TRUST TOPICS REVIEW: UVEITIS SYMPTOMS & TREATMENTS

Strategies for Improving Uveitis Diagnosis, Treatments, and Outcomes

Highlights From TRUST Expert Roundtable Discussion

Roundtable Discussion: *October 18, 2014*

Release Date: *April 6, 2015 /* ***Expiration Date:*** *April 6, 2016*

Faculty | Sunil K. Srivastava, MD (Chair and Moderator)
Thomas A. Albini, MD
Prithvi Mruthyunjaya, MD
Steven Yeh, MD

This educational activity is jointly provided by Dannemiller and MCME Global

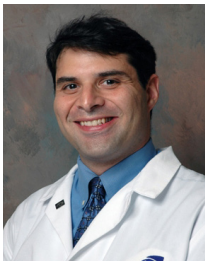
DANNEMILLER M|CME

Supported through an unrestricted educational grant from Santen Pharmaceutical

FACULTY

Sunil K. Srivastava, MD
Chair and Moderator

Staff Physician
Cole Eye Institute
Cleveland, OH

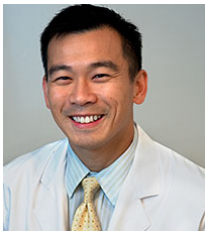


Thomas A. Albini, MD

Associate Professor of Ophthalmology
Bascom Palmer Eye Institute
University of Miami
Miami, FL

Prithvi Mruthyunjaya, MD

Associate Professor of Ophthalmology and Radiation Oncology
Director, Duke Center for Ophthalmic Oncology
Duke University Eye Center
Durham, NC



Steven Yeh, MD

Associate Professor of Ophthalmology
Section of Vitreoretinal Surgery & Diseases
Director, Section of Uveitis and Vasculitis
Emory University Eye Center
Atlanta, GA

TRUST TOPICS REVIEW: UVEITIS SYMPTOMS & TREATMENTS

METHOD OF PARTICIPATION

This activity should take approximately 1 hour to complete. Participants should first read the objectives and other introductory CME/CE information and then proceed to the educational activity. To receive credit for this activity, participants must complete the post-test with a passing score of 80% and then complete the evaluation. Credit is provided through April 6, 2016. No credit will be given after this date. There is no fee to participate in this activity.

In the event you have questions about this activity or are unable to retrieve the certificate, please email cme@dannemiller.com and a certificate will be emailed within 2 weeks.

HARDWARE/SOFTWARE NEEDED TO PARTICIPATE

High speed internet access

CONTENT SOURCE

This continuing education (CE) activity captures content from a TRUST roundtable discussion. TRUST gathers leaders in retina with a focus on uveitis to discuss the latest hot topics and cases in uveitis; the group is led by Dr. Sunil K. Srivastava from the Cleveland Clinic Cole Eye Institute.

ACTIVITY DESCRIPTION

Uveitis is a heterogeneous group of intraocular inflammatory conditions of autoimmune, infectious, neoplastic, toxic/drug-induced, and traumatic etiologies. Due to its heterogeneity, uveitis can be a challenge to diagnose and treat. Although corticosteroids are the mainstay of therapy for noninfectious uveitis, an increased understanding of the pathogenetic mechanisms associated with various forms of noninfectious uveitis has led to alternative modes of treatment to overcome the burden of corticosteroid use. A panel of experts in the field of uveitis met to discuss patient cases within the context of available supporting clinical evidence. Through the review of clinical evidence and real-world case studies by uveitis and retina specialists, this activity highlights the most appropriate diagnostic and treatment strategies based on disease characteristics and actual treatment outcomes. This activity reviews when to treat versus when to refer, how to rule out infection, when to use local versus systemic therapy, when to switch therapies, when to perform surgery, and how to follow up with patients.

TARGET AUDIENCE

This educational activity is intended for uveitis specialists, retina specialists, and comprehensive ophthalmologists who are interested in recent advancements in proper diagnosis, patient selection and treatment decisions, along with the potential consequences of initial treatment with suboptimal or incorrectly applied therapy.

LEARNING OBJECTIVES

Upon completion of this CE case series, participants will be better able to:

- Identify which diagnostic tests and markers of disease progression are most informative for each type of uveitis
- Use topical versus systemic therapies appropriately
- Assess treatment options for noninfectious and posterior noninfectious uveitis and the role of patient selection in optimizing treatment outcomes
- Know how far to take treatment before referring a patient to a uveitis specialist

ACCREDITATION DESIGNATION STATEMENT

This activity has been planned and implemented in accordance with the accreditation requirements and policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint providership of Dannemiller and MCME Global. Dannemiller is accredited by the ACCME to provide continuing medical education for physicians.

Physicians: Dannemiller designates this enduring material for a maximum of 1 *AMA PRA Category 1 Credit*™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Physician Assistants: AAPA accepts certificates of participation for educational activities certified for Category 1 credit from AOA, Prescribed credit from AAFP, and *AMA PRA Category 1 Credit*™ from organizations accredited by the ACCME. Physician assistants may receive a maximum of 1 *AMA PRA Category 1 Credit*™ for completing this program.

DISCLOSURES

Alex Yuan, MD, content reviewer; Jennifer Hodge, Dannemiller's project manager; and Yaremi Koopot, MCME's Director of Medical Education have no financial relationships with commercial interests.

To resolve identified/potential conflicts of interest, the educational content was fully reviewed by a member of the Dannemiller Clinical Content Review Committee, who has nothing to disclose. The resulting certified activity was found to provide educational content that is current, evidence based, and commercially balanced.

Faculty
Dr. Thomas A. Albini is a consultant/advisory board member for Allergan, Clearside Biomedical, Santen, and Valeant.

Dr. Prithvi Mruthyunjaya is a consultant/advisory board member for Allergan.

Dr. Sunil K. Srivastava is a consultant/advisory board member for Allergan, Bausch + Lomb, Clearside Biomedical, and Santen.

Dr. Steven Yeh is a consultant/advisory board member for Bausch + Lomb, Clearside Biomedical, and Santen.

TRUST TOPICS REVIEW: UVEITIS SYMPTOMS & TREATMENTS

OFF-LABEL DISCUSSION

This educational activity may contain discussion of published and/or investigational uses of agents that are not indicated by FDA. The opinions expressed in the educational activity are those of the faculty. Please refer to the official prescribing information for each product for discussion of approved indications, contraindications, and warnings. Further, attendees/participants should appraise the information presented critically and are encouraged to consult appropriate resources for any product or device mentioned in this program.

GRANTOR STATEMENT

This CE activity is supported through an unrestricted educational grant from Santen Pharmaceutical.

TO OBTAIN CE CREDIT

There are no fees for participating and receiving CME credit for this activity. During the period from April 6, 2015, through April 6, 2016, participants must read the learning objectives and faculty disclosures and study the educational activity.

If you wish to receive acknowledgment for completing this activity, please complete the post-test and evaluation on www.dannemiller.com. Upon registering and successfully completing the post-test with a score of 80% or better and the activity evaluation, your certificate will be made available immediately.

DISCLAIMER

The content and views presented in this educational activity are those of the authors and do not necessarily reflect those of Dannemiller. This material is prepared based upon a review of multiple sources of information, but it is not exhaustive of the subject matter. Therefore, health care professionals and other individuals should review and consider other publications and materials on the subject matter before relying solely upon the information contained within this educational activity.

INTRODUCTION

This series of 4 cases discusses how to diagnose, treat, and manage everyday patients who walk into the offices of uveitis and retina specialists, based on the collective experience of 4 physicians with expertise handling patients with uveitis. The potential differences in approach between uveitis and retina specialists are called out.

CASE 1 FROM THE CASE FILES OF DR SUNIL SRIVASTAVA

CASE PRESENTATION

A 50-year-old female who has a 4-year history of uveitis mainly in the left eye presents for a second opinion. She recalls having previous diagnostic testing for infectious uveitis, including tests for syphilis, tuberculosis, and inflammatory markers, and that all of these test results were negative. She states that she is otherwise healthy. Her local physician has treated her eye with steroids, either periocular or intravitreal, and her last steroid injection was 1 month ago. Her vision is 20/20 in the right eye and 20/150 in the left eye.

DISCUSSION

Sunil Srivastava: How aggressive are you at this point with pursuing a diagnosis?

Steven Yeh: Whenever I get a new patient referral, I am vigilant about getting old medical records — both laboratory and radiographic records. Most of my decision making is premised upon what has been done before (eg, which treatments worked, which treatments did not work, and which laboratory tests were performed).

Sunil Srivastava: In this scenario, assume you have the standard set of laboratory results for a uveitis patient in front of you and everything was negative, but the labs were run a few years ago. What would you do next?

Tom Albini: There are certain things that it makes sense to repeat. For example, in a case where I was suspicious of sarcoidosis, I would repeat an ACE [angiotensin-converting enzyme] test. In certain select cases, such as a suspected recurrence of syphilitic disease, it might make sense to repeat RPR [reactive plasma regain]. It would be unnecessary to repeat HLA [human leukocyte antigen] typing, for example.

Steven Yeh: You might also want to run a comprehensive metabolic panel — a CBC [complete blood count]. If you are looking forward from a treatment standpoint, these types of tests will influence whether you can use or exclude certain medications.

Prithvi Mruthyunjaya: Patient history also guides the selection of tests. For example, if there is an issue of travel or potential exposure to an infectious agent, PCR (polymerase chain reaction) testing for infectious uveitis might be appropriate. Unfortunately, it is not uncommon to be lulled into a false sense of security that it is a noninfectious uveitis after multiple tests have come back negative.

Sunil Srivastava: I think we all learned in residency that we must talk to our patients. How do you approach key elements of the history in a uveitis patient even before the exam?

Tom Albini: In this case, I really want to know what kind of uveitis the patient has. Uveitis is a vague term. Has the patient had a history of swelling of the retina? Why were repeated injections necessary? Does she have arthritis? I would look for risk factors for infectious causes. For acute onset, I ask for risk factors for endogenous uveitis, such as recent hospitalizations and immunosuppression. In a chronic case like this, I would focus more on autoimmune phenomena. I would ask the patient about arthritis, rashes, and family history of autoimmune disease to get an idea of where the uveitis might fit within the spectrum of any systemic problems.

Steven Yeh: I also consider the location of the uveitis. Often our patients with uveitis will have ophthalmic symptoms. Pain, photophobia, and eye redness would indicate anterior uveitis with ciliary body inflammation. Complaints of blurred vision and painless changes, such as floaters, would indicate intermediate uveitis. From a systemic standpoint, I focus on pulmonary, dermatologic, and musculoskeletal symptoms.

Sunil Srivastava: Where do you think the knowledge gap is for a retina specialist when this type of patient walks in?

Prithvi Mruthyunjaya: As a retina specialist, a potentially confusing issue is deciding between systemic versus local therapy. A retina specialist would tend to manage immediately with local therapy to the eye, whether it is topical, periocular, or intravitreal, and may miss something that needs to be treated systemically. The concern would be missing something systemic or worse — something potentially lethal like intraocular lymphoma. The retina specialist would tend to treat immediately to improve symptoms but fail to address the underlying systemic cause of the uveitis.

Sunil Srivastava: In asking questions, the patient gave me a positive history of allergy and occasional wheezing and a negative history for headaches, nausea/vomiting, arthritis, rashes, sexually transmitted diseases, chest pain, shortness of breath, coughing up blood, and ulcerations in her mouth or other areas. Upon examination, the left eye had a quiet anterior segment, a PSC [posterior subcapsular cataract], and an unremarkable angiogram (Figure 1). The right eye looked normal and inactive. The OCT [optical coherence tomography] in the left eye highlights a probable previous granuloma or lesion in the macular area. There was some evidence of cystic changes in the macula with an ERM [epiretinal membrane] (Figure 1); the right eye had a normal contour. To put this in an anatomical context, the inflammation appears to involve the back of the eye (ie, posterior or intermediate uveitis).

Photo Courtesy of Dr Sunil Srivastava.

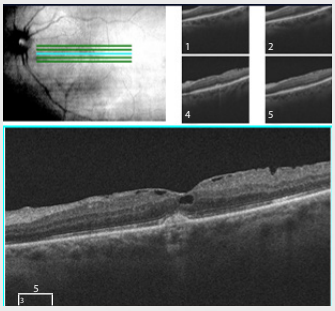


Figure1. OCT Images
OCT of the left eye reveals mild epiretinal membrane, a few intraretinal cysts, and a smooth subretinal pigment epithelium lesion with moderate hyper-reflectance. OCT, optical coherence tomography.

The patient didn't have any symptoms in the right eye, but in my experience unilateral disease is bilateral until proven otherwise. I make sure I always look at both eyes.

Steven Yeh: The tendency with unilateral disease is to think the uveitis is more of a local phenomenon rather than systemic and that local therapy is preferred to systemic therapy.

Prithvi Mruthyunjaya: This highlights another difference in approach between retina and uveitis specialists. The retina specialist typically questions the value of evaluating asymptomatic eyes in more common diseases like macular degeneration, retinal vein occlusion, and DME [diabetic macular edema], whereas in uveitis, it is very important to do a thorough evaluation of both eyes to make sure nothing is overlooked.

Sunil Srivastava: The differential diagnosis I was considering for this patient included multiple sclerosis, inflammatory bowel disease, tuberculosis, sarcoidosis, syphilis, and Lymes disease, when my technician noticed that the patient was wheezing audibly and struggling to talk and answer questions — a tip-off that the uveitis might be the result of sarcoidosis. We repeated the ACE test and her ACE level was high — 73 U/L. The chest CT [computed tomographic] scan showed multiple enlarged lymph nodes. A biopsy of lung tissue confirmed sarcoidosis.

Now that a diagnosis of sarcoidosis has been made, how would you manage the patient?

Tom Albini: Now that we know we are dealing with a patient with sarcoidosis, we can be fairly confident that the uveitis is not caused by something infectious — we know it is not syphilis, which would present similarly. My approach would be to consult with a pulmonologist. Whatever is going to be done at this point to treat the lungs is also going to help the eye. She may be started on methotrexate or on another steroid-sparing agent. If she does not require systemic treatment, I may propose local therapy, since the uveitis is only in the one eye. Even if she does require systemic treatment, I may add local therapy if necessary.

Sunil Srivastava: An important point here is that just because the disease is systemic does not mean systemic therapy is definitively needed at this point. In some cases of sarcoidosis, if the patient's lung disease is inactive or mild, our pulmonologist may recommend close observation — thus, the ocular disease would drive the choice of treatment. Other times, the systemic disease is very active and drives the choice of therapy even if the ocular disease is mild or inactive. It is important to treat based on a team approach.

The retina specialist typically questions the value of evaluating asymptomatic eyes in more common diseases like macular degeneration, retinal vein inclusion, and DME, whereas in uveitis, it is very important to do a thorough evaluation of both eyes to make sure nothing is overlooked.

CASE 2 FROM THE CASE FILES OF DR STEVEN YEH

CASE PRESENTATION

This is a young lady who was 12 years old when she first presented. She complained of floaters in the left eye; the duration of the complaint was several months. There were no symptoms of pain. She complained of some problems seeing the computer at school and had been diagnosed with uveitis and was started on topical prednisolone acetate 1%, twice daily.

DISCUSSION

Sunil Srivastava: Do you think topical steroids of several months' duration are a useful first-line therapy?

Tom Albini: For chronic anterior uveitis, several months of steroids would be better than a steroid-sparing agent, especially if the patient is pseudophakic or has had glaucoma surgery. My typical course for acute uveitis is aggressive topical steroids once every hour or two for 7 days while awake. I would then switch the patient over to either a subtenon (periocular) injection or oral steroids, typically dosed at 1 mg/kg.

Steven Yeh: The other topical therapy that I would consider in patients who have ongoing intermediate uveitis is difluprednate, although there are concerns of IOP [increased ocular pressure] with its use.

Prithvi Mruthyunjaya: Many of our optometry colleagues prescribe difluprednate. For me, it is the equivalent potency of difluprednate twice a day versus prednisolone acetate 4 or 6 times a day. Difluprednate is highly effective, but sometimes it is overtreatment for mild cases of uveitis.

Steven Yeh: The patient is otherwise healthy with no other known medical problems. Her visual acuity was 20/20 in the asymptomatic right eye and 20/40 in the symptomatic left eye. Upon examination, she had trace AC [anterior chamber] cell OD [right eye], 1+ cell OS [left eye]; anterior vitreous disease in both eyes (trace cell OD, 1-2+ cell OS); vitreous opacity and 1+ vitreous haze OS. In her left eye, she had fibrosis over the nerve and an epiretinal membrane, and peripherally, she had a pars plana snowbank with exudates and retinal pigment epithelial changes that suggest she may have had fluid previously as well as neovascularization. From the FA [fluorescein angiogram], you can see that there are leaking vessels (Figure 2).

Sunil Srivastava: It is not uncommon for retina specialists to see a patient with chronic anterior uveitis referred for posterior segment findings. What do you think is going on?

Prithvi Mruthyunjaya: In a situation of pars planitis, the condition is unlikely to be the result of any major infectious or other cause, so it is probably going to be idiopathic. But you still need to go through a differential diagnosis strategy and think about directed laboratory testing. Because this is more than just a couple of snowballs and anterior

Images courtesy of Dr Steven Yeh.

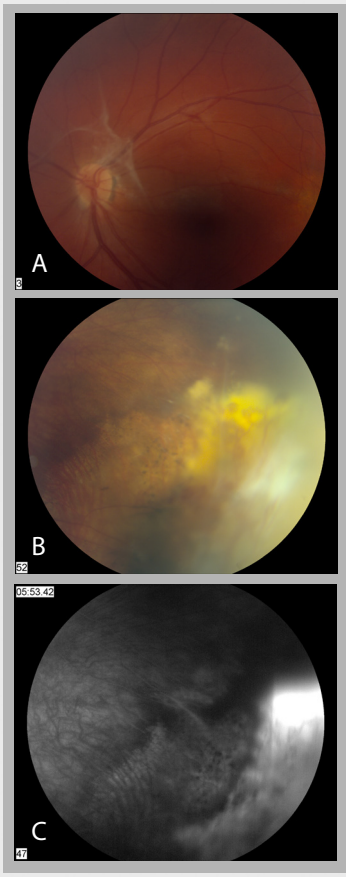


Figure 2. Fundus Photographs
Fundus photograph of left eye shows mild vitreous haze and fibrosis of the posterior hyaloid (A). Inferotemporally, there is a pars plana snowbank with retinal neovascularization (B). Late frame fluorescein angiography shows hyperfluorescence consistent with late leakage in the region of the pars plana (C).

uveitis, there is the question of how to manage the peripheral neovascularization and the inflammation.

Sunil Srivastava: The pigmentary change in the peripheral retina and the presence of an epiretinal [membrane] indicate to me that the inflammation has been there for a while.

Tom Albini: She still has really good visual acuity at 20/40, but the cystoid macular edema with mild retinal thickening is a major concern. I would use more local steroids such as a periocular injection of Kenalog® (40 mg/mL), intravitreal triamcinolone acetonide (2 mg or 4 mg), or an intravitreal dexamethasone implant (700 µg).

Prithvi Mruthyunjaya: My concern is how can I prevent this young patient from needing a vitrectomy in the 20/40 eye.

Tom Albini: The majority of people would think this is not surgical, and doing a vitrectomy for this disease in a 12-year-old with all the possible complications is extremely undesirable — one iatrogenic retinal break in a 12-year-old and there is a good chance the eye will not see well after that surgery. I would stay away from vitrectomy, but then the question is, when is it appropriate to do PRP [panretinal photocoagulation] laser?

You want to control the inflammation before PRP, and my initial approach would be to use steroids, either local or systemic, to get the inflammation immediately under control. If the inflammation is bilateral, I would lean toward using systemic steroids. Once the inflammation is under control, I would switch to a steroid-sparing agent.

I would only recommend vitrectomy as a last resort in a patient this young.

Sunil Srivastava: What outcomes would you follow to determine if the steroid therapy is working?

Tom Albini: There are 3 main outcomes I would want to see: (1) the FA to determine if the vascular leakage has stopped, (2) the exam to determine if the inflammatory cell has cleared, and (3) the OCT to see if the CME [cystoid macular edema] has resolved (assuming she had CME).

Sunil Srivastava: Is there anything you would be particularly worried about in this patient?

Tom Albini: I would really want to see how much nonperfusion there is on the FA, and then would start thinking about treating this patient with PRP (laser).

Prithvi Mruthyunjaya: With the amount of neovascularization seen in her left eye, she's at high risk for vitreous hemorrhage. It would be great if we could reduce the neovascularization. PRP (under anesthesia) is definitely something to think about.

Sunil Srivastava: When considering adding a destructive procedure like PRP, are you supplementing with anything?

Tom Albini: It depends. My usual approach in a patient that has not had a vitreous hemorrhage is to wait for the steroids to quiet the eyes, which typically takes a couple weeks.

Prithvi Mruthyunjaya: I think my move to a laser destructive procedure would probably be even slower, more like 1 to 3 months. I would try local (periocular) steroid therapy first and then systemic. I would wait to see if the neovascularization regresses. If the neovascularization does not regress and if I still see the inflammatory cells, then the eye would have to be completely quiet before I would do a destructive procedure. My concern is that the destructive procedure would cause the inflammation to worsen.

Sunil Srivastava: We all recognize the importance of getting the eye quiet and that this eye needs to be treated. FA and OCT imaging could be used to determine if the eye is quiet.

Steve Yeh: Important outcome measures would include visual acuity, the appearance of vitreous haze, the extent of cystoid macular edema and retinal thickening, and the active appearance of the pars plana snowbank and of the retinal vessels.

Sunil Srivastava: I would lean toward a systemic treatment with possible adjunctive local therapy because this patient already has a secondary complication (the epiretinal membrane and neovascularization) of a long-standing chronic inflammatory disease.

Tom Albini: With systemic treatment in a young patient, I would immediately involve a pediatrician to co-manage the patient. I would want a pediatrician onboard when prednisone is given systemically to a child, and eventually would consider adding a pediatric rheumatologist if the treatment involved steroid-sparing immunosuppression.

Steven Yeh: As Dr Mruthyunjaya described, I moved very slowly towards destructive therapy, but because the snowbank was too thick to have good laser uptake, we performed cryotherapy after the PRP to better treat the border zone.

Sunil Srivastava: I am aggressive with my local therapy at the time of the cryotherapy. For young patients, I have started to move towards injecting the dexamethasone implant because I want 2 to 3 months of therapy. There is a risk of cataract and elevation of intraocular pressure when using this treatment, but I am able to aggressively manage the inflammation during the time of the destructive procedure.

This is a not an uncommon case scenario. It is important to understand that there is time to determine what long-term plan is needed to preserve the child's vision. This case is not an acute emergency. The tactic of starting therapy and then building on top of it is the way to approach a case like this.

We all recognize the importance of getting the eye quiet and that this eye needs to be treated. FA and OCT imaging could be used to determine if the eye is quiet.

Important outcome measures would include visual acuity, the appearance of vitreous haze, the extent of cystoid macular edema and retinal thickening, and the active appearance of the pars plana snowbank and of the retinal vessels.

CASE 3 FROM THE CASE FILES OF DR PRITHVI MRUTHYUNJAYA

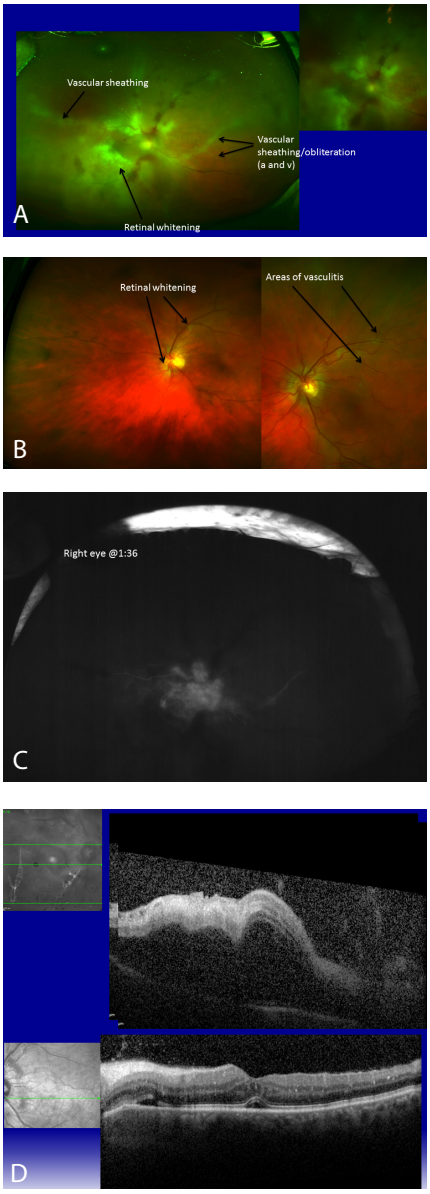
CASE PRESENTATION

A 57-year-old gentleman has 5 days of progressive bilateral vision loss, but the right eye is affected significantly more than the left eye. He has mild ocular pain and discomfort. He is healthy with no past medical history that could be elicited. He smokes, drinks alcohol, and works outside most of the day. He had a few insect bites and scratches from a new puppy. His sexual behavior is low-risk and he notes no unintentional weight loss. He has chronic joint aches and pains but nothing that stands out. He has no oral or genital ulcers, breathing difficulties, rashes, or wheezing.

Examination shows that there is light perception on the right, visual acuity in the left eye is 20/200, 20/60 PH. Intraocular pressure is 11 mm Hg in the right eye (3+ rAPD) and 13 mm Hg in the left eye. He has conjunctival injection but there are no nodules. There are fine keratic precipitates, primarily in the right eye. The anterior chamber has 3-4+ cells, 3+ flare OD and 3+ cells, 2+ flare OS. On the right eye, he has synechiae and focal neovascularization of the iris that is not florid; the anterior vitreous in the right eye has 2+ cells with 1+ haze; the left eye has trace cells.

The wide-field fundus image of the right eye (Figure 3A) demonstrates vascular sheathing and the nerve appears swollen. There is retinal whitening in the macula and perimacular areas, and obliteration of both the arterioles and venules in the mid- and far periphery. The left eye had a more clear view (Figure 3B), but there are some areas of intraretinal whitening and sheathing around vessels (suggestive of early vasculitis) in the posterior pole.

The FA image in Figure 3C shows the initial angiogram of the right eye. By early to mid-frames, we are seeing essentially no peripheral perfusion; centrally, there is abundant fluorescein leakage. The left eye appears to be perfused into the periphery, with the areas with retinal whitening blocking the dye in late frames. There is no macular leakage.



Images courtesy of Dr Prithvi Mruthyunjaya.

Figure 3.
Wide-field Fundus Images
(A) The right eye shows vascular sheathing, confluent retinal whitening, and obliteration of the peripheral vascular beds.

(B) The left eye shows focal areas of intraretinal whitening but preserved retinal architecture.

(C) Mid-phase FA of the right eye shows obliteration of the peripheral vasculature with leakage of retained vessels in the macula. FA, fluorescein angiogram.

(D) OCT image of the right eye (top) shows vitreous opacity and retinal thickening with macular detachment.

The left eye (bottom) shows small pockets of subretinal fluid in the macula and peripapillary region. OCT, optical coherence tomography.

The OCT of the right eye (Figure 3D) shows intraretinal fluid and retinal thickening; the left eye has small pockets of subretinal fluid and intraretinal thickening.

DISCUSSION

Sunil Srivastava: This is an urgent/emergent case. What should we be worried about with this patient, given his sudden vision loss?

Tom Albini: In patients with severe bilateral vasculitis with obliterated circulation in at least one of the eyes, I worry about a systemic vasculitic process that could potentially be lethal. High on my differential diagnosis would be an autoimmune phenomenon. In this case, I would look for markers of systemic inflammation, like C-reactive protein, ESR [erythrocyte sedimentation rate], and complement factors, because there is so much vasculitis. I would want to get a rheumatologist involved if there is systemic inflammation.

With retinal whitening and retinitis, I would also be concerned about infectious causes such as herpes and syphilis, so I would use PCR to help rule out some of the herpetic causes and toxoplasmosis, and I would run a syphilis serology.

Sunil Srivastava: When viral retinitis is in the differential, what diagnostic procedures or treatments should be performed?

Steven Yeh: Because it is important not to miss viral retinitis, namely acute retinal necrosis, the patient would need an anterior chamber paracentesis for PCR analysis.[1] From an autoimmune standpoint, I find that patients who have devastating vasculitis oftentimes have severe systemic vasculitis symptoms on presentation, including shortness of breath indicative of pulmonary vasculitis, skin findings, or kidney disease; they are very sick. It is difficult, because if you are thinking it could be systemic vasculitis, treatment would be high-dose corticosteroids, which could make an infectious disease a lot worse. You could cover for both by placing the patient on corticosteroids and antibiotics/antivirals.

Prithvi Mruthyunjaya: In our differential we considered lymphoma, syphilis, sarcoid, Behcet's, and idiopathic retinal vasculitis—mainly because of the vascular sheathing and the nonperfusion, which are not typically seen for viral retinitis without the hemorrhaging and retinal whitening.

In a case like this, there are multiple potential causes, and the more common ones can be evaluated by retinal specialists. This case became disconcerting when the most common causes came up negative.

The first day, because we were concerned about viral retinitis, vitreous fluid was obtained for PCR and the patient was admitted for IV acyclovir, an intravitreal foscarnet injection was given in the right eye, and the patient was started on topical drops for the AC reaction. By the third day, the vision in the left eye was deteriorating, so intravitreal foscarnet was injected into the left eye while we were waiting for the PCR results.

Tom Albini: To avoid having to admit the patient, valaciclovir 1 g three times a day TID or 2 g TID is an alternative to IV acyclovir.

Prithvi Mruthyunjaya: Numerous laboratory studies (ie, RPR/FTA-Abs, HIV, Lyme, ANCA, ACE, CXR/PPD, ESR, CMP, CBC, CRP, Toxo IgG/IgM, Bartonella titers, and UA) were performed to determine if the origin might be from

Because it is important not to miss viral retinitis, namely acute retinal necrosis, the patient would need an anterior chamber paracentesis for PCR analysis.

infectious or inflammatory causes, but everything came back negative except for slight leukocytosis 12.4 (reference range, 3.2-9.8); and ANA [antinuclear antibody] + of 1:160. We were worried about CNS [central nervous system] vasculitis being involved, so an MRI was performed, but it also came back negative. On day 5, the vitreous PCR came back negative for HSV [herpes simplex virus], VZV [varicella zoster virus], CMV [cytomegalovirus], and *Toxoplasma gondii*.

Tom Albini: The positive ANA makes one think the patient has a vasculitic process, perhaps lupus, but this doesn't look like lupus vasculitis.

Prithvi Mruthyunjaya: The vision continues to deteriorate. On day 5, once we knew the PCR was negative for viral causes, we stopped the IV acyclovir and antibiotic (sulfamethoxazole and trimethoprim) and started him on oral prednisone, 80 mg daily. By day 7, the vitritis was improving and visual acuity in the right eye was stable, although the left eye did worsen slightly. Because we were still worried about the possibility of an infection or lymphoma, we performed a diagnostic vitrectomy in the worse eye: there was no growth on bacterial culture and cytopathology did not uncover lymphoma cells, but he did have atypical lymphocytes.

By day 10, he was getting better subjectively and objectively — the hemorrhaging had decreased, the sheathing was better, and the nerve was less inflamed. But we started to see new areas of whitening in the left eye, so we gave another intravitreal foscarnet injection and, as seen by OCT, the eye responded and was nearly normal. The view of the right eye was now clear. The angiogram of the right eye showed significant destruction of peripheral vasculature, and I was still concerned about the increased risk of retinal neovascularization, concerned about possible Behcet's disease. HLA-B51 was found to be present.

After 4 weeks on oral steroids, vision was 25/100 in the right eye and 20/60 in the left eye. He appeared to be clinically stable.

Would you have altered our testing in any way?

Tom Albini: We still do not know what is going on because almost everything on your differential will get better to some degree with steroids. In cases like this it is difficult to balance the need for steroids and the steroid-induced lymphocyte lysis prior to vitreous biopsy. I prefer to stop steroids 2 weeks prior to a biopsy for lymphoma.

Also, in looking at this case, you could make an argument for an early vitrectomy in the right eye for a diagnostic procedure before starting any steroids. You are exposing the patient to a surgical risk, but you will get the best possible sample for the PCR analysis; it may be your best strategy to save vision in the contralateral eye.

Tom Albini: Did you also do a brain MRI and an LP [lumbar puncture]?

Prithvi Mruthyunjaya: We did a brain MRI but not an LP.

In looking at this case, you could make an argument for an early vitrectomy in the right eye for a diagnostic procedure before starting any steroids. You are exposing the patient to a surgical risk, but you will get the best possible sample for the PCR analysis; it may be your best strategy to save vision in the contralateral eye.

Tom Albini: The LP is very low yield, but it is part of the workup for diagnosing lymphoma. It is a safe procedure and it can make the diagnosis.

Prithvi Mruthyunjaya: This was a frustrating situation since there were a few atypical lymphocytes on the diagnosis vitrectomy while on the steroid. The flow was negative, but it could still be lymphoma suppressed by the steroids.

Sunil Srivastava: You have gotten the patient through the acute crisis; what would you do now?

Prithvi Mruthyunjaya: I would wean him slowly off the oral steroids and consult with a rheumatologist who is familiar with managing uveitis patients.

I would also plan a periocular steroid injection to keep some local therapy in place while he is tapered off the oral steroids and start a steroid-sparing systemic therapy. Bilateral periocular steroid injections would give the patient 2 to 3 months of coverage while a rheumatologist works with him to identify systemically what is going on.

Steven Yeh: This patient is HLA-B51 positive, so it could possibly be Behcet's or an incomplete Behcet's in the absence of other systemic findings. We know that patients with Behcet's disease can lose vision rapidly if they are not taking an immunosuppressive drug.

Sunil Srivastava: At this point I would immunosuppress the patient and look for signs that tell me I am on the right track. If it is viral, you would expect to still have some activity after 2 or 3 weeks, but this patient's right eye looks so much better after 2 weeks. You wouldn't expect a viral disease to improve this quickly and respond to the steroids. I might not inject periocular steroids at this point, because the patient is stable and slowly tapering off systemic steroids. To me, this looks like Behcet's based on the rapid loss of vision, the pale nerve, and that the retina is thin temporally (ie, arterial occlusion). I would probably have him on slow steroids but by month 2, and I would start switching him over and be aggressive with a systemic immunosuppressant.

Prithvi Mruthyunjaya: For retina specialists who see uveitis patients, their comfort level sharply decreases whenever vascular changes present, for example retinal vasculitis, compared with vitreitis and CME. These latter conditions are more directly manageable.

Tom Albini: This is one of those cases where uveitis specialists are more comfortable than retina specialists, because in reality we do not know what this is. I think the rapidity and the cadence here of the inflammation—how rapidly it came, how rapidly it disappeared—strongly suggests Behcet's disease, so I would treat it as Behcet's knowing in the back of my mind that we have not ruled out some of the other possibilities. The nice thing about Behcet's is, once you get the initial inflammation under control with steroids, you can then reduce recurrence with chronic steroid-sparing agents.

Prithvi Mruthyunjaya: When retina specialists encounter systemic vasculitic disease, they should initiate workups, manage the acute situation, and consider a referral to a uveitis specialist.

CASE 4 FROM THE CASE FILES OF DR TOM ALBINI

CASE PRESENTATION

A 50-year-old woman has been experiencing blurry vision and occasional photopsias. Her visual acuity is 20/40 in both eyes, and she has mild cataracts in both eyes. She saw a general ophthalmologist for cataract evaluation, who referred her after detecting vitritis. She has mild anterior chamber cell and mild vitreous cell. There is no cystoid macular edema and no chorioretinal spots. There is also nothing to suggest intermediate uveitis in terms of snowbanks or snowballs.

DISCUSSION

Sunil Srivastava: How do you decide what imaging to order?

Tom Albini: The photopsias suggested retinal inflammatory lesions. Also, she had vitreous cell. As a result of these observations, I was aggressive with imaging and obtained OCT and FA. The FA revealed an unusual pattern of retinal vascular leakage of the primary vessels predominantly in the veins coming off the nerves, and this pattern was symmetric in both eyes. This is a pattern that I see in patients with birdshot retinochoroidopathy (Figure 4).

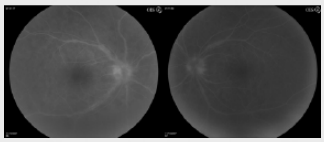
Steven Yeh: ICG (Indocyanine green) angiography also is very important. In this patient, I would have gone forward with FA and ICG with peripheral sweeps.

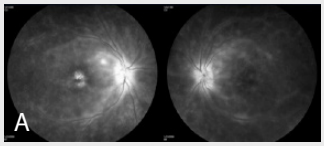
Prithvi Mruthyunjaya: Most retinal specialists would take the patient's history and look at an OCT. If there was no CME, they would look for retinal thickening as a map function. If there was no thickening, then that would be the end of the diagnostic imaging.

Steven Yeh: FA is something that every retina specialist has access to. If the retina specialist had taken an FA, it would have potentially alerted them to additional ongoing vascular disease. Angiography adds to our ability to diagnose disease alongside OCT.

Tom Albini: As a result of the imaging, HLA-A29 testing was obtained and was found to be positive. There is a strong association between HLA-A29 and birdshot retinochoroidopathy. However, she did not have three identifiable lesions in either eye, so technically she did not meet the diagnostic criteria for birdshot. I treated her as birdshot because most of the findings were consistent with this disease. She was initially given oral prednisone and tapered, then started on cyclosporine but developed hypertension. She was switched to mycophenolate but developed hepatic toxicity. She was started on methotrexate + infliximab, but that regimen was stopped due to loss of efficacy; methotrexate + adalimumab and methotrexate + golimumab were not effective. Her rheumatologist suggested methotrexate + corticotropin (13 doses). Finally, methotrexate and a dexamethasone intravitreal implant were tried, and her condition improved. These were consecutive treatments, in order, over a span of about 4 years.

FA





ICG

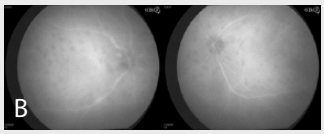


Figure 4.
(A) Fluorescein Angiogram Early and late frame FAs of both eyes reveal vascular leakage diffuse throughout both posterior poles.
(B) ICG angiography demonstrates diffuse multifocal hypofluorescence.

FA, fluorescein angiogram; ICG, Indocyanine green.

Sunil Srivastava: How did you decide something was not working?

Tom Albini: She was symptomatic and could tell when she was controlled and when she was not. For me, the primary outcome measure with this patient was no longer seeing vascular leakage in the FA.

Through all of this, I worked with a rheumatologist and there was a lot of back and forth between the two of us. I had talked to the patient about local treatment from the beginning and after each failure, but she didn't want surgery or an injection. Finally, I talked her into the dexamethasone intravitreal implant, and it worked instantaneously. Now she is happy with this strategy.

Prithvi Mruthyunjaya: How often would you repeat the FA?

Tom Albini: Every 2 to 3 months.

Prithvi Mruthyunjaya: An important point from this case is the diagnostic relevance of FA and that retina specialists should reincorporate using FA for cases of suspected uveitis, given that many have moved away from this diagnostic procedure in favor of OCT.

Steve Yeh: Was it challenging to switch the patient from mycophenolate to methotrexate?

Tom Albini: For this patient, her liver enzymes were elevated with mycophenolate but not with methotrexate. We tried 3 different TNF-α [tumor necrosis factor alpha] blockers in combination with the methotrexate, because there was evidence in the literature that these agents worked for birdshot.[2] Infliximab worked great initially, but then she recurred.

Sunil Srivastava: To me, birdshot retinochoroidopathy is the type of disease that local therapy was made for. When we have to choose between systemic therapy and local therapy, data support the effectiveness of both approaches.[2-6] The unmet need we have right now is sustaining long-term treatment in a relatively young patient. For example, if a 25-year-old patient with bilateral chronic uveitis needs treatment for 40 years, what do you do? The options are not ideal — 40 years of immunosuppressive agents, 13 implants in each eye plus likely CE/IOL [cataract extraction/intraocular lens] and glaucoma surgery, or 80 injections of dexamethasone with probable cataract surgery and glaucoma. Hopefully over the next few years, new therapies will be introduced to address this need.

FA is something that every retina specialist has access to. If the retina specialist had taken an FA, it would have potentially alerted them to additional ongoing vascular disease. Angiography adds to our ability to diagnose disease alongside OCT.

As result of the imaging, HLA-A29 testing was obtained and was found to be positive.

CME EVALUATION AND CERTIFICATE

REFERENCES

1. Harper TW, Miller D, Schiffman JC, Davis JL. Polymerase chain reaction analysis of aqueous and vitreous specimens in the diagnosis of posterior segment infectious uveitis. *Am J Ophthalmol*. 2009;147(1):140-147.

2. Levy-Clarke G, Jabs DA, Read RW, Rosenbaum JT, Vitale A, Van Gelder RN. Expert panel recommendations for the use of anti-tumor necrosis factor biologic agents in patients with ocular inflammatory disorders. *Ophthalmology*. 2014;121(3):785-796.

3. Cervantes-Castaneda RA, Gonzalez-Gonzalez LA, Cordero-Coma M, Yilmaz T, Foster CS. Combined therapy of cyclosporine A and mycophenolate mofetil for the treatment of birdshot retinochoroidopathy: a 12-month follow-up. *Br J Ophthalmol*. 2013;97(5):637-643.

4. Kiss S, Ahmed M, Letko E, Foster CS. Long-term follow-up of patients with birdshot retino-choroidopathy treated with corticosteroid-sparing systemic immunomodulatory therapy. *Ophthalmology*. 2005;112(6):1066-1071.

5. Rush RB, Goldstein DA, Callanan DG, Meghpara B, Feuer WJ, Davis JL. Outcomes of birdshot chorioretinopathy treated with an intravitreal sustained-release fluocinolone acetonide–containing device. *Am J Ophthalmol*. 2011;151(4):630-636.

6. Tomkins-Netzer O, Taylor SR, Lightman S. Long-term clinical and anatomic outcome of birdshot chorioretinopathy. *JAMA Ophthalmol*. 2014;132(1):57-62.