The Occurrence and Proposed Significance of Schnabel Cavernous Degeneration in Uveal Melanoma

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Uveal melanoma (UM) is the most common primary intraocular malignant neoplasm in adults, occurring in 7 per million per year in the United States.1 Multiple chromosomal abnormalities such as monosomy 3 and several genetic mutations have been reported in association with this tumor.2-5 UV light, environmental factors, trauma, and viruses6-10 have been implicated as the underlying cause. Furthermore, uveal nevus, congenital ocular or ocuodermal melanocytosis, and benign diffuse uveal melanocytic proliferation have been suggested as predisposing factors.11-14

It remains uncertain whether there is an association between Schnabel cavernous degeneration (SCD) and UM. Schnabel cavernous degeneration is a rare histopathologic entity that appears as rarefaction and spongiform degeneration of the optic nerve substance posterior to the lamina cribrosa. Associated with a loss of myelin and axons, it is characterized by the presence of hyaluronidase-sensitive acidic mucopolysaccharides within the cavernous spaces.15-17 In a case report by Albert and colleagues,18 a bilateral SCD of undetermined origin was found in a 26-year-old man with bilateral metastatic UM and no history of glaucoma. Sudden and pronounced elevation of intraocular pressure, forcing the vitreous into the cavernous spaces, was historically the main proposed mechanism for SCD.19-25 Subsequently, marked reduction of blood flow of the optic nerve head and resultant ischemia have been proposed as the most important factors in SCD.26

IMPORTANCE Schnabel cavernous degeneration (SCD) has been observed in eyes with uveal melanoma (UM), but, to our knowledge, a definitive study establishing the association between SCD and UM has not been conducted.

OBJECTIVE To explore an association between SCD and UM.

DESIGN, SETTING, AND PARTICIPANTS A historical cohort analysis was performed using histologic slides and related clinical records of cases from the Collaborative Ocular Melanoma Study and Eye Pathology Laboratory at the University of Wisconsin, including 1985 UM eyes, 517 eye bank eyes, and 155 enucleated glaucomatous eyes.

MAIN OUTCOMES AND MEASURES The prevalence of SCD was calculated and compared between each group; subgroup analysis was also conducted of eyes with and without SCD for the prevalence of glaucoma.

RESULTS Schnabel cavernous degeneration was seen in 17 (0.9%) UM eyes, 9 (1.7%) eye bank eyes, and 2 (1.3%) enucleated glaucomatous eyes. No difference was detected between the prevalence of SCD in UM eyes and eye bank eyes (odds ratio [OR], 0.49; 95% CI, 0.22-1.10) or enucleated glaucomatous eyes (OR, 0.66; 95% CI, 0.35-2.89). Subgroup analysis, performed on 421 UM eyes, provided sufficient clinical information to definitively establish the presence or absence of glaucoma. Of the 95 (22.6%) eyes with glaucoma, 11 (11.6%) revealed histopathologic evidence of SCD. Compared with enucleated end-stage glaucoma eyes, this represents a 10-fold increase in SCD in UM eyes with glaucoma (OR, 10.10; 95% CI, 2.17-46.26). The prevalence of glaucoma in UM eyes with SCD, however, was respectively 7- and 15-fold higher than the prevalence of glaucoma in SCD-negative UM eyes (OR, 6.98; 95% CI, 2.51-19.43) and SCD-positive eye bank eyes (OR, 14.67; 95% CI, 1.46-146.97).

CONCLUSIONS AND RELEVANCE Although an association between SCD and UM was not confirmed, subgroup analysis did reveal an increased incidence of SCD in eyes with both UM and glaucoma. This suggests that the occurrence of glaucoma may increase the risk of SCD in eyes with UM.
series by Giarelli et al, SCD was found predominantly in patients who had severe vascular anomalies but no clinical diagnosis of glaucoma. This suggested that a chronic vasculocclusive disease of the proximal optic nerve may be a more significant pathophysiologic factor in SCD in old age than an elevated intraocular pressure. Although unrecognized acute glaucoma, hypotension-induced ischemia, and congenital optic nerve malfunction were considered possible pathogenetic factors in the case by Albert et al, the potential for a pathophysiologic correlation between UM and SCD could not be eliminated. In addition to the case by Albert et al, in a histopathologic report of 12 UM eyes enucleated for sustained high intraocular pressure, Knox et al found SCD in 1 patient with a cavernous infarction of the optic nerve. Schnabel cavernous degeneration was also occasionally noted in UM eyes in the Collaborative Ocular Melanoma Study (COMS), but, to our knowledge, no attempt at establishing prevalence or reporting these cases has been made. In the present study, we reexamined the COMS eyes as well as eyes with UM submitted to the Eye Pathology Laboratory at the University of Wisconsin to explore any possible association between the two entities.

Methods

Archived hematoxylin and eosin–stained slides and available medical records of enucleated eyes with UM from the COMS, as well as histologic slides and medical records of eyes with UM submitted to the Eye Pathology Laboratory at the University of Wisconsin, were reviewed. Histopathologic slides and medical records of eye bank eyes with no known ocular disease and enucleated tumor-free end-stage glaucoma eyes submitted to the Eye Pathology Laboratory at the University of Wisconsin served as our control groups. All slides were examined for the presence of spongiform changes of the disk and optic nerve. In cases with changes suggestive of SCD, the hematoxylin and eosin–stained slides were destained with alcohol and restained with Alcian blue to confirm the presence of acid mucopolysaccharides in the spongiform areas of the optic nerve. Institutional review board approval was obtained from the University of Wisconsin.

The prevalence of SCD in eyes with UM, eye bank eyes, and enucleated glaucomatous eyes was calculated. The association between SCD and UM was investigated using an odds ratio (OR) χ² test. Furthermore, the severity of SCD was graded on a scale of I to IV. When the spongiform degeneration involved less than 25% of the diameter of the optic nerve, it was given a grade I designation, while grades II, III, and IV were assigned to cases with involvement of 25% to 50%, 51% to 75%, and more than 75% of the optic nerve diameter, respectively.

Eyes with UM and eye bank eyes were also evaluated in a subgroup analysis for the presence of glaucoma. The eyes were assumed to have glaucoma when sufficient clinical information clearly stated the diagnosis of glaucoma and at least 2 of the following histopathologic findings: (1) optic nerve cupping on histopathologic evaluation, (2) severe retinal ganglion cell loss, and (3) extensive angle closure as evidenced by iris neovascularization and/or peripheral anterior synechiae on histopathologic examinations. The prevalence of glaucoma in the UM eyes with SCD was then compared with UM eyes without SCD and eye bank eyes with SCD. Last, the prevalence of SCD in UM eyes with glaucoma was compared with the prevalence of SCD in enucleated glaucomatous eyes using the statistical analysis described earlier.

Results

Population Studied and Demographic Data
The histopathologic slides and related records of 1985 UM eyes from 1985 patients (1759 eyes from COMS and 226 eyes from the Eye Pathology Laboratory at the University of Wisconsin), 517 eye bank eyes from 501 individuals, and 155 enucleated glaucomatous eyes from 155 patients were examined. Demographic data from the study groups, as well as the prevalence and grading of SCD in each group, are illustrated in Table 1. The mean age of the patients in the UM group was 59 years, and 56.1% were male. The mean age of the eye bank and enucleated glaucomatous groups was 75 and 49 years, respectively. In total, 57.8% of the eyes in the eye bank group and 51.9% in the enucleated glaucomatous group were from males.

In the subgroup analysis, 421 UM eyes had sufficient clinical information to determine with confidence the presence or absence of glaucoma. The mean age of the patients in this group was 62 years, and 53% were male (Table 2).

SCD of the Optic Nerve
Schnabel cavernous degeneration was detected in 17 of 1985 (0.9%) UM eyes, 9 of 517 (1.7%) eye bank eyes, and 2 of 155 (1.3%) enucleated glaucomatous eyes. All SCD cases showed Alcian blue–positive acid mucopolysaccharides within the cavernous spaces of the optic nerve (Figure). The mean age of SCD-positive cases in the UM, eye bank, and enucleated glaucomatous groups was 67, 84, and 68 years, respectively (Table 1),

<table>
<thead>
<tr>
<th>Studied groups</th>
<th>No.</th>
<th>Sex, %</th>
<th>Age, Mean, y</th>
<th>M:F Ratio</th>
<th>SCD Prevalence, No. (%)</th>
<th>Age, Mean, y</th>
<th>M:F Ratio</th>
<th>SCD Grading in Eyes, No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uveal melanoma eyes</td>
<td>1985</td>
<td>56.1</td>
<td>59</td>
<td></td>
<td>17 (0.9)</td>
<td>67</td>
<td>9.8</td>
<td>14 (82.3) 3 (17.6)</td>
</tr>
<tr>
<td>Eye bank eyes</td>
<td>517</td>
<td>57.8</td>
<td>75</td>
<td></td>
<td>9 (1.7)</td>
<td>84</td>
<td>5.4</td>
<td>4 (44.4) 5 (55.6)</td>
</tr>
<tr>
<td>Enucleated glaucomatous eyes</td>
<td>155</td>
<td>51.9</td>
<td>49</td>
<td></td>
<td>2 (1.3)</td>
<td>68</td>
<td>1.1</td>
<td>2 (100) 0</td>
</tr>
</tbody>
</table>

Abbreviation: SCD, Schnabel cavernous degeneration.
with an even distribution between the two sexes. Compared with the eye bank and enucleated glaucomatous eyes, there was no statistical difference between the prevalence of SCD in UM eyes and eye bank eyes (OR, 0.49; 95% CI, 0.22-1.10; \( z = 1.73; P = .08 \)) or enucleated glaucomatous eyes (OR, 0.66; 95% CI, 0.15-2.89; \( z = 0.55; P = .58 \)).

Prevalence of Glaucoma in the Studied Groups
In the subgroup analysis, 95 of 421 (22.6%) UM eyes fulfilled our criteria for glaucoma, of which 11 (11.6%) revealed histopathologic evidence of SCD. The mean age of SCD-positive cases in glaucoma-positive and glaucoma-negative UM eyes was 66 and 61 years, respectively (Table 2), with an even distribution between the two sexes. All the glaucomatous UM eyes with SCD and both cases of enucleated glaucomatous eyes with SCD revealed degrees of iris neovascularization. Compared with the enucleated glaucomatous eyes, there was a 10-fold increase in SCD in glaucomatous UM eyes (OR, 10.10; 95% CI, 2.17-46.26; \( z = 2.95; P = .003 \)). In addition, there was a 7-fold increase in the prevalence of glaucoma in the SCD-positive eyes compared with the SCD-negative eyes in the UM group (OR, 6.98; 95% CI, 2.51-19.43; \( z = 3.72; P < .001 \)). Glaucoma was found in 1 of 517 (0.2%) eye bank eyes. An approximately 15-fold increase in the prevalence of glaucoma was also discovered in the UM eyes with SCD compared with the eye bank eyes with SCD (OR, 14.67; 95% CI, 1.46-146.97; \( z = 2.28; P = .02 \)).

Grade of SCD and Miscellaneous Histologic Findings
Using the previously described grading system, advanced SCD (grades III and IV) predominated in the eye bank eyes com-

Table 2. Demographic Data and the Prevalence of SCD in a Subgroup of 421 Uveal Melanoma Eyes With Sufficient Clinical Information Regarding the Presence or Absence of a Diagnosis of Glaucoma

<table>
<thead>
<tr>
<th>Subgroup of Patients With Uveal Melanoma</th>
<th>No. of Eyes</th>
<th>Age, Mean, y</th>
<th>Male Sex, %</th>
<th>SCD Prevalence, No. (%)</th>
<th>Age, Mean, y</th>
<th>Male Sex, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Without glaucoma</td>
<td>326</td>
<td>62</td>
<td>53.8</td>
<td>6 (1.8)</td>
<td>61</td>
<td>52.2</td>
</tr>
<tr>
<td>With glaucoma</td>
<td>95</td>
<td>63</td>
<td>51.8</td>
<td>11 (11.6)</td>
<td>66</td>
<td>55.1</td>
</tr>
</tbody>
</table>
pared with the UM group (55.6% vs 17.6%; \( P = .05 \)). None of the enucleated glaucomatous eyes had advanced SCD.

Discussion

In our study, there did not appear to be an association between SCD and UM compared with tumor-free enucleated eye bank eyes and end-stage glaucoma eyes. A high prevalence of glaucoma, however, was demonstrated in the UM eyes with SCD compared with the UM eyes without SCD and eye bank eyes with SCD. This association suggests that glaucoma may be a risk factor in UM eyes for the development of SCD, especially in the form of neovascular glaucoma, which may be associated with a more short-term course. It is interesting that the prevalence of SCD in UM eyes with glaucoma was significantly higher than that of enucleated glaucomatous eyes, indicating that other factors related to UM may play a role in the pathogenesis of SCD.

Cavernous spaces of SCD possess a hyaluronidase-sensitive mucopolysaccharide. This material, demonstrated to be more frequent in the corneoscleral trabeculae of melanoma eyes compared with autopsy eyes, was associated with abnormal cystic changes in the trabecular area. Whether this compound is locally produced or originated from the vitreous has been a matter of debate. It seems that UM has the same effect on the lamina cribrosa beams as it does on corneoscleral trabeculae. In the presence of an abnormal laminar beam microstructure, a ball-valve mechanism may develop, allowing a 1-way flow of the vitreous to the retrolaminar part of the optic nerve in the presence of glaucoma. The herniated vitreous, as the source of hyaluronic acid in the cavernous spaces, may then not only compress the neural filaments but also obliterate the pial septa and induce ischemic necrosis of the optic nerve bundles.

Another possible pathogenetic factor for the occurrence of SCD in UM eyes parallels the process seen in melanoma-associated spongiform scleropathy, a noninflammatory degeneration of the scleral collagen bundles with spongiotic structures observed in UMs. Matrix metalloproteinases, synthesized by the melanoma cells and/or by the melanoma stromal fibroblasts, act as the major mediators of disintegration of scleral collagen bundles into loose fibers in melanoma-associated spongiform scleropathy. The same degenerative mechanism may be involved in the pathogenesis of SCD in UM, in which increased levels of the proteolytic enzymes such as matrix metalloproteinases or downregulation of endothelin in eyes with UM may damage and weaken the collagen fibrils of the lamina cribrosa. This may induce a vulnerable area when glaucoma occurs, which may lead to spongiform degeneration of the retrolaminar optic nerve in eyes with UM.

Compared with the UM eyes, the higher prevalence and severity of SCD in eyes in the eye bank group, which were older, is likely due to age-related changes such as chronic ischemia in the optic nerve that can occur as the result of senile changes and atherosclerosis. Moreover, the retrolaminar portion of the optic nerve is nourished by a complex vascular system composed of end arteries, which makes this area vulnerable to ischemic involution.

The limitations of our study included its retrospective nature and limited clinical information with regard to the presence or absence of glaucoma in most non-SCD glaucoma eyes in the COMS cases. Therefore, our investigations were limited to the analysis of a subgroup of UM cases that had sufficient clinical information with a clear statement about the presence or absence of glaucoma.

Conclusions

Although no association was found between SCD and UM, spongiform changes of the optic nerve may occur in the UM eyes, especially when the eyes become glaucomatous. It can be suggested that in UM eyes with glaucoma, there may be an increased risk of spongiform degeneration of the optic nerve.

**REFERENCES**