Central nervous system cryptococcosis in 3 cats in France

S. PAPAGEORGIOU*, Y. RUEL¹, J.-P. JÉGOU², K. GNIRS¹

¹Clinique Vétérinaire ADVETIA, 5 Rue Dubrunfaut, 75012, Paris, France
²Cabinet Médicochirurgical d’Ophthalmologie Vétérinaire, 39 Rue Rouelle, 75015 Paris

*Corresponding author: stepapageorgiou@gmail.com

SUMMARY

Three cats presenting a central nervous system cryptococcosis in France are reported. The first two cats presented with clinical signs attributed to intracranial disease and the third to cervical myelopathy. Diagnostic imaging (magnetic resonance imaging or computed tomography) was either normal or revealed focal/multifocal nodules within the central nervous system. Latex cryptococcal agglutination test on cerebrospinal fluid was positive for all three cats. The first cat was successfully treated, although a relapse was noted and treatment had to be maintained permanently. The second cat was euthanized before diagnosis was reached. Treatment failed to improve neurological status of the third cat and euthanasia was elected. This case series describes the clinical features, imaging characteristics and outcome of 3 cats with central nervous system cryptococcosis in France, where this affection is rarely reported.

Keywords: cryptococcosis, cat, central nervous system, eye, France

Introduction

Cryptococcosis, mainly caused by Cryptococcus neoformans and Cryptococcus gattii, is the most frequently reported feline systemic mycosis [4]. Cats are most likely infected by inhaling dust containing the airborne fungal yeast form [40]. Infection may result in upper respiratory, cutaneous, ocular and central nervous system (CNS) signs [40]. In the CNS, infection may lead to diffuse meningoencephalitis or granulomatous lesions referred to as «cryptococcomas» [40].

This case series describes the clinical features, imaging findings, and outcome of 3 cats with CNS cryptococcosis. To our knowledge it is the first report of cryptococcosis with brain involvement in France. It is also the first report of computed tomography (CT) findings of brain and spinal cryptococcomas in companion animals.

Case description

CASE 1

A 4.5-year old female Norwegian cat was presented for lethargy, anorexia, pyrexia and a left forelimb lameness progressing to a 4-limb ataxia. The cat was mainly indoor, and living in Paris. Physical examination revealed hyperthermia (39.3°C). Upon neurological examination, postural reaction deficits were detected in all 4 limbs. Spinal reflexes were normal. Cranial nerve testing revealed the absence of a menace response in the left eye with normal direct and consensual pupillary light reflexes. Vision was preserved for both eyes. Behaviour and mentation appeared normal. Cranial nerve testing revealed the absence of a menace response in the left eye with normal direct and consensual pupillary light reflexes. Vision was preserved for both eyes. Behaviour and mentation appeared normal. These neurological findings were consistent with a cerebellar lesion. Ophthalmological examination revealed multiple, small, irregular pigmented foci, consistent with bilateral multifocal granulomatous chorioretinitis (figure 1).

Mots-clés : cryptococcos, chat, système nerveux central, œil, France

RÉSUMÉ

Cryptococcose du système nerveux central chez 3 chats en France


Figure 1: Fundoscopic examination of left eye. Numerous multifocal chorioretinal granulomas of variable size scattered across the fundus.
Routine blood count and chemistry was unremarkable.

Feline leukaemia antigen (FeLV) and feline immunodeficiency virus (FIV) antibody assays were negative (Witness® FeLV-FIV, Zoetis).

Magnetic resonance imaging (MRI) of the brain was performed (MrV, Paramed, 0.22 T) under general anaesthesia. Dorsal T1-weighted, T2-weighted and FLAIR sequences were obtained. T1-weighted transverse images were repeated after IV administration of gadolinium diethylenetriaminepentaacetic acid (0.1 mmol/kg). MRI was normal. Cerebrospinal fluid (CSF) was collected from the cerebellomedullary cistern. The fluid had a total protein concentration of 0.6 g/l (reference value <0.35 g/l) and no pleocytosis. Numerous small (5 µm) yeast organisms that were stripped of their capsules were identified on a Diff-Quick-stained CSF smear. Qualitative latex cryptococcal antigen agglutination test (LCAT) (Crypto-LA II; Fumouze) performed on CSF was positive at a titer of 8.

A diagnosis of CNS cryptococcosis was made. Itraconazole (10 mg/kg q24h orally, Itrafungol®; Elanco) and prednisolone (0.5 mg/kg q24h orally for 3 weeks, Mégasolone® 5 mg, Merial) were initiated. Clinical response to treatment was favourable and the cat was neurologically normal within one month. Three months later the cat developed anorexia and treatment was interrupted. Itraconazole was replaced by Fluconazole (40 mg q12h orally, Trifulcan®; Pfizer). Follow up CSF tap was performed every 2 months for protein, cell count, LCAT and organism identification and was normal. After 11 months of treatment, fluconazole was discontinued. Three months later, clinical signs relapsed and treatment with fluconazole was re instituted at 16 mg per day. Two years and a half later the cat is alive and free of clinical signs. Treatment is maintained.

**CASE 2**

A 4-year old female neutered domestic shorthair cat was presented with a history of head tilt, recurrent episodes of fever and anorexia during the previous month. The cat was an outdoor Parisian cat. Physical examination was unremarkable with the exception of obtundation. Neurological examination revealed a head tilt to the left and an asymmetrical ataxia. Postural reaction deficits were detected on the left side. Spinal reflexes were normal. There was no evidence of an abnormal nystagmus or other cranial nerve deficits. The neurological examination was consistent with left central vestibular disease.

Routine blood count and chemistry was unremarkable.

The cat was anesthetised and CT-scan (Aquilion, Toshiba, 4 slice) was performed. Multiple ill-defined intraxial nodules, hyperdense to the cerebral parenchyma, were identified in the left cerebello-pontine angle, in the thalamus and in the cerebral hemispheres. After IV injection of iodinated contrast medium (2 mL/kg, Telebrix® 35; Guerbet) these lesions presented a strong ring-enhancement associated with diffuse and patchy meningeal enhancement (figure 2). There was a mild mass effect in the frontal area. No abnormality involving the ethmoid sinuses or the cribriform plate was noted. Infectious granulomas were suspected. CSF was collected from the cerebellomedullary cistern, and revealed a protein concentration of 0.4 g/l (reference value <0.35 g/l) and no pleocytosis. Toxoplasma gondii and feline coronavirus serology assay from CSF was negative but qualitative LCAT (Crypto-LA II; Fumouze) was positive at a titer of 4. The cat was euthanized before diagnosis was reached because of dramatic clinical deterioration. Necropsic examination was not allowed.

![Figure 2: CT-scan examination of the brain, soft tissue algorithm, after IV iodinated contrast medium injection. One lesion is visible in caudal fossa (A) and two in rostral fossa (B). They are nodular and ring-enhancing (arrowheads).](image)

**CASE 3**

An 11-year old male neutered domestic shorthair cat was presented for an acute onset of right hemiparesis. The patient was an indoor cat, and lived in Paris. Physical examination was normal. Neurological examination revealed severe right sided ambulatory hemiparesis. There were right-sided postural deficits and spinal reflexes were normal. Examination of cranial nerves was normal, as was the cat's behavior and mentation. These findings were compatible with a C1-C5 myelopathy.

FeLV and FIV antibody assays were negative (Witness® FeLV-FIV, Zoetis).

The cat was anaesthetised and a myelography was performed which revealed no spinal cord compression. A CT-scan (Aquilion, Toshiba, 4 slice) was performed. Pre-contrast study of the cervicothoracic region was normal. After IV injection of iodinated contrast medium (2 mL/kg, Telebrix® 35; Guerbet), a single intramedullary area of enhancement, lateralized to the right side, approximately 1cm long, was visible at the level of C4-C5 vertebras (figure 3). The lesion presented a strong, homogeneous contrast enhancement. Differential diagnosis included intramedullary neoplasia and infectious granuloma. Lumbar tap was performed but CSF was heavily contaminated with blood. CSF was collected from the cerebellomedullary cistern, and revealed no pleocytosis and normal total protein. Toxoplasma gondii and feline coronavirus serology assay from CSF were negative but
qualitative LCAT (Crypto-LA II; Fumouze) was positive at a titer of 4. The sample was insufficient to perform further dilution. A diagnosis of cryptococcosis was made and treatment was instituted with fluconazole (50 mg q12h orally, Triflucan; Pfizer) and prednisolone (1 mg/kg q24h orally, Dermipred 5 mg; Sogeval). Clinical signs progressed to a non-ambulatory tetraparesis rapidly after treatment onset and the cat was euthanized 1 week later due to continuous worsening of his neurological status. Necropsic examination was not allowed.

![Image](image-url)

**Figure 3:** Transversal (A) and sagittal (B) reconstruction of myeloscanner after IV iodinated contrast medium injection. A focal ovoid contrast-enhancing lesion is visible in the right side of the cord at the level of C4C5 (arrows).

**Discussion**

Cryptococcosis, principally caused by *Cryptococcus neoformans* and *Cryptococcus gattii*, is the most frequently reported feline systemic mycosis. Five serotypes of *Cryptococcus* have been recognized: *C. neoformans var grubii* (serotype A), *C neoformans var neoformans* (serotype D), a hybrid of these two varieties (serotype AD), and *C. gattii* (serotypes B and C) [40]. Recently, other varieties appeared to be pathogenic for the cat, namely *Cryptococcus magnus* and *Cryptococcus albidos* [21,22,36].

CNS cryptococcosis is an uncommon but potentially fatal disease. Published reports and studies in feline cryptococcosis are abundant in western Canada, western United States and Australia [7,8,12,17,23,27,31,34,39,43], but very sporadic in Europe [1,5,9,10,11,14,19,24,30]. To the authors’ knowledge only one case of CNS cryptococcosis has been reported in France to date [1].

In both animals and people, inhalation is the primary route of entry into the body. In contrast to humans where cryptococcosis is often associated with immunodeficiency (acquired immunodeficiency syndrome), the disease in dogs and cats occurs in immunocompetent hosts. Cats infected with FeLV or FIV are not considered to be at increased risk for infection but may experience more difficulty in clearing the infection compared with cats not infected with retroviruses [27,29,34,39]. Development of disease requires colonization of the upper respiratory tract in dogs and cats [3]. CNS signs in cats have been reported secondary to respiratory infection and not commonly as primary presenting signs [1,8,27]. All three cats of the present study had CNS signs with no reported history of respiratory signs.

The criteria for an antemortem diagnosis of CNS cryptococcosis include one or more of the following: 1) identification of typical encapsulated yeast-like organisms on CSF cytological examination, 2) a positive CSF fungal culture, 3) a positive measurement of cryptococcal antigens, 4) Isolation of *C. neoformans* outside the CNS and complete regression of the CNS signs with antifungal therapy [2]. LCAT in serum and CSF is highly specific and sensitive and aids both in diagnosis and monitoring animals during and after therapy [15,27,31].

Advanced imaging techniques may assist in the diagnosis of cryptococcosis. Cerebral and spinal cryptococcomas have been described in a few MRI studies in cats [1,13,18,26,30,38,39]. CT-scan modifications in CNS cryptococcosis had never been reported in cats in previous reports. In humans, the most common CT findings included normal studies, multiple nodules (both enhancing or non-enhancing), diffuse cerebral atrophy or hydrocephalus [35]. In the second cat, CT-scan revealed similar lesions with multiple ring-enhancing masses with a mild mass effect. In the third cat, CT-scan revealed a single intramedullary lesion, not visible on pre-contrast examination and presenting a strong, homogeneous contrast enhancement after meglumine ioxitalamate IV injection.

CSF analysis may display mixed or neutrophilic pleocytosis (ranging from 0 to 1440 cells/µL) and an elevated total protein concentration (ranging from 0.08-1.32 g/dL) [39]. However, normal CSF analysis is also reported in some patients [39]. A mild increase in total protein concentration was noted in cases 1 and 2 and CSF analysis was normal in the 3rd case. However, due to blood contamination at the lumbar tap, CSF collection in this case was performed rostral to the site of the lesion, possibly influencing the total nucleated cell count.

Differentiation of *C neoformans* from *C gattii* is possible with a culture on L-canavanine-glycine-bromthymol blue agar [25]. Furthermore, the different strains can be typed by molecular genotyping [33,42]. Culture and species differentiation was not attempted in any of the cases presented in this case series, as for clinical purposes a positive LCAT titer in the CSF associated with signs of CNS disease were considered of diagnostic value. However, a positive culture of the pathogen coupled with a drug susceptibility test would have enabled a better treatment option justification.

Many drugs have been reported for the treatment of cryptococcosis. Amphotericin appears to be an effective agent to treat severe cases of cryptococcosis or cats that fail to respond to azole therapy, especially the ones presenting with neurological signs [34]. The drug’s most important side effect: nephrotoxicity, and the exclusive parenteral administration limit its use [15,29]. For long-term therapy, imidazole compounds can be administered orally, but 5-flucytosine and ketoconazole (as single agents or in combination) have been unrewarding on CNS cryptococcosis [12,17]. These
agents have limited ability to reach effective therapeutic concentrations within the CNS without important side effects [15]. Triazole drugs have increased efficacy, better tissue penetration and reduced toxicity compared to ketoconazole. Itraconazole improved or cured more than 50% of the reported cats with CNS cryptococcosis, even though concentrations in CSF appeared to be low [32]. In the first cat, the drug was effective in resolving the neurological signs, but important adverse effects were reported (weakness, anorexia). Even if fluconazole was found to be less effective in vitro than were ketoconazole and amphoterin B, it has been reported as the treatment of choice for cats with CNS cryptococcosis [27,29]. It has minimal side effects (gastrointestinal signs, bone marrow suppression, hepatotoxicity) and exhibits an excellent penetration of the blood-brain barrier. In vitro studies indicate differences in drug susceptibility between different cryptococcal species and molecular types, as well as between different geographical locations of one molecular type [6,16,20,28,37,41].

Treatment is required for months to years, may be cost prohibitive for many owners and even when continued for long periods of time, does not preclude relapse [7,27,34]. Therapy should be continued until the test becomes negative or ideally until at least two negative tests one month apart are obtained. It has been recommended to periodically evaluate CSF via LCAT, cytologic examinations or fungal cultures for up to 1 year following resolution of clinical signs [15,26]. Unfortunately, animals may relapse, and a negative test does not preclude a relapse or reinfection. The cat described in case 1 relapsed 3 months after treatment was interrupted based on normal total protein, total nucleated cell count and negative LCAT titre in CSF. To detect any early relapses, antigen titre can be monitored every 3 to 6 months after treatment is interrupted [40].

Animals treated early in the course of infection have a fair chance of survival, with involvement of the CNS being the only significant predictor of mortality [8,12,17,23,34]. However, in cases 2 and 3 the delay in diagnosis due to unspecific clinical signs and geographic region unusual for cryptococcosis may have contributed to poor outcome.

Cryptococcosis is a major opportunistic fungal infection in immunocompromised humans [40]. Aerosol exposure of people from organic material rich in bird excreta has been a zoonotic concern [40]. Infected animals do not pose a public health threat to owners and veterinarians as the organism does not aerosolize from sites of infections and therefore the disease cannot be directly contracted, even though precautions should be taken when handling the yeast or infected tissue to avoid inadvertent inoculation [40].

This paper documents the first report of feline cerebral cryptococcosis in France and presents the first CT description of cerebral and spinal cord cryptococcoma. It emphasizes the importance of performing cryptococcal antigen testing in cats with intracranial diseases, even in regions were few cases have been reported so far.

References


CENTRAL NERVOUS SYSTEM CRYPTOCOCCOSIS IN 3 CATS IN FRANCE
