Functional and Anatomical Outcomes of Choroidal Neovascularisation complicating *BEST1* related retinopathy

Abbreviated Title:

Outcomes of CNV in *BEST1* related retinopathy

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KEY WORDS

Autosomal Recessive Best Retinopathy.

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Choroidal neovascularization.

Retina.

Retinal dystrophy.

SUMMARY STATEMENT

Choroidal neovascularization is a rare cause of visual loss in patients with Best disease. Its optimal management is unknown. We highlight novel clinical features of disease and present outcome data suggesting that a better outcome might be obtained with anti-VEGF therapy.

Functional and Anatomical Outcomes of Choroidal Neovascularisation complicating *BEST1* related retinopathy

Abstract

Purpose:

To describe the presenting features and functional outcomes in a series of patients with choroidal neovascularization (CNVM) complicating *BEST1* related retinopathy (Best Disease, BD and Autosomal Recessive Bestrophinopathy, ARB).

Methods:

Retrospective review of consecutive cases at a tertiary care eye hospital. Patients were identified retrospectively over an 11-year period. Records were reviewed to extract demographic, as well as functional and anatomical outcome data.

Results

14 eyes of 12 patients were identified (11 BD, 1 ARB). Median follow up was 2.8 years (range 0.8 to 6). The median age at CNVM discovery was 15.5 years (range 6 to 72). CNVM were active early in the disease course prior to vitelliruption. Seven eyes were treated with intravitreal bevacizumab, 7 eyes were monitored by observation alone. On average patients required a single treatment (median = 1, range 1-10). The median gain in visual acuity (VA) was greater in the treated versus the observed group - 0.46 v 0.17 decimalised units of Snellen Acuity respectively ($p<0.05$ Mann-Whitney U test). Although a significant reduction in central macular thickness (CMT) was evident in both groups, 150μm (treated) and 104μm (observed), active treatment was not associated with greater thinning than observation ($p>0.05$ Mann-Whitney U test).

Conclusions

There is a high rate of spontaneous recovery of *BEST1*-related CNVM, and overall we observed a gain in VA associated with a reduction in CMT. Active treatment, here with intravitreal bevacizumab, is associated with better functional outcomes than observation alone.

Introduction

The bestrophinopathies are a spectrum of inherited retinal dystrophies that result from mutation of the *BEST1* gene. The commonest presentation within this group is Best Disease (BD; Vitelliform Macular Dystrophy; OMIM 153700), a macular dystrophy characterised by bilateral accumulation of subretinal yellow material with later eruption into the photoreceptor layer and symptomatic reduction in vision. This form of the disease is most commonly associated with heterozygous missense mutations usually within the first half of the *BEST1* gene.[1, 2] BD is almost always associated with a reduced light rise of the electrooculogram (EOG).[33] The full-field electroretinogram (ffERG) is normal. In contrast, autosomal recessive bestrophinopathy (ARB; OMIM 611809) associated with bi-allelic *BEST1* variants results in a more widespread retinal disease with multifocal accumulation of subretinal deposit, and abnormalities of the ffERG in addition to a reduced EOG light rise.[4]

In both BD and ARB, central visual acuity may be affected at any stage, although this usually is associated with either intraretinal fluid (IRF) accumulation, disruption of the photoreceptor layer during the vitelliruptive stage of dominant disease, or later atrophy. Rarely, visual decline may be the result of choroidal neovascular membrane (CNVM) formation. Whilst there are a few case reports and small series suggesting that CNVM can be successfully treated with intravitreal injections of recombinant antibodies directed against vascular endothelial growth factor (VEGF) (Ranibizumab, Bevacizumab), there is no evidence to suggest that outcomes are better than conservative management (observation alone).[5-8] Here we report our clinical experience with a cohort of patients with BD and ARB, whose disease has been complicated by CNVM.

Methods

A retrospective review of the electronic patient record system at Moorfields Eye Hospital was performed with the search terms 'Best disease', 'recessive bestrophinopathy', 'choroidal neovascularisation' and 'haemorrhage' covering the time period between 2003 and 2015. The hospital notes were then reviewed both to confirm the diagnosis and document the clinical findings. Only patients with active CNVM were included. CNVM were deemed active if there were two of the following features were present – acute visual deterioration, retinal haemorrhage or exudate, intraretinal fluid, irregular pigment epithelial detachment or evidence of neovascularisation with fluorescein angiography. Presumed inactive CNVM were diagnosed primarily on the basis of subretinal fibrosis and excluded from this study. Patient demographics (including sex and age at CNVM diagnosis) and symptoms were noted. Snellen visual acuity recorded in the clinic was converted into a decimalised value for subsequent analysis. Retinal anatomy was documented with colour fundus photography using a Topcon TRC 50IA retinal camera (Topcon Corporation, Tokyo, Japan) and optical coherence tomography (OCT) using the Spectralis SD-OCT (Heidelberg Engineering, Heidelberg, Germany), with both line and volume scans available for interpretation. Fundus autofluorescence (FAF) images were acquired using the AF mode of the Spectralis SD-OCT using either the 30 or 55 degree lenses. Fundus fluorescein angiography (FFA) was performed using either the Topcon fundus camera or the Spectralis HRA systems.

In order to estimate the period prevalence of CNVM in *BEST1* related eye disease we reviewed retinal images of patients' known to harbour *BEST1* mutations attending between 1.1.2010 and 1.1.2015. Only patients with active disease (as defined above) were included. Numerical data are described using median values and interquartile ranges, and compared using non-parametric analysis (Mann-Whitney U test).

This study was approved by the local research ethics committee, and all investigations were conducted in accordance with the principles of the Declaration of Helsinki.

Results

Cohort demographics

Twelve patients were identified over the study period with a clinical diagnosis of either BD (n=11) or ARB (n=1) complicated by active CNVM. Molecular confirmation of the clinical diagnosis was available in 6/12 cases; genetic testing was not performed in two patients (Table 1). For the molecularly unconfirmed cases, confidence in the clinical diagnosis was high as patients presented with at least two classical features of BD (macular phenotype, reduced EOG, dominant family history). Six patients (50%) were male. Two patients had bilateral CNVM, thus data from 14 eyes of twelve patients were available for analysis. The follow up period ranged from 0.8 to 6 years. One patient was diagnosed with BD as a child but only developed signs of CNVM aged 72 years (Patient 4). The median age at CNVM discovery was 15.5 years (IQR 13 years). For the two patients with bilateral disease, sequential involvement of the fellow eye was observed within 4 years. Figure 1 shows images from the fellow eye of patient 8 to illustrate the natural history of BD uncomplicated by CNVM, for comparison with subsequent figures (Fig. 2-5), which show illustrative images from Patients 2 and 9; salient features will be discussed in the Results and Discussion below.

Premorbid and presenting clinical characteristics

For 11/14 eyes the acuity prior to CNVM discovery was known and documented to be normal in 9/11 (median = 20/20, IQR = 0). 3/14 eyes presented with active disease, consequently the prior acuity was unknown. For 2/11 the baseline visual acuity was already reduced. Patient 4 presented aged 72 with advanced BD; her results will be presented separately. Patient 2 had suffered with prior neovascular disease in the same eye more than two yearspreviously, accounting for her reduced presenting vision. Visual acuity in the fellow eye at the time of CNVM discovery was similar to the pre-CNVM acuity in affected eyes (median 20/20, IQR = 0), strongly suggesting that both eyes were at a similar stage of disease and that neovascularisation occurs relatively early in the disease course. The median visual acuity at CNVM discovery was 20/60 (0.33, IQR = 0.17), overall representing a moderate reduction from baseline, although for individual patients this varied significantly (range = 20/20 to 20/400) (Table 1). The presenting acuity did not appear to be inversely correlated with acuity in the fellow eye. Patient 4 began with acuity of 20/120 right and 20/80 left. Her vision then fell to 20/200 in the right eye as the CNVM became active; 5 years later subretinal scarring resulted in a final acuity of 20/1200. The fellow eye remained at 20/80 throughout the follow up period.

Where SD-OCT scans were available prior to CNVM detection (n= 9), pre-existing SRF was present in seven cases (example shown in Fig. 2A). IRF however was never observed. All patients reported a

symptomatic reduction in their central vision (n=14 eyes). In all cases haemorrhage was noted at some point in the disease course, and was always subretinal in location and found either inside the boundaries of the yellow vitelliform lesion or at its border. Four patients presented in the month preceding hemorrhage detection with new symptoms of dysmorphopsia. In these cases FFA showed no evidence of vascular leakage. It is however possible that they had active neovascular disease at this time that evaded detection with conventional imaging techniques.

Imaging in active disease

Fundus fluorescein angiography (FFA) was requested in 9/14 cases and available for review. In a minority (3/9) late leakage of undetermined origin was evident. The majority (6/9) however demonstrated staining of the hyperfluorescent subretinal deposit thus masking any subtle changes being further characterised. Indocyanine green angiography performed in one case (Patient 12) showed only masking.

Optical coherence tomographic imaging of the retina-RPE-choroidal interface was available for all cases (14 eyes) and demonstrated abnormalities in the four cases that were symptomatic prior to haemorrhage being visualised. The earliest visible changes were at the level of the RPE, with separation from Bruch's membrane due to presumed CNVM (see Figures 2b, 3b, 4e, 5a). The maximal site of RPE elevation was always found in the lower half of the macular lesion (n=14), and often no disturbance was seen in the superior half (see Figure 3A and 3B). Other OCT features observed in patients with CNVM were subretinal fluid (SRF) (n=14), new IRF (n=12), discontinuity in Bruch's membrane (n=7), areas of choroidal excavation (n=4) and presumed photoreceptor outer segment delamination (n=1). At the final follow up visit SRF was still present in all eyes.

Fundus autofluorescence imaging was used to identify subretinal deposition, which was hyperautofluorescent in all cases. Areas with SRF exhibited reduced autofluorescence and when haemorrhage was present the normal autofluorescence was masked to a greater extent than by fluid alone. Inactive CNVM associated with fibrosis and organising haemorrhage that had become depigmented may be mistaken for yellow subretinal deposit seen in typical BD. Autofluorescence was useful in differentiating deposit (hyperautofluorescent) from fibrosis and scarring which are both hypoautofluorescent (Figures 4B and 5D,E show autofluorescence images from the same eye before and after CNV development). Rupture of the RPE resulting from vertical extension of a CNVM was again associated with reduced autofluorescence.

Outcomes

As all the patients identified presented with active CNVM after 2009, treatment with intravitreal bevacizumab (1.25mg/0.05ml) was potentially available to all cases. Seven eyes in this series received active treatment. Three of these patients had neovascular disease in their better seeing eye, as fellow eyes were affected by amblyopia (n=2) or prior CNVM (n=2); factors which may have influenced the decision to use an anti-VEGF agent. The majority (5/7) of treated patients were over the age of 18, perhaps reflecting the ease of administering intravitreal therapy in an adult versus paediatric population where sedation or general anaesthesia may be required. Of the seven treated patients, four had a single injection, one received a second injection, one (Patient 12) had a predetermined course of three 'loading' injections and one (Patient 8) received ten intravitreal treatments. The multiple injections required by Patient 8 may represent partial response to this therapy, membrane recurrence, or the inability to correctly identify an endpoint for treatment. Patient 2 was also thought to have developed late CNVM recurrence surrounding a previously inactive disciform scar.

As a group, the median change in vision after presenting with an active CNVM until the final follow up visit was a gain of 0.34 decimalised Snellen lines (IQR 0.48), equivalent to a change from 20/60 (median presenting acuity) to 20/32. The treated eyes had a median gain in vision of 0.46 (IQR = 0.32), whilst eyes monitored by observation alone also gained vision, recording a more modest increase of 0.17 decimalised Snellen acuity (median gain, IQR = 0.39). This difference was found to be significant (Mann-Whitney U test, $p < 0.05$).

Central retinal thickening was evident in all cases at CNVM discovery, with a median central 1mm macular thickness of 561µm (IQR = 160) (observed) compared to 411µm (IQR = 441) (treated) (Mann-Whitney U test, $p > 0.05$). At final follow up this had reduced to a similar extent in both the groups; 150µm (IQR = 41) (observed) and 104µm (IQR = 240) (treated) (Mann-Whitney U test, $p > 0.05$).

During a five-year interval from 2010-2015, 107 molecularly confirmed cases of *BEST1* related eye disease were recorded at Moorfields Eye Hospital. Molecular genetic testing is offered as an adjunct to the clinical examination, particularly if there is any clinical doubt regarding diagnosis. Testing would not have been offered, or accepted, in a further unquantifiable cohort of patients. Six of these patients later presented with active CNVM, suggesting a minimum prevalence of 5.6% (6/107) during this period.

Discussion

Choroidal neovascularisation is thought to be a rare complication of *BEST1* related retinopathy; however the exact prevalence is currently unknown. [9-13] In this study we have identified 14 eyes from twelve patients who have presented with active choroidal neovascular disease associated with either BD or ARB. Within our own genetic database, this equates to a period prevalence of 5.6%, significantly higher than one may have expected. In the majority of cases, neovascularisation occurred early in the disease course, when visual acuity would otherwise be unaffected. The natural history of these membranes appears to follow a more benign course than those associated with age-related macular degeneration (ARMD), with a median gain of 0.34 decimalised units of Snellen acuity after resolution. Treatment with intraviteal bevacizumab (n=7) was associated with greater visual gain when compared to observation alone (n=7, Mann-Whitney U test $p < 0.05$).

Diagnosing CNVM in the context of *BEST1* related retinopathy is complicated by the presence of pre-existing subretinal deposit, which stains during FFA. We suggest additional features that may aid diagnosis or at least heighten clinical suspicion. Typical disease uncomplicated by neovascularisation is associated with subretinal deposit that organises over time, and often is later accompanied by SRF (Figure 1). The residual deposit becomes distributed in a pattern that is primarily influenced by gravity resulting in a predominantly inferior accumulation (the pseudohypopyon stage). Persistence of the dense deposit inferiorly may result in a greater insult to the inferior retina-RPE complex than that in the superior macula. In keeping with this hypothesis, whenever we were able to identify the neovascular complex it was always sited within the inferior half of the vitelliform lesion (Figures 2-5). In no cases were membranes seen to arise from the superior half of the lesion. In most cases the CNVM develop relatively early in the disease course, prior to vitelliruption, as normal acuity had been recorded within the past seven months in 82% (9/11 eyes), suggesting normal central photoreceptor function. As the membranes grow, they breach Bruch's membrane and distort the RPE resulting in localised detachments (Figures 2b, 3b, 4e, 5a). In the absence of CNVM the RPE should otherwise appear flat and apposed to Bruch's membrane (Figure 1). Bruch's membrane is usually not visible on OCT. RPE detachment results in the two structures now being separately resolved (Figures 2b, 3b, 4e), which are presumed to be the RPE and Bruch's membrane. Type 1 membranes sit below the RPE and in the earliest stages are not perfused.[14] As they mature and support a blood flow they may leak, just as an occult CNVM associated with AMD would. Serous leakage into the sub-RPE compartment may result in fibrosis and RPE hyperplasia without the appearance of frank haemorrhage.[15] This may account for the fibrotic appearance of the macula in some patients with BD rather than the better defined atrophic maculopathy. If this is the case,

CNVM may be a more common complication of BD as both atrophy and fibrosis were recognised as endpoints for this disease when it was originally classified. Should the CNVM breach the RPE becoming a type 2 membrane it can grow within the vitelliform space.[14] Contact with the subretinal surface provides a scaffold for progression, with or without duplication of the RPE. The membrane may bleed into the subretinal as well as sub RPE cavity or leak serous fluid. The presence of definitively new fluid would be hard to detect as SRF is a typical feature of BD in the absence of CNVM, but CNVM activity may additionally result in IRF, not typically seen in BD (Figures 2c, 3a) but present in ARB (Figure 6). As the CNVM contracts it may exert tractional forces on the subretinal surface, and as there is sufficient space within the fluid filled cavity we can occasionally observe a presumed detachment/delamination of the photoreceptor outer segments (present in Figure 3c). Abnormal neovascular networks may also form anastomoses between the retinal and choroidal circulations (Type 3 membranes).

It is likely that a recently developed imaging technique, OCT angiography (OCTA), will offer the best method of visualising well perfused CNVMs, as it is minimally influenced by the presence of subretinal deposit unlike FFA (personal observation, unpublished data). It will be interesting to see in these cases if CNVM anatomy as defined by OCTA correlates to visual outcome, as this may help to provide further prognostic information. If it becomes evident that specific subtypes of CNVM are associated with a better prognosis, or are more responsive to treatment, as is the case in ARMD, this additional information will be particularly helpful in the management of paediatric patients, where organising treatment is not as straight forward as for adults.[15]

Age related CNVM are associated with diffuse thickening of the RPE basal membrane (basal laminar deposit) and secondary dystrophic calcification, whilst pediatric CNVM are not.[16] “Juvenile” membranes are thought to result from a more localised abnormality with a solitary site of subretinal vascular invasion rather than the multifocal vascular breaches that occur with age.[17] This is in keeping with the natural history and prognosis for these membranes being better than for those which occur in ARMD, and may explain why spontaneous regression is reported to be very common in pediatric CNVM.[18, 19] The initial report of visual outcomes in BD complicated by CNVM monitored by observation alone suggested that recovery could be expected in the majority of cases (10/11 eyes in the initial series) with 9/11 eyes recording a final acuity of better than 20/50.[9] Smaller, more focal CNVM may also explain their sensitivity to treatment with anti-VEGF agents, as single treatments are often sufficient.[5-8, 20] Rishi et al have most recently reported their experience treating pediatric CNVM and present data on four patients with BD who were followed up for more than one week.[21] The 3 patients who received treatment showed either an improvement (from 20/200 to 20/120 and

20/20) or stabilisation of vision (at 20/30). One patient with inactive disease was followed by observation only and his vision spontaneously improved (20/200 to 20/30), again highlighting the good visual outcome that may be seen with spontaneous regression of CNV in children. Pediatric CNVM may also complicate structural abnormalities (angioid streaks, choroidal osteoma, optic nerve head drusen, trauma and less commonly myopia), intraocular inflammation (presumed ocular histoplasmosis syndrome, mutifocal choroiditis, toxoplasmosis) or be idiopathic.[21] CNVM are also a rare complication of other childhood-onset forms of inherited retinal disease and have been reported to occur with choroideremia,[22] North Carolina macular dystrophy,[23] and Stargardt disease.[24]

The visual outcomes presented, especially for the untreated group are perhaps surprisingly good, again highlighting the difference with ARMD. In two cases only one treatment was required, suggesting that the membranes are exquisitely sensitive to anti-VEGF or that the disease is monophasic. Endpoints that are valid when treating CNVM associated with ARMD may not be helpful for membranes occurring in the context of BD. We suggest that as SRF can be expected to both pre- and post-date CNVM discovery/activity its usefulness as a biomarker for choroidal neovascularisation is limited. Similarly reliance on automated measurements of central retinal thickness from SD-OCT scans may be unwise, as SRF will be overrepresented within this measurement. This may account for the difference in anatomical and functional outcomes that were recorded here, as patients with typical CNVM recorded better visual outcomes if they received treatment ($p=0.03$), however their central retinal thickness measurements did not mirror these changes. A more accurate use of SD-OCT data may involve segmentation of the retinal sub-layers, recording measurements between the internal limiting membrane (ILM) and ellipsoid zone (EZ), perhaps more representative of IRF. This parameter may correlate better with changes in vision, although our experience of treating patients with ARMD may suggest that this will not always be the case. For ARB even this technique may have limited utility, as IRF is the norm. IRF may also be seen in a minority of cases of end stage BD, so in the setting of significant RPE disease both SRF and IRF may be expected, even in the absence of CNVM, thereby complicating diagnosis.

Surprisingly in one case, haemorrhage secondary to the neovascular membrane did not occur until after the age of 70, whist all other cases were detected under the age of 25 years of age. A number of explanations are possible. Firstly, CNVM occurrence may be independent of disease stage, although in this series 9/14 eyes recorded a normal acuity within the past seven months, suggesting that the majority of photoreceptors were unaffected consistent with the earliest stages of disease. Secondly, this patient may have suffered with prior neovascular complications, and the detected

episode in fact represents a recurrence of disease activity. Finally, the CNVM identified might have occurred independent of the *BEST1* mutation, relating instead to ARMD. As monogenic disorders can show phenotypic overlap with ARMD, and mutations in *BEST1* may be non-penetrant and variably expressed, it is also quite possible that *BEST1*-related retinopathy may masquerade as either neovascular or non-neovascular ARMD.

Lastly, it is important to highlight that the retrospective nature of this study carries with it inherent limitations. Under-ascertainment is likely to have occurred, most evident due to the lack of cases identified prior to 2009. Molecular confirmation of the diagnosis was not available for 8/14 cases, although all did report a dominant family history consistent with BD, and in two cases a reduced Arden ratio was additionally recorded. Absence of randomisation when selecting the intervention may have provided a bias towards treating the more severe cases, although by chance the presenting visual acuities appear to be well matched between the two groups (median = 0.32 v 0.34, decimalsied Snellen). Visual acuity data may also have been influenced by uncorrected refractive error which was not controlled for, but perhaps equally distributed throughout the two groups. Finally, the wide variation in duration of follow up may influence the final acuity, as the natural history of BD is progression to macular atrophy. No such trend was apparent however.

In summary, we present the largest case series to date of CNVM complicating BD and ARB. In this non-randomised retrospective series we have identified that these membranes have a high rate of spontaneous resolution, and additional visual gains may be obtained with the use of intravitreal anti-VEGF therapy. In the vast majority of cases CNVM should be considered as a relatively early potential complication of BD. Occasionally this rare complication may recur. We also highlight novel OCT features seen in both early and late neovascular disease that will facilitate identification of these lesions. Lastly, we suggest that CNVM may be a potentially under-recognised complication of *BEST1*-related retinopathy, and the advent of novel imaging techniques may help to prove this.

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Tables

Table 1. Summary of patient characteristics.

Patient.	ID.	BEST1 variant	Follow up (years)	Eye with CNVM	Age at CNVM discovery	Treatment given? (Number)	Pre-CNVM VA if known (decimalised Snellen)	Presentation VA (decimalised Snellen)	Final Visit VA (decimalised Snellen)
1	29774	p.Arg356X ; p.Ile201Thr	5	OS	12	No	1	0.4	0.95
2	31575	p.Arg218Cys	1.5	OD	9	Yes (1)	0.43*	0.22	0.5
3	1264937	Not known	3	OD	10	No	1	0.05	0.05
4	12171	p.Phe298Val	6	OD	72	No	0.14	0.1	0.016
5	1597719	Not known	2.5	OD	6	No	Not known	0.32	0.66
			3	OS	6			0.2	0.25
6	31286	Not known	3	OS	13	No	1	0.46	0.63
7	29283	p.Ser16Phe	1.5	OS	20	Yes (1)	Not known	0.34	0.8
8	29668	p.Arg105Gly	4 (6)	OD	24	Yes (10)	1	0.66	1^ (0.66)#
9	29781	p.Phe298Val	2	OD	28	Yes (2)	1	0.25,	1
			5	OS	25	No	1	0.1	0.66
10	1787207	Not known	1	OD	18	Yes (1)	1	0.34	1
11	1799554	Not known	0.8	OD	10	Yes (1)	1	0.19	0.8
12	2172661	Not known	0.8	OD	19	Yes (3)	1	0.25	1

*prior CNVM in this eye hence reduced baseline vision

^VA when considered stable after 4th and 8th treatment

#VA at final follow up 6 years later

Figure Legends

Figure 1. Serial images one year apart from the left eye of Patient 8, showing organisation of the pseudo-vitelliform lesion. Left-hand panels show infrared reflectance images, and right-hand panels show corresponding spectral domain OCT scans taken in the same location. *A,* OCT image shows the subretinal deposit or fluid lies in a mound below a largely intact, but irregular outer retinal ellipsoid line. *B*, Image taken one year later shows greater irregularity of the ellipsoid line with some areas of focal hyperreflectivity in the outer nuclear layer.. *C*, Further images taken one year later show approximation between retina and RPE close to the location of the previous hyperreflective areas, likely to be the area of subsequent scarring. At all time points, the RPE lies flat against Bruch's membrane (itself not visible) with no signs of CNVM.

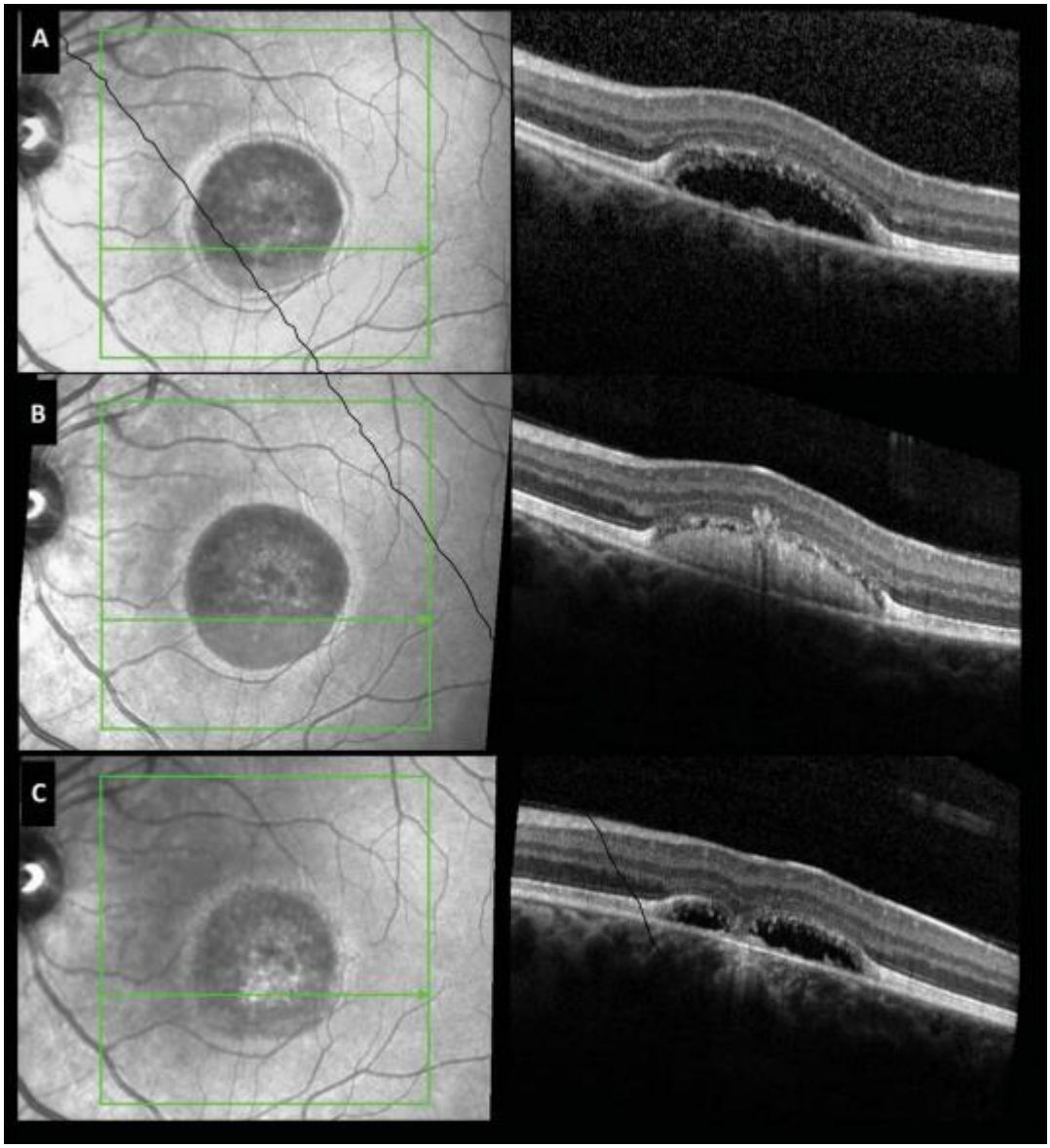
Figure 2. Images from the right eye of Patient 9. *A*, Prior to CNVM development, the RPE lies flat with a shallow foveal detachment. *B*, As the CNVM develops, an irregular RPE elevation becomes evident (white arrow), beneath which Bruch's membrane is now visible. *C*, Signs of active CNVM leakage manifest, with intraretinal fluid, continued presence of subretinal fluid and sub-RPE hemorrhage. This was treated with intravitreal bevacizumab (two injections). *D* and *E*, OCT scans at a later time point showing chronic subretinal fluid superiorly (*D*) and atrophic scarring within the lesion (*E*).

Figure 3. Images from Patient 2 with active neovascular disease in the left eye. *A*, OCT scan taken through the superior part of the lesion demonstrates subretinal fluid (between the RPE and the photoreceptor outer segments), cystic expansion of the ONL so that it merges with the OPL, highlighting fluid probably accumulating between the ONL 'proper' and the axonal component of this layer (Henle's layer) with the OPL band representing the dendritic connections between the photoreceptors and bipolar/horizontal cells. There is also microcystic oedema within the inner nuclear layer. *B*, Scanning at a more inferior location identifies a focal hemorrhagic RPE elevation (arrow), blood within the subretinal space and a small additional bright layer between the subretinal blood and the photoreceptor outer segments themselves immediately below the ellipsoid zone. *C*, OCT scan at a similar location 3 months later. The additional highly reflective layer is now absent. The subretinal space below now contains a broad zig-zag shaped line possibly consistent with delaminating photoreceptor outer segments. *D*, Eight months later the ellipsoid layer is not clearly visible at this same location. *E*, Inferiorly, there is a hypertrophic outer retinal scar and persistence of subretinal fluid.

Figure 4. Images from the left eye of Patient 9 prior to CNVM debvelopment. *A*, Color fundus photograph. *B*, Short wavelength fundus autofluorescence (FAF) image showing hyperautofluorescence of the subretinal deposit. *C*, Fundus fluorescein angiogram (FFA) at 11 s after dye injection. *D*, FFA at 2 min showing staining of the subretinal deposit without clear evidence of active leakage. *E*, OCT image obtained at the same visit.

Figure 5. Subsequent images from the left eye of Patient 9. *A*, *B*, *C*, OCT scans taken 2 months later when the patient developed further symptoms, showing elevation of the RPE with possible breach of this layer (arrow in *A*), haemorrhage and inferiorly disruption of the photoreceptor outer segments, possibly resulting from subretinal fluid. *D*, FAF image shows that this is associated with loss of short wavelength autofluorescence within the lesion and a reduction in autofluorescence inferior to the lesion (associated with photoreceptor disruption). This eye did not undergo treatment. *E*, FAF image 4 years later showing that the inferior hypoautofluorescence is maintained. *F*, OCT scan at the same location suggests some restoration in outer retinal architecture. *G*, OCT through the lesion at the same visit.

Figure 6. Images from a patient diagnosed with ARB showing subretinal and intraretinal fluid in the absence of CNVM. *A* and *B*, OCT scans through the fovea of right and left eye respectively. C and D, OCT scans through locations inferior to the fovea from right and left eye respectively.



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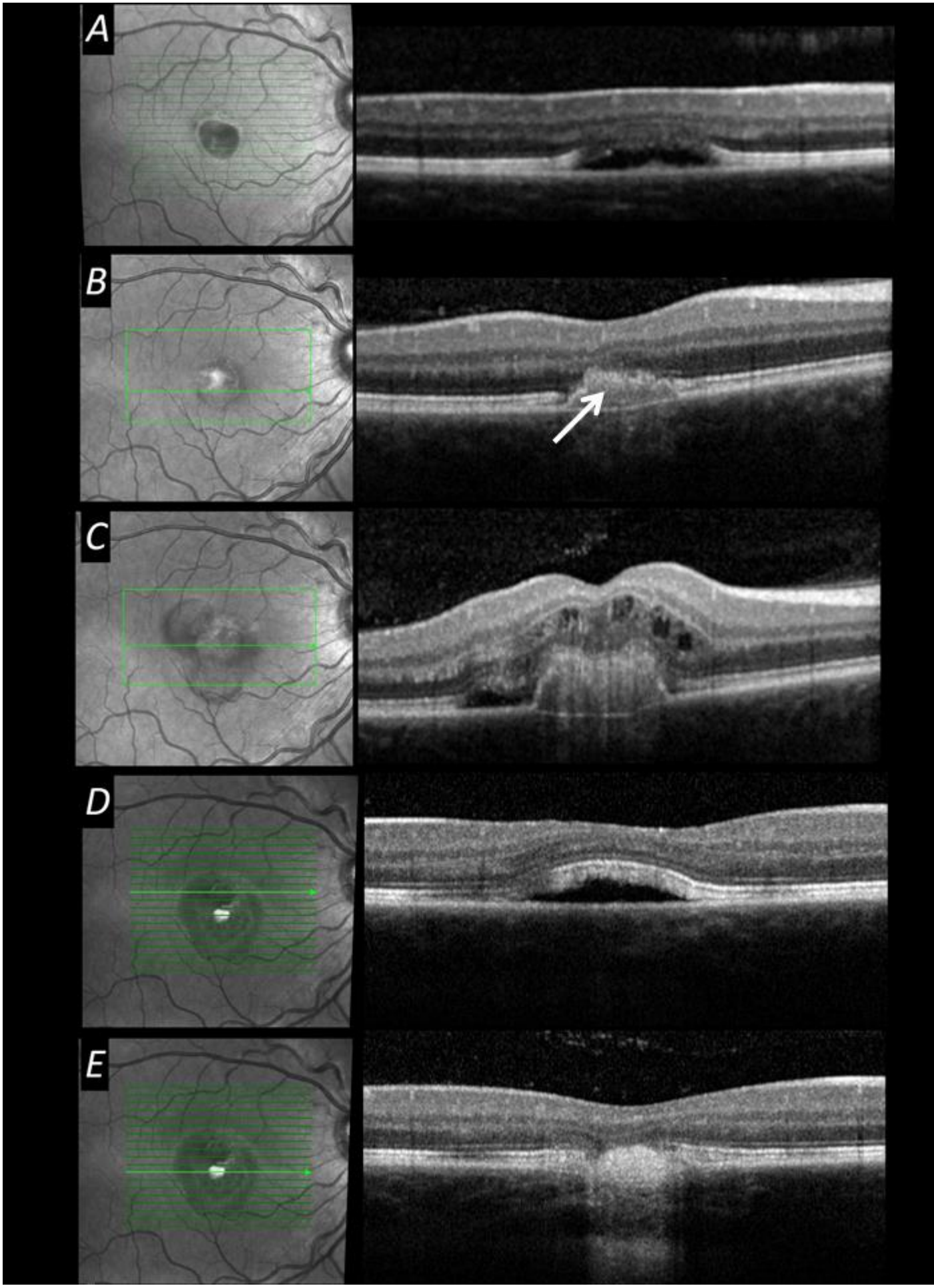
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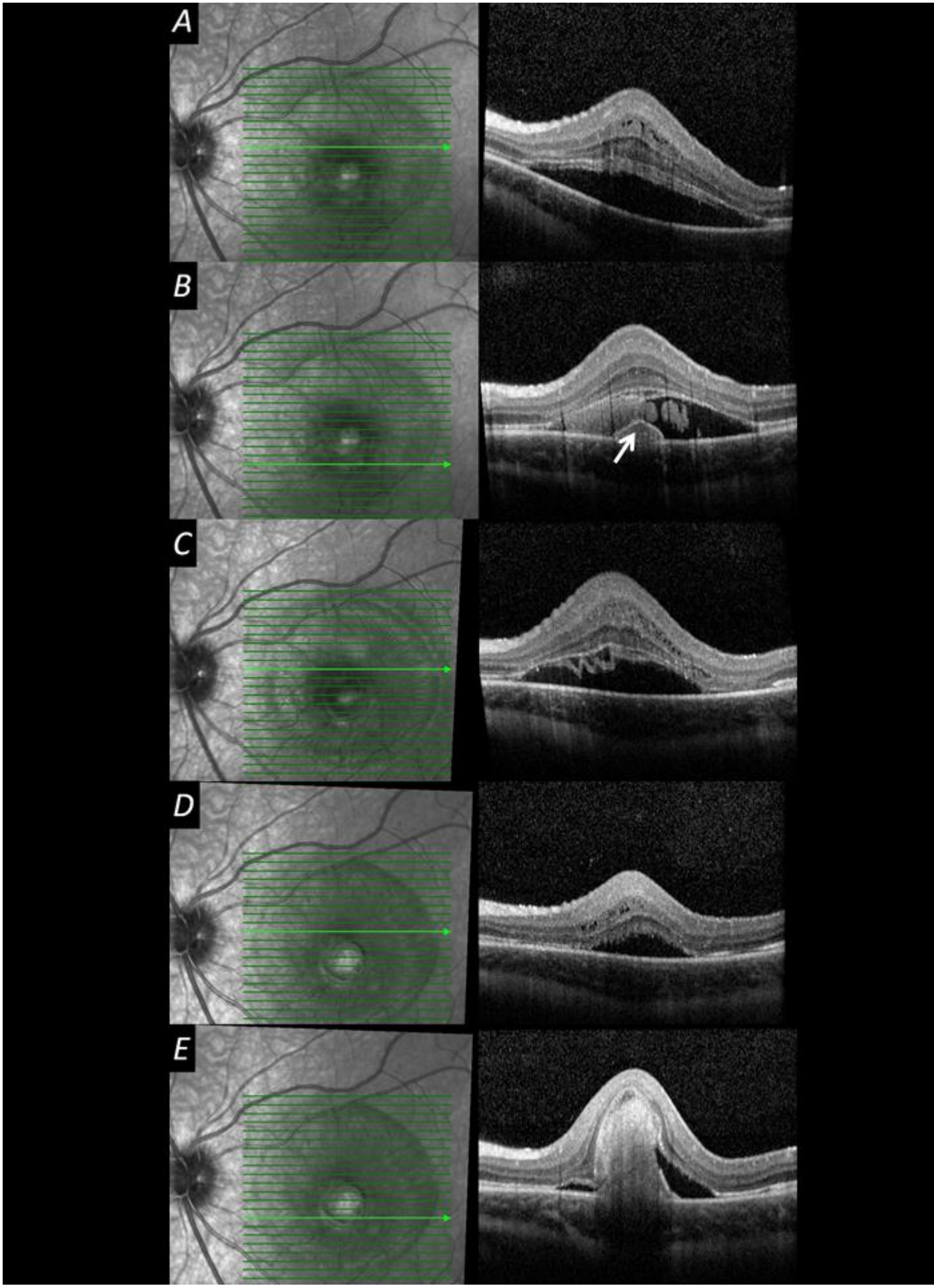
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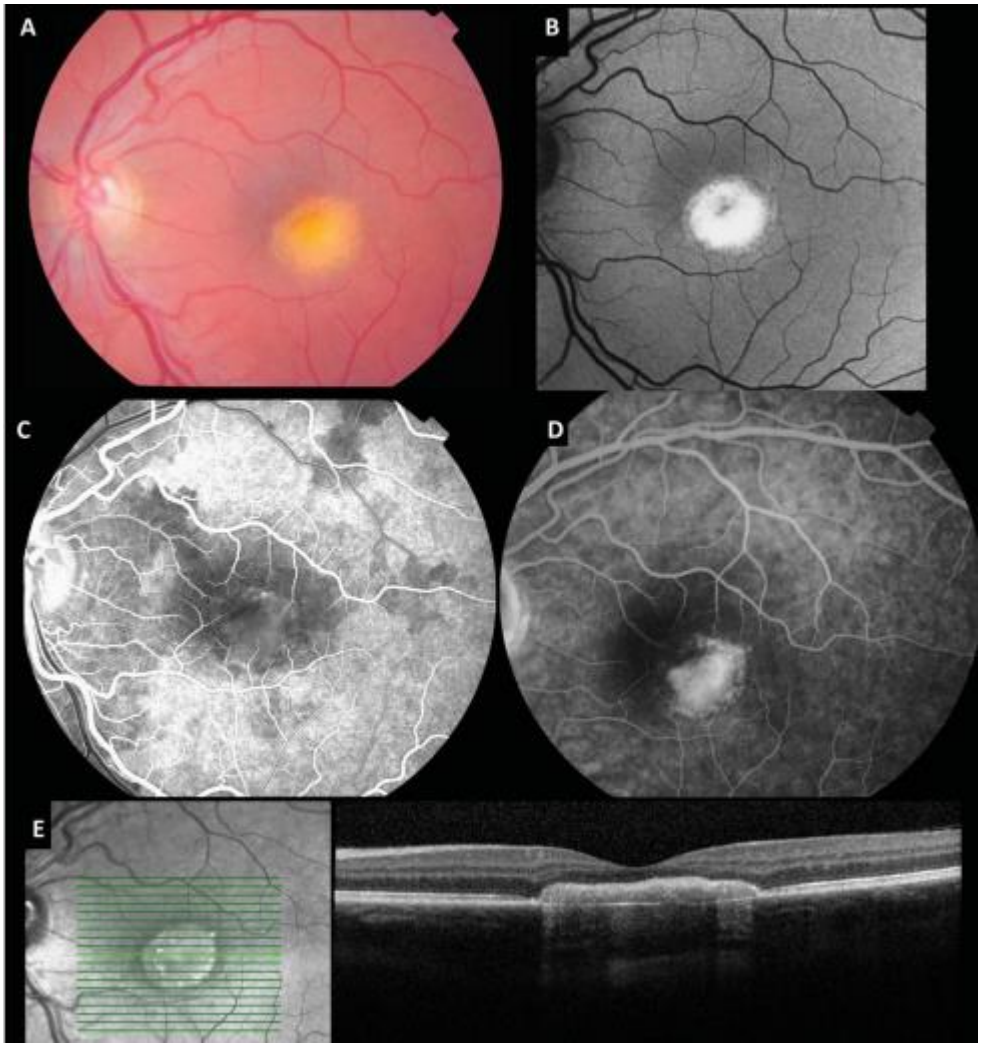

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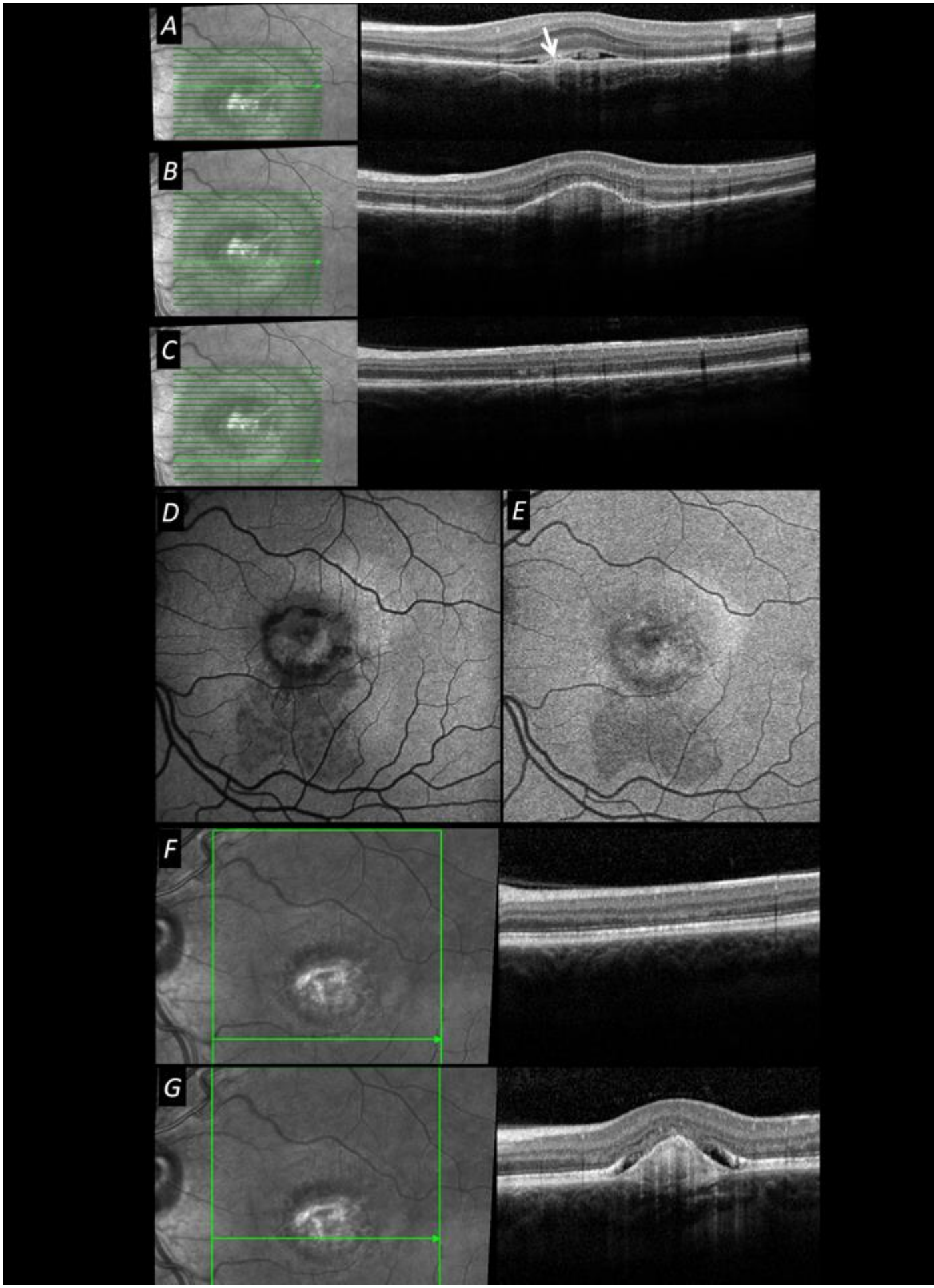
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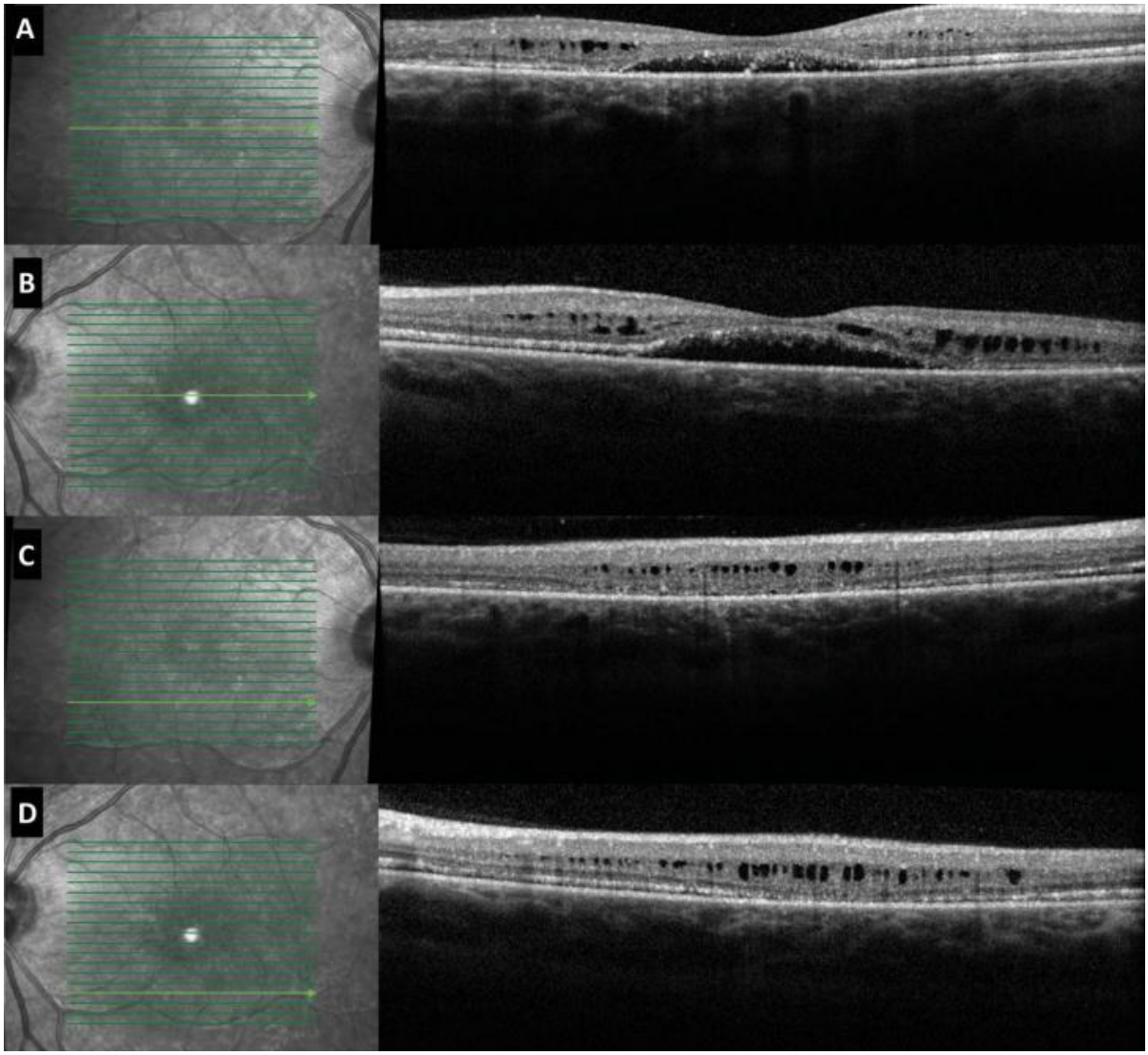

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