# Comparison of histologic lesions of endophthalmitis induced by *Blastomyces dermatitidis* in untreated and treated dogs: 36 cases (1986–2001)

Diane V. H. Hendrix, DVM, DACVO; Barton W. Rohrbach, VMD, MPH, DACVPM;
Philip N. Bochsler, DVM, PhD, DACVP; Robert V. English, DVM, PhD, DACVO

**Objective**—To compare prevalence of organisms and histologic changes in eyes from dogs with blastomycosis that were either untreated or undergoing treatment with itraconazole.

**Design**—Retrospective study.

**Animals**—36 dogs with endophthalmitis associated with blastomycosis.

**Procedure**—Signalment, results of ophthalmic examination, and duration of treatment with itraconazole were extracted from medical records. Histologic sections from eyes were examined for prevalence and viability (ie, budding) of fungal organisms. A scoring system was devised to assess the degree of inflammation.

**Results**—Clinically, all eyes were blind and had signs of severe endophthalmitis. Histologically, the type and degree of inflammation and prevalence of *Blastomyces dermatitidis* were not significantly different between dogs treated with itraconazole and untreated dogs or among groups of dogs treated for different time periods (4 to 14, 15 to 28, or 29 to 72 days). Replication of the organisms in vascular tissues as well as avascular spaces in the eyes was similar in treated and untreated dogs. Lens rupture was seen in 12 of 29 (41%) eyes.

**Conclusions and Clinical Relevance**—Persistence of inflammation in eyes of dogs with naturally occurring blastomycosis is likely attributable to the continued presence of *B dermatitidis*, regardless of the duration of treatment with itraconazole. Lens capsule rupture, a common and previously unreported histologic finding, may contribute to cataract formation and continued inflammation. (*J Am Vet Med Assoc* 2004; 224:1317–1322)

Blastomycosis, a disease caused by the dimorphic fungus *Blastomyces dermatitidis*, occurs primarily in dogs and humans.[1] Blastomycosis is primarily found in North America and occurs most frequently in the Mississippi, Missouri, and Ohio River valleys; the mid-Atlantic states; and the Canadian provinces of Quebec, Manitoba, and Ontario.[1] Infection usually occurs by inhalation of spores produced by the mycelial form growing in soil. Initially, *B dermatitidis* establishes infection in the lungs, from which the organisms spread hematogenously or via the lymphatics to the skin, eyes, bones, lymph nodes, brain, and testes.[1] The yeasts are 5 to 20 µm in diameter; have a thick, refractile, double-contoured cell wall; and are often seen in a characteristic broad-based budding form.[1]

Ocular disease occurs in 30% to 43% of dogs with systemic blastomycosis.[2-4] Ocular infection causes anterior uveitis, panophthalmitis, chorioretinitis, retinal detachment, secondary glaucoma, and optic neuritis.[2,5,6] The most common histologic features of affected eyes are choroiditis and retinal detachment; keratitis, conjunctivitis, inflammation of the periorbital tissues, cataracts, and closure of the drainage angle with changes associated with secondary glaucoma are also seen.[7] *Blastomyces* organisms are observed primarily in the choroid; rarely, organisms have been observed in the anterior segment and retina.[7]

Fifty-four percent of dogs with systemic blastomycosis that are treated orally with itraconazole have no signs of systemic disease 1 year after cessation of treatment.[8] A study[2] of the response of eyes of dogs affected with blastomycosis and treated with itraconazole reported favorable responses in 42% of the eyes. Response varied with the part of the eye affected. Response to treatment occurred in 76% of dogs with posterior segment disease alone, 18% with anterior uveitis, and 13% with endophthalmitis. When endophthalmitis was evident, most dogs were either euthanatized (53%) or treated via enucleation (33%).

The purpose of the study reported here was to compare the prevalence of organisms and histologic changes in enucleated eyes from dogs with blastomycosis that were either untreated or undergoing treatment with itraconazole. Our hypothesis was that *B dermatitidis* continues to thrive in eyes that have persistent endophthalmitis despite administration of itraconazole.

## Criteria for Selection of Cases

Dogs were identified through a search of medical records of the College of Veterinary Medicine, University of Tennessee for the years 1986 through

From the Departments of Small Animal Clinical Sciences (Hendrix), Large Animal Clinical Sciences (Rohrbach), and Pathology (Bochsler), College of Veterinary Medicine, University of Tennessee, Knoxville, TN 37996-4544; Animal Eye Care Associates, 220 High House Rd, Cary, NC 27513 (English); and Immunology Program, North Carolina State University, 4700 Hillsborough St, Raleigh, NC 27609 (English). Dr. Bochsler's present address is Wisconsin Veterinary Diagnostic Laboratory, 6101 Mineral Point Rd, Madison, WI 53705-4494.

Supported by the Companion Animal Fund, University of Tennessee.

Presented in part at the 31st Annual Meeting of the American College of Veterinary Ophthalmologists in Montreal, QC, Canada, 2000.

Address correspondence to Dr. Hendrix.

2001. Requirements for inclusion in the study were a diagnosis of blastomycosis made via cytologic, histologic, or culture testing. In addition, the medical record had to include results of an ophthalmic examination prior to enucleation or necropsy, and ocular tissues had to be available for histologic evaluation. When both eyes from a single dog were available, 1 of the 2 eyes was randomly chosen for inclusion in the study.

## Procedures

Information extracted from the medical records included signalment, ocular examination findings, duration of treatment with itraconazole, and date of enucleation or necropsy. All dogs were examined with a slit-lamp biomicroscope. When the posterior segment could be seen, indirect ophthalmoscopy was used for examination. **Intraocular pressure (IOP)** was obtained via applanation tonometry (reference range, 15 to 25 mm Hg). Many deficiencies of information were apparent on the ophthalmic examination forms. If there was no notation indicating that an ocular tissue had been evaluated, that aspect of the examination was not included in the results.

Paraffin blocks of globes fixed in neutral-buffered 10% formalin or Davidson fixative were collected for each case, and 5-µm sections were cut. Serial sectioning was not done. Sections were stained with H&E and via the Grocott method for fungi.[9] The cornea, anterior chamber, iris, iridocorneal angle, posterior chamber, ciliary body, lens, vitreous body, retina, subretinal space, choroid, and optic nerve were evaluated for inflammation, presence of *B dermatitidis*, and pathologic changes specific to tissue (eg, retinal detachment, preiridial fibrovascular membranes, or cataract formation). Numeric scores were assigned for degree of inflammation by the following scale: 0 = no inflammation; 1 = minimal WBCs in most or all of the tissue with no tissue destruction; 2 = mild infiltrate of WBCs in most or all of the tissue with minimal tissue destruction; 3 = moderate infiltrate of WBCs in most or all of the tissues with intermediate severity of tissue damage; and 4 = marked infiltrate of WBCs with extensive tissue damage. *Blastomyces dermatitidis* or budding of organisms were scored as present or absent in the various sections of the eye if identified by either staining method.

**Statistical analyses**—Inflammation scores for the anterior chamber, iris, posterior chamber, and ciliary body were combined to form a total score for the anterior segment; the vitreous body, retina, subretinal space, and choroid were combined into a total score for the posterior segment. Budding was identified as present in any part of the eye and then subdivided into presence in the vascular and avascular components. The avascular component included the anterior chamber, posterior chamber, vitreous body, and subretinal space. The vascular component included the iris, ciliary body, retina, and choroid. Prevalences of *B dermatitidis*, budding, and inflammation scores from eyes of dogs treated with itraconazole were compared with those of untreated dogs. In addition, we compared eyes of dogs treated with itraconazole for 4 to 14, 15 to 28, and 29 to 72 days. A nonparametric Wilcoxon or Kruskal-Wallis test was used to compare scores among treatment groups, depending on the number of groups compared. Budding was compared among treated and untreated groups by use of the Fisher exact test. Agreement between results of H&E and Grocott staining for revealing organisms was evaluated with a kappa statistic. All analyses were done with a commercial statistical program.[a] All tests were performed as 2-tailed tests; values of $P \leq 0.05$ were considered significant.

## Results

Thirty-six eyes from 36 dogs met criteria for inclusion in the study. Eighteen of 36 (50%) dogs were sexually intact males, 5 (14%) were neutered males, 8 (22%) were spayed females, and 5 (14%) were sexually intact females. Thirty-four dogs were of large breeds and 2 were of small breeds. Thirty-one dogs were purebred and 5 were mixed-breed dogs. Mean age was 4.2 years (range, 8 months to 12 years). Eight dogs were affected bilaterally. Of the 36 eyes included in the study, 30 were enucleated surgically and 6 were removed at necropsy. All eyes were blind at the time of enucleation or death. Eight dogs had been treated with itraconazole for 4 to 14 days (mean, 7.5 days), 6 dogs had been treated for 15 to 28 days (mean, 18 days), and 6 had been treated for 29 to 72 days (mean, 43 days). Sixteen dogs had received no antifungal treatment at the time of enucleation or death. Of the 6 dogs that were euthanatized, 2 had been treated with itraconazole for 4 and 9 days, respectively. Three dogs were euthanatized because of severe bilateral ocular disease, 2 were euthanatized because of respiratory disease, and 1 was euthanatized because of brain involvement.

The most common anterior segment change recorded during examination prior to enucleation or death was anterior uveitis (36/36 [100%]). Changes included corneal edema, aqueous flare, miosis, and iris bombé or synechia. The fundus was not completely visible because of opacities in the cornea, anterior chamber, lens, or vitreous body in 25 of 36 (69%) eyes. Retinal detachment was noted in 10 of 11 eyes in which the fundus was at least partially visible. Twenty-two of 31 (71%) dogs had 1 or more IOP values > 25 mm Hg (mean, 44 mm Hg; range, 30 to 74 mm Hg); 11 of 22 dogs were in the treatment group, and 11 were in the untreated group. Two dogs had IOPs from 14 to 25 mm Hg at all examinations; 7 had low IOPs (mean, 4.4 mm Hg; range, 2 to 6 mm Hg) at 1 or all examinations. All dogs with low IOPs were in the treated group; IOP was not recorded in 5 dogs. All of the eyes used in the study had severe endophthalmitis, and most had panophthalmitis or panuveitis; none of the treated eyes had improved with locally administered ocular treatment and administration of itraconazole. Additional clinical signs included aqueous flare (21/22 dogs [95%]), active chorioretinitis (7/8), miosis (7/9), corneal edema (11/16), buphthalmos (12/20 [60%]), synechia (6/14), vitreal hemorrhage (2/5), hyphema (3/9), iris bombé (2/11), and cataract (1/9). Denominators vary because of variability of data in the medical records.

Histologically, no parts of the eye were spared involvement. Pyogranulomatous inflammation was

the most commonly observed response in both the anterior segment (31/36 [86%]) and posterior segment (36/36 [100%]). Lens rupture, as indicated by an undulating, severed, frayed lens capsule and intralenticular leukocytes, was seen in 12 of 29 (41%) eyes (**Fig 1**). The lens was absent from the histologic section in 7 eyes. An additional 5 eyes had intraocular leukocytes and an intact lens capsule, suggesting a capsule rupture that was not included in the section. Morgagnian globules and bladder cells were evident in 24 of 30 (80%) lenses. *Blastomyces dermatitidis* organisms were seen between cortical lens fibers in 2 ruptured lenses (**Fig 2**). Retinal detachment with subretinal exudate, hypertrophy of retinal pigment epithelial cells, and retinal degeneration were evident in all dogs. Choroidal inflammation was more severe in the nontapetal than in the tapetal choroid in 19 of 36 (53%) dogs, more severe in the tapetal than nontapetal choroid in 1 of 36 (3%) dogs, and equal in degree in 16 of 36 (44%) dogs. Additional histologic findings included, choroiditis (36/36 [100%]), vitreal protein or cells (34/36 [94%]), protein or cells in the anterior chamber (33/36 [92%]), optic nerve inflammation (12/17), and preiridial fibrovascular membrane (18/36 [50%]). The denominators vary because of missing tissues on certain sections. No significant differences in the degree of inflammation in the anterior segment or the posterior segment were observed between treated and untreated groups or among the 3 groups treated with itraconazole for different durations.

*Blastomyces dermatitidis* organisms were observed in 31 of 36 (86%) eyes. Dogs treated with itraconazole had organisms in 17 of 20 (85%) eyes, and untreated dogs had organisms in 14 of 16 eyes. Duration of intraconazole treatment in the 3 dogs with no observed *B dermatitidis* organisms was 7, 7, and 12 days, respectively. Budding of *B dermatitidis* was found in the eyes of dogs from all treatment groups. Budding was seen in 5 of 14 untreated dogs and in 10 of 17 treated dogs. Of the treated dogs, budding was seen in 5 of 5 dogs treated for 4 to 14 days, 2 of 6 dogs treated for 15 to 28 days, and 3 of 6 dogs treated for 29 to 72 days. Budding was seen in the avascular portions of the eye in 10 of 15 dogs treated with itraconazole and in 5 of 12 eyes from untreated dogs ($P = 0.26$). Of the 17 dogs with organisms in the vascular portions of the eye, budding was observed in 5 of 8 eyes from dogs treated with itraconazole and in 1 of 9 eyes from untreated dogs ($P = 0.05$).

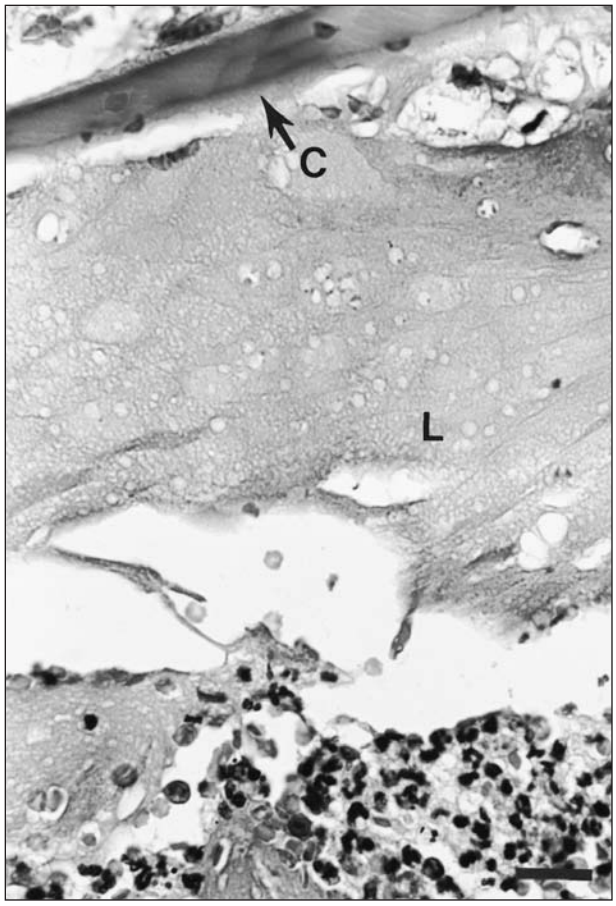


Figure 1—Photomicrograph of a portion of the eye of a dog with endophthalmitis secondary to infection with *Blastomyces dermatitidis*. Notice the lens capsule (C) with liquefaction of subjacent lens fibers, bladder cells, and morgagnian globules (L), all of which indicate cataract development. The lens capsule was ruptured adjacent to this site. Deep to the bladder cells and morgagnian globules, neutrophils are evident among disrupted cortical lens fibers. H&E stain; bar = 25 μm.

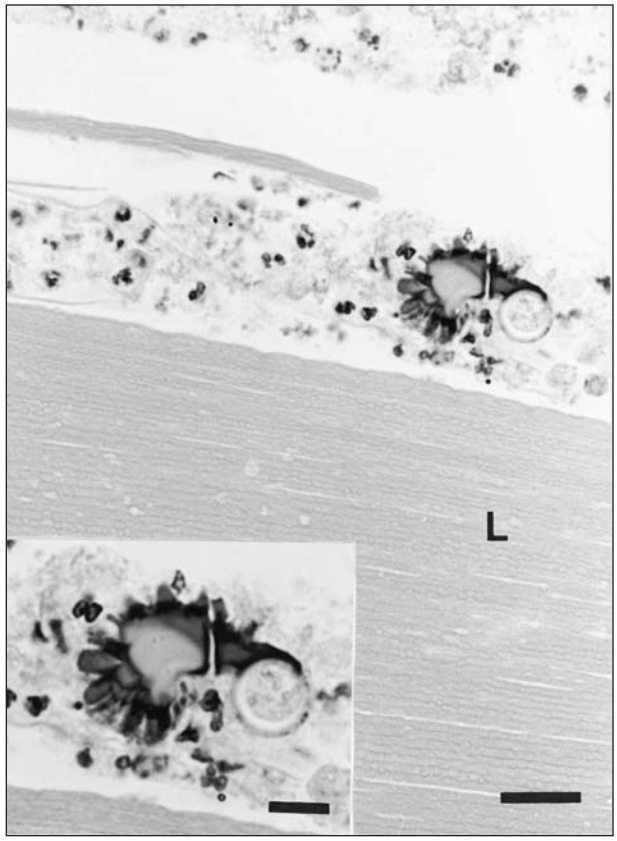


Figure 2—Photomicrograph of a portion of the eye of a dog with endophthalmitis secondary to infection with *B dermatitidis*. Notice the neutrophils and a *B dermatitidis* organism with adjacent Splendore-Hoeppli material (antigen-antibody complexes) located between separated lens fibers. Normal lens fibers (L) are subjacent to the inflammatory material. The lens capsule was ruptured and separated from the lens cortex. H&E stain; bar = 25 μm. Inset: The yeast and Splendore-Hoeppli material are surrounded by neutrophils and debris. H&E stain; bar = 10 μm.

Evaluation of the agreement between H&E and Grocott staining for detecting organisms revealed only a slightly positive association between the stains ($\kappa = 0.3$). Observation or lack of observation of the organisms was the same with both staining techniques for 26 eyes. Organisms were detected by use of only H&E staining in 6 eyes and by use of only Grocott staining in 4 eyes.

## Discussion

Itraconazole is the treatment of choice for most cases of systemic blastomycosis in dogs. Itraconazole causes few adverse effects and has a cure rate of 54%, which is similar to that of amphotericin B and ketoconazole.[8] In another report,[2] 42% of eyes with lesions associated with blastomycosis responded to treatment with itraconazole. However, eyes that are severely affected with anterior segment disease alone or in conjunction with posterior segment disease are much less likely to respond to treatment than eyes with posterior segment disease alone. Although it is not possible to predict with complete accuracy which eyes will respond to treatment at the onset, eyes that respond typically do so within 4 weeks of initiation of itraconazole administration.[2] None of the eyes in our study had responded to treatment.

The dogs in this study were allocated into 3 groups on the basis of the number of days they had been treated with itraconazole at the time of enucleation to detect any possible changes in the eyes that might be related to duration of treatment. The first treatment group was created to include dogs in which serum steady state had not been reached, which occurs at 14 days of treatment with itraconazole.[8] The second group was created because most eyes that respond typically do so by 4 weeks of treatment.[2] The last group was created to include dogs that should be approaching termination of treatment if only mild to moderate lung involvement was initially present.[1] *Blastomyces* organisms were found in similar proportions in the eyes of untreated dogs and dogs undergoing treatment with itraconazole at all stages of treatment. Budding, a sign of active replication, was also observed in most eyes in all groups. Interestingly, budding was observed significantly more frequently in the vascular tissues of the eyes of dogs treated with itraconazole than in untreated dogs. Although we cannot explain this finding, it is unlikely to represent a true effect because there is no biological explanation for induction of budding by itraconazole. Budding indicated that *B dermatitidis* was surviving and replicating in many eyes despite itraconazole treatment.

The observation of *B dermatitidis* organisms within the ocular tissues was variable within a single section and among dogs. The use of both H&E and Grocott staining aided slightly in the detection of *B dermatitidis*.

It is not clear why some eyes respond to treatment with itraconazole and others progress to blindness secondary to glaucoma or retinal detachment or why organisms persist and replicate in eyes despite appropriate treatment. One or a combination of factors may lead to the poor response, including failure of itraconazole to reach sufficient concentrations, ocular immunity, certain features of ocular anatomy, and pathologic changes.

A pharmacologic study[10] has revealed that orally administered itraconazole penetrates into the anterior chamber and vitreous body of rabbits with inflamed eyes. The measured concentrations are greater than the minimum inhibitory concentrations and minimum lethal concentrations for *B dermatitidis*.[11] Although it is assumed that itraconazole penetrates into the inflamed eyes of dogs, this has not been studied.

Immunologically, the persistence of *B dermatitidis* organisms in the eye could decrease the potential to achieve clearance of the organism, even with antifungal treatment. Two immunologic features of the eye could theoretically contribute to survival of the organisms. The first is development of a unique immune response to *B dermatitidis* attributable to processing of antigens via ocular tissues. Antigens presented via the anterior chamber or subretinal space elicit immune responses with suppressed delayed-type hypersensitivity responses and decrease complement-fixing antibody responses.[12-16] This response has been termed **anterior chamber-associated immune deviation (ACAID)**. Although this phenomenon has not specifically been detected in dogs, it exists in most mammals investigated and therefore likely exists in dogs.

The immunologic mechanisms responsible for clearance and elimination of *B dermatitidis* and the interactions between the immune system and organism are incompletely understood. Phagocytosis and killing of organisms mediated by complement, neutrophils, and macrophages are thought to play a key role.[17-20] Results of recent studies[20-23] indicate that adhesion proteins expressed by *B dermatitidis* are critical to the ability to establish a systemic infection and may be the key target of immune responses. Wüthrich et al[22] demonstrated that immunization of mice against the WI-1 adhesion protein of *B dermatitidis* generated a partially protective immune response characterized by the development of a delayed-type hypersensitivity reaction and a strong antibody response. Binding of the WI-1 protein to phagocytes may block normal phagocyte activation pathways required for macrophage activation and complete antigen processing.[24] Results of these studies indicate that specific antibody responses, complement activation, and cell-mediated immunity, notably macrophage activation and delayed-type hypersensitivity, are pivotal for immune clearance of *B dermatitidis*. The development of cell-mediated effector mechanisms may play the most important role. Passive transfer of monoclonal antibodies to the WI-1 binding regions does not provide protection to naive mice.[25] However, enhancement of T-helper type 1 responses and delayed-type hypersensitivity responses by including interleukin 12 in immunization protocols enhances clearance of the organism.[26]

The ability of ocular processing of antigens to suppress the development of delayed-type hypersensitivity responses could therefore be vital. The suppression of delayed-type hypersensitivity and development of a unique immune response to antigens presented via intraocular spaces are systemic. The ACAID response

results in an antigen-specific decrease in delayed-type hypersensitivity responses not only in the eye but also throughout the body. In fact, presentation of antigens via intraocular tissues can suppress delayed-type hypersensitivity reactions even in established immune responses.[27] Consequently, the persistence of *B dermatitidis* antigens in the eye could sustain an immune response that specifically suppresses effector mechanisms critical for the normal elimination of *B dermatitidis*. Therefore, in refractory cases, enucleation of an infected eye may actually aid in clearance of the organism from the rest of the body.

Secondly, ocular tissues may represent a safe haven for the organism. Even with appropriate treatment, the lack of proper immune clearance would greatly hamper elimination of any infectious agent. Part of the eye's unique ability to influence immune responses is attributable to the increased expression of Fas ligand.[28-30] The Fas-Fas ligand system helps regulate immune responses, and binding of Fas on the surface of leukocytes to Fas ligand in ocular tissues can lead to leukocyte apoptosis. Ocular tissues could therefore provide partial protection from an established immune response for *B dermatitidis*, promoting survival of the organism.

Our histologic findings were similar to those previously described and included anterior uveitis, cataract, vitritis, retinal detachment, and choroiditis.[7] In addition, lens capsule rupture, which is a previously unreported histologic finding in dogs with blastomycosis, was observed in 41% of the eyes in this study. Lens capsule rupture has been reported in 1 human case of blastomycosis.[31] Several features of the lens capsule make it resistant to rupture, including elasticity, malleability, thickness, and impermeability to the passage of particulate matter.[32] In humans, as in dogs, most capsular ruptures result from trauma.[33] Capsular rupture secondary to purulent inflammation and intense acute infectious processes is rare in humans and has not been reported in dogs.[32-34] The ruptured lenses seen in our study had inflammatory cells and debris under the capsule and between separated, disrupted lens fibers. The lens capsule was scrolled at the point of rupture. Cataractous changes were invariably present in the lenses. *Blastomyces* organisms were seen within 2 lenses in association with inflammatory cells. We suspect that lens capsule rupture in the dogs reported here was caused by the severe inflammatory processes. Lens capsule rupture may be a mechanism by which severe endophthalmitis is perpetuated in eyes because lens cortical material elicits an unrelenting and unresponsive inflammation.[33]

Our data indicate that *B dermatitidis* organisms were actively replicating in the eyes of dogs with active inflammation, although they were being treated with itraconazole. Lens capsule rupture and the presence of organisms may explain the persistence of endophthalmitis in the eyes of dogs treated with itraconazole. Continuation of treatment with itraconazole may not resolve the inflammation in the eye because of the lack of the ability for the eye to rid itself of *B dermatitidis* and because of the possibility of lens rupture that contributes to persistent inflammation.

[a]SAS/PC, version 8.0, SAS Institute, Cary, NC.

## References

1. Legendre AM. Blastomycosis. In: Green CE, ed. *Infectious diseases of the dog and cat.* 2nd ed. Philadelphia: WB Saunders Co, 1998;371–377.

2. Brooks DE, Legendre AM, Gum GG, et al. The treatment of canine ocular blastomycosis with systemically administered itraconazole. *Prog Vet Comp Ophthalmol* 1991;1:263–268.

3. Arceneaux KA, Taboada J, Hosgood G. Blastomycosis in dogs: 115 cases (1980–1995). *J Am Vet Med Assoc* 1998;213:658–664.

4. Legendre AM, Walker MA, Buyukmihci N, et al. Canine blastomycosis: a review of 47 clinical cases. *J Am Vet Med Assoc* 1981; 178:1163–1168.

5. Buyukmihci N. Ocular lesions of blastomycosis in the dog. *J Am Vet Med Assoc* 1982;180:426–431.

6. Bloom JD, Hamor RE, Gerding PA. Ocular blastomycosis in dogs: 73 cases, 108 eyes (1985–1993). *J Am Vet Med Assoc* 1996;209: 1271–1274.

7. Buyukmihci NC, Moore PF. Microscopic lesions of spontaneous ocular blastomycosis in dogs. *J Comp Pathol* 1987;97:321–328.

8. Legendre AM, Rohrbach BW, Toal RL, et al. Treatment of blastomycosis with itraconazole in 112 dogs. *J Vet Intern Med* 1996; 10:365–371.

9. Luna LG, ed. Methods for bacteria, fungi, and inclusion bodies. In: *Manual of histologic staining methods of the American Institute of Pathology.* 3rd ed. New York: McGraw-Hill Book Co, 1968; 217–241.

10. Savani DV, Perfect JR, Cobo LM, et al. Penetration of new azole compounds into the eye and efficacy in experimental *Candida* endophthalmitis. *Antimicrob Agents Chemother* 1987;31:6–10.

11. Chapman SW, Rogers PD, Rinaldi MG, et al. Susceptibilities of clinical and laboratory isolates of *Blastomyces dermatitidis* to ketoconazole, itraconazole, and fluconazole. *Antimicrob Agents Chemother* 1998;42:978–980.

12. Streilein JW, Niederkorn JY. Induction of anterior chamber-associated immune deviation requires an intact, functional spleen. *J Exp Med* 1981;153:1058–1067.

13. Whittum JA, Niederkorn JY, McCulley JP, et al. Intracameral inoculation of herpes simplex virus type I induces anterior chamber associated immune deviation. *Curr Eye Res* 1982;2:691–697.

14. Streilein JW, Ma N, Wenkel H, et al. Immunobiology and privilege of neuronal retina and pigment epithelium transplants. *Vision Res* 2002;42:487–495.

15. Wenkel H, Streilein JW. Analysis of immune deviation elicited by antigens injected into the subretinal space. *Invest Ophthalmol Vis Sci* 1998;39:1823–1834.

16. Streilein JW. Immunological non-responsiveness and acquisition of tolerance in relation to immune privilege in the eye. *Eye* 1995;9:236–240.

17. Drutz DJ, Frey CL. Intracellular and extracellular defenses of human phagocytes against *Blastomyces dermatitidis* conidia and yeasts. *J Lab Clin Med* 1985;105:737–750.

18. Kozel TR. Activation of the complement system by pathogenic fungi. *Clin Microbiol Rev* 1996;9:34–46.

19. Zhang MX, Klein BS. Activation, binding, and processing of complement component 3 (C3) by *Blastomyces dermatitidis*. *Infect Immun* 1997;65:1849–1855.

20. Klein BS. Molecular basis of pathogenicity in *Blastomyces dermatitidis*: the importance of adhesion. *Curr Opin Microbiol* 2000; 3:339–343.

21. Klein BS, Squires RA, Lloyd JK, et al. Canine antibody response to *Blastomyces dermatitidis* WI-1 antigen. *Am J Vet Res* 2000;61:554–558.

22. Wüthrich M, Chang WL, Klein BS. Immunogenicity and protective efficacy of the WI-1 adhesin of *Blastomyces dermatitidis*. *Infect Immun* 1998;66:5443–5449.

23. Abuodeh RO, Winston V, Scalarone GM. Induction and detection of cell-mediated reactions with different *Blastomyces dermatitidis* antigenic preparations. *Mycoses* 1996;39:85–93.

24. Finkel-Jimenez B, Wüthrich M, Brandhorst T, et al. The WI-1 adhesin blocks phagocyte TNF-alpha production, imparting pathogenicity on *Blastomyces dermatitidis*. *J Immunol* 2001;166:2665–2673.

25. Wüthrich M, Klein BS. Investigation of anti-WI-1 adhesin antibody-mediated protection in experimental pulmonary blastomycosis. *J Infect Dis* 2000;181:1720–1728.

26. Wüthrich M, Finkel-Jiminez BE, Klein BS. Interleukin 12 as an adjuvant to WI-1 adhesin immunization augments delayed-type hypersensitivity, shifts the subclass distribution of immunoglobulin G antibodies, and enhances protective immunity to *Blastomyces dermatitidis* infection. *Infect Immun* 2000;68:7172–7174.

27. Hara Y, Caspi RR, Wiggert B, et al. Suppression of experimental autoimmune uveitis in mice by induction of anterior chamber-associated immune deviation with interphotoreceptor retinoid-binding protein. *J Immunol* 1992;148:1685–1692.

28. Griffith TS, Brunner T, Fletcher SM, et al. Fas ligand-induced apoptosis as a mechanism of immune privilege. *Science* 1995;270:1189–1192.

29. Griffith TS, Yu X, Herndon JM, et al. CD95-induced apoptosis of lymphocytes in an immune privileged site induces immunological tolerance. *Immunity* 1996;5:7–16.

30. Kezuka T, Streilein JW. Evidence for multiple CD95-CD95 ligand interactions in anterior chamber-associated immune deviation induced by soluble protein antigen. *Immunology* 2000;99:451–457.

31. Safneck J, Hogg G, Napier L. Endopthalmitis due to *Blastomyces dermatitidis*. *Ophthalmol* 1990;97:212–216.

32. Yanoff M, Fine BS. Lens. In: *Ocular pathology: a text and atlas*. 3rd ed. Philadelphia: JB Lippincott Co, 1989:347–376.

33. Wilcock BP, Peiffer RL. The pathology of lens-induced uveitis in dogs. *Vet Pathol* 1987;24:549–553.

34. Eagle RC, Spencer WH. Lens. In: Spencer WH, ed. *Ophthalmic pathology*. Vol 1. 4th ed. Philadelphia: WB Saunders Co, 1996;372–437.