Retinal Astrocytic Hamartomas: Unexpected Findings in a Giant Panda

We report the unexpected findings of bilateral retinal astrocytic hamartomas in a giant panda. The eyes of Hsing-Hsing, a giant panda that had renal failure, chronic hypertension, degenerative joint disease, and progressive ulcerative keratitis, were examined grossly and histologically. Most of the findings were related to Hsing-Hsing’s debilitated condition or to normal anatomic variations between giant pandas and humans. These findings included anatomic features typical of a carnivore and metastatic calcification of the cornea and tapetum secondary to renal failure, retinal arteriolar sclerosis and hemorrhage due to hypertension, and bilateral corneal ulcers due to septicemia. Bilateral retinal astrocytic hamartomas were also unexpectedly found. The clinical importance of retinal astrocytic hamartomas is discussed.

Report of a Case. We report a case of retinal astrocytic hamartomas of unknown cause in the eyes of a 28-year-old male giant panda (Ailuropoda melanoleuca). The eyes were obtained from Hsing-Hsing (Figure 1), who was euthanized at the Smithsonian National Zoological Park (Washington, DC) because of advanced renal failure leading to several degenerative conditions including chronic renal failure, degenerative joint disease, chronic epistaxis, decreased mobility, progressive keratitis, and bilateral corneal ulcers with reduced vision. The Smithsonian National Zoological Park (Washington, DC) submitted both eyes to the ophthalmic pathology division at the Armed Forces Institute of Pathology (Washington, DC) for examination in November 1999.

Hsing-Hsing and his mate Ling-Ling came to the United States in 1972 in exchange for a pair of musk oxen, as gestures of goodwill between the United States and the People’s Republic of China. The pandas were instant celebrities seen by millions of people and taken into the hearts of children everywhere.

Ling-Ling died of heart failure in 1992. At her death, she and Hsing-Hsing were aged 23 years and believed to be the oldest giant pandas living outside of the People’s Republic of China. Hsing-Hsing developed arthritis and was castrated to treat a testicular tumor at the age of 26 years. During the last year, he displayed remarkable resilience despite kidney failure and associated symptoms.

Both eyes included findings related to Hsing-Hsing’s physical state, in addition to the unexpected finding of retinal astrocytic hamartomas. There were no other lesions supportive of tuberous sclerosis. There have been only 2 previous reports of ocular pathologic findings in giant pandas, and neither described retinal astrocytic hamartomas.1,2

Astrocytic hamartomas are benign tumors. In humans, these tumors are more commonly associated with tuberous sclerosis (Bourneville disease) and less frequently seen in neurofibromatosis 1 (von Recklinghausen disease) and neurofibromatosis 2 or as isolated occurrences.3,4 These hamartomas are usually found in the retina and optic disc. Because of the strong association between tuberous sclerosis and retinal astrocytic hamartoma in humans,
evidence of tuberous sclerosis is helpful in the diagnosis of astrocytic hamartoma.

Findings. The Left Eye. At gross examination, the left eye measured $18 \times 18 \times 19$ mm, with the cornea measuring $15 \times 15$ mm. There was a central epithelial defect with a stromal opacity that measured $5 \times 3$ mm and band keratopathy. The eye was opened vertically to reveal the panda’s large lens, which had nuclear sclerosis and posterior subcapsular opacities. In the retina, there were 2 small lesions near the optic disc. The first, located inferior to the optic disc, was a $1 \times 3$-mm yellowish stromal opacity with 2 small foci of orange pigment in it, and the second, located superotemporally, was a round hemorrhagic nodule (Figure 2).

Microscopically, the panda’s cornea normally has no Bowman layer. There was extensive calcification of the superficial stroma. Centrally, the cornea was ulcerated, with an infiltrate of acute inflammatory cells in the surrounding stroma. Within the inflamed cornea, Brown-Hopps stain demonstrated bacilli consistent with *Escherichia coli* that was cultured from Hsing-Hsing’s blood. The filtration angle was the type seen in carnivores, with the ciliary body split into 2 leaves by a deep cleft that contained polymorphonuclear leukocytes (Figure 3). The sclera contained a plexus of vessels (circle of Hovius) adjacent to the ciliary body, which drained the aqueous humor into the surface veins. Several cysts were formed by the split between the pigmented and nonpigmented ciliary epithelium or by detachment of the iris pigment epithelium (Figure 3).

The iris stroma was deeply pigmented, and early rubeosis iridis was present. The iris-pigmented epithelium was vacuolated, but periodic acid–Schiff stain did not demonstrate glycogen within the vacuoles. There were 2 small collagenous plaques beneath the posterior lens capsule. The panda’s retina was vascularized, and some of the retinal arterioles were sclerotic, probably secondary to hypertension. The panda had no fovea and no central retinal vessels within the optic nerve. The retinal vessels emanated from the circle of ciliary vessels that surrounded the optic nerve. The small white retinal lesion noted grossly is most consistent with a tumor composed of fibrillar astrocytes. Within the lesion were scattered macrophages containing lipofuscin. The astrocytes replaced the retinal pigment epithelium beneath the lesion. Retinal folds surrounded the tumor (Figure 4). The hemorrhagic lesion was a
The Right Eye. The right eye measured $19/20 \times 20/20$ mm. The cornea measured $15/15$ mm. The cornea was clear except for a central epithelial defect with a stromal opacity measuring $5 \times 3$ mm and band keratopathy. In the retina, about 4 mm inferior to the optic nerve head, was a gray-white $1 \times 2$-mm lesion with orange pigment at its center (Figure 6).

Microscopically, the superficial corneal stroma contained extensive calcification. There was a central ulcer with an infiltrate of acute inflammatory cells in the surrounding corneal stroma. Brown-Hopps stain revealed bacilli within the inflamed cornea. Polymorphonuclear leukocytes were seen within the ciliary body cleft. Several cysts were formed by splitting between the pigmented and nonpigmented ciliary epithelium and detachment of the iris pigment epithelium. The iris stroma was deeply pigmented, with inflammatory cells adherent to the anterior surface. Early rubeosis iridis was present. The iris pigment epithelium contained vacuoles, but no glycogen was visible with periodic acid–Schiff stain. Some retinal arterioles showed hypertensive sclerotic changes.

The small retinal lesion noted grossly was most consistent with proliferated fibrillar astrocytes (Figure 7 and Figure 8). The astrocytes replaced the retinal pigment epithelium (Figure 7). In the center of the lesion were clustered macrophages containing lipofuscin (Figure 8). Results of immunohistochemical analysis with anti-human glial fibrillary acidic protein (GFAP) were negative in both the tumor and the retinal Muller cells. In the upper half of the eye, the choroid had a cellular tapetum that was focally calcified.

Comment. All of what is known about ocular histologic findings in giant pandas is based on reports of pandas that lived and died in captivity. There have been only 2 previous reports of histologic findings in the eyes of giant pandas. Ashton1 reported the normal findings in the giant panda’s eye and the presence of cysts of the ciliary body and peripheral retina, which had degenerated probably because of old age. Similar cysts were seen in the eyes that we examined (Figure 3). Lopez et al2 reported hemangiosarcoma of borderline malignancy on the outer limbus of the left eye in a giant panda from a zoo in Spain. Some of the findings we report here were expected because of the panda’s debilitated state, and some were unique in that they probably represent sporadic unexpected findings. Both provide additional information about ocular disease in pandas.

The giant panda is an unusual species because it is an herbivorous carnivore; therefore, it is not surprising that pandas have the ciliary body and cellular tapetum of a carnivore. On the basis of DNA comparisons, the giant panda is classified as a member of the bear family (Ursidae) and thus is a true carnivore. Other bear species are considered omnivores, but the giant panda is much more selective in its diet and lives almost exclusively on bamboo. This highly selective diet may have contributed to the declining population of giant pandas to near extinction, as humankind has con-
verted bamboo forests to cropland in areas populated by pandas.

The findings of metastatic calcification, hypertension (retinal arteriolar sclerosis and aneurysm), and infection (corneal ulcers and cyclitis) are all sequelae of renal failure and contributed to the panda’s debilitated condition. The retinal hamartomas are surprising and are similar to the ones seen in humans. In humans, astrocytic hamartomas of the retina and optic disc are usually associated with tuberous sclerosis. These are usually congenital lesions that arise from tissue that is present normally and represent aberrations of tissue formation and maturation.

Differential diagnosis of these retinal tumors includes tumor of the retinal pigment epithelium or tapetum. Both of the panda’s tumors arose in the inferior part of the eye where the tapetum is not present. This finding makes the possibility of a tumor of the tapetum unlikely. Furthermore, in a search of Grateful Med, a tumor of the tapetum has not been described in any species. Because antibody to panda GFAP is not available, we attempted to perform immunohistochemical analysis with anti-human GFAP antibody. Because neither the hamartoma nor the panda’s Müller cells reacted, we concluded that panda GFAP does not react with the anti-human GFAP antibody and that the test results were inconclusive. Human tumors of the retinal pigment epithelium have thick continuous basement membranes that are easily detected with the periodic acid–Schiff stain. Periodic acid–Schiff staining of these retinal tumors did not reveal thick basement membranes. One of us (I.W.M.) has seen a human case of tuberous sclerosis in which glial cells from the retinal astrocytic hamartoma replaced the retinal pigment epithelium. These observations and the appearance of the tumors are most consistent with Hsing-Hsing’s 2 tumors being astrocytic.

Although the evidence is conclusive that these 2 tumors were astrocytic, the question of whether they were congenital or acquired tumors is not as well answered.

Factors favoring a congenital tumor are the replacement of the retinal pigment epithelium by tumor cells and the similarity of the retinal folds surrounding the tumor to the folds seen in retinal dysplasia. Factors favoring an acquired retinal astrocytic hamartoma are Hsing-Hsing’s advanced age and the lack of an association with a phakomatosis.

Some investigators state that the presence of an astrocytic hamartoma of the retina in humans is suggestive of tuberous sclerosis. Others conclude that isolated retinal hamartomas are sporadic in the absence of other signs of tuberous sclerosis. The associated findings in humans with tuberous sclerosis include the following: cerebral benign tuberous astrocytic tumors, seizures, mental retardation, shagreen patches, subungual fibromas, café-au-lait spots, and vitiligo. However, in Hsing-Hsing, no other signs of tuberous sclerosis were seen at autopsy. Ulbright et al discussed the differentiation of sporadic tumors from phakomatosis-associated tumors in humans. They concluded that of the 42 previously documented human cases of benign astrocytic tumors of the retina, 57% of patients had tuberous sclerosis, 14% had neurofibromatosis, and 29% did not have a phakomatosis.

Figure 6. Right eye. High-power gross photograph of retinal astrocytic hamartoma. Orange pigment is present in the center of the tumor.

Figure 7. Right eye. Low-power photomicrograph of retinal astrocytic hamartoma. Tumor cells have replaced the retinal pigment epithelium (hematoxylin-eosin).
Retinal astrocytic hamartomas unassociated with a phakomatosis tend to be single lesions in people with a mean age of 27 years, as compared with a mean age of 14.5 years in people with either tuberous sclerosis or neurofibromatosis. With the exception of finding the 2 tumors in Hsing-Hsing, most of the other data indicate that if these astrocytic hamartomas were found in humans they would not be associated with a phakomatosis. Ulbright et al found that in 11 of 11 patients without a phakomatosis the retinal hamartomas were multiple.

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**Adverse Ocular Effects From Over-the-Counter Lice Shampoo**

Lice R Gone (Safe Solutions Inc, Marne, Mich) is available in the United States as a shampoo for the elimination of head lice. The same formulation is available in the United Kingdom as Not Nice to Lice (Safe Solutions UK, Leighton Buzzard, England). We report here 15 cases of severe ocular irritation, including 7 reports of corneal abrasion, secondary to use of this over-the-counter product. Reports were submitted to the National Registry of Drug-Induced Ocular Side Effects and the Food and Drug Administration.

Infestations of head lice can be treated with various agents. Safe Solutions Inc states on its Web site (http://www.licergone.com) that its Lice R Gone shampoo is "essentially harmless to people" and "totally effective against head lice and their nits." Ingredients from the product label include "purified water, anionic/nonionic surfactant blend, glycerin, enzymes, peppermint oil, and peace of mind." The manufacturer states that the protease enzymes present in the shampoo will safely destroy insect exoskeletons.

**Report of Cases.** The 15 case reports are summarized in the Table. The mean ± SD age of patients suffering adverse reactions was 20 ± 15 years (range, 2-54 years). There were 3 males, 7 females, and 5 with sex unknown. Seven subjects' symptoms resolved when they discontinued use of the Not Nice to Lice shampoo (positive dechallenge), and 6 of these subjects' symptoms resolved within 24 hours. All adverse reactions were immediate and included 7 cases of corneal abrasions and 7 separate cases of severe eye irritation. Six patients described severe ocular pain and 6 experienced abnormal vision, with 1 report of blindness (no follow-up data). Six patients instituted immediate irrigation with water, and 1 patient was treated with diphenhydramine hydrochloride. The amount of shampoo used by all patients was per manufacturer instructions.

**Comment.** The 15 case reports of adverse ocular effects reported here should alert clinicians to the possibility of serious ocular complications secondary to use of this over-the-counter preparation. It may not be unusual for eye irritation to occur when a topical solution is used around the eyes (ie, lice shampoo on the head), but it is unusual for the reaction to cause more than transient eye irritation or red eye. Specifically, reports of corneal abrasions are worrisome as patients will need to seek emergent treatment because of severe ocular pain and the risk of a bacterial infection superimposed on the corneal epithelial defect. Corneal abrasions may be due to the proteolytic enzymes present in the shampoo preparation.

Not Nice to Lice is registered as a medical device in the European Union; the manufacturer states that the shampoo will safely destroy insect exoskeletons.