Feline disseminated cryptococcosis

a case report

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Summary

Disseminated cryptococcosis was diagnosed in a cat presenting with severe dyspnoea and multiple cutaneous nodules based on cytology, serology and culture. A 3.5 years old male, castrated, domestic shorthaired cat presented with an acute history of progressive dyspnoea, tachypnoea and anorexia and a history of chronic continuous stridor, stertor and recurrent cutaneous masses.

Nasal and thoracic radiographs showed an increased opacity in the nasal cavity, a diffuse pulmonary infiltrate and a suspected cranial mediastinal mass. Thoracic ultrasound confirmed the presence of several cranial mediastinal masses. Fine needle aspiration of the cutaneous and mediastinal masses revealed the presence of encapsulated yeast cells. Culture confirmed infection with *Cryptococcus neoformans*. Latex Cryptococcus agglutination antigen test was highly positive with a titer of >1:8192. The cat was treated with fluconazole for 15 months until the titer was below detectable levels.

Sammendrag

En kat med svær dyspnø og multiple kutane masser blev diagnosticeret med dissemineret cryptococcose på basis af cytologiske og serologiske undersøgelser samt mykologisk dyrkning.

En 3,5 år gammel, kastreret hankat blev præsenteret med akut, progressiv dyspnø, tachypnø og anorexi. Katten havde haft kronisk stridor og stertor og tilbagevendende kutane masser. Røntgenbilleder fra næse og thorax viste en øget opklaring i næsehulen, en diffus pulmonær infiltrering og en mistænkt kranial mediastinal masse. Den sonografiske undersøgelse af thorax bekræftede forekomsten af flere kraniale mediastinale masser. Finnålsaspiration af de kutane og mediastinale masser viste kapseldannende gærceller. Mykologisk dyrkning bekræftede infektion med *Cryptococcus neoformans*. Latex Cryptococcus Agglutination Antigen Test var kraftigt positiv med en titer på >1:8192. Katten blev behandlet med fluconazole i 15 måneder indtil titeren fandtes negativ.

Feline disseminated cryptococcosis

A case report

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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 cribriform 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, tachypnea 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.

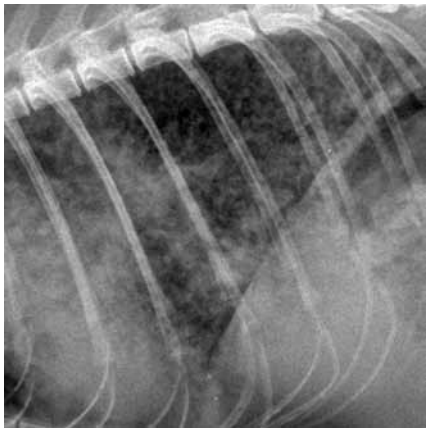


Figure 1. Thoracic radiograph of the cat: detail of thoracic radiograph, latero-lateral projection. Diffuse pulmonary infiltrate with a broncho-interstitial pattern is visible.

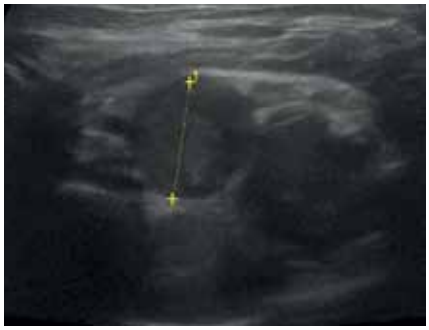
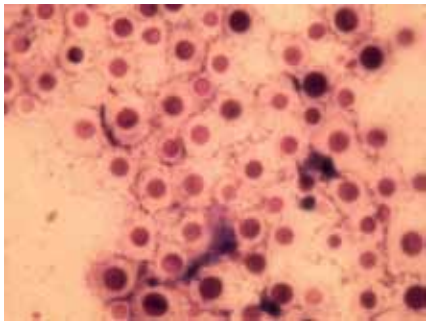


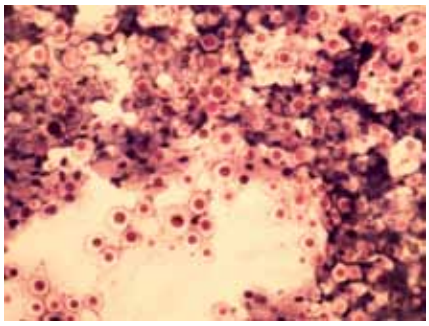
Figure 2. Ultrasonography of the thorax of the cat. There are three approximately 1.5 cm in diameter roughly spherical masses in the cranial mediastinum

Nasal and thoracic radiographs showed an increased opacity in the nasal cavity and a diffuse pulmonary infiltrate with a broncho-interstitial pattern and a suspected cranial mediastinal mass (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 turbinate 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,



3 A: Skin.



3 B: Mediastinal mass.

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 vacuolized macrophages, showing active phagocytosis. Background material consists of a basophilic lightly granulated material, compatible with proteinaceous material.

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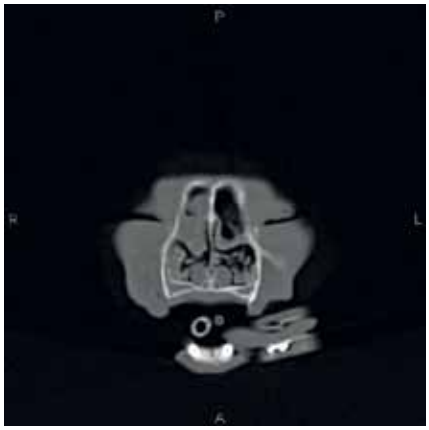

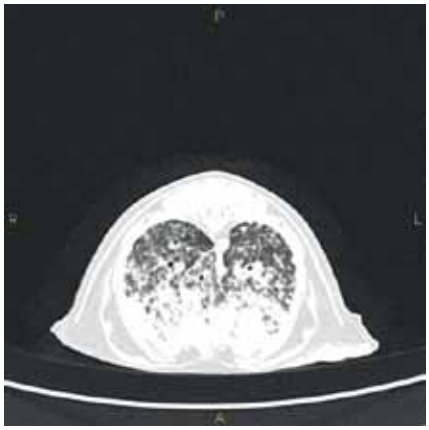

Figure 4. CT nasal cavity and thorax (2 mm slice thickness). A: Nasal cavity: soft tissue filling bilaterally in the nasal cavity and in the left frontal sinus, bilateral nasal turbinate destruction and deviation of the nasal septum. B: Thorax: soft tissues nodules distributed throughout the lungs and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

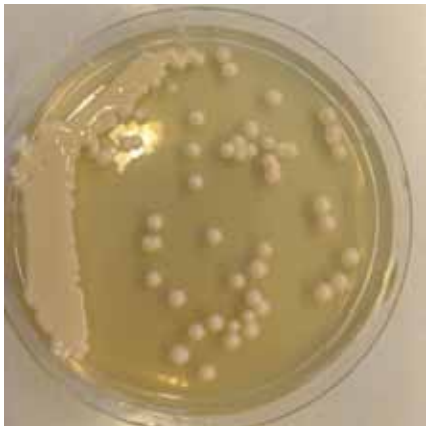

Figure 5. Culture on Sabouraud dextrose agar of isolate from aspirated material from a cutaneous nodule, incubated at for 30°C for 6 days, showing mucoid, grey-white colonies.

Marcy-l'Etoile, France) according to the manufacturer's instructions. Latex *Cryptococcus* agglutination antigen test (LCAAT), performed on blood serum at Athens University, Georgia, USA, was highly positive with a titer of >1:8192.

Treatment with the antifungal fluconazole (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 supplementation. It was bright, alert and responsive, started eating, and was discharged after five 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 to monitor progress of treatment and liver parameters, as increased liver enzyme activity and hepatic toxicity are known as rare side-effects of fluconazole treatment. Liver parameters were within reference range and LCAAT titers were unchanged on all follow-up visits. No clinical side effects to medication were observed. On day 30, the cat was bright, alert and responsive. The cutaneous nodules were unchanged. On day 90, all nodules had disappeared except for one which had decreased in size. On day 150, the last nodule had completely disappeared. The cat's activity level had markedly increased and the only clinical signs were stridor and stertor. Thoracic radiographs were obtained which did not show improvement compared to previous findings. After moving back to the USA, LCAAT titer was tested 15 months after treatment start with levels below detection limit. Fluconazole treatment was discontinued.

Discussion

This presentation of a young cat with chronic respiratory symptoms and cutaneous nodules due to disseminated cryptococcosis 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 diagnoses 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 cryptococcosis 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 ongoing 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 involvement, 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 positively with the disseminated distribution of the disease, as patients with disseminated skin and/or lymph node involvement have significantly higher titers (12). Although the prognosis of cryptococcosis should be considered as guarded, a majority of cats can be expected to be cured, but treatment is protracted and expensive (13). We initiated treatment with fluconazole, an azole antifungal, which is described to be very effective in the treatment of feline cryptococcosis, including cases with advanced, longstanding, or disseminated 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 treatment (2, 12, 15, 16). The cat responded well to treatment and no side effects were observed. Antifungal therapy was continued until the LCAAT titer declined to an undetectable level after 15 months of continued therapy. This was a significantly longer treatment period than described in a previous study where the median duration of treatment with fluconazole in cats

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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