MiraVista
VETERINARY DIAGNOSTICS

CLINICAL REVIEW

Blastomycosis

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See Sykes, J.E. for more detailed information [1].

1. Background
    a. Causative agents: Dimorphic fungi *Blastomyces dermatitidis*, *B. gilchristii* (formerly a cryptic subspecies of *B. dermatitidis*), *B. helicus* (new species rarely found in the Southwest United States and parts of Canada) [2].
    b. Route of infection: inhalation of spores, rarely cutaneous inoculation.
    c. At highest risk: young, large breed dogs with highest rates in Coonhounds, Pointers, and Weimaraners; higher rates in sexually intact males caused by roaming behavior or hunting.
    d. Endemic distribution: Mississippi, Ohio, and Missouri river valleys, VT, Eastern seaboard, Canada (primarily western ON, parts of MB and SK), and areas adjacent to Great Lakes but **may occur outside of endemic areas [2].**
2. Clinical Findings
    a. Pulmonary: ~90% (often accompanied by disseminated findings)
        i. Signs: tachypnea, cough, dyspnea
        ii. Imaging: nodular, referred to as “snowstorm pattern” or interstitial infiltrates. Less frequent: tracheobronchial lymphadenopathy, masses, or cavitary lesions.
    b. Disseminated (extrapulmonary): >50%; may be accompanied by pulmonary involvement
        i. Nonspecific signs: >75%; fever, anorexia, weight loss, lethargy, reduced activity.
        ii. Cutaneous lesions: ~50%; ulcerations with drainage, granulomas, subcutaneous abscesses; especially on nasal planum, face, and nail beds.
        iii. Peripheral lymphadenomegaly: ~40%
        iv. Ocular involvement: ~40%; uveitis, chorioretinitis, optic neuritis, retinal detachment, retinal granulomas, vitritis, glaucoma, lens rupture, panopthalmitis.
        v. Bone lesions: ~20%; lameness, draining lesions, sinus tracts. Imaging reveals osteolytic lesions with periosteal proliferation, usually solitary and distal to stifle and elbow.
        vi. CNS involvement: ~5%; meningoencephalitis, brain lesions, ependymitis with signs of behavioral change, seizures, weakness, ataxia, paralysis, cranial nerve abnormalities.
        vii. Other: <5%: sinonasal, cardiac, gastrointestinal, renal, bladder, testes, prostate, mammary gland.
3. Laboratory abnormalities
    a. CBC: normocytic, normochromic nonregenerative anemia, neutrophilia, monocytosis, lymphocytosis, or lymphopenia.
    b. Serum chemistry profile: mild to moderate hyperglobulinemia due to polyclonal gammopathy, hypoalbuminemia, and uncommonly mild hypercalcemia.
    c. Urinalysis: occasional proteinuria, pyuria, hematuria or cylindruria; rarely yeasts seen on sediment exam.
    d. CSF analysis: increased total nucleated cell counts and increased CSF protein concentration.

4. Diagnosis
    a. Cytology (FNA/impression smear or respiratory specimens) or histopathology
        i. Advantage: FNA or biopsy easy to perform if cutaneous lesions or lymphadenopathy present and most rapid method for diagnosis.
        ii. Disadvantage:
            1. Risk and higher cost if more invasive procedure required in the absence of skin lesions or enlarged lymph nodes (i.e., respiratory specimens or surgical or ultrasound-guided biopsy)
        iii. Sensitivity for transtracheal lavage is 69 – 76% [3, 4] and lung aspirate is 81% [3].
    b. Antigen Detection
        i. Advantage: high sensitivity- 93.5% urine, 87% serum in pathology proven cases [5-7] including those caused by *B. helicus* [2]. Has largely replaced antibody assays for serologic diagnosis. Antigen concentration correlates with severity of infection; used as a marker for monitoring response to treatment. Easy to collect specimens (urine, serum, or other body fluids).
        ii. Disadvantage: very high cross reactivity with *Histoplasma* antigen (96%) [8]. Tests can be initially negative in mild or localized cases so negative result does not exclude diagnosis.
    c. Antibody Detection:
        i. Advantage: useful in cases with more localized or chronic infection (false negative or very weak positive antigen) and histology or cytology not feasible. Antibody EIA has good sensitivity (76 – 95%) [7] and specificity.
        ii. Disadvantage: No commercially available feline Ab EIA. Immunodiffusion (AGID) has low sensitivity (17.4 – 65%) [7]. Although the EIA is highly specific, some false positives may occur in dogs living in endemic area.
    d. Culture:
        i. Advantage: only way to prove the diagnosis. Antifungal susceptibility testing may be performed on cultured isolates.
        ii. Disadvantages: Rarely performed in vet med. Some risk to laboratory personnel, so appropriate facilities are required. Culture requires 1- 3 weeks incubation, up to 5 weeks occasionally. Only used for basis of diagnosis in 12% of cases [9].
    e. Molecular
        i. Fast turnaround time, although no peer-reviewed publications available to assess sensitivity and specificity (making interpretation of results difficult).
        ii. Disadvantage: low incidence of fungemia so whole blood unlikely a desirable specimen. Invasive procedure to obtain respiratory or tissue specimens.
5. Treatment
    a. General
        i. Up to 25% die during 1st week of treatment, mostly those with severe lung disease and respiratory failure [9, 10].
            1. Initial hospitalization for intravenous amphotericin B and respiratory assistance may reduce mortality.

2. Systemic corticosteroids may also be indicated in hospitalized cases with respiratory insufficiency [11].

ii. Outcome poor in cases with CNS involvement or severe respiratory insufficiency

b. Itraconazole: 5mg/kg PO q 12 hours for 3 days (loading dose) then q 24 hours for dogs; higher doses may be required for cats. Alternate-day dosing may be effective in cats [12].

i. Uncomplicated cases: at least 6 months and resolution of signs, resolution or marked improvement of radiographic lesions, and clearance of urine antigen. Relapse occurred in at least 20% of cases in one older study [9]. At least 6 months is recommended in humans [13] and relapse occurred in only 5% of patients [14].

ii. Complicated cases (bone, joints, CNS) or relapse despite appropriate therapy. May require 12 months or more of therapy based on resolution of signs, radiographic lesions, and antigen.

iii. Use only pelletized generic itraconazole or FDA approved products (Sporanox® capsules or liquid, Itrafungol®). Compounded non-FDA approved preparations have poor bioavailability[15], high failure rates and are not recommended.

iv. Testing blood concentration of itraconazole after reaching steady-state (2 weeks in dogs and 3 weeks in cats) is **highly recommended [15].** Some animals require higher or lower itraconazole dose to achieve therapeutic blood level.

c. Fluconazole: 10mg/kg q24h or 5mg/kg q12h. Less effective than itraconazole in prospective clinical trials in humans [13] and is not preferred. Resistance to fluconazole has developed in humans and cats with histoplasmosis [16]. Treatment failure and relapse may be more common with fluconazole in dogs (study not prospective and too small to compare accurately [10]. Fluconazole is not the treatment of choice in dogs [1] or humans [13].

d. Amphotericin B: deoxycholate or lipid-complexed amphotericin B is recommended as initial treatment for cases with severe disease followed by itraconazole to complete therapy [3, 4]. Risk of nephrotoxicity.

e. Terbinafine: no published studies to support terbinafine, not recommended in humans [13]. Has been used anecdotally in vet med, sometimes in combination with other antifungals. PK study in dogs showed blood concentrations >MIC for *Blastomyces* for 18 hours after oral dose (30-35 mg/kg).

6. Monitoring response to treatment

a. *Blastomyces* antigen testing at 3-month intervals during and at 3, 6 and 12-months following discontinuation of treatment, until negative.

b. Imaging: resolution or marked improvement in radiographs, CT or MRI scans.

7. Relapse

a. Diagnosis: recurrent signs and/or increase antigen concentrations

b. Causes: use of compounded itraconazole, subtherapeutic levels of itraconazole, inadequate duration of treatment [9], and use of fluconazole [10, 13].

c. Treatment:

   i. Repeat itraconazole adhering to guidelines above.

   ii. Chronic suppression with itraconazole 5mg/kg administered 3 times weekly could be considered in cases with refractory disease or ongoing environmental exposure.

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