Malignant Medulloepithelioma of the Optic Nerve in a Horse

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Abstract. An 18-month-old Standardbred filly had a large intraocular tumor involving the optic nerve. The tumor was a malignant medulloepithelioma, a rare intraocular neoplasm derived from the primitive medullary epithelium. By light microscopy the tumor had cords and lobules of primitive neuroepithelial cells that formed clefts and true rosettes. Electron microscopy of the rosettes showed a girdle of zonulae adherentes joining the apices of the cells as well as several basal bodies. This is the sixth report of equine intraocular medulloepithelioma, and, to the best of our knowledge, the first intraocular medulloepithelioma arising from the optic nerve head in a horse. Massive involvement of the optic nerve should be suspected when an eye containing an intraocular mass in the posterior segment lacks light perception. In such cases a long segment of optic nerve should be resected.

Medulloepitheliomas are intraocular neuroepithelial tumors thought to arise from the embryonic medullary epithelium of the forebrain and optic vesicles [18, 24]. Uncommon in man [2] these embryonal tumors are rare in domestic animals [16, 20]. Five of the 10 reported cases [5, 6, 13] occurred in horses [5, 6]. Although usually found in the ciliary body, medulloepithelioma may arise in the posterior segment of the eye [1, 10, 17, 19]. This paper reports the light and electron microscopic findings in a malignant nonteratoid medulloepithelioma involving the optic nerve head of an 18-month-old Standardbred filly.

Case History

An 18-month-old Standardbred filly, blind in the left eye, was referred for ophthalmic examination. There was no history of trauma. The horse responded to a threat on the right but not on the left. The left eye was inflamed and congested. The left pupil was fixed and mid-dilated and lacked both direct and consensual reactions. The right pupil did not react consensually. The lens was clear. Although the vitreous was slightly hazy, the posterior segment could be seen easily. The retina was folded inwardly and lacked the usual pattern. A solid pink to gray-white lobular mass occupied about a third to a half of the posterior segment and appeared to involve the optic nerve. Neither hemorrhages nor exudates were seen. The right eye was clinically normal with the exception of the pupillary defect.

Because a malignant intraocular growth was suspected, the left eye was exenterated.
Equine Intraocular Medulloepithelioma

Materials and Methods

The left globe was fixed in Bouin's solution and submitted to the Registry of Ophthalmic Pathology, Armed Forces Institute of Pathology for histologic examination. Paraffin-embedded sections for light microscopy were stained with hematoxylin and eosin (HE), periodic acid-Schiff (PAS), and phosphotungstic-acid hematoxylin (PTAH). In addition, alcian blue and colloidal iron stains for acid mucopolysaccharides, with and without hyaluronidase, were prepared. Tissue for electron microscopy was embedded in epon and stained with uranyl acetate and lead citrate. Preliminary epon thick sections (1 to 2 micrometers) for light microscopy were stained with toluidine blue.

Results

The left globe was 45×44×40 millimeters and had a 9-millimeter segment of enlarged optic nerve. The opaque cornea was 29×33 millimeters. The globe could not be transilluminated and was opened vertically. The anterior chamber and vitreous cavity contained fluffy white material. The lens was in place. A globoid yellow-tan mass about 20×20×20 millimeters arose from the optic nerve head and protruded into the vitreous cavity. The tumor had an encephaloid appearance and prominent blood lakes. A small focus of tumor invaded the peripapillary choroid. An episcleral nodule of tumor was adjacent to the optic nerve, which was massively infiltrated by tumor. There was a shallow serous detachment of the sensory retina.

Microscopic examination of the anterior segment was not remarkable. A large mass protruded from the optic nerve head into the vitreous cavity (fig. 1) and involved the retrolaminar part of the nerve. The tumor was composed of cords and tubules of pleomorphic stratified columnar cells having a neural appearance and forming clefts and occasional true rosettes (fig. 2). The stratified sheet of cells had some degree of polarity. The basal part of the cords rested upon prominent thin bands of hyalinized collagenous stroma resembling very thick basement membrane (fig. 3). The apical cells lining the clefts and rosettes showed a definite external limiting membrane. The collagenous stroma was moderately PAS and alcian-blue positive. These special stains, however, revealed no acid mucopolysaccharide material within the lumina of the rosettes.

Numerous large blood-filled vascular channels and lakes were present. The tumor cells had a definite perivascular arrangement with elongated cytoplasmic processes attached to walls of vessels, which were embedded in a collagenous stroma. The cells were nonpigmented and had a moderate amount of eosinophilic cytoplasm. The nuclei were vesicular and pleomorphic, had prominent nuclear membranes, peripheral chromatin margination and occasionally large nucleoli. Mitotic figures were numerous. The stroma had no cartilaginous or rhabdomyoblastic parts.

The peripapillary retina, which was minimally infiltrated by tumor, was pushed away laterally from the mass in the nerve head. Inferiorly there was a shallow detachment of the retina. Although the tumor cells had focally replaced the retinal pigment epithelium in the juxtapapillary region, invasion through Bruch's membrane into the choroid was not seen. The tumor had massively infiltrated the optic
nerve, reaching its line of surgical resection. The episcleral nodule described grossly was composed entirely of tumor cells.

Epon-embedded thick sections of episcleral tumor demonstrated the presence of true rosettes with lumina lined by a series of dots (inset, fig. 4). By electron microscopy the apices of the cells forming the rosettes were joined by a girdle of zonulae adherentes (fig. 4). Several basal bodies were seen, but no cilia could be detected. The cells abutting connective tissue septa had short profiles of rough-surfaced endoplasmic reticulum and numerous microfilaments. Few mitochondria were present. The hyalinized bands of connective tissue were composed of compacted masses of collagen fibrils that in some areas surrounded endothelium-lined blood vessels. A thin basement membrane was noted between the plasmalemma of the tumor cells and the connective tissue.

A diagnosis of malignant medulloepithelioma of optic nerve head with massive invasion of nerve and extraocular extension was made.

**Discussion**

Neuroepithelial tumors of the ciliary body have been classified into congenital and acquired groups [24]. Occasionally reported in dogs, acquired adenomas and adenocarcinomas arising from the differentiated ciliary epithelium are rare in domestic animals and man [3, 4, 9, 18, 22, 23]. Uncommonly, the embryonic medullary epithelium may give rise to a group of congenital intraocular neoplasms once inaptly termed “diktyomas” [8, 24].

Although intraocular neoplasms are uncommon in the horse [6, 16, 20],

**Fig. 1:** Enucleated eye with large globoid mass protruding from optic nerve head into vitreous cavity and invading retrolaminar part of nerve. AFIP Neg. 77-2104. HE.
intraocular medulloepitheliomas are exceedingly rare. In 1919 an intraocular equine tumor, which was termed a “retinogioma,” was reported [7]. Although cited as a rare example of retinoblastoma in a horse [16], the “retinogioma” was properly reclassified as a malignant medulloepithelioma [5]. Two additional previously unreported tumors have been similarly diagnosed [5]. A medulloepithelioma with orbital invasion was one of two equine intraocular tumors reported in a review of 69 ocular tumors in horses at the University of Iowa [6]. In 1974 the fifth case was reported—an 11-year-old quarter horse with a tumor of the inferior iris leaf and ciliary body [5].

The virtually undifferentiated multilayered medullary epithelium has striking polarity [23]. The cells lining the optic vesicle are joined by a girdle of apical terminal bars comparable to the external limiting membrane of the retina [21], while the cells lining the inner surface of the optic cup produce embryonic vitreous [15, 25]. Polarity also characterizes the multilayered sheets and cords of poorly differentiated neuroepithelial cells found in medulloepitheliomas. The cells, which resemble normal embryonic retina and ciliary epithelium, rest on an abundant,
Fig. 4: Inset: Neuroepithelial rosette with lumen lined by a series of dots. Toluidine blue. Lumen of rosette is shown in electron micrograph. Girdle of zonulae adherentes (ZA). Basal bodies (free arrows). L = lumen of rosette. AFIP Neg. 77-6759.

relatively acellular myxoid stroma rich in hyaluronidase-sensitive mucopolysaccharide [25]. Commonly the sheets of cells form clefts or rosettes. Corresponding to the lumen of the primary optic vesicle, these structures are lined by external limiting membrane and contain no acid mucopolysaccharide [23]. Ultrastructural studies of the rosettes have demonstrated apical terminal bars and nonmotile neuronal cilia [11, 12]. In teratoid medulloepitheliomas the stroma may show rhabdomyoblastic [13, 26], cartilaginous [18], or spongioblastic differentiation.

Although medulloepitheliomas typically arise from the ciliary body, they may also rarely develop from the retina and optic nerve. Malignant medulloepitheliomas involving the optic nerve or retinal stalk in human patients have been reported [1, 10, 17, 19]. The embryonic neuroepithelium lining the invaginating optic vesicle is continuous with that lining the cavities of the embryonic optic nerve and forebrain. Any site lined by neuroepithelium during embryonic life presumably could give rise to medulloepithelioma [10]. Involvement of the ciliary body is most typical since the medullary epithelium remains incompletely differentiated in this region longer than elsewhere [23].

Although metastasis to regional lymph nodes and the lungs has been reported in man [2, 14], medulloepithelioma generally tends to be a locally aggressive neoplasm [18]. The tumor may extend out of the eye and invade the orbit, with occasional fatalities caused by intracranial extension. Metastasis generally follows orbital invasion [2, 24].
In one case, intracranial extension led to the death of the patient despite orbital exenteration, radiotherapy, and chemotherapy [18, 19]. In another [10], the tumor initially involved the optic nerve at the surgical line of transection and ultimately required orbital exenteration and removal of the intracanalicular and intracranial parts of the optic nerve. The patient was alive and well with no evidence of metastasis 18 months after surgery [10].

In both of these cases the visual acuity was no light perception before enucleation. Such severe visual loss associated with an intraocular neoplasm of the posterior segment should suggest involvement of the optic nerve. Secondary retinal detachment is responsible for most visual loss caused by intraocular tumors, with visual field loss corresponding to the area of detachment. Eyes with localized peripheral detachments commonly retain central visual acuity, and light perception may be retained for months or even years in eyes with total detachment.

In our case, lack of both response to threat and pupillary reactions to light in an eye with a shallow, localized detachment should have suggested involvement of the optic nerve and prompted a more extensive resection. Orbital recurrence, intracranial extension or both, undoubtedly will occur because of the presence of tumor at the line of surgical resection of the optic nerve.

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