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Case Series: Discordance Between Visible Retinal Nerve Fiber Layer Defects and Spectral Domain Optical Coherence Tomographic Analysis in Patients with Glaucoma

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Case Series: Discordance Between Visible Retinal Nerve Fiber Layer Defects and Spectral Domain Optical Coherence Tomographic Analysis in Patients with Glaucoma

Abstract

Background: Spectral domain optical coherence tomography (SD-OCT) has become a common modality in glaucoma diagnosis. Ease of use, comfort, and a comparative normative database makes this technology very popular with patients and practitioners. However, despite the sophistication of this technology, it may miss pathologic abnormalities of the retinal nerve fiber layer (RNFL) or be misinterpreted by practitioners based upon comparisons to a normative database.

Purpose: To illustrate discordance between clinical examination and SD-OCT analysis in patients with glaucoma.

Case Reports: Examples of three patients with glaucoma who had photographically and ophthalmoscopically visible RNFL defects who had SD-OCT analyses that fell within a normative database and thus likely to be interpreted as normal, if used in isolation.

Conclusions: Though SD-OCT technology has become common in glaucoma evaluation, over-reliance on this data may lead to false-negative assessment of patients who truly have glaucoma. Spectral domain optical coherence tomography provides valuable adjunctive information for glaucoma evaluation but must be correlated with other clinical assessments such as perimetry, ophthalmoscopy and photography.

Keywords

Retinal nerve fiber layer defects, optic disc photography, optical coherence tomography, discordance

INTRODUCTION

Spectral domain optical coherence tomography (SD-OCT) has established itself as an important, highly relied upon imaging modality in the diagnosis and management of glaucoma, providing high-resolution visualization of ocular microstructures and objective quantification of tissue thickness and change.[1] Recent technological advancements include 3D imaging, reproducible registration, and advanced segmentation algorithms of macular and optic nerve head regions. A review of the evidence to date suggests that retinal nerve fiber layer (RNFL) analysis currently remains the dominant parameter for glaucoma diagnosis and detection of progression while initial studies of macular and optic nerve head parameters have shown promising results.[2] Despite such advancements and use, there exists potential for SD-OCT analysis to not identify true RNFL defects, depending on the parameters examined and characteristics of the abnormalities. Hwang and associates noted that the Thickness Map on the Cirrus SD-OCT showed good correlation to RNFL defects observed with red-free photography, but that Deviation and Clock Hour Maps were less sensitive in detecting abnormalities.[3,4]

The focus of this manuscript is not to discuss individual cases of glaucoma or provide specific guidance on comprehensive utilization of SD-OCT in diagnosing glaucoma. Indeed, there are optic disc parameters and ganglion cell analysis as well as clinical nuances involving Thickness Maps and other features that can allow for better detection of disease when utilized and applied to a comprehensive clinical examination. Additionally, this manuscript is not meant to purport that any branded technology is superior or inferior in glaucoma diagnosis. The focus of this manuscript is to illustrate that commonly used RNFL parameters, when compared to a proprietary normative data base and examined in isolation, may give a false assessment of disease absence in eyes with glaucoma and provide explanations for these occurrences. This report presents a series of patients with visible RNFL defects which were not identified on SD-OCT imaging and provides discussion for discordance and strategies to avoid such false-negative errors.

CASE 1

A 67-year-old woman diagnosed with primary open angle glaucoma (POAG) OS and ocular hypertension OD was treated with latanoprost 0.005% OU. Color optic disc photographs showed an inferior temporal RNFL defect OS (Figure 1a).

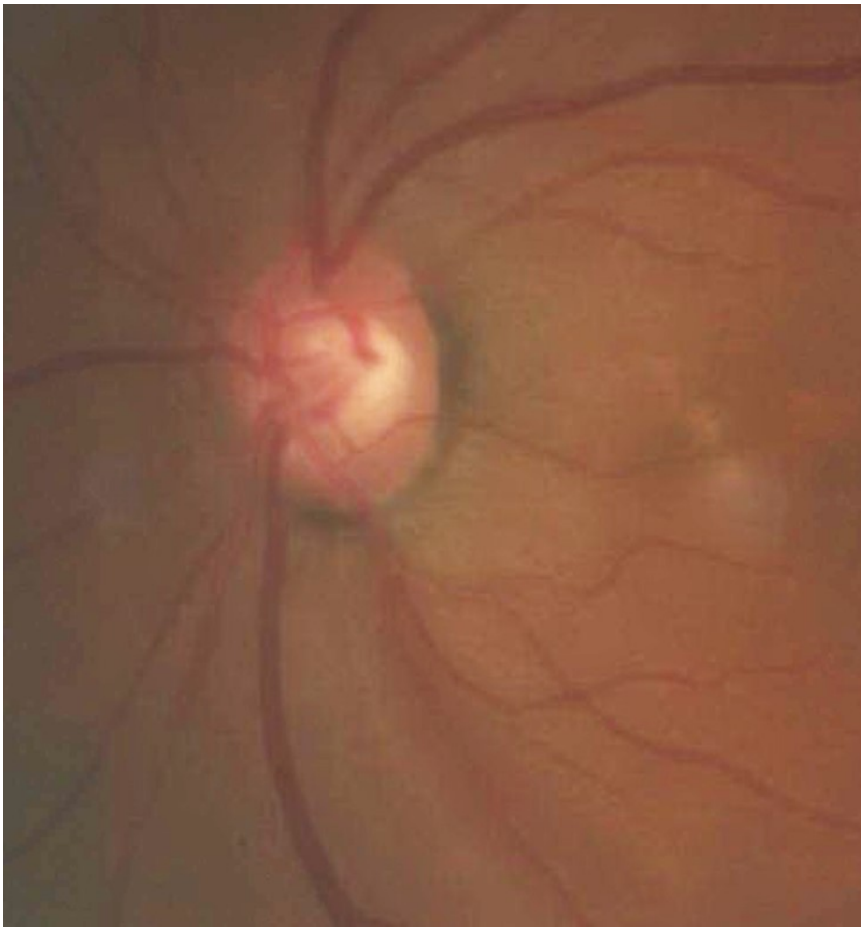

Figure 1a: Case 1 patient with visible RNFL defect inferior-temporal (left) and Cirrus OCT RNFL analysis with Signal strength 7/10 OD, OS.

She had a normal optic disc and RNFL OD. Cirrus SD-OCT (Zeiss, Dublin, CA), when compared to the normative database for this device, showed normal RNFL Thickness, Temporal-Superior- Nasal-Inferior-Temporal (TSNIT), RNFL Quadrants, and RNFL Clock Hours Maps in the region of the defect (Figure 1b).

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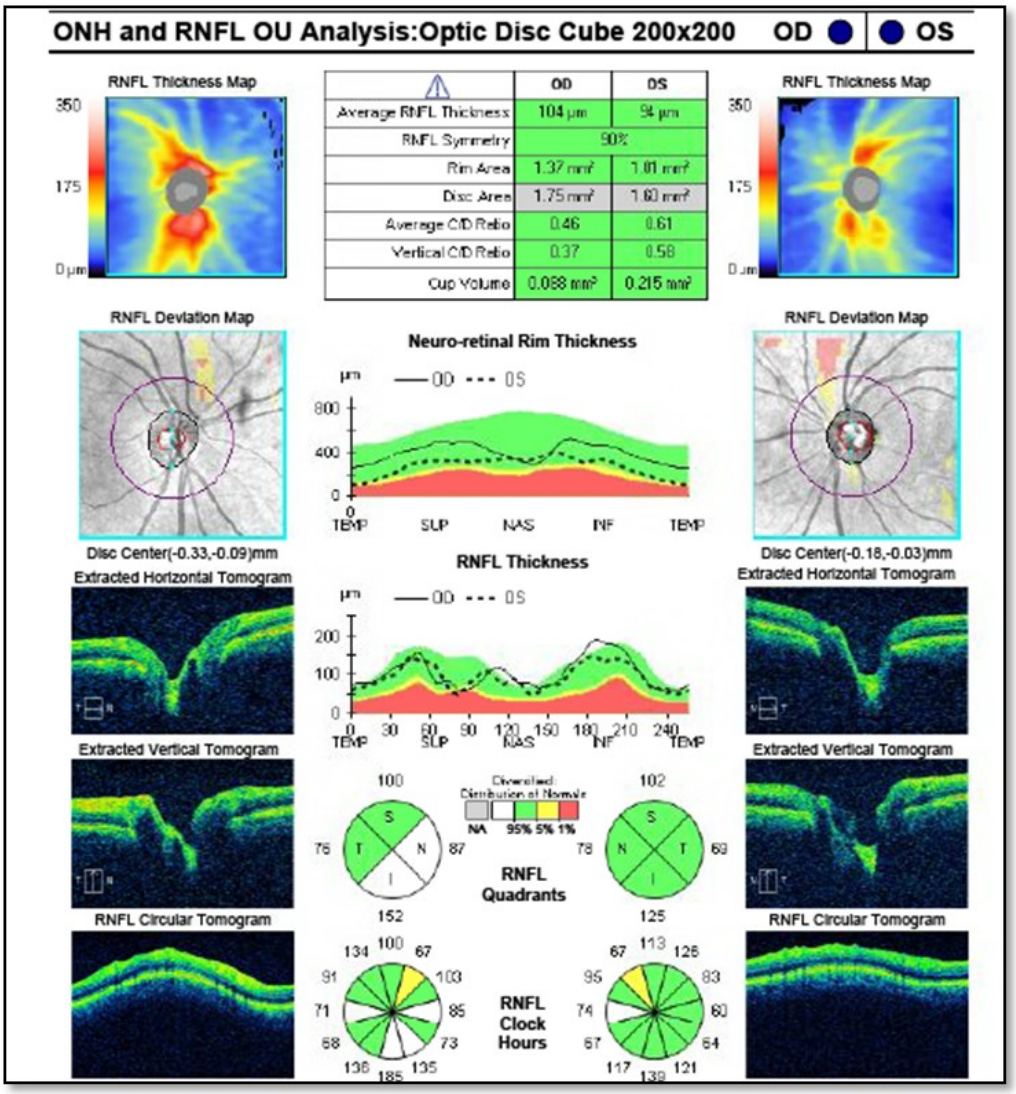

Figure 1b: OCT analysis appears to show no corresponding RNFL defect on Thickness Map, Deviation Map, RNFL Quadrant, or RNFL Clock Hours. All analysis parameters in this area fall within the 95% confidence interval.

Threshold perimetry demonstrated a full visual field OD and a corresponding superior arcuate defect OS (Figure 1c).

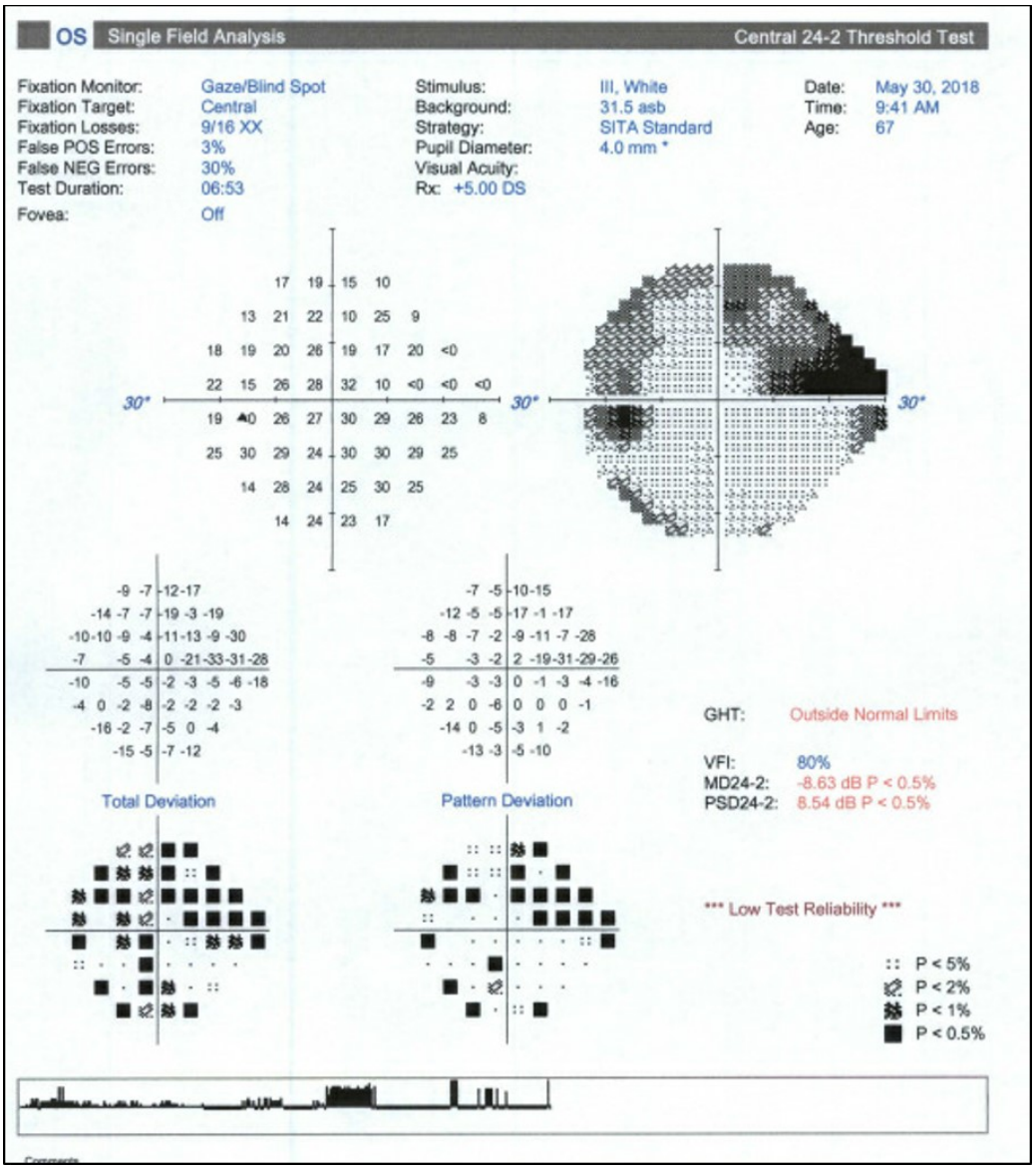

Figure 1c. Corresponding left visual field with superior arcuate defect.

Cirrus SD-OCT analysis presented an objectively normal RNFL analysis when examining the values compared to the normative database, while ophthalmoscopy and optic disc photography revealed a focal wedge-type RNFL defect. Threshold perimetry showed a corresponding functional abnormality OS, indicating true disease.

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CASE 2

A 50-year-old male was referred for a glaucoma evaluation based on suspicious optic discs. He had never been diagnosed with glaucoma previously. His best-corrected visual acuities were 20/15 in each eye and his untreated IOP was 16 mm Hg OU. Ophthalmoscopy and photography of the left eye showed parapapillary atrophy, focal damage to the neuroretinal rim, and an inferior-temporal RNFL wedge defect (Figure 2a).

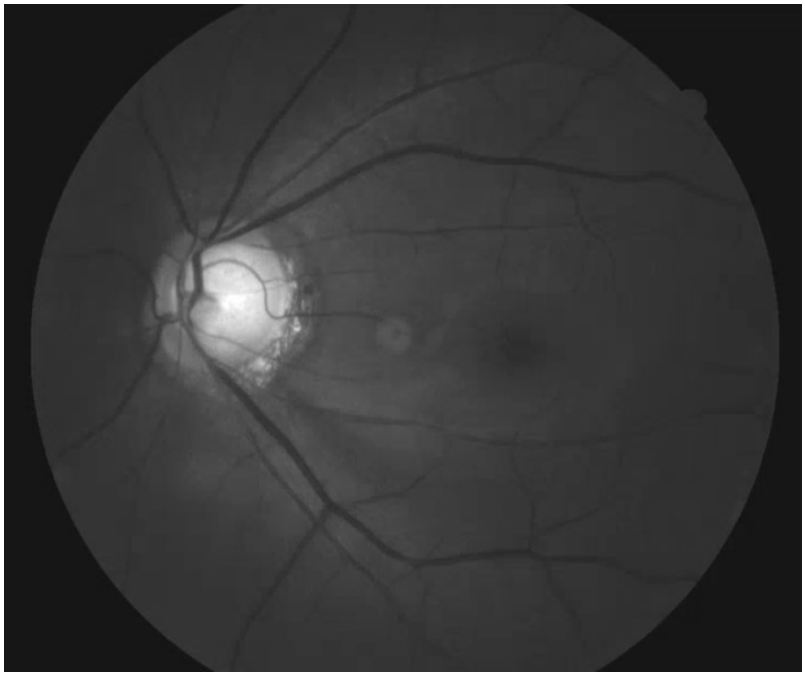

Figure 2a (top): Red-free optic disc photograph of case 2 patient illustrating inferior-temporally located RNFL defect OS.

His right eye revealed parapapillary atrophy and a normal optic disc and RNFL. Inspection of the RNFL Analysis with Cirrus OCT showed a Thickness Map OS with a small discontinuity not extending to the optic disc. The left eye Deviation Map showed a corresponding departure from the normative data base beyond the calculation circle. RNFL quadrants and RNFL Clock Hour Maps were within the normative data range and not flagged as abnormal and would objectively be assessed as normal, based on these parameters (Figure 2b).

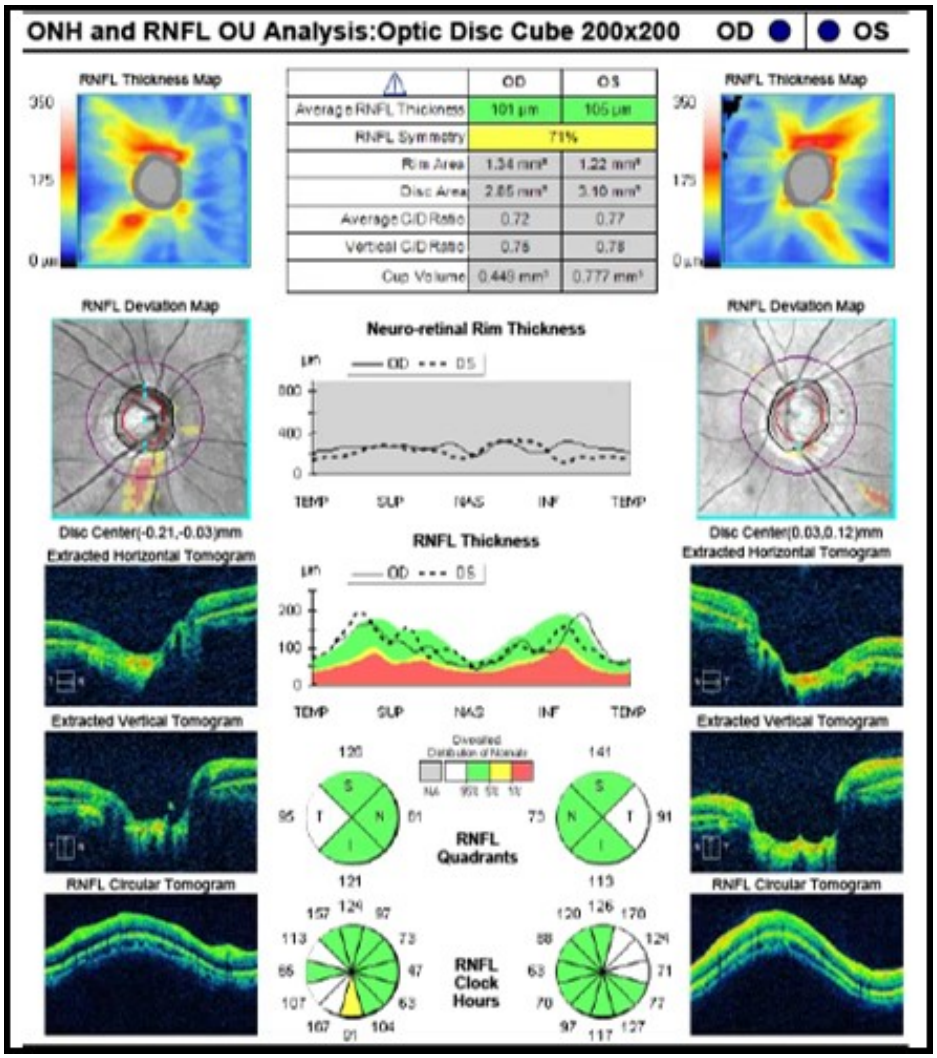

Figure 2b (middle): Cirrus SD-OCT analysis manifesting RNFL discontinuity not reaching the optic disc image on Thickness and Deviation Maps, while showing no statistically significant departures from the normative database on RNFL Quadrant, or RNFL Clock Hours (signal strength 8/10).

Spectralis OCT (Heidelberg Engineering, Franklin, MA) analysis showed all aspects to be within normal limits (Figure 2c).

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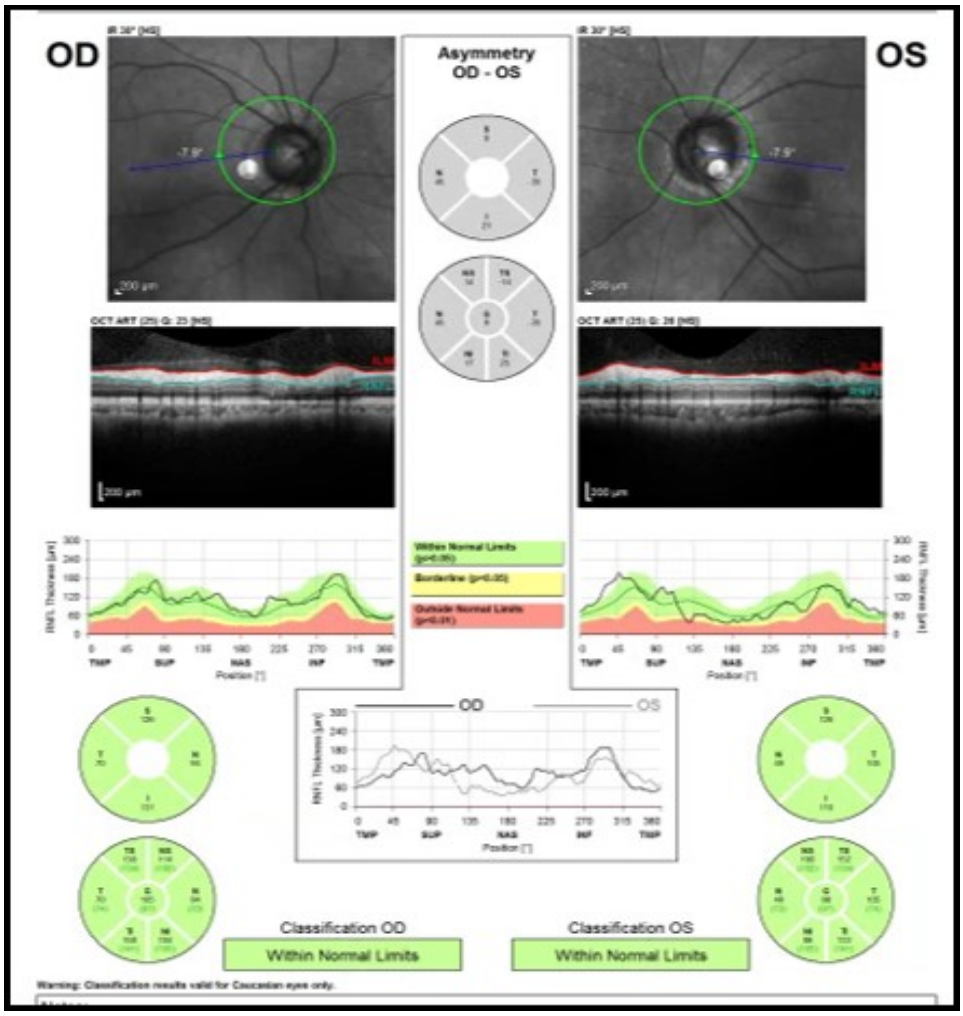

Figure 2c (bottom): Spectralis SD-OCT with all Sector Maps within normal limits (Q: 26).

Both Cirrus and Spectralis OCT analysis failed to objectively identify the clinical RNFL defect. The patient was diagnosed with glaucoma OS based on the optic disc appearance but never returned for further evaluation or treatment.

CASE 3

A 61-year-old female who was previously diagnosed and treated for glaucoma presented for evaluation; she had personally discontinued her topical therapy. Ophthalmoscopy and photography revealed an inferior-temporal RNFL wedge defect OD (Figure 3a).

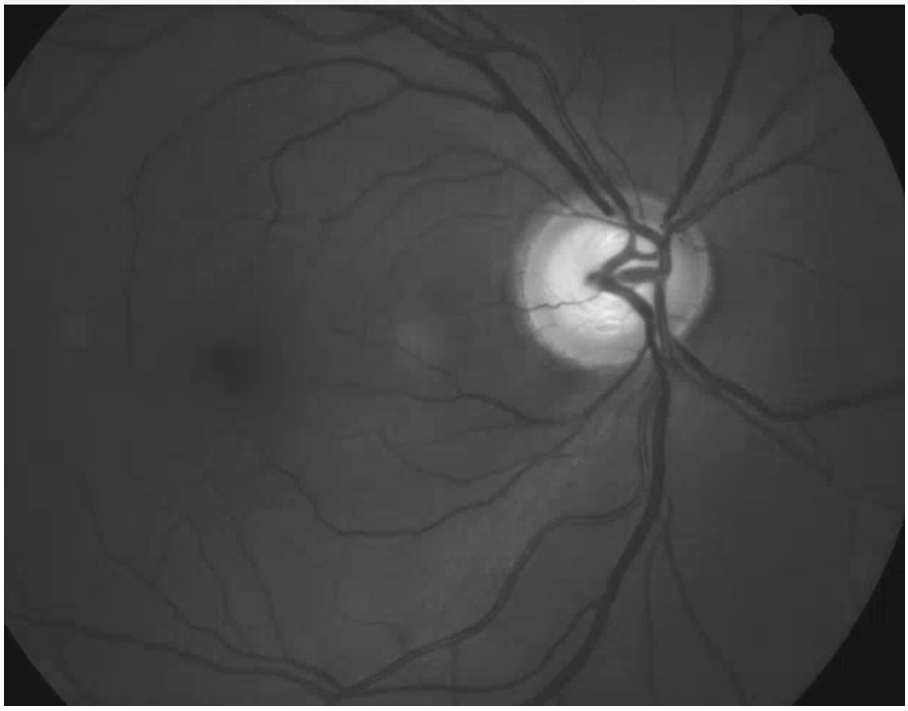

Figure 3a (Top): Red-free optic disc photograph illustrating inferior-temporally located RNFL defect OD.

The left optic disc and RNFL were normal. Cirrus SD-OCT analysis showed a corresponding RNFL abnormality on the Thickness and Deviation Maps, but the TSNIT, RNFL quadrants, and RNFL Clock Hours Maps were within the normative data range and not flagged as abnormal (Figure 3b). Spectralis OCT analysis showed an inferior-temporal abnormality OD and a slight inter-eye asymmetry on the TSNIT Graph. However, all other measured parameters were within the normative data range and not flagged as abnormal (Figure 3c). Threshold perimetry revealed no defects in either eye.

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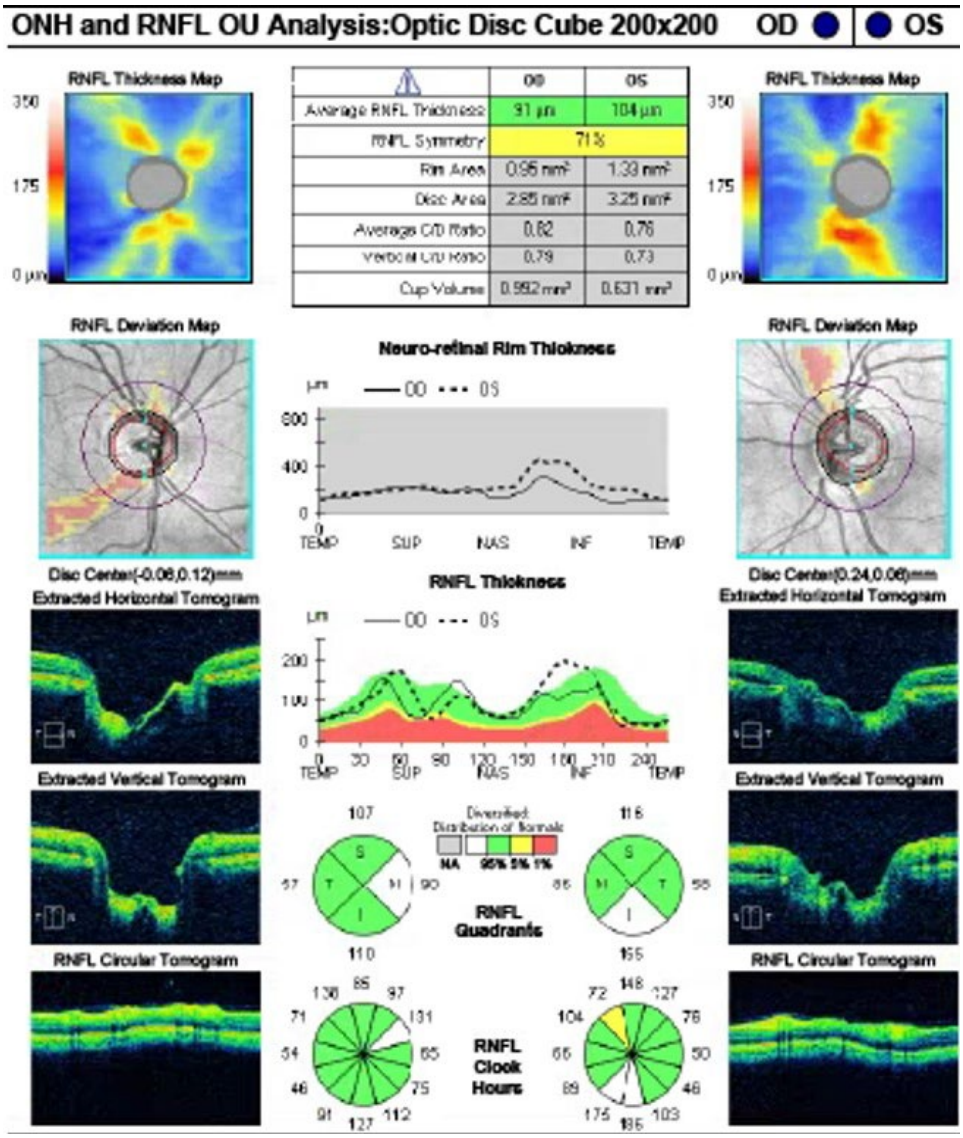

Figure 3b (Middle): Cirrus SD-OCT analysis demonstrating correlating RNFL defect on Thickness and Deviation Map but statistically normal RNFL Quadrant and Clock Hours Maps OD (Signal Strength 8/10).

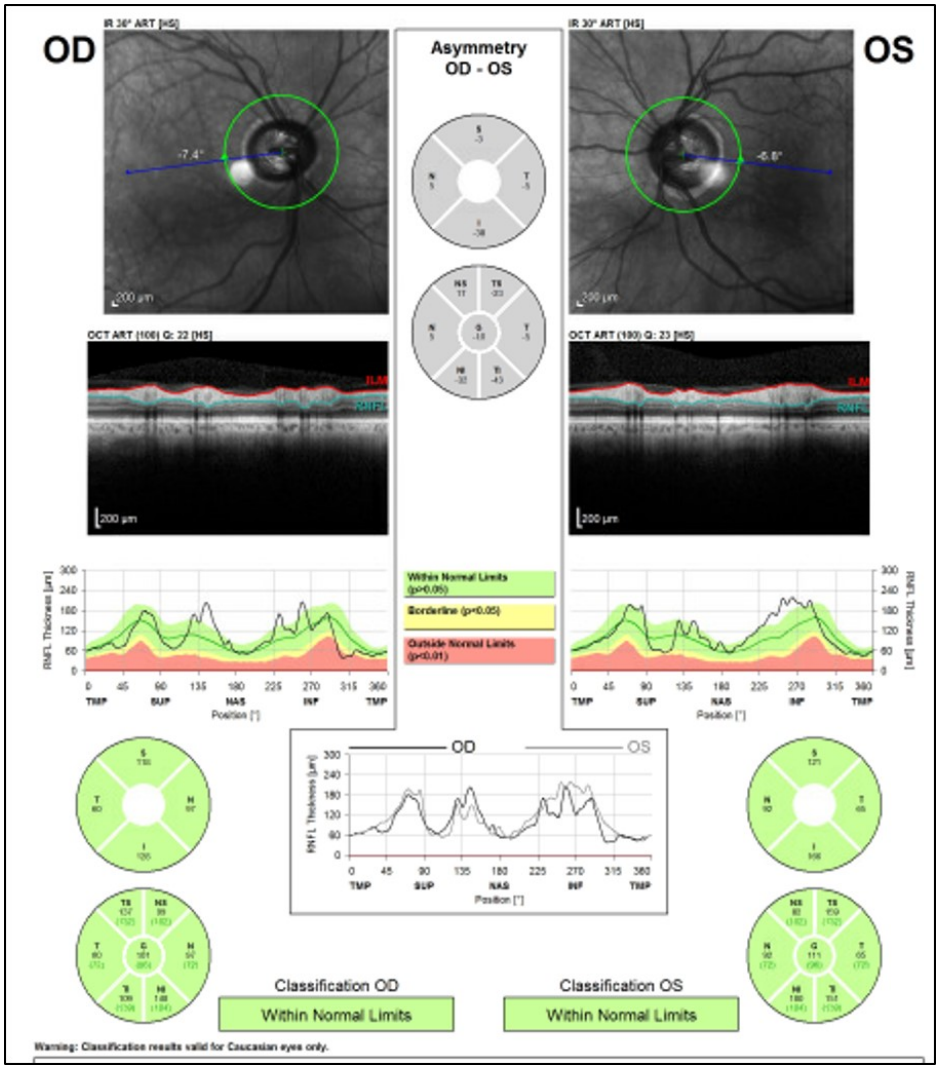

Figure 3c (Bottom): Spectralis SD-OCT analysis showing corresponding abnormality on TSNIT graph but all other corresponding parameters within normal limits (Q:22)

DISCUSSION

SD-OCT has gained widespread acceptance as a valuable imaging modality in the diagnosis and management of glaucoma. Enhanced resolution, reduced acquisition time, and improved scanning protocols allow these devices to generate a quantitative assessment of the RNFL. However, despite such innovative advancements, there remain additional significant factors to consider when interpreting data produced by SD-OCT.

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Our cases illustrate the misrepresentation of true RNFL defects seen funduscopically with false-negative classification of the color-coded maps on SD-OCT that were seemingly without artifacts and fell within the recommended quality imaging scores for each device. When numeric values of the RNFL fall within the "normal" range on the OCT, they could be labeled as "green," despite the presence of glaucoma. Inaccurate optic disc margin delineation and segmentation, along with other acquisition errors, can produce flawed RNFL assessments that could potentially fall within the normative database.[5] Rao and associates conclude increased incidence of false negative classification for preperimetric RNFL defects, small RNFL defects (likely due to averaging the entire sector), and superior quadrant RNFL defects.[6,7] When interpreting the significance of Sector, Quadrant, and Clock Hour displays, or any other global sector analysis, it must be noted that substantial amounts of anatomic area are being averaged together to give an overall value. When this happens, a small RNFL defect may be present, but averaging within the area may result in an overall value that falls within the device's normative database. Also, RNFL defects that are more temporally located in inferior-and-superior temporal glaucomatous damage zones fall in areas that are anatomically thin to begin with and may be within a normative database, thus being classified inappropriately as normal.

It is essential to consider the presence of posterior segment abnormalities that could artificially increase RNFL thickness when utilizing SD-OCT. Epiretinal membrane, proliferative vitreoretinopathy, papilledema, optic nerve drusen, and myelinated nerve fibers, are well-documented conditions that could cause incorrect delineation of the RNFL, resulting in a false-negative assessment of RNFL abnormality.[8,9]

Poor scan quality can also negatively impact SD-OCT ability to detect glaucoma and monitor progression.[5,6] Because a good signal strength was found to improve image quality and reproducibility of the RNFL thickness measurements, clinicians should adhere to manufacturer-specific recommended values when assessing the quality of the scan for any SD-OCT. Additionally, some subjective assessment should be made as to clarity, focus, centration and potential artifacts, such as posterior vitreous detachment and epiretinal membrane that may be visible in the images and B-scans. The quality of images is highly reliant on select patient, operator, and device-dependent factors.[5,8,9] One study comparing the image quality obtained by SD-OCT and fundus photography found that approximately half of the SD-OCT results were of insufficient quality to provide useful clinical information—yet in the same population, disc photographs were satisfactory in nearly all cases.[10]

Another potential contributor to a false negative assessment is the inadequate biometric database for individuals with demographics that are not well-represented including refractive error, sex, age, underlying ocular diseases, and ethnicity.[6-10] In cases of high myopia the RNFL analysis can be affected by the presence of a staphyloma, creating a false determination of overall structural loss. As well, normative databases, scanning protocols, segmentation, and thickness calculation algorithms vary among different manufacturer platforms.[9] Unlike fundus photos that can be compared between cameras, images taken with SD-OCT vary greatly in how a normative database is applied, making inter-device direct comparison inappropriate, though one would expect similar assessment of patients.

Despite normative database limitations, guided progression analysis (GPA) is a practical feature on the SD-OCT, aiding in the detection of progressive RNFL thinning over time.[9] SD-OCT GPA provides a long term comprehensive analysis by including serial scans with a color-coded RNFL thickness change map. This feature is especially helpful when an isolated SD-OCT scan produces values that fall within the normative database, yet other clinical data represents contradictory findings. The drawback is that for a GPA to assist in diagnosis, it is necessary for progression to have occurred. Also, subsequent analyses must all be of sufficient quality and free of confounding artifacts.

Among the different maps produced by the Cirrus SD-OCT, the thickness map has been shown to have the best diagnostic value in identifying RNFL defects present on red-free fundus photographs (as illustrated in case 3).[9] Inter-ocular asymmetry, may also be a significant diagnostic indicator of early glaucomatous damage on SD-OCT RNFL analysis. It has been postulated that RNFL thickness asymmetry beyond 9-12 microns may be indicative of early glaucomatous damage.[9] Of course, use of this parameter is predicated on the quality of the image capture free of artifacts or confounding conditions. In these examples, two of the three aforementioned cases demonstrated inter-eye average RNFL asymmetry between 10-13 microns (Cases 1 & 3). Interestingly, in case 1, the SD-OCT revealed average RNFL thickness asymmetry of 10 microns between eyes and an RNFL symmetry of 90% yet, despite quantitative differences presented, it was green-labeled as normal (Figure 1b).

Some studies show that ophthalmoscopy and red-free fundus photography remain the gold standard of glaucoma imaging due to their portability, ease of use and interpretation, and possibly a large number of images for comparison.[10] Fundus photography with subsequent analysis and sequential optic disc comparison over time has been utilized for decades and thus, has a greater utilization and experience than that of the recently developed SD-OCT. Current SD-OCT is more accurate

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than previous time-domain OCT and further innovations in spectral domain technology such as using multiple circular scans around the optic disc may enhance the accuracy even further.

Conclusions

When diagnosing and managing glaucoma, it is imperative to understand the limitations of SD-OCT RNFL Analysis and to recognize specific factors and instances that could potentially indicate false negative results and incorrect assessment of glaucoma. To improve accuracy when assessing SD-OCT data, implementing a comprehensive approach that includes confirming the name and age of the patient, using only analyses with adequate signal strengths and image quality, verifying refractive error, and recognizing confounding posterior segment abnormalities is crucial. Additionally, utilization of SD-OCT Ganglion Cell Analysis in combination with RNFL Analysis could potentially increase disease detection sensitivity, though there may be similar confounding imaging issues with this assessment as well. Further, optic disc parameters such as found on Cirrus SD-OCT may help discern normal patients from those with glaucoma and assist in interpretation in concert with other analyses. Although SD-OCT encompasses advanced algorithms and progressive technology, it should not be used in isolation and an over-dependence to the exclusion of other clinical findings should be avoided. This manuscript highlights identifiable glaucomatous damage that was not identified with SD-OCT RNFL Analysis in comparison to normative database. A more comprehensive approach including SD-OCT Ganglion Cell and Optic Disc Parameter Analysis along with optic disc photography and clinical ophthalmoscopic evaluation could potentially increase disease detection sensitivity. Spectral domain optical coherence tomography is a vital part of a clinical glaucoma assessment which includes determination of risk factors, threshold perimetry, gonioscopy, and clinical and photographic analysis of the optic disc and RNFL.

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