Original Article

Treatment outcomes of pachychoroid neovasculopathy with photodynamic therapy and anti-vascular endothelial growth factor

Rupak Roy, Kumar Saurabh, Dhaivat Shah, Sugandha Goel

Purpose: To describe treatment outcomes of eyes with pachychoroid neovasculopathy (PNV) with PDT and anti-(vascular endothelial growth factor) VEGF therapy. **Methods:** Retrospective interventional case series. Records of six consecutive cases of PNV were reviewed. Four cases were treated with PDT+ inj ranibizumab. Two cases underwent only PDT. Final visual outcomes and functional outcome including macular status and choroidal thickness were assessed. **Results:** We analysed six eyes of six patients with PNV. There were four males and two females. Mean age of the patients was 56.5 years. Mean duration of follow up was 8.2 months. All patients received reduced fluence PDT. Four patients received ranibizumab along with PDT; mean BCVA at presentation was 0.41 log MAR units and mean BCVA at final follow up was 0.44 log MAR units. There was significant improvement at final follow up (P = 0.03). Mean subfoveal choroidal thickness (SFCT) at presentation was 445 microns and mean SFCT at final follow up was 293 microns. There was a significant reduction at final follow up (P = 0.02). **Conclusion:** PDT with or without ranibizumab appears to be an effective treatment modality for PNV.

Key words: OCT, pachychoroid disease, pachychoroid neovasculopathy

Access this article online

Website: www.ijo.in

DOI: 10.4103/ijo.IJO_1481_18

Quick Response Code:

Advent of newer enhanced depth optical coherence tomography has provided new insights into a variety of chorioretinal disorders.[1] The term pachy, meaning thick, has been derived from the Greek literature. It has been used to describe a group of choroidal findings that point towards a spectrum of related retinal disorders, namely, the pachychoroid spectrum of diseases.[2,3] Pachychoroid vascular changes are believed to underlie the development of focal disruptions in the retinal pigment epithelium (RPE) and Bruch membrane, leading to characteristic features such as choroidal hyper permeability, double-layer sign, dilated choroidal vessels (pachyvessels) and focal or diffuse increase in choroidal thickness. Key features of this entity include pachyvessels and increased choroidal thickness.[3] Pachyvessels are dilated outer choroidal vessels best appreciated on EDI OCT. Various studies have provided normative choroidal thickness across various ethnic groups. It ranges from 260 to 290 microns.[4,5] Diseases included in the pachychoroid spectrum are uncomplicated pachychoroid (UCP), pachychoroid pigment epitheliopathy (PPE), central serous chorioretinopathy (CSCR), pachychoroid neovasculopathy (PNV) and polypoidal choroidal vasculopathy. PNV refers to the occurrence of Type 1 (subRPE) neovascularization in eyes with thick choroid which were previously normal, had PPE or CSCR.[6]

Longstanding RPE changes and possibly RPE detachment can lead to disruption of Bruch's membrane, leading to ingrowth of subRPE choroidal neovascular membranes, resulting in Type 1 CNV. These neovascular membranes overlie areas of thickened choroid with dilated outer choroidal vessels and have been termed 'pachychoroid neovasculopathy', and this pachychoroidopathy suggests that a pathologic choroidal process characterized by dilated outer choroidal vessels and thick choroid is the underlying common denominator.[6] Previous literature described in this genre has focused more on the clinical features of PNV, but no long-term results post treatment have been laid out. Lee *et al*. showed that adjunctive photodynamic therapy (PDT) in eyes with Type 1 neovascularization with thickened choroid that were refractory to anti-vascular endothelial growth factor monotherapy resulted in complete fluid absorption in most eyes, which translated to visual improvement until one year.[7] Hata *et al*. and Matsumoto *et al*. have described treatment outcomes of PNV with ranibizumab and aflibercept.

Treatment outcomes of PNV in Indian eyes are not yet described. The purpose of this study is to report the outcomes of PDT along with injection anti-vascular endothelial growth factor (VEGF) in Indian eyes with PNV.

Methods

We retrospectively analysed clinical and imaging data from a case series of six patients with PNV who had no features of age related macular degeneration (AMD) or other degenerative condition. All patients were examined at a vitreoretinal referral centre based in eastern India. The study period was from June

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Manuscript received: 01.09.18; Revision accepted: 04.06.19

Cite this article as: Roy R, Saurabh K, Shah D, Goel S. Treatment outcomes of pachychoroid neovasculopathy with photodynamic therapy and anti-vascular endothelial growth factor. Indian J Ophthalmol 2019;67:1678-83.

2017 to June 2018. The study was approved by institutional review board and followed the Tenets of Declaration of Helsinki. Demographic data taken from our database included age, gender—best corrected visual acuity (BCVA). All patients underwent comprehensive ophthalmic assessment with slit-lamp biomicroscopy, indirect ophthalmoscopy, colour fundus photography, fluorescein and indocyanine angiography (FFA, ICG) (Heidelberg Spectralis HRA + OCT; Heidelberg Engineering). Spectral domain optical coherence tomography including EDI OCT and blue autofluorescence was performed on all eyes with the Heidelberg Spectralis HRA + OCT. Subfoveal choroidal thickness (SFCT) was defined as the distance from the outer portion of the hyperreflective line corresponding to the RPE to the inner surface of the choroidal-scleral junction and measured with the manual digital calipers function included in the review software. Pachychoroid neovasulopathy (PNV) was defined as absence of drusen on colour fundus, presence of double-layer sign, dilated choroidal vessels with increased SFCT (> 300 microns) on EDI OCT, no specific leaks on FFA, and dilated choroidal vessels on ICG. Double-layer sign on EDI OCT was defined as two reflective bands at the level of RPE, one on top of the other with a small space in between. The upper band corresponds to the RPE, the lower band to basement membrane. On the basis of these diagnostic findings of PNV, patients were subjected to half/reduced fluence PDT followed by anti-VEGF injection (Ranibizumab) or PDT alone. PDT was done encompassing entire area of dilated choroidal vessels corresponding to the double-layer sign seen in OCT. All patients were given option of combination therapy. Two patients decided to have PDT only. Comprehensive ophthalmic assessment with slit-lamp biomicroscopy, indirect ophthalmoscopy and EDI OCT was repeated at the end of one, three and six months and one year.

Statistical analysis was done in SPSS (version 19 Chicago, IL). *P* value less than 0.05 was considered as significant.

Results

We analysed six eyes of six patients with PNV. There were four males and two females. Mean age of the patients was 56.5 years. Mean duration of follow up was 8.2 months. All patients received reduced fluence PDT. Mean PDT spot size was 3,900 microns (2,700–4,500 microns). Four patients received Ranibizumab along with PDT; Mean BCVA at presentation was 0.41 log MAR units and mean BCVA at final follow up was 0.44 log MAR units. There was significant improvement at final follow up ($P = 0.03$). Mean SFCT at presentation was 445 microns and mean SFCT at final follow up was 293 microns. There was a significant reduction at final follow up ($P = 0.02$). Clinical details of study eyes are enumerated in Table 1.

Case descriptions

Case 1

A 53-year-old female patient presented with progressive diminution of vision since two months. The BCVA in right and left eyes were 20/30 and 20/200, respectively. Fundus examination showed an area of shallow neurosensory detachment over the macula in the right eye [Fig. 1A] and RPE alterations at fovea in left eye. Of note, there were reduced tessellations over the posterior pole in both eyes. EDI OCT right eye [Fig. 1B1] shows the characteristic appearance of double-layer sign superior to fovea, and shallow SRF with few serous pigment epithelial detachments at the level of fovea [Fig. 1B2]; left eye had foveal thinning. SFCT in right and left eyes were 0.42 mm and 0.34 mm, respectively. Of significance, there was appreciable focal thickening of choroid with multiple dilated choroidal vessels (pachy vessels) beneath the area having the double-layer sign in the right eye. There was also obliteration of Sattler's layer in the area of largest calibre choroidal vessel. Fundus autofluorescence in right eye [Fig. 1C] shows areas of mixed hypo and hyper autofluorescence over the macula, while left eye showed area of marked hypo autofluorescence over the macula. FFA [Fig. 1D] in right eye showed stippled hyper fluorescence in the late phase superotemporally with no definite leak over macula. ICG [Fig. 1D] in right eye showed dilated choroidal vessels over the corresponding area with late frames showing diffuse choroidal hyperpermeability. In view of these findings, a diagnosis of PNV was made and right eye reduced fluence PDT was done to the superotemporal area [Fig. 1D, white circle]. Two months post PDT, the best corrected snellen visual acuity in right eye was 20/30 with significant symptomatic improvement [Fig. 1E]. The EDI OCT [Fig. 1F1] showed disappearance of double-layer sign and complete resolution of

Table 1: Clinical details of study eyes

A/G	Initial BCVA	Initial SFCT (μ)	EDI OCT Signs			FFA	ICG	Rx	Final BCVA	Final SFCT (μ)	Final OCT
			Double layer	SRF	Pachy-vessel						
53/F	20/30	420	+	+	+	Stippled hyperfluorescence, no leak	Dilated vessel	PDT	20/30	310	No srf, no double layer
56/M	20/40	370	+	+	+	RPE tract, no leak	Dilated vessel	PDT + anti-Vegf	20/25	280	Dry macula
72/M	20/125	510	+	+	+	Late diffuse hyperfluorescence, no leak	Dilated vessel, hotspot	PDT + anti-Vegf	20/60	300	No srf, no double layer
57/M	20/40	520	+	+	+	Staining of focal laser marks, no leak	Dilated vessel	PDT	20/25	280	No srf, no double layer
49/M	20/40	440	+	+	+	window defect	Dilated vessel	PDT + anti-Vegf	20/25	310	No srf or double layer
52/M	20/80	410	+	+	+	window defect	Dilated vessel	PDT + anti-Vegf	20/25	280	Dry macula

A: Age, G: Gender, BCVA: Best corrected visual acuity, SFCT: Subfoveal choroidal thickness, EDI: Enhanced depth imaging SRF: Sub retinal fluid

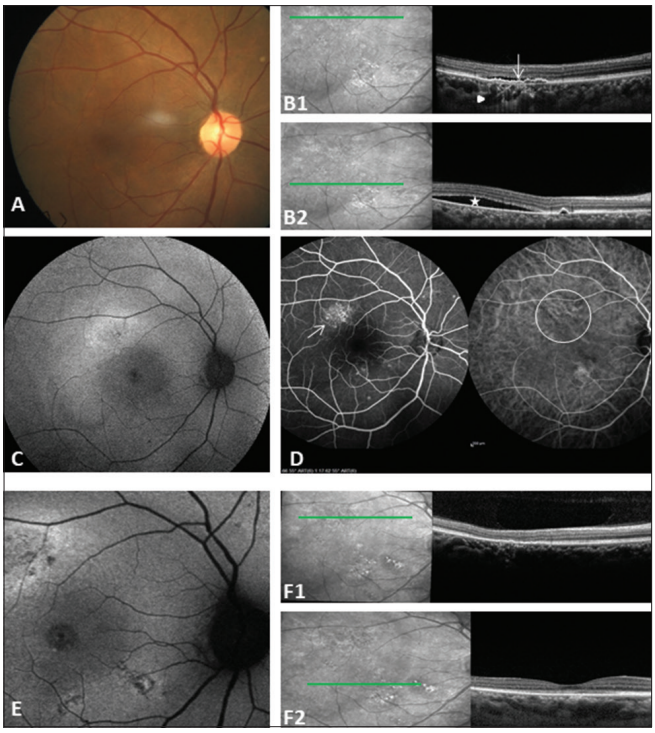

Figure 1: Right eye of Case 1 (A) Colour fundus photograph showing subretinal fluid. (B) EDI OCT shows double-layer sign (white arrow) and thickening of the choroidal vessels (white star). Pachy vessels are seen (white triangle) (C) Blue Auto Fluorescence (BAF) shows areas of mixed autofluorescence. (D) FFA shows stippled hyper fluorescence (white arrow). ICG A shows dilated choroidal vessels (white circle). (E) 2 months post PDT; BAF shows areas of mixed hypo and hyper autofluorescence as before. (F) 2 months post PDT; EDI OCT showed disappearance of double-layer and complete resolution of subretinal fluid

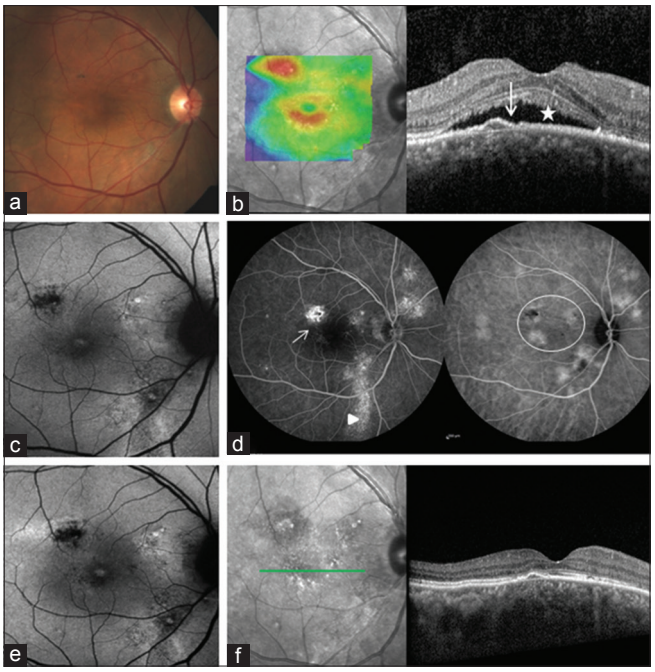

Figure 2: Right eye of Case 2 (a) Colour fundus photograph showing subretinal fluid. (b) EDI OCT highlights the presence of double-layer sign (white arrow) and shows subretinal fluid (white star) (c) BAF shows mixed autofluorescence over macula. (d) FFA shows RPE tracts (white triangle) with areas of late phase hyper fluorescence, but no overt leakage. ICG A shows dilated choroidal vessels in the early phase and a hotspot over macula in late phase (white circle). (e and f) 2 months post PDT; BAF shows areas of hypo autofluorescence over the macula and dry macula and dry macula

SRF at fovea [Fig. 1F2]. There was reduction in the SFCT from 0.42 mm to 0.31 mm. One year post PDT, the patient maintained a vision of 20/30 and EDI OCT was dry.

Case 2

A 56-year-old male patient presented with diminution of vision and metamorphopsia in right eye since two months. He had similar complains before three years for which he had been given three intravitreal injections, of which no details were available. He was known hypertensive on treatment since six years. The BCVA in right and left eyes were 20/40 and 20/200, respectively. Fundus evaluation showed neurosensory detachment at fovea with RPE alterations in the right eye [Fig. 2a] and subfoveal scar in the left eye. On EDI OCT, the right eye [Fig. 2b] showed subretinal fluid with double-layer sign, the left eye showed a schitic retina with a subfoveal scar. FAF [Fig. 2c] in right eye shows areas of hypo autofluorescence over the macula. FFA in right eye showed RPE tracts with areas of late phase hyper fluorescence, but no overt leakage; ICG showed dilated choroidal vessels [Fig. 2d]. In accordance to all these findings, a diagnosis of PNV was made and reduced fluence PDT followed by injection anti-VEGF was advised for the right eye. Two months later, the BCVA in right eye was 20/25. The patient had symptomatically improved and the metamorphopsia had resolved. The EDI OCT [Fig. 2e and f] showed dry macula with SFCT reduced from 0.37 to 0.28 mm. At six months post op, the vision was maintained and the EDI OCT was dry.

Case 3

A 72-year-old male patient came with complain of decreased vision and metamorphopsia in right eye since two months. Right and left eyes had BCVA of 20/125 and 20/80, respectively. The anterior segment examination showed early cortical sclerosis in both eyes. Dilated fundus examination showed RPE alterations in both eyes [Fig. 3a]. On EDI OCT, right eye showed subretinal fluid with double-layer sign with dilated choroidal vessels beneath [Fig. 3b], and left eye showed an epiretinal membrane with no evident vitreoretinal traction. SFCT in right and left eyes were 0.51 and 0.32 mm, respectively. FFA in right eye showed diffuse hyperfluorescence in late phase, but no specific leaks; ICG, right eye showed dilated choroidal vessels [Fig. 3c and d]. On basis of these findings, a diagnosis of PNV was made and reduced fluence PDT followed by injection anti-VEGF was advised in right eye. Two months post op, the BCVA in right eye was 20/60 and patient was asymptomatic. EDI OCT [Fig. 3c,e and f] showed dry macula with disappearance of double-layer sign and reduction in SFCT from 0.51 to 0.30 mm. The patient had no recurrence at six months post op and EDI OCT was dry.

Case 4

A 57-year-old male patient presented to us with complains of metamorphopsia and diminution of vision in left eye since one week. He was a known diabetic and hypertensive on oral treatment since 12 years and had a history of laser treatment in left eye before eight years of which no specific details were available. BCVA in right and left eyes were 20/20

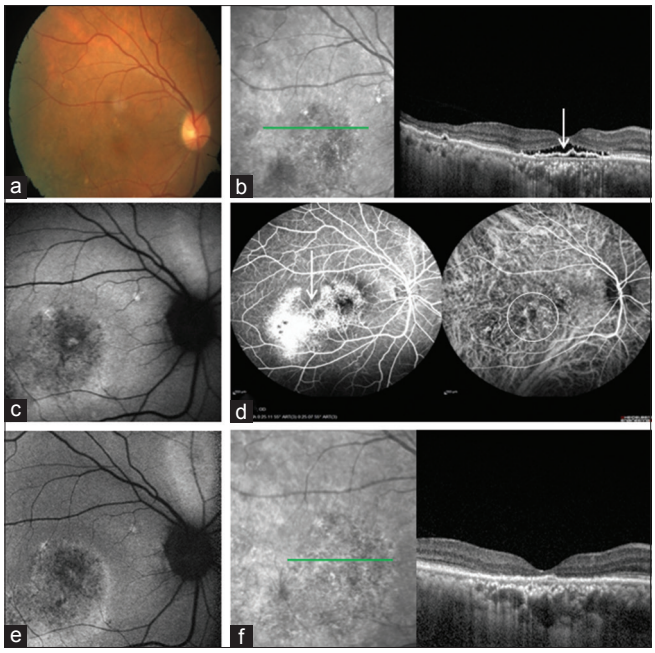

Figure 3: Right eye of Case 2 (a) Colour fundus photograph showing RPE alterations. (b) Enhanced depth imaging optical coherence tomography highlights the presence of double-layer sign (white arrow) and shows subretinal fluid. (c) Fundus autofluorescence shows areas of mottled hypo autofluorescence over the macula. (d) FFA shows area of late phase hyper fluorescence (white arrow), but no specific leakage. ICG A shows dilated choroidal vessels (white circle). (e) 2 months post PDT with anti-VEGF; FAF shows areas of hypo autofluorescence over the macula. (f) 2 months post op; EDI OCT shows dry macula with decrease in the SFCT from 0.51 to 0.30 mm

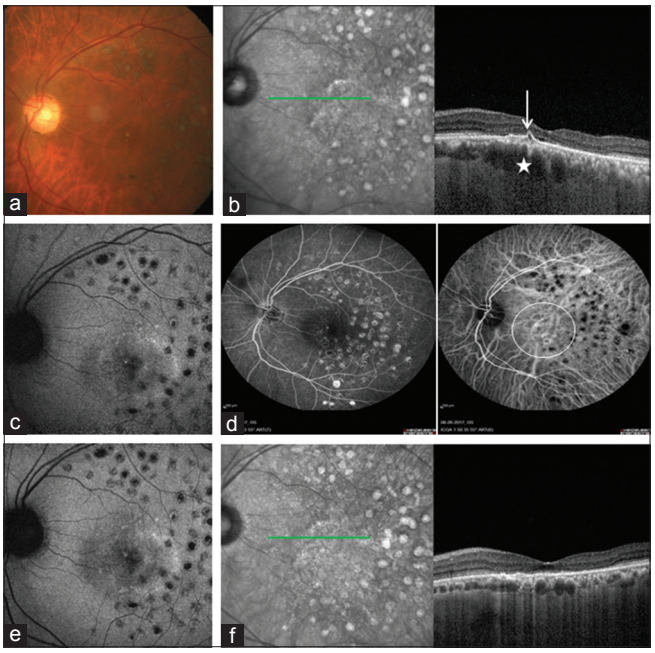

Figure 4: Right eye of Case 4 (a) Colour fundus photograph showing yellowish lesion at posterior pole. (b) EDI OCT highlights the presence of double-layer sign (white arrow) and ilated choroidal vessel termed as pachy vessel (star) with trace subretinal fluid. (c) BAF shows mixed autofluorescence over macula. (d) FFA shows staining of laser marks with no other leakage. ICG A shows dilated choroidal vessels (white circle). (e) 2 months post PDT; BAF shows mixed autofluorescence over the macula. (f) 2 months post op; EDI OCT shows dry macula with decrease in the subfoveal choroidal thickness from 0.52 to 0.28 mm

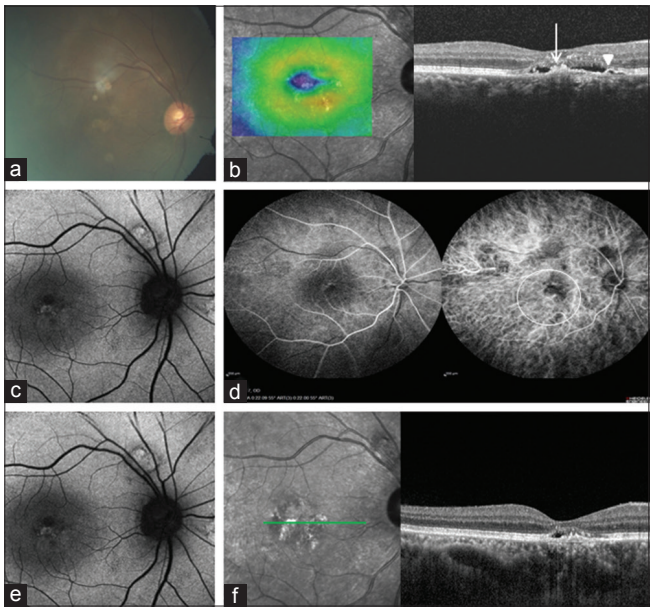

Figure 5: Right eye of Case 5 (a) Colour fundus photograph showing alterations with subretinal fluid. (b) EDI OCT highlights subretinal fluid with hyperreflective deposits (white arrow) in the subretinal space, with double-layer sign (white triangle). (c) BAF shows mixed autofluorescence over macula. (d) FFA shows few window defects and no specific leaks; ICG A shows dilated choroidal vessels (white circle). (e) 2 months post PDT; BAF shows mixed autofluorescence. (f) 2 months post op; EDI OCT shows trace subretinal fluid with decrease in the subfoveal choroidal thickness from 0.44 to 0.31 mm

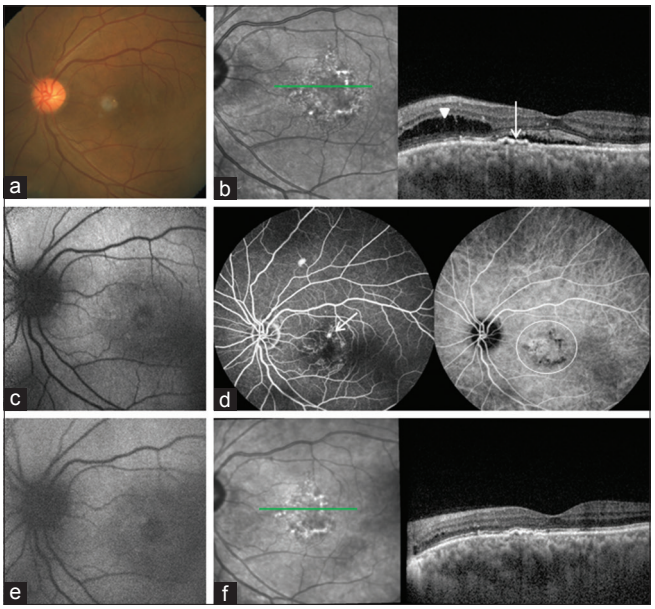

Figure 6: Left eye of Case 6 (a) Colour fundus photograph showing RPE alterations over fovea in the left eye. (b) EDI OCT showing subretinal fluid with double-layer sign (white arrow) and parafoveal intraretinal schitic spaces (white triangle) and dilated choroidal vessels. (c) BAF shows mixed autofluorescence over macula. (d) FFA shows a small leak just adjacent to fovea (white arrow) and multiple other window defects; ICG A shows dilated choroidal vessels (white circle). (e) 2 months post op; FAF shows mixed autofluorescence over macula. (f) 2 months post op; EDI OCT shows dry fovea and decrease in subfoveal choroidal thickness from 0.41 to 0.28 mm

and 20/40, respectively. The anterior segment examination was unremarkable. Fundus examination in right eye showed few microaneurysms over posterior pole; left eye [Fig. 4a] showed laser marks over posterior pole in a C-shaped manner with RPE alterations over fovea. EDI OCT right eye was normal; left eye [Fig. 4b] showed a double-layer sign with trace subretinal fluid and dilated choroidal vessels beneath. Left eye FFA showed late staining of laser marks with no other leakage, and ICG showed dilated choroidal vessels [Fig. 4c and d]. SFCT in right and left eyes were 0.22 and 0.52 mm, respectively. On basis of these findings, a diagnosis of PNV was made and left eye reduced fluence PDT was advised. Two months post PDT, the BCVA in left eye was 20/25 with significant symptomatic improvement. EDI OCT [Fig. 4e and f] showed dry fovea with disappearance of double-layer sign and decreased SFCT from 0.52 to 0.28 mm. At nine months post op, the BCVA was maintained and EDI OCT was dry.

Case 5

A 49-year-old male patient presented with chief complain of decreased near vision and metamorphopsia in both eyes, right more than left, since one month. BCVA in right and left eyes were 20/40 and 20/25, respectively. Anterior segment examination was unremarkable. Fundus exam in right eye showed RPE alterations with subretinal fluid at the posterior pole [Fig. 5a], left eye showed RPE alterations at macula. EDI OCT in right eye showed subretinal fluid with hyperreflective deposits in the subretinal space, with double-layer sign [Fig. 5b]. SFCT in right and left eyes were 0.44 and 0.38 mm, respectively. FFA right eye showed few window defects at macula with no specific leaks; ICG right eye showed dilated choroidal vessels at macula [Fig. 5c and d]. In view of these findings, a diagnosis of right eye PNV was made and right eye reduced fluence PDT along with anti-VEGF was advised. Two months post treatment, the metamorphopsia had significantly reduced. The BCVA in right eye improved to 20/25. EDI OCT [Fig. 5e and f] showed trace subretinal fluid with disappearance of double-layer sign. SFCT decreased from 0.44 to 0.31 mm. At six months follow up, the subretinal fluid had completely resolved and the BCVA was maintained.

Case 6

A 52-year-old male patient presented with complains of recent drop in vision left eye since around one month. He was known diabetic and hypertensive on treatment since four years. The BCVA in right and left eyes were 20/200 and 20/80, respectively. Fundus evaluation showed foveal thinning in the right eye and RPE alterations over fovea in the left eye [Fig. 6a]. On EDI OCT, the left eye [Fig. 6b] showed subretinal fluid with double-layer sign and parafoveal intraretinal schitic spaces, the left eye showed foveal thinning. SFCT measured in right and left eye were 0.22 and 0.41 mm, respectively. FAF [Fig. 6c] in left eye shows areas of mixed autofluorescence over the macula. FFA in left eye showed a small leak just adjacent to fovea and multiple other window defects; ICG showed dilated choroidal vessels in the early phase [Fig. 6d]. In view of these findings, a diagnosis of PNV was made and reduced fluence PDT followed by injection anti-VEGF was advised for the left eye. Two months later, the BCVA in left eye was 20/25 with significant symptomatically improvement. The EDI OCT [Fig. 6e and f] showed dry macula with SFCT reduced from 0.41 to 0.28 mm. At eight months post op, the vision was maintained and the EDI OCT was dry.

Discussion

PNV is considered to be in the spectrum of pachychoroid diseases. Pang *et al*. has described multimodal imaging diagnostic findings of PNV in a series of three cases, but no treatment modality was described. They concluded that PNV falls within a spectrum of diseases associated with choroidal thickening and should be considered as a possible diagnosis in eyes with features of Type 1 neovascularization and choroidal thickening in the absence of characteristic age-related macular degeneration or degenerative change.[6]

Exact pathogenesis of PNV is a matter of research. Enlarged Haller vessel volume and loss of choriocapillaries induces mechanical damage to focal areas of overlying tissues inducing atrophic changes of RPE and a focal break in Bruch's membrane. Theses alterations in the morphology and physiology of the choroid lead to neovascularisation.[8-10]

Hata *et al*. studied nine eyes with treatment-naïve PNV and 21 eyes with treatment-naïve neovascular age related macular degenration (nAMD), and compared initial concentration of VEGF using enzyme-linked immunosorbent assay. The concentration was compared between the two conditions, and its associations with responses to anti-VEGF therapy were investigated. They concluded that mean VEGF concentration in PNV was lower than that in nAMD, suggesting that the way in which VEGF is involved in angiogenesis may differ between PNV and nAMD.[11] Miyake *et al*. have found that patients affected by PVN have a different genetic susceptibility as compared patients with AMD, suggesting a different etiology of the two conditions.[12]

Land mark clinical trials such as MARINA and ANCHOR have established treatment of neovascular AMD with anti-VEGF agents.[13] Various authors have reported treatment of PNV with anti-VEGF agents. Matsumoto *et al*. studied 42 eyes with PNV, which included 28 eyes with and 14 without polypoidal lesions. They evaluated a treat and extend regimen with aflibercept for these patients. They reported significant improvement in BCVA and reduction in central foveal thickness at two years.[14] Perez *et al*. studied the response of eyes with PNV to anti-VEGF injections. Patients were treated with either ranibizumab or aflibercept. The main aim of their study was to evaluate changes in choroidal thickness in patients with PNV treated with anti-VEGF intravitreal injections. They noted a significant reduction in choroidal thickness after anti-VEGF injections. At the 12-month visit, dry macula was achieved in five of nine eyes (55.6 per cent) with PNV and in 16 of 19 eyes (84.2 per cent) with neovascular AMD.[13] However, as reported by Hata and Terao *et al*., the anti-VEGF profile in PNV patient is different from neovascular AMD.[10,15] Thus, it needs different treatment approaches. Lee *et al*. showed that adjunctive PDT in eyes with Type 1 neovascularization with thickened choroid that were refractory to anti-vascular endothelial growth factor monotherapy resulted in complete fluid absorption in most eyes, which translated to visual improvement until one year.[7]

Optimum treatment regimen of PNV is yet to be formulated. Since it is primarily a pachychoroid-driven process, use of PDT

in its treatment seems rational. PDT induces choroidal hypo perfusion, which subsequently leads to reduced choroidal thickness. Though a pachychoroid-driven process, there is evidence of VEGF release in this entity as shown by Hata *et al*. We used combination therapy of PDT and anti-VEGF in eyes with PNV to address both these entities. Four of our cases had PDT + anti-VEGF as primary therapy and had excellent outcome with dry macula, increased vision and decreased choroidal thickness at final follow up. Other two patients did well with PDT alone. PDT as primary therapy of PNV with or without anti-VEGF is yet to be explored. This is the first report of this treatment regimen.

Certainly, there are limitations to our study. Retrospective design, small sample size and lack of OCT angiography are drawbacks of our study. A larger series of patient would also be helpful in establishing a treatment protocol for PNV.

Conclusion

To conclude, we report good anatomical and functional outcomes of eyes with PNV to combination therapy of PDT and anti-VEGF or PDT alone.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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