Review Article :

POLYPOIDAL CHOROIDAL VASCULOPATHY AN OVERVIEW

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INTRODUCTION:

Polypoidalchoroidal vasculopathy (PCV) was first described by Yannuzzi at the Macula Society Meeting in 1982.[3] PCV was earlier recognized as age-related macular degeneration (AMD) with hemorrhage, pigment epithelial detachment (PED) and neurosensory detachment. At present, PCV is defined based on indocyanine green (ICG) angiography findings as " the presence of single or multiple focal nodular areas of hyperfluorescence arising from the choroidal circulation within the first 5 minutes after injection of ICG angiography, with or without an associated choroidal interconnecting vascular network".[5]

Incidence of PCV in Western countries ranges from 4% to 10%, in the Asia-Pacific region from 10% to 48%.[6] Typically PCV presents 1-2 decades earlier than classical AMD.

There is predilection of PCV in male population. Bilaterality, another interesting feature of PCV, is usually defined as the presence of active polyps. Macula is the predominant site for PCV. However, PCV may occur in areas adjacent to the optic nerve head and vascular arcades. PCV is more common in pigmented races i.e., African Americans and Asians. The role of hereditary and environmental factors in its etiology is inconclusive.

PATHOGENESIS :

PCV primarily involves the inner choroidal vasculature. PCV is associated with polyp-like structure projecting from the plane of the inner choroid towards the outer retina or RPE.

Three important factors implicated in the pathogenesis are: - genetics, involvement of choroidal neovascular (CNV) tissue and association of PCV with other diseases.

Phenotypic differences exist between Eastern and Western countries. Epidemiological studies have proven that drusen and incidence of dry AMD are not that common in Asia as compared to Western countries. In the absence of drusen, there is considerable difficulty in identification and management of high-risk group. Thus high-risk groups can't be identified by routine ophthalmic examination.

Various genetic factors responsible for the etiology of PCV:-

1. Complement factor H
2. HTRA I gene (risk of developing wet AMD)
3. Elastin gene (disrupts elastic area of Bruch's membrane)

Although genetic factors may be primarily responsible for the etiology of PCV, sometimes PCV can develop secondary to CNV if additional genetic factors like

HTRA I are involved.

CLINICAL COURSE :

PCV has a remitting and relapsing course with a chronic tendency. PCV causes multiple, recurrent episodes of RPE detachment and

CNV in AMD	PCV
1. More aggressive in growth	1.slow growing, typically waxes and wanes
2. Tendency to grow through RPE	2.grows more in sub-RPE level
3. Grayish membrane	3.reddish mass, polyps
4. Leakage +++	4.leakage ++
5. Fragility +	5.fragility (bleeding) +++
6. Scarring (fibrotic) +++	6.scarring + (unless with secondary CNV)
7. Solitary	7.multiple centers
8. More rapid course with drop of vision	8.a slower course
9. Older in age	9.younger in age
10. Features of AMD	10.not associated with drusen

(reference 3)

neurosensory retina. Causes of visual loss can be fibrosis, disciform scarring, RPE atrophy, chronic cystoids and cystic degeneration, breakthrough vitreous hemorrhage, and phthisis bulbi due to massive suprachoroidal hemorrhage.

Although the overall prognosis for PCV is relatively good, the risk of total blindness due to massive suprachoroidal or vitreous hemorrhage is much higher than in AMD.

PCV has been considered as CNV due to similar angiographic patterns on ICG, elevated levels of VEGF, similar histology, and expression of growth factors and receptor antibodies. However, the increased levels of VEGF in PCV are lower compared with AMD and myopic CNV. Cases that initially present with polypoidal lesions and develop CNV-like features are diagnosed as secondary CNV. Cases that initially present with CNV and later develop polypoidal extensions are diagnosed as polypoidal CNV.

Patients unlikely to develop primary CNV develop secondary CNV much faster. Primary CNV can cause ischemic changes, inflammation, sick RPE and break at Bruch's membrane. These changes can contribute in development of secondary CNV. Secondary CNV can mask the clinical picture and make the treatment response less sensitive, especially to photodynamic therapy (PDT). It also increases risk of persistent recurrent vascular lesions.

Associated conditions with PCV include Systemic hypertension, Sickle cell disease, Severe undetected thrombocytopenia.

In pure or primary PCV, more mature cells were observed with structural abnormalities. Primary PCV was less responsive to anti-VEGF therapy, but showed a good clinical outcome with PDT as it causes remodulation and regression. In PCV combined with CNV, combination therapy is the most optimal treatment.

ANGIOGRAPHIC FEATURES OF PCV:

Hyperfluorescent Polypoidal choroidal lesions on ICGA were considered as the hallmark of PCV. The Polypoidal lesions were classified based on their arrangement into:

a) Solitary

b) Cluster or bunch of grapes

c) Ring

d) Mixes lesions

Heidelberg retinal angiogram (HRA) helps in imaging the branching vascular network (BVN) which actively participates in the pathogenesis of PCV.

ICG is the gold standard for diagnosis of PCV. [10] In PCV, angiography helps in imaging Polypoidal lesions, feeder vessel branching into a network of vessels and leakage. Patients with recurrence of PCV usually have a typical

serosanguineous presentation with Polypoidal lesions, leakage, vascular network and PED. Persistence of Polypoidal lesions should also be considered in patients with leakage. Appropriate laser therapy can settle the leakage in such cases.

The interconnecting channels supplying the Polypoidal lesions are not quiescent channels. Active vessels that leak and bleed usually recur, persist, reactivate and progress. In some cases, the manifestations come from the polyps, while the interconnecting channels are quiescent. In other cases, the Polypoidal lesions are fed by the interconnecting channels and vessels. The lesion grows inside the feeder vessel and causes leakage. These variable manifestations comprise 2 ends of a spectrum.

Highly suspicious signs of PCV rendering ICGA in serosanguinous maculopathy are: [10]

i. Clinically visible orange-red subretinal nodules

ii. Spontaneous massive subretinal hemorrhage

iii. Serous or hemorrhagic pigment epithelial detachments

iv. Notched pigment epithelial detachments

v. Recurrent and chronic atypical clinical course

vi. Features of exudative AMD but absence of soft drusen

vii. Multifocal areas of occult pattern of leaking hyperfluorescence on FA

viii. Features of AMD manifested in younger age group

CLASSIFICATION OF PCV BASED ON CLINICAL PATTERNS:

GROUP 1: (subclinical)

· Asymptomatic with incidental findings during ICGA

· No leakage through the RPE

· No hemorrhage

· RPE atrophy may be present

· Vision is generally good

GROUP 2: (exudative)

· Typical Clinical Polyps

· Focal or diffuse leakage of clear fluid or hard exudates through RPE without hemorrhage

· Well responsive to PDT

GROUP 3: (hemorrhagic)

· Clinical polyps or sub-RPE reddish mass

· CNV-like pattern with hemorrhage

· Rupture of the vessel or profuse vascular leakage

· Absence of hot spots or plaque on ICG

· Absence of drusen and fibrotic scar

GROUP 4: (massive hemorrhagic)

· Rupture of polyps or choroidal vessels

· Massive hemorrhage

· Absence of drusen in the involved and fellow eyes

· Absence of features suggesting other CNVs

· Limited outcome with no standard line of treatment

MODIFIED CLASSIFICATION PROPOSED BY PCV ROUNDTABLE 2008 [(11)]

TYPE 1:- Quiescent- polyps without signs of subretinal or intraretinal fluid or hemorrhage

TYPE 2:- Exudative- without hemorrhage, includes sensory retinal thickening, neurosensory detachment, PED and subretinal lipid exudation.

TYPE 3:- Hemorrhagic- any amount of hemorrhage < 4 MPS disc areas, with or without features described above.

TYPE 4:- Massive hemorrhagic- measuring at least 4 MPS disc area in size, with or without features described above.

DIAGNOSTIC CRITERIA:

The diagnostic criteria for PCV are based on the fundus examination, ICGA findings or both.

A **DEFINITE** case of PCV should meet at least one of the following criteria:

· A protruding orange-red lesion (elevated level of RPE) observed by fundus examination

· A characteristic Polypoidal lesion seen in ICGA.

Polypoidal lesions corresponding to orange-red protruding lesions are characteristic findings of PCV. In ICGA, these lesions are seen as Hyperfluorescent spots in the early phase, which increase in size later. In later stages, these lesions remain unchanged in size and shape.

A **PROBABLE** case of PCV should meet at least one of the following criteria:

· Only an abnormal vascular network is seen in ICGA. (i.e. an abnormal vascular network is present overlying the large choroidal vessels).

· Recurrent hemorrhagic, serous detachments of RPE or both.

The Polypoidal lesions in most eyes are located at the termini of network vessels, and are not a Polypoidal dilatation of vessel termini, but consist of various vascular abnormalities like cluster of microaneurysmal dilatations and loop-like vessels. Pulsation can be detected in network vessels, or in Polypoidal lesions or in both. Pulsation is not a feature of CNV. CD-34 is a marker of vascular endothelium expression in PCV. Dilated vessels are prominent in PCV (but vessels are smaller in CNV in AMD).

Characteristic signs of active PCV:-

A. Clinical evidence of activity includes any of the following clinical signs:

- Neurosensory detachment
- PED
- Subretinal lipid exudation
- Subretinal hemorrhage

OR

B. FA evidence of activity is leaking hyperfluorescence, typically in an "occult" pattern (fibrovascular PED or late leakage of an undetermined source).

OR

C. ICGA evidence of activity is late (defined by 20 min and beyond) leakage and staining of Polypoidal structures.

TREATMENT MODALITIES IN PCV:

Current treatment modalities in PCV: observation, laser, Verteporfin with PDT, transpupillary thermotherapy (TTT), surgery and anti-VEGF agents.

Patients with exudative PCV have a better prognosis than those with hemorrhagic PCV. Also prognosis is better in patients with smaller lesions and a shorter duration of disease.

a) THERMAL LASER PHOTOCOAGULATION:

ICGA guided laser photocoagulation after surgical removal of subretinal blood is beneficial in patients with abundant submacular hemorrhage.

b) SUB-TENON'S TRIAMCINOLONE ACETONIDE:

It helps to decrease exudation of the lesion.

c) VERTEPORFIN THERAPY WITH PHOTODYNAMIC THERAPY:

This causes regression or resolution of polyps by its angio-occlusive mechanism of action, thus causing complete occlusion of polyps and resolution of exudative changes. Common adverse effects due to verteporfin – PDT therapy are subretinal hemorrhage, recurrence of PCV with leakage from BVN and

fibrous scarring. Bleeding may be due to induction of CNV by PDT, and upregulation of VEGF due to PDT.

d) ANTI-VEGF THERAPY:

Anti-VEGF monotherapy is effective in the absorption of subretinal fluid, but less effective in complete regression of polyp lesion. It has been recommended that combination therapy with anti-VEGF and PDT is the optimal modality of treatment.

The initial treatment of PCV should probably be verteporfin therapy with PDT, which leads to regression of Polypoidal lesions. Adjunctive treatment with anti-VEGF can be considered in cases with diffuse leakage from post-PDT BVN.

Anti-VEGF agents in combination with verteporfin may be recommended in cases with:

i. Leakage from BVN as well as polyps

ii. Large amount of subretinal fluid or exudation (PED)

iii. Ambiguous ICGA features between PCV and CNV

iv. Combination lesion of PCV and typical CNV

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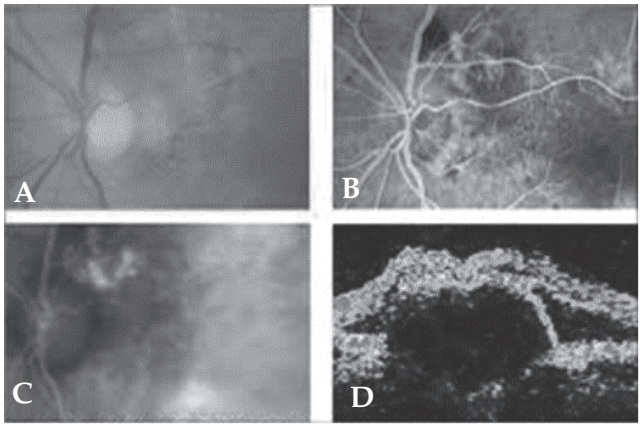

A. Fundus photo

B. Fundus fluorescein angiography

C. Indocyanine angiography

D. OCT