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Clinical features, diagnosis, differential diagnosis and management of idiopathic polypoidal choroidal vasculopathy. 2+2+2+4 D2016

When to suspect the presence of PCV on clinical evaluation?

1. The classical clinical finding of PCV is the presence of reddish-orange subretinal nodules.
2. They can be small, medium, or large in size.
3. The large nodules are easily seen clinically, especially when the overlying retinal pigment epithelium (RPE) is thinned.
4. Apart from polyps, the clinical features more commonly seen include varying degree of serous or serosanguinous PEDs, subretinal hemorrhage, lipid deposition as well as neurosensory retinal detachment in the peripapillary or macular retina.

Clinical classification of polypoidal choroidal vasculopathy

1. Quiescent: Presence of polyp in the absence of any intraretinal or subretinal fluid or hemorrhage
2. Active
    a. Exudative: Absence of hemorrhage; presence of exudation in the form of either serous macular detachment/intraretinal fluid/serous PED/lipid exudation
    b. Hemorrhagic: Subretinal or sub-RPE hemorrhage/ hemorrhagic PED
    c. Mixed: Presence of features of both exudative and hemorrhagic variety.

- Occasionally, PCV can be located outside the posterior vascular arcades and may cause peripheral exudative hemorrhagic chorioretinopathy.
- At times, PCV can also present with breakthrough vitreous hemorrhage.

Symptoms

1. Patients with PCV most commonly present with diminution of vision.
2. Other symptoms include metamorphopsia, floaters, and central scotoma.

Signs

1. Typically, a patient who has symptoms for <3 months may have extensive subretinal exudation and hemorrhage but minimal intraretinal cystic changes and a good visual acuity.
2. The visual acuity being unexpectedly better in PCV than AMD.
3. The better visual acuity has been speculated to be because of minimal intraretinal changes and the possible extrafoveal location in PCV.
4. However, late presentations may have considerable lipid depositions due to protein leakage from the polypoidal vascular abnormalities.
5. In long-standing cases, there may be signs of subretinal fibrosis, pigment epithelial hyperplasia, or atrophic retinal degeneration.

Suspect polypoidal choroidal vasculopathy in the presence of one of the following classical clinical features

1. Reddish-orange subretinal nodules
2. Serosanguineous maculopathy
3. Disproportionate amount of exudation as compared to size lesion
4. Hemorrhagic PED/Spontaneous submacular hemorrhage
5. Nonresponsiveness to anti-VEGF therapy

Differential diagnosis

Age-related macular degeneration (type 1 or type 2), central serous chorioretinopathy, pathological myopia with neovascularization, and choroidal tumors or metastases.

Investigations

A. ICGA

1. Classic clinical features of PCV described above with or without characteristic notched/peaked PED on OCT is an indication to perform an ICGA.
2. ICGA is considered to be the current gold standard for detection and evaluation of PCV
3. The EVEREST study used 3 specific criteria to define the polyps of PCV –
    i. Nodular hyperfluorescence on stereoscopic ICGA (91.8%),

ii. Hypofluorescent halo around the nodule (68.9%),
iii. Pulsation during dynamic ICGA (6.6%).

4. Importance of phases of indocyanine green angiography

1. **First 1 min**: Recognition of AVN, especially feeder vessel in branch vascular network (BVN) which appears very early (Within first 30 s).
2. Dynamic ICGA should be performed as far as possible within the 1st minute to identify pulsatile polyps in addition to defining the extent of AVN.

3. Characterization of Abnormal Vascular Network:

a. Interconnecting channels (IC): AVN appearing within 1 min of dye injection in the absence of feeder vessel
b. BVN: AVN appearing within 1 min of dye injection in the presence of feeder vessel.

4. **First 6 min**: Characterization of polyp: Early nodular hyperfluorescence arising from choroidal circulation noted within the first 6 min of dye injection.
5. They may be either solitary or arranged in strings or clusters.
6. Additional ICGA features include:
   i. Hypofluorescent halo around the hyperfluorescent nodule
   ii. Abnormal vascular channels terminating in the polyps
   iii. Pulsatile filling of polyps (Video ICGA).

7. Based on ICGA, PCV is classified in following subtypes with relation to the location of polyp/AVN

1. Macular
   a. Subfoveal: Below the fovea
   b. Juxtafoveal: Located within 1–199 μ from center of fovea
   c. Extrafoveal: Location 200 μ or more from center of fovea
2. Peripapillary: Located with one disc diameter from the margins of the disc
3. Peripheral: Located outside the arcade

8. Following 10 min: "LGH" can be appreciated well. (Late geographic hypertrophy)
9. Based on ICGA, the location of polyp and AVN should be clearly defined which will help in selecting the best treatment strategy.
10. The total lesion area of PCV is the total area including all polyps and AVN on ICGA.

B. **FFA**

1. FFA should be performed in all patient of PCV at the initial examination to identify the presence or absence of leakage from the AVN which plays a role in prognosticating the disease outcome
2. **Indocyanine green + fundus fluorescein angiography-based classification** of PCV based on prognosis
   a. Polyp + IC
   b. Polyp + BVN without leakage on FFA
   c. Polyp + BVN with leakage on FFA.

C. **OCT**

1. Based on OCT, PCV can be suspected if there is the presence of any one of the following features:
   1. Thumb-like polyp (TLP)/Sharp-peaked PED: Denotes polyp
   2. Tomographic notch in PED: Signifies the polypoidal lesion at margin of PED
   3. Hyporeflective lumen surrounded by hyperreflective ring attached to undersurface of RPE
   4. Double-layer sign (DLS): Presence of two hyperreflective lines on SD-OCT representing shallow irregular RPE elevation and Bruch's membrane, signifying AVN
2. The presence of normal/increased choroidal thickness (pachychoroid) on enhanced-depth imaging OCT (EDI-OCT) provides supportive evidence of PCV and can be used to differentiate it from AMD, in which the choroid is usually thin
3. By identifying classical features of PCV on OCT such as tall-peaked PED, notched PED, DLS, and TLP, it may be possible to suspect PCV and differentiate it from Wet AMD to a large extent.
4. Nonetheless, ICGA remains the gold standard in diagnosing PCV and should be performed if available.

Treatment

1. The treatment of PCV is primarily based on its location, and whether it is active or inactive.
2. The entire PCV lesion including the polyp and AVN should be treated.
3. Treatment modalities for PCV include verteporfin photodynamic therapy (PDT), anti-vascular endothelial growth factor (anti-VEGF) therapy, and thermal laser (TL) photocoagulation.
4. **PCV can be considered active** in the presence of any one of the following features:

1. Intraretinal/subretinal fluid
2. Sub-RPE/subretinal hemorrhage
3. Vision loss ≥5 ETDRS letters
4. Leakage on FFA can be considered as a corroborative feature in defining the disease activity

5. **Indications to treat**
   1. Active symptomatic PCV: Treat
   2. Active asymptomatic PCV: Can consider treatment based on discretion
   3. Inactive PCV: Observe.
6. If there are multiple polyps present on ICGA scattered throughout the posterior pole, but the evidence of activity is limited to only one particular polyp, the panel recommends only the active polyps be treated based on its location.
7. The inactive polyps need close follow-up.

1. Active subfoveal and juxtafoveal PCV and extension of the branching vascular network	Full-fluence PDT with three loading doses of anti-VEGF injection
2. Isolated extrafoveal polyps	Thermal Laser
3. Polyp + AVN in extrafoveal location	TL is associated with the risk of hemorrhage and scotomas. Safer- PDT + Anti-VEGF therapy
4. Extrafoveal PCV	1. Between 200 µ-≤500 µ from fovea = PDT + 3 loading doses of anti-VEGF agents 2. 500 µ-≤1000 µ from fovea = a. Lesion size >1000 µ: PDT + 3 loading doses of anti-VEGF agents b. Lesion size ≤1000 µ: TL + Anti-VEGF 3. Beyond 1000 µ from fovea = TL + Anti-VEGF
5. Peripapillary and peripheral PCV	1. Active symptomatic PCV: TL + Anti-VEGF agent 2. Active asymptomatic PCV: Consider treatment 3. Quiescent PCV: Observe
6. Feeder vessel	Photocoagulation should be certainly considered in cases where it is visible on ICG and it is >500 µ from the center of fovea.

PDT

1. The one major concern regarding the efficacy of PDT for PCV is the recurrence
2. Retinal function, as assessed by multifocal Electroretinography, can be altered by PDT.
3. However, retinal sensitivity in the macular area of eyes with subfoveal PCV improved shortly after PDT.
4. Subretinal hemorrhage can occur after PDT.
5. This is occasionally massive and can lead to vitreous hemorrhage and a poor visual prognosis.
6. Recurrent bullous detachment and chorioretinal anastomosis after PDT have also been reported.

RF PDT

- Should be performed in the following situations:
  1. BCVA ≥20/40
  2. Lesion size >3 DD (Higher chances of bleeding with SF PDT)

Anti- VEGF± PDT

1. Ranibizumab is considered as the preferred anti-VEGF agent based on level I evidence.
2. Although no level I evidence exists for aflibercept use till now, it can also be considered as a primary anti-VEGF agent or in patients refractory to ranibizumab based on physician's discretion.
3. Recent reports of aflibercept suggest that the success rate may be much higher than that reported with ranibizumab, although prospective randomized trials similar to EVEREST are lacking.
4. Off-label use of ziv-aflibercept has also been reported in PCV
5. If initially the extent of lesion is not clearly defned on ICG due to the presence of blocked fluorescence secondary to hemorrhage, it is advisable to initiate anti-VEGF monotherapy alone.
6. Once the hemorrhage clears, ICG + FFA should be performed and if PCV is confirmed, combination therapy with PDT and anti-VEGF agent should be done.
7. Exceptional situations, such as lack of access to PDT and in resource-constrained countries, treat with anti-VEGF monotherapy
8. However, there is a strong possibility that there may be incomplete resolution of polyps, and the number of injections

9. **Indications for initiation with anti-VEGF monotherapy:**

1. Small submacular hemorrhage associated with PCV (<4DD)
2. Thin submacular hemorrhage associated with PCV (<500µm)
3. Polyp extent not clearly defned by ICG
4. Peripapillary PCV

Follow-up

1. ICGA + FFA should be repeated after 3 months to analyze disease activity.
2. **If quiescent,** ICGA + FFA should be repeated again after 6 months and 12 months, respectively.
3. BCVA and OCT should be performed at all follow-up visits.
4. **For incomplete regression of polyps**, retreatment with full-fluence PDT with intravitreal injection of anti-VEGF should be performed.
5. Half-fluence PDT may also be considered if the BCVA is ≥ 20/40.
6. **If FFA/ICGA shows no polyp, but persistence of leaking AVN**, monotherapy with anti-VEGF should be performed

Treatment of recurrence

1. At any of the follow-up visits, if there is a drop in BCVA or appearance of hemorrhage or exudation seen clinically or presence of fluid (subretinal/intraretinal) on OCT, ICG + FFA should be repeated.
2. For recurrence of polyps seen on FFA/ICG, retreatment with full-fluence PDT with intravitreal injection of anti-VEGF should be performed.
3. Reduced-fluence PDT may also be considered if the BCVA is ≥20/40.
4. If FFA/ICGA shows no polyp but the persistence of leaking AVN, monotherapy with anti-VEGF should be executed
5. Nonresponsiveness either due to tachyphylaxis or due to tolerance is known.
6. Switch over to another anti-VEGF or increase in the dose of anti-VEGF injections has been tried by a few

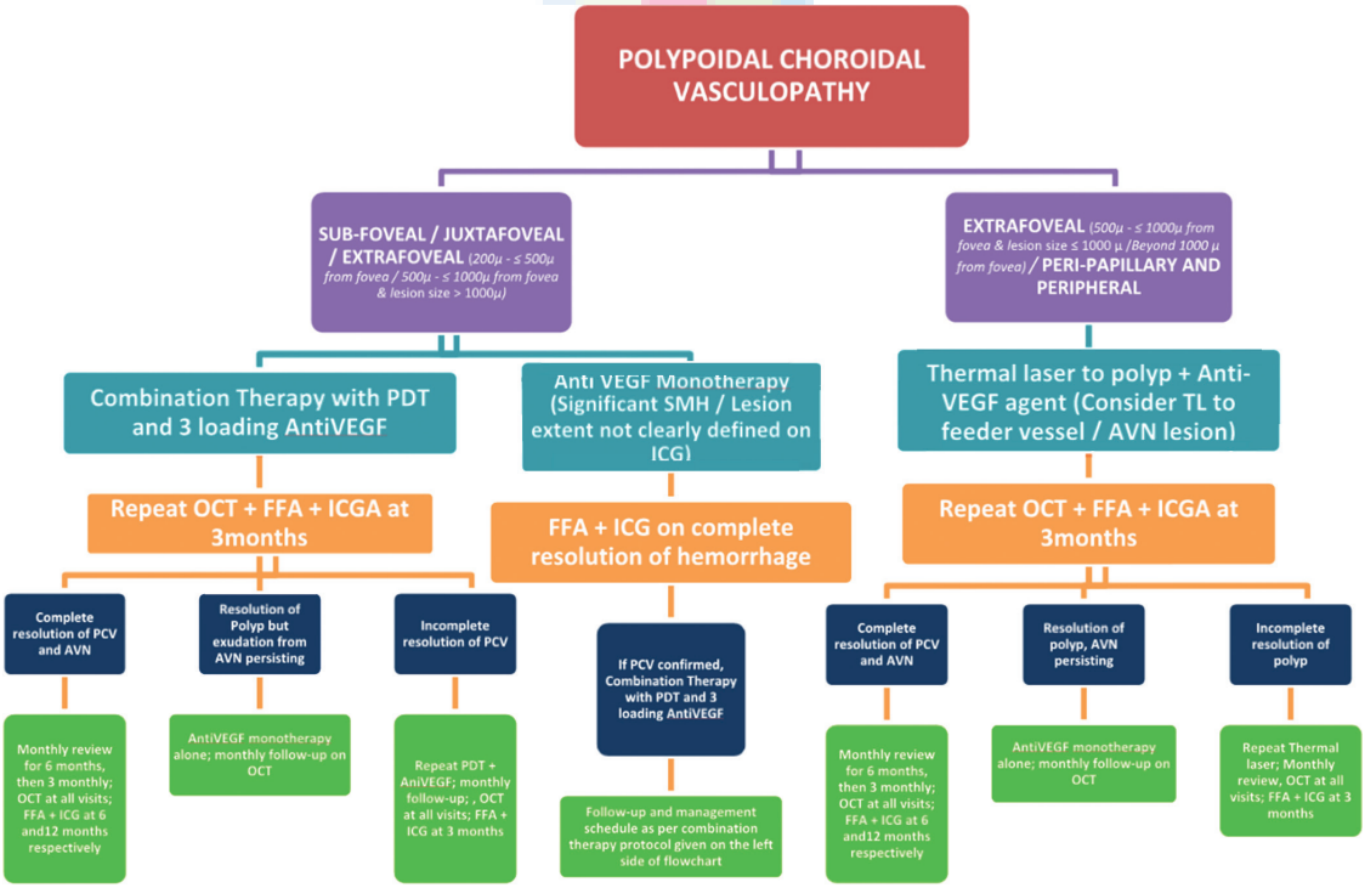

Figure 13: Flowchart for management of PCV based on the updated guidelines

The EVEREST study was the first randomized controlled trial comparing standard fluence (SF) PDT with or without three loading doses of ranibizumab 0.5 mg and ranibizumab monotherapy in PCV.

The primary endpoint was the proportion of patients with complete regression of polyp at 6 months, as determined by ICGA.

The study reported a higher polyp closure rate of PDT with or without ranibizumab compared to ranibizumab alone (77.8% and 71.4% vs. 28.6%).

This study established the efficacy of PDT in the closure of polyps.

One limitation of EVEREST study was the short follow-up period.

To overcome this limitation,

EVEREST II study was designed to assess 24-month outcome of ranibizumab 0.5 mg monotherapy and ranibizumab in combination PDT for macular PCV.

The 12-month data reported better visual acuity gains in combined group (8.3 lines) versus ranibizumab monotherapy group (5.1 lines).

In addition, the polyp regression rate was 69.3% in combination arm, whereas 34.7% in ranibizumab monotherapy arm.

To assess the effect of PDT versus anti-VEGF in terms of visual outcome, the **LAPTOP study**, a multicenter randomized controlled trial was conducted.

Ninety-three patients were randomized to 2 arms: SF PDT monotherapy arm and a ranibizumab monotherapy arm where patients received 3 monthly injections of 0.5 mg ranibizumab.

Additional treatment was performed as needed in each arm.

At 12 months, the study found a higher proportion of patients gaining >0.2 logMAR units in the ranibizumab arm (30.4% vs. 17.0%). In addition, the mean gain in logMAR visual acuity was also greater in the ranibizumab arm at 12 and 24 months.

These 2 trials showed that although PDT may be more effective at polyp closure than anti-VEGF, anti-VEGF therapy seemed to be better for improving or preventing visual loss in patients with PCV.

LAPTOP study from Japan showed that ranibizumab resulted in visual gain from baseline at 24 months, the PDT group did not gain vision.

PLANET study - at 12 months aflibercept monotherapy was non-inferior to aflibercept+PDT in visual outcome.

EPIC study - at 6months aflibercept monotherapy stabilized vision and resulted in resolution of hemorrhagic and exudative complications regression of polyps in around 70% patients.

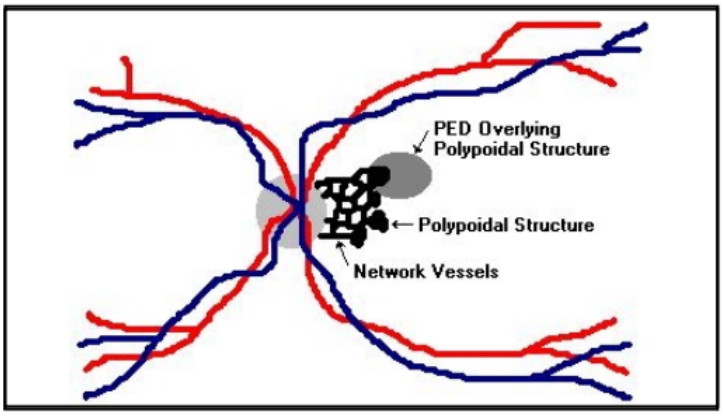

Fig. 3: Diagrammatic representation of PCV

Polypoidal choroidal vasculopathy	
Age at presentation (in years)	25 to 85 years of age (younger and wider range than age-related macular degeneration)
Sex	Males = females
Race	Higher predilection for pigmented races
Locations	Peripapillary, macular or peripheral
Eye involvement	Bilateral > Unilateral
Clinical manifestations	1. A branching network of inner choroidal vessels 2. Terminal, aneurysmal dilations of the vessels 3. Subtle nodular choroidal protrusions 4. Serosanguineous retinal pigment epithelial detachments 5. Exudative retinopathy 6. Vitreous hemorrhage 7. Chronic and recurrent course
Prognosis	Generally good, provided the macula is not involved
Systemic features	No association to systemic disease has been confirmed

Table 1: Differences betweem AMD and PCV

	Neovascular AMD	*IPCV*
Pigmentation	Soft or exudative drusen and/or focal hyperpigmentation	May have subretinal lipid deposits but not drusen
Vessels	Small in caliber and hard to see by ophthalmoscopy (may see dirty-gray membrane)	Larger, distinct organized network of vessels that can be seen clinically
Angiography	Diffuse, late staining of stromal matrix	Late, central wash-out on ICG
RPE detachments	Tend to organize into fibrotic or disciform scars	Often do not leave a scar
Natural History	May have rapid downhill course with severe visual loss	May have more stable, long-term course