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Case Report

Diffuse infiltrating retinoblastoma: A diagnostic conundrum

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ABSTRACT

Purpose: Diffuse infiltrating retinoblastoma (DIR) is characterized by absence of intraocular mass, lack of calcification. It may mimic inflammatory uveitis or exudative retinopathy.
Observations: An eight-years-old boy presented with progressive loss of vision in left eye. Clinical evaluation revealed neovascular glaucoma with a yellow–gray fundal glow, exudative retinal detachment, subretinal exudation and telangiectatic vessels. The presentation was consistent with exudative retinopathy (Coat's disease) but for the presence of a family history of retinoblastoma in the younger sibling. Despite the absence of an intraocular mass or calcification on multimodal imaging, the enucleation was done on the basis of clinical suspicion of retinoblastoma. Histopathology confirmed a diagnosis of DIR.
Conclusions: DIR can pose a diagnostic challenge due to its non-characteristic clinical and imaging features and atypical presentation. A high index of suspicion along with a positive family history was key to diagnosis in our case; histopathology was confirmatory.

1. Introduction

Retinoblastoma is the commonest intraocular childhood malignancy with an incidence of 1 in 14,000 to 20,000 live births. Mean age of diagnosis depends on laterality and heredity; 90% of are diagnosed by three years of age.[1] The presenting symptoms are determined by the size, extent as well as location of the tumour, which can be exophytic (into subretinal space), endophytic (into vitreous cavity), mixed, or diffusely infiltrating (flat lesion along ocular coats). Leukocoria is often the first symptom, along with decreased vision or squinting.[2,3] The differential diagnoses include Coat's disease, persistent fetal vasculature, congenital cataract, coloboma, familial exudative vitreoretinopathy, retinopathy of prematurity, toxocariasis, endophthalmitis, and rare tumours like medulloepithelioma, astrocytic hamartoma. Though they all great morbidity, malignancies have the gravest prognosis, especially if diagnosis is delayed.

Retinoblastoma diagnosis involves clinical evaluation supplemented with ultrasonography and radiological imaging. Presence of calcification within the lesion, demonstrated as high spikes on ultrasonography B-scan, high density on computed tomography (CT) and areas of hypo-intensity on magnetic resonance imaging (MRI) is a diagnostic indicator.[4] Other causes of calcification include phthisis bulbi (in setting of trauma and/or chronic inflammation), hyperparathyroidism (systemic features), choroidal osteoma, drusen or idiopathic; these are distinguished by both demographics and morphology of calcification. In retinoblastoma, calcification is present within the mass or rarely, along sclerochoroidal coats, conforming the globe contour (diffuse infiltrating retinoblastoma, DIR, late stage).[5]

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DIR is uncommon, occurring in about 1-2% of tumours. This plaque like lesion grows slowly towards the anterior segment, does not develop calcification till late stage, and manifests with pseudo-inflammatory complications.[6,7] We present a challenging case of DIR and its clinical and histopathologic correlation. This report adheres to the Declaration of Helsinki and written informed consent of the legal guardians was taken for photographs.

2. Case Description

An eight-years-old boy presented with gradually progressive, painless diminution of vision of left eye (OS) for the past two months. The visual acuity was 6/6 in right eye (OD) and perception of light in OS. Ocular motility range was complete and there was no manifest squint. Slit lamp examination of OS showed ciliary congestion, relative afferent pupillary defect, ectropion uveae, clear lens, and a yellow-gray fundal glow (Fig. 1a). Fundus examination revealed an exudative retinal detachment with a retinal cyst, vitreous haemorrhage, dilated telangiectatic vessels in the temporal periphery and marked subretinal exudation (Fig. 1b). Intraocular pressures (IOP) were 14 and 26 mmHg in OD and OS respectively. Right eye examination was unremarkable. A clinical diagnosis of Coat's disease was formulated. The B-scan confirmed exudative retinal detachment with intraretinal cyst (Fig. 1c). Mild thickening of ocular coats was noted but calcification was not discernible. The optic nerve shadow was unremarkable. While the parents were being counselled, a significant family history was revealed. The child had a deceased younger sibling, who was diagnosed with bilateral retinoblastoma with intracranial extension at the age of two years, four years prior. Our case had not been screened till now. With this significant history, we kept retinoblastoma as a likely diagnosis, even though clinical findings favoured an exudative retinopathy.

An enucleation was performed and histopathological examination was requested. The ocular coats were intact, the eyeball did not demonstrate any transillumination defect and the optic nerve was not thickened. Microscopic evaluation revealed a basophilic, undifferentiated, diffusely infiltrative intraretinal tumour resulting in retinal thickening. A part of the tumour was growing into the vitreous cavity. This region demonstrated cystic spaces and engorged blood vessels. Intraretinal exudation and exudative retinal detachment were noted. Minimal intra-tumoural necrosis was noted, however, there was no calcification. Optic nerve and anterior segment were uninvolved (Fig. 2). A diagnosis of diffuse infiltrating retinoblastoma (DIR) of left eye was confirmed. The clinical TNM staging was cT3c, cN0, cM0, H1 and the pathological TNM staging was pT1. The child is under the care of the paediatric oncologist and at the last follow up, the enucleated socket was healthy and the right eye follow up examination was status quo.

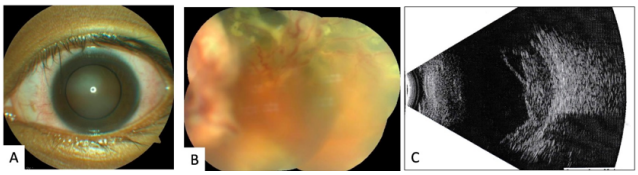

Fig. 1: Clinical Presentation: A: External photograph of the left eye depicting mildciliary congestion, ectropion uveae and a yellow-gray fundal glow. B: Fundus photograph (montage) depicting the retinal detachment, intra and sub retinal exudation and dilated vessels. Overlying vitreous haemorrhage is leading to the media haze. C: B-Scan ultrasound of the left eye confirmed the exudative retinal detachment and mild thickening of the scleral coats. No definite mass lesion or calcification with back shadowing was discernible.

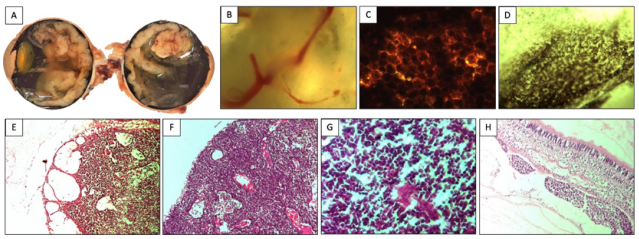

Fig. 2: Histopathology: A:Cut section showing gross thickening of the retina consistent with diffuse infiltrating retinoblastoma; sclera was normal. B: Gross photograph of exudative retinal detachment with preretinal engorged vessel (40x). C: Normal retinal pigment epithelial (RPE) cells (40x). D: RPE proliferation (20x). E: Tumour cells with intraluminal cystic spaces (Haematoxylin and Eosin (H&E), 20x). F: Undifferentiated retinoblastoma cells with intra-tumour blood vessel (H&E, 40x). G: Undifferentiated tumour cells with moderate-severe anaplasia. (H&E, 40x). H: Subretinal seeds (H&E, 40x).

3. Discussion

DIR is uncommon, does not demonstrate typical signs, manifests late and often poses a diagnostic challenge, with up to 56% cases having a wrong initial working diagnoses at time of referral.[6–8] It is characterized by flat retinal infiltration; in late stages, tumour cells may spread diffusely in vitreous, iris, angle and anterior chamber. Majority may be asymptomatic initially, as DIR exhibits a slower growth pattern. In a review on DIR by Traine et al, the mean age at diagnosis was 5.7 years.[8] This is significantly delayed as the average age of presentation for retinoblastoma is 15 months.[1] DIR has a male preponderance, as seen in our case. A positive family history is noted in only 4%; this was present in our case and was in fact an important factor in decision making. Traine et al also reported the symptoms for DIR to be decrease in vision in 48% as compared to leukocoria in 24%, the latter is the commonest presentation for retinoblastoma.[8] Clinical signs include inflammation, congestion, vitreous cells and

raised IOP; our case had congestion and raised IOP.[7,8] Several mechanisms regarding tumour antigen presentation, adhesion, heterotopic precursors and variable immune response have been proposed for the special growth pattern seen in DIR, and research is ongoing.[9] Calcification, which is considered a hallmark of retinoblastoma, is conspicuously absent and thus imaging may not be conclusive.[10] In the presence of uveitis-like picture with anterior chamber cells, a diagnostic paracentesis may be confirmatory. In our case, the suspicion for malignancy was heightened with a positive family history. An enucleation served as a diagnostic and therapeutic procedure. Our case also highlights a missed opportunity. With parental counselling and education about retinoblastoma and its hereditary nature, this child could have been screened at least four years prior, when his younger sibling was detected with retinoblastoma.

4. Conclusion

A high index of suspicion, thorough clinical examination as well as detailed history is important in all paediatric eye diseases. DIR remains a clinical diagnostic challenge and histopathology is confirmatory, and guides further management.

5. Source of Funding

None.

6. Conflicts of Interest

All contributing authors declare no conflict of interest.

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