CASE REPORT

Canine ocular tumors following ciliary body ablation with intravitreal gentamicin

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Abstract
Iridociliary tumors are the second most common primary ocular tumor in dogs and are usually benign. A review of the Comparative Ocular Pathology Laboratory of Wisconsin (COPLOW) database in 2009 suggested a potential correlation between malignant iridociliary epithelial tumors and ciliary body ablation by intravitreal gentamicin injection for the treatment of glaucoma. The purpose of this case series was to determine whether there is evidence of such a correlation in the COPLOW collection. Mining of the COPLOW database revealed that a significant number (39.5%) of canine globes with a history of ciliary body ablation were subsequently diagnosed with primary ocular tumors at enucleation, most commonly iridociliary epithelial tumors and melanocytic tumors. It is possible that neoplasia was present but unrecognized at the time of ciliary body ablation. These tumors had a higher than expected incidence of malignancy. These cases underscore the importance of reserving ciliary body ablation with gentamicin for disease-free eyes.

Key Words: ciliary body ablation, gentamicin, pleomorphic iridociliary adenocarcinoma

INTRODUCTION
Primary ocular tumors in dogs are rare, but when they occur, iridociliary epithelial tumors are the second most common; melanocytic tumors are the first.¹ ² Canine iridociliary epithelial tumors are well characterized and require at least one of the following three criteria to be diagnosed as such epithelial growth extending into aqueous adjacent to ciliary body, iris, or the adjacent inner sclera; a population of pigmented epithelial cells; or a thick basement membrane structure on the cell surface. This basement membrane is periodic acid–Schiff (PAS) positive. Tumors of iridociliary epithelial origin can be further characterized with immunohistochemistry by the presence of vimentin, a distinctive feature for the ciliary epithelium and iridociliary tumors even though it is usually thought of as a marker for mesenchymal differentiation. Iridociliary epithelial tumors can be solid or papillary, pigmented or unpigmented, and invasive or noninvasive.³

The behavior of iridociliary epithelial tumors is largely benign. In a recent review of 702 cases, 84% of canine iridociliary tumors were benign adenomas. Fourteen percent were diagnosed as adenocarcinomas based on the presence of scleral invasion;¹ most of these had the bland cellular morphology of adenomas. Finally, 2.3% (n = 16) displayed marked cellular anaplasia and were diagnosed as pleomorphic adenocarcinomas. There is evidence that this is a malignant variant with metastatic potential.⁴ Four of the 16 cases had received a ciliary body ablation with gentamicin in the affected eye 2–10 months prior to enucleation.⁵

Pharmacologic ciliary body ablation was first described by Vainisi et al.⁶ The authors showed that 25 mg of gentamicin injected into the vitreous lowered elevated intraocular pressures in dogs with chronic glaucoma. Ciliary body ablation is often perceived as an attractive option for the treatment of painful, irreversibly blind eyes because it is relatively inexpensive, avoids the need for surgery and prolonged anesthesia, and can have a cosmetically pleasing outcome. Previously reported negative outcomes of ciliary body ablation include uveitis, pain, corneal opacity, intraocular hemorrhage, cataract formation, and phthisis bulbi.⁷ ⁸ Dexamethasone is often injected concurrently to moderate
inflammation and to avoid or minimize complications.6,7 Chemical ablation of the ciliary body has a reported failure rate of 35%, and of these, 50% do not respond to a second injection.9

The high percentage (25%) of malignant cases with a history of intravitreal gentamicin injection suggests a potential correlation between pleomorphic iridociliary adenocarcinomas and the ciliary body ablation. Chemical ablation by intravitreal injection is generally believed to be contraindicated in cats because of the risk for post-traumatic sarcomas, but there is no perceived association between gentamicin injection and canine ocular tumors. Currently, there are no reports which document any effect on tumor development or tumor response in dogs subsequent to chemical ciliary body ablation in the literature.

MATERIALS AND METHODS

All the globes were submitted to COPLOW between 1983 and 2011 for histopathologic evaluation. Sections were stained with hematoxylin and eosin. When necessary to elucidate cell of origin, globes were stained with PAS or by immunohistochemistry for Melan-A, cytokeratin, vimentin, or glial fibrillary acidic protein (GFAP). Globes were sectioned, mounted, and stained as described previously.3 Two specimens were submitted as hematoxylin- and eosin-stained slides for a second opinion. The COPLOW database was searched for cases including all of the following keywords: Canine, neo (the heading for all neoplastic diagnoses), and gentamicin. This included all abbreviated, generic, and brand names of the drug. Cases were reviewed for suitability (e.g., ‘gentamicin’ referred to intravitreal injection for the treatment of glaucoma, diagnosed neoplasia was intraocular and had been diagnosed in the same eye as had been ablated, etc.). When necessary, submitting veterinarians and referring veterinarians were contacted to complete histories and provide follow-up.

RESULTS

Forty-eight canine globes with a documented history of chemical ciliary body ablation have been submitted to COPLOW. Nineteen of those globes contained primary neoplasias at enucleation. In addition to iridociliary epithelial tumors, melanocytic tumors, spindle-cell tumors of blue-eyed dogs (SCTBED), sarcomas, and a single case of glioma were diagnosed in dogs after ciliary body ablation (Fig. 1). In each case, malignancy was evaluated using established criteria (if available) for the tumor type.3,10–12

Affected dogs ranged in age from 4 to 15 years with an average of 10.3 ± 2.9 years. The elapsed time from ciliary body ablation to enucleation/tumor diagnosis ranged from 3 weeks to 24 months with an average of 6.6 ± 6.3 months (Table 1). Labrador retrievers were overrepresented in the iridociliary epithelial tumor cases (4/6); there were no other breed or sex predilections.

<table>
<thead>
<tr>
<th>Ocular Tumor Types</th>
<th>Iridociliary Epithelial Tumors</th>
<th>Melanocytic Tumors</th>
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</thead>
<tbody>
<tr>
<td>Mean age at enucleation (years)</td>
<td>10.3</td>
<td>11.6</td>
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<tr>
<td>Mean elapsed time from ciliary body ablation to enucleation (months)</td>
<td>6.6</td>
<td>5.8</td>
</tr>
<tr>
<td>Mean elapsed time from enucleation to death (months)</td>
<td>N/A</td>
<td>7.2</td>
</tr>
</tbody>
</table>

Five of the six dogs with iridociliary tumors died or were euthanized within 12 months of enucleation. The average elapsed time between enucleation and death was 7.2 ± 4.3 months with a range of 2–11 months (Table 1). All six of the iridociliary tumor cases exhibited scleral invasion, and four of the 6 (67%) were pleomorphic adenocarcinomas, indicating malignancy. One of these dogs had confirmed metastases at necropsy; two others had suspected metastases. Forty-four percent (4/9) of the melanocytic tumors were malignant melanomas. A fifth was noted to be ‘borderline’ but was diagnosed as melanocytoma. The reported malignancy incidence for melanomas is approximately 20%.10 The glioma was a high grade tumor. The sarcomas had many features similar to the feline ocular post-traumatic sarcoma, a well characterized and malignant ocular neoplasm in cats.

DISCUSSION

A significant portion of canine globes submitted to COPLOW after documented chemical ciliary body ablation were subsequently diagnosed with intraocular tumors (19/48, 39.5%). These were usually melanocytic or iridociliary epithelial tumors; they showed a higher prevalence of...
malignancy and invasiveness than tumors diagnosed in dogs that had never received intravitreal gentamicin.5, 10

A total of 57 globes with a history of chemical ciliary body ablation have been submitted to COPLOW. This includes 48 canine globes (including the 19 with tumors discussed here), seven feline globes, an equine globe, and one wallaby globe. Five of the feline cases were diagnosed with ocular tumors (feline diffuse iris melanoma, post-traumatic sarcoma) subsequent to ciliary body ablation (manuscript in progress). The horse and wallaby globes did not contain ocular tumors.

Chemical ciliary body ablation has historically been recommended for irreversibly blind, painful eyes that are free of inflammation and neoplasia.9 The submission forms for many of these globes report overt inflammation, suspect neoplasia, or an inability to adequately see some or all of the inside of the globe. None of the forms indicate that an ocular ultrasound was performed prior to chemical ablation, which could potentially detect the presence of an occult neoplasm. The presence of ocular disease and the inability to thoroughly examine globes make it feasible that these eyes already harbored malignant or premalignant processes at the time of gentamicin injection. Alterations in the globes’ homeostatic mechanisms after gentamicin administration might expose these neoplastic populations to selection pressures (inflammation, toxic effects of gentamicin) resulting in the preferential survival and/or transformation of specific populations.

Ciliary body ablation likely causes intraocular inflammation secondary to cell death. The release of proteins from damaged and necrotic cells induces cytokines in immune cells that activate oncogenic transcription factors, stimulating tumor cell survival and proliferation. Inflammation can also induce or accelerate tumor angiogenesis, tumor invasiveness, and metastatic dissemination, and chronic inflammation is a predisposing factor for many neoplastic conditions.13

Canine pleomorphic iridociliary adenocarcinomas share morphological similarities to the homologous human tumor (also called pleomorphic iridociliary adenocarcinomas), and human cases frequently have a history of ocular trauma.14–18 A review of the human literature reveals a documented association between ocular trauma and melanoma formation as well.19–21 Furthermore, our sarcoma cases are morphologically very similar to feline post-traumatic sarcoma, a well described and documented tumor type in cats. This suggests a role for inflammation in tumorigenesis or tumor promotion in the cases reviewed.

It is unclear whether inflammation alone can directly induce oncogenic changes or whether it acts indirectly in conjunction with carcinogen exposure.13 It is known that gentamicin is cytotoxic to the ciliary body epithelium, but the exact effects are uncharacterized and the mechanism not understood. The potential for the drug to act as a carcinogen in the presence of marked inflammation (also secondary to gentamicin administration) could create a tumorigenic environment. A case report of a rabbit developing an iridociliary adenoma in a previously quiet eye after mitomycin application might support this theory.22

Alternatively, gentamicin might have toxic or inhibitory effects on pre-existing tumor cells resulting in the selection of clones of cells both resistant to the effects of gentamicin and of more of a malignant phenotype. Recent articles indicate that gentamicin can suppress tumor growth by inducing read-through of premature stop codons in mutated tumor suppressor genes like p53 and adenomatous polyposis coli.23–25 Gentamicin and other aminoglycosides are also being studied as ligands of telomeric sequences that fold on themselves to form unique three-dimensional conformations and inhibit telomerase activity, limiting tumor cell longevity.26 An unrecognized tumor could be comprised of a mixed population: Cells that are susceptible to the inhibitory effects of gentamicin and cells that are resistant. Destruction of the gentamicin-sensitive cells enables the resistant and potentially more malignant cells to proliferate. This potential for tumor promotion by clonal selection underscores the importance of case selection of disease-free eyes for ciliary body ablation.

Whether a correlation exists between ablation with gentamicin and neoplasia is unclear, but the potential has been posited in the literature.27 The relatively small proportion of submissions with a history of ciliary body ablation (57 of approximately 56 000) indicates that very few postablation globes require enucleation, those that do are not commonly submitted for histopathology, or probably, the history of injection is not reported on the submission form.

It is alarming that such a large percentage of the globes submitted after ciliary body ablation were subsequently diagnosed with tumors that are abnormally aggressive. Over one-third of canine globes with a history of chemical ablation suffered a progression of ocular disease severe enough to require enucleation in a matter of months. These dogs were diagnosed with unusually large, malignant, or invasive tumors, and this suggests a possible relationship between ablation with gentamicin and augmentation of pre-existing cancer in this subset of dogs. This association reiterates the importance of reserving ciliary body ablation for disease-free eyes.

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REFERENCES


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