Optical Coherence Tomography in Retinopathy of Prematurity

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Abstract

Retinopathy of prematurity is a vasoproliferative condition characterized by abnormal vascularization of the retina which may lead to tractional retinal detachment. Timely screening and treatment with laser and/or anti-vascular endothelial growth factor agents help prevent blindness. While bedside indirect ophthalmoscopy remains the gold standard for screening, optical coherence tomography has emerged as a new modality for understanding the pathogenesis of retinopathy of prematurity, providing in-vivo monitoring, and evaluating subclinical findings. This chapter provides an overview of optical coherence tomography in retinopathy of prematurity, including available models and adjustments in the neonatal population, differences between preterm, term and adult foveal anatomy, current usages of optical coherence tomography in retinopathy of prematurity as well as descriptions of popcorn retinopathy, macular edema, vitreous bands on imaging.

Keywords

Retinopathy of prematurity · Spectral-domain optical coherence tomography · Preretinal tissue · Plus disease · Vitreous bands · Macular edema of prematurity

9.1 Introduction

Retinopathy of prematurity (ROP) is a disease of premature and/or low birth weight infants, characterized by incomplete retinal vascularization, retinal ischemia, subsequent abnormal neovascularization, and eventually tractional retinal detachment if left untreated. Given timely screening, treatment with laser photocoagulation and/or anti-vascular endothelial growth factor agents prevent blindness.

Grading of disease depends on the location or zone of involvement, severity, or stage of disease, extent of disease, and presence or absence of plus disease [1]. The location of pathology is described as zones I, II, or III (Fig. 9.1). Zone I consists of a circular area with the optic disc as the center and a radius of twice the distance between the optic disc and the macula center. Zone II is an extension of Zone I to the nasal ora serrata. Zone III consists of the remainder of the temporal retina. The severity of disease is described in stages from stage 0 to stage 5.

Stage 1 consists of a demarcation line that distinguishes the vascular retina from the avascular retina. Stage 2 shows the formation of a ridge, and small isolated extraretinal neovascular tufts may be present. Stage 3 is characterized by extraretinal fibrovascular proliferation that grows from the ridge into the vitreous. Stage 4 involves partial retinal detachment that is either extrafoveal (4A) or fovea-involving (4B). Stage 5 shows a total retinal detachment. The extent of disease is the number of clock hours involved. Plus disease con-
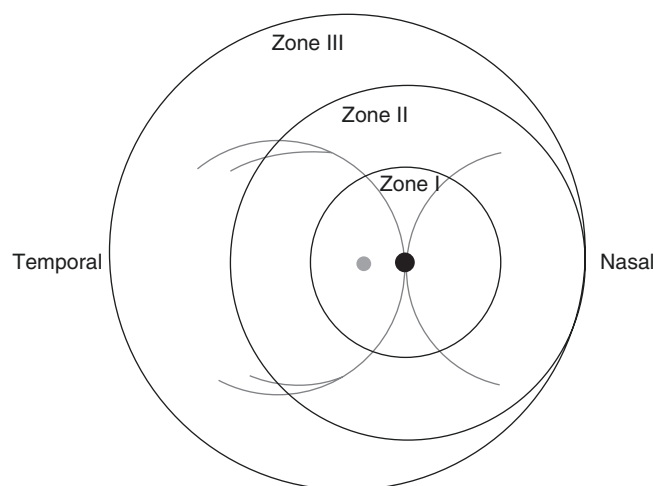

Fig. 9.1 Diagram of zones I, II, and III of retinopathy of prematurity. Images courtesy of Dr. Xi Chen

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sists of venous dilation and arteriolar tortuosity in at least two quadrants [1].

The gold standard for screening is bedside indirect ophthalmoscopy, though other modalities such as fundus photography can be useful supplements. Current screening criteria for ROP includes all infants with a birth weight below 1500 g or gestational age of less than 30 weeks. Infants with birth weights between 1500 g and 2000 g or gestational age greater than 30 weeks who have had unstable clinical courses or additional risk factors should also be screened [2].

Screening for ROP begins at either 4 to 6 weeks after delivery or 31 to 33 weeks postmenstrual age, whoever interval comes later [2]. Follow-up time intervals range from less than 1 week to 3 weeks depending on the severity of the disease found [2]. Screening may cease when full retinal vascularization close to the ora for 360 degrees has been achieved, the patient has reached a postmenstrual age of 50 weeks without detection of prethreshold disease or worse ROP, there is regression of ROP, or if there is vascularization of zone III without previous zone I or II ROP [2].

9.2 SD-OCT

Spectral-domain optical coherence tomography (SD-OCT) uses light interference to produce a cross-sectional image of the anatomy of interest. Various table-top and portable SD-OCTs are available; however, there is logistical and physical difficulty in examining uncooperative young patients and unstable neonates in the intensive care unit [3]. The Envisu (Bioptigen, NC, USA) model is a handheld device that can be used in the office, in the unit, and in the operating room. The advantages of SD-OCT include lack of contact, short imaging time, and the ability to evaluate without anesthesia. Adjustments of imaging protocols such as using shorter scan lengths for shorter axial length, reducing the number of A-scans to avoid unnecessary light exposure, and correcting reference arm position to avoid excessive magnification can all help produce higher quality images in the neonatal population [3]. Maldonado et al provides a reference table for age-specific corrections in neonates and infants to improve image quality [4]. Specific protocols have been proposed to reduce imaging time and patient discomfort [4].

9.3 OCT Difference Between Adult, Term and Preterm Infants

There are a number of differences between the eyes of adults, term infants, and preterm infants found on OCT imaging (Fig. 9.2). As the eye develops, the inner retinal cells migrate outward from the fovea, photoreceptor layers grow inward toward the fovea and the foveal photoreceptor layer thickens

[5, 6]. Compared to term infants, preterm infants have delayed development of photoreceptor inner and outer segments, specifically delayed appearance of the ellipsoid zone in the foveal center and a greater mean distance between the foveal center to the ellipsoid zone [7]. Compared to adults, preterm infants have shallower foveal depression, persistent inner retinal layers, and shorter foveal photoreceptors [6, 8].

Pathology discovered on SD-OCT in infants may prognosticate subsequent visual outcomes. For instance, Rothman et al. found that children who had macular edema on SD-OCT in infancy had worse visual outcomes compared to those who were not found to have macular edema on SD-OCT in infancy [9].

9.4 OCT in ROP

SD-OCT allows for in vivo, cross-sectional analysis and can provide subclinical details undetected by indirect ophthalmoscopy. For instance, Lee et al. performed SD-OCT during routine bedside ROP screenings and found macular cystoid structures in 39% and epiretinal membranes in 32%, none of which were apparent on indirect ophthalmoscopy [10]. Advanced image processing techniques such as segmentation allows for detailed analysis of specific retinal layers [11]. While SD-OCT does not replace gold standard bedside indirect ophthalmoscopy for evaluation of ROP, particularly in more peripheral disease, OCT has advanced the understanding of subclinical disease processes in ROP and enabled in-vivo monitoring of microstructure evolution that has previously only been detectable on histopathology [3, 10].

The hallmarks of each stage of ROP development have been described in greater detail using OCT. In stage 1 disease, the posterior vascular retina shows three inner layers on OCT whereas the anterior avascular retina has one hyperreflective layer [12]. The ridge in stage 2 disease can be seen on OCT as a homogenous thickening of the inner hyperreflective band, with occasional small elevated tufts of preretinal tissue that is likely early pathologic proliferation [12]. Stage 3 disease shows significant thickening of the hyperreflective band and more marked preretinal elevations, sometimes with inner retinal split and focal vitreous traction [12].

OCT can also be used to monitor treatment response, similar to adult disease processes like neovascular age-related macular degeneration. OCT before and after anti-VEGF injection in stage 3 disease showed reduced thickness of inner retinal layers, decreased neovascular elevations, and further extension of three-layered inner retina [12]. OCT can also detect subtle progression despite treatment, such as early tractional retinoschisis in progressive ROP despite laser photocoagulation [13].

A number of specific subclinical SD-OCT changes have been found in infants during ROP screening, including cys-
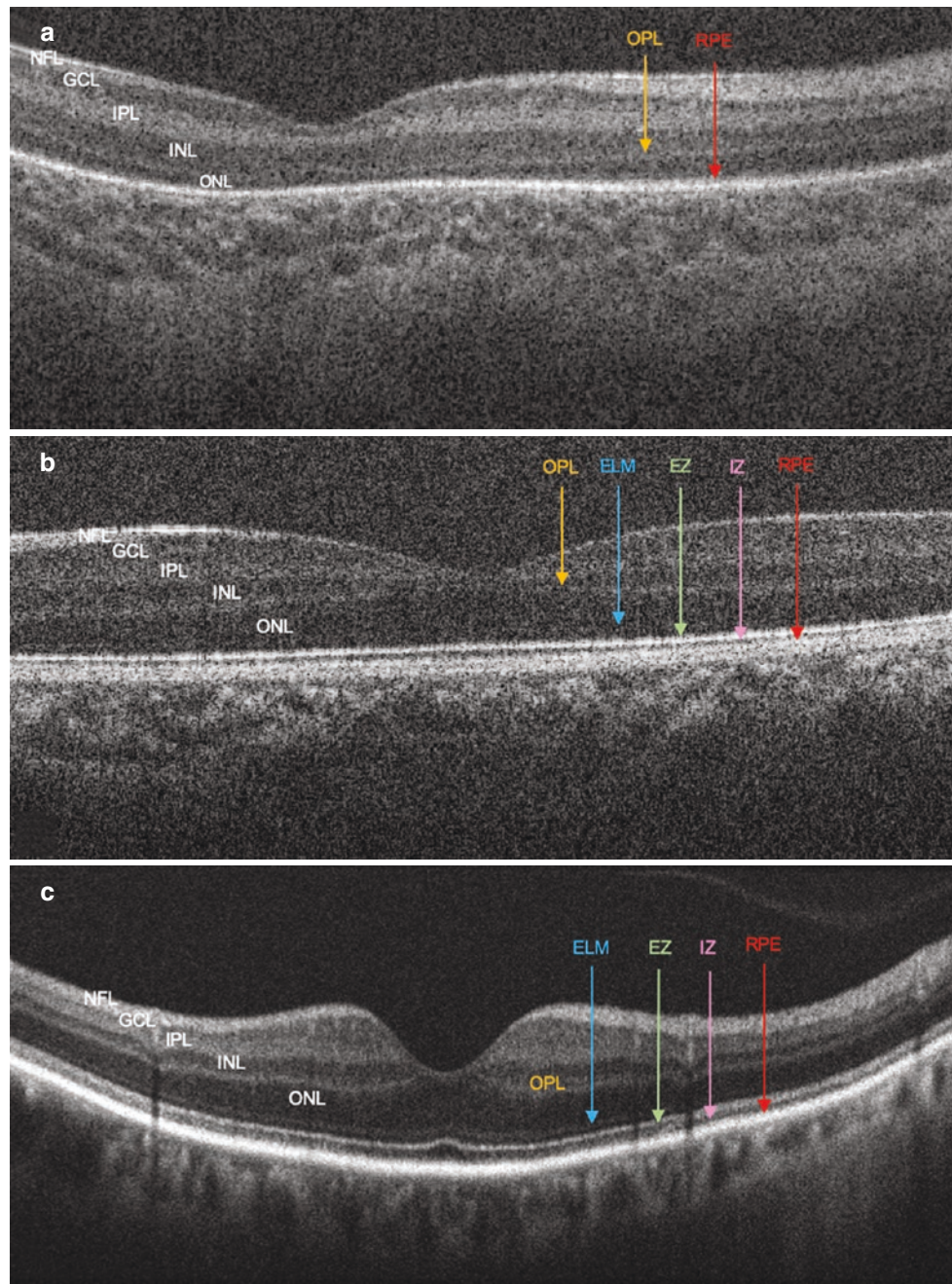
Fig. 9.2 SD-OCT images showing normal foveal anatomy of a premature neonate, full-term neonate, and an adult. (**a**) shows foveal anatomy of a 31 weeks postmenstrual age neonate. Note the persistent, distinct nerve fiber layer, ganglion cell layer, and inner plexiform layers at the foveal center. The photoreceptors structures, including the external limiting membrane, inner segment/outer segment junction, and outer segments are not seen. The foveal depression is more shallow and the inner retinal layers are thicker compared to the outer retinal layers. With development, the ganglion cell layer, inner plexiform, and inner nuclear layers migrate centrifugally whereas the photoreceptors migrate centripetally. (**b**) shows the foveal anatomy of a 40-weeks postmenstrual age neonate. Compared to (**a**), the ellipsoid zone is developed in the periphery, and in the foveal center, the inner retinal cells are migrating centrifugally from the foveal center, and the foveal depression is deepened. The inner retinal layers now appear thinner than the outer retinal layers at the foveal center. The fovea continues to mature over the next decade as continual cone packing and elongation at the foveal center occurs. (**c**) shows the foveal contour of a 72-year-old adult. The foveal contour is deep and the inner retinal layers are thin and indistinguishable at the foveal center. Abbreviations: *NFL* nerve fiber layer, *GCL* ganglion cell layer, *IPL* inner plexiform layer, *INL* inner nuclear layer, *OPL* outer plexiform layer, *ONL* outer nuclear layer, *ELM* external limiting membrane, *EZ* ellipsoid zone, *IZ* interdigitation zone, *RPE* retinal pigment epithelium. Images courtesy of Dr. Xi Chen

toid macular changes, vitreous changes, preretinal tissue and plus disease vascular changes [3, 12, 14, 15]. Each entity is described in detail below.

9.4.1 Macular Edema

Hyporeflective cystoid spaces at the inner nuclear layer level is a frequent finding in premature infants and infants with ROP (Fig. 9.3) [16–18]. This entity has been termed macular edema of prematurity (MEOP), as it is not typically found in full-term infants, though there may be some racial variation [19, 20]. Of the multiple phenotypes found, vertically elongated cysts with a "bulging" foveal contour is common [16]. Vinekar et al. characterize this dome-shaped bulging fovea with intraretinal cystoid spaces separated by vertical septae as "pattern A," and also describe a "pattern B" cystoid macular edema which shows multiple confluent hyporeflective spaces with a more preserved foveal depression [21]. The presence of MEOP has not been found to be associated with ROP outcomes and does not appear to be correlated with the ROP stage [18]. However, eyes with plus disease, stage 3 ROP, and the need for laser treatment have been found to have increased central foveal thickness which is induced by the macular edema [16]. Furthermore, very preterm infants who had cystoid macular edema were found to have poorer motor and language skills compared to those who did not [22]. It has been hypothesized that since the retina represents an extension of the CNS, cellular and developmental events occurring elsewhere in the CNS may manifest in the neuroretinal tissue [22].

9.4.2 Vitreous Pathology

Tractional vitreous bands may be visualized in advanced ROP during vitrectomies. Zepeda et al. used handheld OCT during ROP screenings and found hyperreflective vitreous opacities or vitreous bands in 71% of participants [15]. Vitreous band presence is associated with hyperreflective opacities (Fig. 9.4) [23]. They found an association between the presence of vitreous bands and the presence of epiretinal membranes as well as cystoid macular edema, which suggests a tractional component in the pathogenesis of these entities. There was no association between vitreous band detection and ROP severity [15].
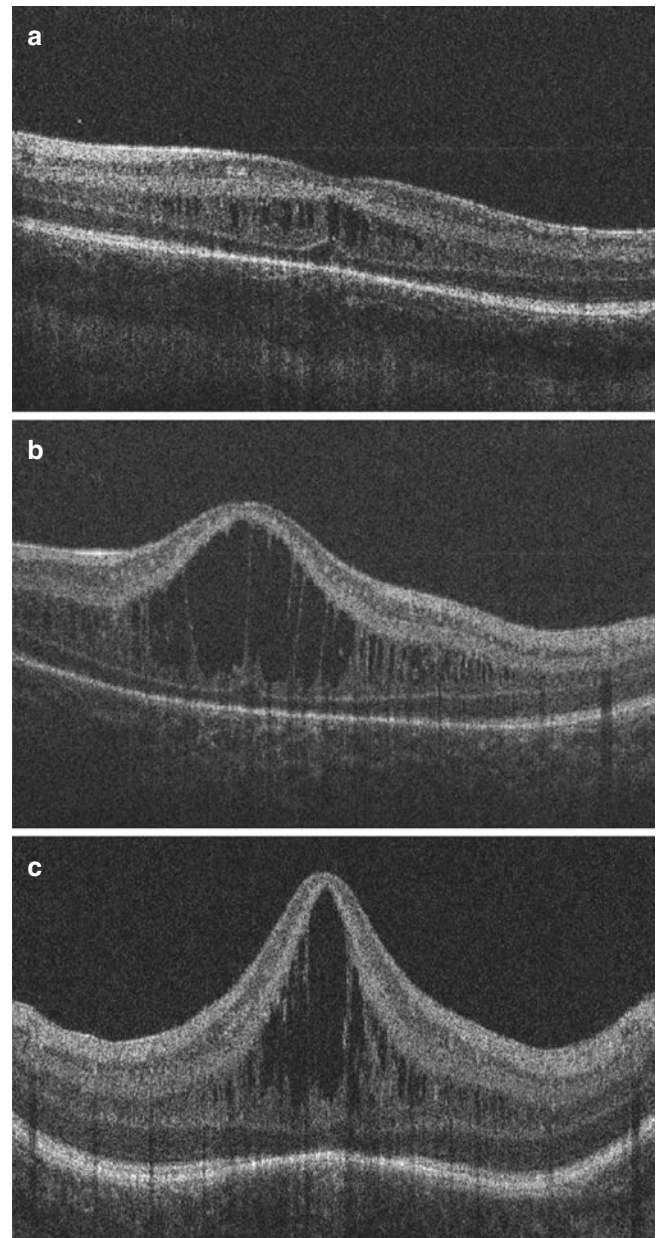

Fig. 9.3 SD-OCT images showing varying degrees of cystoid macular edema in approximately 38-weeks postmenstrual age infants. (**a**) shows mild cystoid macular edema with hyporeflective cystic spaces in the inner nuclear layer with vertical hyperreflective septae, with minimal changes to foveal contour. (**b**) shows moderate cystoid macular edema with vertical elongation of cystic spaces and "bulging" foveal contour. (**c**) shows severe cystoid macular edema with marked bulging of the foveal center. Images courtesy of Dr. Xi Chen
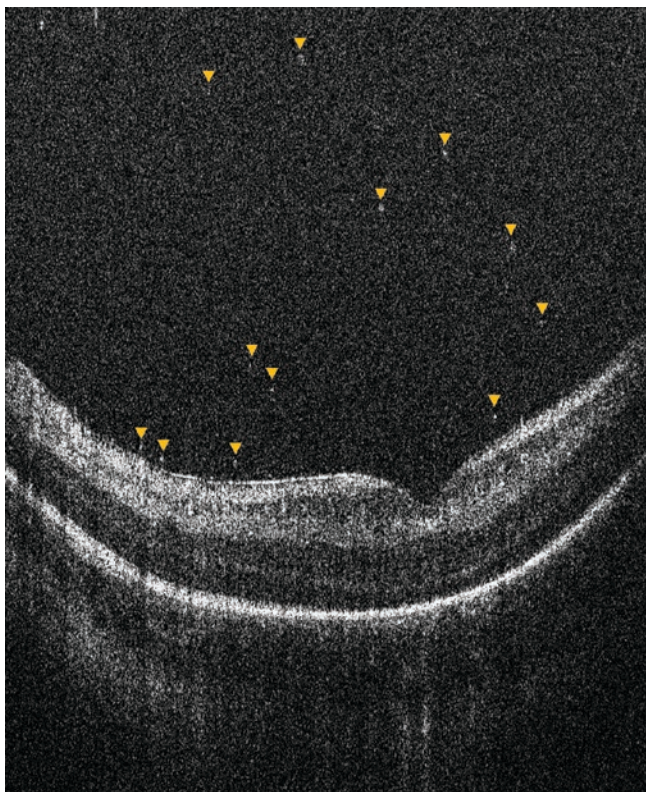
Fig. 9.4 SD-OCT image showing hyperreflective vitreous opacities (yellow arrows) in a 39-weeks postmenstrual age infant. Images courtesy of Dr. Xi Chen

9.4.3 Popcorn Retinopathy/Extraretinal Tissue

The International Classification of ROP makes note of isolated neovascular tufts on the retinal surface found close to the ridge in stage 2 ROP [1], which has been confirmed on OCT (Fig. 9.5) [12, 24]. The presence of these isolated tufts (also known as "popcorn") has been associated with increased risk of zone II, stage 2 disease progressing to stage 3, as well as the development of plus disease and requirement of laser treatment [14]. SD-OCT provides a monitoring modality for these lesions.

9.4.4 Plus Disease

The presence of plus disease is an indication for laser treatment, and the presence of pre-plus disease (a lesser degree of vascular dilation and tortuosity) is associated with the progression of disease requiring laser. However, there is a degree of subjectivity even among experienced examiners [25]. OCT can provide anatomical details of vessel changes in plus and pre-plus disease and possibly aid in more objective differentiation between these clinical entities [3]. OCT is able to evaluate vessel elevation, hyporeflective vessels, and scalloped retinal layers which were significantly associated with plus disease (Fig. 9.5) [26]. Maldonado et al. describes a Vascular Abnormality Score by OCT (VASO) which weighs these characteristics based on common versus uncommon features, and found significantly higher VASO in premature infants with plus disease compared to those with ROP but without plus disease [26].

Moreover, traditional evaluation of plus disease depends on the *en face* view of the posterior pole by indirect ophthalmoscopy or photography, whereas cross-sectional SD-OCT images allow an additional dimension of analysis. For instance, anterior to posterior vessel dilation and tortuosity may be better appreciated on continuous cross-sections [26].

9.4.5 Foveal Involvement

SD-OCT also aids in the differentiation between stage 4A (extrafoveal) and 4B (foveal-involvement) ROP. Foveal abnormalities may impact outcomes in patients with 4A disease and impact treatment outcomes despite anatomic success of detachment repair [27].
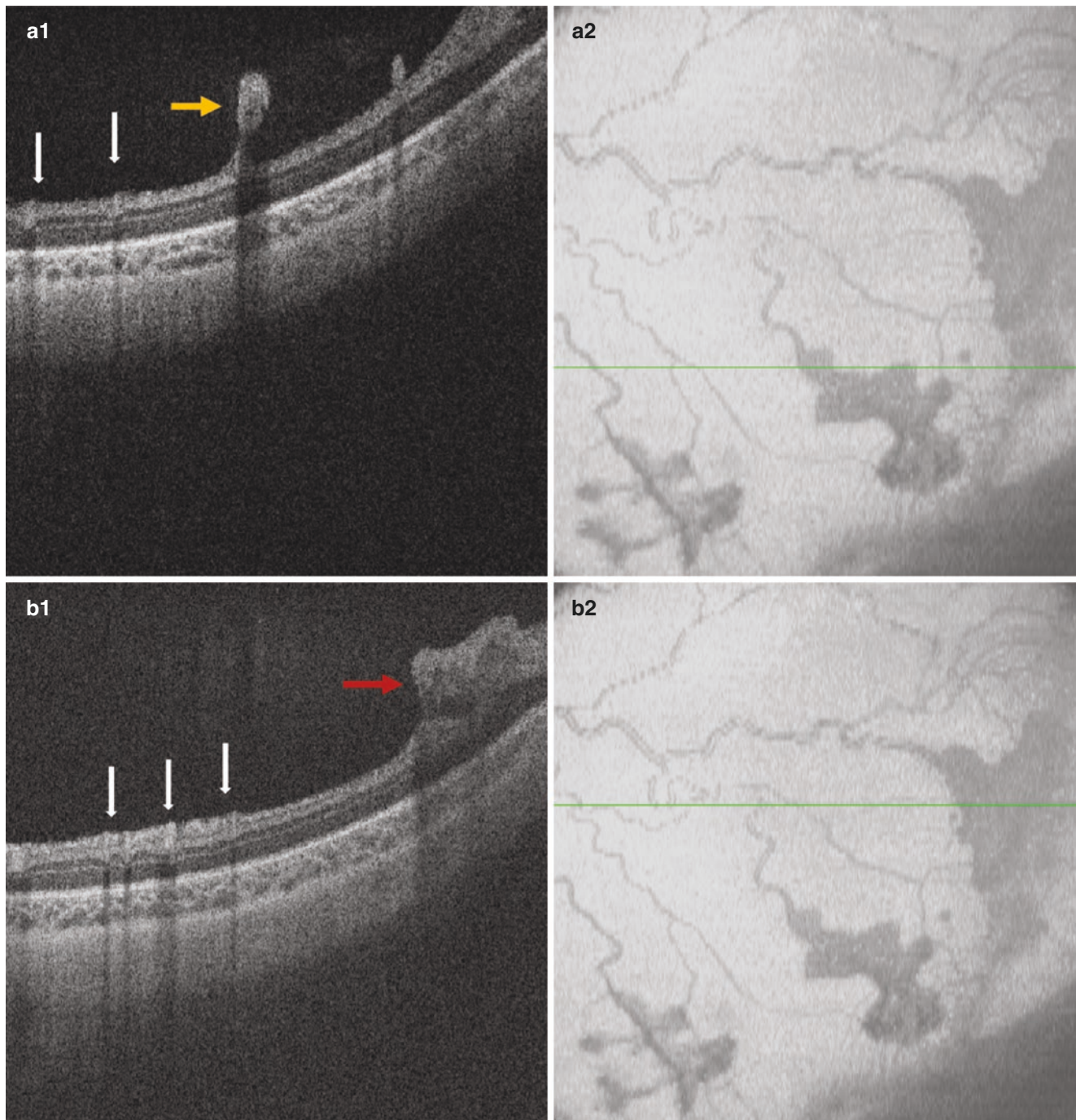
Fig. 9.5 SD-OCT (left) and en face OCT SVP images (right) of a 43-week-old postmenstrual age infant showing plus disease with dilation and tortuosity and peripheral neovascularization with plaque formation confirming stage 3 ROP. The green line on en face OCT SVP in the right column indicates slice location of SD-OCT on the left. (**a1**) shows vessels (white arrows) and "popcorn retinopathy" (yellow arrow). This preretinal neovascular tissue may be present in stage 2 ROP. (**b1**) shows vessels (white arrows) and preretinal neovascular plaques (red arrow) indicative of stage 3 ROP. (**c1**) shows dilated, elevated vasculature (white arrows) with hollow surrounding and continu-ation of the same plaque shown in **b1** (red arrow). The vessels are elevated with subsequent distortion of the retinal layers, which produces a scalloped appearance of the retinal layers. In **c2** at the green line, the vessel of interest appears more dilated compare to surrounding vessels. The VASO score proposed by Maldonado et al. takes into account vessel characteristics including mild versus severe elevation, retinal layer scalloping involving the inner plexiform layer versus outer plexiform layer, any presence of hyporeflective vessels, and any presence of retinal spaces to give a unified score of vessel abnormality. Images courtesy of Dr. Xi Chen
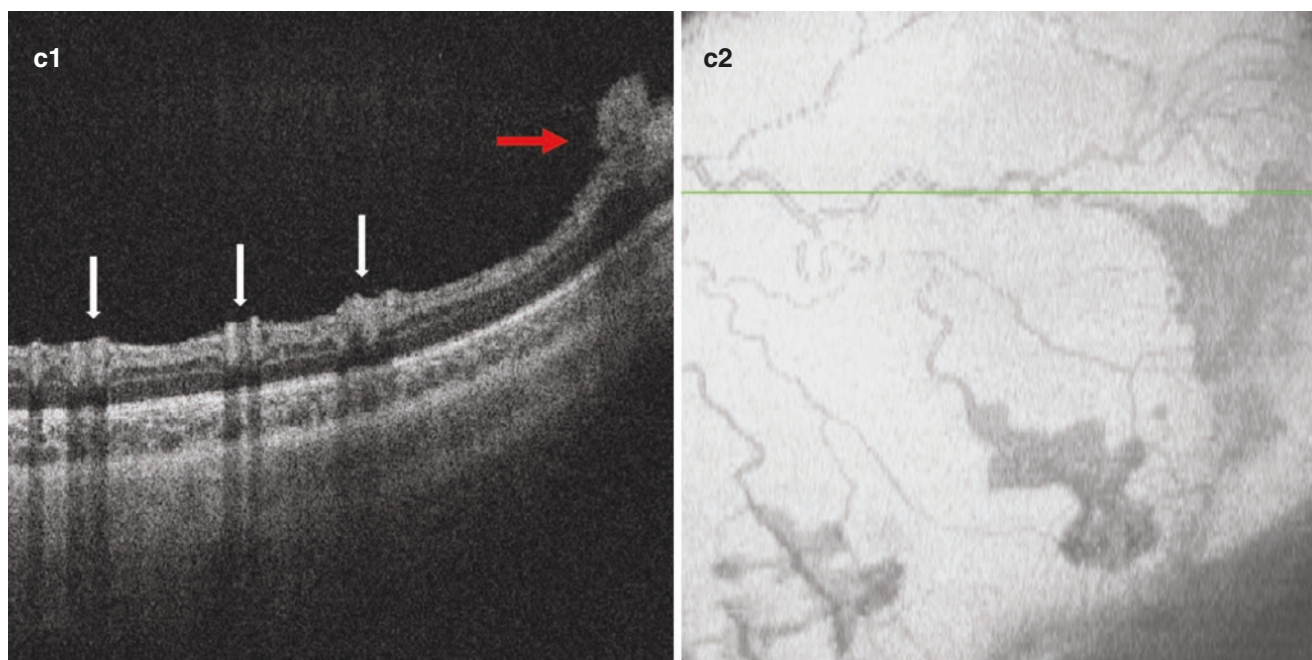
Fig. 9.5 (continued)

9.5 Conclusion

SD-OCT offers in vivo monitoring of retinal structure over time and can identify subclinical details not visible on indirect ophthalmoscopy in ROP. Adapted models and techniques improve the ease and efficacy of imaging in the neonatal population.

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