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Cerebral pyogranulomatous encephalitis caused by *Cladophialophora bantiana* in a 15-week-old domestic shorthair kitten

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Abstract

Case summary A case of cerebral phaeohyphomycosis caused by *Cladophialophora bantiana* is described in a 15-week-old domestic shorthair kitten.

Relevance and novel information Cerebral phaeohyphomycosis is a rare condition in cats caused by dematiaceous fungi. This report describes the clinical and histopathological findings in the youngest case documented in a feline, provides a brief review of aetiology, diagnosis, treatment and prognosis of cerebral phaeohyphomycosis and demonstrates the importance of molecular diagnostics in accurate mycotic species identification.

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Introduction

Phaeohyphomycosis is an infection caused by dematiaceous fungi, a group of fungi that have melanin pigment in their cell walls. Dematiaceous fungi are ubiquitous and found in soil worldwide.¹ Taxonomy is confusing, with frequent name changes reflecting new information in this emerging area of mycoses. The agent in this case, *Cladophialophora bantiana*, has gone through several taxonomical changes in the past, previously named *Cladosporium bantianum*, *Cladosporium trichoides* and *Xylohypha bantiana*.

Several clinical manifestations of phaeohyphomycosis have been reported in cats, most frequently subcutaneous infections.^{2–14} Central nervous system (CNS),^{15–23} pulmonary,²⁴ renal,^{25,26} nasal²⁷ and disseminated^{28–30} infections have also been reported.

CNS phaeohyphomycosis is a rare condition with 11 reported cases in cats.^{15–23,28} Clinical signs of CNS phaeohyphomycosis depend on the location of the infection; they include seizures, vertical nystagmus, cranial nerve deficits, altered mentation, ataxia, head tilt and paresis. Thus far, the youngest reported cases of CNS phaeohyphomycosis in cats have involved 6-month-old cats.^{15,18} The following report is the youngest feline case of phaeohyphomycosis documented to date.

Case description

An approximately 13-week-old, male, entire, domestic shorthair kitten weighing 1.59 kg was surrendered to a Brisbane clinic. Physical examination was unremarkable. After a 1 week isolation period, the kitten was castrated, microchipped, treated for parasites, vaccinated and adopted by a member of the public.

Six days later the kitten presented to the clinic with a 1 day history of vomiting, anorexia and lethargy.

The kitten had lost 170 g since adoption and was subdued. Anisocoria was noted with a mydriatic right pupil. No other significant abnormalities were identified. The

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kitten was started on once-daily subcutaneous amoxicillin/clavulanate (Clavulox; Pfizer) injections at 8.75 mg/kg.

Results of haematological and biochemical testing, pre- and postprandial serum bile acid concentrations and in-house urinalysis are presented in Tables 1 and 2. Absolute lymphopenia and moderate monocytosis were identified. Testing for feline leukaemia virus antigen and feline immunodeficiency virus antibodies was negative (SNAP FIV/FeLV Combo Test; IDEXX).

On day 3 of hospitalisation the kitten developed vertical nystagmus and ataxia, and was euthanased.

Necropsy demonstrated a 1.5 × 1.5 cm dark brown-to-black soft area that predominantly involved the left parietal lobe and extended across the longitudinal fissure to include a 0.5 × 0.5 cm region of the right parietal lobe of the cerebrum (Figure 1). On cut surface the lesion extended 1 cm into subcortical white matter. The left cerebral hemisphere was swollen with flattening and widening of gyri in comparison. The meninges were diffusely slightly reddened. No other gross lesions were identified on examination of the nasal cavity, sinuses, thoracic or abdominal cavities. Histopathology was performed on the brain.

Histological examination (Figures 2 and 3) showed fulminating, focal, pyogranulomatous meningoencephalitis with intralesional pigmented fungus, consistent with phaeohyphomycosis. Leptomeninges and Virchow–Robin spaces were expanded by severe infiltrate of macrophages, lesser neutrophils, lymphocytes, multinucleate giant cells and occasional plasma cells. Leukocytes were often centred on golden-brown pigmented fungi, present extracellularly and within the cytoplasm of macrophages and multinucleate giant cells. Fungal hyphae were 2–5 µm in diameter, poorly septate, sparsely and non-dichotomously branched, and had thin, slightly bulbous walls. Conidiophores were 2–10 µm, oval, present in chains (pseudohyphae), and sometimes showed a thin, translucent capsule. In severely affected areas, leukocytes extended into the adjacent white or grey matter parenchyma. Such regions occasionally showed gliosis, gemistocytic astrocytes, rarefaction and malacia. Rare meningeal veins had fibrin thrombi, rarely containing fungal elements.

Brain tissue was plated on Sabouraud agar and incubated at 28°C for 28 days, until growth of an olivaceous-to-greyish-green woolly fungus was detected. The microscopic morphology showed dark septate hyphae with conidiophores producing long chains of oval conidia. The fungus was given a presumptive identification of *Cladosporium* species and referred for molecular identification.

DNA sequence analysis of the internal transcribed spacer (ITS) 1, 5.8S and ITS2 regions, and the D1/D2 region of the 28S (large subunit) ribosomal DNA gene cluster, using published primers and standard

sequencing methodologies³¹ identified the fungus as *C. bantiana*. The isolate's sequence was compared with those in the ISHAM ITS database and the CBS database using the BLASTn search tool and showed >99.8% identity to MITS1144 and CBS118738, respectively.

Discussion

The most frequently isolated fungus in CNS phaeohyphomycosis in cats has been *C. bantiana*;^{15,17,23,26} however, there have been single case reports of *Verruconis gallopava*,²² *Phoma eupyrena*¹⁶ and *Exophiala jeanselmei*.²⁸ Similarly, in human beings *Cladophialophora* species are responsible for 48% of cases of CNS phaeohyphomycosis.³² *C. bantiana* is regarded as being neurotropic,^{1,33,34} however, there have been two feline cases caused by *C. bantiana* with renal²⁶ and systemic²⁹ involvement without CNS lesions.

This is the youngest feline case of phaeohyphomycosis documented to date. Previously, the youngest have both involved 6-month-old cats.^{15,18} While *C. bantiana* is typically associated with chronic and slowly progressive infections in human³⁵ and veterinary literature,³⁶ it may also cause acute infections.³³ Two reported cases of phaeohyphomycosis in human neonates, who developed clinical signs at 6³⁷ and 7³⁸ days old, respectively, after presumed postnatal infection, illustrate how rapidly clinical infection can develop.

The method of infection is incompletely understood and in most cases the route of entry is not identified. CNS infections are thought to occur via the respiratory route.¹ Ocular²³ and aural³⁹ routes of entry have also been suggested. In this case no gross pulmonary, sinus, aural or skin wounds were identified, and the route of infection was undetermined. Given the strong localisation of the infection to the meninges and the presence of meningeal venous thrombi, meningeal haematogenous entry was considered most likely. Unfortunately, owing to cost constraints, in this case histopathology was only performed on the brain. Histopathology of other tissues such as the nasal cavity, sinuses, hilar lymph nodes, lung and gastrointestinal tract may have better helped define the route of entry and it is recommended that, where possible, gross and histopathological examination of all tissues is performed at necropsy in future cases.

Most feline cases have not identified an underlying cause; however, there have been cases associated with corticosteroid administration¹⁹ and lymphocytic leukaemia.²⁶ Cerebral phaeohyphomycosis has also been described in a dog with persistent lymphopenia.⁴⁰ Risk factors in humans include HIV infection, solid organ and bone marrow transplantation, corticosteroid therapy and trauma; however, over half of human patients do not have an underlying disease or risk factor identified.³² This reflects the ability of dematiaceous fungi to act as primary pathogens. In the present case absolute lymphopenia was identified.

Table 1 Haematological, biochemistry, bile acid and endocrine test results

Parameter	Result	Reference interval
Haematology		
RBC ($\times 10^{12}/l$)	8.2	4.9–10.0
Haemoglobin (g/l)	111	77–156
Haematocrit (l/l)	0.33	0.25–0.48
Reticulocyte (%)	0.1	0.0–0.4
Reticulocyte ABS ($\times 10^9/l$)	8	3–50
MCV (fl)	40	43–55
MCH (pg)	14	13–17
MCHC (g/l)	336	282–333
Platelet count ($\times 10^9/l$)	89 (clumped and adequate)	300–800
WBC ($\times 10^9/l$)	11.8	5.5–19.0
Neutrophils (%)	89	–
Neutrophils ($\times 10^9/l$)	10.5	2.0–13.0
Lymphocytes (%)	0	
Lymphocytes ($\times 10^9/l$)	0.0	0.9–7.0
Monocytes (%)	10	
Monocytes ($\times 10^9/l$)	1.2	0.0–0.6
Eosinophils (%)	1	
Basophils (%)	0	
Blood smear examination	Red cell and white cell morphology normal	
Biochemistry		
Sodium (mmol/l)	147	144–158
Potassium (mmol/l)	4.6	3.7–5.4
Chloride (mmol/l)	113	106–123
Bicarbonate (mmol/l)	17	12–24
Na:K ratio	32	>29.0
Anion gap (mmol/l)	21.6	15.0–31.0
Glucose, serum (mmol/l)	5.1	3.2–7.5
Urea (mmol/l)	8.7	5.0–15.0
Creatinine (mmol/l)	0.07	0.08–0.20
Calcium (mmol/l)	2.3	2.1–2.8
Phosphate (mmol/l)	2.8	1.0–2.3
Ca:P ratio	0.8	1.1–2.3
Protein, total (g/l)	64	60–84
Albumin (g/l)	30	25–38
Globulin (g/l)	34	31–52
A:G ratio	0.9	0.5–1.1
Bilirubin, total ($\mu\text{mol/l}$)	4	0–7
Alkaline phosphatase (IU/l)	69	5–50
Aspartate aminotransferase (IU/l)	42	2–62
Alanine transaminase (IU/l)	111	19–100
Creatinine kinase (IU/l)	192	64–400
Cholesterol (mmol/l)	3.5	2.2–5.5
Bile acids		
Fasting ($\mu\text{mol/l}$)	1	<11
Postprandial ($\mu\text{mol/l}$)	1	<21
Endocrinology		
T4 total (nmol/l)	34	10–60

Entries in bold are outside the reference interval.

RBC = red blood cells; ABS = absolute; MCV = mean cell volume; MCH = mean cell haemoglobin; MCHC = mean cell haemoglobin concentration; WBC = white blood cells; T4 = thyroxine

Table 2 Results of in-house urinalysis

Parameter	Result
Urine-specific gravity	1.042
pH	6.0
Protein	1+
Glucose	Negative
Ketones	Negative
Urobilinogen	1+
Bilirubin	Negative
Blood	Negative

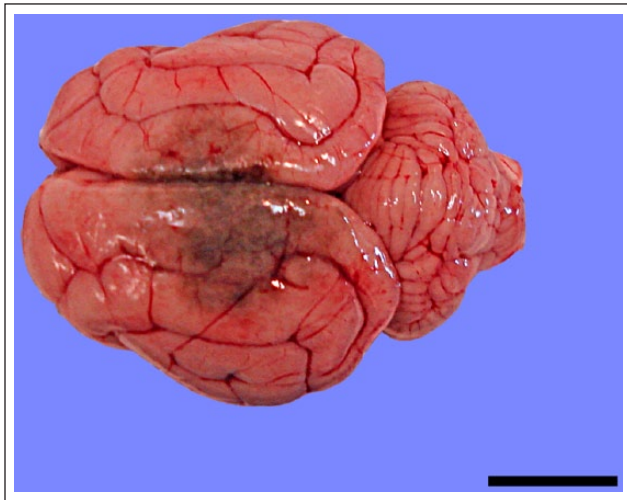


Figure 1 The meninges are reddened and the gyri are swollen and flattened, especially on the left side. There is a dark brown region, which spans the parietal lobes of both hemispheres. Bar = 1.5 cm

Possible explanations for this include stress leukogram, an infection associated, spurious laboratory result or a primary immunodeficiency such as severe combined immunodeficiency, which has been described in human neonates, foals, dogs and mice.⁴¹ The significance of the lymphopenia is unknown.

Standard haematological and biochemical testing in patients with CNS phaeohyphomycosis are generally within reference intervals. In this case monocytosis was considered to be a component of a stress leukogram. Other haematological and biochemical aberrations were considered unlikely to be of clinical significance.

There are no serological tests to diagnose *C bantiana* infection. CT and MRI may reveal changes consistent with intracranial abscessation, ependymitis or meningitis; however, diagnosis relies on biopsies and fungal culture.^{16,25} In the present case the culture isolate was initially incorrectly identified as *Cladosporium* species, despite *Cladophialophora* species' distinctive microscopic morphology. This emphasises the important role of reference laboratories for accurately identifying these rare mycoses and the benefits of sequencing as the gold standard.

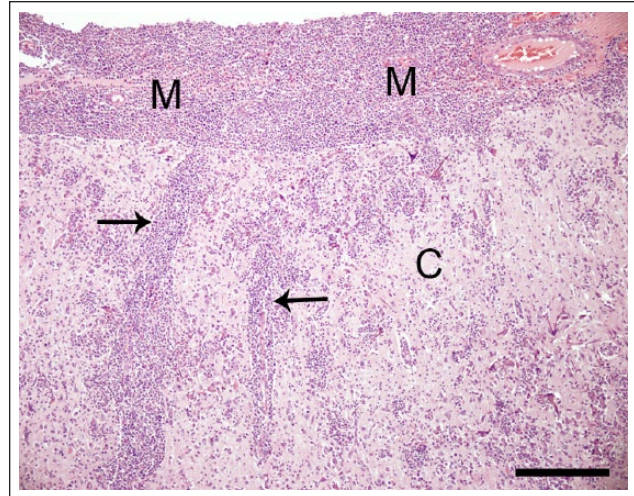


Figure 2 The meninges (M) are markedly expanded by pyogranulomatous leukocyte infiltrate, which extends along Virchow–Robin spaces (arrows) and into the cortical grey matter (C). Haematoxylin and eosin. Bar = 250 µm

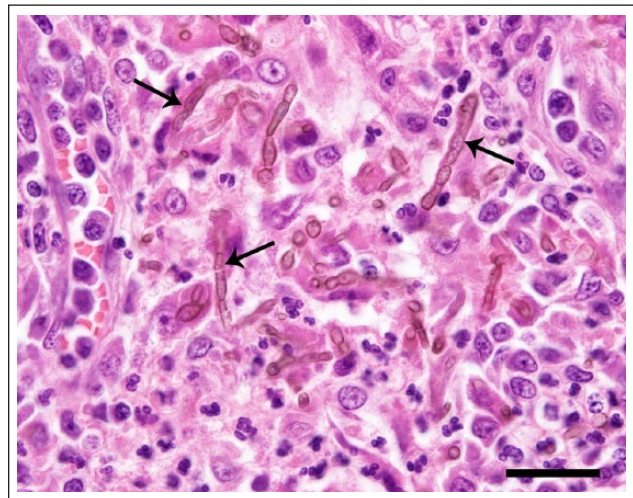


Figure 3 Leukocyte infiltrate predominantly consists of macrophages, and lesser multinucleate giant cells, neutrophils, lymphocytes and plasma cells. The leukocytes are centered on intra- and extracellular fungal hyphae and pseudohyphae (arrows). Haematoxylin and eosin. Bar = 25 µm

Only one feline case⁴² has been diagnosed antemortem; this was achieved by craniectomy subsequent to MRI. In dogs, diagnosis has been achieved antemortem by CT-guided biopsy⁴³ and craniotomy with excisional biopsy following MRI.⁴⁴ Cerebrospinal fluid (CSF) analysis is generally regarded as being non-specific,⁴⁵ but may demonstrate CNS inflammation by increased protein or pleocytosis. In one human case fungal hyphae and conidia were observable cytologically in CSF, and culture grew *C bantiana*.³⁷

There is no standard treatment for CNS phaeohyphomycosis and many different combinations of surgical and

antifungal regimens have been reported. Response to therapy is unpredictable, and in vitro sensitivities may not correlate with in vivo results.^{38,46} Published experience even in the human field is too small to reach definitive conclusions about which antifungal agents are most effective, but a recent review showed treatment with combined itraconazole, flucytosine and amphotericin B to be most effective.³² In this study surgery was not associated with an improved outcome; however, cases where complete excision of brain abscesses was achieved had lower mortality rates than those who underwent therapeutic aspiration or partial excision. Prognosis was reported as poor, with overall mortality rates of 73% in humans, and 100% in untreated cases mortality rates were 100% (as referring to previous study in humans). Two veterinary cases with successful treatment have been reported; one in a dog⁴⁴ and one a cat.⁴² Both were treated with surgical debulking and fluconazole initially, and the dog was changed to voriconazole long-term.

Conclusions

This case report describes a CNS infection with *C bantiana* in a kitten. Cerebral phaeohyphomycosis should not be excluded from the differential list of cats presenting with neurological signs, regardless of age, rapidity of clinical course or immune status. Antemortem diagnosis requires advanced imaging and biopsy in most cases, and correct identification to the species level may be aided by the use of molecular techniques. Despite high mortality rates in humans and cats, long-term survival is possible with aggressive treatment.

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