Cryptococcosis

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Profile

Definition

- Cryptococcosis, the most common systemic mycosis in the domestic cat, is caused by an encapsulated yeast—most commonly *Cryptococcus neoformans* and *C gattii*, both dimorphic, basidiomycetous fungi.
  - *C neoformans*.
    - *C neoformans* var *neoformans*.
    - *C neoformans* var *grubii*.
  - Genotyping via PCR fingerprinting is used to distinguish molecular types and differentiate strains based on geographic location.
    - *C neoformans* var *grubii* isolates are molecular types VNI and VNII.
    - *C neoformans* var *neoformans* is type VNIV with a hybrid type VNIII.
    - *C gattii* isolates are classified as molecular types VGI–VGIV with different genetic subtypes within each VG group representing various strains.
- Reproduction occurs with asexual and sexual phases.
  - Asexual phase is haploid.
  - Sexual phase is by budding.
    - Found within mammalian tissue.
    - Production of basidiospores (ie, infectious component of *Cryptococcus*).

Systems

- Upper respiratory (ie, nasal cavity), skin, lymph nodes, brain, meninges, and eyes are the most common infection sites.
- Other sites include lungs, mediastinum, gingiva, spleen, myocardium, liver, thyroid gland, tongue, and bone.

Geographic Distribution

- Australia, western Canada, and western United States.
  - Although less prevalent, *Cryptococcus* spp can occur in all parts of the world.

Signalment

Species

- Most common in cats and dogs; other mammalian species are susceptible.
- All domestic cats are at risk.

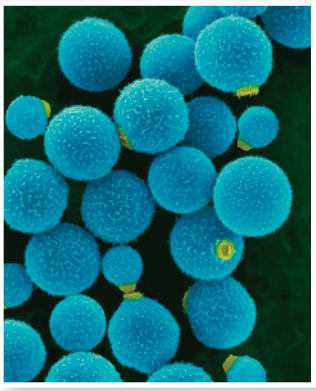
Breed

- Siamese, Birman, and Ragdoll cats were overrepresented in a study from Australia.[1,2]
- No breed predisposition was found in a study in California.[2,3]

Age

- Cats of all ages are known to become infected.
  - Young adult cats appear at increased risk (2–3 years of age).
  - Median age at infection is 6 years.[2-4]
  - Exposure can occur years before infection materializes, so older cats may present with signs.
- Predominantly younger, more active dogs are at increased risk.

MORE ▶



Cryptococcosis, the most common systemic mycosis in domestic cats, is caused by dimorphic, basidiomycetous fungi.

Sex
- No known sex predilection.

Causes
- Inhalation of spores from avian guano or affected soils.
- *C neoformans* is also found in decaying plant matter harboring in some tree hollows.
- *C gattii* has been isolated from air, seawater, freshwater, and tree bark.

Risk Factors
- Cats with retroviruses (ie, FeLV, FIV) are not predisposed to infection with *Cryptococcus* spp, but difficulty responding to therapy and relapse of cryptococcosis may be common.[2,5]
  - These patients may be predisposed to neoplasms (eg, lymphoma, adenocarcinoma, mast cell tumor).
- Opportunistic infections (eg, from *Toxoplasma gondii*) have been reported.

Pathophysiology
- Encapsulated spores (basidiospores) are typically inhaled, initiating infection in the nasal cavities of cats (primarily) and dogs.
- Disease can spread through the cribriform plate, causing meningitis.
  - May involve the optic nerve and eye.
  - May extend into lungs, skin, bones, brain, and other body sites via hematogenous routes.
    - May be detected in the lungs via histopathology without producing clinical signs.
    - Direct contact with open wounds may cause skin lesions.
    - Multiple granulomatous skin lesions are more likely associated with hematogenous spread.

History
- Outdoor cats more susceptible.
- Indoor cats exposed from open windows/doors or indoor plants/soil.
- Transfer from clothing can occur.
- Signs:
  - Sneezing, head shaking, stertor.
  - Inappetence from blocked sinus passages and invasion into the CNS.
  - Blindness.

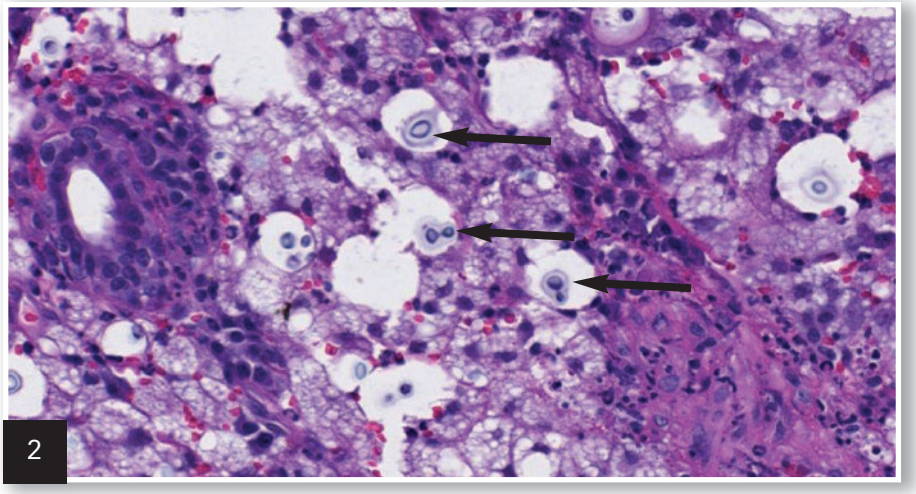
Physical Examination
- Findings in cats (**Figure 1**):
  - Infection with *C gattii* VGI and *C neoformans* var *grubii* may be localized to the nasal cavity.
  - Infection with *C gattii* VGII genotypes can involve multiple organs.
  - Swelling over nasal maxillary of frontal area.
  - Proliferative lesions in the nares.
  - Fungal granulomas in lymph nodes and skin (primarily around head and neck).
  - Mydriasis and optic disc or retinal lesions.
- Findings in dogs:
  - Signs involving multiple organ systems.
  - Neurologic signs, often in conjunction with malaise, are most common:[6]
    - Stumbling.
    - Partial paralysis.
    - Ataxia.
    - Hyperesthesia along dorsum or cervical area.
    - Seizures, sometimes severe.
  - Blindness less common than in cats.
  - Approximately 50% have upper respiratory signs:[6]
    - Epistaxis.
    - Sneezing.
    - Nasal discharge.
  - GI signs.
  - Renal involvement.
  - Cutaneous lesions.

Dx Diagnosis

Definitive Diagnosis
- Cytologic evaluation of tissue samples.
  - Rapid, inexpensive, sensitive test.
  - Does not permit identification of *Cryptococcus* spp.
  - Narrow-based budding yeast capsules evident (**Figure 2**).
- Culture of samples from nasal swab, needle aspiration, cerebrospinal fluid (CSF), lymph nodes, pleural and/or abdominal fluids, urine.
  - Organism grows readily in standard culture media and is not a hazard to laboratory personnel.[2]
  - *Cryptococcus* spp will not grow on dermatophyte medium containing cycloheximide.
  - Use of selective medium can differentiate *C neoformans* group from

1 **(A) Cat presented with classic nasal lesions consistent with cryptococcosis; (B) signs improved after 7 months of treatment with fluconazole.** Courtesy of Patricia Ashley, DVM, DACVD

CSF = cerebrospinal fluid



2

Histopathology sample showing *Cryptococcus* organisms (black arrows). (Hematoxylin and eosin stain, 100× magnification) Courtesy of Michele Stock, DVM, DACVD

C gattii.
- ❑ Immunohistochemical staining cannot distinguish various *C gattii* strains from Pacific Northwest.
- ❑ Can use with titers to evaluate treatment outcome.

- Antigen titers in serum and CSF are highly specific and sensitive.
  - ❑ Aid in diagnosis and determining response to therapy.
    - Initial rise in titers after treatment is expected.
    - Titers should be rechecked 6–8 weeks after initiating therapy.
    - Therapy should be continued until titers are negative; relapse is possible.

Differential Diagnosis

- Infectious rhinitis.
  - ❑ Bacterial.
  - ❑ Viral.
  - ❑ Parasitic.
- Inflammatory rhinitis.
  - ❑ Foreign object.
  - ❑ Lymphoplasmacytic.
  - ❑ Eosinophilic.
  - ❑ Other.
- Neoplasia.
  - ❑ Nasal lymphoma (more common in cats).
  - ❑ Nasal adenocarcinoma (more common in dogs).

Laboratory Findings

- CBC and serum biochemistry findings are nonspecific:
  - ❑ Low-grade nonregenerative anemia.
  - ❑ Lymphopenia.
  - ❑ Monocytosis.
  - ❑ Occasionally elevated globulins (polyclonal gammopathy).
- CSF analysis.
  - ❑ May have encapsulated yeast.
  - ❑ Mild to moderate protein elevations.
  - ❑ Neutrophilic pleocytosis.

Imaging

- Thoracic radiography.
  - ❑ Assess for pulmonary infiltrates, enlarged lymph nodes, mediastinal changes, and effusions from systemic fungal infection.
- Abdominal ultrasonography.
  - ❑ Normal in >80% of cats with cryptococcosis.
  - ❑ Iso-hypoechoic mass lesions in the renal pelvis in cats with renal involvement may be visible.
- MRI.
  - ❑ Helps assess extent of CNS involvement, including mass lesions and optic nerve enlargement.
- CT.
  - ❑ Helps assess destruction of cribriform plate and bony structures of the face.
  - ❑ May have contrast-enhancing mass lesions of the nasal planum; soft tissue and fluid opacification are also possible.
  - ❑ Also helps assess extent of CNS involvement, including mass lesions and optic nerve enlargement.

Tx Treatment

- Supportive care for anorexic and dehydrated patients should be administered as necessary.
- Surgery:
  - ❑ May be beneficial to cats with large accessible cryptococcomas if medications do not penetrate the lesions.
  - ❑ Is controversial as some cats respond to antifungal therapy (see **Medications**, next page).

Nutritional Aspects

- Feeding tubes (eg, PEG, E-tubes) may be indicated to supply nutritional support until inflammation in the nasal passages subsides with antifungal therapy.

Client Education

- Treatment duration is long and owner compliance with medications and follow-up is imperative.
- Zoonotic transmission of *Cryptococcus* from a pet cockatoo to an immunocompromised person has been reported.[7]
  - ❑ Transmission is via aerosol exposure from bird excreta rather than direct contact with the animal.[8]
  - ❑ Cryptococcosis is the most common opportunistic fungal disease of humans with HIV.[8]
- Other sources indicate no zoonotic potential to immunocompetent individuals.[6-9]
- Transmission occurs via shared contaminated environments.[6]

MORE ▶

Medications

Azoles

- Fungistatic compounds that alter cell membrane permeability and allow cell contents to leak into the periphery.
- Fluconazole is treatment of choice for maximum penetration into the CNS, eye, and urinary tract with minimal side effects.
  - ❏ Standard dose for dogs and cats is 5 mg/kg PO q12h until antigen testing of blood or CSF (if CNS disease is present) is negative (mean duration, 8 months).[8]
  - ❏ Some cryptococcal isolates show resistance.
- Itraconazole has been used successfully to treat cryptococcal meningitis.
  - ❏ Cats may experience anorexia, vomiting, and hepatocellular damage (all dose-dependent).
  - ❏ Oral suspension has greater bioavailability and should be dosed lower than tablet formulation (3 mg/kg PO q24h rather than 10 mg/kg PO q24h).
  - ❏ Compounded formulations have been associated with inadequate blood levels.
- For cats with localized disease and resistance to fluconazole, ketoconazole may be preferred by cost-conscious owners.
  - ❏ Standard dose of ketoconazole for dogs and cats is 5–10 mg/kg PO q12–24h until antigen testing of blood or CSF (if CNS disease is present) is negative (~6–18 months).[8]
- Other azoles (eg, voriconazole, posaconazole) are effective but expensive.
  - ❏ Cats may experience neurologic effects from voriconazole.

Amphotericin B

- Fungicidal compound that also disrupts fungal cell membranes.
- Must be given parenterally.
  - ❏ SC protocol may minimize hospitalization and permit outpatient care.
    - 0.5–0.75 mg/kg diluted in large volumes of 0.45% NaCl and 2.5% dextrose 2–3 times/week.
    - Median cumulative dose of 16 mg/kg.
- Newer liposomal and lipid complex preparations are less nephrotoxic than previous formulations.

Flucytosine

- Pyrimidine analog that interferes with fungal nucleic acid synthesis.
- Standard dose (cats only) is 30 mg/kg PO q6h, 50 mg/kg PO q8h, or 75 mg/kg PO q12h, not to exceed 250 mg q6–8h.[8]
- Should not be used as a monotherapy because of risk for resistance.
- May cause bone marrow suppression, GI disturbance, and worsening of preexisting renal insufficiency.
- Should not be used in conjunction with amphotericin B.
- Use only in cats; dogs tend to develop severe cutaneous drug eruptions.

Follow-up

Complications

- Hepatocellular damage associated with chronic ketoconazole and itraconazole administration is possible and warrants monthly monitoring of liver enzymes.
- Renal toxicity associated with amphotericin B is possible and warrants monthly monitoring of renal values and consideration of using liposome-encapsulated formulations of amphotericin B to reduce risk for renal toxicity.

Future Follow-up

- Serum antigen titers should be monitored monthly for seroconversion during treatment.
  - ❏ Patients that seroconvert to a negative status should be retested 1 month after therapy.
  - ❏ Successful treatment occurs when the titer reaches zero.
  - ❏ Treatment may be indicated for months to years.
- For cats in carrier state, periodic antigen testing is warranted.
  - ❏ Antigen titer should decrease by 1 dilution each month during therapy.
    - Failure to achieve this suggests the need for more aggressive therapy (ie, additional medications or change in protocol).[8]

In General

Relative Cost

- Treatment is costly, as it is required for months to years: $$$$$
- Fluconazole and ketoconazole are less expensive than itraconazole.

Cost Key
$ = up to $100
$$ = $101–$250
$$$ = $251–$500
$$$$ = $501–$1000
$$$$$ = more than $1000

Prognosis

- Animals that survive the first 2 weeks of therapy have a reasonable but guarded prognosis.
  - ❏ Rapid rate of improvement in the first month can lead to decreased owner compliance, precluding a higher rate of relapse.
- Relapse is possible.
- CNS involvement is the only significant predictor of mortality. ■ cb

See **Aids & Resources**, back page, for references & suggested reading.

CSF = cerebrospinal fluid