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Case Report

Massive Uveal Relapse of Retinoblastoma Presumed to Be Choroidal Tumorous Involvement: Case Series

Fariba Ghassemi[a, b, c] Masoud Rahimi[a] Hamid Riazi-Esfahani[a, b, c] Alireza Khodabandeh[a, b] Babak Masoomian[a, c] Sara Taghizadeh[a] Shervin Sharifkashani[a, c]

[a]Eye Research Center, Farabi Eye Hospital, Tehran University of Medical Sciences, Tehran, Iran; [b]Retina and Vitreous Service, Farabi Eye Hospital, Tehran University of Medical Sciences, Tehran, Iran; [c]Ocular Oncology Service, Farabi Eye Hospital, Tehran University of Medical Sciences, Tehran, Iran

Keywords
Choroidal involvement · Metastasis · Ocular retinoblastoma · Recurrence · Retinoblastoma metastasis · Uveal relapse

Abstract
We report the choroidal and ciliary body invasion by retinoblastoma (RB) in a salvaged eye after complete and successful primary treatment. Case 1: A 25-month-old boy was referred due to group B RB lesions based on the International Classification of RB (ICRB; groups A–E) in the right eye (OD). His left eye (OS) was enucleated because of advanced group E RB. After 47 months of uneventful follow-up (F/U), a new lesion recurred and was treated with transpupillary thermotherapy. Four months later, a fast-growing pigmented subretinal mass was detected that was treated by brachytherapy with the apical dose of 80 Gy. Three weeks later, the lesion regressed completely, and no recurrence happened after 6 years of F/U. Case 2: A 4-month-old girl with a deletion in chromosome 13 was referred for bilateral RB. OD was enucleated because of unresponsive RB and anterior segment involvement. In OS, group B lesions had multiple recurrences after systemic chemotherapy. After a while, a single mass appeared in the nasal periphery which was controlled well with brachytherapy. Four months later, AC involvement was controlled with IAC, intravitreal, and intracameral chemotherapy, but posterior synechia and cataract appeared later. One year after the last treatment, UBM showed a ring-shaped ciliary body mass. Her parents refused enucleation again, and she received intravenous chemotherapy. Two years later, magnetic resonance imaging showed orbital and optic canal involvement with a deformed globe. In conclusion,

Correspondence to:
Shervin Sharifkashani, shervin.sharif.m.d@gmail.com

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RB recurrence can appear as local choroidal and ciliary body involvement even after a time of complete remission. The role of B-scan and UBM in early diagnosis and successful treatment is valuable.

Introduction

Retinoblastoma (RB) is a primary intraocular malignancy that occurs in 1:17,000 infants on average. Its most common form is unilateral (about 60%) [1]. Historically, enucleation was a kind of RB treatment used in advanced cases (like group E), extensive invasion of the choroid and optic nerve, and extraocular extension [2]. After primary enucleation, the patients may have an orbital recurrence and metastasis rate of 7.9%, which decreased to 1% in those who had received chemotherapy prior to enucleation [3]. Post-laminar optic nerve invasion of RB greatly impacts its metastasis and recurrence [4]. Metastasis to other organs such as the brain, bone, bone marrow, and liver has been mentioned in previous studies, but local metastasis after resection such as orbital recurrence has not been observed [5].

Herein, we report two unusual RB cases in which a time after successful treatment of the primary tumor, a second massive choroidal and ciliary body relapse of RB occurred in their only remaining eye which was well controlled with early diagnosis. The CARE Checklist has been completed by the authors for this case report, attached as online supplementary material (for all online suppl. material, see https://doi.org/10.1159/000531527).

Case Presentation

Case 1

A 25-month-old boy was admitted to Farabi Hospital in January 2012, with a history of bilateral sporadic RB. The left eye (OS) was primarily enucleated because of a very advanced group E tumor based on International Classification of Retinoblastoma (ICRB) [1]. The pathology report showed a well-differentiated RB (size: 18 × 15 × 11 mm) with marked necrosis, diffuse infiltrative condition, without optic disc, optic nerve, and choroidal invasion. In the follow-up (F/U) visit, 2 months later, two new 2 × 2 × 1.5 mm and 1.5 × 1.5 × 1 mm lesions were detected in the right eye (OD) at nasal and super-temporal quadrants (group B). After receiving 8 sessions of systemic intravenous chemotherapy (IVC), both lesions regressed completely. After uneventful F/Us, in the 47th month a new lesion (1 × 0.5 × 0.5 mm) with few granular seeds near the previous lesion, less than 2 mm from the border, appeared and was treated successfully with 2 sessions of local treatment (transpupillary thermotherapy). The seeds disappeared spontaneously (Fig. 1a, b). Four months later, a pigmented subretinal mass (6 × 5 × 3 mm) was detected near the recent recurrence with different internal reflectivities in B-scan (Fig. 1c, d). The retina was intact over the lesion. Magnetic resonance imaging with and without contrast showed an enhancing 4 × 7 × 2 mm lesion in the posteromedial aspect of the OD, touching the medial side of the optic disc. The brain was normal (Fig. 1g, h). After 2 months of missed F/U, the lesion size increased (12 × 10 × 6 mm). The mass was presumed to have tumorous choroidal involvement of RB, and brachytherapy with the apical dose of 80 Gy was performed in OD. Three weeks later, the lesion had regressed completely. Rapid regression of choroidal mass was realistic proof for being RB (Fig. 1e, f).

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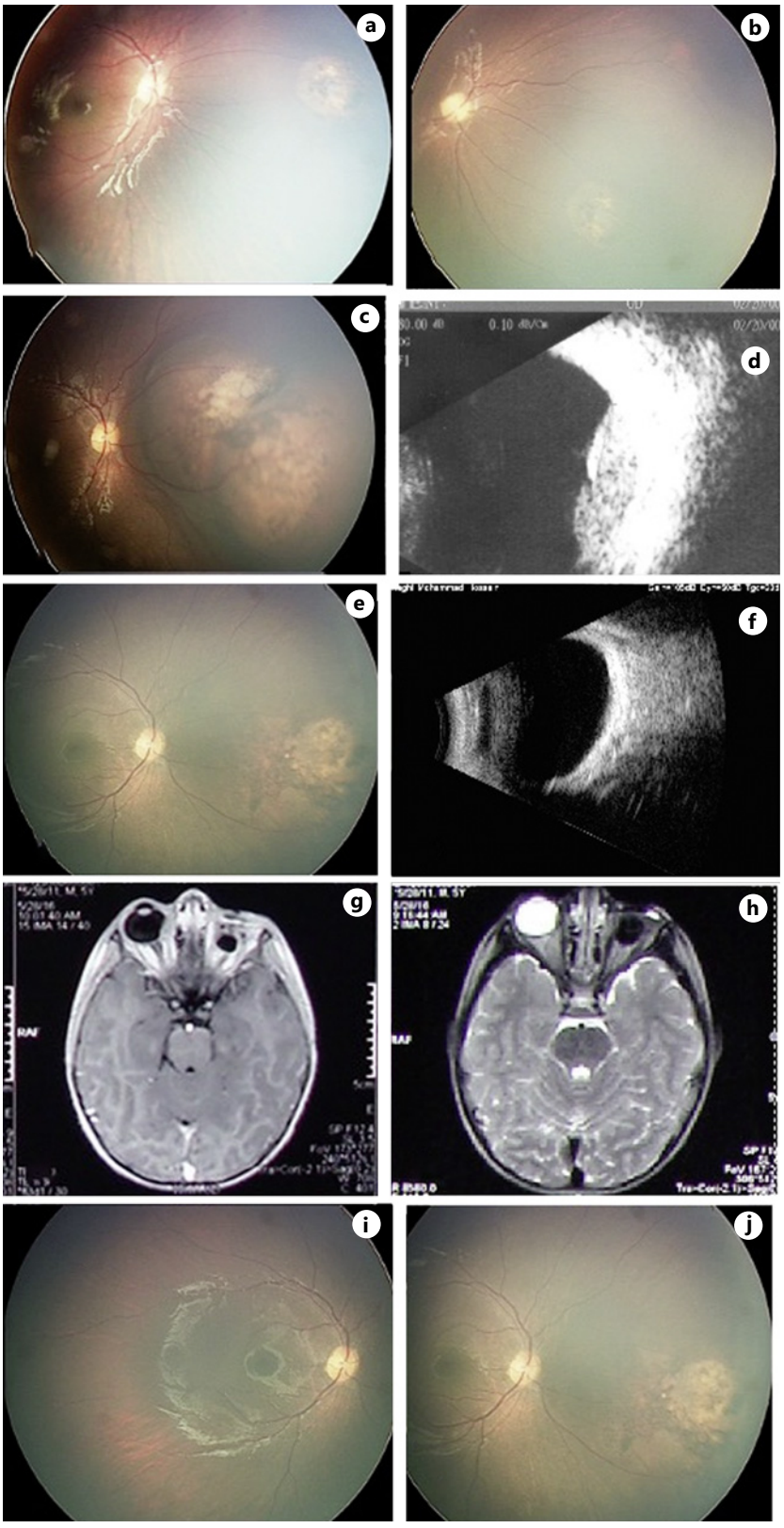

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The patient has been followed for 6 years without any new recurrence. The patient's visual acuity was 20/20 on the last visit without any sign of radiation retinopathy, and the systemic workup was negative for any metastasis (Fig. 1i, j).

Case 2

A 4-month-old girl was admitted to the ocular oncology center of Farabi Hospital in March 2016, with strabismus in OD. On examination, she had bilateral sporadic RB (group E) in OD and group B in OS. She has special facies such as narrowed face and low-set ears, failure to thrive, and developmental delay. In karyotype analysis, chromosome 13 deletion was reported. Systemic chemotherapy was performed with a good response to treatment (8 sessions). Multiple recurrences appeared during IVC and thereafter. Adjuvant local treatments were implemented each time. Eight months after the first IVC, because of incomplete responses and recurrences, another course of IVC was started. New recurrences appeared in OD; therefore, intra-arterial chemotherapy (IAC) was performed twice, but due to recurrence, dense vitreous hemorrhage, anterior segment involvement, and cataract formation, the eye was enucleated in January 2018 (Fig. 2a, b). Histopathology evaluation showed moderately differentiated RB with scant calcification and necrosis. The iris, ciliary body, and anterior chamber were involved. Choroid and prelaminar optic discs were locally invaded. The sclera, post-laminar optic nerve, and surgical margin of the optic nerve were tumor-free. Based on the high-risk histopathology findings, adjuvant chemotherapy was done after enucleation. In January 2020, a single lesion with localized vitreous seeds appeared at the nasal quadrant, and brachytherapy with 106 Ruthenium plaque (60 Gy) was performed (Fig. 2c, f). The lesion disappeared almost completely, but after 4 months, new lesions within the anterior chamber were revealed, and the patient was treated with IAC (once), IVC (8 sessions), and intracameral injection (single session of combined melphalan and topotecan). Due to near-mature cataract and iris atrophy, we had to follow the patient with B-scan and UBM at each visit time. The parents refused enucleation. In January 2021, UBM showed a big ring-shaped ciliary body mass (Fig. 3a–c). The parents again declined enucleation, and another course of IVC was prescribed. After 2 years, the patient was referred with serosanguinous discharges from a deformed eye with a cornea and conjunctival scar. Magnetic resonance imaging showed the orbital and the optic canal infiltration with the tumor, but there was no remarkable proptosis. According to the parent's choice, the patient was followed conservatively and is still alive.

Discussion

These cases demonstrate that RB recurrence can appear in the ipsilateral choroid and uveal tract of the eye as a massive tumor, not as flat infiltration. The most frequent location of ocular metastasis is the choroid [6]. The occurrence of choroidal metastases has increased steadily due to the longer survival of adult metastatic patients and the improvement of diagnostic tools [7]. There is currently no consensus on the treatment strategy.

Fig. 1. a–j A 25-month-old boy with bilateral sporadic RB. The right eye was enucleated because of an advanced RB tumor. **c** He developed a large fast-growing subretinal pigmented mass 51 months after complete remission of primary lesions. **d** The dome-shaped bi-hump lesion had medium internal reflectivity without any calcification. **e**, **f** After brach1ytherapy, the lesion rapidly regressed. **g**, **h** The magnetic resonance imaging showed a dome-shaped lesion at the nasal side of the disc before treatment. **i**, **j** The lesion disappeared completely, and no recurrence and radiation retinopathy were formed during the 6 years of F/U.

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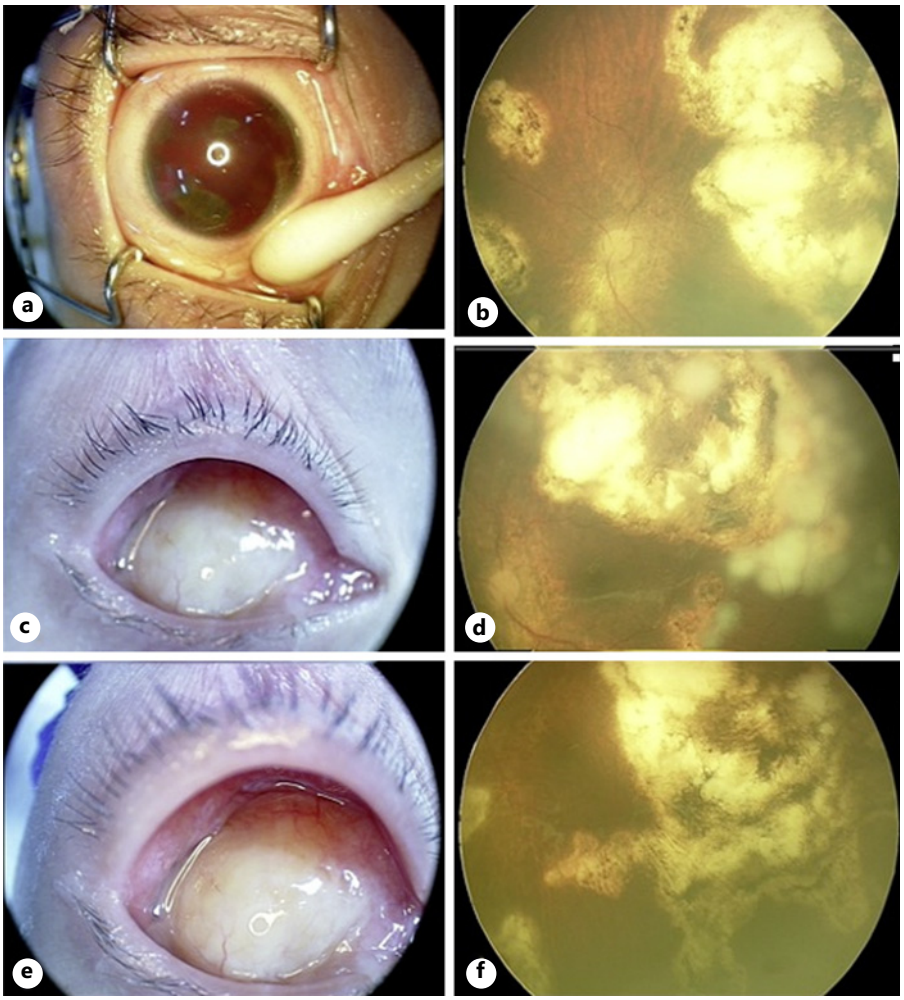

Fig. 2. A 4-month-old with chromosome 13 deletion and bilateral sporadic RB. **a**, **c**, **e** The right eye was enucleated because of a recalcitrant tumor and hyphema and anterior segment involvement. **b**, **d**, **f** The left eye was followed every month, and she had multiple recurrences and all treated by systemic or intra-arterial chemotherapy and local adjuvant treatments.

RB treatment has been promoted recently, which improves the patient's survival rate and decreases the need for enucleation [8]. Heroic efforts were made to save the eyes, especially the only remaining eye. Still, in some advanced cases like Group E, the selective treatment is enucleation for the prevention of systemic metastasis [9]. Some risk factors impact the rate of metastasis and recurrence in the RB. The most important risk factors for metastasis of RB in a row are optic nerve resection site involvement, involvement of the retrolaminar region, and late enucleation [4, 10]. In the literature, isolated choroidal invasion as a risk factor for metastasis is controversial. In some studies, isolated involvement of the choroid was not a risk factor for relapse [11, 12], and in some others, the massive choroidal invasion was a risk factor for metastasis [13]. Bosaleh et al. studied 164 cases and showed that children with massive choroidal invasion had a higher relapse rate but comparable survival to those with focal invasion, provided that aggressive adjuvant chemotherapy was given [14].

Nevertheless, other authors found that the risk of metastasis was increased only if the choroidal invasion was associated with optic nerve invasion [10]. Patients with massive choroidal invasion are frequently given post-enucleation adjuvant IVC as chemoprophylaxis

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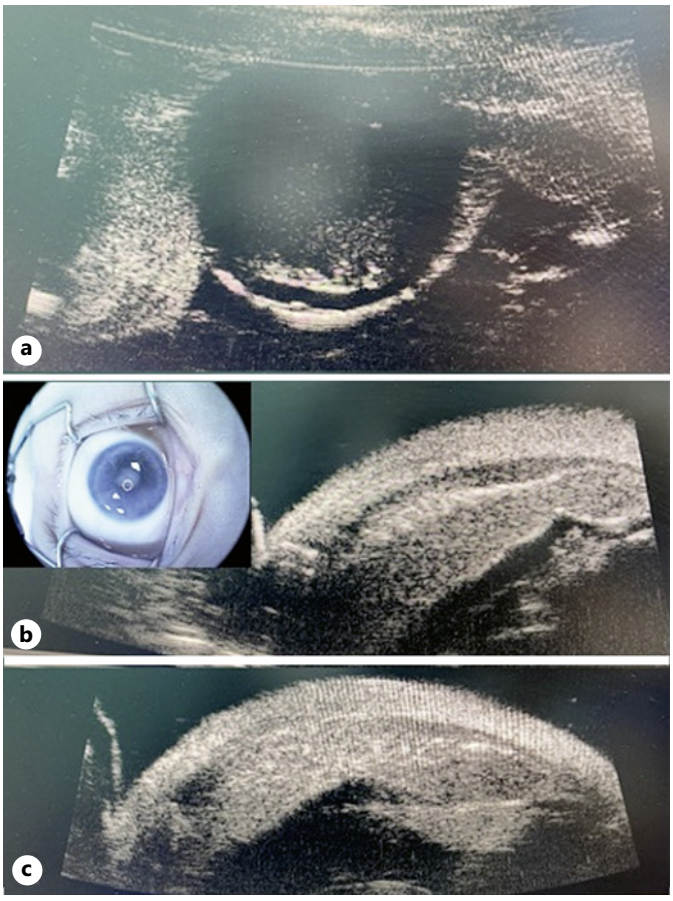

Fig. 3. The second case developed a cataract after 1 year from the last occurrence of the recurrences and anterior segment involvement. She was followed by B-scan and ultrasound biomicroscopy, and 12 months after the previous recurrence, a ring-shaped prominent mass appeared in the ciliary body area, causing the spheroid pattern of the cataractous lens (**a**). The lesion had high internal reflectivity (**a–c**) with a softly undulating surface (**b**) without any calcification in it.

against micrometastases [15, 16]. The reported relapse rate after enucleation of eyes with choroidal invasion varied from 2% to 20% [12–14]. Redler and Ellsworth found that eyes from both surviving and non-surviving patients had a chance of 62% for choroidal invasion [6]. In another study, according to routine histopathological sections through the center of the tumors, choroidal invasion by RB has been reported in 23–62% of enucleated eyes [4]. Shields et al. [13], in a study on 289 eyes, showed that the isolated choroidal invasion was present in 8.4% of the enucleated cases. Increased IOP and iris neovascularization significantly predict the choroidal invasion, and no differences existed between the exophytic and endophytic growth patterns of the tumor and choroidal invasion [13]. The most common forms of RB metastasis with poor prognosis and a survival rate of 28.7% are CNS metastasis, bone metastasis, bone marrow infiltration, and lymph node metastasis [17, 18].

Traditionally, in RB patients, choroidal involvement is often diagnosed through pathology reports, but rarely, the tumorous involvement could be seen clinically as an atypical recurrence of RB that usually does not respond to treatments and with rapid growth [19]. To the best of our knowledge, a few cases of massive and dome-shaped uveal involvement have been reported. In our previous report, we described a rapidly growing dome-shaped choroidal lesion in an already treated RB eye, 10 months after the last treatment. The pathology report showed tumorous

choroidal invasion of RB with the poorly differentiated condition. A very rapidly growing yellowish dome-shaped mass unresponsive to IAC was found with a very fast doubling in size for 2 weeks. Enucleation was considered for her because of the large size and scary rapid growth of the lesion [19]. Chablani reported another single case of conservative treatment of a uveal tract RB relapse, which was treated with Ruthenium-106 brachytherapy [20]. The third report by Stathopoulos et al. [21] had 2 cases. The first one was a 19-month-old girl with multifocal unilateral group B RB, pretreated with IVC, showing a choroidal involvement diagnosed by clinical examination and hand-held optical coherence tomography. She has been under high-dose IVC for concomitant pineoblastoma. The patient was deceased because of treatment complications. Their second case was a heavily pretreated 20-month-old girl with bilateral RB and persistent vitreous seeding in her remaining eye. Three months after intravitreal chemotherapy and thermotherapy, a rapidly growing choroidal hemorrhagic mass was observed inferior to the primary tumor. UBM confirmed the diagnosis, and the lesion was treated with IAC with no recurrence after 36 months.

Three possibilities can explain the tumorous choroidal or uveal recurrence of RB in our patients. First, the choroidal tumor emerged by local invasion of the RB, spontaneously or secondary to laser treatment; by the induced injury to the retinal pigmentary epithelium-Bruch's membrane complex. Second, the choroidal tumor arises after the hematological distribution of the ipsilateral or contralateral RB tumor in the highly vascularized uveal system. Third, both retina and choroidal tissues have had primary tumors (that did not appear in the previous multiple exams under general anesthesia). The recent prospect could pose the possibility of the presence of RB stem cells originally in or migrated to the choroid by any mechanical damage or as an innate process.

Conclusions

This report describes tumorous choroidal and ciliary body involvement of RB in 2 treated patients that were clinically hardly distinguishable from a second primary tumor as melanoma. The lesions were rapidly growing and presented after a period of complete remission. The prognosis of choroidal involvement of RB looks favorable with early diagnosis and comprehensive treatment.

Statement of Ethics

Written informed consent was obtained from each patient's parent for publication of the details of both cases and any accompanying images. The research was conducted ethically in accordance with the Declaration of Helsinki. Ethical approval is not required for this study in accordance with local or national guidelines.

Conflict of Interest Statement

The authors declare that they have no conflicts of interest.

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Author Contributions

F.G.: data collection, manuscript writing, and editing. M.R.: manuscript writing. H.R.-E.: manuscript writing and manuscript editing. A.K. and S.T.: manuscript editing and literature search. B.M.: designing the figures and manuscript editing. S.S.: patient's clinical care, patient's data collection, manuscript review, and supervising the project. All authors read and approved the final manuscript.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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