Feline disseminated cryptococcosis
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Introduction
Cryptococcosis is an opportunistic systemic fungal infection and occurs worldwide, caused by several Cryptococcus (C.) species, which are saprophytic, round, basidiomycetous yeasts with C. neoformans most commonly causing disease (1, 2, 3). Infection occurs in the environment through e.g. pigeon droppings and soil rich in vegetable matter primarily via inhalation through the respiratory system. Cryptococcal basidiospores are considered the main infectious particles due to their small size of 2-3 µm, compared to vegetative, encapsulated cells (4, 5). In the desiccated state, the Cryptococcus organism may be no larger than 1 µm and may survive up to 2 years (2). In infected tissue, and often when cultured, the organism is a variable-sized yeast (3.5 to 7 µm) with a large heteropolysaccharide capsule (1 to 30 µm) (2). The majority of yeasts settle out in the nasal cavity or nasopharynx, where they can produce disease or result in animals becoming asymptomatic carriers of the organism (2).

Dissemination can occur by either direct extension or hematogenous spread (by macrophages), to the skin, lungs, eyes, or central nervous system (CNS) (2, 4, 6). Direct extension from the nasal cavity through the cribiform plate to the CNS or to the paranasal soft tissues and skin is common (2). Cell-mediated immune response results in granuloma formation (2). Direct implantation into skin wounds may also occur. Cryptococcosis is a sporadic infection, but is considered the most common systemic fungal infection in cats worldwide (3). Exposure to outdoor environments is significantly associated with the disease (7, 8, 9). While cryptococcosis in people is most often associated with immunosuppression, the organism appears to be a primary pathogen of immunocompetent cats and dogs (2). An association with feline leukemia virus (FeLV) and feline immunodeficiency virus (FIV) infections in cats has been reported, and prolonged glucocorticoid treatment has been implicated as a predisposing factor in both cats and dogs (2). However, cryptococcosis is
not more common in cats with retroviral infections (7, 8, 10, 11). Diagnostic options of cryptococcosis include cytologic examination, capsular antigen detection, and culture. Cytological finding in aspirates of encapsulated yeast cells is suggestive. Capsular antigen can be demonstrated by Latex Cryptococcus Agglutination Test (LCAAT) (12). Aetiological diagnosis is obtained by culture and mycological characterisation of the isolate.

**Case History**

A 3.5 years old male castrated, domestic shorthaired cat presented to the University Hospital for Companion Animals at the University of Copenhagen with a 5-days history of progressing dyspnoea, tachypnoea and anorexia. The cat was born and raised in California, USA and was imported to Denmark one year previously. It had a history of long-standing respiratory symptoms, described as continuous stridor and stertor and occasionally dyspnoea, and recurrent cutaneous masses, some of which had been surgically removed. There was no history of nasal discharge and cough was only occasionally observed. The cat had been kept indoors for the past year, but had been an outdoor cat prior to that. It was current on vaccinations, but it had not been wormed for the last year. It had been treated with amoxicillin/clavulanic acid (12.5 mg/kg q12h per os) without response for the previous three days.

Physical examination confirmed tachypnoea (respiratory rate 50 breaths/minute) with an increased inspiratory and expiratory effort. Auscultation of the lungs was difficult due to pronounced stridor and stertor. Mucous membranes were pale pink with a capillary refill time of two seconds. The cat had multiple cutaneous, indolent, mobile, firm masses of varying size with a raised, smooth surface, dispersed over the whole body.

The initial therapeutic approach was aimed at addressing the respiratory distress with oxygen supplementation. After the initial stabilization, blood was collected for complete blood count (CBC), serum biochemistry, acid-base chemistry (venous blood sample) and Idexx SNAP® FIV/FeLV Combo Test. CBC and biochemistry did not show any abnormalities except for a mild stress-induced hyperglycemia. Acid-base chemistry did not show any abnormalities either, but as venous blood was used, blood oxygenation could not be assessed. Lactate was in the reference range. FIV and FELV tests were negative.

Nasal and thoracic radiographs showed an increased opacity in the nasal cavity and a diffuse pulmonary infiltrate with a broncho-interstitial pattern (Figure 1). Thoracic ultrasound confirmed the presence of several cranial mediastinal masses (Figure 2). Fine needle aspirates (FNA) of all cutaneous masses were performed and revealed a yellowish gelatinous content. On cytology encapsulated yeast cells were observed (Figure 3).

On day 2, fine needle aspirates of the cranial mediastinal masses and a computed tomography (CT) of the nasal cavity and thorax were performed under general anaesthesia. Recovery from anaesthesia was uneventful. In fine needle aspirates of the mediastinal masses encapsulated yeast cells identical to those from the cutaneous masses were demonstrated (Figure 3).

Computed tomography revealed soft tissue masses in the nasal cavity and frontal sinus, nasal turinate destruction and deviation of the nasal septum, soft tissue nodules distributed throughout the lungs and lung consolidation in the ventral lung field (Figure 4). Aspirated material from a cutaneous nodule was cultured on Sabouraud dextrose agar (CM0041, Oxoid, Basingstoke, Hampshire, England). After incubation at 30° for 7 days, growth was observed of grey-white, mucoid colonies consisting of budding yeast cells with capsule formation (Figure 5). A subculture was identified as *Cryptococcus neoformans* by using the API 20C AUX kit (BioMerieux, 3B: Mediastinal mass.

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**Figure 1.** Thoracic radiograph of the cat: detail of thoracic radiograph, latero-lateral projection. Diffuse pulmonary infiltrate with a broncho-interstitial pattern is visible.

**Figure 2.** Ultrasonography of the thorax of the cat. There are three approximately 1.5 cm in diameter roughly spherical masses in the cranial mediastinum.

**Figure 3.** Cytology from multiple cutaneous lesions and mediastinal masses. There is a massive appearance of circular cryptococcal cells of varying size surrounded by a large capsule. There is an infiltrate of activated highly vacuolated macrophages, showing active phagocytosis. Background material consists of a basophilic lightly granulated material, compatible with proteinaceous material.
Marcy-l’Etoile, France) according to the manufacturer’s instructions. Latex Crypto-
coccus agglutination antigen test (LCAAT), performed on blood serum at Athens Uni-
versity, Georgia, USA, was highly positive with a titer of >1:8192.

Treatment with the antifungal flucon-
zole (10mg/kg q12h PO) was initiated on
day 2 based on the cytological findings.
The cat continued to be stable on cage rest
and did not require further oxygen supple-
mentation. It was bright, alert and responsive,
started eating, and was discharged after
days with instructions to ensure a
quiet, non-stressful environment and
reduced physical activity.

Follow-up examinations were performed
on day 30, 90 and 150. Blood samples for
biochemistry profile and LCAAT titer were
obtained which did not show improvement
compared to previous findings. After mov-
ning back to the USA, LCAAT titer was
tested 15 months after treatment start
with levels below detection limit. Flucon-
zole treatment was discontinued.

**Discussion**

This presentation of a young cat with
chronic respiratory symptoms and cutane-
ous nodules due to disseminated crypto-
coccosis represents a rare case in Denmark,
though the disease is described to have
worldwide significance. In all likelihood,
the infection had been acquired during the
cat’s stay in California, USA, as it had a
history of long-standing respiratory signs.

Regarding the cat’s history, systemic
mycoses were important differential diag-
noses due to a high prevalence in certain
regions in the USA. All findings including
the history of long-standing continuous
upper respiratory tract noise and chronic
recurrent cutaneous nodules could be
explained by chronic disseminated crypto-
coccosis with intranasal, intrathoracic and
cutaneous involvement.

The severe findings on radiography and
CT indicated irreversible chronic intranasal
changes and marked pulmonary pathology
with intrathoracic granulomata which
might prevent full recovery, so that ongo-
ning respiratory sounds and decreased lung
capacity would be expected. The presence
of CNS disease caused by cryptococcosis is
the major factor described to influence
outcome in cats (13). In our case, the cat
did not show any signs of CNS involve-
ment, but as imaging studies of those
regions were not performed, this could not
be definitely ruled out. Our patient had a
LCAAT titer >1:8192 which correlated pos-
itively with the disseminated distribution of
the disease, as patients with dissemi-
nated skin and/or lymph node involve-
ment have significantly higher titers (12).

Although the prognosis of cryptococcosis
should be considered as guarded, a major-
ity of cats can be expected to be cured,
but treatment is protracted and expensive
(13). We initiated treatment with flucon-
zole, an azole antifungal, which is
described to be very effective in the treat-
ment of feline cryptococcosis, including
cases with advanced, longstanding, or dis-
seminated disease (2, 13, 14). Furthermore,
this drug can be given orally. Side
effects in cats can be inappetence and,
rarely, increased liver enzyme activity and
hepatic toxicity (14). On follow-up visits,
liver enzyme activity and LCAAT titers were
measured to monitor progress, evaluate
prognosis, and guide cessation of treat-
ment (2, 12, 15, 16). The cat responded
well to treatment and no side effects were
observed. Antifungal therapy was contin-
ued until the LCAAT titer declined to an
undetectable level after 15 months of con-
tinued therapy. This was a significantly
longer treatment period than described in
a previous study where the median dura-
tion of treatment with fluconazole in cats

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**Figure 4.** CT nasal cavity and thorax (2 mm slice thickness). A: Nasal cavity: soft tissue filling bilaterally in
the nasal cavity and in the left frontal sinus, bilateral nasal turbinate destruction and deviation of the
nasal septum. B: Thorax: soft tissues nodules distributed throughout the lungs and significant consolida-
tion of the lungs in the ventral lung field.

**Figure 5.** Culture on Sabouraud dextrose agar of
isolate from aspirated material from a cutaneous
nodule, incubated at 30°C for 6 days, showing
mucoid, grey-white colonies.
with less severe cryptococcosis was 4 months with a range of 1 to 8 months (13). Due to the advanced disease progression in our patient, a longer treatment period was expected. Despite clinical improvement, resolution of the cutaneous masses and a finally undetectable LCAAT titer, a full recovery with resolution of all respiratory symptoms seems unlikely due to the severe intranasal anatomical changes.

This case report emphasises that it is important to consider cryptococcosis in cats with respiratory symptoms with or without cutaneous involvement due to its worldwide significance, particularly in cats from countries with a high prevalence of cryptococcosis.

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Reference