An unusual variant of diffuse retinoblastoma in an adult

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Case report

A 19-year-old woman was referred to our institution for the evaluation of pearls in the anterior chamber of her left eye in 1987. She had undergone enucleation of the right eye for a retinoblastoma at the age of 22 months. Between 1982 and 1987, she was treated for posterior uveitis in the controlateral eye that failed to resolve. Slit-lamp examination of the eye disclosed small pearls in the anterior chamber (Figure 1). Retinoblastoma cells were found in aqueous fluid aspirated at anterior chamber paracentesis. Evaluation of metastatic dissemination included a chest x-ray, bone marrow aspiration, and cerebrospinal fluid examination were all negative. The neuronal specific enolase level was markedly elevated at 1 000 units. The patient underwent a course of radiotherapy to the left eye up to a total dose of 45 Gy. She remained disease free for 6 months. Multiple small retinoblastoma nodules were then discovered throughout the inner retina and also floating around the anterior chamber. She underwent irradiation with an iodine plaque delivering 40 Gy to the iris.

A RB germline mutation was found in exon 20, 681insTCTGG, with generation of stop codon, 697X. No other cases had been reported in the family suggesting a *de novo* mutation. Three months later, the patient relapsed. She refused enucleation, therefore, chemotherapy combining vincristine and cyclophosphamide was administered but this treatment failed. She was then enrolled in an immunotherapy protocol with Interleukin 2 plus interferon gamma but again treatment results were negative. At this point, the patient refused further treatments and did not turn up for follow-up. Three years later, she presented with a massive exophytic intra-orbital tumor with extra-scleral extension and homolateral pretragal lymph node metastases. A CT scan disclosed an intra-orbital enhancing mass measuring 2×2 cm with anterior, lateral and posterior spread. An extensive work-up revealed no other metastases. The patient was treated with four courses of high-dose ifosfamide (4 g/m^2 d1 to d3 in a continuous infusion). A partial response was observed after the first course. Enucleation with clear margins was performed in September 1992. The histopathologic examination of the operative eye specimen revealed viable foci of tumor cells. The patient received two additional courses of the same chemotherapy regimen and radiotherapy was delivered to the neck lymph nodes (30 Gy). The patient remained disease free for 10 years but she subsequently developed a fatal second cancer (bladder carcinoma).

Retinoblastoma is the most common primary intraocular tumor of childhood [1]. Diffuse infiltrating retinoblastoma is rare, accounting for less than 1.5% of all retinoblastomas [2]. It was first described in 1958 [3] as a tumor infiltrating the retina and exhibiting a flat, diffusely thickening pattern, without development of the white mass typically found in retinoblastoma. The most common initial diagnosis is chronic uveitis. Due to delayed diagnosis, the average age at presentation is 6 years and all patients have unilateral involvement [4]. Associated clinical features are pseudohypopyon, hyphema, iris nodules, and ocular redness. Invasive examinations such as anterior chamber paracentesis, a vitreous tap, and iris biopsy are usually required to make the diagnosis. Computed tomography scans and ultrasonography are not particularly helpful and fail to reveal calcification as in typical retinoblastoma [4]. Diffuse retinoblastoma is characterized by slow progression and poor response to conservative therapy.

This case is unique in several respects: 1) late presentation is uncommon, and unilateral retinoblastoma with late bilateralization (17 years later) is

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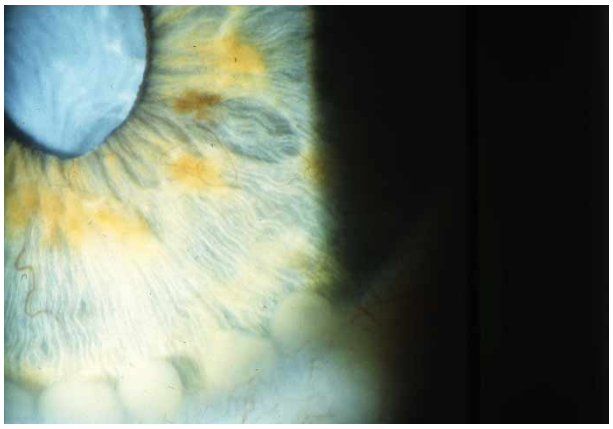

Figure 1. Slit-lamp examination of the eye showing small pearls in the anterior chamber

exceedingly rare [5,6]. Previously existing retinomas or reactivation of a previous spontaneously-arrested retinoblastoma have been suggested as etiological factors [7] ; 2) None of the tumors reported in the literature exhibited the diffuse infiltrating pattern [5,6] ; 3) Despite this usually chemoresistant subtype of retinoblastoma, the combination of an active chemotherapy regimen with high-dose ifosfamide and radical surgery allowed prolonged disease-free survival in this patient. Some tumor regressions have been reported in advanced retinoblastoma with conventional cytotoxic agents such as vincristine, doxorubicin and cyclophosphamide, or more recently with combination carboplatin and etoposide [8]. In conclusion: this variant of diffuse retinoblastoma was initially misdiagnosed because of the involvement of anterior ocular structures with minimal involvement of the retina. Retinoblastoma should be considered in the differential diagnosis of chronic uveitis in any age group.

Conflict of interest

We declare no conflicts of interest.

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Irinotecan-induced central nervous system toxicity. Report on two cases and review of the literature

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