Issue 3

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Clinical Applications in Medical Practice

Daiva Paulaviciute-Baikstiene, Renata Vaiciuliene

Visualisation of Anterior Chamber Angle

There are several ways to evaluate the angle, including direct observation using gonioscopy and imaging the angle with two commonly used commercially available devices (AS-OCT, UBM) (Figs. 1 and 2) [1].

Angle visualisation and assessment may be widely applied in clinical practice: evaluation of angle closure [2], screening of the structural cause (including pupillary block, malignant glaucoma, plateau iris configuration), assessment of the efficacy of a laser iridotomy [3, 4] and dynamic analysis of the iris curvature [5]. These imaging modalities help to find out clinically essential changes in the ACA structures under the light and dark conditions. Along with gonioscopy help to clarify the exact mechanism of angle closure glaucoma in many cases [6]. The criteria for the diagnosis of closed angle in gonioscopy and AS-OCT are different. Non-contact technique describes closed angles as any contact between angle wall anterior to the SS and peripheral iris. For gonioscopy is nonvisibility of posterior pigmented trabecular meshwork [7]. Nolan and collegues reported that the AS-OCT detected more closed angles than gonioscopy. The same investigators determined about 87% of occludable angle quadrants [8]. AS-OCT is also excellent at measuring iris parameters, unlike gonioscopy. Recent studies established that iris volume is an important determinant of angle closure disease [9, 10]. Sakata *et al.* noted that variations in iris configuration and the level of iridocorneal contact may explain some of the differences seen between AS-OCT and gonioscopy [7].

Assessment of ACA width is a key factor determining the susceptibility of a narrow-angle [11, 12].

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The commonly used parameters to quantify normal angle assessment using AS-OCT and UBM are: ACA in degrees, AOD (500 and 750 μm), ARA (500 and 750 μm^2) and TISA (500 or 750 μm^2) (Fig. 3).

- Angle-opening distance (AODn in μm) perpendicular distance from the cornea to iris at n μm from the SS (n typically 500 or 750) [13, 14].
- Angle-recess area (ARAn in μm^2) the triangular area between angle recess, iris and cornea n μm from the SS (n typically 500 or 750) [15].
- Trabecular–iris space area (TISAn μm^2) trapezoidal area between iris and cornea from sclera to n μm (n typically 500 or 750) [16].

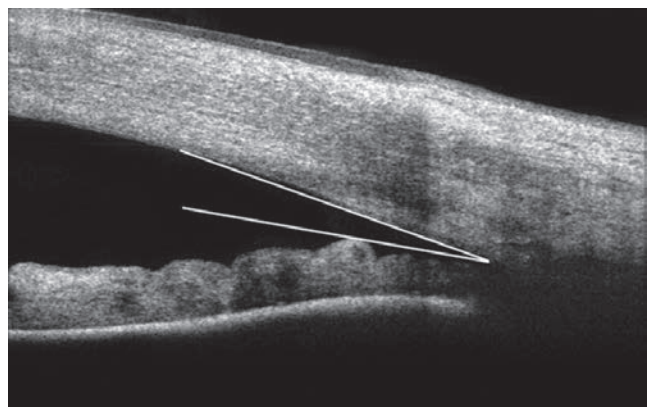


Fig. 1: Visualisation of a narrow angle. Image was performed with anterior segment optical coherence tomography.

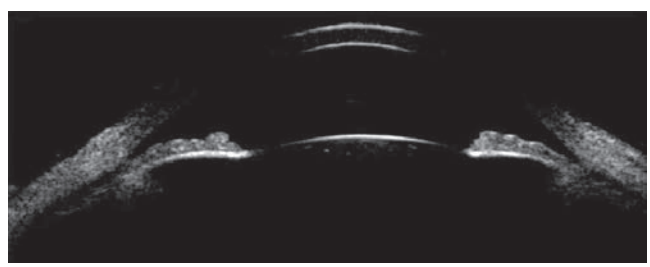


Fig. 2: Visualisation of a narrow angle performed by ultrasound biomicroscopy.

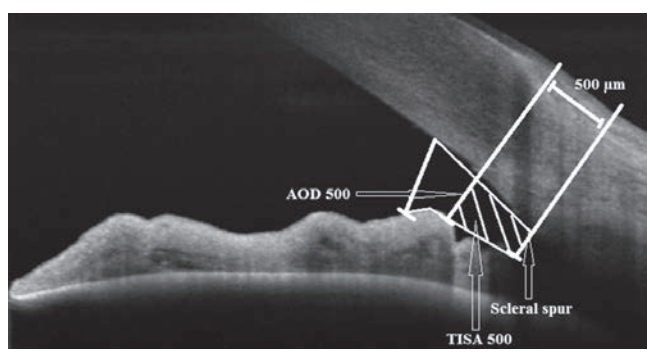


Fig. 3: Measurement of quantitative parameters such as: angle opening distance and trabecular-iris space area. Image was performed with anterior segment optical coherence tomography.

- Anterior chamber angle in degrees the angle recess forms the apex and the two sides of the angle are formed by drawing the lines through the points defining the AOD 500 [17].

Narayanaswamy and colleagues noted that the most useful ACA measurement tool for closed or narrow angles is AOD 750 [2]. Goniometry studies show that in healthy eyes the AOD (500) is 329 μm and ACA about 28° [18]. Meanwhile, in closed or narrow angles AOD (500) is <210 μm and the ACA <18°. Radhakrishnan and colleagues in their prospective observational study of 31 eyes found the criteria, which suggests that occludable angle is when AOD 500 is less than 190 μm [19]. However, AOD measurements could be affected by iris contour, curvature irregularities or presence of peripheral anterior synechiae. Theoretically, ARA is a better indicator compared with AOD, because it measures the entire iris surface [19]. In some situations there is not possible to measure ARA accurately, because of poor visualisation of the SS. Therefore investigators suggested to assess TISA, because it may better represent the actual filtering area and does not require clear visualisation of the angle recess [19]. The same researchers, compared results of AS-OCT and UBM by using the same customized software to conventional gonioscopy under similar room illumination. Measurements for AOD, ARA, and TISA, were similar between both imaging technologies. They also determined high sensitivity and specificity in detecting closed or narrow angles [19]. Nolan and colleagues demonstrated high sensitivity, but low specificity of AS-OCT than with gonioscopy in detection of angle-closure related disease, especially in the superior and inferior quadrants of the eye [8]. Cheon *et al.* established that age could influence the biometric parameters of ACA measured with AS-OCT. Authors noted significant negative slopes with increasing age for AOD, TISA, ARA and ACD [20].

A variety of mechanisms may be involved in the pathogenesis of angle closure [21]. The main anatomic sites where aqueous humour obstruction may occur are shown in Table 1 [21].

Pupillary block (PB) [22] and plateau iris [23] are the most common forms of primary angle-closure glaucoma [23]. PB is the predominant mechanism [1], which is defined as resistance to aqueous flow from the posterior to the anterior chambers. ACA is determined as closed by the presence of contact between the angle wall anterior to the SS and forward bowing of the iris from the root to the pupil margin [14, 22, 24–27]. Previous studies have defined, that eyes with PB have a reduced AOD [28]. Laser peripheral iridotomy (LPI) is the standard treatment for primary angle closure, which eliminates PB. After the procedure, the iris usually flattens out. Imaging devices (UBM, AS-OCT) could help to elucidate the etiology of PB, to assess and to document the iris curvature and ACA change after LPI [29, 30]. The ACA parameters significantly changed after LPI in Lee and colleagues performed study. ACA remained unchanged from 23.9 to 45.7% of closed or narrow angles, after iridotomy. Other investigators also have noted that LPI might

Table 1: Classification of angle closure glaucoma according to Ritch [21].

Angle closure glaucoma	Site of aqueous flow obstruction
Primary pupillary block	Iris
Plateau iris	Ciliary body
Phacomorphic glaucoma	Lens
Malignant glaucoma	Suprachoroidal fluid

not be effective in treating all closed or narrow angles [31]. AS imaging can explain the reasons whereby this procedure is unsuccessful in some angle closure situations such as incomplete LPI, goniosynechiae and plateau iris syndrome. Other multiple causes may contribute to narrow-angle closure following LPI [31–36].

Ultrasound biomicroscopy (UBM) is valuable and for the diagnostic imaging of malignant glaucoma [36] which is characterized by a very shallow AC and a forward movement of the iris lens diaphragm. High posterior lenticular pressure induces forward positioning of the AS structures, and this leads to increased intraocular pressure. UBM and AS-OCT document diminished ACD, anteriorly positioned lens, iris and vitreous, the absence of posterior chamber and uveal effusion [37, 38]. Wang *et al.* in their cross-sectional study demonstrated that in eyes with malignant glaucoma ciliary bodies were more anteriorly rotated and thinner compared with fellow eyes in UBM measurements after trabeculectomy [39].

Approximately one third of eyes with angle closure had plateau iris in studies performed with UBM [40–43]. Possibly enlarged and anteriorly positioned ciliary body compressing the iridocorneal angle and placing the peripheral iris in apposition to the trabecular meshwork [41, 42]. Quigley *et al.* noted that in plateau iris the central depth of the AC is usually normal [38]. UBM and OCT typically demonstrate a thick, flat or slightly anterior bowed iris, but rather steep rise in the iris near its point of insertion [44]. Parc and colleagues comparing the efficacy of AS-OCT and UBM to reveal plateau iris syndrome. They reported that UBM allows visualisation of the ciliary processes position, iris root indentation induced by the ciliary body with loss of ciliary sulcus. Due to blockage of infrared light by iris pigment, AS-OCT is limited with incomplete visualisation of the ciliary body therefore can only visualise indirect signs of plateau iris [45]. Literature suggests that anterior rotation of the ciliary body, best observed with UBM [46].

The angle-closure also can be caused by the intumescent lens. Nongpiur *et al.* reported, that lens vault increases the availability of angle-closure progression, regardless of the lens thickness and location. Imaging modalities can verify the presence of lens swelling pushing forward the iris [37].

Commercially available devices are also benefit in identifying pathology in some forms of secondary glaucoma. To evaluate iris contour and to document the extent of trabecular pigmentation is important in eyes with pigment dispersion syndrome (PDS). This condition is associated with wide open-angle and peripheral iris concavity, causing reverse pupillary block. LPI can help to equalize pressure gradient between anterior and posterior chambers by flattening the iris [47]. Aptel *et al.* identified higher alterations in the contour of the iris in PDS, because of increased iris volume to length ratio, after LPI [48]. Kanadani *et al.* reported that UBM has been used to demonstrate more posterior iris insertion compared to control eyes in PDS [49]. Imaging modalities can be used to assess the iris contour, degree of iridolenticular contact and reverse pressure gradient between two chambers in eyes with PDS [50].

Ultrasound biomicroscopy has even been used to help characterize pseudoexfoliation syndrome by the observation of the pseudoexfoliative material. It looks like as small high-reflective areas in the ACA, on the anterior surface of the lens and under the corneal endothelium. Guo and

colleagues noted that lens zonule nodules and thicker anterior lens capsule were associated with pseudoexfoliation [50].

Therefore imaging technologies allow precise evaluation of iridocorneal angle that is critical to ensure accurate diagnosis and optimal treatment.

Visualisation of Schlemm's Canal

Intraocular pressure (IOP) is regulated by the balance between the formation and outflow of aqueous humour via the trabecular meshwork, Schlemm's canal (SC), veins and collector channels leading to scleral veins [51]. Most often, pressure dependent changes in outflow resistance are located distal to the inner wall of the SC [52]. The resistance of the outflow pathway can result in overdraft aqueous humour and as a result increased IOP [53]. Kagemann *et al.* in their study showed that acute IOP elevations in healthy eyes with open-angles resulted in a reduced SC area demonstrated by high-density OCT [54]. They concluded that the compression of SC is possibly due to a movement of the inner wall towards the outer and might be a result of elevated pressure. AS-OCT or UBM allow for convenient evaluating of the structural and pathophysiological changes in AC structures, such as SC [55–57].

Recent studies suggest that the SC area in healthy patients is significantly larger than in patients' eyes with primary open-angle glaucoma [53, 55, 58]. Kagemann *et al.* found that the SC area varies between 4064 and 7164 μm^2 [59]. They noticed that measurements of the aqueous outflow system could be clinically useful in the establishment of the impact of glaucoma therapies as well as evaluation preoperatively.

The point of a relatively new surgical procedure the canaloplasty effect is circumferential viscodilation and suture tensioning of the SC inner wall, after which the permanent enlargement of the SC occurs and better access to the collector channels [60]. Therefore, this non-penetrating operation reduces the IOP by the reconstruction of the natural aqueous humour drainage. The surgical intervention success depends on this pathway function. In a small number of eyes, this surgery could be unsuccessful due to pathology (e.g., nonreversible collapse collector channels) that cannot be restored [61]. Imaging technologies allow to investigate structural and pathophysiological changes of the SC after canaloplasty and may predict an outcome of the surgery (Fig. 4) [55–57].

Fuest and colleagues explored SC for patients after the non-penetrating glaucoma surgery with spectral-domain AS-OCT and UBM [62]. They found the enlargement of the SC height and width 3 months after canaloplasty. Suture in the SC was detected only in a few cases using AS-OCT, while it was always possible with UBM (probably due to higher reflectivity of polypropylene to ultrasound waves). They concluded that AS-OCT is more useful for imaging superficial conjunctival areas and SC, whereas UBM can detect deeper structures [62].

Paulaviciute-Baikstiene *et al.* visualised SC area before and 1 year after canaloplasty with spectral-domain AS-OCT [57]. The results demonstrated the expansion of the SC area postoperatively with sufficiently low IOP and found a strong negative correlation between the extension of canal and the IOP-lowering effect after surgery [57].

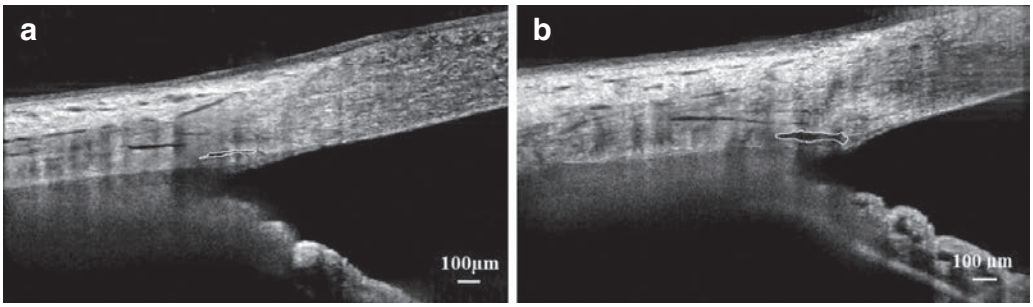


Fig. 4: Schlemm's canal vizualisation before (**a**) and after (**b**) canaloplasty.

Schlemm's canal evaluation with imaging devices may improve the clinical ability to predict the efficiency of a non-penetrating surgery.

Visualisation of Filtering Blebs

Trabeculectomy is "the gold standard" of glaucoma surgery. This intervention is attributed to penetrating filtering procedures, during which time the trabeculo descemet membrane is removed, and a circumventing route to the regular pathway via the trabecular meshwork and the SC is created. The aim of this intervention is to form a subconjunctival accumulation zone of intraocular aqueous (filtering bleb) [63]. Imaging technologies permit a detail noninvasive observation of the inner architecture of the filtering bleb. It is important for the early and late postoperative period.

Slit-lamp investigation includes clinically well-defined parameters of the bleb's external structure and surrounding conjunctival tissue. It is the most commonly used method [64]. Different bleb grading systems including Indiana Bleb Appearance Grading Scale [65], the Moorfields Bleb Grading System [66] and The Wuerzburg bleb classification score [67], based on the bleb classification as described by Picht and Grehn [68, 69] have been published.

The Indiana Bleb Appearance Grading Scale describes four parameters including bleb height (H), extent (E), vascularity (V) and leakage graded with the Seidel test (S). These signs are valued an equal scaling interval (H0–3, E0–3, V0–4, S0–2) (Fig. 5) [65].

The Moorfields Bleb Grading System estimates bleb wall thickness (range from 1 to 10, where 1 equates to visible hole and 3 normal thickness), bleb height (elevation range from 1 to 10, where 3 equates to norma), the proportion of the total bleb area that was diffuse (range 1–10; the percentage of bleb area that is diffuse relative to the size of the demarcated area) and the total width of the bleb (maximum width of bleb [mm]; range from 1 to >10 mm) [66]. This grading system describes vascularity in three places of the bleb (Fig. 6): non-bleb conjunctiva (conjunctiva, which is more than 2 mm from the bleb edge), conjunctiva in the edge and in the centre of the bleb [66].

The Wuerzburg bleb classification score includes evaluation of vascularisation (3 avascular, 2 similar to adjacent conjunctiva, 1 increased, 0 massive), corkscrew vessels (3 none, 2 in one third, 1 in two thirds, 0 entire bleb), encapsulation (3 none, 2 in one third, 1 in two thirds, 0

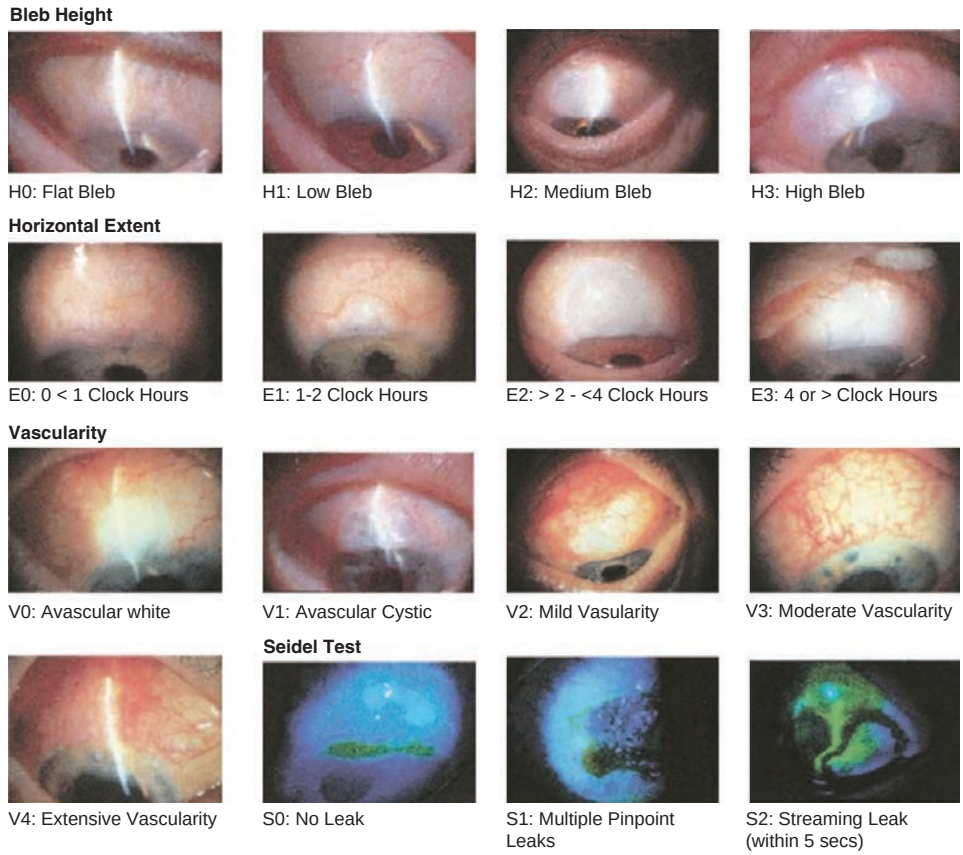
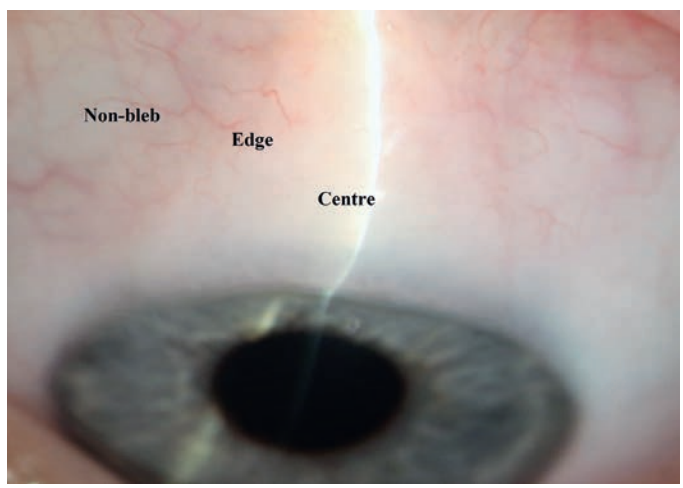


Fig. 5: The Indiana Bleb Grading Scale. *H* height, *E* extent, *V* vascularity, *S* leakage graded with the Seidel test (from Cantor *et al*. [65]).

Fig. 6: Vascularity of the bleb grading zones.



entire bleb) and microcysts (3 entire bleb, 2 lateral or medial of the flap, 1 over the scleral flap, 0 none) [70]. Microcysts and the extent of vascularisation plays a major role in the assessment of trabeculectomy success [71].

Many studies have proven that the morphological findings of filtering bleb correlating with IOP after the trabeculectomy [12, 24, 65, 72, 73]. Blebs with a higher score than 7 points in the early period after penetrating surgery were related with a lower IOP 1 year postoperatively according to the Wuerzburg bleb classification score [70, 71, 74]. Functioning blebs include such parameters: diffuse appearance, mild elevation over the scleral flap, few conjunctival vessels, and microcysts. A small superficial extension, a high degree of elevation, excessive and irregular vascularisation, and an encapsulated shape are failed bleb signs [68, 69]. Blebs with low, small extent and mild vascularity (H1E1V2S0) were found in eyes with higher IOP according to the Indiana Bleb Appearance Grading Scale. It might be related to external subconjunctival fibrosis [65]. Many studies have observed the significance relation between the occurrence of microcysts and reaching the target pressure [65, 68–71, 75]. In contrast, excessive vascularisation shows the interface to higher IOP postoperatively [70, 71]. The most common problem of failing filtering surgery is subconjunctival scarring [76]. Corkscrew vessels are associated with a risk of encapsulation and a higher IOP between 1 and 12 months postoperatively [75]. Thatte *et al*. found a thin, cystic bleb with lower levels of IOP, indicating overfiltration [71].

The description of bleb morphology and function is usually based on the clinician's subjective judgment. Bleb morphology estimation with slit lamp is widely used to predict the possible functionality, but the presence of tissue within the bleb wall complicates the analysis of the internal structures. As a consequence, a more detailed morphologic assessment would improve the ability to characterise features related to the clinical success or failure. AS-OCT and UBM are becoming more commonly used in addition to IOP measurement and slit lamp examination for the objective evaluation of bleb function [63, 77–83]. It is important to understand what features of blebs are associated with failure after glaucoma surgery and would enable clinicians to choose proper treatment and prevent possible complications such as bleb leak or scarring [84–86].

Anterior segment optical coherence tomography (ASOCT) has several advantages in imaging of filtering bleb over UBM: a greater spatial resolution, the absence of any contact with the surface of the eye during the examination, convenience for both the investigator and the patient [87]. Based on Zhang *et al*. the sensitivity and specificity of AS-OCT for predicting a bleb function are significantly higher compared to UBM (92.7% and 83.3% vs. 66.7% and 75.0%) [80], on the other hand, UBM might evaluate deeper tissues.

Previous studies have described many important AS-OCT parameters of bleb structure such as length, height and bleb wall thickness, the wall thickness at the thinnest point, internal fluid-filled cavity length and microcysts that are associated with IOP and bleb filtering function [78, 88–90]. Eyes with good IOP control had higher bleb, with a large internal fluid-filled cavity (cleft volume), thicker walls and microcysts [78, 88–90]. Tominaga *et al*. found a significant correlation between the bleb-wall thickness and IOP, did not find any relationship between the IOP and height of bleb cavity [91]. Kawana *et al*. noticed interface between a high number of microcysts, a

large internal fluid-filled cavity (cleft volume) and good results of trabeculectomy [88]. The study results of Paulaviciute-Baikstiene and colleagues suggest that a higher IOP reduction and better bleb function were associated with higher bleb and thickener wall [78].

Most studies focus on bleb wall reflectivity [77, 78, 90]. It is known, that in the success cases, the wall of bleb has a low reflectivity appearance due to fluffy connective tissue and a weak scarring tendency, whereas, in the failed blebs, a high reflectivity bleb wall was suggestive of dense connective tissue as a sign of marked scarring reaction [77]. Ciancaglini *et al.* presumed that the reflectivity of the wall best represents bleb functionality, rather than the bleb biometric data (e.g., length, height, bleb wall thickness, etc.) [77]. Kokubun *et al.* drew attention to the reflectivity of the bleb wall 2 weeks after trabeculectomy. These reflections were significantly different in blebs that would later succeed or fail. Multiple logistic regression analysis showed that high reflectivity of the bleb wall 2 weeks after trabeculectomy was a risk factor for a negative prognosis at 12 months [90].

Theelen *et al.* explored blebs morphology with slit lamp-adapted OCT and noticed frequently demonstrated multiple hyporeflective layers within Tenon's capsule ("striping" phenomenon) and "shading" phenomenon of the sclera in the first postoperative week in functional filters but not in the failures [82].

Kojima *et al.* reported that the width of the scleral flap opening was another useful, early postoperative predictor of long-term IOP control [92]. Inoue *et al.* in their study with three-dimensional AS-OCT showed that in most eyes with functional blebs could identify the filtration openings from the scleral flap margin into the bleb space [93]. Wound healing may occur with unchanged external bleb appearance, but result in a decreased aqueous outflow from the anterior chamber. In such case, it might not be possible to predict future bleb failure by slit lamp examination. The width of the filtration opening on the scleral flap may be a more sensitive indicator of the surgical failure and to determine a treatment tactic (for example, as needling and laser suture lysis) in the postoperative period [92, 93].

Hirooka *et al.* distribute blebs according to Stratus OCT data in types such as: cystoid-type blebs (showed multiple cysts inside the wall of bleb); diffuse-type blebs (showed low to high reflective areas); layer-type blebs (characterised by a medium to high reflective layer inside the bleb) [83]. Based on this grouping and postoperative IOP, they found that the success rates were 94%, 97% and 75% in the cystoid-, diffuse- and layer-type blebs, respectively [83]. The authors posit that the highly reflecting bleb wall might have fibroblast proliferation and this type of bleb (layer-type) have been seen in eyes with poor IOP control [83].

The most critical period for the blebs' formation is the first postoperative weeks. Procedures to reduce the scarring processes and hold a sufficient filtration through margins of the scleral flap are needed frequently. Various methods may be used to preserve the bleb functionality and the AS-OCT could be a helpful tool to support to choose one of them.

Finger massage is a conventional technique employed after filtering surgery to aid the aqueous humour flow through the artificially created pathway. This procedure promotes the patency of the scleral channel, with the subsequent expansion of the subconjunctival space. The clinical effect of a finger massage can be appreciated with AS-OCT as a scleral opening with the enlarging of the fluid-filled cavity, increasing the bleb wall thickness and a number of microcysts [89].

In addition, the effect of peribleb injection 5-fluorouracil and needling to reduce fibrosis in patients with failing blebs can be evaluated as a decreasing reflectivity and thickening of the wall with multiple intra and subepithelial fluid-filled cavities [89].

Singh *et al*. has proved the AS-OCT possibilities to estimate the effect of laser suture lysis. After the procedure, an increase in total bleb height, with increased bleb wall thickness and separation of the scleral flap from sclera were observed [94].

The advanced diagnostic approach can improve the clinician's ability to understand bleb functionality and in the failed cases to choose management and evaluate their efficacy.

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Source: Paulaviciute-Baikstiene D., Vaiciuliene R. (2019) Clinical Applications in Medical Practice. In: Januleviciene I., Harris A. (eds) Biophysical Properties in Glaucoma. Springer, Cham. https://doi.org/10.1007/978-3-319-98198-7_9.

2

Examples of Optical Coherence Tomography Findings in Glaucoma Eyes with Varying Stages of Severity

Ahmet Akman

Early (Pre-perimetric) Glaucoma

A seventy-year-old male glaucoma suspect referred for glaucoma evaluation. The BCVA was 20/20 OU. The anterior segment exam was normal with grade one nuclear sclerosis in both eyes. The posterior segment exam was normal OU. Intraocular pressures (IOPs) were 32 mmHg OD and 26 mmHg OS without treatment (Figs. 1, 2, 3, 4, 5, and 6).

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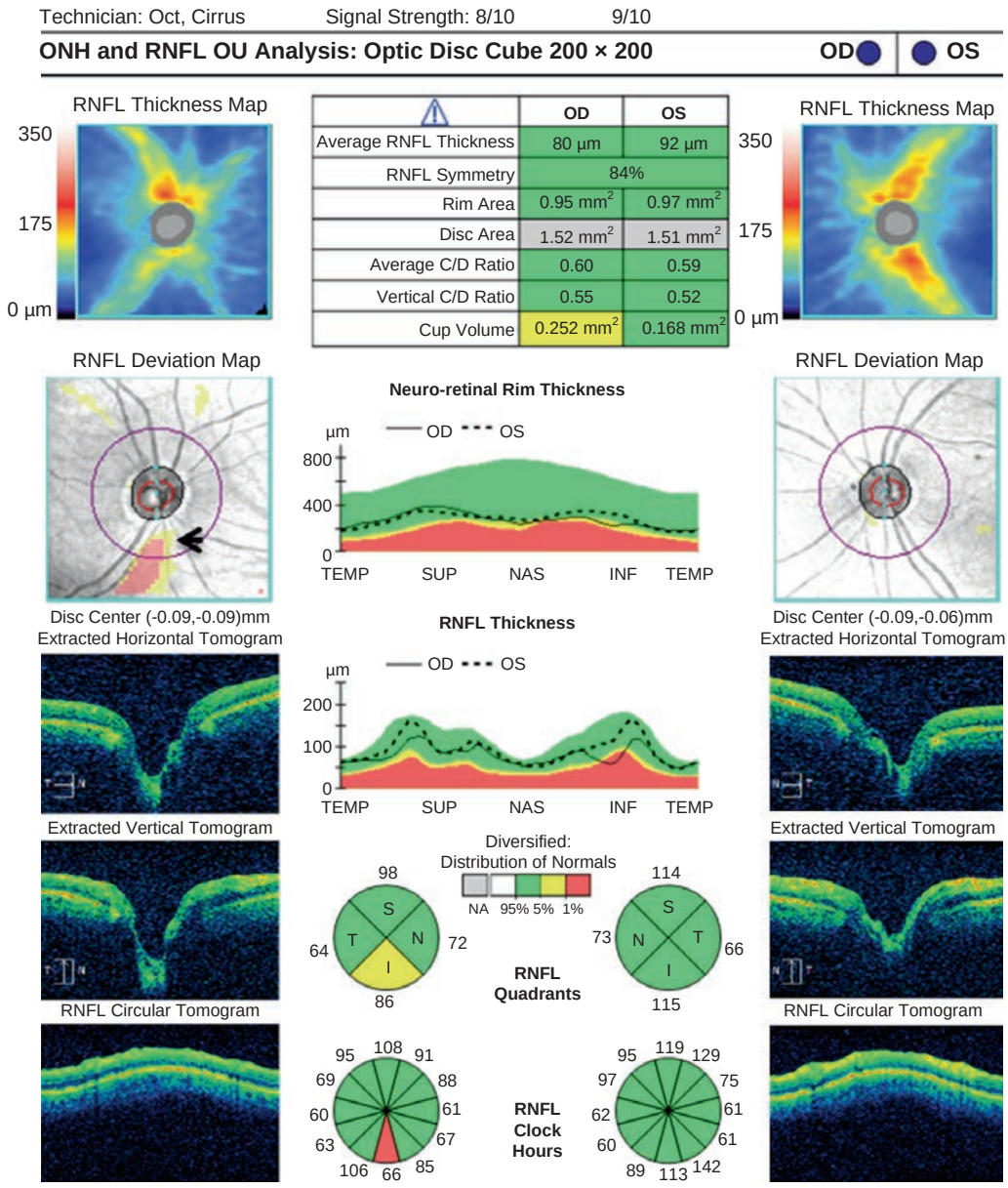


Fig. 1: (Cirrus HD-OCT) This is a good quality OCT scan with SS value of 8 OD and 9 OS; there are no artifacts or anatomical variations. The RNFL thickness map shows that the inferior RNFL bundle is thinner than the superior bundle in the right eye and compared with the inferior bundle of the left eye (see TSNIT curves). Although the average RNFL thickness measurements are still in the normal range in both eyes, there is an inferior RNFL defect on the RNFL deviation map (*black arrowhead*). The TSNIT plot and clock hour graphs also demonstrate this defect at the 6 o'clock position. The only abnormal finding among ONH parameters is the cup volume in the right eye, which is borderline abnormal.

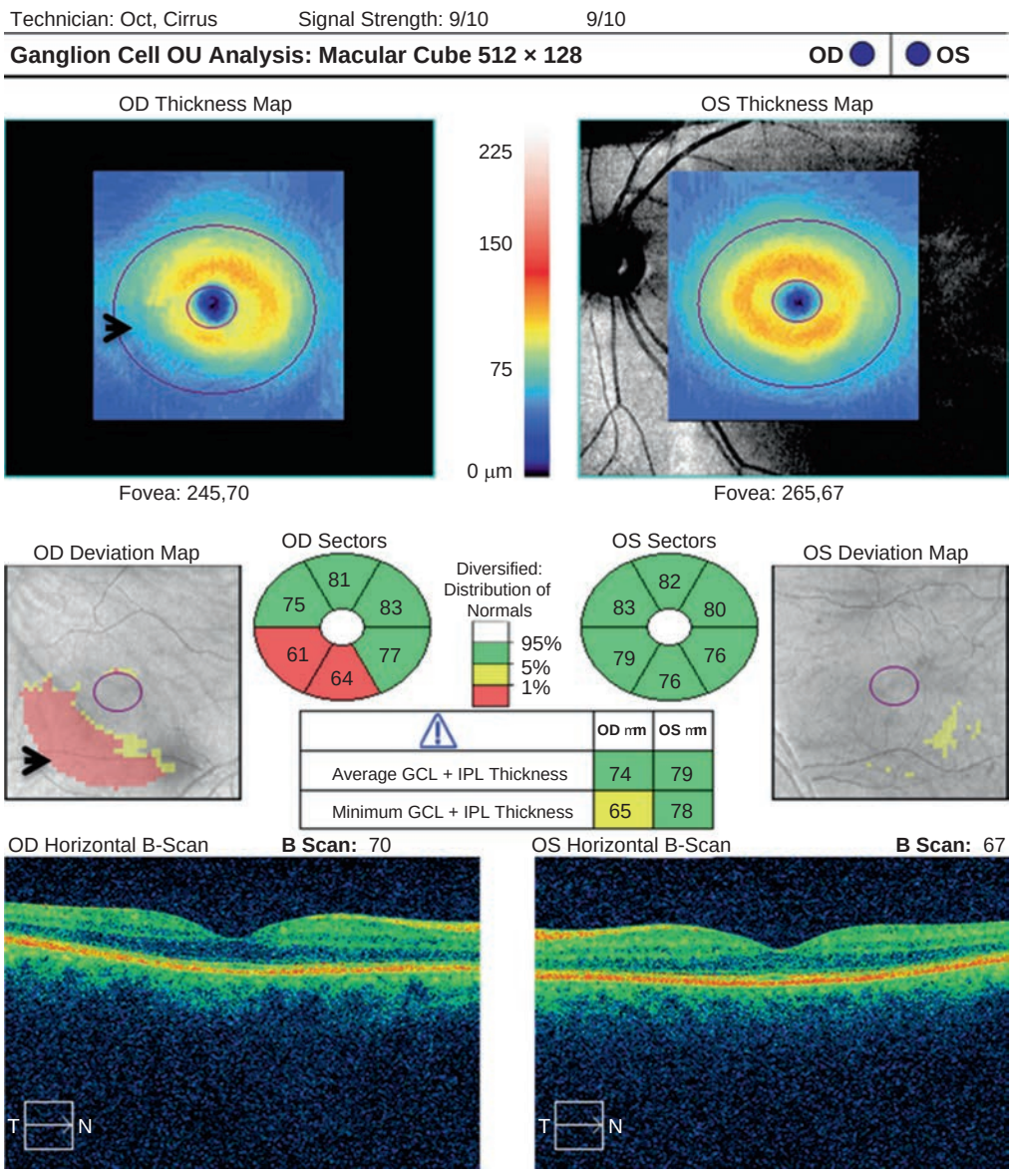


Fig. 2: (Cirrus HD-OCT) macular ganglion cell analysis also shows a local abnormal area in the inferior temporal part of the macula in the right eye (*black arrowheads*), which corresponds to the inferior RNFL defect on the optic disc cube. The inferotemporal and inferior sectors are also abnormal at <1% level and the minimum GCL + IPL thickness is borderline abnormal despite the average GCL + IPL being in the normal range. The right eye with corresponding defects in the peripapillary area and the macula can be classified as early glaucomatous damage as the 30-2 visual field is within normal limits (see below).

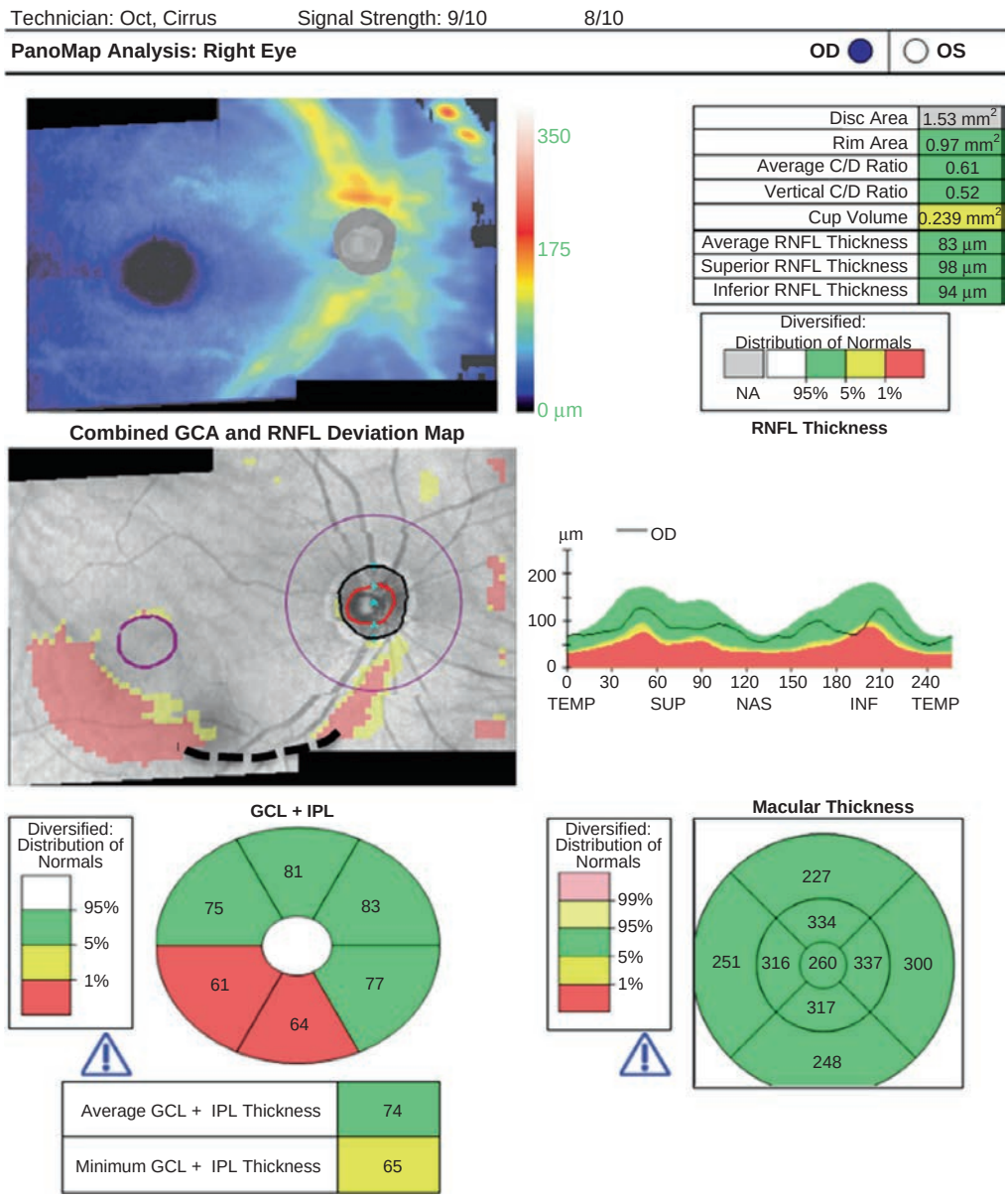


Fig. 3: (Cirrus HD-OCT) The PanoMap analysis shows the peripapillary and macular thinning in a single printout. The area of inferior RNFL thinning appears to be continuous with the region demonstrating macular GCL + IPL thinning, but part of the defect is outside the scan cubes so a gap seems to exist between the peripapillary and macular components of the defect in this printout (*black dashed line*).

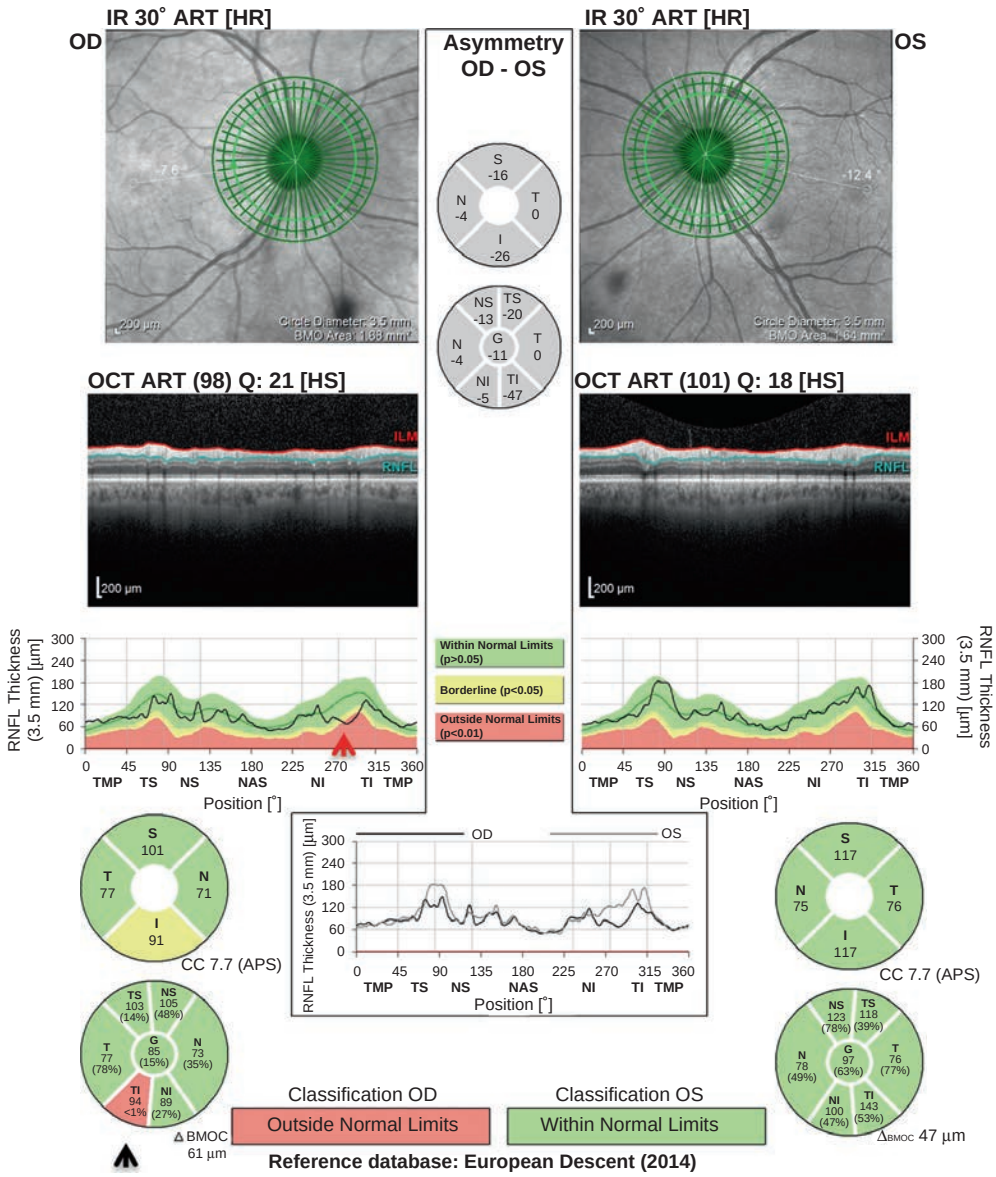


Fig. 4: (Spectralis GMPE module) The Spectralis OCT also demonstrates the RNFL defect in the right eye consistent with the Cirrus HD-OCT. The Garway–Heath sectors locate the defect in the inferior temporal quadrant (*black arrowhead*). The TSNIT graph also shows the defect at around 270–300 degrees (*red arrowhead*).

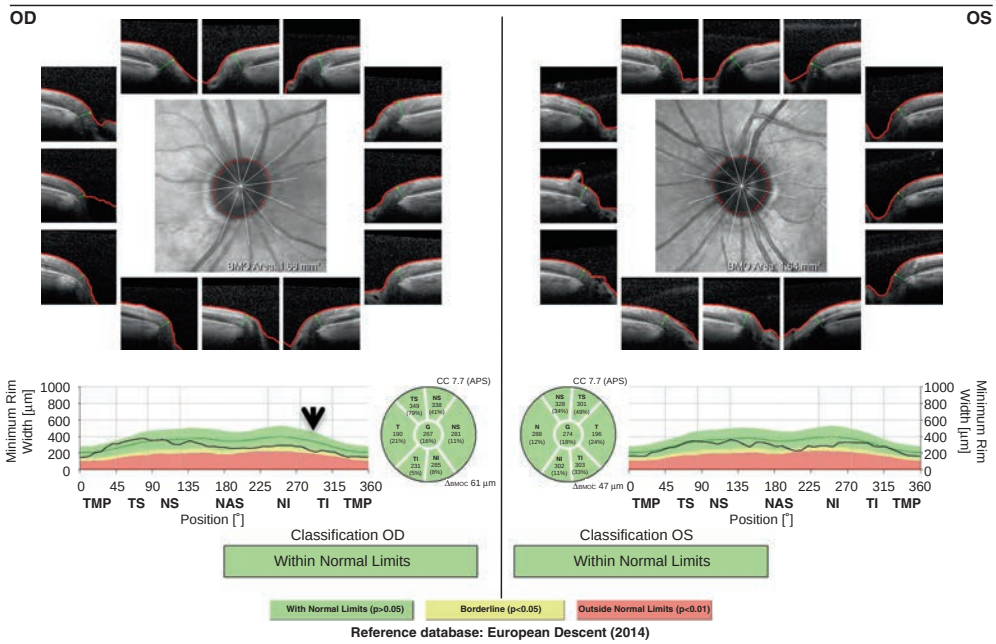


Fig. 5: (Spectralis GMPE module) The Minimum Rim Width analysis demonstrates ONH topography. GMPE analysis is more detailed than the Cirrus HD-OCT ONH findings and although the MRW parameter is borderline in the temporal inferior (TI) quadrant of the right eye in the TSNIT graph (*black arrowhead*), the TI quadrant of the classification chart is still in *green* range as it is a very early and localized defect.

a

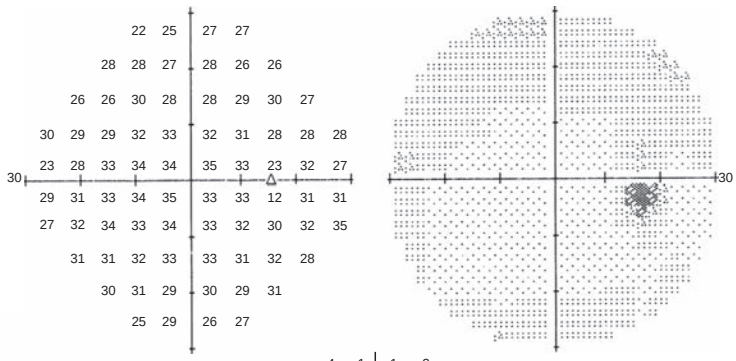
FIXATION MONITOR: GAZE/BLIND SPOT
FIXATION TARGET: CENTRAL
FIXATION LOSSES: 2/16
FALSE POS ERRORS: 3 %
FALSE NEG ERRORS: 0 %
TEST DURATION: 05:33

STIMULUS: III, WHITE
BACKGROUND: 31.5 ASB
STRATEGY: SITA-STANDARD

PUPIL DIAMETER: 5.6 MM
VISUAL ACUITY:
RX: +3.25 DS DC X

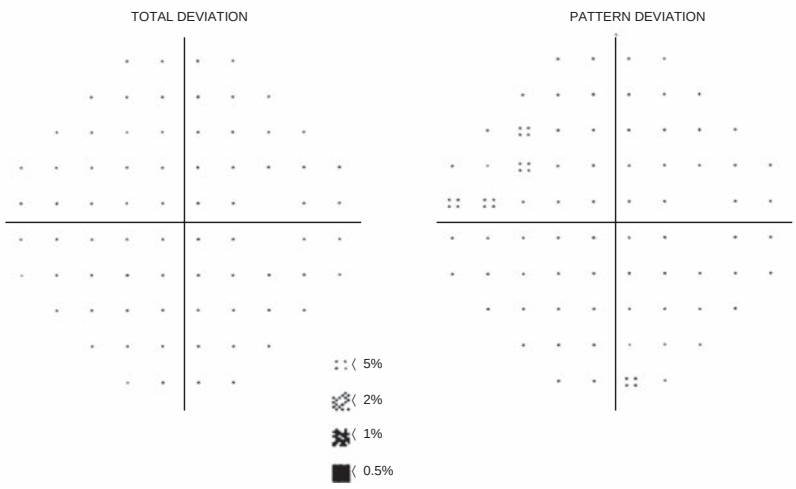
DATE: 04-02-2017
TIME: 07:46
AGE: 69

FOVEA: OFF



GHT
WITHIN NORMAL LIMITS

VFI 100%
MD +1.65 DB
PSD 1.80 DB



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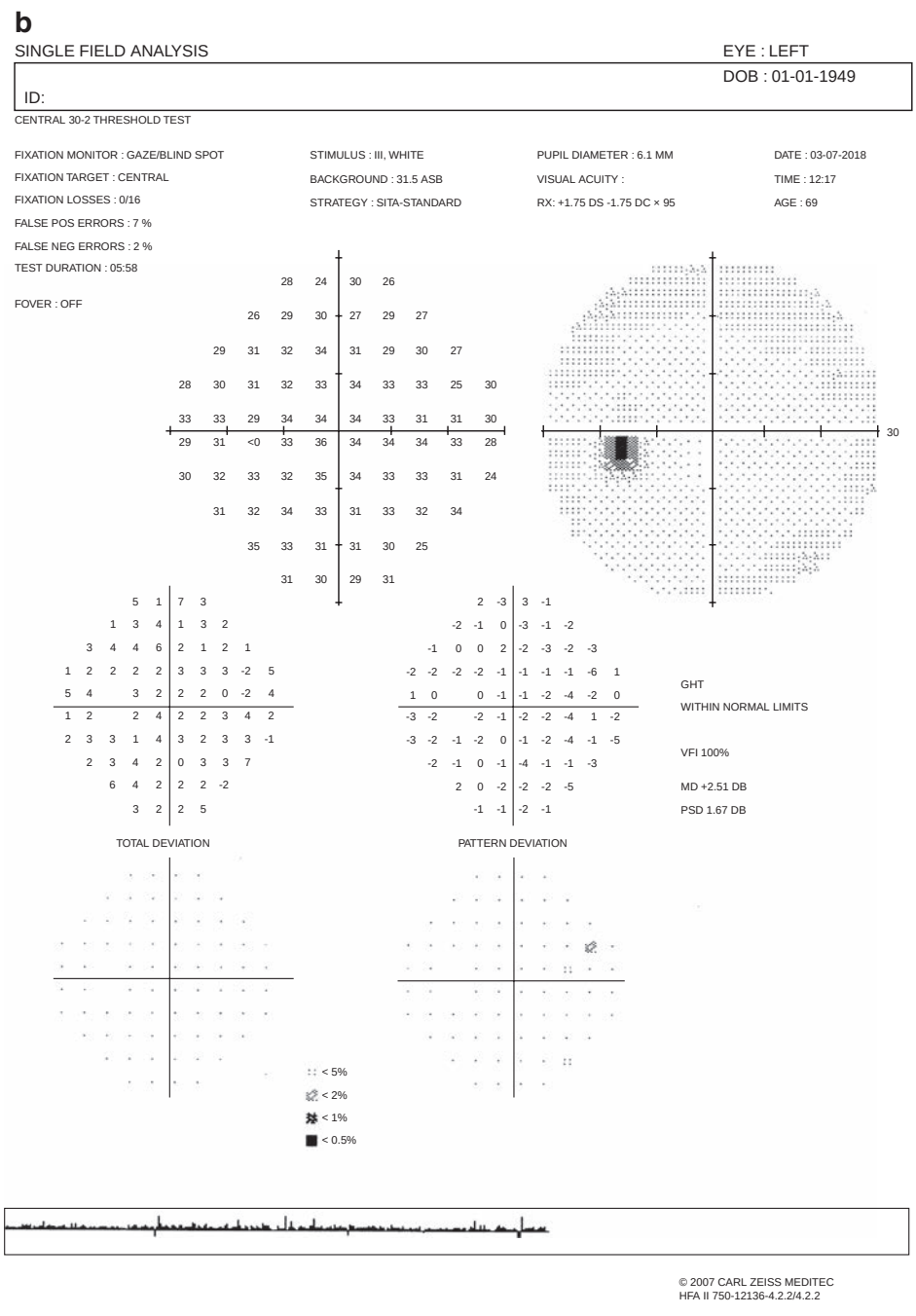


Fig. 6: (**a** and **b**) The Humphrey visual field tests are classified as within normal limits in both eyes.

Conclusion: This case represents an example of early glaucomatous damage, which can be classified as pre-perimetric glaucoma as there is no functional damage on visual field (VF) testing. The retinal nerve fiber layer (RNFL) defect was demonstrated by two different OCT systems; however, both devices failed to show optic nerve head (ONH) topographic damage. Given the high IOP (32 mmHg) and presence of early glaucomatous defects in OCT tests, starting anti-glaucomatous treatment at this stage is a viable option to prevent further damage in the right eye.

Moderate Glaucoma

A seventy-one-year-old male with newly diagnosed exfoliative glaucoma, who had IOP measurements of 22 and 38 mmHg in the right and left eyes, respectively. The anterior segment exam revealed exfoliative material at the pupillary margin and on the anterior lens capsule in both eyes. BCVA was 20/20 OU (Figs. 7, 8, 9, 10, 11, 12, and 13).

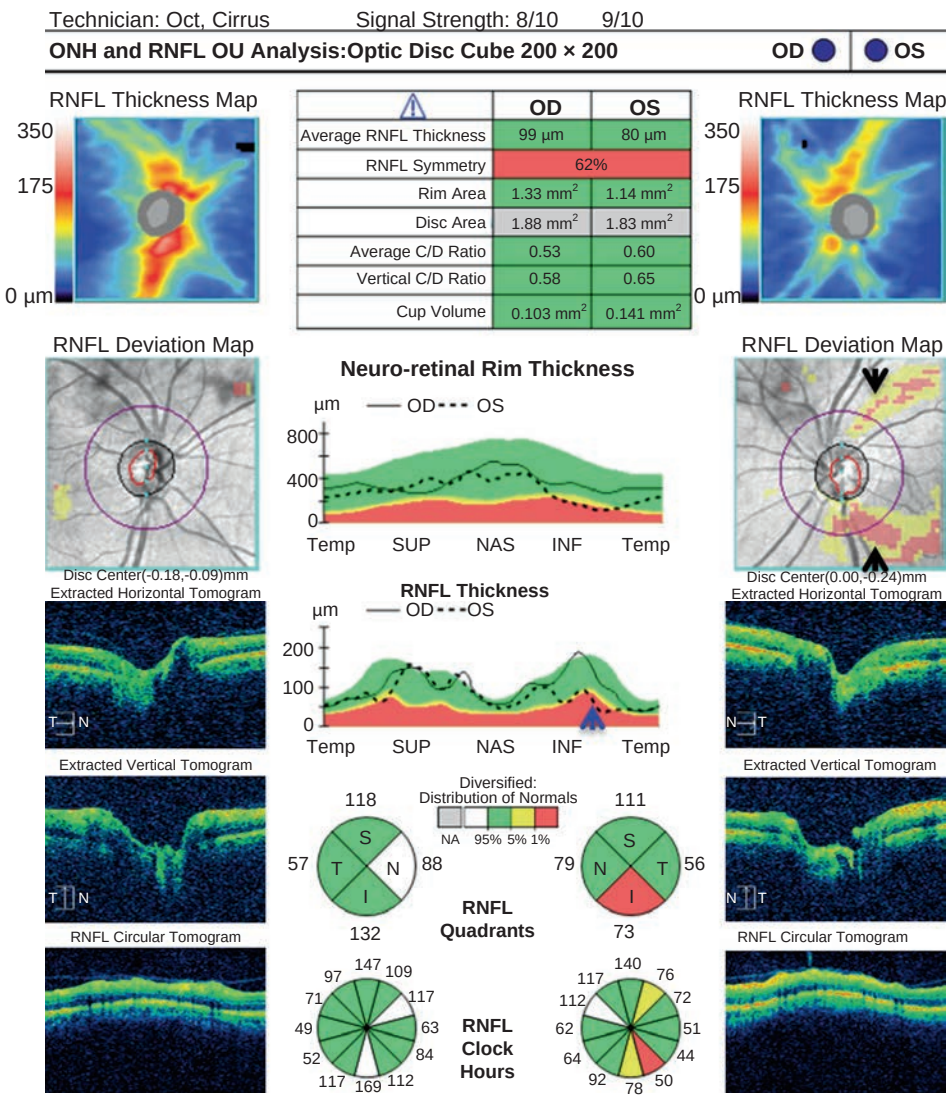


Fig. 7: (Cirrus HD-OCT) Good quality scan with high signal strength (9/10) OU. In the key parameters plot, average RNFL thickness is within normal limits in both eyes although the left eye average RNFL value is 19 µm thinner than that of the right eye. This difference resulted in the RNFL symmetry box being flagged in *red*. The RNFL thickness map of the left eye shows some RNFL loss and the RNFL deviation map, which compares the patient's RNFL measurements to the normative database, reveals definitive inferior RNFL loss and a possible superior RNFL defect (*black arrowheads*). The TSNIT graph demonstrates the inferior RNFL defect in the left eye (*blue arrowhead*). The superior RNFL defect could be a real defect, but it can also be shifted RNFL artifact. Quadrant and clock hour pie graphs confirm the inferior RNFL defect. Although the cup/disc ratios are still in the *green* zone (see the key parameters table), the neuro-retinal rim area TSNIT graph demonstrates neuro-retinal rim loss in the inferior quadrant.

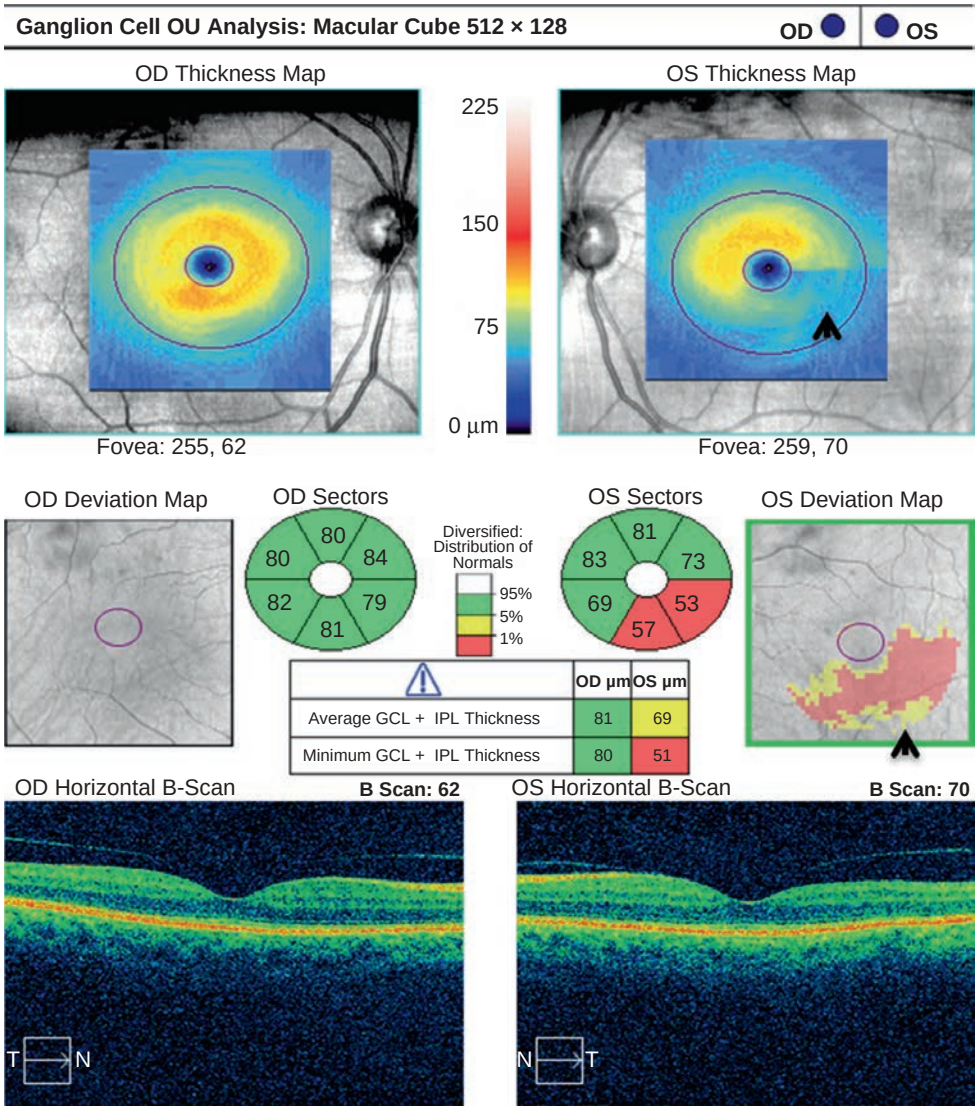


Fig. 8: (Cirrus-HD OCT) Ganglion cell analysis shows normal GCL + IPL thickness in the right eye; a large area of GCL + IPL damage is evident in the inferior and temporal regions of the left macula confirmed by abnormal inferior and inferotemporal sectors and average GCL + IPL thickness (*black arrowheads*). The superior half of the GCL + IPL thickness map is within normal limits.

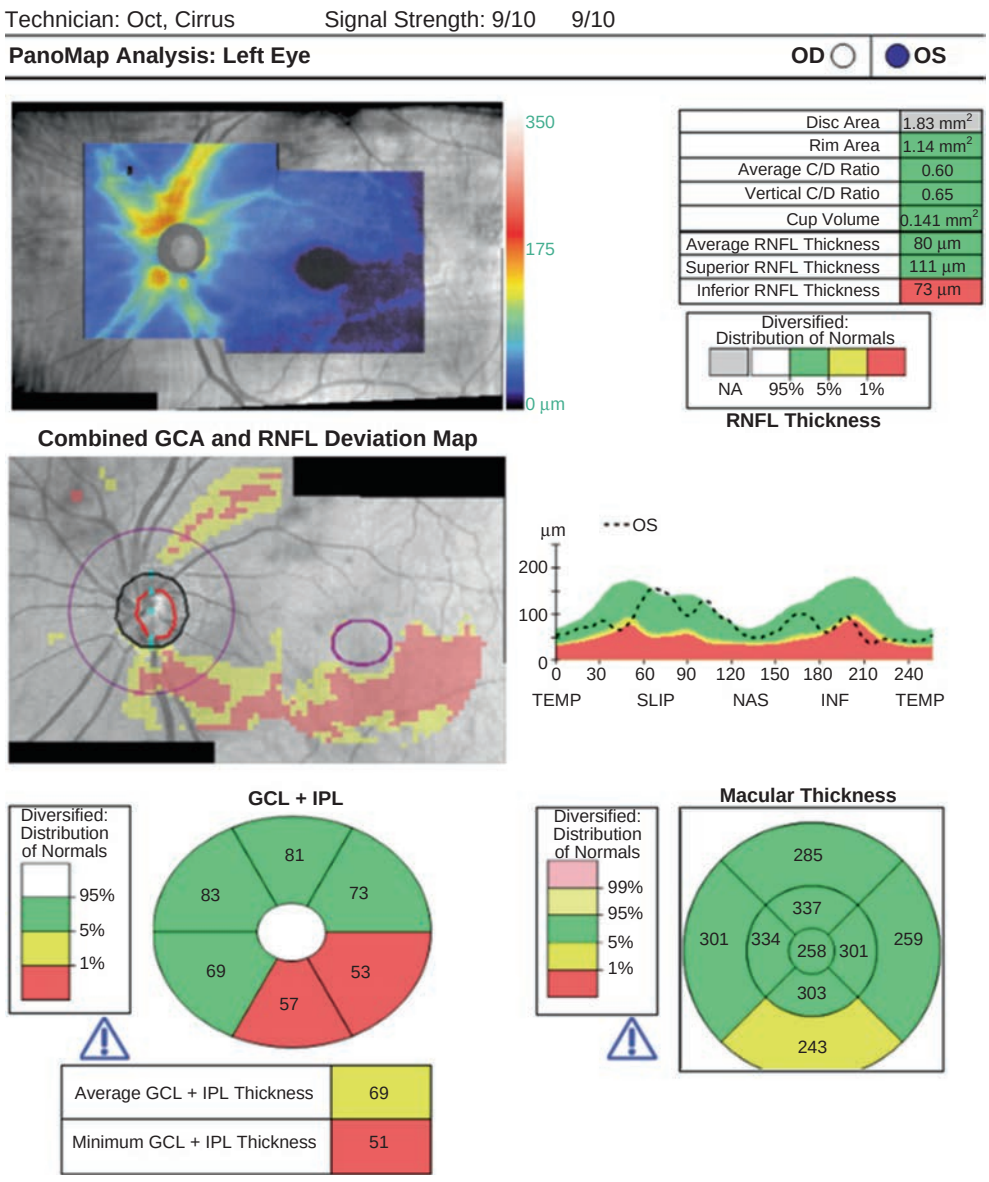


Fig. 9: (Cirrus-HD OCT) PanoMap report of the left eye demonstrates the peripapillary RNFL loss and macular ganglion cell loss in wide-field format.

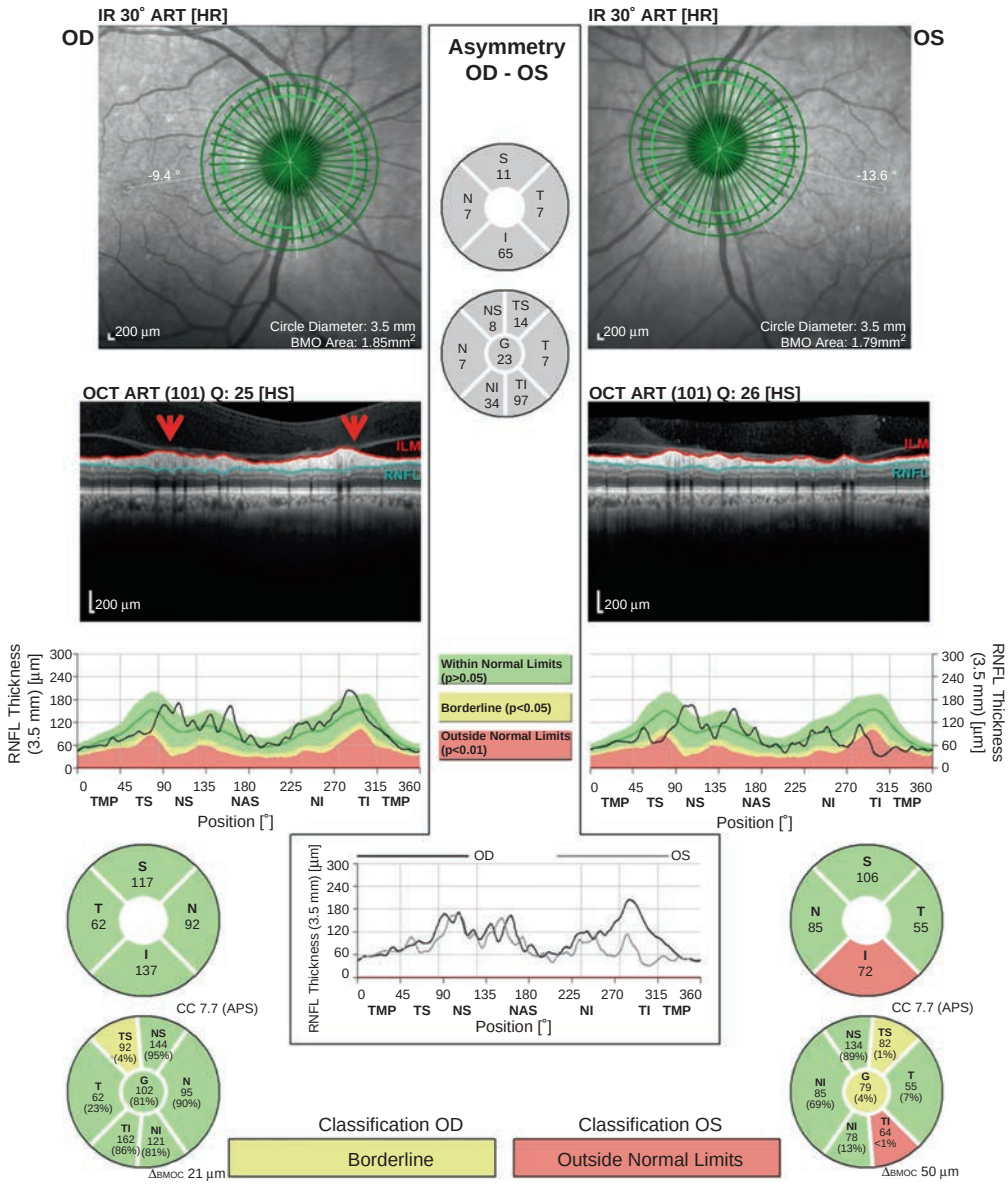


Fig. 10: (Spectralis, GMPE module) Spectralis OCT demonstrates the RNFL loss in the inferior quadrant and in the inferotemporal sector of the left eye. The borderline RNFL finding in the superior temporal sectors of both eyes could be the result of shifted RNFL peaks as the TSNIT graphs show that the RNFL peaks in superior quadrants are not that thin and do not fit the configuration expected from the normative database. Another important point on this OCT printout is the possibility of vitreoretinal traction around the optic nerve head. Vitreous adhesions to the RNFL can be observed in an extended area on the raw OCT image of the right eye. The superior-nasal-inferior adhesions (*red arrowheads*) could be the reason for the thick RNFL values of the right eye on the TSNIT graph. The vitreous/RNFL adhesion and possible traction could hide RNFL loss and may lead to a *green* disease artifact.

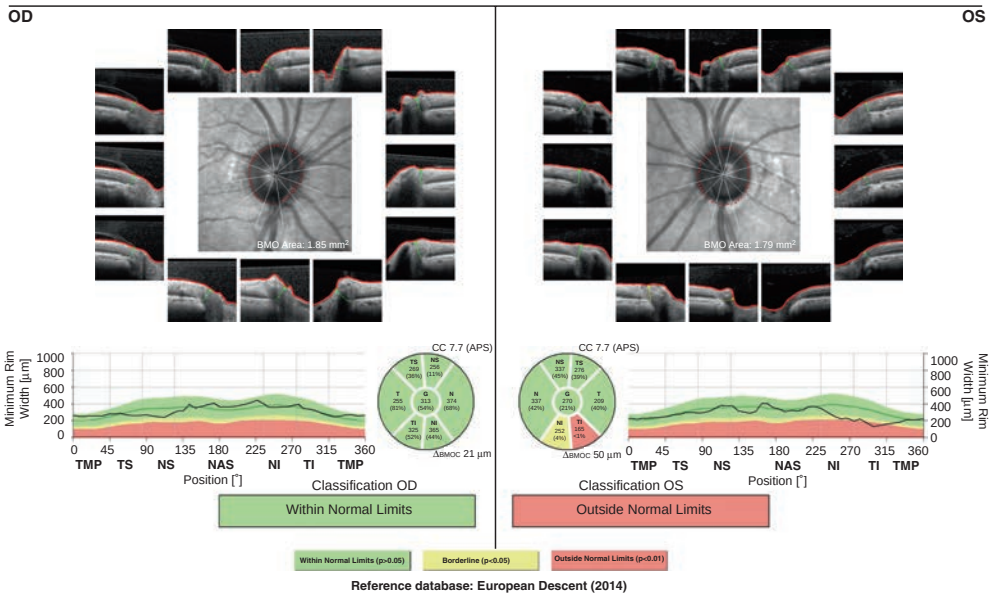


Fig. 11: (Spectralis GMPE module) The Minimum Rim Width analysis demonstrates inferior rim loss in the left eye consistent with the neuro-retinal rim changes observed on Cirrus HD-OCT printout.

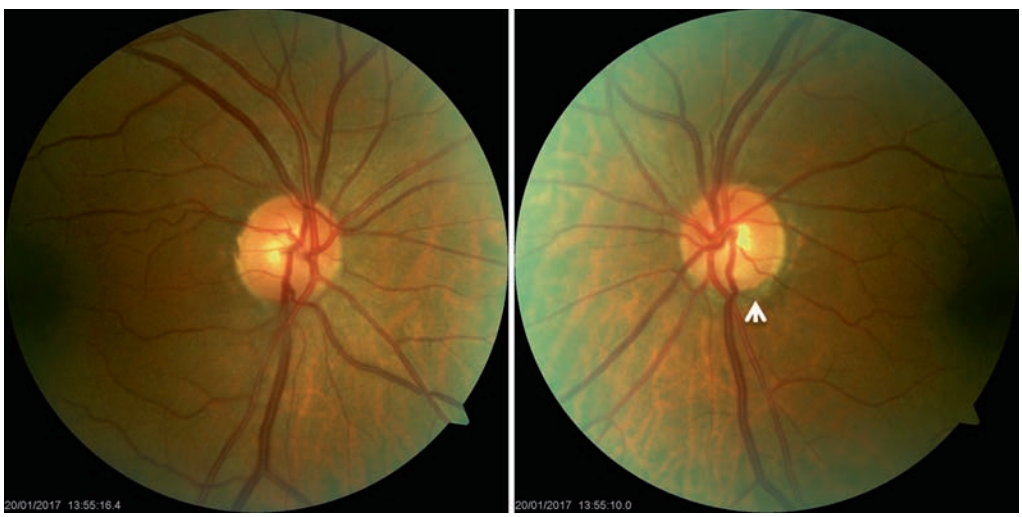


Fig. 12: Inferior notching at the left optic nerve head is evident on the disc photographs (*white arrowhead*).

a

CENTRAL 30-2 THRESHOLD TEST

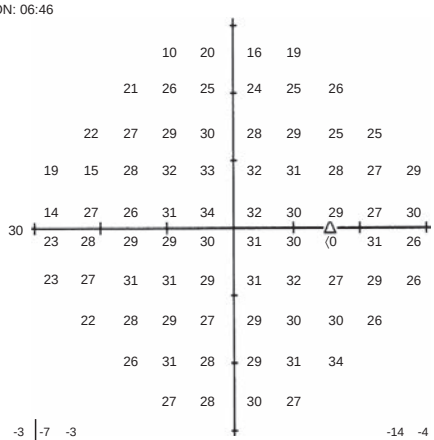
FIXATION MONITOR: BLIND SPOT
FIXATION TARGET: CENTRAL
FIXATION LOSSES: 1/18
FALSE POS ERRORS: 0 %
FALSE NEG ERRORS: 0 %
TEST DURATION: 06:46

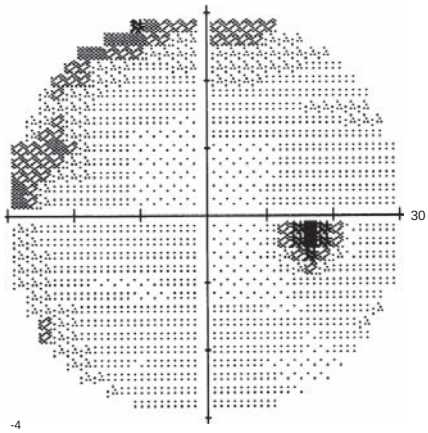
STIMULUS: III, WHITE
BACKGROUND: 31.5 ASB
STRATEGY: SITA-STANDARD

PUPIL DIAMETER: 4.4 MM
VISUAL ACUITY:
RX: +4.00 DS DC X

DATE: 20-01-2017
TIME: 14:18
AGE: 71

FOVEA: OFF





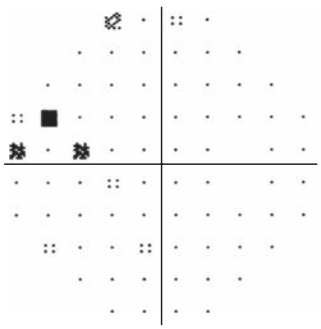
		-13	-3	-7	-3				
		-4	0	-1	-2	0	1		
	-4	-1	0	1	0	1	-2	-1	
-6	-13	-1	1	3	2	2	-1	-1	2
-11	-2	-5	0	2	1	0		-2	2
-3	-1	-2	-3	-2	0	-1		1	-3
-2	-2	0	0	-2	0	1	-3	0	-3
	-5	-1	-1	-3	-2	0	1	-3	
		-1	3	-1	0	2	5		
			1	1	2	0			

			-14	-4	-9	-4			
		-6	-2	-2	-3	-2	0		
	-6	-2	-1	0	-2	0	-3	-2	
-8	-14	-3	0	1	0	1	-2	-2	1
-13	-3	-6	-2	1	0	-2		-3	1
-4	-2	-3	-4	-3	-2	-2		0	-4
-3	-3	-1	-2	-4	-2	0	-4	-2	-4
	-6	-2	-2	-5	-3	-1	0	-4	
		-2	1	-2	-1	0	4		
			0	0	1	-2			

GHT
OUTSIDE NORMAL LIMITS

VFI 98%
MD -0.75 DB
PSD 3.07 DB P〈5%

TOTAL DEVIATION



〈 5%
〈 2%
〈 1%
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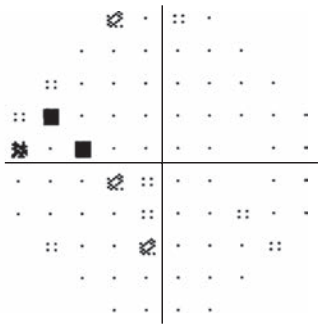
PATTERN DEVIATION



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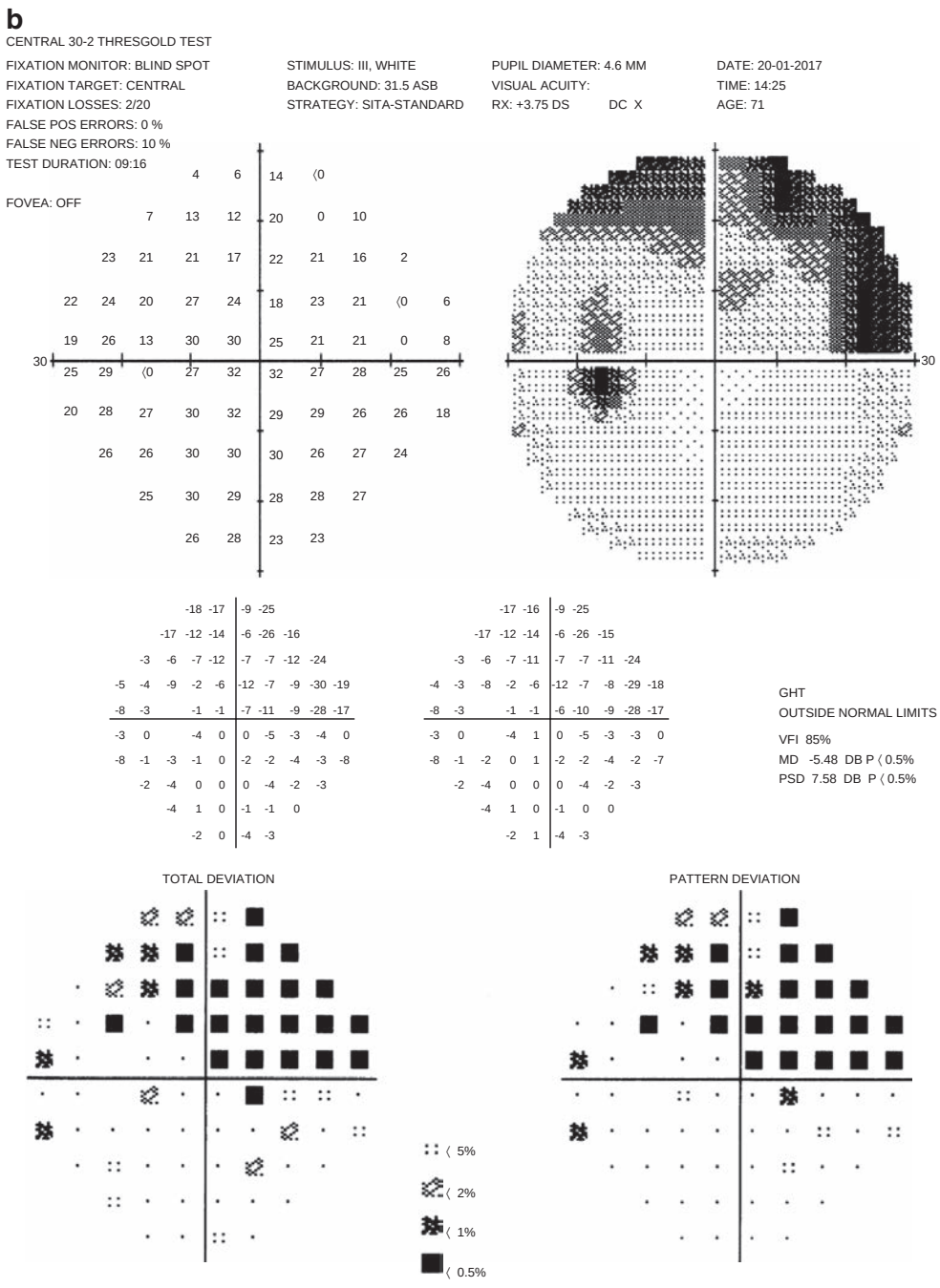


Fig. 13: (**a**) Humphrey visual field of the right eye may be classified as outside normal limits because of an early nasal step. (**b**) Visual field of the left eye shows a dense arcuate defect in the superior hemifield, which is compatible with the inferior RNFL defect. The visual field findings suggest a moderate level of damage.

Conclusion: This case represents a patient with a moderate degree of glaucomatous damage. Both the structural test (OCT) and functional test (VF) show corresponding damage in the left eye. Also, two different OCT devices show similar RNFL loss patterns and neuro-retinal rim damage at the same location. In eyes with moderate damage, both structural and functional tests are important in diagnosing the disease and monitoring the progression. The right eye of the patient must also be followed closely as there is a possibility of green disease.

Advanced Glaucoma

A sixty-eight-year-old female, diagnosed with bilateral primary open-angle glaucoma seven years ago. The right eye underwent two trabeculectomies and the left eye had one trabeculectomy in the last five years. On the last examination, IOP was 16 mmHg in the right eye and 14 mmHg in the left eye (Figs. 14, 15, 16, 17, 18, 19, 20, and 21).

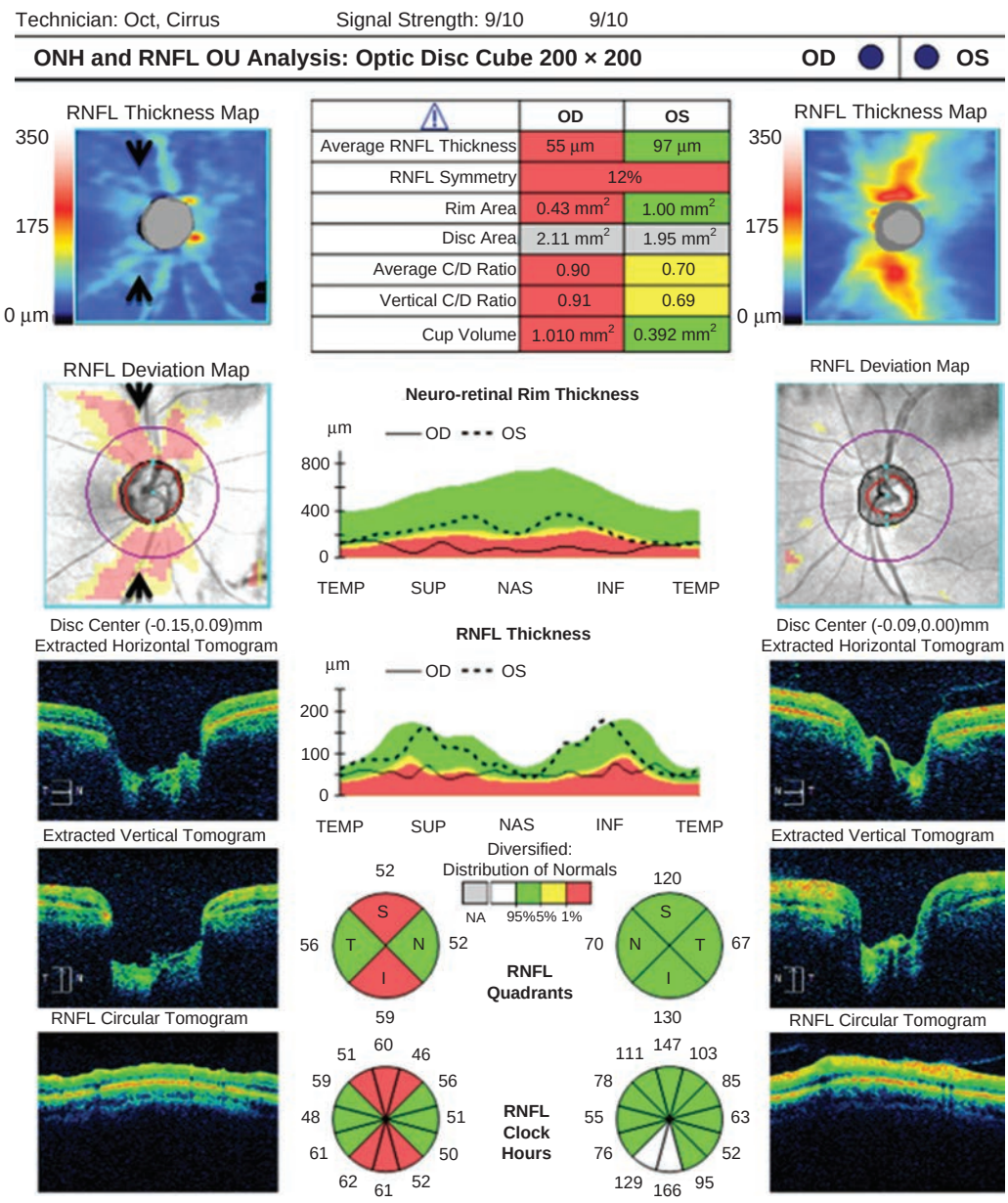


Fig. 14: (Cirrus-HD OCT) Scan quality is excellent (9/10) in both eyes. In the key parameters table, all RNFL and ONH parameters of the right eye are outside normal limits. The RNFL thickness map of the right eye shows advanced RNFL loss and the RNFL deviation map, which compares the patient's RNFL to the normative database, reveals nearly total RNFL loss (*black arrowheads*). The TSNIT graph demonstrates advanced RNFL loss in the right eye in all quadrants. Quadrant and clock hour pie graphs also confirm the advanced RNFL loss evident on the TSNIT graph. Neuro-retinal rim area TSNIT graph also demonstrates advanced neuro-retinal rim loss in all quadrants.

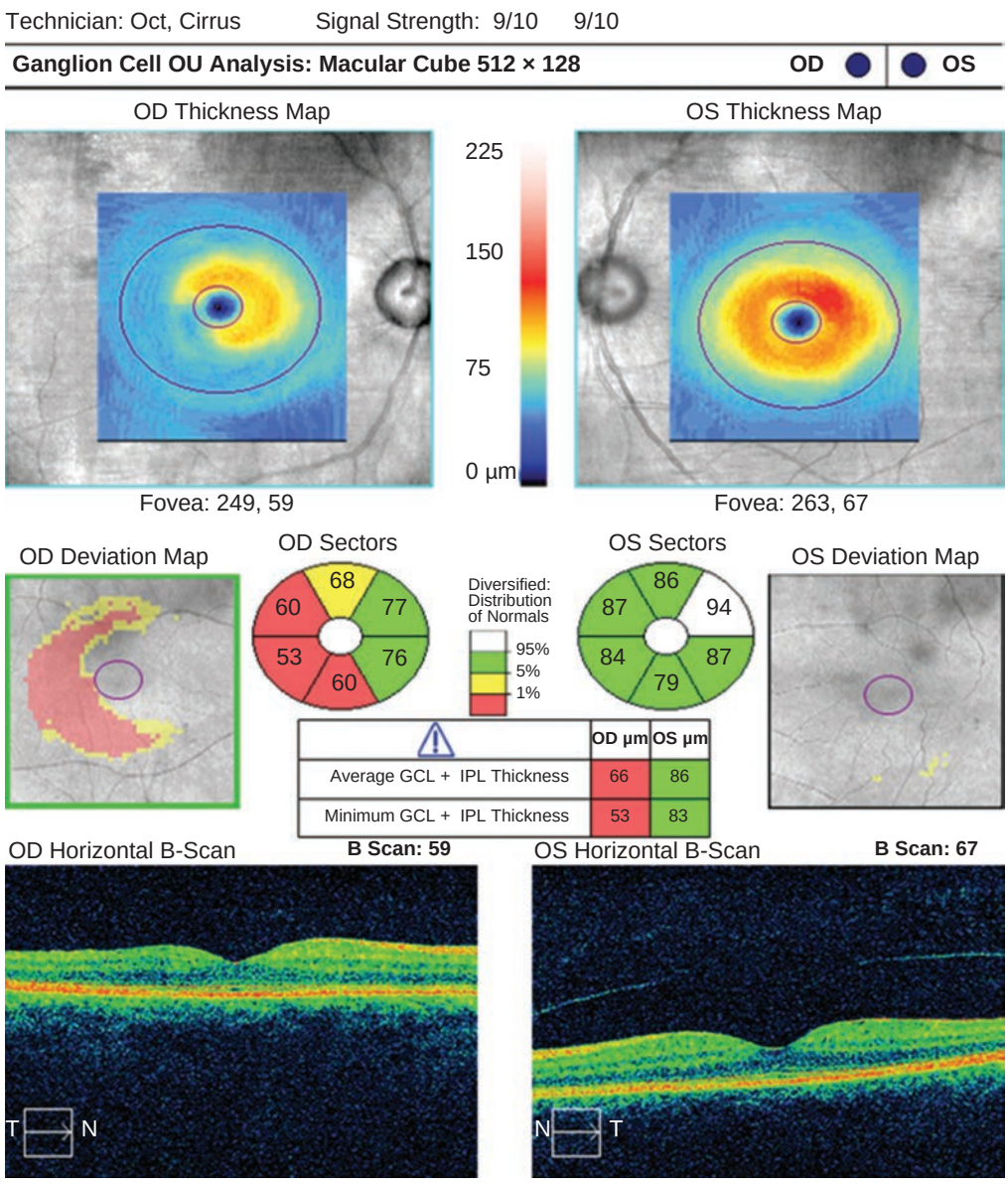


Fig. 15: (Cirrus-HD OCT) Ganglion Cell Analysis shows severely depressed GCL + IPL thickness in the superior and inferior temporal regions of the right eye. The left eye seems within normal limits.

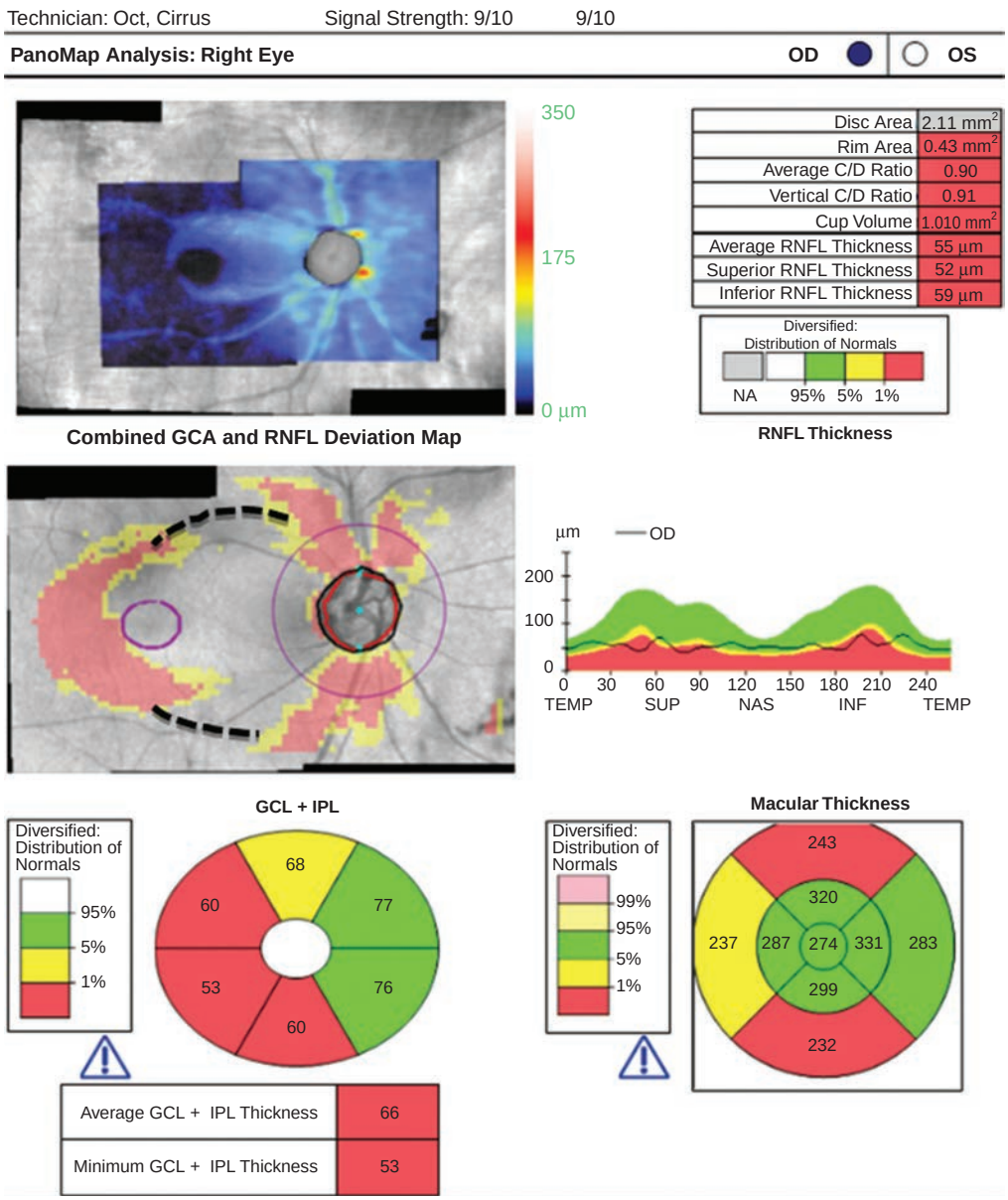


Fig. 16: (Cirrus-HD OCT) PanoMap report of the right eye demonstrates severe RNFL loss around the disc and ganglion cell loss in the macula. OCT uses only the elliptical annulus for comparing the GCL + IPL thickness to the normative database and comparison data for areas outside this annulus are not provided and such regions are not flagged on the GCL + IPL map leading to discontinuity in the RNFL and macular defects (*dashed black lines*).

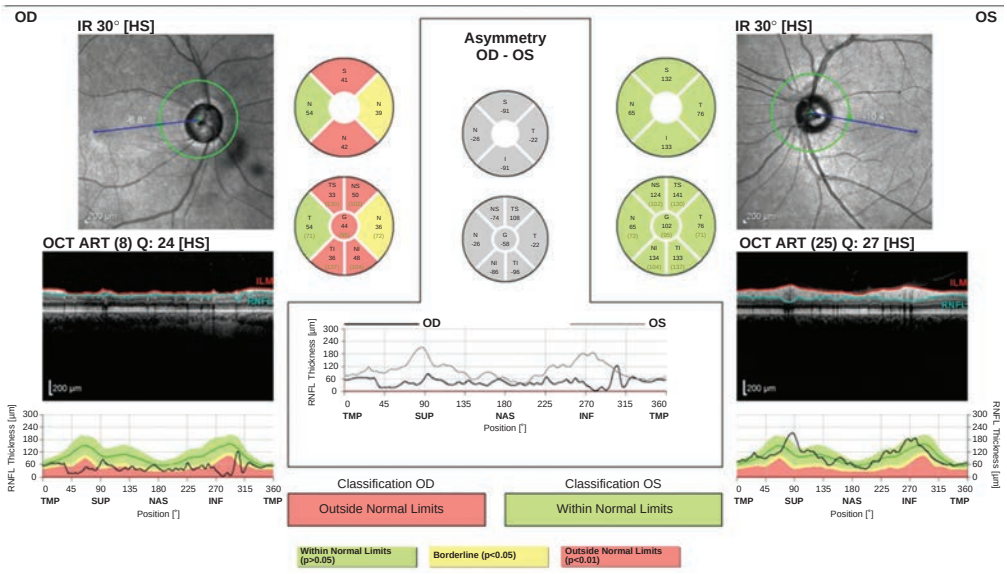


Fig. 17: (Spectralis OCT) The advanced RNFL loss is evident in the right eye. The RNFL TSNIT graph also shows RNFL loss in all quadrants. There is a segmentation error in the inferior quadrant of the right eye which leads to zero micron RNFL thickness between 280° and 300° in the TSNIT plot.

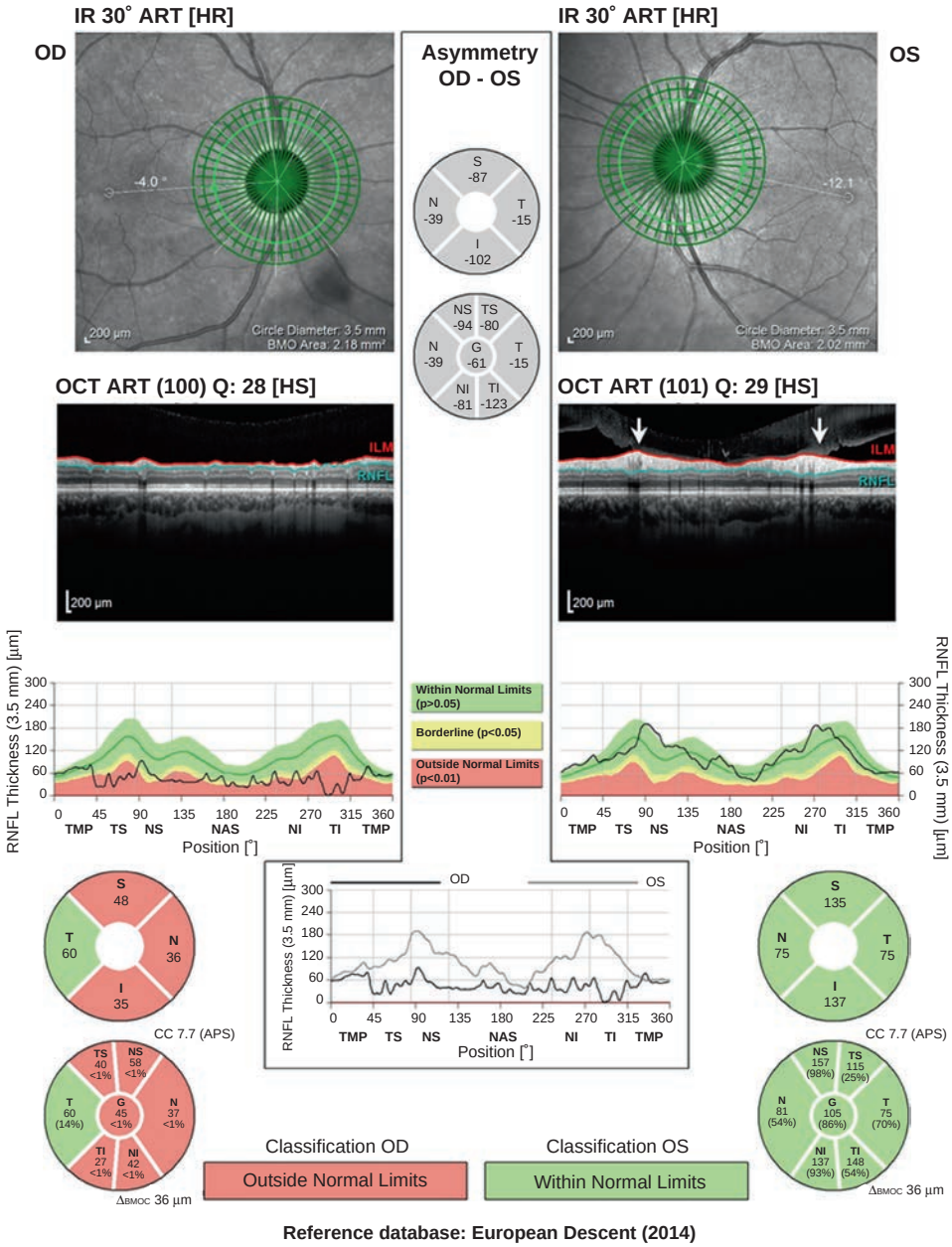


Fig. 18: (Spectralis, GMPE module) Spectralis OCT report with the newer GMPE module also demonstrates RNFL loss in the superior, nasal and inferior quadrants of the right eye. Vitreous/RNFL adhesions can be observed on the raw OCT image of the left eye. These superior-nasal-inferior adhesions (the area between *white arrowheads*) could explain the thick RNFL measurements of the left eye on the TSNIT graph. These adhesions could hide RNFL loss and may lead to a *green* disease artifact.

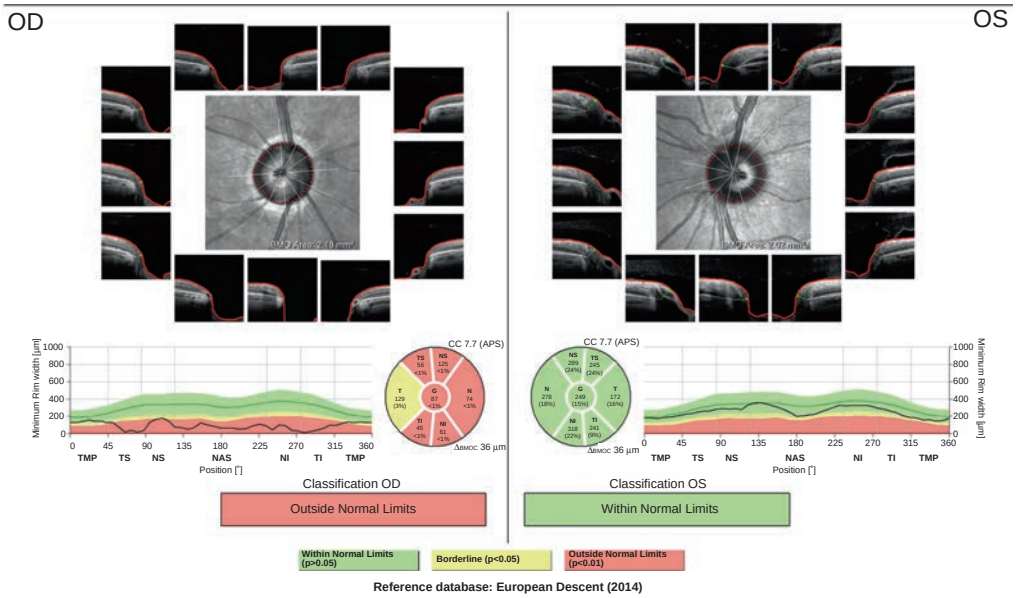


Fig. 19: (Spectralis, GMPE module) The Minimum Rim Width analysis demonstrates loss of neuro-retinal rim in all sectors of the right eye.

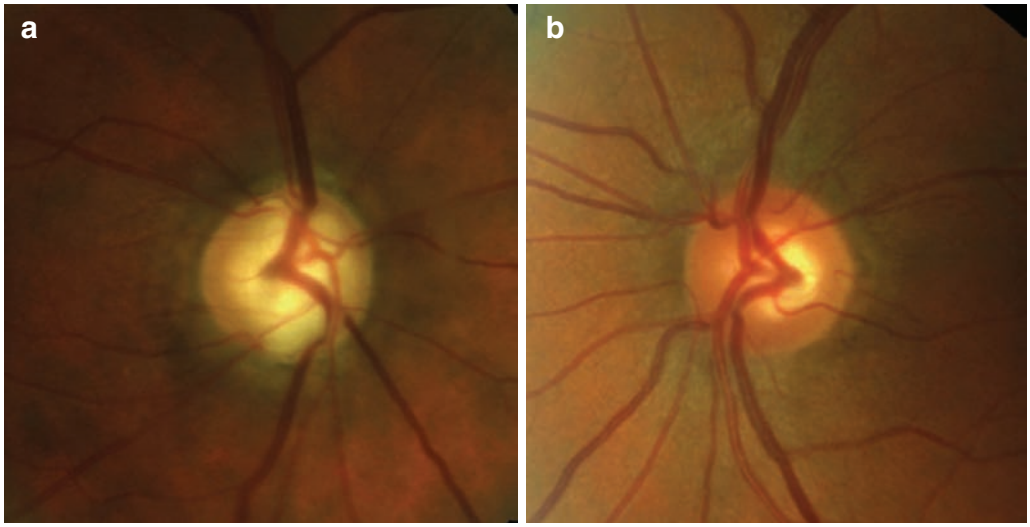


Fig. 20: (**a**) Advanced glaucomatous damage of the right optic nerve head can be seen. (**b**) Left optic nerve head is normal.

a

CENTRAL 30-2 THRESHOLD TEST

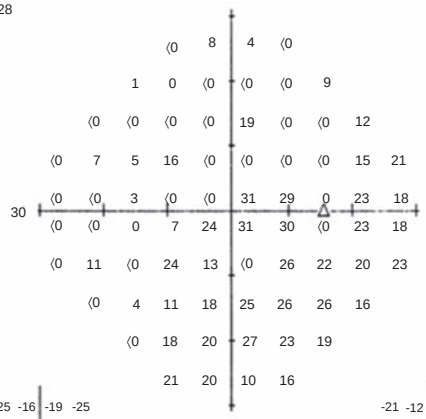
FIXATION MONITOR: BLIND SPOT
FIXATION TARGET: CENTRAL
FIXATION LOSSES: 0/22
FALSE POS ERRORS: 7 %
FALSE NEG ERRORS: 13 %
TEST DURATION: 10:28

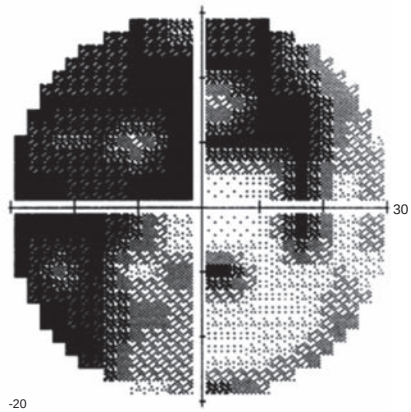
STIMULUS: III, WHITE
BACKGROUND: 31.5 ASB
STRATEGY: SITA-STANDARD

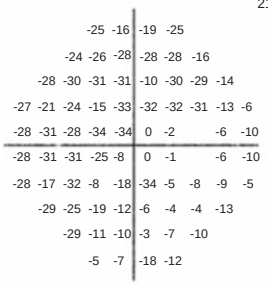
PUPIL DIAMETER: 5.7 MM
VISUAL ACUITY:
RX: +3.25 DS DC X

DATE: 27-12-2016
TIME: 12:58
AGE: 67

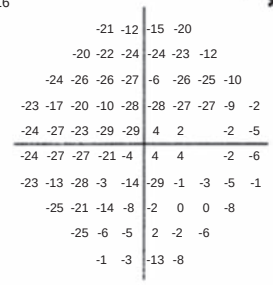
FOVEA: OFF







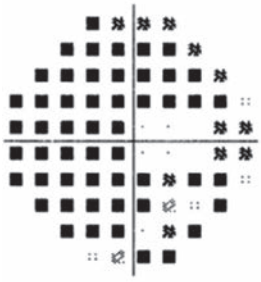
TOTAL DEVIATION



PATTERN DEVIATION

GHT
OUTSIDE NORMAL LIMITS

VFI 45%
MD -18.32 DB P〈0.5%
PSD 13.48 DB P〈0.5%



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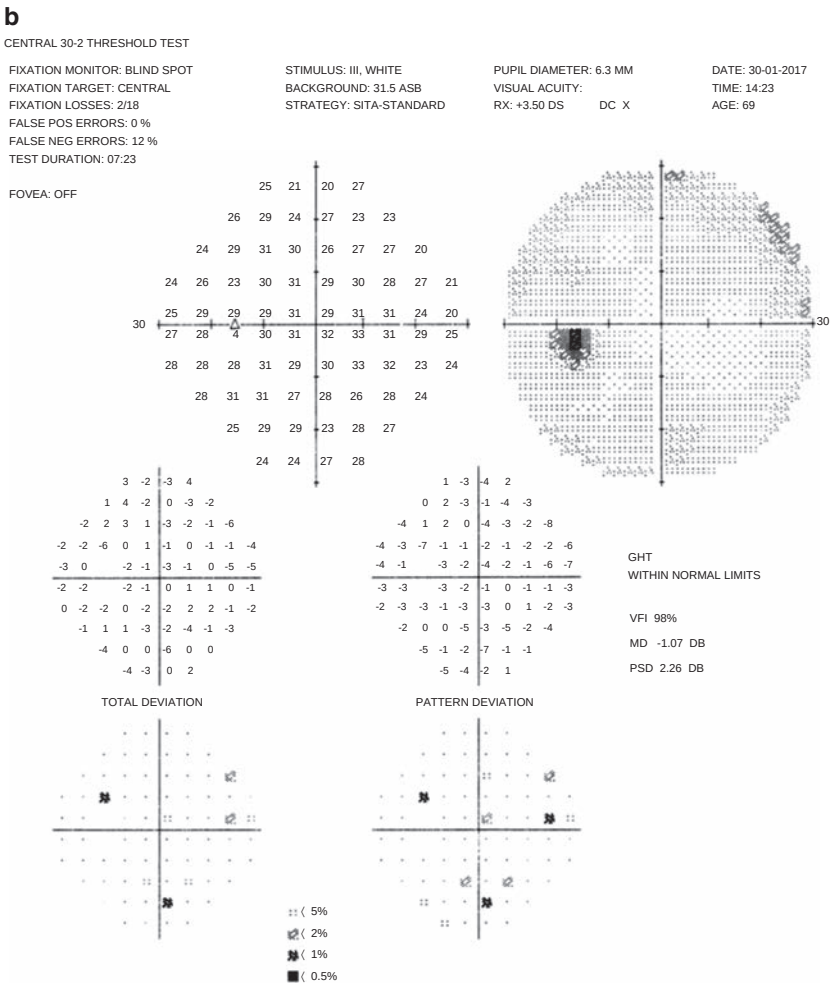

Fig. 21: (**a**) Visual field exam of the right eye shows advanced glaucomatous damage, which is consistent with the OCT findings in this eye. (**b**) The visual field of the left eye is essentially within normal limits.

Conclusion: The RNFL- and ONH-based OCT parameters demonstrate advanced glaucomatous damage in the right eye. Neuro-retinal rim loss in all quadrants is evident on the optic disc photographs and the VF shows advanced glaucomatous damage. Beyond this stage of the disease, the peripapillary RNFL thickness measurements become less important for monitoring the disease as further deterioration is likely difficult to detect due to the floor effect. Macular thickness outcomes frequently reach their measurement floor later than the peripapillary RNFL and hence, GCL + IPL thickness may still be used for monitoring the disease at this stage. Also, functional tests become more important for follow-up at the advanced stage of the disease.

Source: Akman A. (2018) Examples of Optical Coherence Tomography Findings in Glaucoma Eyes with Varying Stages of Severity. In: Akman A., Bayer A., Nouri-Mahdavi K. (eds) Optical Coherence Tomography in Glaucoma. Springer, Cham. https://doi.org/10.1007/978-3-319-94905-5_7.

3

Tumor-associated Glaucoma

Reena Garg, Annapurna Singh, Arun D. Singh

Introduction

Glaucoma secondary to intraocular tumors is not uncommon. The risk of this problem developing depends on the tumor type and location. A review of 2597 patients with intraocular tumors found elevated intraocular pressure in 5% of tumor-containing eyes at the time of diagnosis [1]. Of those eyes, 2111 had uveal melanoma, and secondary IOP elevation was present in 3% of these eyes. Seventeen percent of the melanoma eyes involved the ciliary body, and there were 7% with iris involvement and 2% with choroidal involvement. Two hundred and fifty-six of the 2597 eyes had uveal metastases, and glaucoma occurred in 5% of these patients [1]. Another survey of 227 cases of metastatic carcinoma to the eye and orbit found that glaucoma was present in 7.5% of patients [2]. In a retrospective case series of 144 eyes presenting with iris melanoma, 40% had concurrent glaucoma, which was related to angle infiltration by melanoma, angle neovascularization, and hyphema [3].

Direct invasion of the angle and ciliary body as well as pigment dispersion from uveal melanomas commonly leads to elevated IOP. Tumors that are metastatic to the eye can infiltrate the angle or close the angle by mass effect and are associated with higher rates of glaucoma. Angle neovascularization associated with retinoblastomas can lead to secondary glaucoma. A clinical review of 149 eyes with retinoblastoma found increased IOP in 23% of these eyes, and histologic evidence of glaucoma was present in 50% histopathologic of enucleated eyes in this series [4]. Tumors such as lymphoma, leukemia, benign reactive hyperplasia, medulloepithelioma, iris adenoma, and iris melanocytoma account for a small percentage of intraocular tumors and are

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infrequently associated with secondary glaucoma. These tumors rarely present with elevated IOP as the initial manifestation.

Pathogenesis

Intraocular tumors can present with both open-angle and angle-closure glaucoma through various mechanisms.

Open-angle Glaucoma

There are three principal mechanisms by which intraocular tumors can cause open-angle glaucoma: direct closure of the anterior chamber angle by the tumor mass, tumor cells seeding the anterior chamber angle, and necrotic tumor cells engulfed by macrophages that obstruct the outflow pathways in the trabecular meshwork.

Closure of the anterior chamber angle by mass effect can be caused by many types of tumors, including melanoma, nevus, metastasis, and medulloepithelioma. Extension of melanoma and nevus across the trabecular meshwork can result in increased IOP [1]. In cases of ciliary body or iris melanoma, patients may present with heavy pigmentation in the angle, anterior synechiae, and elevated IOP—mimicking iridocorneal endothelial syndrome [5].

Tumor cells can seed the anterior chamber angle and lead to open-angle glaucoma. Metastatic tumors typically infiltrate the trabecular meshwork, to increase IOP and cause glaucoma (Fig. 1) [1, 6]. Metastases of systemic melanoma can also cause pigmentary dispersion in the angle, resulting in glaucoma. In cases of intraocular melanoma, pigmented cells are dispersed into the anterior chamber and can become lodged in the spaces of the trabecular meshwork, hindering the outflow of aqueous humor (Fig. 2) [7]. Leukemias and lymphomas can result in a pseudohypopyon in the anterior chamber composed of layered tumor cells deposited within the angle resulting in open-angle glaucoma.

The third mechanism is specific to melanotic tumors. Necrotic tumor cells are engulfed by macrophages, which accumulate in the angle to occlude the spaces within the trabecular meshwork and raise intraocular pressure, causing melanomalytic glaucoma [7, 8].

Angle-closure Glaucoma

Angle closure is commonly seen in patients with intraocular tumors. This occurs through three main mechanisms: forward movement of the lens-iris diaphragm, peripheral anterior synechiae formation, and neovascular glaucoma.

Tumor-mass effect can cause forward rotation of the lens-iris diaphragm, leading to closure of the anterior chamber angle. Patients can present with manifestations of acute or chronic angle-closure glaucoma. This is more commonly seen with posterior segment tumors and is frequently

accompanied by retinal detachment. Therefore, any patient with unilateral serous retinal detachment and glaucoma should raise suspicion for underlying malignancy.

Forward movement of the iris by anterior uveal tumors such as ciliary body melanoma can result in occlusion of the trabecular meshwork and PAS formation. Often these tumors are misdiagnosed as primary angle-closure glaucoma resulting in delayed detection of the ciliary body mass and worse prognosis [9]. Massive subretinal hemorrhage can also result in forward movement of the iris and PAS formation and is seen in patients with leukemia or myelodysplastic syndrome [10, 11].

Iris neovascularization (rubeosis iridis) is a common cause of angle-closure glaucoma in intraocular melanomas [1, 7]. Intraocular metastasis, retinoblastoma, and medulloepithelioma can also be associated with neovascularization and secondary glaucoma. Radiation-induced retinal ischemia can lead to neovascularization and is an important cause of glaucoma as this is a common treatment modality for intraocular tumors (Fig. 3).

Clinical Features

Patients with glaucoma are typically asymptomatic; however, glaucoma related to intraocular tumors is frequently associated with presenting ocular symptoms. Iris heterochromia, poor response to IOP-lowering therapy, and serous retinal detachment in a patient with unilateral or very asymmetric glaucoma should alert the clinician to the possibility of an intraocular tumor [6, 12].

Diagnostic Evaluation

A thorough ophthalmic examination including slit lamp biomicroscopy, gonioscopy, transpupillary transillumination, and posterior segment examination is critical. On slit lamp examination, the iris may reveal a melanotic or nonmelanotic lesion, and pigmented cells may be present in the anterior chamber indicative of an anterior or posterior melanoma [7, 8]. The iris may be displaced and may show neovascularization, or the lens can be subluxed or focally opacified.

Direct tumor invasion of the anterior chamber angle may be seen on gonioscopy as well as angle seeding by pigmented or nonpigmented tumor cells or neovascularization of the angle [1, 7, 13]. Malignant melanomas can often show transillumination defects, as shown in a report of 23 ring melanomas, in which 100% patients had transillumination defects [14].

Dilated fundus examination may reveal a choroidal tumor, retinal detachment, or vitreous seeding with tumor cells. In cases of angle closure or occludable angles, dilation should be postponed until after peripheral iridotomy or iridectomy.

Clinical examination alone may not be adequate to provide definitive diagnosis of the tumor. For example, iris nevi and melanomas can be clinically indistinguishable. Fluorescein angiography of the iris, ultrasound biomicroscopy, and anterior segment OCT can be helpful in identifying malignant lesions [15]. Ultrasound biomicroscopy is useful in detecting ciliary body and choroidal tumors, but cannot reliably distinguish between a benign and a malignant lesion

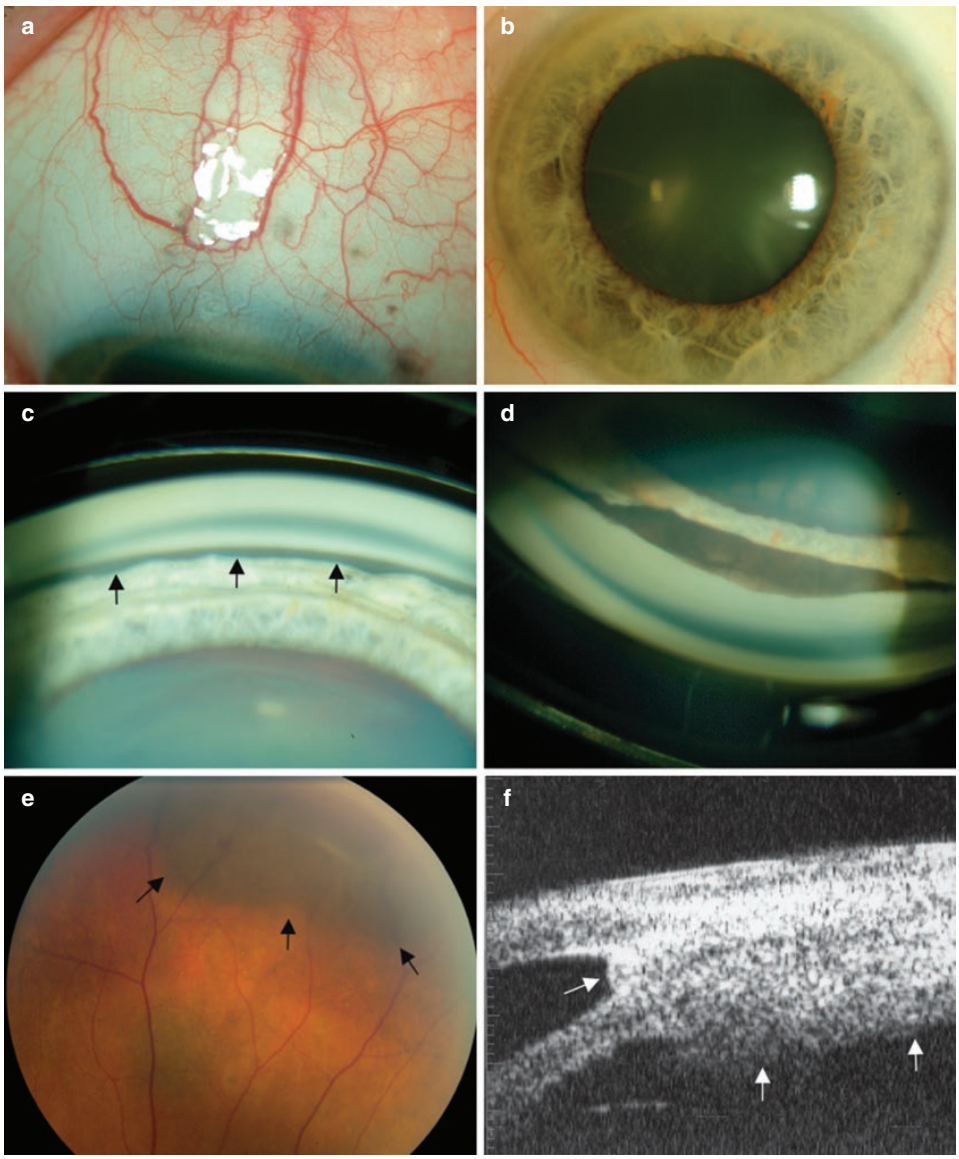


Fig. 1: A 64-year-old woman was diagnosed with ocular hypertension OS. The IOP was 35 mmHg. On external examination, prominent sentinel vessels and episcleral pigmentation were noted superiorly (**a**). The anterior segment appeared normal (**b**). On gonioscopy there was diffuse pigment seeding in the angle (**c**, *arrows*) with an area of tumor extension from 12 to 1 o'clock meridian (**d**). Ophthalmoscopy revealed peripheral choroidal melanoma (**e**, *arrows*). Ciliary body and angle extension were confirmed by ultrasound biomicroscopy (**f**, *arrows*).

[16, 17]. This type of scan can detect tumor growth and extension and is therefore useful for monitoring suspicious lesions and when considering surgical tumor resection [16, 18]. When these modalities are inconclusive, fine-needle aspiration biopsy of the tumor can provide a definitive

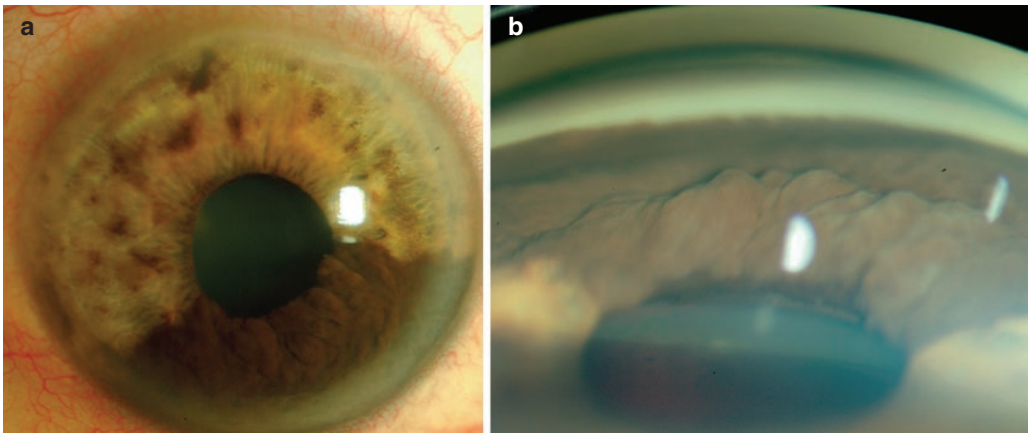
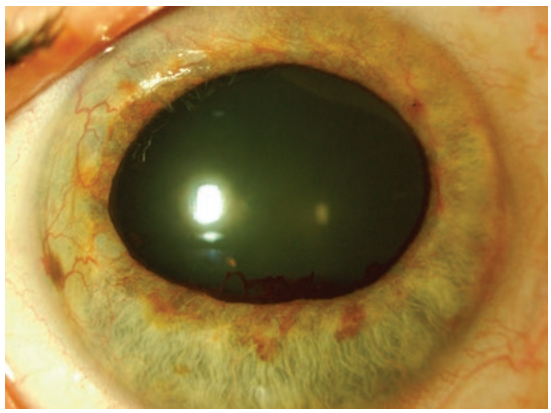


Fig. 2: Diffuse iris melanoma of the lower half of the iris causing secondary glaucoma (IOP = 26 mmHg) (**a**). Gonioscopy confirmed pigment seeding in the angle (**b**).

Fig. 3: Neovascular glaucoma 13 months following iodine-125 plaque radiotherapy for a medium-sized choroidal melanoma.



diagnosis [19, 20]. In cases of suspected vitreoretinal lymphoma, vitrectomy can confirm the diagnosis [21].

Specific Entities

Childhood Glaucoma

Glaucoma in childhood is typically associated with congenital and developmental anomalies, which can usually be easily distinguished from secondary glaucoma secondary to intraocular tumors. In cases of neovascular angle closure, one must consider retinoblastoma, as this is the most common cause of glaucoma in these patients (Fig. 4). Retinoblastoma-associated glaucoma with iris neovascularization as the initial presenting sign has been reported in 7% of cases [22]. Any child with neovascular glaucoma should be evaluated for retinoblastoma. Other

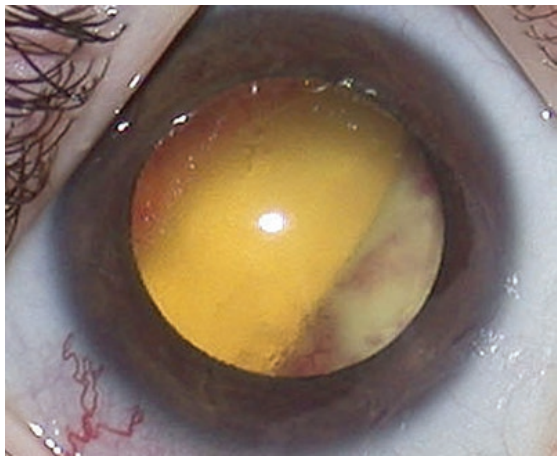


Fig. 4: Neovascular glaucoma associated with Stage E retinoblastoma (as per international retinoblastoma classification). Note ectropion uveae.

conditions that present with neovascular glaucoma include retinopathy of prematurity, persistent hyperplastic primary vitreous, retinal dysplasia, Coats' disease, toxocariasis, and infantile retinal detachment [23]. Additionally, some rare childhood conditions associated with glaucoma include phakomatoses, juvenile xanthogranuloma, and medulloepithelioma.

Sturge-Weber Syndrome

Cutaneous vascular hamartomas or hemangiomas along the distribution of the fifth cranial nerve are the hallmark of Sturge-Weber syndrome, and most patients present with a cutaneous hemangioma, especially of the upper eyelid. Central nervous system involvement can include leptomeningeal angioma and cortical calcifications. Dilated and tortuous episcleral veins and telangiectatic conjunctival vessels are commonly seen on ophthalmic examination [24]. Approximately half of these patients are affected by glaucoma, which is usually secondary to elevated episcleral venous pressure but which can also be the result of anomalous development of the anterior chamber angle, fluid hypersecretion from the ciliary body, and abnormal hemodynamics of the episcleral vasculature (late onset glaucoma) [25]. These patients can also present with congenital glaucoma, which can cause corneal edema, megalocornea, and buphthalmos [26].

Neurofibromatosis Type 1

Hyperpigmented lesions, or café au lait spots and neurofibromas within the peripheral nervous system, are characteristic of neurofibromatosis type Lisch nodules can be seen on anterior segment examination, and elevated IOP can result from iris neovascularization secondary to retinal vasoproliferative tumor or developmental angle anomalies [27]. Neurofibromas of the upper eyelid have been associated with higher rates of glaucoma. Glaucoma occurs more commonly when there is orbitofacial involvement, as revealed by a retrospective chart review of 95 patients diagnosed with NF1 over a 15-year period. Of these patients with facial involvement, glaucoma occurred

only ipsilaterally, with a prevalence of 23%, always with globe enlargement, requiring glaucoma surgery, albeit with a poor prognosis [28].

Von Hippel-Lindau Disease

Neovascular glaucoma can be seen in these patients with neglected or advanced cases of retinal capillary hemangioma.

Juvenile Xanthogranuloma

Ocular manifestations of juvenile xanthogranuloma include lightly pigmented iris lesions, histologically composed of foamy histiocytes and Touton giant cells. These tumors can cause spontaneous hyphema, resulting in secondary glaucoma. Direct invasion of the anterior chamber angle by histiocytes can also lead to elevated IOP and glaucoma. Patients with this condition also have yellow papular skin lesions on the head and neck [29].

Medulloepithelioma

Medulloepitheliomas arise from the nonpigmented epithelium of the ciliary body. They can be benign or malignant and appear as a whitish gray mass of the ciliary body or iris.

Neovascularization of the anterior chamber angle and forward displacement of the iris and PAS formation are common causes of glaucoma in these patients [30, 31].

Adult Glaucoma

Iris Stromal Cysts

Both angle-closure and open-angle glaucoma can be caused by iris stromal cysts whether these cysts occur spontaneously or following surgery or trauma to the eye [32]. Ultrasound biomicroscopy can differentiate iris cysts from malignant lesions [33].

Melanocytoma

Melanocytomas are benign pigmented tumors, which usually affect the optic nerve but which can occur within the iris or ciliary body. These tumors can cause glaucoma by extension into the trabecular meshwork or by dispersion of pigment or necrotic melanocytoma cells [34].

Fuchs' Adenoma

Fuchs' adenoma is a benign tumor of the ciliary body that can involve the iris. Glaucoma can occur as a result of pigment dispersion [35].

Uveal Melanoma

Very advanced choroidal melanomas can cause glaucoma, by pushing the lens/iris diaphragm forward to close the angle. Large tumors with severe retinal detachment can also induce iris neovascularization and neovascular glaucoma. Iris and ciliary body melanomas can cause glaucoma by annular spread around the angle [13]. Tapioca melanomas of the iris are associated with glaucoma which has been reported in a third of these patients [36, 37]. Iris melanomas with secondary glaucoma tend to be diffuse and are therefore associated with increased risks for local tumor recurrence, enucleation, and metastasis [3]. These risks do not occur when glaucoma is coincidental and unrelated to the tumor.

Metastatic Tumors

Intraocular metastases most commonly arise from carcinomas of the lung and breast. These metastases are usually located in the posterior choroid, although they can develop in the iris or ciliary body [38]. Glaucoma is more commonly associated with anterior segment metastases, which tend to cause iris neovascularization and hyphema (Fig. 5) [6].

Leukemia/Lymphoma

Choroidal infiltration by leukemia can cause massive subretinal hemorrhage and acute angle-closure glaucoma [10]. Anterior segment exam may reveal pseudohypopyon or hyphema with resultant open-angle glaucoma [39]. Lymphoma can affect the anterior segment to present as iritis with elevated IOP, although this is rare [40]. Investigation for recurrence of leukemia or lymphoma is essential in these patients presenting with iritis.

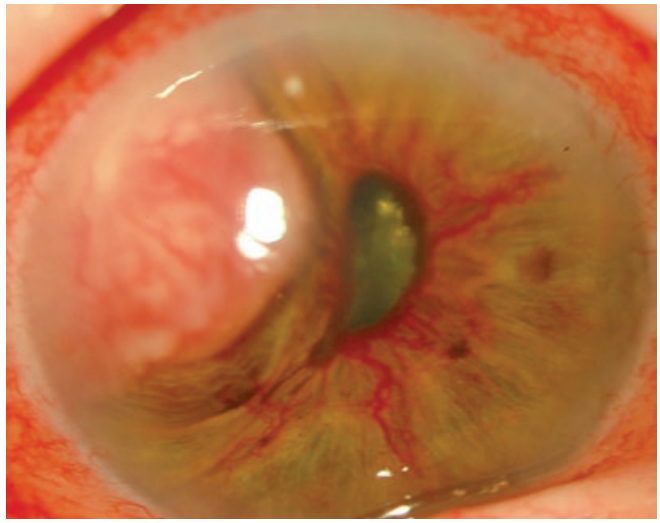


Fig. 5: Iris metastasis from endometrial carcinoma causing neovascular glaucoma.

Myelodysplastic Syndrome/Multiple Myeloma

A few cases of myelodysplastic syndrome presenting with serous retinal detachment and angle-closure glaucoma have been reported [11]. A case of multiple myeloma presenting as iritis has been reported, with cytologic analysis of the aqueous sample revealing neoplastic plasmacytoma cells [41].

Treatment

Treatment of the tumor results in improvement in intraocular pressure in most cases. In patients whose glaucoma does not respond to tumor ablation, management can be difficult [38, 39]. Filtering surgery should be safe in patients with uveal melanoma if the tumor has been successfully treated by radiotherapy or local resection. In cases of retinoblastoma, however, filtering surgery carries the risk of iatrogenic dissemination of the tumor and should be avoided [42, 43]. Laser trabeculoplasty can be considered in these patients, taking care to avoid areas of the anterior chamber angle that involve the tumor. Tumors that are associated with pigment dispersion and secondary glaucoma may respond well to laser trabeculoplasty [44]. A cyclodestructive procedure can also be considered, as the integrity of the anterior chamber is preserved and the procedure can be titrated to some degree [45]. One retrospective review of 27 eyes with secondary glaucoma following radiotherapy for uveal melanoma that underwent cyclophotocoagulation showed sustained intraocular pressure lowering at 24 months, with six of these eyes developing hypotony [46]. Techniques that do not penetrate the anterior chamber including canaloplasty and deep sclerotomy have shown promising results in these patients [47, 48]. Neovascular glaucoma developing after radiotherapy (i.e., "toxic tumor syndrome") can resolve if the offending tumor is excised [49]. In many cases of ciliary body or choroidal melanoma and retinoblastoma associated with glaucoma, patient comfort can be achieved only by enucleation.

When non-penetrating surgery is unsuccessful, penetrating surgery can be considered. Radiotherapy can result in local conjunctival inflammation and scarring, which can compromise trabeculectomy. Minimally invasive techniques such as goniotomy, supraciliary stenting, and others can be considered in these patients. Given the aggressive nature of glaucoma in these eyes, however, tube shunting may be more appropriate. In a case series of 31 patients with elevated IOP, following proton beam radiotherapy for anterior uveal melanoma with documented tumor regression, that were treated with Baerveldt shunt implantation, 86% of patients treated with glaucoma medications achieved adequate IOP control [50]. On follow-up exam, none of these patients had local or systemic dissemination of their tumors.

Patients with Sturge-Weber syndrome-associated glaucoma require special consideration [51]. In patients with high IOP caused by elevated episcleral venous pressure, surgical therapy is frequently required, although these patients have an increased risk of intraoperative choroidal effusion and expulsive hemorrhage [52]. Goniotomy has been successful in some patients and carries a decreased risk of complications. If filtration surgery must be undertaken, appropriate steps to reduce the chance of expulsive hemorrhage, including use of viscoelastic devices, preplacement of scleral sutures, and prophylactic sclerotomy, should be considered.

Table 1: Special considerations for management of tumor-associated glaucoma.

Factor	Comment
Dry eyes	Surface issues, lubrication, punctal plugs
Conjunctival scarring	Choice of surgery
Iris abnormalities	Synechiae, iridectomy
Associated cataract	Combined surgery
Radiation retinopathy	Combined PRP and intravitreal anti-VEGF
Radiation optic neuropathy	Poor visual outcome
Risk of tumor dissemination	Document tumor stability
Immunocompromised status	Risk of infection
Shortened life expectancy	Careful assessment of benefit

Abbreviations: *PRP* pan-retinal photocoagulation, *VEGF* vascular endothelial growth factor

Summary

Open-angle and angle-closure mechanisms can be associated with glaucoma in intraocular tumors. Patients presenting with unilateral glaucoma should be evaluated for associated intraocular tumors. The management of glaucoma associated with intraocular tumors should be individualized and adjusted according to the mechanism of elevated intraocular pressure (Table 1).

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4

Glaucoma Medications' Effect on Ocular Surface

Giedre Pakuliene

Finding a perfect topical drug for glaucoma patients can be a challenging task. A perfect drug must not only be sufficiently effective, but also tolerated well by the patient. Evaluating antiglaucomatous drugs' effects to ocular surface, three major factors must be considered: ocular surface toxicity, inflammation and allergy.

Toxicity—a dose-dependent degree to which a substance can damage the cells.

Allergy—hyperactive immune system reaction to an allergen, to which the individual has become hypersensitive.

Inflammation—a process, by which immune cells react and infiltrate tissues and inflammatory cascades are activated, fighting the foreign material.

Intolerance—inability to tolerate adverse effects of the medication.

Ocular surface tear film lipid layer is significantly thinner for glaucoma patients, comparing to healthy population [1]. This makes glaucoma patients more susceptible to toxic ocular surface damage.

Prostaglandins: The three most frequently used prostaglandin analogues—latanoprost, travoprost and bimatoprost are found to have a similar impact on ocular surface [2]. One of the most common ocular surface reactions to prostaglandins is conjunctival hyperemia [3]. Patients, who use bimatoprost, present with the most frequent hyperemia of all the patients who use prostaglandins, varying from 24% of patients [4] to 70–80% at baseline with a significant decrease at 6 month follow-up [5]. It was thought that conjunctival hyperemia is associated with inflammation; however the lack of inflammatory pathways stimulation in experimental studies and no difference of anterior chamber flare between bimatoprost users and non-users suggest no proof of inflammation. Instead, it is rather associated with nitric oxide mediated vasodilation and is usually temporary [6]. Latanoprost also affects central corneal thickness by corneal gel contraction and compaction of corneal tissue overtime [7].

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Beta-blockers: Timolol is often used to treat glaucoma as a monotherapy or in fixed combinations. The most common adverse effects for ocular surface are burning, itching, foreign body sensation, ocular discomfort, decreased tear production and punctate keratitis [8]. Timolol is shown to cause slowed reepithelization in animal models, as well as increased cytotoxicity and cytostaticity [9]. Timolol, used by glaucoma patients twice daily, is reported to cause punctate keratitis in 6% of cases, despite the preservative used [10]. Timolol and Betaxolol are also reported to cause reduced corneal sensitivity. Low corneal sensitivity increases risk to develop keratitis, therefore patients should be checked regularly [11].

Carboanhydrase inhibitors (CAIs): CAIs can cause increase in central corneal thickness for patients with endothelial pathology in a time dependant manner. CAIs inhibit carbonic anhydrase in endothelial cells and can reduce fluid excretion, which is already compromised, if endothelial cells are damaged [7]. Patients with endothelial pathology should be closely monitored, if CAIs are prescribed, because it can cause corneal decompensation [12]. Brinzolamide is found to create blurred vision after instillation to some of the patients, which is suggested to be caused by tear film instability [13].

Alpha-adrenoreceptor agonists: Brimonidine is a selective second generation alpha-adrenoreceptor agonist. Brimonidine is more likely to cause allergy, than prostaglandin analogues, beta-blockers or CAIs. Ocular allergy is a number one reason of brimonidine discontinuation for patients, treated for glaucoma [14]. Patients, allergic to brimonidine, are more likely to be allergic to timolol or other eye drops and show a decreased tear production, comparing to non-allergic to brimonidine group [15]. Brimonidine is also associated with inflammatory adverse events, such as conjunctivitis and anterior uveitis [16, 17].

Monotherapy is not always effective in glaucoma treatment. Some patients require a combination of two, three or even four antiglaucomatous drugs of different types. Multiple bottles of medications and administration times per day reduce patient compliance. Adverse events sum up with increase in incidence and severity. A combination of these factors becomes a burden to the patient and leads to poor glaucoma treatment and progression of blindness.

Fixed-combination antiglaucomatous medications were created to reduce adverse effects and inconvenience of eye drop instillation. The presence of two substances in one bottle reduces instillation times per day. Using one bottle, instead of two, is more convenient for the patient. Antiglaucomatous medications' preservatives are responsible for a vast amount of adverse effects. Reducing the number of bottles used, also reduces the amount of preservative that reaches the eye surface, therefore, minimizes adverse effects.

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5

The Optic Nerve Damage and Visual Field Change in the Acute Phase of Primary Angle-closure Glaucoma

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After acute onset of primary angle-closure glaucoma (PACG), it is difficult to identify the changes in the optic nerve and retina because of the tissue damage in the anterior segment. What are the characteristics of the visual field and optic nerve damage in PACG? Two cases in which the fundus changes after acute onset of PACG are quite typical are presented in this section. Although the cases are small in number, we believe they are representatives based upon literature review and our observation.

Case 1

Case Presentation

A 33-year-old female patient complained of bulging pain and suddenly decreased vision in her left eye for 1 day. She had experienced ipsilateral headache, nausea, and vomiting. She had no history of vision loss. The patient denied a history of trauma or systemic diseases. A family history was also denied.

On examination, the uncorrected visual acuity (UCVA) was 20/20 OD and 20/200 OS. There was no improvement with refraction. Intraocular pressure (IOP) by standard Goldmann applanation tonometry was 14 mmHg OD and 56 mmHg OS. In the right eye, the cornea was transparent, the depth of anterior chamber was 2.5 CT, the peripheral anterior chamber depth was 1/4 CT, the pupil size was 3 mm, the lens was transparent, and the C/D ratio was 0.4. In the left eye, the examination showed mixed hyperemia, corneal edema, a central anterior chamber depth of

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2.5 CT, a nearly closed peripheral anterior chamber angle, aqueous humor flare, an oval pupil (3.5 mm × 4.5 mm), slow direct light reflex, and loss of fundus details.

The axial length was 21.2 mm in the right eye and 20.9 mm in the left eye.

Final Diagnosis

The final diagnosis was primary acute angle-closure glaucoma (acute phase in the left eye and preclinical phase in the right eye).

Intraocular pressure-lowering drugs were immediately administrated to the patient, including mannitol (via intravenous infusion), oral methazolamide tablets, and topical antihypertensive and antiinflammatory drugs. Anterior chamber puncture was performed in emergency. After the surgery, the IOP was lowered, the UCVA was 20/25 in the right eye, and the pupil size was 3 mm in diameter. Fundus examination showed optic disc edema, multiple infarction foci surrounding the optic disc, and a splinter disc hemorrhage at the supratemporal sector in the left eye (Fig. 1).

Standardized automated perimetry revealed diffuse light sensitivity decrease that was the most severe in the superior visual field in the left eye (Fig. 2).

The patient continued to receive IOP-lowering drugs and topical anti-inflammatory therapies and underwent laser peripheral iridotomy in both eyes. After 1 week of IOP control, the UCVA was 20/22, IOP was 15 mmHg, and the pupil was 3 mm in diameter in the right eye. Re-examination of the left fundus indicated that the optic disc hemorrhage had been absorbed

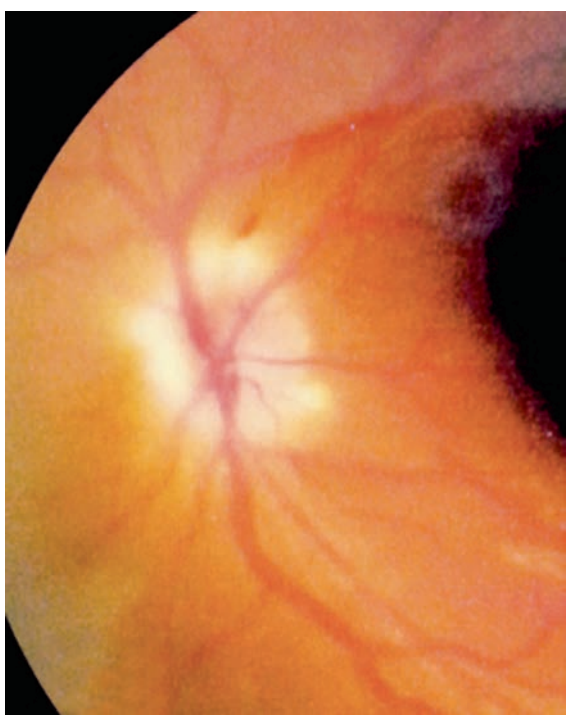


Fig. 1: Fundus photograph. Fundus photograph of the left eye showed multiple infarction foci surrounding the optic disc and a splinter disc hemorrhage at the supratemporal sector.

and the optic disc edema had been relieved, but the infarction foci could still be seen, and an inferotemporal retinal nerve fiber layer (RNFL) defect could be seen (Fig. 3).

Re-examination of the visual field demonstrated a superior visual field defect in the left eye (Fig. 4).

The medication and IOP control were normal. After 3 months, re-examination showed that the UCVA was 20/22, IOP was 15 mmHg, and the pupil was 3 mm in diameter in the right eye. In addition, the optic disc was pale in color with a clear boundary, and there was an inferotemporal wedge-shaped RNFL defect. Re-examination of the visual field showed that the superior visual field defect in the left eye was almost the same as previously seen but slightly improved (Fig. 5).

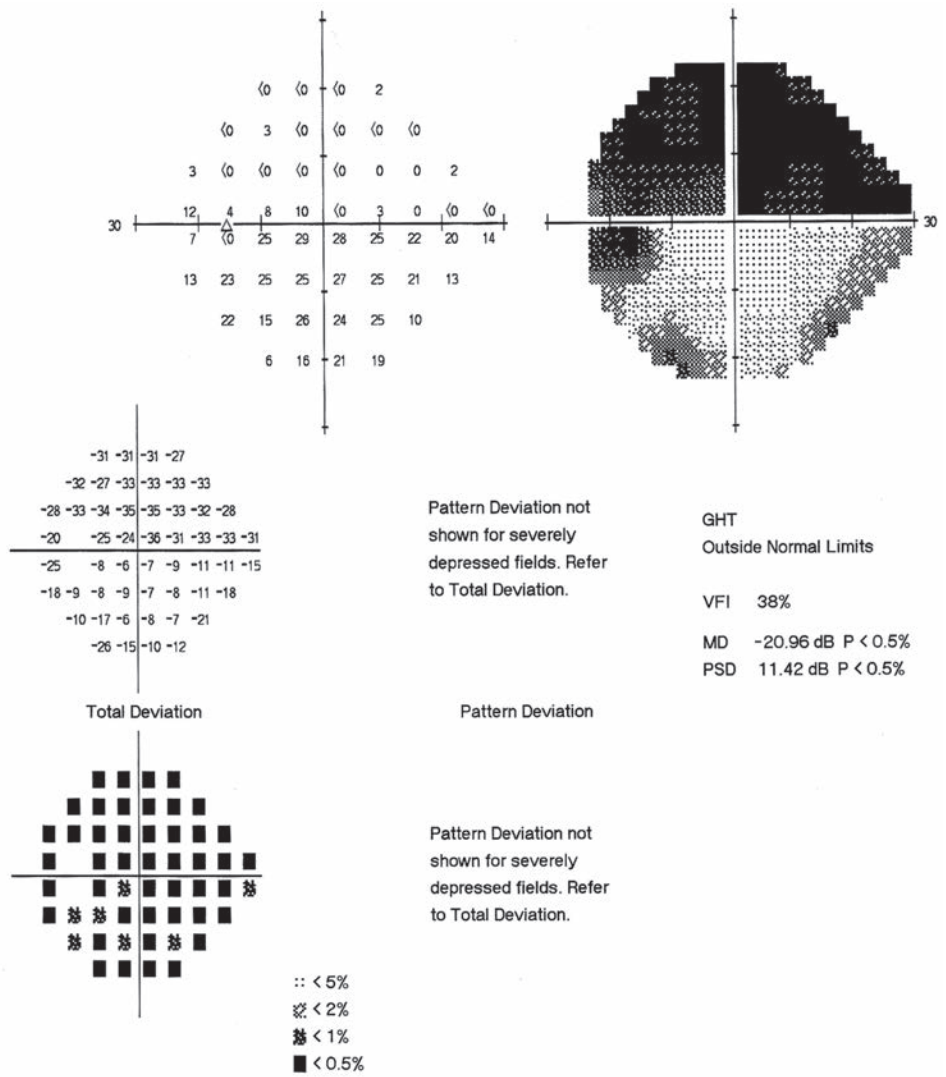
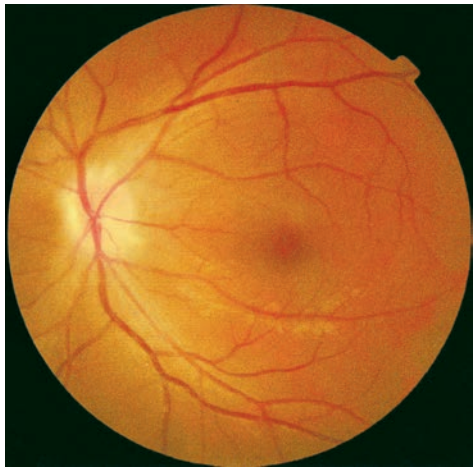


Fig. 2: Humphrey visual field analysis printout. The 24-2 test showed diffuse light sensitivity decrease in the left eye that was the most severe in the superior visual field.

Fig. 3: Fundus photograph obtained during the reexamination after 1 week of IOP control. After 1 week of treatment, re-examination of the fundus showed that the optic disc edema had been relieved, but peripapillary infarction foci and an inferotemporal wedge-shaped RNFL defect could be seen.



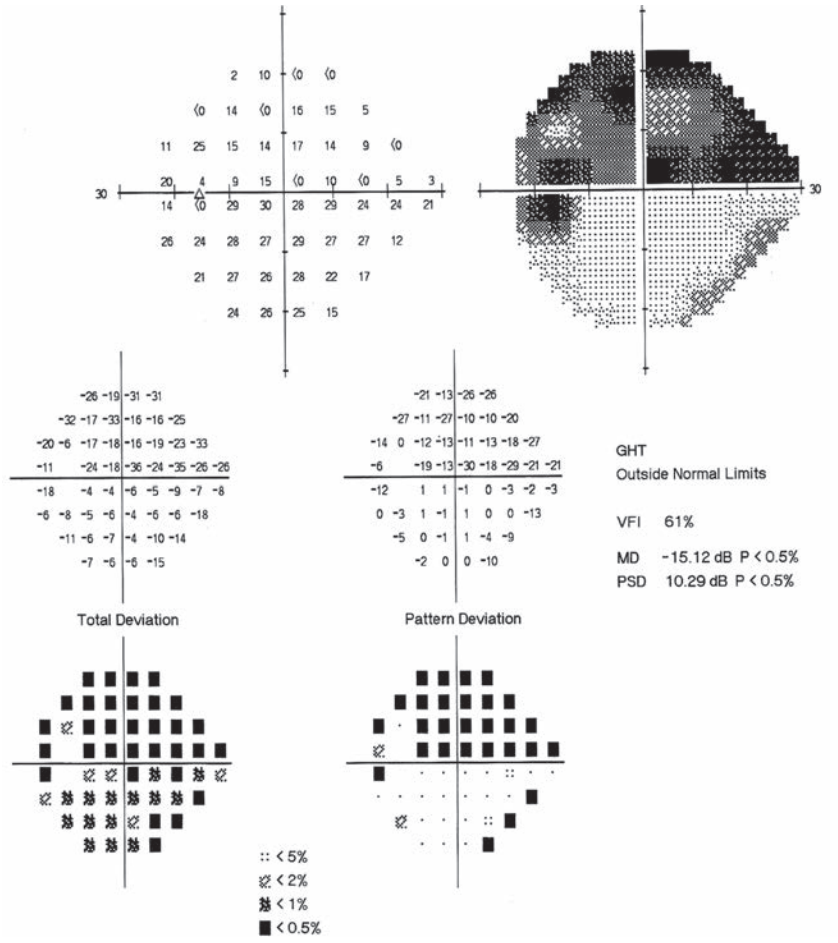


Fig. 4: Humphrey visual field analysis printout obtained during the re-examination after 1 week of IOP control. The 24-2 test showed a superior visual field defect in the left eye.

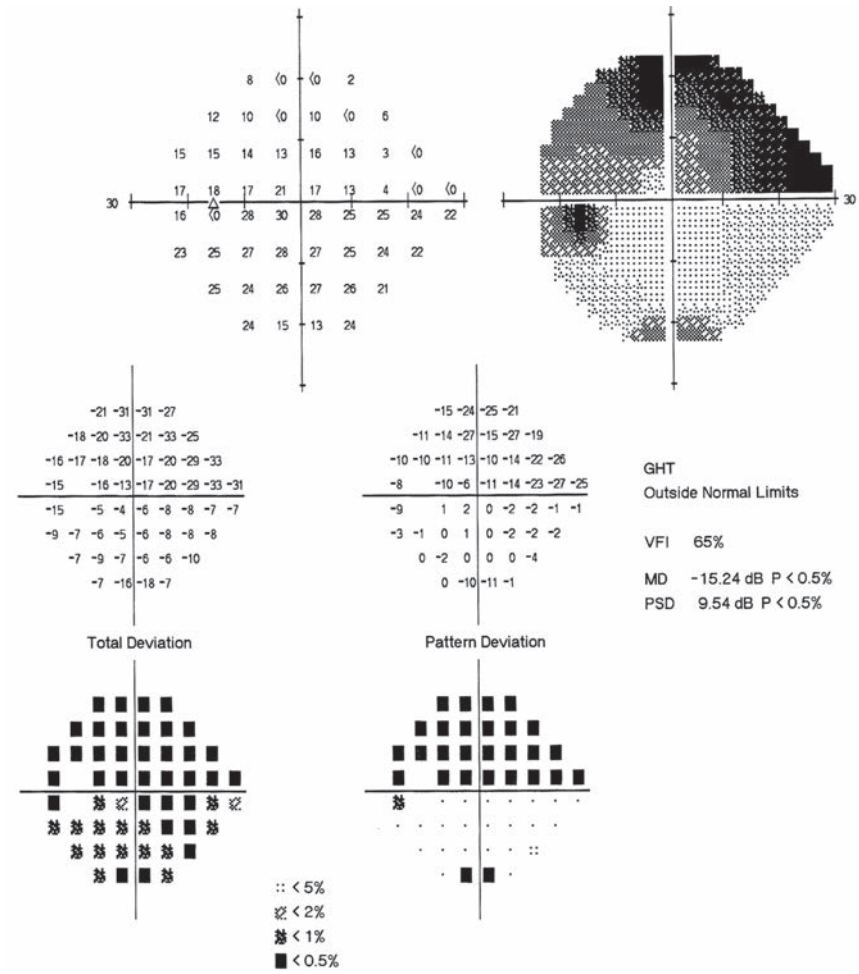


Fig. 5: Humphrey visual field analysis printout obtained during the re-examination after 3 months of IOP control. The 24-2 test of the visual field showed that the superior visual field defect in the left eye was almost the same as previously seen but slightly improved.

Case 2

Case Presentation

A 50-year-old female patient complained of decrease in vision and bulging pain in her right eye for 1 day, which was accompanied by ipsilateral headache. She had experienced a similar onset 2 months before, which was relieved after a rest, and thus the patient did not go for diagnosis and treatment. She had undergone an antiglaucoma surgery in her left eye 5 years before and denied history of other ocular diseases, systemic, or familial diseases.

On examination, the UCVA was 20/60 in the right eye and did not improve with refraction. The UCVA was 20/28 OS, and the best corrected visual acuity (BCVA) was 20/25 OS. IOP by standard Goldmann applanation tonometry was 61 mmHg OD and 15 mmHg OS. In the right eye, there were mixed hyperemia and corneal edema, the depth of anterior chamber was 3 CT, the angle of peripheral anterior chamber closed, the pupil was 3.5 mm in diameter, the direct light reflex was sluggish, the crystalline lens was cloudy, and the fundus was unclear. In the left eye, there was no congestion in the conjunctiva, the superior filtrating bleb was diffused and slightly elevated, the cornea was transparent, the depth of anterior chamber was 3 CT, the incision around the superior iris was unobstructed, the pupil was 3 mm in diameter, the crystalline lens was cloudy, the C/D ratio was 0.3, and the optic disc was pink in color with a distinctive boundary.

Final Diagnosis

The final diagnosis was primary angle-closure glaucoma (acute phase in the right eye; postantiglaucoma surgery phase in the left eye).

Intraocular pressure-lowering drugs were administrated to the patient immediately, including intravenous infusion of mannitol, oral methazolamide tablets, ocular hypertensive eye drops, and antiinflammatory drugs. Anterior chamber puncture was performed in emergency. After the surgery, the IOP was lowered, the UCVA was 20/28, and the pupil was 2 mm in diameter in the right eye. Fundus examination showed optic disc edema and a few temporal bleeding points in the right eye (Fig. 6).

Standardized automated perimetry showed a ring visual field defect in the right eye (Fig. 7). The patient underwent trabeculectomy after IOP of the right eye was under control. The IOP could be maintained in the normal range without any medications after surgery. After 1 month, the reexamination of the visual field showed that the ring visual field defect was the same as previously observed.

Discussion

Both the patients mentioned above had typical symptoms and signs of the acute phase of PACG, and thus the diagnosis was definite; the time from disease onset is 1 day, and active IOP-lowering therapies, including medication, laser, and surgery, were given, thereby having the IOP controlled, yet perimetry and funduscopy indicated that sharp increase in IOP caused significant damage to the optic nerve and retina. This kind of damage and its mechanism are significantly different from those of primary open-angle glaucoma (POAG): edema, infarction foci, and hemorrhagic foci could be seen in the optic disc, and although a nerve fiber bundle induced defect is seen in the visual field, it occurs simultaneously with diffuse decrease in light sensitivity.

In case of acute onset of PACG, the primary cause of optic disc edema is occlusion of the lamina cribrosa, where the nerve fiber axons could not expand due to the presence of dense connective tissue, and continuous influx of axoplasm causes swelling; retinal ganglion cells (RGCs) could not tolerate the blockage of axoplasm delivery, and thus necrosis occurs. Secondly, acute

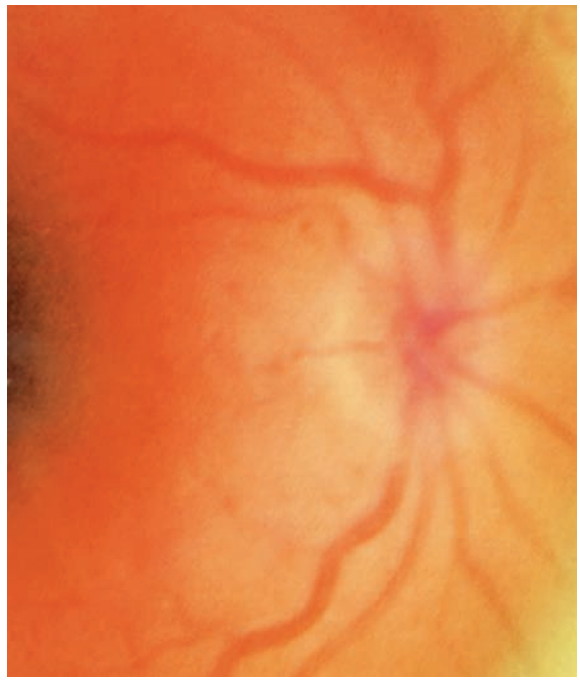


Fig. 6: Fundus photograph. It showed optic disc edema and a few temporal bleeding points.

increase in IOP might cause compression of the lamina cribrosa tissue, leading to distortion and dislocation of it, and the resultant shear force could also block the flow of axoplasm, leading to optic nerve damage [1, 2]. These inferences might explain the significant edema and infarction foci around the optic disc in Cases 1 and 2. In addition, acute increase in IOP could cause change in the local hemodynamics in the optic disc. Local blood supply in the optic disc was from the central retinal artery and the short posterior ciliary artery. In case of acute PACG, sharp increase in IOP causes compression of the vessels in the anterior area of the lamina cribrosa and less blood flow through the optic disc, which disturbs the nutrition and normal physiological function of the axons in the lamina cribrosa; decreased blood supply also impacts the capillary delivery of nutrients into astrocytes; ischemia reperfusion injury would occur on controlling IOP, leading to irreversible ischemia-hypoxia reperfusion injury in the surface capillaries in the optic disc and local retinal nerve fibers [3, 4], so bleeding (Case 2) and RNFL damage could be seen around the optic disc clinically. The ocular vessels of the patients with acute increase in IOP also had abnormal autoregulation, and some vessels had organic lesions, such as lumen stenosis and occlusion, vascular wall degeneration, and necrosis, leading to increased vascular resistance and abnormal regulation. Therefore, in case of acute PACG, retinal nerve fibers around the optic disc would be mainly injured [5], and the resultant visual field defect is still characterized by a nerve fiber bundle induced defect, such as the superior visual field defect and ring visual field defect in Cases 1 and 2.

For the damage of acute PACG, Fig. 8 illustrated on the cellular level the damage mechanisms of the acute tissue ischemia and acute inflammation induced by acute increase in IOP as well as the tissue ischemia-reperfusion injury after the IOP was controlled [6].

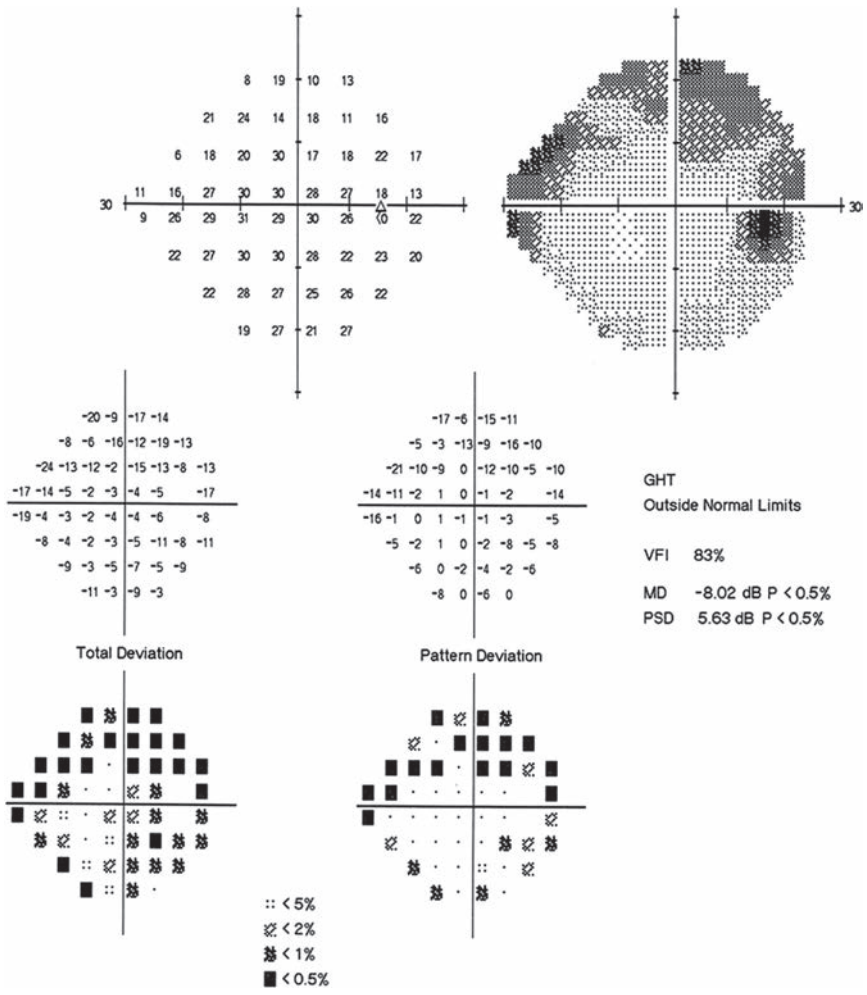


Fig. 7: Humphrey visual field analysis printout. The 24-2 test showed ring visual field defects in the right eye.

Being different from POAG, would acute PACG cause damage to the retina? Anatomically, the retina is divided into ten layers, while the blood supply of the inner five layers and outer five layers is from the central artery system and choroidal vascular system, respectively. The retinal central vascular system is a terminal artery and has no anastomosis with other vascular systems. The main branches of the central retinal artery are distributed in the retinal nerve fiber layers, and small branches from them are distributed in all the inner five layers in the retina. The angles between these branches and trunks are right angles. The supply vessels in the retinal inner nuclear layer and inner plexiform layer were the most distal branches of retinal central arterial capillaries. In acute high IOP, the anatomic site of the most severe ischemia should be the retinal inner nuclear layer, inner plexiform layer, and ganglion cell layer, and thus these three layers would have the most severe injury under ischemia [7–9].

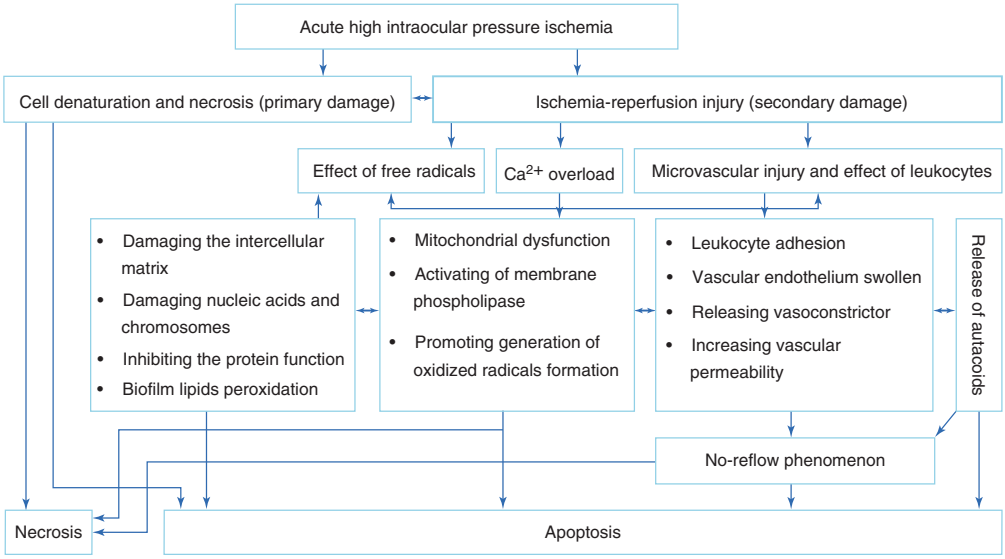


Fig. 8: A schematic overview of the mechanism of tissue damage in the acute phase of acute primary angle-closure glaucoma.

Therefore, the early injury to the inner nuclear layer and inner plexiform layer of the retina would be significant after acute PACG. Although clinical evidences provided by examinations, such as ERG and OCT scan of the macula lutea, were limited, the diffuse decrease in the light sensitivity in early visual field was found in these two patients, indicating damaged retinal function. This required further investigation.

For the damage to the visual field and optic disc due to acute PACG, we still have many problems. For example, there are also such manifestations in non-arterial anterior ischemic optic neuropathy (NAION) as bleeding, edema and even infarction foci in the fundus, and arcuate and flabellate visual field defects connecting with the blind spot caused by RNFL damage. This is very similar to the manifestation of acute PACG. So what are the differences and similarities in the pathological mechanism between the two diseases? We found that most visual field defects occur in the superior quadrant of the central visual field after PACG, although the number of cases observed was quite small. What are the reasons for this? What is the pathophysiological basis of this visual field damage? What is the outcome of visual field damage after IOP is controlled? What are the differences and similarities between the mechanisms of ischemic damage in PACG, POAG, and NAION, as the main change in the optic disc after acute PACG is that the color of the neuroretinal rim tissue became white, which is similar to that in NAION rather than POAG? What is the relationship between the visual field damage and the peak IOP value and its duration time in acute PACG? Is there any damage threshold? All these questions require prospective, large sample size studies for answers and confirmation.

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6

Glaucoma in the Elderly

Joanna H. Queen, Hilary A. Beaver

Case Vignette

An 85-year-old Caucasian man presented for evaluation after an increased intraocular pressure was detected at a community screening for glaucoma. He has a past medical history of severe degenerative arthritis in his hands and suffers from stable angina. Though a widower, he lives independently near his family; he has declined previous suggestions to move in with them or to the local retirement center. On examination, the patient has 20/20 visual acuity OU, an increased intraocular pressure (IOP) of 28 mmHg OU, and glaucomatous cupping of 0.9 OU. Both a confrontation visual field and formal perimetry show a superior arcuate glaucomatous defect OU. At that point, his eye doctor begins a one-eyed trial in the right eye (OD) of timolol GFS 0.5% each morning.

On follow-up evaluation, the patient reports perfect compliance. He reports intermittent blurred vision after placing the new medication. He mentions also a baseline intermittent dizziness due to low blood pressures. On further questioning, he thinks this may be increased with the new therapy. Although he last placed the timolol at 7:00 AM, his intraocular pressures on examination are unchanged and still elevated as during his initial appointment and are equal OU. After questioning, he confirms lid closure and punctual occlusion for 5 min after each drop.

His daughter is present for the current exam and reports that she has witnessed the patient both remembering to take his medication and instilling the drops. When asked to apply an additional drop in the office, the patient elevates his eyes, positions and squeezes the bottle, closes his eyes, and correctly applies correct punctual occlusion. The patient and his daughter are unaware that the process failed to squeeze a drop out of the bottle and into the eye.

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Patient Care

The patient care competency includes the use of preventative care for populations as well as individuals. Treatment and prevention start with diagnosis. We know that the incidence and prevalence of glaucoma increase with advancing age, but because it is often asymptomatic until advanced, the disease can have devastating visual and functional consequences by the time of diagnosis. Glaucoma-related vision loss negatively affects the quality of life and activities of daily living in the elderly, an ever-increasing population in the United States. The elderly are currently increasing at more than twice the rate of the general population; the population over 85 years of age is projected to be 7 times larger in 2050 than it was in 1980. Glaucoma currently affects 2.2% of Americans over age 40 and 7.7% of individuals over age 80. The total number of patients with glaucoma is thus projected to increase by 50% by 2020 [1, 2].

The likelihood of developing glaucoma is affected by race as well as age. Glaucoma is the primary cause of blindness for African-Americans and is three to four times more common than in non-Hispanic whites. This risk is higher still in black patients originating outside of the United States. Other races are increasingly being recognized at increased risk for glaucoma as well. Glaucoma is found in up to 22% of Latinos over age 80 and causes 28.6% of all blindness in the Latin American population. The repercussion to the U.S. population is significant: in the 2010 Census, 50.5 million individuals (16.3% of the population) identified themselves as Latino or Hispanic [2–5].

There is a role for screening at risk populations for eye disease (Fig. 1). Ten percent of the elderly have undiagnosed visual disorders and could benefit from screening. Up to a quarter of patients, over 80 with vision loss are unaware of their disease, including 7% who are blind from

Fig. 1: Application of ophthalmic drops to facilitate examination.

their disease [1, 2]. Compounding this problem, elderly patients with decreased vision may overestimate the quality of their vision, decreasing the likelihood that they will seek ophthalmic evaluation and care [6].

Institutionalized Americans are at a higher risk, with current estimates showing 26% of nursing home residents to have visual impairments [7]. Although half of glaucoma patients in America are undiagnosed, that number increases as high as 75% in Latin Americans for both open-angle glaucoma and for ocular hypertension [5]. There is potential benefit in screening the general elderly population for common diseases such as glaucoma in order to prevent vision loss and the comorbid conditions that accompany the loss of sight. There is increasing attention to performing this vision screening at sites where the elderly frequent, such as senior living facilities, activity centers, and outpatient clinics. These screenings may be performed by traveling nurses. Tonometry is currently one of the recommended means of glaucoma screening. Tonometry can be accomplished with light and inexpensive equipment performed by minimally trained non-ophthalmic personnel but is still underutilized as a glaucoma screening tool [1]. The benefit of public health screening has been studied and has support in the literature [1, 6], but the effect on the rates of vision-related functional impairment and effect on quality of life has been debated. The U.S. Preventive Services Task Force (USPSTF) literature review (2005) found insufficient evidence to recommend for or against screening adults for glaucoma. The USPSTF found "good evidence that screening can detect increased intraocular pressure (IOP) and early primary open-angle glaucoma (POAG) in adults," and "early treatment of adults with increased IOP detected by screening reduces the number of persons who develop small, visual field defects." They agreed that "early treatment of those with early, asymptomatic POAG decreases the number of those whose visual field defects progress" but felt that the overall evidence was not sufficient to determine the "extent to which screening–leading to the earlier detection and treatment of people with IOP or POAG–would reduce impairment in vision-related function or quality of life" [8]. This has led to debate, encouraging screening specifically by eye care professionals. In response to the USPSTF paper, the American Academy of Ophthalmology (AAO) produced a response emphasizing the new evidence for screening and the importance of the role of eye care professionals in screening. The summary of the letter is below:

1. *There is, in fact, a clear chain of evidence that connects glaucoma screening by eye care professionals with meaningful preservation of visual function and quality of life, through the reduction of worsening of glaucoma.*
2. *Community glaucoma screening will result in detection of patients with meaningful loss, since most will already have significant visual field loss in excess of – 4 dB.*
3. *Visual field loss at the – 4 dB level has a demonstrable and clinically significant impact on patient visual functioning and vision-related quality of life.*
4. *There is documented cost-effectiveness from the societal perspective in treating this level of visual field loss.*
5. *Glaucoma screening, defined as including an eye examination that detects all other conditions that threaten sight in the elderly and thus will result in significant benefit for older Americans in key indicators as important as IADL's and ADL's* [9] (Fig. 2).

Fig. 2: Confrontation visual field testing.

The question of the cost-effectiveness in treating glaucoma is a significant one. The direct economic cost of glaucoma to the United States is $2.86 billion annually for doctor, hospital, and drug treatment fees [2]. This estimate does not address the indirect costs of lost productivity, loss of quality of life, depression, institutionalization, and comorbid injury from falls and accidents. Although the geriatric population is already at risk of falling from comorbid medical conditions, glaucoma adds a significant risk for injury and falls. The loss of peripheral vision, particularly loss in the inferior visual fields, increases the likelihood that a patient will run into objects while walking and increases the need for home modification and environmental analysis training [7]. Haymes *et al.* found glaucoma patients to have a threefold increase in annual falls and a sixfold increase in motor vehicle accident (MVA) in the preceding 5 years compared to controls. Glaucoma patients who suffered an MVA were sevenfold more likely judged at fault [10]. The Salisbury Eye Evaluation study found visual field loss to be the primary visual indicator of an increased risk of falling [11]. Several studies have shown binocular visual field loss to be associated with a significantly increased risk of motor vehicle accident [11, 12]. Adequate glaucoma treatment, maximal vision correction and rehabilitation, and fall prevention could decrease both the personal and the social costs of glaucoma in our aging population.

Patient-centered care also applies to the individual and should be considered when performing diagnostic testing on the elderly glaucoma patient. Goldmann applanation and formal visual

field testing, though gold-standard in glaucoma evaluations, have limited utility in patients unable to position comfortably at a slit lamp or visual field perimeter. In addition to physical limitations, even mild cognitive decline can affect visual field results [13]. Assessing the patient as a whole, including both their physical and cognitive limitations, results in a tailored work-up that is more comfortable to the patient and more revealing of true visual deficits and changes for the physician (Fig. 3).

Medical Knowledge

Glaucoma is a significant visual disorder that affects the gamut from first-world to third-world nations. The World Health Organization projects 80 million people to be affected by glaucoma worldwide by 2020, and a recent Cochrane meta-analysis estimates those numbers will climb to over 110 million by 2040 [14]. The worldwide ratio between open-angle and angle-closure glaucoma is approximately 3:1. Of these patients, most bilateral glaucoma blindness in the world is due to angle closure. The overall incidence of glaucoma begins above age 40 and increases sharply with age [15]. The reach of glaucoma as a major cause of vision impairment extends to First World nations and accounts for 10% of blindness in the United States. In the United States, one million elderly over the age of 65 have vision loss from glaucoma, and 75% of those legally blind from glaucoma are over the age of 65 [3].

The elderly at risk for glaucoma are also at increased risk of drug toxicity following treatment for glaucoma (Table 1). Although glaucoma medications are primarily applied as topical

Fig. 3: Formal Humphrey visual field testing.

Table 1: Side effects of glaucoma medication [3, 16, 18].

Medication	Side-effect profile
Alpha adrenergic agonists	Topical allergy, dry mouth, exacerbation of cardiac disease, headache, sleep or gastrointestinal (GI) disturbance, hypertension, fatigue, interaction with MAO inhibitors, and tricyclic antidepressant agents
Beta-2 adrenergic agonists	Topical allergy, aphakic/pseudophakic macular edema
Beta 1 and 2 antagonists	Hypotension, bradycardia, bronchospasm (less in B-1 selective agents), fatigue/loss of exercise tolerance, exacerbation of underlying cardiac disease, masking of hypoglycemia or thyrotoxicosis, depression, impotence, syncope, headache
Carbonic anhydrase inhibitors	Topical: Local allergy, stinging, oral > topical with metallic taste, GI disturbance, idiopathic aplastic anemia, metabolic acidosis, hypokalemia, paresthesias, anorexia, fatigue, kidney stones, depression, weakness, metabolic acidosis
Osmotic diuretics	Exacerbation of underlying cardiac disease, subarachnoid hemorrhage, rapid diuresis
Parasympathetic cholinergic agents	Miosis causing difficulty with dark adaptation and mesopic conditions, cataract, myopic shift, headache, GI disturbance, diaphoresis, dyspnea, hypotension, arrhythmia, weakness, bronchospasm
Prostaglandin analogues	Topical allergy, iris and eyelid pigmentation, growth of lashes, conjunctival hyperemia, uveitis, macular edema, musculoskeletal pain

drops, those drops are adsorbed systemically through the conjunctiva and the nasal mucosa. Drugs administered via the mucosa directly enter the bloodstream without undergoing first pass elimination in the liver. The systemic effective dose of these medications is therefore larger than a similar oral dose. All medications have an increased potential for side effects in the elderly patient. The elderly have a lower muscle-to-fat ratio, less cardiac output, and less effective renal and liver clearance. Older patients have more comorbid medical conditions, including chronic obstructive pulmonary disease (COPD), diabetes, hypertension, cardiac arrhythmias, congestive heart failure, and arthritis that can be adversely affected by the use of topical glaucoma medication [16]. Alpha agonists, in particular, have been found to cause increased morbidity in the elderly due to their ability to cross the blood-brain barrier and cause sundowning, somnolence, and confusion [16]. The elderly take more systemic drugs with which ophthalmic drugs can interact and have lower serum albumin and other plasma-binding sites, such that there is more competition for binding and more free drugs available. Therefore, elderly patients in particular should be instructed on punctal occlusion and lid closure to minimize systemic adsorption of their topical medication. Oral glaucoma medications pose even greater risk for drug-drug interactions and exacerbation of systemic comorbidities, in particular CNS depression/somnolence and exacerbation of chronic kidney disease. Elderly patients on oral carbonic anhydrase inhibitors could be monitored in partnership with their primary care provider with complete blood count (CBC) and kidney function labs [17].

Because elderly patients with glaucoma frequently have comorbid constitutional diseases such as arthritis, they should be instructed and observed performing the correct instillation of their topical medications. Elderly patients with arthritis in their hands, peripheral neuropathy, or generalized weakness can be asked to demonstrate self-administration of drops with a sample of

artificial tears. Although these dropper bottles have different shapes and rigidities, this simple test can give a general confirmation whether the patient is able to self-administer drops.

If there is an observed difficulty with drop instillation, there are a number of options for assisting the patient to better deliver their medication. Difficulty with steady hand positioning can be remedied by purchasing an eye drop guide (a plastic brace that fits around the neck of the bottle and rests on the periorbital skin/orbital rim), many of which are commercially available and inexpensive [19]. Limited neck extension can make placing the eye drop in the inferior fornix difficult. This can be alleviated by having the patient instill their drops lying down (while in bed in the morning and evening is a convenient time for once or twice daily dosed drops) with the neck of the bottle resting on the bridge of the nose and the nozzle over the desired eye. Another benefit of this method is that the patient can close their eyes while administering drops; gravity brings the drop to the medial canthus, the most dependent area of the supine periorbita.

Even with good technique for drop instillation, there remains a large issue with daily compliance [20]. Keeping the bottle near something the patient does every day at the same time (e.g., toothbrush, television remote control) helps with compliance. If the patient takes multiple IOP-lowering drops, it is helpful to provide the patient with a printed grid. The drop name and cap color are written in large letters along one axis and the time to take the drop along the other axis (Table 2). The patient moves the dropper bottle across the grid as they take their drops, visualizing the doses taken and when to take them next. In patients taking more than one eye drop, it can be helpful to mention cap color in addition to medication name, as this is a common way patients identify drops [21].

Elderly patients are also at higher risk for complications after glaucoma surgery including suprachoroidal hemorrhage [23]. As such, a thorough discussion of risks and benefits of any sur-

Table 2: Eye drop medication class by cap color [22].

Medication	Side-effect profile
Adrenergic agonist combinations	Light green
Adrenergic agonists	Purple
Anti-infectives	Tan
Anti-inflammatory, nonsteroidal	Gray
Anti-inflammatory, steroids	Pink
Anti-inflammatory, immunomodulators	Olive green
Beta-blocker combinations	Dark blue
Beta-blocker	Yellow
Beta-blocker (pediatric dose)	Light blue
Carbonic anhydrase inhibitors	Orange
Cytotoxic	Black
Miotics	Dark green
Mydriatics and cycloplegics	Red
Prostaglandin analogues	Teal

gical intervention is necessary. It is important to have this discussion with the patient as well as their family or support system given the increased assistance that is required after glaucoma surgery. Transportation to frequent postoperative clinic appointments, increased drop usage, and blurred vision perioperatively can have profound quality-of-life consequences, particularly if the surgical eye is the patient's better or only eye. It is to the patient's and physician's benefit to plan for these changes ahead of the surgical date to allow for adequate patient assistance.

Interpersonal and Communication Skills

Good communication skills are essential when interacting with the elderly but in particular the older patient with glaucoma. This includes awareness of and recognition of the unique social, economic, physical, and mental needs of elderly patients with glaucoma. For example, a frank discussion of financial resources available for medication might be needed in an elderly patient on a fixed income. The financial hardship created by an expensive branded medication might be sufficient grounds to select a less expensive or generic alternative. The clinician should consider asking the older patient specifically if they prefer generic medication over brand name therapy. In addition, elderly patients are often already dosing systemic medications throughout the day and may prefer a topical drug with multiple dosing to paying additional money for a slow-release, single-use medication. Although patients may talk freely about this aspect of care when the subject is raised by the practitioner, they may be unwilling to broach the subject themselves.

Family members may be able to provide additional valuable information that impacts compliance. They may accompany an elderly patient to their appointments and can be consulted as to the patient's compliance with medication, side effects from medication, and coexistent medical conditions. Some family communication may be nonverbal, and it may be quite helpful to keep them visible while taking a history from the patient. A family member grimacing and shaking their head may be a more helpful indicator of compliance than the patient's verbal pronouncement and can at least raise the question for discussion with the patient about their ability to independently dose their own medication.

The clinician should strive to put the patient at ease. Allowing the patient to share sometimes difficult personal information can have vast implications on compliance and care. A patient who is unable to recall their care plan or to comply with their medication may be unwilling to state this due to the implications on self-reliance, self-sufficiency, and the need for institutional care. It may be difficult to discover a difficulty with medication, as patients with dementia may retain their interpersonal and communication skills far into their disease. A clinician viewed as hurried or uninterested will also not gain the patient's confidence. The patient and their family read nonverbal cues as well as the clinician. Sitting during the interview instead of standing, maintaining good eye contact, and giving the patient ample time to answer a given question will improve communication with the patient. Asking a patient to list the medication they are taking and the dosing of that medicine may be much more informative than asking them to confirm medicines read from the chart. In this age of declining reimbursements leading to more rapid patient encounters,

it is increasingly important to remember the communication competency when dealing with the elderly patient.

Professionalism

Aspects of physician professionalism can affect both the eye care and overall health care of the glaucoma patient. The healthcare provider should recognize and respect the elderly patient's need for independence and show compassion and empathy for the psychosocial aspects of the disease, including fear of blindness and dependency. Although it is important to confirm medical compliance, it is also important to respect patient's autonomy and independence. The clinician in this setting may have to spend more time with the elderly patient with glaucoma to address any social or non-ocular but age-related impediments to care. These adjustments allow the patient to retain dignity through self-reliance, independence, and autonomy but allow the option of adding additional assistance from visiting family members or from home health services.

The professionalism competency also includes ethics and the withholding of medical care. An example of such a choice is seen in the decision to either proceed with surgery or to continue with suboptimal medical management in a poorly controlled, elderly glaucoma patient. Although advanced age and comorbid medical conditions will impact patient care, the decision to treat aggressively or not should be made in discussion with the patient, and if they are not able to make the decision independently, then the discussion should include their family members or other caregivers. The withholding of medical or surgical care based on chronologic age alone is not appropriate and is a form of "ageism." A healthy, spry, independent living 90-year-old may in fact be a better candidate for aggressive treatment than a frail, incapacitated, institutionalized, or terminally ill 70-year-old patient. It is better to outline the benefits and risks of the medical and surgical options, including the effect of advanced age on surgical outcome, and allow the patient to decide on their course of treatment.

Practice-based Learning and Improvement

There is overlap between the practice-based learning and improvement and with the medical knowledge competencies. The clinician should stay abreast of new medical practices and apply these best practices to their own patient care. This would include being facile with the new medicines available for glaucoma and the new surgical options for treating the disease. Most new medications have a limited number of recognized toxicities and contraindications outlined at the time of FDA approval. More of these toxicities become defined with case reports or FDA updates in the months to years after a drug is approved. The clinician should stay abreast of the literature and new drug information and apply this information to the different patient populations with whom they interact (Table 3). In our scenario, this would include recognition of the special pharmacokinetics in the elderly population. Although there may not be specific contraindications in

Table 3: Top questions to ask your elderly glaucoma patient.

1. Do you have asthma, emphysema, or chronic bronchitis?
2. Do you have heart disease, rhythm problems, or heart failure?
3. Do you have hypertension or hypotension? Do you take a beta-blocker?
4. Can you walk up a flight of stairs without stopping for breath?
5. Are you diabetic? Do you get hypoglycemic?
6. Would it bother you if your eyes changed color?
7. Have you ever had inflammation in the eye (uveitis) or macular swelling?
8. Have you had complicated cataract surgery?
9. Are you on antidepressants of any kind?
10. Do you have any allergies to medicines, particularly eye drops? If so, what was the allergy?
11. Are you able to give yourself medication, specifically eye drops?

glaucoma drug therapy simply by age, the clinician should be cognizant of the interaction of comorbid disease and medication toxicity frequently encountered in the elderly [24].

Systems-based Practice

The system of care includes all facilities and individuals that a patient will encounter during the course of their therapy. In this case, the system of care includes the patient, the clinician, the family caregivers, and the skilled home healthcare providers that were refused by the patient. In addition, the local system of care includes the pharmacy where the patient obtains their medication, the primary care practitioner managing their hypertension, and the local hospital and emergency department. The macro system of care includes the pharmaceutical company and industries that make their medication, the insurance agent and company (in this case Medicare and the federal government), any cost-containment policies of these third-party payers, and the health policies of the county, state, and federal government. The clinician should be aware of how their own provision of care is influenced by the other components of the system of care and how to employ those other components to the best advantage of the patient. The clinician should work within their system to provide the best quality care with the most optimal use of the limited resources of the system.

Case Resolution

In this case, observing the patient self-administer drops and improving his technique and compliance were the most important parts of the encounter. The clinician discussed with the patient and family the failure of proper drop application and the option of home healthcare assistance. The patient was adamant about his ability both to remember and to instill his own medications and declined attempts to arrange home health care. The clinician however brokered an agreement to allow the daughter to assist in her father's care. The daughter lives near to her father and has come to all of his appointments and thus gains her father's consent to witness the daily instillation of drops. The daughter

works during the day and so cannot come in late morning, and the patient is "not a morning person," staying up at night and waking after 9:00 AM.

In this case, the clinician changed the medication to a single evening dosing of a prostaglandin analogue. Nighttime dosing of prostaglandins coordinates the schedules of the caregiver and the patient with the optimal dosing for the drug in question. The selection of a prostaglandin lessens the likelihood of postural hypotension in this chronically hypotensive patient, not only decreasing the risk of falls but also lessening the likelihood of inducing nocturnal hypotension and potential side effects such as anterior ischemic optic neuropathy. The solution format of the prostaglandin was preferable in this case as well. Gel-forming solutions can temporarily blur vision and contribute to a fall. Gels are also more difficult to squeeze from a bottle in patients with arthritis or weak finger strength.

Having reviewed the risks and benefits of the new medication and the alternatives to treatment, he is given a written prescription and a follow-up appointment for IOP evaluation in 6 weeks' time. The patient and daughter are instructed to see his primary care physician for evaluation of his dizziness and for a fall prevention assessment.

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