxoplasma serological analysis revealed an IgG titer of 100, and an IgM titer of 20. The clindamycin was discontinued.

Via telephone discussion ten months later (18 months after the initial diagnosis), the owner reported that the cat remained bright and well with no detectable abnormalities.

**DISCUSSION**

This case report describes the successful medical treatment of a young adult cat presented with a left paradoxical vestibular syndrome, in which MRI revealed an extra-axial mass lesion suspected to be a toxoplasma granuloma. In a paradoxical vestibular syndrome, unlike a typical vestibular syndrome, the head tilt and circling is to the opposite side from the lesion. This is due to a loss of cerebellar inhibition of the vestibular nuclei on the affected side. The brain perceives this

unbalanced input as the animal turning to the side of the lesion. The neuro-localisation is the caudal cerebellar peduncle, where the lesion interferes with the afferent and efferent information travelling to and from the vestibulocerebellum (Thomson and others 2012).

The major differential diagnosis for a solitary, extra-axial, homogeneously contrast enhancing mass lesion in the cat brain would be neoplasia, with a meningioma being the most commonly recognised (Tomek and others 2006; Troxel and others 2003). Surgical excision of feline meningiomas is associated with a favourable prognosis and is often the treatment of choice (Cameron and others 2015; Gordon and others 1994; Troxel and others 2003). Two published case reports have each described the surgical excision of a solitary intracranial mass lesion, presumed to be a meningioma, in which postoperative histopathological analysis of the excised tissue instead revealed a diagnosis of toxoplasma granuloma (Falzone and others 2008; Pfohl and Dewey 2005). The MRI findings were of a round mass lesion in the region of the right olfactory bulb and rostral frontal lobe in one case (Pfohl and Dewey 2005), and the left temporal lobe in the second (Falzone and others 2008). The current case report differs in that the mass was located in the caudal cranial fossa. Further studies are required to ascertain if there may be a predilection site for toxoplasma granuloma formation in the feline brain. Falzone et al, 2008 described the mass to be T1-weighted isointense and T2-weighted hyperintense to normal gray matter, as found in the current case report. Furthermore, in all three cases homogenous contrast enhancement of the mass was evident, with contrast extension into the surrounding meninges, creating a dural tail. These imaging features are also typical of those of an intracranial meningioma (Lu and others 2003; Troxel and others 2004). Therefore, cats that present with neurological deficits indicative of a focal brain lesion and where MRI confirms the presence of a mass, a toxoplasma granuloma should be a differential diagnosis, and serological assessment of the toxoplasma titre should be performed prior to pursuing surgical treatment options.

Intracranial lymphoma was another important differential diagnosis for the mass lesion identified on MRI, particularly given the young age of the cat (Troxel and others 2003). The MRI features

of feline intracranial lymphoma are varied, with extra- and intra-axial mass lesions reported, as well as diffuse meningeal infiltration. The mass lesions typically show marked contrast enhancement, peritumoral oedema and variable mass effect (Troxel and others 2004).

In the two reported cases of intracranial toxoplasma granulomas that were surgically excised, clindamycin was administered for 4 to 6 weeks postoperatively but the clinical signs recurred 8 and 20 months postoperatively (Falzone and others 2008; Pfohl and Dewey 2005). MRI was repeated in one case, revealing a presumptive recurrence of the *T. gondii* granuloma (Falzone and others 2008). There are no previous reports of the outcome of medical treatment for feline intracranial toxoplasma granulomatous lesions. In human patients, clinical and MRI improvements have been seen with solitary or multiple CNS mass lesions attributable to toxoplasmosis that are treated medically without surgical debulking (Dannemann and others 1992; Navia and others 1986; Pruitt 2003; Vyas and Ebright 1996). While medical treatment can lead to resolution of clinical signs and MRI lesions, organisms in tissue cysts can survive for the life of the host as slowly dividing bradyzoites (Lappin and others 1989). Hence there is the potential for the disease to recrudesce and for clinical signs to recur. Studies of the long-term response to medical treatment of feline intracranial microscopic and macroscopic toxoplasma granulomas are needed.

Diagnosis of toxoplasmosis is challenging. Various techniques will often be combined to support the clinical suspicion of toxoplasmosis, including serology, CSF analysis for toxoplasma DNA or IgG, and tissue biopsies to assess for the presence of the protozoal organism (Gunn-Moore and Reed 2011). Toxoplasma serology is a very useful complementary diagnostic tool but no serological assay can definitively confirm a diagnosis of toxoplasmosis (Greene 2012). False positive results may arise due to prior exposure, while false negative results can occur early in the disease course or following steroid therapy. Additionally, persistent IgM elevation can occur in some cats without active infection, while others fail to show any detectable IgM response following inoculation (Lappin 2010).



A presumptive diagnosis of intracranial toxoplasma granuloma was made based on the positive serology, the MRI features of the mass and the gross resolution of the lesion on MRI following prolonged clindamycin therapy. Definitive diagnosis would necessitate biopsy of the lesion with direct identification of the parasite by immunohistochemistry (Lappin 2010). Biopsy and histological analysis was not performed in this case due to the perioperative risks associated with surgical biopsy collection, including haemorrhage and neurological deterioration, and the prompt and complete response to medical management. Had it been possible to collect CSF, this may have revealed tachyzoites, or facilitated PCR analysis for the presence of parasitic antigen (Stiles and others 1996). Other differential diagnoses for solitary intracranial mass lesions include neoplasia, fungal granuloma and bacterial abscess. However, the former two would not be expected to resolve with clindamycin therapy, and the MRI features of the mass were not consistent with a bacterial abscess, which would typically be hyperintense compared with normal gray matter on T2-weighted images, hypointense compared with normal gray matter on T1-weighted images with marked ring contrast enhancement (Costanzo and others 2011). Furthermore, no signs of a penetrating injury or local extension of infection, such as from an otitis media, were seen on MRI so again making an abscess less likely (haematogenous spread not excluded).

This case report highlights the potential for resolution of a large suspected intracranial toxoplasma granulomatous lesion with medical treatment and emphasizes the importance of including *T. gondi* in the list of differential diagnoses for single, extra-axial mass lesions in the feline brain.

#### **LEARNING POINTS/TAKE HOME MESSAGES**

- Toxoplasmosis can present as a single, extra-axial mass lesion in the cat brain and is an important differential diagnosis for intracranial neoplasia such as meningioma and lymphoma

- Serological assessment of the toxoplasma antibody titre is recommended in cats presenting with neurological signs, particularly in those with an extra-axial mass on brain MRI, before pursuing more invasive diagnostic or therapeutic procedures
- Large intracranial toxoplasma granulomatous lesions can be successfully managed with medical treatment and while the clinical signs potentially may recur, the case presented here indicates that a long clinical remission is possible without recurrence for a period of 18 months

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