The Recognition of Cavitary Retinoblastoma Tumors: Implications for Management and Genetic Analysis.

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Key Words and Summary

Key Words: Retinoblastoma, Chemotherapy

Summary Statement:
Cavities in retinoblastoma tumors can evolve on systemic chemotherapy. The detection of cavities confer stability and aggressive consolidation therapy is not required.

Structured Abstract

Purpose:
To assess the role of consolidating adjuvant therapy for cavitary retinoblastoma (CRs) and to understand if there is any phenotype- genotype correlation.

Methods:

Patients with retinoblastomas having ophthalmoscopically visible cavities between 2004 and 2014 in whom 4-6 cycles of systemic chemotherapy were given.

Results

Eighteen eyes of 17 patients displayed CRs. This represented 6.8% of 250 patients. Mean age at diagnosis was 13 months; 5 unilateral (29%) and 12 bilateral (71%). The mean (median, range) number of retinoblastoma tumors per eye was 2 (2; 1–6). The number of cavities per tumor was 3 (2, 1–6). Intra-tumoral cavities were seen in the superficial portion of the tumor in 10 eyes (55%). The cavities became visible in 8 eyes (44%) and collapsed in 8 eyes (44%). Two eyes required enucleation due to relapse in non-cavitary tumors. Germline mutations were detected in 14 patients (82%) of whom, four demonstrated mosaicism (29%). The mean follow-up period was 40 (35, 6–120) months.

Conclusion

CRs can be detected following systemic chemotherapy with cavities becoming visible after mean 2 cycles of chemotherapy. They remain stable and do not require aggressive adjuvant therapy. There was no evident phenotype-genotype correlation with mosaicism noted in 29%.

Abbreviations: cavitary retinoblastoma (CR), retinoblastoma (Rb).

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Introduction

Retinoblastoma (Rb) is a life-threatening intraocular malignancy of childhood. Generally, the tumors manifest as a dome-shaped, solid white retinal mass with prominent intrinsic and feeder vessels. Rarely, ophthalmoscopically visible lucent cavities can occur. [1, 2]

These cavitary spaces appear hollow on ultrasonography and hypofluorescent on angiography.[3] Rb tumors are known to respond to chemotherapy[4, 5] often with resolution of retinal detachment and shrinkage of the tumor, but relapse can occur after treatment. The few previous reports on cavitary retinoblastoma (CR) have described its relative chemoresistant and radioresistant features.[2,6] Although the tumor size does not reduce dramatically, they tend not to relapse.[7] Currently, it is common practice to apply consolidation laser to retinoblastoma tumors during systemic chemotherapy.[4,8,9] It has been suggested that prolonged adjuvant therapy is not necessary in CR.[7]

Histopathologically, the cavitary spaces represent areas of photoreceptor differentiation in the area adjacent to the cavitations.[10] This may explain the perception of muted response to therapy and low risk of reactivation.

Despite these interesting findings, there is little in the literature on the genotype – phenotype correlation of CR. In this report therefore, we seek to understand further the clinical phenotype of CR and its natural history, correlate this to genetic findings, and to examine the need for adjuvant therapy once CR occurs.

SUBJECTS

We reviewed the medical records of 250 newly diagnosed patients with retinoblastoma that were managed at the Retinoblastoma Unit at the Royal London Hospital from January 1, 2004, through Dec 31, 2014. This study was approved by Barts Health Clinical Effectiveness Unit (Number 5963), within tenets of the Declaration of Helsinki. Patients with the diagnosis of cavitary retinoblastoma and treatment with systemic chemotherapy were selected for analysis. This was a retrospective, nonrandomized, non-comparative interventional case series.

METHODS

Information collected included demographic details, clinical findings, treatments, and outcome (relapse, globe salvage metastasis and morality). Each patient underwent evaluation for age at diagnosis (in months), sex (male or female), race (White, European or South Asian). Results

of genetic testing (hereditary or non-hereditary) were also recorded.[11] A comprehensive ocular examination under anaesthesia was performed with assessment for laterality (unilateral or bilateral), International Intraocular Retinoblastoma Classification,[12] intraocular pressure (measured by means of Perkins tonometry within the first few minutes of general anaesthesia); status of the anterior chamber, iris, ciliary body, optic nerve, choroid, retina, and vitreous; total number of tumors per eye; total number of cavitary tumors per eye; location of cavitary tumor; total number of cavities within each tumor and location of cavities within each tumor. The presence of associated vitreous seeds (present or absent), percentage of retinal detachment (0-100%), and presence of subretinal tumor seeds (present or absent) was also recorded.

All patients received four to six cycles of systemic intravenous chemotherapy with vincristine (1.5 mg/m2) etoposide (300 mg/m2) and carboplatin (600 mg/m2) which were delivered at three weekly intervals. Trans-pupillary Thermo-Therapy (TTT) was done using Diode Laser (810nm), median intensity used was 350mW (250mW- 500mW) for 9 seconds, and the spot size was 1.2mm.

The diagnosis of CR was based on fundus photography and indirect ophthalmoscopy either at presentation or after chemotherapy. Fundus photographs (RetCam) were compared on first and last follow-up visits. Each cavitary tumor was assessed for tumor regression pattern, and percentage of cavities collapsed. Patient mortality and metastases at the last follow-up examination was also recorded.

RESULTS

Out of 250 (167 unilateral – 67%, and 83 bilateral – 33%) patients with newly diagnosed retinoblastoma, 17 patients (6.8%) had cavitary retinoblastoma at presentation. One child had cavitary tumors in both eyes. Hence, cavitary tumors were found in 18 eyes of 17 patients, (5 unilateral-29% and 12 bilateral -71% patients). The mean patient age at presentation was 14 months (median, 14; range 2 weeks-24months). Ethnicity of the patients was White British 11 patients (64%), White European 4 patients (24%) and South Asian (2 patients, 12%).

In 10 eyes (56%) CR was evident at initial presentation in treatment naive eyes and in 8 eyes (44%) CR was found after two cycles of systemic chemotherapy. The mean (median, range) number of retinoblastoma tumors per eye was 2 (2; 1–6) and number of cavitary retinoblastomas per eye was 1 (1; 1-2). The number of cavities per tumor was 3 (3, 1–6). Associated features were subretinal fluid in 2 eyes (11%), vitreous seeds in 1 eye (5%) and subretinal seeds in 2 eyes (11%). Intra-tumoral cavities were seen in the superficial portion of the tumor in 10 eyes (55%) at presentation. The epicenter of the quadrant of the CR relative to the optic disc was superior to the optic disc in 2 eyes (11%), inferior in 3 eyes (17%) and nasal to the disc in 3 eyes (17%).Cavitary tumors occurred in the macula (temporal to the disc) in 10 eyes (55%), in 7 of which the foveola was affected by the cavity. According to the International Classification of Retinoblastoma, [12] there were no eyes in Group A, 5 eyes (28%) in group B, 3 eyes (17%) in group C, 9 eyes (50%) in group D, and 1 eye (5%) in group E. Germline (hereditary) mutations were detected in 14 patients (82%) of whom 4 demonstrated mosaicism (29%).

TREATMENT

The cavities became visible ophthalmoscopically in 8 eyes (44%) after an average 2 cycles of systemic chemotherapy (FIG 1 and 2). Cavitary tumors were treated with laser transpupillary thermotherapy in 3 eyes in an attempt to prevent future relapse (17%) while in 15 eyes cavitary tumors remained in remission without further direct treatment to that tumor (83%). Other non-cavitary retinoblastoma tumors in eyes that also harboured CR relapsed in 9 eyes (50%), requiring adjuvant treatments (transpupillary thermotherapy, cryotherapy, intraophthalmic artery Melphalan chemotherapy, intravitreal Melphalan, brachytherapy, external beam radiotherapy). In 8 eyes (44%) no adjuvant therapy was given to either cavitary or non-cavitary tumors. Type 3 regression was seen in 10 eyes (56%) mixed type-partially calcified, type 2 in 7 eyes (38%) completely non calcified/grey/fish flesh and type 1 fully calcified in one eye (6%) only respectively.

The natural history of CR was ascertained. Cavities collapsed ophthalmoscopy in 8 eyes (44%) after follow up of 18 (9, 2-48) months. In 5 eyes with collapsed cavities the tumors were involving the fovea (28%), in 2 eyes cavitary tumors were present nasal to the disc and in one eye a cavitary tumor was superior to the disc. Out of 8 eyes with collapsed cavities 6

eyes (75%) received adjuvant treatment for other non cavitary retinoblastoma and vitreous seeds (2-Plaque therapy, 2-Intra-arterial chemotherapy and 2-combined Cryotherapy/ Transpupillary thermotherapy/External beam radiotherapy). Reactivation of vitreous seeds in an eye with a solitary cavitary tumor was seen following systemic chemotherapy requiring enucleation; but there was no evidence of relapse of the cavitary tumor. Enucleation was required in another eye due to relapse of non-cavitary tumors. All 17 patients had at least 6 months of follow-up; (100%), 7 patients have (42%) more than 3 years; and 3 (18.75%) more than 7 years of follow up. The mean follow-up period was 40 (35, 6–120) months. Overall, globe salvage was achieved in 16 eyes (89%). No metastasis or death occurred in any case.

DISCUSSION:

Retinoblastoma with small cavity was first documented in 1952 by Samuels and Fuchs with a suspicion that tumor liquefaction might in fact be a cyst.[6] But the terms *cavitary* retinoblastoma for reference to this entity was first offered by Mashayekhi and coworkers because of the histopathologic absence of definite lining cells.[2] Cavitary retinoblastoma is considered as a rare phenotype, 2.3% of patients.[7] We found cavitary retinoblastoma in 6.8% of the newly diagnosed cases of retinoblastoma and this may be due to the fact that we have recorded cavities unveiled after chemotherapy, rather than on initial presentation, in nearly half of our patients.

Lack of response has been observed with cavitary retinoblastoma, believed to be due to the presence of features of retinoma / retinocytoma (or well-differentiated retinoblastoma) within the mass.[2,13,14] Retinoma is a benign, elevated, grey, translucent retinal mass with cottage cheese–like calcification and hyperpigmented retinal pigment epithelium. Histopathological features include abundant fleurettes and nonproliferative cells.[15]

Retinomas can progress to retinoblastomas but when they present to the ophthalmologist, they are not treated but observed in case of progression. On presentation, they share similarities with treated CRs as they become malignant in only 10% of cases.[16]

In 3 eyes (17%) laser (Transpupillary ThermoTherapy) was done where the tumor had regressed at mean follow up of 6 months. Consolidation was thought beneficial as the surgeon was unaware that the tumor was originally cavitary in nature and therefore bestowed with stability. All CRs (100%) remained stable at the mean follow up of 40 (35, 6–120) months.

In our cohort we observed cavities collapsed in 2 eyes with systemic chemotherapy alone after follow up of 12 months and 20 months respectively while in the other 2 eyes, cavities collapsed after mean follow-up of 3 months where adjuvant treatment (laser, cryotherapy or IAC) was given to both cavitary & non cavitary tumors. Interestingly cavities in 4 eyes collapsed when the noncavitary tumors were treated with adjuvant measures (laser, IAC, brachytherapy) for relapse after mean follow up of 25 (25,2-48) months.

Chemotherapy without additional laser can control 72% of retinoblastoma tumors (CR and non-CR). [5] However it is difficult to predict which tumors will relapse and which will not. As a result, many retinoblastoma surgeons treat all tumors with Type 2 and Type 3 regression with adjuvant therapy in order to create a flat scar. As CRs do not flatten on chemotherapy, this may involve multiple examinations under anaesthesia, large amounts of energy being applied to the eye and detrimental effects on visual function if the tumor is near the foveola. It is thought that eyes have been enucleated in the past as the surgeon was concerned about the lack of response of these tumors to chemotherapy.

In this cohort, 15 of 18 cavitary tumors had no treatment after chemotherapy and did not relapse. Rojanaporn et al[7] stated 4 of 26 tumors had no adjuvant treatment and did not relapse. 3 of 25 (12%) eyes did however relapse and required enucleation although only one had viable tumor on histopathology. In our cases two eyes were enucleated because of relapse in the noncavitary tumor or vitreous seeds (D eyes). We concur that these tumors do not require aggressive therapies following systemic chemotherapy.

Although of 250 patients, 67% were unilateral and 33% were bilateral, in CR cases, it was the reverse: 29% (5/17) were unilateral and 71 % (12/17) were bilateral. This was also the case in Rojanaporn[7] et al's paper (33% unilateral, 67% bilateral). As the majority of unilateral sporadic patients (80%) were enucleated, it is possible that some may have harboured CRs. Also, bilateral cases would have multiple tumor foci and there is a higher chance that one could evolve into a cavitary tumor. Germline (hereditary) mutations were identified in 82% (14/17) of CR patients (in all 12 bilateral patients as would be expected and 2 unilateral patients). 4/14 (29%) of germline cases were mosaic for their RB1 mutations. This figure is higher than expected (8-10% of retinoblastoma germline cases are mosaic for their mutations - Z. Onadim unpublished laboratory data) but the sample size is small. The only other study to perform genetic testing[7] found germline mutations in 11/24 (41%) patients. The higher detection rate may reflect recent innovations in uncovering mosaics.

This paper adds credence to previous work that cavitary retinoblastoma tumors can be observed in a similar manner to retinomas/retinocytomas. The detection of cavities following chemotherapy has not been previously described. Although the numbers are small and some patients were treated with whole eye treatments, we concur that cavities confer stability to these tumors.

STUDY LIMITATIONS

As it is a retrospective study we were unable to acquire the pre and post treatment measurements of the cavities in the CRs via ultrasound. Neither could we perform further immunohistochemistry on the slides of the two enucleated eyes. We only included tumors with cavities that were visible superficially on presentation or became unmasked after chemotherapy. OCT scanning may be helpful in detecting cavities that are deeper and cannot be seen with an ophthalmoscope.

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Figure Legends

Figure 1. Tumor at presentation: no superficial cysts present

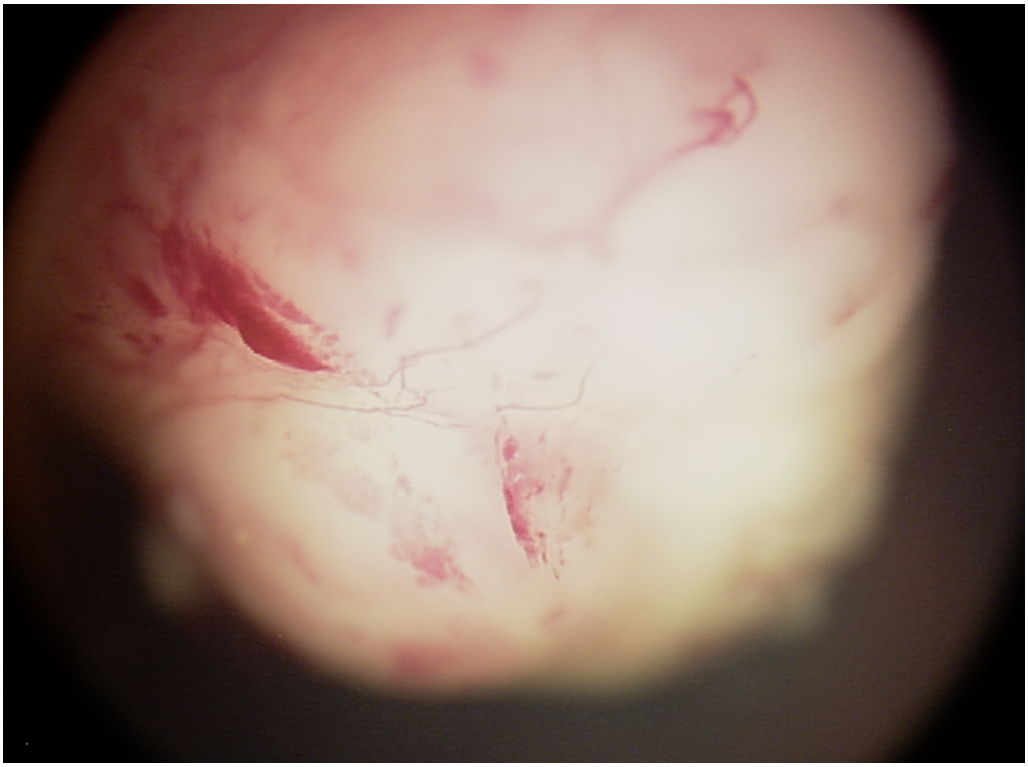

Figure 2. Cysts evident after 2 cycles of systemic chemotherapy (Carboplatin, Etoposide and Vincristine)