Detection and Intraretinal Localization of an ‘Invisible’ Retinoblastoma Using Optical Coherence Tomography

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Key Words

Retinoblastoma · Optical coherence tomography · Ocular oncology

Abstract

Purpose: To report the use of handheld spectral-domain optical coherence tomography (HHSD OCT) to identify and define the intraretinal location of a small retinoblastoma that was not detectable by indirect ophthalmoscopy. **Methods:** This is a retrospective case report of a tumor identified with HHSD OCT in a single patient. **Results:** A 7-week-old male was diagnosed with unilateral group E retinoblastoma in the right eye. An enucleation was completed successfully with histopathologic confirmation of the diagnosis. The normal left eye was monitored for the development of retinoblastoma, and 10 weeks after diagnosis, three new small retinoblastomas were noted in the posterior pole. Identification of the smallest of the three tumors was facilitated by HHSD OCT; it was adjacent to the optic nerve head, and involved the outer nuclear layer, outer plexiform layer, and inner nuclear layer, with the inner retina draping over the tumor. **Conclusion:** HHSD OCT can aid the ocular oncologist in the identification of very small retinoblastomas before they are visible to the eye, which allows for earlier and potentially

vision-sparing treatment of these lesions. Additionally, the ability to identify these very small tumors and to localize them anatomically within the retinal layers may aid in our understanding of retinoblastoma tumorigenesis.

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Introduction

Optical coherence tomography (OCT) was introduced in 1991 [1] and revolutionized the field of ophthalmic imaging. As OCT has evolved, greater resolution and depth of imaging have led to new applications within ocular oncology [2–4]. Handheld spectral-domain OCT (HHSD OCT) allows for imaging in the supine position [5] and therefore is becoming a useful tool in the care of children with retinoblastoma [6]. HHSD OCT has been used to elucidate the retinal anatomy obscured by diffuse tumor seeding [7], to monitor changes in retinal structure during treatment [8, 9], to detect involvement at the optic nerve head [10], and to identify very small retinoblastomas not readily detected by indirect ophthalmoscopy [6, 11, 12]. The ability to identify these early tumors before they are otherwise detectable may not only allow for effective treatment earlier in the course of disease, but may

Fig. 1. **a** Color fundus photograph of the left eye demonstrates 3 retinoblastoma tumors. **b** Color fundus photograph of the left eye demonstrates 3 retinoblastoma tumors labeled Rb1–3, marked by lines through the body of the tumors correlating with the OCT slice. The smallest one, barely visible on fundoscopy, lies just superior to the optic nerve. **c** Spectral-domain OCT of the three tumors shows homogenous dome-shaped masses with overlying inner retinal draping. Tumor No. 3 is located in the outer retina involving the ONL and possibly the OPL. The INL and IPL drape over the tumor. There is also an outer retinal abnormality in all tumors affecting the external limiting membrane (ELM), ellipsoid zone (EZ), and interdigitation zone (IZ). There is shadowing on OCT from the retinal vessels overlying the tumor, which are also seen clinically.

also provide insight into retinoblastoma tumorigenesis [12, 13]. Herein we describe a nearly imperceptible retinoblastoma whose identification by HHSD OCT imaging allowed for early local therapy.

Case Presentation

A 7-week-old child with no past medical history and no family history of retinoblastoma presented with right leukocoria. He was diagnosed with unilateral retinoblastoma, International Classification of Retinoblastoma group E. He underwent enucleation of the right eye without complications and was tested for germline *RB1* mutations. Pathology confirmed moderately differentiated exophytic retinoblastoma without optic nerve, massive choroidal invasion or extrascleral involvement. HHSD OCT of the left eye at diagnosis showed normal retinal anatomy. Screening examinations under anesthesia for the normal left eye were continued at 4–6 week intervals. At 10 weeks after diagnosis, the child was found to have asynchronous, multifocal retinoblastoma, International Classification of Retinoblastoma group B (fig. 1a, b), with two clearly defined lesions on indirect ophthalmoscopy. Intraoperative HHSD OCT (InVivoVue, BiopTigen, Morrisville, N.C., USA) was done with the following settings: rectangular volume length 10 mm; width 10 mm; angle 0; horizontal offset 0; vertical offset 0; A-scans 1,000; B-scans 200; frames 1.

This facilitated identification of the smallest of three new tumors located just superior to the optic nerve (fig. 1b, c). Sequential OCT scans were examined to define tumor position relative to the different retinal layers. The montage in figure 2 shows HHSD OCT images from the superior aspect of the lesion moving inferiorly towards the optic nerve. Sequential OCT scans demonstrated predominant involvement of the outer nuclear layer (ONL), outer plexiform layer (OPL), and the inner nuclear layer (INL) at the apex of the mass.

All lesions were treated in the same session with Argon (532 nm) laser therapy (Iridex, Mountain View, Calif., USA). Testing for germline *RB1* mutation was positive for a heterozygous frame-shift mutation in exon 16 of the *RB1* gene. Given the multifocal tumors involving the macula, the child was referred for intra-arterial chemotherapy.

Discussion

This report demonstrates continued innovation in the use of HHSD OCT for the management of retinoblastoma, and most importantly demonstrates identification of a very small tumor that was not initially detected by indirect fundoscopy. HHSD OCT allowed treatment of this tumor at a very early stage, which potentially spared vision given that

Fig. 2. OCT montage of images through the lesion moving from the superior aspect towards the margin of the optic nerve. **a** The lateral aspect of the larger tumor is seen peripherally. **b** Most superior aspect of the lesion. The INL, ONL, and OPL are shown in **b** and **e** with the OPL and INL seen draping over the edges of the small tumor.

Table 1. Small retinoblastoma tumors reported on OCT

Author(s) [Ref.]	Year	Figure	Layer involved				Retinal draping	Outer retinal abnormality
			ONL	OPL	INL	IPL		
Bremner [13]	2009	1	yes	yes	yes	no	yes	yes
Rootman et al. [6]	2013	2/4A/5	yes	yes	yes	maybe	yes	yes
Shields et al. [2]	2015	1h/i	yes	yes	yes at apex	no	yes	yes
Saktanasate et al. [11]*	2015	B	yes	no	no	no	yes (OPL)	yes (minimal)
Dimaras et al. [12]	2015	4	yes	yes	yes at apex	no	yes (IPL, INL at edges)	yes
Current publication		1	yes	yes	yes at apex	no	yes (IPL, INL at edges)	yes

* Lesion treated with chemotherapy before imaging.

the tumor was located directly adjacent to the optic nerve. Early tumor doubling times have been estimated to be 15 days [14]; therefore, if left undetected, this small tumor may have more than doubled by the next exam, causing greater treatment-related retinal and optic nerve damage.

The very small retinoblastoma detected with HHSD OCT and described in this report adds to the evolving literature on OCT and small retinoblastomas (table 1). Several small tumors detected by OCT were reported as being centered in the INL with extension to other layers [2,

6], whereas larger tumors have full thickness involvement of the retina or an exophytic mass with relatively normal retina overlying the lesions [6, 8, 12]. Other small lesions, however, were reported as having 'outer retinal' involvement with inner 'retinal draping' over an otherwise smooth, round, homogenous mass [2, 12]. To date, only one early lesion detected by HHSD OCT, described by Saktanasate et al. [11], appears to be limited to a single retinal layer, in particular the ONL, with the OPL draped over it. This is, however, a posttreatment image and the presence of tumor in the OPL or INL before treatment cannot be ruled out.

The smallest lesion described in this report has involvement of the ONL, but also involvement of the OPL and the INL at the apex of the mass. The tumor appears to be centered within the ONL and OPL with the INL draping over the sides of the tumor and inner plexiform layer (IPL) draping over the entire mass. There is an additional abnormality of the outer retinal band with loss of the external limiting membrane, inner segment-outer segment junction/ellipsoid zone, and interdigitation zone. The underlying retinal pigment epithelium (RPE) is intact here and additionally, the abnormality does not always traverse the widest extent of the tumor, indicating that the abnormality may not be a shadowing defect as previously described [6] but a tumor-related abnormality. This outer retinal abnormality with intact RPE is also seen in the images of the tumors shown in figures 1 and 2 as well as the other described small retinoblastomas on OCT (table 1).

While these images on their own cannot define the retinal layer that holds the retinoblastoma cell of origin, an ONL origin would be consistent with experimental evidence that retinoblastomas originate from cone photoreceptor precursors in a manner that depends upon the

cone precursor's intrinsically high expression of key oncoproteins that sensitize to the loss of functional retinoblastoma protein [15, 16]. Future OCT images of earlier and smaller tumors may provide more clear evidence of the layer of origin.

OCT has dramatically improved the diagnosis and management of many ophthalmic diseases and is now aiding ocular oncologists in the identification and treatment of small retinoblastomas while they are still 'invisible' on indirect ophthalmoscopy. OCT holds great potential for surveillance of small tumors, monitoring treatment effect, recurrence, and improved visual outcomes with earlier treatment. Additionally, identification of retinoblastomas that are even smaller than those detected to date (table 1) may provide insight into the earliest tumor initiation events as well as approaches to prevent tumorigenesis in genetically predisposed patients.

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Statement of Ethics

This study was conducted in compliance with the rules and regulations of the Health Insurance Portability and Accountability Act as well as in adherence with the Declaration of Helsinki and all other relevant federal and state laws.

Disclosure Statement

The authors declare that they have no conflicts of interests or financial disclosures.

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