Canine ocular neoplasia: a review

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Abstract
Ocular neoplasia is relatively rare in dogs but can have significant impact on vision, comfort, and longevity. Prognosis for life and for the globe varies with tumor type. In this review, the clinicopathologic features of the most common canine ocular neoplasms are detailed, with emphasis on histologic and immunohistochemical characteristics.

Key Words: canine, histopathology, immunohistochemistry, neoplasia, ocular, review

INTRODUCTION
Primary ocular neoplasms are uncommon in dogs relative to neoplasia affecting other organs.1-4 Ocular neoplasms can cause loss or impairment of vision, discomfort, tissue destruction, and metastasis. Ocular neoplasia can be roughly divided into three categories: adnexal/ocular surface, intraocular, and orbital. The impact on the structure and function of the globe, therapeutic options, and prognosis varies with anatomic location of the neoplasm. As in other organs, neoplasms may be primary, arising from the tissue they affect, or secondary, arising from a distant tissue. Secondary neoplasia may be part of a metastatic or multicentric process. Primary ocular neoplasia is more common than secondary neoplasia.1 Of the anatomic sites for ocular neoplasia, intraocular structures are most likely to be affected by secondary neoplasia.1

ADNEXAL/OCULAR SURFACE NEOPLASIA
Periocular skin
Periocular skin is affected by neoplasia similarly to skin elsewhere on the body. There are abundant resources available regarding the diagnosis and treatment of skin neoplasia, hence the discussion here will be deliberately brief.5 Neoplasia with a predisposition for the head and neck areas is more likely to affect the periocular skin, including canine cutaneous histiocytoma, melanocytoma, sebaceous hyperplasia, adenoma and epithelioma, squamous and viral papillomas, trichoblastoma, and others.5 These neoplasms are typically benign. The clinical and histopathologic features mimic those of similar neoplasms at other cutaneous sites. While some neoplasms may regress spontaneously, as in histiocytoma or viral papillomas, other may require therapeutic intervention.6 The slowly progressive nature of some neoplasms, as in melanocytoma, makes benign neglect and careful monitoring a reasonable therapeutic option.7 Surgical excision may be required in some cases where growth of the melanocytoma is noted but comes with the added challenge of maintaining eyelid structure and function.7

Eyelid margin
The meibomian glands of the eyelid margin are the adnexal structure most frequently affected by neoplasia, representing 44-70% of eyelid neoplasms.4,6,8 Histologically, meibomian gland neoplasms can be categorized as adenomas, epitheliomas, and carcinomas, and all of which have a similar clinical appearance. Meibomian gland neoplasms appear clinically as tan, pink, gray, or black masses extending from the meibomian gland orifice. Occasionally, they will erupt through the palpebral conjunctiva. They may have a cobblestone or irregularly textured surface and will often hemorrhage when traumatized. If the tumor mass remains within the gland, it may obstruct the gland orifice, leading to glandular rupture and release of glandular lipid secretions into the surrounding tissue. A marked inflammatory response occurs and may cause the tumor to have a falsely large appearance.

Histologically, meibomian glands adenomas are similar to sebaceous adenomas of the skin (Fig. 1). They are well circumscribed and are often partially exophytic. They are comprised of variably sized lobules of meibomian cells that show normal maturation from small basal reserve cells at the periphery to mature large lipid-laden well-differentiated cells centrally. There are usually multifocal areas of

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cystic degeneration. Mitoses are limited to basal cells and are therefore rare to absent in neoplasms composed predominantly of mature cells. Melanization is variable and usually limited to basal cells. Meibomian adenomas usually include haphazardly arranged ducts that vary in number and size. The ducts are lined by squamous epithelium with scant keratinization. Meibomian gland adenomas can, but are infrequently, categorized as simple or compound/ductal, depending on the extent of ductular differentiation. The overlying epidermis is often hyperplastic and papillomatous and can mimic the appearance of a squamous papilloma. Commonly, rupture and leakage of lipid material elicits peritumoral lipogranulomatous inflammation. The inflammation consists of nodular infiltration of large numbers of macrophages and multinucleated giant cells that often contain acicular birefringent material with multifocal lipid lakes, visible as clear spaces.2,4,5,8–12 The immunohistochemical profile of meibomian gland adenomas has not been established.

Meibomian epitheliomas have histologic features similar to cutaneous sebaceous epitheliomas (Fig. 2). They are well-circumscribed masses composed of densely packed sheets of small basal reserve cells with limited differentiation to lobules or single lipid-laden cells or ducts. The basal cells are small with scant eosinophilic cytoplasm and oval nuclei, stippled chromatin and often multiple nucleoli. The mitotic index is typically high, with >20 mitoses in 10 high-power fields (HPFs). Nuclear atypia and pleomorphism are minimal. The overlying epidermis is often hyperplastic, and lipogranulomatous inflammation may border and infiltrate masses with sufficient lipid content.2,4,5,8–12

Objective criteria to differentiate meibomian adenomas and epitheliomas have not been clearly established. Epitheliomas should have a ‘preponderance’ of basal cells, and some have suggested that 90% of the cells be of the basal type to warrant the diagnosis of epithelioma.5,10 Although mitoses may be numerous, other features of malignancy are not observed with meibomian epitheliomas, and some authors include epitheliomas under the umbrella of benign meibomian adenomas. It is worth noting that some masses with features of meibomian epitheliomas have been published as carcinomas based on the number of mitoses.3,11 True meibomian carcinomas do occur but are quite rare and show unequivocal features of malignancy (i.e. invasion and pleomorphism) in addition to numerous mitoses.2,4,5,8–12 The immunohistochemical profile of meibomian gland epitheliomas has not been established.

The prognosis for life is excellent, and the prognosis for the globe is likewise excellent for meibomian gland adenomas, epitheliomas, and carcinomas with appropriate treatment. Treatment requires removal of the tumor, either by complete excision or by debulking and cryoablation.13,14 Recurrence rates are similar among treatment methods.14

**Conjunctiva**

*Melanocytic neoplasia* Conjunctival melanocytic neoplasms appear clinically as pink to lightly pigmented to darkly pigmented masses of the palpebral, bulbar, and third eyelid conjunctiva. The histologic challenges of diagnosing of conjunctival melanocytic neoplasia as benign or malignant are similar to those at other sites. The mitotic index (MI) has been reported to be the best indicator of malignancy for conjunctival neoplasms, but a definitive cut-off has not been established. Identification of 3–4 mitoses in 10 HPFs has been suggested for mucosal melanocytic neoplasms at other sites and may be useful in the classification of conjunctival melanocytic neoplasia.15,16

Benign melanocytomas are well circumscribed and composed of heavily pigmented cells in which the nuclei are often obscured by the melanin. The growth patterns vary between and within neoplasms, and the cells may be polygonal or spindle. There is minimal anisokaryosis and anisocytosis within each cell type. The MI is usually very low, 0–1 in 10 HPFs. Junctional activity, nests of neoplastic cells within the overlying epithelium, is a common finding. Melanophages may be admixed with the neoplastic cells.2,4,8,9,11,12 The immunohistochemical profile of...
conjunctival melanocytomas has not been established, but they can be expected to have an immunophenotype similar to melanocytomas at other locations and express vimentin, Melan-A, and PNL-2.17–19

Most conjunctival melanocytic neoplasms are malignant.20 The masses are poorly circumscribed with stromal invasion and may be multifocal. The cells are polygonal to spindle cells and form various growth patterns (Fig. 3). Junctional activity is present in most masses where the overlying epithelium is intact. Pigmentation varies between and within neoplasms; malignant melanomas are mildly pigmented when compared to melanocytomas, and some may be amelanotic. There is moderate to severe anisokaryosis and anisocytosis. The MI is typically much higher than 4 in 10 HPFs. Foci of necrosis are common, and melanophages may infiltrate the neoplasms, and the cavernous type with large vascular channels; however, capillary hemangiomas do occur. Rarely, there may be irregular hyperplasia of the overlying epithelium (angio-keratoma).3,11,12,22–29 Hemangiomas are routinely immunopositive for the endothelial cell marker Factor VIII and are immunoreactive for CD31.2,11,16,30,31 Hemangiomas are also immunoreactive for p16, PCNA, and estrogen receptor alpha. Most hemangiomas are immunoreactive for pAkt, and some are immunoreactive for p21, Cyclin D, and telomerase. Hemangiomas are negative for p53.32

Hemangiosarcomas are variably infiltrative masses composed of anastomosing irregularly shaped and sized vascular channels (Fig. 4). The vascular channels are lined by plump endothelial cells that often bulge in the lumen and lack the arrangement of smooth muscle and pericytes that comprise a normal vessel. Pleomorphism is variable, but the neoplastic cells do not have features of normal endothelium. The mitotic index depends in part on cell density within the examined fields, but is usually low. Most conjunctival hemangiosarcomas are well differentiated, and distinction from hemangiomas is not always straightforward.9,11,12,23,24,28,33,34 Hemangiosarcomas, like hemangiomas, are immunopositive for the endothelial cell markers Factor VIII and CD31.2,11,33 In addition, hemangiosarcomas are immunoreactive for p16, PCNA, and estrogen receptor alpha, most for pAkt, and some are immunoreactive for p21 and telomerase. Hemangiosarcomas are negative for p53 and Cyclin D.32

The prognosis for life and for the globe in hemangioma is good, with complete surgical excision being curative in most cases.28 The prognosis for life in hemangiosarcoma is also good; however, there is an increased risk of local recurrence after surgical excision.28 Wide surgical excision with adjunctive cryotherapy has been recommended.28

Mast cell tumors Conjunctival mast cell tumors present clinically as smooth, firm, and subconjunctival masses.35 Local conjunctival hyperemia or conjunctival hemorrhages may be present, and the tumor may fluctuate in size. Conjunctival mast cell tumors are histologically similar to
those in the skin. The masses are typically well circumscribed and composed of sheets of round cells. The cells have distinct borders and often contain cytoplasmic granules. Eosinophils may be admixed with the neoplastic cells. Edema is a common finding. The cytologic features of conjunctival mast cells are most often similar to those of Grade I-II (Patnaik system) or low grade (2-tier system) skin neoplasms. However, some features of the grading systems are difficult to apply to the conjunctiva, and the significance of grading systems developed for cutaneous mast cell tumors has not been determined for conjunctival neoplasms. Similarly, prognostic markers (kit(CD117), kit mutations, ki-67) used in cutaneous mast cell tumors have not been investigated in conjunctival mast cell tumors.

The prognosis for life and for the globe with mast cell tumor is good. While local recurrence is occasionally observed after complete and incomplete excision, metastasis appears rare. Surgical excision is reported to be curative, and adjunctive therapy may or may not be decrease recurrence.

**Third eyelid gland adenoma/adenocarcinoma** Third eyelid gland adenomas and adenocarcinoma appear similar clinically. Protrusion of the third eyelid is noted, with a pink, firm mass expanding the body of the third eyelid. The space-occupying effect of the mass may be associated with exophthalmos, strabismus, or enophthalmos. Most neoplasms of the gland of the third eyelid are histologically malignant. Third eyelid gland adenocarcinomas are expansile and variably infiltrative masses. Some are well differentiated and composed of tubules that resemble normal gland tissue, and others are mostly solid with only rare tubules (Fig. 5). Squamous metaplasia is a common finding. Rare neoplasms include myoepithelial and/or stromal elements. The neoplastic cells are cuboidal to columnar in well-differentiated tubular neoplasms and some solid masses. Small ‘basal’ cells with scant cytoplasm may be a significant component of some solid masses. Pleomorphism is mild even in solid neoplasms. The mitotic index is highly variable. Some masses may be associated with lymphocytic inflammation. Most texts only describe the malignant form, but rare third eyelid gland adenomas have been noted. Third eyelid gland adenocarcinomas are cytokeratin positive.

The prognosis for life with third eyelid gland adenomas and adenocarcinomas is good with complete surgical excision. Metastasis and death in one case with a highly invasive incompletely excised adenocarcinoma has been reported; however, complete excision can be expected to be curative. If removal of the third eyelid alone is sufficient to obtain clean margins, the prognosis for the globe is good; however, exenteration may be required for complete excision.

**Cornea/sclera**

**Epibulbar/limbal melanocytic neoplasms** Epibulbar or limbal melanocytic neoplasms appear clinically as darkly pigmented masses arising from the limbus and expanding into the adjacent cornea and sclera or as masses arising posterior to the limbus and expanding into the adjacent sclera. Limbal melanocytic neoplasms are presumed to arise from the melanocytes that demarcate the limbus at the junction of the corneal stroma and sclera. They expand along the planes of least resistance toward the conjunctiva readily and into the adjacent corneal stroma minimally. Histologically, almost all are benign melanocytomas. These broad-based, nodular neoplasms are composed of discohesive heavily pigmented plump polyhedral cells often admixed with fewer pigmented spindle cells. There is no atypia, and mitoses are rare to absent. Necrosis occurs in approximately 20% of cases. These masses grow by expansion and may extend intraocularly. Rare histologically malignant limbal melanomas have been described, and some otherwise benign neoplasms may include areas with cells that are less pigmented or amelanotic and mitotically active. The immunohistochemical profile of limbal melanocytomas has not been established, but they can be expected to have an immunophenotype similar to melanocytomas at other locations, expressing vimentin, Melan-A, and PNL-2.

The prognosis for life with limbal melanocytic neoplasia is excellent. Limbal melanocytomas have bimodal age distribution, and tumors in older dogs may be particularly slow to progress. Benign neglect and careful monitoring may be warranted in such cases. Surgical excision can preserve the globe in cases with more rapid progression. Photocoagulation may also be effective in arresting tumor progression.

**Corneal squamous cell carcinoma** Squamous cell carcinoma (SCC) of the cornea can have a varied clinical appearance. It may present as a discrete, pink, cobblestone textured mass, or a more diffuse pink mass associated with significant corneal vascularization. SCC is more likely to
occur in corneas with chronic keratitis, and some association with the administration of topical immunomodulators has been proposed.\textsuperscript{54–57} Corneal squamous cell carcinomas have histologic features similar to those in other locations. In the cornea, masses are usually exophytic and variably infiltrative. Approximately 30\% of described cases represent the \textit{in situ} form of squamous cell carcinoma. The neoplasms consist of nests and trabeculae with multifocal dyskeratosis and keratin pearl formation. The neoplastic cells are large, have distinct cell borders and abundant cytoplasm. Mitoses are numerous while pleomorphism is variable. When present, extension in the stroma is superficial. The adjacent corneal epithelium may be hyperplastic/dysplastic and is often pigmented. Corneal stromal inflammation and neovascularization are common findings when the stroma is available for histopathologic evaluation.\textsuperscript{9,11,54–56,58–62} In the few corneal squamous cell carcinomas assessed, immunoreactivity for cytokeratin (1/1), e-cadherin (1/1), and GADD45 (1/1) with rare immunopositive cells for caspase 3 was detected. One of three masses was positive for p53.\textsuperscript{56,61}

The prognosis for life with corneal squamous cell carcinoma appears to be good. The prognosis for the globe is dependent on early detection and surgical intervention. Surgical excision by keratectomy is recommended, and adjunctive therapy may be useful in decreasing recurrence.\textsuperscript{54–58}

\textbf{Other ocular surface neoplasia}

Other neoplasms or masses that may affect the conjunctiva and ocular surface include benign dermoids, squamous and viral papillomas, cysts, and inflammatory masses such as nodular granulomatous episcleritis, onchocerciasis, foreign body reactions, and others. Malignant neoplasms include conjunctival squamous cell carcinoma, which is rare in dogs compared with other species, lymphoma, and transmissible venereal tumor.\textsuperscript{2,4,9,12,57,63–66} Clinical appearance and prognosis vary with tumor type.

\textbf{INTRAOCULAR NEOPLASIA}

\textbf{Uvea}

\textbf{Uveal melanocytic neoplasia} It is difficult to differentiate benign from malignant uveal melanocytic neoplasia based on clinical appearance. Clinically, this tumor type has a variable appearance.\textsuperscript{47,67} Anterior uveal melanocytic neoplasms may appear as a mass expanding the iris and extending into the anterior chamber or as a mass posterior to the iris that anteriorly displaces the iris face. Occasionally, the first clinical sign of an anterior uveal melanocytic neoplasm is thinning of the sclera with a pigmented mass visible expanding into the sclera. Uveitis is usually not a feature of anterior uveal melanocytic neoplasia; however, secondary glaucoma may be present.\textsuperscript{48,68–74} Masses are typically heavily pigmented, but may be nonpigmented. Choroidal melanocytic neoplasms appear as focal pigmented subretinal masses that may be associated with retinal detachment.

Benign uveal melanocytomas are most common in the iris and ciliary body, typically affecting both. A review of two large ocular pathology databases shows that only 6\% of uveal melanocytomas principality affect the choroid (Table 1). Melanocytomas of the anterior uvea readily efface the iridocorneal angle. Many expand along the corneoscleral meshwork which extends anterior to the termination of Descemet’s membrane and blend with the deep peripheral corneal stroma. Scleral and extrascleral extension is common for both anterior uveal and choroidal melanocytomas and is not a feature that is indicative of malignancy.

All melanocytomas have a similar histologic appearance independent of their origin in the iris, ciliary body, or choroid. The neoplasms are composed of variable proportions of heavily pigmented spindle cells and discohesive heavily pigmented plump polyhedral cells (Fig. 6). The spindle cell population has indistinct cell borders, small to moderate amounts of pigmented cytoplasm, and oval nuclei often with one nucleolus. There is minimal anisokaryosis and anisocytosis. Mitoses are rare to absent (<4 in 10 HPF). The plump polyhedral cells are large with distinct cell borders, abundant pigmented cytoplasm, and central to peripheralized round nuclei. There is severe anisocytosis but minimal anisokaryosis. Mitoses are not present in the plump polyhedral cells. These plump polyhedral cells are melanocytes, not melanophages, and contain melanomas/premelanoses. Free individualized pigmented cells may be seen in the anterior and posterior

\begin{table}[h]
\centering
\begin{tabular}{|l|c|c|c|c|}
\hline
\textbf{Neoplasm} & \textbf{Database\ A*} & \textbf{Database\ B*} & \textbf{Total} & \textbf{\%} \\
\hline
\textbf{Uveal melanocytoma (total)} & 1090 & 356 & 1446 & 41.5 \\
\textbf{Anterior uvea} & 1025 & 336 & 1361 & \\
\textbf{Choroidal} & 65 & 20 & 85 & \\
\textbf{Iridociliary adenoma} & 592 & 142 & 734 & 21.1 \\
\textbf{Uveal malignant melanoma (total)} & 334 & 124 & 458 & 13.1 \\
\textbf{Anterior uvea} & 323 & 120 & 443 & \\
\textbf{Choroidal} & 11 & 4 & 15 & \\
\textbf{Lymphoma} & 188 & 30 & 218 & 6.3 \\
\textbf{Metastatic neoplasia*} & 169 & 35 & 204 & 5.9 \\
\textbf{Iridociliary adenocarcinoma} & 116 & 36 & 152 & 4.4 \\
\textbf{Optic nerve meningioma} & 60 & 37 & 97 & 2.8 \\
\textbf{Histiocytic sarcoma} & 54 & 36 & 90 & 2.6 \\
\textbf{Schwannoma of blue-eyed dogs/peripheral nerve sheath tumor} & 43 & 6 & 49 & 1.4 \\
\textbf{Astrocytoma} & 21 & 3 & 24 & 0.7 \\
\textbf{Medulloepithelioma} & 24 & 0 & 24 & 0.7 \\
\hline
\textbf{Total*} & 2691 & 805 & 3496 & \\
\hline
\end{tabular}
\caption{Relative frequency of intraocular and optic nerve neoplasia in dogs in two veterinary pathology databases}
\end{table}

*Database A\textsuperscript{2}; Database B from author PL (Jan 2006-Sept 2012). \textsuperscript{*Excluding lymphoma and histiocytic sarcoma.}
chambers and vitreous. Necrosis and infiltration of melanophages are common. Intraocular hemorrhage, pre-iridal fibrovascular membrane, asteroid hyalosis, and glaucoma are frequent secondary findings. Retinal detachment is expected with choroidal melanocytomas. The immunochemical profile of uveal melanocytomas has not been clearly established, but they can be expected to have an immunophenotype similar to melanocytomas at other locations and express vimentin, Melan-A, PNL-2, etc. 

Uveal melanocytoma may express Cox-2 and monocarboxylate transporter 1. Uveal malignant melanoma is more common in the anterior uvea than in the choroid. Only 3% of uveal malignant melanomas are choroidal in origin. Approximately 25% of anterior uveal melanocytic neoplasms and 15% of choroidal melanocytic neoplasms are malignant (Table 1). The mitotic index is the most reliable parameter in the diagnosis of malignant melanoma. A threshold of four mitoses in 10 HPF is most widely used to establish malignancy in uveal melanocytic neoplasms. As with uveal melanocytomas, expansion along the corneoscleral meshwork in the sclera and in extrascleral tissues is common. Uveal malignant melanomas are composed of spindle cells to polygonal cells (Fig. 7). There is moderate to severe anisokaryosis and anisocytosis. Plump polyhedral cells may be present in low numbers. The spindle and polygonal cells are often only subtly pigmented. Malignant melanomas are less pigmented than their benign counterpart and can be amelanotic. Necrosis and infiltration of melanophages are common. Intraocular hemorrhage, pre-iridal fibrovascular membrane, asteroid hyalosis, and glaucoma are frequent secondary findings. Anterior uveal malignant melanomas that extend in the choroid and choroidal malignant melanoma may cause retinal detachment. There are currently no histologic features that can reliably predict metastasis. In the few reports with immunohistochemistry, uveal malignant melanoma is melan-A immunoreactive with some expression of Cox-1 and Cox-2. Uveal neoplasms are expected to share the immunophenotype of malignant melanomas at other locations.

The prognosis for life with uveal melanocytoma is considered good, although the prognosis for the globe is poor as enucleation is frequently required, particularly in those eyes that develop secondary glaucoma. Photocoagulation has been reported, with variable success in arresting tumor progression. The prognosis for life with uveal malignant melanoma is guarded, and the prognosis for the globe is poor, as enucleation is frequently required, particularly in those eyes that develop secondary glaucoma. The prognosis for a choroidal melanocytic neoplasm is based on its malignancy; most are benign choroidal melanocytomas tend to behave in a benign manner, whereas the more rare malignant tumors have a poorer prognosis.

Ocular melanosis (diffuse uveal melanosis and pigmen-
tary glaucoma) is a unique condition that must be distin-
guished from uveal melanocytomas and malignant melanomas. Clinically, ocular melanosis appears as diffuse pigmentation of the uveal tract. In its early stages, the pigmentation may be discrete and multifocal but inevitably progresses to coalescing, diffuse pigmentation. Pigment may be visible in the fundus and through the sclera. It is unclear if ocular melanosis is truly neoplastic. It is characterized by diffuse uveal infiltration of large, pigment-laden cells predominantly within the anterior uvea.
and anterior sclera without formation of a distinct mass (Fig. 8). Both melanocytes and melanophages contribute to the uveal expansion. The melanocytes have a unique immunophenotype that differs from normal melanocytes with positive immunoreaction for vimentin and variable HMB-45 and microphthalmia transcription factor (MITF) immunoreactivity, but negative staining with Melan-A and S100. The melanophages are CD18 positive.

Iridociliary neoplasia Clinically, neoplasia of the ciliary body epithelium appears as nonpigmented to lightly pigmented pink masses that may protrude into the pupillary aperture and displace the iris face anteriorly. Dyscoria, lens subluxation, cataract, and retinal detachment may be observed, and secondary glaucoma may be present. Benign tumors cannot be clinically differentiated from malignant tumors. Benign ciliary body adenomas typically arise from the ciliary body epithelium and may involve the iris. Most expand in the posterior chamber, and some will extend in the ciliary body and iris. The masses are predominately nonpigmented, but pigment can be found in some neoplastic cells of most neoplasms. A small subset of benign iridociliary tumors is heavily pigmented. The neoplasms are composed predominately of cords and nests with tubules, solid sheets, and occasionally cysts (Fig. 9). Tubules and cysts may contain hyaluronic acid. The cuboidal cell population has distinct cell borders, moderate amounts of cytoplasm, and oval nuclei. There is usually mild anisokaryosis and anisocytosis although scattered cells may exhibit some atypia. Mitoses are uncommon (usually less than 5 in 10 HPF). Neoplastic cell produces PAS-positive basement membrane material. Intraocular hemorrhage, pre-iridal fibrovascular membranes, asteroid hyalosis, and glaucoma are frequent secondary findings.

Mimicking normal neuroepithelium, iridociliary adenomas are immunoreactive for vimentin and neuron-specific enolase (NSE) with variable immunopositivity for S100, glial fibrillary acidic protein (GFAP), and desmin. There is also immunoreaction to telomerase reverse transcriptase (TERT), and some neoplasms express cytokeratins.

Malignant iridociliary neoplasms (ciliary body adenocarcinomas) are similar to their benign counterpart. They typically arise from the ciliary body epithelium and will extend in the ciliary body and iris, and malignant iridociliary neoplasms will invade the sclera (Fig. 10). Invasion of the sclera is a major criteria of malignancy for malignant iridociliary neoplasms. Approximately 15% of iridociliary neoplasms can be classified as malignant (Table 1). The masses are predominately nonpigmented, but pigment can be found in some malignant iridociliary tumors. The neoplasms are composed predominately of nests and cords often with solid sheets. Tubules and cysts are less common than in benign tumors. The cuboidal cell population has distinct cell borders, moderate amounts of cytoplasm, and oval nuclei. There is moderate to severe anisokaryosis and anisocytosis. The mitotic index is highly variable and can be low but is typically increased compared with benign tumors (more than 5 in 10 HPF). Production of PAS-positive basement membrane material is usually present in at least portions of the mass. There is currently no histologic feature that can reliably predict metastasis. Intraocular hemorrhage, pre-iridal fibrovascular membrane, asteroid hyalosis, and glaucoma are frequent secondary findings.

Iridociliary adenocarcinomas are immunoreactive for vimentin, NSE and TERT with variable immunopositivity for S100, cytokeratin, GFAP and desmin. Malignant iridociliary neoplasms have increased TERT expression and are more likely to express cytokeratin than benign tumors.

The prognosis for life with ciliary body adenomas and adenocarcinomas is good, although the prognosis for the globe is poor as enucleation is required in most cases. Surgical excision, chemotherapy and photocoagulation have been reported as therapeutic options.

Medulloepitheliomas are less common than ciliary body adenomas/adenocarcinomas. Clinically, medulloepitheliomas have a similar presentation to ciliary body adenomas.
and adenocarcinomas. Retinal detachment may be present depending on the location from which the tumor arises. Medulloepitheliomas are rare neoplasms of the canine globe that typically arise from the ciliary body. The neoplastic cells form loose sheets and poorly organized multilayered rosette-like structures with a central cavity. True Flexner–Wintersteiner and Homer–Wright rosettes may be present. The neoplasms are composed of small hyperchromatic stellate to round cells similar to those found in other primitive neuroectodermal tumors. Some areas may have features resembling ciliary processes or retina. Medulloepitheliomas may be termed teratoid when the neoplasm contains heterotopic elements that are not normal derivative of the ocular embryonic development. Medulloepitheliomas are immunoreactive for TERT with limited immunopositivity for cytokeratin, vimentin and CD99. One case was negative for S100, NSE, triple neurofilament (TNF), GFAP, synaptophysin and ki-67. The prognosis for life is generally good, although metastasis is reported, and the prognosis for the globe is poor as enucleation is required in most cases. Medulloepitheliomas are immunoreactive for TERT with limited immunopositivity for cytokeratin, vimentin and CD99. One case was negative for S100, NSE, triple neurofilament (TNF), GFAP, synaptophysin and ki-67. The prognosis for life is generally good, although metastasis is reported, and the prognosis for the globe is poor as enucleation is required in most cases.

**Schwannomas of blue-eyed dogs (peripheral nerve sheath tumors, ‘spindle cell tumors of blue-eyed dogs’)** The clinical appearance of schwannomas of blue-eyed dogs/peripheral nerve sheath tumors is infrequently described in the peer-reviewed literature. Moreover, some of these neoplasms may not be recognized clinically and are diagnosed when histopathology of the enucleated globe is performed. Histologically, they typically arise in the iris and extend in the ciliary body. The morphologic, immunohistochemical and electron microscopy findings are all consistent with a schwannoma. The masses are nonpigmented and composed of interlacing bundles, streams and whorls. Antoni A and B patterns are usually recognized. The spindle cells have indistinct cell borders, scant amounts of cytoplasm and oval nuclei. Pleomorphism and mitotic index are variable. Approximately half of the neoplasms are well differentiated with a low mitotic index. Other masses may show marked atypia with numerous mitoses. Intraocular hemorrhage, pre-iridal fibrovascular membranes, and glaucoma are frequent secondary findings. Schwannomas of blue-eyed dogs/peripheral nerve sheath tumors are immunoreactive for vimentin and S100. Most are immunopositive for GFAP and PGP 9.5. There is variable expression of laminin, GADD5, p53, PCNA, anti-UVssDNA, and TERT. The neoplastic cells are immunonegative for MITF, CD34, skeletal muscle actin and TNF, and usually immunonegative for Melan-A, smooth muscle actin and desmin. The prognosis for life for this tumor type is not well understood with only one published case of metastasis, however the prognosis for the globe is considered poor as enucleation is required in most patients.

**Metastatic neoplasia** The clinical appearance of metastatic neoplasia is variable, and may include anterior uveitis, discrete masses of the uveal tract or secondary glaucoma. Lymphoma and histiocytic sarcoma are the most common metastatic neoplasms to the canine globe (Table 1). Mammary adenocarcinomas are the most common secondary epithelial neoplasms. Hemangiosarcoma, malignant melanoma and osteosarcoma are common nonleukocytic sarcomas that spread to the eye. Metastases most often involve the iris and ciliary body in dogs. There are two general patterns of metastasis to the canine globe: diffuse expansion and effacement of the uveal tract and mass formation or multifocal expansion of the uveal tract often with carpeting of the iris and ciliary body. Lymphoma and histiocytic sarcoma will typically expand and efface the anterior uveal tract. Lymphoma will also readily extend in the choroid and retina or other structures. Carcinomas and nonleukocytic sarcomas more often will form multifocal masses and occlude blood vessels. Many will carpet or line the iris and ciliary body occasionally extending to cover the posterior cornea or retina (Fig. 11). Immunohistochemistry may be helpful to determine the histogenesis of poorly differentiated metastases. The prognosis for life varies with the tumor type. The prognosis for the globe is considered poor as enucleation may be required, blinding sequelae such as retinal detachment.
may develop or painful sequelae such as glaucoma may occur.

**Retina/optic nerve**

**Astrocytomas (gliomas)** Clinically, astrocytomas appear as a discrete mass in the fundus or more frequently, retinal detachment with secondary vitreal hemorrhage, hyphema, and glaucoma. Astrocytomas may arise in the retina or optic nerve and often involve both. Approximately 40% will invade the choroid. The masses are nonpigmented and composed of interlacing bundles and fascicles with a delicate fibrovascular stroma (Fig. 12). The spindle cells have indistinct cell borders, moderate amounts of fibrillar eosinophilic cytoplasm, oval nuclei and often multiple nucleoli. Pleomorphism and mitotic index are variable but most masses are high grade astrocytomas with severe anisokaryosis and anisocytosis and high mitotic index. Retinal detachment, intraocular hemorrhage, pre-iridal fibrovascular membrane and glaucoma are frequent secondary findings. Astrocytomas are immunoreactive for vimentin, most are immunopositive for GFAP, and there may be expression of NSE and S100. The prognosis for life is considered good with rare regional invasion reported, although the prognosis for the globe is poor as enucleation is required in most patients.

**Lobular orbital adenomas** Clinically, lobular orbital adenomas present as exophthalmos, third eyelid protrusion, subconjunctival mass effect, and periocular swelling. Lobular orbital adenomas arise from the lacrimal or salivary glands. The neoplasms are multilobular and composed of nests and acini with scant stroma. The lobules lack ducts, and this feature is essential to making the diagnosis of lobular orbital adenoma. The cuboidal cell population has distinct cell borders, moderate amounts of cytoplasm that is often granular, and oval nuclei. There is minimal anisokaryosis and anisocytosis, and the cells essentially have features of normal tissue. Mitoses are absent. The immunohistochemical profile of lobular orbital adenomas has not been established. The prognosis for life with lobular orbital adenoma appears guarded, as local recurrence is common. The prognosis for the globe is guarded to poor, as enucleation is recommended to decrease recurrence.

**Other orbital neoplasia** Any of the tissue components of the orbit may give rise to neoplasms such as osteosarcoma, multilobular tumor of bone, fibrousarcoma, liposarcoma, rhabdomyosarcoma, salivary-lacrimal adenocarcinoma, metastatic disease, and others. The features of these neoplasms are similar to those at other sites.

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**REFERENCES**


