Transforming Growth Factor β in Retinoblastoma-Related Cataract

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Objective: To analyze the histopathology and expression of transforming growth factor β (TGF-β) in retinoblastoma with and without cataractous changes.

Methods: Twenty patients with unilateral retinoblastoma underwent enucleation. None of these patients had received preoperative chemotherapy or radiotherapy. Formalin-fixed, paraffin-embedded tissue sections were examined histologically for the presence of morgagnian globules or liquefaction of lens fibers; TGF-β was immunolocalized using an anti-TGF-β antibody.

Results: Two globes showed several morgagnian globules and liquefaction of the lens fibers, representing cataractous changes. One patient had posterior subcapsular cataract; the other, anterior polar cataract. In both cases, prominent cytoplasmic immunoreactivity for TGF-β was detected in retinoblastoma cells. In contrast, 3 patients showed histologic evidence of minor cataractous changes. The globes with either minor or no cataractous changes revealed minimal to no expression of TGF-β.

Conclusions: These results suggest that TGF-β produced by retinoblastoma cells may induce cataract formation.

Clinical Relevance: The growth factors produced by retinoblastoma cells may lead to associated pathologies, such as cataracts, in the ocular structures. This study implies that when a child presents with a unilateral cataract, retinoblastoma should be excluded as the primary diagnosis.

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Table. Clinicopathologic Characteristics of Retinoblastoma Cases

<table>
<thead>
<tr>
<th>Case No./Sex/Age, y</th>
<th>Eye</th>
<th>Lens</th>
<th>Morgagnian Globules</th>
<th>Tumor Infiltration</th>
<th>Necrosis</th>
<th>Tumor Cells, %</th>
<th>TGF-β Positive Cells (%)</th>
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</thead>
<tbody>
<tr>
<td>1/4/2</td>
<td>L</td>
<td>PSC</td>
<td>+ +</td>
<td>+ +</td>
<td>12 × 9</td>
<td>26</td>
<td>28</td>
</tr>
<tr>
<td>2/4/1</td>
<td>R</td>
<td>APC</td>
<td>+ +</td>
<td>+ +</td>
<td>12 × 10</td>
<td>49</td>
<td>50</td>
</tr>
<tr>
<td>3/4/1</td>
<td>L</td>
<td>Minor</td>
<td>+</td>
<td>−</td>
<td>16 × 11</td>
<td>54</td>
<td>95</td>
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<tr>
<td>4/4/1</td>
<td>L</td>
<td>Minor</td>
<td>+</td>
<td>−</td>
<td>14 × 14</td>
<td>68</td>
<td>133</td>
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<tr>
<td>5/4/1</td>
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<td>+</td>
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<td>−</td>
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<td>−</td>
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<td>−</td>
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<td>50</td>
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<td>63</td>
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<td>−</td>
<td>17 × 13</td>
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<td>−</td>
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<td>−</td>
<td>−</td>
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<td>−</td>
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<td>16/4/1</td>
<td>L</td>
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<td>−</td>
<td>−</td>
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<tr>
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<td>−</td>
<td>14 × 10</td>
<td>9</td>
<td>13</td>
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<td>−</td>
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<td>9</td>
</tr>
<tr>
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<td>−</td>
<td>−</td>
<td>13 × 4</td>
<td>49</td>
<td>25</td>
</tr>
<tr>
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<td>−</td>
<td>−</td>
<td>11 × 9</td>
<td>47</td>
<td>46</td>
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</table>

**STATISTICAL ANALYSIS**

Statistical evaluations were performed using the t test. Significance for all tests was P < .05.

**RESULTS**

**DEFINITE CATARACT ASSOCIATED WITH RETINOBLASTOMA IN 2 CASES**

The Table summarizes the clinicopathologic profiles that were revealed in this study. Two retinoblastoma cases showed histologic evidence of cataract (cases 1 and 2). One 2-year-old girl (case 1) and one 1-year-old girl (case 2) with both diagnosed retinoblastoma and neovascular glaucoma in the left and right eyes, respectively, underwent enucleation. No systemic anomalies or metabolic disorders were observed. Neither of the patients had cataracts in the unaffected eyes. In each of the affected eyes, the anterior chamber was shallow and the angle was closed. The iris revealed rubeosis iridis. Marked newvascularization of the iris was present with ectropion uvea. The vitreous cavity was partially obliterated by a grayish-white mass arising from the retina.

In case 1, the lens showed significant cataractous changes, forming morgagnian globules within the entire cortex with the exception of the anterior portion (Figure 1A and B). Posteriorly, wide liquefaction of the lens fibers was seen (Figure 1B and C), while the nucleus remained intact. The posterior lens capsule was thickened where lens epithelial cells migrated (Figure 1C). In case 2, liquefaction was present beneath the anterior lens capsule (Figure 1D). No cataractous changes were observed in the posterior side of the lens. Examination of the tumors revealed undifferentiated retinoblastoma (Figure 2A) with a necrotic area and multiple foci of calcification in both cases. The retina adjacent to the tumor tissue was detached. Retinoblastoma cells invaded the vitreous cavity and were present in the vicinity of the posterior capsule (Figure 1C). Microscopic rupture of the lens capsule was not detected in either case.

**MINOR CATARACTOUS CHANGES IN 3 CASES OF RETINOBLASTOMA**

Three cases showed histopathologic evidence that could be classified as minor cataractous changes (cases 3-5). Several morgagnian globules existed near the posterior capsule (Figure 1E). The number of morgagnian globules was low, and the extent of the lens change was small in this group compared with that in the definite group. Liquefaction was observed beneath the posterior capsule (Figure 1F), but the area of liquefied change was limited in this group.
IMMUNODETECTION FOR TGF-β IN RETINOBLASTOMA TISSUES

The number of TGF-β-immunopositive tumor cells was markedly high (80%) in 2 cases (cases 1 and 2), showing association of cataract with the retinoblastoma. Immunohistochemical analysis demonstrated cytoplasmic immunoreactivity for TGF-β in most of the tumor cells, including those in the vitreous cavity (Figure 2A and B). In contrast, no TGF-β was expressed in the detached retina adjacent to the tumor (Figure 2C and D). Compared with the findings seen in the definite cataract group, the rate of cases positive for TGF-β was low in those with retinoblastoma, representing minor cataractous changes, and in those with no cataractous changes (Table).

ASSOCIATION BETWEEN TUMOR SIZE, NECROSIS, AND CATARACTOUS CHANGE

In this study, statistical analysis was performed between retinoblastoma cases with (n=5, cases 1-5) and without (n=15, cases 6-20) cataractous changes. The mean tumor size, calculated by multiplying the anterior-posterior and horizontal dimensions, was 156.4 mm² (standard deviation [SD], 39.6 mm²) in those with cataractous changes and 116.8 mm² (SD, 65.5 mm²) in those without cataractous changes (P=.22). The mean necrotic area was 83.8 mm² (SD, 40.9 mm²) (mean rate of immunopositive cells, 50.8% [SD, 15.5%]) in cases with cataractous changes and 55.1 mm² (SD, 35.6 mm²) (mean rate of immunopositive cells, 44.2% [SD, 14.8%]) in those without cataractous changes (P=.06 in size, P=.45 in percentage).

COMMENT

These 2 conditions, retinoblastoma and congenital cataract, are believed to be unrelated; however, anterior polar cataract has been reported to occur in association with retinoblastoma. Because it is very unlikely that congenital cataracts of any type are related to retinoblastoma, the presence of the cataracts found in this series is unusual. In the present study, 2 patients showed the presence of definite cataracts (cases 1 and 2) in their eyes that contained retinoblastoma. Case 1 had a posterior subcapsular cataract intermingled with morgagnian globules in her left eye, implying that the histological findings of the cataract are typical.

It is likely that retinoblastoma cells upregulate vascular endothelial growth factor, which causes neovascular-
As shown in the Table, the 3 patients with retinoblastoma and only minimal cataractous changes (cases 3-5) demonstrated no upregulation of TGF-β. The pathogenesis of minor cataractous changes in eyes containing retinoblastoma is unclear from the current study. Size of the tumor and extent of necrosis did not correlate with the lens changes when comparing eyes with and without cataractous changes, as there was no statistically significant difference in size of the tumor (P = .22) and extent of necrosis (P = .06 in size, P = .45 in percentage). These results suggest that the extent of tumor growth and necrosis in retinoblastoma may not be associated with pathogenesis of cataractous changes. However, expression of TGF-β may play a role in the development of the lens changes with typical histologic features of well-developed cataract.

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REFERENCES


Figure 2. Hematoxylin-eosin staining and immunodetection for transforming growth factor β (TGF-β) in retinoblastoma and the detached retina adjacent to the tumor. A, Tumor cells diffusely proliferate without forming Flexner-Wintersteiner rosettes, representing undifferentiated retinoblastoma in case 1. Cytoplasmic immunoreactivity for TGF-β is observed in retinoblastoma cells (B) but not in the detached retina (D). C, Inner nuclear layer gets thin in the detached retina in conjunction with retinoblastoma tissue.

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