

## CASE REPORT

# Cerebral cryptococcal granuloma in a cat

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A 7-year-old cat was presented for seizures. Cerebrospinal fluid cytology and serology were consistent with a diagnosis of toxoplasmosis. The cat was treated with clindamycin but seizures continued and additional neurological signs developed over 6 months. A mass lesion was identified in the left cerebral hemisphere using magnetic resonance imaging (MRI). The lesion enhanced after gadolinium and a tumour was considered likely. Histologically, the lesion proved to be a cryptococcal granuloma and retrospective serology confirmed that the cat had cryptococcosis at its initial presentation. This report provides the first description in the veterinary literature of the MRI appearance of a cerebral cryptococcoma and emphasises the importance of performing cryptococcal antigen determination in cats with signs of intracranial disease.

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A 7-year-old spayed domestic shorthaired cat presented with a history of having two seizures in the previous 6 weeks. During the seizures, the cat lost consciousness, paddled its limbs, rolled and urinated. There were no pre-ictal signs but the cat was weak and unable to walk normally in the post-ictal period.

Physical examination was unremarkable although there was evidence of overgrooming on the ventral abdomen. Neurological and ophthalmological examinations were considered normal. Abnormalities in routine haematology included a mild leucocytosis due to a mature neutrophilia. Plasma biochemistry revealed a slight increase in creatine kinase activity, consistent with muscle damage in a seizing patient. Urine was obtained by cystocentesis and a low number of bacteria were detected with microscopic examination; a light growth of a haemolytic *Escherichia coli* was cultured from the urine. Feline leukaemia antigen and feline immunodeficiency virus antibody assays were negative.

The cat was anaesthetised and cerebrospinal fluid (CSF) collected from the cerebellomedullary cistern. The fluid was clear and colourless with a protein concentration of 0.34 g/l and  $13.33 \times 10^6$  cells/l, comprising 30% monocytes and macrophages, 64% lymphocytes and 6% neutrophils. CSF culture was not performed. Recovery from anaesthesia was prompt but after extubation the cat started to paddle and bite its paws and became cyanotic before developing opisthotonos. Propofol was administered intravenously (iv) and the cat was re-intubated. However, it still exhibited extensor rigidity when extubation was attempted. The rigidity was controlled initially with midazolam (0.2 mg/kg iv) and subsequently with phenobarbitone (6 mg/kg iv) but mild limb paddling and excessive licking and leg biting continued. As the CSF pleocytosis suggested inflammatory intracranial disease, serum was submitted for toxoplasma serology. The *Toxoplasma gondii* specific immunoglobulin G (IgG) titre by immunofluorescent assay was 160 and the immunoglobulin M (IgM) titre was greater than or equal to 160. A tentative diagnosis of cerebral toxoplasmosis was made. Seizure activity resolved over 24 h and the cat was

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discharged from the hospital on clindamycin treatment (20 mg/kg twice daily orally (PO) for 4 weeks).

Two weeks later, another seizure was observed and the anticonvulsant phenobarbitone was added to the treatment (3 mg/kg once daily PO for 4 days increasing to 5.5 mg/kg daily PO in divided doses after 10 days). Toxoplasma serology four weeks later demonstrated the IgG titre had increased to greater than or equal to 640; the IgM titre was unchanged. One week after cessation of clindamycin treatment, another seizure occurred and a further 28-day course of clindamycin (20 mg/kg twice daily PO) was prescribed and phenobarbitone treatment was continued.

Six months after the initial examination, the cat presented for further evaluation. It had continued to seizure once every month, with each seizure lasting about 30 s. The owners commented that it usually held its head to the left when having a seizure. Two days before presentation, the cat had become anorexic, adipic and was observed straining to urinate and defaecate. It also started shivering, circling to the left, growling when handled and seemed poorly responsive to sound.

Physical examination revealed a very depressed cat with a dull coat and dry mucous membranes. It circled to the left and was mildly ataxic. Neurological examination revealed an absent menace response in the right eye, despite normal direct and consensual pupillary light reflexes, and subtle deficits in right fore- and hindlimb postural reactions. Spinal reflexes and proprioceptive positioning were considered normal. Prehension difficulties were observed although the cat could chew and swallow food placed in its mouth. The neurological findings were consistent with a lesion in the left prosencephalon and magnetic resonance imaging (MRI) of the brain was recommended.

With the cat anaesthetised, a GE Vectra II 0.5 Tesla scanner with a human wrist surface coil was used to obtain T1-weighted gradient echo sequence (SPGR) images in the sagittal, transverse (axial) and dorsal (coronal) planes (Fig 1a, b) and transverse T2-weighted images (Fig 2). T1-weighted transverse images were repeated after administration of gadolinium diethylenetriaminepentaacetic acid (Gd-DTPA) (0.1 mmol/kg) (Fig 3). A large intra-axial lesion (3×2×1.8 cm) was observed in the left cerebral hemisphere. The lesion was irregular in outline with a multi-lobed appearance. Increased signal density

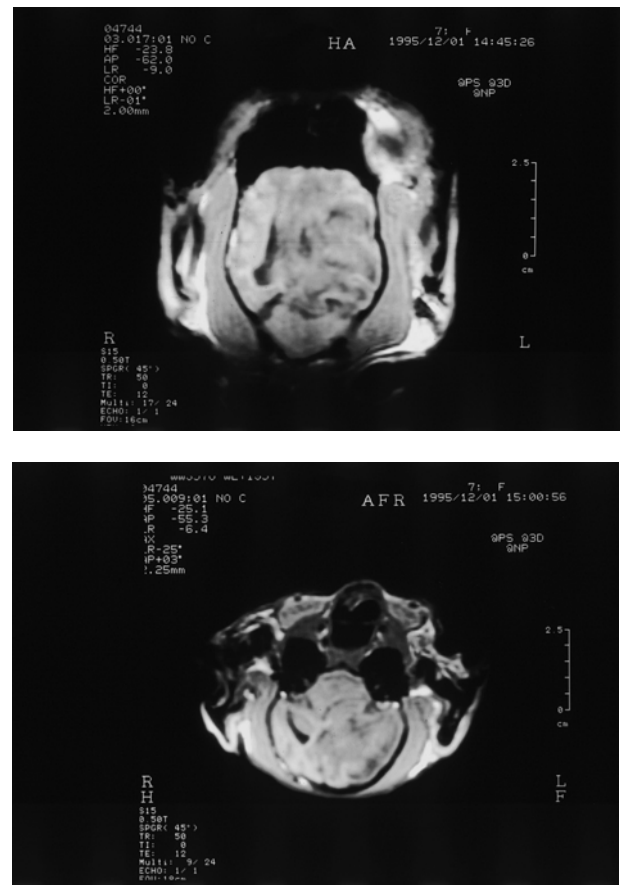
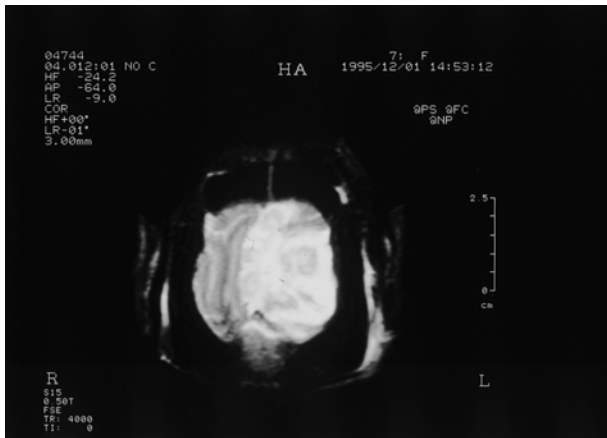
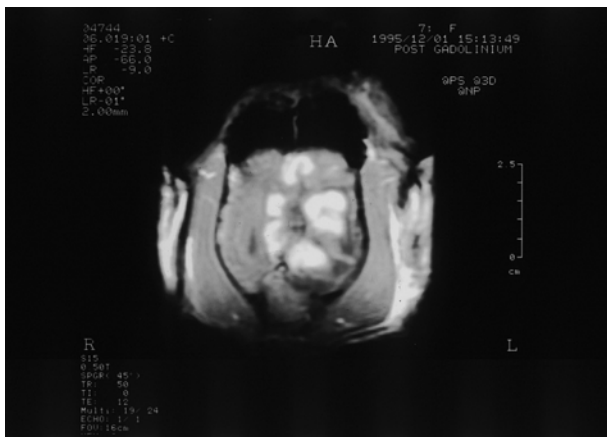


Fig 1. Transverse (a) and dorsal (b) SPGR images (50/12/45°) showing the hypo-intense lesion with mass effect compressing the lateral ventricle and producing subfalcine and descending transtentorial herniation.

on the T2-weighted images, interpreted as extensive surrounding oedema, was noted throughout the left cerebral hemisphere and there was considerable associated mass effect with compression of the left lateral ventricle and displacement of the midline structures towards the right. There was descending transtentorial herniation on the left compressing the dorsal aspect of the left cerebellar hemisphere and there was also subfalcine herniation. After Gd-DTPA, there was considerable gyriform enhancement in the margins of the mass and evidence of central necrosis. No other lesions were detected and there was no abnormality involving the ethmoid air cells or the cribriform plate. In view of the slowly progressive clinical signs, the location of the lesion, the extensive image enhancement after Gd-DTPA and the relatively well circumscribed nature of the single large lesion, meningioma and glioma were considered the most likely diagnoses. Excisional biopsy of the lesion was declined and euthanasia was performed.



**Fig 2.** Transverse (axial) FSE T2-weighted image (4000/110:TR/TC) showing a lobulated mass lesion in the left hemisphere with marked surrounding oedema and central fluid accumulation. There is a severe mass effect with subfalcine herniation.



**Fig 3.** Transverse (axial) SPGR contrast enhanced T1-weighted image (50/12/45°) at the same level as Fig 1. There is enhancement in the subcortical white matter at the margin of the central fluid density cavity producing a striking lobulated appearance to the lesion.

The mass identified by MRI corresponded histologically to several cryptococcal pyogranulomas enveloped by broad zones of oedema and gliosis. The large but variably sized inflammatory foci were present in the left dorsomedial, dorsal and dorsolateral cerebrocortical hemisphere, involving the gyri cinguli, splenialis, suprasplenialis marginalis, ectomarginalis (suprasylvianus) and ectosylvius (Fig 4). The foci involved both parietal and temporal lobe cortical grey and white matter of the corona radiata, with several foci extending into the overlying leptomeninges to produce adhesions between apposed gyri. There was no extension of

infection to involve the lumen of the compressed left lateral ventricle.

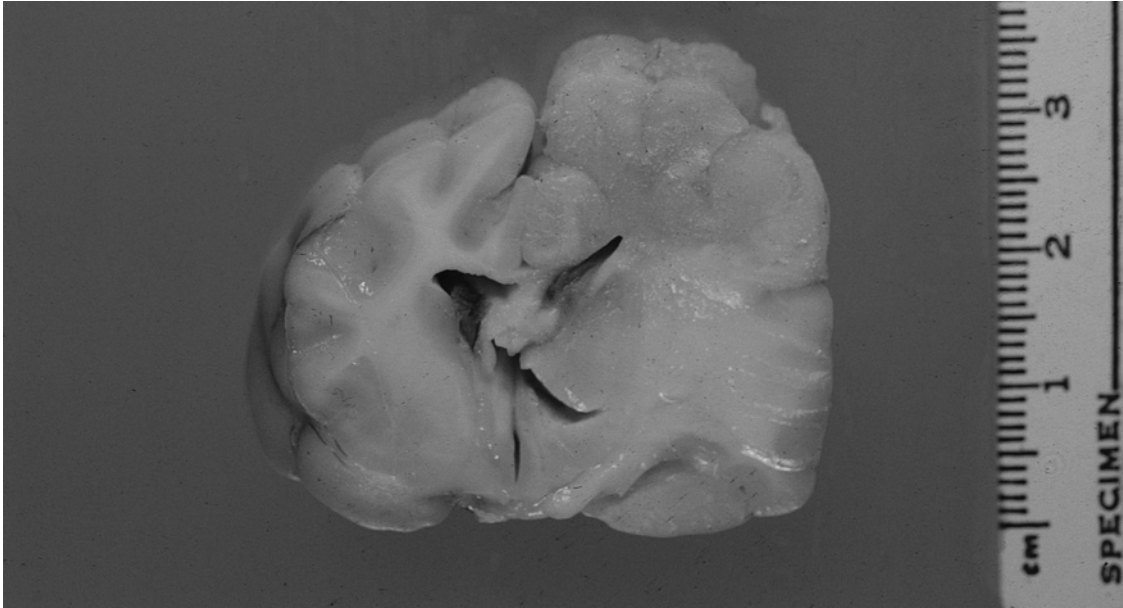
Cryptococcal organisms were present in moderate to regionally high numbers and were of typical appearance, being pale basophilic, round to ovoid structures surrounded by thick clear capsules which stained strongly with periodic acid Schiff. Narrow-based budding was infrequently observed (Fig 5). The organisms were up to 30  $\mu\text{m}$  in diameter, including the capsule. In some areas, there was only a mild neutrophilic response to high cell density sheets of yeasts. In most areas, however, there was intense suppurative to pyogranulomatous exudate enveloping small clusters of yeasts. Dense aggregates of lymphocytes and occasional plasma cells were scattered around the periphery of the inflammatory foci and were also present focally in the overlying leptomeninges and as thick cuffs in the Virchow–Robin spaces of the surrounding neuropil. Broad zones of moderate to severe oedema and reactive gliosis were present in the cortex adjacent to the infectious foci and extending to the margins of the left lateral ventricle and into the left medial corpus callosum. Moderate to severe oedema also radiated into the left dorsolateral and lateral thalamus, corona radiata, internal capsule and corpus striatum. Much of the white matter and, to a lesser extent, grey matter of the left dorsomedial and dorsal cerebral cortex was reduced to glial scar tissue rich in fibrous gemistocytes.

Cryptococcal organisms in the histological sections were typed as *Cryptococcus neoformans* var. *neoformans* using immunohistochemistry. This new method utilises monoclonal antibodies directed against variety specific capsular antigens (Krockenberger et al., in preparation). A latex cryptococcal antigen agglutination test (LCAT) titre was determined retrospectively on stored serum from the initial presentation and was found to be 32, indicating that cryptococcal infection had most probably been responsible for all the cat's clinical signs.

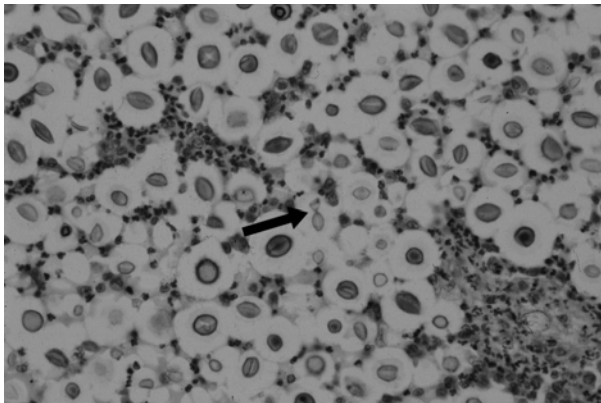
## Discussion

Diseases of the feline central nervous system can be difficult to diagnose as neurological examinations are often difficult to perform and interpret, CSF cytology is typically neither sensitive nor specific and imaging studies are expensive and not easily accessible. This report describes a cat with cerebral disease in which CSF cytology,





**Fig 4.** Transverse section of the brain at the level of the third ventricle and optic tract. Enlargement, distortion and grey discolouration of grey and white matter of the left parietal cortex and left dorsolateral thalamus, with compression of the left lateral ventricle and right displacement of midline structures. Marked expansion of the corona radiata, internal capsule, corpus striatum and lateral thalamus due to reactive oedema and gliosis is evident.



**Fig 5.** Left dorsal cerebral cortex. Aggregates of cryptococcal yeasts surrounded by clear halos representing polysaccharide capsules, with infiltrating neutrophils. Central arrow demonstrates narrow-based budding of a yeast. (Haematoxylin and eosin, magnification  $\times 230$ ).

serology for *Toxoplasma gondii* and MRI led to incorrect diagnoses.

The seizures for which the cat initially presented were almost certainly referable to a small cerebral cryptococcal granuloma. The lesion presumably acted as an epileptogenic focus but was not large enough to cause signs of prosencephalic dysfunction that could be appreciated on routine neurological examination. The neurological signs which developed as the cat deteriorated were consistent with expansion of a mass

lesion in the left prosencephalon. Lesions in this area can result in contralateral menace and postural reaction deficits. The right-sided postural reaction deficits result from interference with ascending conscious proprioceptive pathways or descending upper motor neurons in the left prosencephalon (Glass et al 1996). The overgrooming and agitated licking and biting of the skin associated with seizure activity were consistent with a disturbance to thalamocortical pathways concerned with cutaneous sensation and nociception. Circling towards the side of the lesion is common with prosencephalic lesions (Oliver & Lorenz 1983, Glass et al 1996) and it was interesting that seizure activity invariably resulted in a left head tilt, an ipsilateral vestibular sign. Prosencephalic lesions have also been reported to cause inappropriate urination (Glass et al 1996) but it is not known whether the straining in this case was related to neurological disorder or a lower urinary tract problem. The cat's clinical signs at the final presentation were almost identical to those described by Glass et al (1996) in a cat with a single, large cryptococcal granuloma documented by computerised tomography (CT) imaging and excisional biopsy.

Central nervous system cryptococcosis is a particularly important neurological problem in humans with acquired immunodeficiency syndrome (AIDS). There are numerous reports of MRI findings in humans with intracranial

cryptococcosis but mostly with respect to patients with AIDS (Tien et al 1991, Mathews et al 1992, Andreula et al 1993, Miszkiel et al 1996, Sánchez-Portocarrero & Pérez-Cecilia 1997). Magnetic resonance imaging in humans with intracranial cryptococcosis usually demonstrates meningitis or meningoencephalitis, dilated Virchow–Robin spaces, cyst-like structures (gelatinous pseudocysts) and granulomas (cryptococcomas) (Andreula et al 1993, Ostrow & Hudgins 1994, Miszkiel et al 1996). Lesions are usually hyperintense on T2-weighted scans and have intermediate to low signal intensity on T1-weighted sequences. The lesions are usually in the basal ganglia, thalamus or midbrain and range from 3 mm to several centimetres in diameter (Andreula et al 1993, Ostrow & Hudgins 1994, Miszkiel et al 1996). Enhancement of cryptococcomas or the leptomeninges after Gd-DTPA is not typical (Mathews et al 1992, Andreula et al 1993, Ostrow & Hudgins 1994, Miszkiel et al 1996) although it has been reported (Tiens et al 1991). Doubling the dose of Gd-DTPA has been reported to cause more reliable enhancement (Andreula et al 1993). The reason for this lack of enhancement has been attributed to a poor inflammatory response due to the unique character of the organism and its protective polysaccharide capsule or, more likely, as a result of the profound immunosuppression involved in the majority of human cases of cryptococcosis (Yu et al 1995, Miszkiel et al 1996). Contrast enhancement has been reported in an immunocompetent human patient (Yu et al 1995) and in a dog (Tiches et al 1998).

There are relatively few MRI reports of cryptococcal mass lesions in humans as the frequency of these lesions in AIDS patients is very low (Sánchez-Portocarrero & Pérez-Cecilia 1997). When the literature was reviewed, 9% of HIV patients had focal cerebral mass lesions attributed to cryptococcosis (but which could have been due to other pathology such as toxoplasmosis or lymphosarcoma) compared with 23% of immunocompetent patients (Sánchez-Portocarrero & Pérez-Cecilia 1997). This difference could be related to a difference in cryptococcal varieties involved, as cryptococcosis in immunocompromised humans appears to be almost exclusively due to *Cryptococcus neoformans* var *neoformans* whilst 74% of infections in immunocompetent patients are due to *Cryptococcus neoformans* var *gattii*, (Mitchell et al 1995). Cerebral cryptococcomas have been reported in one study as only occurring with var *gattii* infections (Speed 1993, Speed & Dunt 1995) and

extrapolating from the human pathology and radiology studies, it was thought that var *gattii* was most likely in this cat. Although culture was not performed, the organism was typed as var *neoformans* by immunohistochemistry. This suggests that cryptococcal mass lesions may reflect a competent cell-mediated response rather than cryptococcal variety.

To our knowledge, this is the first description of MRI of a cerebral cryptococcal granuloma in a cat. Cryptococcosis was not suspected in this patient because of the size and site of the lesion and the intense enhancement on T1-weighted images after Gd-DTPA. This report serves to highlight a number of issues in the diagnosis of CNS disease in cats. *Cryptococcus* organisms were not seen in the cat's CSF, but organisms are only found in 40–70% of human cases (Dimech 1991) and 60% of veterinary cases (Meric Taylor 1998) of CNS cryptococcosis. The lack of organisms and the relatively subtle pleocytosis may have been because the infection resulted in a cryptococcal granuloma with only late extension to involve the leptomeninges; human patients with solitary cerebral lesions can have normal CSF (Mitchell et al 1995). Culture of the CSF may have been rewarding although negative results of culture have been recorded in human patients with CNS cryptococcosis (Speed & Dunt 1995). As a provisional diagnosis of toxoplasmosis was made on the basis of the CSF analysis and serology, cryptococcosis was dismissed as a diagnostic possibility and a LCAT was not performed. It was later revealed that the toxoplasma IgM test procedure used had very low specificity although the rising toxoplasma IgG titre serology was certainly typical of a recent infection with *T gondii*. The presence of infection does not necessarily correlate with clinical disease (Dubey 1994) and the relatively poor response to prolonged clindamycin treatment should have indicated that toxoplasmosis was unlikely to be responsible for the cat's signs.

A LCAT following pronase treatment (Stockman & Roberts 1983, Medleau et al 1990) should be performed routinely as part of the diagnostic investigation of intra-cranial disease in cats. The LCAT is a sensitive and specific test. It is simple, accessible, inexpensive, and, in this cat's case, would have eliminated the need for CSF collection (a procedure not without risk in cats with intracranial disease) and expensive imaging studies. Interestingly, cryptococcal antigen was not detected in the serum of one cat with a cerebral cryptococcal granuloma (Glass

et al 1996) although it was demonstrated retrospectively in our case. If treatment for cryptococcosis had been instituted at the first presentation, the cat's disease may well have resolved. Should imaging be performed in cats with CNS disease, the presence of a single, large, contrast-enhanced cerebral lesion should not preclude a diagnosis of cryptococcal granuloma. Differentiation of cryptococcomas from other brain lesions may be possible in the future with magnetic resonance spectroscopy based on the high levels of  $\alpha,\alpha$  trehalose present in the cryptococcal lesions (Dzendrowski et al 1999).

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