The presence of baseline hyperreflective spots in macular hole significantly correlated with the visual acuity improvement at 9 and 12 months. The mean improvement from baseline best corrected visual acuity score found to be greater in eyes without baseline hyperreflective spots.[30]

External limiting membrane (ELM) is probably the first element of the outer retina to be restored after macular hole surgery followed by restoration of ellipsoid portion of the inner segment (EIS). Complete ELM would be the anatomical foundation for the migration process of the photoreceptors aiming at closing the MH. EIS line reconstruction seems to be the best prognostic factor for a good visual rehabilitation after MH surgery.[31]

CONCLUSION :

Current treatment options for MH management discussed in this review allow to achieve high rate of macular closure and improved visual recovery. Use of repeated OCT could be helpful for defining the duration of prone positioning and visual recovery postoperatively.

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Paul Anton Cibis *is pioneer in retinal detachment surgery specifically, the introduction of silicone oil as a hydraulic dissecting instru- ment to separate membranes from the retina and which remains as a vitreous substitute tamponading the detached retina.*

Central Serous Chorioretinopathy (CSCR)

Rohit Agarwal

Definition :

Central maculopathy characterised by idiopathic circumscribed serous retinal detachment of neurosensory retina from the retinal pigment epithelium (RPE)

- Typically affects one eye.
- Common in young or middle aged men 20-45 years
- Male : female- 6:1

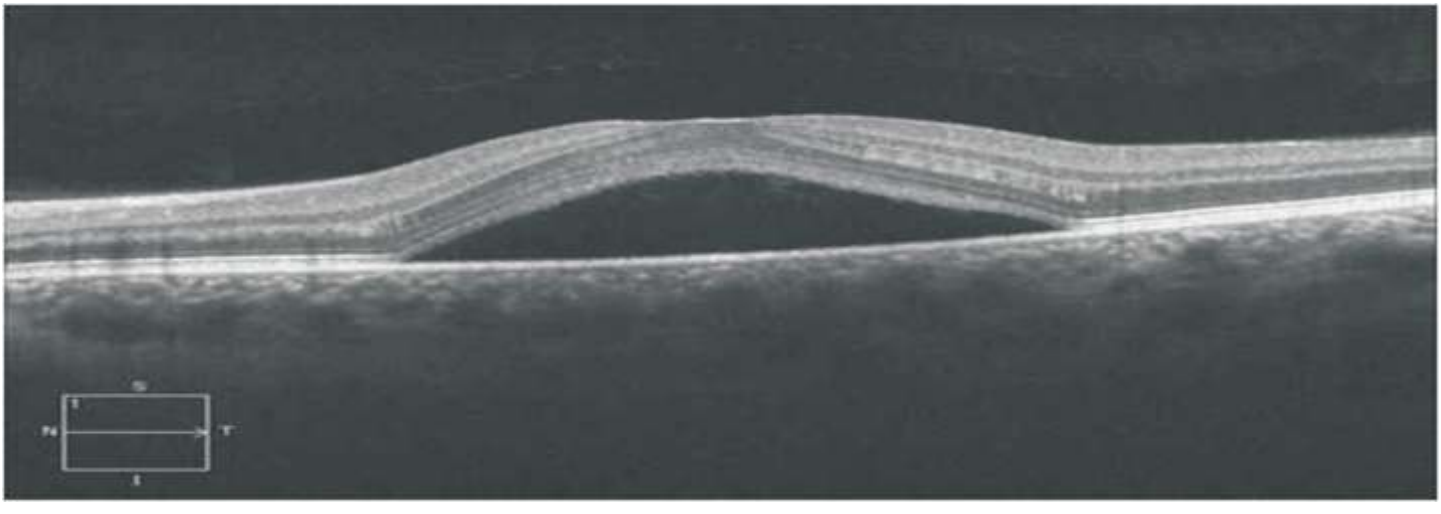

Figure 1 : OCT scan of the macula showing Neurosensory detachment

Risk Factors and Associations With CSCR :

1. Systemic conditions :

- Type A personality (M/C)
- Emotional stress
- Systemic hypertension
- Gastroesophageal reflux disease
- Pregnancy
- Organ transplantation
- Systemic lupus erythematosus
- Tobacco use
- Alcohol use
- Membranoproliferative glomerulonephritis type II
- Helicobacter pylori infection
- Autoimmune disorders

2. Medications :

- Corticosteroids
- Psychopharmacological medications
- 3, 4-methlyenedioxymethamphetamine
- Antacids and anti-reflux medications
- Over-the-counter sympathomimetics
- Antibiotics
- Antihistamines
- Sildenafil citrate

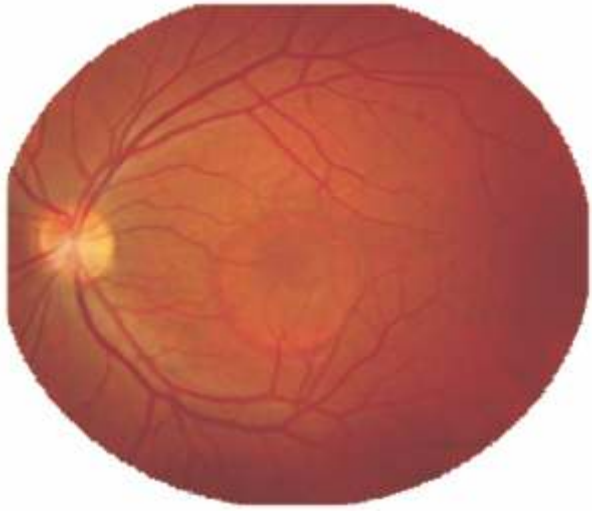

Figure 2 : Furdus Photograph showing Foveal New a Sensorus detachment

Vitreo Retina Consultant
Rohit Eye Hospital and Child Care Centre, Indore

Classification of CSCR :

1. Acute CSCR
2. Chronic CSCR

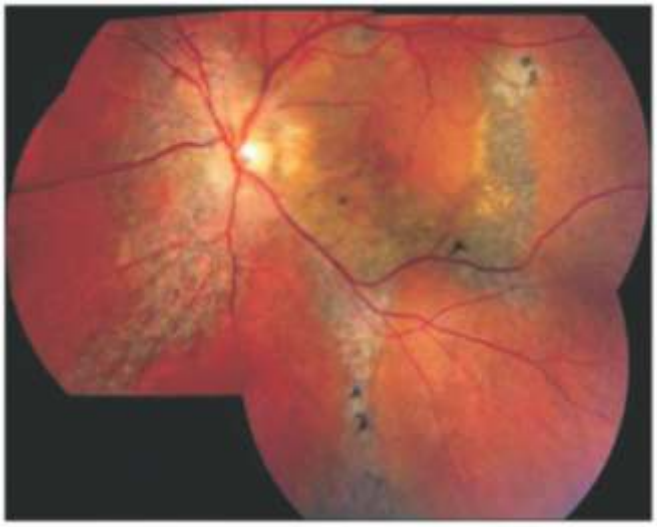

Figure 3 : RPE Tracking

Histologically CSCR (Spitnaz classification)classified as -

Type 1 : Detachment of sensory retina

Type 2 : RPE detachment

Type 3 : Intermediate type- both sensory retina and RPE detachment

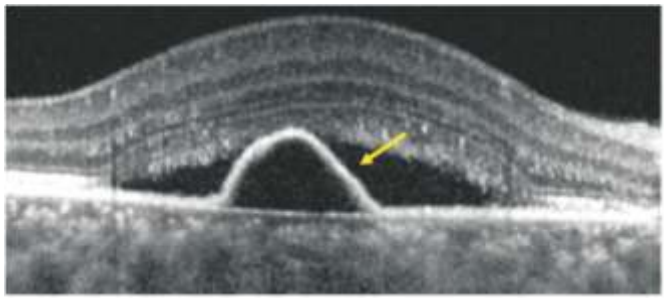

Figure 4 : Serous PED with NSD

Pathogenesis :

1. Historically, it was believed that a simple breakdown of the bloodretinal barrier at the RPE level was responsible for the leak-does not explain the beneficial effect of the permanent RPE barrier breakdown produced as a result of laserphotocoagulation.
2. Later it was suggested that pathologically hypersecreting RPE cells cause fluid accumulation, but this theory fails to explain the widespread choroidal hyperpermeability seen with ICGA.
3. The theory that choroidal hyperpermeability plays an important role- as seen on EDI-OCT. Increasing evidence implicates an abnormal choroidal circulation as the cause of CSCR. Choroidal fluid passes through an opening in the RPE and produces a serous retinal detachment.

Clinical Features :

Symptoms :

- U/L blurring
- Metamorphopsia
- Micropsia
- Mild dyschromatopsia
- Impaired dark adaptation

Signs :

- V/A : 6/9-6/18, may improve with weak convex lens due to acquired hypermetropia.
- Round/oval detachment of sensory retina
- SRF: clear/turbid
- Small PEDs, small patches of RPE atrophy and hyperplasia- Indicates site of previous lesions -typically seen on FAF
- Relative scotoma
- Chronic form:
  - o seen in 5% of cases, in older individuals receiving long term steroid therapy
  - o Atrophic changes present, fluid can track down in a gravity dependent fashion- gravitational tract- best seen on FAF (and FA)- can occasionally progress to bullous CSR
- · Optic disc- may show a pit

Course :

1. Spontaneous resolution within 3-6 months with return to normal-near normal v/n in 80%, recurrence in 50%.
2. Minority: chronic course lasting > 12months, prolonged detachment- photoreceptor and RPE degeneration- loss of v/n.
3. Bullous CSR: large/ single or multiple serous retinal and RPE detachments.

Diagnosis :

- Mostly Clinical, can be confirmed with imaging.
- The presence of cystic retinal degeneration, fine RPE mottling, or RPE clumping suggests chronicity of the present episode or a history of a previous CSCR episode

Investigations :

1. Amsler grid : metamorphopsia corresponding to neurosensory detachment.
2. OCT : optically empty NSR elevation.

   Other findings : small RPE detachment, precipitates on posterior surface of detached retina(hyperreflective dots) and thickened choroid.

3. OCTA : reveals CNV in the presence of CSCR.
4. FA :

a) Used to exclude the presence of other pathologies that produce serous retinal detachments and to confirm the diagnosis.

b) Classically, dye from the choroid leaks through a focal RPE defect and pools in the subretinal space. In >75% of patients, this pooling occurs within 1 DD of fovea.

c) 2 PATTERNS SEEN :

« Smoke stack :

- less common(10%)
- Early phase: small hyperfluorescent spot due to leakage of the dye through RPE.

Figure 5 : Smoke Stack leakage on FFA

- Late phase: dye passes through the subretinal space and ascends vertically to the upper border of detachment and then spreads laterally until entire area is filled with dye.

« Ink blot:

- More common
- Early phase: hyperfluorescent spot
- Late phase: spot gradually enlarges centrifugally until the area is filled with dye.

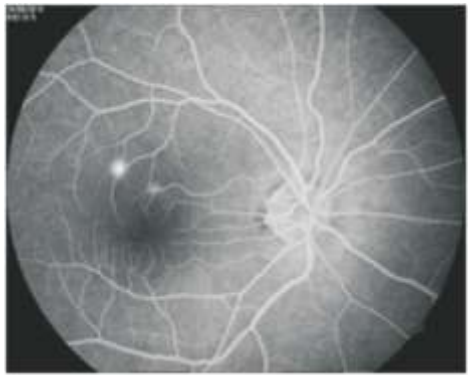

Figure 6 : Ink blot leakage on FFA

5. ICGA :

- When FA is atypical, ICGA can help exclude the presence of other pathology.

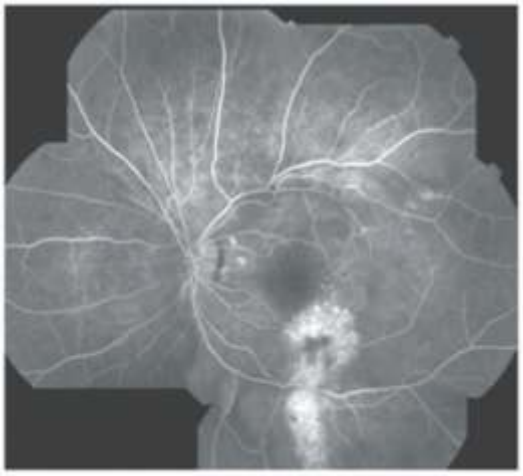

Figure 7 : RPE tract

- Bilateral multifocal hyperfluorescent areas-appear during the midphase.

6. FAF :

- Focal decrease in FAF at the leakage site and at the sites of old lesion.
- Gravitational tract.

Differential Diagnosis :

- CNVM
- VKH
- Optic disc pit
- Posterior scleritis
- RRD
- PCV
- Choroidal hemangioma/melanoma/metastasis

Treatment :

1. Observation:as majority resolve spontaneously.
2. Withdrawal of corticosteroid treatment.
3. No medical treatment has shown to be effective. Recently, mineralocorticoid antagonists (eplerenone) and rifampin have been proposed as safer alternatives to local treatments.
4. Local treatment:

- Laser treatment- Guidelines:

o Unresolving CSR >/= 4months

o If spontaneous recovery does not occur in a month in a patient with/ without h/o recurrent CSCR in the same eye or if the other eye a/w visual loss due to previous episode of CSR.

o For patients with occupational needs for binocular vision (pilots, surgeons)

- o In the acute stage, photocoagulation at the site of leakage can result in resolution of SRF in 3-4 weeks.
- · Micropulsed diode laser: good results and less retinal damage on OCT as compared to conventional photocoagulation.

Laser treatment should be avoided if the leak occurs within 200 µm of the centre of the FAZ.

Technique :

Green-wavelength laser to produce a light gray scar over the focal RPE leak.

612 laser burns of 50-200 µm spot size at =0.1-second duration and power ranging from 75-200 milliwatts (mW) are used.

Complications :

Permanent RPE change at the site of the laser scar- central scotoma and CNV.

Complications may be reduced by using larger spot sizes, employing lower power, and avoiding the capillary-free zone.

Only definite benefit -decrease the duration of the neurosensory detachment.

- PDT (photo dynamic therapy)-
- o 30-50% of the dose used for CNV in conjunction with 50% light intensity -complete resolution.
- o Effective for both chronic CSCR (>6 months) with diffuse decompensation of the RPE lacking focal FA leaks&acute CSCR with focal RPE leaks.

5. Anti-VEGF
6. Other aspirin, beta-blockers, mifepristone, eplerenone-questionable effect.

Harvey A. Lincoff *(1920-2017), MD, was a pioneer of retinal detachment surgery.*

During his lauded career, Dr. Lincoff shifted the paradigm of retinal detachment repair with the development of revolutionary techniques and instruments. Decades after their introduction, many of his advancessuch as the use of cryopexy and a method for locating retinal holesremain gold standards.

Prior to his passing, Dr. Lincoff served as professor emeritus and director of retinal research at the New York Presbyterian Hospital-Weill Cornell Medical Center. He authored more than 200 papers and book chapters, and received numerous international awards and honors, including the Academy's inaugural Charles L. Schepens Lecture and medal in 2008..

Retinal Pigment Epithelial Detachment : A Review

Reetika Saxena[1], Amit H Palkar[2]

Abstract :

Retinal pigment epithelial detachment is one of the most common clinical findings seen in neovascular age related macular degeneration, polypoidal choroidal vasculopathy and central serous chorioretinopathy. There are four types of retinal PEDs - drusenoid, serous, fibrovascular and hemorrhagic PEDs. They often co-exist with choroidal neovascularization, fluid, exudates, hemorrhage and complicate into RPE atrophy, rip or scarring. Identifying the underlying pathology of the macular condition is essential to plan management. Multimodal imaging helps understand the type, extent, level of lesion and features of PED lesion. Optical coherence tomography (OCT) is the most frequently used investigation technique to study retinal PEDs, besides fluorescein angiography (FA), indocyanine green angiography (ICGA) and recently optical coherence tomography angiography (OCTA). Thus guiding in the treatment, predict and monitor response at follow-up. There is a paucity in literature with regards to the treatment of Retinal PEDs, as it has seldom been a focus in study trials of neovascular AMD, CSCR or PCV. Few studies have conducted post-hoc analysis of patients in nAMD trials to understand the course of disease with anti-VEGF therapy. We review the literature to describe concisely the pathogenesis, classification of retinal PEDs, its associated features that point to retinal diseases, multimodal imaging, and treatment.

Introduction :

Retinal Pigment Epithelial Detachments (PEDs) are defined as a distinct separation of the retinal pigment epithelium (RPE) from the underlying Bruch's membrane layer. A number of retinal diseases are associated with PEDs, most commonly neovascular age-related macular degeneration (nAMD) and may be identified in 63% to 80% of eyes with nAMD.[1,2] The positive finding of a retinal PED on clinical examination may be either isolated or usually associated with choroidal neovascular membrane (CNV), fluid, lipid exudation, hemorrhage, RPE rip, fibrosis or atrophy. The study of the PEDs and associated features help decode the underlying pathology, plan the treatment management and establish long term prognosis. This short review describes the pathogenesis, classification of retinal PEDs, its associated features that point to retinal diseases, multimodal imaging, and treatment.

Pathogenesis :

Anatomical apposition between retina, RPE and Bruch's Membrane is essential for nutritional support of photoreceptors and good visual function. Any structural change in the Bruch's membrane generates a diffusion barrier between RPE and the choriocapillaris, leading to fluid accumulation under RPE. Also, these changes establish a pro-angiogenic and pro-inflammatory environment. The reduced exchange of signaling molecules between the neighboring tissues leads to inflammation, drusen formation and to choroidal neovascularization.[3] Moreover, long term separation of RPE from the underlying Bruch's Membrane/ choriocapillaris complex results in a decline in RPE function and the death of photoreceptors over time.

Types of Retinal PEDs and Features :

Most PEDs are initially asymptomatic, sometimes induce hyperopia ,often have diminution of central vision or cause metamorphopsia. Diagnosis is largely based on a thorough fundus examination with multimodal imaging in order to understand layered details and underlying cause.

A multimodal imaging facilitates understanding pathophysiology of retinal PEDs, including fluorescein angiography (FA), indocyanine green angiography (ICGA), optical coherence tomography (OCT), and OCT angiography (OCTA). However, OCT is the most commonly used imaging technique and useful in identifying the type of PED, to evaluate, guide, predict treatment response and follow up.

Retinal PEDs are usually found in ocular diseases like Central Serous Chorioretinopathy (CSCR), Neovascular AMD (nAMD) and Polypoidal Choroidal Vasculopathy (PCV). An isolated PED is often idiopathic or indicates a hyperpermeable choroid, but rarely seen as an isolated ocular manifestation in systemic diseases. Table.1 summarizes etiologies of retinal PEDs.

Identifying the type of retinal PED and its characteristics helps

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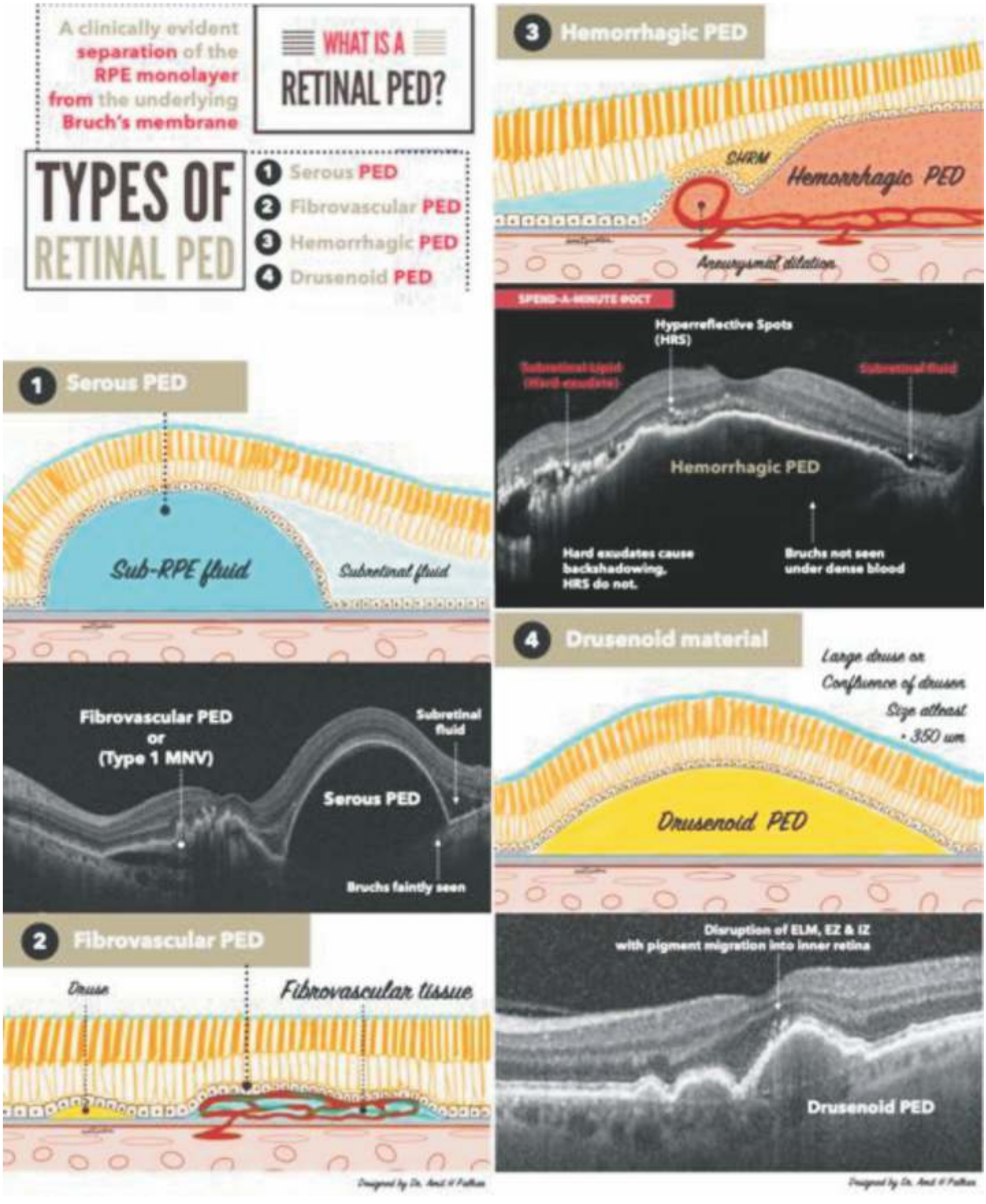
A clinically evident separation of the RPE monolayer from the underlying Bruch's membrane
WHAT IS A RETINAL PED?
TYPES OF RETINAL PED
1 Serous PED
2 Fibrovascular PED
3 Hemorrhagic PED
4 Drusenoid PED
3 Hemorrhagic PED
SHRM
Hemorrhagic PED
Aneurysmal dilation
SPEND-A-MINUTE #OCT
Hyperreflective Spots (HRS)
Hemorrhagic PED
Hard exudates cause backshadowing. HRS do not.
Bruchs not seen under dense blood
1 Serous PED
Sub-RPE fluid
Subretinal fluid
Fibrovascular PED or (Type 1 MNV)
Subretinal fluid
Serous PED
Bruchs faintly seen
4 Drusenoid material
Large druse or Confluence of druse Size atleast > 350 um
Drusenoid PED
2 Fibrovascular PED
Druse
Fibrovascular tissue
Disruption of ELM, EZ & IZ with pigment migration into inner retina
Drusenoid PED

Figure 1

Table. 1

Ocular	Degenerative	ARMD
	Pachychoroid spectrum	PCV, CSC
	Idiopathic	Small multifocal idiopathic PEDs
Systemic	Renal associations	Tubulo-interstitial nephritis and uveitis syndrome, Type II membranoproliferative glomerulonephritis
	Inflammatory	Systemic lupus erythematosis, inflammatory bowel disease, sarcoidosis
	Infectious	Blastocystis hominis, post streptococcal syndrome, neurosyphilis
	Neoplastic	Paraproteinemias (cryoglobulinemia, IgA or IgM gammopathies), Waldenström macroglobulinemia, large cell nonHodgkin lymphoma (ocularcentral nervous system form), choroidal nevi, acute myeloid leukemia
	Iatrogenic	Pamidronate, hemodialysis, organ transplantation

in the diagnosis of the retinal disease under evaluation. There are predominantly four types of Retinal PEDs - Drusenoid, Serous, Fibrovascular, and Haemorrhagic PED. (Figure 1)

Drusenoid PED is a large drusen or a confluence of soft drusen, with a size at least 350 µm as defined by the Age-Related Eye Disease Study. They are characterized by the accumulation of extracellular lipid-rich deposits between the RPE and Bruch's membrane and are associated with an increased risk of

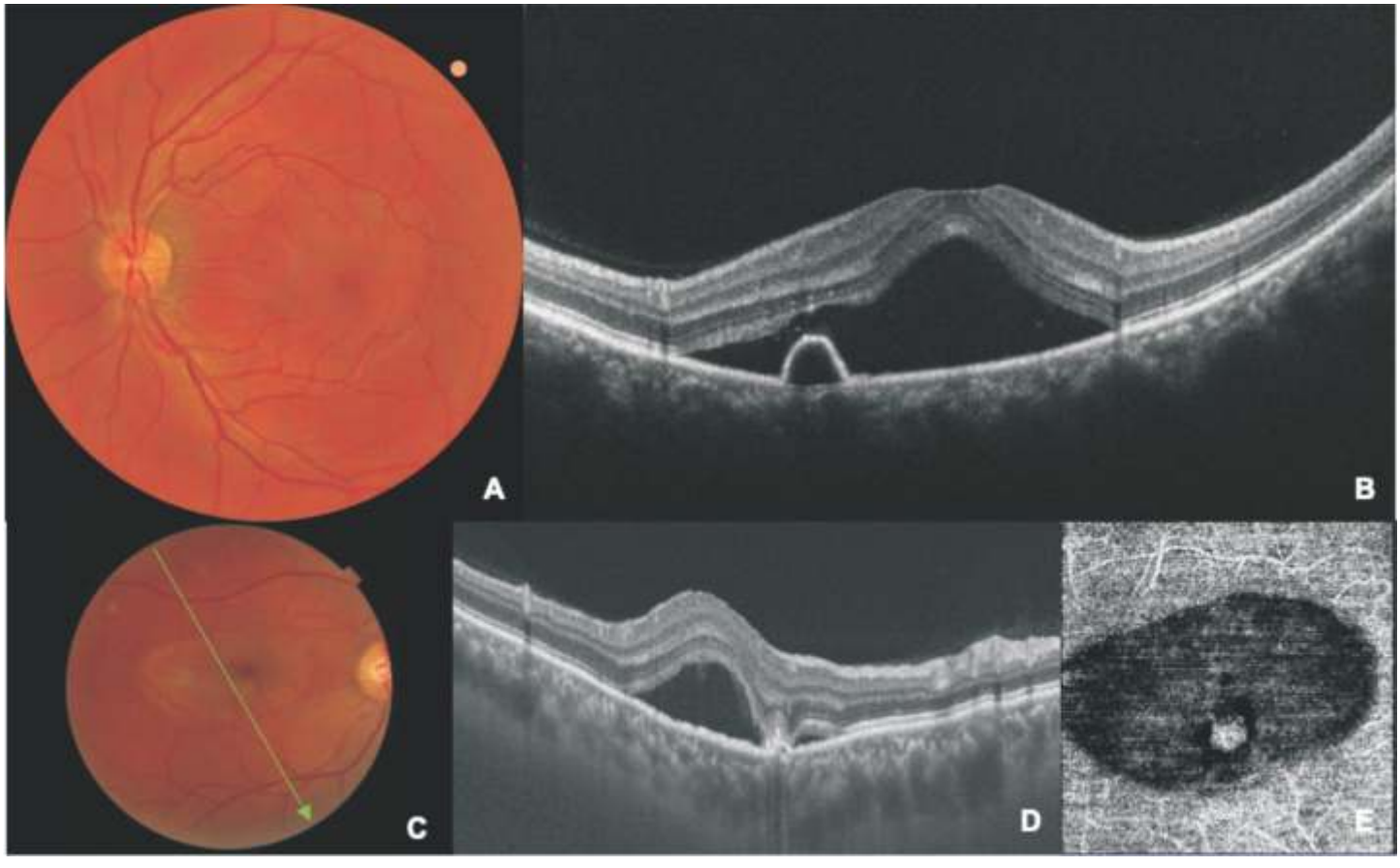

Figure 2. (A) Fundus photo of left eye showing a large neurosensory detachment with subretinal fluid and OCT (B) demonstrating an underlying Avascular Serous PED with a microrip at the apex with few hyper-reflective dots. Note the distinct separation of the RPE and Bruch's Membrane. (C) Fundus photo of right eye showing a large horizontally oval subretinal fluid with a yellowish lesion inferior to fovea. OCT- Bscan (D) reveals a small flat irregular PED (FIPED), raising a suspicious neovascularization process. (E) OCTA confirmed the presence of a CNV at the FIPED.

progression to advanced AMD.[4,5] OCT shows undulating elevations of RPE with faint hyperfluorescence in early phases and no leakage in late phases of FA, unless associated with underlying CNV. On ICGA, drusenoid PEDs show homogeneous hypofluorescent lesion during the early phase and remain hypofluorescent throughout the transit.[6]

Serous PED is a fluid collection between RPE and Bruch's membrane and it occurs as sharply demarcated elevation of the RPE. The fluid collection is due to increased choriocapillaris leakage and decreased RPE pump function. Neovascular AMD and CSCR are two of the most common conditions associated with serous PED. Avascular serous PEDs are seen in acute CSCR. Leakage from microrips in these PEDs are attributed to subretinal fluid (SRF). However, Vascular serous PEDs indicate nAMD and should be looked for in chronic CSCR.10 (Figure 2) FA in serous PED shows early hyperfluorescence that increases in intensity as the angiogram progresses, but the extent and size of hyperfluorescence remains constant. In acute CSCR, microrips in PEDs may appear as pinpoint leakages in early phases of FA. Irregular blocked hypofluorescence may be seen in long standing PEDs due to pigment migration along the walls of the PED. The dye eventually pools into an avascular serous PED in the late stages. On the contrary, vascular Serous PEDs are usually picked up on FA when stippled hyperfluorescence is noted at the edge of a PED, suggesting the presence of an underlying neovascular membrane. These PEDs often fill irregularly and may appear notched due to presence of the membrane. ICGA demonstrates only minor diffusion into a PED and hence, may have value to distinguish between vascular and avascular lesions. ICGA is helpful in studying choroidal hyperpermeability in PEDs with CSCR and planning photodynamic therapy (PDT).[8]

Fibrovascular PED is a characteristic lesion of nAMD consisting of a CNV growing through the Bruch's membrane into the sub-RPE space, separating RPE monolayer and its basement membrane from the inner collagenous layer of Bruch's membrane. Gass suggested PED with a notch, presence of

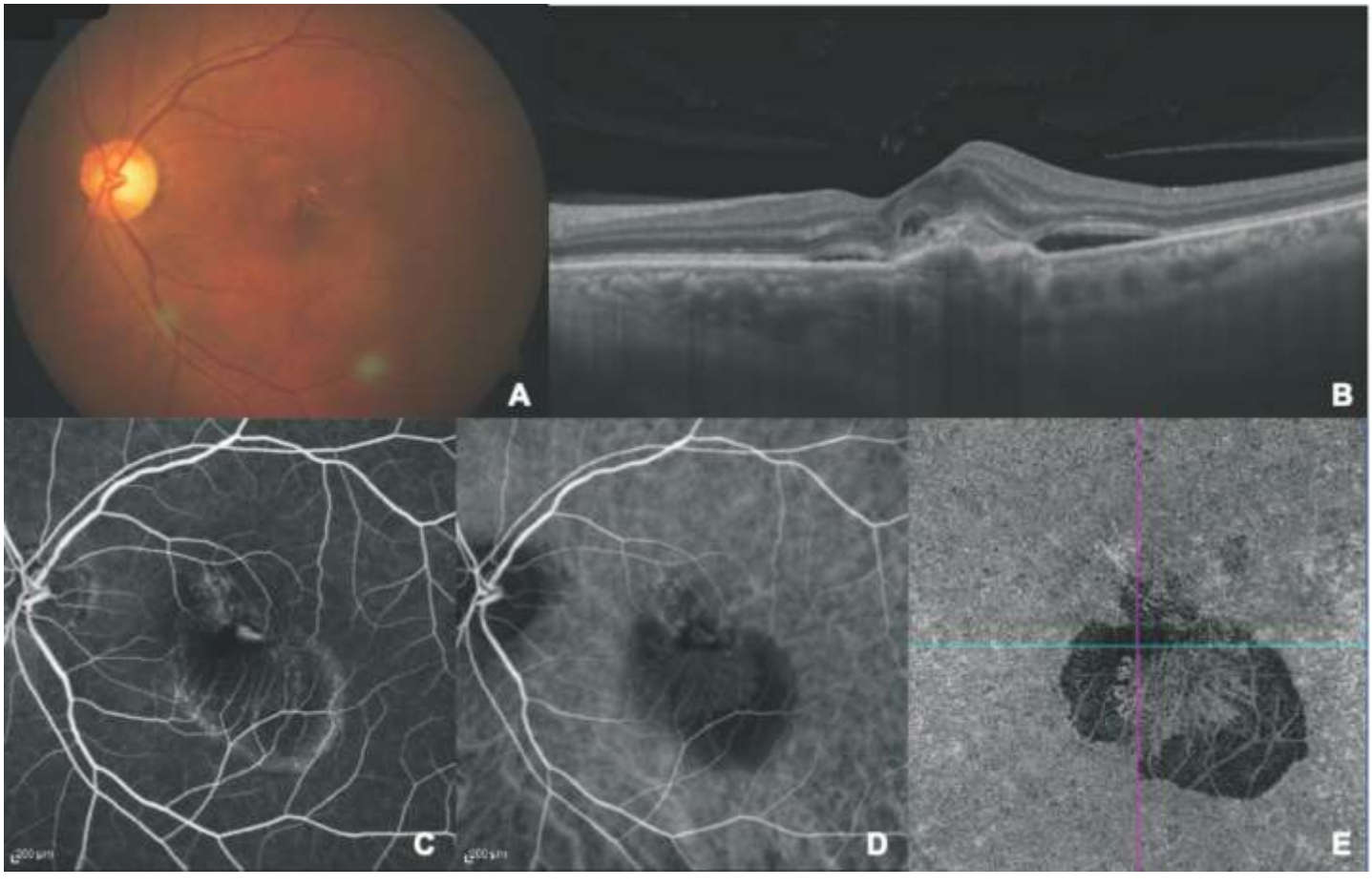

Figure 3. (A) Fundus photo of left eye shows pigmentary changes at the macula with a greyish lesion at the fovea. (B) OCT demonstrates a fibrovascular PED with mild hyperreflective signal between the RPE and Bruch's Membrane suggestive of a CNV below the RPE, subretinal hyper-reflective material (SHRM) over the PED and subretinal fluid around the PED lesion. (C) FA shows typical stippled hyperfluorescence with filling of the dye in the subretinal space but (D) the ICGA and (E) OCTA reveals an underlying large network of sub RPE vessels in arborizing pattern.

subretinal or sub-RPE hemorrhage at edge of PED, yellow subretinal and intraretinal exudates are tell-tale signs of underlying CNVM.[9] Cytokines such as vascular endothelial growth factor (VEGF) cause breakdown of ocular retinal barrier and thus leak. When the leakage overwhelms the local RPE ability to remove fluid, it accumulates to form subretinal fluid (SRF) and intraretinal fluid (IRF). Chronic leakage of fluid causes precipitation of lipoproteins in the subretinal or intraretinal space to form lipid exudates. And extravasation of blood from the neovascular complex results in sub-RPE, subretinal and intraretinal heme. (Figure 3)The early FA of vascular or fibrovascular PEDs reveal a minimal, irregular degree of sub-RPE stippled hyperfluorescence that slowly increases over several minutes to produce staining of the RPE, which Gass initially defined as occult CNV. Both in serous and Fibrovascular PED, leakage of ICG in the late phases or focal "hot spots" may be indicative of an underlying associated CNV. Optical Coherence Tomography Angiography (OCTA) has emerged as a noninvasive tool to decipher underlying vascular membranes in PEDs using altered flow signals on cross sectional OCTA and vascular complexes on Enface OCTA.[10]

Hemorrhagic PEDs are seen in both, nAMD and PCV, caused by the bleeding of hyalinized polypoidal vessels into the sub-RPE space. They are characteristically associated with a branched vascular network with polypoidal lesions of PCV. (Figure 4) These PEDs, when large in size, are prone to RPE rips. Eyes with blunt trauma also develop choroidal rupture with hemorrhagic PED and subretinal heme. FA shows sharply delineated blocked choroidal fluorescence both in early and late phase. ICGA demonstrates only minor diffusion into a PED, however it has immense value in delineating the branched vascular network (BVN) with polypoidal lesions of PCV.[11]

Natural Course and Complications :

In the natural course of retinal PED, the lesion enlarges in size and volume over several months and later regresses with either RPE atrophy, disciform scarring or RPE rip or tears. Serous avascular PEDs and drusenoid PEDs usually progress to RPE atrophy. Approximately 50% of patients with newly diagnosed PEDs experience significant loss in visual acuity (>3 lines) 1 year from diagnosis without treatment.[12] Fibrovascular PEDs eventually fibrose into disciform scarring and RPE atrophy. Fibrosis is a part of the wound healing response, in response to numerous cytokines and factors such as transforming growth factor beta 1, pigment epithelial growth factor, and connective tissue growth factor (CTGF). Fibrotic tissue is associated with lesion contraction; it has been proposed that a balance between VEGF and CTGF may control the behavior of fibrovascular tissue. Higher levels of VEGF in relation to CTGF may promote vascular growth, while decreases in the ratio may lead to increased fibrosis, disciform scar and contracture of that tissue (angiofibrotic switch). Hemorrhagic PEDs progress to disciform scar faster than non hemorrhagic subtypes.[6] RPE rip (or tear) generally develops in large PEDs, especially hemorrhagic PEDs. PEDs with a

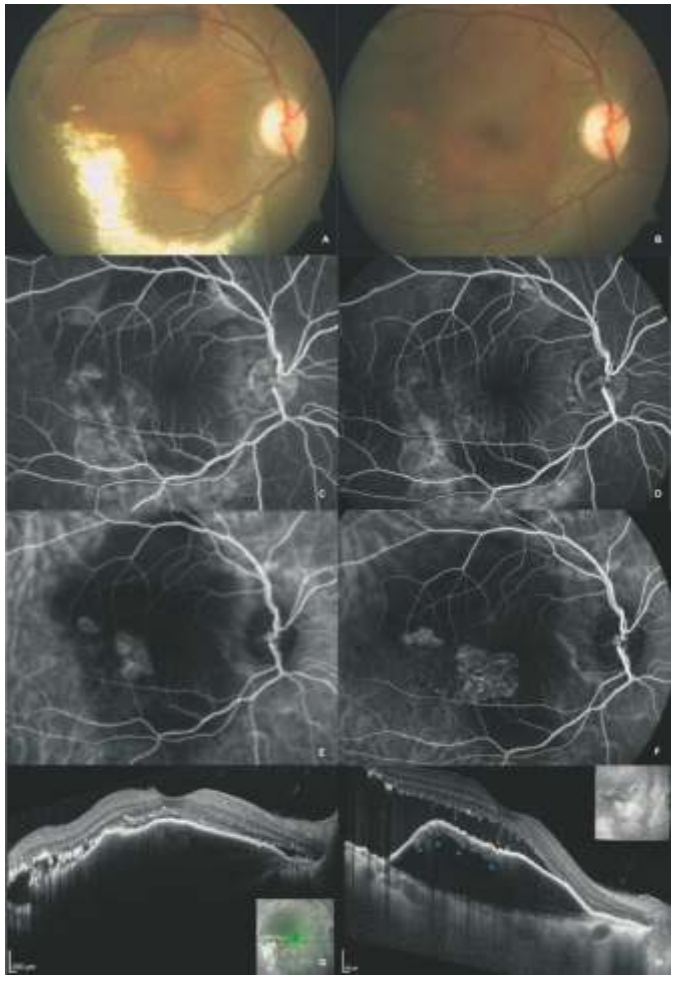

Figure 4.A 51-year-old woman with diminution of vision (OD-20/30) had (A) hemorrhages both in the sub-RPE and subretinal space extending to the arcades with massive exudation. (C) FA shows blocked fluorescence due to subretinal and sub-retinal pigment epithelium hemorrhage with stippled hyperfluorescence inferotemporal to fovea, which is identified as branching vascular network with polypoidal lesions at the temporal edge of the lesion in ICGA (E). (G) The OCT B-scan shows a subfovealhemorrhagic PED, with minimal subretinal fluid and hyperreflective hard exudates. She received intravitreal aflibercept monotherapy and status post five injections, (B) exudation, subretinal and sub-retinal pigment epithelium hemorrhage reduced clinically, with persistent stippled fluorescence in fluorescein angiography (D), better delineation of branching vascular network with ICGA (F). (H) OCT B-scan demonstrates subretinal fluid, PED with serous conversion and reduction in size and branching vascular network abutting the retinal pigment epithelium (blue asterisk).

baseline vertical height >550 microns and an increased surface area were associated with a higher risk of RPE tear, after intravitreal Anti-VEGF injections.[13,14] These rips of RPE are caused by a tractional dehiscence of the RPE monolayer. RPE rips lead to acute flattening of PED, with sudden severe vision drop in rips involving fovea. (Figure 5)

neovascular AMD). Except for lifestyle changes and the use of vitamin supplements, there are limited treatment options available for intermediate. Recently, subthreshold micropulse laser (SML) 577 nm yellow laser has demonstrated collapse of large drusenoid PEDs, without obvious visual loss, by avoiding long separation of RPE from the underlying Bruch's Membrane

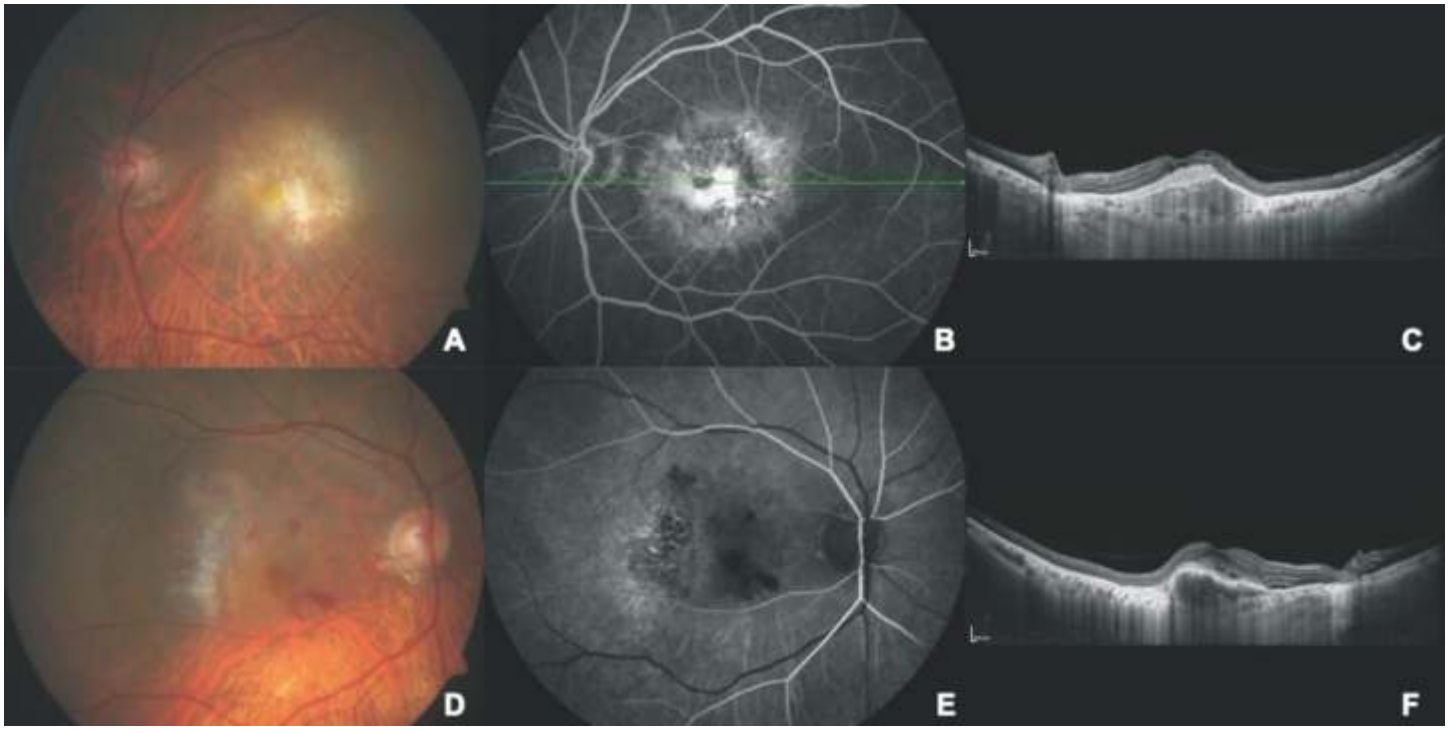

Figure 5. (A) Fundus photo of left eye shows disciform scarring at the macula, seen as (B) intense hyperfluorescence in the late phase in FA due to staining of the tissue. (C) OCT Bscan demonstrates a multi-layered PED with RPE atrophy and SHRM. The overlying retina shows few cystic changes. (D) Fundus photo of the right eye shows a crescentic greyish white lesion with clear choroidal vessels due to de-roofing by the RPE rip. Nasal and superior to the rip, heme specks are noted indicating CNV activity. (E) Early FA demonstrates the transmission defect due to absence of RPE over the rip and blocked fluorescence from the heme. (F) OCT shows the curled up RPE temporal to the fovea with the bare choroid in contact with the overlying retina.

Differential Diagnosis :

Dome-shaped elevations of the choroid and the overlying RPE in eyes with choroidal melanoma, metastasis, and hemangioma can mimic a PED on OCT and EDI OCT. Subretinal infiltration of lymphoma in Non Hodgkins Lymphoma cases can also present as multiple RPE elevations. Acquired vitelliform disorders, paraneoplastic vitelliform disorders and dehemoglobinized subretinal blood may also clinically look similar to PED.[6]

Treatment :

Treatment of retinal PEDs involves primary treatment of the underlying cause of the retinal PED. AREDS Report No.28 mentions that, in the absence of baseline advanced AMD, within 5 years, 42% drusenoid PED eyes develop advanced AMD (19% central geographic atrophy (GA) and 23% choriocapillaris complex and alleviating RPE damage.[16]

Avascular Serous PEDs are often asymptomatic and usually observed at regular intervals to look for development of any subretinal fluid and/or flat irregular PED (FIPED). In acute CSCR, conservative management or mineralocorticoid receptor antagonists lead to resolution of serous PEDs. Intravitreal antiVEGF is not useful in avascular serous PEDs, because the fluid accumulation between RPE and choriocapillaris is caused by the hydrophobic barrier of Bruch's membrane, not CNV.[17] However, anti-VEGF therapy is indicated in patients with chronic CSCR with persistent SRF with subfoveal fibrin or FIPED. Also, these eyes show longer symptom duration and thicker subfoveal choroidal thickness than those with focal PED. SML and Photodynamic Therapy (PDT) (Standard protocol, half dose, half fluence) is effective in SRF reduction and CNV resolution in FIPED, but known to cause RPE atrophy,

secondary CNV, chronic choroidal hypoperfusion and pigmentary changes.

Vascular Serous PEDs, Fibrovascular PEDs and Hemorrhagic PEDs present with sudden onset decrease in central vision and warrant treatment. In the past, total ablation of the PED lesion with laser photocoagulation was performed for treatment of vascularized PED. The progression of the membrane would halt, but functional outcomes of this treatment were not satisfactory due to laser scars.[18] The applicability of PDT or other modalities has decreased day by day with the herald of intravitreal anti-VEGF pharmacotherapy. Current treatment protocols include intravitreal injection of anti-VEGF agents for the treatment of fibrovascular and hemorrhagic PED in nAMD and PCV.

PEDs are an important marker of disease severity and progression in neovascular AMD and equally most challenging to resolve anatomically with treatment. Currently, there are few prospective studies that demonstrate effective therapy for PEDs associated with neovascular AMD. These analyses are limited by the use of time-domain OCT or do not focus specifically on eyes with PED, providing incomplete information regarding PED outcomes.[19] HARBOR trial was conducted to evaluate the potential beneficial effects of both a higher dose and pro re nata (PRN) dosing of Ranibizumab in patients with subfoveal neovascular AMD. Neither the higher dose nor the more frequent dosing showed a significant change in mean BCVA from baseline to month 12 and month 24.[20] But the study failed to mention any effect on the PED in these patients. In order to understand the effect of ranibizumab in PEDs, Sarraf et al performed a post hoc subgroup analysis of the HARBOR trial.[19] They analyzed the effect of baseline PED status (present or absent) and height on visual and anatomic outcomes in patients with nAMD treated with standard-dose (0.5 mg) versus high-dose (2.0 mg) ranibizumab on a monthly or PRN dosing regimen. They concluded Ranibizumab 0.5 mg given monthly or PRN effectively treated PEDs in patients with neovascular AMD, and significant vision gains resulted regardless of PED status and height at baseline. But there was no additional vision benefit with a higher dose of ranibizumab (2.0 mg).

Another approved intravitreal VEGF-trap therapy for treatment of neovascular AMD, Aflibercept, has been studied in patients with PED. In the VIEW trial, 75% of patients had baseline PED in all study groups, although the study was limited by the use of time-domain OCT. The PED resolution was observed in 28 to 39.5% patients at 1 year, but no significant change in BCVA.[21] Infact, VIEW 2 trial showed a decline in the vision in the eyes with PED, secondary to the occurrence of intraretinal cystoid changes.[22] In the HARBOR data, there was an approximately 3-fold higher rate of macular atrophy development in patients with complete flattening of PED compared with patients with persistent PED at month 24 (44% vs. 17%). This supports the idea that treatment to resolve PEDs completely may not be necessary because more macular atrophy is seen when the PED is resolved completely.[19]

The post hoc HARBOR analysis had approximately one-third of patients with a flattened PED 1 month following the initial ranibizumab injection. Lower baseline PED height was associated with PED flattening. However, at 2 years, PED flattening was not associated with vision outcomes. Although in patients, whose PED flattened at 1 month and were treated as needed, were more likely to receive fewer injections by month 24.[23]

RPE tears occurred in 5% with a PED at baseline in HARBOR patients; however, this rate increased to 14% with larger PEDs. Patients with larger PEDs, especially greater than 550 microns, receiving anti-VEGF experience a higher rate of RPE tears.Also, large hemorrhagic PEDs in PCV are amenable to RPE tears , post injection subretinal hemorrhage and vitreous hemorrhage.[11] However, unlike nAMD, the effect of anti-VEGF therapy on PED in PCV has not been explored extensively and is a potential avenue of research.

To conclude, PEDs can be associated with a wide range of disorders, be asymptomatic or can lead to severe vision loss. To treat or observe depends on vision loss, identifying the type of retinal PED, associated features and finding the underlying disease. RPE tears can be sudden, severe, sight threatening complications with or without treatment of PED. Macular scarring and atrophy is responsible for long term vision loss. Proper pretreatment counseling helps better understanding between the patient and the treating physician.

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Retinitis Pigmentosa : A Comprehensive Review

Deepali Fauzdar

Introduction :

Retinitis Pigmentosa (RP) is a group of inherited retinal disorders (IRDs) associated with primary abnormality of the photoreceptor-RPE complex, initially affecting the rods with later involvement of cones, and is subjectively characterized by night blindness and a loss of peripheral vision, and objectively by a grossly reduced or extinguished full-field ERG. RP can be typical/ non-syndromic (ocular features only) or Atypical/ syndromic (with systemic features). Here we will discuss Clinical Features, Diagnostic evaluation, Management and Newer Modalities of treatment of RP under trial.

Epidemiology and Etiology :

The worldwide prevalence of RP estimated to be 1 in 4000. The age of onset, progression, degree of visual loss and associated features are variable and depends on the inheritance pattern. The modes of inheritance have been described are sporadic (no family history, the most common cases), autosomal recessive(AR), autosomaldominant (AD) (best prognosis), X-linked recessive (XLR) (least common group with worst prognosis). RP represents broad spectrum of genetic and phenotypic heterogeneity, at least 150 genes have been identified, associated with syndromic and non-syndromic RP.

Clinical Features :

Symptoms :

Patients present with a history of night blindness or nyctalopia and a difficulty in visual adaptation at night or in dim illumination.[1] Patients may also have difficulty with peripheral vision in dim light. Photopsia is not uncommon. Family history of RP may be present. The difficulty with night vision may begin in early childhood, or patients may notice it in the second or third decade of life. By the age of 30 years, over 75% of patients are symptomatic.

Clinical Triad :

The classic clinical triad (Figure-1)of RP includes :

1. Bone-spicule retinal pigmentation
2. Arteriolar attenuation
3. Waxy optic disc pallor

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Clinical Sign :

1. Visual acuity varies in all type of RP, may be normal for many years, as central vision is preserved but contrast sensitivity affected at early stage.
2. Peripheral vision problems are initially noticed only in the dim light, but later these problems are noted under all conditions.[2]
3. Fundus findings may differ according to the stage of the disease. At a very early stage arteriolar narrowing (The attenuated vessels seen in patients with RP are believed to be due to either reduced metabolic demand or vasoconstriction and reduced blood flow resulting from a hyperoxic state after the loss of oxygen-consuming photoreceptors),[3,4] fine dust-like intra-retinal pigmentation seen. At a later stage perivascular bonespicule pigment seen.
4. Pigmentary changes begin in the mid peripheral retina and then extend anteriorly as well as posteriorly, giving rise to a ring scotoma.[5,6] Pigmentation consists of retinal pigment epithelium cells that have detached and migrated to the inner retina after photoreceptor death.[7]
5. Waxy pallor of the optic disc may be there. Disc pallor does not correlate with visual acuity.
6. Advanced stage of RP shows unmasking of the large choroidal vessels, tessellated fundus, prominent arteriolar attenuation, and marked optic disc pallor.
7. Macular involvement may occur in the form of cystoid macular edema, surface wrinkling of the internal limiting membrane, ERM formation and atrophic changes may contribute to early vision loss.[8]
8. Posterior sub-capsular cataract is common in all forms of RP, found in at least 50% of patients with RP.
9. Associated Ocular features include Optic nerve head drusen, Open-angle glaucoma, Keratoconus, Myopia (frequently encountered), low grade intermediate uveitis, posterior vitreous detachment and vitreous debris.

Features of Syndromic RP :

1. **Usher's Syndrome :** AR, genetically heterogenous, sensorineural deafness, vestibular dysfunction

2. **Bassen-Kornzweig Syndrome :** Abetalipoprotenemia, AR, ptosis, ocular motility disturbances, spinocerebellar ataxia, acanthocytosis, fat malabsorption
3. **Refsum's Disease :** (Heredopathia-atactica-polyneuritiformis), AR, nyctalopia, salt-and-pepper fundus, hypertrophic peripheral neuropathy, cerebellar ataxia, deafness, icthyosis, cardiac arrhythmias, elevated CSF protein
4. **Cockayne's syndrome :** Salt-and-pepper type pigmentary retinopathy, arteriolar attenuation, optic nerve pallor, childhood dwarfism, prematurely aged appearance, bird-like facies, disproportionately large hand and feet, mental retardation
5. **Kearns-Sayre Syndrome :** Mitochondrial Myopathy, external ophthalmoplegia, ptosis, pigmentary retinopathy, complete heart block
6. **Bardet-BiedlSyndrome:** Bull's eye maculopathy, in few case bone-spicules, mental handicap, polydactyly, obesity, hypogenitalism, renal abnormalities
7. **Laurence-Moon Syndrome :** Choroidal atrophy, spastic paraplegia, mental handicap, hypogenitalism
8. **MucopolySaccharidoses :** Lysosomal enzyme deficiency involve in mucopolysaccharides degradation, AR, pigmentary degeneration of retina, optic nerve head swelling, corneal stromal infiltrate, glaucoma, facial coarseness, skeletal abnormalities, heart disease
9. **Friedreich's Ataxia :** AR, pigmentary retinopathy, vestibular nystagmus, optic atrophy, cerebellar ataxia, absence of tendon reflex, scoliosis, cardiomyopathy

Investigations :

1). Visual Field Testing and Perimetry :

Initially, there is a mid-peripheral field defect showing full or partial ring scotoma, which extends anteriorly as well as posteriorly, leaving only a central island of vision in the late stages.[2]

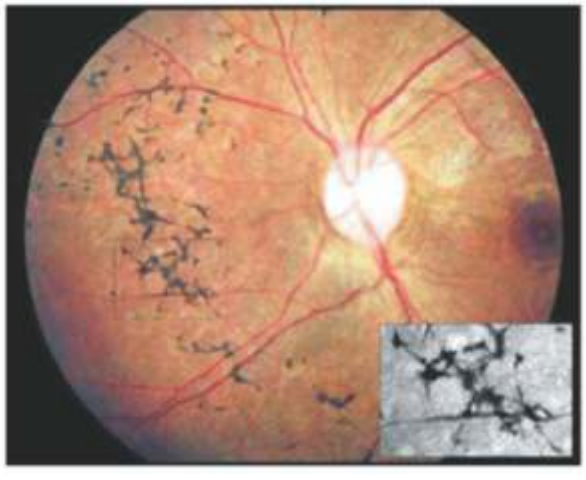

Figure-1 : The classic clinical triad of waxy optic disc pallor, arteriolar attenuation, and bone-spicule pigmentation.

2). Dark Adaptommetry :

A prolonged dark adaptation is seen in almost all cases and dark adaptometry can be used in early detection and screening.[1] Elevation of the rod as well as the cone segment of the dark adaptation curve occurs.

3). Full Field ERG :

ERG is considered the gold-standard modality for diagnosing RP, establishing baseline function and monitoring RP progression. This may be significantly subnormal even when the fundus shows minimal changes. Full-field ERG findings in RP patients include decreased rod amplitude, maximum, oscillatory, cone and flicker responses. Initially, individuals with RP have a decreased scotopic response (dim light response in dark adaptation) reflecting rod dysfunction, followed by prolonged B-wave implicit times. The eventual involvement and loss of cone photoreceptors leads to reduced amplitude of the photopic/cone (bright light response in light adaptation), maximum(combined rod and cone response to maximum intensity light in dark adaptation) and 30 Hz flicker responses. ERG responses may be wholly extinguished in advanced stages of the disease(Figure-2).

4). OCT :

OCT can identify retinal morphological changes in patients with RP. At early stage of the disease it shows disorganization of the outer retinal layers.With disease progression, decreased thickness of the outer nuclear layer can be observed.[9] At a late stages of RP the complete loss of both the outer segment and the outer nuclear layer is seen, with the inner retinal layers remaining relatively well preserved.[10] OCT is also used to monitor the presence and progression of CME, macular cysts, ERM and macular holes in patients with RP.

5). Fundus Auto-fluorescence :

FAF is commonly used to assess disease stage and progression. In FAF, areas of hypo-autofluorescence representing atrophy of photoreceptors have been found to correlate with visual field defects.[11] Several FAF patterns are considered typical in RP, such as a hyper-autofluorescent ring or an abnormal central hyper-autofluorescence(Figure-3).[12] This hyper-autofluorescent ring, also named the Robson-Holder ring, delineates the border between normal and disrupted inner and outer segment junctions.[10]

6). Genetic Testing :

In today's era, genetic testing is mainstay in the diagnosis and management of RP. By identifying the causative genetic mutation in a patient we can establish specific diagnosis of RP,

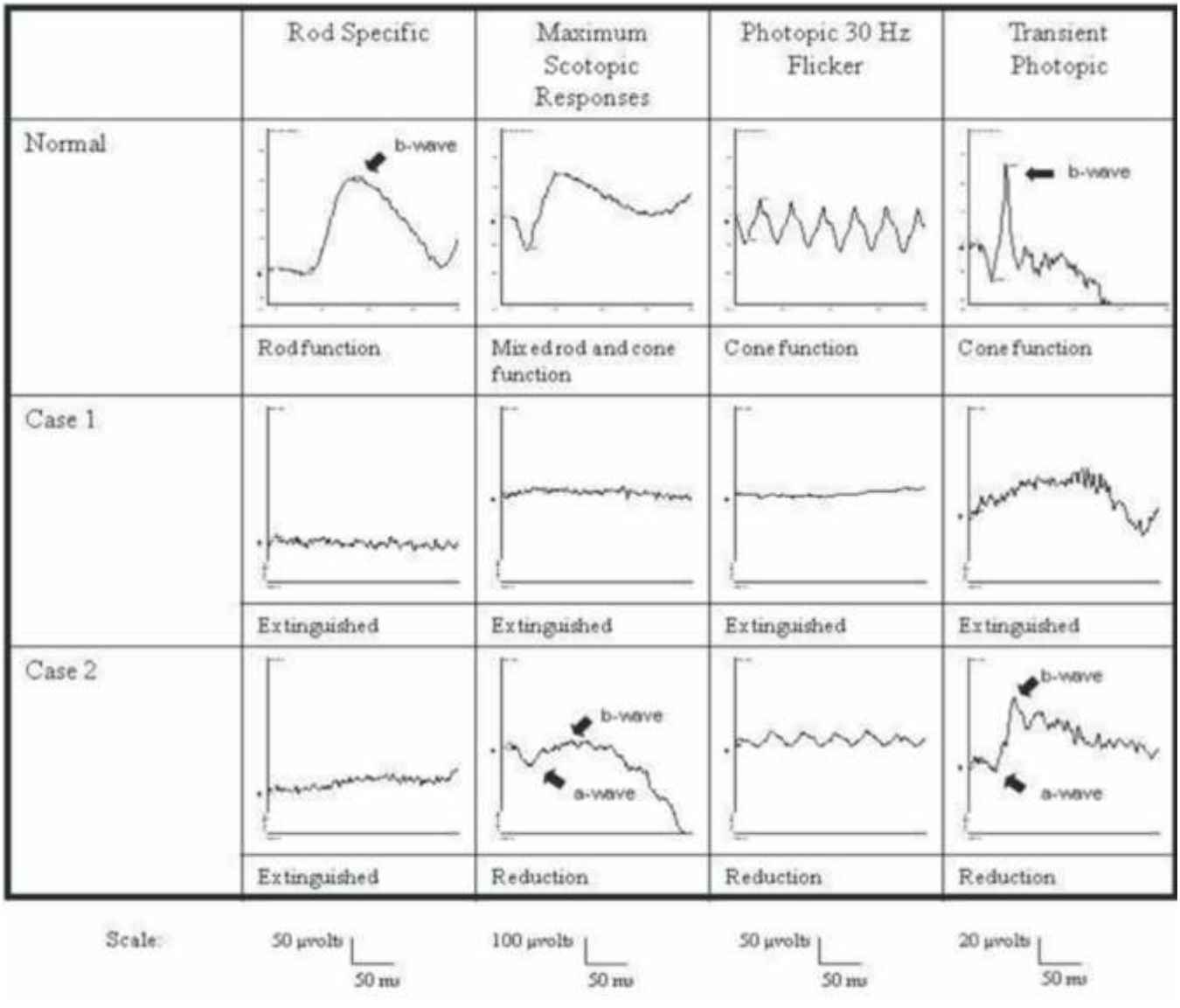

Figure-2 : Full-field ERG findings were consistent with severe generalized rod-cone dysfunction affecting the rod system more than the cone system standardized ERG traces from a normal individual are shown for comparison.

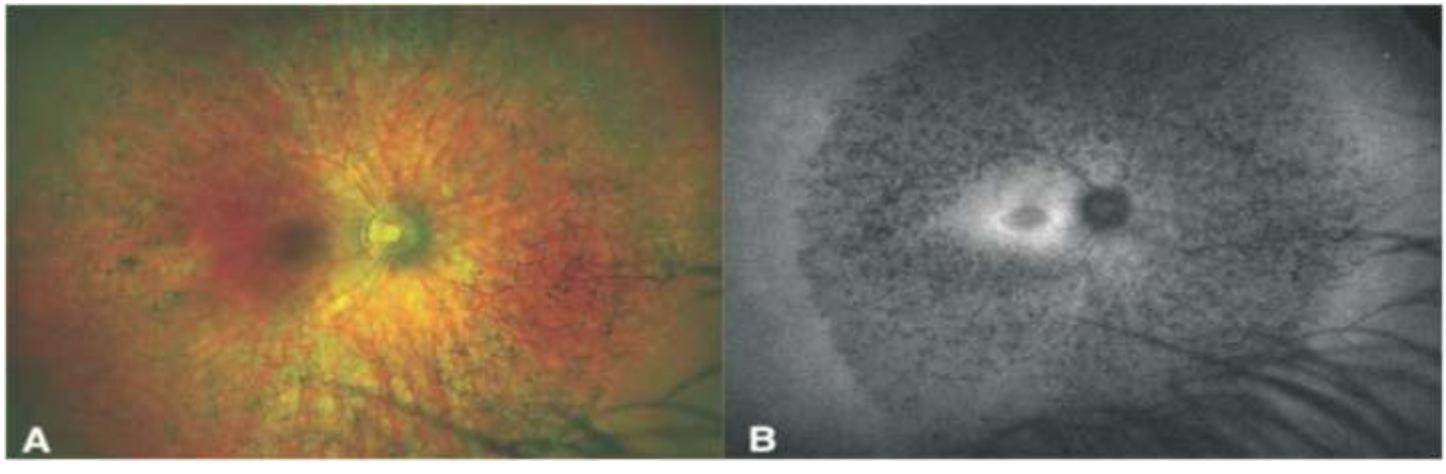

Figure-3 : A) Fundus photography of the right eye shows classical findings of bone spicule pigmentation, attenuated blood vessels and optic nerve pallor. B) Fundus auto-fluorescence photograph of the same eye, showing an ellipsoid-shaped hyperautofluorescent ring.

which often impacts prognosis, management, genetic counselling and risk of transmission to offspring. However, causative genetic variants are identified in about 60 percent of cases, leaving a significant portion of cases with an undetermined genetic etiology.[13] Some pitfalls are also there with genetic testing, such as false-positive rates, and differences in content and coverage of next-generation sequencing panels and other currently available genetic tests.[14] Therefore; pre-test phenotyping, consisting of a detailed medical history and reviewing diagnostic tests and imaging, is fundamental prior to ordering genetic testing; in co-ordination with a genetic counselor, who can assist in panel selection and communicating test results to patients, as well as education on prognosis.

Prognosis and Management :

About 25% of patients with RP become legally blind in both eyes, rarely they lose total vision. Half or even more of patients have visual acuity of 6/12 or better in at least one eye. Only a few patients younger than 20 years of age have a visual acuity of 20/400 or less. However by the age of 5O years, a significant proportion of patients will have a visualacuity of approximately 20/400.

1. Yearly follow-up is recommended to detect a treatable cause of fall of vision, such as cystoid macular edema or cataract.
2. CME associated with RP can be treated with topical carbonic anhydrase inhibitors (CAI), patients that do not respond well to topical therapy may require an oral CAI, which is initially tried in a dose of 125 mg twice a day for 2 months to confirm its beneficial effect.[15]
3. Perimetry should be performed at regular intervals to assess visual field changes.
4. Cataract surgery can improve vision to some degree in patient with cataract.
5. In high myopic patient with RP, glass prescription and regular peripheral retina examination is also important.
6. Sunglasses should be worn outdoor to prevent light sensitive further damage to photoreceptors-RPE.
7. Patient instructed to keep a bright torch with him. This can be very useful for searching in darks.
8. Providing Low-vision devices and rehabilitation of patients facing difficulty in their daily chores. For reading and writing near visual aids such as lighted magnifiers and closed-circuit televisions are useful.
9. The role of oral high dose vitamin A therapy in slowing the rate of progression of typical RP remains controversial.[16,17]
10. Patients can be advised to use supplements such as lutein and zeaxanthin, which have been found to aid in slowing disease progression and are safe for patients.
11. An Omega-3-rich diet containing docosahexaenoic acid can further slow disease progression.[18]
12. Potential retino-toxicdrugsshould be avoided.

Newer Modalities for Treatment of RP :

There is no known prescription cure for the disease at present. But considerable progress has been made in the genetics of RP, and treatment modalities are being studied in both animal models of retinal degeneration and humans, giving retina specialists and their patients reasons for hope.

1). Luxturna :

In 2017, Luxturna (voretigeneneparvovec, Spark Therapeutics), an adeno-associated virus (AAV2) vector carrying an RPE65 cDNA, became the first FDA-approved gene therapy for an inherited retinal disorder. Designed for the treatment of RPE65-related Leber's Congenital Amaurosis and a small percentage of cases of autosomal recessive RP (~2 percent).

2). Gene Therapy :

Genetic therapy remains the most promising approach for the treatment of IRDs. Gene therapy involves replacement of defective genes with functional ones by using gene augmentation, silencing, editing. Therapies can be delivered to the subretinal space through viral vectors, commonly AAVs (adeno-associated virus), to provide a functional copy of a gene (augmentation) or to correct a mutation (editing). The retina's immune-privileged environment, as well as its accessibility for surgical procedures, make it a suitable candidate for this type of approach. [19]

3). Stem Cell Therapy :

Several types of stem cells, such as retinal progenitor, embryonic, induced pluripotent and mesenchymal, are being studied as a potential treatment modality in retinal dystrophies. Pre-clinical studies have shown advantageous effects of stem cell treatment, such as replacing damaged cells, adding nutritional support to remaining functioning cells, protecting retinal vascularity and promoting synaptic connections.[20]

4).Optogenetics :

This is an emerging technology that employs optimized opsins, light-sensitive proteins that can modulate neural activity in retinal cells, using existing neural synapses to act as artificial photoreceptors.[21] Opsin genes, such as channel-rhodopsin, can be transfected into non-photoreceptor cells, such as retinal ganglion cells, through commonly used vectors, such as AAV, via subretinal injection.

5). Retinal Implants :

Retinal implants are being developed and implanted at various centers in the world. There are two types of implants, either epiretinal or subretinal. The basic concept is microchip implantation of electrodes on the retina or below it. They are stimulated by light, converting them to electric signals. Then these electric impulses induce biological visual signals in the remaining functional retinal cells and which are transmitted through the optic nerve to the brain.[22,23]

6). Gene Editing :

Gene editing employing the CRISPR/Cas9 system is an emerging approach for future therapies for IRDs. In brief, the CRISPR system acts as molecular scissors that cut out a portion of the damaged gene and replace it with a wild-type sequence. Results of in vitro retinal cell and in vivo mouse studies are promising, showing a slowed progression of RP.[24]

7).Growth factors :

Treatment with specific growth factors may be a way to slow RP progression in people with mild or later-onset disease as suggested by animal models of retinal degenerations. Currently, research includes ciliary neurotrophic factor (CNF) encapsulated cell technology but seems to be controversial. [25]

Conclusion :

In conclusion, retinitis pigmentosa remains a leading cause of hereditary visual impairment. Diagnosis is made through a combination of clinical symptoms, diagnostic and functional assessments, and genetic testing. While treatments remain elusive, we as ophthalmologists should give these patients a positive ray of hope as well address their clinical situation. We must tell them that the researchers around the world are relentlessly working for them and some cure already rising on the horizon, will definetly be available in clinical practice in near future.

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Sohan Singh Hayreh *(November 6, 1927 September 29, 2022) was an ophthalmologist, clinical scientist, and professor emeritus of ophthalmology at the University of Iowa. As one of the pioneers in the field of fluorescein angiography, he was generally acknowledged to be a leading authority in vascular diseases of the eye and the optic nerve. For over 60 years, Hayreh was actively involved in basic, experimental, and clinical research in ophthalmology, publishing over 400 original peer-reviewed articles in various international ophthalmic journals, six classical monographs and books in his field of research, and more than 50 chapters in ophthalmic books. He made many seminal observations dealing with the ocular circulation in health and disease, the optic disc and the optic nerve, retinal and choroidal vascular disorders, glaucomatous optic neuropathy, fundus changes in malignant arterial hypertension, ocular neovascularization, rheumatologic disorders of the eye, and nocturnal arterial hypotension. He was an elected fellow of the National Academy of Medical Sciences.*

Angoid Streaks

Pratik Mahajan[1], Dipty Shah[2]

Introduction :

Angioid streaks is the term used to describe visible irregular lines that spread radially form the optic nerve, with a variable width which funduscopically seem red-brown. It is their similarity to retinal vessels that is responsible for their name, consequent atrophy of the RPE above them. Calcium deposits make Bruch's membrane more brittle and less resistant to trauma (external, muscle traction, pressure on the eye), being responsible for the choroidal ruptures involved in these patients.Latest theories demonstrate an absence of a systemic

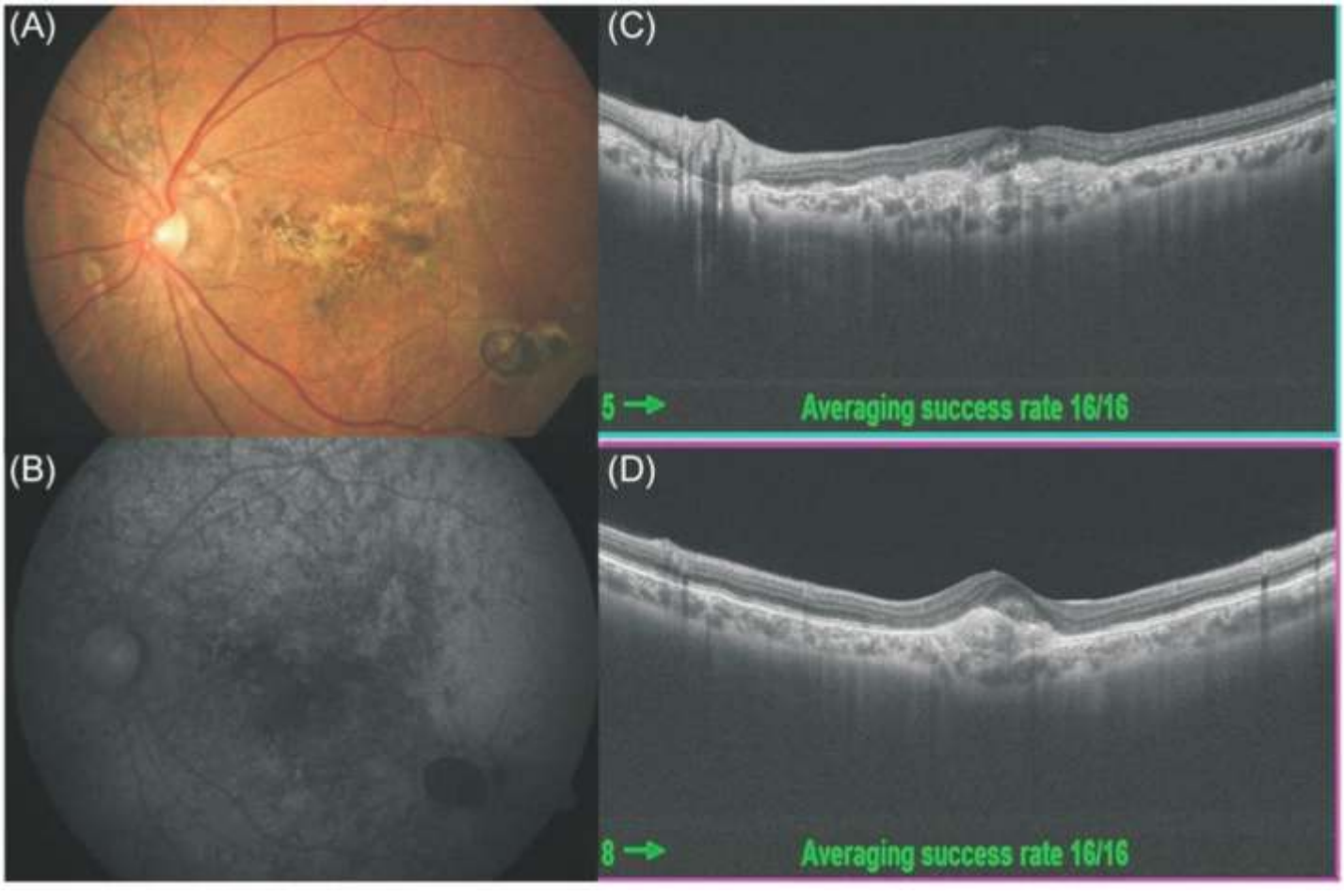

Figure 1 : Fundus photograph (A) and autofluorescence (B) images of an eye with angioid streaks and scarred choroidalneovascular membrane which is confirmed on SS-OCT scans-horizontal (C) and vertical (D).

They were first described in 1889 by Doyne during the exploration of traumatized eyes. Angioid streaks are the ophthalmoscopic manifestations of calcific degeneration and irregular breaks in Bruch's membrane together with a antimineralization factor that leads to the calcification of Bruch's membrane and other connective tissues that are rich in elastic fibers.

A case of angiod streaks may or may not have a systemic association. Systemic associations of angioid streaks include pseudoxanthomaelasticum, EhlersDanlos and Marfan syndromes, Paget's disease, acromegaly and several blood dyscrasias like thalassemia, spherocytosis, and sickle-cell anemia. Patients showing this disease are usually

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asymptomatic until complications arise. The most frequent of them is the development of traumatic CNV, and prognosis depends on the macular involvement.

Ocular Manifestations and Clinical Course :

Angioid streaks are funduscopically diagnosed and identified as irregular subretinal breaks or dehiscences that radiate from the optic nerve whose width is reported to vary from 50 to 500 μm. They may remain stable or increase in size, but they do not regress. Similar to choroidal ruptures, patients stay asymptomatic as long as the macular area is not involved. Patients suffering from angioid streaks are very susceptible to choroidal breaks after the mildest of traumas, and 72.86% of cases present with CNV. These patients usually evolve to legal blindness as more than 70% of the cases are bilateral. The early phase is characterized by metamorphopsia and/or blurred vision (ranging from 20/20 to light perception, depending on the location of the break) after mild trauma. The most common finding at this stage is a subretinalhaemorrhage involving the macular area, which will later reveal CNV after a break in Bruch's membrane at the affected spot. Fundus autofluorescence, fluorescein angiography (FFA), indocyanine green angiography (ICGA), and optical coherence tomography (OCT) may help identify areas of angioid streaks or their complications.

Treatment :

There is no effective treatment to prevent the development of angioid streaks. Spaide et al suggested the possibility that pyrophosphates could be used to treat pseudoxanthomaelasticum looking to halt abnormal mineralization of tissue including that seen in Bruch's membrane, and so prevent the development of breaks and angioid streaks. Current therapeutic approaches are focused on the management of complications. PDT, surgical extraction, laser photocoagulation, macular translocation, and transpupillary thermotherapy (TTT) were used with variable results and no significant long-term benefits. On the other hand, anti-VEGF intravitreal injections have surged as a new option during the last years as several studies have shown their potential benefits for the treatment of angioid streak-related CNV and seem to be able to stop the progression of CNV with significant improvement in visual outcomes. Tilleul et al state that this kind of CNV seems to be more similar to myopia-related CNV than age-related macular degeneration (AMD), needing fewer injections than wet AMD. This group also highlights the importance of monitoring patients suffering from complications in one eye so as to be able to identify and treat the fellow eye in case of involvement as soon as possible and so prevent foveal scarring.

*In 2016, **Dr. Mark S Humayun** received the National Medal of Technology and Innovation from President Barack Obama for his innovative work and development of the Argus II.*

White Dot Syndromes : An Overview

Kushagra Jain

Introduction :

The white dot syndromes constitute a group of inflammatory chorioretinopathies. The common, defining clinical feature is the presence of multiple, discrete, white lesions located at the deeper levels of the retina choroid.[1] Several of the white dot syndromes are associated with a viral prodrome, and an etiology is lacking for these conditions. Typically seen in young, otherwise healthy adults, the white dot syndromes most often present with symptoms of photopsia, floaters, decreased night vision, blurred vision, and visual field loss.[2] These conditions can be acute in onset or transient without long-term visual consequence. White dot syndromes share many similar clinical features, including the "tell-tale" chorioretinal lesions, several distinct clinical features, and diagnostic testing findings that allow for additional characterization.

The term White dot syndromes has been generally used to describe the following diseases: [3]

- Acute Posterior Multifocal Placoid Pigment Epitheliopathy (APMPPE)
- Serpiginous choroidopathy
- Multiple Evanescent White Dot Syndrome (MEWDS)
- Birdshot Retinochoroidopathy
- Multifocal Choroiditis and Pan uveitis Syndrome (MCP)
- Punctate Inner Choroidopathy (PIC)
- Acute Zonal Occult Outer Retinopathy (AZOOR)

See Table 1.

These conditions are conventionally recognized as distinct identities, and some suggest that they represent a spectrum of chorioretinal disease.[4]

Etiology :

The etiology of the white dot syndromes remains unknown. Several entities are associated with a viral prodrome, suggesting a potential viral or infectious etiology. Similar to most autoimmune conditions, an unknown trigger is thought to precipitate an inflammatory or autoimmune process in the posterior eye.[5] The white dot syndromes represent a primary ocular process and are not associated with systemic inflammatory or autoimmune disease. An increased prevalence of such conditions has been demonstrated in several subgroups of patients with white dot syndrome (i.e., AZOOR).[6] Birdshot chorioretinopathy is highly associated with the presence of the HLA-A29 haplotype.[7] This correlation is so prominent that the absence of this haplotype, even within the presence of typical clinical features, should prompt consideration of an alternative diagnosis.

Table 1. White Dot Syndromes

	Sex	Pathology	Laterality	Size	Morphology	Location	Color	A/C	VIT	FA	EOG	ERG	Prognosis	Etiology	Treatment
APMPPE	-	RPE Choroid	Bi	Large	Placoid	Posterior pole	White scar	+	50%	Early blockage Late stain	↓	↓	80% good	50% viral	None
Serpiginous	-	Choroid RPE	Bi	Large	Serpiginous	Disc Macula	Gray-yellow	-	30%	Loss of chorio-capillaries	↓		Poor	?	None Immuno-suppressives
MEWDS	F>M (4:1)	RPE Retina	80% Uni	100–200 µm	Granular macula	Perifoveal	Gray-white	-	+	Early "wreath"	↓	↓	Recover	50% viral	None
Birdshot	F>M (2:1)	Choroid RPE	Bi	100–300 µm	Ovoid	Posterior equator	Creamy, no pigment	30%	100%	Vessel leak Mac-ON		↓	Chronic	S-Ag CMI	CSA
MCP	F>M (3:1)	Choroid RPE	80% Bi	50–350 µm	Punched out	Multifocal	Yellow pigment ring	52%	98%	Early stain		↑↓	Poor	EBV?	Steroids Acyclovir?
PIC	F>M	Choroid RPE	Bi	50–100 µm	Discrete; well-circumscribed	Posterior pole	Yellow-white	-	-	Early stain			May develop subretinal fibrosis	EBV?	Steroids?
AZOOR	F>M	Outer retina	Bi	Large	Large zones of RPE	Midperiphery	Bone spicule	-	+/-	Mild leakage	?	↓	Good in 1 eye	?	None

A/C = Anterior chamber cell, CMI = Cell-mediated immune response, CSA = Cyclosporine, EBV = Epstein-Barr virus, EOG = Electro-oculogram, ERG = Electroretinogram, FA = Fluorescein angiogram, S-Ag = S-antigen, VIT = Vitritis

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Epidemiology :

With a few exceptions (birdshot chorioretinopathy,

serpiginous choroiditis), white dot syndromes present in young, otherwise healthy, adults below the age of 50.[1] Gender differences allow for further characterization of these entities, with a female predominance recognized in birdshot chorioretinopathy, MCP, PIC, AZOOR, and MEWDS.[2] The incidence of white dot syndromes in a community-based population was 0.45 per 100,000 per year, consistent with their description as rare disease entities.[8]

Acute Posterior Multifocal Placoid Pigment Epitheliopathy :

APMPPE is an acute-onset bilateral inflammatory disease causing decreased vision in one eye first and often in the second eye days later. It presents with yellow, creamy, placoid lesions in the macula at the level of the retinal pigment epithelium (RPE) (Fig 1). APMPPE occurs in otherwise healthy young adults in the second to third decades of life, with no sex predilection. The etiology is unknown, but a viral prodrome occurs in about one third of patients.

Diagnosis is based on clinical history and ophthalmoscopic features. The fluorescein angiographic changes seen in the acute phase of the disease characteristically demonstrate blockage of fluorescence in the early frames, with even, diffuse late staining. Controversy exists concerning whether APMPPE is a result of primary disease of the pigment epithelium or is caused by obstruction of choroidal circulation with secondary pigment epithelial reaction. No evidence has shown that corticosteroids or any other medications are beneficial. Most patients start to experience improvement in the fundus appearance in 1-2 weeks. Visual acuity recovery occurs within weeks, and this disease has a generally good visual prognosis. [10]

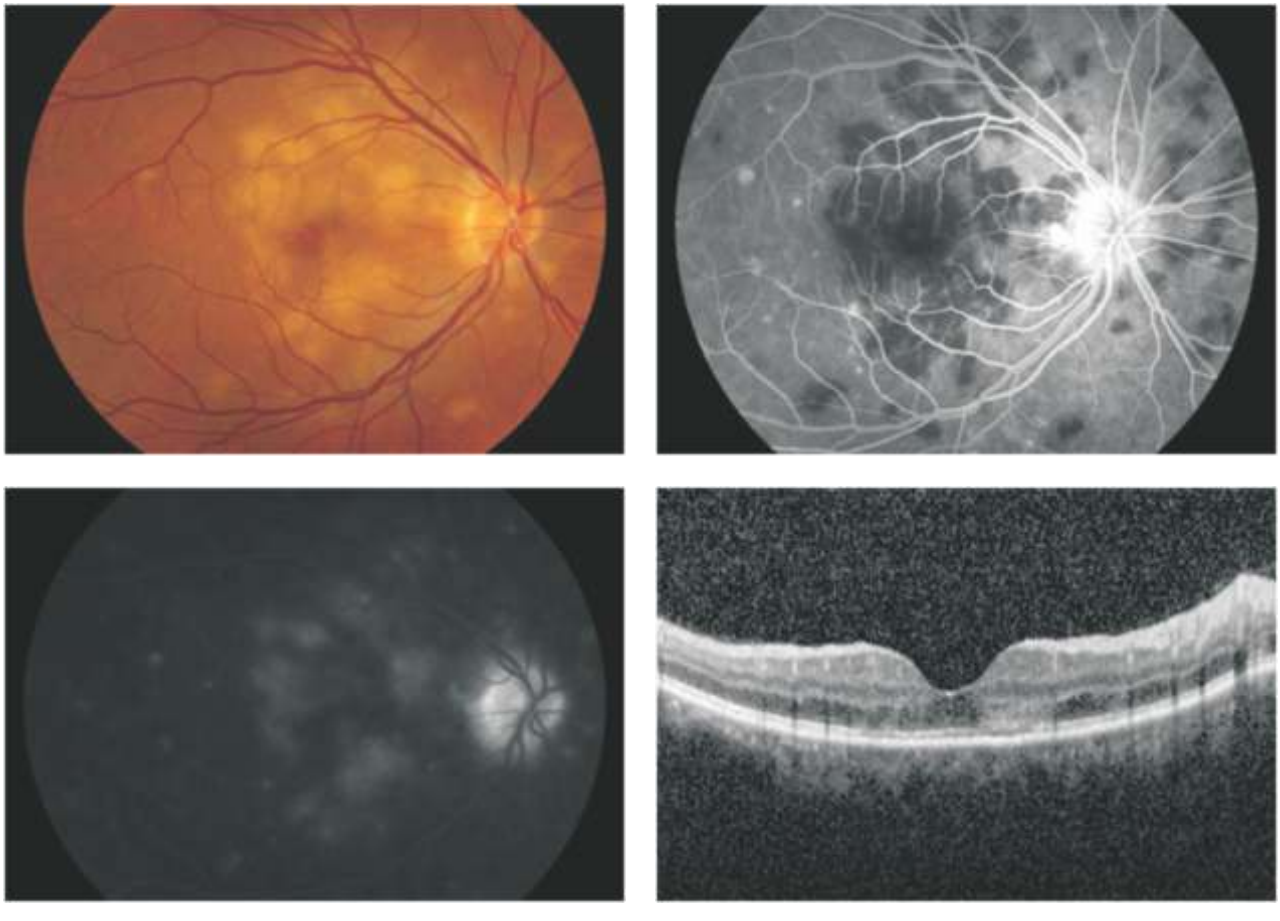

Figure 1: Acute posterior multifocal placoid pigment epitheliopathy (APMPPE). A. Multiple creamy yellow-white lesions throughout the macula. There is mild vitritis on exam and mild disc edema. B. Laminar phase of fluorescein angiogram demonstrating early hypofluorescence of the lesions. C. Late phase of fluorescein angiogram demonstrating late staining of lesions. D. Optical coherence tomography OD: Disruption of the outer retinal layers.

Serpiginous Choroidopathy :

Serpiginous choroidopathy, also known as geographic choroiditis or helicoid peripapillary choroidopathy, is a recurrent inflammatory disease of the choroid that causes a serpiginous (pseudopodial) or geographic (maplike) pattern of

scars in the posterior fundus (Fig 2). Patients complain of decreased visual acuity and central or paracentral scotomata.

Acute-onset lesions have a geographic zone of gray-yellow discoloration of the RPE, which spreads centrifugally outward from the optic disc and macula in a jigsaw-like pattern. These lesions are hypofluorescent in the early phases but stain in the later phases on angiography and may appear similar to the lesions of APMPPE. Unlike APMPPE, however, serpiginous choroidopathy is a chronic and recurrent disease. As active areas become atrophic over weeks to months, new lesions can occur elsewhere or contiguously with atrophic lesions. Dense scotomata corresponding to involved areas develop in all patients, and the second eye may be affected months or years later. Rarely, choroidal neovascularization (CNV) may develop at the margin of an area of chorioretinal atrophy.

Treatment with immunosuppressive agents, systemic corticosteroids, or acyclovir has been attempted, but the results of this treatment are generally poor. More potent combination immunosuppressive treatment with mycophenylate, cyclosporine, azathioprine, and prednisolone appears to halt disease activity in some patients and should be initiated immediately if serpiginous choriod opathy is suspected. When lesions spread to involve the center of the macula, visual acuity remains at a very low level.[11]

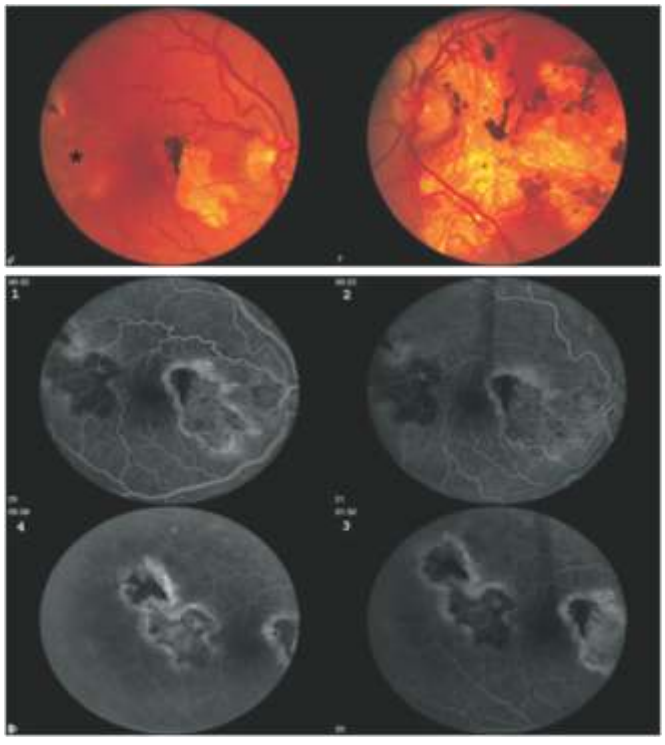

Figure 2 : Serpiginous choroidopathy. A. Fundus photos, OU. Atrophic scars are evident in both eyes. The fuzzy, gray-cream colored geographic area of serpiginous reactivation is seen temporally in the right eye (*). B. Fluorescein Angiogram: There is blockage of fluorescence in the early frames of the right eye in the area of the active disease. In the late frames (labeled numbers 3 and 4), the margins of this area hyperfluoresce.

Multiple Evanescent White Dot Syndrome (MEWDS) :

Multiple evanescent white dot syndrome (MEWDS) is thought to be an inflammatory outer retinal disease. The typical patient with MEWDS is a healthy middle aged female age 15-50 years. There is a gender disparity as women are affected with MEWDS four times more often than men. Roughly 30% of patients have experienced an associated viral prodrome.

Patients present with acute, painless, unilateral change in vision. They may notice photopsia, dyschromatopsia, or a temporal or paracentral scotoma. Majority of the cases have unilateral involvement, but bilateral MEWDS has been

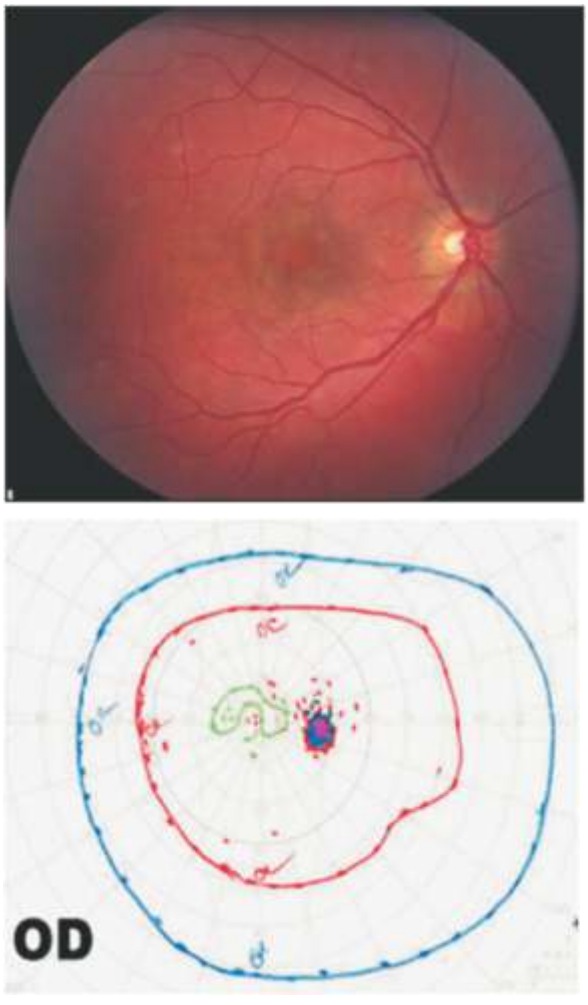

Figure 3 : Multiple evanescent white dot syndrome (MEWDS). A. Fundus Photo - Note the orange, granular changes in the central RPE and multifocal white dot changes. B. Goldman visual field (GVF) testing slightly enlarged blind spot and mildly reduced paracentral visual field overall.

described and is usually asymmetric. Though the onset is acute, the disease is typically self limiting and recurrences are rare. Visual prognosis is excellent. On fundus exam (Fig 3), one sees flat, multifocal, grey-white lesions (100-200 microns), appearing to reach as deep as the RPE. Typically lesions are found outside the fovea in the posterior pole. A characteristic finding in MEWDS is an orange-yellow fovea with granularity. One might also note optic disc edema, mild vitritis (usually posterior vitreous cells), mild anterior chamber flare, a relative afferent pupillary defect and an enlarged blind spot. Sheathing of retinal veins and superficial retinal hemorrhages are rarely seen.

Since MEWDS is a self-limited disease, with almost all patients regaining good visual acuity within 3-9 weeks, no treatment is recommended. Photopsia and scotomata gradually resolve and the lesions will disappear and may be replaced by mild pigment mottling or chorioretinal scarring. MEWDS typically is a self-limited disease, however, patients with MEWDS may have persistent blind spot enlargement. While it is uncommon, 10% of patients may also experience a recurrence. The prognosis is relatively good for these patients.[12]

Birdshot Retinochoroidopathy :

Birdshot retinochoroidopathy, commonly referred to simply as “birdshot”, is a rare form of posterior uveitis which mainly affects the retina and choroid. The disease occurs in women more often than men, typically Caucasian, and most often between the ages of 30 and 60 year. “Birdshot” can be a severe and blinding disease if unrecognized or undertreated. Infection, by virus or bacteria, in susceptible individuals is thought to act as a trigger, with the disease then being self-propagated by an autoimmune mechanism.

The most common complaints are floaters and flashes, blurry or hazy vision, sometimes described as looking through murky water, decreased color and/or night vision. Examination reveals vitritis (100%), a variable degree of disc edema and vascular sheathing, and characteristic yellow ovoid "birdshot" chorioretinal lesions most numerous in the nasal retina (Fig 4). The ERG is reduced or extinguished. The fluorescein angiogram is often unremarkable, and the choroidal lesions appear more visible on ophthalmoscopy. One interesting fluorescein angiographic phenomenon that is seen in patients with this condition is the presence of "quenching;' whereby dye appears to disappear rapidly from the retinal circulation. Approximately 90% of patients are HLA-A29 positive.

Vision loss may be caused by cystoid macular edema (CME; in approximately one third of patients), optic atrophy, or, rarely, macular CNV The disease is chronic, bilateral, and prone to recurrent episodes of inflammation. The dexamethasone/ fluocinolone acetonide intravitreal implant has been shown

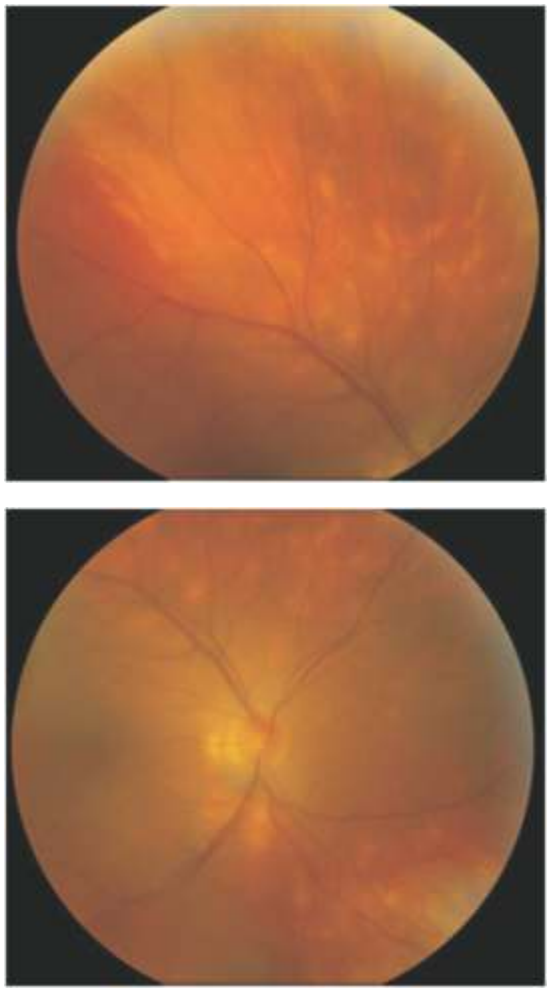

Figure 4 : Fundus photographs reveal mild vitritis and multiple ovoid, cream-colored lesions at the level of the choroid and retinal pigment epithelium (RPE) in the post-equatorial fundus distributed mostly in the nasal retina.

prospectively to decrease recurrences of inflammation and visual loss in birdshot retinochoroidopathy. Disease progression may be assessed electroretinographically by monitoring the 30-Hz-flicker implicit time. Visual acuity outcomes depend on the nature and extent of the disc and macular disease.[13]

Multifocal choroiditis and Panuveitis Syndrome (MCP) :

MCP is a bilateral disease that predominantly affects women between the second and sixth decades. Symptoms include decreased vision, floaters, photopsia, and visual field defects such as an enlarged blind spot. Patients present with a bilateral vitritis, disruption of the peripapillary RPE, and multifocal choroiditis (Fig 5).

The multiple yellow choroidal lesions later evolve into chorioretinal scars similar to the "punched-out" lesions seen in ocular histoplasmosis(OHS). However, unlike patients with

OHS, patients with MCP have some degree of vitritis and often mild anterior segment inflammation. Topical, periocular, and systemic corticosteroids may help to reduce the choroidal and vitreous inflammation, whereas more potent immuno-modulation may be necessary for lesions threatening fixation. However, MCP is a diagnosis of exclusion, and infectious etiologies such as syphilis and tuberculosis should be ruled out prior to initiating immunomodulation. Subfoveal CNV occurs in approximately 20% of affected eyes and is the leading cause of visual loss. Epiretinal membrane formation and CME may also be late complications. The risk of visual loss may be reduced by controlling inflammation and by prompt treatment of CNV. Visual outcomes in MCP are often poor.[14,15]

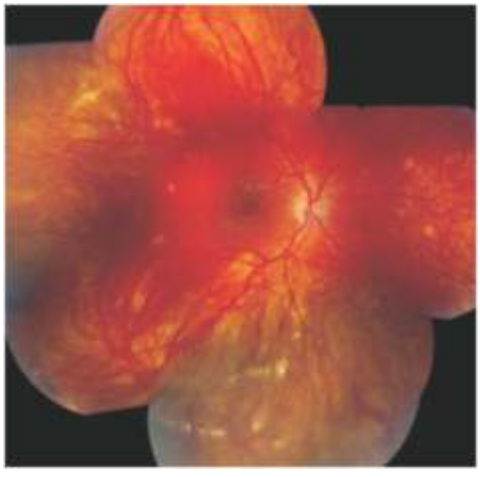

Figure 5 : Multifocal choroiditis and panuveitis syndrome

Punctate Inner Choroidopathy (PIC) :

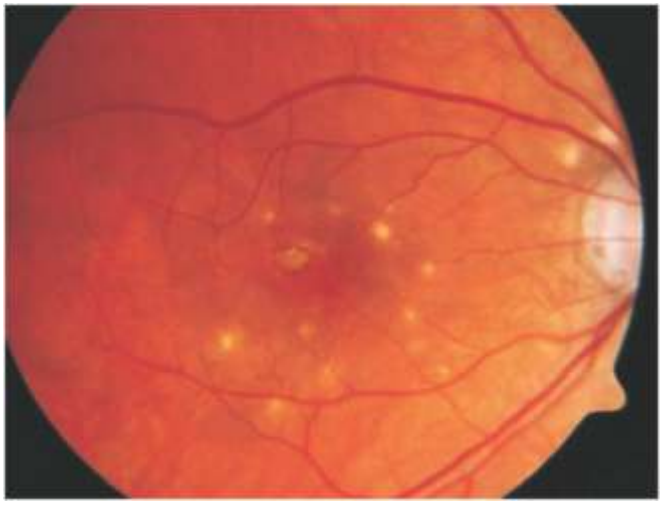

Figure 6 : Punctate inner choroidopathy(PIC)

PIC tends to occur in young patients with myopia. More than 90% of these patients are women. Patients present with symptoms of bilateral loss of central visual acuity, as well as prominent photopsia and scotomata.

Fundus examination during the acute phase shows small (100-300 μm) round yellow-white lesions at the level of the RPE or inner choroid that may coalesce and form a serous retinal detachment (Fig 6). Scotomata usually correspond to the location of these lesions. Mild optic disc edema may be visible, but iritis and vitritis are not seen. The lesions fill and stain during the late phase of fluorescein angiography, especially if a

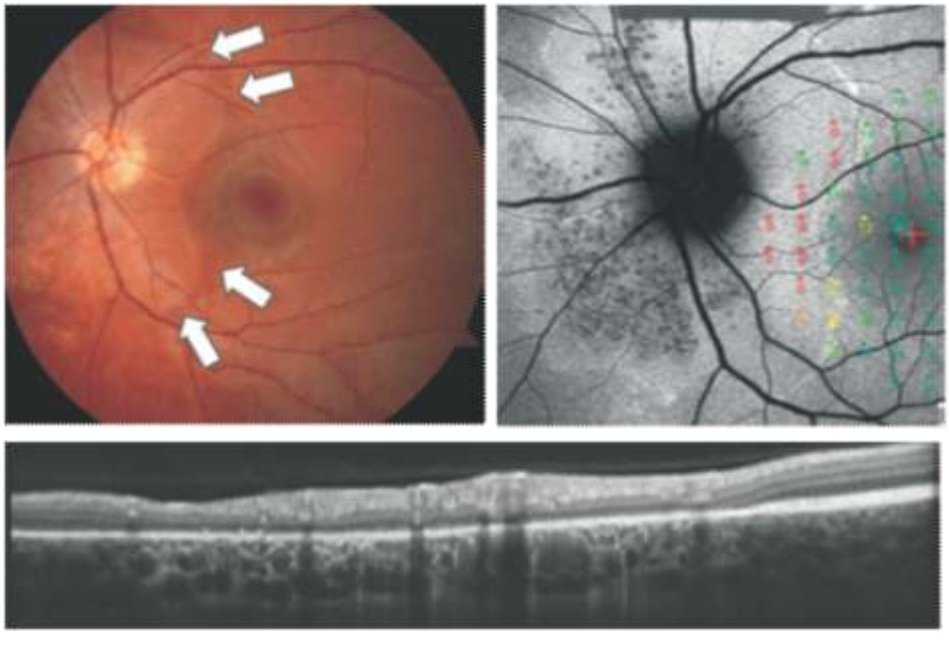

Figure 7 : A case of resolving acute zonal occult outer retinopathy (AZOOR). Note the wavy line (arrows) bordering the involved and healthy areas on fundus autofluorescence (FAF); superimposed microperimetry (MP) shows decreased sensitivity in the involved area. Optical coherence tomography (OCT) shows thinning of the retina[17]

serous detachment is present. Lesions later become atrophic yellow-white scars, which may become pigmented or enlarge over time. These scars appear very similar to those seen in OHS and multifocal choroiditis.

Oral and periocular corticosteroids have been used without adverse effect in patients with PIC, but spontaneous improvement usually occurs without treatment. The prognosis for visual acuity is generally good, and the condition seems not to recur. However, one third of eyes develop CNV within a site of old scarring; some of the CNV involutes spontaneously. Photopsia may persist for years.[16]

Acute zonal occult outer retinopathy(AZOOR) :

AZOOR, a presumed inflammatory disorder, damages broad zones of the outer retina in one eye or both eyes. AZOOR usually occurs in young women, with an acute onset in one eye. Initial symptoms include photopsia, visual field loss, and sometimes an enlarged blind spot. The fundus may appear normal on initial presentation, or mild vitritis may be seen (Fig 7). Angiography may show retinal and optic nerve head capillary leakage, especially in patients with evidence of vitritis. The ERG often shows decreased rod and cone amplitudes under both photopic and scotopic conditions. Visual field testing may show scotomata, which can enlarge over weeks or months. Some patients recover from AZOOR, whereas others have persistent large visual field defects. Permanent visual field loss is often associated with late development of fundus changes. Depigmentation of large zones of RPE usually corresponds with scotomata; narrowed retinal vessels may be seen within these areas. The late fundus appearance in some patients may resemble cancer-associated retinopathy or retinitis pigmentosa. Most patients retain good vision in at least 1 eye. No treatment has any proven benefit.[4]

Thankfully, many white dot syndromes are self-limited and do not require treatment. Still, exceptions exist, and, in these circumstances, treatment often involves the use of systemic immunosuppressive therapy. Coordination of care between an ophthalmologist specializing in chorioretinal disease and a rheumatologist is often needed for optimal care. Consideration should be given to case conferences or joint clinics to facilitate such coordination.[18] An interprofessional healthcare team coordinating between the patient's family clinician, ophthalmology specialists, and nursing staff will lead to optimal results through accurate diagnosis, patient education, and in some instances, based on the particular variant, active intervention.

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Posterior Uveitis

Sachin Barhanpurkar

Posterior uveitis is an entity that has varied etiologies. Since posterior uvea is close to the vitreous, retina and optic nerve they may get affected simultaneously and hence proper and timely intervention is a must. Proper clinical examination and investigations can help reach correct diagnosis.

How to approach a patient of Posterior uveitis :

History :

A proper history helps reach to get important evidence regarding the disease. A relevant medical history, social history, associated medications and family history can help diagnose early.

The following points can help clinch the diagnosis :

1. Type of uveitis (posterior or pan uveitis)
2. Associated retinitis , chorioretinits or only choroiditis
3. Associated optic nerve or retinal vessel involvement.
4. Do the clinical features fit into infective or non infective entity
5. Associated anterior segment inflammation vitritis or complications
6. Associated systemic features.
7. Any recurrence and response to treatment.
8. Immune status
9. Masquerade syndrome.

Posterior uveitic diseases can be classified based on :

1. Etiology

A. Infective

- Toxoplasmosis
- Toxocariasis
- Tuberculosis
- Syphilis
- Bartonella
- Viral
- HIV

B. Non infective

- APMPPE
- MEWDS
- GHPC
- MFC
- PIC
- Birdshot Choroidopathy
- POHS
- SFU
- DUSN
- Retinal Pigment Epithelitis
- Sarcoidosis

2. Based on characteristics of lesion

- Choroiditis
- Retino choroiditis
- Neuroretinits
- Retinitis
- Granuloma
- Mass lesions (Masquerading as uveitis)

Investigations that help in diagnosis :

§ Color fundus photography, FFA, ICS, OCT, USG

o Fundus photo helps in diagnosis and for serial documentation of lesions. FFA helps in understanding the activity of lesion. It helps in detecting the disease sequelae like neovascularization, non perfusion, vascular staining, flower petal appearance in Cystoid macular edema and CNVM activity.

o ICG helpful for deeper choroidal lesions , CNVM and in presence of retinal hemorrhages.

o OCT is non invasive and non contact method to detect CME, ERM, CNVM, Macular hole

o B Scan useful for hazy media, in type of RD, , increased choroidal thickening like VKH and posterior scleritis.

§ Laboratory investigations: Routine and specific investigations for particular etiology are done. They are more useful for detecting infective than in non-infective conditions. In cases of diagnostic dilemma intraocular fluid evaluation for PCR are helpful.

§ Systemic examination

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How to approach to a case of posterior uveitis:

1. Identification of the particular fundus picture
2. Confirm with specific investigations
3. Treatment of the primary cause with anti-infective agent
4. Use of systemic steroids as additional anti-inflammatory therapy
5. Avoid periocular/ intravitreal steroids
6. In diagnostic dilemmas, intraocular fluid for antibodies or PCR for identification.

Infective Posterior Uveitis :

The infective disease comprise bacterial, viral, protozoal, and helminthic organisms. Each have typical characteristics that help in diagnosis. Some organisms have distinctive pattern of growth.

Posterior segment infections with focal fundus lesions:

Ocular Toxoplasmosis:

Toxoplasma gondii is a protozoan parasite that infects up to a third of the world's population. It is the most common infective cause of posterior uveitis in immunocompetent patients. Most cases are subclinical or benign. There would be a history of contact with pets, ingestion of raw uncooked food or contaminated water. Transplacental transmission is the only form of human to human transmission.

Clinical Features :

Presentation is in the form of retinochoroidits which is unilateral in 72-83% of cases. Inflammation occurs due to activation of cysts deposited in or near the retina. Focal necrotizing retinitis is a characteristic lesion. Although peripheral retinochoridal scars are more common (82%), posterior pole is vulnerable to infections (50%).

Infection	Color	Level	Site and location	Other
Focal Bacterial Endogenous endophthlmitis	Yellow white	Flat or slightly elevated, full thickness retina with variable RPE involvement	Small ,large lesions produce diffuse infections	Uncommon presentation of endogenous endophthalmitis
Syphilis	Yellow to orange	Outer retina and choroid	Outer temporal macula or diffuse retinal involvement	Minimal RPE involvement and scarring
Tuberculosis	White	Choroidal nodules, periphlebitis, serpigenous like lesions	Miliary to large nodules, geographic	May be solitary , apnophthalmitis may occur
CMV Retinits	Yellow white usually with hemorrhage	Superficial, granular with central pigmentary scarring	Variable, often 15% of retina or more at diagnosis	May be multifocal or solitary expanding patch
Necrotizing herpetic retinitis	White to yellow	Thick layer of necrosis with vascular occlusion and pigment disruption	Peripheral, confluent with rapid centripetal spread	Variable arteritis and optic neuritis
Toxoplasmosis	Grey to white or pale yellow	Thick layer of inflammatory swelling	Usually small, recurrence at edge of pigmented scar, may spread diffusely	Acquired disease without preexisting scar is possible. Characteristic OCT appearance of full thickness retinal opacification
Candidiasis	White	Subretinal base with penetration through retina and vitreous	Small to moderateretinal lesions and focal vitreous opacities	Solitary or multiple panophthalmitis may be seen
Aspergillus infection	Yellow white	Chorioretinal plaque	Predilection to involve macula	Intense inflammation and intravascular spread

Congenital Toxoplasmosis :

Ocular manifestation may be the only presentation without any systemic disease. Typical punched out macular cicatricial lesion with central necrotizing zone including retina choroid and vitreous is diagnostic (Photo 1) Re-activation of toxoplasma in the form of satellite lesion may be seen.

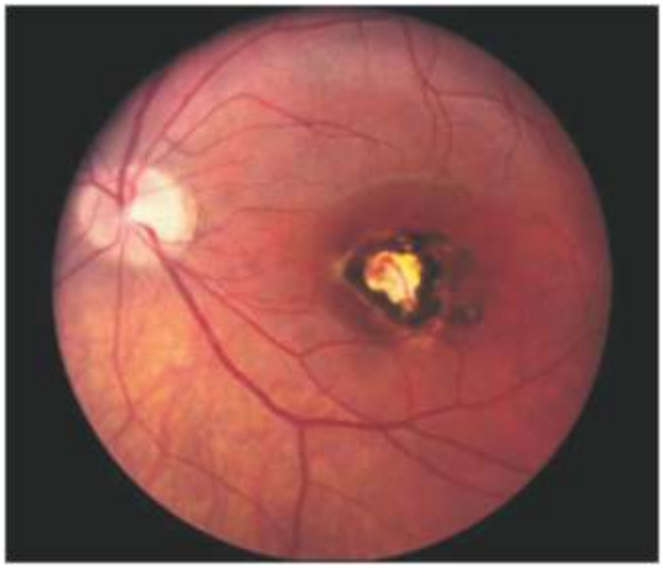

Figure 1 : Congenital Macular scar

Acquired Toxoplasmosis :

Presentation: patient presents with diminished vision / floaters. Macular involvement with headlight in the fog appearance (photo 2) of focal necrotizing retinochoroiditis with overlying vitritis is typical presentation. Initially lesion starts in superficial retina and gradually involves all layers and surrounding vitreous, sclera and adjacent uvea. Yellow white lesion with hazy borders is seen in periphery. The lesions may be of varied sizes. Adjacent choroiditis , hemorrhage , vitiritis may be seen. Vasculitis may be seen close to an active lesion and is due to antigen-antibody complex deposition or mononuclear cell infiltrates in vessel wall. Kyrieleis arteriolitis may also be seen which are exudates/ periarterial plaques.

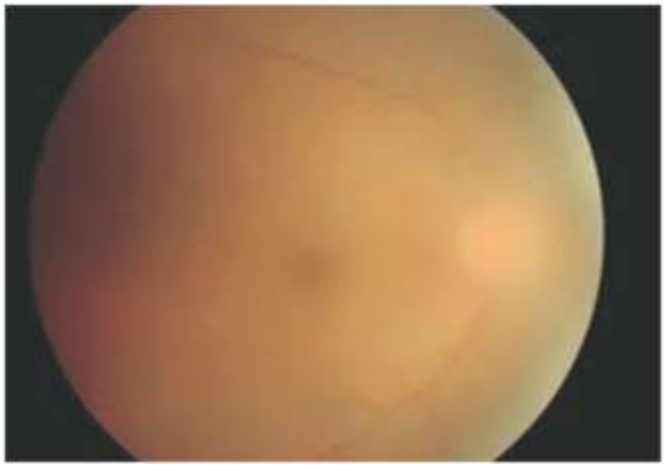

Figure 2 : Headlight in the fog appearance

Healed scar with well defined borders around central chorioretinal atrophy is characteristic.

It may also present with serous detachment, neuritis, papillitis, disc hemorrhage, venous engorgement and macular star. In immunocompromised patients punctate outer retinal toxoplasmosis or necrotizing retinitis lesions mimicking viral retinitis may be seen.

Complications may be seen in the form of glaucoma (most common), cataract, vitreous hemorrhage, RD, CNVM or optic atrophy.

Diagnosis :

Mainly clinical, FFA, ICG ,OCT are complimentary.

Anti toxo antibody utres detected by several techniques like Sabin Feldman dye test (Gold Std), complement fixation antibody test, IFAI, ELISA (most common investigation done).

IgG and IgM levels detect whether infections are chronic or acute. IgM appear after 1st week of infection and then declines, IgG levels raise till 6-8 weeks and then declines and stay forever. However antibody levels may be low and hence undiluted samples should be used. Sometimes false positive titre may be seen and hence clinical signs should be considered before taking decision.

PCR test and Goldman Witmer coefficient analysis are an important tool. In dilemma aqueous and vitreous samples for detecting toxoplasma DNA for confirmation may be taken.

Treatment :

Current therapies target only the trophozoites. Treatment targeting cysts are not yet found. Pyrimethamine and sulfadiazine combination are most effective. Others include Clindamycin and Azithromycin. Systemic steroid also to be added to the regimen to reduce inflammation. Anterior uveitis treted with topical steroids and cycloplegics.

Immunocompromised patient require long term prophylaxis till immune status improves. Toxoplasma CNVM is treated with PDT. Persistent Vitreous opacities or vitreo traction are managed with vitrectomy.

Anti Toxoplasma drugs :

1. Trimethoprim + Sulphamethaxazol DS tab 160mg /800 mg one tab daily for 6 weeks
2. Pyrimethamine (100mg 1st day, 75 mg- 2nd day, 50 mg- 3rd day followed by 25 mg once a day daily) + Sulfadiazine (4 gm daily in divided dose every 6 hours) for 4-6 weeks
3. Clindamycin : 300 mg 6 hourly dose / max 1.8 gm / day for 6 weeks

4. Spiramycin : 2 gm/day in divided doses
5. Azithromycin loading dose 1 gm- 1st day then 500mg once daily for 3 weeks
6. Atovaquone 750 mg every 6 hours for 4-6 wks

Anti toxoplasma therapy in special situations :

Pregnancy

I trimester : spiramycin + sulfadiazine.

II trimester(>14 weeks) : Spiramycin + Sulfadiaxine + Pyrimethamine + Folinic acid

III trimester : Spiramycin + Pyrimethamine+ Folinic acid

Newborn

Pyrimethamine, Sulfadiazine and folinic acid

Ocular Toxocariasis :

Caused by ingestion of larva of dog (Toxocara canis) or cat(Toxocara Cati) round worm. It is seen in children with pica or those who are in close contact with pets. Diagnosis based on positive history of contact with pets. Humans are end hosts. The infection leads to focal granulomatos reaction n many organs. Ocular manifestation may be seen as:

- Granuloma in peripheral retina and vitreous
- Posterior pole granuloma
- Chronic endophthalmitis
- Optic nerve involvement
- Anterior segment involvement

Typical presentation is in the form of peripheral granuloma with TRD with chronic endophthalmitis like picture. Early lesions show intense vitreous haze. Long standing mass show atrophy and hyperplasia of RPE cells. White-grey white granulomas around fovea and optic disc may be seen. Dead larva appear as dark grey areas within whitish mass at the posterior pole. CNVM/ sub retinal toxocara granuloma should be ruled out.

Diagnosis :

Diagnosis is mostly clinical, ELISA test for Toxocara Excretory Secretory Antigen (Tes-Ag) is highly specific. Raised Anti-Tes Ag IgE levels indicate acute toxocara infection or progressive inflammation. Raised IgG levels confirm past infection or present infection with minimum inflammation. Toxocara GW co-efficient analysis from aqueous or serum can be of value in diagnosis.

Differential Diagnosis :

Retinoblastoma / endophthalmitis / pars planitis/ Coats disease/ Familial Exudative Vitreo retinopathy

Treatment : Quiescent clinical presentation usually do not require any treatment. In rare cases where there is eye involvement with visceral larva migrans, anti helminth (albendazole) along with systemic steroids. Complications may be treated with vitrectomy, cryo or laser .

Larva may be removed surgically or by laser photocoagulation.

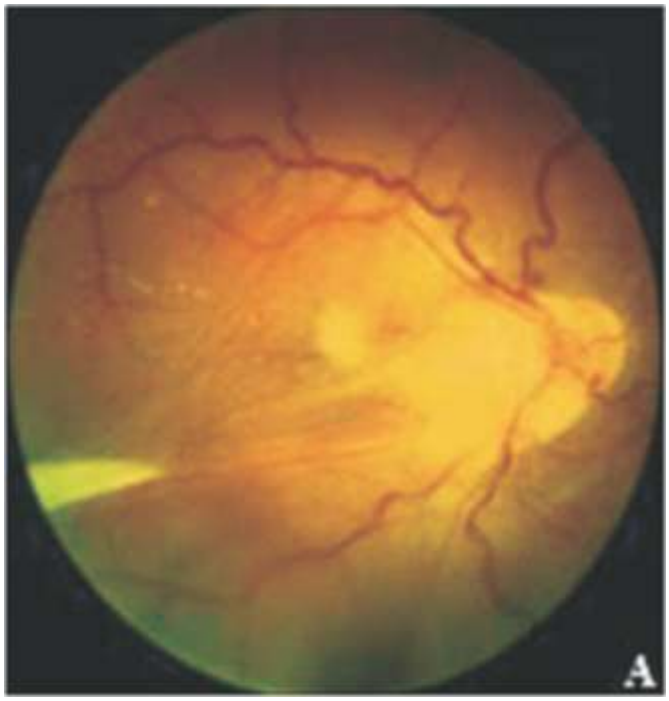

Figure 3 : Toxocara Granuloma

Tubercular Posterior Uveitis :

Ocular TB can be primary where eye is the initial site of entry.

Secondary spread is by hematogenous spread and that includes tubercular uveitis. Hypersensitivity to tubercular protein may cause retinal vasculitis. Only 1.4% of patient with systemic TB have tubercular uveitis .

Presentation :

Most common presentation is disseminated multiple tubercles (earliest sign). Circumscribed yellow white grey lesions deep in choroid of size 0.5- 3 mm in diameter may be seen.

Another form is single tubercle (also known as focal choroiditis) may be seen(D/D melanoma). In immuno-suppressed individuals multiple choroidal tubercles may be seen as in cases of miliary tubercles . In the case of mass lesion elevated with overlying serous detachment may be seen. Choroidal tubercle may give rise to sub retinal abscess (Photo 4). Clinically may resemble retinal vasculitis, intermediate uveitis , panuveitis and neuroretinitis.

Diagnosis :

FFA : active choroiditis may give a ring of fire appearance in subretinal abscess or granuloma. Vasculitis with associated