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REVIEW

Pachychoroid neovasculopathy: a type-1 choroidal neovascularization belonging to the pachychoroid spectrum—pathogenesis, imaging and available treatment options

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Abstract

Purpose The purpose of this paper is to provide a meaningful literature review about the epidemiology, pathogenesis, imaging and treatment of pachychoroid neovasculopathy (PNV).

Methods A computerized search from inception up to December 2019 of the online electronic database PubMed was performed using the following search string: "pachychoroid neovasculopathy". The reference list in each article was scanned for additional relevant publications.

Results PNV is a type-1 choroidal neovascularization, overlying focal areas of choroidal thickening and dilated choroidal vessels. It can develop in patients affected by pachychoroid pigment epitheliopathy or chronic central serous chorioretinopathy. The absence of drusen, the presence of pachydrusen, younger age of onset and choroidal thickening distinguish it from neovascular age-related macular degeneration (AMD). PNV incidence and prevalence data are lacking. Its pathophysiology is not fully understood, but angiogenic mechanisms involved in neovascular AMD may be different from those in PNV. Due to optical coherence tomography (OCT) improvements, PNV can be diagnosed more easily than before. In particular, PNV shows a shallow pigment epithelium detachment with an undulating retinal pigment epithelium over a subfoveal choroidal thickening, associated with vein enlargement in Haller's layer (named pachyvessels) and choriocapillaris thinning. On OCT angiography, PNV reveals tangled hyper-reflective filamentous neovessels in the choriocapillaris itself. The current first-line PNV treatment is intravitreal anti-VEGF (vascular endothelial growth factor) injections with a treat-and-extend regimen. In particular, aflibercept shows a higher rate of fluid absorption than others. In the case of fluid recurrence or persistence, photodynamic therapy is a valid alternative.

Conclusion Ongoing research into pathophysiology and imaging improvements may be helpful in defining prognostic criteria and stratifying patient risk, allowing responsible monitoring and management of PNV.

Keywords Pachychoroid neovasculopathy · Pachychoroid disease · Intravitreal anti-VEGF · Photodynamic therapy

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Introduction

Described by Pang and Freund in 2015, pachychoroid neovasculopathy (PNV) is a new clinical entity characterized by type-1 choroidal neovascularization, overlying focal areas of choroidal thickening and

dilated choroidal vessels [1]. The absence of drusen, the presence of pachydrusen, choroidal thickening and younger age of onset distinguish PNV from neovascular age-related macular degeneration (AMD), suggesting a different aetiopathogenesis [2]. Pachydrusen is a homogeneous subretinal pigment epithelium (RPE) deposit, larger than 125 μm, typically presented as a singular lesion, usually located outside the fovea, with no tendency to aggregate and without focal hyperpigmentation on its surface at fundus examination [3]. Furthermore, patients affected by pachychoroid pigment epitheliopathy (PPE) or chronic central serous chorioretinopathy (CSCR) can develop PNV or polypoidal choroidal vasculopathy (PCV). Therefore, PNV resides on the pachychoroid spectrum of disease, which also encompasses CSCR, PPE and PCV [1, 4]. All these diseases share characteristic choroidal alterations named pachychoroid; however, each one is a different disease. CSCR is defined as serous retinal detachment with or without pigment epithelial detachment (PED) lasting more than four to six months. PPE is a condition that is usually asymptomatic, characterized by RPE changes over the pachychoroid [2]. Finally, PCV is a variant of type-1 neovascularization characterized by a branching vascular network with terminal aneurismal (polypoidal) dilations, which can potentially bleed [2, 4]. It is important to note that PNV can also be extramacular, as recently reported by Gupta et al. in their review of a series of extramacular choroidal neovascular membranes [5].

Epidemiology

PNV is a newly defined choroidal neovascularization, so it could have been misdiagnosed as neovascular AMD. Recently, a report by Miyake et al. reviewed 200 consecutive Japanese patients with neovascular AMD. Only 80.5% of them were affected by neovascular AMD, the other 19.5% instead affected by PNV. The PNV group was significantly younger (68.7 vs 75.6, $P = 0.000051$), with a higher subfoveal choroidal thickness. Moreover, the authors observed a higher frequency of the *CFH* rs800292 G allele in AMD patients and a similar frequency of the *CFH* rs800292 A allele between the PNV group and normal Japanese subjects, validating the hypothesis of a different pathogenesis between PNV and neovascular AMD [6]. Hosoda et al. examined the correlation of choroidal thickness in PNV and neovascular AMD patients with *CFH* rs800292 allele frequency. In particular, an increased G allele frequency was noted in neovascular AMD patients, who usually have a thinner choroid, and an increased allele A frequency in PNV patients, who have a thicker choroid [7]. Dansigani et al. compared 12 single-nucleotide polymorphisms (SNPs) of the *CFH*, *ARMS2*, *CFHR4*, *CFHR5*, *FI3B*, *C3*, *CFB* and *C2* genes among PNV patients, neovascular AMD patients, pachychoroid patients without neovascularization and healthy subjects. They confirmed that PNV patients were ten years younger than those with neovascular AMD and differentiated them into neovascular and non-neovascular pathways based on genotype. The only SNP that showed a difference between neovascular AMD and PNV groups was rs2274700 of *CFH* [8].

Pathogenesis

It has been speculated that choroidal vessel expansion, named pachyvessels, could cause choriocapillaris ischaemia and RPE dysfunction, leading to neovascular proliferation [1, 9]. Nevertheless, the role of pachydrusen in the cascade of events is yet to be clarified. In particular, the presence of pachydrusen may cause RPE dysfunction, inducing choriocapillaris atrophy and arteriovenous shunting, with resultant choroidal vessel dilatation [10]. In contrast, choroidal vessel dilation associated with choriocapillaris atrophy could damage overlying tissues, allowing extracellular deposition of homogeneous material, the pachydrusen [11].

Moreover, evaluation of macular vortex vein morphology in PNV patients has shown dilation and a lack of horizontal separation through the macula between superior and inferior drainage areas, with the development of collateral veins that link the superior and inferior vortex veins. Collateral vein formation could compensate for choroidal venous congestion [12–14].

Nevertheless, to date, PNV pathogenesis has not been fully explained. Several reports have only confirmed a different angiogenic mechanism between neovascular AMD and PNV. In particular, Hata et al. reported lower VEGF-A (vascular endothelial growth factor A) levels in PNV patients than in neovascular AMD patients [15]. Terao et al. recently analysed

cytokine profiles in aqueous humour samples from PNV patients, comparing them to neovascular AMD and healthy subjects. Proinflammatory cytokines, such as IL-6 (interleukin 6), IL-8 (interleukin 8) and MCP-1 (monocyte chemoattractant protein 1), and VEGF-A, typically upregulated in the neovascular AMD group, were not upregulated in the PNV group. In contrast, the VEGF-A concentration was similar between the PNV and healthy groups. Moreover, in PNV patients, a lack of correlation between cytokine levels and anti-angiogenic treatment response has been noted, whereas a negative association is typical in neovascular AMD patients [16].

Another aspect that supports a different pathogenesis between PNV and neovascular AMD is the choroidal structure response to anti-VEGF treatment. The choroid is mainly composed of stroma and vessels without a well-organized structure, so clearly identifying all its layers is not easy. Sonoda et al. published a detailed protocol to differentiate and quantify the choroidal luminal area from the stromal area using the open access software ImageJ (National Institutes of Health, Bethesda, Maryland, USA; available at https://imagej.nih.gov/ij/). In particular, increased age and greater ocular axial length seemed to be correlated with reductions in luminal and stromal areas and the luminal-to-stromal area ratio [17]. Azuma et al. performed this choroidal analysis in 21 PNV patients and 34 neovascular AMD patients one month after intravitreal injection (aflibercept or ranibizumab). They also measured the area of choroidal neovascularization with fluorescein angiography (FA), foveal thickness with OCT and best-corrected visual acuity (BCVA). In neovascular AMD, improvement in BCVA was positively related to a smaller choroidal neovascularization (CNV) area at baseline, a greater reduction in choroidal luminal area and fewer aflibercept injections. These findings were not confirmed in PNV patients, validating the hypothesis of a non-VEGF-dependent mechanism responsible for PNV [18].

In conclusion, PNV pathogenesis is not fully understood, and compared to neovascular AMD, VEGF may play a different role, or other angiogenic factors may be involved.

Imaging

Fundus autofluorescence (FAF) in PNV displays patchy areas of granular hypoautofluorescence with scattered, distinct hyperautofluorescent specks due to RPE changes overlying pachyvessels, as in other pachychoroid spectrum diseases [6] (Fig. 1).

FA, like FAF, does not allow easy differentiation of pachychoroid spectrum disease (CSCR, PPE, PCV and PNV). In particular, neovascular AMD, CSCR and PNV display diffuse leakage and RPE atrophy. PNV shows late hyperfluorescence in the form of late leakage of uncertain origin, as does neovascular AMD, being both type-1 neovascularizations.[19, 20]. However, eyes with PNV do not exhibit classical serous macular detachment or characteristic changes in FAF, such as the descending tract seen in CSCR [2].

Indocyanine green angiography (ICGA) shows diffuse hypercyanescence in the mid- and late phases, proving choroidal hyperpermeability, which may be related to choriocapillaris structural damage, typical of the pachychoroid spectrum [21, 22]. It is notable that choroidal hyperpermeability is usually greater in PPE and CSCR than in uncomplicated

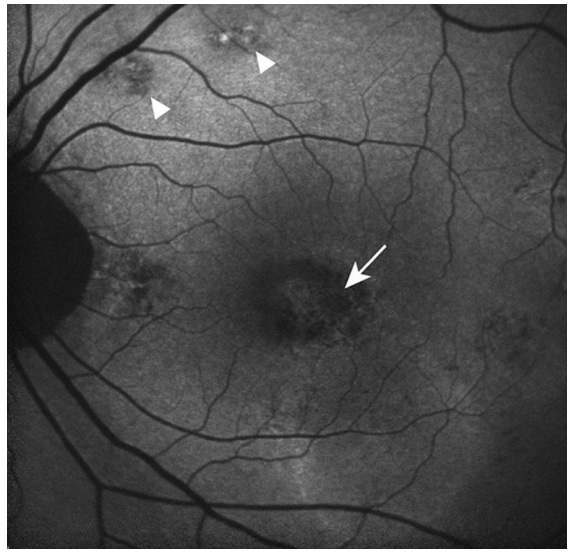

Fig. 1 FAF in a patient affected by PNV. FAF displays patchy areas of granular hypoautofluorescence with scattered, distinct hyperautofluorescent specks associated with choroidal vessel dilation (arrowheads) and a choroidal neovascularization lesion (arrow). Reproduced with the permission from reference [6]. This work is edited (Figure 3 cropped) and licensed under CC-BY license

pachychoroid phenotypes, though the choroidal vessel density and choroidal thickening are comparable [23]. Moreover, ICGA displays a late-staining plaque in PNV, as this is a type-1 neovascularization, which is fundamental for distinguishing PNV from PCV. Polypoidal choroidal vasculopathy is indeed characterized by hypercyanescent nodules with surrounding hypocyanescence in the initial phase that become hypercyanescent in the mid-late phase due to the leakage of terminal aneurismal dilations [2, 24]. In addition, in the case of quiescent neovascularization, which is well detectable on FA but without intraretinal/subretinal exudation on OCT, PNV and neovascular AMD have different behaviours on ICGA [25]. The latter is characterized by late plaque hypercyanescence, while PNV shows hypercyanescence only in the early–mid-ICGA phase, followed by late wash-out [26] (Fig. 2).

On OCT, PNV is characterized by a shallow irregular pigment epithelium detachment (PED), named the "double-layer" sign, where the upper hyper-reflective band corresponds to RPE and the lower one to Bruch's membrane, over a thick choroid [27, 28]. In particular, the presence of heterogeneously hyper-reflective material in the sub-RPE space further suggests the presence of neovascularization. Moreover, small peaked PED may develop at the margin of PNV, within which aneurismal lesions may be identified with OCT or ICGA. It is important to note that areas of type-1 neovascularization are spatially correlated with areas that display pachychoroid features [2].

Recently, optical coherence tomography (OCT) developments, such as enhanced depth OCT (EDI-OCT) or swept source OCT (SS-OCT), have allowed a detailed analysis of the choroid, leading pachychoroid disease to become a definite morphologic entity instead of a simple choroidal thickening. Consequently, in PNV, all the typical characteristics of pachychoroid spectrum disease can be found: First, there is a subfoveal choroidal thickness over 200 µm or an extrafoveal choroidal peak thicker than 50 µm compared to the subfoveal choroidal thickness [6, 29–31]. Second, a widespread or localized (in one or two quadrants) presence of pachyvessels (vein enlargement in Haller's layer) can be noted, correlating with choroidal thickening areas. A pachyvessel's peculiar characteristic is keeping its calibre constant towards the posterior pole and ending abruptly, unlike

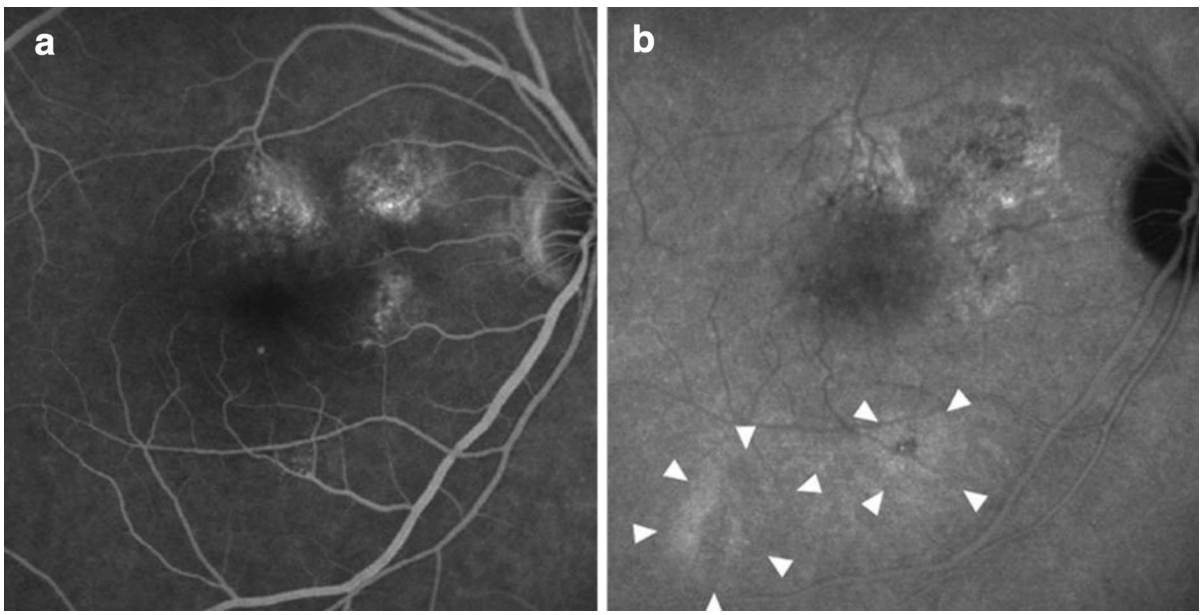

Fig. 2 FA and ICGA in a patient affected by PNV. **a** FA shows a type-1 neovascularization as late hyperfluorescence in the form of late leakage of uncertain origin. **b** Late phase of ICGA displays hypercyanescence of PNV and choroidal vascular hyperpermeability (arrowheads). Reproduced with the permission from reference [6]. This work is edited (Figure 5 cropped) and licensed under CC-BY license

physiological choroidal vessels, which taper before ending. Moreover, pachyvessels retain their large calibre, as they pass through the PPE, CSCR or PNV disease focus [2, 32]. Third, thinning of the choriocapillaris can be noted over the pachyvessel area, attesting to atrophy of the choriocapillaris and Sattler's layer and the possibility of developing a pachychoroid disease with a normal or reduced choroidal thickness [8]. Lastly, the presence of pachydrusen can be revealed, usually presented as a singular lesion, larger than 125 μm, with a scattered outer border, more defined compared to soft drusen [3]. Recently, Baek et al. elucidated the pachydrusen distribution in the pachychoroid spectrum. Usually, it is located peri- or parafoveally rather than subfoveally; in particular, perifoveal lesions are more prevalent in PNV. Moreover, the number of pachydrusens per eye was higher in PNV and PCV (PPE 1.38 ± 0.99, CSCR 1.36 ± 0.73, PCV 1.95 ± 1.24, PNV 1.84 ± 1.05 $P = 0.036$), supporting the hypothesis of sequential processes of disease progression, from PPE and CSCR to PNV and PCV [10]. Therefore, in pachychoroid spectrum disease, a complete morphological choroidal evaluation should be performed instead of only measuring the choroidal thickness. Interestingly, Lee et al. measured subfoveal choroidal thickness and performed a choroidal analysis using the protocol described by Sonoda et al. in patients affected by CSCR, PNV, PPE, or myopic choroidal neovascularization and healthy subjects. Subfoveal choroidal thickness was greater in CSCR, PNV and PPE than in healthy subjects (467.05 μm, 399.35 μm and 411.50 μm vs 282.61 μm, respectively, $P < 0.001$, $P = 0.002$ and $P < 0.001$), but no differences were noted among pachychoroid groups. Moreover, the luminal area increase was correlated with subfoveal choroidal thickness in the PNV and CSCR groups. It is also important to note that significant stromal area reduction was reported in the CSCR group compared to the PNV and PPE groups, validating the hypothesis of different pathogenic processes in pachychoroid spectrum diseases [33] (Fig. 3).

Finally, neovascularization can be highlighted noninvasively with optical coherence tomography angiography (OCTA), which shows an entangled vascular network between RPE and Bruch's membrane, with well-defined margins and irregular shapes [34]. According to several studies, OCTA may detect choroidal neovascularization more frequently than the combination of OCT, FA and ICGA [35–38]. However, Arf et al. reported that OCTA could not identify neovascularization in 11.8% of eyes with PNV, but it

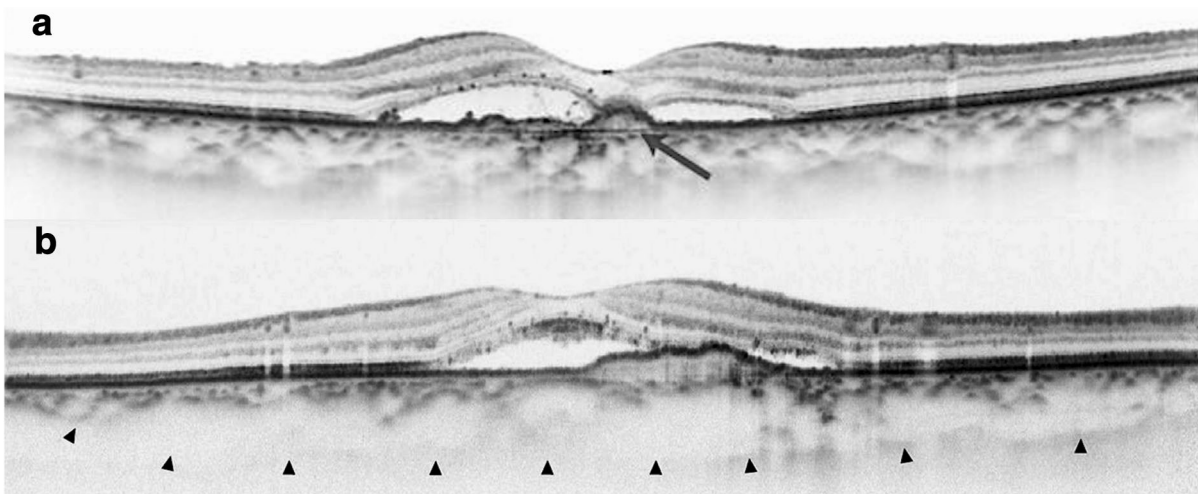

Fig. 3 EDI-OCT in two patients affected by PNV. **a** In the first patient, EDI-OCT shows a PNV as a shallow irregular PED (the "double layer sign") (arrow) associated with subretinal fluid, a thick choroid and no drusen. **b** In the second patient, EDI-OCT shows the "double layer sign" with subretinal fluid over a thick choroid (arrowheads) (subfoveal choroidal thickness 353 μm). Reproduced with the permission from reference [6]. This work is edited (Figure 4 and Figure 5 cropped and contrast increased) and licensed under CC-BY license

Table 1 Imaging in PNV

Imaging technique	Role	Main features
FAF	RPE changes evaluation	Patchy areas of granular hypoautofluorescence with occasional distinct hyperautofluorescence specks
FA	Not specific for PNV evaluation	Diffuse hyperfluorescence and late leakage with undetermined origin
IGCA	Proves choroidal hyperpermeability and characterizes PNV lesion	Diffuse hypercianescence in mid-late ICGA phases and late staining plaque. In case of quiescent neovascularization PNV shows early–mid-hypercianescence followed by late wash-out
OCT	Allow characterization of PNV	Pigment epithelium detachment named "double-layer" sign (the upper hyper-reflective band corresponds to RPE and the lower one to Bruch's Membrane); small peaked PED at the margin of PNV
EDI-OCT or SS-OCT	Allow detailed analysis of choroid	Increased subfoveal choroidal thickness (over 200 μm), pachyvessels, thinning of choriocapillaris, perifoveal pachydrusen
OCTA	Confirm the presence of neovascular lesion; evaluate the spatial correlation between choriocapillaris blood flow and pachyvessels	Hyper-reflective filamentous neovessels, between retinal pigment epithelium and Bruch's membrane, with well-defined margin and irregular shape

FAF fundus autofluorescence, *FA* fluorescein angiography, *IGCA* indocyanine green angiography, *OCT* optical coherence tomography, *EDI-OCT* enhanced depth OCT, *SS-OCT* swept source OCT, *OCTA* OCT angiography, *PNV* pachychoroid neovasculopathy, *PED* pigment epithelium detachment

could be identified on ICGA images. Therefore, they suggested that dye angiography remains the gold standard for identifying neovascularization, especially in treatment-naïve patients [39]. OCTA is a noninvasive imaging technique, so it should be considered a useful tool in guiding the frequency of follow-up examinations and treatment decisions in pachychoroid disease [26] (Table 1).

Recently, to allow easier detection and better management of PNV, Miyake et colleagues proposed four diagnostic criteria (all must be met) using multimodal imaging methods [6]:

- CNV in either eye on FA;
- Subfoveal choroidal thickness $\geq$ 200 μm in both eyes on EDI-OCT or SS-OCT;
- No drusen or only non-extensive (limited to an area less than 125 μm in diameter) hard drusen (diameter $\leq$ 63 μm) (Age-Related Eye Disease Study (AREDS) category 1);
- Choroidal vascular hyperpermeability (hypercyanescent focal area in the middle ICGA phase) or RPE anomaly (patchy areas of granular hypoautofluorescence with scattered, discrete hyperautofluorescent specks) or the presence of dilated choroidal vessels below CNV or a history of CSCR.

The subfoveal choroidal thickness reported in the literature ranges from 200 to 395 μm [2, 29–31]. To make the above-mentioned criteria more inclusive, some authors chose the lowest thickness value reported. They also suggested that all CNVs with extensive hard drusen, soft drusen, pseudodrusen, focal hyperpigmentation or geographic atrophy should be considered neovascular AMD, highlighting that choroidal thickness per se is not the most important criterion for defining the pachychoroid disease phenotype [6]. Finally, since PNV may respond differently to photodynamic therapy (PDT) or anti-VEGF therapy, discriminating it from neovascular AMD is of great importance, and these criteria make fundamental headway in achieving this goal [6].

Treatment

Anti-VEGF therapy

PNV is a recently described clinical entity; therefore, studies about treatment efficacy and safety are few, with limited follow-up and a small number of participants.

In neovascular AMD, intravitreal anti-VEGF has been shown to be effective in reducing the subfoveal choroidal thickness, suggesting a possible therapeutic role in PNV regardless of the pathogenesis [15, 40, 41].

Miyaki et al. treated 22 PNV and 86 neovascular AMD patients with three intravitreal ranibizumab injections monthly. The rate of dry macula did not differ significantly between the two groups (90.9% vs 83.7% $P = 0.51$). However, the PNV group had a longer retreatment-free period ($P = 0.0095$) at one year of follow-up [6].

Padron-Péréz et al. treated 18 PNV patients with anti-VEGF intravitreal injections, matching each patient's treated and untreated eyes to assess variation. Subfoveal choroidal thickness decreased significantly from 317.7 µm to 266.9 µm ($P \leq 0.001$) at 12 months of follow-up, without a significant BCVA improvement. Interestingly, subfoveal choroidal thickness decreased according to the number of intravitreal injections (rs = 0.762, $P < 0.001$), but it remained stable in the untreated eye group [42].

Matsumoto et al. reviewed 42 eyes with PNV and 60 with neovascular AMD that were treated with a treat-and-extend intravitreal aflibercept regimen (2 mg/0.05 ml) and followed up for 24 months. Both groups showed a significant BCVA and central macular thickness (CMT) improvement from baseline, but without significant intergroup differences. However, PNV patients required fewer injections (13.2 ± 0.5 vs 13.8 ± 0.4, $P < 0.05$) and showed a greater reduction in subfoveal choroidal thickness (54 µm vs 29 µm, $P < 0.05$) [43].

Azuma et al. treated 21 PNV patients with a single aflibercept or ranibizumab intravitreal injection, evaluating them one month after treatment. The BCVA improvement was not statistically significant (LogMAR -0.05 $P = 0.17$), and subfoveal choroidal thickness was only measured at baseline (306 ± 80 µm) [18].

Cho et al. enrolled 205 patients, 22 with PNV and 183 with neovascular AMD, treating them with three anti-VEGF injections (2 mg/0.05 ml of aflibercept or 0.5 mg/0.05 ml of ranibizumab) monthly, followed by pro re nata injections in case of CNV or subretinal fluid (SRF) persistence. No significant differences in terms of BCVA improvement or CMT were shown between groups, though the PNV group did have a younger age, better BCVA at baseline, a lower retreatment rate after the loading dose (59.1% vs 80.9% $P = 0.018$), a lower injection rate (4.2 vs 4.9 $P = 0.031$) and a longer treatment-free period (6.1 vs 4.3 months, $P = 0.006$) [44].

Jung et al. compared the efficacy of a loading dose of three intravitreal aflibercept (2 mg/0.05 ml) injections versus three intravitreal bevacizumab (0.5 mg/0.05 ml) injections in 54 PNV patients. After three months, the aflibercept group showed a significantly higher subfoveal choroidal thickness reduction (35 µm vs 9 µm, $P = 0.013$) and a complete fluid reabsorption rate (82.6% vs 51.6% $P = 0.018$); nevertheless, BCVA improvement and CMT reduction were similar. Patients not responding to bevacizumab at three months switched to aflibercept, and 86.7% obtained complete fluid reabsorption. Interestingly, patients who did not respond to aflibercept or bevacizumab were treated with PDT, showing completely dry macula in 100% of cases three months after treatment, without fluid accumulation recurrence within 1 year of follow-up. At the end of follow-up, the mean BCVA and CMT of all 54 patients had significantly improved (BCVA from 0.45 ± 0.25 to 0.26 ± 0.25 LogMAR, $P < 0.001$ and CMT from 337 ± 53 µm to 251 ± 68 µm $P < 0.001$) [45].

Finally, anti-VEGF therapy has also been used in the treatment of extramacular PNV. In particular, Gupta et al. treated only two patients out of four because PNV exudation increased and patients complained of photopsia. One patient showed no response to the treatment, and the other patient presented stable exudation but resolution of the photopsia. Visual acuity remained stable in all cases during follow-up [5].

PDT therapy

PDT induces choroidal hypoperfusion, which should reduce choroidal thickness. As a treatment for PNV, it was first described by Pang et al. They treated two

Table 2 PNV treatment results

Study (year)	Patients enrolled	Age	Previous therapy	Regimen	Drugs	Follow-up (months)	Baseline BCVA (logMAR)	Follow-up BCVA (logMAR)
Miyaki et al. [6]	22	68.5 ± 8.5	None	3 injections monthly	Ranibizumab 0.5 mg	12	n/a	n/a
Padron-Perez et al. [42]	18	68.3 ± 7.0	None	treat-and-extend	Aflibercept 2.0 mg or Ranibizumab 0.5 mg	12	0.4 (SD n/a) Range (0.8–0.1)	0.3 (SD n/a) Range (0.9–0.1)
Matsumoto et al. [43]	42	67.5 ± 1.3	None	treat-and-extend	Aflibercept 2.0 mg	24	0.20 ± 0.05	0.11 ± 0.05
Azuma et al. [18]	21	73.7 ± 9.8	None	1 intravitreal injection	Aflibercept 2.0 mg or Ranibizumab0.5 mg	1	0.54 ± 0.39	0.48 ± 0.42
Cho et al. [44]	22	62.5 ± 7.8	None	pro re nata		12	0.50 ± 0.32	0.31 ± 0.28
Jung et al. [45]	54	64.0 ± 7.6	None	treat-and-extend	Aflibercept 2.0 mg or Ranibizumab0.5 mg	3	0.45 ± 0.26	n/a
					In particular 31 with Ranibizumab		0.46 ± 0.24	0.38 ± 0.31
					In particular 23 with Aflibercept		0.43 ± 0.26	0.27 ± 0.21
Lee and Lee [46]	28	66 ± 8.0	At least 4 anti-VEGF intravitreal injections in the past 6 months	Standard fluence	PDT	3	0.42 ± 0.31	0.34 ± 0.30
Roy et al. [47]	6	56.5	None	Half fluence	2 PDT	8.2	0.41	0.44
					4 PDT followed by 1 Ranibizumab 0.5 mg			

Study (year)	Improvement	Baseline CMT (μm)	Follow-up CMT (μm)	Improvement	Baseline SFCT (μm)	Follow-up SFCT (μm)	Improvement
Miyaki et al. [6]	n/a	n/a	n/a	n/a	310 ± 53	n/a	n/a
Padron-Perez et al. [42]	Not significant $P = 0.38$	n/a	n/a	n/a	317.7 ± 39.9	266.9 ± 56.3	Significant $P < 0.001$
Matsumoto et al. [43]	Significant $P < 0.001$	257 ± 16	154 ± 10	Significant $P < 0.001$	342 ± 16	288 ± 15	Significant $P < 0.001$
Azuma et al. [18]		n/a	n/a	n/a	306 ± 80	n/a	n/a
Cho et al. [44]	Significant $P = 0.021$	373 ± 184	195 ± 137	Significant $P < 0–001$	324 ± 92	n/a	n/a

Table 2 continued

Study (year)	Improvement	Baseline CMT (μm)	Follow-up CMT (μm)	Improvement	Baseline SFCT (μm)	Follow-up SFCT (μm)	Improvement
Jung et al. [45]	n/a	337 ± 53	n/a	n/a	436 ± 83	n/a	n/a
	Significant	332 ± 54	276 ± 60	Significant	438 ± 78	429 ± 75	Significant
	$P = 0.002$			$P < 0.001$			$P = 0.042$
	Significant	345 ± 52	264 ± 83	Significant	433 ± 93	399 ± 96	Significant
	$P = 0.013$			$P = 0.004$			$P < 0.001$
Lee and Lee [46]	Significant	342 ± 63	241.6 ± 60.0	Significant	386 ± 80	350 ± 91.1	Significant
	$P = 0.040$			$P < 0.001$			$P < 0.001$
Roy et al. [47]	Significant	n/a	n/a	n/a	445	293	Significant
	$P = 0.030$						$P = 0.020$

BCVA best-corrected visual acuity, *CMT* central macular thickness, *SFCT* subfoveal choroidal thickness

patients with PNV with standard fluence PDT and showed a modest SRF improvement after intravitreal anti-VEGF therapy. The first patient achieved a complete SRF resolution for 4 months. The second group showed a definite SRF reduction without complete reabsorption. Afterward, both continued to receive anti-VEGF [1].

Dansingani et al. published a case report of a 54-year-old female with a history of CSCR for 4 years. She developed a PNV and was treated with eleven intravitreal injections of aflibercept followed by half-fluence PDT. At one year of follow-up, SS-OCT showed persistent serous macular detachment, with stabilization of the irregular pigment epithelium detachment and pachyvessels [27].

Lee and Lee recently treated 28 eyes with PNV with PDT, refractory to at least four intravitreal anti-VEGF injections performed in the last six months. At three months of follow-up, complete fluid absorption was observed in 85.7% of cases, with a mean BCVA improvement from 20/53 to 20/44 ($P = 0.04$) and subfoveal choroidal thickness reduction from 386 μm to 350 μm ($P < 0.001$). At one year, 60.7% of patients were free of recurrent fluid accumulation, and BCVA improved $\geq$ 0.3 LogMAR in 96.4% [46].

Roy et al. reviewed six consecutive cases of PNV, four treated with PDT and intravitreal ranibizumab injection and two with PDT alone. The median follow-up was 8.2 months. BCVA and subfoveal thickness significantly improved from the initial presentation to the final visit, from 0.41 to 0.44 LogMAR units ($P = 0.03$) and 445 μm to 293 μm ($P = 0.02$) [47] (Table 2).

Other treatments

Recently, a subthreshold micropulse laser (SML) has been suggested as a valid alternative to PDT in CSCR treatment by the PACORES (Pan-American Collaborative Retina Study) group and others [48–50]. SML generates a high peak temperature around RPE intracellular melanosomes, avoiding any damage to photoreceptors. The exact mechanism of action of SML is not fully understood; it is believed that SML stimulates RPE metabolism, improving its function, but it should also suppress VEGF production and upregulate angiogenic inhibitors [51–54]. Therefore, SML could play a role in PNV treatment, but no study has been published on it yet.

Another therapeutic option could be thermal argon or diode laser ablation for extramacular PNV, though not for macular PNV due to scarring and subsequent central scotoma development; however, to date, no report has been published [5, 55].

A final second-line treatment could be transpupillary thermal therapy. In this modality, a laser of wavelength 810 nm is mainly absorbed in the choroid, allowing an effective treatment of pachychoroid diseases [56–58]. To date, no report has been published, so its potential role has not yet been proven.

Conclusion

PNV is a new clinical entity belonging to the pachychoroid spectrum that is frequently misdiagnosed as neovascular AMD. For this reason, epidemiological data are lacking, and its pathogenesis is not fully understood. PNV patients are usually younger than neovascular AMD patients and have a history of CSCR or PPE. Additionally, patients with neovascular AMD could have a history of CSCR or PPE.

Nevertheless, in current clinical practice, imaging improvements, such as SS-OCT, EDI-OCT and OCTA, have allowed a better characterization of PNV and have helped ophthalmologists make proper diagnoses, even in cases of quiescent neovascularization. In particular, it is important to remark that PNV is a type-1 neovascularization, with no drusen or only non-extensive hard drusen, over an area of increased subfoveal thickness.

Treatment is based on intravitreal anti-VEGF injections, the same as for neovascular AMD, with a loading dose of three monthly injections, followed by additional injections if needed. Usually, PNV patients have a longer retreatment-free period than AMD patients and require fewer injections during the follow-up. According to reported results, aflibercept seems more effective in fluid reabsorption than other anti-VEGF agents, but the BCVA is similar after treatment. PDT is a second-line treatment with significant efficacy in terms of fluid absorption in patients non-responsive to anti-VEGF.

Nevertheless, ongoing research into pathophysiology may further benefit the care of patients presenting with PNV. Finally, diagnostic improvements may be helpful in defining prognostic criteria and stratifying patient risk to promote better disease management.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Informed consent Informed consent was not applicable in this study.

Human and animal rights This article does not contain any studies with human participants or animals performed by any of the authors.

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