The Pathogenesis and Significance of Pre-iridal Fibrovascular Membrane in Domestic Animals

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Abstract. Histologic examination was made of 1,419 globes from domestic animals (964 dogs, 374 cats, 41 horses, and 40 cattle) with ocular disease; pre-iridal membranes (rubeosis iridis) were found in 98. The membranes originated as endothelial budding from the anterior iridal stroma and seemed to mature into fibrous or fibrovascular membranes that were often followed by hyphema or, occasionally, glaucoma. Pre-existent disease in the 98 affected globes included chronic endophthalmitis (27/98), chronic glaucoma (24/98), anterior uveal melanoma (15/98), ciliary body adenoma (14/98), neoplasms metastatic to the eye (8/98), and chronic retinal detachment (6/98). In terms of likelihood of occurrence, pre-iridal membranes seen in 21% (6/21) of globes with retinal detachment, 19% (14/75) of those with ciliary body adenomas, 14% (24/167) of those with chronic glaucoma, and 10% (15/158) of those with anterior uveal melanoma. They were detected with greatest relative frequency in horses (9/41) followed by dogs (83/964), cats (5/374) and cattle (1/40). These membranes, which are rarely detected by clinical examination, probably form in response to angiogenic factors released by ischemic retina, by neoplasms, or by leukocytes involved in ocular inflammation.

Key words: Neovascular glaucoma; pre-iridal membranes; rubeosis iridis.

The presence of fibrovascular membranes on the anterior surface of the iris was described in the human eye as early as 1928 and was called rubeosis iridis because of its clinical appearance of iridal reddening. In human beings, it is a frequent lesion, occurring in about 20 percent of enucleated globes. It is most frequently encountered in human patients with diabetic retinopathy, with central retinal vein occlusion, or with primary intraocular neoplasms. The stimulus for the neovascularization is unknown but is assumed to be one or more angiogenic stimulating factors released by hypoxic retina, by tumor cells, or by some component of host response (macrophages?) to the presence of the injured retina or the neoplasm. Some examples of rubeosis iridis appear to be much less specific and probably occur as a result of chronic uveitis in a manner similar to the development of granulation tissue elsewhere in the body. Regardless of the precise nature of the stimulus, the new vessels originate from the superficial stroma of the iris and spread across the iridal surface, accompanied by pericytes and fibroblasts. The interendothelial junctions are immature and leaky, so that serous effusion, or even hemorrhage (hyphema), is a frequent complication. Glaucoma may result when the new vessels cover the face of the filtration angle (neovascular glaucoma) or cause fusion of the iridal root to the peripheral cornea (peripheral anterior synechia). Attempts to reproduce the lesion in nonhuman animals have met with variable success. Ligation of the optic nerve or diathermy of vortex veins, retinal veins, or iridal surface of rabbits was unsuccessful, but ligation of long ciliary arteries resulted in mild rubeosis. Accompanying anterior segment necrosis limited the usefulness of the last-mentioned model. Irradiation of aphacic monkey eyes resulted in the development of pre-iridal membranes several years after irradiation, as did prolonged experimental hypotony. Vitrectomy and serous retinal detachment reliably stimulated rubeosis iridis in cats 1 to 2 months after the surgery. Rubeosis iridis has not been described as a spontaneous clinical entity in domestic animals, but it has been seen histologically in canine globes with ciliary body tumors or with blastomycosis. We have noted, in animal globes enucleated for a wide variety of reasons, that pre-iridal fibrovascular membranes are much more frequent than the available literature would suggest. The purpose of this report is to describe the circumstances under which these membranes develop and their significance to the eyes in which they occur.

Materials and Methods

Canine (964), feline (374), equine (41), and bovine (40) globes were obtained by surgical enucleation or at necropsy from animals with clinically detected intraocular disease. Each
globe was fixed in the 10% neutral buffered formalin or in Bouin's fluid and was processed routinely for paraffin embedding. Sections from the mid-sagittal plane of each globe were cut at 6–8 μm, stained with hematoxylin and eosin (and usually with periodic acid-Schiff reagent), and examined by light microscopy. Those globes with pre-iridal fibrovascular membranes were segregated for more detailed study. Specifically, each globe was classified as to the major disease present, the various structural alterations, and the apparent significance of the iridal membranes as determined from the clinical history, ophthalmic clinical examination, or histologic lesions.

Three canine globes that had been fixed in formalin were examined by scanning and transmission electron microscopy. The iris and iridocorneal angle were dissected from the remainder of the globe, post-fixed in 2.0% paraformaldehyde and 2.0% glutaraldehyde, and examined using routine ultrastructural techniques.

### Results

Pre-iridal fibrovascular membranes were identified in 98 of the 1,419 globes studies. It was seen with greatest relative frequency in horse eyes (9/41) followed by dog (83/964), cat (5/374), and cow (1/40). The membranes were found most frequently in globes with primary diagnoses of chronic endophthalmitis (27/98), chronic glaucoma (24/98), ocular melanoma (15/98), ciliary epithelial tumors (14/98), and other neoplasms (8/98). When correlated to other intraocular lesions, rubeosis iridis was found in 21.4% of the globes with retinal detachment, 18.7% of those ciliary body tumors, 14.4% of those with glaucoma, 9.6% of globes with melanoma, 6.0% of those with chronic inflammation, and 5% of globes with neoplasms other than ciliary body tumors or melanomas (Table 1).

The membranes were of three types: cellular, vascular, and fibrous. Membranes with a mixture of these tissues were frequently encountered. Cellular membranes consisted of a thin layer of plump spindle-shaped cells on the face of the iris, sometimes, clearly continuous with endothelial cells of the anterior iridal stroma (Fig. 1). Vascular membranes consisted of ramifying delicate blood vessels, presumably a later stage of the cellular membrane (Fig. 2). The fibrous membranes were rarely purely fibrous, with most having at least some vascular component. A structure intermediate between fibrous and vascular was the most frequently seen type of membrane (Fig. 3). Most covered the entire surface of the iris with no predisposition for pupillary or basal zones.

Lesions attributed to the presence of the pre-iridal membrane included hyphema, evasion or inversion of the pupillary margin, and occlusion of the pupil or of the filtration angle. Hyphema was particularly frequent (56.7% of eyes with rubeosis), but varied widely in its severity. Many cases were probably the result of hemorrhaging from the fragile new blood vessels during enucleation. Three types of involvement of the filtration angle were seen: spanning of an open angle and open ciliary cleft by a thin fibrovascular membrane spread across the face of the pectinate ligament; spanning of an open angle but a collapsed trabecular meshwork; and spanning of a closed, collapsed angle and cleft with the pre-iridal membrane contributing to a peripheral anterior synchia. The latter two categories were consistently associated with glaucoma (Figs. 4–6).

Effects on the pupil were dependent upon the location and maturity of the pre-iridal membrane. In 25 globes with a mature, predominantly fibrous, membrane confined to the anterior surface of the iris, there was evasion of the pupillary margin with adhesion of the free margin of the iris to the iridal face (ectropion uveae). In 40 globes the iridal membrane extended through the pupil and ramified on the posterior surface of the iris, and, in 19 of these, there was posterior inversion of the iridal free border [entropion uveae

### Table 1. The prevalence of pre-iridal membranes in animals eyes.

<table>
<thead>
<tr>
<th>Primary Diagnosis</th>
<th>Number Studied</th>
<th>Pre-iridal Membranes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dog</td>
<td>Cat</td>
<td>Horse</td>
</tr>
<tr>
<td>Retinal detachment</td>
<td>16</td>
<td>6</td>
</tr>
<tr>
<td>Ciliary epithelial neoplasm</td>
<td>63</td>
<td>12</td>
</tr>
<tr>
<td>Chronic glaucoma</td>
<td>136</td>
<td>29</td>
</tr>
<tr>
<td>Idiopathic ocular hemorrhage</td>
<td>24</td>
<td>5</td>
</tr>
<tr>
<td>Uveal melanoma</td>
<td>109</td>
<td>48</td>
</tr>
<tr>
<td>Endophthalmitis</td>
<td>283</td>
<td>131</td>
</tr>
<tr>
<td>Other intraocular neoplasms</td>
<td>95</td>
<td>61</td>
</tr>
<tr>
<td>Retinal degeneration</td>
<td>71</td>
<td>42</td>
</tr>
<tr>
<td>Congenital anomalies</td>
<td>35</td>
<td>3</td>
</tr>
<tr>
<td>Other (including perforating corneal ulcers, ocular trauma, eyelid or orbital neoplasms)</td>
<td>132</td>
<td>37</td>
</tr>
</tbody>
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Pre-iridal Membranes

(Fig. 7). Growth of the membrane across the pupil or the formation of iridolenticular adhesions (posterior synechiae) were infrequently seen. The extent of membrane in different sections from the same globe could, however, be quite variable. Different portions of iris within the same globe or even the same section could have membranes that were predominantly vascular or predominantly fibrous, covering or sparing the filtration angle, and located on the anterior or posterior surface of the iris.

Four canine globes (one with ciliary body tumor and three with chronic retinal detachment) had neovascularization on the inner (vitreal) surface of the retina as well as on the iris.

Discussion

The most surprising result of this study is the frequency with which we were able to identify pre-iridal membranes in domestic animals with ocular disease, despite the rarity of their recognition by clinical examination. The prevalence is particularly high in horses, associated with chronic uveitis (periodic ophthalmia) and/or retinal detachment. This prevalence in horses may be related to the case with which the poorly vascularized equine retina becomes hypoxic following detachment, or it may simply be related to the horse's tendency to form exuberant granulation tissue as part of a chronic inflammation.

Failure to clinically recognize the lesion may be explained by concurrent severe disease in the cornea or anterior chamber, which makes examination of the iris difficult or impossible. In addition, the dark brown iris of most animals is a difficult background against which to detect a fibrovascular membrane, and the name "ruberosis" is probably not appropriate in these species inasmuch as reddening is not likely to be seen. Finally, failure to identify the membranes may result from the assumption, by clinicians and pathologists, that such membranes do not occur in the eyes of nonhuman animals. With some chagrin, we admit that many of our cases were found only on review of cases from our own files, where the lesion had lain undiscovered for years!

We are convinced that the vascular, fibrovascular, and fibrous types of membranes represent nothing more than a maturation sequence. The nature of the cellular membrane is less clear. A few examples were unequivocally of endothelial origin, but in many globes we could not determine whether the thin cell layer was endothelial, fibroblastic, or even histiocytic. Our unproven speculation is that it represents the earliest phase of a pre-iridal vascular membrane.

The pathogenesis of membrane development is probably related to the diffusion of angiogenic and fibroblastic stimulatory factors from chronic inflam-
Fig. 4. Delicate fibrovascular membrane traverses the filtration angle in a dog, creating peripheral anterior synechia, and probably causing the glaucoma. HE.

Fig. 5. Extension of a fibrovascular membrane across the face of the pectinate ligaments (arrow) was the only lesion identified as a cause for the glaucoma in a canine globe. HE.

Fig. 6. Scanning electron micrograph, dog. Thin cellular membrane (arrow) creates an imperforate filtration angle. C = peripheral cornea; I = iridal stroma.

Fig. 7. Ectropion uveae caused by delicate fibrovascular pre-iridal membrane (arrow); dog. The pupillary border is everted and adherent to the anterior surface of the iris. HE.

formation, neoplasms, or ischemic retina. Because the globes included in our study usually had advanced disease with more than one major alteration (for example, neoplasm plus chronic uveitis and retinal detachment), it is not possible for us to determine a precise pathogenesis for the pre-iridal membrane in most specimens. Nonetheless, some examples seemed quite clear and uncomplicated. Ciliary body neoplasms, for
example, were usually small, well-differentiated, and were seen in globes that were otherwise normal—except for the presence of a pre-iridal membrane. Similarly, a few globes had retinal separation but few other changes, except for the pre-iridal membranes.

The significance of the membranes seems to vary widely. Hyphema and glaucoma were the two major complications. Spontaneous unilateral hyphema has long been associated with intraocular neoplasms, and perhaps the development of rubeosis iridis explains the development of the hyphema in those cases where the neoplasm itself is not particularly vascular.28 In those globes with both glaucoma and rubeosis, it was difficult to determine which had happened first and whether there was a causal relationship between them. When the two lesions occurred in globes of dog breeds predisposed to primary glaucoma and in which there was no other lesion to explain the development of the rubeosis, we presume that the rubeosis results from glaucoma-induced retinal hypoxia. Conversely, we have seen several cases in which the glaucoma could only be explained by the growth of the membrane across the filtration angle, resulting in either occlusion of the face of the trabecular meshwork by the continuous endothelium or in angle narrowing as the membrane matured and contracted.

References


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