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Original Article

Evaluation of Clinical Findings, Optical Coherence Tomography, Fundus Fluorescein Angiography, and Indocyanine Green Angiography Imaging in Patients with Polypoidal Choroidal Vasculopathy

Ruveyde Garip,[1] Dilek Yasa,[2] Abdullah Ozkaya[3]

[1]Department of Ophthalmology, Trakya University, Faculty of Medicine, Edirne, Turkey
[2]Department of Ophthalmology, Beyoglu Eye Training and Research Hospital, Istanbul, Turkey
[3]Department of Ophthalmology, Sisli Memorial Hospital, Istanbul, Turkey

Abstract

Objectives: The aim of this study was to describe clinical findings as well as spectral-domain optical coherence tomography (SD-OCT), fundus fluorescein angiography (FA), and indocyanine green angiography (ICGA) findings of polypoidal choroidal vasculopathy (PCV).

Methods: This retrospective, observational case series included 144 eyes of 103 patients who were diagnosed with PCV between January 2014 and August 2016. Best corrected visual acuity, 90-diopter lens slit-lamp fundus biomicroscopy examination findings, color fundus photography, SD-OCT, FA, and ICGA findings were evaluated at the time of diagnosis.

Results: Sixty-six patients (93 eyes, 64.1%) were male and 37 (51 eyes, 35.9%) were female. Sixty-two (60.2%) patients had unilateral involvement. The most common SD-OCT finding was retinal pigment epithelial detachment (PED). Red-orange subretinal lesions were seen in 20 eyes (13.9%). There was a single polyp in 21 (14.6%) eyes, and more than 1 polyp in 123 (85.4%) eyes observed with ICGA imaging. The polyps were located in the peripapillary area in 10 (6.9%) eyes, the macular area in 91 (63.2%) eyes, and the extramacular area in 1 (0.7%) eye. A significant branching vascular network was seen in the ICGA images of 112 (77.8%) eyes.

Conclusion: In this study, the majority of patients were male, with unilateral macular polyps. A serous PED and an exudative pattern were the most common clinical manifestations. SD-OCT showed specific findings for PCV, but ICGA was the most useful test for diagnosis.

Keywords: Indocyanine green angiography, optical coherence tomography, polyps.

Introduction

Polypoidal choroidal vasculopathy (PCV) is an idiopathic disorder characterized by the presence of polypoidal or aneurysmal hyperfluorescence with or without a branching vascular network (BVN) visible with indocyanine green angiography (ICGA), and leads to the development of recurrent serosanguinous retinal pigment epithelial detachments (PED) (1–3). PCV is considered a peculiar phenotype of neovascular age-related macular degeneration (nAMD) by some (4), or a distinct clinical entity by others (5, 6). Although PCV and nAMD share common clinical findings and risk factors, PCV has revealed differences in terms of natural his-

Address for correspondence: Ruveyde Garip MD. Trakya Universitesi Tip Fakultesi, Goz Hastaliklari Anabilim Dali, Edirne, Turkey
Phone: +90 506 328 89 87 **E-mail:** ruveydegarip@gmail.com

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tory, treatment protocol, and prognosis. Multimodal imaging is necessary for an accurate differential diagnosis between PCV from nAMD (7).

Interethnic differences in PCV in terms of clinical and demographic characteristics have been established. According to the literature, PCV affects Asians more than Caucasians (8). The disease has a male predilection in the Asian population, unlike in Caucasians, where there is a female dominance (9). Unilateral involvement is more common in the Asian population (10).

There are publications on PCV frequency, and clinical and imaging findings in Asia and Europe. However, there are insufficient data on the clinical and imaging findings of the disease in Turkey. The aim of this study was to define the clinical and imaging findings of patients who were followed up in a single clinic with the diagnosis of PCV.

Methods

This study was conducted according to the principles of the Declaration of Helsinki and was approved by the Human Research and Ethics Committee of Trakya University School of Medicine. Written informed consent was obtained from the participants before enrollment.

This retrospective, observational case series included patients who were diagnosed as having PCV between August 2014 and January 2016. The demographic characteristics of the patients were recorded. The best corrected visual acuity (BCVA), 90-diopter lens slit-lamp fundus biomicroscopy examination findings, color fundus photography, spectral-domain optical coherence tomography (SD-OCT), fundus fluorescence angiography (FA), and indocyanine green angiography (ICGA) findings were evaluated at the time of diagnosis.

The diagnostic criteria for PCV were the presence of early subretinal ICGA hyperfluorescence plus at least 1 of the following angiographic or clinical findings: nodular appearance of the polyp on stereoscopic viewing, hypofluorescent halo around the nodule, abnormal vascular channels supplying the polyps, orange subretinal nodules corresponding to the hyperfluorescent area on ICGA, and massive submacular hemorrhage, according to the EVEREST study (11).

All of the patients who were diagnosed with PCV were included in the study. Patients with macular disease in the eye with PCV, such as high myopia (>-6 diopters), angioid streaks, ocular histoplasmosis, central serous chorioretinopathy or idiopathic choroidal neovascularization, were not included. Patients with uveitis, glaucoma, proliferative retinopathies, tumor, amblyopia, or epiretinal membranes were also excluded. Also among the criteria for exclusion were uncontrolled systemic hypertension and diabetic retinopathy, allergy to fluorescein or indocyanine green dye, and media opacity that would prevent fundus evaluation.

Clinical Evaluation

The presence of PED, PED characterization (hemorrhagic PED), subretinal hemorrhage, scar tissue, lipid deposition, hard exudates, the presence of red-orange subretinal lesions, and the presence of vitreous hemorrhage were evaluated in the fundus examination. According to these findings, the disease was divided into 3 groups: hemorrhagic pattern (with vitreous or retinal hemorrhage), exudative pattern (with serous PED or exudations), and silent polyps (without hemorrhage or intraretinal fluid).

Spectral-Domain Optical Coherence Tomography

SD-OCT was performed using the Heidelberg Retinal Tomograph (HRT; Heidelberg Engineering GmbH, Heidelberg, Germany). The presence of PED, peak-like elevation of the retinal pigment epithelium (RPE), presence of tomographic notch sign ("V"-shaped depression between 2 PEDs or at the margin of a large PED), polyp presence (a rounded hyporeflective area repre¬senting the polyp lumen within hyperreflective lesions ad¬hered beneath the retinal pigment epithelium), double-layer sign (consisting of 2 hyper-reflective lines, representing the RPE and Bruch's membrane), and fluid accumulation were evaluated.

Fluorescein Angiography

Fundus FA was performed using a scanning laser ophthalmoscope (Heidelberg Retina Angiograph 2; Heidelberg Engineering GmbH, Heidelberg, Germany). The presence of window defects, pooling due to PED, hemorrhage-related blockage, and the presence of hyperfluorescence that could be compatible with a choroidal neovascular membrane (CNV) were evaluated. The appearance of CNV was classified as occult (ill-defined areas of irregular staining or poorly demarcated areas of leakage in the late phase of angiogram) or classic (well-demarcated areas of intense hyperfluorescence appearing early and showing progressive leakage).

Indocyanine Green Angiography

All of the ICGA scans were performed using a scanning laser ophthalmoscope (Heidelberg Retina Angiograph 2; Heidelberg Engineering GmbH, Heidelberg, Germany). Polypoidal hyperfluorescence (polyp appearance), number of polyps, polyp formation, polyp localization, and choroidal branching vascular network (BVN) were evaluated on ICGA images. BVN was evaluated in the early phases of ICGA and polypoidal hyperfluorescence was assessed in the middle phases of ICGA. Polyp formations were classified as single, clustered, string, and separate clusters. Two or more polyp entities in the same region were evaluated as a cluster. Clusters formed in different regions were evaluated as separate clusters. At least 2 polyps with linear alignment were evaluated as string polyps. The polyp appearance was divided into 2 categories: Large, single, nodule-shaped polyps were

defined as nodular polyps, and small, aneurysmal dilatations, such as hyperfluorescent spot clusters, were defined as hyperfluorescent dots.

Polyp localization was divided into 4 groups: peripapillary (lesions in which more than half of the lesions were located in the area 1500 μm from the optic disc), macular (lesions located within the area 6000 μm from the center of the foveal avascular zone, except for the peripapillary zone), extramacular, and mixed locations. The location was determined according to the area that contained at least 50% of the lesion area.

Statistical Methods

All of the statistical tests were performed using IBM SPSS Statistics for Windows, Version 20.0 (IBM Corp., Armonk, NY, USA). Baseline characteristics are presented as mean±SD. The descriptive statistics methods used included calculation of the average, median, minimum and maximum values, and the frequency of qualitative data was evaluated as a percentage.

Results

General Information

A total of 144 eyes of 103 patients were included in the study. Thirty-seven of the patients were female (51 eyes, 35.9%) and 66 were male (93 eyes, 64.1%). The mean age was 69.8±9.7 years (range: 35-90 years). Sixty-two (60.2%) of the 103 patients had unilateral involvement. Bilateral involvement was seen in 41 (39.8%) patients. Of the cases with bilateral involvement, 14 (34.2%) were female and 27 (65.8%) were male.

Fundus Examination Findings

There was a hemorrhagic pattern in 39 (27%) eyes and an exudative pattern in 99 (68.8%) eyes. Six (4.2%) of the patients had silent polyps. The most common clinical manifestation was serous PED, seen in 120 (83.3%) eyes. Red-orange subretinal lesions were observed in 20 (13.9%) eyes. There was subretinal hemorrhage in 35 (24.3%) eyes, scar tissue in 44 (30.5%) eyes, lipid deposition in 50 (34.7%) eyes, hard exudates in 48 (33.3%) eyes, and RPE changes in 9 (6.2%) eyes. Vitreous hemorrhage was observed in 1 (0.7%) eye.

Spectral-Domain Optical Coherence Tomography Findings

PED was identified in 120 (83.3%) eyes, and was the most common SD-OCT finding. A tomographic notch sign was seen in 79 (54.9%) eyes, a sharp PED peak was noted in 76 (52.8%) eyes, polyps were found in 60 (41.7%) eyes, and a double-layer sign was observed in 85 (59.0%) eyes (Fig. 1). Subretinal fluid only was found in 59 (41.0%) eyes, intraretinal fluid only was seen in 15 (10.4%) eyes, and mixed- type fluid accumulation was observed in 50 (34.7%) eyes. No fluid was observed on SD-OCT at the time of diagnosis in 19 (13.2%) eyes.

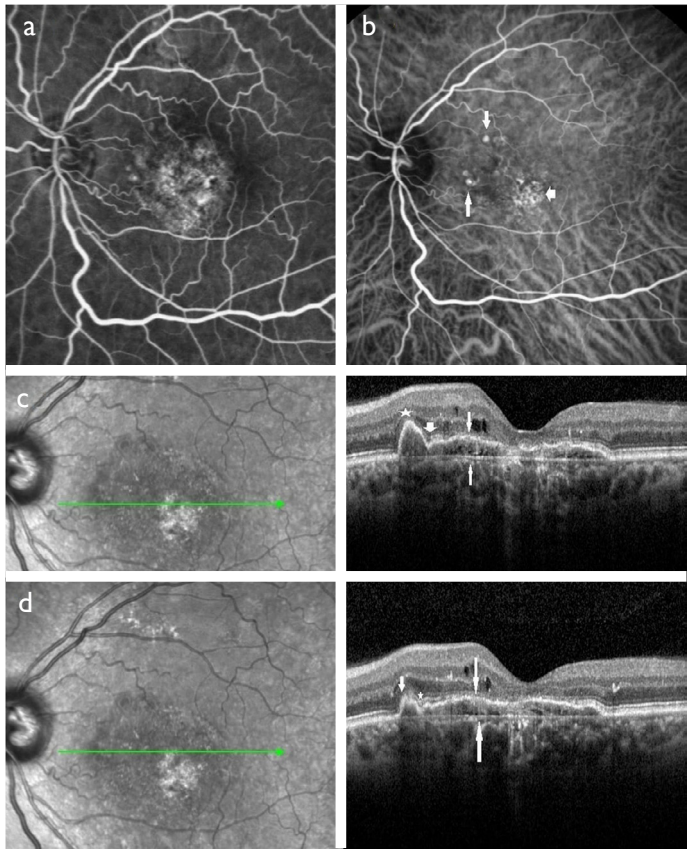

Figure 1. (a) Fundus fluorescein angiography image; **(b)** Polypoidal lesions with a nodular form (thin arrows) observed with indocyanine green angiography, polypoidal lesions in the form of a cluster of hyperfluorescent spots (short, thick arrow), and a branching vascular network; **(c)** Spectral-domain optical coherence tomography images of peak-like elevation corresponding to a polypoid lesion seen on the pigment epithelial detachment (PED) (star), a tomographic notch mark (short, thin arrow), and double-layer sign (thin, tall arrows); **(d)** Peak-like elevation corresponding to a polypoid lesion on the PED (short, thick arrow), tomographic notch (star), and double-layer sign (long arrows).

Fluorescein Angiography Findings

FA imaging revealed hyperfluorescence-like occult CNVM in 87 (60.4%) eyes and hyperfluorescence-like classical type CNVM in 14 (9%) eyes. Forty-three (29.9%) eyes had no appearance of CNVM. In these eyes, there were findings such as window defects, RPE detachment-related filling defects, and staining due to fibrous scarring. In 38 (26.4%) eyes, hyperfluorescence spots were observed.

Indocyanine Green Angiography Findings

In 112 (77.8%) eyes, ICGA showed a typical BVN and polyp-like aneurysmal dilation in the terminal branches. There was a single polyp in 21 (14.6%) eyes and a large number of

polyps in 123 (85.4%) eyes. The mean number of polyps was 9.66±8.27 (range: 1-36). A nodular polyp was present in 49 (34%) eyes. ICGA revealed aneurysmal dilatations observed as hyperfluorescent spot clusters in 60 (41.7%) eyes. Thirty-five (24.3%) eyes had mixed-type polyps. In addition, cluster formation was observed in 66 (45.8%) eyes. There were separate clusters in 40 (27.8%) eyes, and string-like polyps in 5 (3.5%) eyes (Fig. 3). Twelve (8.3%) eyes had polyps interspersed with independent zones.

Examination of the polyp locations indicated that there were peripapillary polyps in 10 (6.9%) eyes, macular polypsin 91 (63.2%) eyes, and extramacular polyps in 1 (0.7%) eye. The other 42 (29.2%) eyes had a mixed location. A significant BVN was seen in 112 (77.8%).

Discussion

In our study, 37 patients were female (51 eyes, 35.9%) and 66 were male (93 eyes, 64.1%). It was observed that the disease was significantly more frequent in men than women in our study. It is known that PCV affects darkly pigmented individuals and Asians more than Caucasians (10, 12). PCV has a male predilection in the Asian population, unlike in Caucasians, where there is a female dominance (9, 13). The incidence of disease among females in Asian populations varies between 22-37%. However, the rate varies between 52-65% in white patients (10). According to this study, the disease occurred significantly more frequently in men than women and this finding is consistent with Asian studies (Table 1). The age range of the patients in previous literature reports was 21–93 years, and the mean was 68.4 years (10). In our study, the mean age was 69.8 years (min-max: 35-90), which was compatible with the previous studies.

According to Asian publications, the incidence of bilateral involvement varies between 9% and 18%, whereas the frequency varies between 21% and 55% in the white population (10). In our study, bilateral involvement was present in 41 (39.8%) patients. Unilateral involvement was seen in 62 (60.2%) patients. The rate of bilaterality was higher than that

Table 1. Comparison of findings with polypoidal choroidal vasculopathy studies among various racial groups

Authors	Ethnic group	Number of patients	Male ratio (%)	Bilaterality (%)	Polyp location (%)
Uyama et al. (21)	Japanese	32	69	9	Macular=94 Peripapillary=9
Lafaut et al. (22)	White	36	47	61	Macular=49 Arcade=13 Peripapillary=36
Scassellati-Sforzolini et al. (12)	European	19	47	21	Macular=53 Peripapillay=37 Periphery=10
Sho et al. (23)	Japanese	100	63	10	Macular=84.5 Peripapillary=7.2
Wen et al. (8)	Chinese	37	73	14	Macular=62 Arcade=21 Peripapillary=14 Midperiphery=3
Ladas et al. (24)	European	22	59.1	54.5	Macular=32 Peripapillary=68
Byeon et al. (14)	Korea	79	78.5	24	Macular=87.8 Peripapillary=5
Hou et al. (16)	Chinese	204	60.3	21	Macular=68 Arcade=15 Peripapillary=5 Multiple=11
Our results	Turkey	103	64.1	39.8	Macular=63.2 Peripapillary=6.9 Periphery=0.7 Mixt=29.2

reported in Asian-based studies, and the bilaterality ratio was found to be close to that reported in studies of white races (Table 1).

In a study conducted in India with 47 eyes, Anantharaman et al. (9) reported that serous macular detachment and serous PEDs were the most common clinical manifestations in PCV. They observed an exudative pattern in 34 eyes and a hemorrhagic pattern in 13 eyes. In another study conducted in Korea, an exudative pattern was seen in 51 (52%) of the 98 eyes, a hemorrhagic pattern was found in 34 (34.7%) eyes, and a diffuse hemorrhagic pattern was observed in 13 (13.3%) eyes (14). In this study, 99 (68.8%) eyes had an exudative pattern and 39 (27.11%) eyes had a hemorrhagic pattern. Silent polyps were seen in 6 (4.2%) patients. In our study, the most common pattern was an exudative pattern and the most common clinical finding among our patients was a serous PED (83.3%). Our findings were consistent with previous studies.

Polypoidal lesions can appear as red-orange nodular RPE elevations on fundus biomicroscopic examination. This finding suggests PCV; however, it is not diagnostic. Small PEDs without polyps may also cause the same appearance (15). Hou et al. (16) reported that they detected red-orange color polypoid lesions in 25 (10.2%) eyes. In our study, red-orange subretinal lesions were seen in 20 (13.9%) eyes, consistent with previous research.

ICGA is considered the gold standard imaging method for diagnosing PCV, but it is an invasive technique, it includes a risk of developing allergies to indocyanine green dye, and it is still not accessible in some areas. Therefore, noninvasive diagnostic criteria were needed (3). Previous studies have described some SD-OCT findings that may be specific for the diagnosis of PCV. The most common OCT findings are PEDs with a sharp peak, with or without associated smaller PEDs, which may cause a tomographic notch sign (10). The peaked elevation of the PED and the moderate hyperreflectivity within this elevation usually correspond to the polyp itself, whereas the hyporeflective area, surrounded by RPE-associated hyperreflectivity, corresponds to the polyp lumen (17, 18). Polypoidal lesions can be seen under the RPE and are associated with the posterior surface of the RPE (19). The V-shaped depression between 2 PEDs is called the tomographic notch (18). The double-layer sign is an SD-OCT finding that consists of 2 hyperreflective lines corresponding to the RPE and Bruch membranes. It is thought that the double-layer sign originates from fibrous tissue harbored by the BVN (17, 20).

De Salvo et al. (18) reported that 91.9% of patients had a sharp peak elevation observed on the PED, 100% of the patients had a tomographic notch sign, and 94.6% of the patients had a hyporeflective polyp lumen. In another study evaluating OCT findings of patients with PCV in Korea, 93.2% of the patients had multiple PEDs, 85% had a sharp peak elevation on the PED, 86.4% had a tomographic notch, and 47.6% had a hyporeflective lumen of the polyp (19). In our study, 79 (54.9%) eyes showed a tomographic notch sign, and 76 eyes had a sharp peak on the PED (Fig. 1). Typical hyporeflective lumen in the PED and a hyperreflective area around it (corresponding to the polyp itself) was observed in 60 (41.7%) eyes (Fig. 2). Our rates were found to be lower than those of previous studies. In our study, we included all patients in whom we found polyps and BVN on ICGA, with or without fundus findings. We also included patients with disciform scarring and coexisting exudative age-related macular degeneration. The SD-OCT findings were masked and these inclusions may have contributed to our lower results. The double-layer sign was first described by Sato et al. (20), who reported that they had found a double-layer sign in 26 (59%) eyes of 44 eyes. In our study, 85 (59.0%) eyes had a double-layer sign, which is consistent with previous studies (Figs. 1, 2).

In the majority of PCV cases, the FA findings are similar to occult or sometimes classical CNV (1). Window defects due to RPE atrophy may be seen. In some cases, hyperfluorescent spots may be observed in the area where polypoidal structures are present (10). Imamura et al. (19) reported that PCV may be seen with FA in cases where the polypoidal vascular component is large and the accompanying RPE is atrophic. In our study, 87 (60.4%) eyes had hyperfluorescence suggesting occult CNV and 14 (9%) eyes had early hyperfluorescence, as in the classic type CNV. Forty-

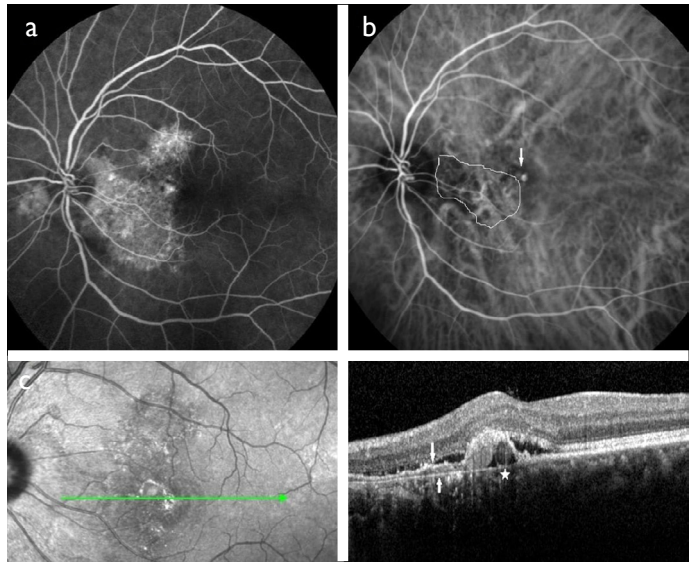

Figure 2. (a) Fundus fluorescein angiography image; **(b)** Indocyanine green angiography images of a polypoidal lesion (arrow) and branching vascular network (circled area), **(c)** the polyp lumen with retinal pigment epithelial detachment (star), and double-layer sign (arrows).

three eyes (29.9%) had no CNV appearance. In these eyes, there were findings such as window defects, filling defects connected to the RPE detachment, and scar staining due to fibrous scarring. In 38 (26.4%) eyes hyperfluorescent spots were observed. It was thought that the hyperfluorescent spots seen with FA corresponded to PCV lesions. When FA results were compared with ICGA images, it was seen that the hyperfluorescent dots observed with FA corresponded to the PCV areas in ICGA. There were no findings that could affect imaging, such as subretinal hemorrhage and exudation. Window defects due to RPE atrophy were also observed.

ICGA is the gold standard imaging method for the diagnosis of PCV. In ICGA, PCV lesions are characterized by characteristic polypoid lesions, with or without branching vascular networks. It has been reported that PCV lesions are seen more frequently in the macular region (62-94%) in Asian-based studies. In American and European studies, peripapillary PCV is reported more frequently (18-75%) than in Asian studies (10). In our study, we observed a peripapillary location in 10 (6.9%) eyes, a macular placement in 91 (63.2%) eyes, an extramacular location in 1 (0.7%) eye, and mixed locations in 42 (%29.2) eyes. Our results are similar to those of Asian-based studies (Table 1). The most common location of PCV lesions was determined to be the macular area. The reason for the differences between different ethnic groups is unclear. However, differences in genetic and environmental factors are thought to lead to these outcomes (2).

In this study, we observed that, 21 (14.6%) eyes had a single polyp, 66 (45.8%) eyes had cluster formations, 5 (3.5%) eyes had string-like formations, and 40 (27.8%) eyes had separate clusters. Polyps were interspersed with independent zones in 12 (8.3%) eyes (Fig. 3). The most common polyp configuration was clustering polyps. Uyama et al. (21) suggested that hemorrhage and liquid accumulation were more frequent in grape-like clusters and that these eyes had a higher risk of severe vision loss. The authors noted that the disease persisted with recurrent bleeding and leakage that results macular degeneration and visual loss in these patients.

PCV was first described as 2 distinct components: a BVN external to the choriocapillaris, and terminal aneurysmal dilations sometimes seen clinically as reddish-orange subretinal lesions. Wen et al. (8) reported seeing a BVN in 64% of 42 eyes. In the EVEREST study conducted with 61 patients, the incidence of BVN was 75.4% (11). In our study, there was a similar BVN ratio of 77.8% (112 eyes) (Fig. 2).

In our study, the majority of patients were male. PCV was predominantly unilateral, and most of the lesions were located in the macular region. A serous PED and an exudative pattern were the most common clinical manifestations.

OCT angiography (OCT-A) is a new and noninvasive

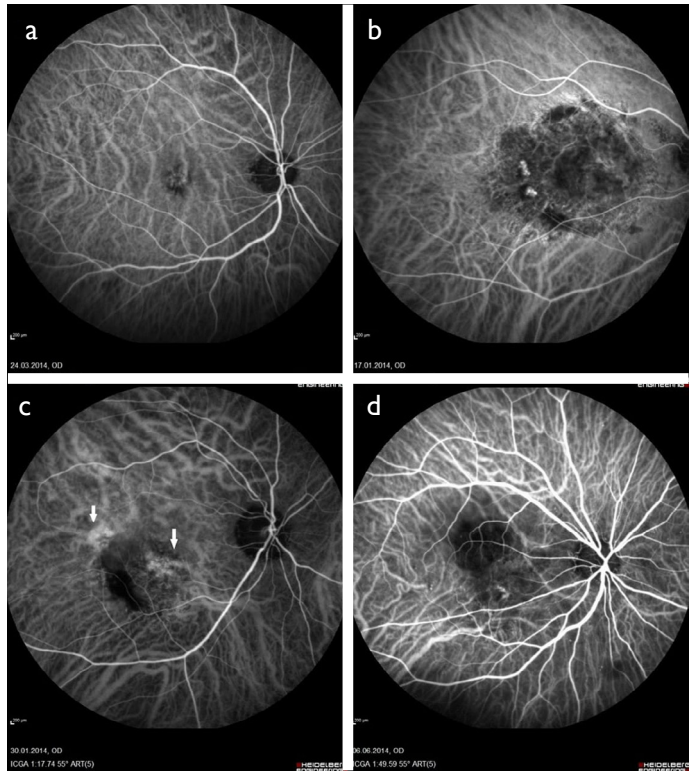

Figure 3. Polyp configurations observed with indocyanine green angiography: **(a)** single cluster, **(b)** and **(d)** string-like polyps, **(c)** separate clusters.

imaging tool that detects the blood flow in the retina and structural changes simultaneously using a split-spectrum, amplitude-decorrelation algorithm OCT-A allows visualization of retinal microvasculature and the morphology of vessels in the inner/outer retina and in the choroid (25). In OCT-A images, BVN is seen as a hyper-flow lesion, while a polypoidal lesion is seen as a round, hypo-flow structure in many cases (26). Several studies have compared the application of OCT-A and ICGA in the detection of polyps and BVN. It has been shown that OCT-A revealed BVNs better than ICGA. In contrast, it cannot show polypoidal lesions as clearly as ICGA (27).

The limitation of this study was the lack of OCT-A images. Patients diagnosed with PCV before 2016 were included in the study and due to the retrospective nature of the study, no OCT-A images were available. Nonetheless, we believe that our study is descriptive in terms of demographic data, OCT, FFA, and ICGA images.

PCV is an important disease that can be confused with age-related macular degeneration. The clinical and imaging findings of each should be well known to avoid misdiagnosis since there are differences between the 2 diseases in terms of treatment and prognosis. In the present study, we found that PCV had a male predilection, with mostly unilateral and polypoidal lesions located in the macular area. The most

common clinical finding was a serous PED. SD-OCT showed specific findings for PCV, but ICGA was the most useful test for diagnosis.

Disclosures

Ethics Committee Approval: The Scientific Research Ethics Committee of Trakya University School of Medicine provided the ethics committee approval for this study (09.12.2019-TÜTF-BAEK 2019-421).

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

Authorship Contributions: Involved in design and conduct of the study (RG, DY, AO); preparation and review of the study (RG, DY, AO); data collection (RG, AO); and statistical analysis (RG, DY).

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