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Polypoidal choroidal vasculopathy

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Abstract

This article presents a literature review of studies by Russian and foreign researchers regarding polypoidal choroidal vasculopathy (PVC). It discusses the epidemiological and clinical characteristics, diagnostic features, and current treatment methods of PVC and the results of clinical studies. PCV is a subtype of neovascular age-related macular degeneration (AMD) with specific characteristics such as predisposition to certain races, clinical features such as serosanguineous complications of differing severities, tendency to relapsing course of neovascularization, and development of secondary serosanguineous exfoliation. PVS is most frequently observed in patients aged 50–65 years, and its prevalence among Caucasians and Asians is 4%–9.8% and 23.9%–54.7%, respectively. PCV is diagnosed using fluorescein angiography, indocyanine green angiography, and optical coherence tomography. One of the aims of initial treatment of PCV is polyp regression. According to the expert group on PVC, to achieve polyp regression, the use of laser coagulation and photodynamic therapy must affect both polyps and the vasculature. Treatment with laser coagulation, photodynamic therapy (independently and in combination with angiogenesis inhibitors), and monotherapy with angiogenesis inhibitors have been demonstrated in population studies. Regardless of the resultant diagnosis of PCV, treatment protocols require further investigation. Furthermore, additional studies are necessary for evaluating the long-term correlation among initial polyp regression, relapses, response to repeated therapy, and functional results.

Keywords: polypoidal choroidal vasculopathy, age-related macular degeneration, photodynamic therapy, antiangiogenic therapy, diagnosis.

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Polypoidal choroidal vasculopathy (PCV), first described by Yannuzzi in 1982, is characterized by the presence of polypoidal subretinal vascular foci accompanied by a serosanguineous detachment of the retinal pigment epithelium (RPE) [1]. PCV was initially designated as idiopathic PCV. Subsequently, Kleiner et al. described specific hemorrhagic lesions of the macular area, which were characterized by recurrent subretinal hemorrhages and hemorrhages under RPE, in middle-aged African-American women. They named this condition the posterior uveal hemorrhagic syndrome [2].

Yannuzzi et al. suggested that choroidal vasculopathy was an independent disease that was characterized by the formation of multiple recurrent serosanguineous detachments of RPE and the sensorineural retina accompanied by hemorrhages, particularly from the polypoid components of pathologically altered vessels [3]. Later, the new term of PCV was introduced.

According to current concepts, PCV is an independent form of neovascularization, with specific characteristics such as predisposition to patients of certain races and clinical features such as varying degrees of serosanguineous complications, a tendency to a relapsing course of neovascularization, and the appearance of secondary serosanguineous detachments [4]. Some experts currently characterize PCV as a subtype of neovascular age-related macular degeneration (AMD), but others consider it as a separate disease [5, 6].

Early reports suggested that PCV mainly affects middle-aged women [3], but subsequent reports stated that PCV develops in both sexes (more often in Asian men than in Asian women) [7]; PCV is most often diagnosed in patients aged 50–65 years [5]. According to studies reported by different authors, PCV prevalence among Caucasian patients with presumed AMD amounted to 4%–9.8%, whereas that among Asian patients with presumed AMD amounted to 23.9%–54.7%, which was higher [4, 5, 7, 8].

The epidemiological and clinical characteristics of PCV among African-American, Asian, and Caucasian patients may vary. Although most Japanese patients with PCV were males (71%), the opposite was observed among European patients (75% female). In addition, in 92% of Japanese patients, PCV occurred in the central macular area, whereas in European patients, an equal frequency of foci was observed in the macular and peripapillary

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regions. Only 14% of Japanese patients had bilateral lesions, in contrast to 32% of European patients. These differences suggest the presence of genetic polymorphisms that predispose to PCV development in different races [6].

Clinical presentation and diagnostic aspects. PCV is clinically characterized by hyalinization and peripapillary macular or peripheral polypoid expansions of the pathological choroidal vascular bed under RPE. It is accompanied by serous exudates and hemorrhages, which can lead to the detachment of RPE and occasionally, the sensorineural retina [3, 9].

A typical manifestation of PCV in a patient with symptoms for at least 3 months is extensive subretinal exudates and hemorrhages with minimal cystic retinal changes and good visual acuity. In patients with symptoms persisting for >3 months, obvious lipid deposits that result from extravasation of proteins from active aneurysmatic elements of polypoid vascular foci are noted [6].

The size of polypoid foci may vary from small to medium or large. The detachment of RPE is often combined with the presence of polypoid structures. Microfractures and ruptures can arise on the edges of serosanguineous RPE detachments. Following spontaneous resolution of acute serosanguineous complications, the signs of subretinal fibrosis may be observed, along with hyperplasia of the pigment epithelium and atrophic degeneration [10, 11]. As a rule, the presence of PCV in one eye implies a high risk for bilateral lesions [6].

PCV foci can also be located peripherally and are usually only diagnosed with the development of serosanguineous detachment and vitreous hemorrhage. PCV can also develop in the eyes along with other macular changes. Among Japanese patients with PCV, 23% presented with soft drusen in the macular zone along with polypoid vascular anomalies [4, 12].

Methods of visualization. Fluorescein angiography (FAG), indocyanine green angiography (IGA), and high-resolution optical coherence tomography (OCT) are the main diagnostic techniques for visualizing PCV.

FAG. It is not as effective as other forms of fluorescent imaging for visualizing PCV. In most patients with PCV, including Caucasians, pronounced ocular fundus pigmentation obscures the underlying choroid. In patients with newly developed PCV and serosanguineous complications, it is possible that the polypoidal choroidal vascular abnormalities become obscured. Nevertheless, in patients with extensive polypoidal choroidal vascular changes, FAG may be useful for the visualization of PCV; however, it does not enable the assessment of the entire lesion zone as a whole [6].

IGA. IGA is an informative tool for visualizing vascular abnormalities with PCV [13]. The high penetrating power of light waves of approximately 800 nm and the high binding capacity of indocyanine green with blood plasma proteins provide high-resolution visualization of choroidal vessels [6]. During the development of active proliferation, leakage, and hemorrhages, indocyanine stains fibrin in the late phase of angiography. In the early phase of IGA, pulsation of polypoid vessels can sometimes be observed [14]. Yuzawa et al. noted that PCV was characterized by changes in choroidal vessels, with focal dilatation, narrowing, and vascular tortuosity that forms branched three-dimensional vasculature [15]. The Japanese Study Group of Polypoidal Choroidal Vasculopathy determined the presence of orange-red subretinal nodes with their corresponding hyperfluorescence localization in IGA as a diagnostic criterion for PCV. The authors detected acinus clusters on IGA, which appeared similar to hyperfluorescent nodes in the early phase of IGA with amplified hyperfluorescence intensity in the late phase [16].

OCT. The value of OCT in PCV diagnostics is based on the recording of the changes around the polypoid foci. High-resolution OCT demonstrates that polypoid foci are located under the pigment epithelium on the inside of RPE detachment [6]. Sato et al. revealed reflective layers comprising RPE and one or several highly reflective lines under RPE in the region of a branched vasculature [17]. C-scans, which can be reconstructed from linear B-scans in numerous spectral OCT devices, can display a phenomenon that Imamura et al. termed as the "hematocrit sign," which is the separation of blood into its cellular and serous components. Sometimes the *en face* projection enables the identification of the pathological vasculature as a whole in the form of multiple interconnected polypoidal foci and can reveal a vasculature that is designated as a "bola sign" (boleadoras is an African hunting missile weapon) [6]. Because polypoid foci that are visualized with IGA often correspond to the localization of the pigment epithelium detachment on OCT, some researchers believe that the leakage from polypoid foci located under the pigment epithelium leads to its detachment [10].

Current approaches to therapy. Polyp regression, as confirmed by angiography, is considered to be an aim of initial therapy of active

PCV [5]. Despite the probability of spontaneous resolution of PCV foci, polyp preservation along with an active disease process poses the risk for a subsequent rupture and leakage. In a retrospective study, the natural course of PCV was assessed in 14 eyes for an average of 39.9 months, and only 50% of the eyes showed a stable course with relatively favorable outcomes, whereas the other 50% developed hemorrhages and leakage, which were associated with a worse prognosis [18].

Residual branched vasculature can be a source of recurrent PCV after photodynamic therapy (PDT) with verteporfin, and the ability of PDT to cause occlusion of these abnormal vessels remains controversial (19–21). According to the expert group on PCV, the use of both laser coagulation and PDT could affect both polyps and the vasculature [5]. Treatment of an asymptomatic vasculature in the presence of active polyps is considered to be more controversial.

The long-term risk for relapses or occurrence of new polyps after complete regression owing to treatment has not been completely characterized. In a 12-month study of the frequency of relapses, particularly owing to the development of new foci, complete regression of the initial polypoid foci was observed in 95% of cases, with new polyps being formed in 9% of cases and polyps recurring in 5% [21]. Honda et al. revealed the mean time to the development of relapses was 11.0 ± 7.5 months [22].

Following the initial PCV therapy, monthly monitoring for 6 months has been recommended, with subsequent monitoring frequency determined by the attending physician based on the individual characteristics of the patient [5]. According to previous studies, the criteria for repeated treatment included leakage based on FAG, exudative changes based on OCT, or the persistence or relapse of polyps based on IGA results [23, 24].

Role of laser coagulation in treating PCV. A previous study showed that thermal laser coagulation performed under the guidance of IGA stabilized or improved vision in 55%–100% of eyes, whereas a visual acuity decreased in 13%–45% of eyes [15]. Considering the destructive nature of whole-focus laser coagulation compared with targeted laser coagulation of polyps, this approach has limited applications in subfoveolar and juxtafoveolar PCV [5]. This opinion was confirmed by a minor retrospective study with the conclusion on advantages of laser coagulation in treating PCV of extrafoveolar localization [25].

Results of PDT monotherapy with verteporfin. When the results of 17 studies on PDT monotherapy with verteporfin with level III evidence were analyzed, 12 showed improved or stabilized vision in 80% of eyes [26, 27]. Lee et al. [25] described stabilized or improved vision in only 58.5% of cases, which was explained by the presence of laser coagulation in anamnesis. In another long-term study, loss of visual acuity in 37.0% of eyes at 3 years after PDT monotherapy with verteporfin was associated with the subsequent development of recurrent polypoid foci and the propagation of pathological vasculature [27].

Combined PDT with verteporfin and antiangiogenic therapy. In the EVEREST study, patients with symptomatic PCV underwent PDT monotherapy with verteporfin, 0.5 mg ranibizumab monotherapy, or a combination therapy. The treatment included standard PDT under IGA guidance on the first day and/or intravitreal ranibizumab injections at a dose of 0.5 mg with repeated treatment between 3 and 6 months according to predetermined anatomical and functional criteria. Combination therapy and PDT monotherapy with verteporfin had greater efficacy compared with ranibizumab monotherapy in achieving complete polyp regression at 6 months after initiating therapy. In the combination therapy group, a more pronounced improvement was observed in the indices of uncorrected visual acuity and the thickness of the central zone of the retina [23].

A retrospective study showed a significant improvement in the mean values of uncorrected visual acuity after PDT combined therapy with verteporfin and ranibizumab after 3 and 12 months ($p < 0.01$), but this improvement was observed only in patients who did not previously undergo treatment (naive patients) [28].

According to a study by Romano et al. [29], in eyes in which relapse occurred after a previous therapy with PDT and verteporfin, stabilization was noted, but vision did not improve. Resolution of recurrent or persistent fluid accumulation was achieved after administering several injections of an antiangiogenic drug in the eyes with polyp regression with the use of PDT but preservation of exudation from the branched vasculature [30].

In genetic studies, association between the genotype and the results of PCV therapy was demonstrated. The clinical response to PDT with verteporfin significantly differed in patients with variants of the *SERPINF1* gene, which encodes the pigment epithelium-derived factor [31].

Monotherapy with antiangiogenic drugs. The interest in antiangiogenic drugs as a treatment for exudates in PCV is because of the high expression levels of Vascular Endothelial Growth Factor (VEGF) in the endothelial cells of pathological vessels in PCV cases [32]. Existing data indicate that at least in the short term, antiangiogenic monotherapy reduces hemorrhage and exudates but may be less effective in reducing the size and number of PCV foci and the vasculature [33]. In a larger prospective cases series, the response of polypoid foci to ranibizumab monotherapy was effective, and the resolution or improvement of PCV was observed in 78.0% of cases [34].

Kawashima et al. [35] compared the efficacy of aflibercept in 15 patients with AMD and 26 patients with PCV who were not responsive to ranibizumab treatment. After 6 months of aflibercept therapy, visual acuity improved by one line in patients with PCV, whereas no significant changes were observed in patients with AMD. In addition, OCT revealed that 80% of patients with PCV showed no signs of activity compared with 46.7% of patients with AMD ($p = 0.024$).

Ijiri et al. [36] evaluated the initial response to aflibercept in 33 patients with PCV without any previous treatment. After 3 months of treatment, the average visual acuity increased by 8.9 letters according to the Early Treatment Diabetic Retinopathy Study charts. In addition, OCT revealed that in 97% of cases, there was no exudation, and IGA revealed that in 48% of cases, complete regression was achieved.

Saito et al. [37] administered aflibercept to43 cases of PCV refractory to ranibizumab. Three months after changing to aflibercept, the average visual acuity significantly improved ($p = 0.0074$), and the polyps disappeared in 50% of cases.

Despite the results achieved in PCV diagnostics, treatment protocols still require further studies. Additional research on the long-term association among initial polyp regression, relapses, response to repeated treatment, and functional outcomes is necessary.

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