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ANTERIOR CHAMBER EXTENSION OF RETINOBLASTOMA

Case Report, Part 1

In 2009, a girl aged 4 years 5 months noticed blurry vision. A well-baby clinic found her vision to be 20/30, OD, and 20/125, OS. It had been 20/40 in both eyes at age 4. The parents also noted abnormal whiteness on the iris. An ophthalmologist in the nearest hospital found cells and precipitates in the anterior chamber, a whitish iris tumour, vitreous cells, and a large retinal tumour, OS, and diagnosed a unilateral retinoblastoma.

At examination under anaesthesia in the Ocular Oncology Service, Helsinki University Hospital, her right eye was normal save for a small hypertrophy of the RPE. The IOP was 16 mmHg, OD, and 19 mmHg, OS. The cornea was clear. At 11 o'clock, a white vascularised shallow tumour extended across the iris. Multiple partly vascularized deposits resided in the inferior angle, and single cells and satellites in the vitreous. A solid tumour that was 10.7 mm thick and measured 14.8 mm and 16.7 mm in smaller and larger diameter, respectively, was found in the nasal retina. The optic disc and macular area were visible and uninvolved.

A diagnosis of a typically non-cohesive late-onset, group E, retinoblastoma was made. Primary proposal was enucleation, routine for anterior chamber extension, and adjuvant chemotherapy given extensive seeding of the chamber angle. Because of potential for macular vision, an alternative strategy with chemoreduction and, as needed, intraocular methotrexate already in use for vitreous seeding in Helsinki was discussed, with secondary enucleation in case of no response or inadequate response. The family preferred the latter.

Eight cycles of vincristine, etoposide, and carboplatin (VEC) were eventually given in another University Hospital after a negative bone marrow aspiration and systemic evaluation had excluded metastases. Already after the 1st VEC cycle, the anterior chamber foci had all but vanished leaving anterior synechiae behind, the vitreous was clearer, and the primary tumour smaller. Sectoral posterior subcapsular cataract existed where it had touched the lens. The retina had detached, however. We suspected that the regressing tumour had left a hole behind. Minor vitreous haemorrhage had occurred. After the 2nd cycle, the anterior chamber was clear, and the main tumour had calcified to quarter size. The detachment behaved like a rhegmatogenous one.

No-drainage surgery was scheduled after the 3rd cycle. The anterior segment was quiet. Vitreous seeds had sharpened. The base of the retinal tumour was cryocoagulated, which helped to lower the IOP through indentation. Twin radial 5.5 mm buckles under single sutures were applied to match the tumor diameter to cover a hole in any position, and gradually tightened. An anterior chamber tap was negative for tumour cells.

After the 4th cycle, the retina was attached. Minor new bleeding over the tumour and in the vitreous were noted. After the 5th cycle, delayed by 2 weeks because of diarrhoea, a small recurrent focus was seen in the inferior angle and another one at the pupillary margin. A small greyish area was seen at the margin of the calcified tumour. Intraocular, high-dose intravenous, and intra-arterial chemotherapy options were discussed.

The parents preferred added intraocular chemotherapy. Injections of methotrexate divided in the anterior chamber and the vitreous were given, the former via a long intracorneal track. After the 6th injection, the anterior chamber was clear. After the 6th VEC cycle, vitreous seeds were all sharp, and the greyness at the calcified tumour margin had resolved. Maintenance methotrexate injections followed. Complete regression was confirmed at the 7th and 8th VEC cycles as well as when methotrexate was discontinued after 1 year.

She was reviewed monthly. Visual acuity was 20/200. Optical coherence tomography showed a rugged macular photoreceptor layer and RPE with intraretinal pigment migration from prior retinal detachment. At 5 months post VEC, recurrent small vitreous spheres were discovered. Secondary enucleation and whole eye salvage radiotherapy were discussed as options. After due consideration, the parents chose the former, and the eye was removed 2 weeks later. By that time, a 1.5 mm recurrence had appeared in the chamber angle.

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The eye measured 22 mm in diameter with a 2 mm optic nerve stump and was sectioned vertically. Calcified primary tumour measured 7 mm in diameter. The periocular tissues and cornea were normal. The optic nerve head and choroid were free of tumour. The retina outside the tumour displayed degenerative changes and intraretinal pigment migration, likely in macrophages.

In addition to pyknotic tumour cells and macrophages, the anterior vitreous had viable small satellites and single tumour cells. They were also seen the in posterior and anterior chamber, and single cells adhered to the corneal endothelium. Small tumour nodules were found on anterior iris stroma and another viable nodule in the chamber angle infiltrated the root of the iris, trabecular meshwork, and adjacent ciliary body. Its center was necrotic. Plenty of sections were screened without any tumour cells in Schlemm's canal, aqueous veins, or episclera. However, in still further sections, single small round cells along the inner surface of Schlemm's canal were detected that had hyperchromatic nuclei rather than nuclei with finely dispersed chromatin like in tumour cells in the other locations. Immunostaining for synaptophysin in two stepped sections nevertheless identified a few immunopositive tumour cells in Schlemm's canal.

Case Report, Part 2

The paediatric oncologists were informed about the histopathology. They elected not to administer adjuvant chemotherapy after a screening MRI of the orbit, head and neck, cerebrospinal fluid, bone marrow with anti-GD2, and bone scans were negative. The same was true 6 months after enucleation. An MRI was negative also at 9 months. One year after enucleation, the socket remained normal clinically and by MRI.

One year 3 months after enucleation, hepatic and bone metastases were detected. The orbit was normal. High-dose chemotherapy with bone marrow rescue resulted in remission by 6 months, maintained at 1 year. A month later, bone marrow relapse was detected that failed to respond to treatment. She died at age 9 years.

Comment

Anterior chamber involvement, which occurs generally in 2-5% of eyes with retinoblastoma, is debated as a risk feature for metastasis [1-3]. A web-based, non-validated survey in 2020 found that of 24 referral centers with ocular oncologists and pathologists in 16 countries, only 52% considered anterior chamber seeds a high-risk feature, as compared to postlaminar optic nerve (100%) or massive choroidal invasion (93%) [4].

Histopathologic reports of *anterior chamber seeds* are exceptional [5]. However, in May 2022, Jakati and Kaliki studied clinical types of aqueous seeds and histopathologic characteristics in 25 primarily enucleated eyes with retinoblastoma and classified them according to Munier [6]. Type 1 "dust" (36%) were individual tumour cells mixed with macrophages and nonviable tumor cells. Type 2 "spheres" (32%) were round foci with or without a central core of necrosis surrounded by viable cells. Type 3 "clouds" (32%) represented viable and nonviable tumour cells, macrophages, and erythrocytes sedimented at the chamber angle. Seeds were associated with invasion of posterior chamber (72%), trabecular meshwork (40%), Schlemm's canal (16%), iris (52%), ciliary body (56%), choroid (massive in 36%), sclera (4%), and postlaminar optic nerve (28%) in almost all eyes (92%). Especially type 3 seeds were associated with ciliary invasion (41% vs. 88%). During a median follow-up of 4 years, 3 patients (12%) developed metastases; they had massive choroidal and postlaminar optic nerve invasion as well. The authors thought that association of aqueous seeding with other high-risk histopathologic features suggests a cautious approach to their conservative management.

A previous retrospective study of 14 eyes with clinicopathological correlation for *vitreous seeds* reported that 8 untreated and 6 previously treated eyes showed similar histopathologic features, but treated eyes had more type 1 and 3 seeds [7]. The authors concluded that knowledge of underlying histopathology of each seed type is fundamental as it may aid in understanding clinical response to treatment.

In our patient, type 2 and 3 seeds were unquestionably associated with frank uveal invasion, evidenced by the neovascularised nodules. Anterior chamber with or without intravitreal chemotherapy with melphalan and topotecan [8-10], as well as a bicameral melphalan infuson have been described [3,11] for aqueous seeds since 2017, allowing epi- but not intraciliary invasion; for the latter plaque radiotherapy is proposed [3,12]. Our patient received methotrexate before use of melphalan was published in 2012. The vascularised nodules initially responded to systemic and seeds to intraocular chemotherapy. Infiltration of the ciliary body at the angle and vitreous relapse both may have contributed toward the two recurrences in the anterior chamber. The seeds most commonly originate from the vitreous and ciliary body invasion is most treatment-resistant.

Here metastases developed in the absence of evident choroidal or optic nerve invasion suggesting spread through Schlemm's canal, either primarily or upon the two anterior chamber recurrences, was responsible.

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