Non-Indocyanine Green Angiography Diagnostic Criteria in The Differential Diagnosis of Polypoidal Choroidal Vasculopathy

Jale Mentes[1]

ABSTRACT

Purpose: Polypoidal choroidal vasculopathy (PCV) is a disease characterized by a branching neovascular network and polypoidal lesions typically originating from the internal choroidal vessels, and is a subtype of neovascular age-related macular degeneration (nAMD). It is important to make a differential diagnosis due to high prevalence of PCV in all populations and differing clinical course and treatment from nAMD. Although indocyanine green angiography (ICGA) is considered as gold standard in the diagnosis of PCV, it is an invasive method, impractical, and has limited access in many clinics. Therefore, non-invasive, less time-consuming, reliable and easily reproducible diagnostic methods are needed for diagnosis of PCV. In recent years, it has been suggested that there are typical findings for the diagnosis of PCV on spectral-domain optical coherence tomography (SD-OCT) and color fundus images (CFIs), and that the diagnosis can be made with a very high accuracy without ICGA. In this article, typical CFI and SD-OCT findings for the differential diagnosis of PCV were described. In addition, findings supporting the diagnosis of PCV on other noninvasive imaging modalities such as fundus autofluorescence (FOF) and optical coherence tomography angiography (OCTA) were also noted.

Keywords: Branching neovascular network, Color fundus photography, Fundus autofluorescence, Indocyanine green angiography, Optical coherence tomography angiography, Polypoidal choroidal vasculopathy, Polypoidal lesion, Spectral domain optical coherence tomography.

INTRODUCTION

Polypoidal choroidal vasculopathy (PCV), which was first described by Yanuzzi in 1982, is characterized by aneurysmal dilatation which are termed as polypoidal lesions (PL) and branching neovascular network (BNN) typically originating from inner choroidal vessels beneath retinal pigment epithelium (RPE). Clinically, PCV is associated with serous and hemorrhagic detachments of pigment epithelium and recurrences; currently, it is considered as a subtype of neovascular age-related macular degeneration (nAMD).[1-8]

In previous studies on PCV, it was reported that PCV prevalence shows great variations across countries, ethnicities and races and that it is higher in yellow race and Asian populations (40-60% but lower in Caucasians (10-20%).[4-9] In recent studies using ICGA, it was shown that PCV prevalence is high not only in yellow race and Asian populations but also in all populations including Caucasians.[3]

Today, it is known that anti-VGEF agents alone, used in the treatment of nAMD in widespread manner, are not completely effective to treat PCV and to control disease activity. In clinical trials, it was shown that PLs were not completely closed with recurrences in most cases by anti-VGEF monotherapy; thus, there is need for different therapeutic strategies and combination therapies.[3,8,10,11] Menteş et al. found that PCV rate was 63.9% in nAMD cases with inadequate response to treatment with 6 doses of anti-VGEF monotherapy.[12] Owing to high PCV prevalence in all populations and clinical course and treatment differing from nAMD, it is important to make differential diagnosis in clinical practice and use different management strategies in these cases.

1- Prof. MD, Private Doctor

Received: 27.08.2023
Accepted: 02.09.2023
J Ret-Vit 2023; 32: 163-172
DOİ:10.37845/ret.vit.2023.32.28

Correspondence Adress:
Jale Mentes
Alsancak mah., Ziya Gökalp Blv. No: 28, Kat: 4, D: 8, Konak, İzmir, Türkiye
Phone: +90 232 463 5284
E-mail: jale.mentes@ege.edu.tr

The ICGA is considered as the gold standard in the diagnosis of PCV; however, it is an invasive and time-consuming imaging modality requiring a special dye and device; thus, it is not routinely employed in many ophthalmology clinics and the diagnosis of PCV is overlooked in daily practice.[1,3-17] Given that, it has been suggested that there is need for non-invasive, less time-consuming, reliable and reproducible diagnostic modalities other than ICGA in the diagnosis of PCV in recent years.[1,3,8-11] Spectral-domain optical coherence tomography (SD-OCT) is a non-invasive imaging modality which is widely used in the diagnosis and management of cases with nAMD in clinical practice and provides high-resolution images in a rapid and reliable manner. In recent years, there are studies proposing that findings typical for the diagnosis of PCV exist in SD-OCT and color fundus images and that the differential diagnosis between PCV and typical nAMD can be made with high sensitivity by using these findings without need for ICGA.[1,3-5,8-11,13-17]

In this manuscript, we discussed typical color fundus imaging and SD-OCT findings for diagnosis and differential diagnosis of PCV in the eyes with PCV confirmed by ICGA. In addition, findings favoring the diagnosis of PCV on other noninvasive imaging modalities such as fundus autofluorescence (FOF) and optical coherence tomography angiography (OCTA) were also noted.

NON-INVASIVE IMAGING TECHNIQUES IN THE DIFFERENTIAL DIAGNOSIS OF PCV

Clinical Examination and Color Fundus Photography

In clinical examination or color fundus imaging, the most typical finding for diagnosis of PCV is the presence of orange-reddish, round subretinal nodules (Figure 1A, 3A, 5A, 6A, 7A). The subretinal nodules may be localized at macula or peripapillary region and even at peripheral retina in rare instances. In addition, findings suggestive for PCV also include serous PEDs (Figure 2A, 6A), hemorrhagic PEDs (Figure 3A), neurosensory serous detachment and exudation (Figure 4A) and massive bleeding.[1,3-8,13,16] The hemorrhage may be intravitreal, subretinal or sub-RPE. In PCV, lack of drusen, pigmentary changes, geographic atrophy and disciform scars which are typical for nAMD are other striking findings.[1,3-5,13]

Optical Coherence Tomography

Based on recent studies and experiences, there is a consensus that there are valuable findings for diagnosis and differential diagnosis of PCV on both B-scan and en-face (C-scan) SD-OCT and that PCV diagnosis can be made with high sensitivity (89%) and specificity (85%) in the guidance of these findings.[3,5,7,14]

For discriminating PCV from a typical nAMD, the major SD-OCT finding is that both BNB and PL, components of PCV) are localized between RPE and Bruch's membrane. In addition, it is generally accepted that the presence of at least two of B-scan OCT findings below has extremely high diagnostic value for PCV.[1,3,5,7,11,13-17]

It has been reported that typical SD-OCT appearance for the lesion defined as PL on ICGA is **"a sharp, spiking PED"** on B-scan. This PED is termed as "thumb-like protrusion", which is delineated as a sharp or spiking protrusion pushing RPE layer in inverse-U. It is typical that PED content is mid-reflective, a distinguishing feature from other PEDs (Figure 1C, D, 2C, 3C, 5C, 6C, 7C). For PL, another typical B-scan SD-OCT finding is defined as **"denticulated or multi-lobular PED".** This finding generally appears in the presence of PL-related, sharp PED adjacent to a serous or hemorrhagic PED. The serous PED has a dome-like appearance which seems to be blank optically while small, sharp PL-related PED adjacent to serous PED has mid-reflective content. In most instances, there is a **V-shape** depression or notch between two PEDs (Figure 3C). In addition, it has been reported that presence of serous or hemorrhagic PED alone is a suspicious finding, warranting evaluation of PL at adjacent areas. Typical B-scan SD-OCT finding for BNB is **"Double-Layer Sign".** It is defined as presence of mid-reflective material between hyper-reflective, slightly swollen, undulated RPE and hyper-reflective Bruch's membrane (Figure 1C). It was reported that this finding seen in nAMD eyes with type 1 NV had a higher diagnostic value favoring PCV in the co-existence of sharp, spiking PED. [1,3,5,7,11,13-17]

The en -face (C-scan) SD-OCT, providing horizontal images where retina parallels to vitreous, is another helpful imaging modality for identifying components of PCV, namely PL and BNN.[1,3,5,17] On en-face images, PL is typically visualized as a bright, hyper-reflective round or oval ring. Its contents is typically mid-reflective. In active polyps, there is subretinal fluid surrounding the ring (Figure 1E). In the presence of serous PED, PLs are visualized as a smaller ring which is hyper-reflective at periphery with mid-reflective content adjacent to larger ring. This finding is termed as **"Snowman"** (Figure 2D). BNNs typically appear as hyper-reflective, irregular, geographic RPE elevations which are generally adjacent to PL or PED (Figure 1E, 2D).

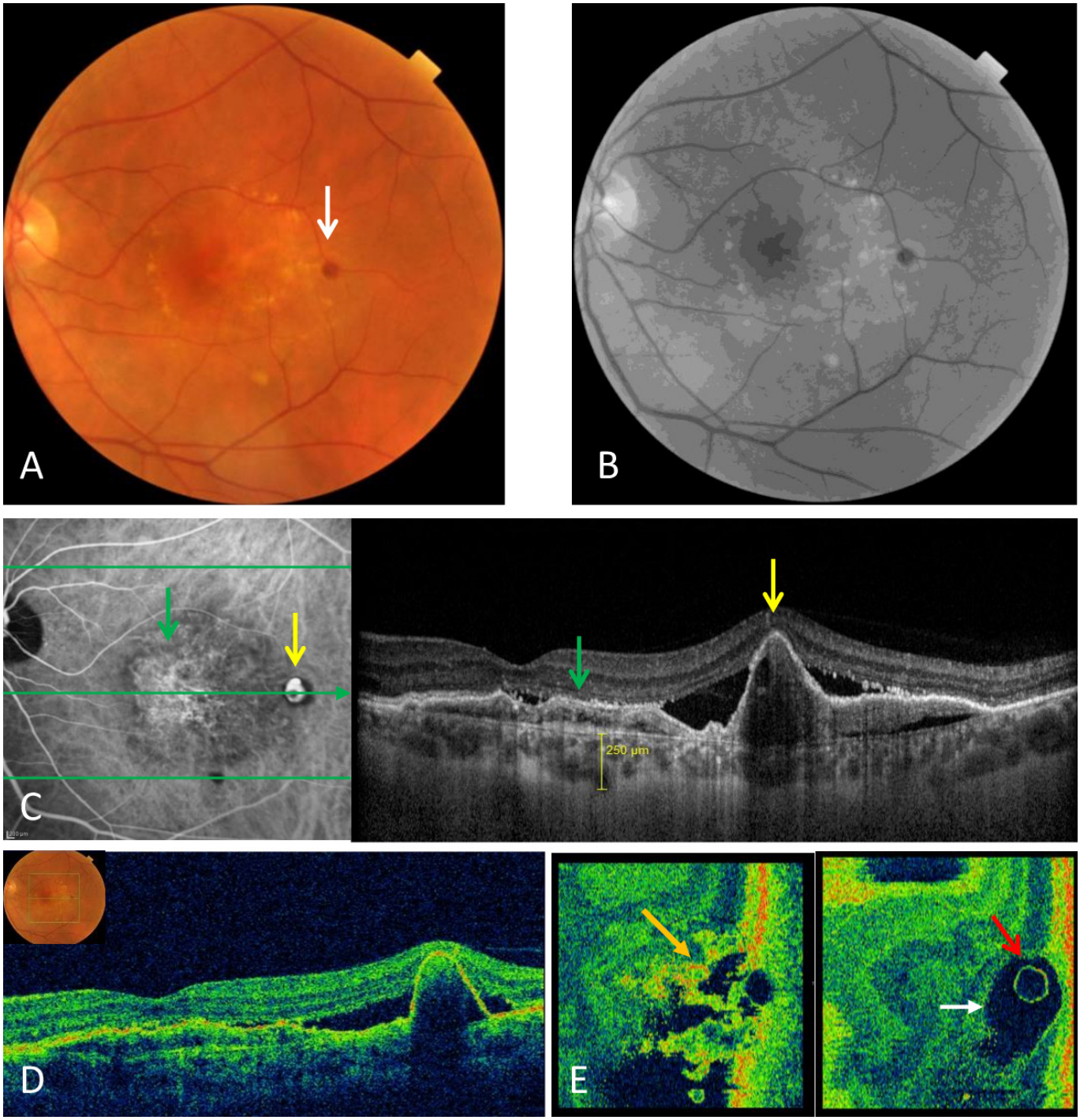

Figure 1: *A 71-year-old male patient with PCV,* **A)** *Color fundus photograph; orange nodule (white arrow)* **B)** *Infrared photograph* **C)** *SD-OCT guided by ICGA; a hypercyanine PL on ICGA and sharp peaked PED on OCT (yellow arrows), branching neovascular network (green arrows)* **D)** *SD-OCT* **E)** *En face OCT; branching neovascular network (orange arrow), PL (red arrow) and subretinal fluid (white arrow).*

Fundus Autofluorescence

FOF imaging visualizes natural fluorescence formed by lipofuscin granules within RPE via conventional short-wave (688 nm) cSLO technique, which is a non-invasive, rapid, reliable and reproducible tool providing valuable information in the diagnosis of PCV as it is the case in many diseases involving outer retinal layers. In several clinical trials, it was reported that PL and BNN have characteristic FOF patterns and can be visualized by 88-92% and 97-100%, respectively.[5,7,18-21]

Öztaş et al. identified 4 distinct FOF patterns at areas corresponding to localization of PLs on ICGA in eyes diagnosed as PCV by ICGA.[18] The most typical pattern was a central, well-defined, round, confluent

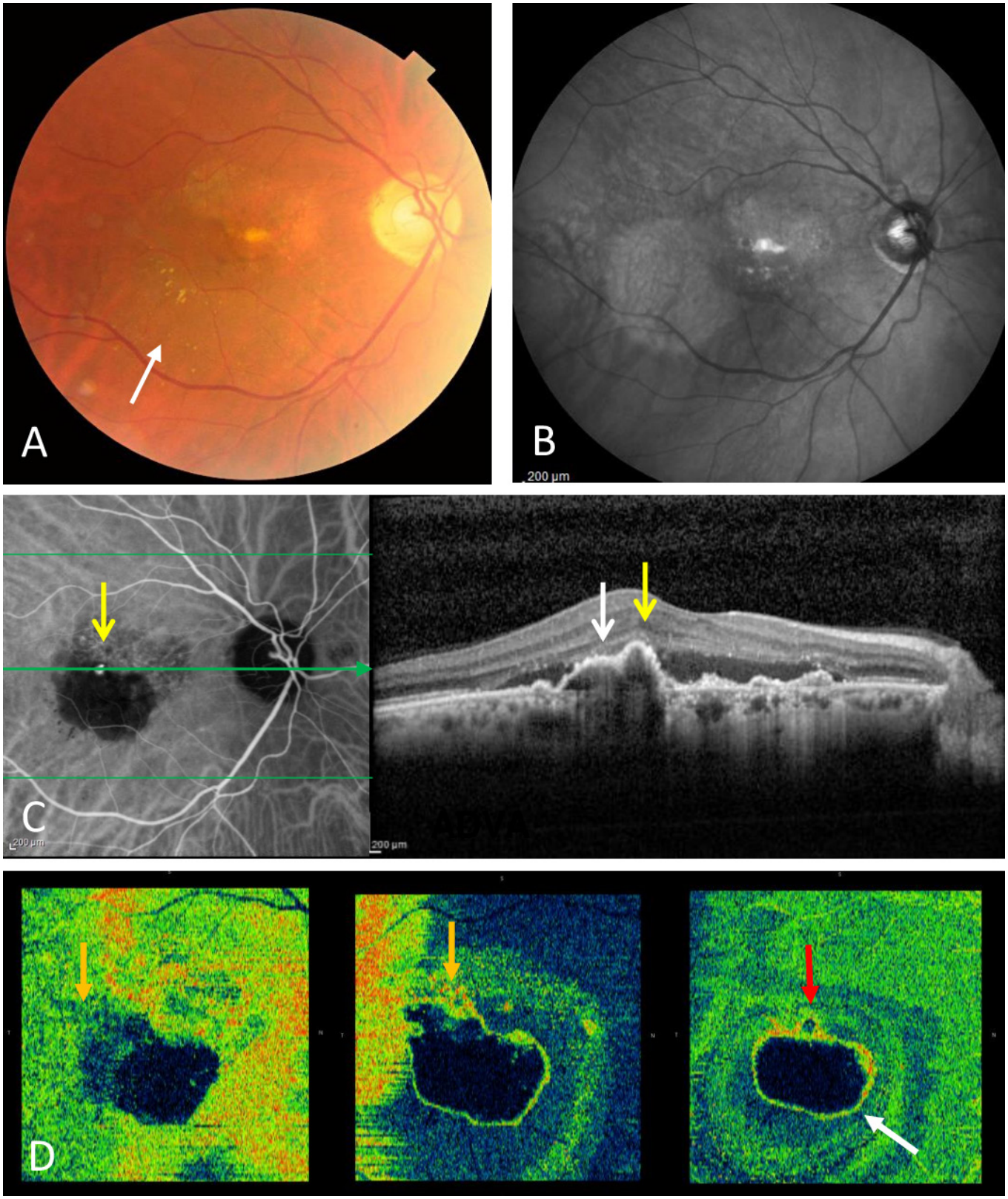

Figure 2: *A 65-year-old male patient with PCV,* **A)** *Color fundus photograph; a serous PED (white arrow)* **B)** *Infrared photograph* **C)** *SD-OCT guided by ICGA; a hypercyanine PL on ICGA, sharp peaked PED (yellow arrows) and serous PED (white arrow) on OCT* **D)** *En face OCT; branching neovascular network (orange arrows), PL (red arrow) and serous PED (white arrow);* ***«snowman view».***

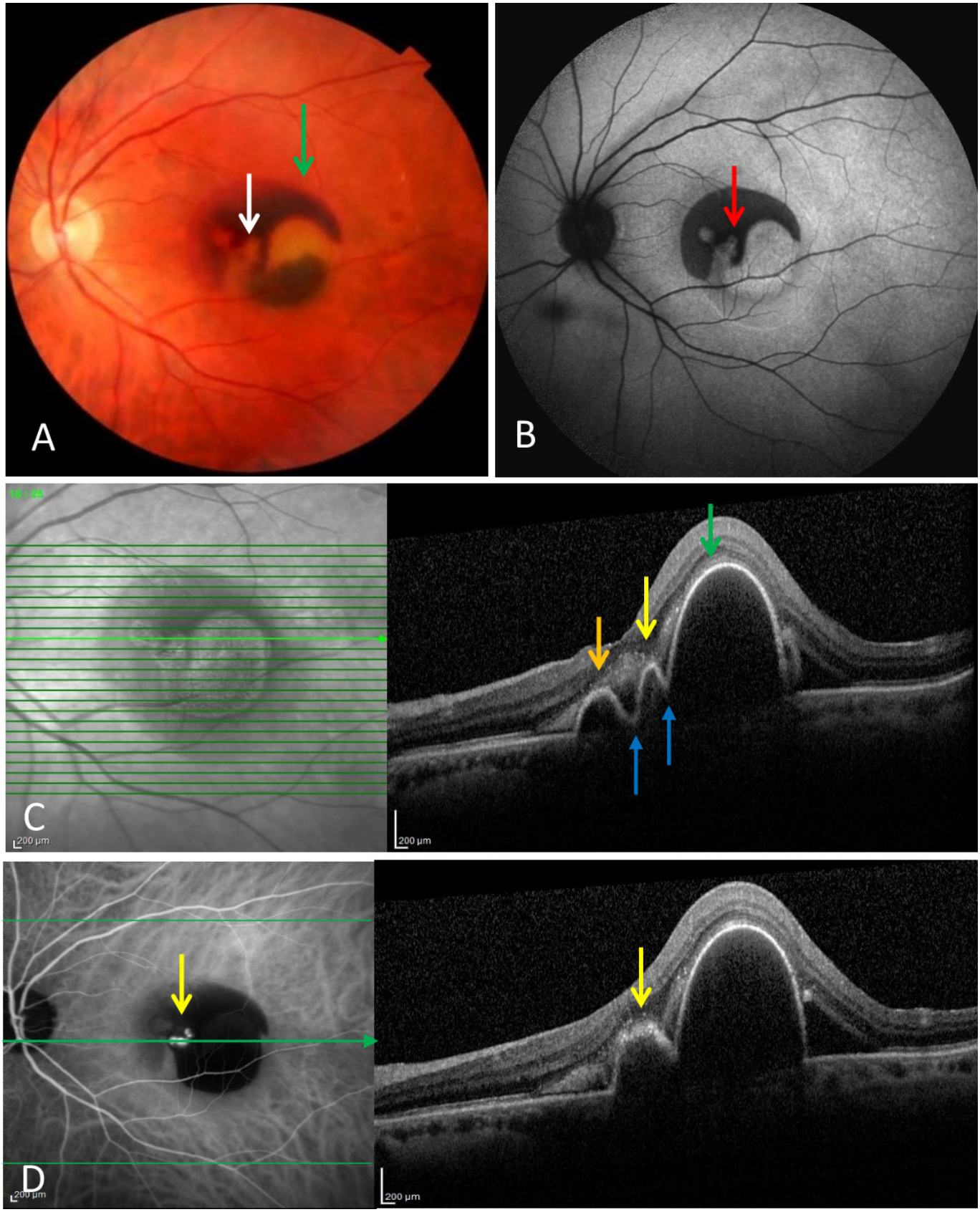

Figure 3: *A 55-year-old male patient with PCV,* **A)** *Color fundus photograph; a hemorrhagic PED (green arrow) and orange nodule (white arrow)* **B)** *FAF image; a round hyperautofluorescent area in the center and a hyporautofluorescent ring surrounding it (red arrow)* **C)** *SD-OCT; sharp peak PED with medium internal reflectivity typical for polipoidal lesion (yellow arrow), hemorrhagic PED (green arrow), serous PED (orange arrow), notches between hemorrhagic, serous PEDs and PL (blue arrows), multilobular PED* **D)** *SD-OCT guided by ICGA; a hypercyanine PL on ICGA and sharp PED on OCT (yellow arrows).*

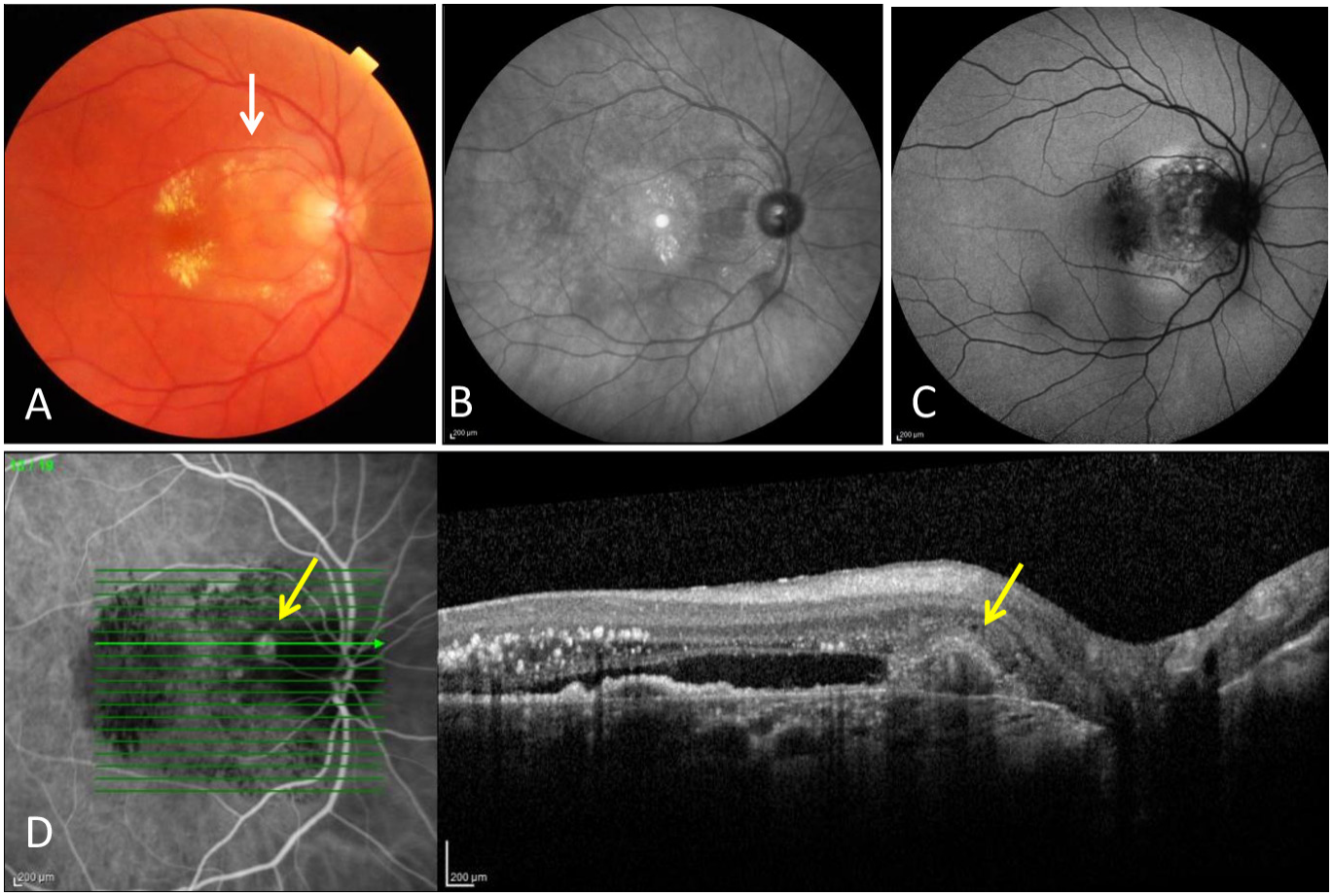

Figure 4: *A 70-year-old female patient with PCV,* **A)** *Color fundus photograph; neurosensorial serous detachment and exudation in the maculopapillary region (white arrow),* **B)** *Infrared photograph* **C)** *FAF image* **D)** *SD-OCT guided by ICGA; a hypercyanine polipoidal lesion adjacent to the optic disc on ICGA and sharp peaked PED on OCT (yellow arrows).*

hypo-autofluorescent area with a surrounding, hyper-autofluorescent ring (72%) while second most common pattern was a central, well-defined, round, confluent hyper-autofluorescent area with a surrounding, hyper-autofluorescent ring (8%) on contrary to above-mentioned pattern (Figure 3B, 6C). Authors reported that confluent hypo-autofluorescent or granular hypo-autofluorescent patterns might be present in limited number of eyes and that the blocked auto-hyperfluorescence in the presence of hemorrhage might hamper FOF images. They also found that BNNs had typical granular hypo-autofluorescence on FOF images (Figure 5B).

It has been hypothesized that the fact that PL and BNN have patterns on FOF imaging can be explained by changes in lipofuscin distribution within RPE resulting from cellular damage in RPE over time due to continuous mechanical stress and pressure on RPE layer induced by PL and BNN.[5,18-21]

Optical Coherence Tomography Angiography

OCTA is a novel, non-invasive and reproducible imaging modality that provides layered visualization (en face technique) of vascular structures of retina and choriocapillaris using intravascular erythrocyte movements without requiring dye injection.[1,17,22-24]

In clinical trials on sensitivity and specificity of OCTA in the diagnosis of PCV, there is consensus that it is not always possible to visualize PLs using en face and structural OCTA due to slow and variable blood flow within PLs (60-75%); however, cross-sectional OCTA has higher sensitivity (90%). It was reported that, on en face and structural OCTA, typical appearance for PLs is round or oval, hyper-reflective RRPE rings with mid-reflective content just above Bruch's membrane (Figure 6E-H, 7D-G).[1,7,15,17,22-24] It was emphasized that BNN en face ad structural OCTA image alone was not typical for PCV when failed to visualize PLs and that BNNs appeared as a vascular network similar to type 1 NV at the level or RPE and Bruch's membrane.

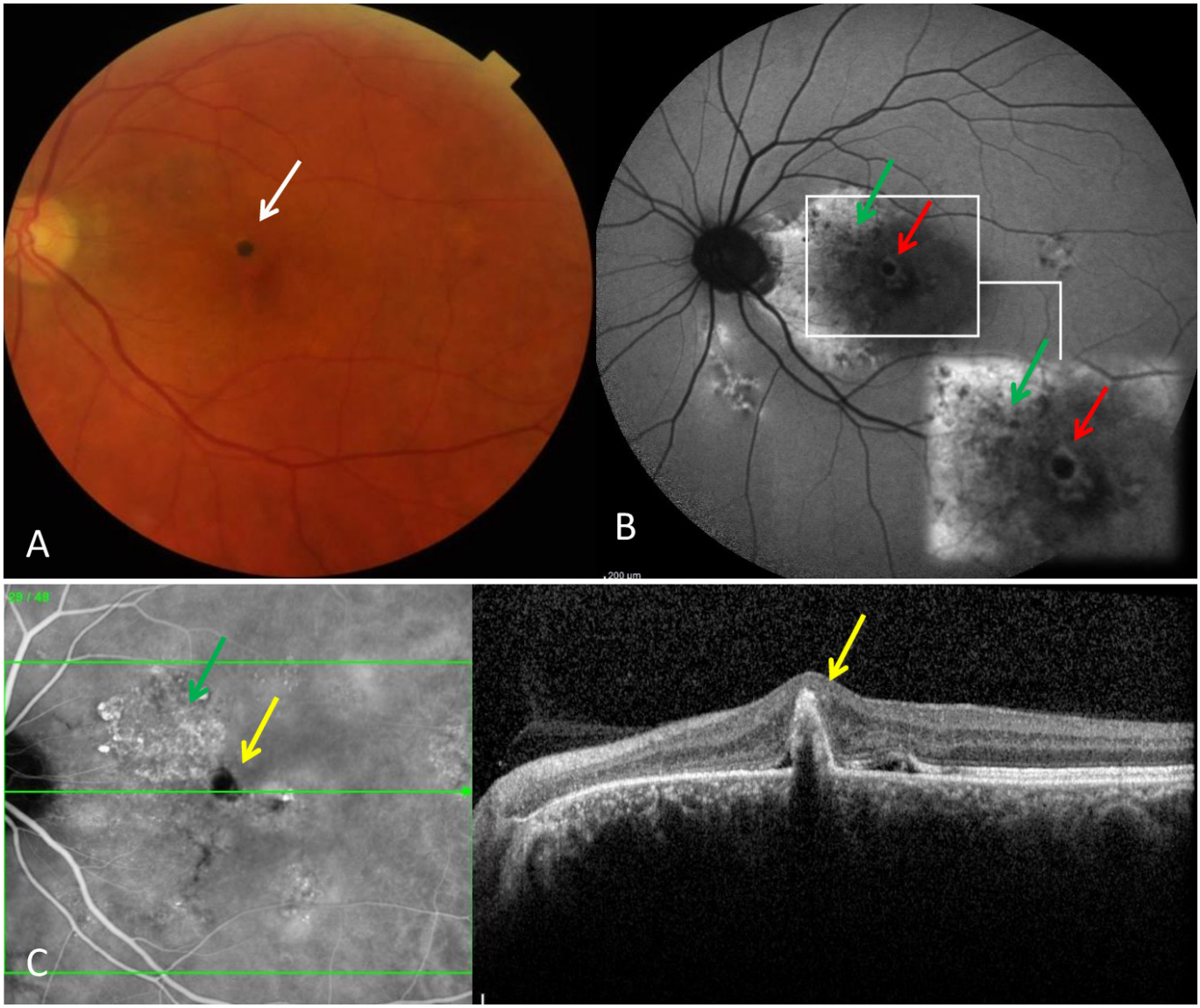

Figure 5: *A 62-year-old male patient with PCV, A) Color fundus photograph; a dark nodule (white arrow) B) FAF image; a well-circumscribed confluent hypoautofluorescent area of PL with a hyperautofluorescent ring surrounding it (red arrows) and granular hypoautofluorescence at the site of branching neovascular network (green arrows) C) SD-OCT guided by ICGA; atypical staining active polypoidal lesion (yellow arrow) and branching neovascular network (green arrow) on ICGA and sharp peaked PED on OCT (yellow arrow).*

In conclusion, due to low sensitivity, the role of OCTA in the diagnosis and differential diagnosis of PCV can be defined as provision of complementary information to other imaging modalities and multi-modal diagnosis.[1,17,22-24]

CONCLUSION

The ICGA, which was considered as gold standard method for diagnosis of PCV, is now deemed as an imaging modality which should be solely used in atypical cases and clinical trials due to its invasive and time-consuming nature as well as need for specific dye and device and is not routinely used in clinical practice. In recent years, there is a consensus on that there are very typical findings for PCV diagnosis on non-invasive imaging modalities including SD-OCT, color fundus images, FOF and even OCTA and that PCV diagnosis can be made with >90% sensitivity without ICGA by considering all these imaging modalities in a multimodal process. Obviously, future studies should aim to further develop non-ICGA multimodal imaging criteria for diagnosis and differential diagnosis of PCV.

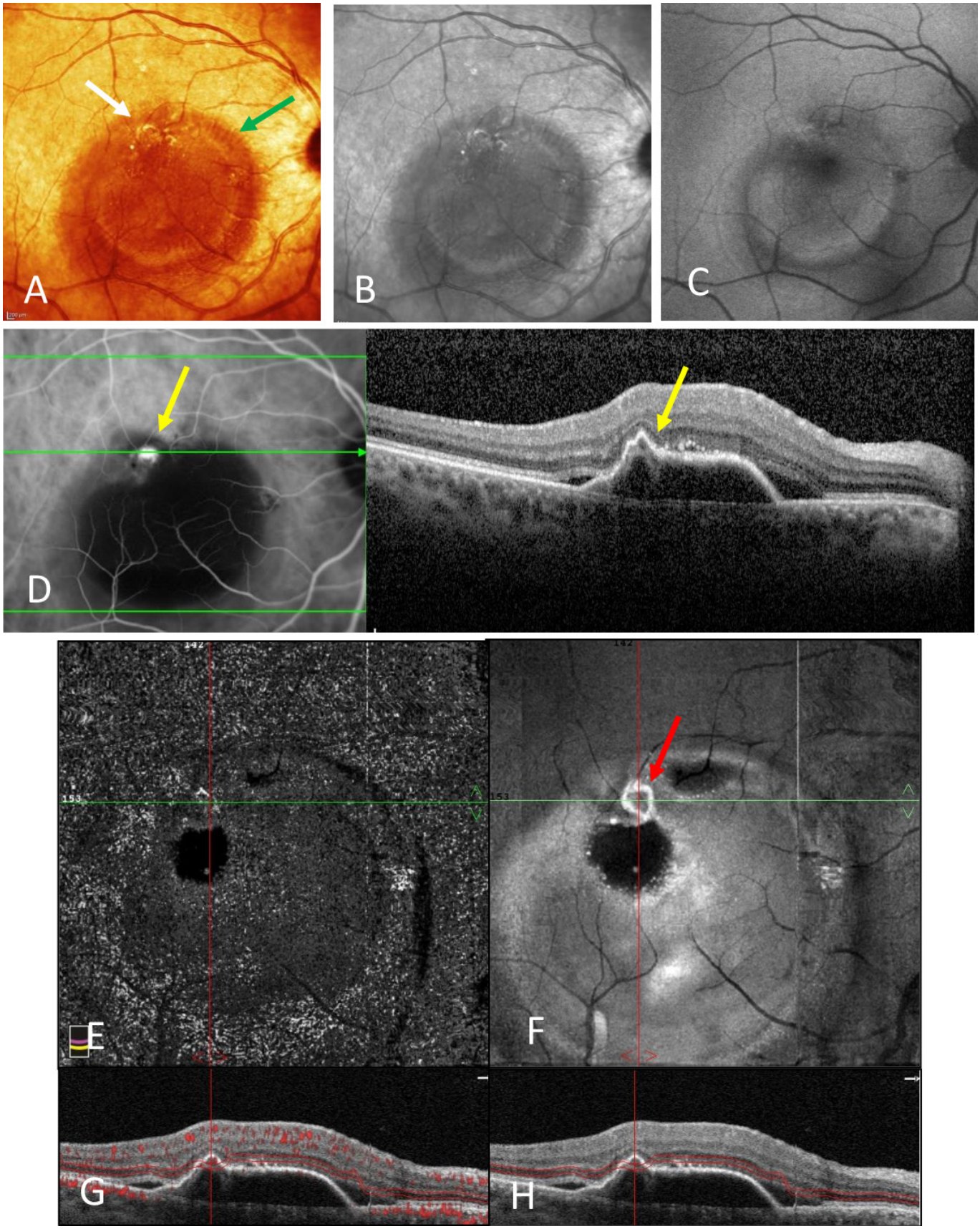

Figure 6: A 64-year-old female patient with PCV, A) Color fundus photograph; orange nodüle (white arrow) and serous PED (green arrow) B) Infrared photograph, C) FAF image D) SD-OCT guided by ICGA; a hypercyanine PL adjacent to the serous PED on ICGA and sharp peaked PED on OCT (yellow arrows) E) En Face OCTA F) Structural OCTA; polipoidal lesion appear as a hyperreflective RPE ring with medium internal reflectivity (red arrow) G, H) Cross-sectional OCTAs.

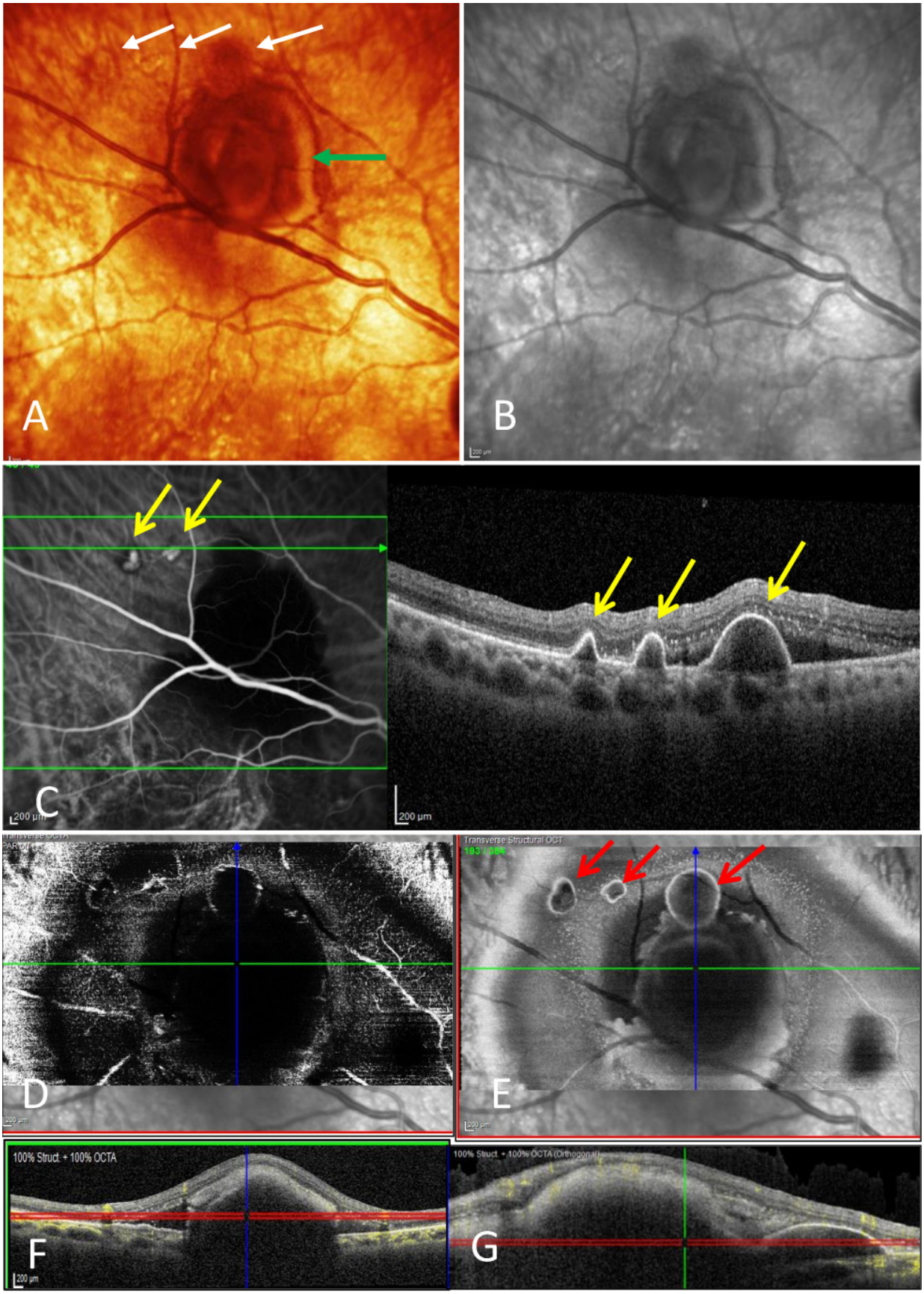

Figure 7: A 72-year-old female patient with PCV, A) Color fundus photograph; orange nodüles (white arrows) and hemorrhagic PED (green arrow) above the macula B) Infrared photograph C) SD-OCT guided by ICGA; There are two polipoidal lesions on ICGA, but three sharp peaked PEDs are seen on OCT (yellow arrows) D) En Face OCTA E) Structural OCTA; Three hyperreflective RPE rings of polipoidal lesions, their internal reflectivity is medium (red arrows) F, G) Cross-sectional OCTAs.

REFERENCES

1. Sheth JU, Narayanan R, Anantharaman G, et al. Updated guidelines for the management of polypoidal choroidal vasculopathy: Recommendations from the Indian Polypoidal Choroidal Vasculopathy Panel and the Vitreoretinal Society of India. Indian J Ophthalmol. 2022; 70:3102-11.
2. Yannuzzi LA, Sorenson J, Spaide RF, et al. Idiopathic polypoidal choroidal vasculopathy (IPCV). Retina 1990; 10:1-8.
3. Cheung CMG, Lai TYY, Teo K, et al. Polypoidal choroidal vasculopathy: consensus nomenclature and non-Indocyanine green angiograph diagnostic criteria from the Asia-Pacific Ocular Imaging Society PCV Workgroup. Ophthalmology 2021; 128:443-52.
4. Anantharaman G, Sheth J, Bhende M, et al. Polypoidal choroidal vasculopathy: Pearls in diagnosis and management. Indian J Ophthalmol. 2018; 66: 896-908.
5. Zhao J, Chandrasekaran PR, Cheong KX, et al. New concepts for the diagnosis of polypoidal choroidal vasculopathy. Diagnostics 2023; 13:1680.
6. Wang Y, Gu X, Chen Y. Advances in multi-modal non-invasive imaging techniques in the diagnosis and treatment of polypoidal choroidal vasculopathy. Front. Med. 10:1221846. doi: 10.3389/fmed.2023.1221846
7. Lam WC, Choudhry N, Wong D. Polypoidal choroidal vasculopathy in Canada, Can J Ophthalmol. 2020; 55:199-211.
8. Cheung CMG, Lai TYY, Ruamviboonsuk P, et al. Polypoidal choroidal vasculopathy: definition, pathogenesis, diagnosis, and management. Ophthalmology 2018; 125:708-24.
9. Permadi AC, Djatikusumo A, Adriono GA. Optical coherence tomography in diagnosing polypoidal choroidal vasculopathy. Looking into the future: A systematic review and meta-analysis. Int. J. Retin. Vitr. 2022; 8:14.
10. Salvo G, Vaz-Pereira S, Keane PA, et al. Sensitivity and specificity of spectral-domain optical coherence tomography in detecting idiopathic polypoidal choroidal vasculopathy. Am J Ophthalmol. 2014; 158:1228-38.
11. Kokame GT, Omizo JN, Kokame KA, et al. Differentiating exudative macular degeneration and polypoidal choroidal vasculopathy using OCT B-Scan. Ophthalmology Retina 2021; 5:954-61.
12. Menteş J, Barış ME. İntravitreal Anti-VEGF tedavisine yetersiz cevaplı neovasküler tip yaşa bağlı maküla jejenerasyonlu gözlerde polipoidal koroidal vaskülopati sıklığı, Turk J Ophthalmol. 2022; 52:338-41.
13. Chaikitmongkol V, Kong J, Khunsongkiet P, et al. Sensitivity and specificity of potential diagnostic features detected using fundus photography, optical coherence tomography, and fluorescein angiography for polypoidal choroidal vasculopathy. JAMA Ophthalmol. 2019; 137:661-7.
14. Liu R, Li J, Li Z, et al. Distinguishing polypoidal choroidal vasculopathy from typical neovascular age-related macular degeneration based on spectral domain optical coherence tomography. Retina 2016; 36:778-86.
15. Cheung CMG, Yanagi Y, Akiba M, et al. Improved detection and diagnosis of polypoidal choroidal vasculopathy using a combination of optical coherence tomography and optical coherence tomography angiography. Retina 2019; 39:1655-63.
16. Yang J, Yuan M, Wang E, et al. Noninvasive multimodal imaging in diagnosing polypoidal choroidal vasculopathy. BMC Ophthalmol. 2019; 19:229.
17. De Carlo TE, Kokame GT, Kaneko KN, et al. Sensitivity and specificity of detecting polypoidal choroidal vasculopathy with en face optical coherence tomography and optical coherence tomography angiography. Retina 2019; 39:1343-52.
18. Öztaş Z, Menteş J, Nalçacı S, et al. Aktif polipoidal koroidal vaskülopatili gözlerde fundus otofloresans özellikleri, Turk J Ophthalmol.2016; 46:165-8.
19. Yamagishi T, Koizumi H, Yamazaki T, et al. Fundus autofluorescence in polypoidal choroidal vasculopathy. Ophthalmology 2012; 119:1650-7.
20. Suzuki M, Gomi F, Sawa M, et al. Changes in fundus autofluorescence in polypoidal choroidal vasculopathy during 3 years of follow-up. Graefes Arch Clin Exp Ophthalmol. 2013; 251:2331-7.
21. Zhao X, Xia S, Chen Y. Characteristic appearances of fundus autofluorescence in treatment-naive and active polypoidal choroidal vasculopathy: a retrospective study of 170 patients. Graefes Arch Clin Exp Ophthalmol. 2018; 256:1101-10.
22. Chan SY, Wang Q, Wang YX, et al. Polypoidal choroidal vasculopathy upon optical coherence tomographic angiography. Retina 2018; 38:1187-94.
23. Wang Y, Yang J, Li B et al. Detection rate and diagnostic value of optical coherence tomography angiography in the diagnosis of polypoidal choroidal vasculopathy: A systematic review and meta-analysis. J Ophthalmol. 2019; 2019:6837601.
24. Fujita A, Kataoka K, Takeuchi J, et al. Diagnostic characteristics of polypoidal choroidal vasculopathy based on B-scan swept-source optical coherence tomography angiography and its interrater agreement compared with indocyanine green angiography. Retina 2020; 40:2296-303.