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MICROSCOPIC LESIONS OF SPONTANEOUS OCULAR BLASTOMYCOSIS IN DOGS

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INTRODUCTION

There are numerous reports (Wolf, Schwartzman and Sautter, 1958; Treviño, 1966; Simon and Helper, 1970; Wilson, van Dreumel and Henry, 1973; Carlton, 1974; Carlton and Austin, 1976; Peiffer, Gelatt and Mehlhoff, 1978; Legendre, Walker, Buyukmihci and Stevens, 1981; Buyukmihci, 1982) documenting ocular involvement in generalized infection of dogs with *Blastomyces dermatitidis*. Although some of the reports (Wolf *et al.*, 1958; Treviño, 1966; Simon and Helper, 1970; Wilson *et al.*, 1973; Carlton, 1974; Carlton and Austin, 1976; Peiffer *et al.*, 1978) on ocular involvement in blastomycosis describe the histological features, analysis of these reports reveals that only 8 dogs actually had involvement of the globe. All had well-advanced ocular disease. In our estimation, in only 4 of the dogs (Wolf *et al.*, 1958; Treviño, 1966; Carlton, 1974; Carlton and Austin, 1976) were the pathological changes described well enough to characterize the ocular abnormalities. In none was there a correlation between the presence of the organism and the inflammatory changes. Because of the small number of cases and their advanced nature, no determination could be made as to the route of ocular infection, pathogenesis, or typical manifestations.

The purpose of this report is to describe the various microscopic changes that occur within the globe in ocular blastomycosis, by using a series of naturally occurring cases with a wide range of severity. From this study we hoped to understand the natural pathogenesis of ocular blastomycosis and determine if there was a predilection of the organism for a particular ocular tissue and to correlate its presence with ocular inflammatory changes.

MATERIALS AND METHODS

The clinical and diagnostic features for the dogs used in this study have been described elsewhere (Buyukmihci, 1982). From 13 dogs, 16 globes were obtained during surgery or at necropsy. Most tissues were removed several weeks after ocular disease was first noticed. Fixation was usually by immersion in Zenker's-acetic acid solution but a few specimens were fixed in neutral buffered 10 per cent formalin. Sagittal histological sections of paraffin-embedded globes included the pupil and optic disk. Serial or step-sectioning was not done. Haematoxylin and eosin (HE) and periodic acid-Schiff (PAS) stains were routinely used.

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RESULTS

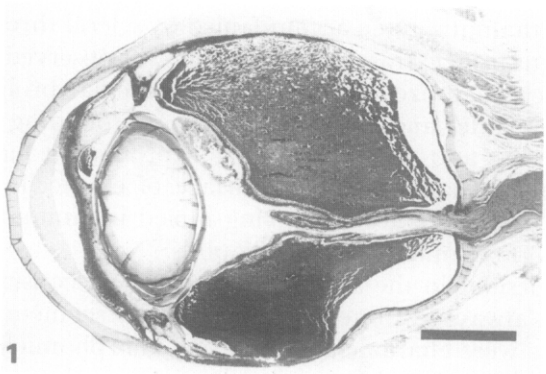
Various degrees of involvement of all three coats of the eye were seen. In the most severe cases, there was extension into the peri-bulbar tissues. The severity of the inflammation and sequelae, such as degeneration of various tissues, increased with the duration of ocular involvement. The severity and extent of the inflammatory lesions in the posterior segment, especially in the choroid, were particularly noteworthy.

Choroiditis and separation of the sensory retina from its epithelium secondary to exudation were usually the most consistently observed lesions (Fig. 1). Choroidal inflammation appeared to centre on the choriocapillaris of the non-tapetal choroid. Curiously, the tapetal choroid was either spared or only minimally inflamed. The most striking feature of the choroidal inflammatory infiltrate was the tendency to extend through Bruch's membrane and the retinal epithelium into the space created by exudation and retinal separation. In these cases, the choroid itself was often minimally involved, whereas the infiltrate was extensive [Fig. 2(a)]. The infiltrate consisted of a confluent mat of histiocytes often containing *B. dermatitidis* organisms which were best demonstrated with the PAS method. Foci of neutrophils were commonly encountered among the histiocytes and often surrounded degenerated organisms. This pyogranulomatous mat frequently extended circumferentially, coating the inner aspect of the choroid-retinal epithelial complex and the scleral aspect of the separated sensory retina [Fig. 2(b)]. Neovascularization of this infiltrate from the choroid and outer layers of the retina was present in most cases (Figs 2(a) and 3). The centre of the sub-sensory retinal cavity was occupied by non-adherent histiocytes, neutrophils and free or phagocytosed *B. dermatitidis* organisms suspended in an eosinophilic and often granular exudate. Marked haemorrhage into this cavity was commonly observed and always accompanied retinal necrosis and frequently neovascularization from the retina and choroid. In only two cases was the pyogranulomatous infiltrate largely confined to the choroidal tissues without marked extension into the sub-sensory retinal cavity. Langhans' giant cells were frequently seen within the inflammatory infiltrate in the choroid.

Retinitis, whereas it was an almost constant feature, was usually far less severe than choroidal involvement and was limited to lymphocytic and plasmacytic perivascular cuffing (Fig. 4). Infiltration of the retina with histiocytes and neutrophils was not prevalent unless retinal necrosis was present. These latter cases generally had severe panophthalmitis. Rarely were *B. dermatitidis* organisms found within the retina.

Fig. 1. Uveitis with separation of sensory retina from retinal epithelium by massive exudation. HE Bar = 5 mm.

Fig. 2. (a): The non-tapetal region of the choroid (C), showing destruction of retinal epithelium by massive inflammatory infiltrate into the sub-sensory retinal space; neovascularization (arrowhead) is present. The choroid essentially is spared. Organisms appear as clear circular spaces. HE. Bar = 48 μm.
(b): Degenerating and inflamed sensory retina coated on the scleral side with inflammatory infiltrate containing many organisms. HE Bar = 44 μm.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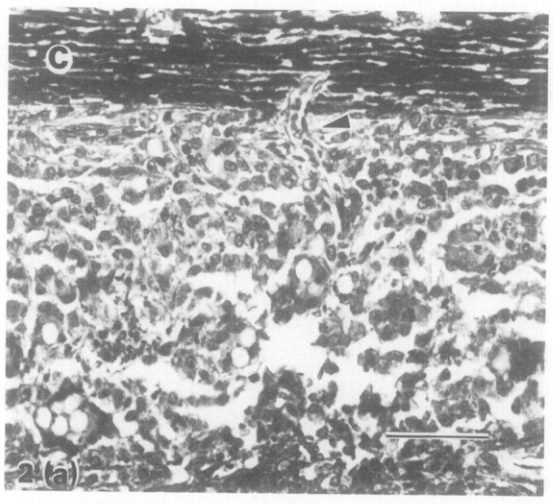
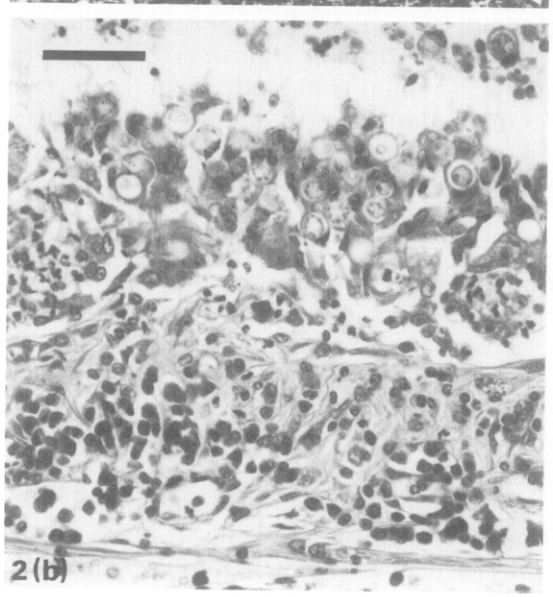

C
2 (a)


2 (b)

Severe panophthalmitis, often accompanied by scleral thrombophlebitis and periorbital cellulitis from extrascleral extension, was observed in five cases. The last of these was characterized by marked fibrovascular proliferation amongst the extra-ocular muscles and connective tissue surrounding the globe. These particular cases were also noteworthy in that prominent basophilic club-like deposits frequently radiated from the surface of extracellular *B. dermatitidis* organisms (Fig. 5) and the accompanying mixed inflammatory cell infiltrate was marked by a predominance of neutrophils.

Inflammatory lesions in the anterior segment were constantly present, but they were almost always less intense than posterior segment lesions. Keratitis and conjunctivitis were characterized by a polymorphonuclear inflammatory cell response in early cases and a mixed cell response in later cases. In the older lesions, the cornea was also invaded by blood vessels. Hyperaemia and oedema of the ciliary processes and mixed cellular infiltrate of lymphocytes, plasma cells and histiocytes into the ciliary body and perivascular tissues of the iris were commonly encountered. There was new vessel growth (rubeosis iridis) on the anterior surface of the iris in most cases (Fig. 6). Essentially, all of these cases also had neovascularization in the posterior ocular tissues. Occasionally, there was entropion uvea, in which the pupillary border of the iris was inverted and adherent to its posterior surface. In the cases with severe panophthalmitis, the posterior surface of the iris was often ulcerated, with marked exudation of cells and proteinaceous fluid into the posterior chamber. Histiocytes and neutrophils predominated in these lesions. Organization of these posterior chamber exudates by new vessels and fibroblasts originating in the posterior aspect of the iris was also observed. *Blastomyces dermatitidis* organisms were infrequently encountered in the anterior ocular tissues.

Sequelae to the ocular inflammation included cataract, anterior and posterior synechiae and, in 7 cases, closure of the drainage angle. The last of these led to, or was associated with, glaucoma. The eyes in these cases were enlarged and had loss of retinal ganglion cells and optic nerve degeneration, most likely the result of glaucoma, although post-neuritis degeneration was sometimes a complicating factor.

DISCUSSION

The study of this series of eyes with blastomycosis resulted in observations not previously appreciated or reported: (1) centring of the inflammatory process on the choriocapillaris, (2) relative sparing of the tapetum; (3) minimal involvement of the choroid proper despite massive exudation beneath the sensory retina; (4) neovascularization of the sub-sensory retinal exudate; (5) propensity of the organisms for the choroid and lack of invasion of the retina; (6) presence of scleral thrombophlebitis and peri-orbital cellulitis from extrascleral extension; (7) intense inflammation in the anterior ocular tissues without the presence of organisms; (8) almost always greater inflammatory response in the posterior ocular tissues than in the anterior tissues of the same eye; (9) development of rubeosis iridis, even in eyes with very little inflammation of the iris and (10) the correlation of rubeosis iridis with

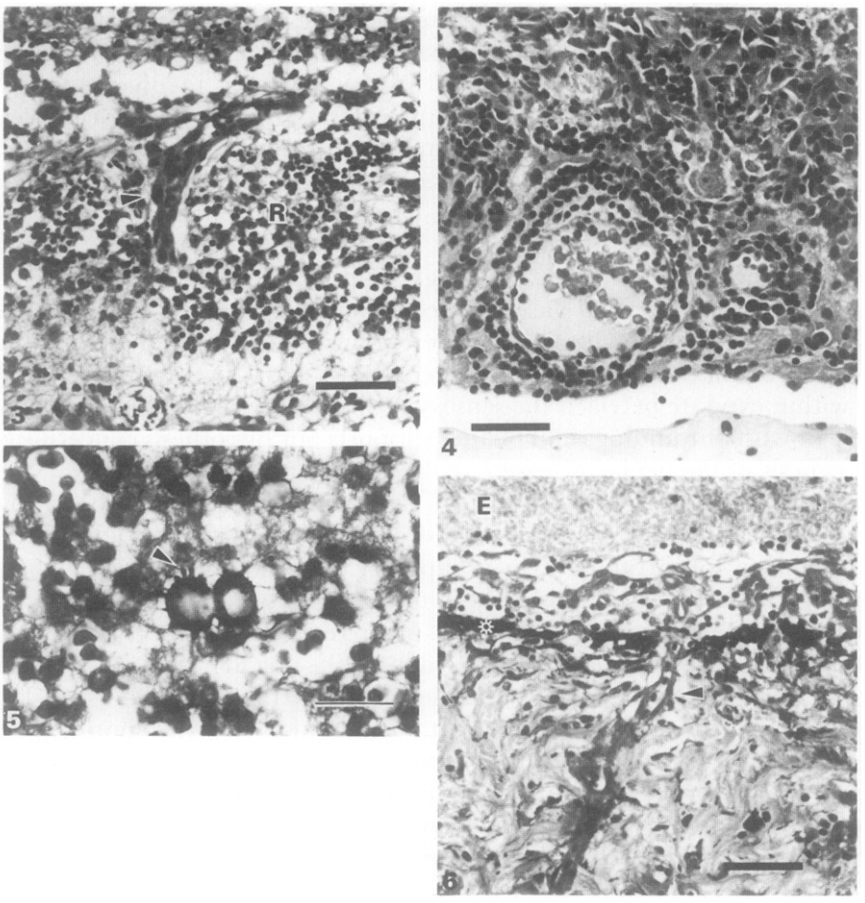


Fig. 3. Neovascularization (arrowhead) from sensory retina (R) into adjacent infiltrate. HE Bar = 48 μm.

Fig. 4. Perivascular infiltration of retina with lymphocytes and plasma cells. HE Bar = 48 μm.

Fig. 5. Basophilic club-like deposits (arrowhead) on surface of organism. HE Bar = 18 μm.

Fig. 6. Neovascularization of anterior surface of iris. Feeder vessel (arrowhead), anterior border layer of iris (asterisk), anterior chamber exudate (E). PAS Bar = 44 μm.

neovascularization and other pathological changes in the posterior ocular tissues. It also provided us with an opportunity to develop a reasonable hypothesis for the source and pathogenesis of ocular infection.

Our experience suggests that the eye is a major target for the organism. Perusal of the literature raises doubts as to whether the eyes of infected dogs were always examined and whether a thorough examination was made in most reports not dealing directly with the eye. There is considerable variation from one report to another with respect to the prevalence of ocular involvement and we believe that this has led to the erroneous impression that the eye is not frequently involved.

The earliest lesions involved only the choroid. With increased duration of

infection, there was involvement of surrounding tissues. Breakdown of the retinal epithelium with exudation beneath the sensory retina occurred. Sometimes, however, there appeared to be minimal involvement of the choroid. In these cases, the organisms apparently invaded through the retinal epithelium, resulting in retinal separation and massive exudation and inflammation in the space created. There was no evidence of dissemination from retinal vessels. In several reports (Treviño, 1966; Carlton, 1974; Carlton and Austin, 1976; Peiffer *et al.*, 1978), there were statements that organisms were present within the retina. This might imply that the organism may reach the eye through the retinal vasculature. In only two reports (Treviño, 1966; Peiffer *et al.*, 1978) is the location of the organism documented in this regard. Inspection of the micrographs, however, shows that the organisms actually were within exudate between the sensory retina and retinal epithelium. This is consistent with our findings and further supports our hypothesis concerning the pathogenesis of the ocular disease.

The reason for the propensity of *B. dermatitidis* invasion of the choroid is unexplained. Initial localization of the organism in the choroid could not simply be due to entrapment in a capillary bed; if this were the case, the organism should become established in other regions of the eye with the same degree of frequency as in the choroid. Moreover, localization of organisms essentially did not occur in the retina which, in the dog, derives its blood supply from the same ciliary vessels as the choroid (Martin and Anderson, 1981). Regional blood flow may be a factor; it is much higher in the choriocapillaris than in the retina (Ernest, 1980). This may result in distribution of organisms to the inner choroid at a rate higher than elsewhere so that a critical concentration for growth may be reached early. The fact that choroidal arterioles are large and open up abruptly into the centres of the capillary lobules may be significant. Even if this is somehow linked to the increase in susceptibility of the choroid, it does not explain why the tapetal region is relatively spared.

A striking feature of the ocular changes in this series of dogs with blastomycosis was the extensive inflammation of anterior ocular tissues not invaded by *B. dermatitidis*. Although alluded to once (Carlton, 1974), this seems not to have been previously adequately appreciated. This has important clinical relevance since the organism is found only rarely in the anterior chamber and paracentesis of this cavity would not necessarily be diagnostic. The severity of the inflammatory process was directly correlated with the duration of the ocular posterior segment disease. The inflammation in the anterior ocular tissues could have been due to the release of diffusible mediators such as prostaglandins and other vasoactive compounds from inflammatory or other cells in the posterior ocular tissues. The consistent finding of greater inflammation and destruction of posterior than of anterior ocular tissues supports this hypothesis. The finding of rubeosis iridis in eyes without a great deal of anterior segment inflammation also supports the notion of a diffusible angiogenic factor from the diseased retina (Gartner and Henkind, 1978; Stefansson, Landers, Wolbarsht and Klintworth, 1984). The clinical significance of the rubeosis iridis was reduced, however, because of the

destruction of posterior segment tissues secondary to inflammation in these eyes.

From the variety of lesions seen in this series of cases, the following seems to be the typical pathogenesis of ocular blastomycosis. The organism reaches the eye haematogenously. For unknown reasons, it becomes established in the choriocapillaris. At this point, it may break through the choriocapillaris and retinal epithelium, where it elicits an inflammatory reaction between the sensory and epithelial portions of the retina, with little disturbance of the choroid. More commonly, it incites intense inflammation within the choroid before, or while extending into, other tissues. The inflammatory response in the ocular posterior segment triggers a secondary inflammatory response in the anterior ocular tissues where it is unusual for organisms to localize. Changes in the anterior ocular tissues lead to compromised outflow of aqueous humour resulting in glaucoma which is a prominent feature of advanced cases. Extension of the inflammatory process into the periorbital tissues seems to be the result of extension from a locus within the choroid.

SUMMARY

Ocular tissues from 13 dogs with naturally-occurring blastomycosis were examined histologically. Choroiditis and separation of the sensory retina from its epithelium were the most prominent lesions, although all three coats of the eye were always involved. Severe panophthalmitis was associated with a marked exudative reaction within the ocular tissues. Whereas inflammation of the anterior ocular tissues was often intense, it was rarely associated with the presence of *B. dermatitidis*. Sequelae to the ocular inflammation included cataract, synechiae, rubeosis iridis, and closure of the drainage angle. The last of these resulted in glaucoma and resulting degeneration of the optic nerve.

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