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The Significance of the Discordant Occurrence of Lens Tumors in Humans versus Other Species

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Abstract

Purpose—The purpose of this study was to determine in which species and under what conditions lens tumors occur.

Design—A review of data bases of available human and veterinary ocular pathological material and the previously reported literature.

Participants—Approximately 18,000 patients who had ocular surgical specimens submitted and studied at the University of Wisconsin School of Medicine and Public Health (UWSMPH) between 1920 and 2014 and 45,000 ocular veterinary cases from the Comparative Ocular Pathology Laboratory of Wisconsin (COPLOW) between 1983 and 2014.

Methods—Material in two major archived collections at the University of Wisconsin medical and veterinary schools were studied for occurrence of lens tumors. Tumor was defined as “a new growth of tissue characterized by progressive, uncontrolled proliferation of cells.” In addition, cases presented at 3 major eye pathology societies (Verhoeff-Zimmerman Ophthalmic Pathology Society, Eastern Ophthalmic Pathology Society, and The Armed Forces Institute of Pathology Ophthalmic Alumni Society) from 1975 through 2014 were reviewed. Finally, a careful search of the literature was carried out. Approval from the IRB to carry out this study was obtained.

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Main Outcome Measures—The presence of tumors of the lens.

Results—The database search and literature review failed to find an example of a lens tumor in humans. In contrast, examples of naturally occurring lens tumors were found in cats, dogs, rabbits, and birds. 4.5% of feline intraocular and adnexal neoplasms (234/5153) in the veterinary school database were designated as feline ocular post-traumatic sarcoma (FOPTS), a tumor previously demonstrated to be of lens epithelial origin. Similar tumors were seen in rabbit eyes, a bird, and in a dog. All four species with lens tumors had a history of either ocular trauma or protracted uveitis. The literature search also revealed cases where lens tumors were induced in zebrafish, rainbow trout, hamsters, and mice, by carcinogenic agents (methylcholanthrene, thioacetamide), oncogenic viruses (SV40, HPV-16), and genetic manipulation.

Conclusions—Our results suggest that lens tumors do not occur in humans. In contrast, following lens capsule rupture, a lens tumor can occur in other species. We hypothesize that a genetic mechanism exists which prevents lens tumors in humans.

Over the last century, the perceived absence of lens tumors in patients has been remarked upon in the literature although never rigorously confirmed.^{1–4} If true, this absence is noteworthy and possibly remarkable because all dividing cells, even in invertebrates – including metazoan hydra – can develop genetic mutations giving rise to tumors.⁵ In fact, limitations on the presumed non-occurrence of lens tumors have accumulated. Malignant tumors of the lens can be induced with carcinogens,⁶ oncogenic viruses,⁷ and engineered genetic defects in transgenic animals.^{8–10} More strikingly, malignant tumors of the lens can spontaneously occur in other species of non-human vertebrates.^{11–18} During the last 25 years, considerable knowledge has accumulated regarding the “regulatory circuits” that must be disrupted in order for a cell to become malignant. The purpose of the present study was to determine in which species and, under what conditions, lens tumors occur by studying human and veterinary pathologic material available to us, combined with a review of the literature. Confirmation of the absence of lens tumors in humans is an important first step in determining the mechanism by which human lens epithelial cells are exempted from tumor formation.

Methods

To determine in which species and under what conditions lens tumors occur, we carried out the studies listed below. Our working definition of a “tumor” was a new growth of tissue characterized by progressive, uncontrolled proliferation of cells.¹⁹

1. A review of the University of Wisconsin School of Medicine and Public Health (UWSMPH) human ocular pathology archival collection containing approximately 18,000 specimens and reports accumulated between 1920 and 2014.
2. A review of the UW School of Veterinary Medicine’s Comparative Ocular Pathology Laboratory of Wisconsin’s (COPLOW) collection of the more than 44,000 animal ocular pathology specimens received between 1983 and 2014.
3. A review of cases presented at three major U.S. ophthalmic societies: the Verhoeff-Zimmerman Ophthalmic Pathology Society; the Eastern Ophthalmic Pathology Society, and the Armed Forces Institute of Pathology Ophthalmic Alumni Society.

This review covered the period from 1975 through 2014. Representative histopathology slides, photomicrographs, and protocols are available in the teaching collection of the UWSMPH Ocular Pathology Laboratory. Senior members of these societies were queried regarding lens tumors encountered during their careers.

4. A thorough electronic literature search was carried out using the variation of the terms “Lens, Crystallin” [Mesh] and “Neoplasms” [Majr]. The reference list for each article was reviewed seeking additional articles regarding human or animal lens neoplasms and abnormal proliferations. All articles found in this search were reviewed in detail.

Results

Spontaneous lens tumors (“naturally occurring” tumors) in humans

No case of a malignant or benign tumor of the lens was found in any of the human archival ocular pathology collections reviewed, nor described in the literature. Nor had other senior members of the eye pathology societies seen such a case in their professional experience.

Examples of overgrowth involving benign proliferation of lens epithelium both within the lens capsule and intraocularly through ruptured lens capsules (figure 1) were observed, as well as the commonly encountered mild to moderate proliferation of lens epithelium, sometimes with fibrous metaplasia, in lenses with posterior capsular opacification. In no instance was the histologic appearance suggestive of a benign or malignant tumor.

“Spontaneous lens tumors” in non-human species

The veterinary database review identified 234 examples of lens tumors, all diagnosed as malignant. Malignant tumors of the lens occurred most commonly in cats and comprised 4.5% of intraocular and adnexal neoplasms in that species.

An additional 29 spontaneous lens tumors in non-human species have been reported in the literature. The initial case was reported by one of the authors of this paper (DMA and associates) in 1983.¹¹ The following year, Dubielzig reported 3 cases of lens malignancy in the feline eye following ocular trauma.¹² In a subsequent study, it was established that rupture of the lens capsule was a major risk factor for development of the tumor and, on the basis of the histologic appearance, the name “feline ocular post-traumatic sarcoma” (FOPTS) was suggested.¹³ Regional lymph nodes, lung and brain were principle sites of metastases.¹³ The time between the injury and diagnosis of the tumor ranged from 1 to 17 years with an average of 6.4 years. A tissue culture study of the tumor cells raised the possibility of pigment cells as a source of the tumor,¹⁴ but positive immunohistochemical staining for crystalline α A, a protein highly specific for the lens, confirmed its lens epithelial origin.¹⁵ A loss of p16 regulation was suggested as a factor in the pathogenesis of these tumors.

A summary of previously unreported lens malignancies in non-human species in the COPLOW collection is given in Table 1. All cases showed evidence of lens capsule rupture,

and most had some degree of uveitis. Although these are considered “spontaneous lens tumors,” all occurred after rupture of the lens capsule. Table 2 summarizes the cases described in the literature. A representative clinical picture and photomicrograph of a feline lens tumor is shown in figure 2. Other species described with lens tumors similar to that seen in cats include rabbits and birds (figures 3 and 4). It should be noted with regard to documented length of time between injury and recurrence and presence of metastases that veterinary work-ups and medical histories are generally more limited than those available for humans.

Induced lens tumors in non-human species

Carcinogens—Dame Ida Mann was a distinguished ophthalmologist who, in the mid-twentieth century, provided fundamental knowledge regarding genetics and embryology as they relate to eye diseases. Mann was intrigued by the fact that mitoses occur in the lens epithelium throughout life and into old age, but lens tumors at that time had not been described in humans or in other species. In 1947, she reported induction of experimental malignant tumors in the lenses of mice with methylcholanthrene.³ In 1966, Von Sallmann et al. reported the development of massive malignant-appearing proliferations of the lens epithelium in rainbow trout given a diet rich in thioacetamide.⁶

Oncogenic viruses and transgenics using oncogenes—In 1969, Albert et al. observed malignant transformation of lens epithelium of hamsters when infected with an oncogenic virus (Simian Virus 40).⁷ Subsequently, a coding sequence of SV-40T antigens was fused to the murine α crystalline promoter to establish a transgenic line of mice that developed invasive lens tumors. Another transgenic mouse line was developed using genes producing proteins (E6 and E7) found in human papilloma virus 16 (HPV E6 and E7).

More recently, N-ethyl-N-nitrosourea (ENU)-induced mutants of zebrafish have been developed that exhibit tumor-like proliferation of the lens epithelium, without progression to malignancy: the zebrafish mutant “bumper”²⁰ and the zebrafish mutant “Occhiolino.”²¹

Discussion

In the past 25 years, it has been demonstrated that a critical factor involved in the development of cancer is genetic mutation in dividing cells.²² Tomasetti and Vogelstein, in fact, recently demonstrated that for many types of cancer, there is a strong quantitative correlation between cancer risk and the lifetime number of divisions of the normal stem cells that maintain that tissue’s homeostasis.²³ Accordingly, they calculated that two-thirds of cancers are due to random mutations arising during DNA replication in normal, non-cancerous stem cells.²³ These mutations can alter the function of the gene leading to oncogenes that cause or contribute to cancer formation.²²

During the last quarter century, a major focus of cancer research has been to search for mutations that cause various types of cancer. Mutations, however, can also result in the deactivation of genes that inhibit cancer formation: tumor suppressor genes. Researchers are increasingly aware of the need to look for genes that prevent cancer. Nor is this search limited to cancer research. Systematic searches of genetic databases have identified genes

that offer partial protection from Type 2 diabetes, Alzheimer's disease, osteoporosis, and heart disease.²⁴

Cancer of the lens appears to be a prime candidate for identifying a cancer inhibiting gene or genes in humans. Lens cancer as discussed above is a tumor that occurs in other species but does not occur in humans. As described in the Results section, zebra fish mutants show tumor-like phenotypes, suggesting that the responsible genes may be in the pathway causing transformation of lens epithelium cells. Once those responsible genes are identified, it will be valuable to study their roles as well as their mammalian counterparts.

At present, to the best of our knowledge, there have been no genetic studies of spontaneous lens tumor. With current genetic techniques it should be possible to identify the genes involved in lens tumor formation in these other species, and use these as candidate genes in identifying the genes responsible for preventing cancer in the human lens.

Cancer epidemiologists reserve the term "environmental" to designate factors that are non-hereditary. A number of such environmental factors have been suggested regarding the absence of lens tumors in humans^{1,2,25,26}: the blood aqueous barrier; the lens capsule; lack of blood supply that can be recruited for tumor growth; factors related to lens metabolism, and ultraviolet absorption by the lens. All of these, however, are also found in species that develop lens cancer.

Alternative, but, we believe, far less likely possibilities are 1) lens tumors in other species are caused by oncogenic viruses not present in humans, and 2) the possibility that tumors arising in humans might present as a cataract and be discarded during routine lensectomy, thereby preventing the tumor's recognition in humans.

The fact that rupture of the lens capsule appears to be a major risk factor in lens tumors in animals is intriguing. Trauma involving the lens epithelium in humans is very common because the lens epithelium is traumatized during modern extracapsular cataract extraction; the most commonly performed surgical procedure in humans.²⁷ Despite the frequent surgical injury to the lens epithelium, and its typical benign proliferation postoperatively to form a Soemmerring's ring-type secondary cataract, no benign or malignant lens tumors have been documented. We hypothesize that a genetic protective mechanism exists. Identifying this mechanism may be of value in better understanding the genetics of human cancers.

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References

1. Sachs E, Larsen RL. Cancer and the lens. *American journal of ophthalmology*. 1948; 31(5):561–564. [PubMed: 18861156]
2. Ullrich K, Casson RJ. Does anybody care that the crystalline lens never gets cancer? *Clinical & experimental ophthalmology*. 2013; 41(8):812. [PubMed: 23566233]

3. Mann I. Induction of an Experimental Tumour of the Lens. The British journal of ophthalmology. 1947; 31(11):676–685. [PubMed: 18170388]
4. Seigel GM, Kumer A. The Enigma of Lenticular Oncology. Digital Journal of Ophthalmology. 2001; 7(4)
5. Domazet-Loso T, Klimovich A, Anokhin B, et al. Naturally occurring tumours in the basal metazoan Hydra. Nature communications. 2014; 5:4222.
6. Von Sallmann L, Halver JE, Collins E, Grimes P. Thioacetamide-induced cataract with invasive proliferation of the lens epithelium in rainbow trout. Cancer research. 1966; 26(8):1819–1825. [PubMed: 5923180]
7. Albert DM, Rabson AS, Grimes PA, Von Sallmann L. Neoplastic transformation in vitro of hamster lens epithelium by simian virus 40. Science (New York, NY). 1969; 164(3883):1077–1078.
8. Chen Q, Hung FC, Fromm L, Overbeek PA. Induction of cell cycle entry and cell death in postmitotic lens fiber cells by overexpression of E2F1 or E2F2. Investigative ophthalmology & visual science. 2000; 41(13):4223–4231. [PubMed: 11095619]
9. Zheng HC, Nakamura T, Zheng Y, et al. SV40 T antigen disrupted the cell metabolism and the balance between proliferation and apoptosis in lens tumors of transgenic mice. Journal of cancer research and clinical oncology. 2009; 135(11):1521–1532. [PubMed: 19466455]
10. Mahon KA, Chepelinsky AB, Khillan JS, Overbeek PA, Piatigorsky J, Westphal H. Oncogenesis of the lens in transgenic mice. Science (New York, NY). 1987; 235(4796):1622–1628.
11. Woog J, Albert DM, Gonder JR, Carpenter JJ. Osteosarcoma in a phthisical feline eye. Veterinary pathology. 1983; 20(2):209–214. [PubMed: 6573055]
12. Dubielzig RR. Ocular sarcoma following trauma in three cats. Journal of the American Veterinary Medical Association. 1984; 184(5):578–581. [PubMed: 6706803]
13. Dubielzig RR, Everitt J, Shaddock JA, Albert DM. Clinical and morphologic features of posttraumatic ocular sarcomas in cats. Veterinary pathology. 1990; 27(1):62–65. [PubMed: 2309385]
14. Wong CJ, Peiffer RL, Oglesbee S, Osborne C. Feline ocular epithelial response to growth factors in vitro. American journal of veterinary research. 1996; 57(12):1748–1752. [PubMed: 8950429]
15. Zeiss CJ, Johnson EM, Dubielzig RR. Feline intraocular tumors may arise from transformation of lens epithelium. Veterinary pathology. 2003; 40(4):355–362. [PubMed: 12824506]
16. Carter RT, Giudice C, Dubielzig RR, Colitz CM. Telomerase activity with concurrent loss of cell cycle regulation in feline post-traumatic ocular sarcomas. Journal of comparative pathology. 2005; 133(4):235–245. [PubMed: 16154137]
17. McPherson L, Newman SJ, McLean N, et al. Intraocular sarcomas in two rabbits. Journal of veterinary diagnostic investigation: official publication of the American Association of Veterinary Laboratory Diagnosticians, Inc. 2009; 21(4):547–551.
18. Dickinson R, Bauer B, Gardhouse S, Grahn B. Intraocular sarcoma associated with a rupture lens in a rabbit (*Oryctolagus cuniculus*). Veterinary ophthalmology. 2013; 16(Suppl 1):168–172. [PubMed: 23734573]
19. Mosby's Medical, Nursing, & Allied Health Dictionary. Sixth. Elsevier Health Sciences; 2005.
20. Schonthal HB, Franz-Odenaal TA, Hodel C, et al. The zebrafish mutant bumper shows a hyperproliferation of lens epithelial cells and fibre cell degeneration leading to functional blindness. Mechanisms of development. 2010; 127(3–4):203–219. [PubMed: 20117205]
21. Aose, M.; Greiling, TMS.; Djajadi, HR., et al. The Formation of a Second Lens in the Mutant Zebrafish, Occhiolino. Association for Research in Vision and Ophthalmology; Fort Lauderdale, FL: May 3. 2010 2010
22. Hanahan D, Weinberg RA. The hallmarks of cancer. Cell. 2000; 100(1):57–70. [PubMed: 10647931]
23. Tomasetti C, Vogelstein B. Cancer etiology. Variation in cancer risk among tissues can be explained by the number of stem cell divisions. Science. 2015; 347(6217):78–81. [PubMed: 25554788]
24. Friend SH, Schadt EE. Translational genomics. Clues from the resilient. Science. 2014; 344(6187):970–972. [PubMed: 24876479]

25. Mal'tsev EV. Hypothetic "tumorous immunity" of the lens. *Oftalmologicheskii zhurnal*. 1977; 32(3):231–233. [PubMed: 876607]
26. Folkman J, Merler E, Abernathy C, Williams G. Isolation of a tumor factor responsible for angiogenesis. *The Journal of experimental medicine*. 1971; 133(2):275–288. [PubMed: 4332371]
27. Report to the Congress: Medicare Payment Policy. 2015. p. 2015<http://www.medpac.gov/documents/-reports>. Accessed 3/31/2015

Figure 1.

(A) Iris and anatomical angle demonstrate lens epithelial proliferation and deposition of lens material and basement membrane on the posterior and anterior surfaces of the iris (arrow). This patient developed angle closure (asterisk). Also note the Soemmering's ring cataract. Hematoxylin and Eosin (H&E) staining. Photo used courtesy of Alan D. Proia, MD (Duke University School of Medicine). (B) Anterior pyramidal cataract with entrapped lens epithelial cells and basement membrane deposition among avascular fibrous material (arrow). H&E staining. Photo used courtesy of Harry S. Brown, MD (University of Arkansas)

Figure 2.

(A) Clinical photograph of a feline eye containing a lens tumor. The globe also shows changes resulting from trauma and uveitis, and the presence of a developing neoplasm. (B) Feline lens tumor. Photomicrograph showing the wrinkled remnants of lens capsule and neoplastic cells both inside (In) and outside (Out) of the lens capsule. A PAS positive membrane suggestive of lens capsule surrounding individual cells or clusters of cells. Alcian blue and PAS staining.

Figure 3.

Rabbit eye with lens tumor. (A) Low magnification photomicrograph shows the wrinkled lens capsule. The arrowhead indicates a tear in the lens capsule. Neoplastic tissue is seen both within (*) and outside of the lens capsule. H&E staining. (B) High magnification of same tumor sampled from a deeper section with neoplastic cells present both inside the lens capsule (top) and outside the lens capsule (below). Numerous tumor cells are surrounded by a Periodic acid-Schiff (PAS) positive membrane suggestive of lens capsule. Alcian blue PAS and staining.

Figure 4.

King penguin lens tumor. (A) Photomicrograph of neoplastic and proliferating lens epithelial cells within the wrinkled lens capsule. Polygonal neoplastic cells are surrounded by a thin PAS positive membrane suggestive of lens capsule. Alcian blue and PAS staining. (B) Photomicrograph showing polygonal neoplastic lens epithelial cells embedded in the corneal lamellar stroma. They demonstrate the deposition of PAS positive membranes interpreted as lens capsule. Alcian blue and PAS staining.

Table 1

Summary of key features in previously unreported cases from COPLOW

Genus/Species	Number of cases	Age (years)		Sex	Time between traumatic event and the development of		Metastasis	Extraocular invasion
		Median	Range		Median	Range		
<i>Felis catus</i>	234	12	0.75–20	138 male, 83 female, 13 unknown	5 (n=196)	0.83–17	Present (n=3); Absent (n=9); Unknown (n=226)	Present (n=140); Absent (n=81); Unknown (n=13)
<i>Aptenodytes patagonicus</i> (King penguin)	1	37	37	1 male	2.5		No metastases noted at autopsy	Unknown
<i>Canis lupus familiaris</i> (Apricot poodle)	1	10	37	1 male	Unknown		No workup described	None

Table 2

Summary of key features in published cases of lens tumors in animals

Genus/Species	Publication	Age (years)	Sex	History of eye trauma	Time between traumatic event and the development of lens tumor	Metastasis	Extraocular Invasion
1 felis catus (domestic cat)	Woog J, et. al 1983	10	F	Positive	8 years	Not stated	Orbital invasion
3 felis catus (domestic cats)	Dubielzig DD, et. al 1984	10, 12, 13	M, F, M	Positive	10 years, "several years", Not stated	Not stated	Optic nerve invasion in all three cases
13 felis catus (domestic cats)	Dubielzig DD, et. al 1990	Not stated	Not stated	Positive	"many months" to 10 years	One cat, disseminated	Optic nerve invasion in 8 of 12 cases
9 felis catus (domestic cats)	Zeiss CJ, et. al 2003	Not stated	Not stated	5 cases	Unknown	Not stated	Not stated
2 Oryctolagus cuniculus (Rabbits)	McPherson L, et. al 2009	5, 8	F, M	Not stated	Unknown	Not stated	Extrascleral extension into extraocular muscles in both cases
1 Oryctolagus cuniculus (Rabbit)	Dickenson R, et. al 2013	7	F	Not stated	Unknown	Not stated	Not stated