Retina Pathology of a Failed External Beam-Radiated Group Vb Retinoblastoma

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We report on a 7-month-old boy who suffered from retinoblastoma with presentation of a white pupillary reflex in his right eye. Initial examination showed a large subretinal and intraretinal mass nasally with extensive vitreous seeding of tumor cells (Group Vb in the Reese-Ellsworth classification). External beam radiation therapy (EBRT) was applied in hopes of preserving the eye, and significant regression with disappearance of vitreous seedings and a prominently decreased tumor mass with localized calcification were documented. Unfortunately total retinal detachment was subsequently identified 3 months after irradiation. The patient ultimately underwent enucleation, and histopathology revealed significant calcification within the residual tumor without marked necrosis; a preretinal fibrous membrane with focal vascular thickening was noted, which implied a partial but incomplete effect of EBRT for this group Vb retinoblastoma. We describe the histopathological findings of the failure of irradiation for a group Vb retinoblastoma, and emphasize the importance of early application of EBRT treatment for a retinoblastoma. *(Chang Gung Med J 2002;25: 542-7)*

Key words: retinoblastoma, external beam radiation therapy.

Retinoblastomas are the most common intraocular tumor in childhood. Although the management of retinoblastomas has shifted toward focal conservative treatment, external beam radiation therapy (EBRT) continues to be an important and effective method which permits preservation of ocular and visual potential when treating less-advanced retinoblastomas, especially when there is diffuse vitreous subretinal seedings.[1] Herein, we report on irradiation of a group Vb retinoblastoma which underwent enucleation, and describe the histopathological findings of the irradiated eye.

CASE REPORT

This patient was a 7-month-old male who had experienced a normal gestation delivery. He was in excellent health until his parents noticed a white pupillary reflex in the right eye. He was examined by a local ophthalmologist, and a diagnosis of retinoblastoma was made. The patient was immediately referred to our hospital. At that time he could localize a 15-mm target with his left eye. Fixation of his right eye was markedly diminished; however, he could localize a large red light with that eye. The

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optokinetic nystagmus test with a 4-cm stripe was negative. No deviation was revealed by the Hirschberg test. An intraocular tumor was detected in his right eye with ultrasonography. Computed tomography (CT) scans of the right orbit confirmed the presence of a calcified intraocular mass (Fig. 1). One week later, the patient was examined with indirect ophthalmoscopy under general anesthesia. A large subretinal and intraretinal whitish mass was identified nasally, which extended posteriorly from the ora serrata to the region of the optic nerve and macular area (Fig. 2). Extensive vitreous seeding of tumor cells was noted (Group Vb in the Reese-Ellsworth classification). The lens and anterior chamber were unremarkable. Examination of the left eye revealed nothing outside of normal limits.

The systemic work-up, including lumbar puncture, bone marrow biopsy, and brain and left orbit CT scans, was unremarkable.

In an attempt to maintain useful vision and control the tumor, the child was treated with external beam radiation therapy (EBRT) employing a total

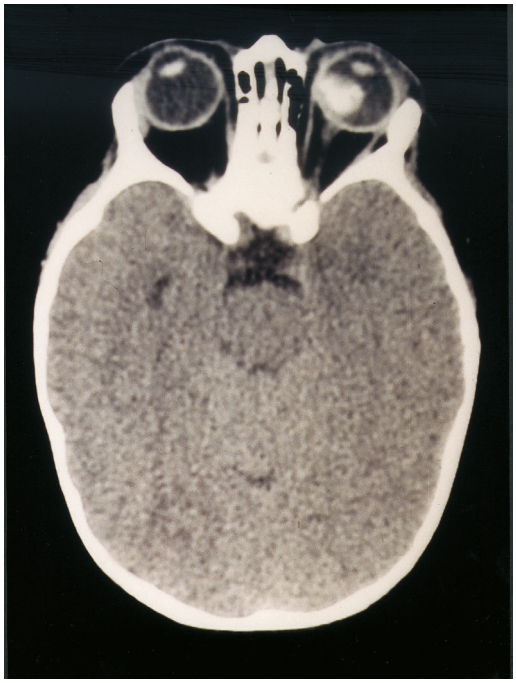

Fig. 1 Axial CT scans showing a calcified intraocular mass.

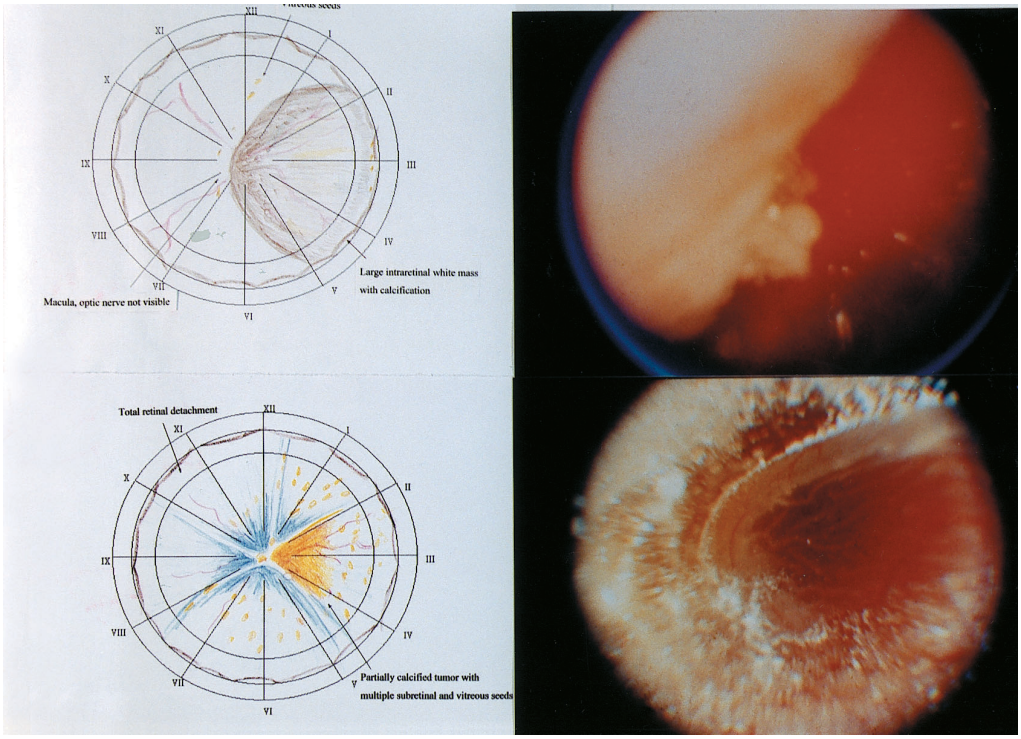

Fig. 2 Photography and fundus drawing of the right eye at presentation (top) and after irradiation (bottom).

dose of 4570 cGy, administered in 25 fractions using doses of 180-190 cGy over a period of 5 weeks.

Retinal detachment in his right eye was noted by the child's radiation oncologist 3 weeks after starting the EBRT. Radiation therapy was continued in the hope that the retina might reattach and to decrease the amount of viable tumor that would be present at the time of enucleation. Total retinal detachment with a funnel configuration was confirmed under general anesthesia 7 weeks later (Fig. 2). A calcified intraocular mass located in the nasal quadrant anterior to the equator was again noted. Multiple calcified flecks were seen within the lesion. Adjacent to the tumor and throughout the anterior retina and vitreous, small white punctate lesions were identified, which were thought to be regressed tumor seeds. The optic disc and macula could not be visualized due to the retinal detachment. No abnormalities were identified in the anterior segment. Examination of the left eye was unremarkable. The right eye was enucleated 2 months later.

Histopathological findings

Gross examination:

The right eye was received in formalin. The horizontal meridian measured 20.5 mm, and the vertical meridian measured 20.0 mm. The cornea and superior aspect of the sclera had collapsed, which caused an artifactual shortening of the anterior-posterior meridian which measured 14.0 mm. The horizontal and vertical dimensions of the distorted cornea measured 10.5 ¡ 9.5 mm, respectively. No iris neovascularization was noted. A 4.0-mm-long portion of the optic nerve with a diameter of 3.5 mm was present.

A transillumination defect was identified with a fiber optic illuminator. This defect was located at approximately 4~5 o'clock and was 7.0 mm posterior to the corneoscleral limbus and 8.0 mm anterior to the optic nerve. The anterior and vertical posterior lengths of the defect were 4.5 and 3.0 mm, respectively. The eye was trisected at the superior and inferior limbus at a slightly oblique angle to include the area with the transillumination defect in the center section. An intraocular tumor was present corresponding to the transillumination defect. The retina was totally detached, and appeared thickened with a white-tan color adjacent to the mass.

Microscopic examination:

Histopathological examination disclosed a tumor with features typical of a retinoblastoma (Fig. 3). The cells were characterized by round nuclei, inconspicuous nucleoli, and scant amounts of cytoplasm. Occasional Flexner-Wintersteiner rosettes were present. Significant calcification was noted within the mass, but marked tumor necrosis

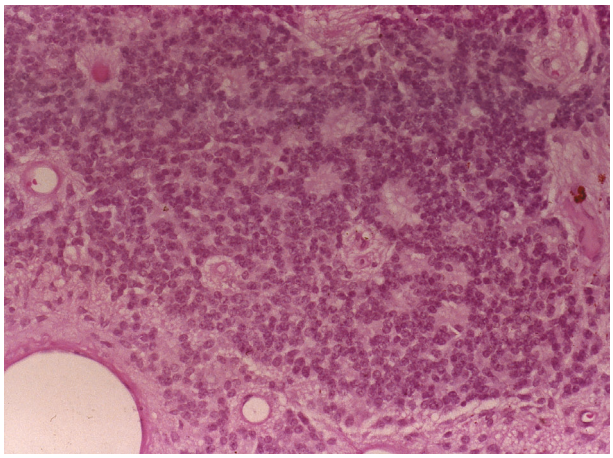

Fig. 3 Clusters of typical cells of the retinoblastoma (round nuclei, inconspicuous nucleoli, and scant amount of cytoplasm) and typical Flexner-Wintersteiner rosettes. (H&E, ¡ 200)

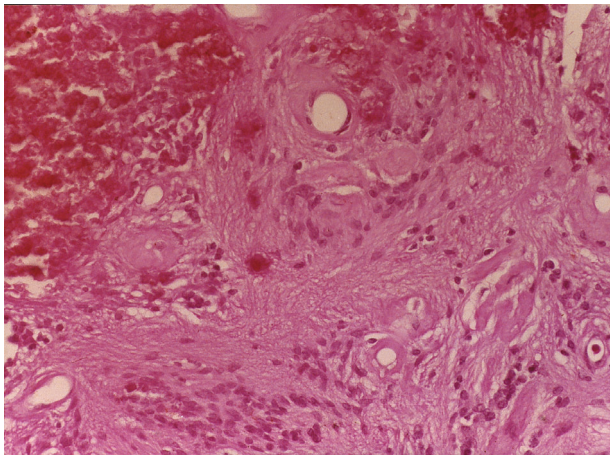

Fig. 4 Significant gliosis and irregular thickening of capillaries by fibrillary materials. (H&E ¡ 200)

was not identified. A preretinal fibrous membrane was noted along the periphery of the tumor, and focal vascular thickening due to deposition of fibrillary material was identified in the retina (Fig. 4). Posterior migration of epithelial cells and fragmentation of the lens material were present. The anterior segment was unremarkable. No tumor was present in the optic nerve.

DISCUSSION

EBRT has evolved into an eye-conserving and vision-preserving treatment for retinoblastomas, especially when the retinoblastoma is an extremely radiosensitive tumor, and particularly when there is extensive vitreous or subretinal seedings.[1] Since the first documented cure of a retinoblastoma using treatment with irradiation in 1918,[2] various EBRT techniques have been reported. The specific treatment modality depends on the location and the size of the retinoblastoma, the presence of vitreous seeding, the number of tumors, and the status of the contralateral eye.[3] Side effects of EBRT tend to be dose related and include chronic dry eye, radiation cataract, vitreous hemorrhage (from unsupported tumor vessels in a shrinking tumor, or from radiation-induced neovascularization), radiation retinopathy (RPE mottling, retinal vascular occlusion, microaneurysm, and exudate), optic nerve ischemia (late radiation damage to small vessels within the optic nerve), poor orbital bone development, and, most seriously, radiation-induced second cancer.[4-7] The rate of eye preservation depends mainly on the stage of the disease (91% for group 1 retinoblastomas; 29% for group V).[8] The traditional standard treatment of an eye with a Reese-Ellsworth group V retinoblastoma has been either enucleation or EBRT, although the globe salvage rate was limited to 8%~25%[9] in older series. Recently with marked improvements in adjunctive therapy and chemotherapy, the globe salvage rate for group V retinoblastomas has increased up to 66%~78%.[8-10]

EBRT was initially given in our case in hopes of preserving the globe. Unfortunately, total retinal detachment developed thereafter. Enucleation was therefore performed as the standard treatment for an advanced group V retinoblastoma with failed EBRT and the occurrence of total retinal detachment.

On biopsy, the histopathological findings revealed a residual uncontrolled tumor with characteristics of a retinoblastoma, with no prominent necrosis. Significantly regressed vitreous seeds and calcification were found within and surrounding the residual mass. A preretinal fibrous membrane as well as prominent focal vascular thickening along the periphery of the retina were concomitantly noted, which implied a partial but incomplete effect of EBRT for this advanced group Vb retinoblastoma.

Marcus[2] and Egbert et al.[10] described the most-consistent histopathological findings for irradiated retinoblastomas, which consist of abnormalities of the retinal vessels (thickening of the vascular wall with deposition of PAS-negative fibrillary material) and ciliary arteries (myointimal proliferation and lumen narrowing). Choroiretinal and neuroglial scars, cataracts, retinal vascular occlusions, neovascularization, preretinal proliferative changes,[2,11] and diffuse optic nerve atrophy[10] have all been reported in irradiated eyes.

EBRT with or without adjunctive therapy provides effective eye-preservation treatment for an advanced retinoblastoma, particularly with vitreous seeding. However, it may fail. From the retina pathology of this unsuccessful case (group Vb), if EBRT is to be used as a treatment modality, it should be applied to earlier groups.

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以放射線治療視網膜母細胞瘤之視網膜病理解剖

譚欣媛　陳賢立　陳成彥　李文浩

本病例爲7個月大的男孩以右眼出現白色瞳孔反射作爲右眼視網膜母細胞瘤之初步表現。眼部檢查發現一個大型視網膜腫瘤，並有廣泛的玻璃體癌細胞轉移，符合Reese-Ellsworth第五期之分類。初步先採用放射線治療；起初有明顯的腫瘤消退，但3個月後病情擴展成全視網膜剝離，故隨即施與眼球摘除術。病理解剖可見明顯鈣化的殘餘腫瘤，並在腫瘤周圍有纖維化及血管增生，顯示放射線治療對此第五期視網膜母細胞瘤有著不完全的療效。本篇以視網膜病理解剖的角度，來佐證放射線治療對於視網膜母細胞瘤治療之重要性。(長庚醫誌 2002;25: 542-7)

關鍵字：視網膜母細胞瘤，放射線治療。

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