Focal pulmonary granuloma caused by Cladophialophora bantiana in a domestic short haired cat

NATASHIA EVANS*, MARCUS GUNEW†, RHETT MARSHALL†, PATRICIA MARTIN‡ & VANESSA BARRS*

*Valentine Charlton Cat Centre, Faculty of Veterinary Science, The University of Sydney, New South Wales, †The Cat Clinic Mount Gravatt, Queensland, and ‡Department of Veterinary Pathology, Faculty of Veterinary Science, University of Sydney, New South Wales, Australia

Introduction

Phaeohyphomycoses is a collective term referring to infections caused by over 100 different species of fungi that display dark-walled hyphae in culture [1]. Cladophialophora bantiana belongs to this group and has been previously known as Torula bantiana, Cladosporium bantiana, Xylohypha bantiana, Cladosporium trichoides and Xylohypha emmonsii. It has a worldwide distribution [2], with infection most commonly observed in humans, less frequently in cats and sporadically in dogs [3–7]. Infections have been reported in immunocompromised and immunocompetent individuals.

While C. bantiana is considered to be a highly neurotropic fungus, cutaneous and disseminated infections have also been reported [8–10]. In humans, wide surgical resection combined with systemic antifungal therapy provides the best chance of long-term survival [4] but even with aggressive therapy mortality rates in humans approach 70% [11].

This report describes the diagnosis, treatment and outcome of an isolated pulmonary granuloma caused by C. bantiana in a 12-year-old neutered male domestic short haired cat with long standing diabetes mellitus.

Case report

A 12-year-old male neutered domestic short haired cat presented with a 4-week history of coughing that had been unresponsive to a two week course of oral doxycycline (Vibravet, Pfizer). The cat lived both indoors and outdoors and had been diagnosed 2 years previously with diabetes
mellitus. The latter was well-stabilized on 1.5 to 2 international units of glargine insulin administered subcutaneously (Lantus, Sanofi Aventis) twice daily. Although the physical examination was unremarkable, thoracic radiographs revealed a 4 × 5 cm radiopaque soft-tissue mass in the right caudal lung lobe. Fine-needle aspirate biopsies of the mass were collected under general anaesthesia. Cytological evaluation using a modified Giemsa-Wright stain (Diff Quik, Fronine Laboratory Supplies) revealed branching septate brown fungal hyphae within epithelioid macrophages, neutrophils and occasional lymphocytes. These results are consistent with mycotic pneumonia and pyogranulomatous inflammation. Haematology, biochemistry and urinalysis data were unremarkable. Serological tests for feline immunodeficiency virus (FIV) and feline leukaemia virus (FeLV) were negative (IDEXX Snap FIV/FeLV combo test). Abdominal sonography and survey radiographs of the axial and appendicular skeleton were unremarkable. A right lateral thoracotomy was performed and the right caudal lung lobe resected en bloc. A concerted effort was made to get a clear surgical margin and prevent contamination while removing the lobe, but this could not be guaranteed as granulomatous tissue extended to the ligament site (Fig. 1).

Histopathology revealed that the majority of lung parenchyma was replaced by large aggregates of epithelioid macrophages that were interspersed with moderate numbers of lymphocytes and occasional plasma cells. Epithelioid macrophages surrounded areas of necrosis and debris with numerous neutrophils and brown pigmented branching septate hyphal elements. This was consistent with marked pyogranulomatous mycotic pneumonia. Fresh tissue from the mass was inoculated onto Sabouraud’s dextrose agar and incubated at 25 and 37°C. After 4 days there was a moderately heavy growth of a black filamentous fungus. The mold was subcultured to potato dextrose agar to encourage conidial formation, but none was observed. PCR and sequence analysis of the 18S ribosomal RNA gene of the isolate was performed. The amplified sequence (443 bp) demonstrated 98% identity to sequences of the dematiaceous fungus Cladophialophora bantiana deposited in the GenBank database (GenBank (NCBI) database accession number GQ258793.1) using the Basic Local Alignment Search Tool (Blast). In vitro susceptibility testing of the isolate was not performed due to poor conidial formation and technical difficulty associated with susceptibility testing of hyphae [21].

The cat had an unremarkable post-operative recovery and the cough was not noted again. Therapy was commenced with itraconazole 10 mg/kg orally once daily. After 4 weeks the cat became inappetant and repeat serum biochemistry revealed an elevated alanine aminotransferase (ALT) twice the normal reference range (244 mmol/l, 19–100 mmol/l). Itraconazole was discontinued and posaconazole was commenced at 2.5 mg/kg twice daily PO with food (Noxafil, Schering Plough). This was well tolerated, and was continued for 7 months post operatively. At the time that posaconazole was discontinued there was no clinical evidence of recrudesced infection.

Four weeks after discontinuing posaconazole the cat became inappetant. Repeat biochemistry revealed a moderate ALT elevation (1011 mmol/l, 19–100 mmol/l). On abdominal sonography approximately 50% of the liver was of mixed echogenicity and a 5 cm diameter mass was seen in the right lateral lobe of liver. Histopathology of a Tru-Cut biopsy of the mass revealed changes consistent with hepatocellular carcinoma. Surgical resection of the liver mass was considered unlikely to be successful based on the sono-graphic findings and the owner elected palliative care. Five months after diagnosis of hepatocellular carcinoma, the owner elected to euthanase the cat and gave permission for a limited post mortem involving examination of the thoracic and abdominal cavities but not the central nervous system. No gross abnormalities consistent with fungal infection were seen on inspection of the thorax and abdomen. Samples of lung and liver were submitted for histopathology. Sections were stained with haematoxylin and eosin (H & E) and periodic acid schiff (PAS). Lung tissue was also stained with van Gieson stain. Histopathology of the lung revealed moderate emphysema. No fungal elements or inflammatory infiltrate was detected. Liver sections consisted of multiple small to very large round to oval islands of poorly differentiated highly pleomorphic cells with a complete loss of normal liver architecture. There were no sinusoids, hepatocyte plates, portal tracts or even central veins in the proliferating tissue. Marked anisocytosis and anisokaryosis were present. The mitotic rate was very high (58 per 10 high power fields). No fungal elements were detected. These changes confirmed the antemortem

Fig. 1 Resected lung lobe with black pigmented edges.

© 2011 ISHAM, Medical Mycology, 49, 194–197
diagnosis of hepatocellular carcinoma. Based on these post mortem results there was no evidence of recurrence of infection 13 months after the original diagnosis.

**Discussion**

This is the first reported case of an isolated pulmonary fungal granuloma caused by *C. bantiana* without dissemination or neurological system involvement in a domestic cat. It is also the first report of the administration of the antifungal posaconazole for treatment of *C. bantiana* in a cat and it is the first non-cutaneous infection in a cat to achieve long term survival.

* *C. bantiana* is a rare cause of cerebral, cutaneous and disseminated infections. Over 70 cases have been documented in humans worldwide. Infection appears to be more common in tropical and subtropical areas [11]. It is considered to be a neurotropic fungus since the vast majority of human infections affect the central nervous system. While the portal of entry is not always obvious, cutaneous infections are suspected to be the result of direct inoculation into a wound or via a penetrating injury. Systemic or central nervous system infection is suspected to result from inhalation of conidia and haematogenous spread [2]. Inhalation was likely the portal of entry in this case as the granuloma was located in the lung.

To our knowledge infections caused by *C. bantiana* have been described in felids on 14 occasions, which includes 13 domestic cats and one snow leopard. Reported cases have involved the central nervous system (CNS, *n* = 8) [2,3,13–15], disseminated infections (*n* = 2) [12], a cutaneous infection (*n* = 1) [9], an ocular infection (*n* = 1) [17] and pyelonephritis (*n* = 1) [16]. Four cases were diagnosed antemortem (ocular, pyelonephritis, disseminated and cutaneous infections), with the remaining 10 cases diagnosed post mortem. The only cat to survive longer than 7 months had a cutaneous infection and was treated initially with anti-fungal therapy, then by incomplete surgical resection. Following surgical resection the cat also had episodes of relapse when antifungal therapy with fluconazole (Diflucan, Pfizer) was discontinued. It is not reported how long this cat survived. Of the remaining cases diagnosed antemortem, one died within 1 week of diagnosis despite treatment with ketoconazole [12], and one was euthanased after 7 months of treatment with itraconazole [16]. The remaining case had a 6-month disease-free interval following surgical excision alone before developing neurological signs and was euthanased. A post mortem examination was not performed [17]. While there is very little published information regarding factors that may influence therapeutic outcome, it is likely that infections where complete surgical excision is able to be performed carry a better prognosis.

In this case the affected lung lobe was resected but clear margins could not be guaranteed as fluid leaked from the lung lobe at the ligation site. Given the gross pigmented appearance of the fungus within the liver lobe, empirical anti-fungal therapy was commenced immediately post operatively. Itraconazole was initially chosen because of its reported efficacy against filamentous fungi [18,19] and its ready availability. Itraconazole is also generally well tolerated by cats [18]. Susceptibility testing was not performed by the reference laboratory due to lack of conidial formation. Susceptibility testing of hyphae is possible but is technically demanding and often unsuccessful. In one study only 12 of 50 attempts to prepare inoculums suspensions for susceptibility testing from the hyphae of filamentous fungi were successful [21]. Due to lack of susceptibility testing, posaconazole was chosen empirically when the cat did not tolerate itraconazole therapy. Posaconazole is a third generation azole that is well tolerated in humans. Recent murine models have shown prolonged survival of mice infected with *C. bantiana* when treated with posaconazole in comparison to those treated with micafungin, amphotericin B, 5-flucytosine and voriconazole [20].

Of interest in this case is the history of diabetes mellitus, which may have been a predisposing factor for fungal infection. Both immunocompromised and immunocompetent humans are represented in case reports of infections due to *C. bantiana*. However, diabetes mellitus was found to be a predisposing factor in a retrospective review of 40 patients with intracranial fungal granulomas [22]. Diabetic humans are also considered to have an increased susceptibility to infections caused by mycobacteria. A recent study found altered cytokine expression in diabetic patients with tuberculosis compared with non-diabetic patients. This effect was even more marked in poorly controlled diabetics [23]. Other than one case of disseminated infection in a cat being treated with chemotherapy for lymphoma, in none of the previous cases involving felids were the animals reported to be immunocompromised [16].

This case report describes the diagnosis and successful therapy of a cat with a pulmonary fungal granuloma caused by *C. bantiana*. Surgical excision followed by a 7-month course of the antifungal posaconazole resulted in a disease-free interval greater than 12 months.

**Acknowledgements**

The authors thank Schering-Plough for supplying posaconazole free of charge for therapy and Dr Derek Spielman of Veterinary Pathology Diagnostic Services for the histopathological interpretation in this case.

**Declaration of interest:** Posaconazole was supplied by Schering Plough.
References


This paper was first published online on Early Online on 24 September 2010.