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Central posterior hyaloidal fibrosis – A novel optical coherence tomography feature associated with choroidal neovascular membrane

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ABSTRACT

Purpose: To describe a novel optical coherence tomography (OCT) finding at the vitreomacular interface (VMI), and report its association with advanced choroidal neovascularisation (CNV).

Observations: Optical coherence tomography (OCT) scans performed at three retinal imaging centres at Amanat Eye Hospital, Pakistan from May 2016 till May 2021 were reviewed. A specific change at the vitreomacular interface was noted consisting of abnormal hyper reflectivity at the point of attachment of the posterior hyaloid membrane to the foveal center which appears to 'fill in' the foveolar depression.Eight eyes of eight patients were identified. All affected eyes had advanced CNV and persistent vitreofoveolar adhesion. In all eyes, the foveal contour (concavity) was maintained and there was no inner retinal surface wrinkling which differentiates this OCT feature from vitreomacular traction or epiretinal membranes. The authors propose the term Central Posterior Hyaloidal Fibrosis (CPHF) for this specific OCT finding.

Conclusions and Importance: Central Posterior Hyaloidal Fibrosis (CPHF) is a newly reported OCT finding associated with advanced CNV, which may represent a possible profibrotic influence of a choroidal neovascular membrane to the overlying posterior hyaloid adhesion.

1. Introduction

Choroidal neovascularisation (CNV) is the long term consequence of numerous ocular diseases, including but not limited to age related macular degeneration (AMD), high myopia, inflammatory eye disease, angioid streaks and retinal scars (from ocular trauma or retinal laser). Development of CNV invariably leads to significant visual disturbances regardless of the underlying disease. The exact pathophysiology of CNV is poorly understood.[1,2]

Several reports have suggested VMI changes as a possible 'starting point' in the development of CNV[3,4], however, the cause – effect relationship of VMI status with CNV is a longstanding debate.[5] Both vitreomacular adhesion (VMA) and vitreomacular traction (VMT) have been reported to play a role in the development of CNV.[6,7] On the other hand, posterior vitreous detachment seems to reduce the incidence of CNV. It has been proposed that VMA promotes the development of CNV by inducing chronic low-grade inflammation, by maintaining macular exposure to cytokines or free radicals in the vitreous gel or by interfering in *trans*-vitreous oxygenation and nutrition of the macula.[8]

In this case series, we present a novel OCT feature pertaining to vitreomacular interface in eyes with advanced CNV and by analyzing its appearance on optical coherence tomography (OCT) imaging, hypothesize about its relationship to the coexisting CNV.

2. Methods

This is a retrospective observational case series. Retinal imaging centres (affiliated with Amanat Eye Hospital, Pakistan) located in three cities (Islamabad, Rawalpindi and Peshawar) act as referral points for patients in northern Pakistan and perform scans as per requests of referring ophthalmologists. A total of 14564 OCT scans of 8234 patients (performed between May 2016 till May 2021) were reviewed by a

Abbreviations: AMD, Age related macular degeneration; VMI, Vitreomacular interface; VMA, Vitreomacular adhesion; VMT, Vitreomacular traction; CNV, Choroidal neovascularisation; SD- OCT, Spectral domain Optical Choroidal Tomography; CPHF, Central Posterior Hyaloidal Fibrosis.

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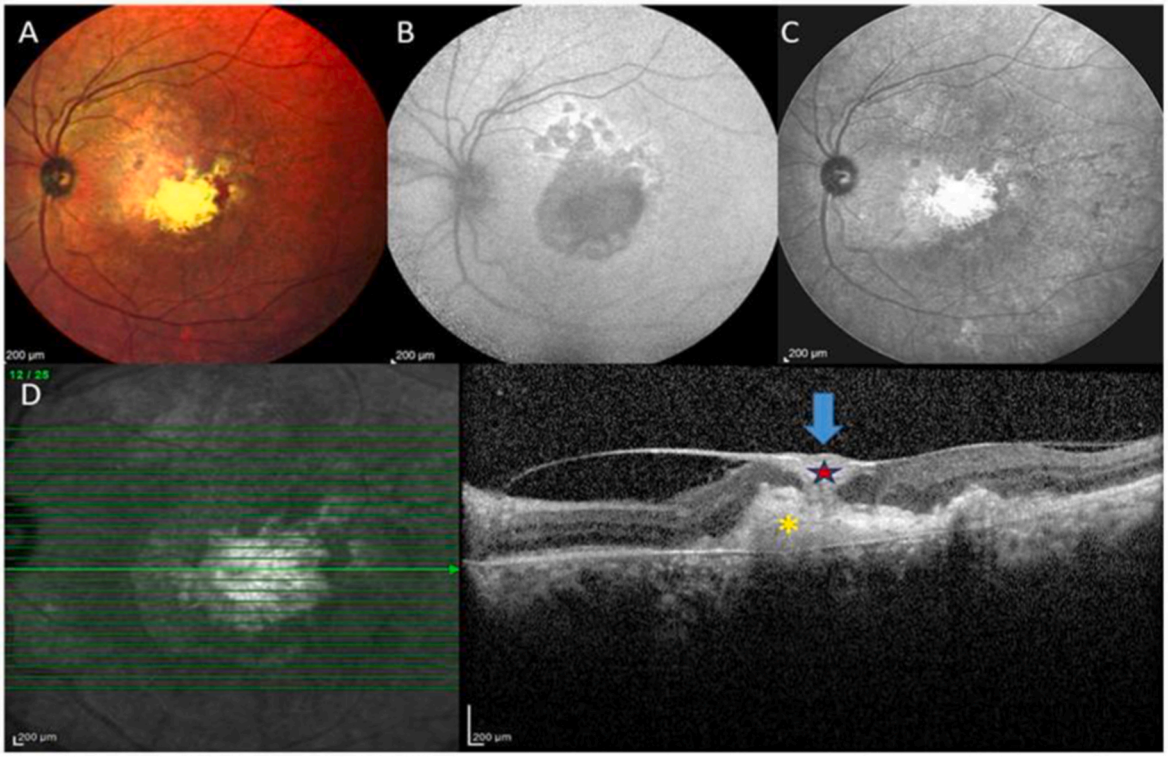

Fig. 1. A) Multicolor image of left eye of Case A shows subfoveal CNV with prominent inner retinal surface fibrosis. B) Fundus autofluorescence image shows RPE atrophy extending beyond the lesion with increased autofluorescence at the margins consistent with AMD. C) Infrared image. D) The horizontal central line scan shows a hyper-reflective subretinal lesion consistent with CNV (*). A partially detached posterior hyaloid membrane with persistent attachment to the foveal center (blue arrow) and abnormal hyper reflectivity leading to a 'filled in' appearance of the foveolar depression (red star). (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

retinal specialist (HK) for the presence of a novel OCT finding, Central Posterior Hyaloidal Fibrosis (CPHF). CPHF was defined as abnormal hyper reflectivity at the point of attachment of the posterior hyaloid membrane to the foveal center that appears to 'fill in' the foveolar depression without affecting foveolar contour (concavity) in the absence of any wrinkling of inner retinal surface (Fig. 1).

824 scans were excluded due to either poor image quality or other pathologies known to influence VRI (Vitreoretinal surgery, macular hole, neurosensory retinal detachment). Eight eyes of eight patients of CPHF were identified for further analysis.

Patient age, gender and clinical history were reviewed from the clinical record. Slit lamp examination findings were studied. OCT data sets as well as fundus images of both eyes of patients was further analysed by three retinal imaging experts (PK, BL and HK) for the presence of CNV and/or other retinal pathologies and for a possible etiology of CNV in these cases. Fluorescein angiography and OCT angiography was additionally performed in 2 cases to confirm choroidal neovascularisation within suspicious subretinal hyper reflective material on OCT. This research adhered to the tenets of the declaration of Helsinki and approval was obtained from the institutional review board.

2.1. Protocol for scan acquisition

Retinal scans were performed using either Heidelberg SPECTRALIS SD-OCT (Heidelberg Engineering, Germany), Optovue AVANTI SD - OCT (Fremont, CA) or TOPCON TRITON Swept Source OCT (Topcon, Japan) depending upon the availability at the specific imaging centre. Macular 6 × 6mm scans centered on the fovea were acquired using fast macular scans protocol (25 horizontal b-scans protocol) on Spectralis. On the Topcon as well as the Optovue OCT systems, the same area of macula was scanned using the 5x5 crosshair and raster protocols.

3. Results

13740 scans were available for interpretation. Eight eyes of eight patients with CPHF were identified. Six out of eight patients were male and two out of eight were female. Mean age was 66.3yrs (range 55–79yrs) [Table 1]. Duration of loss of vision in affected eyes ranged from 24 to 50 months. Visual acuity ranged from 6/60 to hand movement (LogMAR +1.0 to +1.5). Diagnoses ranged from AMD (4 eyes), angioid streaks (1 eye), myopia (1 eye) and idiopathic (2 eyes). Diagnosis of CNV in these eyes was made after taking into account the clinical symptoms, observing the multicolor fundus photographs and review of OCT scans by three retinal experts. In all patients, affected eyes showed clear media (except contralateral eye of one case). Significant central macular fibrosis was first noted on slit lamp examination and then recorded on multicolor fundus pictures. There was no retinal vascular pathology in these eyes and no sign of inflammation. Contralateral eye showed drusen in cases of AMD and other signs as described in Table 1 and Figs. 4 and 5.). Fundus fluorescein angiography was available for the affected eye of case C, which showed an extensive central macular scar showing late staining pattern hyperfluorescence and no apparent leakage. (Fig. 6). OCTA was available to study in the affected eye of case D, which showed abnormal blood flow between the RPE and Bruch's membrane on angioflow and an abnormal network of capillaries on en face OCT corresponding to the subfoveal pigment epithelial detachment on SD OCT (Fig. 7).

Vitreofoveal adhesion was observed in all eight eyes with CPHF. CPHF itself was defined as abnormal hyper reflectivity at the point of attachment of the posterior hyaloid membrane to the foveal center that appears to 'fill in' the foveolar depression In all patients, CPHF was present in only one eye (Figs. 4 and 5) although in one patient, the fellow eye could not be examined or scanned due to mature cataract. CPHF can be distinguished from other VRI abnormalities such as epiretinal

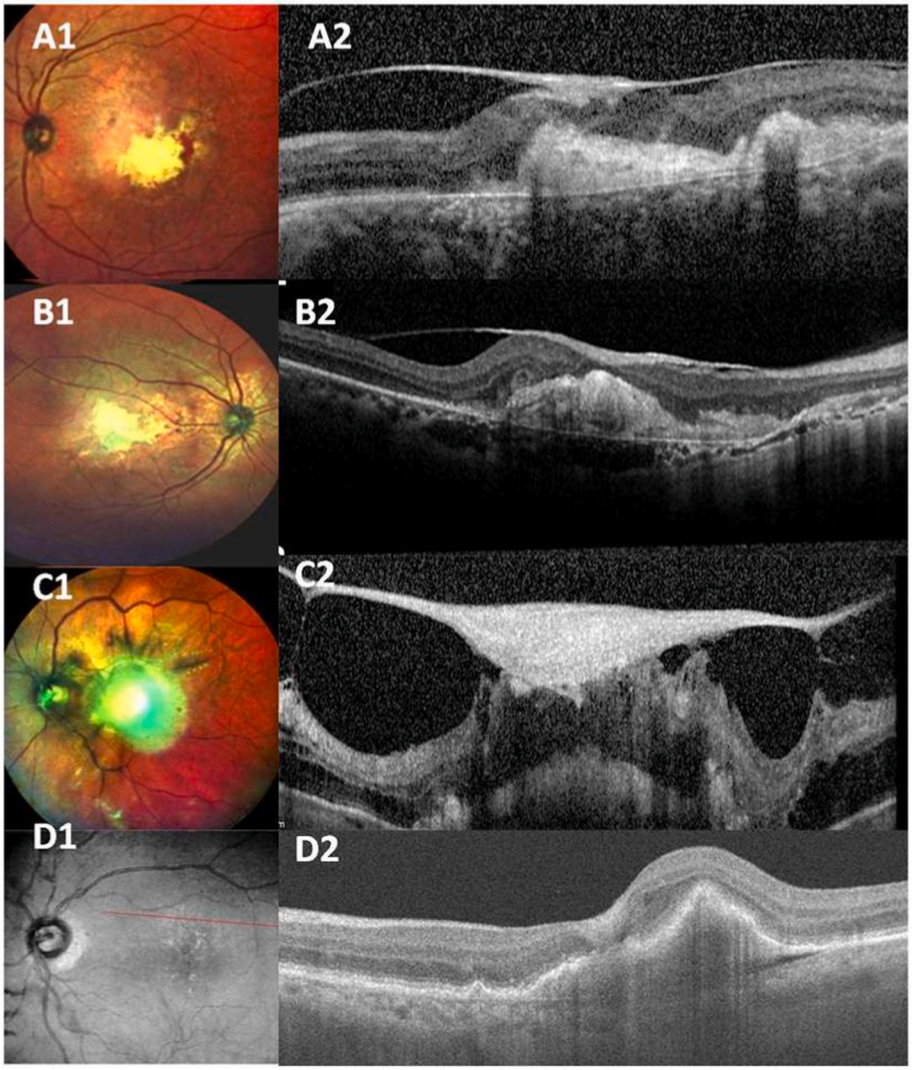

Fig. 2. Multicolor fundus pictures (A1-D1) of affected eyes of cases A-D. A2-D2 shows central line scans with CPHF.

membrane and vitreomacular traction as described below.

In this case series, all eyes with CPHF exhibit a smooth inner retinal outline on OCT despite considerable overlying fibrosis. This feature distinguishes it from epiretinal membranes where even faint membranes tend to cause inner retinal surface wrinkling. Only in case C, focal tenting of distant points is seen in the nasal and temporal peripheral macula-likely secondary to anteroposterior traction from the posterior hyaloid membrane. However the retinal surface within the area of the central vitreofoveal adhesion involved in the CPHF process is smooth. The fovealor contour (concavity) in all eyes with CPHF is maintained despite considerable overlying fibrosis. This feature distinguishes CPHF from cases of vitreomacular traction which usually leads to distortion/obliteration of the foveal concavity in early stages (Fig. 8). In two out of eight cases (F1 and H2) the hyper reflectivity noted within the CPHF was 'non homogenous', although this could not be correlated with any distinct clinical/OCT feature.

Out of the eight eyes identified, two eyes exhibited outer retinal tubulation (Figs. 2 and 3), three eyes showed signs of current activity (intraretinal/subretinal fluid), three eyes were treatment naïve and three eyes had received previous intravitreal anti VEGF treatment. For two out of eight eyes, clinical data regarding treatment was unavailable.

4. Discussion

In this case series, we present a distinct OCT feature, which to the best of our knowledge has not been described in published literature. We propose the term "central posterior hyaloidal fibrosis" (CPHF). The authors theorize that CPHF indicates accentuated fibrosis of the posterior hyaloid membrane at its point of attachment to the foveal center in cases of advanced CNV.

The foveal center may be vulnerable to this process for a number of reasons. Firstly, the fovea is a point of physiologically stronger adhesion of the posterior hyaloid. Studies have established that presence of underlying CNV may enhance this adhesion.[9] Maggio et al. assessed the prevalence of vitreomacular adhesion (VMA) in treatment naive eyes with exudative AMD in comparison with eyes with nonexudative AMD and age-matched controls and were not able to demonstrate any significant difference in the prevalence of VMA in any group. They also reported that there was no difference in the rate of *de novo* CNV development in eyes with or without VMA and found a lower incidence of spontaneous release of VMA over time in eyes affected by exudative AMD. The results of this study suggest that a stronger adhesion of the posterior hyaloid membrane to the foveal center might be a consequence rather than a cause in eyes with CNV, possibly through release of inflammatory mediators. We further speculate that there may be an increase in profibrotic mediators in some eyes with advanced CNV that

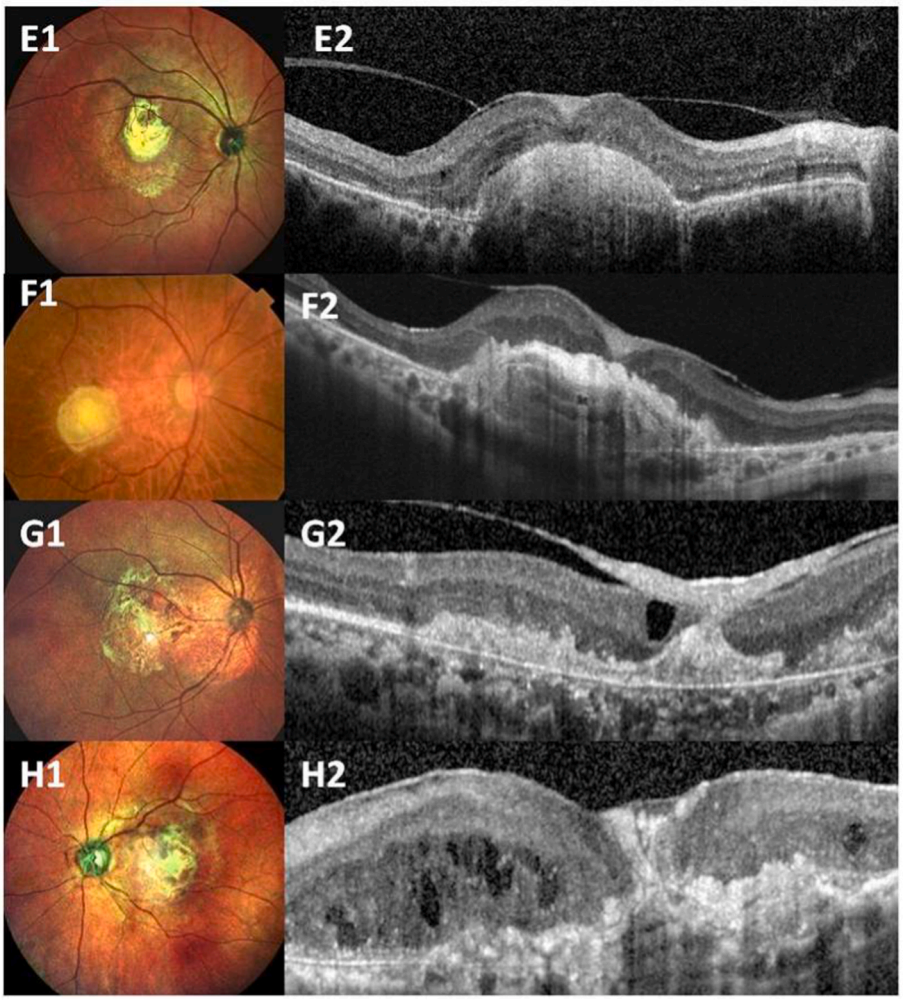

Fig. 3. Multicolor fundus pictures (E1-H1) of affected eyes of cases E-H. E2-H2 shows central line scans with CPHF.

may cause this unusually adherent posterior hyaloid to thicken at the foveola resulting in "filling in" of foveolar depression. It is also possible that the cases described here are extreme examples of a more common interaction of the neovascular process with the vitreomacular interface, which could potentially be relevant to the clinical course of this common sight-threatening condition. Additionally, the physiological extrusion of inner retinal layers at the fovea makes it the thinnest point in the macular area. This may further facilitate a bidirectional transretinal transport of proinflammatory/profibrotic mediators between the CNV lesion and the inner retinal surface.

In addition to the biochemical aspect of this phenomenon, there may also be a mechanical influence. Tsunoda et al.[10] first described outer retinal changes in the OCT scans of cases with vitreomacular traction (ERM and VMT) namely the 'cotton ball sign' and hypothesized that these may be due to inward traction at the fovea. Sarraf et al. then elaborated a central bouquet of Muller cells at the fovea and postulated that they might be responsible for transmitting forces from vitreofoveal adhesion to the outer retina resulting in anatomical changes and development of OCT features like the cotton ball sign, foveal detachment and a vitelliform lesion.[11] It is possible that as an advanced CNV matures and contracts due to fibrosis, transretinal transmission of forces originating in subretinal space may influence the overlying attached posterior hyaloid.

The mechanical dynamics of CPHF appear distinct from other VMI abnormalities when assessed on OCT. The earliest sign of anteroposterior traction due to VMT is the obliteration/distortion of the normal fovealor depression followed by intraretinal cysts/schisis. In contrast, cases of CPHF described in this case series exhibit thickening of the hyaloid that appears to fill in the foveolar depression rather than obliterate it and no macular schisis or macular detachment was seen. Other VMI abnormalities such as epiretinal membranes and taut posterior hyaloid membranes seen in diabetic maculopathy tend to present with inner retinal surface wrinkling early in the disease. Despite considerable thickening of the posterior hyaloid, CPHF does not exhibit this wrinkling (Fig. 8).

VMI status in cases of CNV has been seen to affect the response to anti VEGF treatment mainly due to the tractional effect that would resist resolution of underlying intraretinal edema.[12,13] However, given the retrospective nature of this case series, we were not able to statistically analyse any such influences.

This study lacks longitudinal analysis. All cases included in this case series had CPHF on presentation and previous scans were not available. Serial scans ranging from few weeks to few months showed no frank change in OCT features. These patients were counseled regarding the visual prognosis and no treatment was offered for this retinal condition. Further avenues for research would include isolating features of CNV that may encourage the process of CPHF and to study the relationship/impact of this change on anti VEGF treatment. Studies are needed to support the hypothesis that CPHF is an abnormally accentuated fibrotic process. To this end it would be valuable to undertake analysis of cytokine profile from vitreous biopsies in such cases and, if possible, comparative histological analyses of the posterior hyaloid face in the presence and absence of CPHF.

Table 1
Clinical Summary of patients with central hyaloidal fibrosis (affected eyes are shaded grey).

Case no.	Gender	Age (yrs)	OCT findings OD with possible diagnosis	OCT findings OS with possible diagnosis	Visual Acuity		Treatment given to affected eye	Vitreoretinal interface in affected eye
					OD	OS		
1	F	58	Reticular pseudodrusen (Non exudative AMD)	Advanced CNV with fibrosis (exudative AMD)	20/25	20/200	Treatment Naive	Partial PVD with persistent VMA
2	M	56	CNV with fibrosis (cause unknown)	Dense Cataract /No view	CF 3m	NA	Multiple intravitreal inj Bevacizumab	Partial PVD with persistent VMA
3	F	78	Drusen (Non exudative AMD)	Advanced CNV with fibrosis (exudative AMD)	20/30	HM	Treatment Naïve	Partial PVD with persistent VMA
4	M	69	Drusen/ no RPE atrophy (Non exudative AMD)	Advanced CNV (exudative AMD)	20/40	20/200	Multiple Ranibizumab injections	No PVD
5	M	55	CNV with fibrosis (cause unknown)	No abnormality detected	20/100p	20/20	Intravitreal Ranibizumab injections	Partial PVD with persistent VMA
6	M	79	Advanced CNV with scarring (possibly myopic CNV)	SHREM with small hemorrhage (Small CNV / coin hemorrhage)	CF 1m	20/60	Treatment Naive	Partial PVD with persistent VMA
7	M	59	CNV with scarring (AMD?/ inflammatory?)	Submacular fibrosis	CF 2m	CF 2m	Not known	Partial PVD with persistent VMA
8	M	76	Advanced fibrotic CNV (exudative AMD)	Advanced fibrotic CNV (Exudative AMD)	CF 1m	HM	Not known	Partial PVD with persistent VMA

AMD= Age related Macular Degeneration, CNV = choroidal nevascularisation, PVD= Partial Vitreous Detachment, VMA= Vitreo-Macular Adhesion, RPE= Retinal Pigment Epithelium, F= Female, M= Male, HM= Hand movement, CF= Counting Fingers

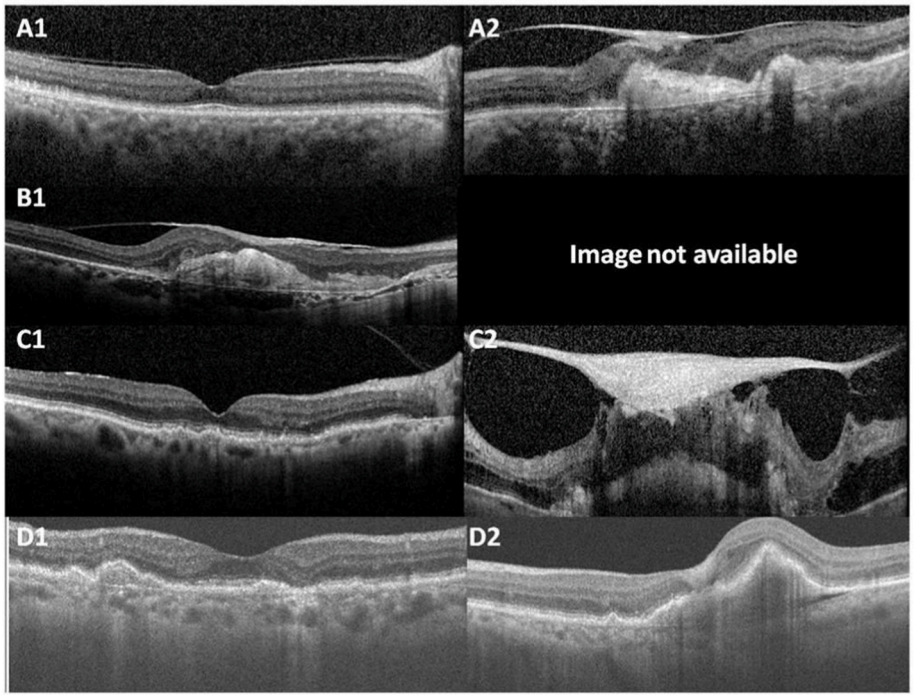

Fig. 4. Composite picture showing involved (A2, B1, C2, D2) and fellow eyes of cases A-D (A1, B2, C1, D1).

5. Conclusion

In this study we have presented a series of patients describing a novel OCT feature seen exclusively with advanced CNV, a phenomenon we have termed central posterior hyaloidal fibrosis (CPHF). This may represent a possible profibrotic influence of CNV on the overlying VMI. Furthermore, it supports earlier theories of transretinal biochemical as well as mechanical communication.

Patient consent

Written consent was obtained from all patients to use their data for

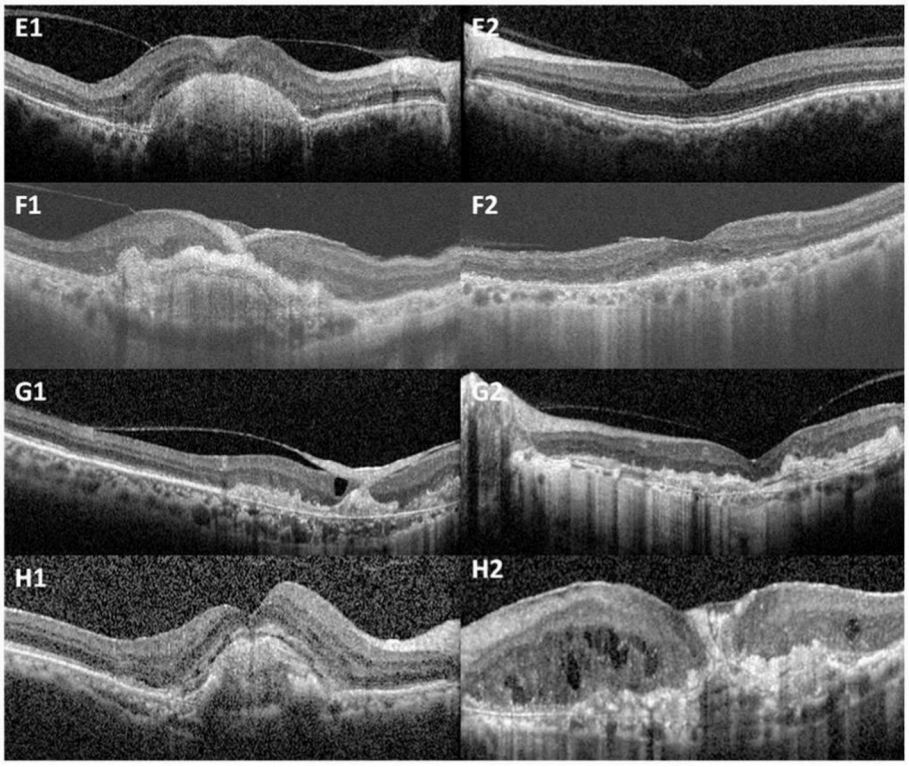

Fig. 5. Composite picture showing involved (E1,F1,G1,H2) and fellow eyes of cases E-H (E2,F2,G2,H1).

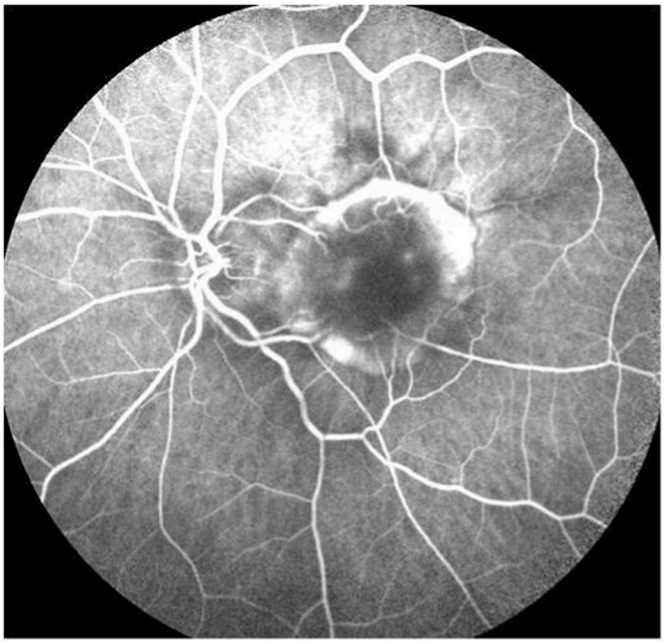

Fig. 6. Fundus fluorescein angiography of the affected eye of case C, indicating an extensive central macular scar showing late staining pattern hyperflourescence and no apparent leakage.

this case series. Prior approval was obtained from the institutional review board for this case review.

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Disclosure

All authors have no financial disclosures.

Intellectual property

We confirm that we have given due consideration to the protection of intellectual property associated with this work and that there are no impediments to publication, including the timing of publication, with respect to intellectual property. In so doing we confirm that we have followed the regulations of our institutions concerning intellectual property.

Research ethics

We further confirm that any aspect of the work covered in this manuscript that has involved human patients has been conducted with the ethical approval of all relevant bodies and that such approvals are acknowledged within the manuscript.

IRB approval was obtained (required for studies and series of 3 or more cases).

Written consent to publish potentially identifying information, such as details or the case and photographs, was obtained from the patient(s) or their legal guardian(s).

Authorship

All listed authors meet the ICMJE criteria.
We attest that all authors contributed significantly to the creation of this manuscript, each having fulfilled criteria as established by the ICMJE.

We confirm that the manuscript has been read and approved by all named authors.

We confirm that the order of authors listed in the manuscript has been approved by all named authors.

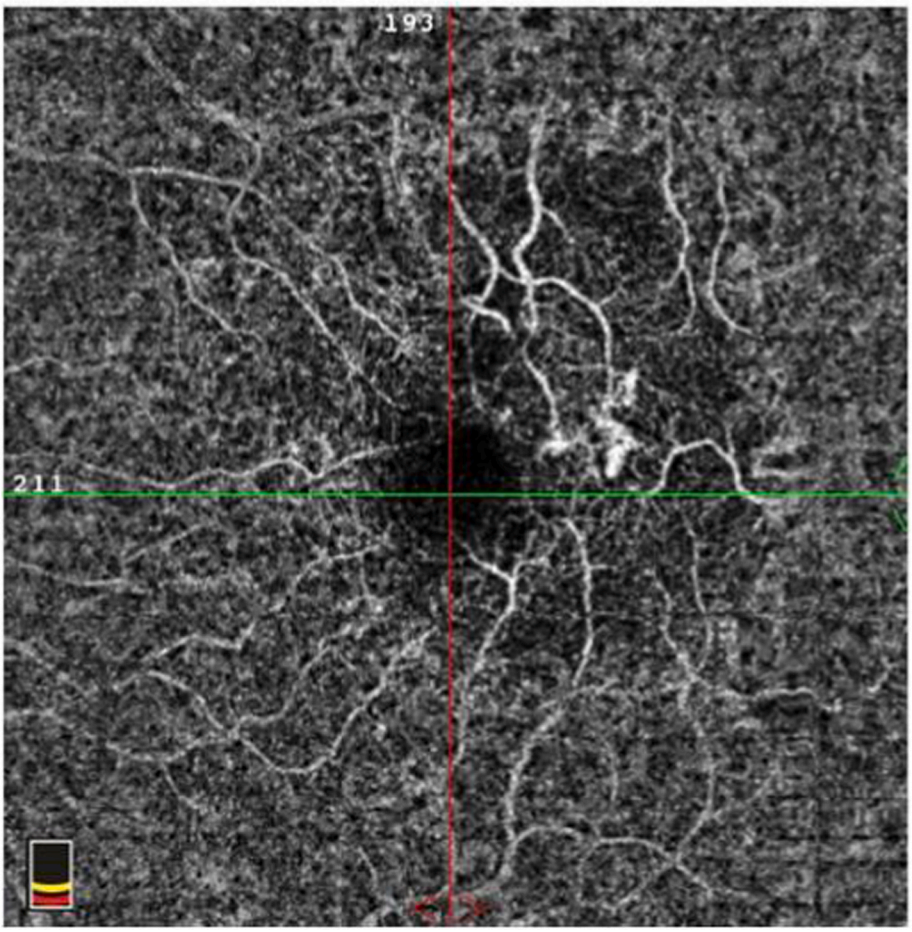

Fig. 7. OCT angiography of affected eye of case D, showing an abnormal blood flow between the RPE and Bruch's membrane on angioflow and an abnormal network of capillaries on en face OCT corresponding to the subfoveal pigment epithelial detachment on SD OCT.

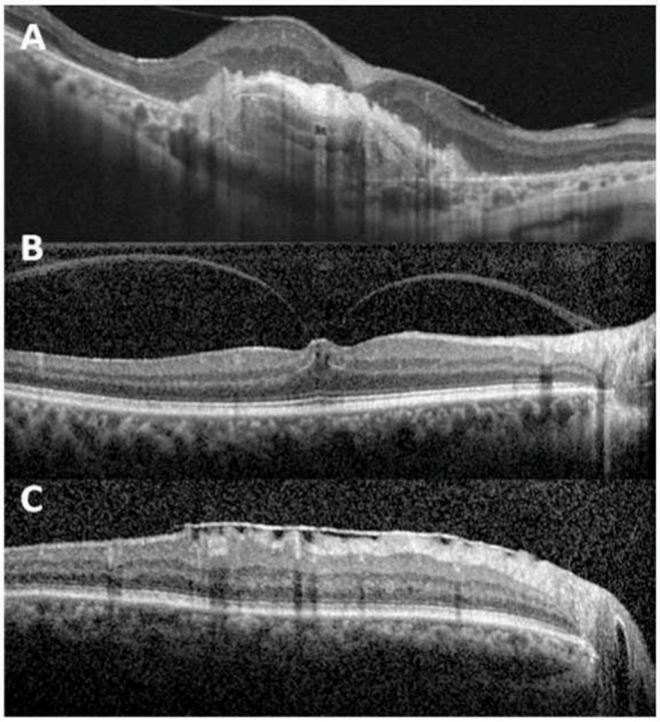

Fig. 8. Comparison of anatomical features of eyes with CPHF (A), VMT (B) and ERM (C). Lack of inner retinal surface wrinkling and maintenance of the foveolar concavity distinguish CPHF from other VMI variations.

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Author contributions

All authors attest that they meet the current ICMJE criteria for authorship. The individual author contributions are as follows. Hina Khan: Conceptualisation, data curation, RA analysis, Methodology, Project administration & supervision and write up. Rida Amjad: Software, write up. Pearse A Keane: Data analysis, Alastair K Denniston: Methodology and write up (original draft), Brandon J Lujan: Data Analysis, Write up Review and Editing.

Declaration of competing interest

The authors declare no conflict of interest.

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