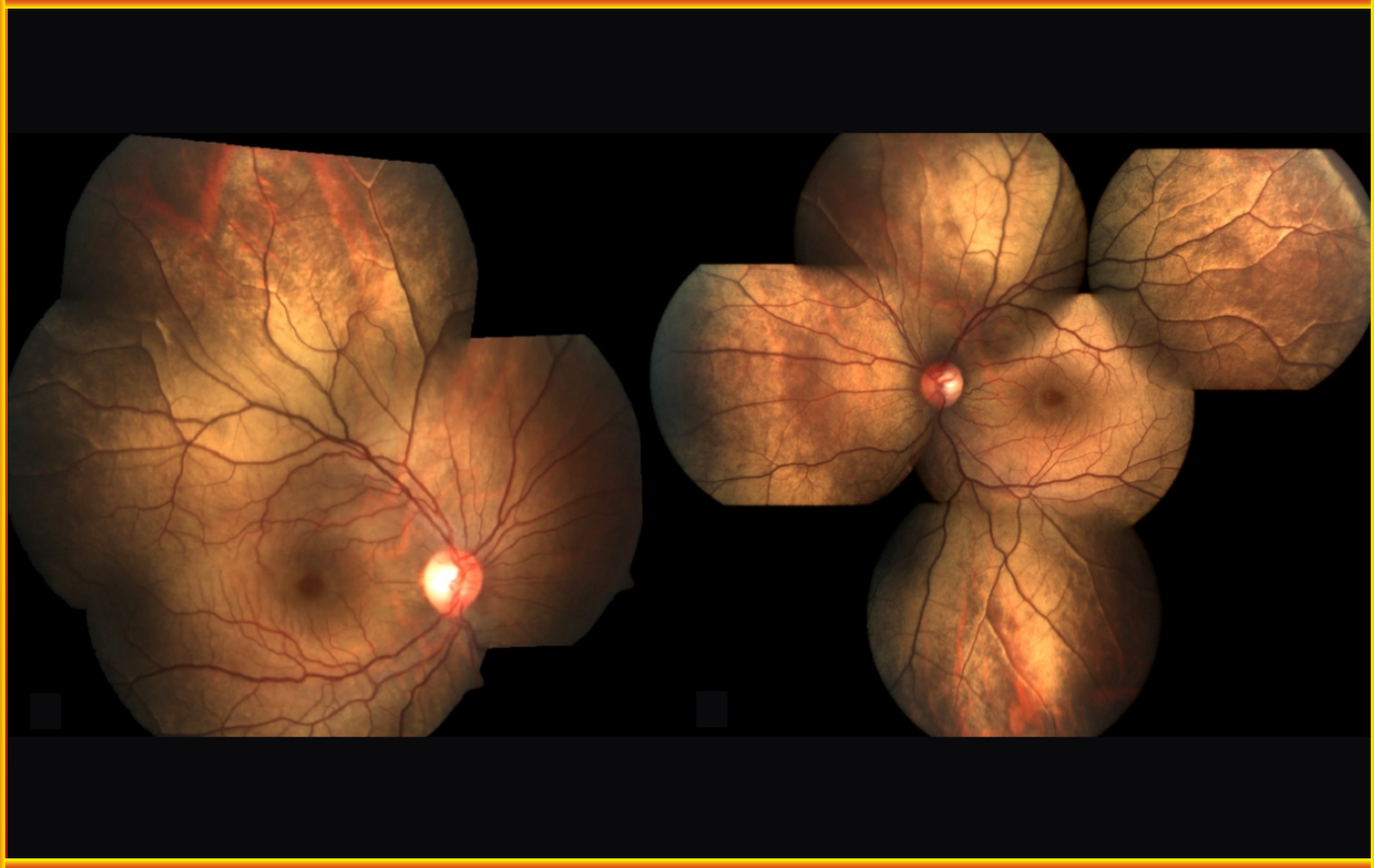
SEPTEMBER 2021

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 the world opens up more and monsoon spreads its wings across and normalcy now seems a rality let us wish everyone a safe and normal year ahead. This year too our conference will be a virtual one with important announcements coming in soon. Meanwhile this month our newsletter offers important views on Ocular tuberculosis by none other than Dr Narsing Rao and SoumyavaBasu.

The spotlight takes the uveitis discussions forward with a spotlight moderated by Aniruddha Agarwal and a host of eminent uveitis specialists on challenging scenarios in uveitis.

Once again wish you all a very happy oncoming festive season and a safe year ahead

Regards and best wishes

Shobhit Chawla
President
VRSI

From the Honorary Secretary's Desk

Dr. Raja Narayanan
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Dear Friends:

Greetings from VRSI. We are delighted to bring out the next edition of 2021 Newsletter. I am sure that your practices have picked up after slowing down due to the second wave of COVID. The abstract submission for VRSI annual conference is open now. We have invited renowned speakers for the conference, and all of us are looking forward to releasing the final scientific program soon.

We are getting excellent responses 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 have opened submissions for interesting short videos which would add another dimension to our educational activity.

An excellent issue of VRSI Newsletter has been compiled by Dr. Anand Rajendran. I am sure that you will find their articles 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. Please do send me your valuable suggestions, on how we could improve the interaction with VRSI members on any aspect of clinical care, education, research, industry relation and regulatory updates. Stay safe, and we shall meet online again very soon.

Regards

Raja Narayanan
Hon. General Secretary
VRSI

From the Convenor, Scientific Committee's Desk

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Dear Friends and Colleagues

As the planet recovers and emerges from the scourge of the pandemic, it is time for better tidings. After the success of the 1st Virtual VRSI Meet last December, the next edition – the Virtual VRSI 2021 is around the corner and is scheduled to be held from Dec 16-19 2021. The Abstract Submitter is open and we are delighted to see the tremendous response thus far. We have a galaxy of renowned international stalwarts and eminent national faculty for the event. We welcome and urge all members to participate and send in their submissions and make the event an even greater success.

It has been a pleasure bringing out the September edition of the VRSI Newsletter 2021, one that is focussed on Uveitis. We have Dr. Narsing Rao, an internationally acclaimed Uveitis specialist along with Dr. Soumyava Basu, giving us a an erudite account on Intraocular Tuberculosis in the 'StalwartSpeak' section. The Spotlight article of the issue, anchored by Dr. Aniruddha Agarwal, along with an eminent panel of national experts, focusses on Challenging Scenarios in Uveitis. In the Innovator's Isle section, Dr. Prabu Baskaran and our team describe an interesting DIY innovation to tackle the menace of fogging in Vitreoretinal surgery. Dr. Niranjan Sahoo holds forth on the utility of the NAVILAS laser in the Retina Tech Section. Finally, we have an interesting case report from Dr. Chitaranjan Mishra to round off this issue.

We look forward to engaging with all of you in VRSI's webinars as well as the Virtual VRSI Meet 2021.

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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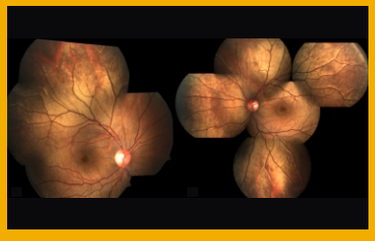
A WINNER OF THE VRSI IMAGING CONTEST



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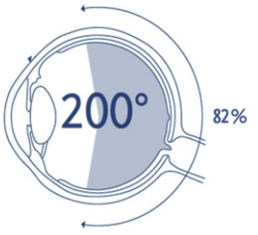

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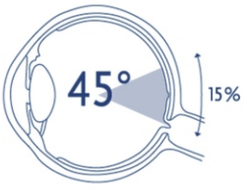

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STALWARTSPEAK

Intraocular TB: Making strides on the bench and bedside

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Intraocular tuberculosis (IOTB) has been a widely discussed topic at various academic fora, especially in endemic countries such as India. Most of these discussions have been guided by expert opinions and personal biases. However, the past two decades have seen a remarkable shift in the approach to understanding IOTB. This shift in our understanding has come from systematic documentation and analysis of clinical records, application of new ocular imaging modalities and molecular diagnostics, and laboratory research on animal models and human samples. The impact of this clinical and bench research can be broadly divided into the following categories: recent recognition and documentation of clinical signs, new imaging observations, outcomes of anti-TB therapy (ATT) and adjuvant therapies, histopathological studies and studies on animal models and human ocular samples.

Amongst the clinical signs, serpiginous-like choroiditis (SLC) or multifocal serpiginoid choroiditis has been recognized as a significant finding of IOTB. 1The importance of this morphologic change in diagnosis of IOTB is supported by therapeutic response to anti-tuberculosis agents and molecular evidence primarily from intraocular fluid analysis.2,3The morphological diagnosis of serpiginous-like choroiditis is almost exclusively associated with IOTB in TB-endemic countries, although it has also been linked to other infectious and non-infectious entities.4 SLC can be distinguished clinically from the autoimmune serpiginous choroiditis, which is rarely found in India.5 Since being reported from India in 2003,1 SLC has been widely recognized as a presenting sign of IOTB across the world, in both TB-endemic and non-endemic countries. In non-endemic countries, SLC is seen mainly in individuals of who migrated from endemic regions.

The other important clinical signs have been identified in TB retinal vasculitis. These include presence of subvascular retinitis lesions (active or healed), focal vascular tortuosities, and vascular occlusion.6 Together, these clinical signs and SLC have high predictive value for IOTB in TB-endemic countries and increase the pre-test probability of IOTB in patients with immunological or radiological evidence of systemic TB infection.7

Almost in parallel to the identification of clinical signs, new imaging tools have become necessary adjuncts to the clinical evaluation of IOTB. These imaging tools include wide field fundus photography and autofluorescence, optical coherence tomography (OCT), OCT-angiography, apart from the

conventional fluorescein angiography and indocyanine green angiography. 8Multi-modal imaging (MMI) with these tools assists in identifying disease patterns and extent, complications and sequelae, and response to treatment.9 These imaging tools have also provided unique insights into the pathogenesis of IOTB. For example, MMI has revealed the involvement of outer retina, retinal pigment epithelium and choriocapillaris in SLC, and the changes that occur in response to treatment.

Another major advancement has been in the molecular diagnosis of IOTB. This has progressed from conventional polymerase chain reaction (PCR) to nested PCR, real-time quantitative PCR, reverse transcriptase PCR for RNA, and normalized quantitative PCR.10-12 This has been accompanied by introduction of new primers, alone or in combination (multi-targeted PCR).10Non-PCR techniques such as loop mediated isothermal amplification (LAMP) assays have also been applied and promise to be cost-effective tools for molecular diagnosis of IOTB. 13 Despite these advances, molecular techniques are yet to find widespread acceptance in clinical practice. Possible reasons include the relative ease of clinical diagnosis of IOTB in endemic countries, difficulties in aqueous or vitreous sampling, lack of access to PCR facilities, and false negative (due to inadequate/inappropriate sample) or false positive results (due to bystander TB-DNA in TB-endemic countries).12

All the above advances have led to development of diagnostic criteria for initiation of ATT in IOTB. Most studies have noted therapeutic efficacy of 80-90% in preventing recurrent inflammation after completion of ATT.14The multicentric Collaborative Ocular Tuberculosis Study (COTS) recently proposed consensus-based guidelines from 81 uveitis experts across the globe, for initiation of ATT in TB choroiditis, intermediate uveitis, panuveitis, retinal vasculitis and anterior uveitis.15, 16 These guidelines should ensure uniformity in treatment of IOTB and provide comparable data for future analysis. The role of adjunctive therapy in IOTB has also been investigated. This includes corticosteroid therapy, either systemically or locally with sustained release dexamethasone.17These are particularly critical in treatment of TB-SLC, which is prone to paradoxical worsening after initiation of ATT.18 In addition, intravitreal anti-vascular endothelial growth factor (VEGF) such as bevacizumab has been used in management of refractory choroidal granuloma.19

Histopathological studies of enucleated globes and ocular tissue biopsies have provided insights into the nature of inflammatory response in IOTB. Two such relatively recent studies includea series of five eyes from India (1995),20 and another series of 42 eyes, from the United States (2011).21 Both the studies showed the presence of extensive granulomatous inflammation with necrosis but very few bacilli (1-2) in ocular tissues. More recent studies have also demonstratedintra-retinal granuloma formation in TB retinal vasculitis,22 and inner choroidal granulomatous inflammation with necrosis and photoreceptor damage in TB-SLC.23The granulomatous inflammation in the eye has also been foundin animal models that were systemically infected with mycobacteria. In the guinea pig model, the animals were infected with aerosol containing TB bacilli, and granulomatous inflammation noted in the eye after 56 days.24 The intraocular granuloma were also found to produce large quantities of VEGF.25 More recently, the zebrafish embryo model has been used to demonstrate dissemination of mycobacteria from the systemic circulation into the eye, across the blood retinal barriers, as well as the early interactions between the bacilli and the host immune system.26,27

Unlike the above histopathologic reports of uveal granulomatous inflammation, a well-documented IOTB histologic study with special stains and quantitative PCR of dissected Retinal Pigment Epithelium (RPE) revealed presence of Mtblocalized to RPE layer with underlying choroidal granulomatous inflammation with necrosis.28Finally, in vitro studies in RPE cell cultures and from human vitreous samples have provided further insights into the host microbial interactions in IOTB. The RPE cells have emerged as a sanctuary for mycobacteria which phagocytose the mycobacteria but are not bactericidal thus allowing the bacteria to survive in the cells for a long time.29Another significant observation has been the presence of both TB-specific and retinal antigen specific (autoreactive) T-cells in the vitreous samples of IOTB patients.30 The autoreactive T-cells are more pro-inflammatory and are resistant to cell death, thus prolonging the inflammatory response. Further dissection of this dual immune response (anti-mycobacterial and autoimmune) in different stages and clinical presentations of IOTB will help in tailoring the diagnostic and therapeutic strategies for patients.

Thus, there have been significant advances in nearly every aspect of IOTB – both at the bench and on the bedside. However, there are several gaps that need remain to be filled. For example, a multicentric prospective study to validate the criteria for initiation of ATT. Similarly, the duration of ATT for IOTB also needs to be defined through prospective studies with adequate sample size. Considering the rapidity of progress and huge interest in the field across the globe, it is likely that we will meet these objectives very soon.

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SPOTLIGHT

Challenging scenarios in infectious and non-infectious uveitis

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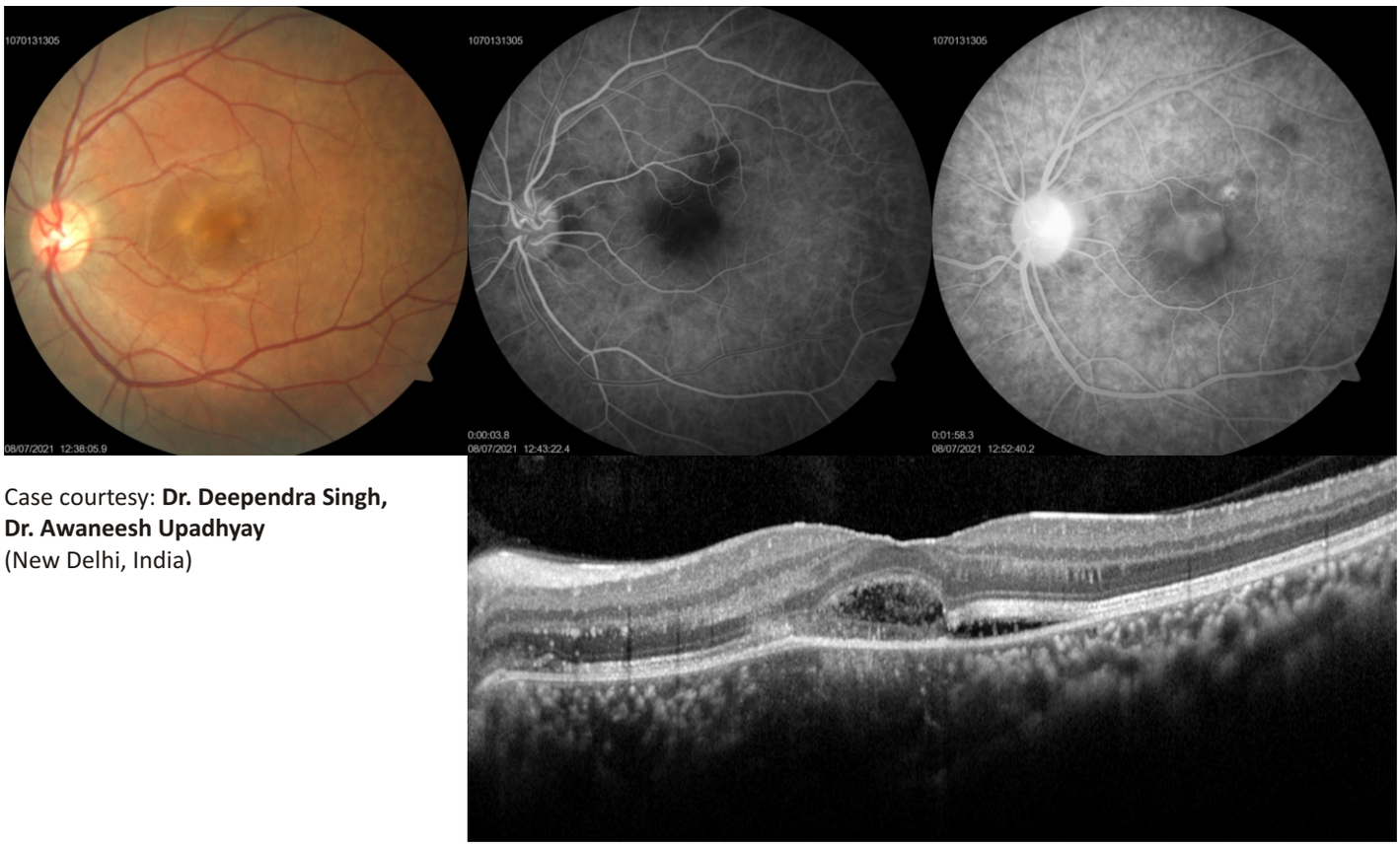
Case 1

Macular choroiditis

26-year-old male with sudden decrease in vision in left eye for the past two days. VA: 20/150. No investigations done. No treatment initiated.



Case courtesy: **Dr. Deependra Singh, Dr. Awaneesh Upadhyay**
(New Delhi, India)

Questions:

1. **Eyes with macular choroiditis present a unique challenge needing emergent diagnosis/treatment. How do you proceed with the evaluation and treatment of such cases?**
2. **Since macular choroiditis can often have subretinal fluid, do you manage it differently?**
3. **Looking at the above clinical scenario, what would be your phenotype diagnosis of the uveitis?**

1. Eyes with macular choroiditis present a unique challenge needing emergent diagnosis/treatment. How do you proceed with the evaluation and treatment of such cases?

HNS/SG: Unilateral inflammation in a young patient is highly suspicious for infectious uveitis, so the first step will be to perform a diagnostic panel to rule out infections especially tuberculosis and syphilis. If infection is suspected or found the treatment should be targeted towards the underlying infection.

AF: The first step is to differentiate infectious etiology from immune etiology. Immune etiologies usually show "typical" clinical features and easily identifiable on exploring the fundus, for example choroidal lesions in Birdshot are usually multiple, mostly nasal and with accompanying retinal vasculitis; or acute posterior multifocal placoid pigment epitheliopathy (APMPPE) lesions are plaque-like lesions, multifocal and circumscribed to the posterior pole. An immune disease that could be considered in case of a macular choroiditis could be sarcoid. Once a "typical" immune clinical picture has been ruled out, an infection (or a masquerade, i.e., metastasis) has to be considered. The number one cause in infection is tuberculosis. Syphilis should be always considered. Infrequent infectious etiologies may be considered depending on the clinical history and the immune status of the patient. Hence, tuberculosis, sarcoidosis and syphilis would be at the top of the list.

AG: In my opinion, the patient has monofocal choroiditis lesion in the macula. On fluorescein angiography (FA), it shows an initial hypofluorescence and in the late frames, it shows two types of hyperfluorescence, due to the staining of outer retinal fluid and the subretinal fluid. It would have helped if an indocyanine green angiography (ICGA) had been done to see if there are more lesions in the choroid that have not been picked up on FA. My gut feeling is this patient has a few more lesions. The optical coherence tomography (OCT) has many interesting features in this patient.

a. The inner retina is normal up to the external limiting membrane ruling out any retinitis.

b. Vitreous cells are not made out. There is a horizontally oval lesion in the choroid which is elevating the RPE and the outer retina.

c. Temporal to the fovea there is a thin layer of subretinal fluid.

d. Just anterior to the choroidal lesion there is disorganization of all the layers of the outer retina.

e. there is bacillary layer detachment with intraretinal fluid collection in the inner segments of the photoreceptors.

f. There appears to be infiltration of the retina just anterior to the choroidal lesion.

g. there are many hyperreflective dots in the outer retina in the juxtapapillary area. My interpretation of this OCT: It is an inflammatory pathology and most likely a tubercular granuloma. My workup would include: Mantoux test, QuantiFERON TB-Gold plus test, computerized chest tomography (contrast-enhanced), syphilis serology. I would also do a baseline blood sugar level, complete blood counts, and liver function tests. There is no evidence of retinitis so I will not order investigations for toxoplasma, herpes or zoster virus.

JB: My initial work-up in these patients would be to obtain a complete panel of ophthalmic imaging. These would include: fundus photograph (conventional, not ultra-widefield), fundus autofluorescence, FA and swept-source OCT. I would work up for TB (Mantoux, QuantiFERON TB Gold test and high resolution CT chest) and syphilis.

PM: I would like to proceed with a complete ophthalmic and systemic evaluation followed by an ordering of tailor-made investigations for these cases. Systemic history of fever, evening rise of temperature, loss of weight, any other systemic focus of infection including SARS CoV-2 infection and vaccination history in view of current pandemic. In addition to color fundus photography and OCT images, I would like to get the fundus autofluorescence imaging with or without ICGA which will also help us in the management. Since it is a macular lesion closer to the fovea, I would like to start the patient on systemic steroids at the earliest after ruling out associated systemic infections such as syphilis, HIV, tuberculosis and SARS CoV-2.

BM/RM: Eyes with macular choroiditis needs emergency evaluation with baseline evaluation and additional tests. The baseline evaluation we all know includes apart from complete hemogram, tests for tuberculosis and syphilis. In this specific macular lesion, we shall also include test for toxoplasma IgG, IgM for itsatypical presentation, measles IgGsuspecting subacute sclerosing panencephalitis (SSPE). The clues for dengue titers, chickungunya titers, rickettsia titers can also be considered in appropriate clinical setting. Appropriate multi modal imaging of the lesions can be a useful addition like any posterior uveitis. If needed cerebrospinal fluid tap for Measles IgG and IgM can be attempted if there is neurological deterioration with neurologist opinion on electroencephalogram (EEG). OCT features during the course of the disease like rapid full thickness retinal involvement with destruction, thinning and atrophy in a very hyperacute manner should alert the clinician to apply the Dyken's diagnosticscriteria for SSPE.

2. Since macular choroiditis can often have subretinal fluid, do you manage it differently?

HNS/SG: Inflammatory subretinal fluid will often respond to oral or periocular corticosteroid. Once infection is ruled out, corticosteroid treatment should be initiated. In a young person, regional corticosteroid injections may be tolerated, with the awareness of the increased risk of intraocular pressure (IOP) rise and progression of cataract. However, it would be a good idea to avoid local corticosteroids if the clinical picture or etiology is not very clear. In such cases a trial of systemic steroids may be a safer approach as systemic steroid effect weans off quicker once it is discontinued.

AF: The treatment will depend on the cause; both tuberculosis and syphilis will need antibiotics and I always add steroids (even pulse 250-500 mg methylprednisolone if there is foveal involvement).I do not manage differently when subretinal fluid is present.

AG: Macular choroiditis needs urgent treatment. Once the labs have been sent, and without waiting for the reports, I would start the patient on oral corticosteroids at 1mg/kg body weight. I would add anti-tubercular therapy if any test for tuberculosis is positive. The labs would also rule out possible sarcoidosis, chances of which, anyway, are minimal with this OCT picture. Unlike sarcoid granuloma, tubercular granulomas tend to infiltrate the overlying outer retina. I would like to rule out syphilis in all patients of uveitis because it can mimic any phenotypes of uveitis.

JB: As the lesion is over the fovea. I would manage it with intravenous methylprednisolone 1 gram daily for 3 consecutive days. followed by oral steroid. I would consider anti-TB treatment if Mantoux or QuantiFERON TB gold test.

PM: I treat like any other choroiditis. However, in the present situation due to COVID-19 pandemic, I will make sure that there is no associated central serous chorioretinopathy component before starting the patient on systemic steroids.

BM/RM: Presence of subretinal fluid in macula needs appropriate full dose titration of ocular inflammation with oral steroids. If infections are ruled out, posterior subtenon corticosteroids can be given. However, their use is controversial in infectious conditions, and they are employed based on the previous response to steroids.

3. Looking at the above clinical scenario, what would be your phenotype diagnosis of the uveitis?

HNS/SG: Highest in the differential is tubercular uveitis. Depending on patient characteristics and past medical history Vogt-Koyanagi-Harada's syndrome, sarcoidosis, and drug-induced uveitis are also possible.

AF: The retinography shows a round, choroidal lesion with subretinal fluid and yellowish components; the lesion has early hypofluorescence and late hyperfluorescence and leakage of the optic disc, as well as a hyperfluorescent focal lesion above the main round lesion is observed. Structural OCT shows bacillary detachment and subretinal fluid as well as an area of hyperreflectivity of the outer retina next to the bacillary detachment. The RPE is pushed by a choroidal hypo-reflective lesion with associated disturbance of the normal dotted pattern of the choriocapillaris. I would say that this is a choroidal granuloma and if the patient had any evidence of tuberculosis, I would give anti-tuberculous treatment with steroids.

AG: My phenotype diagnosis ismacular chorioretinitis.

JB: I would not label a particular diagnosis. I would keep a differential diagnosis of macular serpiginous choroiditis and unilateral acute idiopathic maculopathy (UAIM).

PM: Considering the phenotype, the possibility of macular choroiditis is there as well as the possibility of unilateral acute idiopathic maculopathy can be considered.

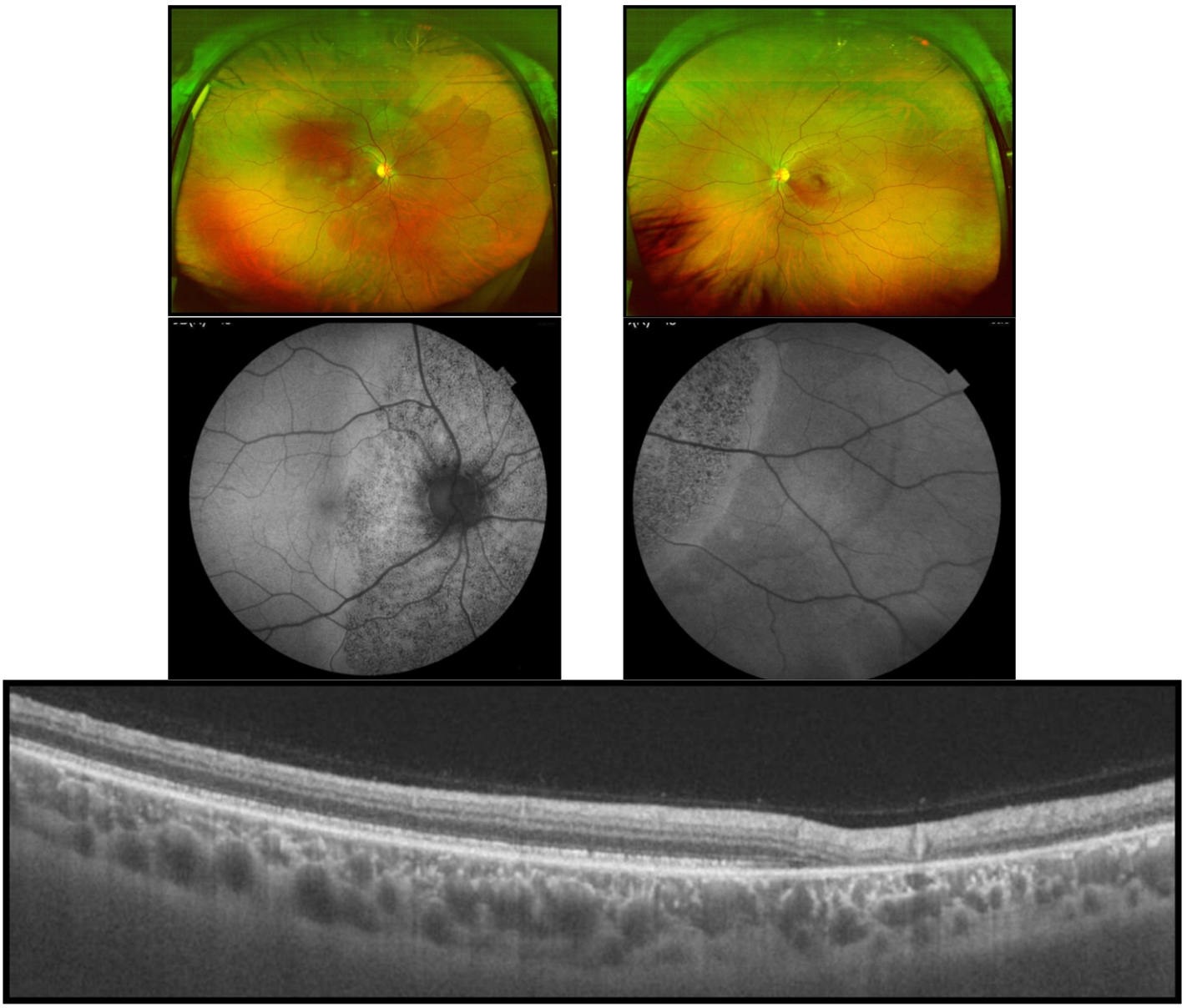
BM/RM: The phenotype diagnosis should focus on SSPE, toxoplasma, atypical macular serpiginous choroiditis which is less likely and delineated by imaging and progression of clinical findings and lab reports coupled with response to treatment

The case of macular choroiditis highlights the importance of emergent diagnosis and management of these patients to prevent permanent vision loss. Experts agree that our patient has choroiditis, and the imaging revealed a choroidal granuloma. In such cases, it is important to identify the phenotype and rule out retinitis (due to toxoplasmosis, SSPE, and other causes). Unilateral acute idiopathic maculopathy is an important differential diagnosis. These patients benefit from emergent corticosteroid therapies.

Case 2

AZOOR

24-year-old young male with scotoma in the right eye. Says he sees black spot in front of the right eye since ~ 1 year



Questions:

1. **Please tell us the phenotypes of uveitis where you consider an infection due to RNA viruses**
2. **What are the hallmark features of AZOOR, specifically how not to confuse with autoimmune retinopathy?**
3. **Do you treat AZOOR with antivirals?**

1. Please tell us the phenotypes of uveitis where you consider an infection due to RNA viruses

HNS/SG: Most common cases of viral posterior uveitis in the USA are caused by DNA viruses especially herpetic family. In the given case, salt and pepper mottling of the retina does raise suspicion for rubella retinopathy (rare).The large placoid areas on color photo and the loss of outer retinal layers should prompt syphilis testing. Other differential diagnoses include non-uveitic entities such as retinal degeneration and cone-rod dystrophies.

AF: In my clinical practice, I have almost never considered an RNA virus as an etiologic agent of a uveitis case. The most frequent viral etiology in my experience is herpes virus group, which are DNA virus. Herpes virus infections present with a typical clinical picture of acute retinal necrosis (peripheral necrotic lesions, peripheral arteritis, vitritis and papillitis) which are usually caused by varicella zoster virus or herpes simplex 1.In a clinical picture of hemorrhagic vasculitis and/or granular retinitis in an immuno suppressed patient (transplant/HIV), cytomegalo virus infection needs to be considered.

AG: Acute zonal occult outer retinopathy (AZOOR) is a disease mostly seen in Caucasians. I have had no personal experience of AZOOR even though I was actively looking out for this diagnosis ever since it was described by Don Gass. I believe some anecdotal cases have been reported from India.

JB: Foveolitis and exudates with hemorrhage can be seen in Dengue and Chikungunya virus associated post-fever retinopathy. These are the RNA viral infections that I have encountered in my practice.

PM: Phenotypes of uveitis associated with RNA viruses are viral anterior uveitis, Fuchs' heterochromic iridocyclitis (thought to be associated with rubella), posterior uveitis which can be in the form of white dot syndromes, salt and pepper retinopathy, retinal vasculitis andpost-fever retinitis.

BM/RM: The phenotype of AZOOR typically involves a myopic female in the middle age group. However, in this male patient care needs to be taken to apply the diagnostic criteria proposed by Gass. History of prodromes of viral illness helps us to incline towards viral etiology, although the pathognomic characteristics of viral etiology are difficult to identify. Large scale studies on this controversial area are needed. We sincerely admit that in the practice of one and half decade we have seen few single digit patients only.

2. What are the hallmark features of AZOOR, specifically how not to confuse with autoimmune retinopathy?

HNS/SG: AZOOR has been described as having outer retinal layer loss that can be identified on fundus autofluorescence as a zone of hypo-autofluorescence surrounded by a ring of hyper-autofluorescence. OCT also confirms the loss of outer retinal layers. Autoimmune retinopathy (AIR) is characterized by complete absence of fundus lesions, absence of intraocular inflammation, presence of serum antiretinal antibodies and ERG abnormalities with no other possible organic cause for the visual abnormalities. Both AZOOR and AIR can have autofluorescence, OCT and ERG abnormalities, but AZOOR tends to stabilize over time and AIR continues to progressively have loss of photoreceptors.

AF: The characteristic AZOOR lesion is the trizonal lesion; the three areas or zones may be distinguished on fundus autofluorescence, OCT and ICGA. A hyper-autofluorescent line demarcating the AZOOR lesion is frequently observed. On fundoscopy, the AZOOR lesion is observed as peripapillary areas of retinal pigment abnormalities; this lesion is typically unilateral (though bilaterality may develop) and progresses, though rarely involves the fovea. These described abnormalities would correspond to the established/chronic lesions, however, in the acute stage changes are milder. In acute cases, the examination may be normal or show a faint whitening of the peripapillary retina surrounded by a whitish line. The OCT will show disruption of ellipsoid zone and outer nuclear layer. Autofluorescence will show hyper-autofluorescence. Autoimmune retinopathy shows more diffuse abnormalities, resembles retinitis pigmentosa and no trizonal lesion is observed.

AG: My description of AZOOR is largely based on the extensive lectures by Dr. Anita Agarwal who was associated with Dr.Gass. AZOOR is predominantly seen in young myopic females who present with shimmering scotomas after a viral prodrome. The fundus examination is mostly normal in the early stages, the disease is asymmetrical bilateral. Characteristic enlargement of the blind spot and permanent scotoma is seen on the perimetry with significant ERG changes. On autofluorescence imaging, a characteristic hyper-autofluorescent line is seen at the progressive edge of the lesion. There is a zonal loss of RPE, choriocapillaris and outer segments of photoreceptors in the affected zones. Viral prodromes are not uncommon before the onset of many autoimmune disorders also. The presence of anti-retinal antibodies is not evidence of either the AZOOR or AIR (cancer-associated retinopathy i.e., CAR; melanoma associated

retinopathy i.e., MAR or non-neoplastic autoimmune retinopathy). Unlike the AZOOR where the lesion is seen in contiguity with the optic disc, the lesions in AIR are predominantly periarterial as described by Dr. Narsing Rao.

JB: Trizonal autofluorescence, enlargement of blind spot, central scotoma are hallmark features of AZOOR. ERG is markedly abnormal as well. AIR commonly produces negative wave forms. Clinically, I often find it important differentiating the two entities based on a history of paraneoplastic and melanoma associated retinopathy. In AIR, antiretinal antibodies (anti-recoverin antibody) are positive.

PM: AZOOR is a rare white dot syndrome, affects young and middle-aged individuals (mostly women), characterized by loss of zones of outer retinal function. Symptoms include acute onset photopsias and subjective visual field losses. The fundus is initially normal with field defects, oritcan present with striking trizonal pattern of fundus autofluorescence due to distinct patterns of retinal pigment epithelial involvement, which may beself-limiting or progressive. Thinning of photoreceptor cell layer with loss of the outer segments and abnormal inner retinal lamination with enlargement of blind spotare seenin AZOOR. Exact etiology is not known. A viral infective agent with subsequent immune alteration of the photoreceptors is postulated. Progressive reconstitution of the ellipsoid zone on OCT with resolving outer retinal changes are seen in AZOOR. Autoimmune retinopathyusually presents with normal looking fundus, presence of antiretinal antibodies, progressive loss of vision associated with loss of photoreceptors and ERG changes.

BM/RM: The hallmark features of AZOOR depends on the stage of AZOOR and theclassical trizonal pattern seen in fundus autofluorescence, OCT, FA/ICGA findings, electrophysiological tests, adaptive optics findings. Thorough evaluation and investigations to rule out paraneoplastic syndromes and AIRare mandatory.

3. Do you treat AZOOR with antivirals?

HNS/SG: There are reports in literature that associate AZOOR with possible latent viral infections and treat with valacyclovir. I only add valacyclovir if there is a history of prior viral infection or if the patient tests positive for serum herpes simplex IgM.

AF: No treatment has been shown to halt the progression of AZOOR, however, I prefer treating with steroids / immunosuppressive drugs rather than antimicrobials.

AG: No specific RNA virus has been detected in these patients and I do not think there is a role of any antiviral therapy least of all the acyclovir. Treatment is corticosteroids and other immuno suppressive agents.

JB: I treat AZOOR with immunosuppressives and steroids. Standard treatment is still not established. Few reports are present in literature regarding antivirals with questionable efficacy.

PM: Earlier I used to treat with empirical course of antiviral therapy with systemic steroids in suspected viral trigger etiology of AZOOR. But now, I am not treating with empirical antivirals in AZOOR since it is due to post-infectious autoimmune response. I treat them with systemic steroids and systemic immunosuppressive therapy.

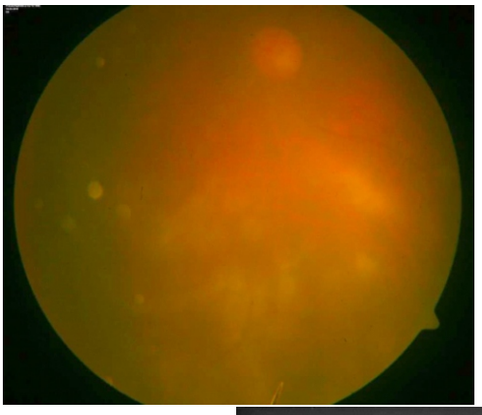
BM/RM: The treatment of AZOOR is controversial with no level 1 evidence available. We start antiviral agents along with oral steroids which may or may not improve the natural course of the disease. We explain the pros and cons of the lacunae in existing ocular literature and proceed with the treatment. Typically, such patients seek a second opinion from another reputed uveitis experts as well.

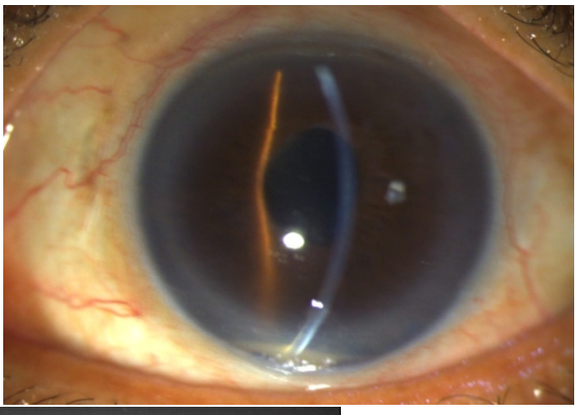
RNA viral infections such as dengue fever, chikungunya, among others are challenging in diagnosis and management. The epidemiology aids in the diagnosis, coupled with supportive laboratory assays. In the case of acute zonal occult outer retinopathy (AZOOR), the clinical manifestations are reminiscent of a post-infectious inflammatory condition. Therefore, these patients are typically treated with corticosteroids and immunosuppressive therapies without the need for antiviral treatment. The clinical manifestations, especially the trizonal pattern on autofluorescence help in clinching the diagnosis.

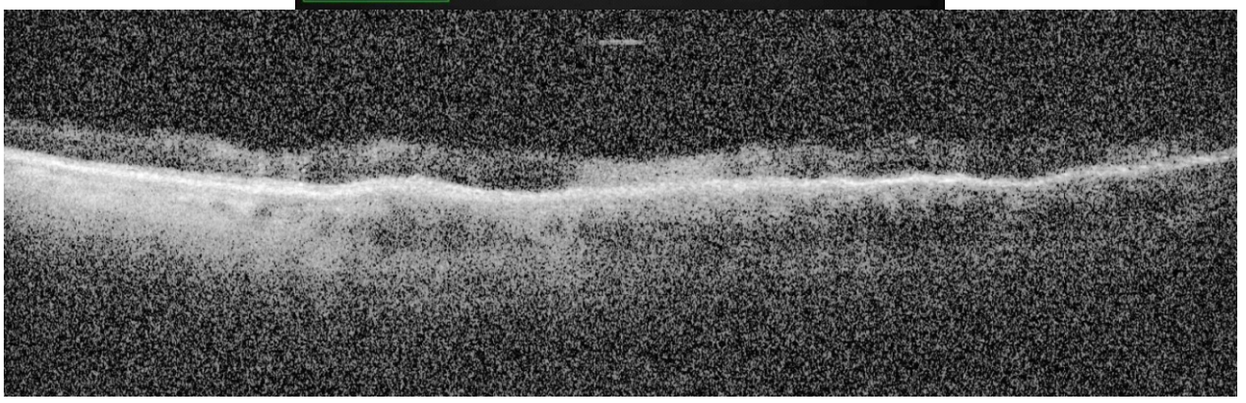
Case 3

CMV Retinitis

A 71-year-old diabetic patient was diagnosed with multiple episodes of anterior uveitis. For CME, he received intravitreal triamcinolone. A discrete retinitis patch noted. Underwent diagnostic PPV – CMV PCR strongly+. Received oral valganciclovir. Not immunocompromised. Developed hypopyon while oral antivirals ongoing.







Questions:

1. **In non-HIV CMV retinitis, do you encounter immune reconstitution, and development of such reactive uveitis?**
2. **Do you ever treat CMV retinitis with steroids/immunomodulators?**
3. **How often do you encounter resistance to valganciclovir? How do you diagnose and treat them?**

1. In non-HIV CMV retinitis, do you encounter immune reconstitution, and development of such reactive uveitis?

HNS/SG: CMV retinitis has increasingly been seen in the non-HIV population – among patients immunosuppressed following transplants or on immunosuppressive medications. CMV retinitis can present even in the absence of CMV viremia. These patients typically require induction doses of systemic antivirals +/- intraocular ganciclovir, and then remain on maintenance doses for prolonged period.

AF: Immune reconstitution uveitis (IRU) develops in HIV positive patients with CMV retinitis who have a substantial increase of CD4 several weeks after starting HAART (highly active antiretroviral therapy). It also may occur in patients taking immunosuppressive drugs when they leave these medications (and recover their normal immunity); in the case presented the mechanism could be related with a recovery of the local immune response when triamcinolone started losing its effect.

AG: CMV retinitis is a well-known complication of the use of intravitreal triamcinolone (IVTA) and dexamethasone implants. In the elderly, there is an age-related immune senescence leading to immune dysfunction which is usually responsible for infections and malignancy. The use of the IVTA in the elderly patient leads to profound local immunosuppression in the eye that may lead to CMV retinitis. When the CMV retinitis is seen in the context of HIV (when the CD+4 helper T cells count declines below 50 cells/µl) there are no inflammatory signs, and the media is clear. On the other hand, patients who develop CMV retinitis due to local immunosuppression due to IVTA or a dexamethasone implant, show a significant inflammatory reaction in the vitreous cavity. Non-HIV immune reconstitution inflammatory syndrome is seen in immunocompromised patients who have received an organ transplant, and TNF-α inhibitors and in patients with tuberculosis (in the pre-HIV era).This happens due to a shift in the balance between anti-inflammatory and pro-inflammatory cells (CD4+ helper T cells) to the continued presence of the dead or alive microorganisms. While the patient under consideration here is not systemically immunocompromised but has profound local immunosuppression which has allowed the migration of CMV into the retina and setting up inflammation. Breakdown of the blood ocular barrier has likely allowed the naïve CD4+ cells into the vitreous cavity and resulted in a massive inflammatory reaction including hypopyon. Recently, Downes et alhave reviewed the subject of non-HIV CMV retinitis extensively.

JB: Yes, it can be seen in organ transplant CMV retinitis. I have seen CMV retinitis in a case of bone marrow transplant. However, the CD4 count should be done if there is suspicion for HIV.

PM: Yes, I have seen immune reconstitution in non-HIV CMV retinitis in cases who received IVTA for refractory diabetic macular edema and in post renal transplant on systemic immunosuppressive medications.

BM/RM: Yes, non-HIV patients can have immune reconstitution like any other infectious uveitis. We needto meticulously ruleout non-HIVcauses of immune suppression like severemalnutrition, undetected malignancies, advanced aging, uncontrolled diabetes, metabolicmasquerades.

2. Do you ever treat CMV retinitis with steroids/immunomodulators?

HNS/SG: Like most infectious uveitis, there is an increase in intraocular inflammation following the institution of antivirals. This post-infectious uveitis requires a course of oral steroid and usually does not require long-term immunomodulation. Depending on the amount of area involved with retinitis, a vitrectomy and silicon oil may be required to prevent retinal detachment in the future.

AF: No, I never use steroids/immunomodulators to treat CMV retinitis.

AG: The use of steroids or immunomodulators depends on the level of inflammation. Evaluating the presence of various cytokines in the vitreous fluid would help establish a proinflammatory response in this patient. It may be possible to show a skewed balance between the proinflammatory cytokines such as IFN-γ, IL-17A/IL-17F/IL-22 and anti-inflammatory cytokines like TGF-β/IL-10, IL-4/IL-10. In the past, this reaction has been mistaken even for endogenous endophthalmitis. I think the treatment, in this case, should be systemic corticosteroids to induce cytopenia.

JB: Never. We do not give steroids or immunosuppression unless there is immune recovery uveitis.

PM: In routine CMV retinitis cases, I do not use steroids/immunomodulators.But,I have treated CMV retinitis with steroids in immune recovery uveitis and immunomodulators in cases ofCMV retinitis associated with cancers or aggressive autoimmune diseases. We have treated them with systemic and intravitreal ganciclovir therapy along with systemic steroids with or without maintenance dose of

systemic immunosuppressive therapy to save the life of the patient in these situations

BM/RM: We typically see CMV retinitis in immune suppressed and very rarely in immunocompetent individuals. In patients with CMV retinitis who develop CME or choroidal neovascularization, we give intravitreal ganciclovir and steroids to prevent flare up of antecedent CMV retinitis. Steroids per se are not given for CMV retinitis. Intravitreal steroids may be detrimental in the treatment of CMV retinitis.

3. How often do you encounter resistance to valganciclovir? How do you diagnose and treat them?

HNS/SG: Infrequently patients are resistant to ganciclovir and require foscarnet. It is advised to work closely with an infectious disease specialist in such cases.

AF: In my clinical practice, I have not encountered a case of resistance, which I would suspect in recurrent cases despite a proper valganciclovir treatment. In my opinion, these cases should be managedclosely with an infectious disease specialist

AG: Valganciclovir is a prodrug of ganciclovir available for oral use. CMV resistance to ganciclovir / valganciclovir is known especially if the UL97 or UL54 gene mutation is present. If the patient is not responding, I would suggest the use of intravitreal foscarnet / cidofovir which unlike ganciclovir do not require phosphorylation to convert into the active form to block the viral DNA polymerase.

JB: Quite uncommon. I give intravitreal foscarnet in such cases.

PM: Very rare. I have encountered resistance to valganciclovir in one case where i have subjected the DNA of the CMV virus to Sanger's sequencing to identify mutation (targeted genes UL97 & UL54)responsible for ganciclovir resistance. Using Human CMV AD169 (Accession: X17403.1) as reference sequence, insertion of threonine was observed in our case. Ganciclovir resistance cases can be treated with foscarnet / cidofovir. Recently newer drug lotermovir 480 mg/day is also available to treat resistance to valganciclovir cases.

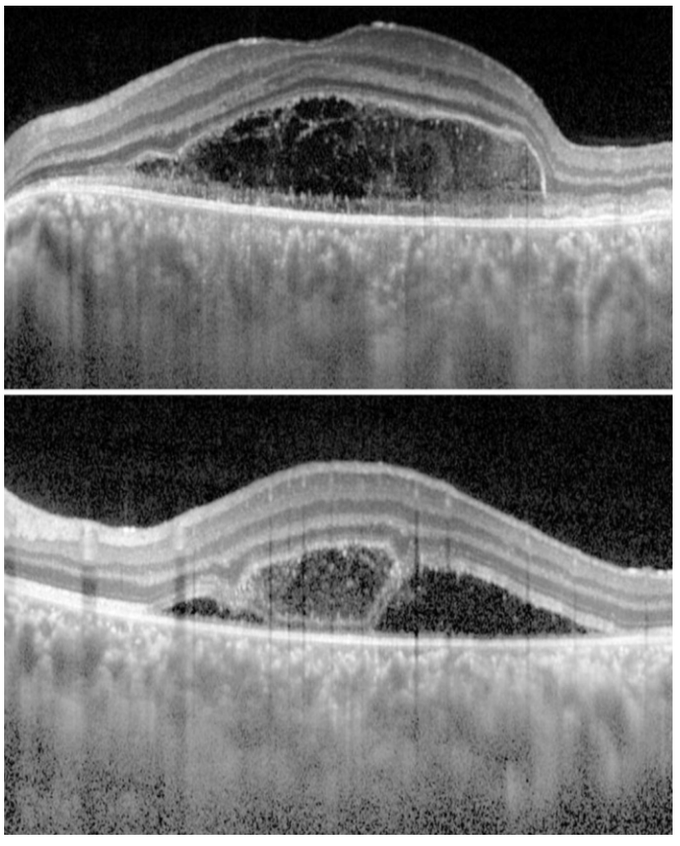
BM/RM: We have not encountered resistance to ganciclovir in our practice. But if it is suspected, drug compliance adequately ensured and repeat vitreous tap with qPCR proves a definite rise in copy number, we have intravitreal foscarnet or a combination treatment in the reserve plan. We are cognizant of the fact that sequencing of the CMV UL97 (phosphotransferase) and UL54 (DNA polymerase) genes for mutations known to confer resistance is performed to predict drug resistance all three drugs (ganciclovir, foscarnet, and cidofovir), respectively. Primers and probes used were previously described by Sanchez and Storch et al.

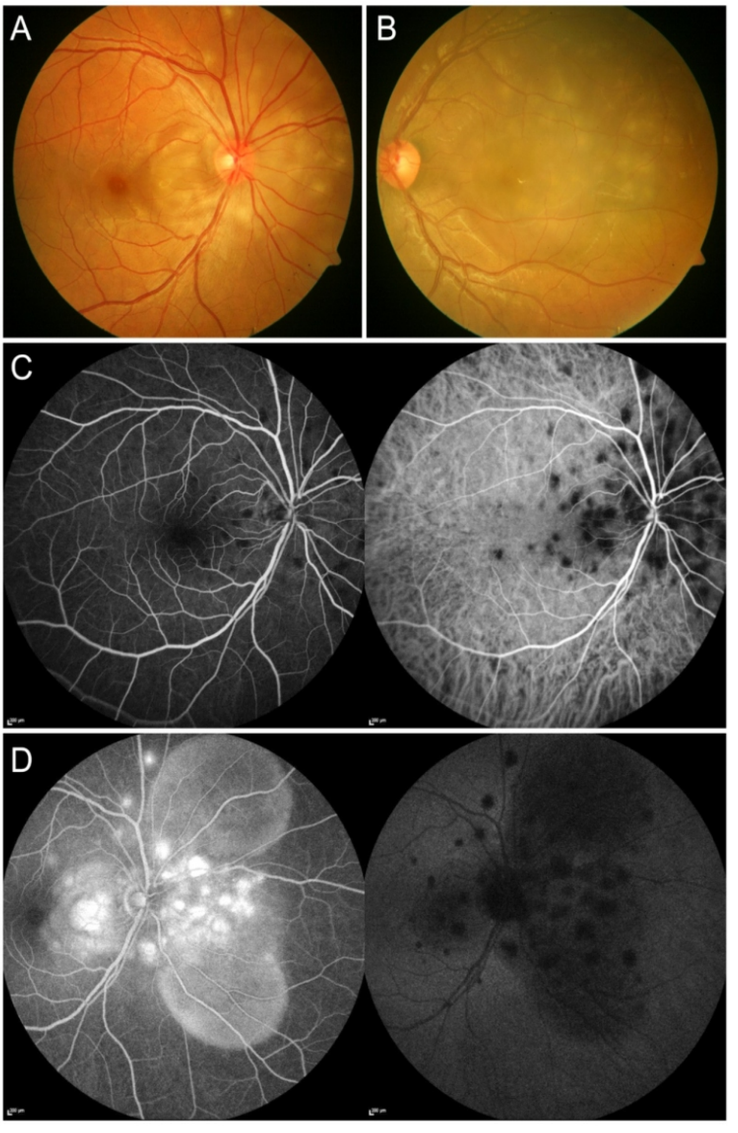
Cytomegalovirus (CMV) retinitis is one of the most common opportunistic infection in patients with low CD4 T cell counts in the setting of HIV/AIDS. However, CMV retinitis is also being increasingly recognized in conditions of systemic immunosuppression due to solid organ transplantation, uncontrolled diabetes mellitus, prolonged corticosteroid / immunosuppressive therapies, among others. CMV retinitis needs therapy with ganciclovir, keeping in mind possibility of suboptimal response due to resistance (though rare). The patients may develop immune recovery uveitis (more common in HIV patients), needing topical or oral corticosteroids.

Case 4

VKH disease

A 33-year-old female (Asian Indian) presented with bilateral multifocal serous retinal detachment with deep yellow choroidal stromal lesions. OCT showed subretinal fluid. Fluorescein and indocyanine green angiography are typical for Vogt-Koyanagi-Harada's (VKH) disease.





Questions:

1. **Please share your pearls in differentiating VKH from CSC/other non-uveitic serous detachments.**
2. **Do you pay attention to the OCT compartmentalization of fluid (bacillary layer detachment)? Please elaborate.**
3. **Do you always rely and perform indocyanine green angiography? What are the advantages of doing it?**

1. Please share your pearls in differentiating VKH from CSC/other non-uveitic serous detachments.

HNS/SG: CSC and VKH can be a diagnostic dilemma as they both present with serous detachments at the macula and have thick choroid on EDI-OCT, however the treatment is diametrically opposite, where you avoid corticosteroid in CSC and need corticosteroid in VKH. The classic patterns for each of these entities on FA and ICGA help distinguish the two clinically.

AF: VKH shows usually multiple and bilateral serous detachments which is very infrequent in CSC (usually unilateral and with one solitary serous detachment); in case of doubt, I always search for cells in the vitreous cavity; there will not be an evident vitritis, but some cells are always present in VKH. Another pearl is when assessing FA: leakage of the optic disc is universal in VKH, and it does not happen in CSC. Other signs typical of VKH in FA is the "stary night" appearance due to multiple pinpoint leakage. On ICGA, round hypofluorescent lesions (choroidal granulomas) are evident in VKH. Finally, I always ask for meningitic symptoms, such as headache when suspecting VKH.

AG: In my experience, bilateral multifocal serous retinal detachments in young Asian women are the hallmark of VKH disease. If you can detect signs of inflammations in the anterior chamber or the vitreous then there is no other diagnosispossible except VKH. Only if you actively seek a history of prodromal symptoms patients would come forward with headache, neck stiffness, among others. If you do not ask, they will not tell you! It is unusual for young women to present with bilateral CSC. There are no signs of inflammation in CSC ever. In my experience women who develop CSC happen to be working women and are domestically or professionally driven type A personalities. They will not volunteer to provide this history and you must actively seek it. In VKH, EDI-OCT will show a diffuse choroidal thickening which is maximum in the peripapillary choroid and tapers anteriorly. In the past, we looked for this thickening on USG. In CSC, you may see a choroidal thickening which is known as pachychoroid, characterized by atrophy of the choriocapillaris and large pachy-vessels of Haller's layer and a normal Sattler's layer. In the VKH disease, there are no pachy-vessels and there is a diffuse thickening of the entire choroid.

JB: Close differential diagnosis for VKH is central serous chorioretinopathy (CSC) and bilateral posterior scleritis. FA and OCT are quite characteristic. In VKH, starry sky pattern and pockets of the subretinal fluid in the late phase of FA are characteristic. In CSC, point leak with increased hyperfluorescence with staining is seen in late phase. In posterior scleritis, the sclero-choroidal thickening sometimes with T-sign is seen.

PM: On fundus examination, detection of a dark spot within CSC is an important clinical sign to differentiate from yellowishchoroiditis lesions in VKH. FFA and ICGreveal early choroidal stromal hyperfluorescence, hypofluorescent dark dots and early pinpoint hyperfluorescence with late pooling of dye with disc leakin VKH, and choroidal hyperfluorescence and focal leaks with a smokestack or inkblot pattern in CSC.OCT reveals hyper-reflective dome-shaped elevation of the RPE suggestive of pigment epithelial detachment (PED) with RPE bumps in association with subretinal fluid in CSC, posterior vitreous cells with bacillary layer detachment, intraretinal cystic spaces with septae withchoroidal bulge in VKH disease with multiple hyper-reflective lesions in the retina. OCTA shows presence of dense dark areas at the level of the choriocapillaris in CSC, irregular, areas of mixed hypo- and hyper-reflectance with ill-defined margins in chronic CSC andmultiple, round-to-oval, well-defined, variably sized hyporeflective areas suggestive of choriocapillaris flow void in VKH disease.

BM/RM: The nuances of delineating CSC from inflammatory pathologies are interesting and nicely covered in the guest article by Dr. Anand Rajendran in the first edition ofUSI newsletter. What we apply in practice is to look for discleak, markers of inflammation in clinical examination using the VKH diagnosticcriteria, 10 OCT signs of VKH (if present), history of prodromes of VKH, response to treatment, correlation of multimodal imaging including the differential choroidal thickening in B- scan. This is pertinent in cases of incorrect diagnosis of VKH or CSC developing in a setting of high dose oral steroids.

2. Do you pay attention to the OCT compartmentalization of fluid (bacillary layer detachment)? Please elaborate.

HNS/SG: Subretinal fluid in VKH is very sensitive to corticosteroid and will resolve soon with treatment. Prolonged and chronic fluid pockets can disrupt the underlying photoreceptor leading to poor quality of vision even after the fluid has resolved.

AF: Bacillary layer detachment (BLD) is almost universal in VKH. The above-mentioned pearls together with the BLD on OCT help to stablish the diagnosis in all cases of VKH. Treatment (3 intravenous methylprednisolone pulses followed by oral prednisone and always one conventional immunosuppressive

drug from the beginning in my clinical practice) resolves the BLD and the visual acuity recovers.

AG: You may see a bacillary detachment in VKH disease indicating a collection of fluid in the myoid layer of the inner segment of photoreceptors, essentially splitting of myoid and ellipsoid zones of the inner segments. Some of the reported cases have had, VKH, APMPPE, toxoplasma retinochoroiditis, CSC in SLE, trauma, among others. It is believed that in acute events, the subretinal fluid is forced into the neurosensory retina mostly due to its acute exudative inflammatory nature. It is a reversible phenomenon with the control of inflammation, and I do not believe that it has any diagnostic or prognostic value. It created buzz for some time due to its being a novel discovery on OCT, but the phenomenon has been known to ocular pathologists for several decades.

JB: Yes,very much – the sign of bacillary layer detachment is of interest. One can see subretinal septae and thickened choroid, especially the posterior pole.

PM: Yes, bacillary layer detachment occurs due to separation of myoidzone from ellipsoid zone of the photoreceptor layer. It is present in VKH disease and other inflammatory conditions of the retina, and it is not seen in idiopathic CSC.

BM/RM: Yes, the compartmentalization of inflammatory fluidcausing bacillary layer detachment is significant but there are other differentials of bacillary layer detachment well. We pay holistic attention to all the signs, and the sensitivity and specificity of bacillary layer detachment alone needs to be proven in a large-scale trial.

3. Do you always rely on and perform indocyanine green angiography (ICGA)? What are the advantages of doing it?

HNS/SG: ICGA helps identify choroidal inflammation and guide response to treatment, by demonstrating health of choroid, beyond what can be visualized on EDI-OCT.

AF: I do not always perform ICGA, just in case of doubtful cases. A typical situation where it may be helpful is when there are no serous retinal detachments. OCT will surely show choroidal thickening and RPE undulations and ICGA will confirm the diagnosis showing round, multifocal hypofluorescent lesions corresponding to choroidal granulomas. An advantage of ICGA versus OCT is that the former provides information about the real extension of the disease whereas OCT only provides assessment of the macular area. However, due to practical reasons, in my clinical practice for long term monitoring of inflammatory activity, I perform OCT to assess choroidal thickening in every follow-up visit.

AG: While ICGA may have a limited role in the diagnosis of VKH disease, it has a profound role in the management of VKH. Major complications of VKH including sunset glow fundus appearance, choroidal thinning and choroidal neovascular membrane formation are all linked to a premature tapering of corticosteroids and immunosuppressive therapy while a subclinical persistent inflammation is continuing. It is believed that the reason for the VKH disease entering a chronic recurrent phase is due to premature tapering of therapy based on clinical, FA and OCT parameters. FA is a poor tool in assessing diseases of the choroid. Once you start treatment with corticosteroids, the first to resolve is the serous fluid with consequent improvement in visual acuity and the next is the decrease in choroidal thickness seen on OCT. Both these phenomena do not tell us whether the inflammation is continuing in the choroidal stroma. The only way at present to ensure that choroidal inflammation has completely subsided before tapering of steroids is to show by ICGA the disappearance of the hypofluorescent lesions in the choroid. No doubt, ICGA is an invasive tool, I look forward to studies prospectively comparing the ICGA and OCTA for monitoring the complete disappearance of inflammatory activity in the choroidal stroma. It is to be noted that VKH is an inflammatory disease of the choroidal stroma and not merely the choriocapillaris. I am not sure that beyond the choriocapillaris, the current generation of OCTA machines can unequivocally demonstrate the flow voids in the choroidal stroma and provide information comparable to the ICGA.

JB: I do not find any great advantage of performing ICGA routinely in patients with VKH. FA and swept source OCT are very characteristic in these patients. I do SS-OCT to follow-up these cases.

PM: Yes, I prefer to get the ICGA, but it will not be possible in all the cases. ICGA helps us to differentiate VKH from CSC. In VKH, we get hypofluorescence in active stromal choroiditis whereas in CSC there is increased vascular permeability. In VKH disease, ICGA is used to monitor the response to treatment.

BM/RM: We do both FA and ICGA in uveitis imaging unless contraindicated or financial constraints. However, the quality of ICGA imaging is evolving now and need to be clinically correlated. Wesolely avoid relying on one imaging methodalone, although it is reasonably indicated to detect the iceberg

phenomenon of VKH and discerning the end point of VKH treatment. Extent of involvement is clearly delineated by ICGA especially in chronic cases.

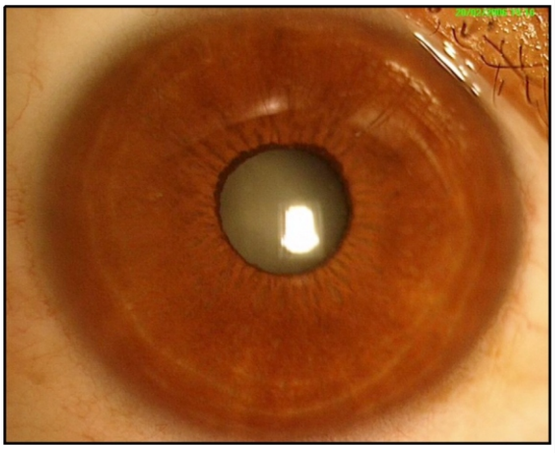
Often, Vogt-Koyanagi-Harada's (VKH) disease and central serous chorioretinopathy (CSC) can be confused, since both present with bilateral exudative retinal detachments. The treatment for these two conditions is diametrically opposite. Hence, it is critical to be sure of the diagnosis because patients with CSC should not receive corticosteroids, and patients of VKH benefit with emergent corticosteroids (often intravenous pulse). Multimodal imaging plays an important role in the diagnosis. The key features in VKH on FA are starry sky pattern with multifocal RPE leaks, multiple round-to-oval deep choroidal granulomas appearing hypofluorescent in ICGA, and hypo-reflective on EDI-OCT. OCTA shows multiple hyporeflective areas in the choriocapillaris slab in VKH. In CSC, there would be multifocal points of leakage with inkblot or smoke-stack pattern, without disc hyperfluorescence. Bacillary layer detachment is a novel feature on OCT in VKH characterized by a split in the inner photoreceptor myoid zone.

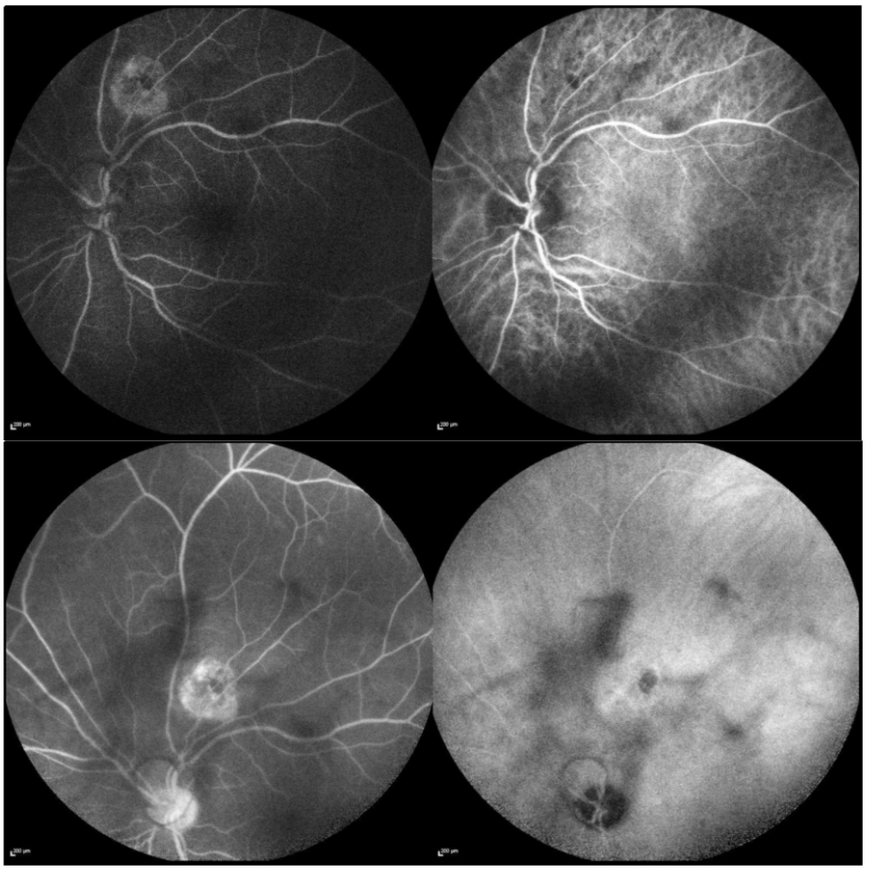
Case 5

Fuchs Uveitis

32-year-old Asian Indian female with unilateral floaters had occasional cells, flare +, vitritis + and a superior chorioretinal lesion.

Treated over a year with steroids and azathioprine; methotrexate added recently. However, it was fuchs requiring no treatment !





Questions:

1. **In patients with Fuchs uveitis, how do you approach to a correct diagnosis in the presence of significant vitritis ?**
2. **Chorioretinal scars can occur in Fuchs uveitis (like this patient). How do you approach such cases ?**
3. **What are the features on fluorescein angiography one can expect in Fuchs uveitis ?**

1. In patients with Fuchs uveitis, how do you approach to a correct diagnosis in the presence of significant vitritis?

HNS/SG: The classic features of Fuchs' uveitis are unilateral chronic low grade anterior chamber cell with iris nodules, keratic precipitates, cataract, and low-grade vitreous inflammation. Heterochromia and iris atrophy may be present as well. In the presence of significant vitreous inflammation, the best method is to perform complete lab work up ad rule out an infectious cause. In an older person, malignancy should also be in the differential. Young patients can be really bothered by vitreous opacities and veils, even in the absence of active vitreous inflammation.

AF: In my opinion, the key signs in Fuchs' uveitis are diffuse stellate keratic precipitates and absence of synechiae. The observation of significant vitritis (though usually vitreous opacities rather than vitritis is what is observed) is infrequent and may confound but considering the anterior segment findings (diffuse stellate keratic precipitates), it should not be a problem for making a correct diagnosis of Fuchs. If vitreous opacities are visually significant, vitrectomy is indicated.

AG: The major challenge in Fuchs' uveitis is to tell the difference between Fuchs' and intermediate uveitis. Most of the cases of Fuchs' uveitis get diagnosed as Intermediate uveitis and get over treated. The standard textbook nomenclature in the past has been Fuchs' heterochromic uveitis. If you are looking for heterochromia you are likely to miss the diagnosis of Fuchs' uveitis, because at least in the brown irides, it is very difficult to tell the difference between the colors of two eyes, the normal and the one with Fuchs'. This is precisely the reason why the accepted nomenclature now is Fuchs' uveitis. How I do look for Fuchs' uveitis:

a. Iris atrophy in FU affects the crypts first and these become dull, lose sharpness, and become shallow. The way I would do it in the clinic is to toggle the slit lamp quickly and repeatedly from one eye to the other and compare the iris pattern in the two eyes. Also, look for the iris transillumination. Best noted at the pupillary border as the pupillary ruff is the first one to atrophy. You might see Koeppe's nodule at the pupillary border as well as pinhead-sized iris nodules in the iris stroma.

b. Next is to look for the glassy stellate keratic precipitates that are seen all over the corneal endothelium, unlike the keratic precipitates that are seen in other types of uveitis which are typically present in the Arlt's triangle. Unless you look for keratic precipitates in Fuchs' uveitis, you will not notice them.

c. The third feature of Fuchs' uveitis is the posterior subcapsular cataract. It is a mistaken belief that intermediate uveitis is commonly complicated by posterior subscapular cataracts. It is not true. Posterior subcapsular cataract is a hallmark of Fuchs' uveitis. Patients of Fuchs' uveitis present to the clinic due to visual disturbances caused by posterior subcapsular cataract and not due to the floaters by the vitreous opacities. Patients of Fuchs' become aware of bothersome floaters only after cataract surgery and are now being offered vitrectomy (minimally invasive) as these cannot be wished away by any other means.

d. Patients of Fuchs' uveitis do not have cystoid macular edema which is a hallmark of intermediate uveitis.

JB: I see that whether I am not missing intermediate uveitis. I look for snowballs and snow banking.

PM: Fuchs uveitis is a clinical diagnosis. It is characterized bythe absence of acute symptoms of severe pain, redness, photophobia; presence of characteristic small, white stellate keratic precipitates distributed widely, across the endothelium; low-grade anterior chamber inflammation; diffuse iris stromal atrophy with or without heterochromia; absence of posterior synechiae prior to cataract surgery; presence of cells and opacities in the anterior vitreous. It can be associated with the presence of abnormal vessels in the irido-corneal angle, opacities in the crystalline lens, fundus lesions and/or scars and secondary glaucoma. Fuchs' uveitis with significant vitritis in the absence of cystoid macular edema that did not undergo cataract surgery can be confirmatory criteria for the diagnosis of Fuchs' uveitis in the presence of significant vitritis.

BM/RM: We investigate all our patients of Fuchs' uveitis for pseudo-Fuchs'as described in Stephen Foster's textbook of uveitis. Typically, the closer differentials encountered in our practice are rubella, toxoplasma, sarcoidosis, syphilis which we had handled by specific diagnostic tests appropriately targeted upon in a clinically relevant scenario.

2. Chorioretinal scars can occur in Fuchs uveitis (like this patient). How do you approach such cases?

HNS/SG: Chorioretinal scars can be monitored with fundus autofluorescence and OCT. There is no need to treat a patient with an inactive scar.

AF: I do not change my approach, that is: I never treat inflammation, just complications (cataract, hypertension, vitreous opacities)

AG: I would ignore the chorioretinal scars in patients with Fuchs' uveitis. At one time it was thought that these scars were caused by toxoplasma. I doubt if anyone has seen a case of active toxoplasma retinochoroiditis in Fuchs' uveitis.

JB: I agree. I do not do anything different than usual Fuchs' uveitis.

PM: Chorioretinal scarsin Fuchs' uveitis can be observed. Toxoplasmosis has been reported in association with chorioretinal scars in Fuchs' uveitis.

BM/RM: The posterior segment associations of Fuchs' uveitis like toxoplasma, TORCH virus infections are seen in our practice. If proven inactive by appropriate imaging, we explain the patients the need for careful follow-up. The appropriate treatment of cataract and glaucoma if associated are meticulously done. We focus on careful application of diagnostic

criteria of Fuchs' uveitis and the markers of poor prognosis as elegantly described in the literature. Fuchs' uveitisisan aberration in ACAID pathway and is aspectrum of heterogeneousseverity which needs to be addressed based on the specific scenario. It is easily overlooked and need not be painted in the same color of the brush. This strategy is often used for any uveitis condition.

3. What are the features on fluorescein angiography one can expect in Fuchs uveitis?

HNS/SG: Most patients with Fuchs' uveitis will have a normal fluorescein angiogram. There have been reports of disc leakage and peripheral small vessel leakage, but they are uncommon.

AF: Optic disc hyperfluorescence and peripheral vascular leakage have been demonstrated in Fuchs' uveitis; it is important to remember this to avoid misdiagnosis with other entities.

AG: On FA, there may be a mild optic disc staining in Fuchs' uveitis but no cystoid macular edema. On the other hand, in intermediate uveitis, there is cystoid macular edema, and no optic disc staining.

JB: One may see peripheral vasculitis, which is also seen in intermediate uveitis. I do not do FA in Fuchs' uveitis.

PM: FA can reveal disc staining/disc hyperfluorescence, peripheral vascular leakage and staining of chorioretinal atrophic patches in Fuchs' uveitis

BM/RM: FA finding of vascular leaks in Fuchs' uveitis may or may not indicate active inflammation. It needs clinical correlation and approach as indicated. The unique points in FA findings of Fuch's uveitis are:[a] optic disc hyperfluorescence not proportional to vitritis, [b] increased disc hyperfluorescence can be found even in a very mildvitritis. Hence, we need to be holistic, and tailor make the treatment. The etiologies for peripheral vascular leaks are: [a]Breakdown in blood-retinal barrier, and [b] traction by the vitreous. We focus these are present and proceed accordingly. We do not perform vitrectomy despite advances in the surgical procedures. We strictly avoid periocular or intraocular, oral steroids in Fuchs' uveitis as it can flare up uveitis as per Foster's textbook!

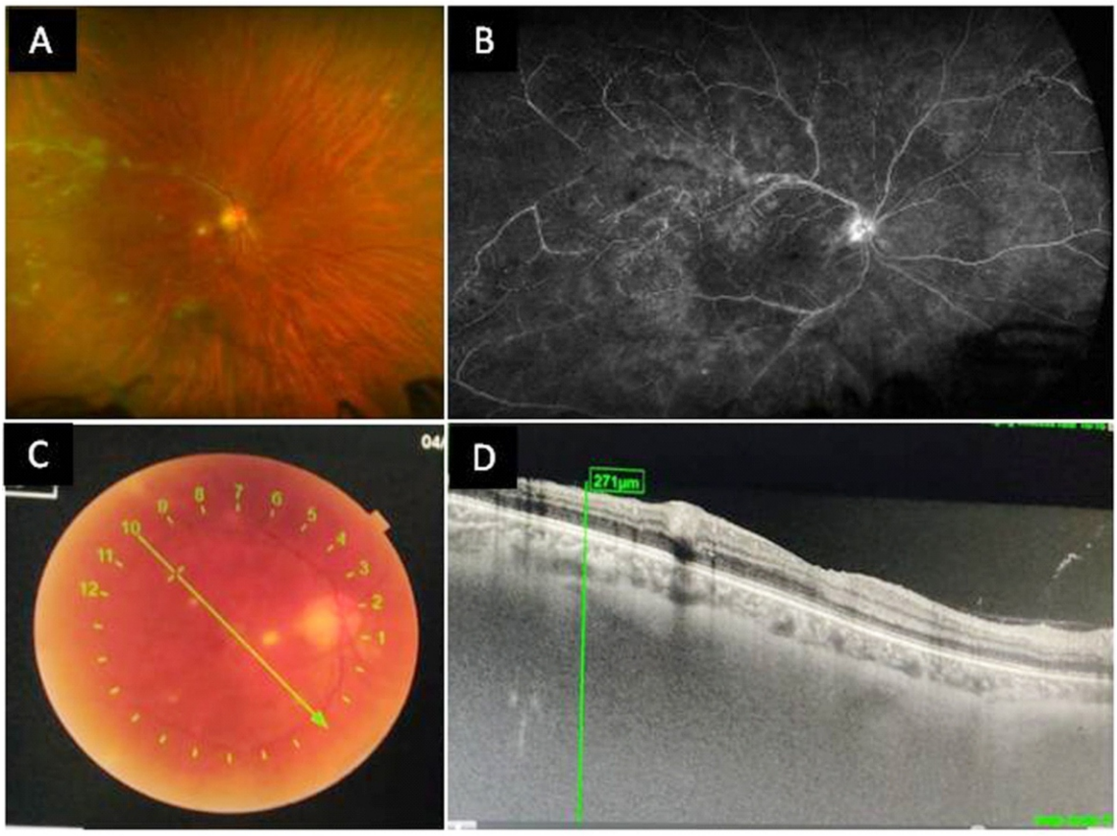
Fuchs' uveitis syndrome (FUS) is a non-inflammatory uveitis mimicker in which there is iris atrophy, heterochromia (but not in all cases), stellate keratic precipitates distributed all over the cornea, posterior subcapsular cataract, and glaucoma in 50% cases. Often misdiagnosed as viral anterior uveitis, it can be mistreated with prolonged topical corticosteroids resulting in worsening of cataract/glaucoma. This case highlights the posterior segment manifestations of FUS, which are often less understood. Vitritis and inactive chorioretinal scars are common in FUS and must not be treated with corticosteroids or immunosuppressive therapies. These patients require only observation, treatment for cataract and glaucoma, and floaterectomy for bothersome vitritis.

Case 6

Retinal vasculopathy?

A 36-year-old female was recently diagnosed with systemic lupus erythematosus. She has typical features of malar rash and ANA positivity. The patient has disturbance in vision in both eyes

Fluorescein angiography shows early vasculopathy.



Questions:

1. **What are the fluorescein angiographic features that help differentiate true vasculitis from vasculopathy ?**
2. **In patients with SLE and other vasculopathies, how do you treat eyes with occlusive vasculopathy ?**
3. **What are the key posterior segment features one should detect in eyes with vasculopathies ?**

1. What are the fluorescein angiographic features that help differentiate true vasculitis from vasculopathy?

HNS/SG: Vasculitis implies inflammation of the retinal vessels and is associated with leakage from large vessels. In Lupus, there is more of an occlusive pattern due to inflammation of the small vessels and ischemia.

AF: Retinal vasculitis and vasculopathy of other origin (i.e., hypertensive) may show similar funduscopic signs like hemorrhages, soft and hard exudates, and ischemic complications like neovascularization. FA allows to objectivate an inflammatory origin by showing leakage of blood vessel walls and leakage in other structures like optic nerve or macular area (macular edema).

AG: I think the term 'vasculopathy' is used especially about renal involvement in SLE, a major target organ, wherein the histopathology of the glomeruli may show a variety of lesions including fibrinoid necrosis, sclerosis, subendothelial immune complex deposition, thrombosis, occluded arterioles,

arteriosclerotic changes, and vessel wall inflammation. These lesions in the kidneys can be as categorized as non-inflammatory vascular immune complex deposits (vasculopathy), inflammatory (necrotizing) vasculitis, thrombotic microangiopathy, and degenerative/arteriolar sclerosis. [Seshan SV. Lupus vasculopathy and vasculitis what is the difference and when do they occur. Pathology case reviews 2007; 12(5):214-221.]Vasculopathy is an umbrella term used when you do not have a histopathological diagnosis of vessel wall inflammation. The term vasculitis cannot be used in the absence of histological evidence of vessel inflammation. There are very few histopathological reports of eye involvement in SLE. In the absence of histopathological evidence, it is not right to call the retinal arterial changes in SLE vasculitis. The mere presence of perivascular infiltrates is no sign of inflammation as the leucocytes have been shown to move in and out of the vessel walls without any sign of inflammation. The immune complex deposits are non-inflammatory and have been shown on pathology in autopsy eyes of patients with SLE choroidopathy. Immune complex deposits have also been demonstrated in animal models of SLE wherein they lead to vascular occlusions. Most of the lesions in the retina are either due to hypertension or non-inflammatory immune complex deposition or APLA. The immune complex deposition in the vessel wall may show as focal staining of the vessel wall. In patients with SLE, APLA syndrome may present as frosted branch angiitis. Recently, there are many reports on the use of OCTA to evaluate retinal vasculitis. So far, it has been used to look for perivascular retinal thickening as a surrogate marker for leakage from the retinal vessels. I am sure it should be possible to look for vessel wall thickening or thrombus formation or immune complex deposits in SLE vasculopathy on OCTA.

JB: Vasculopathy shows staining on FA, whereas vasculitis shows leakage.

PM: There will bedisc leak and vascular leakage(diffuse, segmental, and focal)characterized by perivascular hyperfluorescence which may be associated with capillary dropouts with new leaky vessels on FA in true vasculitis. FA in occlusive vasculopathy is characterized byocclusion of the retinal vessels with extensive areas of capillary drop out areas with telangiectasia of the retinal vessels with neovascularizationin the retina. Disc leak and perivascular leakage will help us to differentiate true vasculitis from vasculopathy.

BM/RM: Delineating active vasculitis from vasculopathy (caused by SLE) is crucial. In the active vasculitis there is inflammatory exudation and leakage, cuffing and sheathing of vessels which can be segmental or diffuse. The perivascular inflammatory exudates need to be delineated from the cotton wool spotsseen due to microinfarcts caused by retinal vasculopathies. In retinal vasculopathies caused by circulating immune complexes there can be vascular occlusion without the characteristic inflammation of the retinal vessels, retinal swelling/retinal exudation, or intraocular inflammation like described above. True retinal vasculitis in SLE is rare. The immune complexes in SLE are not able to permeate the tight endothelial junctions of retinal vessels an degress of immune complexes and ingress of leukocytes do not occur typically. Basically, in retinal vasculopathies the ocular inflammation is typically secondary and not primary as in a typical retinal vasculitis caused by tuberculosis, sarcoidosis, Behcet's, viral, toxoplasma, among others. Interested readers can look at the basics of the classification of retinal vasculitis.

With these basics in mind, if we look at the FA there can be easy understanding that FA of vasculopathies can have vascular occlusion which can be diffuse, focal with extensive non-perfusion areas without typical perivascular leaks. Severe cases can have extreme degrees of retinal and choroidal ischemia. The perivascular area which is relatively clear needs careful attention compared to the brisk perivascular leaks and exudation of primary retinal vasculitis. Interestingly, focus on the basic involvement of arteriole or venule. Leakage from the arteriole or venule might occur in SLE. Do remember, SLE, polyarteritis nodosa, and Wegener's granulomatosis, Churg-Strauss syndrome and cryoglobulinemia involves the arterial ends. Please do note that there can be some overlap of predominantly vasculopathy and vasculitis as well. The 3 patterns of FFA findings described in literature on SLE are Opticdisc vasculitis, Cotton wool spots with occlusions, rare perivascular leaks.

Retinal vasculitis, with inflammation of the retinal arterioles or venules, tends to have poorer visual outcomes and present in an acute fashion. A large percentage of these patients have concomitant antiphospholipid antibodies including anticardiolipin and lupus anticoagulant. Histopathologic specimens proved fibrinoid change with thrombus formation without a true arteritis as well.

In the related APLA syndrome, there can be a perivascular leak due to fibrovascular proliferations which should not be confused with primary retinal vasculitis. There comes the nuance to distinguish inflammatory sheathing coined as

perivascular "cuffing'' from non-inflammatory sheathing described in Foster's textbook of uveitis. Targeted diagnostic work up based on the above clinical setting with the active involvement of rheumatologists can save the patients from a huge battery of tests.

2. In patients with SLE and other vasculopathies, how do you treat eyes with occlusive vasculopathy?

HNS/SG: Rapid initiation of systemic immunosuppression is required to prevent permanent vision loss from vascular occlusion. Ischemic peripheral areas can get panretinal photocoagulation to prevent CNV from developing in the areas of ischemia.

AF: In depends on the severity and extension of the ischemia. Severe cases with involvement of posterior pole need and urgent approach with intravenous methylprednisolone pulses or intravitreal dexamethasone implants or even intravenous cyclophosphamide pulses for the acute phase, followed by conventional immunosuppressive drugs and or biologics (typically anti-TNF agents though other options like Rituximab may be considered depending on the systemic disease). Less severe cases may be managed with oral steroids plus immunosuppressive drugs and or biologics.

JB: I treat very aggressively with immunomodulatory therapy with laser photocoagulation of ischemic areas and neovascularization.

PM: Occlusive retinal vasculopathy cases are treated with systemic steroids, systemic immunosuppressants, laser photocoagulation, and anticoagulation therapy.

BM/RM: Eyes with occlusive vasculopathy due to SLE needs elegant control of inflammation first before we treat the non-perfusion areas with panretinal photocoagulation. Violation of this basic rule had resulted in violent flare up of anterior or posterior segment inflammation in our real time practice. Though anti-coagulants are suggested by the rheumatologists and in the literature, the beneficial effects are not crystal clear. The rheumatologists carefully rule out the differentials of SLE and typically titrate the inflammation with high dose steroids and immunosuppressants and of late biologicals/biosimilars are handy with or without a systemic marker of inflammatory activity. Please note that in clinical trials, rituximab did not prove its efficacy in controlling inflammation unlike other autoimmune conditions. Belimumab targeting BLyS has promising effects with priority FDA approval like Voclosporin which is the first oral therapy for SLE with proven efficacy. The common error we see in our practice is we should not stop short with steroids alone. It needs both as we need to understand that both steroids and immunosuppressives are required before the immunosuppressive action kick in in 4-6 weeks. As always titration of inflammation is thekey step of treatment success. If panretinal photocoagulation is required as an emergency, it can be done under periocular or intraocular steroid cover as well.

3. What are the key posterior segment features one should detect in eyes with vasculopathies?

HNS/SG: Signs of retinal ischemia such as cotton wool spots, retinal hemorrhages, retinal emboli and vascular occlusion and sclerosis may be seen in patients with retinal vasculopathies.

AF: Systemic vasculitis (granulomatosis with polyangiitis, polyarteritis nodosa, among others) very rarely associated with retinal vasculitis. Anterior segment disease (such as scleritis and episcleritis) are the most common ocular findings. The key posterior segment features of retinal vasculitis would be vessel sheathing, soft exudates, retinal hemorrhages, occlusive events (both arterial and venous), optic disc edema, vitritis and associated neovascular complications.

AG: A major manifestation of SLE in the eye is cotton-wool spots seen in 3-29% depending upon the systemic activity of SLE. Cotton-wool spots are a sign of significant systemic activity and neuropsychiatric SLE. The cotton wool spots in SLE may result from occlusion of terminal arterioles due to hypertension or deposition of immune complexes or micro thrombus formation due to endotheliilitis and APLA. Retinal vasculopathy or microangiopathy appears as a more appropriate descriptive term for these lesions. Only uncommonly the retinal arterioles or veins may also show partial or complete occlusion by thrombosis, most of them due to a close association of SLE with lupus anticoagulant and the antiphospholipid syndrome (APLA syndrome). These cases show a diffuse vessel wall staining of the retinal veins. If the arterioles are thrombosed there is non-perfusion of the capillaries in its distribution territory and extensive areas of capillary non-perfusion. Occlusion of the terminal arterioles by fibrin emboli is seen on FA as capillary stumps. Both the central retinal artery and vein may be thrombosed. In these cases, there is no or minimal evidence of inflammation.

JB: Cotton wool spots, retinal hemorrhages, microaneurysms, sheathing of retinal veins are the classical features on examination.

PM: Posterior segment manifestations of retinal vasculopathy include cotton-wool spots, retinal vascular attenuation, intraretinal hemorrhages, retinal vascular occlusions (artery or vein occlusions or both),capillary non-perfusion of the retina, retinal neovascularization, exudative maculopathy and rarelyoptic atrophy.

BM/RM: The extent of retinal vascular and macular ischemia needs to be documented with ischemic indices available after FA. Do look carefully for neovascularization on the disc, retina and elsewhere in the eye as well. Do note the arm-retina time and the delay happening in the retinal and choroidal phases as well. Careful multimodal correlation in the context of clinical picture is crucial to discern the holistic picture of disease severity, depth, and the extent of involvement. While the milder form of retinal vasculopathy is mediated by immune-complex deposition and inflammation, the more severe vaso-occlusive disease stems from fibrinoid degeneration/necrosis without significant inflammation.

Retinal vasculopathy in systemic lupus erythematosus (SLE) can result in sight-threatening manifestations, including proliferative disease leading to tractional detachments and vitreous hemorrhage. True retinal vasculitis must be differentiated from retinal vasculopathy due to SLE and other causes, both clinically and angiographically. True retinal vasculitis typically presents with sheathing, hemorrhages, occlusion, and early leakage on FA. In retinal vasculopathy, there can be occlusion, but only late staining of the vessel wall on FA. In addition, other signs of inflammation such as optic nerve head hyperfluorescence will be absent. Cotton-wool spots and ischemic vein occlusions are common in retinal vasculopathy. Search for an underlying cause such as APLA, SLE, and other hematological disorders is necessary to guide the management.

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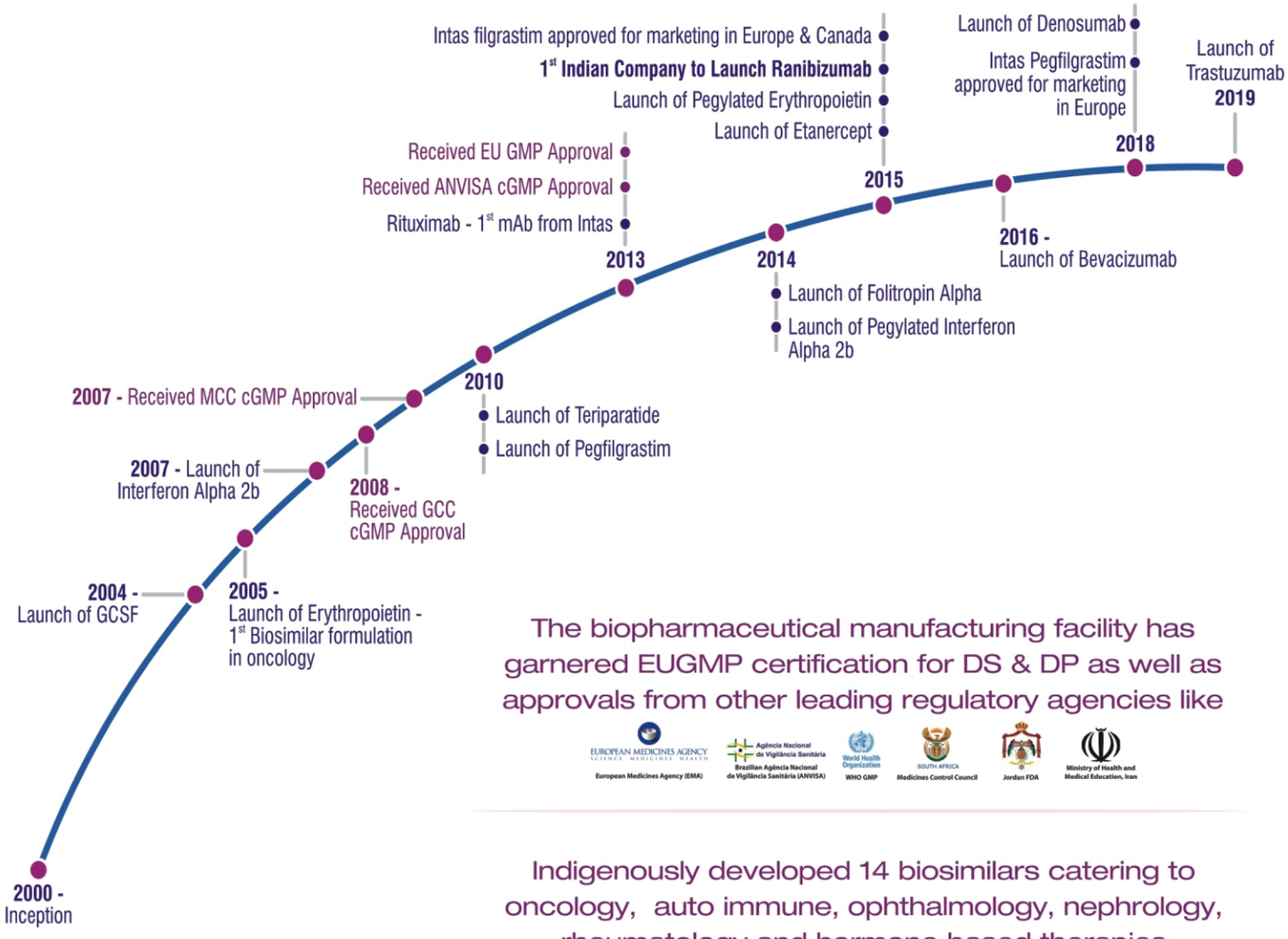

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INNOVATOR'S ISLE

A Novel Do-It-Yourself Anti-fogging Device For Vitreo Retinal Surgeries

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Introduction:

Adequate visualization of the retina is of paramount importance for a safe and efficient vitreoretinal surgery. The wide-angle viewing system (WAVS) using the non-contact front lens has become popular among vitreo-retina surgeons. They eliminate the need for an assistant to hold the lens and provides a flexible viewing angle to the surgeon.(1) However, at times, the under surface of front lens gets fogged due to condensation of hot exhaled air escaping through the eye drape near the medial canthus area. This significantly decreases the intraoperative visibility of the retina. There are a few antifogging devices described in literature to mitigate this problem. We describe a novel antifogging device based on filtered air flow.

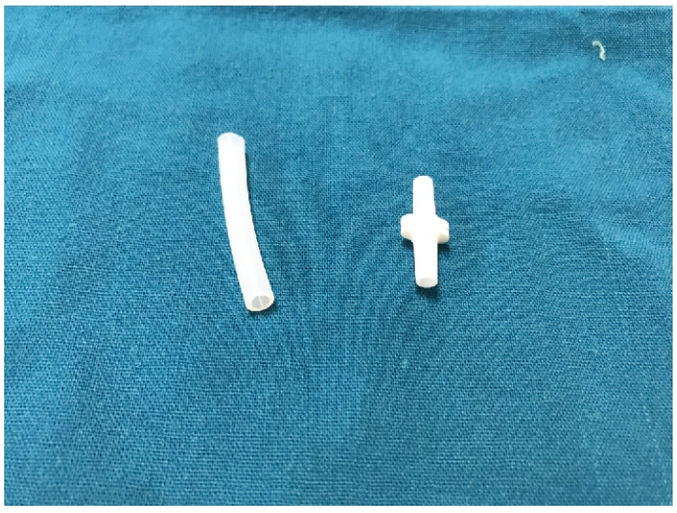
Materials and methods:

Herewith we describe our device which consists of three components: 1: Air pump 2: Two Micropore filters with short tubing and adaptors and 3: Sterile long vitrectomy tubing.

Air pump:

A simple electrically operated aquarium air pump is used to generate air flow. It is light in weight and portable (380 gm, 15x11x6 cm) (Figure1). This is the only component which needs to be procured outside an operation theatre set up. There is an option of increasing the air flow if needed. The outlet can be connected to the air filter using a short tubing and an adaptor. (Figure 2) We used trimmed pieces from a phacotubing set as short tubing. The plastic adaptors are readily available in vitrectomy packs.

(1) Aquarium air pump



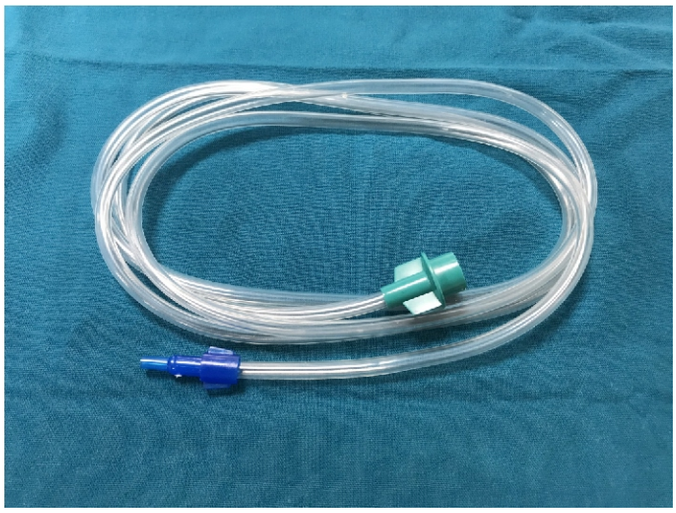
(2) Short phaco tubing set and adaptor

Filter:

We used gas filters which are made of poly tetra fluoro ethylene (PTFE) material (Sartorius, Germany)of filter size is 0.2 microns. (Figure 3) These are readily available with gas tamponade procedures. The inlet is connected to the pump using an adaptor. We have made use of two gas filters in our model which are connected one after the other. The outlet is connected to a long tube. These gas filters are readily available in any retina theatre for doing pneumoretinopexy procedures. Tubing:

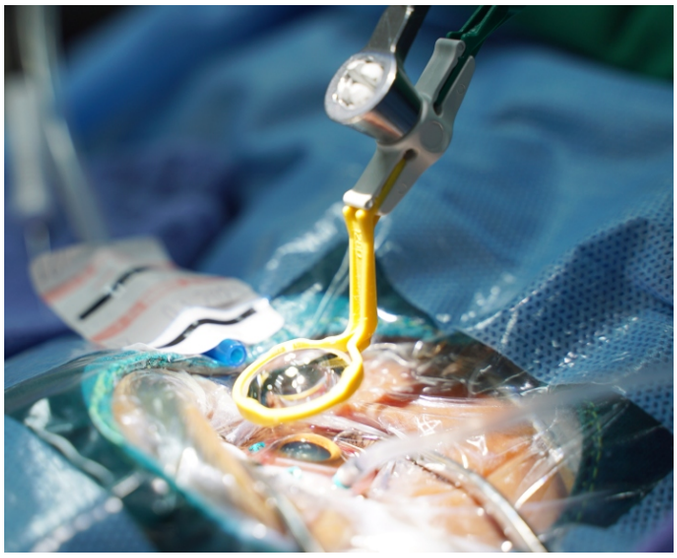
This long tube is the only sterile component in the device. The infusion tubing is available in any vitrectomy pack and can be

(3) Gas filters of poly tetra fluoro ethylene (PTFE) material (Sartorius, Germany) of filter size 0.2 microns.

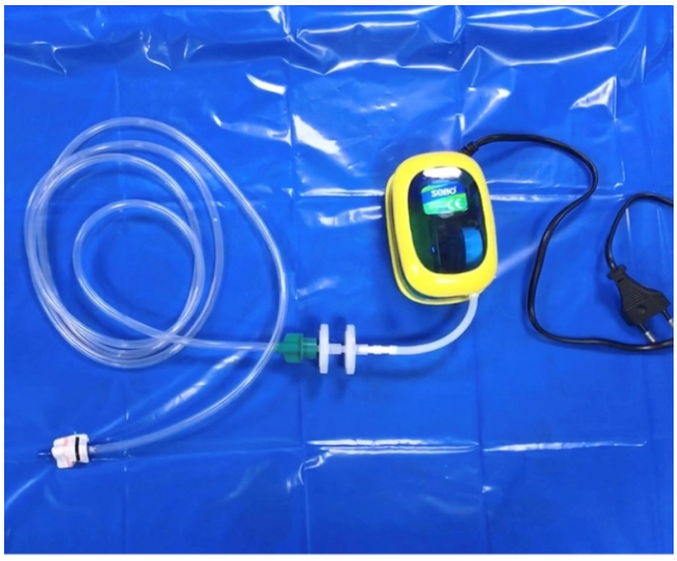


(4) Sterile vitrectomy tubing set of Dutch ophthalmic research centre, Netherlands.

used for this purpose. The end that is usually fixed to the cassette needs to be connected to the gas filter and other end is kept over the eye drape on the nasal bridge of the patient. We have used infusion tubing set of Dutch ophthalmic research centre, Netherlands. (Figure 4) Depending on the type of vitrectomy tube set used, an additional phaco tubing segment and adaptors can be incorporated in case the filter end does not fix with the long tubing. The sterile end is attached to the surgical field such



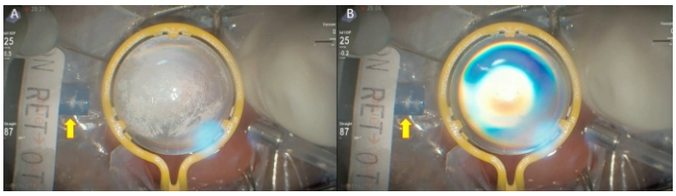
(5) Picture showing the sterile vitrectomy tube placement over the nasal bridge of patient during vitrectomy.



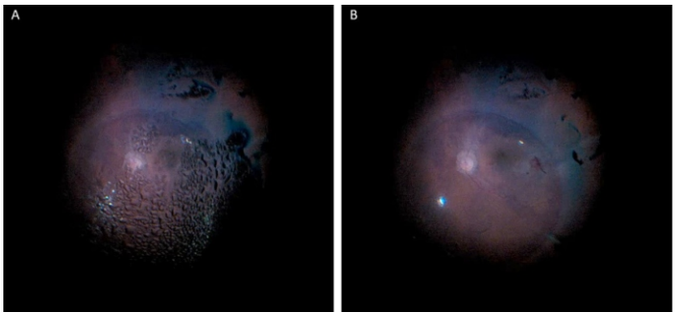
(6) Assembled device.

that it is directed towards the front lens and not towards the cornea. (Figure 5) This is to avoid drying of cornea and to achieve maximum defogging effect. Sterilization indicator stickers can be used to stick the sterile end of the tube to the eye drape over the nasal bridge. (Figure 6)

(7) Sabouraud dextrose agar media showing comparable colonies (colony count < 20) between the test and control plates.



(8) A: Intraoperative front lens fogging. Sterile tube of antifogging device attached on the nasal bridge (yellow arrow)
B: Clear front lens after the device is switched on. Sterile tube of antifogging device attached on the nasal bridge (yellow arrow)



(9) A: intraoperative hazy view of the retina due to fogging of front lens
B: Clear view of the retina after the device is switched is on.

Discussion:

The wide-angle viewing system offer a panoramic view of the surgical field which increases the safety and efficacy of vitreo-retina surgeries. Among the two types of WAVS, the non-contact variety consists of keeping a front lens close to the cornea during surgery. Often, the hot exhaled air by the patient escapes the surgical drape and condenses on the front lens causes fogging during intraoperative procedures. Fogging interrupts the vitreo-retina surgeon during pars plana vitrectomy and hinders surgical performance. Traditionally, a cotton plug is kept nasally as a wedge to obstruct the exhaled air from reaching the front lens. Viscoelastics have also been used to prevent condensation. However, both these methods are effective for a short duration and require frequent replacement. Lee et al suggested warming of lens in normal saline before surgery. However, the effect did not last longer.(2) Gurnani et al suggested the role of an anti-fogging solution in eye pieces of ophthalmic microscopes.(3) The solution being unsterile, cannot be used for the front lens of the WAVS. Kusaka et al made a device which can be mounted on the 128D lens of the Resight system. The device was connected to a vacuum pump to clear the condensed water droplets.(4) The device is custom made for the Resight system and hence maynot be used universally for all WAVS. Italso adds on to the bulk ofthe lens which may hamper manoeuvrability especially in the nasal region. Uwaydat et al suggested the use of a 14FR latex urinary catheter connected to a wall suction outlet. It may be a challenge in reconstructing the suction outlet in a relatively smaller set up.(5)

Our model is based on the concept of blowing filtered air jet from an air pump over the front lens. This effectively clears the condensed micro water droplets from the under surface of the front lens. Our device is made from readily available resources available in any vitreo-retina theatre set-up. Only the aquarium air pump is procured externally and is easily available. The 0.2 micron filters ensure filtered air into the surgical field. We have used two filters in our device and validated it by blowing the filtered air from the device on Sabourauds dextrose agar plates. The results yielded insignificant number of colonies (<20 count) and was comparable with the control plate used. (Figure 7)The final component is the infusion tubing of a standard vitrectomy pack. Hence the device does not incur any additional cost. Uwaydat et al kept the sterile end of the urinary catheter near the medial canthus area. In our device, the sterile end of the tubing is kept over the nasal bridge to achieve the optimal height needed for directing the air jet towards the front lens. Unlike the device described by Kusaka et al, our device doesn't add any bulk to the front lens and doesn't cause any hindrance in surgical manoeuvrability. We have successfully used this model in over 100 PPV surgeries and have not faced any fogging or safety issuesin any of those surgical procedures. (Figure 8-9) The device has certain limitations. First, the sterilization stickers used to attach the sterile end of the long tubing can get wet during surgery and cause misdirection of the tube. Hence, they may need to be replaced by a new sticker or an additional arteryforceps can be used to further stabilise the position. Second, the open-end diameter of the long infusiontubing may vary in size which may require an additional short tube and adaptors.

To conclude we believe that our device is a simple, safe, easy to assemble andcost-effective which canbe made from readily available resources.

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RETINA TECH

NAVILAS: A new frontier in retina laser

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Introduction

Laser treatment for retinal diseases has undergone significant changes in recent years. While laser in the form of focal, grid or pan-retinal photocoagulation (PRP)used to be the mainstay of treatment in most of the retinal diseases, the advent of anti-vascular endothelial growth factors (anti-VEGF) has resulted in a gradual shift of preference towards these agents. Nonetheless, lasers still hold a vital position in the management of retinal vascular disorders, especially as an adjunct to anti-VEGF agents. The greatest challenge with PRP is the speed of laser and the pain perceived by the patient, whereas avoiding sensitive areas like optic disc and fovea is the major concern in posterior pole lasers. The navigated laser systems have been developed to circumvent these problems and make the experience easier for both the patient and the ophthalmologist.

The NAVILAS(OD-OS, Teltow, Germany) system was introduced in 2009 as an ophthalmic scanning slit based laser photocoagulator with a laser delivery system coupled with multimodal imaging. The navigation function offered by the device allows for accurate and faster delivery of laser. The ability to pre-position the laser beam upto far periphery of the retina with continuous readjustment of the laser beam with eye movements is one of the unique features of this system.

Components on the laser system

1) A digital fundus camera providing high definition real time images of the retina

2) A photocoagulating and microsecond pulsed subthreshold laser system

3) A retinal eye tracking system

Fundus camera

The fundus camera utilizes a white-light slit illumination projected through ophthalmoscope optics that pans across the imaged area at a rate of around 25 times per second using a motorized mirror.[1] The reflected light again passes through the ophthalmoscope optics and gets captured onto a 2-dimensional digital imaging sensor.

Optoelectronic blocking of stray light by a sensor results in a reflection free fundus image.[1] The image is then transferred to a digital display after checking for data corruption and interruption. This allows for a smoother real-time image of retina. The image overlay function in the machine superimposes fundus fluorescein angiography (FFA) or infrared image with the live fundus image in order to plan the areas to be lasered. This whole system obviates the need for looking through an

eyepiece.The imaging system has three imaging modes :True-color (including non-mydriatic snap), Infrared (treatment default) andFFA mode (posterior pole). The field of view can vary from 50°/30°/10°(static) tomore than 110° (dynamic).

Laser delivery system

The laser system optical zoom is a laser telescope that allows for application of laser spots of different diameters. An X-Y scanner used for deflecting the treatment laser beam to position the laser spots within the field of view on the retina can be controlled by a micro-manipulator by the user.[1]Illumination and imaging beams are transmitted through a dichroic mirror, while the laser beam is coupled into the imaging beam via the mirror only during treatment mode.[1] A pattern delivery system, similar to that seen in PASCAL laser, isavailable in the unit, from which the user can select single-spot, rectangular, circle, and arc patterns. Laser is performed in infrared mode and can be changed to the color image in between. This "toggle" function allows for alternating between the color image and infrared image which can be used to assess the intensity of burn that can be then titrated appropriately. Its custom made no-tilt contact lens reduces ellipticity of peripheral laser spots. Both 532 nm (Diode-pumped solid state frequency-doubled Nd:YVO) and 577 nm [optically pumped semiconductor (OPSL)] laser machines are commercially available. The aiming beam uses a 635 nm diode laser. Spot size can be adjusted from 50-500 µm (75-750 µm peripheral spot size) with an adjustable power and duration range of 50-2000 mW and 10-4000 ms respectively. Micropulse laser function uses 50-500 µs pulse duration (duty cycle: 5 %, 10 %, 15 %) and is one of the most salient features. **(Figure 1A)**

Clinical applications

- **The Navilas laser system** is indicated in all conditions where conventional laser has been used. These include photocoagulation for the treatment of diabetic macular edema, proliferative diabetic retinopathy, retinal venous occlusion, lattice degeneration, retinal tears, retinal detachments, choroidal neovascularization etc.

- **The imaging system** can also be used to acquire colour, infrared and fundus fluorescein angiography.

Planning and treatment

Planning of treatment protocol varies significantly between posterior pole treatment and PRP. Several modifications have to be made both to the laser settings and the optical unit before laser can started.

Posterior pole laser

Localisation of target pointis done by graphically marking the area of treatment (microaneurysms for single-spot focal treatment and areas of diffuse leakage for grid pattern photocoagulation) on the FFA image **(Figure 1B).** The reference FFA image can be an image taken in the NAVILAS machine itself or can be imported from an external hard drive. The laser parameters are entered according to the type of treatment and the areas of "caution zone" are marked. The system carefully avoids these caution zones during laser application. The positioned points are displayed and overlaid on the live fundus image during laser treatment phase. The NAVILAS system automatically advances the aiming beam to the next marked

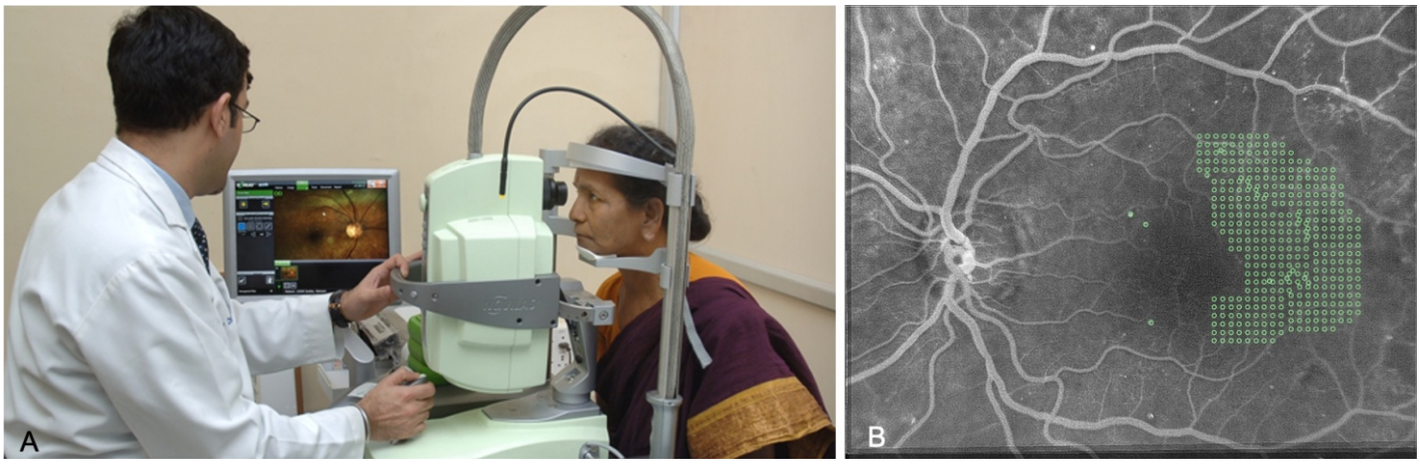

Figure 1: (A) Figure showing the entire assembly of NAVILAS system along with the positioning of patient and ophthalmologist. (B) Example of pre-planning macular laser in a case of diabetic macular edema.

point after laser has been applied. However, while adjustments in X-Y directions is accurate, focussing in the z-axis is extremely difficult.[2]This information becomes particularly concerning while treating thicker maculae. Therefore, it is recommended that navigated laser photocoagulation be performed under dry retinal conditions following either intravitreal anti-VEGF or steroid injection.

Navigated laser PRP

Unlike posterior pole laser which is contact lens free, a wide-field contact lens has to be used during PRP. The Navilas laser system provides an exchangeable PRP objective that has to be used along with the custom PRP contact lens.[3] The patient's eye, the contact lens, and optical head must be aligned for acquiring the best possible image. Coverage of the retina up to equator can be achieved with no/minimal tilt of the lens. With the PRP optics, NAVILAS images a static field of 63° x 50° (80° diagonal), but by moving the laterally or vertically , a dynamic field of around 136° can be achieved. Focusing is guided by an optical focus finder. Two bars of infrared light are projected on the retina which line up vertically with optimum focus, but move apart horizontally when out of focus.[3]

The system also has a provision of pattern positioning on the retinal image which is independent from the image acquisition. This system uses galvanometer scanners which can be controlled by the user with the help of base joystick or by drawing the patterns on the touch screen. The navigated laser system allows for both short and long pulse duration laser treatment. When using shorter pulses, the spot size variation is similar to that seen with conventional laser machines, due to the reduced impact of eye movements on laser exposure. However, the eye tracking function of NAVILAS helps in eliminating undue variation in spot size when using longer duration pulse. Even the peripheral laser spots have been reported to be far less elliptical than that seen in conventional pattern laser due to advanced optics that compensates for optical aberrations originating from the periphery of lens and contact lens tilt.[4]The laser scars observed in NAVILAS system are also more uniform compared to pattern laser system.[4]

Advantages:

- Provides high-resolution wide field imaging of the retina throughout treatment
- Multimodal images like FFA, ICG and OCT retinal thickness maps taken on other devices can be imported and integrated into the treatment planning
- Computer based treatment planning which can be performed either directly with the touchscreen, or by using buttons on the base and joystick.
- Provision for blocking sensitive areas like fovea and optic disc and the active eye tracking make it extremely safe.
- Documentation of the treatment protocol along with the settings used for treatment can be recorded and printed for future reference.
- Handy tool for learning during which both the trainer and trainee can watch the screen when the laser is being performed

Disadvantages

- Difficulty with moderate and dense cataracts
- Unavailability of indocyanine green angiography and autofluorescence imaging
- High cost of the machine

Safety and accuracy

The unique advantage of the NAVILAS system over conventional laser lies in its accuracy, speed of treatment and patient comfort. In terms of accuracy, it significantly out-performs conventional laser, with 96% of applications falling within 100 micron of the target spot.[5] This makes it highly efficient in the treatment of posterior pole pathologies. Similarly, on comparison of time taken per 100 spots, studies have demonstrated a significant reduction in treatment time as compared to PASCAL laser, especially when using a 30ms treatment protocol.[4, 6]Once "locked" into the correct position, not much action is usually required in order for the entire marked area of laser to be completed. Thus, it is the initial planning and positioning, that has a bit of learning curve. The precision of laser delivery, provision for marking "caution zone" and the eye-tracking facility, makes NAVILAS extremely safe. Navigated laser also improves patient comfort both in focal and peripheral treatments as compared to conventional laser. The benefits arise from the fact that a contact lens is not required for posterior pole treatments owing to the advanced digital visualisation system. Also, as treatment takes place under infrared light, it improves patient fixation and comfort level.[4]

Indications

Diabetic Macular edema

Neubauer et al. demonstrated a lower retreatment rates with navigated laser in the first 8 months as compared to conventional laser, in cases where focal laser is indicated.[7] Similarly, the CAVNAV study showed a lower mean number of injections required in eyes treated with navigated focal photocoagulation following three loading doses of anti-VEGF agents, as compared to anti-VEGF monotherapy (42% lesser retreatment rates).[8]And this benefit persisted even over the course of 4 years. The enhanced accuracy of the navigated laser system appeared to play a role in the durability of the treatment response.

Central serous chorioretinopathy

NAVILAS is highly effective in the treatment of CSCR with resolution rates ranging from 50-100 % according to various studies.[9, 10] Apart from the accurate application of laser to the leakage site, the micropulse laser setting allows for treatment of even sub-foveal leaks. Ambiya et al. demonstrated a resolution rate of around 60% at 3 months, in eyes with sub-foveal leak treated with 5%DC micropulse laser.[11]

Other diseases

NVILAS has also been used in the treatment of retinal vein occlusions[12], neovascular age-related macular degeneration[13] and retinal breaks.

Telemedicine and education

A recent concept of telemedicine application of NAVILAS has also been described wherein an image from one center can be sent to an image reading center where the treatment plan can be mapped out and sent back to the treating center for laser implementation,[14]or laser can be remotely controlled over a 5G network[15]. Finally, the “Navigate” application acts as an excellent educational tool for fellows and residents to practice and understand appropriate treatment plans.

Conclusion:

NAVILAS offers a fast, precise and safe alternative to conventional laser equipment. However, the lack of any head to head comparison between the various laser platforms in terms of treatment outcomes raises questions regarding its superiority. Nonetheless, NAVILAS has opened new doors in laser technology. With its real time imaging, automatic accurate laser delivery system and eye-tracking system, NAVILAS has the potential to become the future of retinal laser.

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Conflicts of interest: There are no conflicts of interest.

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CASE REPORT

OCTA characterization of choroidal neovascularization in dome-shaped maculopathy and treatment response with anti-VEGF

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Abstract:

A 74-year-old female presented with defective vision in left eye (OS) for 3 months with a best-corrected visual acuity (BCVA) of 20/80. She was pseudophakic in both eyes (OU) with tessellated fundus and macular pigmentary changeOS. A diagnosis of dome-shaped maculopathy was established OU using optical coherence tomography (OCT), with Type 1 choroidal neovascularization OS confirmed on OCT and OCT angiography (OCTA). Despite multiple anti-vascular endothelial growth factor injections, subretinal fluid OS resolved only partially. At final follow-up, BCVA OS deteriorated to 20/200 despite attenuation of peripheral neovascular arcade on OCTA with treatment.

Keywords:

Anti-VEGF, choroidal neovascularization, dome-shaped maculopathy, OCTA, serous retinal detachment

Introduction:

Dome-shaped maculopathy (DSM) is a morphological entity described on optical coherence tomography (OCT) as an abnormal forward convex protrusion of the macula within a posterior staphyloma in highly myopic eyes. 1–3It has also been demonstrated inemmetropes, hypermetropes4 and eyes without staphyloma. 5Macular complications which can compromise vision in DSM include serous retinal detachment (SRD), choroidal neovascularization (CNV), pigment epithelial detachment (PED), retinal pigment epithelium (RPE) atrophy, foveoschisis, macular hole and lamellar MH. 5–12Eyes with thicker choroid, greater dome height and vertical domes are more likely to develop SRD in DSM. 6,13

With the evolution of retinal imaging, non-invasive OCT angiography (OCTA) has been assuming greater importance in identifying neovascular process established on gold-standard

techniques like fluorescein angiography (FA) and indocyanine green angiography (ICG). 14–16In this report, we describe a case of bilateral DSM in non-myopic, non-staphylomatous eyes with Type 1 CNV-associated SRD in the left eye and the role of OCTA in assessing response to therapy in such eyes.

Case presentation:

A 74-year-old lady with Type 2 diabetes and hypertension presented to our tertiary care centre with defective vision in left eye (OS) for 3 months. Her best-corrected visual acuity (BCVA) was 20/20 in right eye (OD) and 20/80 OS. Intraocular pressures were 12 mm Hg OD and 10 mm Hg OS. She was pseudophakicin both eyes (OU) and fundus exam revealed gross tessellation with prominent choroidal vasculature OU with bilateral peripapillary atrophy, dull foveal reflex OD and macular pigmentary change OS [Fig. 1 A and B]. No drusen were seen in either eye. Axial lengths were measured as 23.1 mm OD and 23.04 mm OS and B-scan ultrasound ruled out posterior staphyloma OU.

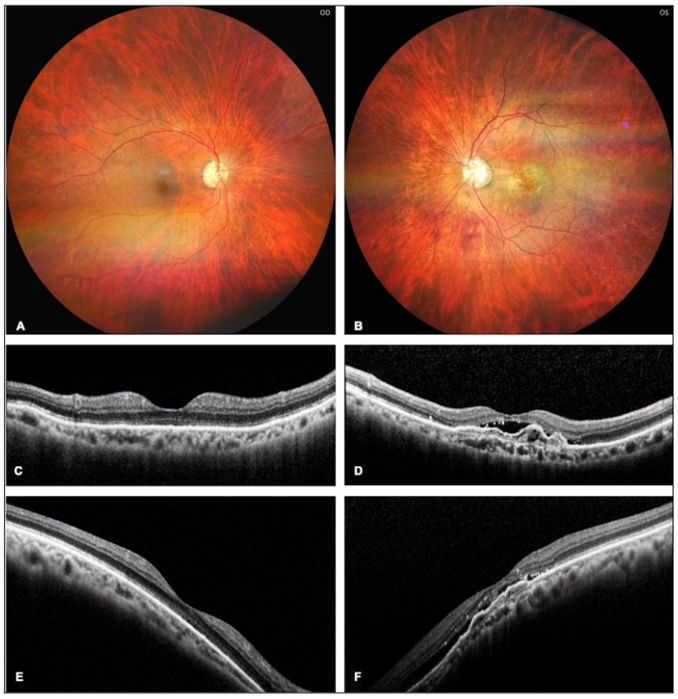

Figure 1: Color fundus photography of right (A) and left eye (B) showed grossly tessellated fundus with pigmentary change at macula in left eye. Vertical and horizontal raster scan on spectral-domain optical coherence tomography (SD-OCT) of right (C and E) and left eye (D and F) showed dome-shaped maculopathy with a vertically oriented dome. In addition, left eye also showed an irregular retinal pigment epithelium detachment (PED) associated with an overlying serous retinal detachment (SRD) and underlying dilated choroidal vessels (D and F).

Spectral-domain optical coherence tomography (SD-OCT) scan (Spectralis, Heidelberg Engineering, Heidelberg, Germany) revealed a macular bulge at the posterior pole OU, suggesting DSM **[Fig. 1 C - F]**. The macular bulge height (as measured from the apex of the bulge to a tangential line drawn from the outer border of the retinal pigment epithelium at the borders of the bulge)6 was 153 µm OD and 147 µm OS. Subfoveal choroidal thickness (SFCT) was measured as 250 µm OD and 302 µm OS. In addition, OS revealed a subfoveal and parafoveal irregular PED consisting of non-homogenous, mild to moderate hyper-reflectivity, with an overlying SRD **[Fig. 1 D and F]**. FA was unremarkable OD, while a focal, ill-defined, early stippled hyperfluorescence with leakage in the late phase was noted OS, suggesting a Type 1 CNV.

The patient received 3 consecutive monthly intravitreal ranibizumab (IVR) injectionsOS, however, BCVA OS remained unchanged, with persistence of SRD [Fig. 2A] and the SFCT was 276 µm. At this stage, OCTA revealed a Type 1CNVwith large caliber central trunk underlying the SRD and the corresponding OCT B-scan showed neovascular flow through the lesion [Fig. 2. B and C]. The need for continued anti-vascular endothelial growth factor (anti-VEGF) therapy was emphasized to the patient. However, citing financial constraints the patient elected for off-label use of intravitreal bevacizumab (IVB) injection and underwent 5 consecutive monthly IVB injections with OCT scans showing a variable response. At the final follow-up, BCVA OS was 20/200. SRD had only partially regressed while the subfoveal irregular PED persisted **[Fig. 2D]** and the SFCT measured 240 µm.

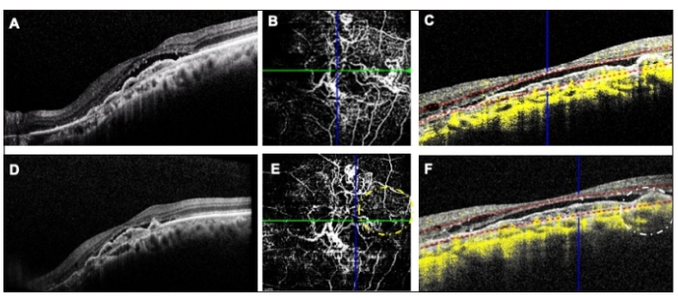

Figure 2: SD-OCT and OCT angiography (OCTA) of left eye after three intravitreal ranibizumab injections (A-C). SRD persisted (A) and a type 1 CNV with large caliber central trunk was noted beneath SRD (B) with flow signal through the lesion on OCT B-scan (C). At final visit, SRD had partially resolved (D). OCTA (E) revealed significant attenuation of peripheral neovascular arcade (yellow circle) temporal to the central trunk as shown by reduction in neovascular flow signal through the lesionand reduction of choroidal vascularity below the lesion on OCT B-scan (white circle) (F).

OCTA showed a significant attenuation of the peripheral neovascular arcade temporally **[Fig. 2E]** as seen by a decrease in the neovascular flow signal through the lesion on OCT B-scan **[Fig. 2F]**, with minimal change in caliber of the central trunk.

Discussion:

The occurrence of SRD in DSM may be secondary to altered dynamics of the choroidal vasculature due to compression from scleral thickening or macular bulge, RPE dysfunction or CNV formation. 5,7–9,17,18 CNV-related SRD in DSM eyes has been shown to respondtoanti-VEGF or photodynamic therapy (PDT).5,8,18 However, primary DSM-related SRD without a CNV may show variable response to several treatment approaches. 17,19,20

Agarwal et al 18 reported a highly myopic patient with a vertical dome, having mixed (type 1 and type 2) CNV and SRD, identified by swept-source OCTA. In their case, the patient could achieve complete drying of macula with just one anti-VEGF injection. However, in our case, SRD only partially regressed, even after multiple anti-VEGF injections. We also noted significant attenuation of peripheral arcades of the neovascular complex on OCTA after multiple injections, which indicated that the CNV had responded to treatment. Hence, we believe that the persistent SRD might have been related to primary DSM-related subretinal fluid which was not amenable to treatment, as recorded by previous authors. 2,19

There is no unified consensus yet regarding effective treatment options for chronic SRD 2,17,19–22 seen commonly in DSM eyes without CNV. 6,10Several author groups have tried treating this chronic fluid with observation 17, anti-VEGF 2,17,19, PDT2,17,19,21, sub-threshold micropulse laser 20 and mineralocorticoid receptor antagonists 17,19,22, with variability in their treatment responses. Few authors believe that this fluid may be a protective factor towards visual acuity in such patients. 23 However, visual acuity in our patient probably worsened due to progressive retinal damage by CNV.

In summary, we report a rare instance of CNV in a non-myopic eye with DSM, which we documented on OCTA on multiple follow-ups. We also recorded SRD in the DSM eye which was not amenable to the prolonged anti-VEGF therapy targeted towards treating the CNV. OCTA may help us in understanding the ultrastructural morphology of CNVs in such eyes, and enable us in differentiating the pathogenesis of SRD in DSM eyes, thereby helping us prognosticate such patients.

DECLARATION OF PATIENT CONSENT

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given his consent for his images and other clinical information to be reported in the journal. The patient understands that his names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed

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Notes

Notes

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