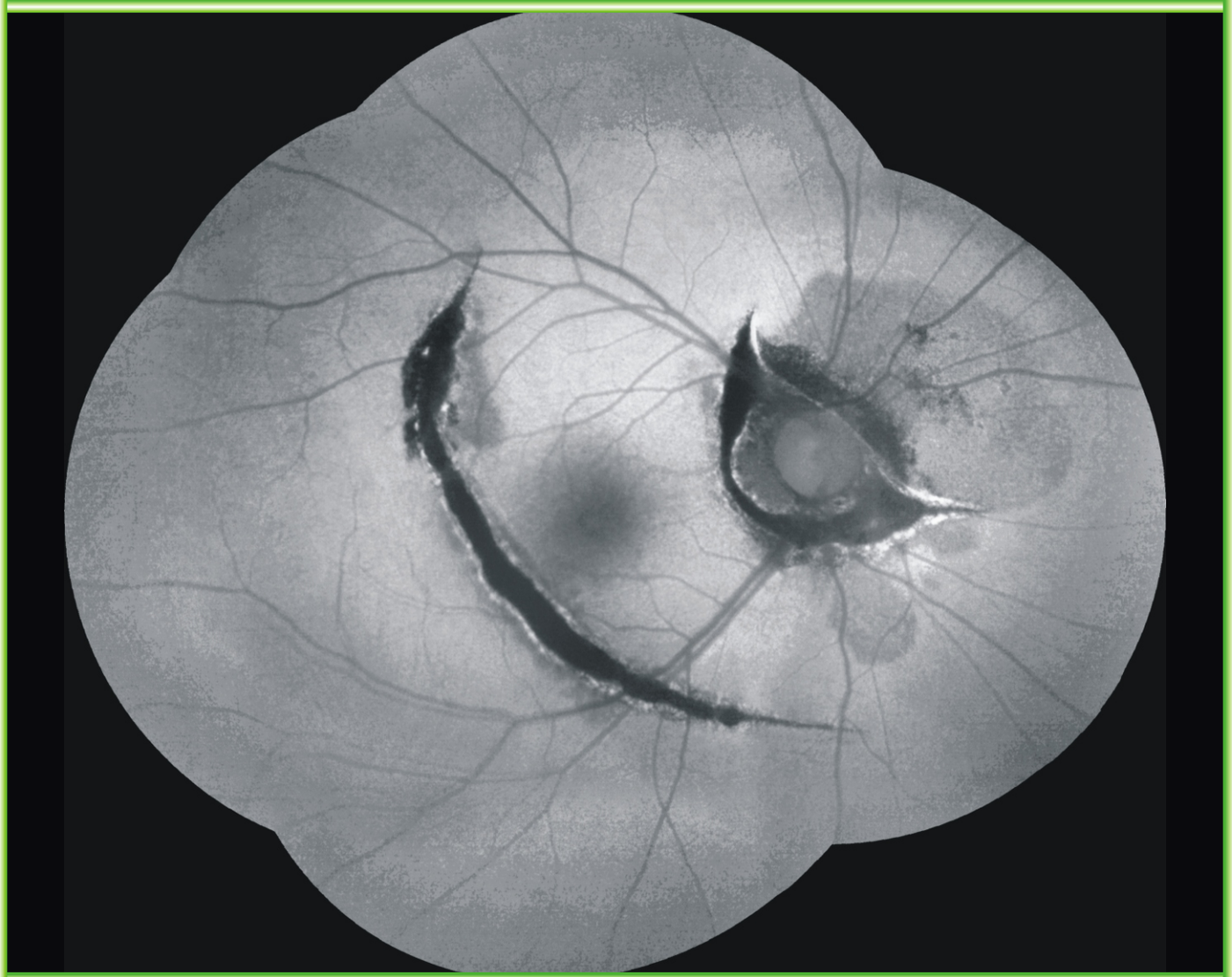
MARCH 2021

The Official Newsletter of the

VITREO RETINAL SOCIETY-INDIA



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Contents

From the President's Desk

Dr. Shobhit Chawla
Medical Director and Chief - Vitreo Retinal Services
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Dear friends

As this year unfolds new hopes and a new normal, hope in the form of safety for all propelled by the vaccine and a new normal of cautious living. The governing council of VRSI will take a balanced decision on the way to conduct the annual meeting this year. We will have clarity by June 2021. Meanwhile let us enjoy and enhance our knowledge on non ICGA diagnosis of Polypoidalchoroidalvasculopathy from our Stalwart for this edition Gemmy Cheung. Manoj Soman has created an interesting set of challenging scenarios in Neovascularmacular degeneration. Once again I thank our Scientific Convenor and all members of Governing council for making this last year of uncertainty into a year of fruitful learning for all .

Regards and best wishes

Dr. Shobhit Chawla
President
Vitreo-Retinal Society of India

From the Honorary Secretary's Desk

Dr. Raja Narayanan
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Dear Friends:

VRSI is delighted to bring out the first edition of 2021 Newsletter. I am sure that your practices have picked up after slowing down due to COVID last year. Many of the members have reported seeing more severe retinal diseases, partly due to delayed treatment. VRSI has worked with various authorities to get insurance approval for anti-VEGF drugs, and is also working with other Societies such as the Diabetes and Endocrinology Societies to promote inter-disciplinary care for diabetic patients.

We are also getting excellent response for VRSI Imaging contest, lead by Dr. Madhana Gopal. This gives an opportunity for retina specialists to share their interesting images with the VRSI members. We hope to open submissions for interesting short videos which would add another dimension to our educational activity.

An excellent issue of VRSI Newsletterhas been compiled by Dr. Anand Rajendran.I am sure that you will find theirarticles extremely valuable for your daily practice. I take this opportunity to request you all to submit your interesting images, cases, articles and innovations to the VRSI newsletter, which will help improve the scientific knowledge base of our members. Stay safe, and we shall meet onlineagain very soon.

Regards
Dr. Raja Narayanan
Hon. Secretary
Vitreo-Retinal Society of India

From the Convenor, Scientific Committee's Desk

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Dear Friends and Colleagues

After a year combatting the COVID pandemic that has had the planet in its throes, we look forward with hope and cheer to better times in 2021. I would also take the opportunity to thank all the faculty, speakers and attendees for contributing and making the VRSI Virtual Meet 2020 such a stupendous success. It has been a pleasure bringing out the opening issue of the year - the March edition of the VRSI Newsletter 2021. In this issue, we have Dr. Gemmy Cheung, an internationally acknowledged expert in Imaging, penning valuable pearls on how one may distinguish PCV from Neovascular AMD using non-ICGA diagnosticsin the 'StalwartSpeak' section. The Spotlight article of the issue, anchored by Dr. Manoj Soman, is focussed on the Challenging Scenarios in Neovascular Macular Degeneration, with an eminent panel of national experts holding forth on a slew ofcomplex situations. In the Innovator's Isle section, Dr. Divyansh Mishra, describes his creation –the Smartphone Mobile Indirect Ophthalmoscope. The Retina Tech Section has Dr. Ashish Kamble highlighting the role and value of Microperimetry in Macular Imaging. Dr. Dhananjay Shukla, in his unique style, describes his Top 7 Impactful articles of the Year in the Retina Roundup 2020, cherry-picked from our monthly Retina Roundup bulletins. Dr. Kshitij Tamboli, in a lighter vein, provides us an poetical take on our speciality. Finally aninteresting case report from Dr. Puja Maitra rounds off this issue.

We look forward to contributions from all members to future issues. We are thankful to all the members for the appreciation and hope to see the same enthusiastic response and support to VRSI activities.

Dr. Anand Rajendran
Convenor
Scientific Committee
Vitreo-Retinal Society India

Guidelines - Manuscript Submission for VRSI Newsletter

Original articles:

These include randomized controlled trials, intervention studies, studies of screening and diagnostic test, outcome studies, cost effectiveness analyses, case-control series, and surveys with high response rate. The text of original articles amounting to up to 3000 words (excluding Abstract, references and Tables) should be divided into sections with the headings Abstract, Key-words, Introduction, Material and Methods, Results, Discussion, References, Tables and Figure legends.

Case reports / Challenging case /Innovations / Instruments /Techniques :

New, interesting, challenging, rare cases, innovations, instruments and techniques can be reported. They should be unique and providing learning point for the readers. Manuscripts with clinical significance or implications will be given priority. These communications could be of up to 1000 words (excluding Abstract and references) and should have the following headings: Abstract (unstructured), Key-words, Introduction, Case, Discussion, Reference, Tables and Legends in that order.

The manuscript could be of up to 1000 words (excluding references and abstract) and could be supported with up to 10 references. Case Reports could be authored by up to four authors.

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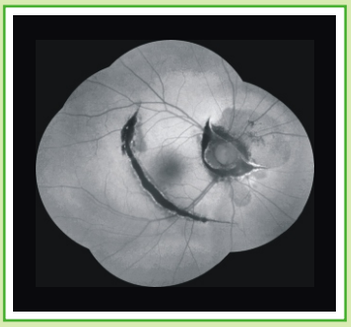

The Cover page Image :

Winner of the VRSI Jan 2021 Retina Image Contest - "Traumatic Choroidal Tear - An Autofluorescence Montage"

Image Description :

This is an ocular fundus autofluorescence montage image of traumatic choroidal tears in the parafoveal and peripapillary areas due to injury with a cricket ball. FAF brings out the deeper details of the retinal pigment epithelium and choroidal splitting in such cases much more vividly than color or red-free images.

Image contributed by

Dr. Mukesh Porwal, Rajkot

STALWART SPEAK

Can we differentiate PCV from typical neovascular AMD without ICGA?

Dr. Gemmy Cheung
Dr. Chinmayi Himanshuroy Vyas
Singapore National Eye Center
Singapore

INTRODUCTION

Polypoidal choroidal vasculopathy (PCV) is a subtype of neovascular age-related macular degeneration (nAMD) characterized by nodular dilatations arising from neovascular networks that ramify mainly in the subretinal pigment epithelial space.[1-5] It has been estimated that up to 50% of nAMD cases in Asia are of the PCV subtype, whereas this proportion is estimated to range between 10% and 20% in White populations.[6-9]

The recent clinical trials EVEREST II and the PLANET have reported significant improvement in visual outcomes with Anti-vascular endothelial growth factor (VEGF) therapy for management of PCV.[10-14] However its effect on polypoidal lesions closure has been variable, leaving clinicians uncertain as to the long-term outcomes of PCV treatment.[13-14] Few clinical series describing the treatment outcomes of nAMD also noted a poorer response to anti-VEGF monotherapy in eyes later found to have PCV variant.[15-16] For these reasons, distinguishing PCV from typical nAMD is desirable and clinically important.

Indocyanine green angiography (ICGA) is considered as the current gold standard modality for diagnosis of PCV, however it is an invasive and a time-consuming procedure.[4,17,18] Moreover ICGA performed with flash systems that capture single frames are less sensitive for diagnosis of PCV.[8,9]

In contrast, spectral-domain OCT provides high-resolution images, is quick and non-invasive, ubiquitously available and is the mainstay imaging method for diagnosis and monitoring of nAMD activity and guiding retreatment. More recently, it has been proposed that a combination of nonICGA-based features may yield high sensitivity and specificity for differentiating PCV from typical nAMD eliminating the need for ICGA.[19-29]

APOIS PCV WORKGROUP

The Asia-Pacific Ocular Imaging Society (APOIS) PCV Workgroup was formed as an associate member society of the Asia-Pacific Academy of Ophthalmology to promote the application of ocular imaging in the understanding and management of PCV worldwide.

An international panel of retina experts in age-related macular degeneration was assembled as a part of the APOIS Workgroup. The consensus panel members were selected from Asia, Europe, and North America on the basis of previous notable scientific contributions to the field of retinal imaging in nAMD and PCV. The first publication from this workgroup was recently published in Ophthalmology.[30]

Consensus Nomenclature

Initially, consensus meetings were held to discuss the

nomenclature, terminology, and diagnostic criteria for PCV, and based on these discussions, consensus was achieved for an updated nomenclature reflecting the latest understanding based on advances in imaging technologies and histologic reports.

The panel's consensus was that PCV should be considered a variant of type 1 neovascularization within the age-related macular degeneration spectrum. For describing the lesion components, the terms polypoidal lesion and branching neovascular network were recommended. Specifically, the term polypoidal lesion (PL) was preferred over 'polyps' as multimodal imaging and histological studies have shown that these lesions are vascular in nature with a central lumen for blood flow, as opposed to solid, fleshy lumps in true polyps. The term 'aneurysmal lesion' was also discussed within the panel. The consensus was that while some lesions do show aneurysmal appearance, many polypoidal lesions have complex configuration and internal structure. Some appear to be a coil of vessels with localized dilatation within segments. Without histology, the panel felt the resolution by current imaging modalities is not adequate to confirm that all these lesions are aneurysms.

Regarding the branching neovascular network, the panel recommended updating the widely used term 'branching vascular network' to branching neovascular network in order to recognize the neovascular nature. This follows multimodal imaging and histological studies which place this lesion in a plane above the Bruchs' membrane and below the retinal pigment epithelium. Hence, the term branching neovascular network clarifies that this lesion is not intrachoroidal. Another term, 'pachychoroid neovasculopathy' was also discussed. The panel recommended this term should be reserved for etiologic discussion.

Non Indocyanine Green Angiography Diagnostic Criteria

The panel further evaluated the performance of a set of non-ICGA features based on combinations of spectral-domain (SD) OCT and fundus photography to differentiate PCV from typical neovascular AMD compared to ICGA as gold standard. An initial list of 11 signs were selected based on literature review and suggestions by panel members. These features were evaluated by the panel members in a masked manner in a test set of eyes with PCV and typical nAMD. The performance of each feature in differentiating the two lesion subtypes was evaluated (Table-1).

Nine out of the initial 11 features were retained for analysis of combination set(summarized in Table-2, examples included in figure-1). Combination of sub-RPE ring-like lesion, en face OCT complex RPE elevation, and sharp-peaked PED was selected as the final diagnostic set (AUC 0.90, sensitivity 0.75, specificity 0.91, positive predictive value 0.93, negative predictive value 0.68). This scheme was validated (accuracy of 82%) in an independent dataset of 80 eyes selected from Singapore and Italy to ensure the validity in both Asian and white populations.

For clinical application, we recommend this diagnostic set of 3 features can be applied as a screening tool (Table-3). When all 3 features are present, the likelihood of PCV is high (PPV 0.93). If anti-VEGF monotherapy is used, these cases should be evaluated at month 3. If initial response is suboptimal, an ICGA should be considered to confirm the diagnosis of PCV. Management options to consider for sub-optimally controlled PCV include switching anti-VEGF agent and combining anti-VEGF therapy with photodynamic therapy. It is also worth noting that the negative predictive value of this diagnostic set is 0.68. Hence eyes which do not display these features may still be harbouring PCV, particularly lesions with small, equivocal polypoidal dilatations.

Future directions

The APOIS PCV workgroup aims to continue to study clinically relevant questions related to PCV. In the next project, the group plan to evaluate non-ICGA based diagnostic criteria in previously treated eyes. Other areas which the group have plans to explore include comparison of choroidal background and macular atrophy between Asian and white populations.

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Table 1: performance of individual criteria from highest to the lowest AUC

	AUC (95% CI)	Sensitivity	Specificity	PPV	NPV
1. Sub-RPE ring-like lesion	**0.83 (0.76-0.89)**	**0.81**	**0.87**	**0.88**	**0.79**
2. Enface OCT-complex RPE elevation	**0.82 (0.75-0.88)**	**0.80**	**0.84**	**0.85**	**0.79**
3. Sharp-peaked PED	**0.79 (0.71-0.85)**	**0.79**	**0.79**	**0.79**	**0.79**
4. Orange nodule	0.74 (0.67-0.81)	0.69	0.84	0.88	0.61
5.Complex or Multilobular PED	0.67 (0.59 -0.75)	0.76	0.68	0.61	0.81
6.Thick choroid with dilated Haller's layer	0.71 (0.63-0.78)	0.63	0.74	0.81	0.54
7.Double layer sign	0.65 (0.57-0.73)	0.78	0.60	0.42	0.88
8.Extensive subretinal hemorrhage	0.60 (0.57 – 0.72)	0.62	0.58	0.64	0.72
9.Fluid compartment	0.56 (0.48– 0.64)	0.57	0.52	0.41	0.65

The top 3 criteria (in bold) were selected in the final diagnostic set

TABLE 2. non indocyanine Green angiography features evaluated for predictive value of polypoidal choroidal vasculopathy

	Features	Detailed description
	OCT features	
1	Sharp peaked PED (Fig 1A)	• Narrow-peaked PED, with inverted "V" configuration. Also described as "thumb-like protrusion" • Sharp vertical incline >70 on at least 1 side • Height: base-to-width ratio >1
2	Sub-RPE ring-like lesion (Fig 1B)	• Round structure seen under PED • May have hyporeflectivecenter and hyperreflective outline • Reflectivity of center may vary in intensity
3	Complex multi-lobular PED (Fig 1C)	• Notch in PED, resembling an "M" (white arrow) • Multilobular PED
4	Double layer sign (Fig 1D)	• Undulating RPE line that is separated from BM line underneath
5	Thick choroid with dilated haller's layer vessels (Fig 1E)	• Thick choroid for age and axial length or refractive error • Any eye with subfoveal choroid thickness ≥300 mm • Dilated Haller's layer vessels that occupy the full thickness of the choroid with attenuation of overlying choriocapillaris (white arrowheads denote the scleral choroidal interface)
6	Fluid compartment (Fig 1F)	• Predominant SRF with or without mild IRF
7	Enface OCT complex RPE elevation (Fig 1G)	• Hyperreflective branching vascular network connecting multiple PEDs
	Fundus CFP features	
8	Extensive subretinal hemorrhage (Fig 1H, black arrow)	• Subretinal or sub-RPE hemorrhage≥4 DD
9	Orange nodule (Fig 1H, asterisk)	• One or more orange subretinal round elevation

CFP= colour fundus photography ; DD= disc diameter ; IRF = intraretinal fluid ; Ped pigment epithelial detachment ; RPE = retinal pigment epithelium ; SRF= subretinal fluid

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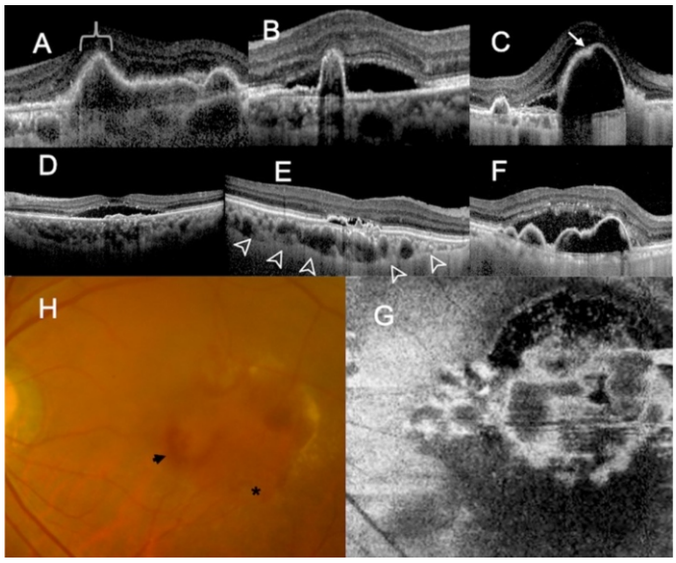

Figure-1: Nine features evaluated for non indocyanine Green angiography diagnosis of polypoidal choroidal vasculopathy. Refer to table 2 for detailed description. (**A-F**) Cross sectional OCT based features, (**G**)1 feature based on en face Oct, and (**H**) features based on colour fundus photography. A, Sharped peaked pigment epithelial detachment (PED). B, Sub-retinal piment detachment ring-like lesion. C, Complex or Multilobular PED (notch within the outline of PED , white arrow). D, Double layer sign or shallow, irregular retinal pigment epithelium (RPE). E, Thick choroid with dilated Haller's layer vessels (choroidal interface highlighted by white arrowheads). F, Predominance of subretinal fluid. G, complex RPE elevation observed with en face OCT. H, Extensive subretinalhemorrhage (black arrow) Orange nodule (asterisk)

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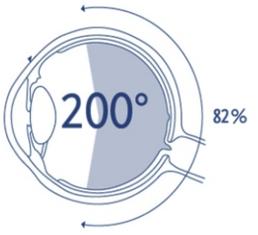

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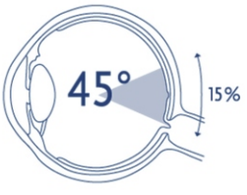

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SPOTLIGHT

Challenging Scenarios in Neovascular Macular Degeneration

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CASE 1

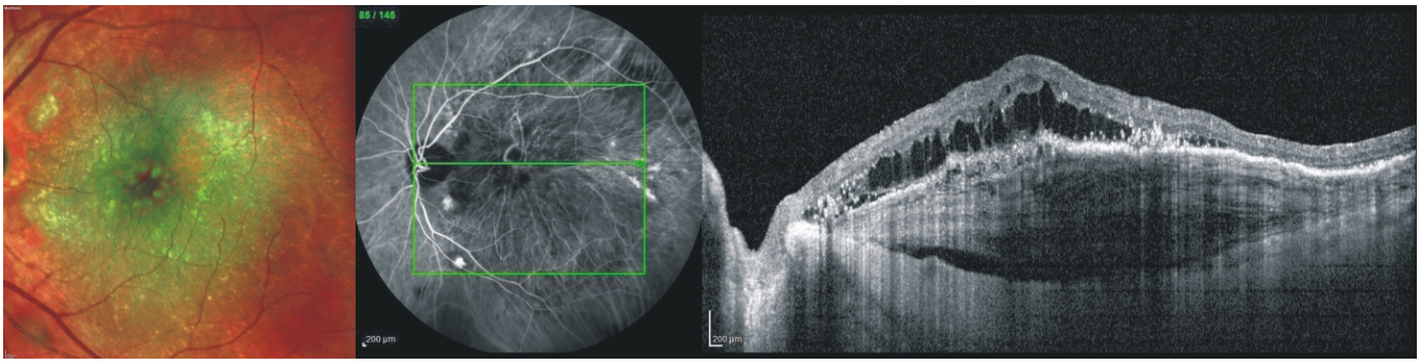
MS : 55 yr old male presented with defective vision in his only seeing eye. The other eye had lost vision due to a recent postinjection endophthalmitis. The BCVA was CFCF in the phakic and cataractous right eye and 6/24p in the pseudophakic left eye. The right eye ultrasonography revealed closed funnel RD. The left eye was treated with 12 antiVEGF Ranibizumab injections elsewhere over a period of 3 years and at presentation he had an occult CNVM with a diffuse PED with multilayering.

1. **Do we need to switch therapy considering the fact that he is a nonresponder or consider the case as inadequately treated**

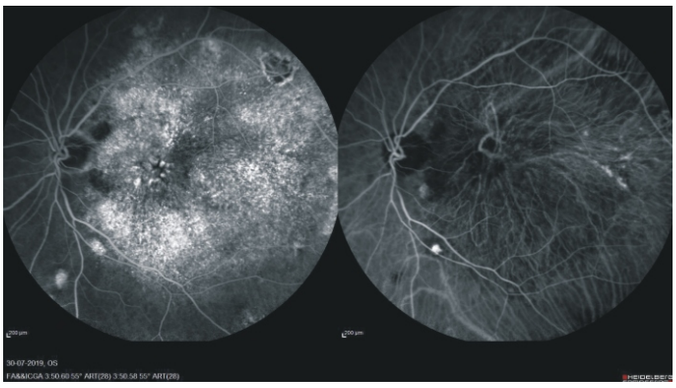
MPS : It is possible that the patient has been sub optimally treated considering 12 injections/3 years. However, there is active disease, only eye, large network and possible PCV. Considering all above, prefer switching the patient to aflibercept (loading dose followed by T&E. If the response is subnormal, I will consider adding intravitreal steroid (PCV, presence of hypereflective dots). One however needs to consider the risk of steroid induced elevated IOP in this one-eyed patient.

PS : I would consider switch to another anti-VEGF. Presence of multilayering suggests chronicity and considering that it is PCV that we are dealing with, current literature shows that Aflibercept gives better response especially when considering monotherapy.

DG : I think it would be reasonable to switch and include PDT



Multicolor image reveals greenish hue to the occult CNVM area with exudation suggestive of chronicity. SD OCT reveals irregular RPE, underlying zone of CNVM tissue with multilayering lamellae underneath. Note the choroidal cleft seen.



Combined FFA/ICG angiography revealed a large extensive occult leakage with polps seen inferiorly on FFA and a mature centrifugally spreading network with inferior polyp staining on ICGA.

with the goal to both reduce the persistent exudation and reduce the treatment burden. Depending on the response to PDT,I would also consider switching to aflibercept in this case. EVEREST II study showed that combination therapy was superior to Ranibizumab monotherapy in improving BCVA and better in achieving complete polyp regression.

GM : To differentiate a non-responder from inadequate treatment, I would look at the number and interval since the last Ranibizumab injection. If the patient had received at least 3 monthly injections 1 month prior to the presentation, I would consider him as non-responder with persistent IRF and consider switching to Aflibercept injection. If he had received irregular treatments, then I may repeat Ranibizumab to see the therapeutic response and plan accordingly.

RC : I believe that the patient is perhaps not a total Non-responder but showing a partial response because he maintains 6/24 vision over 3 years. If cost is not an issue, it would be worthwhile trying Aflibercept. If a better and more sustained response is seen with the switch, then this can be continued.

RR : I will consider switching to a different Anti VEGF, preferably Aflibercept

2. Is traditional PDT safe in such large lesions or do we target the mature feeder vessels

MPS : I would not consider a standard PDT for this lesion, considering the size of lesion which can result in large area of RPE atrophy. If at all, targeted PDT to feeder vessel can be considered. The lesion does seem to have a central feeder. One needs to look at the early phase of ICG angiogram to identify the feeder vessel.

PS : I would not prefer to do PDT for such a large occult CNV. Laser photocoagulation of the extrafoveal polyps can certainly be done to reduce the number of injections.

DG : I would prefer half fluence PDT in such cases. If the response is suboptimal, I would consider repeating another half fluence PDT.

GM : Reduced fluence PDT combination treatment is currently reserved for Anti VEGF non-responders in Wet AMD and is best directed towards the central feeder vessel to reduce the treatment area and thereby reducing the associated risks while achieving effective regression of CNVM.

RC : PDT may be deleterious in such large lesions. I am hesitant in giving very large PDT spots especially where the exact fovealcentre cannot be spared.

RR : I will refrain from doing PDT over such a large lesion.

3. Does Multilayering merit a different therapeutic approach

MPS : Multilayering has been shown to be associated with chronic anti-VEGF therapywith preservation of vision. Primary therapy in these eyes would still be anti-VEGF therapy with regular follow-up.

PS : Multilayering of PED in Type 1 CNV usually reflects chronicity of disease probably due to suboptimal response inspite of multiple antiVEGF injections. The fibrotic component increases and the contractile forces can some times lead to massive subretinal haemorrhage. Switching antiVEGF injections can some times show a better response.

DG : Multilayering is seen in vascularized PEDs and is thought to represent subRPE lipid due to the chronic exudation and are often seen with CNV adherent to the RPE monolayer. They represent a more unstable morphology and may need chronic treatment. In such cases with persistent exudation it is also important to exclude intraretinal and subretinal pseudocysts, which may not indicate active exudation.

GM : Multilayering of FVPED is a sign of progressive sub RPE fibrosis of the neovascularization and hence a sign of disease stability, suggesting that this patient may require a less aggressive treatment course.

RC : I have seen a few cases of multilayered PED that may have more than one element of CNV. These cases may thus be more resistant with a poorer prognosis and may require more injections to maintain visual acuity

RR : I feel that Multilayered PEDs do not merit a different therapeutic approach. It just represents localization of the neovascular process in the sub RPE space and hence can be considered a better prognostic indicator.

4. What is the importance of choroidal clefts?

MPS : Choroidal clefts have been associated with increased risk of RPE tear, subretinal hemorrhage and poor vision. Hence a close follow up and judicious use of anti-VEGF agents will be required, balancing between keeping the macula dry vs. aggravating complications such as RPE tear and subretinal hemorrhage.

PS : Choroidal clefts seen on structural OCT scans are known to form due to combination of factors like the contractile forces of the sub RPE material and leakage from the subRPE active lesion. These are often associated with presence of subretinal fluid as well and suggest presence of activity and hence the need for treatment. Also, these are known to be associated with suboptimal response to anti-VEGF, subretinal fibrosis, higher risk of RPE tears and poor visual outcomes.

DG : The subRPE CNV is thought to lead to contractile and hydrostatic forces which leads to development of these clefts. While it is not clear if clefts are significant by themselves, there is some thought that they may be a risk factor for complications such as RPE Rip or subretinalhemorrhage which adversely impact vision.

GM : Choroidal cleft formation is seen in FVPED while on anti VEGF therapy and follows progressive sub RPE fibrosis of the neovascularization.

RC : The exact importance of choroidal clefts is not clear. These may be a result of contraction of fibrovascular tissue under the PED or due to misdirection of subretinalfluid. In some studies, a higher risk of RPE RIP is also reported. This has to be kept in mind and counselled, but the overall management essentially remains the same.

RR : Choroidal cleftis an imaging finding that occur probably due to contraction of the multilayered CNVM tissue complex. Though the presence of choroidal clefts does not alter mytherapeutic approach, I have noted disappearance of choroidal clefts after anti VEGF injections.

TAKE HOME PEARLS

Type 1 or occult CNVMs often require chronic anti VEGF therapy compared to type 2 (Classic CNVM) or type 3 CNVM (RAP). Before changing anti VEGF agents, it is important to assess if the patient is inadequately treated or is a real non responder. Inadequately treated patients are those with poor compliance and may be given the benefit of continuing treatment with the same drug with a standardised protocol unless there are obvious indications for a switch. Though standard PDT has been advocated in PCV eyes, there is now a growing interest in reduced fluence PDT especially in large lesions. Retreatment if required could however, include standard PDT and targeting the feeder vessels. Multilayered PEDs are seen commonly in type 1 CNVM eyes who undergo chronic anti VEGF therapy and are believed to be sequestered CNVM with good preservation of vision. These eyes are essentially managed by anti VEGF therapy, though switching agents may help in resistant cases. Choroidal clefts may be due to mechanical effect or represent exudative process. The latter responds to anti VEGF therapy and can be identified by co existant exudative features in the subretinal and intraretinal compartment. Choroidal clefts have been often associated with a high risk of RPE tears, subretinal hemorrhage, subretinal fibrosis and poor vision and merits careful follow up.

CASE 2

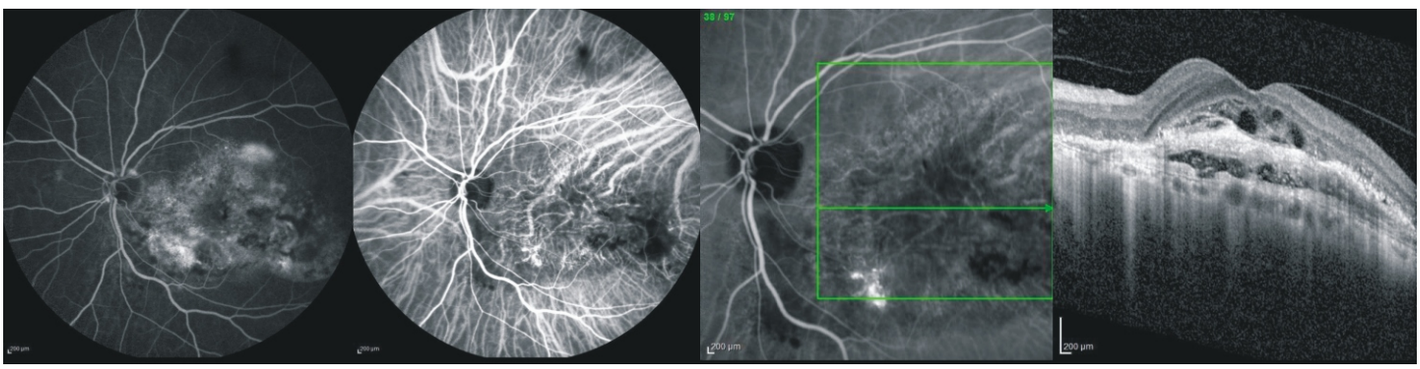
MS : 64 year old gentleman presented with recent onset defective vision in his left eye. The BCVA was 6/12 in his right eye and 5/60 in his left eye. He is a known diabetic on insulin and OHA and gives history of angioplasty 6 months back and minor stroke 2 years back. He discontinued both eyes antiVEGF treatment after the cardiac event. He had received 2 Ranibizumab injections in the right eye and 3 injections in the left eye prior to the cardiac event. He is currently on dual antiplatelets. Combined FFA/ICGA angiography and SD OCT was done.

1. **Treating the right eye; Do we restart loading dose or will a PRN schedule suffice. Is PRN more safe than TAE in such situations?**

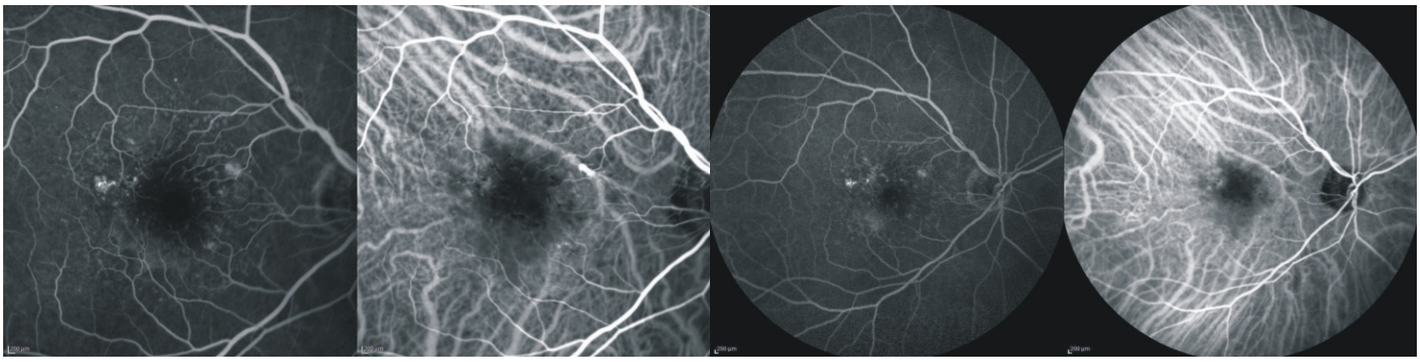
MPS : Considering that there is SRF and this is the better eye, this eye needs treatment. As the cardiovascular event was 2 years back and angioplasty 6 months back, it may be advisable to restart the therapy with loading dose followed by T&E at least. Though increased anti-VEGF exposure may be associated with increased systemic risk, this has not been borne out of studies. In fact, Chakravarthy et al have shown discontinuous treatment to be associated with more systemic adverse events and mortality.

PS : Considering the systemic risk factors, monthly loading dose can be avoided. After the first injection itself, the patient can be on the treat and extend regime instead of PRN with slowly increasing the interval between the injections. Once good resolution is seen, one can shift to observe and extent.

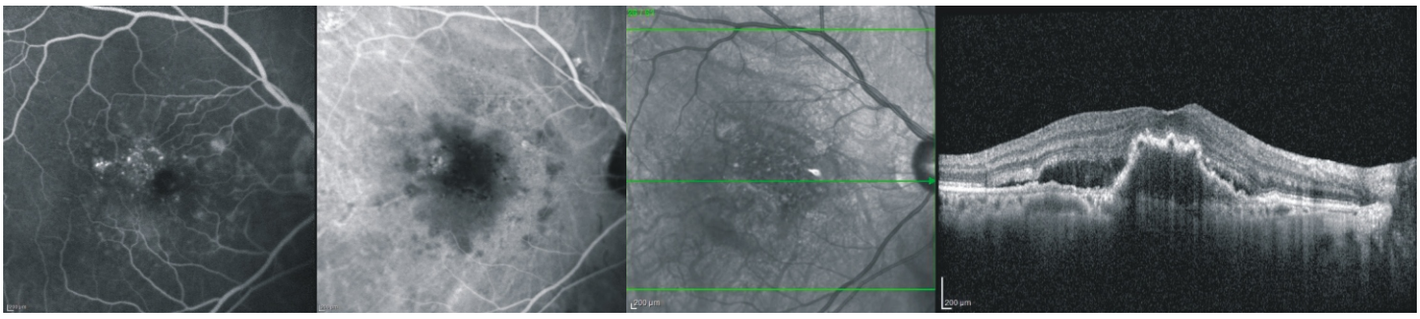
DG : I would start with a single dose and assess response. It is difficult to stratify risk between PRN and TAE since we don't know how many injections he would need.



Left eye of the patient with predominantly scarred CNVM with residual IRF



Right eye of the patient with combined FFA/ICG angiography (early and Mid frames)revealing juxtafoveal occult leakage and focal hyperfluorescent lesions extrafoveally on FFA and ICGA revealing an illdefined juxtafoveal network and no evidence of polyps.



Right eye of the patient with combined FFA/ICG angiography late frames revealing juxtafoveal leakage on FFA and staining of the network on ICGA. SD OCT reveals irregular PED with internal reflectivity and SRF.

GM : Since the RE shows a small network, this eye may require less aggressive treatment considering his systemic risk and I prefer to treat him on a PRN basis in consultation with his cardiologist.

RC : For the right eye, PRN schedule can be followed. If response is good and sustained for few months, then the same can be continued. If injections are required very frequently, PDT may be added to treat the juxtafoveal lesion.

RR : I will start with a loading dose followed by TAE regimen

2. **When can we give antiVEGF after an ATE and do we need a physician clearance for all patients who are advised anti VEGF therapy? What is your protocol on stopping antiplatelets ?**

MPS : Studies have suggested resuming treatment after 3 months but I wait until 6 months. Physician clearance is more of a placebo effect as there is no defined parameter by which the safe period or safety in a given patient can be determined. Consideration to altering anti-platelet agent therapy may be given in patients with hypertension towards minimizing risk of retinal / subretinal hemorrhage, but not for administering intravitreal injections. Trials on association between subretinal hemorrhage and anti-platelet agents have yielded contradictory results. Also one needs to remember that these drugs may have been prescribed for potentially lifesaving reasons and it may not be possible to stop them to reduce the risk of subretinal hemorrhage.

PS : Usually a period of 6 months after a ATE is considered safe. Physician clearance for all patients who are advised anti-VEGF therapy is not necessary. But an active effort to take history regarding any cardiac or thromboembolic

events recently should be taken and documented. Antiplatelets have not been found to increase risk of subretinal hemorrhage especially if the lesion size is less than 1DD and hypertension is kept under control. However in the presence of any risk factors if one considers to stopantiplatelets, they should be stopped at least 72 hours before the treatment.

DG : I do not stop any blood thinners for anti-VEGF therapy. I also do not delay anti-VEGF after ATE if vision will be impacted. However if the exudation can be controlled with intravitreal steroids, or can be observed, I offer that and defer anti-VEGF for a year.

GM : Though stopping anti-platelets is not required for anti-VEGF injections, physician clearance is preferred for patients with ATE risks. I would consider treating such patients earliest by 3 months after an ATE event.

RC : Anti-VEGF can be given after 6months, perhaps even after 3 especially if one-eyed. I don't think physicians can provide a clear answer to the basis of clearance or no clearance to ocular anti-VEGF therapy. Thus after waiting for 3-6 months, which may be sufficient for collateral development , a calculated risk of giving the anti-VEGF can be undertaken. I would not stop any antiplatelets for an intravitreal injection

RR : Usually I wait 6 months after an episode of ATE. I take a cardiologist clearance before injecting in these patients. I don't stop anti platelets prior to Anti VEGF injections.

3. How do we manage the left eye. Is it worth giving more antiVEGF injections in partially scarred CNVM (especially considering the fact that he had multiple ATE events).

MPS : I would wait to see the effect of treatment in the right eye as there is a possibility of cross-over beneficial effect as well in the left eye. If the vision recovery in the right eye is good and adequate to suit patient's needs, we can desist from treating the left eye. Waiting will also allow increasing the safety window before considering treating the left eye.

PS : Priority should be given to safeguard the vision of the better eye. With a BCVA of 5/60in the right eye, I don't think it is really worthwhile to chase the SRF or the IRF in this eye, especially considering the fact that he had multiple ATE events.

DG : It would be reasonable to consider treating the left eye but only after the right eye exudation is controlled.

GM : Since the LE shows a partly scarred CNV post treatment, this eye may be considered for a less aggressive treatment considering his systemic risk. I would prefer to treat him on a PRN basis in consultation with his cardiologist.

RC : Considering the multiple ATE events and the fact that the right eye now requires anti-VEGF therapy, I would probably not treat the left eye further. But if only the left eye was involved I would assess the structural integrity of the retinal layers of the eye with scarred CNV. If the retinal layers appear good on OCT, I would go ahead with atleast one anti-VEGF. If it does not improve vision at all then I would offer no further treatment. Sometime we do find a good response and in such cases treatment could be continued. If vision is 3/60 or less it is reasonable to assume that the patient is not using much of the central retina and it may not be worthwhile injecting, especially if the OCT is also very disorganized.

RR : I would not advise any further injection in left eye

4. How do you define good vs poor responder?

MPS : Good responder is one who shows complete / partial resolution of fluid, improved / maintenance of vision over the course of injections. Consideration for switch can be taken after 3 injections. At least a minimal change in the OCT parameters after the first or second injection will make me persist with the same agent.

PS : A morphological poor response can be defined as less than 25% decrease or no change in parameters like SRF, CRT or IRF on OCT, seen after 1 month of anti-VEGF injection. Any increase in OCT parameters or an increase in size of lesion inspite of treatment is also taken as poor response. Poor functional response can be defined as no improvement or less than 5 ETDRS letters improvement in BCVA after 1 month of anti-VEGF treatment. “Recalcitrant CNV” has been defined as persistence of IRF or SRF on SD-OCT at <30 days after the last of six injections at monthly intervals.

DG : Good responders are those with resolution or significant improvement in fluid following 3 injections. Poor responders would include those who had <25% reduction

in central subfield thickness with persistent fluid following 3 injections.

RC : Improvement in visual acuity and reduction of both IRF and SRF indicate a good response. In poor responders or non-responders both may not change. Other than the immediate response to a single injection one should also consider the amount of time the effect of the intravitreal lasted. In patients who require an injection every 4-6 weeks, alternate anti VEGF agents, PDT or addition of steroid may be required. In those who maintain remission for 3-4 months the ongoing therapy might itself be sufficient.

RR : To me good response means absence of SRF, IRF and reduction of retinal thickness more than 75% from baseline anatomically. Functionally a gain of more than 5 letters on ETDRS scale is considered a good response. Poor response is defined as less than 25 % decrease in retinal thickness, persistent or increase in SRF /IRF or PED height. Functionally a decline or less than 4 letter gain can be considered as poor response.

TAKE HOME PEARLS

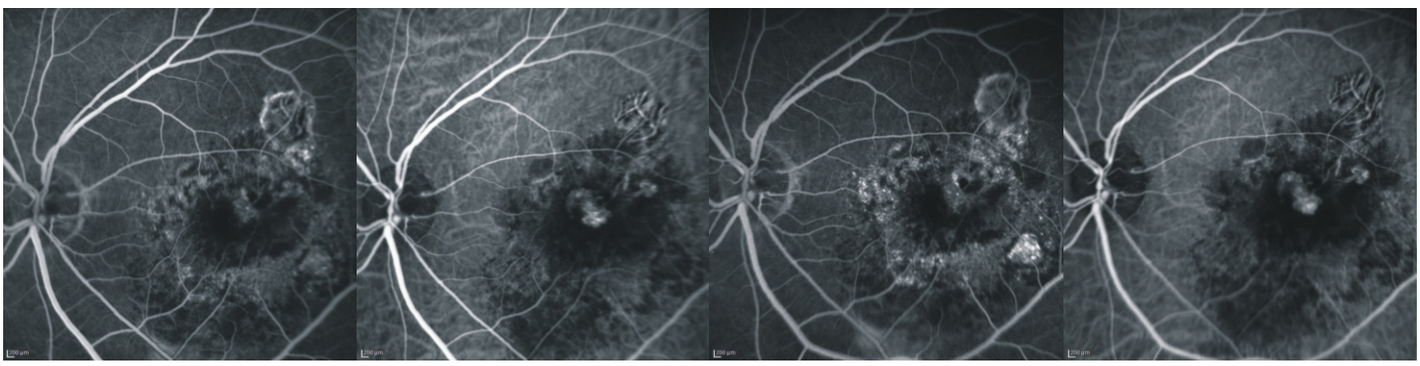
After a documented ATE, anti VEGF agents are best avoided for 3-6 months. Though there is no need to stop antiplatelets before anti VEGF injections, they have to be used with caution in hypertensives with large CNVM lesions due to the risk of possible subretinal hemorrhage. Obtaining a physician's opinion before anti VEGF therapy is not mandatory but in situations where there is a past ATE, it may be prudent to discuss the same with the treating physician. Good response to anti VEGF therapy includes anatomical and visual criteria after atleast 3 consecutive injections. Anatomical criteria includes complete resolution or partial resolution of fluid (IRF> SRF) and attaining atleast 25% reduction of the fluid and l thickness. Visual criteria includes demonstration of visual improvement of atleast 5 letters from the baseline. Often clinicians look for these changes even after the first or second injections which could give them a guide as to how the agent is working in that particular case.

CASE 3

MS : 60 year old gentleman presented with recent onset metamorphopsia. He has no systemic diseases and gave H/O RTA 11 years back and was treated conservatively for his eye problems then. The BCVA was 6/9 in the right eye and 6/12 in the left eye. The right eye had a mild cataract and few drusenoid deposits. The left eye revealed evidence of subfoveal occult disease. A combined FFA/ICG angiography and OCT was done. OCT revealed SHRM with multipeaked PED with variable internal reflectivity. The temporal smaller polyp showed pulsations

What are the treatment options

1. **AntiVEGF Monotherapy or combination therapy with PDT. When and what do you treat with traditional laser in PCV.**



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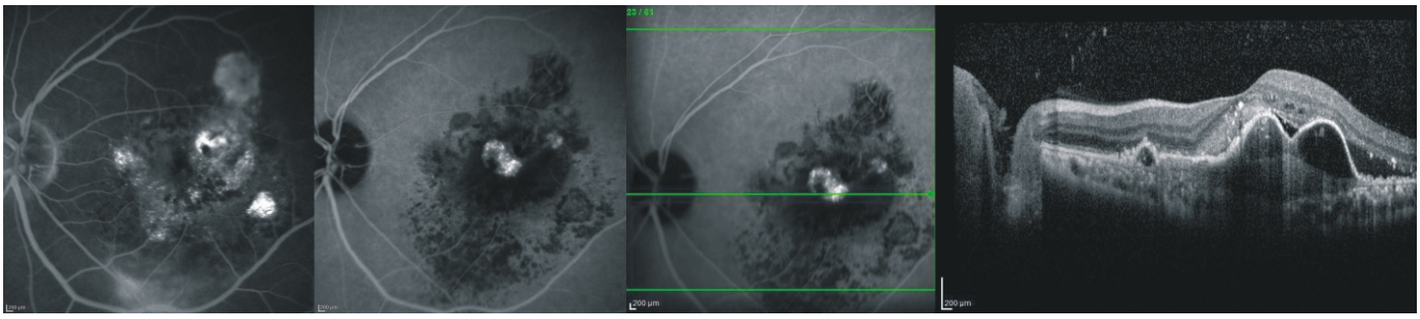

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MPS : I tend to prefer anti-VEGF monotherapy with aflibercept initially. I am using PDT less often these days due to limited availability of the dye and laser equipment, better visual results with anti-VEGF monotherapy and frequent recurrences despite PDT in some patients. Traditional laser is preferred in extrafoveal single polyps / cluster with only SRF involving fovea. However I would not laser when the leaking polyp is part of the PED complex which involves the fovea.

PS : In presence of PEDs, PDT is best avoided. One can start with monotherapy, preferably with Aflibercept. Once there is significant decrease in the PEDs, PDT can be considered for subfoveal polyps to reduce the number of injections required. Focal laser to the extrafoveal polyp can be combined with monotherapy. This can be done in beginning itself and I find it very useful in the management of PCV.

DG : I would use either anti-VEGF monotherapy or combination with PDT.

GM : In view of the good vision and presence of SHRM, I would Initiate Aflibercept monotherapy with 3 loading doses and keep deferred PDT as an option based on the response as per the Planet study guidelines. Temporal extramacular polyps may be treated with Focal Laser.

RC : I would start with monotherapy and depending on the patients affordability, I would suggest Aflibercept or Ranibizumab. The extrafoveal polyps can be dealt with direct focal laser. If after a few injections, the disease seems to be becoming chronic and the central polyps also persist, I might add PDT. The availability of PDT however is currently a problem in India.

RR : I will do Combination therapy in this case. I use tradition thermal laser for well definedextrafoveal polyps.

2. Role of full fluence vs low fluence PDT currently in PCV

MPS : I would prefer to use half fluence PDT currently. In eyes where there is associated subretinal hemorrhage or PED with turbid fluid masking the complex, I may prefer standard PDT.

PS : Reduced fluence PDT has been shown to be equally effective in the PCV and safer. There is a less incidence of massive subretinal hemorrhage and RPE tears with low fluence PDT.

DG : I would perform half-fluencePDT and repeat it as needed.

GM : Though the evidence based recommendation for PCV is standard Fluence PDT, in cases with good vision (better than 6/12), reduced Fluence PDT is preferred. I would reserve Standard fluence PDT for any recurrences.

RC : I generally prefer full fluencePDT for PCV and do half fluencePDT in CSCR

RR : Currently standard fluence PDT is preferred in PCV.

3. Is there a preferred antiVEGFagent and protocol in eyes with such PEDs?

MPS : I would prefer to start with aflibercept in PCV associated disease but in some patients, have found aflibercept resistant disease to respond to ranibizumab as

well. In the presence of associated hypereflective foci, I believe that addition of intravitreal steroid to anti-VEGF agents may aid in treating resistant disease.

PS : In AMD patients with PED that are refractory to Ranibizumab and Bevacuzumab, switch over to Aflibercept may show the desired response. Increased potency of CNV contraction with Aflibercept should however be kept in mind. Though the risk of RPE rips is lower with any of the antiVEGF agents as compared to PDT, the patients should be counselled regarding the same. Risk of RPE rips is particularly high in eyes with height of PED more than 400-600 microns especially with loading dose. These patients should be followed up more closely

DG : There is some data that Aflibercept and Brolicizumab may show a better anatomical response in such eyes.

GM : I would Initiate Aflibercept monotherapy with 3 loading doses and would follow up as per the Planet study guidelines.

RC : Aflibercept would be the preferred agent, but in my practice cost constraints are huge and I end up using Bevacizumab itself in many of these cases.

RR : Aflibercept is the preferred Anti VEGF agents in this setting. I would like to practice a Treat and Extend protocol which has shown promising response in the management of PCV

4. Importance of pulsating polyps and late wash out effect of polyps? Do thinner choroid PCVs behave differently?

MPS : Pulsating polyps are associated with increased risk of hemorrhage. I am not sure of the significance of late wash out effect of polyps. The association between thin choroid and PCV is being recognized as an entity recently and we need to define this entity better and study these cases in greater detail for robust evidence. At present these can only be personal impressions which can be erroneous.

PS : Pulsating polyps have been associated with increased risk of subretinal haemorrhage. Late wash out effect is seen in nonleaky polyps that do not retain dye in the late phase of ICG. Thinner choroid PCV or non pachychoroid PCV are seen more in older age group, associated with drusen and AMD like features and more responsive to antiVEGF than pachychoroid PCV.

DG : Pulsations are helpful to distinguish polyps from other lesions such as large micro-aneurysms, RAP and prominent choroidal vessels. Scared complexes also will not show pulsations. The Everest study had reported that polyps with pulsations may have a higher association with subretinal hemorrhage. Thinner choroids may be more prone to choroidal ischemia and thrombosis after PDT.

GM : Pulsatile Polyps is early frames of ICGA is a classic diagnostic feature of PCV on Video ICG angiography and polyps may demonstrate late wash out or late leak into the sub RPE Space. Polyps seen in thin Choroids, sometimes referred to as 'Polypoidal CNV', behaves more like Wet AMD to treatment and PDT should be used with caution in these eyes in view of the higher risk for choroidal ischemia.
RC : I have not really looked into this aspect

RR : Pulsating polyps have a higher risk of hemorrhagic complications. I have not noticed any difference in treatment response between PCV with thin vis a vis thicker choroid.

TAKE HOME PEARLS

PCV eyes are best managed with Aflibercept monotherapy these days as PDT is currently unavailable freely in our country. A loading dose followed by TAE protocol is recommended but there is always a fear of missed recurrences in our set up with TAE protocols. Eventhough standard PDT has been documented to be effective in multicentric trials, retinologists nowadays use reduced fluence PDT more frequently. Recurrent lesions can be treated with repeat PDT and standard PDT is often adopted. Extrafoveal polyps can be treated with conventional laser photocoagulation and can be added even at baseline while planning antiVEGF treatment in these eyes. Identification of Pulsating polyps are important as these eyes have a high risk of developing massive subretinal hemorrhage and help us identify active disease while evaluating chronic cases. Late wash out phenomenon identified on ICGA is a useful sign which may indicate not so active polyps. PCV eyes with thinner choroids behave just like traditional AMD eyes. These eyes may be associated with drusens, are good responders to anti VEGF therapy and carry a greater risk of choroidal ischaemia after PDT.

CASE 4

MS : 51 yr old male smoker presented with metamorphopsia of the right eye of recent onset. The BCVA was 6/9 in the right eye and 6/6 in the left eye. The right eye fundus revealed a serous PED with overlying reflectivity on OCT. There was no IRF or SRF on OCT. Combined FFA/ICG was done which revealed focal hyper fluorescence on FFA with subsequent irregular pooling of PED. The ICG also confirmed the focal hot spot and late staining of the PED content. OCTA revealed an abnormal network extension at the DCP.

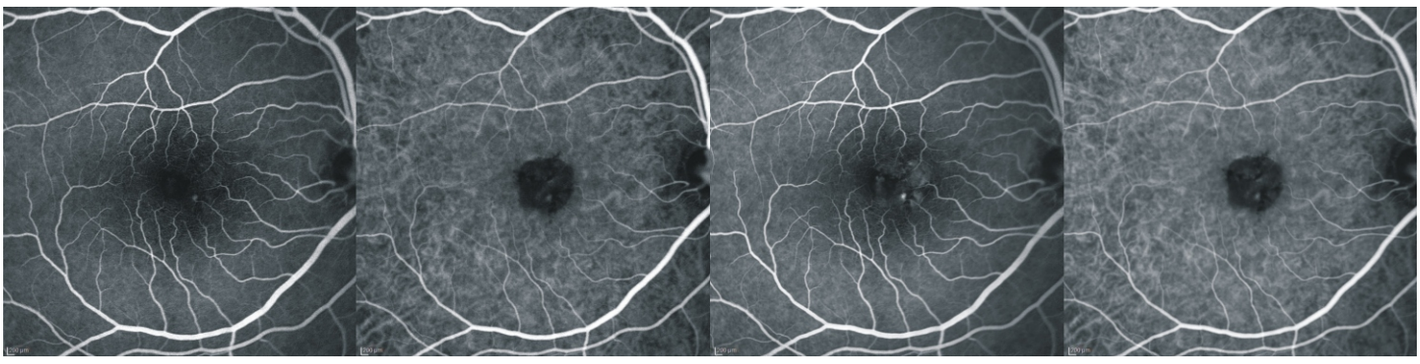
1. **What is the best approach to deal with this lesion? Observe or active intervention**

MPS : Considering that the patient is recently symptomatic, some IRF seen (I can see one temporal to the intraretinal component and a sliver nasally) and a network on OCTA, I would prefer to treat the patient.

PS : On the structural OCT scan, pigment on top of the PED (showing underlying shadowing) suggests chronicity of the lesion. Treatment can be initiated if any progression of lesion in form of SRF or IRF is seen at a close 2 weekly follow up.

DG : I would observe this eye at this stage.

GM : I would consider this case as Vascularised Serous PED subtype of neovascular AMD (with acquired vitelliform deposits), as OCTA shows abnormal network at the nasal edge of the PED. Though the close differential in this case would be Type 3 CNVM with focal hyper-reflective intraretinal lesion with after-shadowing, I do not see the classic Intraretinal cystic fluid, intraretinal hemorrage or



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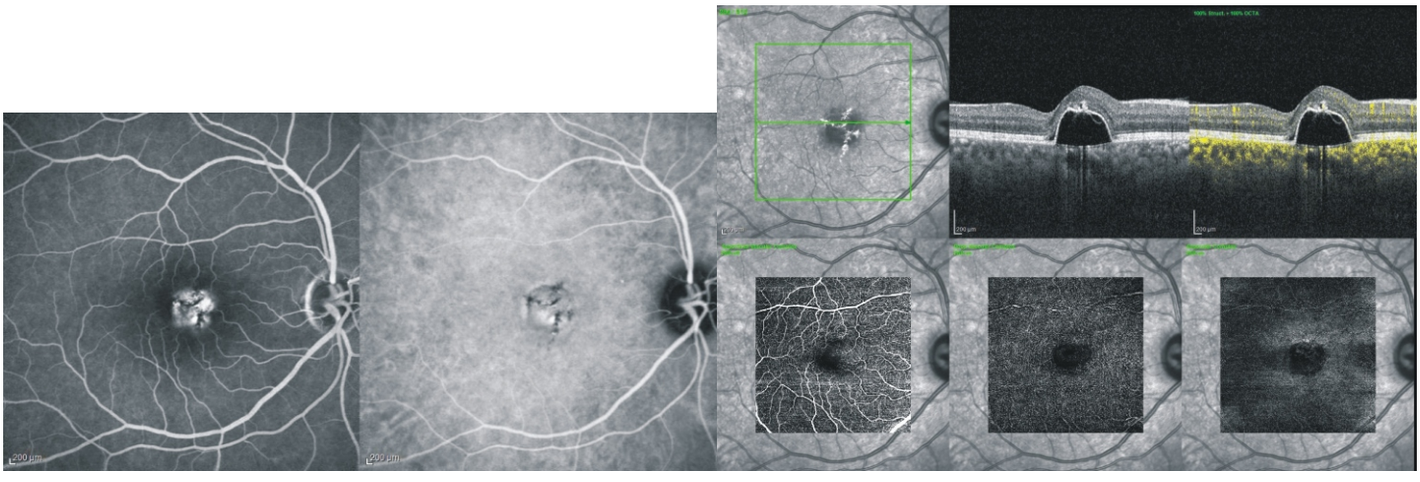


8.52 OCTA

right angled dipping of foveal vessels in this case which probably indicates an early stage. Vascularised PEDs have shown considerable flattening with anti-VEGF inections, especially Aflibercept. If the patient is keen and symptomatic, I would start Aflibercept injections on a PRN basis based on treatment response.

RC : Here you are alluding to a very early identification of a type 3 lesion. I have not picked up many such early cases. But looking at this I would probably advice intravitreal anti-VEGF to prevent worsening and progression to advanced stages

RR : I would like to observe this patient very closely. If the patient develops IRF or SRF or drop in vision, I will plan treatment .

2. Is combination therapy better than anti VEGF monotherapy in type 3 CNVM?

MPS : VEGF monotherapy appears to give similar or better results than combination therapy. Combination with PDT may in fact have an adverse effect on vision due to leakage of dye intraretinally.

PS : Type 3 CNVMs are known to respond well to Anti VEGF monotherapy. The number of injections required to dry up a Type3 CNVM is usually less than Type 1 CNVM.PDT is best avoided because of increased risk of geographic atrophy. In fact even antiVEGF injections in these eyes are associated with increased RPE atrophy.

DG : Type 3 CNVMs are quite sensitive to anti-VEGF therapy

GM : Type 3 CNVM is best treated with anti-VEGF injections and Combination therapy with reduced fluence PDT is reserved for refractory cases.

RC : I have mostly used Anti VEGF monotherapy in these eyes. I have found that younger patients do respond well.

RR : I prefer Anti VEGF monotherapy in type 3 CNVM .

3. What are the associated findings seen in type 3 CNVM eyes?

MPS : Type 3 CNVM are likely to have intraretinal exudation, intra and pre retinal hemorrhages along with a pigment epithelial detachment in stage 2 and 3 and intraretinal neovascularization alone in stage 1. Often Stage 3 disease is associated with a vascularized pigment epithelial detachment and retinochoroidal anastomosis. Telangiectatic vessels may be seen around the intraretinal neovascularization in stage 1.

PS : Associated findings include Intraretinal hemorrhages on fundus examination, mid and late phase hot spot on FFA and ICG an, right angles vessel dipping into RPE on FFA and ICG. Based on typical OCT findings, a type 3 lesion is divided into stages by Freund and Sarraf et al.

Stage 1: presence of cystoid changes and hyperreflective foci in DCP (usually the first sign), subtle OPL disruption, retinal subsidence or descent of the OPL towards the RPE with preservation of the outer retina. Stage 2: Disruption of the inner segment ellipsoid zone and the RPE. Stage 3: Infiltration through the RPE with the development of a serous or mixed serous drusenoid PED and formation of a retinochoroidal anastomosis. On OCTA an early type 3 lesion can present as small “tuft of high flow tiny vessels with curvilinear morphology”

DG : Associated findings include Intraretinal hemorrhage, exudation, cystoid edema on OCT often with fibrin within the cystic spaces.

RC : A deep retinal haemorrhage or associated pseudodrusen may be more commonly seen in eyes developing a type 3 MNV

RR : Intraretinal fluid, intraretinal hyperreflective foci, PED, CME and intraretinal small hemorrhages are associated finding in type 3 CNVM.

4. What is the best way to treat serous PEDS associated with CNVM?

MPS : Vascularized serous pigment epithelial detachments may often need treatment. If associated with good vision and a quiescent CNVM (treatment naïve) one can watch closely for occurrence of intraretinal or subretinal fluid or decrease in vision. When these occur, anti-VEGF therapy can be instituted.

PS : The serous PEDs seen in type 3 lesions respond well to antiVEGF agents. However, the visual gains in these eyes are limited by the increased risk of formation of fibrotic scars as well as GA. Excessive treatment with antiVEGF agents can cause increased GA while delay in treatment may lead to subretinal hemorrhage and subretinal fibrosis.

DG : I would treat these eyes Cautiously. Large serous PEDs have a risk of developing RPE RIPS.

GM : As Vascularised PEDs have shown considerable flattening with anti-VEGF inections, especially Aflibercept, I would inject on a PRN basis based on treatment response.

RC : I would initially treat with Anti VEGF monotherapy. Suubsequently I would assess the area of PED notch on ICG and OCTA- If there seems to be an fibrovascular element there, I may add PDT to that part. However I would not like to give a large spot of PDT to the entire extent of a larger PED.

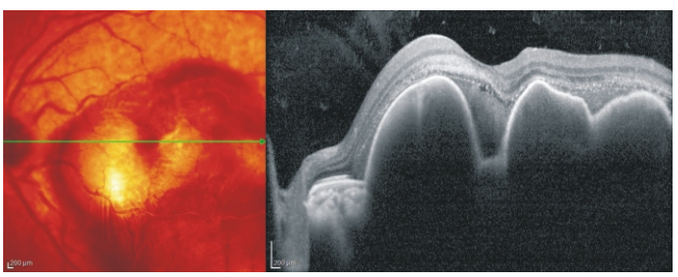
RR : Serous PED with CNVMs are difficult to treat. They are resistant to Anti VEGF agents alone. Combination of Anti VEGF and PDT has shown some response in literature. Currently I would closely observe new serous PEDs that do not produce vision loss or not associated with retinal thickening, hemorrhage, or subretinal fluid.

TAKE HOME PEARLS

Type 3 CNVMs are characterised by intraretinal fluid, intraretinal hemorrhage, telagiectactic vessels and variable reflective PEDs depending on the stage of the disease. The typical appearance of hot spot on FFA/ICGA is diagnostic. OCTA helps to identify early networks in the DCP level with typical high flow curvilinear tuft vessels. These eyes are best managed with antiVEGF monotherapy. PDT carries a risk of greater RPE atrophy in these eyes which even otherwise have a high association of geographic atrophy. Many of these eyes have associated retinal pseudodrusens as well. Serous PEDs with CNVM often needs anti VEGF therapy (Both Aflibercept and Brolucizimab seems to be promising) but show poor visual results. Vascularised PEDs with quiescent CNVMs are observed closely and need active treatment when they become symptomatic with associated fluid on OCT.

CASE 5

MS : 52 year old lady presented with sudden onset defective vision in her left eye. The BCVA was 6/6 in her pseudophakic right eye and CF1 M in her phakic left eye. She is a known hypertensive on poor control of BP and gives history of NSAID use for arthralagia for the last 3 years. She was not on antiplatelets. Her right eye fundus was normal and the left eye revealed fresh subretinal hemorrhage with underlying PEDs. Multicolor imaging with OCT and Combined FFA/ICGA angiography was done.



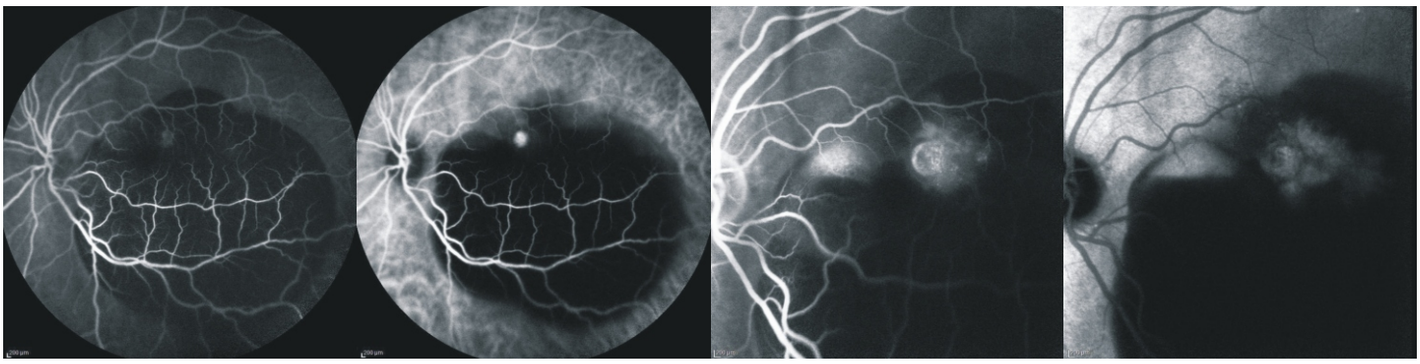
Multicolor image with SD OCT

What are the treatment options;

1. **AntiVEGF monotherapy, Pneumatic displacement, tPA injection, combination therapy.**

MPS : Considering the presence of significant subretinal hemorrhage, I would prefer a combination of pneumatic displacement with anti-VEGF agent. tPA may not be necessary as the subretinal blood component is not too thick and I feel that the elevation is more due to sub RPE blood, which may not be treatable with tPA. The fovea is between the elevations due to hemorrhagic RPE detachment and hence visual recovery and improvement in metamorphopsia may occur only after resolution of the PED's.

PS : The left eye has subretinal as well as subRPE haemorrhage. Since it is recent in onset one can try to displace the hemorrhage away from the macula using pneumatic displacement along with tPA injection and intravitrealantiVEGF.



Combined FFA/ICG angiography; Early and late frames

DG : I would opt for subretinaltPA alone. Pneumatic displacement is also a good option.

GM : Here we have a case of PCV with hemorragic PEDs and thick Subretinal hemorrage at the macula of> 5 disc areas. The best option would be a combination therapy of Intravitreal Injection of antiVEGF, 0.2-0.3 cc C3F8 gas and tPA50µg along with AC paracentesis, followed by 5 days face down position. For thinner submacular bleeds, monthly AntiVEGF injection +/- Pneumatic displacement, may suffice.

RC : I commonly do intravitrealt PA with intravitreal gas injection in such cases. In a few cases I have done vitrectomy with subretinal injection of a cocktail of tPA, air and Anti-VEGF. Both give good results if the bleed is not more than 10-14 days old.

RR : This is a typical case of PCV with subretinal hemorrhage. I would prefer combination therapy of Anti VEGF and pneumatic displacement. Since the bleed looks fresh tPA is not warranted.

2. What is your preferred gas? Have you noticed any risk with pneumatic displacement? Tips to prevent complications

MPS : I usually use C3F8, as small volume of gas is enough and when combined with additional anti-VEGF injection +/- tPA, IOP management is easier. Risks are PVD induction, retinal tears, retinal detachment, vitreous hemorrhage, macular hole, endophthalmitis, elevated IOP etc., Not all complications can be prevented but, one useful tip is that if there are any potential areas of retinal tear formation such as a lattice, these can be barraged prior to the intravitreal injection.

PS : One can use expansile undiluted C3F8 or SF6 depending upon how long the temponade is necessary. But it must be expansile gas especially in absence of vitrectomy. I prefer C3F8. The risk of breakthrough hemorrhage causing vitreous hemorrhage is significant in these eyes. This should be explained to the patient before the procedure because it can result in further decrease in vision. Also, eyes with PCV can have recurrent massive hemorrhage in some cases leading to bleed in all layers of the eye and no perception of light. Systemic hypertension must be kept under control and one must look for other systemic contributing factors to excessive bleeding(eg; NSAIDtherapy) and change such inciting medications under guidance of the treating physician.

DG : I generally use C3F8 gas. Gas can cause a retinal tear in eyes without a PVD. There can also be vitreous hemorrhage with large subretinal hemorrhage even in the absence of a break. During the pneumatic procedure, perform anterior chamber paracentesis. Also consider using a 27g needle if you want to reduce fish-eggs and move the eye after injection so that the injection site is away from the highest point prior to withdrawing the needle.

GM : I prefer 0.2-0.3 cc C3F8 gas

RC : For pneumatic displacement, I use C3F8. Though it stays longer, the injection quantity is less than SF6. So if we were

to combine gas with tPA and anti-VEGF the total volume is less and IOP can be better managed. I have seen one case that developed a macular hole post resolution of the bleed. While removing the needle ensure that this part of the eye is not the highest, otherwise gas may escape through the needle tract. Also careful management of IOP is important. One can administer pre-op Mannitol, do paracentesis during the procedure and give post op Acetazolamide in such cases.

RR : I am comfortable with C3F8 gas. Sometimes breakthrough vitreous hemorrhage can occur, though it can also occur as part of the natural history of the disease or following Anti VEGF injection.

3. Any preference for antiVEGF therapy and why?

MPS : My preference would depends on the etiology of the subretinal hemorrhage. If PCV is suspected aflibercept is preferred. If it is AMD, Ranibizumab / Aflibercepti preferableand Bevacizumabcan bean alternative. Also in a previously treated patient, I would prefer using the sameanti-VEGF agent the patient responded to earlier (if this history is available).

PS : TheantiVEGF I would prefer to use is Bevacizumab or Ranibizumab if I am using tPA as well. Aflibercept when combined with tPA in presence of plasmin may undergo cleavage and its antiangiogenic property may be compromised. I do not have any experience with Brolucizumab in this clinical setting.

DG : I would consider Aflibercept due to the associated large PEDs.

GM : If patient can afford,my choice of antiVEGF is Aflibercept for PCV, as Aflibercept monotherapy has been shown to be an effective alternative to PDT combination.

RC : I have mostly used Bevacizumab or Ranibizumab in such cases.

RR : I would prefer Aflibercept because of its superior efficacy in this setting .

4. When do you prefer to use tPA or surgical evacuation? Is vitrectomy for secondary vitreous hemorrhage consequent to AMD/PCV different?

MPS : The choice of treatment will depend on duration of hemorrhage, thickness of the hemorrhage, presence or absence of associated vitreous hemorrhage, other eye status, ability to maintain position and predominant site of hemorrhage sub retinal or sub RPE. Significant vitreous hemorrhage will obviously necessitate a vitrectomy. Hemorrhages thicker than 500microns and extending beyond the arcades are preferably managed with vitrectomy, subretinal tPA with subretinal air, subretinal anti-VEGF and partial fluid air exchange. Surgical evacuation wherein a large temporal retinotomy is created for evacuation of the clot is being performed less commonly due to the risk of subsequent retinal detachment and PVR. However, in one-eyed patients with extensive subretinal hemorrhage, I may consider this option. Vitrectomy for secondary vitreous hemorrhage is different as

1. The blood is ochre colored and can obscure the retinal details significantly; this associated with an adherent peripheral opaque vitreous and possibly areas of irregular elevated retina due to sub retinal hemorrhage(peripheral PCV), can increase the risk of retinal break formation and retinal detachment. 2. When associated with retinal detachment, it may be difficult to decipher if the detachment is only exudative or associated with a break, the rhegma can be difficult to make out due to the underlying chorioretinal scarring. 3. Visualization of the infusion cannula can be difficult in these cases and one may have to use a longer infusion cannula. 4. These eyes are prone to develop ghost cell glaucoma.

PS : Recent onset of bleed as in this situation can be treated with intravitrealtPA and antiVEGF with pneumatic displacement. In cases of history of bleed of more than 7-14 days duration, surgical evacuation may be necessary. If breakthrough vitreous hemorrhage is seen PPV will be necessary. Such vitreous haemorrhage is usually dense and does not absorb on its own. During surgery the posterior vitreous is usually stuck to the retinal surface and no PVD is present. Surgery has to be slow and careful, cutting the vitreous in layers till slowly some view of the retina is present. Once a thin layer of vitreous remains, high suction to induce PVD can be used. The aim should be to clear the

visual axis. Excessive peripheral trimming because of an opaque “vitreous skirt” can cause iatrogenic retinal break formation. These patients should be monitored for post op increase in IOP as ghost cell glaucoma is oftenbe seen in these eyes.

DG : I would consider evacuation with a retinectomy only if the hemorrhage is massive and not amenable to displacement. Secondary vitreous hemorrhages usually clears but if vitrectomy is required attempt to remove the vitreous hemorrhage only and not the subretinal blood unless it is subfoveal.

GM : Pneumatic displacement, especially triple therapy, has risk of early IOP hike due to the injection volume and expansile gas which is best taken care by AC paracentesis and oral acetazolamide for the 1st day post treatment. Break-through vitreous hemorrage is particularly problematic in PCV, despite pneumatic displacement, in many eyes. Such vitreous hemorrhages may be dense and usually lack PVD. A careful clearance of layered blood and PVD induction is required, which may be combined with subretinal injection of tPA and gas fill for inferior displacement of blood especially if significant submacular bleed has detached the macula

RC : I have never had to do a surgical evacuation but I have tried subretinal injection of the cocktail in cases where the bleed is quite large. We get aliquots of tPA from our dispensing pharmacy and so it does not cost too much to the patientand we generally add tPAto all intravitreal gas injections. The commonly used dose is 50-75 microgram for an intravitrealinjection and less than 20 microgram for a sub-retinal injection. In this dose I have not really seen any inflammation or side-effects

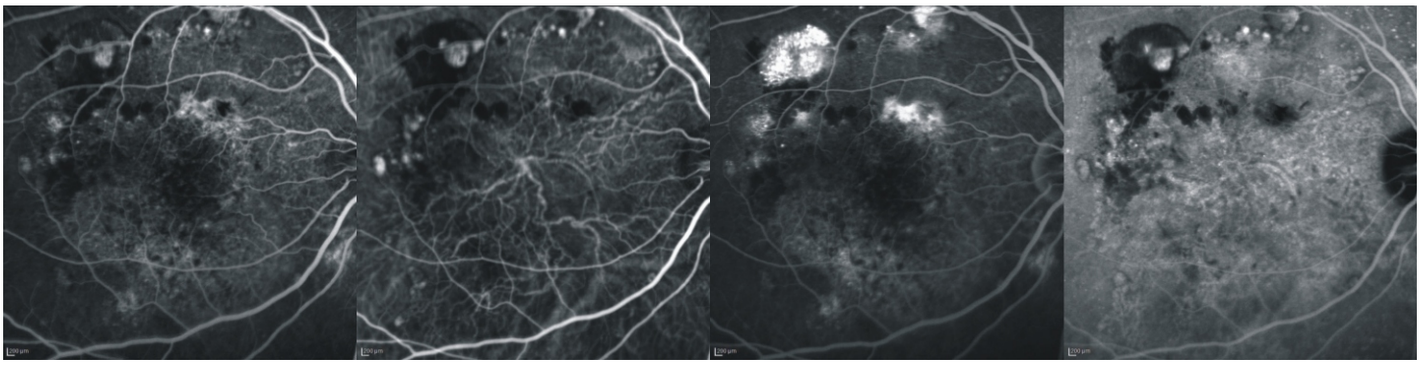
RR : PA is preferred if the blood is clotted. I usually do surgical evacuation in case of massive bleed spanning across the arcades. Viterous hemorrhage secondary to AMD /PCV tend to be very dense. Surgically I don't find any difference in treating vitreous hemorrhage in these eyes, the principles remain the same.

TAKE HOME PEARLS

Recent significant subretinal haemorrhage in neovascular AMD or PCV may be an indication for pneumatic retinopexy. Most surgeons prefer 0.2-0.3 cc C3F8 because a lesser volume can be injected compared to SF6. This is a concern especially when anti VEGF agents or tPA is added to prevent secondary glaucoma. tPA (intravitreal dose; 50 microgm, subretinal dose; 20 microgm) is used specifically when the subretinal haemorrhage is thicker and older but is not useful in sub RPE bleeds. The choice of antiVEGF would depend on the pathology associated. However Aflibercept may have to be avoided when tPA is given as Aflibercept is believed to loose its antiangiogenic property in the presence of plasmin. Keeping the risk of secondary glaucoma in mind, these eyes may require preoperative priming and postoperative medications. Many of these eyes also develop vitreous haemorrhage subsequently. PCV eyes may have a propensity to develop subsequent massive bleeds and poor vision. Eyes with vitreous haemorrhage do not resolve easily, often do not have PVD and needs Vitrectomy. Vitrectomy should be cautious in these eyes and a careful PVD induction with less aggressive peripheral skirt trimming is suggested. Surgical evacuation through a retinotomy is attempted in massive subretinal haemorrhage with clots unless unavoidable.

CASE 6

MS : 63 yr old female presented with metamorphopsia of the right eye of 5 months duration. She had lost vision in her left eye due to scarred CNVM. The BCVA was 6/12 in the right eye and HM in the left eye. The right eye revealed a flat irregular shallow PED on OCT. There was no IRF or SRF on OCT at the foveal region. There was a thumb shaped PED with SRF basal cuff around extrafoveally. Combined FFA/ICG was done which revealed extrafoveal occult leakages with visualization of the polyps on FFA. The ICG confirmed multiple polyps and a BVN with feeder at the centre.



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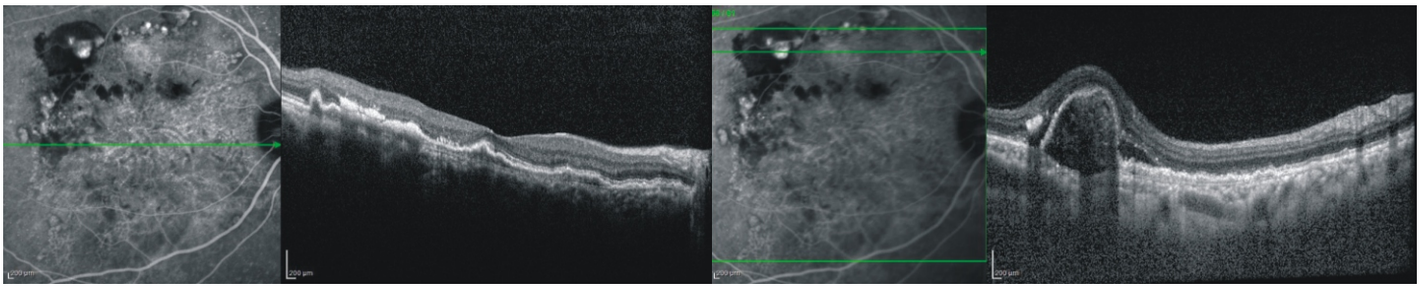

1. How do we differentiate FIPED, SIRE and DLS

MPS : DLS has been shown to occur in pachychoroid associated CSCR, pachychoroid neovasculopathy (PNV) and polypoidal choroidal vasculopathy (PCV). Hypereflective space between the RPE and Bruch's is associated with DLS in PCV and PNV and hyporeflective in CSCR. Thus studying the DLS may give a clue to the etiology of the DLS. In contrast FIPED is a finding in PCV and increase in FIPED is an early sign of subsequent exudation and these patients need to be followed up closely. FIPED has been described as shallow detachment of the RPE from Bruchs membrane filled with partial or complete hyperreflectivity with a minimum horizontal and maximum vertical dimension of 500 microns and 100 microns respectively. SIRE describes eyes with large drusen and is an indicator of the presence of an underlying non-exudative macular neovascularization. Thus DLS can be present in various AMD subsets; the space between the DLS can give an indication to the etiology of the DLS. SIRE (AMD) and FIPED (PCV) are OCT signs indicating potential for future exudation, thus necessitating closer follow up.

PS : DLS or the "double layer sign" is the sign on structural OCT formed by the accumulation of fluid between the basement membrane of the RPE and the inner boundary of the Bruch's membrane/choriocapillaris complex. SIRE or Shallow irregular RPE elevations are RPE elevations of greatest transverse linear diameter of>100 microns, irregular RPE elevation with a height of less than100 microns and a variable internal or subRPE reflectivity. These are the elevations in patients with AMD that usually have an underlying non exudative MNV as seen on OCTA. So eyes with the SIRE sign need more frequent follow up and diligent Amsler chart monitoring. Also, these characteristic features of SIRE help to differentiate neovascular RPE elevations from nonneovascular RPE elevations like drusen or serous RPE detachments. FIPED or flat irregular Pigment epithelial

detachment is a term used generally in the setting of chronic central serous retinopathy. A hyperreflective sub RPE space usually harbours a type 1 CNV. Though DLS was originally described in eyes with PCV to represent an underlying branching vascular network, it is now understood that it can be seen in AMD as well as other pachychoroid diseases and can harbor a type 1 CNV that can be identified on OCTA.

DG : DLS represents two highly reflective layers that consists of RPE and another highly reflective layer beneath the RPE. These eyes are associated with branching vascular network in PCV.

FIPED refers to PED with dimpled or irregular surface, usually used in reference to central serous retinopathy and may be avascular as well. Shallow, irregular RPE elevation above Bruchs (SIRE) denotes RPE elevations with a greatest transverse linear dimension of 1000 µm or more, an irregular RPE layer with a height of predominantly less than 100 µm, and a nonhomogenous internal reflectivity.

GM : DLS is the structural OCT sign, shallow irregular separation of RPE from the Bruch's membrane with intervening hyper-reflectivity, suggesting the presence of BVN of PCV. However, OCT shows similar Shallow RPE elevations (SIRE) <100µ in ARMD, suggesting the presence of subclinical macular neovascularization (MNV) overlying thin choroids and Flat Irregular PED (FIPED) in Chronic CSC suggesting the presence of subtle MNV overlying thick choroids. OCTA is particularly sensitive in picking-up these MNVs, which may be missed on routine angiography, when SD-OCT shows SIRE, FIPED or DLS signs.

RC : I think it is just a question of terminology with not too much clinical relevance between these terms. Definitely a double layer sign at the edges of a PED should make one think of a possibility of a BVN at that place. Flat or shallow PEDs are just other ways of looking at a double layer sign. A trapezoidal PED may be linked more to type 3 MNV and a thumb like PED, is more common in PCV.

RR : DLS or double layer sign was described by Sato et al. They described two layers on OCT, one the RPE layer and the other the bruchs membrane. The DLS with internal hyperreflectivity may harbour early type 1 choroidalneovascularisation (CNV).SIRE or shallow irregular RPE elevation quantified DLS as a RPE elevation more than 1000 micron in length. They also may harbour type 1 CNVM. FIPED is a similar finding in the setting of CSCR and signifies the same.

2. **What is the line of management; observe or active management (one eyed having lost due to a similar disease process)**

MPS : Considering the presence of a large BVN with peripheral active polyps and sub retinal hemorrhage, it is preferable to treat this eye as a spontaneous massive subretinal hemorrhage may occur and cause abrupt loss of vision in this one eyed patient. Photocoagulation of peripheral active polyps under cover of anti-VEGF agents would be preferable.

PS : Since the patient is symptomatic and single eyed, treatment would be required using combination of different modalities. Careful thermal laser to the extrafoveal polyps with intravitrealantiVEGF injections would be appropriate to begin with.

DG : I would treat and assess the response to antiVEGF therapy

GM : Peripheral active polyps warrants treatment with Focal Laser+/-anti-VEGF, considering the risk of possible subretinal or vitreous hemorrage.

RC : Laser can be done for the extrafoveal component. The mature vessel like BVN at the centre will stay. But as long as it is not causing RPE decompenstion and fovea remains dry, I feel that there is no need to inject. Serial close follow up is essential

RR : Since the patient has no sub foveal disease activity I will observe the patient

3. **PRN vs TAE protocol; Is TAE necessary in such situations**

MPS : A maintenance injection 3 or 4 monthly may be required to maintain this eye to minimize risk of unexpected subretinal hemorrhage.

PS : Considering the large BVN and multiple polyps with sero-sanguinous PED, TAE with close follow up would be a

good approach to follow initially. Once disease stabilizes, one can try to decrease the antiVEGF injections and treat PRN. Recurrences are frequently seen in such eyes

DG : I would not prefer TAE regime as long as the frequent visits required for PRN are acceptable to the patient.

GM : Treat and extent protocol is controversial in PCV due to the unpredictable nature of polyp inactivation and I believe that extension to 4 monthly injection visits without monitoring visits may risk a surprise fresh bleed with vision loss. However, in wet AMD, TAE is particularly helpful to patients and physicians in the long term with fewer visits.

RC : I would start injecting only when the disease becomes exudative. Subsequently I will follow a PRN schedule if fovea becomes dry again in 2-3 weeks after the first injection.

RR : I feel that PRN is good enough for these situations if need be.

4. **Does such thin SRF amount to disease activity? What are the types of SRF that may be observed while managing CNVM.**

MPS : As in this patient, SRF becomes significant to treat due to presence of subretinal hemorrhage which indicates active disease. Subfoveal SRF in a patient during course of adequate and appropriate treatment with stable, good vision can be observed. This is not to be the case in a naïve eye in a patient who has lost the other eye to scaring.

PS : Though there isn't much SRF under the fovea, the extrafoveal polyp superotemporal to fovea appears active and may need treatment. However minimal fluid in the range of 100-200 microns that persists inspite of optimal antiVEGF therapy can be closely observed in a patient who maintains a strict follow up.

DG : Yes it may be disease activity but does not necessarily have to be treated. The CATT study showed that eyes with subfoveal SRF had better visual outcomes at 2 years than those with extrafoveal SRF or no SRF. Thus a small amount of SRF may be safely observed.

GM : Persistent subtle SRF (< 100µ) may be tolerated while on TAE regime without risking VA loss.

RC : Thin SRF does not indicate that some disease activity is happening always. Also it is probable that the rate of fluid leak or exudation from the CNV complex is being compensated by the RPE and the disease is still not a full blown exudative neovascular disease. I have tried injecting in some of these cases which have a double layer sign developing withlittle fluid. In some the fluid reduced but later bounced back to the same level with the visual symptoms remaining the same and in some it did not budge. So now I follow them and start injecting only when there is definite evidence of the fluid increase on OCT.

RR : Emerging evidence support that thin or scanty SRF can be tolerated in the management of CNVM. However any SRF associated hemorrhages, drop in vision or increased retinal thickness must be treated.

TAKE HOME PEARLS

FIPED (Flat irregular PED) is separation of the RPE from the bruchs of minimal horizontal extent of 500 microns and maximum height of 100 microns, typically described in chronic CSCR eyes and may be hyporeflective or hyperreflective, the latter denoting underlying type 1 CNVM. DLS (Double layer sign) refers to separation of the RPE from the bruchs, typically described in PCV and pachychoroid eyes and is usuallyhyperreflective, denoting underlying type 1 CNVM. SIRE (Shallow irregular RPE elevation) is a term which refers to separation of the RPE from the bruchs, typically described in AMD eyes with confluent drusens and is usually hyperreflective, denoting underlying quiescent CNVM. The importance of these lesions is that they need close follow up and could turn into exudative neovascularisation. Large tomographic centrally dry macular BVNs with active extrafoveal polyps may be managed with laser treatment to polyps along with antiVEGF therapy because they stand a risk of massive subretinal haemorrhage. Aflibercept is the preferred agent in PCV eyes and the protocol best suited to the patient can be adopted. In a treatment naïve eye any new SRF merits treatment. However in a patient on regular antiVEGF therapy and good follow up some SRF to the tune of 100-200 microns can be tolerated if visual acuity remains stable and no other evidence of disease activity like subretinal haemorrhage exists.

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INNOVATIVE MODE OF ACTION[16-22]

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ABBREVIATED PRESCRIBING INFORMATION

EYLEA™ SOLUTION FOR INTRAVITREAL INJECTION IN VIAL. Approved name(s) of the active ingredient(s) One ml solution for intravitreal injection contains 40 mg aflibercept. Each vial provides a usable amount to deliver a single dose of 50 µl containing 2 mg aflibercept. Indication EYLEA™ is indicated for the treatment of neovascular (wet) age-related macular degeneration (wetAMD). Dosage Regimen wAMD The recommended dose for EYLEA™ is 2mg aflibercept , equivalent to 50µl. EYLEA™ treatment is initiated with one injection per month for three consecutive months, followed by one injection every 2 months. There is no requirement for monitoring between injections. Long term (after the first 12 months of treatment), it is recommended that patients continue to be treated with EYLEA™ every 2 months. Method of administration Intravitreal injections must be carried out according to medical standards and applicable guidelines by a qualified physician experienced in administering intravitreal injections. Following intravitreal injection patients should be instructed to report any symptoms suggestive of endophthalmitis (e.g. eye pain, redness of the eye, photophobia, blurring of vision) without delay. Each vial should only be used for the treatment of a single eye. Contraindications Know hypersensitivity to aflibercept or to any of the excipients, active or suspected ocular or periocular infection, active severe intraocular inflammation. Special warnings and special precautions for use Endophthalmitis and retinal detachments may occur following intravitreal injections. Patients should be instructed to report any symptoms suggestive of endophthalmitis or retinal detachment without delay and should be managed appropriately. Increases in intraocular pressure have been seen within 60 minutes of an intravitreal injection. There is a potential risk of immunogenicity and arterial thromboembolic events following intravitreal use of VEGF inhibitors. EYLEA™ should not be used in pregnancy unless the potential benefit outweighs the potential risk to the foetus. Women of childbearing potential have to use effective contraception during treatment and for at least 3 months after the last intravitreal injection of aflibercept. Undesirable effects Very common: Conjunctival hemorrhage, eye pain. Common: Retinal pigment epithelial tear, detachment of the retinal pigment epithelium, cataract, cataract cortical, cataract nuclear, cataract sub capsular, corneal erosion, corneal abrasion, intraocular pressure increased, vision blurred, vitreous floaters, vitreous detachment, injection site pain, foreign body sensation in eyes, lacrimation increased, eyelid edema, injection site hemorrhage, punctate keratitis, conjunctival hyperemia, ocular hyperemia. For full listing of undesirable effects, please refer to the full product insert. For further prescribing information, please contact Bayer Zydus Pharma Private Limited, Bayer House, Central Avenue, Hiranandani Estate, Thane, Maharashtra, India Pin-400607. Email: medicalinfo.india@bayerzyduspharma.com. Source: Based on CCDS / Version 10 / 19 Apr 2016; PI Rev 03 Nov 2016. Date of revision of API, 17 Nov 2016. For the use of healthcare professionals only.

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INNOVATOR'S ISLE

Indigenous do it yourself hands free smartphone mobile indirect ophthalmoscope "HF-SMIO"

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Dr. Mayur Kulkarni

Introduction:

The smartphone assisted indirect ophthalmoscopy can be performed with holding the phone in one hand and condensing lensin other or devices that allow the condensing lens to be mounted on them, thereby freeing one hand from holding the lens. However, It is difficult to perform maneuvers such as scleral depression.1-4 The article of head mounted digital camera for indirect ophthalmoscopy by Arong Wang et al 5was an inspiration to develop DIY "HF-SMIO", it helps to view the display of the smartphone attached to the head band and thus one hand can be utilized to focus the +20Dlens and the other hand can be utilized for scleral indentation.

Materials & methods:

Here with we describe the making of the ''DIY HF SMIO'' assembly. It consists of 1.Headband of a discarded Indirect ophthalmoscope [Figure 1 A],2.A flexible arm of a flexible table lamp [Figure 1 B],3.Universal mobile holder [Figure 1 D],4.Counter balance made with in house material [Figure 1 D].

First the flexible arm is attached to the universal mobile phone holder using the discarded T junction of the slit lamp attachment for the fixation light [Figure 2 A]. There is an additional aluminium plate to support flexible arm assembly attachment to the head mount [Figure 2B].Once assembled, the arm holding the mobile phone can be bent as required [Figure 2C].The tightening knob of the head band is removed to allow fixing the counter weight. The counter balance can be made out of discarded material- here we have used a slit lamp, lamp housing stuffed with metal counter weights. The screw holding the circum knob of the headband is secured [Figure 2D].The knob functionality is reassessed by rotating the circum knob for tightening and loosening the head band. The counter balance assembly is made in house using a discarded plastic plate with some serrations. The cup is a discarded lens cover of a microscope with some counter outward serrations. The weights are some random solid metal objects. The cup with weights are twisted onto each other as a counter balance assembly [Figure 2 E]. The reason for having the counter balance is to avoid slippage of the head mount with the mobile phone weight, without which

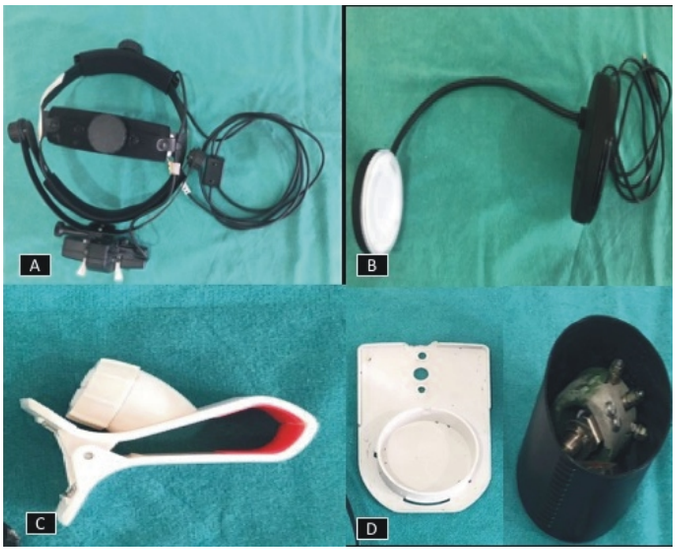

Figure 1

A. Figure showing the headband of a discarded Indirect ophthalmoscope.

B. Figure showing a flexible table lamp.

C. Figure showing a universal mobile holder.

D. Figure showing counter balance made with in house material.

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that the headband tends to slip and there can be exaggerated after movements of the holding assembly with examiner's head movement [Figure 2E].The approximate weight is double the weight of mobile phone and the flexible arm.

Indirect ophthalmoscopy of the preterm infants diagnosed as having ROP was performed and the fundus images were captured using HF-SMIO. Images were captured using iPhone 5S (Apple Inc., Cupertino, CA, USA) utilizing the default video camera with continuous flash on mode placed in the universal adaptor. The live video on the phone screen helps us see what we are doing, the 20D lens (Volk) was utilized as in indirect ophthalmoscopy and the retinal/ peripheral retinal lesions even with indentation without the need of assistance were recorded. A total of 25 eyes of 15 preterm infants diagnosed to have ROP were included in the study. Five eyes (16.66%) were excluded due to poor pupillary dilatation or inability to image due to logistic issues. HF-SMIO was used to document ROP in 25 eyes diagnosed as ROP, 24 (96%) of the eyes had very good quality images [Figure 3 A-C] except one eye had poor quality images

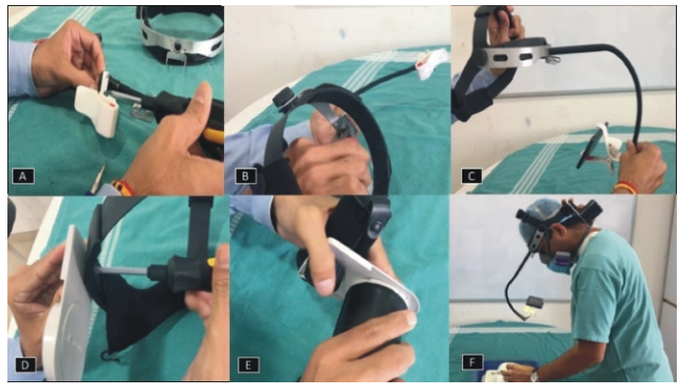

Figure 2

A. Figure showing the flexible arm is attached to the universal mobile phone holder using the T junction.

B. Figure showing an additional aluminium plate attached to support flexible arm assembly to the head band.

C. Figure showing the arm holding the mobile phone can be bent as required.

D. Figure showing the attachment of the counter balance base plate with the screw holding the circum knob of the headband is secured.

E. Figure showing the counter balance assembly twisted onto each other made with the discarded lens cover of a microscope with some counter outward serrations. The weights are some random solid metal objects.

F. Figure showing the final assembly of HF- SFMIO.

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due to the vitreous haze due to vitreous haemorrhage without plus disease (child was having history of very severe intra ventricular haemorrhage -Terson's Syndrome) [Figure 3 D].

Discussion:

We hereby demonstrate the construction and use of a simple inexpensive and do it yourself solution “HF-SMIO” it uses a headband and mounts a digital camera with its display in front of the user using a flexible arm at an appropriate distance to avoid accommodation. The camera's aperture acts as the only observation path, with the user performing ROP screening and viewing directly on the display screenso “what you see is what you are doing”[Figure 4 A].Using our solution is as good as using an actual indirect ophthalmoscope e.g., head positioning,

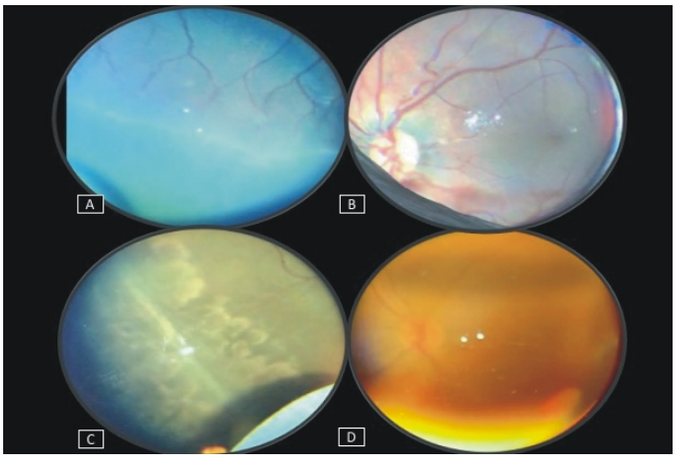

Figure 3

A. Figure showing a ridge at the junction of vascular & avascular retina.

B. Figure showing pre retinal hemorrhage without plus disease.

C. Figure showing regression of the neovascularization over the ridge and some remnants of the fibrous ridge with laser spots post 1 month laser.

D. Figure showing poor quality images due to the vitreous haze due to vitreous haemorrhage without plus disease (child was having history of very severe intra ventricular haemorrhage - Terson's Syndrome).

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manipulation of the condensing lens to reduce glare, one hand being free for indentation and manipulation as is required for ROP screening. The biggest advantage is to utilize it to teach adequate technique of visualization of the periphery in ROP using indentation [Figure 4 B].The DIY HFSMIO can be utilized to image anterior segment photo using 20 D lens [Figure 4 C].The DIY HFSMIO can be utilized for viewing , training & teaching the Residents or fellows can be trained by viewing the live video on the smart phone without again subjecting the neonate for the risk of examination with indentation [Figure 4 D].

The article by Aaron Wang et al was our inspiration which proposed a new method for an Indirect Ophthalmoscope Camera (IOC) 5, utilizing the phone attached to the head band with a small plate, the drawback of the method was that the camera is very close to the eyes. The shortcoming of our study is that the sample size is very small & the images were taken by the

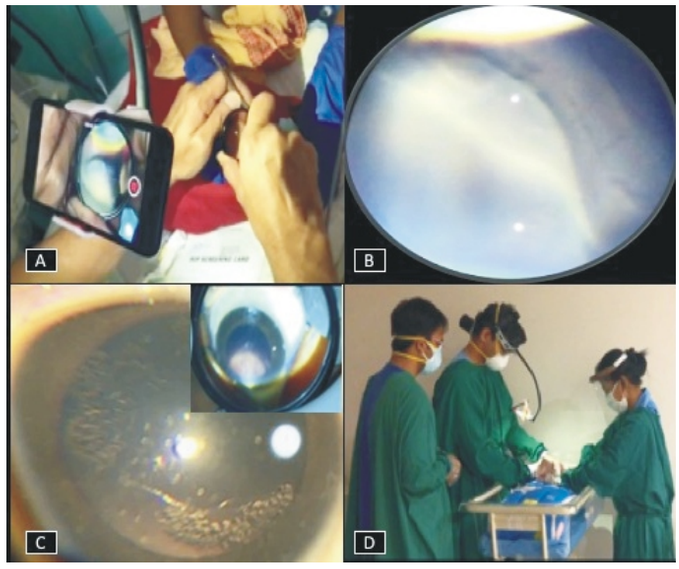

Figure 4

A. Figure showing the DIY HFSMIO recording the ROP examination performed with utilizing the other had for indentation with wire vectis.

B. Figure highlights the technique of indentation. The ridge can be missed with over exaggerated indentation. For adequate peripheral visualization with indentation the indentation has to be just enough to cause a small mound in the periphery so as to visualize the whole lesion.

C. Figure showing anterior segment photo showing cataract formation while doing laser using 20 D (figure in the inset).

D. Figure showing the DIY HFSMIO can be utilized for viewing , training & teaching the Residents or fellows can be trained by viewing the live video on the smart phone without again subjecting the neonate for the risk of examination with indentation.

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expert, the technique can have some learning curve but can be overcome by practise, the images had minimal reflexes due to the LED light from the smart phone is a diffuse light. The smart phones having a the cameras close to the LED can only be utilized for this technique.

Conclusions:

Our DIY -HF-SMIO is alow-cost assembly can be easily adopted by ophthalmologists, as it preserves the way in which the

indirect exam is performed. As one hand is free it can be utilized for indentation. The videos / screen shots captured are readily available for discussion with the patient and other care givers.

Financial support and sponsorship:

Nil.

Conflicts of interest:

There are no conflicts of interest.

Acknowledgements:

Retina department, Dr Mahesh P Shanmugam Sir for the idea of DIY - HFSMIO. Biomedical team Sankara Eye Hospital, Bangalore for the help in assembling the device, All the NICU we are associated for ROP screening Rainbow Children's Hospital; Marathalli, Apollo Cradle; Kundanahalli gate, Columbia Asia; Whitefield, Sakra World Hospital, Femint Hospital, Whitefield.

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RETINA TECH

Microperimetry Biofeedback Training – A new tool for Visual Rehabilitation

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Visual field assessment (perimetry) is a very commonly performed Vision Function test in ophthalmological practice. Visual fields were generally measured using the manual technique (confrontation) or Automated Perimetry (e.g. Humphry Visual Field Analyser). These systems are very well established for conditions such as glaucoma (1) but in cases of central visual field loss these systems felt inadequate because of the following reasons:

1. The center of fixation as shown in the Visual Field analyzer may not be the center of the fovea in case of central scar, eccentric fixation, or unstable Fixation.

2. The point-to-point correlation of Visual field scotoma with the corresponding retinal area is very difficult.

3. It is inadequate to detect very small scotoma

4. The quantification of retinal sensitivity during follow-up tests does not necessarily reflect the threshold of the same area previously tested.

5. The exact correlation between retinal morphologic changes and retinal sensitivity was not met.

Microperimetry provides the solution for the above-mentioned problems and can provide proper Functional visual information of related pathology. Apart from this Microperimetry can also provide data about the fixation stability of the patient by monitoring Fixation in real-time.

When there is a loss of central vision, the ocular motor system loses its reference positionwhich is at the fovea in the normal eyeleading to difficulties in ocular motor control. Most patients adapt to their impairment by using the healthy eccentric parts of the retina for fixation; these eccentric retinal areas are called preferred retinal loci or PRLs and they play the role of a “pseudo-fovea” (2) (3)(4)

Usually, PRLs are formed in the functional area which is located closest to the Anatomical fovea. PRLs are not fixed, they can change based on tasks. Most of the patients with bilateral loss of vision, find it very difficult to read as they have to constantly move their head to find PRL for comfortable reading. In cases where PRLs are constantly changing, or there is unstable fixation, Microperimetry Biofeedback Training can help these patients to achieve acceptable PRL and can increase Reading Speed. (5)

Fixation Stability in Microperimetry is measured by calculating the area of an ellipse which encompasses the cloud of fixation points for a given proportion (63% or 95%) based on standard deviations of the horizontal and vertical eye positions during the

fixation attempt. This is called Bivariate Contour Ellipse Area (BCEA). The smaller the area, the better is the fixation stability.

Microperimetry biofeedback training (MBFT) is a visual rehabilitative strategy based on fixation stability improvement reinforcing or creating a new preferential fixation locus.

We have done Biofeedback Training using MAIA (Macular Integrity Assessment, iCARE) Machine which is a Third generation microperimeter (Figure1).

We do the Training in the following steps:

1. We do Expert test 4-2 Threshold Strategy, at least 3 times on different days to avoid Learning Defects. This maps the scotoma (Black dots), areas of poor retinal sensitivity (Towards Red shades), Good Sensitivity (Towards Green shades), Fixation in Real-Time (Dark blue dots), PRL (Blue dot with 'F' label)

2. We select a new PRL relocation Point, called PRT (Preferred Retinal target), which is at the point of better Retinal sensitivities and nearer to the fovea. It should not be within the area of the scotoma.

3. The patients undergo 10 sessions of training weekly once, each training lasting for 10 min.

4. During training,the machine gives audio feedback which increases attention modulation helping the brain to detect the PRT.

5. At the end of Training, Expert test was done to assessthe new PRL.

Biofeedback Training is based on the Motor neuro-rehabilitation Principle. Motor neuro-rehabilitation aims to improve a patient's functional abilities, replacing skills that have been lost fully or partially. A general neuro-rehabilitation mechanism of action is the potentiation of a group of latent neuronal connections that are utilized repeatedly during challenging behavioral practice. The repeated and persistent practice, over several weeks, of a challenging movement facilitates neural synapsis, which may result in lasting physiological changes in motor neural networks. (6) (7) (8)

We are sharing one such case. 67-year-old Gentleman came

Figure 1

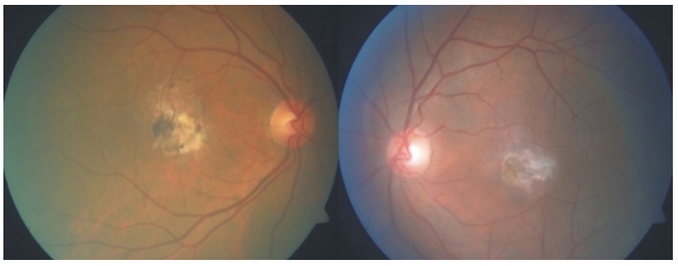

Figure 2

with defective vision in both eyes for 3 years, BCVA Both eyes 6/18p. He had a Bilateral macular Scar secondary to ARMD (Figure 2). There is no sign of activity on OCT and No Flow on OCT-A. He underwent MAIA Biofeedback training as described earlier. Figure 3 and Figure 4 shows Pre (Left side pane) and post (Right side pane) Training Findings of Right eye and Left eye Respectively. The upper pictures show the distribution of retinal sensitivity and Fixation data. Middle Pictures shows an improvement of retinal sensitivity around the PRL and Lower Pictures show reduction BCEA i.e. improvement of fixation stability.This results in improvement of His reading Speed from 23 letters in 1 min to 37 letters in 1 min. (N36 Font Size Tamil Letters). The patient also recognized that distance vision is better in quality and sharpness and he could recognize faces more clearly.

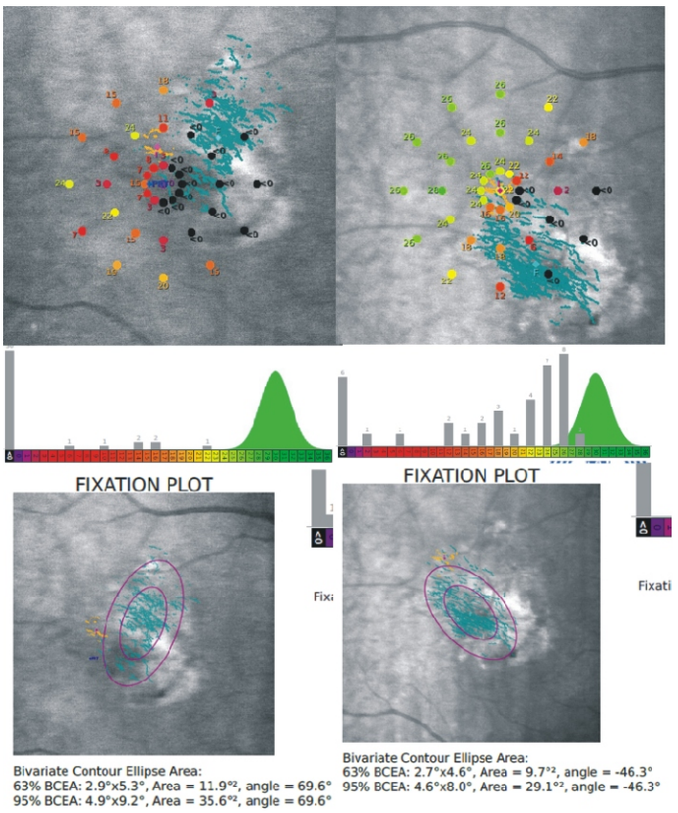

Figure 3

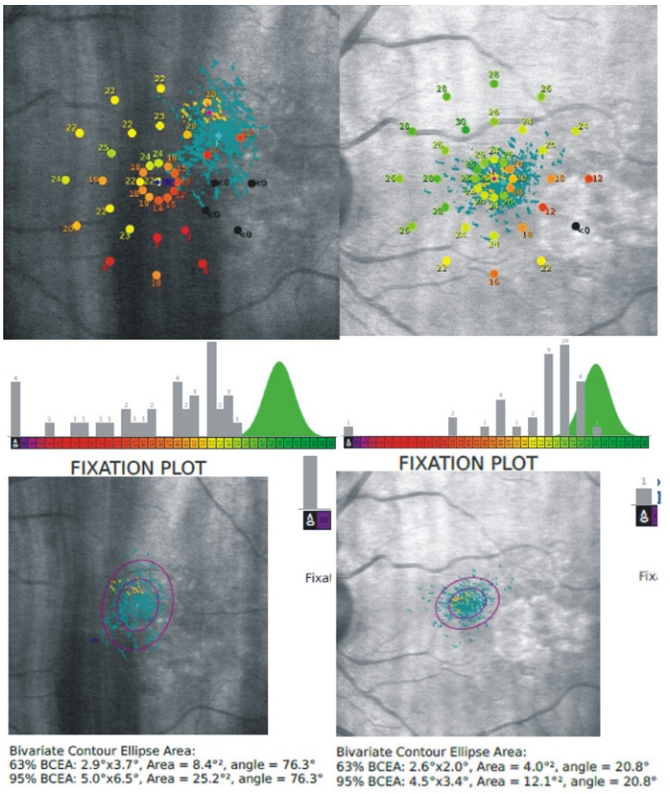

Figure 4

To conclude, Microperimetry Biofeedback Training can be offered to patients with non-progressive Bilateral or Unilateral central vision loss. This is a very good rehabilitation technique that can improve the quality of life in selected cases.

Acknowledgement:

The work done presented here is at Aravind Eye Hospital, Madurai, Tamilnadu (India). I acknowlege the guidance of Dr. Kim Ramasamy, Dr. Anand Rajendran and Dr.RenuRajan.

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RETINA ROUNDUP 2020

My Top 7 Impactful Articles of the Year

Dr. Dhananjay Shukla
Consultant
Retina-Vitreous Service
Ratan Jyoti Netralaya
Gwalior

1. COVID-19 & Eye / Retina

COMMENTS :

This is undoubtedly the elephant in the room! Unfortunately, I am still searching for it in 2021. For us, the most relevant piece could be Retinal findings in patients with COVID-19 (Lancet, May 12, 2020; Marinho et al), but they reported wispy, insignificant findings, which were blown away by an editorial in EYE (**Vavvas et al, Eye 2020;34:21532154**) as unreliable as well. I also broadened the net and looked at Ophthalmic findings in COVID-19 (Wu et al. JAMA Ophthalmol2020;138:575-578& Zhou et al. Ophthalmology. 2020;127:982-983) but again, Wu, Zhou & others reminded Ms. Irene Kuo of a Rashomon Moment (Commentary, **Ophthalmology 2020;127:984-985**) for their contradictory findings. To cut the story short, COVID-19 causes red eye and watering like common cold, and eye specialists are at risk because they go close to patients to examine eyes. Raise your hand if you did not know it already!

2. Wang D, Au A, Gunnemann F, Hilely A, Scharf J, Tran K, Sun M, Kim JH, Sarraf D. Pentosan-associated maculopathy: prevalence, screening guidelines, and spectrum of findings based on prospective multimodal analysis. Can J Ophthalmol 2020 Apr;55:116-125.

ABSTRACT

OBJECTIVE :

To describe the prevalence and spectrum of multimodal imaging findings of pentosanpolysulfate sodium (PPS)-associated maculopathy and to recommend dosage-related screening guidelines.

DESIGN :

Cross-sectional study.

METHODS :

Patients previously or currently treated with PPS at University of California, Los Angeles, were randomly ascertained and prospectively screened for PPS-associated maculopathy with multimodal retinal imaging. Daily and cumulative dosages of PPS exposure were calculated for each patient. Images were studied to identify the characteristic findings of toxicity. The prevalence of PPS-associated maculopathy and screening guidelines were determined.

RESULTS:

The prevalence of PPS-associated maculopathy in this cohort

was 20% (10/50 patients). Both average duration of PPS therapy and average cumulative dosage were significantly lower in the unaffected (6.3 ± 6.6 years, 691.7 ± 706.6 g) versus the affected groups (20.3 ± 6.6 years, 3375.4 ± 1650.0 g, $p < 0.001$). Near-infrared reflectance (NIR) illustrated characteristic punctate retinal pigment epithelium (RPE) macular lesions early. Fundus autofluorescence (FAF) showed speckled autofluorescence in the posterior pole with peripapillary extension. Co-localization with optical coherence tomography (OCT) displayed focal RPE thickening and, in more severe cases, RPE atrophy in the macula and even the periphery.

CONCLUSIONS:

A prevalence of 20% in this study cohort suggests a significant risk of macular toxicity for PPS-treated patients. Characteristic alterations are best detected with FAF and NIR. More significant PPS exposure was associated with more severe atrophy. We recommend an initial baseline eye examination to include OCT and, most importantly, NIR and FAF with annual retinal imaging thereafter especially with cumulative dosages approaching 500 g. Patients exposed to greater than 1500 g of PPS are at significant risk of retinal toxicity.

COMMENTS :

PentosanPolysulfate Sodium or PPS is an FDA approved staple for chronic bladder pain and irritation (interstitial cystitis) for over 2 decades; but stormed into ophthalmic headlines when NierajJain 1st observed macular pigment epithelium stippling (RPE, not unlike hydrochloroquine or HCQ maculopathy) in patients on PPS for long (**Pearce WA, Chen R, Jain N. Ophthalmology 2018;125:1793-1802**). Sarraf and colleagues sum up the literature, peg prevalence at a shocking 20% (considering how commonly the drug is prescribed) and advise screening when cumulative dose exceeds half a kilo. There are several parallels with HCQ: the drug targets RPE preferentially; the visual loss is severe, irreversible and continues many years after discontinuing the drug; and early diagnosis, though critical, is too subtle for biomicroscopy. The earliest signs are best seen with near-infrared reflectance imaging and a bit later but more definitively by autofluorescence imaging.

3. Reid GA, McDonagh N, Wright DM, Yek JTO, Essex RW, Lois N. FIRST FAILED MACULAR HOLE SURGERY OR REOPENING OF A PREVIOUSLY CLOSED HOLE: Do We Gain by Reoperating?-A Systematic Review and Meta-analysis. Retina 2020;40:1-15.

ABSTRACT :

PURPOSE:

To evaluate repeated surgery for idiopathic full-thickness macular hole that failed to close (FTC) after first surgery or reopened (RO) once originally closed.

METHODS:

Systematic review and meta-analysis. Pubmed. gov and Cochrane Library were searched for studies in English presenting outcomes of idiopathic full-thickness macular hole that FTC or RO (case reports/series of <5 cases excluded).

OUTCOME MEASURES:

Anatomical closure, postoperative best-corrected visual acuity, intraoperative / postoperative complications, and patient-reported outcomes. Meta-analysis was performed on aggregate and available individual participant data sets using the metafor package in R.

RESULTS:

Twenty-eight eligible studies were identified. After reoperation, pooled estimates for anatomical closure were 78% (95% confidence interval 71-84%) and 80% (95% confidence interval 66-89%) for FTC and RO groups, respectively. On average, best-corrected visual acuity improved in both groups. However, only 15% (28 of 189 eyes) of FTC eyes achieved best-corrected visual acuity of ≥6/12. The pooled estimated probability of ≥2-line best-corrected visual acuity improvement was 58% in the FTC group (95% confidence interval 45-71%); meta-analysis was not possible in the RO group. The most common complication was cataract.

CONCLUSION:

Reoperation for FTC or RO idiopathic full-thickness macular hole achieved a clinically meaningful visual acuity improvement in more than half of patients; high levels of vision (≥6/12), however, were uncommon.

COMMENTS :

Vitrectomy for macular hole has evolved to become one of the most rewarding retinal surgeries. Large, chronic macular holes remain refractory to treatment, however. This review takes a hard look at failed macular hole surgeries, reassures that it is worthwhile to try again, but warns that recovery of good vision (≥6/12) is uncommon (about 15%). When deciding on WHAT to do in re-surgery, unfortunately there was no clear winner. As internal limiting membrane (ILM) had already been peeled in >80% cases during primary vitrectomy, the most common procedure was the use of long-acting gas/silicone oil: alone, or with additional ILM peeling. Free ILM grafts were uncommon (about 5%), probably because of difficulty of the procedure.

4. Monés J, Srivastava SK, Jaffe GJ, Tadayoni R, Albini TA, Kaiser PK, Holz FG, Korobelnik JF, Kim IK, Pruente C, Murray TG, Heier JS. Risk of Inflammation, Retinal Vasculitis, and Retinal Occlusion-Related Events with Brolucizumab: Post Hoc Review of HAWK and HARRIER. Ophthalmology. 2020;15:S0161-6420(20)31075-7.

ABSTRACT

PURPOSE :

An independent Safety Review Committee (SRC), supported by Novartis Pharma AG, analyzed investigator-reported cases of intraocular inflammation (IOI), endophthalmitis, and retinal arterial occlusion in the phase 3 HAWK and HARRIER trials of brolucizumab versus aflibercept in neovascular age-related macular degeneration (nAMD).

DESIGN:

A post hoc analysis of a subset of data from two 2-year, double-masked, multicenter, active-controlled randomized phase 3 trials (NCT02307682, NCT02434328).

PARTICIPANTS:

Patients (N = 1817) with untreated, active choroidal neovascularization due to age-related macular degeneration in the study eye were randomized and treated in HAWK/HARRIER. The SRC reviewed data from cases of investigator-reported IOI (60/1088 brolucizumab-treated eyes; 8/729 aflibercept-treated eyes).

METHODS:

The SRC received details and images (color fundus photography, fluorescein angiography, and OCT) for all investigator-determined cases of IOI, retinal arterial occlusion, and endophthalmitis. Cases were reviewed in detail by ≥2 readers, then adjudicated by the SRC as a group.

MAIN OUTCOME MEASURES:

Within this patient subset: incidence of IOI, signs and incidence of retinal vasculitis and/or retinal vascular occlusion, and visual acuity loss; time since first brolucizumab injection to IOI event onset; and frequency of visual acuity loss after brolucizumab injection by time of first IOI event onset.

RESULTS:

Fifty brolucizumab-treated eyes were considered to have definite/probable drug-related events within the spectrum of IOI, retinal vasculitis, and/or vascular occlusion. On the basis of these cases, incidence of definite/probable IOI was 4.6% (IOI + vasculitis, 3.3%; IOI + vasculitis + occlusion, 2.1%). There were 8 cases (incidence 0.74%) of at least moderate visual acuity loss (≥15 ETDRS letters) in eyes with IOI (7 in eyes with IOI + vasculitis + occlusion). Of the 8 cases, 5 experienced their first IOI-related event within 3 months of the first brolucizumab injection (increasing to 7/8 within 6 months). Incidence of IOI in aflibercept-treated eyes was 1.1%, with at least moderate visual acuity loss in 0.14%.

CONCLUSIONS:

This analysis of IOI cases after brolucizumab injection identified signs of retinal vasculitis with or without retinal vascular occlusion and an associated risk of visual acuity loss. The findings will help physicians to evaluate the risks and benefits of brolucizumab treatment for nAMD.

COMMENTS :

Another elephant I kept chasing across the room was the safety of Brolucizumab: Good, Bad or Ugly? The above post hoc review fit the bill best among the host of polarized publications. They mention the risk of ANY intraocular inflammation (IOI) as about 4% (!) though the authors assure that less than 1% were sight-threatening (occlusive vasculitis). It is notable that thoughthe

incidence any IOI was about 1% with aflibercept, though authors point that the "overall rates of moderate or severe visual loss were similar (7+%!!) for both brolucizumab and aflibercept." Theyprobably clubbed the visual from loss drug-related complications with the visual loss due to the treated disease. Another alarm bell was that inflammation could occur after an uneventful 1st dose as well...and as late as 18 months. The authors recommend patient monitoring for complications to be more comprehensive than routinely performed. As reports of IOIcontinue to hit PubMed, in a mostly no-Mediclaim, resource-starved,poor follow-up,developing world setting with availability of safer alternatives, the above data appears to be a red signal, at least for me.

5. **Joseph DP, Ryan EH, Ryan CM, Forbes NJK, Wagley S, Yonekawa Y, Mittra RA, Parke DW, Emerson GG, Shah GK, Blinder KJ, Capone A, Williams GA, Eliott D, Gupta OP, Hsu J, Regillo CD. Primary Retinal Detachment Outcomes Study: Pseudophakic Retinal Detachment Outcomes: Primary Retinal Detachment Outcomes Study Report Number 3. Ophthalmology. 2020;127:1507-1514.**

ABSTRACT

PURPOSE:

This study evaluates outcomes of comparable pseudophakicrhegmatogenous retinal detachment (RRD) treated with pars plana vitrectomy (PPV) or PPV with scleral buckle (PPV-SB).

DESIGN:

Multicenter, retrospective, interventional cohort study.

PARTICIPANTS:

Data were gathered from patients from multiple retina practices in the United States with RRD in 2015.

METHODS:

A large detailed database was generated. Pseudophakic patients with RRD managed with PPV or PPV-SB were analyzed for anatomic and visual outcomes. Eyes with proliferative vitreoretinopathy, giant retinal tears, previous invasive glaucoma surgery, and ≤90 days of follow-up were excluded from outcomes analysis. Single surgery anatomic success (SSAS) was defined as retinal attachment without ongoing tamponade and with no other RRD surgery within 90 days.

MAIN OUTCOME MEASURES:

Single surgery anatomic success and final Snellen visual acuity (VA).

RESULTS:

A total of 1158 of 2620 eyes (44%) with primary RRD were pseudophakic. A total of 1018 eyes had greater than 90 days of follow-up. Eyes with proliferative vitreoretinopathy, previous glaucoma surgery, and giant retinal tears were excluded, leaving 893 pseudophakic eyes eligible for outcome analysis. A total of 461 (52%) were right eyes. A total of 606 patients (67%) were male, with a mean age of 65±11 years. Pars plana vitrectomy and PPV-SB as the first procedure were performed on 684 eyes (77%) and 209 eyes (23%), respectively. The mean follow-up was 388±161 days, and overall SSAS was achieved in 770 eyes (86%). Single surgery anatomic success was 84% (577/684) for PPV and 92% (193/209) for PPV-SB. The difference in SSAS between types of treatment was significant (P = 0.009). In eyes with macula-on RRD, SSAS was 88% in eyes treated with PPV and 100% in eyes treated with PPV-SB (P = 0.0088). In eyes with macula-off RRD, SSAS was 81% in eyes treated with PPV and 89% in eyes treated with PPV-SB (P = 0.029). Single surgery anatomic success was greater for PPV-SB than PPV for inferior (96% vs. 82%) and superior (90% vs. 82%) detachments. Mean final VA was similar for PPV (20/47) and PPV-SB (20/46; P = 0.805).

COMMENTS :

This is a contrarian study against the universal bias for primary vitrectomy (MIVS) for retinal detachments. For most RDs, or at least for the uncomplicated RD sans PVR, GRT and trauma, we expect MIVS to suffice. So did the participating surgeons who preferred primary vitrectomy in three-fourths of the cases. But they found that a belt buckle substantially improvedthe single-surgery re-attachment rates, not just for inferior and macula-OFF RD, but also for superior and macula-ON RD. This finding would mean MIVS is meaningless in most RDs: what's the point in 25 or 27G MIVS if one still needs a 360-degree peritomy for belt buckle?But here is the catch: there were 60-plus surgeons from 5 centers, which most likely entailed a host of inexperienced or trainee surgeons in the fray. But THAT is also

what makes the results more universal. The details like base dissection, 360-degree laser were not addressed (the latter has been addressed in a later PRO study, there are 12 versions now), but it one has to grudgingly admit that this study ensures excellent outcomes for vitrectomy in pseudophakic RD with a simple, accessible addition of an encircling band.

6. Bhavsar KV, Michel Z, Greenwald M, Cunningham ET Jr,, Freund KB. Retinal injury from handheld lasers: a review. SurvOphthalmol. 2020 Jul 3:S0039-6257(20)30103-X

ABSTRACT

Retinal photic injury induced by handheld lasers is a burgeoning public health concern due to the wider accessibility of high-powered devices. Retinal damage from thermal energy can cause potentially severe and permanent vision loss in children and young adults who are particularly vulnerable because of comorbid behavioral, learning, and psychiatric impairments. Understanding the spectrum of specific clinical and imaging features of such laser injuries aids in prompt and accurate diagnosis. Multimodal retinal imaging is important for the identification of the outer retinal abnormalities that characterize this condition. We reviewed 171 reported cases in the English and non-English language literature published from 1999, when handheld laser injury was first described, to December, 2018. Risk factors, demographic and clinical characteristics, as well as multimodal imaging findings, were collected and summarized. These findings both provide insights for public health awareness and guide areas of future investigation.

COMMENTS :

Flouting the laser safety regulations, powerful handheld lasers (>>5mW) are widely available as toys nowadays: close to 90% of these injuries were reported in the last decade, mostly from lasers purchased on the internet. The most dangerous laser wavelengths are blue and blue-green (more inherent energy). The injuries were mostly unintentional, related to play or pranks in children, and thankfully mild (vision 20/50 or better). When injuries are more severe and in adults, they were likely to be intentional (e.g., self-inflicted) and psychiatric consultation may be in order. Optical coherence tomography revealed the classic outer retinal band interruptions in most (esp. mild) cases. The visual prognosis was excellent in mild cases, and surprisingly, also in laser-induced macular holes after vitrectomy. Besides parent awareness and physician education, the authors emphasized strict government regulations penalizing dangerous and falsely labeled handheld lasers.

7. Sharma A, Kumar N, Kuppermann BD, Bandello F, Loewenstein A. Understanding biosimilars and its regulatory aspects across the globe: an ophthalmology perspective. Br J Ophthalmol. 2020;104:2-7

ABSTRACT

PURPOSE:

This article aims to analyse the key regulatory guidelines across the globe concerning biosimilars. Materials and methods: Review of the current literature.

RESULTS:

Biosimilars are well regulated with the majority of regulators having enforced the guidelines for the development and approval, and new biosimilar drugs are appearing on the horizon to provide a therapeutic option to a wider population base because of its cost-effectiveness and proven safety. Due to their extensive analytical data, clinical data and pharmacovigilance studies, their development should not be considered similar to generic drugs.

CONCLUSION:

This review discusses the biosimilars, their regulation globally and their difference from generics from ophthalmic perspective.

COMMENTS :

We keep fielding queries about new biosimilars mushrooming about the Indian Retina landscape. This review addresses some of the questions and concerns. And biosimilars abound in USA, Europe and Korea as well, as the innovator molecules' market monopoly nears expiry. While Europe leads globally in biosimilar regulation and development, it is relieving to see that the Indian government regulations are among the most rigorous and still time efficient. While the ranibizumab biosimilar Razumabremains the only brand approved for ophthalmic application, several others are in the pipeline. Biosimilars are typically about 25% cheaper than the innovator molecules, which is indeed good news for the cash-strapped, uninsured suffering masses in India.

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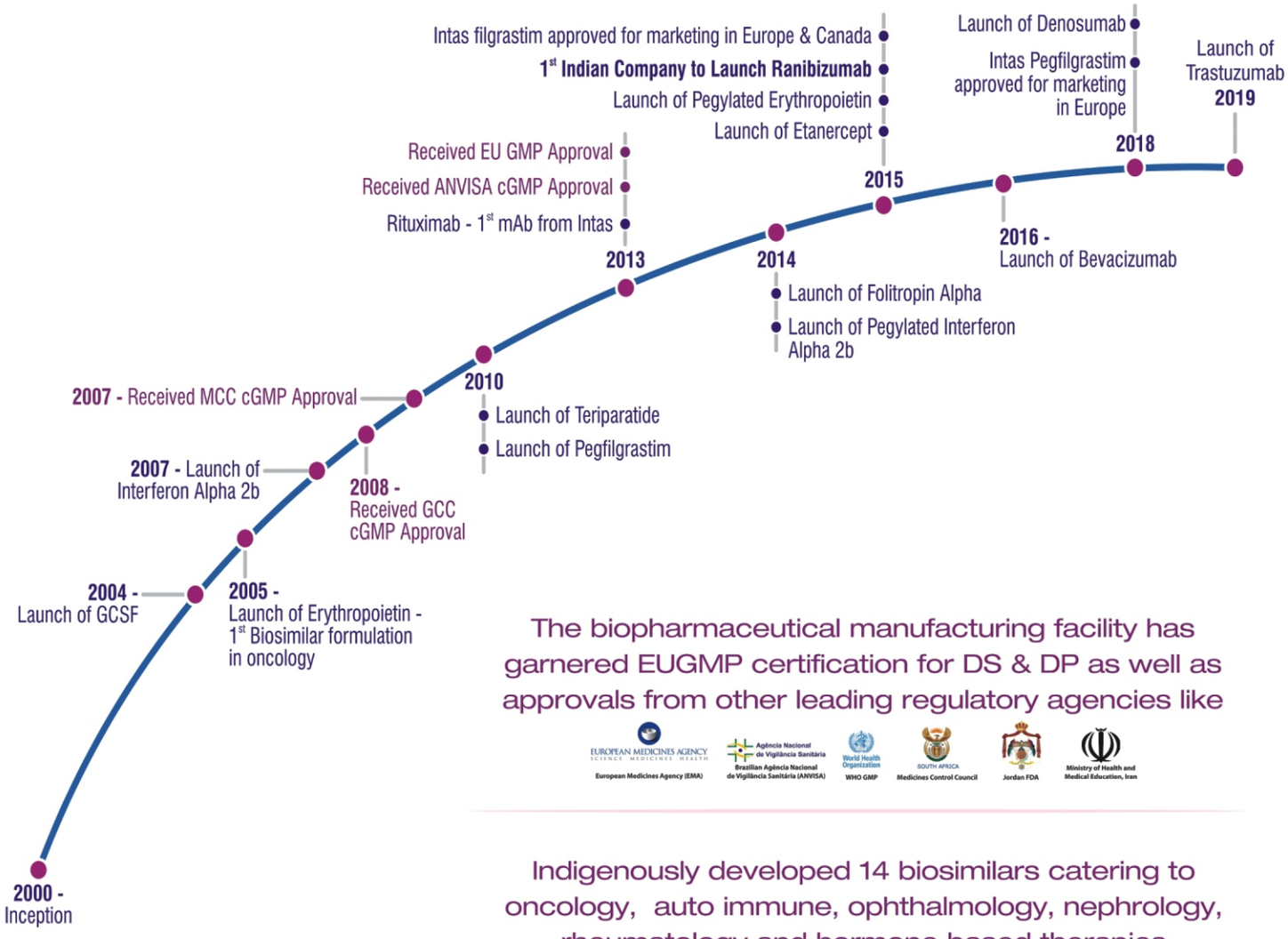

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Author

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Bangalore.

A VR fellow had a dream!
"Two title letters" denied to be one team!!

If V was the key or R was crucial?
On this,he was asked to be judicial!

"Well i am the vision, u r just a media"
'R' claimed.... wasnatures clear criteria

'V' proved himself a social!
Said, "I allow my clearance i am so cordial"!!

"Substitution of my solitude
And i don't get enough gratitude! "

"R is the stiffer one
Always makes the patient run!"

"I help him stay attached
My service to eye is unmatched!"

"Culprit is V causes breaks in me! "
R exclaimed .....
"When he wants to separate and be free!"

"Why do i pay price for his senile ageing?"
"Changes are seen in my imaging!!"

"I have so much to me,
All the 10 layers reside happily!!"

"V Is the baddie,
He causes PVD"!

"Every now and then traction and pull"
"His character is awful!!"

Decision was tough!
Both teams fought rough!!

Judge noted flashes!
Humbled them to stop the clashes!!

Said you together are my life!
Both valuable tosurgeons'knife!!

To be a court, I have no stamina!
I honor u both, before i get ocular angina!!
And be a good fellow of Vitreoretina!!

CASE REPORT

Dasatinib associated Periocular Reaction Post Scleral Buckle Surgery

Dasatinib induced periocular complication

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Abstract:

A young diabetic with Chronic myeloid Leukemia (CML) in remission on dasatinib developed severe periorbital hemorrhage and edema following uneventful scleral buckle for post-vitrectomy rhegmatogenous retinal detachment (RD). Dasatinib, a tyrosine kinase inhibitor, was presumed to be the cause of unanticipated post-operative complication. The patient improved with conservative management including systemic steroidsand canthotomy and cantholysis. Subsequent intraocular surgery (phacoemulsification) was uneventful when the drug was temporarily discontinued in the perioperative period. We believe that this is the first report in literature that describes sudden hemorrhagic periocular complications of dasatinib following ophthalmic surgery.

Introduction:

We report of a juvenile diabetic who developed sight threatening orbital hemorrhage after uneventful scleral buckling that is attributable to use of Dasatinib in the presence of normal hematological parameters. This report highlights the further management, the need for careful analysis of systemic parameters and pharmacological considerations in planning subsequent surgery to avoid similar occurrence

Case Report:

A34 year old diabetic male presented with progressively worsening vision in the right eye for 3 months and decrease in vision in left eye since 1month with past history of having

undergone unsuccessful vitreo retinal surgery in his right eye(OD) elsewhere (performed for advanced diabetic traction retinal detachment). He was treated for CML 4 months back and was in remission with tablet dasatinib 50mg once daily for the past 2 weeks. His systemic medications included two antidiabetic medications- linagliptin 5 mg once daily and empagliflozin 10 mg once daily.

He presented with vision of Perception of light (PL) in ODwith dense vitreous cavity hemorrhage and ultrasonography(USG) showed an underlying RD (figure 1A).

The left eye(OS) had visual acuity of counting finger at 1meter,intraocular pressureof 14 mmHg, controlled with timolol maleate 0.5% and brimonidine 0.2% for secondary glaucoma. There was no rubeosis. Fundus showed densevitreous haemorrhage and USG showed anunderlying RD (figure 1B). He underwent 25 G pars plana vitrectomy and membrane dissection under peribulbar anaesthesia (PA) after bevacizumab was injected 2 days before to reduce the vascularity of the fibro vascular tissue. The post-operative period was uneventful. At two monthspost-operative visit, he regained 6/9 vision. The posterior pole showed residual fibrous tissue above upper arcade that was minimally distorting the macula (Figure 1 C). The peripheral fundus revealed a nasal retinal detachment due to a retinal break between 8 and 9 o'clock in the periphery (figure 1 D). He underwent scleral buckling (SB) with #279 solid silicone tyre in 2 quadrants (superonasal and inferonasal) and #240 encircling band with externaldrainage of subretinal fluid and intravitreal injection of 0.4 ml of 100 % Sulfur hexafluoride (SF6) gasunder peribulbar anaesthesia (PA) using bupivacaine and hyaluronidase. On first post-operative day the patient complained of severe pain. Examination revealed PL vision, gross lid edema, chemosis, sub conjunctival haemorrhage, hyphaema and high digital tensionwith restricted ocular movements (figure 2A). The intradermal skin test for hyaluronidase sensitivity was negative. Patient underwent blood investigations for coagulation profile including factor VIII and XIII which were normal. Magnetic resonance imaging features were suggestive of peri bulbar and retro-bulbar hemorrhage. He was initially givenoral non-steroidal anti-inflammatory drugs and subcutaneous injection of 10 milligram of vitamin K. In view of clinical severity and inadequate response, and after consultation with the internist and oncologist, 500 milligrams of intravenous methyl Prednisolone (IVMP) was administered twice a day for 3 days

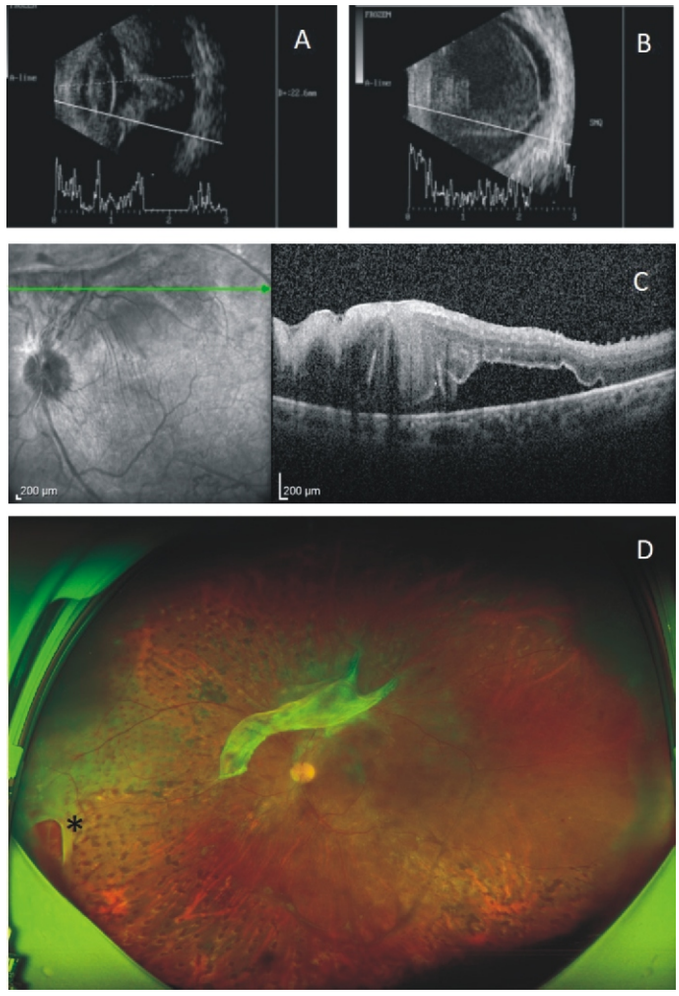

Figure 1:

A. Ultrasonography of the right eye showing a membrane echo attached to the optic nerve head suggestive of retinal detachment with funnel configuration

B. Ultrasonography of the left eyeshowing a membrane echo attached to optic nerve head suggestive of retinal detachment, with hyperreflective dot echoes in vitreous cavity suggestive of vitreous haemorrhage

C. Optical coherence tomography showing localized extramacular traction corresponding to the area of proliferation.

D. Ultra-widefield fundus image (Optos) of the left eye showing nasal retinal detachment with dry residual proliferations superior to disc.

and then switched to oral steroids. A lateral canthotomy and cantholysis was also performed to reduce orbital pressure (figure 2B)in view of further clinical worsening. He showed gradual improvement and resolution of the orbital edema and hemorrhage over the next few weeks(figure 2 C, D), with BCVA improving to 6/60,N10. The retina was well attached with good buckle indentation (figure2C). The IOP was well controlled with timolol maleate 0.5%, brimonidine 0.2%and brinzolamide 1%.

Nine months later he underwent Phacoemulsification with Intraocular lens implantation under PA as before. This time, after consultation with the oncologist, tablet dasanitib was withheld for 1 week prior to the surgery and restarted 1 week after the surgery. The surgery and post-operative period was uneventful. BCVA was 6/18N6 at 6 weeks follow up with attached retina which was maintained at last follow up14 months after the last surgery.

Discussion:

Dasatinib inhibits multiple tyrosine kinases by competitive inhibition at the enzyme's ATP-binding siteand is an US Food and drug administration (FDA) approved second-generation multitarget kinase inhibitor of BCR-ABL oncogene.[1,2] It is the drug of choice in Chronic Myeloid Leukemia (CML) patients who are resistant to treatment with Imatinib Mesylate.[1]Dasatinib also inhibits other kinases including platelet-derived growth factor receptor (PDGFβ).[1]It exhibits reduced selectivity but is325 fold more potent than imatinib and has been found efficacious in patients with CML resistant or intolerant to imatinib. [3,4]

Dasatinib has a plasma protein binding of 96% and it is known to be distributed in the extravascular spacecontributing to fluid retention, a common side effect reported in 50% of patients on oral Dasatinib.[1] The risk of periorbital edemais reported to be 5-

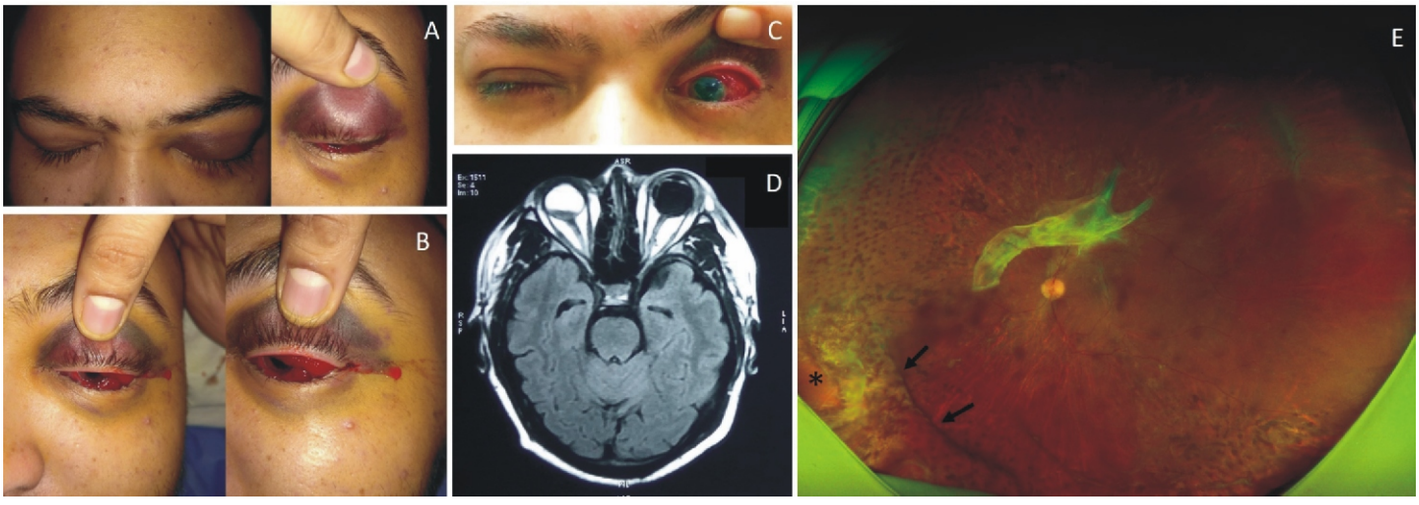

Figure 2:

A. External photograph showing left sided ecchymosis of eyelids with conjunctival chemosis seen on forceful eye opening
B. External photograph post lateral canthotomy + cantholysis, showing left sided ecchymosis of eyelids with conjunctival chemosis, with some improvement in extraocular movements.
C. External photograph showing resolution of severe conjunctival chemosis 1 week after canthotomy + cantholysis .
D. MRI T1 weighted image showing resolution of retro-orbital hematoma on the left side, 3 weeks post canthotomy+ cantholysis.
E. Ultra-widefield fundus image(Optos) of the left eye showing attached retina with break at 8 o' clock position (*) well supported by scleral buckle indent (arrow), peripheral laser scars and dry residual proliferations superior to disc.

10% according to the BC Cancer Agency Cancer Drug Manual.[1,2] However such cases are not reported in ophthalmic literature. Imatinib Mesylate, a drug belonging to the same group, although structurally distinct, is better known to cause periorbital edema in about 70-% patients.[5]

Dasatinib is known to be associated with an increased risk for bleeding episodes but post-operative/ operative site complications are less described. [1] A case of dasatinib induced bilateral spontaneoushyphaema has been reported in a patient of CML also on low dose aspirin and clopidogrel.[6] In this case a possible mechanisms of platelet dysfunction, alterations in thrombin formation and disruption of vascular endothelial integrity has been proposed.[6] To our knowledge this is the first case report of haemorrhagic complication with features of fluid retention triggered by surgery.

The development of these suspected drug related complications suspected after SB could be attributed to the recent onset of intake of drug, the peak concentration 0.5-3 hours after oral intake, or to the extraocular and orbital manipulation during SB compared to micro incision vitrectomy surgery (MIVS).

The choice of surgical procedure was due to the phakic status, clear lens, location of the break and the fact that no intraocular manipulation was planned. A reattachment rate of69% has been reported with similar detachments post vitrectomy with use of intravitreal gas injection.[7]In the absence of a bleeding diathesis, the possibility of peribulbar block related complication was the initial diagnosis, however the worsening over a week despite aggressive medications indicated that this was unlikely. Pulse steroid therapy using 3-6 pulses in considered in many systemic inflammatory conditions for faster clinical recovery. [8]

The terminal half-life of dasatinib is 5-6 hours and considering that a drug takes around 4-5 half-life for elimination, around 30 hours is required for its complete washout. Keeping this in mind a safe period of withholding the drug of 1 week before the surgery was advised by the oncologist during the second surgery which was uneventful.

Ocular complications can be associated with many systemic drugs and therefore a detailed medical history may give us new insights, especially with newer pharmacological formulations with lesser known side effect profiles. Even in the post-operative period a high level of alertness is required to differentiate unusual events like orbital edema that occur spontaneously due to surgical manipulation, from those precipitated by systemic medications. This case report emphasizes the need to either alter the medications or surgical plan while performing ocular/orbital surgery in patients on dasatinib or any medication of this class of drugs.

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Notes

Notes

Notes

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*Based on bench lab testing.

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