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CASE REPORT

Brainstem phaeohyphomycosis due to *Curvularia lunata* (*Cochliobolus lunatus*) in a cat

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A 13-year-old female neutered domestic short-hair cat was presented with chronic progressive vestibular ataxia, lethargy and anorexia. Clinical examination revealed bilateral mucopurulent nasal discharge. Neurological examination revealed obtundation, a right head tilt, ambulatory tetraparesis, generalised vestibular ataxia, decreased postural reactions in all limbs, right Horner's syndrome, spontaneous conjugate jerk rotatory nystagmus and right positional ventral strabismus. Neuroanatomical localisation was observed in the right central vestibular system. Computed tomography revealed a solitary ill-defined contrast-enhancing mass lesion at the level of the right cerebellopontine angle. Cerebrospinal fluid (CSF) analysis revealed mild mononuclear pleocytosis and fungal elements. CSF culture was positive for *Curvularia* spp. Further tests for underlying diseases were all negative. The cat was treated with antibiotic and antifungal treatment, but it deteriorated rapidly and was euthanased. Necropsy of the brainstem mass lesion revealed pyogranulomatous inflammation. Panfungal polymerase chain reaction (PCR) targeting the internal transcribed spacer (ITS) region and subsequent sequencing identified *Curvularia lunata* in the formalin fixed brain tissue. This is the first report of brainstem phaeohyphomycosis by *Curvularia lunata* (Pleosporales) in a cat. In addition, this is the first report among animal and humans where fungal elements of *Curvularia lunata* were found in the CSF cytology. Opportunistic fungal pathogens should be always considered within the differential diagnoses list in cats with neurological signs and advanced imaging findings compatible with solitary mass lesions in the brain. In feline patients with pyogranulomatous meningoencephalitis and a

suspicion of a fungal aetiology, panfungal PCR for the ITS region and sequencing should be performed regardless of the absence of fungal elements in histopathology.

Keywords eumycetoma; feline; fungal meningoencephalitis; mononuclear pleocytosis; solitary granuloma

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Fungal meningoencephalitis is sporadic in cats and can be manifested as diffuse or multifocal meningoencephalomyelitis, ventriculitis or solitary granuloma, with or without sinonasal involvement or as a part of a disseminated disease.¹ *Aspergillus* spp., *Cladophialospora bantiana*, *Coccidioides* spp., *Cryptococcus* spp. and *Blastomyces dermatitidis* have been described to cause solitary mass lesions (granulomas) in the brain with or without extracranial lesions.^{1,2}

Phaeohyphomycosis describes a heterogeneous group of mycotic infections caused by dematiaceous or pigmented filamentous fungi that contain melanin in their cell walls and grow as hyphae or as a mix of yeast cells and hyphae in the host's tissues.³ Phaeohyphomycetes are found in soil, wood and decomposing plant debris worldwide, and they cause opportunistic infections of the skin and subcutaneous tissue in cats. Although systemic disease is usually rare, ingestion or inhalation of spores might result in extracutaneous disease.⁴ Feline central nervous system (CNS) phaeohyphomycosis is rare; however, it has been described to be caused by *Cladophialospora bantiana*, *Ochroconis gallopavum*, *Exophiala jeanselmei* and *Fonsecaea multimorphosa*, and *Cladophialospora bantiana* is particularly neurotropic.^{1,4,5} CNS phaeohyphomycosis due to *Curvularia* spp. has not been reported in cats. This is the first case report of phaeohyphomycosis by *Curvularia lunata* in the CNS (brainstem) in a cat. In addition, this is the first report among animals and humans where fungal elements of *Curvularia lunata* were found in CSF cytology.

Case report

A 13-year-old female neutered, client-owned, indoor/outdoor, domestic short-hair cat was presented for a 20-day history of progressive ataxia and a 3-day onset of lethargy and anorexia.

Clinical examination revealed bilateral mucopurulent nasal discharge, whereas otoscopy and ophthalmoscopy were unremarkable. Nasal passage examination revealed no pathological findings

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(e.g. masses) other than a mildly erythematic nasal mucosa and the above-mentioned discharge. On neurological examination, the cat appeared obtunded but responsive. Posture and gait analysis revealed a right head tilt, ambulatory tetraparesis and generalised vestibular ataxia (rolling to the right). Postural reactions were decreased in all limbs. Cranial nerve assessment revealed right Horner's syndrome, spontaneous conjugate jerk rotatory nystagmus and right positional ventral strabismus. Spinal reflexes and muscle tone were intact. The cat appeared to be comfortable upon palpation of the skull and vertebral column. Neuroanatomical localisation was observed in the right central vestibular system.

Differential diagnoses for an adult cat with chronic progressive lateralised central vestibular signs included (1) inflammatory encephalopathy (infectious meningoencephalitis, meningoencephalitis of unknown origin), (2) neoplasia or (3) degenerative encephalopathy (e.g. feline spongiform encephalopathy).

Complete blood count revealed mild neutrophilia ($15.8 \times 10^3/\mu\text{L}$; reference interval, $3.0\text{--}13.4 \times 10^3/\mu\text{L}$) without left shift, whereas the remaining parameters were within normal limits. Serum biochemistry was within normal limits. Serology for feline immunodeficiency virus (FIV) antibodies and Feline Leukemia Virus (FeLV) antigen (ELISA Snap test) was negative. Urinalysis was within normal limits, whereas aerobic bacterial culture was negative. Cytology of a nostril swab revealed neutrophilic inflammation with an abundance of epithelial cells.

Computed tomography (CT) [Optima CT520, GE Hangwei Medical Systems, Beijing, China] of the skull revealed a solitary ill-defined

contrast-enhancing mass lesion at the level of the right cerebellopontine angle (Figure 1).

Cerebellomedullary cisternal CSF analysis revealed mixed mononuclear cell pleocytosis (total nucleated cell count $10 \text{ cells}/\mu\text{L}$; reference interval, $0\text{--}5 \text{ cells}/\mu\text{L}$), whereas protein levels were not evaluated. A differential leukocyte count performed on a cytospin preparation of the CSF revealed 65% large mononuclear cells, 32% small lymphocytes and 3% non-degenerate neutrophils. There were rare elongated oval microorganisms, measuring approximately $6\text{--}8 \times 2\text{--}3 \mu\text{m}$, with thin walls and clear to lightly basophilic interior that appeared darker centrally (Figure 2). The described microorganisms were considered morphologically consistent with fungi. Although these fungi did not have morphological features of common contaminants, the scenario of them being contaminants could not be ruled out at that stage. Aerobic bacterial culture of the CSF was negative.

In light of a potential mycosis and given the clinical severity of the cat and the endemism of fungi in the country, fungal cultures were performed in Sabouraud dextrose agar (SDA) with chloramphenicol from the CSF, urine, bronchoalveolar lavage fluid, external ear canals lavage fluid, nasal mucosa, conjunctiva and bile.

The cat was hospitalised for a total of 17 days and was treated with intravenous fluid therapy (crystalloids) and empirical antibiotics (marbofloxacin, $5 \text{ mg}/\text{kg}$, PO, q 24 h) while awaiting the fungal culture results. Gradual improvement was noticed, and the cat was discharged. At that stage, given the clinical improvement of the cat and the lack of fungal culture results, antifungal treatment was not

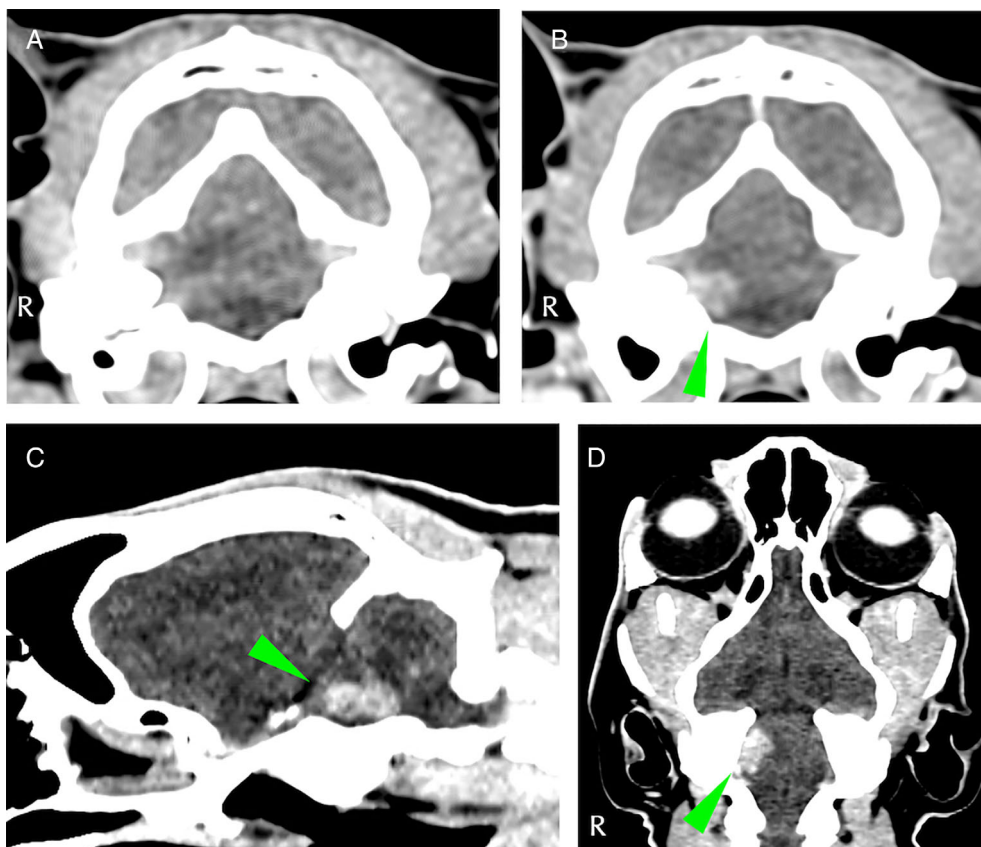


Figure 1. Computed tomography (soft tissue window) of a cat with brainstem phaeoophomycosis by *Curvularia lunata*. Transverse pre-contrast image (A) at the level of cerebellum and brainstem, where no lesion is evident. A $4.6 \times 3.1 \text{ mm}$ contrast-enhancing lesion (arrowhead) with ill-defined periphery is evident at the level of right cerebellopontine angle at the post-contrast sagittal sequence (B). The same lesion (arrowhead) is evident on the sagittal (C) and dorsal (D) post-contrast sequences.

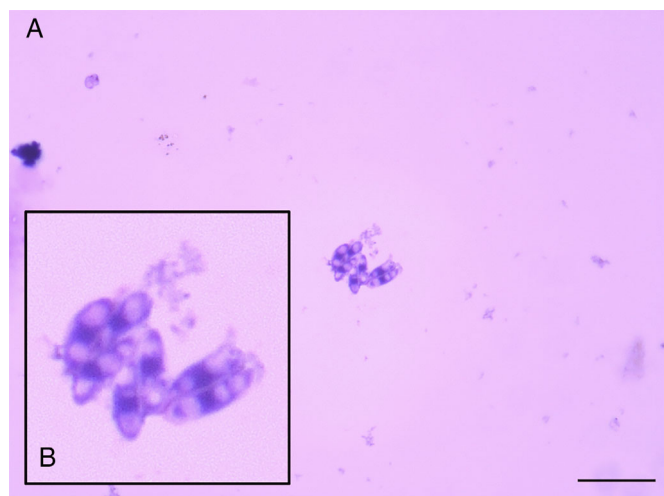


Figure 2. Cerebellomedullary cisternal cerebrospinal fluid cytological examination of a cat with brainstem phaeohyphomycosis by *Curvularia lunata*. (A) There is a small group of seven elongated oval microorganisms, measuring approximately 6–8 × 2–3 μm, with thin walls and clear to lightly basophilic interior that appeared darker centrally [cytospin preparation, original magnification ×1000, Giemsa stain, scale bar = 20 μm]. These microorganisms can be identified as fungal elements. (B) Electronically magnified picture of the fungal elements.

considered necessary. One week later, the cat was readmitted due to deterioration consisting of anorexia, lethargy and recurrence of neurological signs. On readmission, clinical examination revealed cachexia, whereas neurological examination revealed obtundation and non-ambulatory tetraparesis. Empirical treatment with fluconazole (50 mg/cat, PO, q 24 h) and osmotic treatment with mannitol (1 g/kg, IV, bolus) were initiated; however, the cat progressively deteriorated within a week, developed decerebellate rigidity and then was euthanased at the request of the owners. As CSF cultures require long incubation times, at day 19, they turned positive for a saprotrophic dark-pigmented fungus, which was identified by microscopy as *Curvularia* sp. The rest of the fungal cultures were negative apart from the one from the nasal mucosa, which was positive for *Aspergillus* section *Flavi*.

Postmortem gross examination of the cat revealed a whitish, ill-defined mass of gelatinous consistency on the right cerebellopontine angle compatible with granuloma or neoplasia (Figure 3). The rest of the brain had no remarkable lesions, whereas the serous membrane of the small intestine had multiple randomly distributed white nodules 2–4 mm in diameter, and the liver presented multifocal whitish and friable foci. Histopathology of the internal organs was not performed, and therefore, a subclinical disseminated pyogranulomatous inflammation cannot be ruled out. Histopathology of the brain, with haematoxylin–eosin (HE) and periodic acid–Schiff (PAS) stain, revealed cavitation (malacia) accompanied by a severe granulomatous reaction at the level of the right cerebellopontine angle. Inflammatory cells comprised large numbers of macrophages (often epithelioid) and lymphocytes with few plasma cells and neutrophils admixed with amorphous cellular debris. Reactive gemistocytes and mildly increased number of glial cells were observed on the neuropil adjacent to the granulomatous area (Figure 4). Convincing hyphae

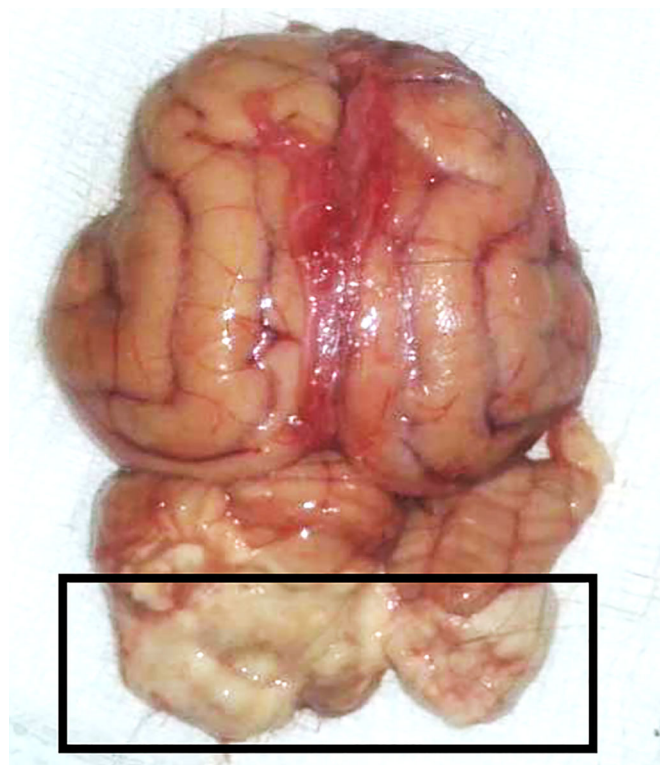


Figure 3. Postmortem gross examination of the brain (dorsal aspect) of a cat with brainstem phaeohyphomycosis by *Curvularia lunata*. There is a whitish, ill-defined mass of gelatinous consistency on the right cerebellopontine angle, which represents the fungal granuloma (rectangular).

were not observed in the histological sections performed. Polymerase chain reaction (PCR) on the formalin-fixed paraffin-embedded (FFPE) slides of the brain were negative for *Candida* spp. and *Aspergillus* spp.; however, the panfungal PCR targeting the entire internal transcribed spacer (ITS) region was positive.⁶ Sequencing of the ITS PCR product and subsequent BLAST (<https://pubmed.ncbi.nlm.nih.gov>) showed homology of 98.99% with *Cochliobolus lunatus*, the teleomorph of *Curvularia lunata*.

Discussion

Curvularia spp., a melanin-producing dematiaceous fungus,⁷ is mainly a saprotrophic pathogen of plants; however, some species can cause infection (phaeohyphomycosis) in humans and animals.⁸ *Curvularia* spp. is able to infect both immunocompetent and immunosuppressed humans, mainly in tropical and subtropical areas.⁸ *Curvularia lunata* is the most commonly reported species to cause clinical signs in humans⁸; it represents the anamorph, whereas its teleomorph (sexual state) is *Cochliobolus lunatus*, and they are the same biological entity.⁷ The major manifestation of phaeohyphomycosis by *Curvularia* spp. in mammals is the cutaneous *eumycetoma* or *eumycotic mycetoma*, that is, pyogranulomatous nodules that contain tissue grains or granules composed of dense fungal mass of ubiquitous soil fungal saprophytes and necrotic debris. These fungi are invading the host via wound contamination, such as

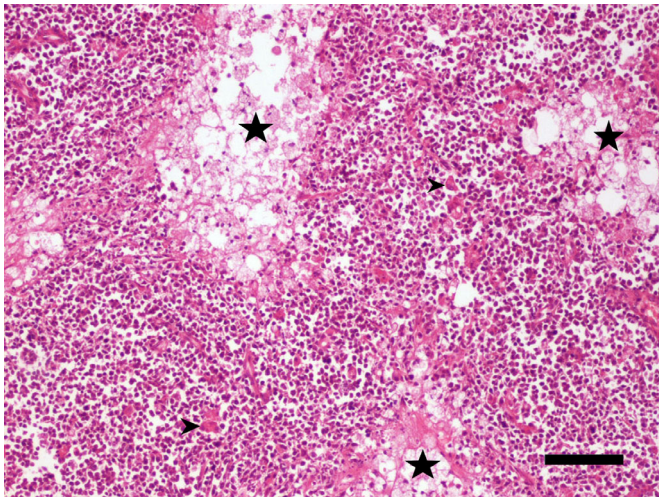


Figure 4. Histopathological microphotographs of the brainstem of a cat with brainstem phaeohyphomycosis by *Curvularia lunata* revealing cavitation (malacia) (stars) accompanied by a severe granulomatous reaction at the level of the right cerebellopontine angle. Inflammatory cells comprised of large numbers of macrophages (often foamy reflecting phagocytosis of lipid-laden malacic tissue) and lymphocytes with fewer plasma cells and neutrophils admixed with amorphous cellular debris. Reactive gemistocytes (arrowheads) and mildly increased number of glial cells were observed on the neuropil adjacent to the granulomatous area (original magnification $\times 100$, haematoxylin–eosin stain, scale bar = 100 μm).

a contaminated splinter or fight injury.⁹ Interestingly, *Curvularia lunata*, *C. pallescens*, *C. clavata* and *C. geniculata* have been sporadically reported to cause meningoencephalitis in either immunocompetent or immunocompromised humans, mainly affecting the forebrain but also the brainstem.¹⁰ In dogs, *Curvularia lunata*, *C. geniculata* or *C. spicifera* (syn. *Bipolaris spicifera*) cause cutaneous/subcutaneous,^{11–16} osseous¹⁷ or abdominal¹⁸ granulomas; corneal ulceration;^{19,20} or disseminated systemic disease with cutaneous, cardiac and renal involvement.^{21,22} CNS involvement of *Curvularia* spp. has been reported in a dog with central vestibular signs and concurrent renal involvement,²³ whereas the fungus has been found in histopathological sections of the brain of a neurologically normal dog with cutaneous phaeohyphomycosis by *Curvularia spicifera*.²² In cats, *Curvularia lunata* and *C. spicifera* (syn. *Dreschlera spicifera*) have been sporadically reported to cause cutaneous/subcutaneous granulomas.^{11,24,25} The cat reported in this study manifested central vestibular signs that progressed to cerebellar due to a granuloma located at the right cerebellopontine angle. No underlying disease was found ante- and postmortem, and the cat was also negative for FIV/FeLV. Mucopurulent rhinitis was considered a secondary infection to a potential immunosuppression the fungal CNS disease caused. Factors predisposing cats to phaeohyphomycoses include immunosuppressive drugs; concurrent disease; or age-related, non-specific loss of immunity; however, no obvious immunosuppression has been found in most reported cases. In these cases, it is believed that the pigment of phaeohyphomycetes played an important role in their virulence and pathogenicity as it aids fungal evasion of the host immune response by preventing hydrolytic enzymatic attack and scavenging of free radicals liberated by phagocytic cells during then oxidative burst.⁴

Magnetic resonance imaging of the brain in humans with CNS phaeohyphomycosis by *Curvularia* spp. demonstrated a solitary, homogeneously contrast-enhancing lesion with mass effect and perilesional oedema mainly in the forebrain but also in the medulla oblongata¹⁰ and diffuse contrast-enhancing meningoencephalitis-like²⁶ or haemorrhage-like lesions²⁷ within the forebrain. In CT, focal intraparenchymal hypodensity within the forebrain with accompanying perilesional haemorrhage, oedema and midline shift has been described.²⁸ Pituitary fossa mucocele with associated optic nerve atrophy²⁹ and sellar mass that is uniformly contrast enhancing mimicking meningioma,³⁰ have been reported as uncommon localisations of the fungus. Destruction of the anterior cranial fossa floor in the CT³¹ or nasal involvement with osseous erosion of the cribriform plate and medial walls of orbits²⁶ can accompany the main lesions.

A mild mononuclear cell pleocytosis was detected on the CSF cytological examination, a finding that was consistent with fungal disease. CSF analysis has not been widely performed in human cases with CNS mycosis by *Curvularia* spp. Where performed, cytology was either unremarkable,³⁰ or it revealed neutrophilic pleocytosis,^{10,32} whereas fungal cultures of CSF were usually negative.^{10,30,33} In the current cat, CSF fungal culture was positive for *Curvularia* spp. based on phenotypic features. In cats, *Cryptococcus* spp. is mainly identified in the CSF, whereas other fungi are only seen sporadically.¹ This is the first report among humans and animals to describe and demonstrate fungal elements of *Curvularia* spp. in the CSF cytology. The positivity of *Aspergillus* section *Flavi* in the culture of the nasal mucosa could be attributed to a potential secondary mycosis by *Aspergillus* spp. due to immunosuppression by the phaeohyphomycosis. There is a high incidence of concurrent fungal disease and aspergillosis in feline cases, indicating that immunosuppression may play a role in predisposing cats to this disease.³⁴ On the other hand, in the absence of macroscopic and imaging lesions within the nasal and sinus cavities that could be more consistent with sinonasal aspergillosis, the rhinitis of the current case could be attributed to other non-fungal pathogens. In addition, *Aspergillus* spp. can be found on mucosal surfaces of healthy animals, and infection can only be diagnosed by samples taken from a deeper layer of tissue.³⁵

Antemortem and postmortem diagnostic tests failed to reveal an underlying disease in our feline patient. Serology for FIV/FeLV was also negative, although these are usually negative in feline CNS mycoses.¹ The cat in this case seemed to be an apparently immunocompetent patient; however, a lack of histopathology from other organs (especially those with macroscopic lesions) make this assumption presumptive, as well as classification of phaeohyphomycosis as focal or disseminated (although subclinical) impossible.

In humans, aspiration cytology, transcranial brain biopsy and surgical biopsy are usually used for the diagnosis of CNS phaeohyphomycosis by *Curvularia* spp. In histopathology with HE, the pigmentation of these species might not be evident. Fontana-Masson stain might be necessary to demonstrate the melanin pigment, whereas Grocott-Gomori's methenamine silver or PAS stains can be used to highlight the fungal wall. Fungal elements are observed as yeast-like structures and septate hyphae, and they can be found

throughout the lesion.³⁶ In humans, the presence of a CNS-encapsulated mass with purulent material, histopathologically characterised by lymphocytes, polymorphonuclear leukocytes and red blood cells, leads to the nomenclature of 'brain abscess' in the literature.¹⁰ In dogs with extraneural phaeohyphomycosis by *Curvularia* spp., features of pyogranulomatous inflammation are evident.²²

Identification of the fungus species in most of the studies in humans is based on phenotypic criteria (e.g. conidia morphology and growth pattern in the fungal culture, hyphae in histopathology), but this may be incorrect as recent studies revealed the absence of correlation between morphological and molecular identification.⁸ Fungal culture of affected tissues can be performed using media such as SDA, Czapek Dox agar, brain–heart infusion broth, blood agar or potato dextrose agar.⁷ In addition, because of the ubiquitous nature of these fungi, they are often considered contaminants,⁸ and thus, clinical correlation should be performed carefully. Serology modalities are not commercially available for these species. Therefore, molecular methods are the diagnostic modalities of choice for the diagnosis of CNS mycoses. Specifically, a panfungal PCR is recommended in the affected tissue (e.g. histopathological specimen) for the identification of the ITS region of the nuclear ribosomal RNA gene that is present in all fungal genera, and then, DNA sequencing for species identification is performed.⁷

CNS phaeohyphomycosis is fatal, and only surgical removal of the compressive granuloma could provide survival in both humans and animals.¹ Surgical removal of the *Curvularia* granuloma is followed by antifungal treatment with a combination of an amphotericin B and an azole, such as voriconazole, in humans, whereas antibiotic or surgical treatment alone is not recommended.¹⁰ Voriconazole is neurotoxic in cats, so amphotericin B combined with fluconazole and adjunctive corticosteroids would be an alternative treatment for cats.¹ In our case, fluconazole was used due to its successful effect against CNS fungal disease³⁷ and its broad availability on the market. Fluconazole, however, was not a successful choice as it is not active against filamentous fungi. Amphotericin B would be a better option for empirical treatment against filamentous fungi; however, it was not an option at that time as it was a human hospital medication, and its availability is limited due to antimicrobial resistance; it is significantly nephrotoxic particularly for cats;³⁷ and at the time of empirical treatment, the filamentous form of the fungi was not known.

A major limitation of this study is that fungal elements were not found in the examined histopathological sections stained with HE and PAS. Retrospectively, the paraffin blocks were not retrievable for re-review and further special staining. Therefore, the theory of contamination could not be completely ruled out. However, in the authors' opinion, this is considered unlikely given that: (1) on admission, CSF analysis revealed mononuclear pleocytosis and presence of fungal elements that microbiologically identified as *Curvularia* spp.; (2) after several days, the postmortem histopathological examination of the brainstem revealed pyogranulomatous inflammation, which is compatible with fungal infection; and (3) the panfungal PCR performed on FFPE tissue was positive, and subsequent sequencing was consistent with the teleomorph of *Curvularia lunata*. Consequently,

there were strong arguments to support a diagnosis of fungal aetiology for the brainstem granuloma.

In conclusion, *Curvularia lunata* should be considered an opportunistic pathogen that can cause fungal meningoencephalitis in immunocompetent or immunosuppressive cats, and it should always be included in the differential diagnoses list for mass lesions in the brain of a cat with neurological signs. CSF cytology could be a useful diagnostic modality where phaeohyphomycetes could be observed. Even if histopathological examination is comprehensive, it can fail to identify fungi due to the relative paucity of fungal organisms, and therefore, molecular methods such as panfungal PCR for ITS and sequencing should be performed for a precise identification of the fungal species in cases of pyogranulomatous meningoencephalitis regardless of whether organisms are identified on histopathology. CNS phaeohyphomycoses are fatal, and thus, surgical intervention of mass lesions should be considered. This is the first case report to describe brainstem phaeohyphomycosis due to *Curvularia lunata* in cat and demonstrate it in CSF cytology.

Conflicts of interest and sources of funding

The authors declare no conflicts of interest or sources of funding for the work presented here.

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