Original Article

Lateral elongation of flat irregular pigment epithelial detachment: A novel optical coherence tomography biomarker in polypoidal choroidal vasculopathy

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Purpose: To explore novel Optical Coherence Tomography (OCT) biomarkers and precursor lesions in Polypoidal Choroidal Vasculopathy (PCV). **Methods:** This retrospective cohort study included 76 treatment naïve fellow eyes of PCV. Focus was given to analyse the various morphological changes in the clinically unaffected fellow retina during the follow-up period. **Results:** 11 fellow eyes (14.47%) developed disease activity in the form of Sub Retinal Fluid (SRF) or Intra Retinal Fluid (IRF) within a mean follow-up of 17 months. All 11 eyes (100%) showed the presence of flat irregular pigment epithelial detachment (FIPED) and a peculiar property of lateral elongation of FIPED during disease activity. A positive correlation with the disease progression was found for the same ($P < 0.0001$). The mean horizontal dimension of the flat irregular PED at the enrolment was 1984 ± 376u and the mean expansion of FIPED at SRF formation was 461 ± 152u. ICG taken at the time of disease activity in the fellow eye revealed branching vascular network (BVN) in 9 (81.8%) eyes, polyps in 7 (63.6%) eyes, a combination of both in 5 (45.4%) eyes. Type one BVN with interconnecting channels showed faster disease progression than type two BVN. Eye tracking ICG illustrated that BVN corresponded to the FIPED in OCT and polypoidal lesions developed at the end of expanding FIPED. **Conclusion:** Flat irregular pigment epithelial detachment with its characteristic property of lateral elongation may be considered as a precursor lesion for PCV and as a novel OCT biomarker for the disease activity. Fellow eyes with FIPED need close monitoring to identify development of disease activity at the earliest.

Key words: Branch vascular network, flat irregular pigment epithelial detachment, lateral elongation, polypoidal choroidal vasculopathy

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Polypoidal Choroidal Vasculopathy (PCV) can manifest as a sudden exudative maculopathy or haemorrhagic maculopathy or as a combination of both.[1] PCV adheres to the tomographical features of pachychoroid spectrum including a thick choroid on enhanced depth imaging, dilatation of outer choroidal vessels in the Hallers layer (pachyvessels) associated with focal attenuation and compression of the choriocapillaries and the middle choroidal vessels in the Sattler layer.[2]

The disease is highly prevalent in Asian population. Clinic-based case studies have shown the proportion of PCV based on Indocyanine green angiography (ICG) findings is between 20% and 60% in Asian population and between 8% and 13% in European patients.[3-6] Pooled prevalence of PCV in white patients with exudative Age-related Macular Degeneration (AMD) is 8.7%.[7] Polypoidal choroidal vasculopathy is not so rare, it is thought to be in 1 out of 11 patients of diagnosed exudative AMD.[7]

One of the most common differential diagnosis of PCV is exudative or wet Age Related Macular Degeneration. Soft confluent drusens and reticular pseudo drusens are the known precursors of wet AMD.[8] The significance of presumptive risk factors of PCV has not been clearly addressed till now. Identifying the precursor lesions might contribute to comprehend the pathophysiology of PCV. Studying the contralateral eye of unilaterally active PCV patients might be one of the measures to investigate the precursor lesions, because the probability of contralateral involvement is higher than the probability of normal age-matched person developing PCV.[8-10] The aim of the current study was to explore novel Optical Coherence Tomography (OCT) biomarkers and precursor lesions in Polypoidal Choroidal Vasculopathy (PCV).

Methods

We retrospectively analysed the electronic medical records of patients diagnosed with unilateral polypoidal choroidal vasculopathy who presented to our institute between June 2013 and May 2017. Approval from the ethics committee review board was obtained. The research followed the tenets of the Declaration of Helenski. Ethics committee approval obtained on 19 July 2017.

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Study eyes were the uninvolved treatment naïve contralateral eyes of PCV with a minimum follow-up of one year. Diagnosis and case selection of PCV was made purely based on Everest criteria. Bilateral involvement at the time of enrolment were excluded from the study.

Focus was given to analyse the various morphological changes in the clinically unaffected contralateral retina during the follow up period. SDOCT features including the retinal Pigment Epithelial Detachment (PED), Ellipsoid Zone (EZ) disruption, subretinal deposits, subretinal fluid were analysed. The pigment epithelial detachment profile was studied. PED were classified into serous PED (an area of sharply demarcated, dome-shaped serous elevation of the retinal pigment epithelium), drusenoid PED (bumpy RPE elevations with uniform hyper reflectivity within the elevated RPE), flat irregular PED (shallow detachment of the RPE from bruchs membrane with a partial or complete hyperreflective fill gap in between with a minimum horizontal and maximum vertical dimension of 500 microns and 100 microns respectively). The horizontal and vertical dimensions of the PED was measured in each follow-up. Development of subretinal fluid in any macular section was noted and its relationship to the PED was noted. Choroidal thickness was measured using the inbuilt caliper as the distance from the outer portion of hyperreflective RPE to the inner portion of hyperreflective zone corresponding to the sclerochoroid junction in the enhanced depth imaging. In the same image, pachyvessels were noted and the dimensions were measured.

Morphology of the choroidal vasculature was studied using ICG angiography which was repeated at the time of disease activity in the other eye. The presence of polyps, pulsatility, branching vascular network (BVN), choroidal hyperpermeability, and late geographic hypercyanescence on ICGA were looked for. Active polyp was defined as nodular hypercyanescence appearing within first 6 minutes with a surrounding hypohalo and leak in Fluorescein Angiogram (FFA). Quiescent polyps were defined as nodular hypercyanescence without a leak in FFA. Typically the early phase of the ICG angiogram (First one minute) reveals a distinct network of vessels within the choroid, called as Abnormal/Branching Vascular Network (AVN/BVN). The evidence based guidelines defined 2 types of Branching vascular network; Type 1 defined as "Abnormal vascular network appearing within 1 minute of dye injection in the presence of feeder vessel". Type 2 BVN as only interconnecting channels or indistinct network without a feeder vessel.[11,12] Late Geographic Hyperfluorescence (LGH) was defined as a hyperfluorescent lesion with clearly demarcated geographic margin, 10 min after the injection of ICG dye with a rosette-pattern and these strongly support the diagnosis of PCV.

Disease activity in the contralateral eye was considered when subretinal fluid (SRF) or intraretinal fluid (IRF) develops in the macular scan compared to the previous quiescence phase. Any morphometric changes in the inner or outer retina and choroidal vasculature during this transformation phase were analysed and dimensions were measured.

Statistical analysis

The data obtained from the patients were recorded and analysed. Results relating to categorical variables were expressed as counts and percentages. Two proportion Z test was used to find the difference in the two proportions. The results were considered statistically significant if P value < 0.05.

Results

Demographic characteristics: Refining through the inclusion-exclusion criteria, 76 treatment naïve fellow eyes of polypoidal choroidal vasculopathy were enrolled in the study. The mean age of the study group was 64.4 ± 5.7 years (range being 52-78 years). Female sex predilection was noted in the sex ratio 3:2. There were 51 females (67%) and 25 males (33%) in the study. The mean follow-up duration was 34 months.

Out of the 76 contralateral eyes, 11 eyes (14.47%) developed disease activity in the form of subretinal or intraretinal fluid. This amendment happened before the clinical onset of exudative or haemorrhagic maculopathy in all cases. The mean duration between the quiescence phase and the development of fluid in the subretinal space was about 15 months (range being 6-22 months). The changes in these 11 eyes will be given importance in the present study [Table 1].

SDOCT findings

Outer retinal layer analysis

At initial examination, SDOCT revealed Pigment Epithelial Detachment in 26 eyes. Of which 11 eyes had flat irregular pigment epithelial detachment (FIPED). 10 eyes had serous PED and 5 eyes had drusenoid PED. Of which the presence of subretinal fluid was found in all the eyes with flat irregular pigment epithelial detachment (P value <0.0001). The mean length of the detachment at the initial examination was 1984 + 376u. All of these cases showed a lateral expansion or increase in the horizontal dimension of the detachment when disease activity was detected by the presence of subretinal fluid in the follow up scans. Mean lateral expansion of flat irregular detachment from the quiescent phase to SRF formation was around 461 ± 152u in a mean duration of 15 ± 6 months. The mean lateral dimension of the flat irregular detachment at the time of disease activity was 2336 ± 228u. The flat irregular detachment was associated with an overlying focal ellipsoid zone disruption in 7 eyes. Flat irregular PED were mostly extrafoveal and superior in location.

Choroidal morphology analysis on SD OCT

The mean subfoveal choroidal thickness of the study population by enhanced depth imaging was 352 ± 74u. On subgroup analysis, the mean subfoveal choroidal thickness on the disease activity group (n = 11) was 347 ± 45u. 80.26% (61 eyes) showed presence of pachyvessels. All the 11 eyes (100%) with disease activity had pachyvessels at initial examination. On the subgroup analysis on eyes with disease activity, the mean diameter of the largest subfoveal pachyvessel was 147 + 35u. On follow-up examinations, the size of the pachyvessels showed a statistically significant increase in size on the eyes which later developed disease activity. The mean diameter increased from 147 + 35u to 172 + 46u. (P < 0.002). Pachyvessels at the flat irregular PED measured 144 + 31u at the time of initial examination which increased to 185 + 28u. (P < 0.002). In eyes with disease activity, the dimension of pachyvessels at flat irregular pigment epithelial detachment was found to more than that of subfoveal and extrafoveal foci. Two eyes showed increased peripapillary choroidal thickness with peripapillary pachyvessels. In those eyes, the subfoveal

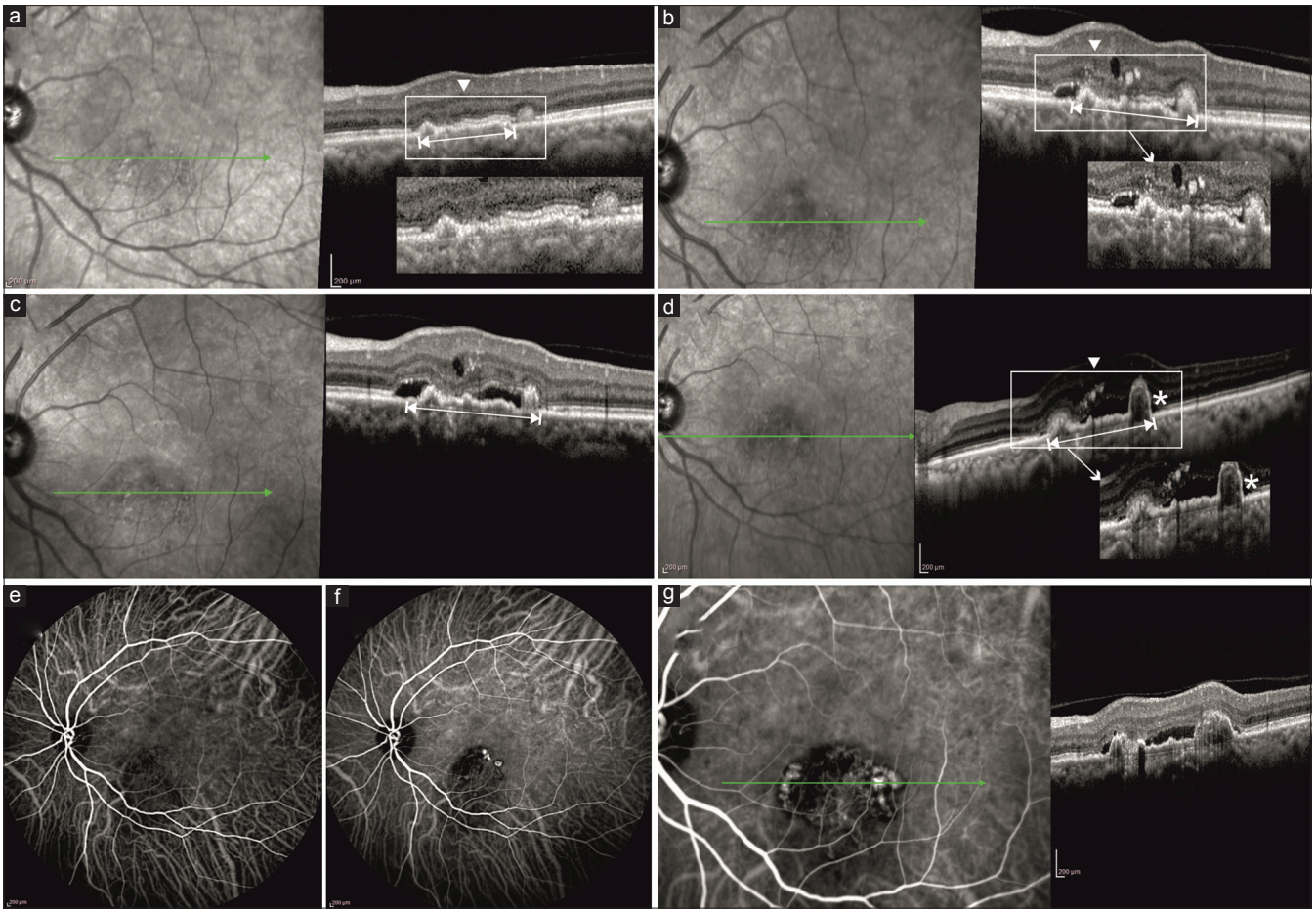

Figure 1: Sequential SDOCT demonstrating the gradual expansion of Flat irregular pigment epithelial detachment (FIPED) in the unaffected fellow eye of 63-year-old female diagnosed as PCV (a) SDOCT imaging showing a FIPED located inferior to fovea measuring 1535u. (b and c) 6th, 8th month followup OCT showing lateral expansion by 127u and 428u with SRF, IRF formation. (d) Asterisk showing Polypoidal lesion developing at the end of FIPED. (e) ICG at 3rd month shows normal circulation. (f and g) 8th month ICG and Eye tracking ICG shows polyp with type 1 BVN with a feeder vessel; BVN corresponding to the FIPED

choroidal thickness (329 ± 26u) was found to be lesser than the peripapillary choroidal thickness (361 + 32u).

Indocyanine green angiography analysis

Since ICG had been performed only when clinically indicated, the time interval between dye angiography and OCT was not controlled. Initial ICG examination revealed polyp in 7 eyes and BVN in 9 eyes. A combination of BVN and polyps were found in 5 fellow eyes. The presence of a nodular hyper which appears within early frames of ICG with a surrounding hypohalo suggestive of active polyp was noted in 2 fellow eyes with disease activity. Early nodular hyper without a surrounding halo and absence of leak in fluorescein angiography was noted in 5 fellow eyes. The distinct network of vessels Branching vascular network (BVN) appearing within very early frames of ICG recorded in dynamic ICG was found in 9 fellow eyes. 7 eyes in our series had type 2, or the BVN without feeder vessel. In one case, the ICG turned out to be inconclusive. Nevertheless, some of the contralateral eyes without disease activity showed the presence of choroidal hyperpermeability and late geographical hypercyanescence (LGH). Choroidal hyperpermeability was noted in 11 eyes (16.92%), LGH in 13 eyes (17.2%), dilated choroidal vessels at posterior pole in 19 eyes (25.1%).

Eye tracking ICG revealed that the branching vascular network corresponded to the area of the flat irregular PED and polyps developed at the end of expanding flat irregular PED. Type 1 BVN with interconnecting channels showed faster progression of SRF formation; mean duration being 8 ± 4 months whereas Type 2 BVN without interconnecting channels showed a slow progression of disease activity; the mean duration being 15 ± 6 months. ($P < 0.001$) [Figs. 1-3]. One of the pivotal observation was the absence of clinical exudation or haemorrhage or serosanguniopathy in the eyes between the quiescent phase and disease activity.

Discussion

Since 1982, the first reporting of polypoidal choroidal vasculopathy by Dr.Yanuzzi, the disease has been understood way farther. Although it has been first described as a variant of choroidal neovascularisation, now it is clearly understood that the disease is a part of pachychoroid spectrum and supposedly arises from the changes in the inner choroidal vascular layers.[13-15] Till date, the disease is not understood in totality, and the precursor lesions have still not been addressed. Our study was to elucidate any such precursor lesions so that the underlying pathophysiology could be made much easier and

Table 1: Baseline, Demographic and Morphometrical Data of the Eleven Fellow Eyes with Early Disease Activity

Patient	Age	Sex	BCVA at the time of enrolment	BCVA at the time of disease activity	FIPED at quiescent phase (μ M)	Location of FIPED	FIPED (μ M) at the time of disease activity	EZ disruption	Subfoveal largest pachyvessel	Largest pachyvesselat the FIPED	Duration to disease activity (Months)	BVN	Polyp	EDI subfoveal	SRF	IRF	CVH
1	68	M	20/25	20/30	2793	Superior	3226	Yes	156	145	19	Type 2	No	429	Yes	No	Yes
2	69	M	20/20	20/20	1008	Superior	1123	Yes	134	163	11	Type 2	Yes	280	Yes	No	Yes
3	64	F	20/40	20/40	2210	Inferior	2592	No	123	98	9	Type 1	Yes	298	Yes	Yes	Yes
4	56	F	20/20	20/25	1986	Peripapillary	3257	No	99	136	13	Type 2	Yes	331	Yes	Yes	Yes
5	63	F	20/30	20/30	2277	Superior	2385	No	164	153	14	Type 2	No	365	Yes	No	Yes
6	55	M	20/20	20/20	1510	Inferior	1824	Yes	178	97	18	Type 2	No	349	Yes	Yes	No
7	53	F	20/30	20/40	1764	Superior	1998	Yes	81	143	15	NIL	Yes	297	Yes	No	No
8	75	F	20/25	20/30	1535	Inferior	1662	No	131	121	6	Type 1	Yes	357	Yes	Yes	Yes
9	57	M	20/30	20/30	2347	Superior	2668	Yes	89	126	20	Type 2	No	396	Yes	Yes	Yes
10	67	F	20/25	20/30	2440	Superior	2751	Yes	142	140	15	NIL	Yes	435	Yes	No	Yes
11	57	F	20/20	20/20	1957	Peripapillary	2235	Yes	96	124	22	Type 2	Yes	279	Yes	Yes	Yes

BCVA=Best corrected visual acuity; FIPED=Flat irregular pigment epithelial detachment; EZ=Ellipsoid zone; BVN=Branching vascular network; EDI=Enhanced depth imaging; SRF=Subretinal fluid; IRF=Intraretinal fluid; CVH=Choroidal vascular hyperpermeability

Figure 2: Sequential SDOCT imaging in a 68-year-old female (a) SD OCT illustrating a FIPED of 2277u. Zoomed image illustrates partially hyperreflective fill FIPED with focal loss of ellipsoid zone. Note the large hallers layer vessels (arrows) compressing the sattler and choriocapillaries; pachyvessels underneath FIPED. (b and c) 9th, 14th month follow up OCT image shows a lateral elongation of the FIPED by 323u with subsequent SRF, IRF formation. (d and e) ICG taken at 11 and 14 months illustrates dilated choroidal vessels at the foveal zone and small Type 2 interconnecting vascular network respectively

crucially to pick up the disease at the earliest possible time even before the clinical attributes of the disease occurs.

Our study included the contralateral treatment naïve eyes of PCV. Bilateral PCV have been reported in 15-20% of the eyes

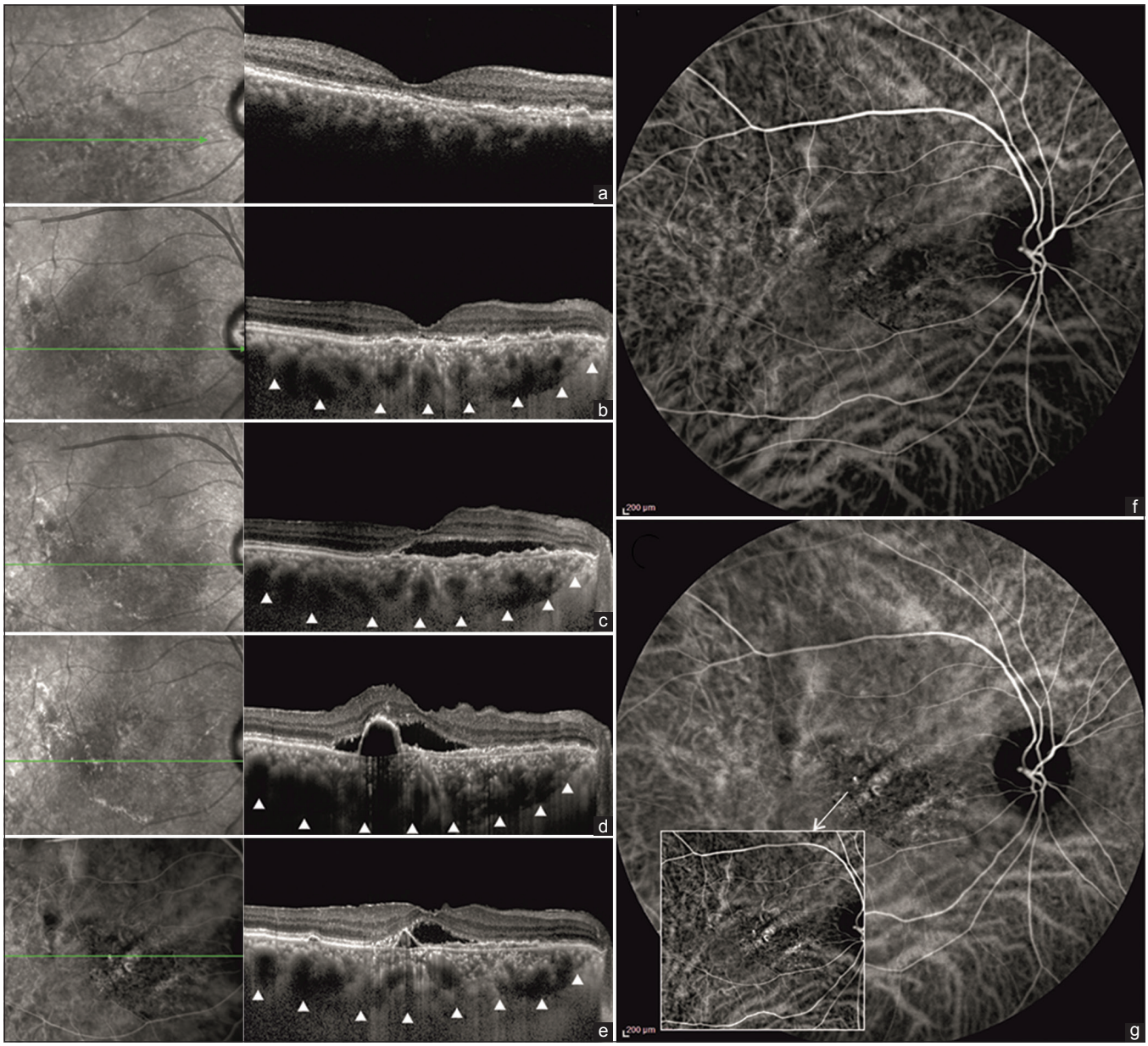

Figure 3: Sequential SDOCT imaging in the right of 59-year-old female, left eye diagnosed as PCV (a) SD OCT illustrating a FIPED of 1986u. Note the peripapillary location. (b and c) 6th, 12th month follow up OCT shows expansion of FIPED subfoveally with increase in SRF subsequently. (d) 15th month follow up SDOCT shows an optically clear PED at the end of expanding of FIPED. (e) 16th month Eye tracking ICG shows polypoidal lesion at the end of PED. (f and g) ICG taken at 11 and 15 months illustrates dilated choroidal vessels at the foveal zone with a subfoveal polyp and a BVN

within one year of the onset.[16,17] This study revealed bilateral involvement in 14.47% of the eyes. Female sex predilection was noted in the ratio 3:2. At the time of diagnosing the earliest disease activity in OCT, all the eyes had a Logmar vision of 0.18 or better, possibly because of the extrafoveal location and minimal intraretinal changes. Pachychoroid disease spectrum typically present with sudden onset of defective vision as serous, exudative or haemorrhagic maculopathy. Later on, the disease sweeps into irreversible vision loss. This clearly explains there exist an ample time for the disease to set into the vision threatening stages. The exact time of development of disease in the contralateral eye and the reason behind it could not be predicted. This undoubtedly explains the need of identifying the disease at the earliest.

On scrutinising the morphometrical changes in the contralateral eyes of PCV, we could find 11 fellow eyes with early development of subretinal fluid. The subretinal fluid development preceded the development of intraretinal fluid. 11 fellow eyes were associated with the presence of flat irregular PED and moreover strongly blended with the peculiar property of the lateral expansion of flat irregular PED. The same was associated with a significant *P* value (*P* value <0.0001) with statistically significant positive correlation with disease activity. All the flat irregular PED studied had a partial or complete hyperreflective fill and none had a total hyperreflective PED. Average lateral expansion of flat irregular detachment from the disease free to SRF development was around 461 + 152u microns. The mean lateral dimension of the flat irregular

detachment at the time of activity was 2247 + 314u microns. Earliest among the 11 eyes to develop SRF was within 6 months and the latest was 22 months. Pachyvessels adjacent to the flat irregular PED showed statistically significant increase in diameter at the development of SRF. Whereas, pachyvessels in the fellow eyes without disease activity could not reveal a statistically significant increase in the size of vessels.

The occurrence of flat irregular pigment epithelial detachment in chronic central serous retinopathy and CNVM have been documented by various research groups.[18-23] Song and *et al.* have documented that ''low to flat'' empty PED in chronic CSCR are not linked to CNVM but related to the chronicity of the disease. But all the cases in the series studied were hyporeflective flat PED.[18] Hage *et al.* found the correlation between the avascular flat irregular pigment epithelial detachment in chronic CSCR and to differentiate it from the type one CNVM.[19] Our study demonstrates the association between the flat irregular PED and PCV disease progression.

Dynamic video ICG and the simultaneous eye tracking OCT demonstrated that branching vascular network corresponded to the flat irregular PED. Out of the 11 eyes which had disease progression in the contralateral eye ICGA could find BVN in 9 fellow eyes. Two fellow eyes which had type 1 BVN with the feeder vessel showed faster elongation of the flat irregular PED and early development of SRF with in a mean duration of 8 ± 4 months. Whereas the other 7 fellow eyes with the type 2 BVN, interconnecting anomalous channel without a feeder vessel showed slow and gradual expansion of the flat irregular PED; mean (SD) duration being 15 ± 8 months. This attributes to the fact that Type 1 BVN with a feeder vessel and faster expansion of flat irregular PED needs close monitoring than the other variant.

Danasingani *et al.*[20] have revealed that shallow irregular pigment epithelial detachments in eyes with pachychoroid features may harbour neovascular tissue. They demonstrated the same by studying the flat or shallow irregular PED with OCT Angiography. The same group suggested that in eyes with pachychoroid features, the finding of a shallow irregular pigment epithelial detachment on OCT has greater diagnostic value for type 1 neovascularization. Even though we couldn't utilise OCT Angiography, our study strongly supports the same by providing the evidence of BVN which corresponded to the flat irregular PED.

Flat irregular PED showed a significant positive correlation with the presence of BVN, Polyps, Choroidal hyperpermeability and late geographical hypercyanescence which all are known putative intrinsic factors in PCV. ICGA could identify polypoidal lesions in 7 fellow eyes. Location wise, 4 polypoidal lesions were macular. Extrafoveal location was the commonest followed by sub foveal and peripapillary region. The location predilection was similar to those described by Imamura *et al.*[24] The polyps are seen in the macular region in 92% of Asians while there is an even distribution of polyps in the macular and peripapillary location amongst the Whites.[24] These variations among ethnicities could be because of some genetic susceptibility among the pigmented races.

On eye tracking ICGA, the unique finding was that the polyps developed at the edge of the expanding flat irregular pigment epithelial detachment. This finding correlated with the Akitaka and *et al.* study group in which they retrospectively studied the haemorrhagic and serous PED in 93 PCV eyes.[25] They mentioned that 65% of the polypoidal lesions are located at the margin of PED and make a visible notch in the accompanying tomography. Fernandes and *et al.* reported that the hot spot in ICG was located at the margin of the PED in 11 out of 12 study eyes.[26,27] It was interesting to note that even with the presence of polypoidal lesions in the subretinal pigment epithelium space, there were no clinical signs of haemorrhagic or exudative maculopathy. It has been hypothesised that the branching vascular network infiltrates through the bruchs into sub RPE space and terminates into polypoidal lesion and the enhanced exudatic activity of the lesion later on develops into large or extralarge serosanguinous PED. According to our study, the expanding flat irregular PED may be considered as the tomographical finding of the encroaching BVN.

All the contralateral study eyes which developed disease activity showed certain distinct characteristics: 1) flat irregular detachment of the pigment epithelium from the bruchs membrane with a partially or complete hyperreflective fill in between, 2) lateral expansion or elongation of the flat irregular detachment from the quiescent phase to the disease activity, 3) appearance of subretinal fluid over the expanding flat irregular detachment, 4) absence of clinical maculopathy with preservation of good vision even with appearance of subretinal fluid, 5) presence of pachyvessels adjacent to the expanding flat irregular PED with definite increase in the size of the vessels, 6) presence of either polypoidal lesions or branching vascular network with or without feeder vessel in the ICG, and 7) emergence of polypoidal lesions at the end of the expanding flat irregular detachment.

We do acknowledge the potential limitations of this analysis including the retrospective nature of the study, incomplete multimodal imaging in few cases as the study eyes were contralateral uninvolved eyes, the manual mode of measurements, the relatively small sample size and the lack of OCT Angiography information. Use of OCTA in the area of expanding FIPED will enlighten more about the pathophysiology of the disease. Future studies looking at a larger sample size may be definitely helpful to further characterize this disease and determine when and where exactly to intervene therapy to these eyes so that vision can be preserved without further loss and to thereby define an optimum treatment approach. Even today, the most common utilised imaging modality in retinal diseases is OCT; so to have an OCT biomarker in PCV holds significance.

Conclusion

In conclusion, lateral elongation of the flat irregular pigment epithelial detachment may be considered as a novel OCT biomarker in polypoidal choroidal vasculopathy. We urge clinicians to pay close attention to this SD OCT finding in order to predict disease progression, so that fellow eyes can be saved at the right time.

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Conflicts of interest

There are no conflicts of interest.

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