Spontaneous regression of bilateral retinoblastoma

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SUMMARY A 24-year-old black man was found to have bilateral, spontaneously regressed retinoblastoma that had previously been misdiagnosed as post-traumatic chorioretinal scarring. His son and half-brother both had bilateral viable retinoblastoma. The ophthalmoscopic and fluorescein angiographic features of this patient’s fundus lesions included a calcified, whitish mass located centrally in one of the scars and a fine residual vascularity in another of the fundus lesions. The authors review the pertinent literature on spontaneous regression of retinoblastoma.

Spontaneous regression is an uncommon but well-described feature of retinoblastoma, which is estimated to occur in approximately 2 of every 100 tumours. Clinical diagnosis of spontaneous regression can be made with relative certainty only in patients having viable retinoblastoma in the same or the opposite eye or in patients with a pathologically confirmed family history of retinoblastoma.

Unilateral, unifocal spontaneous regression of retinoblastoma is uncommon; bilateral multifocal spontaneous regression of retinoblastoma is even rarer. Yet several cases of this type have been reported. In many of the previously reported cases the eye (or eyes) containing the spontaneously regressed tumour has been phthisical and blind. Only a few reports describe preservation of the eyes and retention of useful vision in both eyes. Even fewer of these cases have been well illustrated graphically.

This paper describes the case of a man with bilateral, spontaneously regressed retinoblastoma who retained useful vision in both eyes. The appearance of these lesions is illustrated with clinical photographs and fluorescein angiograms.

Case report

A 24-year-old black man (patient IIb in Fig. 1) was seen when his son was examined (patient IIIb in Fig. 1). He was found to have 3 lesions in the left fundus and one lesion in the right fundus. The son (patient IIIb) had just been found to have bilateral viable retinoblastoma. Inquiries into the family history revealed that the patient’s half-brother (patient Ila in Fig. 1) had also had bilateral retinoblastoma and had previously undergone enucleation of one eye and photocoagulation and cryotherapy of a peripheral lesion in the opposite eye. Histopathological examination of the enucleated eye demonstrated a well-differentiated retinoblastoma.

Patient IIb reported having had poor vision since childhood in his left eye. A previous ophthalmic examination performed elsewhere had revealed exotropia, for which the patient had undergone horizontal rectus muscle surgery 5 years before our first examination. A macular lesion had been noted in the patient’s left eye prior to this surgery, but it was diagnosed as a post-traumatic chorioretinal scar resulting from unrecalled ocular trauma. The patient’s family history was negative at that time.

Ocular examination on the Oncology Service at
Wills Eye Hospital revealed his best corrected visual acuities to be 6/5 in the right eye and 6/60 in the left. Intraocular pressures, measured by application tonometry, were normal. External examination disclosed conjunctival scars over the horizontal rectus muscles of the left eye. Slit-lamp biomicroscopy revealed no anterior segment abnormalities. Fundus examination of the right eye (Fig. 2A) showed a 3x2 mm minimally elevated grey-white lesion located about 9 mm superior to the fovea (Fig. 3A). The fluorescein angiogram of this lesion showed retinal pigment epithelial window defects (Fig. 3B). The overlying retinal circulation was intact, and there was no indication of a specific tumour circulation. The left fundus (Fig. 2B) contained 3 lesions. A 7.5x6 mm irregularly pigmented grey-to-black lesion was present in the macula (Fig. 4A). Near the centre of this lesion was an irregular, whitish, slightly elevated mass. There was an associated loss of the papillomacular nerve fibre layer. Fluorescein angiography demonstrated retinal pigment epithelial window defects without a retinal tumour vessel pattern (Fig. 4B). The second lesion in the left eye (Fig. 2B) was an 8x7 mm whitish-grey, gliotic-appearing, slightly elevated mass located about 5 disc diameters inferior to the fovea (Fig. 5A). The fluorescein angiogram of this lesion showed small, relatively discrete retinal pigment epithelial window defects as well as a finely branching pattern of small retinal tumour vessels (Fig. 5B). The third lesion was a very small, calcific nodule adjacent to the ora serrata at the 6:15-o’clock meridian (Fig. 2B).

A plasma carcinoembryonic antigen (CEA) test on patient IIb was slightly elevated at 3-7 ng/ml (normal range 0–2.5 ng/ml); the half-brother, patient IIa, had a plasma CEA of 6.8 ng/ml. (SI conversion: ng/ml= μg/l.) The parents of patients IIa and IIb were examined ophthalmoscopically and were found to have no fundus lesions. Patient I’, the father of both patients IIa and IIb, had a normal plasma CEA level.

Discussion

A number of well-documented cases of spontaneously regressed retinoblastoma have been reported in the literature. Many of the unilateral cases have been diagnosed on the basis of histopathological findings in patients with unilateral phthisis bulbi of unknown aetiology. The characteristic histopathological features of spontaneously regressed retinoblastoma in such eyes include calcified tumour cell nests and necrosis of the surrounding retina. Some patients with spontaneous tumour regression in a phthisical
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Fig. 3A

Fig. 3 A. Atrophic chorioretinal lesion in right fundus of patient IIb. B. Venous phase of fluorescein angiogram showing retinal pigment epithelial window defects.

Eye have been found to have viable retinoblastoma in the fellow eye. A rare patient has even been found to have bilateral spontaneous tumour regression presenting as nontraumatic phthisis bulbi during childhood. Spontaneously regressed retinoblastomas in otherwise normal eyes have also been reported. Many such cases were diagnosed on the basis of a positive family history of retinoblastoma or the histopathological identification of retinoblastoma in the fellow eye.

Fig. 4A

Fig. 4 A. Macular lesion in left eye of patient IIb. Note calcific retinal foci centrally within lesion. B. Recirculation phase fluorescein angiogram of macular lesion, which demonstrates retinal pigment epithelial window defects without tumour vessels.
eye.4-7,9-19 Other cases have been diagnosed by ophthalmoscopic observation of characteristic lesions in the fundi of patients with no family history of retinoblastoma.20-23 The diagnosis of retinoblastoma must be considered presumptive in these cases.

The typical ophthalmoscopic appearance of spontaneously regressed tumours is generally described in terms of standard postirradiation regression patterns.8 The macular lesion in our patient’s left eye was consistent with a type I regression pattern with pronounced retinal-pigment epithelial alterations, and the inferior midperipheral lesion in this eye was similar to the type II regression pattern. The small, far peripheral inferior lesion in the left fundus appeared to be an entirely calcified type I lesion, but the small lesion in the right eye showed persistent fine tumour vessels. This observation is consistent with our findings in previously irradiated eyes with type I and type II tumour regression patterns.24

Regressed retinal tumours in otherwise normal eyes have been detected in both unilateral and bilateral cases of retinoblastoma.3-5 7,9,11,19-23 Most of these eyes have retained useful vision, and many, containing one or more regressed tumours, have had normal visual acuity because the lesions were in extramacular locations. Our patient had normal vision in his right eye, which contained a single totally regressed extramacular tumour. However, his visual acuity was impaired in the left eye because of the macular location of one of the 3 regressed tumours.

There are several theories about the pathogenesis of spontaneous regression of retinoblastoma. One of the most popular is that regression occurs because of vascular insufficiency in a rapidly growing tumour.1,25-26 According to this theory the tumour outgrows its blood supply, becomes necrotic, and subsequently regresses. Another theory suggests that an immunological mechanism may be responsible for spontaneous tumour regression. Histological deposits found in some retinoblastomas that have undergone spontaneous necrosis appear to be immune complexes,27 and increased levels of circulating immune complexes have been found in some retinoblastoma patients.28 Both our patient and his half-brother had

Table 1  Comparison of spontaneously regressed retinoblastoma in a phthisical eye and spontaneously arrested retinoblastoma (retinoma)

<table>
<thead>
<tr>
<th>Age at detection</th>
<th>Spontaneously regressed RB</th>
<th>Spontaneously arrested RB</th>
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<tbody>
<tr>
<td>Status of involved eye</td>
<td>Childhood to adulthood</td>
<td>Adulthood</td>
</tr>
<tr>
<td>Status of other eye</td>
<td>Phthisis bulbi</td>
<td>Useful eye</td>
</tr>
<tr>
<td>1. Viable RB</td>
<td>1. Viable RB (40%+)</td>
<td></td>
</tr>
<tr>
<td>2. Retinoma</td>
<td>2. Retinoma (25%+)</td>
<td></td>
</tr>
<tr>
<td>4. Phthisis bulbi</td>
<td>4. Phthisis bulbi</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Mechanism of development</th>
<th>Spontaneously regressed RB</th>
<th>Spontaneously arrested RB</th>
</tr>
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<tbody>
<tr>
<td>Obstruction of central retinal artery</td>
<td>Mutation of partially differentiated retinoblast</td>
<td></td>
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Table adapted from Gallie et al.21
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elevated CEA, an antigen originally described in patients with gastrointestinal malignancies.29 Some family relations of patients with retinoblastoma have been found to have elevated CEA, the ‘CEA family syndrome.’30 Whether there is any relationship between CEA levels and an immunological mechanism is unknown. There is no conclusive evidence that either the vascular or the immunological theory is correct.

We believe that the lesions in the patient described are regressed retinoblastomas, because they share ophthalmoscopic features and patterns known to occur in retinoblastomas following irradiation. However, 2 other suggestions can be made as to the nature of these fundus lesions. The first is that they are spontaneously arrested rather than spontaneously regressed retinoblastomas.11 Smith considers that the histological and ophthalmoscopic appearance of these lesions is different from that found in regressed tumours after irradiation.11 However, we do not know of any report of a growing, viable retinoblastoma which stopped growing spontaneously and assumed the appearance shown in his article.

The second suggestion is that proposed by Gallie and coworkers31 (Table 1), who feel that this lesion is a nonprogressive retinoblastoma, a benign tumour which they have termed a retinoma. Their hypothesis is that a retinoma results when a genetic mutation occurs in a partially differentiated retinoblast. Had this mutation occurred in an immature cell, it would presumably have resulted in a viable, progressive retinoblastoma. No experimental or histopathological evidence has been presented, however, to show that this embryological sequence of events is correct.

Our patient had previously been misdiagnosed as having a post-traumatic chorioretinal scar, presumably as a result of a prior unrecalled ocular injury. The presence of calcified retinal foci within this macular chorioretinal scar, however, suggested the diagnosis of regressed retinoblastoma. We believe that ophthalmologists should be familiar with the characteristic appearance of regressed tumours and that they should consider retinoblastoma in the differential diagnosis of patients with typical fundus lesions. Correct identification of retinoblastoma at the time of our patient’s examination for strabismus might have stimulated ophthalmoscopic examination of his son and half-brother at an earlier age. Then appropriate therapy32 could have been initiated earlier and the chances of salvaging the eyes and preserving vision would have been better.

This work was supported in part by the Pennsylvania Lions Sight Conservation and Eye Research Foundation, Inc., the Retina Research and Development Foundation, the Ocular Oncology Fund, and the Research Department, Wills Eye Hospital, Philadelphia, Pennsylvania.

References

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doi: 10.1136/bjo.66.11.685

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