5 Current Understanding of Polypoidal Choroidal Vasculopathy

An Overview on Clinical and Genetic Aspect of Polypoidal Choroidal Vasculopathy

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Abstract

Polypoidal choroidal vasculopathy (PCV) is a common subtype of age-related macular degeneration (AMD) in Asians. PCV is characterized by branching vascular networks and polypoidal lesions in the choroidal vasculature. Since it was first described four decades ago, there is significant progress in the diagnosis, etiopathogenesis, and treatment of PCV. The progress was driven by the advancement of multimodal imaging including indocyanine green angiography and optical coherence tomography, genome-wide association studies, and animal model investigations. There is clear evidence that PCV has distinct clinical characteristics, natural histories, and treatment outcomes compared with the wet type AMD that is typical in Western populations. In this review, we summarize the current understanding of PCV with a focus on the parallel studies from the clinical setting and animal models.

Keywords

Polypoidal choroidal vasculopathy · Age-related macular degeneration · Choroidal neovascularization · Exudative age-related macular degeneration · Pachychoroid neovasculopathy

5.1 Introduction

Age-related macular degeneration (AMD) is a leading cause of irreversible blindness in the elderly. Approximately 8.7% of the worldwide population suffers from AMD, with the number of cases expected to rise from around 196 million in 2010 to around 288 million in 2040 [1]. Wet AMD (also called neovascular AMD, or nAMD) includes choroidal neovascularization (CNV) and polypoidal choroidal vasculopathy (PCV). CNV describes the growth of new blood vessels from the choroid into the subretinal space whereas PCV refers to choroidal vessel abnormalities (e.g., polypoidal dilations) [2]. PCV is a common subtype of wet AMD in Asian populations while CNV is the typical subtype in Western populations. PCV is frequently associated with recurrent hemorrhagic or exudative pigment epithelium detachment (PED). The clinical course of PCV

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G. Prakash, T. Iwata (eds.), *Advances in Vision Research, Volume III*, Essentials in Ophthalmology,
https://doi.org/10.1007/978-981-15-9184-6_5

is generally more stable and visual outcomes are more favorable compared with CNV. The current anti-VEGF therapy is less effective in treating PCV compared with classic CNV. Research from genetic, clinical, and animal model investigations have shed light on the pathophysiological mechanism of PCV. We will discuss these areas in this review.

5.2 Epidemiology and Global Perspective

PCV has ~four-fold higher prevalence in pigmented races (e.g., African, Japanese, Chinese, and other Asians) than the non-pigmented races like Caucasian [2]. This is clearly opposite to the incidences of CNV in the Caucasian population. The estimated prevalence of PCV is 22.3%–61.6% among Asians [3] in contrast to 8%–13% of CNV in Caucasians [4]. There is a marked male preponderance of 63%–78.5% and only 5.9%–24.1% have bilateral disease. In Caucasians, women are predominantly affected at a ratio of 4.7:1 [4]. PCV is generally diagnosed in patients between the ages of 50 and 65 years though it can range from the 20s to 80s. The average affected age among the Korean, Chinese, Japanese, and the Indian population is 60–65 [5]. The average age of onset in Caucasians is 75.4 years [6]. 92% of Japanese patients' PCV occurs in the central macula, whereas there is an even distribution of macular and peripapillary location in Europeans. Only 14% of Japanese patients develop bilateral disease, in contrast to 32% of Europeans [2].

5.3 Etiopathogenesis

Smoking is a known risk factor for AMD and also appears to be an important risk factor for PCV. Two population-based studies in the Japanese demonstrated that cigarette smoking is associated with an odds ratio of 4.4 and 4.87 for PCV when compared with normal controls [7, 8]. Various inflammatory cytokines and systemic factors are associated with PCV and CNV and may cause PCV and CNV by compromising the capacity of the immune system to handle immunological stress and resulted in an immune imbalance. Systemic serum biomarker analysis has been used to differentiate between PCV and CNV. Subhi et al. found that inflammatory C-reactive protein (CRP) protein in the plasma of PCV patients was elevated but other inflammatory cytokines interleukin (IL)-1β, IL-6, IL-8, IL-10, and tumor necrosis factor receptor 2 (TNF-R2) were similar to the healthy controls [9]. Other studies reported elevated proinflammatory cytokine levels, including IL-1b and IL-23, in aqueous and vitreous samples, which support a role for inflammation in PCV [10, 11]. Increased plasma homocysteine levels are linked to retinal diseases such as retinal vascular occlusion and diabetic retinopathy [12–14]. In the Chinese PCV population, 1 μmol/L of increase of plasma homocysteine to the basal level increases the 1.5-fold risk to develop PCV [15]. Because higher levels of homocysteine had been linked to endothelial injury and increased oxidative stress [16, 17], it was hypothesized that elevated levels of homocysteine may induce injury to choroidal arteries and cause aneurysmal like dilations (polyps) and arteriosclerosis of choroidal vessels in PCV [15]. In addition, increased levels of matrix metalloproteinase (MMP 2 and MMP 9) were detected in PCV lesions, and both MMPs were increased in the serum of PCV patients, suggesting that they may have a role in the pathogenesis of PCV [18, 19].

In Clinic, PCV patients typically presented with inner choroidal vasculature abnormalities accompanied by extensive exudation, bleeding, and proteinaceous leakage followed with lipid deposition from active polypoidal vascular lesions [2, 20]. Surgically extracted specimens from PCV patients showed thickened and complete or partial obstruction of hyalinized choroid vessels walls due to the extravasation of plasma protein and deposition of basement membrane-like material beneath the Bruch's membrane [21, 22]. Stagnation of blood was evidenced by the presence of blood cells in the vascular cavity, and adherence of neutrophils to the inner ves-

sel walls [22]. Microscopic examination identified degenerative changes in the inner elastic layer and arteriosclerotic nature of the choroid vessels. An increase of deposition of basement membrane-like material together with collagen fibers in the arteriolar walls was also featured in the PCV specimen [23]. Complete or varying severe to a partial loss of α-SMA was detected in the hyalinized vessels in the PCV specimen [22]. Moreover, exudative changes around the vessels were more significant in PCV compare to the CNV portion of the excised specimen. CD34, an endothelial cell marker, immunostaining was found to be discontinuous in PCV while the CNV portion of tissue was presented with in continuity in vascular endothelium [22]. Recently based on the histopathological features of the autopsy tissue obtained from a 60-year-old African American woman with PCV, Tso M et al. suggested that PCV may be a venous stasis choroidopathy condition [24]. They observed that PCV is composed of dilated vascular channels consisting of thin wall venules intertwined with arteriosclerotic choroidal arterioles. Occlusion of these choroidal vascular channels might give rise to choroidal stasis and ischemia leading to serous RPE detachment and a sub-RPE neovascular membrane. Gross dilatation of the choroidal venules and capillaries in the sub-RPE neovascular membrane leads to the characteristic "grape like" structures, a unique clinical feature in this disease entity. Tso M et al. hypothesized that choroidal venular stasis is one of the primary causes of PCV pathogenesis.

Based on genome-wide association studies implicating the involvement of high temperature requirement factor A1 (HTRA1), a multifunctional secreted serine protease that is ubiquitously expressed in mammalian tissues, in AMD including PCV [25–29], we generated the first PCV model by transgenically expressing human HTRA1 in mouse RPE [30, 31]. Increased expression of HTRA1 induced two key features of PCV, polypoidal dilations (polyps) and branching vascular network (BVN), in transgenic *hHTRA1*$^{+}$ mice. BVN (Fig. 5.1a, red circles) and polyps (Fig. 5.1a, blue arrows) begin to appear ~1 min after ICG injection in the early phase (0–4 min) and become more distinct in the middle phase (6–15 min) and late phase (18–22 min) with the fading of the choroidal vasculature. More lesions started to appear in the middle phase (Fig. 5.1a, black arrows). On funduscopy, polypoidal lesions appear as reddish-orange nodules (Fig. 5.1b, middle row, white arrowhead; bottom row, red box). A cluster of polypoidal lesions, which faded at the late phase of ICGA, appears on the fundus as a cluster of reddish-orange nodules (Fig. 5.1b, bottom row, red box). Hemorrhagic (Fig. 5.1b, middle row, white stars) and serous (Fig. 5.1b, bottom row, white asterisks) PEDs, RPE degeneration (Fig. 5.1b, bottom row, yellow arrow) as well as yellowish hard exudates (Fig. 5.1b, middle row, green arrow) were observed near the lesion site. These phenotypes share remarkable similarities to the well-established clinical features of human PCV. By performing comprehensive genetic, histopathological, imaging, and molecular biological studies on the *hHTRA1*$^{+}$ PCV mouse model in combination with analysis on human PCV specimens, we demonstrated that HTRA1 mediated degradation of elastin in choroidal vessels is critical for the development of PCV, which exhibited destructive extracellular matrix remodeling and vascular smooth muscle cell loss [18]. Compared with weak PCV, severe PCV exhibited prominent immune complex deposition, complement activation, and infiltration of inflammatory cells, suggesting inflammation plays a key role in PCV progression. Based on this study, we proposed a two-stage process for PCV pathogenesis: PCV initiation is mediated by increased HTRA1 activity while progression is driven by chronic inflammation.

5.4 Clinical Features

Although both PCV and CNV are related to choroidal vasculature, they are different in clinical nature. In CNV, abnormal choroid vessels break the Bruch's membrane (BM) and grow into the sub-RPE or subretinal space, while PCV arises

within the inner choroidal vasculature and characterized by the formation of branching vascular networks (BVN) that terminates in aneurism like polypoidal lesions. PCV was characterized as a variant of a type 1 neovascularization in which the abnormal choroid vessels are located in the sub-RPE space [2]. In the early phase of PCV, patients typically presented with extensive subretinal exudation and bleeding with minimal cystic changes and negligible impact on the retina function. PCV may progress to an advanced phase very quickly due to proteinaceous leakage followed with lipid deposition from active polypoidal vascular lesions with a significant impact on the retinal function [2, 20].

Although fluorescein angiography (FA) is routinely used in the diagnosis of CNV, the use of FA in PCV is limited since FA is not able to reli-

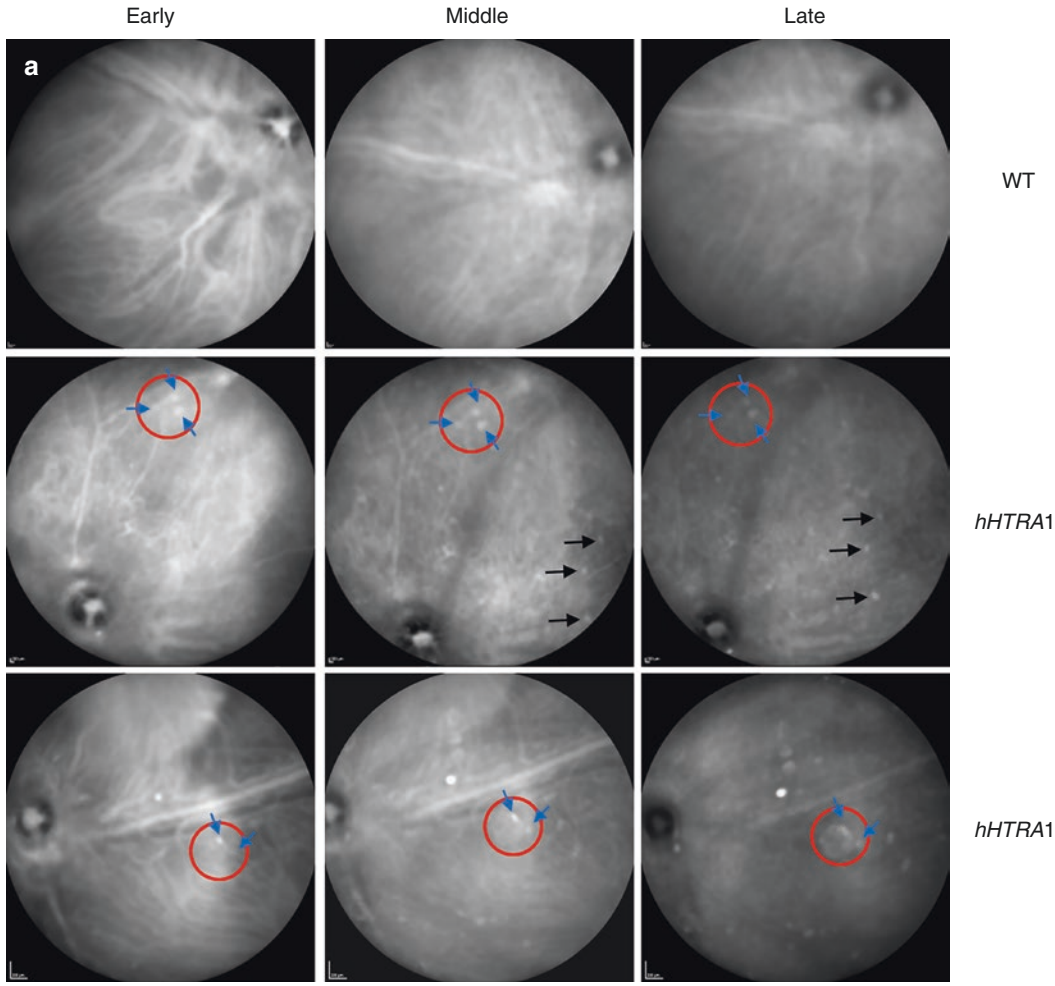

Fig. 5.1 ICGA and funduscopic features of PCV lesions in *hHTRA1*$^{+}$ mice. (**a**) Angiographic features of *hHTRA1*$^{+}$ mice on time course ICGA. The early, middle, and late phases of ICGA were recorded for wild-type (WT) control and *hHTRA1*$^{+}$ mice. *hHTRA1*$^{+}$ mice developed polyp dilations (blue arrows) and BVN (red circles) from the early phase. More lesions started to appear in the middle phase (black arrows). (**b**) Funduscopic examination of WT control and *hHTRA1*$^{+}$ mice. In *hHTRA1*$^{+}$ mice, reddish-orange nodules, which correspond to PCV lesion structures based on ICGA, are indicated (middle row, white arrowhead; bottom row, red box). Hemorrhagic (middle row, white stars) and serous (bottom row, white asterisks) PEDs, RPE degeneration (bottom row, yellow arrow) as well as yellowish hard exudates were observed near the lesion site (middle row, green arrow). Reproduced from Invest. Ophthalmol. Vis. Sci. 55, 3842–3850. Copyright the Association for Research in Vision and Ophthalmology

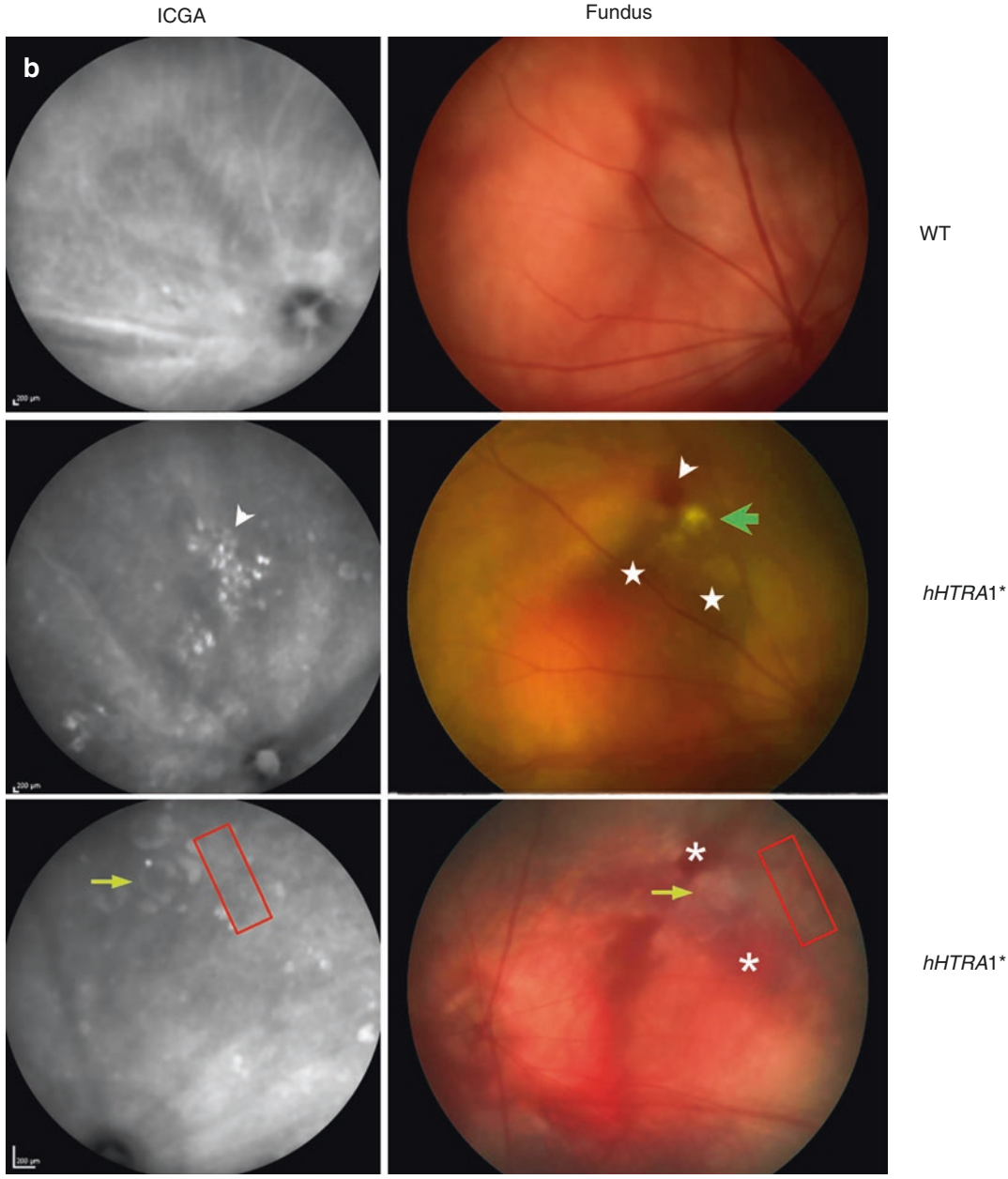

Fig. 5.1 (continued)

ably detect polys. Indocyanine green angiography (ICGA) is considered the gold standard for the diagnosis of PCV due to its capability to image the posterior choroidal vasculature [2]. Polyps (single or multiple) can be detected in the early phase of ICGA. BVN and other features can be visualized with confocal scanning ophthalmoscopy. On fundoscopy, the presence of orange-red subretinal nodules with corresponding ICG hyperfluorescence is characteristic of PCV [32]. Both FA and ICGA are required to differentiate PCV from CNV. FA can detect occult choroidal neovascularization (CNV) while ICGA can visualize of the abnormal polypoidal lesions.

Optical coherence tomography (OCT) imaging is especially useful to detect subretinal fluid, PED, and polypoidal lesions [2, 33]. In addition to BVN and polyps, other clinical features such as late geographic hyperfluorescence (LGH) [34, 35] and hyperfluorescent plaque [36, 37] have been visualized in PCV eyes based on ICGA.

By examining the PCV phenotypes (e.g., lesion type, distribution) of the PCV model *hHTRA1*$^{+}$ mice by a variety of in vivo imaging techniques (ICGA, funduscopy, and SD-OCT), we found the *hHTRA1*$^{+}$ mice exhibit additional features that are present in PCV and wet type AMD, e.g., LGH, plaque, and PED, in addition to BVN and polyps [31]. SD-OCT located the lesions in the choroid while round protrusions of the RPE can be detected, which is consistent with polypoidal lesions. It is intriguing that male *hHTRA1*$^{+}$ mice exhibit more severe types of lesions (e.g., LGH and PED) than females. This is reminiscent of the higher incidence of PCV in males than females in Asians although the opposite is true for Europeans [2, 3]. In particular, we are the first to perform ICGA on PCV animal models by tail-vein injection of ICG to obtain high-quality ICGA comparable to human studies in terms of the three phases (early, middle, and late) of angiography [31, 38]. By using this technique, the polyps can be detected in the early "fill-in" phase of ICGA, most lesions become visible in the middle phase and more distinct in the late phase with the fading of surrounding vessels (Fig. 5.1a). This technique is also useful to distinguish between different types of lesions, e.g., LGH vs. plaques. This animal model will provide an invaluable tool for future mechanistic and translational studies (e.g., drug screening) of PCV and other forms of choroidal vasculopathies.

Recently, a new clinical entity of type 1 neovascularization termed pachychoroid neovasculopathy associated with choroidal thickening, but lacking soft drusen and other typical AMD findings, was reported [39]. Some investigators suggest PCV falls within the pachychoroid spectrum of conditions including pachychoroid pigment epitheliopathy, central serous chorioretinopathy, and PCV [40–43]. These studies provide some evidence that PCV is a pachychoroid-driven disorder with findings of similar choroidal features and the occurrence of polypoidal lesions in eyes lacking typical AMD features [36, 42, 44]. However, several studies also suggested that pachychoroid as an underlying cause for focal choroidal excavation [40], geographic atrophy named as pachychoroid geographic atrophy [43], peripapillary exudative changes named as peripapillary retinoschisis [41], peripapillary pachychoroid syndrome [45], and pachydrusen [46]. Further studies are necessary to clarify the relationship between pachychoroid neovasculopathy and PCV.

5.5 Genetic Aspects

Genetic association studies from Chinese and Japanese populations indicated that genetic loci related to AMD such as the complement cascade, inflammatory pathway, extracellular matrix/basement membrane regulation pathway, and lipid metabolism are associated with PCV [3, 47]. A recent study on the SNP meta-analysis in East Asian population revealed that eight genes linked to CNV including *HTRA1*, age-related maculopathy susceptibility2 (ARMS2), complement system factor H (CFH), factor B (CFB), component 2 (C2), Super killer viralicidic activity 2-like (SKIV2L), and cholesterol ester transfer protein (CETP) are also significantly associated with PCV [48]. Particularly, numerous studies have shown that genetic loci in chromosome 10q26 surrounding HTRA1 and ARMS2 are strongly associated with AMD including PCV [25, 27–29, 49–52]. However, a series of studies on the influence of AMD-associated polymorphisms on the expression of ARMS2 and/or HTRA1 have yielded conflicting results [29, 53–58]. However, recent studies started to provide evidence that variants in the promoter region of HTRA1 can transcriptionally upregulate HTRA1 [59, 60]. Transgenic expression of HTRA1 or ARMS2 in mouse has shown that overexpression of HTRA1 but not ARMS2 induced PCV and CNV [30, 31, 59, 60]. Furthermore, we showed that HTRA1

protein was significantly increased in RPE and degenerating choroidal vessels of PCV lesions in human specimens, suggesting HTRA1 likely plays a causal role in PCV pathogenesis [18]. Interestingly, a rare missense (Lys329Arg) variant of the FGD6 gene in the Han Chinese population was found to be significantly associated with PCV but not with CNV. FGD6-Arg329 promoted more abnormal vessel development in the mouse retina than FGD6-Lys329, suggesting that oxidized phospholipids and FGD6-Arg329 might act synergistically to increase susceptibility to PCV [61]. A GG missense variant at rs5882 in the CETP locus was found to have a 3.53-fold increased risk of PCV compared with the AA genotype. PCV patients with the rs5882 GG genotype had lower serum high-density lipoprotein levels than the AA genotype [62]. The CFH Y402H polymorphism might also have a synergistic effect on cigarette smoking to further increase the risk of PCV [63]. The c.6196A > G variant in the IGFN1 gene was found to be significantly associated with only PCV (combined $p = 7.1 \times 10^{-11}$, odds ratio = 9.44), but not with CNV (combined $p = 0.683$, odds ratio = 1.30). The minor allele G conferred an increased risk of PCV [64].

5.6 Clinical

Depending on the state of PCV (active or inactive), several treatment options, e.g., thermal laser photocoagulation (TLP), verteporfin PDT (vPDT), anti-VEGF therapy, and various combinations of these therapies are available. ICGA-guided direct TLP, which targets both polyps and BVN (whole lesion with polyps), has been shown to either stabilize or improve the vision. However, Recurrence of polyps, the formation of subsequent CNV, exudation or hemorrhage, and atrophy at the fovea have been observed with TLP therapy [65–67]. In vPDT, verteporfin (a photosensitizing agent) produces a photochemical reaction when activated by nonthermal laser in the far-red spectrum and produces selective vascular occlusion by thrombosis [68]. Visual outcome of vPDT treated PCV eyes was stable for 2 years but the effect gets diminished with time and PCV re-occurs within 3–5 years post vPDT. Post-PDT subretinal hemorrhage, massive suprachoroidal hemorrhage, RPE tears, and microrips at the margin of the PED are the reported complications of PDT for PCV. PDT alone is ineffective in causing regression of the BVN or in resolving exudative activity arising from the BVN, but when combined with anti-VEGF compounds demonstrated better visual outcomes [69, 70]. Anti-VEGF drugs, bevacizumab (a full-length anti-VEGF antibody) or Ranibizumab (an antibody fragment with smaller size), decreases the exudation and improve or stabilize vision but has minimal to no change in polyp regression [71, 72]. The newer anti-VEGF drug, Aflibercept (a soluble decoy receptor fusion protein consisting of the binding domains of VEGF receptors 1 and 2), demonstrates improved visual outcome and causes poly regression [73–75]. However, long-term study is needed to fully assess the efficacy of this treatment. Pigment epithelial tears, post-injection subretinal hemorrhage and vitreous hemorrhage, and RPE atrophy are few complications reported. Because anti-VEGF drugs reduce the exudation from polypoidal lesions arising from the BVN and vPDT causes thrombosis of the polypoidal lesions, a combination of the two therapies produces better long-term visual outcomes. In the EVEREST study, PDT and ranibizumab combination increased the polyps closure rate to (77.8%) compared to PDT alone (71.4%) [76] whereas Ranibizumab monotherapy can close only 28.6% polyps. In addition, PDT alone is ineffective in causing regression of the BVN or in resolving exudative activity arising from the BVN [76]. The EVEREST II study revealed that the combination therapy (PDT with ranibizumab) achieved superior BCVA gain (8.3 vs. 5.1 letters; $p = 0.013$), along with superior anatomical outcome, including higher polyp closure rate (69.3% vs. 34.7%; $p < 0.01$) and a higher proportion with the absence of disease activity (79.5% vs. 50.0%) at month 12 compared with ranibizumab monotherapy [77].

5.7 Summary

Significant advances have been made in our understanding of PCV in terms of genetics, pathophysiology, and treatment strategy. We have gained improved knowledge regarding the difference between PCV and CNV. The principal therapies for PCV are laser photocoagulation, PDT, and anti-VEGF drugs. The best-reported treatment combines PDT with anti-VEGF drugs [78]. The combination therapy of PDT and anti-VEGF drugs have achieved good results in polyp closure. However, one major concern regarding PDT is the high rate of recurrence or the development of new polypoidal lesions [69, 70]. On the other hand, long-term use of anti-VEGF therapy can lead to anti-VEGF resistance [79–81], and long-term blockade of VEGF signaling in retinal diseases may have detrimental side effects [82, 83]. Therefore, the development of novel drugs that prevent or reduce both BVN and polypoidal lesions could have a considerable impact on the current therapeutic strategy. Animal models have played an essential role in the development of anti-VEGF drugs for CNV. The availability of a PCV animal model should facilitate the development of new treatment for PCV [18, 31].

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