

Uveitis 2018

Uveal Blues in Chicago

Program Directors

Albert T Vitale MD and Hatice N Sen MD MHSc

In conjunction with the American Uveitis Society



McCormick Place
Chicago, Illinois
Saturday, Oct. 27, 2018

Presented by:
The American Academy of Ophthalmology



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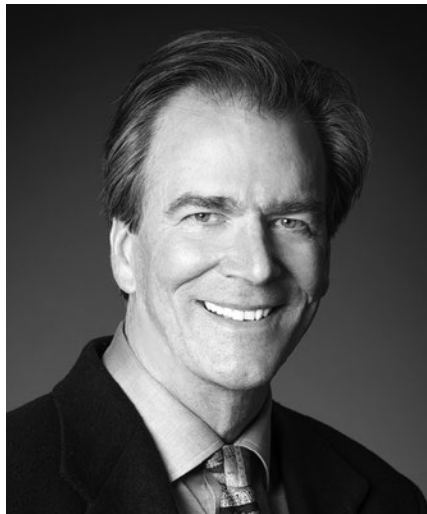
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2018 Uveitis Subspecialty Day Planning Group

On behalf of the American Academy of Ophthalmology and the American Uveitis Society,
it is our pleasure to welcome you to Chicago and Uveitis 2018: Uveal Blues in Chicago.



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CME Credit

The Academy's CME Mission Statement

The purpose of the American Academy of Ophthalmology's Continuing Medical Education (CME) program is to present ophthalmologists with the highest quality lifelong learning opportunities that promote improvement in physician practices, resulting in the best possible eye care for their patients.

2018 Uveitis Subspecialty Day Learning Objectives

Upon completion of this activity, participants should be able to:

- Identify the challenges in recognizing the various forms of ocular inflammatory diseases, including anterior, intermediate, posterior, and pan uveitis
- Construct a differential diagnosis for various forms of uveitis
- Classify the principles of diagnosis for ocular inflammatory disorders in order to initiate appropriate disease-directed evaluations
- Describe the important and appropriate role of immunomodulatory therapy for patients with selected ocular inflammatory diseases, and also for patients with steroid-dependent inflammation
- Describe the potential new treatments for uveitis and ocular inflammatory diseases, including selected therapeutic agents now in development

2018 Uveitis Subspecialty Day Target Audience

The intended audience for this program is uveitis surgeons, comprehensive ophthalmologists with an interest in anterior segment, and allied health personnel who are performing or assisting with uveitis surgery.

2018 Uveitis Subspecialty Day CME Credit

The American Academy of Ophthalmology is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide CME for physicians.

The Academy designates this live activity for a maximum of 7 *AMA PRA Category 1 Credits*[™]. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Teaching at a Live Activity

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- Register in advance and pick up your badge onsite if materials did not arrive before you traveled to the meeting;
- Register onsite; or
- Scan the barcode on your badge as you enter an AAO 2018 course or session room.

CME Credit Reporting

South Building Level 2.5 and Academy Resource Center

Attendees whose attendance has been verified (see above) at AAO 2018 can claim their CME credit online during the meeting. Registrants will receive an email during the meeting with the link and instructions on how to claim credit.

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The CME credit reporting receipt is not a CME transcript. CME transcripts that include AAO 2018 credits entered at the Academy's annual meeting will be available to Academy members through the Academy's CME web page (www.aao.org/cme-central) beginning Thursday, Dec. 13.

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The Academy provides nonmembers with verification of credits earned and reported for a single Academy-sponsored CME activity. To obtain a printed record of your credits, claim CME credits onsite at the CME Credit Reporting kiosks. Nonmembers choosing to claim online through the Academy's CME web page (www.aao.org/cme-central) after December 13 will have one opportunity to print a certificate.

Proof of Attendance

The following types of attendance verification are available during AAO 2018 and Subspecialty Day for those who need it for reimbursement or hospital privileges, or for nonmembers who need it to report CME credit:

- CME credit reporting/proof-of-attendance letters
- Onsite registration receipt
- Instruction course and session verification

You must have obtained your proof of attendance at the CME Credit Reporting kiosks onsite, located in South, Level 2.5, and in the Academy Resource Center.

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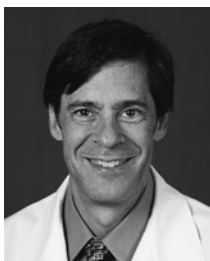
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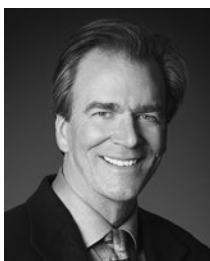
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To ask a question during the meeting, follow the directions below.

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- Filter by Meeting – Uveitis Meeting
- Select Current Session
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- Click Submit Question



Uveitis Subspecialty Day 2018: Uveal Blues in Chicago

In conjunction with the American Uveitis Society

SATURDAY, OCT. 27

7:00 AM CONTINENTAL BREAKFAST

8:00 AM Welcome and Introductions Albert T Vitale MD*

Section I: Basic Blues

Moderator: Albert T Vitale MD*

8:05 AM	Epidemiology and Diagnostic Approach to Uveitis	Russell W Read MD PhD*	1
8:20 AM	Local Therapy: Steroids and Beyond	Susan L Lightman FRCOphth FRCP PhD*	2
8:35 AM	Systemic Therapy: Steroids and Conventional Immunomodulatory Therapy	Douglas A Jabs MD MBA	3
8:50 AM	Systemic Therapy: Biologics	Eric B Suhler MD MPH*	4
9:05 AM	Advocating for the Profession and Patients	David W Johnson MD*	5

Section II: Up-Front Blues—Anterior Uveitis

Moderator: Nisha Acharya MD*

Panelists: Lyndell Lim MBBS FRANZCO MRANZCO*, Todd P Margolis MD PhD*, Peter J McCluskey MD*, Elisabetta Miserocchi MD,* and Daniel V Vasconcelos-Santos MD PhD

9:10 AM	Differential Diagnosis of Anterior Uveitis	Todd P Margolis MD PhD*	8
9:20 AM	Case Presentation	Thuy A Doan MD	9
9:30 AM	Case Presentation	Jessica G Shantha MD*	12
9:40 AM	Case Presentation	Gerami D Seitzman MD	16
9:50 AM	Case Presentation	Thellean K Leveque MD	18
10:00 AM	Panel Discussion and Audience Interaction		
10:05 AM	REFRESHMENT BREAK and AAO 2018 EXHIBITS		

Section III: Stepladder Blues—Intermediate Uveitis

Moderator: Steven Yeh MD*

Panelists: Mark S Dacey MD*, Janet Louise Davis MD*, Henry J Kaplan MD*, Justine R Smith MD*, and Manfred Zierhut MD*

10:35 AM	Medical and Surgical Approach to the Treatment of Intermediate Uveitis	Janet Louise Davis MD*	22
10:45 AM	Case Presentation in Intermediate Uveitis	Akbar Shakoor MD	24
10:55 AM	Case Presentation in Intermediate Uveitis	Marissa G Larochelle MD	27
11:05 AM	Case Presentation in Intermediate Uveitis	Sumit Sharma MD*	30
11:15 AM	Case Presentation in Intermediate Uveitis	John A Gonzales MD	32
11:25 AM	Panel Discussion and Audience Interaction		
11:30 AM	LUNCH and AAO 2018 EXHIBITS		

* Indicates that the presenter has financial interest. No asterisk indicates that the presenter has no financial interest.

Section IV: Focal and Multifocal Blues—Posterior Uveitis

Moderator: Wendy M Smith MD

Panelists: Grace A Levy-Clarke MD*, Debra A Goldstein MD*, Careen Yen Lowder MD PhD,*
Alan Gary Palestine MD, and Ilknur Tugal-Tutkun MD*

12:40 PM	Posterior Uveitis—When to Worry about Systemic Disease	Alan Gary Palestine MD	34
12:50 PM	Case Presentation in Posterior Uveitis	Bryn M Burkholder MD	36
1:00 PM	Case Presentation in Posterior Uveitis	Lucia Sobrin MD*	39
1:10 PM	Case Presentation in Posterior Uveitis	William R Tucker MBBS	42
1:20 PM	Punctate Inner Choroidopathy and Multifocal Choroidopathy With Panuveitis—Separate Entities or Spectrum of the Same Disease? Pro	Debra A Goldstein MD*	46
1:25 PM	Punctate Inner Choroidopathy and Multifocal Choroidopathy With Panuveitis—Separate Entities or Spectrum of the Same Disease? Con	Lee M Jampol MD	47
1:30 PM	Panel Discussion and Audience Interaction		

Section V: Mystery Blues—Infectious, Noninfectious, and Masquerades in Panuveitis

Moderator: Phoebe Lin MD PhD*

Panelists: Thuy A Doan MD PhD, Gary N Holland MD, Michal Kramer MD,
Ramana S Moorthy MD, and Narsing A Rao MD

1:35 PM	Is it Infectious or Not? Pearls and Pitfalls	Ramana S Moorthy MD	48
1:45 PM	Case Presentation in Panuveitis	Marion Ronit Munk MD PhD*	51
1:55 PM	Case Presentation in Panuveitis	Kathryn L Pepple MD PhD	54
2:05 PM	Case Presentation in Panuveitis	Laura J Kopplin MD PhD	57
2:15 PM	Case Presentation in Panuveitis	Amde Selassie Shifera MD PhD*	59
2:25 PM	Panel Discussion and Audience Interaction		
2:30 PM	REFRESHMENT BREAK and AAO 2018 EXHIBITS		

Section VI: Modal Blues Variations—Imaging in Uveitis

Moderator: Sunil K Srivastava MD*

Panelists: Amani Fawzi MD, Vishali Gupta MBBS, David Sarraf MD*, and Rajiv E Shah MD*

3:00 PM	Multimodal Imaging Options in Uveitis	Glenn J Jaffe MD*	62
3:10 PM	Case Presentation	Francesco Pichi MD	63
3:20 PM	Case Presentation	Purnima S Patel MD	66
3:30 PM	Case Presentation	Dilraj Singh Grewal MD*	70
3:40 PM	Case Presentation	Ann-Marie Lobo MD*	72
3:50 PM	Panel Discussion and Audience Interaction		

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Section VII: Operational Blues—Surgery in Uveitis

Moderator: Emil Mitchel Opremcak MD

Panelists: Thomas A Albini MD*, Keith Barton MB BCH*, and James Philip Dunn Jr MD*

3:55 PM	Cataract Surgery in Uveitis	James Philip Dunn Jr MD*	74
4:05 PM	Glaucoma Surgery in Uveitis	Keith Barton MB BCH*	75
4:15 PM	Diagnostic Fluid, Tissue Sampling, and Processing in Uveitis	Thomas A Albini MD*	76
4:25 PM	Panel Discussion and Audience Interaction		

Section VIII: Avant-Garde Blues

Moderator: Hatice N Sen MD MHSc

4:30 PM	Primary Mortality Results of the SITE-1,2 Cohort Study	John H Kempen MD*	79
4:39 PM	Late Breaking Developments: FAST Trial Results	Nisha Acharya MD*	
4:48 PM	Fluocinolone Acetonide Intravitreal Implant Trial Results	Quan Dong Nguyen MD*	80
4:57 PM	Late Breaking Developments: POINT Trial Results	Jennifer E Thorne MD PhD*	81
5:06 PM	Suprachoroidal Delivery of CLS-TA for Uveitic Macular Edema: Results of the Phase 3 PEACHTREE Trial	Rahul Khurana, MD	82
5:15 PM	Reflections on a Career in Uveitis: Where We Have Been and the View Forward	C Stephen Foster MD*	84
5:30 PM	Conclusion and Thank You	Hatice N Sen MD MHSc	

* Indicates that the presenter has financial interest. No asterisk indicates that the presenter has no financial interest.

Epidemiology and Diagnostic Approach to Uveitis

Russell W Read MD PhD

I. Describe the Disease

- A. Careful, comprehensive history of present illness, past medical history, family history, and social history
- B. Careful, comprehensive examination, descriptive
 - 1. Anatomical (anterior, intermediate, posterior, pan)
 - 2. Temporal (sudden vs. insidious onset; limited vs. persistent duration)
 - 3. Pathological (granulomatous vs. nongranulomatous)

II. Develop the Differential From the Descriptive Naming

- A. Keep it simple! Thinking in dichotomies may help.
 - 1. Infectious vs. noninfectious
 - 2. Malignant vs. nonmalignant
- B. If it isn't infectious and it isn't malignant, then it's autoimmune (unless it's drug induced or traumatic).

III. The Differential Drives the Diagnostics

Common things are common (but don't forget the zebras).

A. Minimum begins with:

- 1. Syphilis tests: *Treponema pallidum* antibodies; TP-PA / MHA-TP
- 2. Tuberculosis
 - a. QuantiFERON-TB Gold
 - b. PPD
- 3. Sarcoid: Chest X-ray

B. Additional tests based on the differential

- 1. Low back pain, young Caucasian
 - a. HLA-B27
 - b. Sacroiliac joint X-rays
- 2. Creamy yellow-white fundus lesions: HLA-A29
- 3. Vasculitis
 - a. ANCA
 - b. Lupus panel
- 4. Intermediate uveitis: Ask about multiple sclerosis symptoms, family history (consider MRI)

IV. Establish a Leading Candidate Diagnosis

- A. Develop and implement a therapeutic plan.
- B. Constantly assess success and reassess diagnosis and plan.

Local Therapy: Steroids and Beyond

Susan Lightman FRCOphth FRCP PhD

Introduction

Local therapy gives medication to the eye where we need it to be without the need for additional systemic therapy. Topical therapy in the form of drops, creams, and gels is widely used to manage anterior uveitis, corneal / conjunctival infections, and raised IOP. Injections in or around the eye can be given in patients with uveitis with unilateral disease, in patients with unilateral / bilateral disease on maintenance-dose systemic therapy in whom one eye has relapsed, or in patients with bilateral disease to replace the need for systemic therapy where giving this causes issues. There are two main routes of administration—periocular and intraocular. Steroids for periocular use include methylprednisone (Depo-Medrone) and triamcinolone. For intraocular use we have steroids—dexamethasone, triamcinolone, dexamethasone implant (Ozurdex), fluocinolone implant (Retisert), fluocinolone injectable implant (Iluvien)—all of which have been used successfully with variations in the time of effect. Soluble dexamethasone is rarely used now as it stays for a very short time within the eye. Other nonsteroid agents for injection into the uveitic eye include methotrexate, anti-VEGF agents, and biologics.

Clinical Trial Data

Trials have shown that there is no difference in efficacy or side effects giving regional steroids by different periocular routes¹ and that intraocular triamcinolone is very effective but with greater side effects including cataract formation and raised IOP.^{2,3} Ozurdex has shown efficacy and a longer duration of action even when given repeatedly.^{4,5} The POINT trial compared periocular triamcinolone, intraocular triamcinolone, and Ozurdex and will report this year. The MUST trials have shown equal visual outcome of local treatment with Retisert and systemic therapy up to about 5 years, and then after that vision is slightly better preserved with systemic therapy, with macula disorders causing more visual loss in the local treatment group.⁶

Individual small series have shown efficacy of intraocular methotrexate, especially useful in steroid responders,⁷ and of various anti-VEF agents.⁸ The MERIT clinical trial is ongoing and compares intraocular methotrexate, ranibizumab, and Ozurdex in the control of cystoid macular edema in quiet eyes. Iluvien has also shown some promise,⁹ and the outcome of longer clinical trials with this drug are awaited. The use of systemic biologics is spreading, and they are very effective. Their use when delivered into the eye is controversial, with some studies showing a good response and others not.¹⁰

Going forward? We await the results of the ongoing trials, but please could we have a nonsteroid that is easily injectable, lasts a few months at a time, and doesn't have ocular side effects?!

References

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6. Kempen JH, et al. Association between long-lasting intravitreal fluocinolone acetate implant vs systemic anti-inflammatory therapy and visual acuity at 7 years among patients with intermediate, posterior, or panuveitis. *JAMA*. 2017; 317(19):1993-2005.
7. Taylor SR, Banker A, Schlaen A, et al. Intraocular methotrexate can induce extended remission in some patients in noninfectious uveitis. *Retina* 2013; 33:2149-2154.
8. Gulati N, Forooghian F, Lieberman R, Jabs DA. Vascular endothelial growth factor inhibition in uveitis: a systematic review. *Br J Ophthalmol*. 2011; 95(2):162-165.
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10. Pulido JS, Pulido JE, Michet CJ, Vile RG. More questions than answers: a call for a moratorium on the use of intravitreal infliximab outside of a well-designed trial. *Retina* 2010; 30(1):1-5.

Systemic Therapy: Steroids and Conventional Immunomodulatory Therapy

Douglas A Jabs MD MBA

Selected Readings

1. The Multicenter Uveitis Steroid Treatment (MUST) Trial and Follow-up Study Research Group. Association between long-lasting intravitreal fluocinolone acetonide implant vs systemic anti-inflammatory therapy and visual acuity at 7 years among patients with intermediate, posterior, or panuveitis. *JAMA* 2017; 317:1993-2005.
2. Jabs, DA, Rosenbaum JT, Foster CS, et al. Guidelines for the use of immunosuppressive drugs in patients with ocular inflammatory disorders: recommendations of an expert panel. *Am J Ophthalmol*. 2000; 130:492-513.
3. Jabs DA. Immunosuppression for the uveitides. *Ophthalmology* 2018; 125:193-202.

Systemic Therapy: Biologics

The Basics

Eric B Suhler MD MPH

Definition: Biologic Response Modifiers

- Therapeutic proteins designed to block the activity of immunoactive molecules
- Most commonly recombinant antibodies or antibody-derived proteins that block cytokines, cytokine receptors, cell surface proteins, or other bioactive proteins

Commercially Available Biologics

Tumor necrosis factor blockers

- Five commercially available
- Monoclonal antibodies: adalimumab (Humira; AbbVie) and infliximab (Remicade; Janssen) with most published experience
- Adalimumab
 - Has been FDA approved for the treatment of adult noninfectious intermediate, posterior, and panuveitis since June 2016.
 - Also with excellent randomized clinical trial evidence for juvenile idiopathic arthritis uveitis in children
- Infliximab also effective in numerous uncontrolled case series
- Few smaller case series suggest benefit of the monoclonal antibodies golimumab (Simponi; Janssen) and certolizumab (Cimzia; UCB).
- Etanercept (Enbrel; Amgen)
 - A fusion protein against all TNF isoforms
 - Has been demonstrated less effective in the treatment of uveitis than the monoclonal Abs

Other Agents in Development for Ocular Inflammatory Disease

B-cell blocker

- Rituximab (Rituxan; Genentech / Roche)
 - Effective in case series for scleritis and orbital inflammation
 - Some suggestion of benefit for uveitis, ocular cicatricial pemphigoid
 - Also used for primary vitreoretinal lymphoma

IL-6 blockers

- Tocilizumab (Actemra; Genentech / Roche): case series suggesting benefit in uveitis and uveitic macular edema
- Sarilumab (Kevzara; Sanofi / Regeneron): suggestion of benefit in STOP-UVEITIS study

Costimulation blockers

- Abatacept (Orencia; BMS): Published series suggest low efficacy signal and question benefit in specific disease subpopulations.

IL17 blockers

- Secukinumab (Cosentyx; Novartis): failed to show benefit in numerous large RCTs for uveitis

IL12/23 blocker

- Ustekinumab (Stelara; Janssen); currently under study at the NEI

JAK inhibitors

- Filgotinib: subject of current multicenter RCT for uveitis

2018 Advocating for the Profession and Patients

Uveitis Subspecialty Day

David W Johnson MD

Ophthalmology's goal to protect sight and empower lives requires active participation and commitment to advocacy from every ophthalmologist. Contributions to the following three critical funds are a part of that commitment:

- OPHTHPAC® Fund
- Surgical Scope Fund (SSF)
- State Eye PAC

Please join the dedicated community of ophthalmologists who are contributing to protect quality patient eye care for everyone. The OPHTHPAC Committee is identifying Congressional Advocates in each state to maintain close relationships with federal legislators in order to advance ophthalmology and patient causes. At Mid-Year Forum 2018, we honored nine of those legislators with the Academy's Visionary Award. This served to recognize them for addressing issues important to us and to our patients. The Academy's Secretariat for State Affairs is collaborating closely with state ophthalmology society leaders to protect Surgery by Surgeons at the state level.

Our mission of "protecting sight and empowering lives" requires robust funding of both the Surgical Scope Fund and the OPHTHPAC Fund. Each of us has a responsibility to ensure that these funds are strong.

OPHTHPAC® Fund

OPHTHPAC is a crucial part of the Academy's strategy to protect and advance ophthalmology's interests in key areas, including physician payments from Medicare and protecting ophthalmology from federal scope-of-practice threats. Established in 1985, OPHTHPAC is one of the oldest, largest, and most successful political action committees in the physician community. We are very successful in representing your profession to the U.S. Congress.

Advocating for our issues in Congress is a continuous battle, and OPHTHPAC is always under financial pressure to support our incumbent friends as well as to make new friends among candidates. These relationships allow us to have a seat at the table with legislators who are willing to work on issues important to us and our patients.

The relationships OPHTHPAC builds with members of Congress is contingent on the financial support we receive from Academy members. Academy member support of OPHTHPAC allows us to advance ophthalmology's federal issues. We need to increase the number of our colleagues who contribute to OPHTHPAC and to the other funds. Right now, major transformations are taking place in health care. To ensure that our federal fight and our PAC remain strong, we need the support of every ophthalmologist to better our profession and ensure quality eye care for our patients.

Among the significant impacts made by OPHTHPAC are the following:

- Secured relief from the burdens and penalties associated with the existing Medicare quality improvement programs for 2018
- Halted applications of MIPS penalties to Part B drug payments to physicians
- Convinced CMS to revisit drastic cuts to retina and glaucoma surgical codes
- Halted the flawed Part B Drug Demonstration
- Derailed an onerous global surgery payment data collection plan
- Continued efforts in collaboration with subspecialty societies to preserve access to compounded and repackaged drugs such as Avastin

Contributions to OPHTHPAC can be made here at AAO 2018, or online at www.aao.org/ophthpac by clicking "Join." You can also learn more by texting "OPHTH" to 51555.

Leaders of the American Uveitis Society (AUS) are part of the American Academy of Ophthalmology's Ophthalmic Advocacy Leadership Group (OALG), which meets annually in January in Washington, D.C., to provide critical input and to discuss and collaborate on the Academy's advocacy agenda. At the January 2018 OALG meeting, panel discussions took place on the outlook for Medicare reimbursement and implementation of the Merit-based Incentive Payment System (MIPS), as well as specialty research related to the IRIS™ Registry. In addition, meeting participants discussed the changing paradigm for optometric scope battles, held a roundtable to discuss challenges for surgical subspecialties, and considered how telemedicine could impact ophthalmology.

At Mid-Year Forum 2018, the Academy and AUS ensured a strong presence of uveitis specialists to support ophthalmology's priorities. Ophthalmologists visited members of Congress and their key health staff to discuss ophthalmology priorities as part of Congressional Advocacy Day. The AUS remains a crucial partner with the Academy in its ongoing federal and state advocacy initiatives.

Surgical Scope Fund

Thanks to contributions to the 2018 Surgical Scope Fund (SSF) from ophthalmologists across the country, the Academy's Surgery by Surgeons initiative has had a successful year preserving patient surgical safety and surgical standards in state legislatures across the country. The SSF is key to the Academy's Surgery by Surgeons campaign. *If you have not yet made a 2018 SSF contribution*, visit our contribution booth at AAO 2018 or contribute online at www.aao.org/ssf. If you already have made that 2018 contribution, please consider making a crucially needed supplemental contribution.

The SSF provides grants to state ophthalmology societies in support of their efforts to derail optometric surgery proposals that pose a threat to patient safety. Since its inception, the Surgery by Surgeons campaign and the SSF, in partnership with

state ophthalmology societies, has helped 34 state/territorial ophthalmology societies reject optometric scope-of-practice expansion into surgery.

To date in 2018, thanks to financial resources from the SSF, the Surgery by Surgeons campaign has netted patient safety and surgery standard preservation victories in the following battleground states:

- Florida
- Iowa
- Maryland
- Mississippi
- Nebraska
- North Carolina
- South Carolina
- Vermont
- Virginia

The 2018 battle is far from over, though. For example, California, Illinois, Massachusetts, and Pennsylvania are currently under assault. Furthermore, as of submission of this update in June 2018, the optometric surgery push had sprouted in six additional states.

Dollars from the SSF are critical in the state surgery campaigns. In each of these legislative battles, the benefits from SSF distributions are abundantly clear. The best lobbyists and public relations consultants are contracted as necessary. Additionally, media campaigns (including TV, radio, and social media) are launched to educate the voting public when needed. This helps to secure success in protecting patient safety by thwarting optometry's attempts at expanding its scope of practice to include surgery privileges.

Each of these endeavors is very expensive, and no one state has the resources to wage one of these battles on its own. Ophthalmologists must join together and donate to the SSF to fight for patient safety when a state faces a scope battle over optometric surgery.

The Secretariat for State Affairs thanks the AUS for joining state ophthalmology societies in contributing to the SSF in 2017 and looks forward to its continued financial support. Subspecialty organizations like the AUS complete the necessary SSF support structure for the creation and implementation of successful Surgery by Surgeons campaigns.

State Eye PAC

It is increasingly important for all ophthalmologists to support their respective State Eye PACs because campaign contributions to legislators at the state level must come from individual ophthalmologists and cannot come from the Academy, OPHTHPAC, or the SSF. The presence of a strong State Eye PAC providing financial support for campaign contributions and legislative education to elect ophthalmology-friendly candidates to the state legislature is critical, as scope-of-practice battles and many regulatory issues are all fought on the state level.

ACTION REQUESTED: Advocate for Your Profession & Your Patients

Academy SSF contributions are used to support the infrastructure necessary in state legislative / regulatory battles and for public education. State PAC and OPHTHPAC contributions are necessary at the state and federal level, respectively, to help elect officials who will support the interests of our patients. Contributions to *each* of these three funds are necessary and help us protect sight and empower lives. SSF contributions are completely confidential and may be made with corporate checks

or credit cards, unlike PAC contributions, which must be made by individuals and are subject to reporting requirements.

Please respond to your Academy colleagues and be part of the community that contributes to OPHTHPAC, the Surgical Scope Fund, and your State Eye PAC. Please be part of the community advocating for your patients now.

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Surgical Scope Fund	OPHTHPAC® Fund	State EyePAC
To derail optometric surgical scope of practice initiatives that threaten patient safety and quality surgical care	Ophthalmology's interests at the federal level Support for candidates for U.S. Congress	Support for candidates for state House, Senate, and governor
Political grassroots activities, lobbyists, PR and media campaigns	Campaign contributions, legislative education	Campaign contributions, legislative education
No funds may be used for campaign contributions or PACs.		
Contributions: Unlimited Individual, practice, and organization	Contributions: Limited to \$5,000	Contribution limits vary based on state regulations.
Contributions are 100% confidential.	Contributions above \$200 are on the public record.	Contributions are on the public record depending upon state statutes.

Differential Diagnosis of Anterior Uveitis

Todd Margolis MD PhD

History

- Acute / chronic
- Recurrent
- Unilateral / bilateral
- Other systemic disease

Symptoms: Beyond Classic Pain, Redness, Photophobia, and Blurred Vision

- Careful review of systems
- Loss of accommodation or pain on accommodation
- Symptoms may be minimal
 - Juvenile idiopathic arthritis (JIA)
 - Herpes simplex
 - Herpes zoster
 - Cytomegalovirus (CMV)
 - Fuchs

Signs: Beyond Cell and Flare

- Loss of corneal sensation
- Band keratopathy
- Endotheliitis
- Hypopyon
- Nodules (Busacca, Koeppe)
- Type / distribution of keratic precipitates
- Iris atrophy
- Acute rise in IOP
- Trans-trabecular meshwork vessels
- Conjunctival granuloma / enlarged lacrimal gland
- IOL position

Syndromes vs. Pathogenesis

These should not be confused!

A syndrome is defined by a collection of findings, not by a pathogenic cause.

For many uveitic syndromes, the cause(s) was/were not originally known. We now know the cause of many of these syndromes (eg, Fuchs heterochromic cyclitis secondary to CMV, iridocorneal endothelial syndrome secondary to herpes simplex virus, etc.). Understanding this is critical to diagnosing and managing these conditions.

Differential Diagnosis of Pediatric Anterior Uveitis

JIA > idiopathic > tubulointerstitial nephritis and uveitis syndrome (TINU)

Differential Diagnosis of Adult Anterior Uveitis

Idiopathic > HLAB27/AS > herpes / Fuchs > trauma

Selected Readings

1. Smith JA, Mackensen F, Sen HN, et al. Epidemiology and course of disease in childhood uveitis. *Ophthalmology* 2009; 116:1544-1551.
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Case Presentation: Stuttgart to San Francisco

Thuy Doan MD

CASE PRESENTATION

- 36-year-old white man
- > 15-year history of chronic bilateral anterior uveitis
- Symptoms: blurred vision and floaters (left > right). No pain.
- Ocular history: chronic topical steroid usage, no improvement with oral methotrexate and high-dose systemic Prednisone for 1 year, CE/IOL both eyes
- Current medications: brimonidine / timolol (Combigan) b.i.d. both eyes, prednisone acetate 1% b.i.d. O.D. and q.i.d. O.S.
- Ocular examination
 - VA: 20/20 O.D. and 20/25 O.S.
 - IOP: 17/28 mmHg with applanation
 - Fine diffuse keratic precipitates O.U.
 - Anterior chamber 0.5+ cells, no flare O.D.; 1+ cells, no flare O.S.
 - Patchy peripheral iris atrophy O.U.
 - Posterior chamber IOL with trace posterior capsule opacification O.U.
 - 0.5+ anterior vitreous cells, no haze O.D.; and 2+ AV cells mixed with pigment, 1+ haze O.S.
 - Epiretinal membrane O.S. but fundus otherwise unremarkable O.U.

DIAGNOSIS & TEACHING POINTS

Differential Diagnosis

- Viral-associated anterior uveitis
 - Herpetic (herpes simplex virus [HSV] / varicella zoster virus [VZV] / cytomegalovirus [CMV]) anterior uveitis
 - Rubella-associated anterior uveitis
- HLA-B27-associated uveitis
- Syphilitic uveitis
- Masquerade syndrome
- Undifferentiated / idiopathic

Workup

Anterior chamber (AC) tap for HSV / VZV / CMV polymerase chain reaction (PCR). Diagnostic and therapeutic vitrectomy for cytology and flow cytometry, repeat HSV / VZV / CMV PCR. Leftover aqueous fluid was subjected to metagenomics deep sequencing (MDS) at the Proctor Foundation. MDS captured the entire rubella virus (RV) genome.

Final Diagnosis, Clinical Course, and Outcome

This was a case of Fuchs heterochromic iridocyclitis (FHI) 2/2 chronic RV infection. The patient was taken off of systemic antiviral medication and topical steroids. Glaucoma drops were used to manage IOP elevation. His vision maintained at 20/20 O.U. on his last visit at Proctor. No additional surgeries were required. This case had to be reported to the California Department of Public Health and the CDC because rubella RNA was detected in the eye, suggesting live and replicating virus.

Teaching Points

- Hypertensive anterior uveitis is infectious until proven otherwise.
- FHI is commonly a unilateral disease, but 20%-80% can have bilateral involvement.
- FHI is associated with RV or CMV infection.
- Vitreous opacities are common.
- Failure to consider the disease as a diagnosis is an important factor for delay in diagnosis of FHI.
- Iris abnormalities can be subtle or challenging to appreciate, especially in patients with brown irides.
- Intraocular fluid testing is useful in cases with atypical presentation. Repeat if necessary.
- MDS allows for the detection of any pathogen in small amounts (as little as 20 microliters) of aqueous or vitreous fluid.

Disease Discussion

I. Epidemiology

- A. The prevalence of herpetic anterior uveitis is ~0.5/100,000 person-years.
- B. Prevalence is increased with increasing age.

- C. The prevalence of FHI in the United States is low and has dramatically decreased due to effective and successful vaccination programs.
- D. The prevalence of FHI at tertiary centers in Europe can be as high as 7%.

II. Clinical Features

A. Viral uveitis (herpetic and FHI)

1. Unilateral or bilateral
2. Keratic precipitates extending beyond the equator (stellate or pleomorphic)
3. Iris atrophy
4. Elevated IOP
5. Reduced corneal sensation

B. FHI (above in addition to the following features)

1. Heterochromia may not be appreciated.
2. Cataract in up to 90% of the patients
3. Vitreous opacities are not uncommon.
4. Iris nodules
5. Amsler vessels on gonioscopy or Amsler sign (small hemorrhage in AC after minor trauma) in cases of FHI

III. Differential Diagnosis

Herpes simplex anterior uveitis, VZV, CMV, Posner-Schlossman syndrome, HLA-B27-associated uveitis (usually with posterior synechiae and low IOP)

IV. Diagnosis

- A. Constellation of clinical findings
- B. Response to empiric antivirals, with the exception of FHI
- C. Intraocular fluid for molecular tests
 1. HSV / VZV / CMV PCRs
 2. Rubella RT-PCR and Goldmann-Witmer coefficient assay in Europe only
 3. MDS for all pathogens at the Proctor Foundation (accepting samples)

V. Etiology / Pathogenesis

- A. Reactivation of herpetic viruses or immune response to viral antigen in the AC
- B. Chronic RV infection in Europe and CMV and RV in Asia

VI. Management

- A. Herpetic: oral antiviral medications (acyclovir, valacyclovir, famvir, or valganciclovir for CMV), topical steroids, and oral antiviral prophylaxis

- B. Rubella-associated uveitis: do-no-harm approach, careful monitoring of IOP, cataract surgery for cataract (same perioperative management as non-uveitic cataract), therapeutic vitrectomy for vitreous opacities

VII. Prognosis

These patients generally do well with the appropriate management. Glaucoma-associated complications are the rate-limiting factors for poor vision in these patients.

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3. de Groot-Mijnes JD, de Visser L, Rothova A, et al. Rubella virus is associated with fuchs heterochromic iridocyclitis. *Am J Ophthalmol.* 2006; 141: 212-214.
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Case Presentation: It's Always Something, and Then Some

Jessica Shantha MD

CASE PRESENTATION

An 8-year old white female patient presents with decreased vision in her left eye. Prior annual eye exams showed 20/20 vision in both eyes. She was diagnosed 2 years prior with uveitis, with the most recent flare 1 year ago.

Medications

Naproxen

Family History

Negative

Review of Symptoms

- Positive for arthritis in the past
- Negative for fevers, weight loss, hearing loss, oral ulcers, cold sores, cough, diarrhea, blood in stools, rashes, lower back pain, weakness / numbness, recent travel

Examination

- Visual acuity: O.D. 20/20, O.S. 20/50
- Pupils: O.D. reactive, O.S. nonreactive with posterior synechiae
- IOP: O.D. 26, O.S. 23
- Anterior segment
 - O.D. nasal and temporal band keratopathy, fine keratic precipitates, 1+ cells
 - O.S. nasal and temporal band keratopathy, large keratic precipitates, 1+ cells, posterior synechiae nearly 360 degrees, few clock hours open
- Fundus exam
 - O.D. cup-to-disc ratio 0.3, normal macula, vessels, and periphery
 - O.S. cup-to-disc ratio 0.3, blunted foveal light reflex, vessels, and periphery, limited view 2/2 to posterior synechiae
- OCT
 - O.D. normal
 - O.S. cystoid macular edema

DIAGNOSIS AND TEACHING POINTS

Differential Diagnosis

- Juvenile idiopathic arthritis (JIA)
- HLA-B27–associated anterior uveitis
- Tubulointerstitial nephritis and uveitis syndrome (TINU)
- Blau syndrome
- Sarcoidosis
- Infectious: viral (herpetic), toxoplasmosis, tuberculosis
- Idiopathic anterior uveitis

Investigations

- ANA: positive
- Rheumatoid factor: negative
- HLA-B27: negative
- ACE/lysozyme: negative
- QuantiFERON-TB Gold: negative
- FTA-ABS / RPR: negative
- Chest X-ray: negative

Final Diagnosis, Clinical Course, and Outcome

Chronic bilateral anterior uveitis with cystoid macular edema in the left eye associated with juvenile idiopathic arthritis oligoarticular (JIA)

- Started on difluprednate q.i.d. O.U. and methotrexate 22.5 mg weekly, folic acid 1 mg daily
- Cystoid macular edema resolved with vision O.S. 20/25
- Anterior uveitis O.U. uncontrolled on methotrexate, initiated adalimumab 20 mg every 2 weeks given persistent inflammation. Adalimumab was increased to weekly dosing given inadequate control.
- Initiated infliximab infusions 5 mg/kg every 4 weeks, continued on methotrexate 22.5 mg weekly, folic acid 1 mg daily. Intermittent steroid drops.
- Developed ocular hypertension O.U., which was thought to be due to topical steroids and treated with dorzolamide-timolol (Cosopt) b.i.d. O.U.
- Developed visually significant cataract O.S. with visual acuity of CF. Inflammation controlled.
- Underwent cataract surgery O.S. with IOL placement, intraoperative IV solumedrol with perioperative prednisone 1 mg/kg 3 days before surgery and tapered accordingly
- At last follow-up, visual acuity 20/25 O.U. with normal IOP and quiet inflammation without cystoid macular edema. Currently she is maintained on methotrexate 15 mg weekly, folic acid 1 mg daily, and infliximab infusion 5 mg/kg every 8 weeks. She is off all topical steroids.

Teaching Points

- JIA patients can develop many complications of untreated inflammation leading to vision loss that include band keratopathy, cystoid macular edema, uveitic cataract, and glaucoma.
- In pediatric patients, we must be cognizant of the development of amblyopia.
- These patients usually require systemic immunosuppressive medications with close follow-up with ophthalmology and rheumatology.
- Cataract surgery should not be performed until uveitis is controlled for at least 3 months on an acceptable long-term regimen.

Disease Discussion

I. Introduction

- A. JIA is the most common systemic association with pediatric uveitis.
- B. Definition: Onset of chronic arthritis (greater than 6 weeks) in child less than 16 years of age
- C. Subtypes
 1. Oligoarticular JIA: uveitis 30%
 2. Polyarticular JIA: uveitis 5%-10%
 3. Systemic onset JIA: uveitis < 1%
 4. Enthesitis-related arthritis: uveitis 7%-15%
 5. Psoriatic arthritis: uveitis 10%-20%
- D. Uveitis is more commonly seen in oligoarticular, ANA positive, and rheumatoid factor negative subtypes.
- E. Uveitis can precede systemic disease in 3%-7% of patients.

II. Epidemiology

- A. Prevalence varies in pediatric uveitis patients, ranging from 15% to 67% at different centers.
- B. In patients with a diagnosis of JIA, uveitis occurs in 11%-30% of patients.
- C. Risk factors for uveitis development: young age, female gender, ANA positivity, HLA-B27 positivity, oligoarticular disease
- D. Siblings of patients with JIA have a 15- to 30-fold higher risk of JIA compared to the general population.
- E. Risk factors for vision loss: presence of uveitis before arthritis, ophthalmic complications present at initial diagnosis, short duration between arthritis onset and uveitis, young age, male, multiple episodes of inflammation

III. Clinical Features

- A. Asymptomatic chronic anterior uveitis (most common feature)
- B. Complications develop from inadequate treatment of inflammation and secondary to local corticosteroids.
- C. Band keratopathy, posterior synechiae, cataract, glaucoma, hypotony, cystoid macular edema, epiretinal membrane, optic nerve edema

IV. Pathogenesis

- A. Multifactorial
- B. Autoimmune condition
- C. Activation of T-cells

V. Diagnosis

- A. History
- B. Physical exam
- C. Laboratory investigations: CBC, ESR, CRP, ANA, rheumatoid factor, HLA-B27, rule out syphilis and TB

VI. Management

- A. Screening guidelines: Based on subtype, age, and laboratory testing
 1. Initial screening, within 6 weeks of diagnosis of JIA
 2. Oligoarticular JIA, enthesitis-related arthritis, psoriatic arthritis under 11 years of age: ophthalmic exam every 3-4 months
 3. Polyarticular JIA, ANA positive, under 10 years of age: ophthalmic exam every 3-4 months
 4. Polyarticular JIA, ANA negative, under 7 years of age: ophthalmic exam every 3-4 months

B. Local

1. Topical corticosteroids are used to treat initial flares and recurrent disease.
2. Long-term use is cautioned due to side effects.
3. One study showed that use of topical corticosteroids at dose of 3x/day or less was associated with lower risk of cataract development.

C. Medical

1. Systemic corticosteroids for complex disease, not responding to topical therapy but not acceptable for long-term therapy
2. Indication for systemic immunosuppressive therapy include active joint disease, recurrent or chronic uveitis, inadequate uveitis control, steroid responder
3. Goal: long-term inflammatory control

4. Multiple classes of immunosuppression

- a. Antimetabolites: methotrexate (first-line therapy), azathioprine, mycophenolate mofetil
- b. Biologics: adalimumab, infliximab, rituximab, tocilizumab, abatacept
- c. Alkylating agents: cyclophosphamide, chlorambucil

D. Surgical

1. Cataract extraction
 - a. Quiet for at least 3 months
 - b. Perioperative, intraoperative, and postoperative oral corticosteroids may be required.
 - c. Lens implantation vs. aphakia
2. Glaucoma surgery
 - a. Failed topical treatment
 - b. Goniotomy, draining devices, trabeculectomy procedure
3. Band keratopathy
 - a. EDTA chelation
 - b. Phototherapeutic keratectomy

VII. Prognosis

Patients need long-term management with an ophthalmologist and rheumatologist to decrease the burden of ocular complications and vision loss in this at-risk population.

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Case Presentation: Eyes of Horus

Gerami Seitzman MD

CASE PRESENTATION

38-year-old female patient referred for management suggestions for chronic bilateral anterior uveitis

History of Present Illness

- Age 25: Presented elsewhere with redness and photophobia O.U. Treated with prednisolone drops O.U.
- Age 35: Re-presented with photophobia and floaters O.U. Records indicate bilateral granulomatous anterior uveitis and vitreous cell. Topical therapy was attempted and was insufficient. Oral prednisone was initiated. Uveitis flared with prednisone decreases below 20 mg.
- Age 36: Rheumatologist initiated azathioprine (dose unknown.) Patient was able to taper off oral prednisone completely.
- Age 37: Bilateral granulomatous anterior uveitis returned O.U. on oral azathioprine. Prednisone restarted. Unable to taper without recurrence.
- Age 38 (16 weeks prior to presentation): Patient starts 40-mg adalimumab every 2 weeks. Continues 50-mg azathioprine with slow oral prednisone taper. Patient on 20-mg oral prednisone when she presents for a second opinion.

Past Medical History

Unremarkable

Review of Systems

- Cold sores
- 55-lb weight gain from prednisone

Examination

- VA: 20/20 O.U.
- IOP: 22 O.U.
- External exam: moon facies
- Anterior chamber: Posterior synechia O.U.; no cell
- Vitreous: No vitreous haze, no active vitritis
- Retina: Normal

DIAGNOSIS & TEACHING POINTS

Differential Diagnosis

- Differential diagnoses of currently controlled, but with prior evidence of, prior bilateral granulomatous anterior uveitis include sarcoidosis, idiopathic, Behçet disease, Vogt-Koyanagi-Harada syndrome, and sympathetic ophthalmia
- Infectious and neoplastic etiologies are possible but unlikely as they are not likely to be controlled with current immunosuppressive regimen.

Additional Positive Review of Systems

- Patient had tattoos placed 2 years prior to initial episode: 2 on her neck, 2 on her forearms.
- With flares of uveitis, her tattoos swell and sometimes the lymph nodes in her neck enlarge.

Workup (Prior to Presentation)

- FTA/RPR: nonreactive
- HLA B27: negative
- ACE: within normal limits
- CBC: within normal limits
- PPD: negative
- Chest X-ray: within normal limits

Final Diagnosis and Outcome

Bilateral granulomatous anterior uveitis with concurrent onset of raised and indurated tattooed skin. Clinically inactive on systemic immunosuppression. Continued slow taper of oral prednisone advised. Uncertain if removal of tattoos at this point would have a meaningful clinical response.

Discussion of Disease

I. Coincident Uveitis and Tattoo Induration

- A. First described in 1952: bilateral anterior uveitis, tattoo granulomas, systemic sarcoidosis
- B. 1969. Case series of 3: Three of 3 cases were bilateral anterior uveitis, 1/3 with retinitis tattoo granulomas, *no* systemic sarcoidosis.
- C. 2014. Case series of 7. Five of 7 bilateral nongranulomatous anterior uveitis, tattoo granulomas. Two of 7 bilateral granulomatous panuveitis. *No* systemic sarcoidosis.
- D. Tattoo swelling may proceed or occur simultaneously with uveitis.

II. Common Features

- A. Bilateral intraocular inflammation
- B. Anterior uveitis is more common than panuveitis.
- C. Black ink tattoos
- D. Granulomatous and nongranulomatous

III. Treatment Options

- A. Some cases are responsive to treatment with topical and/or oral steroids with taper.
- B. Most cases tend to be chronic or recurrent. Chronic immunosuppression is recommended for these cases.

IV. Tattoo Statistics

- A. 29% of the U.S. population has one or more tattoos (Harris Poll 2015.)
- B. 69% of those with tattoos have 2 or more.
- C. 40%-47% of millennials have a tattoo (Pew-Research Center 2013).

V. Tattoos can have a variety of histopathologic findings.

- A. This includes non-necrotizing granulomas.
- B. Immunopathology evaluation could be more consistent with delayed type hypersensitivity, especially in cases where tattoo swelling precedes uveitis.

VI. Questions

- A. Is this coincidence, or is this an inciting environmental antigen causing inflammation in a genetically susceptible host?
- B. Is this entity distinguishable from sarcoidosis? Could this represent an initial presentation? Does making the distinction matter clinically?

VII. Tattoo Pigments

- A. Black ink ingredients include soot, carbon, ash, nickel, and iron.
- B. Tattoo pigments migrate into lymph nodes.

VIII. Tattoo Removal

Management could include removal of tattoo; however, uveitis could still persist. If tattoos are extensive, expense and need for skin grafting may preclude this option. If removal of tattoo is pro-inflammatory, it could worsen the course of inflammation.

Selected Readings

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Case Presentation: Rubbernecking at the Whiplash

Thellea K Leveque MD

CASE PRESENTATION

History of Present Illness

44-year-old white female patient presented with 3 days of rapidly increasing unilateral eye pain with redness, photophobia, and blurred vision. No flashes or floaters. Never had anything like this before, but did have pink eye diagnosed and treated by her primary care doctor in the same eye about 2 years ago.

Past Medical History

- Borderline hypertension
- Basal cell carcinoma removal
- Hypothyroidism
- Whiplash injury in car accident 15 years ago
- Myopia, wears glasses

Medications

- Levothyroxine
- Ibuprofen
- Multivitamin

Family/Social History

Nonsmoker, rare use of alcohol. Works in fundraising / non-profit. No children. No family history of autoimmune disease. Dad had chronic low back pain.

Review of Systems

Chronic neck and left shoulder pain since car accident, improves somewhat with NSAID use / physical therapy / warm showers. No low back pain, no morning stiffness, no hip, knee or other joint pains, normal bowel habits, no oral or genital ulcers, no history of cold sores, no skin rashes, no shortness of breath or cough, travel to Canada for work, and to Germany in college.

Physical Examination

- Visual acuity 20/20 O.D., 20/40 O.S.
- IOP 14 mmHg O.D., 11 mmHg O.S.
- Right eye normal
- Left eye:
 - Anterior: 2+ conjunctival injection, trace corneal edema, medium keratic precipitates mostly in Arlt triangle, 2+ cell and 1+ flare, scattered posterior synechiae, clear lens
 - Posterior: 1+ anterior vitreous cell, no haze, minimal optic disc edema, blunted foveal light reflex, OCT confirms macular edema

DIAGNOSIS & TEACHING POINTS

Differential Diagnosis

- HLA-B27–associated anterior uveitis
- Undifferentiated (idiopathic)
- Sarcoidosis (typically granulomatous inflammation)
- Behçet disease (would expect oral / genital ulcers / skin findings)
- Tubular interstitial nephritis with uveitis, TINU (typically bilateral)
- HSV (typically associated with high eye pressure and diffuse keratic precipitates)
- Syphilis (always on the differential because it can present in any form of uveitis and has important treatment implications)

Workup

- HLA-B27 +
- Syphilis IgG –
- Chest X-ray normal

Final Diagnosis, Clinical Course, Outcome

- Primary diagnosis: HLA-B27–associated acute anterior uveitis
 - Aggressive initial treatment with topical and/or oral steroids with long, slow taper
 - Lyse the posterior synechiae in the office with cycloplegia
 - Topical cycloplegia over course of treatment
 - Watch eye pressure with aggressive topical steroid use
 - There is mixed data on the efficacy of topical / oral adjunctive NSAID therapy.
 - Ultimately, the eye findings completely resolved with tapering treatments lasting 8-10 weeks.
 - Referral to rheumatology for evaluation of seronegative spondyloarthritis.

- Secondary diagnosis: axial spondyloarthritis, *not just whiplash*
 - Neck pain, indolent course, and absent radiographic findings are more common in women.

Teaching Points

- Only a minimal differential diagnosis and initial workup are required based on the classic clinical presentation and review of systems.
- Despite being in the posterior segment, the involvement of the optic nerve, macula, and anterior vitreous do not call for reclassification of the uveitis as intermediate, posterior, or panuveitis.
- Over one-half of patients with acute unilateral anterior uveitis will be positive for HLA-B27.
- About three-quarters of patients with HLA-B27 acute anterior uveitis have an associated systemic inflammatory disorder, with ankylosing spondylitis being the most common diagnosis.
- Seronegative spondyloarthritis (SpA) represents a spectrum of inflammatory rheumatic disorders* in which both peripheral and axial joints might be affected. They are diagnosed based on characteristic clinical manifestations, laboratory abnormalities, and imaging features and display variable onset, presentations, and progression.
- Although ankylosing spondylitis is still thought to be about twice as common in men, diagnosis in women has increased due to expansion of diagnosis criteria and a greater understanding of sex differences in disease presentation.
- Systemic and ophthalmic disease may be asynchronous in their activity, and ophthalmologists and rheumatologists may have different treatment recommendations.

Table 1. Associations in HLA-B27 Patients, by the Numbers

Systemic Disease	HLA-B27 Prevalence (%)	Systemic Developing AAU (%)	B27-AAU Developing Systemic (%)
Ankylosing spondylitis	90	20-30 (more common in men)	55-90
Reactive arthritis	40-80	12-37	8-21
Psoriatic arthritis	40-50	7-16	3-4
Enteropathic arthritis	35-75	2-9 (more common in women)	1-7
Undifferentiated SpA	70	-	5-21

Abbreviation: SpA, Seronegative spondyloarthritis.
Adapted from Chang, McCluskey, Wakefield, 2005.⁴

***Diseases in the Seronegative Spondyloarthritis Family**

- Axial spondyloarthritis
 - Ankylosing spondylitis
 - Nonradiographic axial spondyloarthritis
- Peripheral spondyloarthritis (affecting mostly arms and legs)
- Reactive arthritis
- Psoriatic arthritis
- Enteropathic arthritis / spondylitis associated with inflammatory bowel diseases
- Undifferentiated spondyloarthritis

Disease Discussion**I. HLA-B27 Acute Anterior Uveitis (AAU)****A. B27 basics**

1. The HLA-B gene, located on the short arm of chromosome 6, codes for a class I major histocompatibility complex (MHC) molecule involved in presentation of antigenic peptides to T cells.
2. The HLA-B gene demonstrates genetic variation in humans with hundreds of alleles, each given a number (eg HLA-B27).
3. The HLA-B27 locus is highly polymorphic, with over 100 subtypes that may vary with ethnicity. For example, the HLA-B27*05 allele is present in almost 90% of HLA-B27-positive individuals of Northern European descent.

B. Prevalence of HLA-B27 in different populations

1. The large majority of patients with HLA-B27 positivity will not become ill. Only about 1% of individuals will manifest inflammatory diseases.
2. Important to remember for pretest probability
 - a. Pawaia tribe in Papua New Guinea (53%)
 - b. Haida tribe of the Pacific Northwest (50%)
 - c. Northern Scandinavia (14%-16%)
 - d. Non-Hispanic whites in the U.S. (7.5%)
 - e. Mexican Americans (4.5%)
 - f. African Americans (2%-4%)
 - g. Chinese (2%-9%)
 - h. Arab populations (2%-5%)
 - i. Japanese (< 1%)

C. Epidemiology

HLA-B27-positive AAU is the most common form of uveitis in Europe and North America, being roughly 4 times as common as intermediate or posterior uveitis.

D. Clinical features of B27-AAU

1. May have explosive onset
2. Limited duration (about 8-10 weeks)
3. Recurrent with variable severity / frequency
4. First episode usually between age 20 and 40
5. Unilateral alternating, may favor one eye over the other
6. ± hypopyon
7. ± posterior synechiae
8. ± mild optic disc edema
9. ± macular edema
10. Slightly low eye pressure

E. Treatment

1. Corticosteroids: topical, periocular, oral
2. Limited data on utility of NSAID use
3. Refractory or frequently recurring cases may be treated with nonbiologic immunomodulatory therapy or TNF inhibitors.
4. The TNF inhibitor etanercept is less efficacious than infliximab and adalimumab and may even be proinflammatory.

F. Complications

1. Steroid-induced cataract, ocular hypertension
2. 360 posterior synechiae → iris bombe → glaucoma
3. Macular edema
4. Untreated: cyclitic membrane, hypotony, IOL complications

II. Axial Spondyloarthritis (axSpA)

- A. Represents a spectrum of disease encompassing nonradiographic arthritis of the spine (nr-axSpa) and traditional ankylosing spondylitis (AS)
- B. Frequently present and undiagnosed at the time of first episode of uveitis
- C. Beware the extra-axial manifestations: cardiovascular diseases (2%-10% of patients with AS), pulmonary apical fibrosis, inflammation of jaw, neck, ribs, etc.
- D. Gender differences
- E. Burden of underdiagnosed disease
- F. Treatment
 1. Physical therapy, NSAIDs, TNF inhibitors for axial disease
 2. Sulfasalazine or methotrexate for peripheral disease

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Medical and Surgical Approach to the Treatment of Intermediate Uveitis

Janet Louise Davis MD

I. Correct Diagnosis

Vitreous cells present, presumed lymphocytes

- A. Yes: This is intermediate uveitis, although it may be a masquerade of vitreous hemorrhage, retinal detachment, lymphoma, or other

1. Other signs of inflammation present

- a. Retinal vascular leakage on wide-angle angiography
 - i. Macula-involving
 - ii. Posterior to the equator
 - iii. Anterior to the equator
 - iv. Small vessel leakage (characteristic and notable) vs. large vessel staining (may be present but with less prognostic significance)
- b. Macular edema
 - i. OCT thickening or cysts; can follow OCT map
 - ii. Angiographic only; discretion in treating this but likely prognostically important
- c. Pars plana exudate; if prominent, less chance of associated extraocular disease such as multiple sclerosis or sarcoidosis
 - i. With neovascularization
 - ii. Without neovascularization
 - iii. Vitreous hemorrhage present
 - (a) Visually significant
 - (b) Not visually significant
- d. Anterior segment inflammation

2. Fellow eye involved

3. No other signs of inflammation: Consider diagnostic vitrectomy for masquerades

- B. No: This is not intermediate uveitis; see other lecture.

II. Step 1 Treatment

- A. Step 1 treatment is cryoretinopexy to areas of elevated peripheral retina or neovascularization from ora to anterior zone 3 with laser photocoagulation to areas of flat retina posterior to any clock hours of pars plana exudate.

- B. Step 1 treatment is most appropriate for I.A.1.c. i, ii, or iii (a) patients

- C. Step 1 treatment can be combined with Steps 2-4 for more severe disease than IIA.

III. Step 2 Treatment Is Corticosteroids

- A. Injection corticosteroids are appropriate for nonpediatric age group with mild disease or as adjunctive therapy.

1. Caution with structural complications of cataract and glaucoma
2. Caution with intermittent therapy of a chronic disease
3. Subtenon administration of 40-mg triamcinolone acetonide may give longer duration; may be less effective for controlling retinal vascular leakage or macular edema than intravitreal injection of 4-mg triamcinolone acetonide or 0.7-mg dexamethasone.

- B. Oral corticosteroids are most appropriate as a 3-month tapering bridge therapy to systemic therapy but can be considered for 3-month tapering course as monotherapy to assess response. Preferred to injections for I.A.1.c.ii bilateral disease.

- C. Add to Step 1 for IIB patients

IV. Step 3 Treatment Is Noncorticosteroid Systemic Immunomodulatory Therapy

- A. See: Guidance on Noncorticosteroid Systemic Immunomodulatory Therapy in Noninfectious Uveitis: Fundamentals of Care for Uveitis (FOCUS) Initiative. *Ophthalmology*. 2018; 125(5):757-773.

1. Usual start is drug therapy: methotrexate, mycophenolate, or azathioprine
2. Biologic therapy is usually added to drug therapy: adalimumab.

- B. Treatment criteria are to treat until below treatment threshold with no macular involvement and minimal stage 3 vascular leakage on wide-angle angiography.

1. Treatment outcomes are angiography and other inflammatory markers.

2. Lack of progress in 3-6 months warrants treatment change.

3. Treatment continued for 1 year past remission on drug with slow taper

- C. Best medical judgment critical for assessment of outcomes and treatment changes

- D. Step 1 is often omitted if Step 2 or 3 is chosen as the initial therapy.

- V. Step 4 Treatment Is Pars Plana Vitrectomy
 - A. Always combined with Step 1 before or during surgery
 - B. Usually preceded by or combined with Step 2
 - C. Often preceded by Step 3
 - 1. Systemic immunosuppression (Step 3) can usually be phased out within 6 months of Step 1+Step 4.
 - 2. Unilateral patients on Step 3 treatment may have the inflammation in the fellow eye “unmasked” as Step 3 treatment is withdrawn.
 - D. Step 4 is equivalent to Step 3 in the classic stepladder, but more contemporary practice is to select preferred treatment with strong consideration of patient preferences and circumstances.
 - E. Step 4 + Step 1 is preferred therapy for I.A.1.c.iii(a) patients
 - 1. Think of the stepladder more as a way to categorize patients based on severity.
 - 2. Think of the various treatments as a playbook of strategies to achieve the best outcome for the individual patient.

Case Presentation in Intermediate Uveitis: Roid Rage!

Akbar Shakoor MD

CASE PRESENTATION

History of Present Illness

- 18-year-old East Asian woman presents with 3-year history of blurry vision, floaters, both eyes

Past Ocular History

- None

Past Medical History

- Bipolar depression and 3 prior suicide attempts
- Admitted to University Hospital for suicidality and major depression

Medications

- Lamotrigine, quetiapine

Review of Systems

- Reviewed 14 systems, negative except for above

Exam

- BCVA: O.D., 20/400; O.S., 20/300
- IOP: 17, 19
- Anterior segment: O.D., 1+ cell; O.S., tr cell
- Fundus
 - O.D.: 2+ vitreous cell, 1+ vitreous haze, inferior vitreous hemorrhage, macular edema. Multiple areas of retinal periphlebitis. Mild disc edema. Cystoid macular edema (CME)
 - O.S.: 2+ vitreous cell, trace vitreous haze, alteration of peripheral vascular caliber with subtle periphlebitis

Imaging

- OCT
 - O.D.: Massive CME with subretinal fluid
 - O.S.: Massive CME
- Fluorescein angiography
 - O.U.: Disc leakage and “fern-like” periphlebitis. Area of inferior retinal neovascularization with vitreous hemorrhage O.D. Area of inferior peripheral retinal nonperfusion was noted O.D.

DIAGNOSIS AND TEACHING POINTS

Differential Diagnosis

Intermediate uveitis with vasculitis

- Infectious
 - Tuberculosis
 - Syphilis
 - HIV
 - HTLV-I, HTLV-II
- Noninfectious / inflammatory
 - Multiple sclerosis–associated
 - Sarcoidosis
 - Granulomatous polyangiitis (vasculitis)
 - Systemic lupus erythematosus (vasculitis)
- Masquerade syndromes
 - Primary intraocular lymphoma

Workup

- Laboratory
 - CBC, CMP, QuantiFERON-TB Gold, fluorescent treponemal antibody-absorption (FTA), rapid plasma reagin (RPR), angiotensin converting enzyme (ACE), lysozyme, HIV, viral hepatitis, antineutrophil cytoplasmic antibody (ANCA), double-stranded DNA, ANA
- MRI: Unremarkable

Treatment and Course

- After appropriate laboratory testing, a slow taper of oral prednisone was started (in consultation with patient's psychiatrist) with concurrent initiation of corticosteroid-sparing immunomodulation. Mycophenolate mofetil 1 g PO b.i.d.
- Patient reported improvement in symptoms but also reported recurrent suicidal ideation, aggression, and psychosis.
- Prednisone was decreased to 20 mg daily, and intravitreal corticosteroids were injected with incomplete resolution of CME in both eyes.
- No corticosteroid steroid response was noted.
- Laser was performed to area of retinal nonperfusion O.D.
- Over the next few months, mycophenolate dose with increased to little effect.
- Adalimumab was added, with improvement in CME but not complete resolution.
- Patient developed dense vitreous hemorrhage O.D.
- Pars plana vitrectomy with augmentation of peripheral laser and fluocinolone acetonide implant (Retisert) O.D.
- Pars plana vitrectomy with augmentation of peripheral laser and fluocinolone acetonide implant (Retisert) O.S.
- Vision stabilized to 20/60 O.U. with resolution of CME. Limited by macular atrophy O.U.

Disease Discussion

I. Summary

- A. 18-year-old with severe bilateral intermediate uveitis complicated by massive CME, vitreous hemorrhage and macular atrophy.
- B. Unable to tolerate steroid due to suicidal ideation

II. Intermediate Uveitis

- A. Inflammation localized to the vitreous and peripheral retina.
- B. First described in the literature as chronic cyclitis by Fuchs in 1908
- C. Standardization of Uveitis Nomenclature Working Group: Primary site of inflammation is the vitreous. May be associated with systemic disease, such as multiple sclerosis or sarcoidosis.
- D. Pars planitis (~50%): Considered a subset of intermediate uveitis characterized by the presence of snowbanks or snowballs in the absence of an infectious etiology or a systemic disease. This primary form accounts for over 50% of patients with intermediate uveitis.

III. Epidemiology

- A. Intermediate uveitis accounts for 4%-8% of uveitis seen in tertiary setting. Up to 25% of pediatric referrals.
- B. Onset: Children and young adults
- C. No racial predilection; equal incidence in men and women
- D. Bimodal distribution: second decade and third-fourth decade
- E. Children: worse presenting visual acuity and often more severe disease

IV. Presentation

Blurred vision, floaters, photopsias, paracentral scotomata

V. Pathogenesis

- A. Immunogenetics: No HLA association
- B. Antigenic basis of disease so far unknown

VI. Ophthalmic Findings

- A. Vitreous cell and haze
- B. Retinal vasculitis, CME (28%-50%), uveitis glaucoma (15%), cataract (15%-20%), optic nerve edema
- C. Retinal nonperfusion with neovascularization in retinal periphery and optic nerve head, vitreous hemorrhage (6%-28%), epiretinal membrane

- D. Late findings include cyclitic membranes, tractional or rhegmatogenous retinal detachment (3%-22%), hypotony, and phthisis bulbi.

VII. Imaging: Fluorescein Angiography

- A. Diffuse leakage in “fern-like” pattern
- B. CME
- C. Peripheral retinal nonperfusion
- D. Retinal neovascularization with or without tractional membranes and vitreous hemorrhage

VIII. Differential Diagnosis

- A. Inflammatory
 - 1. Sarcoidosis
 - 2. White dot syndromes
 - 3. Retinal vasculitis
 - 4. Infectious uveitis

IX. Treatment Options

- A. Steroids
 - 1. Oral
 - 2. Injectable corticosteroid
 - 3. Corticosteroid implant
- B. Immunomodulatory therapy
 - 1. Antimetabolites
 - 2. T-cell inhibitors
 - 3. Biologic response modifiers

Case Presentation in Intermediate Uveitis: Fire on the Snowbank

Marissa Larochelle MD

CASE PRESENTATION

History

- An 8-year-old male patient was referred for evaluation of decreased vision O.S. Patient had noted blurred vision O.S. at distance and near starting 1 month prior. Mother of child stated that his depth perception seemed off—he had been bumping into the sides of things lately. Denied redness, pain, flashes or floaters.
- Review of symptoms: cough/cold symptoms several weeks prior to onset of eye symptoms
- Prior medical history, family history and social history: Unremarkable

Exam

- BSCVA: O.D. 20/200, O.S. 20/20
- IOP: O.D. 13, O.S. 15
- Pupils: O.D. irregular, O.S. round and reactive; no afferent pupillary defect
- Slit lamp exam
 - O.D. with clear cornea, posterior synechiae at 5 and 7 o'clock, 1+ anterior chamber cell, 3+ vitreous cell, 2+ haze, hemorrhage inferiorly
 - O.S. with clear cornea, trace anterior chamber cell and 1+ vitreous cell with minimal haze

Fundus exam

- O.D. with possible small NV on nerve, inferior snowbank with neovascularization partially obscured by preretinal hemorrhage
- O.S. with well-consolidated inferior vitreous opacities, otherwise unremarkable

Imaging

- Macular OCT within normal limits O.U., no macular edema
- Fluorescein angiography performed during exam under anesthesia (EUA): peripheral fern-like retinovascular leakage O.D. > O.S. Late nerve leakage O.D.

DIAGNOSIS AND TEACHING POINTS

Differential Diagnosis

- Tuberculosis, syphilis, Lyme (regional), *Bartonella*, EBV, toxoplasmosis (atypical), *Toxocara*, tubulointerstitial nephritis and uveitis syndrome (TINU), sarcoid, collagen-vascular disease, MS associated, JIA associated, idiopathic pars planitis
- Other causes of vitreous hemorrhage in pediatric population: occult trauma, regressed ROP, familial exudative vitreoretinopathy (FEVR), persistent fetal vasculature syndrome (PFV), retinoblastoma, Coats disease, leukemia, retinal tear

Workup

- CBC, CMP, ACE, lysozyme, RPR, FTA-Abs, QuantiFERON Gold, ANA, RF, HLA-B27, urine beta-2 microglobulin, toxoplasma IgG and IgM, *Toxocara*, *Bartonella*: all negative or within normal limits

Final Diagnosis

- Idiopathic intermediate uveitis / pars planitis

Clinical Course

- Topical steroids O.U. and cycloplegia O.D. to treat anterior inflammation
- EUA with subtenon triamcinolone acetate (STK; Kenalog) O.D. and peripheral laser photocoagulation to inferior retina O.D.
- Next visit: VA O.D. improved to 20/60; O.S. 20/20; IOP O.D. 18, 10 O.S. (mild IOP rise / asymmetry with STK)
- Refraction with pediatric ophthalmology: VA 20/30 O.D., 20/20 O.S.
- Possible component of mild deprivation amblyopia
- Plan to start systemic immunomodulatory therapy if he recurs
- Has been followed for 1.5 years without recurrence; final VA O.D. 20/25, O.S. 20/20

Teaching Points

- Pars planitis in children can present as vitreous hemorrhage.
- Bilateral but very asymmetric disease can occur.
- Some eyes can be monitored without treatment (good visual acuity, no structural complications).
- Peripheral retinal ablation can induce remission of pars planitis in some patients.

Disease Discussion

I. Epidemiology

- A. Intermediate accounts for 8%-22% of uveitis patients.
- B. Primarily affects patients from childhood through fourth decade
- C. No clear gender predilection

II. Presentation

Often minimal symptoms including blurred vision and floaters, but no pain / redness or photophobia unless anterior segment inflammation also occurs

III. Clinical Features

- A. Primary site of inflammation is the vitreous (1-4+ vitreous cell/haze); can have mild anterior chamber inflammation
- B. Vitreal yellowish-white aggregates (snowballs); periphlebitis, exudates on the pars plana (snowbank); Do scleral depression
- C. Complications: macular edema, ocular hypertension, retinal vascular leakage, cyclitic membrane formation, neovascularization, vasoproliferative tumor, epiretinal membrane, retinal detachment, optic nerve involvement
- D. Vitreous hemorrhage occurs as a complication in children much more frequently than adults (28% vs. 6%).

IV. Etiology

- A. Rule out infectious (syphilis, TB, Lyme, *Bartonella*)
- B. Idiopathic likely T-cell mediated
- C. Always consider sarcoid and MS-associated and ask review of systems, specifically for these, at each follow-up

V. Diagnosis

Clinical diagnosis with aid of multimodal imaging (macular OCT, fluorescein angiography)

VI. Treatment

- A. When to treat vs. observe
- B. Treatment options
 - 1. Topical steroids for anterior segment inflammation
 - 2. Periocular steroid injections
 - 3. Oral prednisone
 - 4. Systemic immunomodulatory therapy
 - 5. Vitrectomy and/or peripheral retinal ablation

VII. Special Considerations in the Pediatric Age Group

- A. Risk of vision loss unbeknownst to the patient, especially unilateral
- B. What injections can be performed in the office setting?
- C. Utilizing an EUA
- D. Treating amblyopia

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Case Presentation in Intermediate Uveitis

Sumit Sharma MD

CASE

A 16-year-old white female patient with intermediate uveitis and optic nerve edema was referred for persistent uveitis with a negative workup including MRI brain. Refracted to 20/20 but felt her visual acuity was “weird.” Has been treated with topical and oral steroids over the past year for recurrent uveitis. Prior workup including ACE, *Bartonella* Abs, Lyme, syphilis titers, ACE, HLAB27, and MRI brain were all negative. She was referred to rheumatology to start on methotrexate and to us for a second opinion on her uveitis as she could not be tapered below 30 mg of prednisone without flaring.

On presentation she was on 40 mg prednisone and prednisolone drops b.i.d. O.U. Review of systems was completely negative.

Physical Findings

- BCVA with refraction: O.D. 20/20; O.S. 20/20
- IOP: O.D. 15; O.S. 13
- No afferent pupillary defect
- Quiet anterior chamber
- 2+ vitreous cell O.U.
- 2+ optic nerve edema O.U.
- Inferior snowballs with snowbanks O.U.
- Fluorescein angiography shows diffuse late peripheral leakage and optic nerve leakage in both eyes.

nephritis and uveitis syndrome in young patients with uveitis. *JAMA Ophthalmol.* 2015; 133(2):140-145.

DIAGNOSIS AND TEACHING POINTS

Differential Diagnosis

- Pars planitis
- Sarcoidosis
- Juvenile idiopathic arthritis
- Inflammatory bowel disease–associated uveitis
- Psoriatic arthritis
- Syphilis
- TB
- Tubulointerstitial nephritis and uveitis syndrome

Workup

Urinalysis and urine beta 2 microglobulin, basic metabolic panel

- Urinalysis showed low molecular weight proteinuria.
- Urine beta 2 microglobulin: 3138
- Creatinine 0.99 (GFR estimated 64, based on pediatric correction for height and weight)
- Evaluation with pediatric nephrology and decision not to do a biopsy based on clinical characteristics and overall minimal renal dysfunction.

Final Diagnosis, Clinical Course and Outcome

Tubulointerstitial nephritis and uveitis syndrome (TINU)

Teaching Points

- Patients with otherwise undiagnosed etiology of uveitis should have an evaluation for urine function to include a urinalysis and urine beta 2 microglobulin (not blood). The creatine level should be corrected for the patient's height and weight in the pediatric population.
- Treatment should include an evaluation with a nephrologist.

Discussion

I. Introduction

- A. TINU was first described in 1975 by Dobrin et al.
- B. It is defined as occurrence of tubulointerstitial nephritis (TIN) and uveitis in a patient in the absence of other systemic diseases that can cause either interstitial nephritis or uveitis
- C. It is felt to be an immune-mediated process that can be caused by drugs or infections, but many cases remain idiopathic.

II. Demographics

- A. TINU was originally felt to be mostly a bilateral, sudden-onset uveitis affecting children more than adults and more common in girls.
- B. It is increasingly being recognized that TINU can occur in any age range and can cause any type of uveitis; however, most cases are bilateral.

III. Symptoms

- A. TINU can be a life-threatening condition due to severe acute kidney injury.
- B. Most patients present with either nonspecific symptoms such as fever, rash, flank pain / tenderness, or fatigue, or they are completely asymptomatic except for ocular symptoms.

IV. Diagnosis

- A. Diagnosis of exclusion
- B. Urine (not blood) beta 2 microglobulin is elevated as tubulointerstitial nephritis worsens.
- C. There is felt to be an association with HLA-DRB1, but HLA testing is not indicated.
- D. Urinalysis can be normal or can show red blood cells / red blood cell casts.
- E. Proteinuria can be present, but albuminuria is absent as glomerular pathology is not common.
- F. Urinary and/or peripheral blood eosinophilia may be present.
- G. Renal biopsy is needed to confirm the diagnosis.
- H. Renal biopsy will show tubulointerstitial necrosis and/or fibrosis with preserved glomeruli, interstitial edema, and cellular infiltration of predominantly CD4-positive lymphocytes.
- I. Need to exclude other systemic diseases that can cause both renal and ocular inflammation

V. Differential Diagnosis

Sarcoidosis

VI. Treatment

- A. In cases with mild kidney dysfunction, oral steroids may be sufficient to control inflammation, but most patients will need long-term systemic immunosuppression to control the renal disease.
- B. Ocular inflammation can be controlled with local therapy as needed.

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Case Presentation in Intermediate Uveitis: These Floaters Just Won't Go Away!

John Gonzales MD

CASE PRESENTATION

37-year-old white man with 5-year history of floaters O.U. Prior investigative tests including QuantiFERON-TB Gold, treponemal antibody, and chest X-ray were negative. Prior to referral to our center he had received a vitrectomy that had negative studies, including cytopathology. He was diagnosed with intermediate uveitis, which responded to oral and topical corticosteroids. Patient was started on antimetabolite therapy and then advanced to infliximab due to lack of complete response of his uveitis. Despite advancement in therapy his intraocular inflammation eventuated to a robust amount of anterior chamber cell with plaque-like lesions in the anterior chamber of the right eye. At this point the visual acuity in the right was counting fingers, with IOP of 40 mmHg. There was no view to the posterior segment; B-scan ultrasonography demonstrated a mild vitritis, but no retinal detachment, choroidal thickening, masses, or posterior scleritis. The left eye exhibited visual acuity of 20/40, IOP of 13 mmHg, and 1+ anterior chamber cell with no flare. There was 1+ anterior vitreous cell, no vitreous haze, and no posterior segment lesions.

Differential Diagnosis

- Infectious
 - Tuberculosis
 - Syphilis
 - Endogenous endophthalmitis
- Noninfectious
 - Intermediate uveitis
 - Sarcoidosis
 - Undifferentiated anterior / intermediate uveitis

Workup

- CT chest: pulmonary nodule of undetermined clinical significance (infectious disease consulted)
- MRI brain: unremarkable
- Laboratory
 - QuantiFERON Gold: negative
 - Treponemal antibody: negative
 - CBC with differential: within normal limits

DIAGNOSIS AND TEACHING POINTS

Infliximab was discontinued due to worsening condition and concern for an infectious etiology.

Anterior chamber paracentesis was negative by directed polymerase chain reaction and metagenomic deep sequencing (MDS) for infectious pathogens. Anterior chamber washout was performed with biopsy of plaque-like material; this was positive for diffuse large B-cell lymphoma on cytopathology and immunohistochemistry. MDS identified mutations associated with lymphoma development.

Discussion

I. Introduction

- A. Primary vitreoretinal lymphoma (PVRL) is a subset of primary central nervous system lymphoma (PCNSL).
- B. PVRL may affect the subretinal space, the vitreous, and the optic nerve.

II. Epidemiology

- A. Immunocompetent and immunodeficient patients may develop PVRL. Historically, reactivation of latent Epstein-Barr virus has mediated the development of PVRL in immunodeficient patients, while most immunocompetent cases have not been related to an infectious pathogen.
- B. Classically, immunocompetent patients may develop disease in their fifth to sixth decades of life, while immunodeficient patients developed disease much earlier. However, with the use of anti-retroviral therapy in AIDS patients, the incidence of PCNSL and PVRL has declined.
- C. There is a slight female preponderance of disease.

III. Clinical Symptoms and Signs

- A. Patients typically complain of floaters and blurry vision.
- B. Vitritis, anterior chamber cell, or subretinal involvement may be seen.
- C. The vitritis responds to systemic and local steroids, which allows this entity to masquerade as a noninfectious uveitis.
- D. When subretinal lesions exist, OCT can identify hyper-reflective lesion between retinal pigment epithelium and Bruch membrane.

IV. Differential Diagnosis

- A. Intermediate uveitis
- B. Tuberculosis
- C. Syphilis

V. Diagnosis

- A. Cytopathology or molecular testing of ocular tissue (aqueous, vitreous, or chorioretinal biopsy)
- B. MRI brain to evaluate for CNS disease

VI. Management

- A. Coordinate with neuro-oncologist
- B. Chemotherapy vs. radiation: Treatment has been evolving, with improved outcomes.

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Posterior Uveitis—When to Worry About Systemic Disease

Alan G Palestine MD

I. Goals of the Presentation

To explore how and when to evaluate the relationship of systemic disease and posterior uveitis using general principles and specific examples

II. Posterior Uveitis

- A. Involves retina and/or choroid as the primary site for inflammation but may have inflammation in the anterior chamber and/or vitreous. Fifteen percent to 30% of uveitis is classified as posterior uveitis.
- B. Toxoplasmosis and sarcoidosis are the most common diagnoses.
- C. Many diverse clinical presentations involving dots, spots, plaques, etc. A plethora of disease names, syndromes, acronyms, and eponyms. However, true understanding of the etiology may be lacking.
- D. May be localized to the eye or be associated with disease in other organs

III. Systemic Disease and Posterior Uveitis

- A. Always worthwhile to search for systemic disease associations, but do not be disappointed when there are none.
- B. Causation, association, and unrelated coexistence have different implications when considering systemic disease. Syphilis is an example of a causative systemic disease; Behçet syndrome has associated inflammation in multiple organs; Hashimoto thyroiditis coexists in patients with posterior uveitis but is not clearly related.

IV. Reasons to Look for Systemic Disease

- A. To attempt to unify multiple patient symptoms into one diagnosis:
Patients and doctors always want to know why a disease has occurred. Sometimes there is a clear etiologic agent (usually infectious), sometimes we can associate multiple symptoms into one umbrella diagnosis, and sometimes we have no answer.
- B. To avoid undertreating non-ocular involvement
- C. To access therapies that may be approved only for systemic diseases
- D. To create collaborative interspecialty management to avoid duplication

V. Mechanisms of Posterior Uveitis: Examples of Localized / Systemic Disease

- A. Mechanical: intraocular foreign body / ocular ischemic syndrome

- B. Malignant: B cell lymphoma – may be localized only to the eye or involve the brain

- C. Infectious: recurrent ocular toxoplasmosis / syphilis

- D. Immune driven: multiple evanescent white dot syndrome (MEWDS), birdshot chorioretinopathy (BSCR) / sarcoidosis, Behçet

- E. Genetic: ADNIV (CAPN5 mutation) / Blau syndrome (NOD2 mutation)

VI. How to Search for a Systemic Disease

- A. Extraocular involvement may not be symptomatic. Define the location, course, and progression. History, clinical findings, and imaging drive the workup. Does the clinical disease meet the criteria for a disease known to have no systemic associations, like punctate inner choroidopathy or birdshot? Final diagnosis not always achieved on the first visit.
- B. Detailed history is the most useful tool. Most syndromes do not present with simultaneous multisystem findings; rather, they evolve over time.
- C. Extensive vs. targeted laboratory workup? Many systemic diseases such as Behçet syndrome have no associated tests that establish the diagnosis.
- D. Doing many tests may yield false positive results and is costly. Positive predictive value (PPV) is the likelihood that a positive lab test is actually related to the patient's uveitis. Testing should be based on clinical findings and differential diagnosis.

VII. Laboratory Testing and Posterior Uveitis

- A. Most patients should have a syphilis serology and radiographic chest imaging; both have a high PPV. Other testing when clinically appropriate.
- B. HLA typing is most useful to confirm A29+ in BSCR, but only if the appearance is clinically consistent. Other HLA associations are weaker.
- C. Viral serologies are rarely useful and are most useful when negative unless patient has systemic symptoms of active systemic infection.
- D. TB QuantiFERON testing has a PPV of 11% in uveitis overall, but a 95% PPV in clinical serpiginous choroiditis, hence serpiginous-like tuberculous choroiditis.
- E. Antineutrophil cytoplasmic antibody (ANCA) reasonable in retinal vasculitis (occlusive). ANA, ESR, and RF are rarely helpful. Atypical clinical appearance or response justifies more testing.

VIII. Summary

- A. Define the disease clinically as to location, course, and progression, then make an initial hypothesis and a differential diagnosis. Does it meet the criteria for a known disease that has no systemic association?
- B. Detailed history and focused testing to confirm initial hypothesis
- C. Revisit initial hypothesis as disease evolves or fails to respond to treatment
- D. Always consider the possibility that there is more than just ocular inflammation, but accept that none may be found.

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Case Presentation in Posterior Uveitis: Sarcoidosis

Bougie Nights

Bryn Burkholder MD

CASE PRESENTATION

A 37-year-old Filipino male patient presents with painless, blurred vision and floaters in the left eye for 6 months. The right eye has been entirely asymptomatic.

Past medical history is notable for borderline diabetes, treated with diet and exercise modification. On review of systems, he reports a chronic cough for the past few months. He has never smoked or used alcohol or illicit drugs. He works in maintenance. He was adopted and emigrated from the Philippines in 1987.

On initial examination, uncorrected acuities are 20/20 O.D. and 20/25 O.S. Pupils, pressures, motility, and confrontation fields are normal. Examination of the right eye is entirely unremarkable. Slit lamp examination of the left eye is notable for 1+ pigmented cell in the anterior vitreous. Fundus examination reveals prominent midperipheral, perivenous sheathing and exudates. There are scattered, diffuse intraretinal hemorrhages, as well as old vitreous hemorrhage adjacent to the inferotemporal arcade. Wide-field angiography demonstrates segmental leakage along the retinal veins, with marked nonperfusion in the superior and temporal midperiphery and periphery.

DIAGNOSIS AND TEACHING POINTS

Differential Diagnosis

Sarcoidosis, Behçet disease, pars planitis, antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis, systemic lupus erythematosus, tuberculosis, multiple sclerosis, syphilis, Lyme disease

Workup

Negative FTA-Abs, ANCA, PPD; normal urinalysis. Chest x-ray demonstrates mediastinal and hilar adenopathy, as well as peribronchial infiltrates and nodular opacities of the left upper lobe and right lung base.

Patient Follow-up and Clinical Course

The patient was referred to a pulmonologist, who performed a bronchoscopy. Hilar lymph node biopsy demonstrated noncaseating granulomas, consistent with sarcoidosis. The patient was started on a course of high-dose oral prednisone with a slow taper. He also underwent laser photocoagulation to the left eye. At the end of his course of oral prednisone, he had no active ocular or pulmonary disease and has been monitored without recurrent inflammation for five years.

Discussion

I. Sarcoidosis

A. Introduction

1. Multisystem disease characterized by chronic granulomatous inflammation
2. Most commonly affects the lungs, but also may cause inflammation in eyes, skin, heart, and nervous system
3. Definitive diagnosis made by tissue biopsy demonstrating noncaseating granulomas

B. Ocular disease

1. Clinical presentation
 - a. 25%-50% of patients with systemic sarcoidosis have eye involvement.
 - b. May affect any structure of eye and orbit
 - c. Most common ocular manifestation is anterior uveitis.
 - d. Has many and varied presentations, but common clinical findings include granulomatous keratic precipitates, vitreous snowballs, perivenous sheathing and exudates ("candle wax drippings"), and peripheral retinochoroidal nodules
2. Retinal periphlebitis is found in 29%-37% of patients with sarcoidosis-associated uveitis.
 - a. May be ischemic or nonischemic (more common)

- b. Periphlebitis often segmental

3. Diagnosis

- a. Chest x-ray may demonstrate hilar adenopathy or pulmonary infiltrates.
- b. Chest CT is more sensitive but carries increased risk from radiation.
- c. ACE and lysozyme levels may be useful adjuncts but are nonspecific.

4. Treatment

- a. Corticosteroids (topical / oral / periocular / intravitreal) are a mainstay of therapy.
- b. Antimetabolites, particularly methotrexate, may prevent vision loss.
- c. Biologic agents, specifically adalimumab and infliximab, may be effective for refractory disease.

II. Retinal Vasculitis

A. Introduction

1. 15% of patients with uveitis have retinal vasculitis.
2. A very small percentage of patients with retinal vasculitis have systemic vasculitis (1.4%).

B. Pathophysiology

1. Etiology unclear
2. Histologic studies demonstrate perivascular infiltration of lymphocytes.
3. May be thrombotic or obliterative (from inflammatory infiltrate)
4. Vascular occlusion leads to increased vascular endothelial growth factor (VEGF), causing neovascularization and increased vessel permeability.

C. Clinical features

1. Exam findings may include vascular sheathing, perivascular infiltrates, intraretinal hemorrhage.
2. Complications include macular edema, ischemia, neovascularization, vitreous hemorrhage, retinal detachment, and neovascular glaucoma.
3. More than 2 quadrants of retinal ischemia is associated with an increased risk of neovascularization.
4. Ischemic vasculitis is associated with higher risk of vision loss (from macular edema, ischemia) than nonischemic vasculitis.

D. Treatment

1. Laser photocoagulation and intravitreal anti-VEGF agents may be useful in patients with ischemic disease.
2. Immunosuppression may reduce risk of vision loss.

Teaching Points

- Because sarcoidosis has a wide variety of clinical presentations, it should be considered in the differential diagnosis for all patients with uveitis or orbital inflammation.
- Sarcoidosis may cause a retinal periphlebitis that, in some cases, may result in retinal ischemia.
- Corticosteroids are often first-line treatment for sarcoidosis-associated uveitis. The use of immunosuppression has been associated with a reduced risk of vision loss.
- Laser photocoagulation and/or intravitreal anti-VEGF agents may be used to treat retinal ischemia and its complications.
- Systemic therapy for sarcoidosis-associated eye disease may be coordinated with a pulmonologist or other specialist.

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Case Presentation in Posterior Uveitis: Birdshot

More Than Meets the Eye

Lucia Sobrin MD

CASE PRESENTATION

A 54-year-old white woman first noted a floater and shimmering lights in her left eye 6 months prior to presentation. At that time, she was examined by a local retina specialist and found to have a normal examination. Then, 2 months prior to presentation, she subsequently developed new floaters in the right eye and blurred vision in both eyes while on vacation in New Mexico. She was examined by a retina specialist in New Mexico, who diagnosed her with a hemorrhagic posterior vitreous detachment in the right eye. Her symptoms persisted upon her return home and she went to see her local retina specialist again, who referred her for further evaluation.

Her past medical history included systemic *Ehrlichia* infection treated with doxycycline 12 years prior. Review of systems was unremarkable. Her vision was 20/32 in the right eye and 20/40 in the left eye. There was no afferent pupillary defect. Anterior segment examination was normal. There was 2+ vitreous cell and disc hyperemia in both eyes. Otherwise the retinal examination was felt to be within normal limits. OCT showed no retinal cystic changes. Fluorescein angiography showed retinal vascular leakage along the arcades in both eyes. Indocyanine green angiography showed multiple hypocyanescent spots throughout the fundus.

DIAGNOSIS AND TEACHING POINTS

Differential Diagnosis

- Birdshot chorioretinopathy
- Sarcoidosis-associated posterior uveitis
- Idiopathic posterior uveitis and retinal vasculitis
- Syphilitic posterior uveitis
- Primary vitreoretinal lymphoma

Workup

Serologic testing showed a mildly elevated ACE level of 57 (normal range: 8-53). HLA-A29 was positive. CXR, anti-treponemal antibodies, Lyme IgM and IgG, and CBC were normal/negative.

Final Diagnosis, Clinical Course, and Outcome

Birdshot chorioretinopathy

Goldmann visual field testing was normal. Full-field electroretinogram was normal in the right eye and both cone and rod signals were slightly diminished in the left eye. The patient was treated with oral prednisone with significant improvement in symptoms and improvement in visual acuity to 20/20 in both eyes. Symptoms recurred with prednisone tapering, and she was then transitioned to mycophenolate mofetil for longer term therapy. During the follow-up period, the birdshot lesions became more apparent on examination.

Disease Discussion

I. Epidemiology

- A. Typically a disease of middle age: mean age = 50 years
- B. More common in patients of European descent
- C. Female predominance
- D. No clear systemic disease association

II. Clinical Diagnosis

- A. Most common symptoms: blurred vision, floaters, photopsias
- B. Central visual acuity is often excellent at disease onset and does not necessarily reflect the extent of disease. Patient's complaint of poor vision is often out of proportion to measured visual acuity.
- C. Ophthalmic findings
 1. Lesion characteristics
 - a. Typical birdshot lesions are ill-defined, cream-colored choroidal lesions, most often seen in the nasal postequatorial fundus and exhibiting a radial distribution from the nerve.
 - b. Early in the disease course, the lesions are often not easily visible, and this can lead to a delay in the diagnosis.

2. Associated findings in acute stage

- a. Vitritis, often mild to moderate
- b. Retinal vasculitis
- c. Optic disc inflammation
- d. Cystoid macular edema

3. Associated findings in the chronic/late stage

- a. Choroidal neovascularization
- b. Epiretinal membrane
- c. Optic atrophy
- d. Peripheral retinal atrophy

4. Imaging; often crucial to making the diagnosis

- a. Fluorescein angiography: Commonly leakage is seen, predominantly along the arcade vessels.
- b. Indocyanine green angiography: May reveal hypofluorescent spots in the absence of clinically apparent spots and be useful in early diagnosis. Even when some spots are visible on examination, indocyanine green angiography often shows more spots than those seen on examination.

5. HLA-A29 testing

- a. One of the strongest associations between HLA type and disease in all of medicine
- b. 7% of the white population is positive for HLA-A29.
- c. HLA-A29 positivity in the absence of characteristic clinical findings of birdshot chorioretinopathy should not result in a diagnosis of birdshot chorioretinopathy.

III. Differential Diagnosis

A. Immune-mediated

1. Sarcoidosis
2. Idiopathic posterior uveitis and retinal vasculitis
3. Multifocal choroiditis and panuveitis

B. Infectious

1. Syphilis
2. Tuberculosis
3. Lyme disease

C. Neoplastic: intraocular lymphoma

IV. Disease Assessment

Ancillary testing is crucial to assessing disease severity and monitoring disease course.

- A. Many of the typical markers we use to monitor other forms of posterior uveitis are less useful in monitoring patients with birdshot chorioretinopathy.
 1. Central visual acuity can be preserved until late in the disease course, while the peripheral retina is being severely damaged.
 2. The vitritis in some cases is relatively mild, and thus significant changes in vitreous cell may not occur.
 3. The birdshot lesions themselves may not resolve, even if the disease is well controlled.
- B. Several ancillary tests are useful to monitor disease.
 1. OCT
 - a. To monitor for macular edema and choroidal neovascularization
 - b. Enhanced depth imaging OCT may show choroidal thickening (with active choroidal inflammation) or thinning (in chronic disease).
 2. Fundus autofluorescence: Macular hypoauto-fluorescence is associated with poorer visual outcomes.
 3. Fluorescein angiography, to evaluate for retinal vasculitis
 4. Indocyanine green angiography, to monitor choroidal inflammation. In some, spots may resolve with treatment.
 5. Visual field testing and electroretinography, to assess peripheral retinal function

V. Treatment Goals

- A. Resolution of macular edema
- B. Resolution of retinal vascular leakage

- C. Preservation of retinal function as measured by visual field testing and electroretinography:

Presence of visual field and electroretinographic abnormalities at the time of initial diagnosis are an indication of existing functional retinal damage and should prompt more aggressive treatment.

- D. Induction of long-term remission

VI. Treatment Options

- A. Antimetabolites: methotrexate, mycophenolate mofetil, azathioprine
- B. T-cell transduction inhibitors: cyclosporine, tacrolimus
- C. Biologics: infliximab, adalimumab, daclizumab, intravenous immune globulin, tocilizumab
- D. Sustained-release steroid implants

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Case Presentation in Posterior Uveitis: Behçet or Other Systemic “Third Time Lucky”

William R Tucker MBBS

CASE PRESENTATION

History

- 30-year-old white male of Italian descent with sudden onset of blurred vision and floaters in the right eye
- Six-year history of bilateral recurrent alternating panuveitis with retinal vasculitis
- Otherwise fit and healthy at initial diagnosis
- Panuveitis responded to high-dose oral corticosteroids but flared multiple times at tapering to low dose (5 mg prednisone).
- Started mycophenolate mofetil 1 g b.i.d. treatment 6 years previously, and tacrolimus 2 mg b.i.d. added 3 years previously. Despite these he continued to flare on steroid taper below 5 mg.
- Abdominal pain, bowel cramping, and diarrhea present intermittently throughout but worsened significantly 1 year previous. Colonoscopy reveals geographic ulceration and biopsy has transmural inflammation consistent with Crohn disease.
- Infliximab infusions 6 weekly and mesalazine started for Crohn disease diagnosis; subsequent ocular quiescence and tapering off prednisone / tacrolimus / mycophenolate, guided by gastroenterologists, 6 months prior to new flare.
- Continues infliximab / mesalazine at presentation

Examination

- VA with correction: O.D. count fingers, O.S. 20/40
- No relative afferent pupillary defect
- O.S. clear with no intraocular inflammation
- O.D. circumciliary flush, 1+ anterior chamber cells, 2+ vitreous haze/cells, no visible chorioretinal lesions but macula edema, perivenular sheathing and visible retinal ischemia peripherally

Imaging

- OCT O.D.: Macula edema with intraretinal cystic change
- Fundus fluorescein angiogram O.D.: Hot disc, macula ischemia, retinal vasculitis with widespread ferning, inferotemporal retinal ischemia

DIAGNOSIS AND TEACHING POINTS

Additional History

- Mouth ulcers at initial presentation
- Behçet disease assumed until Crohn disease diagnosed and rapid quiescence with disease-modifying antirheumatic drugs and biologic

Differential Diagnosis

Bilateral panuveitis, retinal vasculitis, and GI tract involvement

- Behçet disease
- Crohn disease with panuveitis / retinal vasculitis
- Endogenous endophthalmitis
- Sarcoidosis
- Tuberculosis
- Whipple disease

Workup

- Normal CBC, renal function, liver function
- Negative: treponemal serology, QuantiFERON Gold, *Borrelia* serology, toxoplasma serology, HIV
- Normal ACE, rheumatoid factor
- Negative ANA, antineutrophil cytoplasmic antibody (ANCA), anti-cardiolipin, anti ds-DNA, anti-RNP, anti Ro/La
- Chest X-ray clear
- No PAS staining or other evidence of Whipple disease on duodenal biopsy. No malabsorption.
- Positive HLA-B27 and HLA-B51

Final Diagnosis

- Behçet disease and severe ocular involvement (with concurrent Crohn disease)

Clinical Course

- Admitted to hospital for 3 days of intravenous methylprednisolone 1 g/day
- Discharged on 80 mg prednisone and mycophenolate 500 mg b.i.d. restarted
- Infliximab auto-antibodies detected
- Started adalimumab 40 mg every 14 days
- Prednisone tapered off over next 12 months
- Last visit quiescent on adalimumab / mycophenolate
- VA: O.D. 20/200, O.S. 20/20

Teaching Points

- More than one systemic condition can occur simultaneously in patients.
- Trust good clinical judgement, and remember, the initial clinical presentation can be the best time to make the diagnosis before confusion from chronicity, complications, and medication side effects cloud the picture.
- Infliximab is a very effective medication but requires additional immunosuppression to ensure neutralizing auto-antibodies don't develop.

Disease Discussion (Behçet Disease)

I. Introduction

- A. Named after Hulusi Behçet, a Turkish dermatologist who first described the triad of recurrent oral aphthous ulcers, genital ulcers, and hypopyon uveitis
- B. Also known as Adamantiades-Behçet syndrome or Silk Road disease
- C. Multisystemic small-vessel vasculitis characterized by obliteration of arteries, veins, and capillaries
- D. Most common manifestations include mucous membrane lesions of the GI tract, ocular inflammation, and inflammatory arthritis. Cardiovascular and neurological system involvement can lead to fatal consequences of aneurysm or obliterative cerebral vasculitis.

II. Epidemiology

- A. As the name suggests, there is a much higher prevalence in countries along the Silk Road, the ancient trade route between Europe, the Middle East, and Asia. Rare in United States and Africa but it is well documented that cases occur.
- B. Young adults (25-35 years), no gender predilection, but a more severe course in males
- C. Over half of Behçet disease patients will have ocular features.

III. Clinical Features

- A. Systemic features, included in the diagnostic criteria below
- B. Ocular features
 1. Chronic recurrent nongranulomatous uveitis
 2. 60% develop panuveitis, but anterior, intermediate, posterior uveitis can also occur.
 3. Hypopyon: smooth, shifting, and present in relatively quiet eyes (cold hypopyon)
 4. Retinal vasculitis can affect arteries, veins, and the capillary bed (ferning). There can be chorioretinal infiltrates and frank ischemic retina due to multifocal occlusive and necrotizing retinal vasculitis.
 5. Other findings include cystoid macula edema, optic nerve head edema, retinal hemorrhages, distinct retinal artery, and retinal vein occlusions.
 6. Less common anterior findings: recurrent conjunctivitis, episcleritis, scleritis
 7. End stage: obliterated white retinal arterioles with chorioretinal atrophy and optic disk pallor
 8. Complications: neovascularization, cataract and glaucoma

IV. Differential Diagnosis

A. Infectious

1. Syphilis
2. Endogenous endophthalmitis
3. Tuberculosis
4. Acute retinal necrosis

B. Noninfectious

1. HLA-B27 associated severe uveitis with hypopyon and posterior involvement
2. Sarcoidosis
3. Systemic lupus erythematosus
4. ANCA-associated vasculitis
5. Multiple sclerosis-associated intermediate uveitis and retinal vasculitis

C. Masquerade

1. Leukemia
2. Lymphoma

V. Diagnosis (International Study Group Guidelines)

A. Oral aphthous ulcers at least 3 times in 12 months and 2 of these 4:

1. Genital ulcers
2. Skin lesions
3. Ocular inflammation
4. Pathergy reaction

B. Behçet's Disease Research Committee of Japan

1. Major criteria
 - a. Recurrent oral aphthous ulcers
 - b. Skin lesions (erythema nodosum, folliculitis)
 - c. Genital ulcers
 - d. Iridocyclitis (with hypopyon)
 - e. Posterior uveitis with retinal vasculitis
2. Minor criteria
 - a. Arthritis
 - b. Epididymitis
 - c. GI involvement
 - d. Vascular involvement (thrombosis)
 - e. Neurologic symptoms
3. Complete: all major criteria
4. Incomplete
 - a. 3 major criteria
 - b. 2 major and 2 minor criteria
 - c. Ocular disease + 1 major criteria

d. Ocular disease + 2 minor criteria

e. Suspect: 2 major criteria

f. Possible: 1 major criteria

VI. Etiology and Pathogenesis

- A. HLA-B51 is present in 50%-80% but is not an essential diagnostic marker.
- B. The lack of patients in large populations (eg, Brazil) suggests environmental factors must interact with HLA-B51 in susceptible populations. Putative factors include mycobacterial heat shock protein and organophosphates.
- C. Innate immune cells (neutrophils) are found to be highly activated, suggesting a possible autoinflammatory mechanism for the disease.

VII. Management

A. Medical

1. Anterior uveitis
 - a. Topical steroids
 - b. Periocular steroid injections
2. Posterior segment-involving uveitis
 - a. Intravitreal steroid injection
 - b. Oral corticosteroids
 - c. Immunosuppressants
 - i. Azathioprine
 - ii. Cyclosporin
 - iii. Mycophenolate mofetil
 - iv. TNF inhibitors (increasingly used as first-line therapy in the presence of posterior involvement occlusive retinal vasculitis, retinitis)
 - v. Interferon alpha-2a (use in Europe is more widespread)
 - vi. Alkylating agents

B. Surgical

1. Treatment of complications
 - a. Cataracts
 - b. Glaucoma
 - c. Retinal detachment

VIII. Prognosis

- A. Systemically: Good in absence of neurological or cardiovascular involvement
- B. Ocular: With stronger first-line therapy such as biologics, prognosis may have improved, with 10%-15% deteriorating to VA <20/200 after 5 years. Thirty years ago this figure was 50%+.

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Punctate Inner Choroidopathy and Multifocal Choroidopathy With Panuveitis—Separate Entities or Spectrum of the Same Disease? Pro

Debra A Goldstein MD

NOTES

Punctate Inner Choroidopathy and Multifocal Choroidopathy With Panuveitis—Separate Entities or Spectrum of the Same Disease? Con

Lee M Jampol MD

NOTES

This image shows a single sheet of white paper with horizontal ruling lines. The lines are evenly spaced and run across the width of the page. There are no margins, text, or other markings on the paper.

Is It Infectious or Not? Pearls and Pitfalls

Ramana S Moorthy MD

I. Uveitis Classification: Noninfectious vs. Infectious

A. Noninfectious uveitis

1. “Auto-immune”
2. Underlying systemic immunologic abnormalities and idiopathic cases account for the majority of cases.

B. Infectious uveitis

1. Viral

- a. Herpes group viridae (anterior uveitis, viral retinitis)
- b. HSV1 and 2; varicella zoster virus (VZV), cytomegalovirus (CMV), ? Epstein Barr (EBV)

2. Bacterial

- a. Syphilis
- b. Tuberculosis
- c. Lyme disease
- d. Bartonellosis
- e. Rickettsial diseases
- f. **Endophthalmitis

3. Fungal

- a. *Candida*
- b. *Aspergillus*
- c. Histoplasmosis
- d. Coccidioidomycosis, blastomycosis

4. Protozoal: toxoplasmosis

5. Helminthic

- a. Toxocariasis
- b. Diffuse unilateral subacute neuroretinitis (DUSN)
- c. Onchocerciasis, cysticercosis

II. The Keys to Determining if the Uveitis Is Infectious or Not

- A. *Obtain an accurate and thorough history and perform a thorough ophthalmic and physical exam.*
- B. Laboratory testing or tissue biopsy may *then* confirm and narrow differential. Labs are not a substitute for a thorough history and physical examination.
- C. However, if infection is suspected, cultures and polymerase chain reaction (PCR) are diagnostic and crucial for proper management.

III. Key Considerations

A. Systemic illness

1. Fevers, chills, weight loss
2. Other organ systems: lungs, GI tract, lymphadenitis / lymphangitis
3. Poor nutrition: malnourished, hyperalimentation
4. Immunocompromised
 - a. Cancer (leukemia / lymphoma)
 - b. Iatrogenic: chemotherapy, indwelling catheters
 - c. Acquired: HIV

B. Local factors

1. Recent surgery
2. Trauma

C. Laterality

1. Unilateral cases: consider HSV, VZV, CMV, toxocariasis, toxoplasmosis
 - a. IOP elevation: herpetic disease and toxoplasmosis
 - b. Sectoral iris atrophy: VZV or HSV
 - c. Corneal scarring / edema: HSV and VZV
 - d. Characteristic clinical features
2. Unilaterality is not always helpful; many noninfectious entities present unilaterally.
 - a. HLAB27+ anterior uveitis
 - b. Scleritis

D. Non-ocular clinical clues: Cutaneous

1. Vesicular and/or dermatomal rash: HSV/VZV
2. Palmar or plantar exanthematous rash: secondary syphilis
3. Erythema chronicum migrans: Lyme borreliosis

IV. Still Not Sure? Pattern Recognition of the Uveitis

- A. Toxoplasmosis: unilateral, focal retinochoroiditis
- B. VZV/HSV anterior uveitis: corneal scars, iris atrophy, IOP increased, diffuse keratic precipitates (KPs)
- C. Late-onset endophthalmitis: pseudophakia, history, capsular opacities
- D. *Aspergillus* endophthalmitis: necrotic granuloma in posterior pole and “hyaloidal hypopyon”

- E. CMV retinitis: one of four patterns – “pizza pie,” granular, brushfire, frosted branch angiitis
- F. Toxocariasis: peripheral granuloma, focal macular granuloma, diffuse endophthalmitis
- G. Bartonellosis: Focal choroiditis or neuroretinitis
- H. Necrotizing herpetic retinitis: VZV, HSV 1& 2
 - 1. Acute retinal necrosis (ARN): peripheral areas of confluent retinal necrosis, occlusive retinal arteritis, vitritis and anterior chamber reaction, immunocompetent host
 - 2. Progressive outer retinal necrosis (PORN): areas of confluent retinitis in periphery, minimal vitreous haze and inflammation, immunocompromised host (esp. HIV)
- I. Tuberculous uveitis: tuberculous serpiginoid choroiditis
- J. Hypopyon
 - 1. Congealed and immobile; think infection or HLAB27
 - 2. Mobile: consider Behçet disease
- V. Diagnostic Testing: Combine With Clinical Appearance
 - A. Serology
 - 1. Syphilis: treponemal-specific tests most useful
 - 2. *Toxoplasma*: anti-Toxoplasma antibody
 - a. IgG (recurrent)
 - b. IgM (acquired)
 - 3. QuantiFERON-TB: interferon gamma release assay (or T-Spot TB)
 - 4. Lyme serology, confirmed by western blot
 - 5. Toxocariasis: anti-toxocara IgG antibody
 - 6. Bartonellosis: anti-*Bartonella quintana* or *henselae* IgG and IgM titers
 - 7. Anti-HSV/VZV/CMV antibody titers are only helpful if negative for ruling out a diagnosis.
 - B. Cultures and Gram stains
 - 1. Vitreous and aqueous
 - 2. Useful for bacteria and fungi, not as much for viridae
 - C. PCR can be done to identify the following:
 - 1. HSV 1&2, VZV, CMV, EBV
 - 2. *Toxoplasma gondii*
 - 3. *Mycobacterium tuberculosis* (65 kDa sAg)
 - 4. *Borrelia burgdorferi* (41 kDa flagellin gene)
 - 5. *Propionibacterium* (Pa1, rPa2, rPa3 antigens)
 - 6. Fungi (28S rRNA gene)
 - 7. *Tropheryma whipplei* (16S rRNA gene)
- 8. Intraocular lymphoma (IgH gene, Myd88 L265P mutation)
- 9. Yield varies with site based on clinical presentation. Aqueous vs. vitreous
- D. Multiplex PCR and next-generation sequencing
- E. Deep genomic sequencing
- VI. Therapy
 - A. Specific antibiotic
 - 1. Essential
 - 2. Antiviral, antibacterial, antiprotozoal, etc.
 - B. Later addition of corticosteroids; essential
 - 1. Soon after antibiotic therapy initiated
 - 2. Host immune response and inflammation is more damaging than infectious agent
 - 3. *Never use corticosteroids alone for suspected infectious uveitis.* Particularly avoid intravitreal, periocular; they cannot be removed.
- VII. Still Not Sure Whether the Uveitis Is Infectious?
 - A. Do not make it *irretrievably worse. Primum non nocere.*
 - 1. Avoid regional or intraocular corticosteroids if infection is not adequately ruled out!
 - 2. Choose the most serious infectious condition and treat; systemic and/or intraocular antimicrobials
 - 3. Frequent topical corticosteroids with cycloplegics
 - 4. Eg, hypopyon in an otherwise healthy young male
 - B. Lack of response or worsening to corticosteroids suggests infectious or masquerade etiology.

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Case Presentation in Panuveitis: And the Debate Continues . . .

Marion Ronit Munk MD PhD

CASE PRESENTATION

One Saturday evening an 18-year-old white male patient presented in our emergency clinic with painless blurred vision of his left eye for 2 days. The right eye was asymptomatic. Past medical history was unremarkable, as was family history. Patient denied any medication. Alcohol intake was reported to be on a regular basis. He denied having any pets. No travel outside Europe was reported. He was emmetropic, no glasses.

He also reported that he had just entered the army 6 months previously and that he had undergone an extensive workup, including serology of various infectious diseases.

Examination

- BCVA O.D.: 20/16 without correction, O.S.: 20/40 without correction
- IOP with contacts: O.D.: 16, O.S.: 19
- Slit-lamp examination was notable for 0.5+ cells O.S., no keratic precipitates, no posterior synechiae. O.D. was unremarkable.
- O.S.: 1+ vitreous cells, no haze; O.D.: normal
- Dilated fundus exam: O.D. normal; O.S.: blurred disc margin, multifocal yellowish chorioretinal lesions temporal to the fovea; adjacent to that another diffuse, fluffy grayish / yellowish subretinal lesion

DIAGNOSIS AND TEACHING POINTS

Differential Diagnosis

- TB-associated chorioretinitis
- Ocular toxoplasmosis
- *Toxocara*
- Idiopathic CNV
- Secondary CNV after trauma / punctate inner choroidopathy (PIC) / unifocal choroiditis / multifocal choroiditis
- Syphilis
- Sarcoidosis

Workup

Laboratory

- Monocytosis, CRP normal
- Negative: fluorescent treponemal antibody-absorption test (FTA-ABs) and RPR, QuantiFERON-Gold, ACE / lysozyme / IL2 within normal range, chest X-ray
- As patient tested seronegative for toxoplasmosis 6 months earlier and evaluation of aqueous paracentesis with polymerase chain reaction (PCR) was not possible on the weekend, toxoplasmosis serology was obtained in the emergency clinic, which was found to be IgG- and IgM-positive with intermediate IgG avidity (53%).

As serologic panels suggested a recent toxoplasmosis infection, patient was started on Bactrim Forte 2/day. Two days later in clinic dilated fundus exam revealed 2 small hemorrhages adjacent to lesion. The indocyanine green angiography (ICGA) showed hypofluorescent lesions in the posterior pole O.S. Fluorescein angiography (FA) O.S. revealed a classic choroidal neovascular membrane (CNVM) temporal to the fovea. OCT O.S. showed subretinal fluid, intraretinal fluid, and a subretinal hyper-reflective material; the inner retinal layers were intact.

Final Diagnosis and Outcome

Secondary CNVM in multifocal choroiditis with panuveitis (vs. PIC)

After diagnosis, patient received intravitreal ranibizumab injections and vision improved to 20/20. Bactrim Forte was stopped.

Teaching Points

- Toxoserology and IgG avidity testing is not useful to diagnose ocular toxoplasmosis (OT), as approximately 1/3 of the world population has been exposed to this pathogen and only around 2% will present with OT. Twenty-seven percent of toxoplasmosis IgM testing can remain positive for more than 2 years or may be false positive, as in cases of an underlying rheumatological disorder.
- OT is a diagnosis based on clinical assessment. When clinical presentation is not clear, an anterior chamber or vitreous paracentesis for toxoplasmosis PCR should be performed. Some studies suggest higher sensitivity with vitreous paracentesis. Multimodal imaging, including OCT, ICGA, and FA, may help in order to rule out or verify OT.
- An IgG avidity of > 60% is indicative of older primary toxoplasmosis infection (≥ 4 months ago). However, a low toxoplasmosis IgG avidity may persist longer, due to immunodeficiency or after toxo therapy.
- The correlation between *Toxoplasma gondii* antibodies and OT is often not very strong.
- In immunocompromised patients or in patients with leukemia, serum IgG may even stay negative.
- Even if a patient converts from seronegative to a positive IgM, IgA, and IgE, as well as low IgG avidity, it is likely that the patient has had *T. gondii* infection without ocular involvement. Clinical presentation must lead diagnosis of OT.
- There are genotypic differences between infecting parasites: *T. gondii* exists in 3 main clonal lineages (strains I, II, and III). While *T. gondii* type I strains seem to dominate severe OT in immune competent patients, OT in immunocompromised patients may be caused by any parasite type. However, sexual recombination allows much larger parasite diversity, and more than 130 atypical genotypes have been characterized with differences in virulence.
- The retina rather than the choroid is the primary site of *T. gondii* infection.
- Usually OT presents with severe vitritis; only in immunocompromised patients, vitritis may be mild / missing.

Discussion of Disease

I. Ocular Toxoplasmosis

- Usually primary retinal infection with secondary granulomatous choroiditis with vitritis
- Most common cause of posterior uveitis worldwide
- May have white spots along arterioles (Kyrleis plaques)
- The diagnosis is clinical, but if unclear presentation, aqueous or vitreous paracentesis with Toxo PCR or with Goldmann-Witmer coefficient should be performed.
- Treatment targets tachyzoites in retina during active disease, without effect on *Toxoplasma* bradyzoite cyst, which remains dormant.
- Punctate outer retinal toxoplasmosis with CNVM has also been described as a variant of ocular toxoplasmosis.
- Treatment indication: Lesions that threaten macula, papillomacular bundle, or optic nerve
- Treatment possibilities
 - Oral: Bactrim Forte (trimethoprim-sulfamethoxazole), clindamycin, sulfadiazine, pyrimethamine, atovaquone, and steroids
 - Alternative, intravitreal: clindamycin \pm intravitreal dexamethasone

II. Multifocal Choroiditis with Panuveitis vs. PIC: Historical Description of PIC

- A. Onset usually between 20 and 40
- B. Predominantly myopic women
- C. More than 50% develop CNVM.
- D. Present with small yellowish lesions in posterior pole which form over weeks into punched-out atrophic scars
- E. Differential diagnosis: presumed ocular histoplasmosis syndrome, multifocal choroiditis (MFC) with panuveitis, sarcoidosis, syphilis, TB
- F. Treatment: Steroids (peri-intra and systemic), immunosuppressives; for secondary CNVM: anti-VEGF
- G. Differentiation between MFC and PIC is still a matter of discussion, as MFC extends beyond the posterior pole, with more inflammation, older age, more often treated with and more responsive to immunomodulatory therapy.

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Case Presentation in Panuveitis: A New Haircut?

Kathryn L Pepple MD PhD

CASE PRESENTATION

Clinical Presentation

35-year-old white male with 2-day history of vision loss, photophobia, and left eye pain. Past medical history positive for hypothyroidism, on levothyroxine for many years. No family history of eye disease or autoimmunity. Sexual history positive for sexual contact with multiple male and female partners in the past 3 months. No IV drug use, no foreign travel or TB exposure risk. Review of systems positive for fatigue and gradual hair loss over the past 3-4 months.

Examination

- External exam: scant eyebrow hair and patchy, thinned hair on his head
- Vision O.D. 20/40, O.S. 20/400
- O.D.: granulomatous keratic precipitates (KP), 1+ anterior chamber cell and flare, 1+ anterior vitreous cell, 0.5+ vitreous haze, vascular sheathing and superior temporal arterial occlusion
- O.S.: Granulomatous KP, 4+ cell, < 1 mm hypopyon, synechiae, 4+ vitreous haze and vitritis
- Fluorescein angiogram of the right eye: superior temporal filling delay in branch arteriole and mixed venous and arteriolar vasculitis

DIAGNOSIS AND TEACHING POINTS

Differential Diagnosis

- Infectious: TB, herpetic retinal necrosis, endogenous bacterial or fungal
- Panuveitis
- Inflammatory: Sarcoidosis, Behçet disease

Lab Evaluation, Diagnosis, Clinical Course

- + Syphilis IgG and RPR (1:128). HIV+, QuantiFERON Gold negative, chest X-ray normal
- Patient was treated with 2 weeks of IV penicillin. After 24 hours of therapy, 60-mg oral prednisone daily was started with a planned taper. Vision in the right eye declined to 20/70, but vision in the left eye recovered to 20/30 with only a mild residual epiretinal membrane.

Final Diagnosis

Syphilitic panuveitis with retinal arteriole occlusion and alopecia

Discussion of Disease

I. Introduction

- A. Syphilis must be considered in the differential of all patients with uveitis due to its protean manifestations, availability of effective treatment, and terrible consequences of inappropriate treatment with corticosteroids.
- B. Causative agent is the gram-negative spirochete *Treponema pallidum*.

II. Epidemiology

- A. After a low in 2000, incidence of syphilis infection has been increasing since 2010.
- B. Highest risk groups are men that have sex with men (MSM), and patients coinfecting with HIV.
- C. Uveitis occurs in around 5%-10% of patients with syphilis infection.
- D. Syphilis is identified as the cause of ~1% of cases presenting to tertiary uveitis care centers.

III. Clinical Features

- A. Stages of syphilis infection and the classic manifestations associated with each stage include:
 1. Primary disease: painless chancre
 2. Secondary disease: palmar plantar rash
 3. Latent: none
 4. Tertiary: Cardiac and neurosyphilis
- B. Ocular syphilis can occur at any stage, but is common during secondary syphilis.

- C. Syphilis can present with a wide range of presentations in the eye, from interstitial keratitis to anterior, intermediate, posterior, or panuveitis with granulomatous or nongranulomatous features.
- D. Findings are typically bilateral but may be asymmetric or unilateral.
- E. Other classic systemic findings can suggest the diagnosis prior to confirmatory serologic testing. This patient demonstrated patches of nonscarring alopecia with a “moth-eaten” appearance that is pathognomonic for secondary syphilis, but not common (~5% of patients).

IV. Diagnosis

- A. Treponemal-specific serologic or CSF testing, but can also be made by polymerase chain reaction from ocular samples.
- B. The CDC recommends “reverse sequence testing” with a treponemal-specific test performed first (FTA-ABS or Syphilis IgG ELISA), followed by a reflexive nontreponemal test (RPR).
- C. Lumbar puncture and CSF analysis should be used for the diagnosis and monitoring of neurosyphilis.
- D. All patients with syphilitic uveitis should be tested for HIV due to high rates of coinfection.

V. Etiology and Pathogenesis

- A. Syphilis is contracted primarily through sexual transmission of the spirochete, or maternal-to-fetal infection in utero.
- B. Uveitis develops after hematogenous spread from the primary infection.
- C. Tissue damage and ocular complications result from pathogen-induced cytotoxicity and the host immune response.
- D. Spirochete death after antibiotic treatment can generate a paradoxical worsening of ocular inflammation or a systemic inflammatory condition resembling sepsis known as the Jarisch-Herxheimer reaction.

VI. Management

- A. Antibiotic
 1. The only 2 CDC-approved treatment options for syphilitic uveitis are:
 - a. 18-24 million units IV penicillin G daily for 2 weeks
 - b. 2.4 million units IM penicillin G plus 500 mg probenecid q.i.d. for 2 weeks

2. Systemic treatment of infection with an approved neurosyphilis regimen should begin immediately upon diagnosis; comanagement with an infectious disease specialist is beneficial to ensure an appropriate regimen and compliance.

3. Sexual partners need to be tested and treated.

B. Anti-inflammatory

1. Topical corticosteroids and cycloplegia can begin immediately for anterior manifestations.
2. Oral steroid pulse and taper for severe posterior inflammation or Jarisch-Herxheimer reaction may be required.

VII. Prognosis

- A. Variable, depending on degree of inflammation and development of permanent structural complications during untreated infection, but many patients will have good visual recovery.
- B. Delayed identification and treatment and use of local corticosteroid prior to antimicrobial therapy can lead to devastating outcomes.

Selected Readings

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Case Presentation in Panuveitis: The Da Capo Blues

Laura J Kopplin MD PhD

CASE PRESENTATION

History

- 43-year-old male patient presenting with bilateral blurred vision and photophobia for 1 week
- Past ocular history: Left optic nerve edema 1 year prior; patient deferred workup, monitored with partial recovery of vision and resolution of edema
- Past medical history: diabetes mellitus type 2, dyslipidemia
- Review of symptoms unremarkable

Examination

- Vision: 20/200 O.D., 20/150 O.S.
- Right afferent pupillary defect
- Anterior segment: granulomatous keratic precipitates (KPs), posterior synechiae and trace cell O.U.
- Vitreous cells and snowballs O.U.
- Nasal macular edema O.D.
- Right optic disc edema with peripapillary hemorrhages, left optic nerve pallor
- Fluorescein angiogram
- Right optic disc leakage
- Bilateral petaloid macular leakage
- Vascular leakage O.D. > O.S.

DIAGNOSIS AND TEACHING POINTS

Differential Diagnosis

- Syphilis
- Tuberculosis
- Bartonella
- Lyme
- Sarcoidosis
- Multiple sclerosis
- Idiopathic

Workup

- Negative / normal: RPR, TPA, QuantiFERON Gold, bartonella IgM/IgG, Lyme, CBC, ALT, AST
- Elevated ACE (89)
- Chest X-ray: bilateral hilar prominence concerning for adenopathy
- Chest CT: bilateral hilar and mediastinal lymphadenopathy, bilateral noncalcified pulmonary nodules
- MRI brain / orbits: multiple white matter lesions, atrophy of the left optic nerve
- Lumbar puncture: no oligoclonal banding
- Mediastinal lymph node biopsy: lymphoid tissue with small noncaseating granulomas

Final Diagnosis and Clinical Course

Sarcoidosis anterior and intermediate uveitis with optic disc edema

- Intravenous methylprednisolone 1g x3 days
- Oral prednisone taper
- Mycophenolate 1000 mg b.i.d.
- Recent initiation of Humira due to worsening pulmonary and ocular symptoms with prednisone taper

Disease Discussion

I. Introduction

Systemic inflammatory disorder characterized by non-caseating granulomas

II. Epidemiology

- A. Ocular symptoms are presenting feature in 20%-30% of cases.
- B. Bimodal incidence: 20-30 and 50-60 years
- C. More common in Scandinavian and African American ethnicities

III. Clinical Ocular Features

- A. International Workshop on Ocular Sarcoidosis criteria
 1. Mutton-fat KPs / small granulomatous KPs / iris nodules (Koepe / Busacca)
 2. Trabecular meshwork nodules / tent-shaped peripheral anterior synechiae
 3. Vitreous snowballs / strings of pearls

4. Multiple chorioretinal peripheral lesions

5. Nodular or segmental periphlebitis (candlewax drippings)

6. Optic disc nodules / granulomas, isolated chorioidal granuloma

7. Bilaterality

B. Other ocular structures: scleritis, conjunctiva (granulomas), lacrimal gland (sicca), orbital tissue

C. Cranial neuropathies

IV. Diagnostic Testing

- A. Gold standard: biopsy identifying noncaseating granulomas
- B. Laboratory testing: ACE, lysozyme, liver enzymes, serum calcium
- C. Imaging: chest X-ray, chest CT, gallium or PET scans

V. Etiology and Pathogenesis

- A. Genetic: family history of sarcoidosis, HLA-DRB1
- B. Environmental vs. microbial antigen trigger

VI. Management

Ocular disease may drive treatment.

- A. Initial therapy with local and systemic corticosteroids
- B. Antimetabolites as first-line steroid-sparing treatment
- C. Biologic therapy (TNF inhibitors) for refractory disease

VII. Prognosis

- A. Ocular disease may not correlate with systemic activity.
- B. Worse prognosis with chronic uveitis, intermediate and posterior uveitis, development of glaucoma

Selected Readings

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Case Presentation in Panuveitis: Seeing Spots

Amde Selassie Shifera MD PhD

CASE PRESENTATION

History

- 30-year-old white female
- Chief complaints: Sudden onset bilateral blind spots, flashes, and shimmering lights of 1 day
- History of present illness
 - Approximately 4 weeks prior to presentation, patient developed an upper respiratory infection with fever, chills, and cough. Chest X-ray was negative; no rapid strep test done. Symptoms resolved without specific treatment.
 - Approximately 2 weeks prior to presentation, patient developed bilateral lower abdominal pain, flank pain, dysuria, vomiting, and diarrhea. Urinalysis and urine cultures were negative. She was treated with nitrofurantoin. Her urinary symptoms and gastrointestinal symptoms resolved after about a week (1 week prior to onset of her presenting symptoms).
- Review of systems
 - History of recurrent painful oral ulcers since her teenage years
 - History of localized swelling after venipunctures
 - No recent vaccinations
- Past medical history
 - Postural orthostatic tachycardia syndrome (POTS) diagnosed in her teenage years after she began having blackout spells; central line in place for weekly nutritional supplementation
 - Ehlers-Danlos syndrome diagnosed about 3 years prior to presentation
 - Gastroesophageal reflux disease
 - ? Mast cell disorder
 - Status post ablation for supraventricular tachycardia
 - Atlantoaxial instability

- Family and social history
 - History of scleroderma in a brother, and history of Sjögren syndrome in a sister
 - Mixed ancestry of French, Swiss, English, and Native American origins

Examination at Presentation

- Visual acuity near without correction: 20/20 and 20/20
- IOP 11/10 mmHg
- No relative afferent pupillary defect in both eyes
- Confrontational visual fields: normal for both eyes
- Anterior chamber: 1+ cells O.D. and 1+ cells O.S.
- Vitreous: 1-2+ cells O.D. and 2+ cells O.S.
- Retina: Scattered intraretinal hemorrhages and perivascular sheathing and perivascular white lesions O.U.; sheathing and white lesions largely perivenous

Ophthalmic Imaging at Presentation

- Fluorescein angiography: Blocking in both eyes from intraretinal hemorrhages
- OCT of macula
 - Vitreous opacities in both eyes
 - Very small hyper-reflective deposits in the outer retina O.U.

DIAGNOSIS AND TEACHING POINTS

Differential Diagnosis

- Case summary: Sudden onset bilateral panuveitis with very short-lasting retinal hemorrhages and perivascular sheathing / white lesions (and persistent focal outer retinal disruptions) in a patient with an antecedent upper respiratory infection and suspected antecedent urinary and gastrointestinal infection
- Possible diagnoses
 - Infectious: syphilis; infective endocarditis
 - Immunologic / inflammatory: Adamantiades-Behçet disease; sarcoidosis
 - Neoplastic: leukemia
 - Drug-induced panuveitis
 - Postinfectious panuveitis

Workup (Within 1 Month of Presentation)

- Workup for infectious diseases
 - Serology negative for HIV, West Nile virus, syphilis, toxoplasmosis, *Bartonella henselae*, *Bartonella quintana*, hepatitis (HAV, HBV, HCV), coccidioidomycosis, and Lyme disease
 - ELISPOT assay negative for tuberculosis
 - Blood bacterial and fungal cultures negative
 - Transthoracic echocardiogram negative for vegetations
- Workup for immunological / inflammatory diseases
 - Serum negative for ANA, ANCA, rheumatoid factor (RF), and cardiolipin antibody; dilute Russell viper venom test normal
 - Serum ACE and lysozyme normal
 - Serum negative for NMO IgG
 - Serum C3 normal, C4 borderline low
- CSF analysis
 - 1 WBC, 4 RBC, glucose 60, protein 39
 - Oligoclonal bands: CSF/Serum Banding Pattern 4: oligoclonal IgG bands in the CSF that are identical to those present in the corresponding serum
 - CSF negative for VDRL, Lyme antibodies, *Cryptococcus neoformans* antigen
 - CSF polymerase chain reaction negative for human herpes virus 6, cytomegalovirus, herpes simplex virus, Epstein-Barr virus, varicella zoster virus, and enterovirus
 - CSF bacterial and fungal culture negative
- Chest CT: No nodules or intrathoracic lymphadenopathy
- MRI brain and orbits negative
- MRI cervical and thoracic spine: No abnormal signal or enhancement

Final Diagnosis, Clinical Course, and Outcome

Postinfectious panuveitis, unidentified microbial etiology

- On day of presentation
 - Started on prednisolone drops while awaiting the results of investigations
- Four days after presentation
 - Intraretinal hemorrhages and retinal perivascular sheathing / white lesions completely resolved O.U.
- One week after presentation
 - Anterior chamber inflammation resolved O.U.
- One month after presentation
 - OCT macula: Focal areas of outer retinal disruption in both eyes
 - Fundus autofluorescence: Bands of increased autofluorescence that appear to radiate from the disk along the blood vessels
- Four months after presentation
 - Started on a course of oral prednisone (in light of outer retinal changes and the patient having not received systemic steroid treatment)
 - Tapered off over a period of 4.5 months
- Five months after presentation
 - Vitreous cells resolved O.U.
- Eleven months after presentation
 - Humphrey visual field (HVF) O.D.: Persistent defects in superonasal and superotemporal quadrants; mean deviation (MD) −4.65
 - HVF O.S.: Persistent defects in superotemporal and inferotemporal quadrants; MD −5.85
- 16 months after presentation
 - BCVA: 20/25 and 20/32
 - Signs of angioid streaks in both eyes on fluorescein angiography
 - No evidence of recurrence of inflammation after initial episode, despite being off immunosuppressive treatment

Teaching Points

- Consider the possibility of postinfectious uveitis; inquire for antecedent infections; antecedent infections could be subclinical.
- Systemic steroids could be considered once active infection has been ruled out or appropriate anti-microbial chemotherapy has been instituted.
- No need for long-term immunosuppressive treatment in cases with postinfectious uveitis once the acute episode has subsided.

Discussion of Disease

- Postinfectious uveitis is extremely rare.
- The very low incidence suggests that it occurs only in susceptible individuals, possibly due to a rare genetic predisposition.
- Certain syndromes of forms of postinfectious uveitis, some well-described and others presumed
 - Post-streptococcal uveitis
 - Multiple evanescent white dot syndrome (MEWDS)
 - Acute posterior multifocal placoid pigment epitheliopathy (APMPPE)
 - AMN
- Major possible pathogenic mechanisms
 - Molecular mimicry resulting in immune-mediated damage to retinal and uveal tissues as a result of adaptive immune response to inciting microbial agent
 - Direct damage of uveal and retinal tissues as a result of delayed infection by the inciting microbial agent

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Multimodal Imaging Options in Uveitis

Glenn J Jaffe MD

I. Background

A. Uveitis is a group of diseases.

1. Imaging methods must be tailored for specific disease.
2. Specific imaging is based on the specific type of uveitis, or group of conditions that are considered in the differential diagnosis, to provide maximum diagnostic information and to minimize unnecessary testing.

B. Imaging purposes

1. To establish diagnosis
2. To monitor treatment
3. To assess safety and efficacy of clinical trial interventions

II. Specific Imaging Modalities

A. Fluorescein angiography

1. Cystoid macular edema
2. White dot syndromes
3. Vogt-Koyanagi-Harada syndrome (VKH)
4. Sympathetic ophthalmia
5. Posterior scleritis
6. Placoid syphilitic uveitis
7. Acute multifocal posterior pigment epitheliopathy
8. Serpiginous choroiditis

B. Indocyanine green angiography

1. White dot syndromes
2. VKH
3. Sarcoid
4. Acute multifocal posterior pigment epitheliopathy
5. Serpiginous *choroiditis*

C. Color fundus photography

1. Monitor change in chorioretinal lesions
2. Can use ultrawide-field imaging or multi-field standard photography

D. Ultrasonography

1. Useful when media opacity precludes imaging by other methods
2. Particularly helpful for presurgical planning

E. Fundus autofluorescence

1. Helpful to monitor retinal pigment epithelial cell absence or dysfunction

2. Monitor disease activity

3. Monitor disease progression

F. OCT

1. Assess tissue thickness

- a. Retinal thickness
 - i. Cystoid macular edema
 - ii. Retinal thinning
- b. Subretinal tissue thickness
 - i. Choroidal neovascularization
 - ii. Subretinal fibrosis
- c. Choroidal thickness
 - i. VKH
 - ii. Posterior scleritis
 - iii. Sympathetic ophthalmia

2. Assess morphological characteristics

- a. Vitreoretinal interface changes
 - i. Epiretinal membrane
 - ii. Vitreomacular traction

3. Assess retinal microstructure

- a. Inner retinal layers
 - i. Retinal nerve fiber layer
 - ii. Ganglion cell complex
 - iii. Inner nuclear layer
- b. Outer retinal layers
 - i. External limiting layer
 - ii. Ellipsoid zone
 - iii. Photoreceptor outer segments

4. Determine fluid

- a. Intraretinal fluid
- b. Subretinal fluid
- c. Choroidal fluid

5. Hyper-reflective dots

6. Anterior chamber cells

7. Vitreous cells

8. OCT angiography

9. Determine vascular flow

10. Determine blood vessel location in depth slab

Case Presentation: The Tip of the Choroidal Iceberg

Francesco Pichi MD

CASE PRESENTATION

History

- 54-year-old man was referred for a second opinion for a choroidal mass in the left eye compatible with a choroidal melanoma.
- On previous examination, a B-scan showed a 6x11-mm mass with low reflectivity and fluorescein angiography showed late diffuse hyperfluorescence; on MRI the lesion was hyperintense relative to the vitreous in T1 and hypointense in T2.
- Past ocular history: unremarkable
- Past medical history: none
- Review of symptoms: noncontributory
- Family history: negative for ocular disease or malignancy

Examination

- Visual acuity: 20/25 in O.D., 20/70 in O.S.
- IOP: 10 mmHg in O.D., 11 mmHg in O.S.
- Anterior segment examination O.D.: normal
- Anterior segment examination O.S.: keratic precipitates, trace anterior chamber cells, no iris nodules or synechiae
- Fundoscopy O.D.: normal with a clear vitreous and no retinitis, choroiditis, or vasculitis
- Fundoscopy O.S.: 1+ anterior vitreous cells, cystoid macular edema, along inferior arcade yellow-greyish mass with overlying subretinal fluid

DIAGNOSIS AND TEACHING POINTS

Differential Diagnosis

Choroidal granuloma secondary to sarcoidosis, choroidal tuberculous granuloma

Ophthalmic Imaging

- Fundus autofluorescence showed speckled hyperautofluorescence of the mass, surrounded by an hyperautofluorescent halo.
- OCT confirmed the presence of cystoid macular edema; scan along the inferior arcade of O.S. showed a choroidal mass that on enhanced depth imaging (EDI) appeared hyperintense. The overlying retinal pigment epithelium was mottled, and there was hyper-reflective subretinal exudation on above the lesion. Subretinal fluid surrounded the choroidal mass.
- On indocyanine green angiography the choroidal mass was hypofluorescent with a speckled halo of hyperfluorescence.

Systemic Workup

- All initial laboratory investigations were negative.
- ACE and QuantiFERON-TB were negative.
- Chest CT did not reveal any granulomatous lung disease but showed an interrupted and asymmetric soft tissue thickening of all segments of the aorta.
- PET total body was performed and showed tibial sclerotic osseous lesions that were biopsied.

Final Diagnosis, Clinical Course, and Outcome

Choroidal infiltration and secondary uveitis in Erdheim-Chester disease

- Immunohistochemical staining of the bone lesion biopsied confirmed the diagnosis.
- The patient was sent to nephrologist to exclude kidney involvement.
- An 8-week course of prednisone was initiated, starting at 80 mg PO daily.
- After 4 months, the anterior inflammation had completely resolved as well as the cystoid macular edema.
- Upon final B-scan examination, the lesion had shrunk to 3-mm height x 8-mm width.
- Final visual acuity was 20/20 in O.S.

Disease Discussion

I. Introduction

- A. Erdheim-Chester disease (ECD) is a rare clonal neoplastic disorder that causes hyperactivation of inflammatory pathways resulting in non-Langerhans cell histiocytosis
- B. It can affect the skeletal, cardiac, pulmonary, endocrine, cutaneous, and nervous systems

II. Ocular Involvement

- A. Visual symptoms have been reported in 3% of ECD patients.
 1. Extraocular involvement (orbital) is reported in 25%-30% of osseous or CNS disease.
 2. Intraocular involvement is rare, with only 5 published case reports, 4 of which demonstrated choroidal infiltration.

III. Differential Diagnosis Through Imaging

- A. Choroidal melanoma: The initial MRI and B-scan could have pointed toward a choroidal melanoma. However, the clinical presence of intraocular inflammation and cystoid macular edema on OCT made this diagnosis unlikely.
- B. Choroidal granuloma: On EDI-OCT a choroidal granuloma usually appears hyporeflective; in ECD, the choroidal infiltration consists of histiocytes that have a hyper-reflectivity in EDI-OCT.
- C. Bilateral diffuse uveal melanocytic proliferation (BDUMP): Fundus autofluorescence can help differentiate these 2 entities; in ECD, the choroidal infiltration leads to a speckled but uniform pattern of hyperautofluorescence, compared to the “leopard-spots” pattern of hyper- and hypofluorescence in BDUMP.

IV. Management

- A. Intraocular involvement with subretinal fluid and choroidal masses shows a reasonable response to:
 1. Intravitreal anti-VEGF
 2. Systemic corticosteroids
 3. Systemic chemotherapy (cladribine, anakinra, sorafenib, interferon-alpha)
- B. The discovery of a high frequency of BRAF^{V600E} mutations in ECD has opened new targeted therapies with vemurafenib and MEK inhibitors for the systemic disease.

V. Prognosis

- A. Ocular prognosis is good if the choroidal involvement is not in the macula.
- B. Systemic prognosis is poor, with mortality rates of 43% after 32 months of follow-up.

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Case Presentation: “It Just Keeps Coming Back”

Purnima S Patel MD

CASE PRESENTATION

History

- A 30-year-old white female patient presented with a 3-month history of painless flashing lights and loss of her superior visual field in her left eye. She was treated by her local retinal physician with oral prednisone, with recurrent inflammation with taper. She also had dry eye symptoms in both eyes.
- Past medical history
 - Atrial fibrillation
 - Basal cell carcinoma (left arm)
 - Irritable bowel syndrome
- Medications
 - Mirena intrauterine device
 - Prednisone 20 mg
- Review of systems
 - Night sweats for 3 months
 - Dry mouth
- Social history: The patient previously lived in Tanzania, where she tested positive for an amoeba and typhoid fever.
- Family history
 - Factor V Leiden (maternal cousins)
 - Unknown clotting disorder (father)

DIAGNOSIS & TEACHING POINTS

Differential Diagnosis

Coagulopathy, infectious, autoimmune vasculitis

- Primarily arteritis
 - Systemic lupus erythematosus
 - Polyarteritis nodosa
 - Syphilis
 - Acute retinal necrosis
 - Progressive outer retinal necrosis
 - Idiopathic retinal vasculitis and renal
 - Chug-Strauss syndrome
- Primarily phlebitis
 - Sarcoidosis
 - Multiple sclerosis
 - Behcet disease
 - Birdshot chorioretinopathy
 - HIV paraviral syndrome
 - Eales disease
- Arteritis and phlebitis
 - Toxoplasmosis
 - Relapsing polychondritis
 - Granulomatosis with polyangiitis
 - Crohn disease
 - Frosted branch angiitis

Workup

- Hypercoagulable workup including PT, dPT, thrombin time, INR, protein C and S, antithrombin III activity, factor II antibody, factor V Leiden, fibrinogen: all negative
- Autoimmune work-up including ANA (positive, 1:320), C3/C4 (low), ANCA (myeloperoxidase antibody, serine protease 3), RF, anti ds DNA, anti-Smith, Anti-SSA/SSB, anti-RNP, anticardiolipin, lupus anticoagulant (negative), ESR and CSR normal on mycophenolate mofetil
- Infectious workup including FTA-ABS and QuantiFERON Gold negative
- Imaging
 - MRI without evidence of CNS vasculitis
 - TTE: LVEF 55%-60% (normal), mild tricuspid valve regurgitation, mild mitral valve regurgitation

Final Diagnosis and Outcome

Lupus-associated retinal vasculitis complicated by resultant branch retinal artery and vein occlusions with development of macular edema and retinal neovascularization

- This patient was diagnosed with systemic lupus erythematosus (SLE) 5 years prior to presentation to ophthalmology. She was started on hydroxychloroquine but she discontinued therapy after 1 year.
- On the ophthalmology service, the patient had active vasculitis with branch retinal artery and vein occlusions on clinical examination and fluorescein angiography. The vasculitis was active on prednisone doses lower than 20 mg; therefore, mycophenolate mofetil was started at 1 g PO b.i.d. The prednisone 20 mg was kept on board.

- However, the patient continued to have leakage. The prednisone was increased to 40 mg, and the mycophenolate mofetil to 1.5 g PO b.i.d.
- The patient developed macular edema, for which she received aflibercept injection.
- She developed retinal neovascularization, which was treated with panretinal photocoagulation with regression.
- She was tapered off oral prednisone and maintained on mycophenolate mofetil 1.5 mg b.i.d.
- Her inferotemporal leakage ultimately improved; however, she developed new leakage of the superotemporal vein which was treated with a dexamethasone implant injection and a plan to escalate immune modulatory therapy to a TNF-blocker.

Teaching Points

- Retinal vasculitis is a serious, vision-threatening manifestation of SLE requiring systemic immunosuppression.
- Retinal imaging with fluorescein angiography is essential with posterior segment involvement to diagnose and follow disease activity.
- Close monitoring is required to follow disease activity and adjust systemic immunosuppression.
- Because of the systemic nature of disease, collaboration among specialists (ophthalmologists, rheumatologists, nephrologists, neurologists, dermatologists, etc.) is often required.

Discussion of Disease

I. Introduction

Systemic lupus erythematosus (SLE) is a chronic, autoimmune, multisystem connective tissue disorder with prominent autoantibody production and relapsing and remitting clinical course.

II. Epidemiology

- A. The incidence of SLE ranges from 1.8-20 cases per 100,000 per year and is 9 times higher in women.
- B. While SLE is more common in people of African and Asian descent, thromboembolic events are more common in white patients.
- C. Average age of onset is 30.
- D. Ocular manifestations occur in up to one-third of patients.

III. Pathogenesis

- A. SLE is a complex disease process, with dysregulation of the immune system at multiple levels, including defects in the innate and adaptive immune systems, apoptotic clearance, cytokines, T-cell signaling, and B-cell immunity.

- B. Two major theories exist on how antibody overproduction causes tissue damage:
 - 1. Immune complex deposition in end-organ capillary beds activates immune / inflammatory responses.
 - 2. Autoantibodies cross-react with normal proteins, causing tissue damage.

- C. The exact mechanism of vascular occlusion is unclear; however, some suggest that immune-complex deposition, complement activation with microvascular thrombosis, and fibrinoid degeneration of the vascular wall are involved.

IV. Clinical Manifestations

- A. The spectrum of clinical manifestations can have a large range of variation from patient to patient and in the same patient over time.
- B. At least 3 different clinical presentations have been recognized:
 - 1. Chronic active
 - 2. Relapsing-remitting
 - 3. Quiescent

V. Ocular Manifestations

- A. SLE can affect the periorbital, ocular adnexa, eye, and optic nerve.
- B. The most common manifestation is keratoconjunctivitis sicca, which can be found in up to one-third of patients. The majority of patients endorse at least 1 dry eye symptom.
- C. Uveitis is uncommon as an isolated manifestation of SLE.
- D. Scleritis is rarely necrotizing but can manifest as nodular or diffuse and anterior and/or posterior. The scleritis typically presents as painful and can be potentially vision threatening, requiring prompt treatment.
- E. The most visually devastating complications occur secondary to optic nerve involvement and retinal vasculopathy.
- F. Lupus retinopathy is a common manifestation of systemic disease, occurring in up to 29% of patients. The most common pattern of retinopathy is microangiopathy similar to diabetes, with the earliest findings being cotton-wool spots and retinal hemorrhages. A strong correlation exists between the presence of retinopathy and central nervous system (CNS) disease.
- G. Retinal edema, hard exudates, microaneurysms, arterial narrowing, venous engorgement, and vascular tortuosity have all been reported.

- H. Retinal vasculitis with inflammation of the arterioles or venules tends to have poorer visual outcomes and often presents in an acute fashion. Fluorescein angiography frequently demonstrates arterial and capillary nonperfusion, leakage from neovascular fronds, and staining of the walls of involved vessels. Retinal vascular complications are typically bilateral but can present unilaterally.

- I. Central retinal vein occlusion and arterial occlusive disease have been reported.

- J. Lupus choroidopathy with exudative retinal detachments is rare. It is generally seen in patients with highly active disease, including CNS vasculitis and nephropathy, as well as uncontrolled blood pressure.

- K. Optic nerve disease is a rare manifestation of SLE, presenting as optic neuritis and ischemic optic neuropathy with vision typically worse than 20/200.

VI. Diagnosis

- A. Systemic Lupus International Collaborating Clinics classification criteria for systemic lupus erythematosus: Requires ≥ 4 criteria (at least 1 clinical and 1 immunologic) or biopsy-proven lupus nephritis with positive ANA or anti-dsDNA.
- B. Ocular involvement may be clinically silent, and so all patients with SLE should undergo careful eye examination. In addition to a complete ophthalmic examination (ocular vital signs, slit-lamp biomicroscopy, and dilated fundus examination), one or more special tests may be required, including multimodal imaging (OCT, fluorescein and/or indocyanine green angiography, autofluorescence imaging), visual field testing, and electroretinography.

VII. Management of Ocular Manifestations

- A. Significant ocular involvement including orbital inflammation, scleritis, peripheral ulcerative keratitis, retinal vasculitis, choroiditis, and optic nerve involvement warrant systemic therapy.
- B. Corticosteroids are the mainstay of acute treatment because they are fast acting and effective. High-dose steroids should only be used short term.
- C. Antimalarials such as chloroquine and, more commonly, hydroxychloroquine are highly effective in curtailing future flares with fewer side effects than alkylating agents. However, these therapies can cause irreversible vision loss secondary to drug-induced maculopathy, for which patients require screening and monitoring according to the 2016 AAO guidelines.
- D. Early and aggressive treatment is warranted for patients with retinal vasculitis given the correlation with CNS vasculitis to prevent high level of morbidity and mortality.

- E. Periocular steroid injections have a role in unilateral or asymmetric disease; however, they should be used with caution and avoided in patients with scleritis.
- F. Steroid-sparing immunosuppressive agents are used in a large proportion of patients due to treatment failure or harmful side effects of corticosteroids. Methotrexate, mycophenolate mofetil, cyclosporine A, azathioprine, chlorambucil, and cyclophosphamide have all been used with varying degrees of success.
- G. Recently, newer biologic agents targeting specific molecules in B- and T-cell activation have been employed with clinical improvement.

VIII. Prognosis

- A. Visual prognosis is dependent on ocular manifestations, severity, and level of disease activity.
- B. In cases of retinal vasculitis, permanent loss of visual acuity is likely due to retinal ischemia.

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Case Presentation: Should We Stop the Leak?

Dilraj Grewal MD

CASE PRESENTATION

History

- 45-year-old Indian male photographer referred for floaters and possible “floaterectomy”
- Past medical history:
 - Sarcoidosis diagnosed by skin biopsy 5 years ago; no other organ involvement
 - Degenerative disc disease
- Past ocular history: Has had cryo for retinal tear previously
- Review of systems: Generally negative. No neurological symptoms.
- Medications: Doxycycline for sarcoidosis

Examination

- VA 20/25 O.D. and 20/25 O.S.
- IOP 13 and 14 mmHg
- Anterior chamber: Deep and quiet
- Lens: 1+ nuclear sclerosis and mild posterior subcapsular cataract both eyes
- Vitreous cavity: 1+ anterior vitreous cell, no vitreous haze
- Fundus examination with few vitreous opacities, inferior snowballs and snowbanks in both eyes, cryo scar left eye

DIAGNOSIS AND TEACHING POINTS

Case Discussion

- Imaging
 - OCT: ERM in both eyes and no cystoid macular edema (CME) in either eye
 - Wide field fluorescein angiography (WFFA): Perivascular leakage and late disc leakage both eyes, no peripheral ischemia
- Differential diagnosis: Sarcoid, TB, idiopathic causes, syphilis
- Workup: ACE elevated to 115, interferon-gamma release assay (IGRA) for TB, syphilis immunoglobulin G, anti-neutrophil cytoplasmic antibody negative

Clinical Course

- Month 4: Examination unchanged but slightly increased perivascular leakage on WFFA. OCT, without cystoid macular edema (CME). Vision unchanged. Discussed treatment initiation but he refused.
- Month 8: Clinical examination unchanged but further increased perivascular leak on WFFA. Symptomatically he had persistent floaters. Now with CME by OCT in the right eye. He still continues to defer treatment.

Discussion of Imaging Findings

- Peripheral retinal vascular leakage on WFFA reveals increased pathology and leakage outside the ETDRS standard fields compared with conventional angiography.
- Peripheral vascular leakage correlates with degree of inflammation and presence of angiographic CME.

- We typically rely on morphologic and functional findings to guide treatment decisions, and it still remains unclear whether presence of peripheral vascular leakage alone necessitates treatment initiation or augmentation.
- While there is no standardized definition for activity determined by leakage alone, leakage may act as a surrogate marker for inflammation and influence the grading of disease.
- There is ongoing work on developing quantitative metrics for retinal vasculitis and perivascular leakage that may help us better predict long-term visual and clinical outcomes and better guide therapeutic decisions.

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Case Presentation: A Pregnancy Complicated by Multiples

Ann-Marie Lobo MD

CASE PRESENTATION

History

- History of present illness: 30-year-old woman who was 14 weeks pregnant noted sudden vision loss in her right eye followed by her left eye 4 weeks after a flu-like illness and a urinary tract infection treated with ciprofloxacin.
- Past medical history: pre-eclampsia with prior pregnancy, Bells palsy
- Ocular history: high myopia
- Medications: multivitamins
- Review of systems: headaches
- Visual acuity: 20/200 O.U.
- No afferent pupillary defect
- Slit lamp exam: normal
- Mild vitreous cells O.U.
- Bilateral hypopigmented chorioretinal lesions in posterior pole
- OCT: subretinal elevation / fluid O.U. with hyper-reflectivity and thickening of retinal pigment epithelium (RPE)

DIAGNOSIS AND TEACHING POINTS

Differential Diagnosis

- Multifocal choroiditis / punctate inner choroidopathy
- Acute posterior multifocal placoid pigment epitheliopathy
- Macular serpiginous
- Presumed ocular histoplasmosis syndrome
- Syphilitic posterior placoid chorioretinitis
- TB-associated serpiginous choroiditis

Workup

- Normal: FTA-Abs, QuantiFERON-TB Gold, rubella, HIV, VZV, ACE, lysozyme, toxoplasma IgM/IgG
- Referred to neurology for evaluation of headaches: normal MRI/MRA and LP
- Referred to uveitis: subsequent evaluation with bilateral macular scars
- Fundus autofluorescence: hypoautofluorescent dots with surrounding hyperautofluorescent rim
- OCT angiography (OCT-A): choroidal neovascularization O.U.

Final Diagnosis

Multifocal choroiditis (MFC) with choroidal neovascular membranes O.U.

Clinical Course, and Outcome

- Started on systemic corticosteroids, discussed anti-VEGF therapy but decision made to postpone until after delivery
- Intravitreal bevacizumab following delivery
- Immunosuppressive therapy

Disease Discussion: Imaging in MFC

I. Introduction

- A. MFC is an inflammatory chorioretinal disease of unknown etiology.
- B. Most often described in young, myopic women
- C. Can be associated with development of CNV in up to 75% of patients
- D. Visual prognosis most often depends on development of CNV and optic atrophy.

II. Multimodal Imaging in the Evaluation of MFC

- A. Spectral domain OCT: subretinal / sub-RPE elevation with hyperreflectivity of subretinal space and disruption of ellipsoid zone
- B. Autofluorescence: hyperautofluorescent ring around hypoautofluorescent center

C. OCT-A

1. Network of hyper-reflective vessels on outer retinal and choriocapillaris images
2. May not be able to distinguish between clinically active and inactive CNV lesions

D. Advantages of multimodal imaging in MFC

1. Noninvasive
2. May help to distinguish between inflammatory lesions and CNV when compared to conventional fluorescein angiography

III. Treatment of MFC and Inflammatory CNV

- A. Anti-VEGF therapy: Use in pregnancy has been reported, but no definitive guidelines available and potential for maternal / fetal complications (spontaneous abortion, pre-eclampsia) still needs to be considered.
- B. Corticosteroids
- C. Steroid-sparing immunosuppression

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Cataract Surgery in Uveitis

J P Dunn MD

I. Preoperative Preparation

- A. Strict control of uveitis for ≥ 3 months
 - 1. Corticosteroids
 - a. Topical
 - b. Periocular
 - c. Intravitreal
 - d. Sustained release
 - e. Systemic
 - 2. Immunosuppressive agents
- B. Resolution of macular edema
 - 1. Control of uveitis
 - 2. Intravitreal anti-VEGF agents
 - 3. Regional corticosteroids: Intravitreal are more effective than periocular.
- C. Rule out other causes of decreased vision if possible:
 - 1. Epiretinal membrane
 - 2. Glaucoma
 - 3. Irregular astigmatism
 - 4. Optic neuropathy
 - 5. Retinal atrophy / scarring
 - 6. Retinal scarring / epiretinal membrane peel
 - 7. Retinal ischemia
- D. Consideration of combined surgery
 - 1. Pars plana vitrectomy
 - 2. Glaucoma surgery
 - 3. Chelation of band keratopathy
- E. Informed consent: realistic expectations for both patient and surgeon

II. Intraoperative Considerations

- A. Achieving adequate pupillary dilation
 - 1. Pharmacologic
 - 2. Viscosynechiolysis
 - 3. Push-pull techniques
 - 4. Iris hooks
 - 5. Pupil expanders
- B. Minimize intraocular inflammation
 - 1. Iris trauma from phaco tip
 - 2. Possible adverse effects of femtolaser capsulotomy
 - 3. Thorough removal of lens cortex / nuclear fragments
 - 4. Thorough removal of viscoelastic
- C. Use of capsular staining
 - 1. Trypan blue is very helpful in most cases.
 - 2. Requires adequately dilated pupil
 - 3. Staining under the viscoelastic
- D. Perioperative anti-inflammatory / vascular stabilizing therapy
 - 1. Intravenous corticosteroids
 - 2. Subtenon triamcinolone acetonide (TA) at end of case
 - 3. Intravitreal preservative-free TA at end of case
 - 4. Intravitreal anti-VEGF therapy

III. Postoperative Care

- A. Aggressive anti-inflammatory therapy
 - 1. Topical corticosteroids
 - 2. Topical NSAIDs to reduce pseudophakic cystoid macular edema
 - 3. Topical cycloplegics to prevent recurrent synechiae
- B. Taper oral corticosteroids carefully.
- C. Maintain immunosuppression as necessary.
- D. Monitor fellow eye in bilateral cases.

Glaucoma Surgery in Uveitis

Keith Barton MBBCh

Background

IOP elevation is common in uveitis (10%-20% of cases in subspecialty uveitis clinics). Multiple mechanisms provide a diagnostic challenge. IOP elevation may vary from an intermittent, short-term response to corticosteroid usage to acute angle closure with severe irreversible visual loss.^{1,2}

Roughly 10% of patients have chronic IOP elevation, among whom a corticosteroid response is responsible in less than 20%.³ Surgical intervention is more frequently required than in primary glaucoma, and the swings in pressure that result tend to be much greater.

When to Consider Surgery? How to Identify the Patient Who Is Likely to Need Surgery

IOP elevation in patients with uveitis is often episodic, leading to uncertainty about when to intervene surgically. The requirement for surgical intervention varies, from patients with very high IOP and virtually normal optic discs to those with low IOP but advancing field loss.

Those with lower IOP levels and progressive glaucomatous disc and field damage represent no diagnostic dilemma. The challenge is in deciding when to intervene in those with significant episodic IOP elevation without significant optic disc cupping.

In general, three parameters can be used to help predict the likely future requirement for surgery: the angle appearance, optic disc asymmetry, and the type of uveitis.

Surgical Intervention

The Secluded Pupil

Secondary acute angle closure from a secluded pupil is very different from that in primary angle-closure glaucoma. Laser iridotomy is often inadequate or even counterproductive, and incisional surgery is frequently required.⁴ There are a number of methods for performing surgical iridectomy, and these may be combined with viscogoniolysis.

Open Angle or Chronic Angle Closure

Both open angle and chronic angle closure are managed using options similar to those used in primary glaucomas, though the IOP response is often different and the outcomes are influenced by the chronic inflammatory disease. Preoperative and postoperative inflammation must also be managed.

Trabeculectomies, aqueous shunt, and minimally invasive glaucoma surgery (MIGS) procedures all perform differently in uveitis, and these will be compared and contrasted.^{1,2,5}

Trabeculectomy performed in patients with uveitis has a higher risk of both early hypotony and late failure. Early hypotony may be prevented by tight suturing of the scleral flap

and selective postoperative suture release, whereas late failure is more easily avoided by careful case selection. In general, in the author's practice, trabeculectomy may be very successful when restricted to those with good preoperative inflammatory control, no previous incisional surgery, and relatively short-term use of glaucoma medication. The factor that most influences trabeculectomy success appears to be lens status, when high failure risk patients such as those with juvenile idiopathic arthritis (JIA) or neovascularization are excluded.

Aqueous shunts work well in uveitis, to the extent that case selection for the type of shunt is also important. In those with chronic severe uveitis from early childhood, the author still prefers to use a single-plate Molteno implant, finding that other, larger-plate implants may result in chronic hypotony. On the other hand, many of those with less severe, but chronic uveitis in adulthood require a Baerveldt 101-350, the Ahmed valve being insufficient to achieve long-term pressure control. Uveitis have been included in large, randomized clinical trials of aqueous shunts (9% of the combined Ahmed vs. Baerveldt and Ahmed Baerveldt comparison studies), but the numbers have been insufficient for stand-alone analysis.⁶ Prior studies have shown good long-term success of shunts in uveitis.⁷

In general, the newer devices offer more modest IOP-lowering efficacy than traditional surgery, though the author has found a useful role for Xen and InnFocus MicroShunt in patients who are at low risk of scarring, but with high IOP levels and mild glaucomatous optic disc damage.⁵

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Diagnostic Fluid, Tissue Sampling, and Processing in Uveitis

Thomas Albini MD

Anterior Chamber or Vitreous Fluid Analysis

- Polymerase chain reaction (PCR) for herpes simplex 1 (HSV1), HSV2, varicella zoster virus (VZV), and cytomegalovirus (CMV) has a high sensitivity and specificity from either anterior or posterior chamber fluid and is useful for definitive diagnosis of viral retinitis when the diagnosis cannot be made based on clinical presentation.
- PCR for toxoplasmosis has higher sensitivity from vitreous than from anterior chamber fluid. This can be essential in diagnosing atypical toxoplasmosis. On rare occasions patients may have reactivation of toxoplasmosis in the setting of concurrent infection with another organism. PCR is essential in identifying this phenomenon.
- Syphilis and toxocariasis antibody can be detected in intraocular fluid, although the sensitivity and specificity of this test is not known. Almost always the diagnosis of syphilis can be made on the basis of clinical findings and treponemal and nontreponemal serologic tests.
- PCR for *Mycobacterium tuberculosis* from intraocular fluids is very specific but not sensitive. Optimal primers vary according to geography, and optimal PCR strategy has not been established.
- Pan-primers for bacterial, fungal, and/or mycobacterial species have been used on ocular fluids and provide a faster time to diagnosis. The tests are not well studied and difficult to obtain.
- Culture of intraocular fluids remains the gold standard for diagnosis of endophthalmitis. Almost always vitreous specimens are obtained.
- Cytokine analysis for IL-6 and IL-10 can help distinguish lymphoma (high IL-10 to IL-6 ratio) from other inflammatory disease (low IL-10 to IL-6 ratio).
- MYD88 variant is increasingly used as a biomarker of primary intraocular lymphoma.
- Gene rearrangement can identify monoclonal populations of lymphocytes and suggest lymphoma.
- Flow cytometry can identify atypical cell populations, such as high prevalence of B-cells, or kappa- or gamma-restricted B-cells.
- Cytology with PAP stain or H&E stain. Cytology remains the gold standard for the biopsy of lymphoma. Specimens can be obtained from the anterior chamber, vitreous cavity, or subretinal fluid. Selection of fluid source needs to balance the surgical risks of the procedure with the chance of identifying malignant cells in a particular anatomic location in specific patients. Thorough preoperative assessment including multimodality imaging should be used to identify the exact location of cellular infiltrate.

Table 1. Special Stains Employed in Evaluation of Chorioretinal Biopsy

Stain	Molecular Target and Characteristics	Suspected Diagnosis and Comments
Gram	Cell wall peptidoglycan	Bacteria, <i>Candida</i> , <i>Cryptococcus</i>
Acridine orange	DNA and RNA	Rapid detection of bacteria, <i>Mycobacteria</i> , and fungi in normally sterile specimens
<ul style="list-style-type: none"> • Ziehl-Neelsen stain • Fite's stain • Auramine-rhodamine stain 	<ul style="list-style-type: none"> • Mycolic acid – acid fast • Mycolic acid – acid fast • Fluorescent cell wall – reddish yellow 	<ul style="list-style-type: none"> • Mycobacteria stain bright red • Weak acid fast • Requires fluorescence microscope
Geimsa	DNA	Leukocytes, bacteria (differentially stains human and bacterial chromatin)
Grocott's methenamine silver (GMS)	Cell wall polysaccharide components	Fungi (living and dead). <i>Pneumocystis jirovecii</i>
Periodic acid-Schiff	Glycogen and other polysaccharides	<ul style="list-style-type: none"> • Living fungi stain magenta. • Macrophages in Whipple disease
Warthin–Starry stain	Unknown target	<ul style="list-style-type: none"> • <i>Bartonella</i> • <i>Borrelia</i> • <i>Helicobacteria</i> • <i>Legionella</i> • <i>Treponema pallidum</i>

(table continues on next page)

Table 1. Special Stains Employed in Evaluation of Chorioretinal Biopsy (contined)

Stain	Molecular Target and Characteristics	Suspected Diagnosis and Comments
Calcofluor white (CFW)	Cellulose and chitin	Fungi and parasitic organisms
Von Kossa stain	Phosphate	Dystrophic calcification
S-100 antigen	Calcium binding protein	Schwannomas, ependymomas, astroglomas, almost all benign and malignant melanomas and their metastases
HMB-45 antigen	Neuraminidase sensitive oligosaccharide side chain of a glycoconjugate present in immature melanocytes	Melanocytic tumors
Melan-A antigen	Transmembrane protein expressed in skin, retina, cultured melanocytes, melanomas and angiomyolipomas	Melanoma
Leukocyte common antigen CD45	Transmembrane protein tyrosine phosphatase	All leukocytes
T-lymphocyte antigen CD2, CD3, CD5, CD7	Surface glycoprotein	Pan T cells
T-lymphocyte antigen CD4	Surface glycoprotein	<ul style="list-style-type: none"> T helper cells, monocytes, macrophages, and dendritic cells. Mycosis fungoides
T-lymphocyte antigen CD8	Surface glycoprotein	Cytotoxic T-cells, natural killer cells, and dendritic cells
B-lymphocyte antigen CD19	Cell surface molecule that assembles with the antigen receptor of B lymphocytes	Pan B cells
B-lymphocyte antigen CD20	Cell surface molecule involved with development and differentiation of B-cells into plasma cells. Progressively increased concentration with B-cell maturity.	<ul style="list-style-type: none"> B cells, B cell lymphomas Target molecule for anti-CD20 monoclonal antibody treatment of lymphoma (rituximab)
B-lymphocyte antigen CD22	Sugar binding transmembrane protein, which specifically binds sialic acid with immunoglobulin. CD22 functions as an inhibitory receptor for B cell receptor (BCR) signalling.	B cells, early B cells, B cell lymphomas
<ul style="list-style-type: none"> MUM 1 CD138 	Plasma cell markers	Plasma cells
<ul style="list-style-type: none"> Kappa Lambda 	Immunoglobulin light chains	<ul style="list-style-type: none"> Monoclonal lymphoid populations Normal K:L ratio 1.1
Polyclonal antibodies	Specific infectious targets	<ul style="list-style-type: none"> Toxoplasmosis, Strain 56 Cytomegalovirus, immediate early antigen and early antigen Herpes simplex virus, multiple antigens Varicella zoster virus, multiple antigens
Monoclonal antibodies, CDC ¹	Specific infectious targets	<i>Cryptococcus</i>
Cytokeratin stains	Keratin containing intermediate filaments found in the intracytoplasmic cytoskeleton of epithelial tissue	Metastatic carcinoma

Biopsy of Retina, Choroid, and/or Iris

Biopsies should always be preplanned following multimodality imaging to determine the most likely source of diagnostic tissue. Focused planning is required. What tissue will be biopsied? Which tests will be performed? How will this information contribute to the patient's care? Multiple biopsy sites can increase the diagnostic yield in some cases.

The pathologist is ideally one who is qualified as an ophthalmic specialist. The main reason to consult with the pathologist beforehand is to make sure that the specimen is handled properly, both by the surgeon, who must decide to submit the specimen fresh or in a variety of fixatives depending on the planned analyses, and by the pathologist. Some fixatives, such as 2.5% glutaraldehyde and 2% paraformaldehyde for electron microscopy, must be made fresh. Fine-needle aspiration biopsy may benefit from prior arrangement so that the cytopathologist can review the specimen intraoperatively to confirm that adequate material has been obtained. Finally, warning a pathologist that his or her lab will be receiving a minute specimen may help prevent mishandling.

Ordinarily, vitreous specimens for diagnosis of intraocular lymphoma are unfixed. Fine needle biopsy specimens of other tumors are also submitted unfixed. Diagnostic biopsies of retina or choroid are generally fixed preparatory to histologic examination. The vast majority of the time, fixation in formalin is adequate as slides can be de-paraffinized and stained with immunohistochemical reagents or subjected to in situ hybridization. Formalin-fixed tissue is probably the most versatile way to preserve a small specimen. It is less damaging to cell surface proteins than 95% ethyl alcohol, which would negate further staining with immunohistochemical reagents. Glutaraldehyde and paraformaldehyde is used if electron microscopy is planned, but situations in which it is necessary are few, mainly confirmations of novel infections.

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Primary Mortality Results of the SITE-1,2 Cohort Study

John H Kempen MD

NOTES

Fluocinolone Acetonide Intravitreal Implant: Results Across Clinical Trials

Quan Dong Nguyen MD MSc

Introduction

Glucocorticoids have been used to manage ocular inflammatory disease since the 1950s and, along with systemic immunosuppression, are the mainstay of noninfectious uveitis treatment. A product that is relatively simple to administer in office and delivers corticosteroid directly to the intended site of action for an extended period may offer significant treatment benefits.

Clinical Trials

Two double masked, randomized, prospective, sham-controlled trials were designed to test the hypothesis that a single injection of a fluocinolone acetonide intravitreal insert (FAi) capable of delivering daily microdoses of drug for 3 years can reduce the proportion of patients that have a recurrence of noninfectious posterior uveitis.

- Trial 1: PSV-SAI-001, *N* = 129 at 33 multinational sites
- Trial 2: PSV-SAI-005, *N* = 153 at 15 Indian sites

12-Month Efficacy Outcomes

Uveitis Recurrence

Twelve-month uveitis recurrence rates were significantly reduced in both trials. Trial 001 recurrence rates were 37.9% (FAi) and 97.6% (sham). Trial 005 recurrence rates were 36.6% (FAi) and 71.2% (sham).

Adjunctive Medications to Treat Ocular Inflammation

Eyes in the sham treatment group were more likely to receive rescue treatment for intraocular inflammation and were more likely to require multiple adjunctive treatments during the first 12 months of each trial.

Macular Edema

Resolution of macular edema was reported at 12 months in approximately 70% of eyes randomized to FAi treatment vs. 50% of eyes randomized to sham treatment.

Central foveal thickness was reduced in both groups. Rapid reduction was observed in FAi-treated eyes, particularly in Study 001, where baseline foveal thickness was greater.

BCVA

At 12 months, both groups showed approximately 1-line improvement in BCVA.

Conditional post hoc analyses showed that BCVA improvements in the FAi-treated eyes were particularly evident in eyes that were enrolled with greater amounts of macular edema and vitreous haze.

Evaluating BCVA at the last visit before ophthalmic anti-inflammatory rescue treatment demonstrates the impact that the multiple adjunctive treatments in the sham group had on 12-month BCVA.

Twelve-Month Safety Outcomes

IOP

Mean IOP was similar in the 2 treatment groups. Medication to lower IOP was used by approximately 25% of subjects in both treatment groups in Study 001 and by approximately 50% of subjects in both treatment groups in Study 005.

Cataract

Cataract extractions were more frequent in FAi-treated eyes in both studies. The difference in Study 001 (33% vs. 5%) was more pronounced than in Study 005 (18% vs. 9%).

Other Adverse Events

Other adverse events were generally reported at rates lower than 10% in both groups. Cystoid macular edema was reported more frequently in the sham treatment group, and transient hypotony was reported more frequently in the FAi treatment group.

Conclusion

These results indicate that long-term continuous control of noninfectious posterior uveitis can be accomplished with an office-based intravitreal injection. Side effects are consistent with those expected from a corticosteroid treatment and are manageable with standard therapies.

The studies will continue for an additional 2 years.

Late Breaking Developments: POINT Trial Results

Jennifer E Thorne MD PhD

NOTES

[illegible]

Suprachoroidal Delivery of CLS-TA for Uveitic Macular Edema: Results of the Phase 3 PEACHTREE Trial

Rahul N Khurana MD

I. Study Overview

A. Significance of uveitic macular edema

1. The leading cause of vision loss in uveitis
2. Affects nearly 40% of uveitis patients
3. May persist despite adequate control of uveitis

B. Design

Phase 3, randomized, masked, sham-controlled, multicenter study to assess the safety and efficacy of 4 mg of CLS-TA administered via suprachoroidal injection compared to a sham control in the treatment of subjects with macular edema associated with uveitis

C. Inclusion and exclusion criteria

1. Key inclusion

- a. Noninfectious uveitis: any etiology / disease diagnosis within uveitis
- b. Any geographic location including anterior, intermediate, posterior, and pan
- c. Diagnosis of macular edema due to uveitis with central subfield thickness (CST) of at least 300 microns
- d. BCVA: ≥ 5 ETDRS letters (20/800) and ≤ 70 ETDRS read (20/40) in the study eye
- e. Any level of inflammatory activity in evaluating anterior chamber cells or flare and vitreous haze on the SUN scales, that is, active or controlled disease

2. Key exclusion

- a. Any active ocular disease or infection in the study eye other than uveitis
- b. IOP >22 mmHg or uncontrolled glaucoma

II. Efficacy Results

A. Mean change in BCVA at Week 24:

Primary endpoint of this study was met, indicating a higher proportion of subjects in the CLS-TA arm (46.9%) who gained ≥ 15 EDTRS letters in BCVA from baseline compared to the control arm (15.6%). This proportion was statistically significant ($P < .001$), indicating that subjects treated with suprachoroidal CLS-TA had greater improvement in vision from baseline compared to subjects in the control arm undergoing sham procedures.

B. Mean change in CST at Week 24:

The secondary endpoint of mean change from baseline in CST at Week 24 showed a mean reduction from baseline of $152.6 \mu\text{m}$ in CST at Week 24 in CLS-TA arm compared to a $17.9 \mu\text{m}$ mean reduction in the Control arm, which was statistically significant ($P < .001$).

C. $\geq 20\%$ reduction in CST at Week 24:

At Week 24, a $\geq 20\%$ reduction in excess CST from baseline was observed in a higher proportion of subjects in the CLS-TA arm (57%) compared to the control arm (13%).

D. Resolution in CST:

At each monthly visit from baseline, a higher percentage of subjects in the CLS-TA arm showed resolution in their retinal thickness (<300 microns) compared to the control arm, with 57% in the CLS-TA arm vs. 9% in the control arm at Week 24.

E. Resolution in signs of inflammation

In addition to evaluating changes in BCVA and in macular edema at each visit, the PEACHTREE trial enrolled subjects with any level of inflammation on the 3 SUN scales, namely, anterior chamber cells, anterior chamber flare, and vitreous haze. For example, over approximately 70% or more of the subjects had vitreous haze in each of the arms of this trial. Signs of inflammation were evaluated at every visit, including at the Week 24 primary endpoint visit. The data suggest that suprachoroidal CLS-TA provides outcomes that could be useful.

1. Percentage of subjects with resolution (scores of zero) of anterior chamber cells at Week 24 was 72% in the CLS-TA arm and 17% in the control arm.
2. Percentage of subjects with resolution (scores of zero) of anterior chamber flare at Week 24 was 74% in the CLS-TA arm and 20% in the control arm.
3. Percentage of subjects with resolution (scores of zero) of vitreous haze at Week 24 was 69% in the CLS-TA arm and 23% in the sham arm.

III. Safety Results

A. Serious adverse events (SAEs): Three SAEs were reported, but none were considered related.

1. Sialadenitis
2. Post-traumatic compression fracture of first lumbar vertebra body
3. Retinal detachment

B. Ocular AEs $\geq 5\%$ in the study eye include the following:

1. Cataracts
2. Cystoid macular edema / macular edema
3. Eye pain / injection site pain
4. Ocular hypertension / IOP increased
5. Uveitis
6. Vitreous detachment

C. Details of interest from two of these AEs, IOP and cataracts

1. Elevated IOP

- a. Total incidence of IOP AEs related to corticosteroid (includes increased IOP, ocular hypertension, and glaucoma AEs): 13.1%, with 11.5% in the CLS-TA arm and 15.6% in the control (sham) arm
- b. All AEs in the control arm occurred following rescue corticosteroid treatment.
- c. All but 1 subject in the CLS-TA arm were given IOP-lowering topical drops.
- d. No surgeries were associated with any AEs of elevated IOP.

2. Cataracts

The progression of cataracts (includes cataracts, cataracts subcapsular, and cataracts nuclear) was comparable in both arms, with 7.3% in the CLS-TA arm and 6.3% in the sham arm.

Reflections on a Career in Uveitis: Where We Have Been and the View Forward

C Stephen Foster MD

- I. Herbs
- II. Fever Therapy
- III. Leeches and Blood-letting
- IV. Cycloplegia (1840)
- V. Corticosteroids (1949)
- VI. Nitrogen Mustard (1950, Roda-Perez)
- VII. Methotrexate (1966, Wong)
- VIII. Other Antimetabolites and Alkylating Agents (1970 Onward)
- IX. Biologic Response Modifiers (2001)
- X. Tolerance / Regulatory T Lymphocytes (2018)

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