

Diffuse anterior retinoblastoma: current concepts

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Abstract: Diffuse anterior retinoblastoma is a rare variant of retinoblastoma seeding in the area of the vitreous base and anterior chamber. Patients with diffuse anterior retinoblastoma are older than those with the classical types, with the mean age being 6.1 years. The original cells of diffuse anterior retinoblastoma are supposed to be cone precursor. Patients most commonly present with pseudouveitis, pseudohypopyon, and increased intraocular pressure. The retina under fundus examination is likely to be normal, and the clinical features mimic the inflammation progress, which can often lead to misdiagnosis. The published diffuse anterior retinoblastoma cases were diagnosed after fine-needle aspiration biopsy running the potential risk of inducing metastasis. The most common treatment for diffuse anterior retinoblastoma is enucleation followed by systematic chemotherapy according to the patient's presentation and clinical course. This review summarizes the recent advances in etiology (including tumorigenesis and cell origin), pathology, diagnosis, differential diagnosis, and new treatment. The challenges of early diagnosis and prospects are also discussed.

Keywords: pathology, microenvironment, treatment, diagnosis

Introduction

Retinoblastoma is a common intraocular malignancy in infancy or childhood, presenting the typical clinical features leukocoria (white reflections in pupil) and strabismus, with an incidence rate of approximately one in 15,000–20,000 live births worldwide.¹⁻⁶ Most sufferers are diagnosed at less than 5 years old, with a median age of 18 months.^{1,2,4} Two centuries ago, retinoblastoma was first reported by Haye et al who described it as a neuroectodermal tumor within retina.^{5,6} According to different criteria, retinoblastoma can be classified as sporadic or familial and as unilateral or bilateral, respectively.^{7,8}

Retinoblastoma was also the first disease demonstrating a genetic defect in cancer research, and *RBI* is the only gene in which mutations are known to cause heritable predisposition to retinoblastoma.³ *RBI* gene is localized to chromosome 13q1.4 and has an autosomal dominant pattern of inheritance.^{9,10} In both heritable and sporadic cases, biallelic mutations of the *RBI* tumor-suppressor gene initiate tumor growth.^{8,11-14,15} Normally, pRb encoded by *RBI* gene plays important roles in preventing the progression of the cell cycle from G1 to S phase through inhibiting E2F transcription factors (E2Fs) which act as important transcription regulators in eukaryotes.^{12,13,16-18} The pRb function is modulated by phosphorylation which is mediated by cyclin-dependent kinase (CDK)-cyclin complexes.¹⁹⁻²¹ And retinoblastoma does not originate from intrinsically death-resistant cells as previously thought. When *RBI*-deficient retinoblasts undergo p53-mediated apoptosis and exit the cell cycle, subsequently, MDMX (Mdm2 p53 binding protein homolog) protein overexpresses following *MDMX* gene amplifies, which are strongly selected for during tumor progression as a mechanism to suppress the p53 response in *RBI*-deficient retinal cells.²²⁻²⁵

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Retinoblastoma originates from cone precursors and performs various growth patterns, including: endophytic, exophytic, mixed endophytic–exophytic, intraretinal, diffuse infiltrating, and spontaneous regression/arrest (retinocytoma/retinoma).^{26–30} Among these, diffuse infiltrating retinoblastoma is a rare type which has seed involvement of the retina with free tumor cells entering the aqueous humor, infiltrating the vitreous, and diffusely implanting on the anterior segment.^{31–35} Diffuse anterior retinoblastoma is an anterior variant of diffuse infiltrating retinoblastoma which results in tumor cells in the aqueous humor disseminating from inferior peripheral intraretinal focus seeding in the area of ciliary body, vitreous base, and anterior chamber.^{36–43} Features such as invisible retinal mass and anterior segment lesion infiltration mimic inflammatory processes in the anterior segment, which often leads to misdiagnosis of uveitis and endophthalmitis unless anterior chamber paracentesis or tissue sampling is performed.^{44,45} Therefore, the average onset age of diffuse anterior retinoblastoma is higher than that of the classical types.³⁶

Historical review

Two centuries ago, Hayes first published a description of a neuroepiblastic tumor of the retina, which was later named as “retinoblastoma” in 1767.^{1–3} “Diffuse infiltrating retinoblastoma” was first suggested by Ashton in 1958 to describe the unusual nature of a flat neoplasm that seldom formed tumor masses in retina.^{31,32} Afterwards, Jijelava and Grossniklaus reported a case which was characterized by anterior chamber pseudohypopyon without visible retinal mass and finally named as “diffuse anterior retinoblastoma” in 1998.³⁶ It was once believed that diffuse anterior retinoblastoma was unilateral and non-heritable, until 2009, when Crosby et al presented a case exhibiting a germline mutation of *RBI* that indicated that diffuse anterior retinoblastoma may in fact be heritable.³⁷ Overall, a total of six cases have been reported; since then, little has been published on anterior diffuse retinoblastoma.

Effect of microenvironment

Microenvironment is considered to exert significant effects on the tumor progression for classical retinoblastoma.⁴⁶ For example, under hypoxic conditions, active HIF-1 heterodimeric complex binds to core DNA sequences at the hypoxia response element, and thus activates multiple target genes including VEGF.^{46,47} Therefore, coordinate upregulation of HIF-1 and VEGF is involved in tumor angiogenesis, which induces neovascularization from the preexisting vessels, increasing the supply of nutrients to promote the proliferation and survival of tumor cells in a

hostile microenvironment.⁴⁷ To investigate the microenvironmental factor of tumorigenesis involved in diffuse anterior retinoblastoma, Crosby et al performed immunofluorescent stainings both on the intraretinal tumor and on tumor cells in the aqueous humor.³⁷ Both types of sample were positive for vascular endothelial growth factor (VEGF) and negative for inducible nitric oxide synthase (iNOS) and hypoxia-inducible factor 1 (HIF-1); however, transforming growth factor β (TGF- β) was positive in the aqueous humor tumor cells only. The results indicate that VEGF expressed by the intraretinal tumor did not appear to be mediated by HIF-1 or iNOS, which are the common pathways of ischemia mediating angiogenesis.³⁷ The TGF- β superfamily possesses three major functions in growth regulation and development: inhibit proliferation (of most cells, but can stimulate the growth of some mesenchymal cells), exert immunosuppressive effects, and enhance the formation of extracellular matrix.^{48,49} Among the functions, inhibition of growth by TGF- β stems from a blockage of the cell cycle in the late G1 phase participates in G1 arrest with retinoblastoma proteins and members of the cyclin/CDK CDKI families.^{50,51} TGF- β also inhibits cell proliferation through inducing the synthesis of 4EBP1 and CDKIs (p15, p21, and p57).⁵² The combination of 4EBP1 and eIF4E (eukaryotic initiation factor 4E) suppresses the protein translation, and CDKIs inhibit cell cycle progression through inhibiting activity of the cyclin–CDK complex which is essential for G1/S transformation, contribute to phosphorylation of retinoblastoma proteins, and thus lead to tumor formation.^{51,52} Additionally, TGF- β also inhibits expression of Cdc25a phosphatase, which is necessary for cyclin–CDK complex activation and negative regulation of factors including Id protein, E2F, and c-Myc driving the cell cycle progression and cell proliferation.^{49–51} Crosby et al speculated tumor seeds in aqueous humor acquire TGF- β as a survival factor to aid in tumor formation and migration.³⁷

Pathology

Under microscope, the tumor cells infiltrated diffusely throughout the anterior chamber, anterior vitreous, and posterior cornea are always in the forms of singles, clumps, or islands, which are similar to those seen in the earlier fine-needle aspiration biopsy (FNAB). They have small round basophilic shapes; high nuclear-to-cytoplasmic ratios; hyperchromatic nuclei; and presence of nuclear pyknosis and karyorrhexis, which suggests the existence of necrosis.

Pathologically, retinoblastoma consists of cells with round, oval, or spindle-shaped nuclei that are approximately

twice the size of lymphocytes forming the structure of rosettes. The rosettes include Homer Wright and Flexner–Wintersteiner (FW) rosettes, dependent on the stages of retinal differentiation, and these two rosettes are exclusively found in retinoblastoma.⁵³ The lumen corresponds to subretinal space and stains with alcian blue (HR-AMP) that contains cytoplasmic extensions from the tumor cells. The cells surrounding the lumen are joined near the apices by intracellular connections (zonulae adherent), which are analogous to the external limiting membrane of retina. FW rosettes are not pathognomonic because they also occur in malignant medulloepitheliomas and some pineal tumors.^{53,54} Taking into account all reported cases, Homer Wright rosettes were present in two cases whereas FW rosettes were present in two other cases.^{37,38,41,42}

On electron microscopy, tumor cells have a high nuclear-to-cytoplasmic ratio, rare nucleoli, glycogen granules, intercellular junctions, sparse intracytoplasmic filaments, chromatin clumping, and cilia in the 9+0 configuration (cilia-like structures with a ring of nine doublet microtubular structures but no central component) that is characteristic of retinoblastoma and retinal photoreceptors.

At present, there is not a standard consensus regarding immunohistochemical staining for retinoblastoma diagnosis, and the protocols performed in each case varied. However, several biomarkers were commonly used and manifested similar results. Neuron-specific enolase ([NSE] a glycolytic enzyme essentially confined to neurons) is observed positive in neuron processing of all layers in normal retina.^{55,56} NSE was positive in two cases,^{38,39} which indicates that diffuse anterior retinoblastoma was of neuronal origin. Synaptophysin (a neuron-associated integral membrane glycoprotein of presynaptic vesicle) is concentrated in synaptic connections, while, in retinoblastomas, they exist in rosette-forming cells and in both plexiform layers.^{54,55} Synaptophysin was positive in two cases indicating a photoreceptor-like differentiation of this tumor. Vimentin, which immunolabels cells that undergo epithelial-to-mesenchymal transition, was positive in Grossniklaus et al³⁸ indicating acquisition of infiltration and metastasis ability in diffuse anterior retinoblastoma. Negativity in remainder biomarkers such as S-100 and glial fibrillary acidic protein (GFAP) also possesses significance. In normal retina, S-100 protein and GFAP are positive in astrocytes and Muller cells, while the reaction of these proteins are devoid in retinoblastoma tumor cells, which supports the view that retinoblastomas are composed of neuron-committed cells. S-100 was negative in three cases, and GFAP was negative in two cases. Moreover, mouse monoclonal anti-cytokeratin (MAK-6), AE1/AE3, leukocyte

common antigen, and cluster of differentiation molecule 34 (CD34) each stained negatively in one case report.

Diagnosis and differential diagnosis

Diffuse anterior retinoblastoma is usually unilateral, and the average age of the disease is approximately 6.4 years.³⁶ It was once believed that diffuse anterior retinoblastoma was sporadic, until 2009, when Crosby et al reported a germline mutation which had been previously reported in heritable retinoblastoma.³⁷ In most cases, children present with pseudouveitis or pseudohypopyon, which mimic the inflammation process that often leads to misdiagnosis. Overall, a total of six cases have been reported; the clinical descriptions and pathological examinations are summarized in Table 1.

Redness, visual blurring, and iris depigmentation are often the chief complaints of the initial visits, and primary diagnosis can mistakenly lead to conjunctivitis, so children with the above symptoms should receive comprehensive examinations without only antibacterial eyedrops. Keratic precipitates and white fluffy exudates, which are common clinical features of granulomatous uveitis or *Toxocara* endophthalmitis, could also be noticed in such patients under slit-lamp examination.^{36–40} Gonioscopy can reveal a partly closed anterior chamber angle attributing to the obstruction of the trabecular meshwork from cellular debris.⁴⁴ Commonly, intraocular pressure (IOP) of the patients is elevated, and the average IOP is about 35 mmHg, which can be explained by neovascularization of the iris and/or infiltration of tumor cells into Schlemm's canal or the trabecular meshwork.⁴⁴ Some glaucomatous atrophy could also be noticed in corneal epithelium, optic nerve, and retina. Ectropion uveae can be occasionally identified, which results from fibrovascular tissue on the anterior surfaces of the iris leaflets.⁴² Fundus exam is likely to be normal, but one case identified a small peripheral retinal mass at the initial optical examination.³⁷ B-scan echography is always unable to detect a retinal mass or calcification.³⁸

Differential diagnosis of diffuse anterior retinoblastoma is broad, including medulloepithelioma, sarcoidosis, idiopathic uveitis, metastatic neuroblastic tumor, fungal endophthalmitis, pars planitis, *Toxocara* endophthalmitis, leukemia, lymphoma, juvenile rheumatoid arthritis-associated uveitis, and retinoblastoma.^{56,57} Among these diseases, medulloepithelioma is the most significant one to be distinguished.

Medulloepitheliomas are typically malignant nonhereditary embryogenic neoplasms of the medullary epithelium almost always occurring in the ciliary body.⁵⁸ Secondary glaucoma from iris neovascularization actually occurs more frequently with medulloepithelioma, occurring in 60% of

Table 1 Clinical descriptions and pathological examinations

| Authors (year) | Eye | Age/sex | Chief complaints | Slit-lamp examination | IOP and VAC | Fundus examination | US imaging | Misdiagnosis/initial diagnosis | Diagnosis tool | Treatment | Immunohistochemical stains | Follow-up |
|---|-----|---------|---|--|---|--|---|--------------------------------|--|---|---|---|
| Garner et al ³⁹ (1987) | OD | 7 y/F | Redness, blurring of vision | "Severe anterior uveitis with large iris nodules and cells and opacities in the anterior vitreous" | IOP 44 mmHg (after treatment for granulomatous uveitis) VAC 6/60 | Unknown | Unknown | "Granulomatous uveitis" | Biopsy of iris, lens excision | Initial treatment: topical corticosteroids, oral prednisone 5 mg TID, sub-Tenon's injection of methylprednisolone, lens excision Treatment after diagnosis: enucleation, orbital radiotherapy, adjuvant chemotherapy | (+)NSE (-)S-100 (-)GFAP | Recurrent orbital retinoblastoma 8 months after enucleation; no sign of further recurrence at 12 months |
| Grossniklaus et al ³⁸ (1998) | OD | 6 y/F | Unknown | November 1995: 4+ anterior chamber cells; May 1996: 4+ anterior chamber cells, a small "hypopyon", 1+ to 2+ vitreous cells; June 1996: dense "hypopyon" with 4+ anterior chamber cells and 4+ vitreous cells | November 1995: IOP 28 mmHg; 20/30-2 May 1996: IOP 34 mmHg; VAC 20/70+1 June 1996: IOP 43 mmHg; vision by hand motions | Normal appearing retina, cells in inferior vitreous | Posterior vitreous detachment, no retinal detachment or mass | | Anterior chamber fine-needle aspiration biopsy | November 1995: topical prednisolone, dexamethasone 0.1%, betaxolol HCl 0.5%, thiabendazole for 3 days, oral prednisone May 1996: topical prednisolone q1 - 2H, dorzolamide HCl TID, timolol maleate 0.25% qHS, diclofenac sodium QID, dexamethasone qHS; enucleation June 1996: rimexolone q1 - 2H, α -clonidine 0.5% TID; enucleation | (+)NSE (+)Vimentin (-)Cyokeratins (MAK-6, AE1/AE3) (-)GFAP (-)S-100 | Unknown |
| Crosby et al ³⁷ (2009) | OS | 9 y/F | Blurry vision, redness, discoloration of iris | Pseudohypopyon | IOP 34 mmHg VAC 20/60 | A possible small, inferior, peripheral mass in her left retina | Unknown | | Anterior chamber fine-needle aspiration biopsy | Enucleation | (+)TGf- β (+)VEGF (-)iNOS (-)HIF-1 α | Unknown |
| Longmuir et al ⁴¹ (2010) | OD | 8.5 y/M | "Unilateral anterior uveitis" | Keratic precipitates; 3-4+ cells; "less prominent flare", small hypopyon, multiple nodules on iris and angle | IOP 46 mmHg VAC 20/40 | No retinal abnormalities or masses detected | Iris root thickening to 1 mm for 360°, mild anterior vitreous opacities | | Anterior chamber fine-needle aspiration biopsy | Initial treatment: topical prednisolone 1% q1H, topical dorzolamide HCl, timolol maleate, brimonidine, scopolamine HBr 0.25%, oral prednisone 30 mg PO q day Treatment after diagnosis: enucleation, six cycles of vincristine, carboplatin, etoposide, external beam radiation (4,140 cGy total) | (+)VEGF (-)iNOS (-)HIF-1 α (+)Synaptophysin (-)Leukocyte common antigen (-)CD34 | No recurrence at 5 y |

| | | | | | | | | | | | |
|-----------------------------------|----|-------|--|---|-------------|-------------------------|--------------------------|--|--|--|--------------------------------------|
| Khetan et al ⁵² (2011) | OS | 3 y/F | Unresolving anterior uveitis with secondary glaucoma | Conjunctival congestion, pupil sluggishly reactive to light, "white, fluffy exudates" | IOP 31 mmHg | Normal appearing retina | Normal | Anterior chamber fine-needle aspiration biopsy | Initial treatment: topical prednisolone 1% q4H, homatropine BID, timolol maleate 0.5% + brimonidine acetate 0.2% BID | Unknown | No recurrence at time of publication |
| Herwig et al ⁵³ (2011) | OS | 3 y/M | Discoloration of iris | Pseudohypopyon | IOP 26 mmHg | Normal appearing retina | No mass or calcification | Anterior chamber fine-needle aspiration biopsy | Treatment after diagnosis: enucleation Enucleation, six cycles of carboplatin, etoposide, vincristine | (+)Synaptophysin (+)NSE (-)S-100 | No recurrence at 5 months |

Abbreviations: BID, twice a day; HBr, hydrobromide; IOP, intraocular pressure; OD, right eye; OS, left eye; PO q day, per oral daily; q1 – 2H, every 1–2 hours; q4H, every 4 hours; qHS, nightly before sleep; QID, four times a day; YAC, visual acuity; M, male; F, female; y, years; NSE, 2-phospho-D-glycerate hydrolase; GFAP, glial fibrillary acidic protein; TGF- β , transforming growth factor- β ; VEGF, vascular endothelial growth factor; iNOS, inducible nitric oxide synthase; HIF-1, hypoxia-inducible factor 1.

cases.⁵⁹ Though nonteratoid medulloepitheliomas have been suggested to express NSE and synaptophysin, suggesting that they may be of neuronal origin, they also perform positive in biomarkers of GFAP, S-100, and vimentin, indicating that nonteratoid medulloepitheliomas may be multi-potential tumors, different from retinoblastoma composed of neuro-committed cells. Diffuse anterior retinoblastoma and medulloepithelioma are nearly indistinguishable on imaging, because both neoplasms are hyperintense to the vitreous on T1-weighted images and hypointense on T2-weighted images and enhance either uniformly or heterogeneously.^{60,61}

Making a correct diagnosis still remains the greatest challenge in the management of the disease. Since this variant of retinoblastoma is extremely rare, the absence of an obvious retinal mass easily leads to misdiagnosis. In addition, since the diagnosis of diffuse anterior retinoblastoma relies upon an FNAB, which possesses the potential danger of aggressive tumor spreading, pursuing particular clinical hint presentation and seeking a diagnostic tool which could confirm the diagnosis without amplifying the tumor dissemination are of crucial importance.

Management

Attribute to the previous misdiagnosis, the majority of patients in the cases received topical corticosteroids to anti-inflammation and medications lowering the IOP due to the increased IOP, which were not beneficial to diffuse anterior retinoblastoma.^{37,38,41,42} Accordingly, all the published cases performed enucleation followed by systematic chemotherapy.

The reported diffuse anterior retinoblastoma cases were unilateral and possessed anterior segment invasion, which are the absolute criteria for enucleation because these eyes have very limited visual potential in a prolonged period. The tumoral avascular features of this variant, which involves the anterior chamber and basal vitreous, are either poorly controlled by conventional therapies or beyond any conservative treatment, while traditional solid vascularized retinal tumors are easily accessible to various treatment modalities.^{62,63} In addition, these aggregations of tumor cells are virtually inaccessible to focal treatments and are highly radio resistant due to their hypoxic nature.⁶⁴ So diffuse tumor cell control cannot be accomplished with any of the available modalities without enucleation, and the risk of keeping a blind eye cannot be justified when there is a risk for tumor spread and metastasis. Vital elements of enucleation include minimizing globe trauma and obtaining a long section of optic nerve in order to avoid seeds in it.

Following enucleation, histopathology should be examined to evaluate hints or presence of metastatic. High-risk cases include those with tumor invasion posterior to the

lamina cribrosa of the optic nerve, those with 3 mm or greater of choroidal invasion, and those with a combination of any degree of optic nerve and uveal invasion,⁶⁵ and additional systematic chemotherapy and consolidation are required to control the diffuse infiltrating seedings.⁶⁶ Although intravenous chemotherapy protocols vary slightly between institutions, many centers are currently treating intraocular retinoblastoma with carboplatin, vincristine, and etoposide as a three-drug regimen given in two to six cycles.⁶⁷

But to probe into the chemotherapy regimens and determine the standard chemotherapy, we still need more long-term clinical trials to investigate the therapeutic effect of treatment options that are individual or as a combination such as intravenous chemotherapy, intra-arterial chemotherapy, and intravitreal chemotherapy and thus to make further adjustment of management including selecting the appropriate adjuvant chemotherapy methods and deciding the number of the chemotherapy cycles, which is beneficial for the survival rate and living quality of the patients. Therefore, modern centers are treating retinoblastoma with a variety of modalities and individualizing the therapy according to the patient's presentation and clinical course.

No recurrences of tumor were reported in any of the published cases, though the accurate survival rate is difficult to extract because of the lack of long-term follow-ups.

Conclusion

Diffuse anterior retinoblastoma is a rare variant of diffuse infiltrating retinoblastoma that occurs unilaterally in children between the ages of 3 and 9 years. The majority of cases are nonhereditary; however, there is one reported case in a child with a germline mutation of the *RB1* gene. FNAB should only be performed at highly specialized centers with experienced ophthalmologists and ophthalmic pathologists as a last resort to narrow the differential diagnosis due to the risk of tumor dissemination. Simultaneously, exploring the particular clinical hint presentation and seeking diagnostic tools other than FNAB that could confirm the diagnosis without amplifying the tumor dissemination are of importance. Additionally, making adjustment of management such as selecting the appropriate adjuvant therapy methods is crucial for the survival rate and living quality of the patients. Detailed, long-term case reports following diagnosed children are still lacking.

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Disclosure

The authors report no conflicts of interest in this work.

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