Original Article

Pachydrusen in polypoidal choroidal vasculopathy in an Indian cohort

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Purpose: To report the prevalence of pachydrusen and their relationship with subfoveal choroidal thickness (SFCT) and large choroidal vessel layer thickness (SF-LCVT) in eyes with polypoidal choroidal vasculopathy (PCV) and their fellow eyes. **Methods:** The case records of 50 patients (99 eyes; 59 PCV and 40 fellow eyes) were retrospectively analyzed for the presence of pachydrusen and other drusen types such as soft drusen. The diagnosis was established using colour fundus photography and optical coherence tomography (OCT). SFCT and SF-LCVT were measured and correlated with the different types of drusen. **Results:** The mean age of the study cohort was 62.26 ± 10.67 years and included 27 males and 23 females. Pachydrusen and soft drusen were seen in 14 (PCV: 8 and fellow eyes: 6) and 8 eyes (PCV: 2 and fellow eyes: 6) respectively. The mean SFCT and SF-LCVT in the eyes with and without pachydrusen was not significanty different (280.29 ± 103.11 μ vs. 292.63 ± 87.17 μ; $P = 0.63$ and 180.57 ± 59.20 vs. 173.73 ± 54.86 μ; $P = 0.67$, respectively). The pachydrusen were most commonly located near the vascular arcades and showed scattered distribution pattern. Though SFCT and SF-LCVT was lower in the eyes with soft drusen compared to eyes with pachydrusen, it failed to reach statistical significance (SFCT, $P = 0.1$ and SF-LCVT, $P = 0.06$). **Conclusion:** The prevalence of pachydrusen in PCV and their fellow eyes is lower in Indian population suggestive of ethnic variations. SFCT and SF-LCVT was not noted to vary signifcantly in eyes with and without pachydrusen in this study cohort.

Key words: Choroidal thickness (CT), large choroidal vessel thickness (LCVT), optical coherence tomography (OCT), pachydrusen, polypoidal choroidal vasculopathy (PCV), soft drusen

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Drusen are the extracellular deposits located between retinal pigment epithelium (RPE) and bruch's membrane and have been commonly described in age related macular degeneration (AMD).[1-4] The classical description of drusen in age related eye disease study (AREDS) was based on the size and number of drusen.[3] The classification included small, intermediate, and large drusen based on the size of drusen.[3] Other morphological descriptions have also been used such as hard and soft drusen based on whether drusen are discrete or confluent.[4] Spaide recently described a different type of drusen which are large sized (>125 μ) but have a different morphology, distribution pattern compared to the previously described large drusen in AREDS. Moreover, these drusen were associated with thickened choroid hence termed as pachydrusen.[5]

Pachychoroid spectrum is a recently described group of disease entities which are characterized by thickened choroid.[6] The presence of large choroidal vessel leads to the compression of medium choroidal vessel and choriocapillaris.[6,7] Polypoidal choroidal vasculopathy (PCV) falls under the category of the pachychoroid spectrum disorders and was previously considered a subtype of AMD.[8-10] It is more common in Asians and African-Americans as compared to Caucasians.[9] The prevalence of PCV in the presumed AMD eyes of Chinese (24.5%), Japanese (54.7%), Korean (24.6%), and Taiwanese population (49%) showed significant ethnic variations.[11-14] EVEREST study defined the diagnostic criteria of PCV which included the presence of aneurysmal dilatations called polyps with or without branching vascular network (BVN).[15]

Few studies have studied the prevalence of pachydrusen in AMD with prevalence ranging from 8.4% (unpublished data) to 11.7%.[5] It will be interesting to study the pachydrusen (which is associated with thickened choroid) in eyes with PCV, which is itself associated with thicker choroid. Lee *et al*. have reported the prevalence rates of 50% for pachydrusen in eyes with PCV and their fellow eyes in their study in South Korean population.[16] They also noted that the subfoveal choroidal thickness was significantly thicker in pachydrusen group as compared to other drusen types such as soft drusen or subretinal drusenoid deposits.[16] Our study focuses on the prevalence of pachydrusen in PCV and their fellow eyes and associated changes in subfoveal choroidal thickness (SFCT) and large choroidal vessel layer thickness (SF-LCVT) in Indian population.

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Methods

We retrospectively studied the consecutive patients with a diagnosis of PCV in at least one eye. The study included patients visiting the retina clinic of a tertiary center based in South India from April 2016 to July 2018. Institutional Review Board (IRB) approval was taken and all the study protocols conformed to the tenets of Declaration of Helsinki.

Treatment naïve eyes of PCV were included in the study. We analyzed the records of a total of 99 eyes (50 patients) with a diagnosis of PCV in at least one eye. PCV was diagnosed on the basis of criteria defined in EVEREST study. The presence of focal hyperfluorescence with polyps and BVN on indocyanine angiography (ICGA) confirmed the diagnosis of PCV.[15] Other additional criteria including serosanguinous pigment epithelial detachments (PED) on optical coherence tomography (OCT), presence of orangish nodular lesions or submacular hemorrhages on fundus photograph supported the diagnosis.

The exclusion criteria consisted of patients having refractive error more than 6D, other intraocular pathologies such as uveitis, diabetic retinopathy, or other retinal vascular disorders, advanced glaucoma, history of previous vitreoretinal surgeries and/or laser photocoagulation. Presence of media opacities like cataract or vitreous hemorrhage or significant submacular hemorrhage which prevented accurate assessment of fundus pathology and assessment of drusen at posterior pole were also excluded from the study.

All patients underwent comprehensive ophthalmological examination which included best corrected visual acuity (BCVA) in logarithm of minimum angle of resolution (logMAR), slit lamp examination, indirect ophthalmoscopy, fundus photography (Zeiss Visupac® FF4 and FF450-plus, Carl Zeiss, Dublin, CA), swept-source optical coherence tomography OCT (SS-OCT; Topcon DRI OCT Triton® plus) and indocyanine green angiography (ICGA) or fluorescein angiography (FFA) (HRA-II; Heidelberg Engineering, Dossenheim, Germany, Zeiss Visupac® FF4 and FF450-plus, Carl Zeiss, Dublin, CA).

Image analysis

The colour fundus photographs (50 degrees field of view involving the disc and macula) and OCT images were evaluated independently by two observers (RC, JC). In case of discrepancy in the observations, the final decision was reached after mutual consensus. PCV was classified in exudative and hemorrhagic subtypes based on the predominant clinical appearance as per the previous classifications.[10,17]

Drusen were classified on the basis of morphological description and location of the drusen in OCT. Soft drusen were identified as yellowish confluent deposits with irregular, ill-defined margins commonly involving the macula and posterior pole. Rarely, these drusen were associated with pigmentary changes on their surface. OCT scans showed presence of sub -RPE deposits. Pachydrusen were identified on color fundus photograph by their yellowish white appearance, large size (>125 μ), and location of distribution. The various locations described for the pachydrusen are peripapillary, near arcades, and macular while the distribution pattern can be solitary, scattered, or clustered. The eyes with presence of both small, hard drusen/soft drusen and pachydrusen were included in the pachydrusen group. SFCT was measured subfoveally from the outer border of RPE to the inner border of choroido-scleral interface (CSI). Subfoveal large choroidal vessel layer thickness (SF-LCVT) was measured as the perpendicular distance between margin of CSI and inner border of a large choroidal vessel near to the fovea with a diameter of at least 100 μ.[18]

The data were tabulated and the mean with standard deviation were calculated using SPSS software (version 22; IBM Corp., New York, NY). The variation of SFCT and SFLCVT was also compared in the various sub-groups of PCV using independent *t*-test in normal distribution and Mann-Whitney test in non-parametric distribution pattern. *P* value ≤0.05 was considered statistically significant.

Results

A total of 99 eyes of 50 patients (one eye phthisical) were studied. The study group comprised of eyes with PCV (59) and their fellow eyes (40). A total of 9 patients had bilateral PCV. The mean (± standard deviation [SD]) age of the patients was 62.26 ± 10.67 years and the study group included 23 males and 27 females. The baseline characteristics are detailed in Table 1. The mean (±SD) BCVA of the study eyes was 0.52 ± 0.66 logMAR. In the cohort, 80 eyes were phakic (43 clear lens and 37 senile cataract). One eye was aphakic and 18 were pseudophakic.

The mean (±SD) SFCT and SF-LCVT were 290.83 ± 89.18 μ and 174.73 ± 55.24 μ respectively in the study population. The mean (±SD) SFCT (286.91 ± 83.26 μ) and SFLCVT (170.58 ± 58.51 μ) in PCV eyes were not significantly different from the SFCT (296.56 ± 98.03 μ; *P* = 0.59) and SFLCVT (180.79 ± 50.21 μ; *P* = 0.37) in the fellow eye as shown in Table 2.

Among the 50 patients (99 eyes) studied, pachydrusen were found in 14 eyes (14.14%) while 8 eyes (8.08%) had presence of soft drusen. The prevalence of pachydrusen in PCV and fellow eyes was comparable with presence of pachydrusen in 8 PCV eyes (13.56%) and 6 non-PCV fellow eyes (15%). Out of the 8 PCV eyes with pachydrusen, 4 eyes had hemorrhagic PCV and 4 had exudative PCV.

Table 1: Shows the baseline characteristics of the study eyes including patients of polypoidal choroidal vasculopathy (PCV) and their fellow eyes

Parameters	Number (*n*)
Number of eyes studied	99
Number of eyes with PCV	59
Age (in years)	62.26±10.67
Sex	23 males; 27 females
Bilaterality	9 patients
Visual acuity (in logMAR)	0.52±0.66
SFCT (in microns)	290.83±89.18
SFLCVT (in microns)	174.73±55.24
Pachydrusen (incidence)	14.14%
Soft Drusen (incidence)	8.08%
Hemorrhagic vs Exudative PCV	41 (69.49%); 18 (30.51%)

logMAR, logarithm of minimum angle of resolution; SFCT, subfoveal choroidal thickness; SFLCVT, subfoveal large choroidal vessel layer thickness

The mean SFCT was 280.29 ± 103.11 μ in the eyes with pachydrusen as compared to 292.63 ± 87.17 μ in those without pachydrusen—a difference that was not found significant ($p = 0.63$). The mean SFLCVT was 180.57 ± 59.20 μ in the eyes with pachydrusen as compared to 173.73 ± 54.86 μ in those without pachydrusen—a difference that was again not found significant ($p = 0.67$). Eyes with pachydrusen were also not found to have a difference with soft drusen in terms of mean SFCT (280.29 ± 103.11 μ Vs 200.13 ± 114.18 μ; $P = 0.1$) and mean SFLCVT (180.57 ± 59.20 μ vs. 130.5 ± 53.37 μ; $P = 0.06$).

The distribution patterns of pachydrusen were also detailed with respect to the location and arrangement of drusen. The most common location was near the vascular arcades (9 eyes), peripapillary (3 eyes) and macular (2 eyes) whereas the arrangement pattern for pachydrusen was scattered (6) followed by clustered (4) and solitary drusen (4). Representative cases are shown as Figs. 1 and 2. Three eyes had presence of both soft drusen and pachydrusen and were included in the group with pachydrusen.

FFA and ICG were done for 43 (out of 50) —a total of 86 among 99 eyes. Cases in which the diagnosis was straightforward based on clinical and OCT signs, ICGA was not performed. Pachydrusen showed mild hyperfluorescence in both FA and ICGA in majority of the patients (8/14 eyes). However, 6 eyes with pachydrusen showed early and late hypofluorescence in both FA and ICGA [Figs. 1 and 2].

Discussion

The prevalence of pachydrusen in PCV and their fellow eyes in our study involving Indian cohort was 14.14% which is significantly lesser compared to similar study by Lee *et al*. in Korean population where they have reported a prevalence rate of 50%.[16] This difference could be due to the ethnic variations and difference in morphological expression of the disease in different population. This is supported by the fact that variable incidence rates of PCV in Asian (24%–54%) and Caucasian (4%–13%) eyes have been shown in various publications.[11,13,19-21]

Eight eyes had presence of soft drusen (2 PCV eyes and 6 non-PCV fellow eyes). The SFCT and SF-LCVT though not statistically different, it showed a tendency towards reduced CT in eyes with soft drusen as compared to eyes with pachydrusen. Spaide first described pachydrusen in eyes with non-neovascular AMD with a prevalence rate of 11.7% in Caucasian population.[5] We have reported the prevalence of pachydrusen (8.4%; 12/143 eyes) in AMD was in Indian population (unpublished data). Spaide hypothesized that the presence of different types of drusen may have a direct correlation with CT. SDD, soft drusen and pachydrusen were present in thin choroid, choroid with normal thickness, and thickened choroid, respectively.[5]

Previous authors have characterized the pachydrusen and differentiated them from soft drusen based on the complex and irregular shape with a well-defined outer border.[5,16] The description of pachydrusen is based on the choroidal thickness, size of drusen, and its distribution. The common locations described are peripapillary, near vascular arcades, and macular with distribution pattern such as solitary, scattered, and clustered.[16] In our series, the most common pattern seen was scattered pachydrusen near the vascular arcades.

The similar prevalence of pachydrusen in PCV and non-PCV eyes suggests bilaterally symmetrical distribution pattern and that pachydrusen may not be directly involved in the disease activity and clinical manifestation of the disease. This observation was also seen in the study by Lee *et al*.[16] Similarly, pachydrusen were seen in both hemorrhagic (4 eyes) and exudative PCV (4 eyes) with no preponderance for any subtype. Though pachydrusen in most of the eyes showed an early and late mild hyperfluorescence, 6 eyes showed a hypofluorescence in both FFA and ICGA. The variation in staining pattern of different types of drusen has been shown in multiple studies and appears to correlate with their chemical composition.[22,23]

Recently, PCV has been classified in the pachychoroid spectrum related disorders and has been associated with increased choroidal thickness.[6,7] The fellow eyes of PCV were

Table 2: Shows the comparison of baseline and choroidal parameters in different subgroups: Polypoidal choroidal vasculopathy (PCV) and non-PCV fellow eyes; eyes with pachydrusen and without pachydrusen

Parameters	PCV eyes	Fellow eyes
Number of eyes	59	40
Visual acuity (logMAR)	0.76±0.73	0.16±0.28
SFCT (in microns)	286.91±83.26	296.56±98.03
SFLCVT (in microns)	170.58±58.51	180.79±50.21
Pachydrusen	8 eyes (13.56%)	6 eyes (15%)
Soft Drusen	2 eyes (3.39%)	6 eyes (15%)
Parameters	**Pachydrusen**	**Eyes with no pachydrusen**
Number of eyes	14	86
PCV vs Non-PCV	8 PCV eyes (57.14%)	51 PCV eyes (59.30%)
	6 NPCV eyes (42.85%)	35 NPCV eyes (40.69%)
Hemorrhagic vs Exudative PCV	4 (50%); 4 (50%)	37 (72.54%); 14 (27.45%)
BCVA	0.28±0.32 logMAR	0.58±0.73 logMAR
SFCT	280.29±103.11 μ	292.63±87.17 μ
SFLCVT	180.57±59.20	173.73±54.86
Soft Drusen	1 eye (7.14%)	7 eyes (8.14%)

logMAR, logarithm of minimum angle of resolution; SFCT, subfoveal choroidal thickness; SFLCVT, subfoveal large choroidal vessel layer thickness

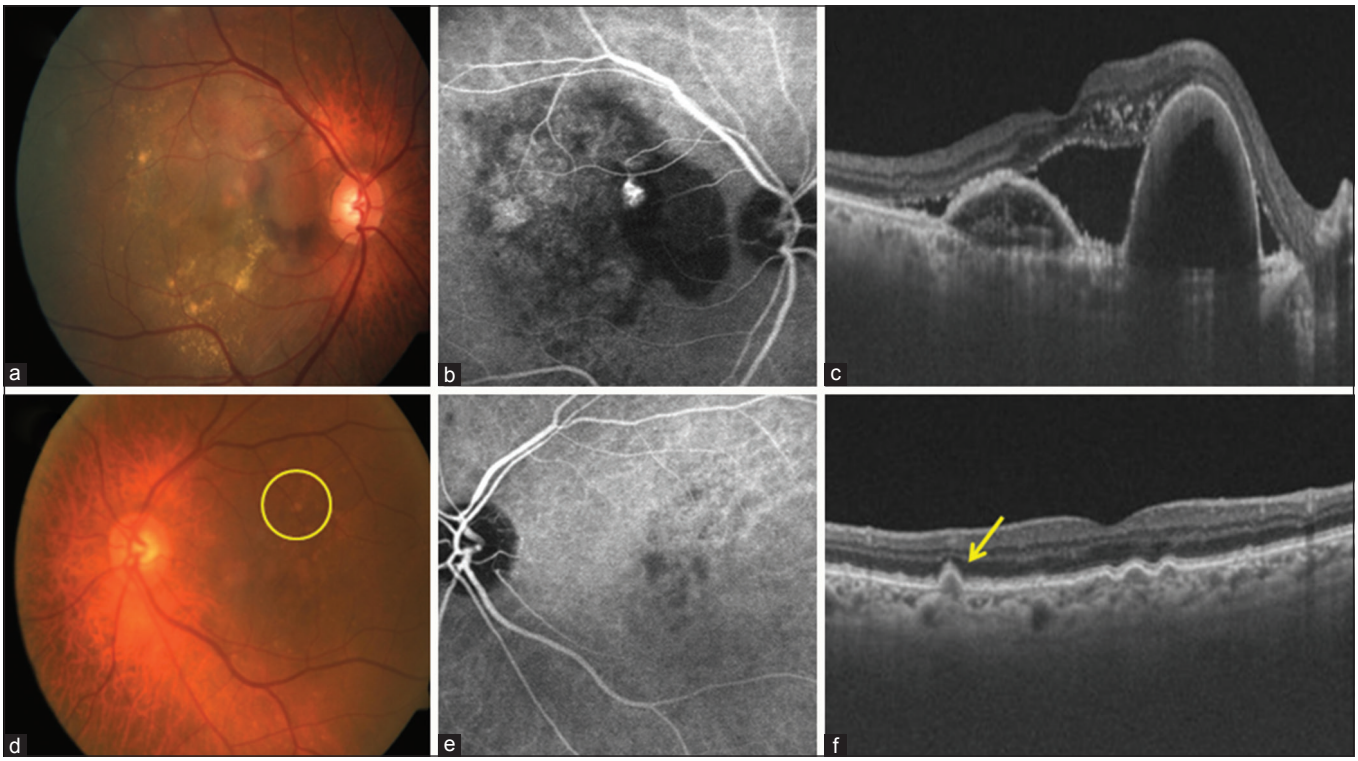

Figure 1: Fundus photograph (a) shows subretinal heme nasal to fovea and subretinal exudation whereas (d) shows subfoveal small, hard drsuen and pachydrusen superior to fovea (yellow circle). Late phase indocyanine angiography (b, e) shows focal hyperfluorescence suggestive of polyp in right eye and hypofluorescence corresponding to pachydrusen in left eye. OCT (c) shows PED, subretinal fluid and intraretinal hyperreflectivity. Vertical OCT scan (f) shows homogenous deposit at sub RPE level with pachydrusen (arrow). SFCT was 318 and 286 microns in right and left eye respectively

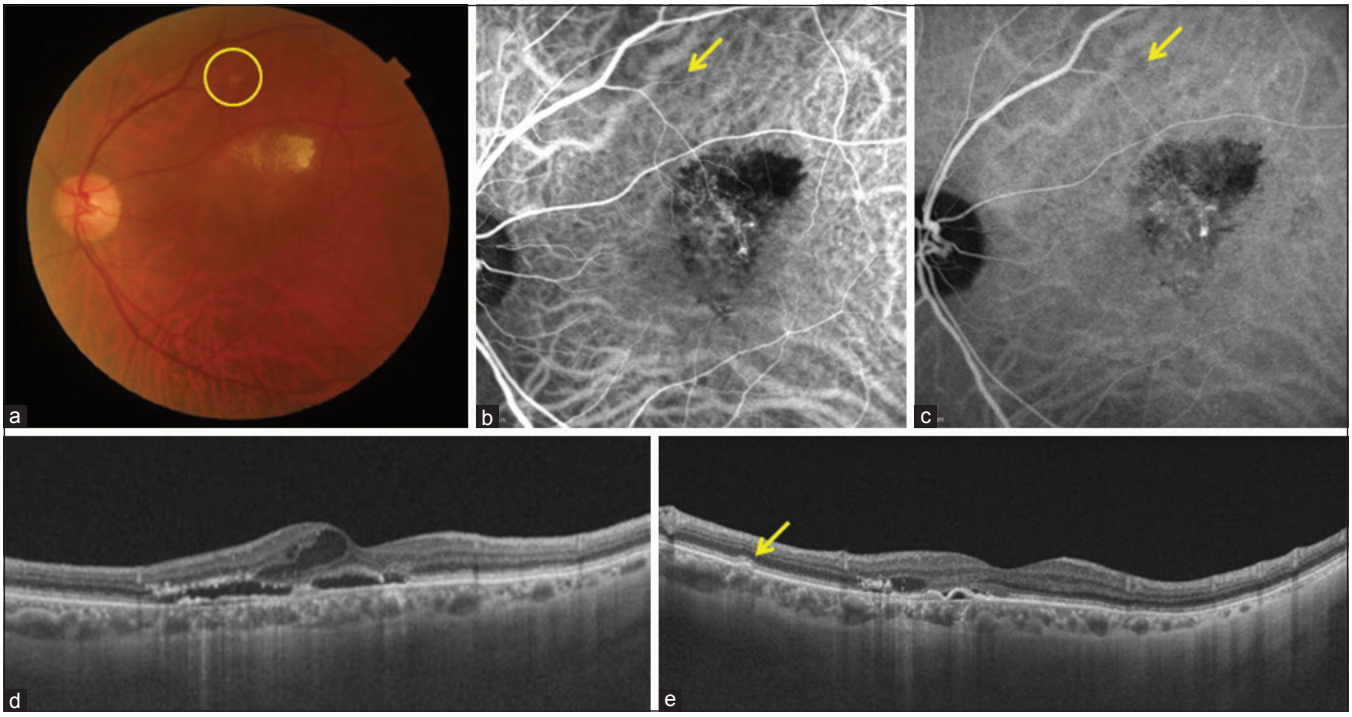

Figure 2: Fundus photograph (a) of an eye with PCV showing pachydrusen (yellow circle) with hard exudates superior to fovea. Early and late phase ICGA (b, c) show branching vascular network, focal hyperfluorescence due to polyp and hypofluorescence corresponding to pachydrusen (arrow). OCT showed intraretinal, subretinal fluid, subretinal hyperreflectivity and PED with SFCT of 206 microns (d). The corresponding vertical OCT scan (e) shows homogenous deposit below retinal pigment epithelium (RPE) suggestive of pachydrusen (yellow arrow)

noted to have a slightly higher SFCT and SF-LCVT which was not statistically significant as compared to eyes with PCV. This suggests that the CT changes happen bilaterally in eyes with PCV and the asymptomatic fellow eyes. Lee *et al*. have reported slightly higher SFCT in fellow eyes of PCV as compared to the PCV eyes.[16] We also noted similar findings in eyes with and without pachydrusen with no significant difference between the two groups. The above two observations show the nonadditive effect of PCV and pachydrusen related to CT.

The results of previous study in nonexudative AMD eyes may not be applicable to eyes with PCV as eyes with AMD and PCV show different pathophysiology along with difference in CT. PCV is associated with increase in choroidal vascular hyperpermeability and presence of pachyvessels.[6,7,24-26] On the other hand, AMD is characterized by choroidal thinning.[26,27] Moreover, previous reports have also shown reduced number of drusen in eyes with PCV as compared to the AMD.[11,28,29]

The results need to be analyzed considering the limitations of this study. The study was retrospective, cross-sectional and included a small number of patients. The data were obtained from the visiting patients in a referral hospital. This does not provide the true estimates of the prevalence of pachydrusen in the population. The study lacks longitudinal follow up of the patients which could have provided more information on the natural progression of drusen and their effects on CT and LCVT.

Conclusion

The current study provides an outlook regarding the newly described type pachydrusen in eyes with PCV and their fellow eyes. Whether these represent a morphological variation of drusen in these eyes or carry prognostication potential in terms of visual acuity and course of the disease is unclear at present. Future, longitudinal studies focused on these aims may provide more insight into the pathogenesis and natural course of these drusen.

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Conflicts of interest

There are no conflicts of interest.

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