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RARE SYSTEMIC MYCOSES IN CATS: BLASTOMYCOSIS, HISTOPLASMOSIS AND COCCIDIOIDOMYCOSIS

ABCD guidelines on prevention and management

Albert Lloret, Katrin Hartmann, Maria Grazia Pennisi, Lluis Ferrer*, Diane Addie, Sándor Belák, Corine Boucrault-Baralon, Herman Egberink, Tadeusz Frymus, Tim Gruffydd-Jones, Margaret J Hosie, Hans Lutz, Fulvio Marsilio, Karin Möstl, Alan D Radford, Etienne Thiry, Uwe Truyen and Marian C Horzinek

Overview: Rare fungal infections, including those hitherto not reported in Europe, may occur sporadically in non-endemic areas, or imported cases may be seen.

Infections: Blastomycosis is mainly seen in North America; no cases have been reported in Europe. Histoplasmosis, which is endemic in the eastern US, Central and South America,has been diagnosed in Japan and Europe. Coccidioidomycosis is endemic in the southwestern US, Central and South America; only one imported case has been reported in Europe. The primary mode of transmission is inhalation of conidia or spores from the environment.

Disease signs: Most feline cases present with a combination of clinical signs (mainly respiratory, along with skin, eye, central nervous system and bone). Lymphadenopathy and systemic signs may be present.

Diagnosis: Diagnosis is based on fungal detection by cytology and/or histology. Commercial laboratories do not routinely perform fungal culture. Diagnosis of coccidioidomycosis, which is more difficult, may be supported by antibody detection.

Treatment: Treatment consists of prolonged systemic antifungal therapy, with itraconazole as the first-choice agent for histoplasmosis and blastomycosis. The prognosis is good if owner compliance is adequate and adverse drug effects do not occur.

Prevention: Cat owners travelling to endemic areas should be warned about these diseases. There is no zoonotic risk.

Fungal properties and epidemiology

Rare systemic fungal infections in Europe are blastomycosis (caused by Blastomyces dermatitidis), histoplasmosis (caused by Histoplasma capsulatum) and coccidioidomycosis (caused by Coccidioides immitis). In endemic areas, these infections are more frequent in dogs; scientific data for cats are scarce and mainly based on a few retrospective case series or reports.

These diseases are endemic in some areas of the Americas, but in recent years more cases have been reported from non-endemic areas. At risk are mainly outdoor, free-roaming cats with access to fungal organisms in the soil. However, an outbreak of blastomycosis has been reported in an urban non-endemic area (Chicago, Illinois), in five indoor cats; unusual drought was suggested as the most likely cause.

Histoplasmosis has also been diagnosed in indoor cats, associated with exposure to contaminated soil linked to construction work, potted plants and unfinished basements. The first reported cases of histoplasmosis in Europe and Japan have been published in recent years. In both cases diagnosis was confirmed by post-mortem examination, involving histology, special stains and immunohistochemistry.

Italy, Germany and Turkey should be considered endemic areas for histoplasmosis, as suggested by the European Confederation of Medical Mycology Working Group.

Few case reports and one case series of coccidioidomycosis have been published so far, and only in endemic areas. One case in a cat imported from the USA has been diagnosed in Portugal.

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**Pathogenesis**

Fungal systemic mycoses are not contagious among cats, with infection occurring after the organism is contracted from the environment. Inhalation of aerosolised conidia or spores establishes a primary infection site in the lungs; thereafter, yeast dissemination to the lymphatic, skeletal and central nervous (CNS) systems occurs, as well as to the eyes and skin, with pyogranulomatous inflammation.9

**Clinical presentation**

Systemic mycoses generally produce a combination of clinical signs related to the target sites of infection, including the respiratory tract (which is usually the primary focus), bone, CNS, eyes, lymph nodes and skin.1,9

- **Blastomycosis** Cats usually show pneumonia (dyspnoea, tachypnoea, coughing) and skin disease (non-ulcerated dermal masses or large abscesses) and non-specific signs like fever, lethargy, anorexia and weight loss.10,11 Chorioretinitis and common CNS signs may also be present in cats with disseminated disease.11 CNS infection rarely occurs without evidence of systemic disease.12 Lymph node involvement is not a common feature.10,12 Abnormal blood values are non-specific, indicative of an inflammatory process. In one cat with pulmonic and cutaneous blastomycosis, hypercalcaemia and increased levels of calcitriol were found, which returned to normal after treatment.14 Thoracic radiographs mainly demonstrate nodular interstitial to alveolar patterns and areas of consolidation. Diffuse bronchial patterns are also observed.10,14 Immunosuppression and retroviral infection have not usually been present in the cases reported.9,10

- **Histoplasmosis** Cats usually show pneumonia, gastrointestinal disease and sometimes progressive disseminated disease.13,16 Cases have also been reported of disseminated infections without respiratory signs.16,17 Intestinal involvement may occur, with pyogranulomatous lesions in the small bowel and mesenteric lymph node enlargement.5 In disseminated disease, the liver, lymph nodes, eyes and bone marrow are affected. One case of disseminated histoplasmosis presenting as an acquired skin fragility syndrome has been reported.18

- **Coccidioidomycosis** Cats usually show skin, respiratory, musculoskeletal, neurological and ocular signs.19,20 Ocular disease (anterior uveitis, granulomatous chorioretinitis, blindness) has been diagnosed in cats without systemic signs.21

**Diagnosis**

Diagnosis is usually based on the demonstration of yeast cells in affected tissues by cytology and/or histology.1,9,15

**Cytology**

The characteristic morphology of the yeast cells (B dermatitidis – thick-walled, 8–12 μm cells without a capsule; H capsulatum – round to oval intracellular yeast cells with a basophilic centre surrounded by a light halo) is in most cases sufficient to confirm the diagnosis. Respiratory tract (by lung fine needle aspiration or bronchoalveolar lavage), skin, lymph node (not in blastomycosis) and bone marrow (histoplasmosis) samples are most suitable for diagnosis.9,15

Cytology is less reliable for the diagnosis of coccidioidomycosis.19,21,22

**Histopathology**

Histology is needed for diagnosis when cytology fails, especially in coccidioidomycosis.22 Pyogranulomatous inflammatory responses and the presence of yeasts with the typical morphology in each case are diagnostic. Special staining for fungal organisms (periodic acid-Schiff, Gridley’s or Gomori methenamine silver) may improve the sensitivity.5,15,22

**Culture**

Culture is the gold standard for diagnosis, but is not frequently performed in practice. Concerns about the potential risks to laboratory personnel handling the samples should govern the procedures.

**Other tests**

Tests have been developed for the detection of blastomycosis antigen in blood and urine of dogs and humans.23 The highest sensitivity is achieved by testing both blood and urine. Cross-reactions occur with histoplasmosis, as the antigen is identical for both organisms; the test may therefore be seen as an assay to screen for both mycoses.24 Antigen detection tests have also been used to monitor response (including duration of response) to treatment.23,25 Antigen testing has not been critically evaluated in cats, and recommendations about its use cannot be given.

Assays to detect antibodies against these fungal organisms have been developed, but they are of low sensitivity and specificity for blastomycosis and histoplasmosis, not discriminating between current disease and previous exposure.1,9

In contrast, serology using an agar gel immunodiffusion test is the basis for the diagnosis of feline coccidioidomycosis. High
sensitivity (83%) has been established in cats by a retrospective study [EBM grade III].19 False-negative results may be expected in the first 2 months of acute infection. Coccidioidomycosis is usually diagnosed by a combination of serology, cytology and/or histopathology.19,21,22

Treatment

No prospective studies exist on the treatment of feline systemic mycoses. Available data on treatment are based on retrospective studies and case reports.

Itraconazole is currently the treatment of choice for blastomycosis and histoplasmosis [EBM grade III].1,16,26 Amphotericin B and fluconazole may be used as well, especially in severe cases or those with CNS signs [EBM grade III].1,16 In a study of eight cats with histoplasmosis, long-term itraconazole treatment was well tolerated and cured all the patients [EBM grade III].15

Ketoconazole or fluconazole have been used most frequently in feline coccidioidomycosis [EBM grade III].1,19 In a recent report of cats with ocular coccidioidomycosis, fluconazole was effective, although long term treatment was necessary in one case [EBM grade IV].21

Table 1 lists the treatment options for these infections.

There are no vaccines available.

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Conflict of interest

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References

Itraconazole, administered over several months, is the first-line treatment for blastomycosis and histoplasmosis, and fluconazole for coccidioidomycosis.

KEY POINTS
- Cat owners travelling to endemic areas should be warned about these rare systemic mycoses. Practitioners in Europe should consider these infections in cats coming from endemic areas.
- Italy, Germany and Turkey should be considered endemic areas for histoplasmosis, based on recommendations made by the European Confederation of Medical Mycology Working Group. So far only one cat with histoplasmosis has been reported from Italy.
- Respiratory involvement is common and frequently the primary site of infection. Dissemination may occur to skin, gastrointestinal system, lymph nodes, liver, CNS, eye and bone.
- Fine-needle aspirates and cytology are of high sensitivity in the diagnosis of blastomycosis and histoplasmosis.
- Itraconazole, administered over several months, is the first-line treatment for blastomycosis and histoplasmosis, and fluconazole for coccidioidomycosis.

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