CME Monograph

GLOBAL APPROACHES FOR MANAGING NONINFECTIOUS UVEITIS OF THE POSTERIOR SEGMENT

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This continuing medical education activity is jointly provided by **New York Eye and Ear Infirmary of Mount Sinai** and MedEdicus LLC.

New York Eye and Ear Infirmary of Mount Sinai

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This continuing medical education (CME) activity captures content from a CME symposium held on November 10, 2017, in New Orleans, Louisiana.

ACTIVITY DESCRIPTION

This monograph provides an update on the differential diagnosis of noninfectious uveitis of the posterior segment (NIU-PS), current and emerging treatments for patients with NIU-PS that can be managed by the retina specialist who is not a uveitis specialist, and NIU-PS cases that need referral to a uveitis specialist.

TARGET AUDIENCE

This educational activity is intended for European, Asia/Pacific, and US ophthalmologists caring for patients with noninfectious uveitis of the posterior segment.

LEARNING OBJECTIVES

Upon completion of this activity, participants will be better able to:

- Use diagnostic assessments to differentiate between infectious and noninfectious uveitis of the posterior segment
- Describe which patients with noninfectious uveitis of the posterior segment would be referred to a uveitis specialist
- Review evidence-based systemic treatments for patients with noninfectious posterior uveitis
- Apply information on the mechanism of action and safety and efficacy data for emerging agents in clinical trials for local therapy to the management of patients with noninfectious uveitis of the posterior segment

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INTRODUCTION

Uveitis involving the posterior segment is a collection of infectious and noninfectious diseases that can be limited to the eye or that represent a manifestation of a systemic disease. The approach to management depends on the specific diagnosis established using information collected through clinical history, ophthalmic examination, imaging, and selective use of laboratory testing.

The following case-based discussions of actual patient scenarios present considerations for the diagnosis and management of uveitis involving the posterior segment.

CASE 1. DIAGNOSTIC CHALLENGE: INFECTIOUS OR NONINFECTIOUS UVEITIS?

From the Files of Bahram Bodaghi, MD, PhD

A 42-year-old Italian female presented on a Friday afternoon. She had a history of bilateral posterior white dot syndrome and extensive choroiditis in the right eye, for which she was receiving oral corticosteroids and cyclosporine A. She was referred by her treating ophthalmologist with a request to switch her therapy to adalimumab for relapsing uveitis in the left eye.

Fundus imaging showed extensive choroiditis in the right eye ***(Figure 1A)****. Fundus and red-free fundus images from the left eye showed a new lesion close to the fovea that was consistent with the patient's symptoms of visual loss and metamorphopsia* ***(Figures 1C and 1D)****. Fluorescein angiography (FA) disclosed an active lesion in its distal part, close to the fovea* ***(Figure 1F)****.*

Discussion

This case represents a true emergency situation because of the proximity of the lesion to the fovea, but first, it is necessary to rule out an infection or masquerade syndrome before initiating therapy. Most cases of infectious uveitis can be diagnosed on the basis of clinical appearance.[1] For example, retinal necrosis, especially if it is unilateral in an immuno-competent patient or bilateral in an immunosuppressed patient, should raise suspicion for an infectious disease: herpetic retinitis, syphilis, and toxoplasmosis would be at the top of the list. Placoid retinal lesions are pathognomonic of syphilis. Iris transillumination, reduced corneal sensation, and intraocular pressure (IOP) elevation are signs of herpetic uveitis, but might be absent in herpetic retinitis. Tuberculosis can cause a serpiginous-like chorioretinopathy.

Lim and colleagues used laser confocal microscopy to categorize keratic precipitates (KPs) according to morphologic characteristics and reported that cluster and nodular presentations were associated with active infectious

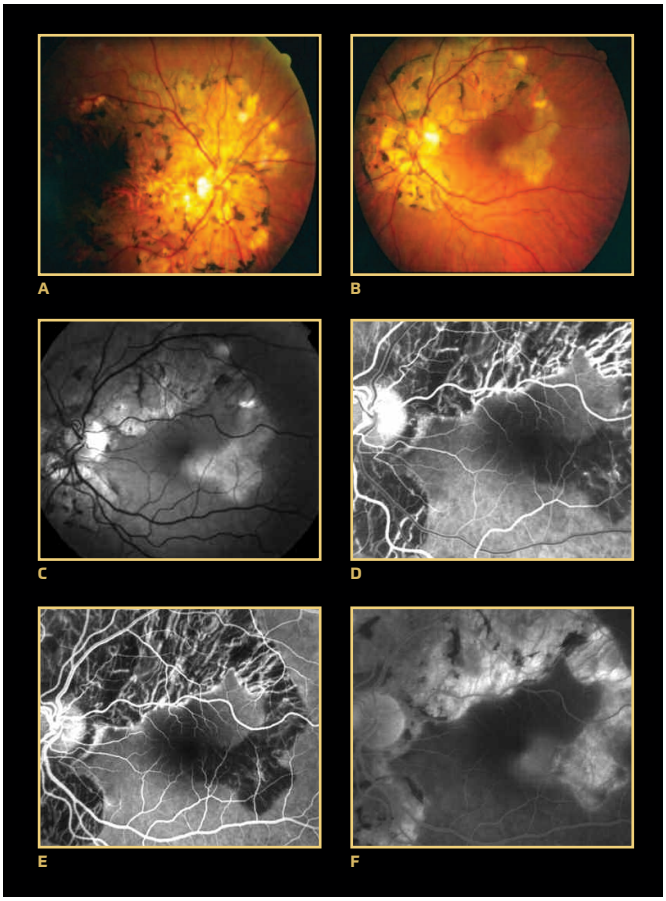

Figure 1. (A-C) Fundus and red-free photographs showing extensive serpiginous choroiditis in both eyes, with a creamy active macular lesion (OS). (D-F) Fluorescein angiography discloses an active lesion OS, with absence of border pigmentation and progressive leakage of the distal part, close to the fovea.

uveitis.[2] Further study is needed to confirm this initial report, and confocal microscopy is not widely available. Diffuse KPs, however, suggest herpetic uveitis, and a granulomatous unilateral pattern of KPs with a focal lesion in the back of the eye is strongly suspicious of toxoplasmosis.[2,3]

In this case, the presence of areas of pigment alteration with atrophy is characteristic of serpiginous choroiditis, which should raise suspicion for tuberculosis.[1] Other conditions to consider in the differential diagnosis include acute posterior multifocal placoid pigment epitheliopathy (APMPPE) because it can also cause bilateral chorioretinal scarring, and both ampiginous choroidopathy and relentless placoid chorioretinitis or ampiginous choroidopathy because of the progressive nature of the disease.

Conventionally, no treatment is given for APMPPE, but the possibility for progression into the more severe serpiginous-like form must also be considered, particularly in patients in the developing world. It has been observed during the follow-up of patients diagnosed with APMPPE that, in some cases, the multiple lesions that are present coalesce to form a large scar resembling the scar seen in serpiginous choroiditis. Sarcoidosis is also included in the differential diagnosis because it can mimic primary choriocapillaropathies.

Case Continued

A laboratory workup was ordered; it included a complete blood count, erythrocyte sedimentation rate, angiotensin-converting enzyme, and chest x-ray, all of which were normal. Rapid plasmin reagin (RPR) and fluorescent treponemal antibody absorption tests were also negative. Herpes simplex virus immunoglobulin G was positive. A purified protein derivative (PPD) skin test was positive (9-mm induration), and the interferon-gamma release assay was positive.

The patient was diagnosed with tuberculous serpiginous-like choroiditis. She was prescribed isoniazid 5 mg/kg/d and rifampin 10 mg/kg/d, both for 24 weeks, and pyrazinamide 25 mg/kg/d and ethambutol 20 mg/kg/d for 8 weeks.[4] Corticosteroid treatment, beginning with pulses of intravenous methylprednisolone, followed by oral prednisone, was initiated rapidly after initiation of antibiotics because of the immediate threat to vision.

Discussion

Syphilis serology (RPR and fluorescent treponemal antibody absorption) and chest x-ray are almost always appropriate in the workup of chorioretinitis to help rule out syphilis and sarcoidosis, respectively; both disorders are among the masquerade syndromes. In general, however, other serologic testing has low specificity as a diagnostic evaluation because a significant percentage of the population will test positive for many infectious causes of uveitis, including herpes simplex virus, varicella zoster virus, cytomegalovirus, and even toxoplasmosis. When an infectious etiology is strongly suspected in a patient with an inflammatory component in the vitreous, or especially in the anterior chamber, polymerase chain reaction testing from aqueous or vitreous sampling is helpful to establish a specific diagnosis.

Computed chest tomography might be preferred over plain radiography for pulmonary evaluation when tuberculosis is suspected in patients with uveitis.[5] Other diagnostic tests for tuberculosis include the PPD skin test and the serum interferon-gamma release assay. Clinicians should recognize that the interferon-gamma release assay might be falsely negative in people who are coinfested with parasites.[6] Therefore, it is worth performing the PPD test when evaluating patients in regions where parasite infestations are endemic, whereas the interferon-gamma release assay alone can be ordered in nonendemic areas, such as the United States.

Tuberculous Serpiginous-Like Choroiditis

The clinical appearance, lack of response to immunosuppressive therapy, and diagnostic testing in this case support the diagnosis of tuberculous serpiginous-like choroiditis. This condition was originally described by Gupta and colleagues in a paper published in 2003.[7] The clinical features for differentiating tuberculous serpiginous-like choroiditis include the presence of vitritis and multifocal lesions in the posterior pole and periphery. Patients also tend to come from highly endemic regions.[8]

Treatment for tuberculous serpiginous-like choroiditis is specific with an antitubercular regimen, and because of the threatening nature of the lesion in the left eye, the patient in this case was also started on corticosteroid treatment once the anti-infective treatment was established. Data from the Collaborative Ocular Tuberculosis Study (COTS) showed that of the 962 patients enrolled at 25 centers worldwide,[9] 262 had serpiginous choroiditis (COTS, unpublished data). Serpiginous choroiditis was more commonly observed among immigrants than in nonimmigrants, and had a poorer prognosis among immigrants, perhaps because their uveitis was suspected to have an autoimmune etiology instead of being related to tuberculosis.

Case Continued

*The lesion in the left eye healed after a few weeks **(Figure 2)**. The corticosteroid was slowly tapered, and cyclosporine was discontinued. The patient continued on prednisone 5 mg/d. She remained relapse-free during 10 years of follow-up, and best corrected visual acuity (BCVA) in her left eye was 20/20 at her last visit.*

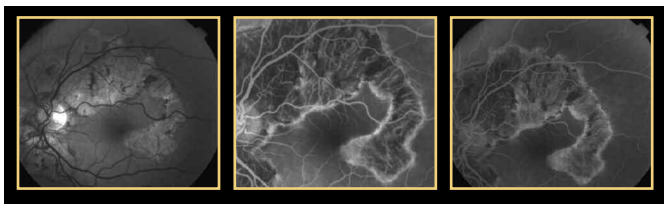

Figure 2. Red-free photograph and fluorescein angiography 3 months after starting therapy, showing inactivation of the lesion with the hyperfluorescent border and absence of leakage. Note the immediate juxtafoveal scar.

Take-Home Points

An infectious etiology or masquerade condition must always be ruled out before starting corticosteroid therapy in an eye with uveitis involving the posterior segment. Serpiginous choroiditis is usually associated with tuberculosis, and patients with this diagnosis should receive a full antimicrobial regimen for *Mycobacterium tuberculosis* infection.

CASE 2. DECIDING WHEN TO REFER TO A UVEITIS SPECIALIST

From the Files of Diana V. Do, MD

*A healthy 27-year-old Asian man who works in Silicon Valley presented complaining of blurry vision in both eyes. He stated the problem began a few weeks prior. Visual acuity was 20/100 OD and 20/80 OS. Fundus examination revealed serous retinal detachments involving the macula and changes at the level of the retinal pigment epithelium (RPE) in both eyes **(Figure 3)**.*

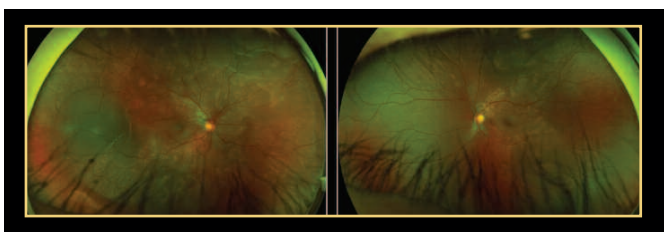

Figure 3. Fundus autofluorescence shows serous retinal detachments in both eyes

The patient had no other complaints nor any remarkable findings on clinical examination or history, which included specific querying about neurologic/auditory symptoms (eg, headaches and tinnitus) and dermatologic issues.

Imaging studies included optical coherence tomography (OCT), FA, and fundus autofluorescence. On OCT, both eyes showed a massive amount of subretinal fluid, with extensive septae between the outer retina and the elevated part of the retina ***(Figure 4)****. Fundus autofluorescence showed multiple areas of RPE involvement bilaterally* ***(Figure 5)****, and the FA showed multiple pinpoint dots of hyperfluorescence at the level of the RPE* ***(Figure 6)****. The RPR test result was negative.*

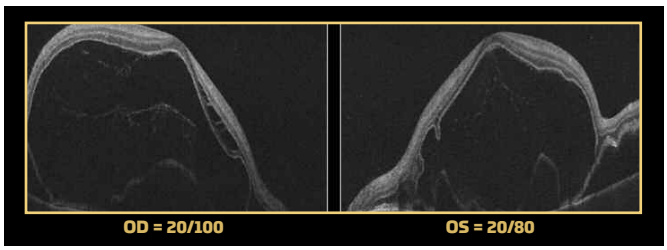

Figure 4. Subretinal fluid as shown on optical coherence tomography

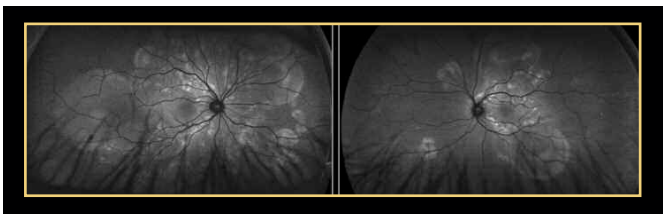

Figure 5. Areas of retinal pigment epithelium involvement are present bilaterally on fundus autofluorescence

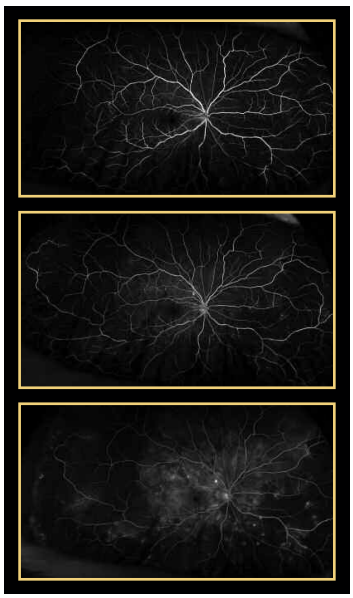

Figure 6. Multiple pinpoint dots of hyperfluorescence

On the basis of the findings from the clinical examination and imaging, the patient was diagnosed with Harada disease (ophthalmic manifestation), a component of the Vogt-Koyanagi-Harada (VKH) syndrome.

Discussion

A variety of imaging methods are available to identify specific pathologic features that will help to establish the diagnosis in an eye with posterior uveitis. The imaging should be tailored to the individual patient and can also help with management of the uveitic condition. Optical coherence tomography can help identify cystoid macular edema (CME), subretinal fluid, and disturbances in the outer retina.[10] Fluorescein angiography identifies active uveitis, macular edema, choroidal neovascularization, retinal vasculitis, and areas of ischemia. Fundus autofluorescence provides information on RPE health, and indocyanine green angiography is useful for characterizing the choroid and choroidal circulation.

The laboratory evaluation of patients with uveitis should be guided by clinical judgment that takes into account which tests are most likely to be positive or to influence management. Hypertensive choroidopathy can be considered in the differential diagnosis of suspected VKH syndrome/Harada disease. Infection should always be ruled out, and infectious etiologies that would be included in the differential diagnosis in this case include Lyme disease because of the bilateral serous retinal detachment and tuberculosis because it can also lead to a similar clinical presentation. It is also worthwhile to routinely test for syphilis because it can present in a variety of ways and is readily treatable with a variety of antibiotics.

Vogt-Kayanagi-Harada Syndrome

VKH is a multisystemic autoimmune inflammatory disorder. It typically occurs in people with darker pigmented skin who are of Hispanic, Middle Eastern, or Asian descent, and it is characterized by uveitis that is often accompanied by neurologic/auditory and cutaneous manifestations.[11] The diagnosis is based on clinical findings and exclusion of other etiologies. The ophthalmic features (often referred to as Harada disease) in this case that are consistent with VKH include serous retinal detachments, pinpoint areas of leakage on FA, and outer retina septae identified on OCT.[12,13] Exudative subretinal detachment also occurs with central serous chorioretinopathy, but central serous chorioretinopathy is less likely to be bilateral and is not associated with subretinal septae.[13]

Case Continued

Because of the clinical presentation and decreased vision, the patient was started on intravenous methylprednisolone 1 g/d for 3 days and then switched to oral prednisone 60 mg/d, with slow tapering. Both the exudative detachment and subretinal fluid were dramatically reduced when the patient returned after 1 week ***(Figures 7 and 8)****, and visual acuity (VA) improved to 20/40 OU. Follow-up continued, and the patient was scheduled to return for his next visit when he reached a prednisone dose of 30 mg/d.*

Discussion

Systemic treatment is indicated for Harada disease/VKH because it is a systemic disease that typically affects both eyes. The treatment can be initiated with a corticosteroid.

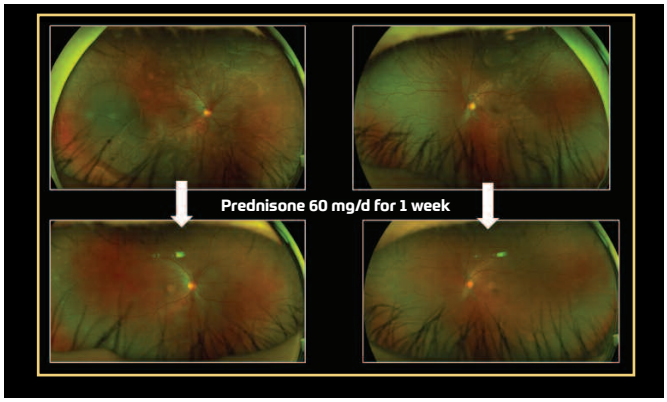

Figure 7. Retinal detachment before (top row) and after (bottom row) treatment

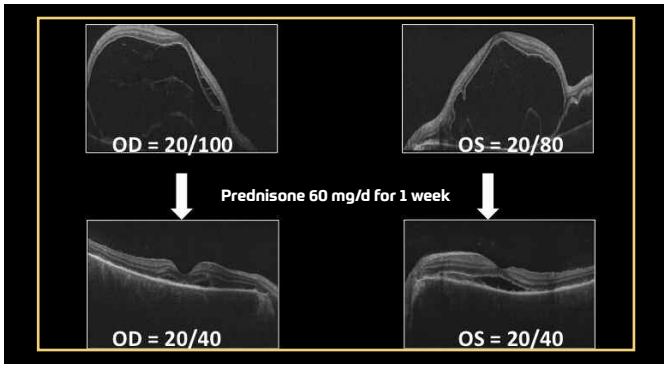

Figure 8. Subretinal fluid before (top row) and after (bottom row) treatment

There are no clinical trials that compare intravenous and oral corticosteroids. Treatment for VKH has been initiated with a prednisone dose ≥ 100 mg/d.[14,15] This is an ultra-high dose with the potential for causing ischemic necrosis of bone and a subsequent need for hip replacement surgery.[16] Treatment initiation with pulsed intravenous methylprednisolone 1 g/d for 3 days, followed by oral prednisone 60 mg/d, is safer.[17]

The corticosteroid-tapering regimen should be tailored to the disease response. In this case, the prednisone dose was tapered slowly, with the goal of discontinuing treatment after 3 to 6 months.

For patients with VKH, a second immunomodulatory agent can be added as needed on the basis of the efficacy and safety of corticosteroid monotherapy. Indications for adding immunomodulatory treatment are failure to completely respond to treatment within 1 month as the taper is under way, development of significant side effects from the corticosteroid, anticipated need to maintain the patient on oral prednisone at a dose exceeding 10 mg/d, or presence of a pre-existing medical condition (eg, uncontrolled diabetes or hypertension) that makes the individual a poor candidate for long-term corticosteroid therapy.[17]

Referral to a Uveitis Specialist

Retina specialists might consider referring patients with uveitis to a uveitis specialist if the patient is not responding to initial treatment or requires chronic immunomodulatory therapy. Consultation with a uveitis specialist should also be considered for patients who present with a diagnostic dilemma and for those with uveitis associated with systemic disease.

Take-Home Points

Multimodal imaging can be helpful for accurate diagnosis of posterior segment uveitis. VKH responds well to oral corticosteroids. Other immunomodulatory agents might be helpful for recurrent and chronic cases. Referral to a uveitis specialist might be considered when the diagnosis is uncertain and for patients who present with treatment challenges.

CASE 3. SYSTEMIC VS LOCAL TREATMENT OF UVEITIS

From the Files of Vishali Gupta, MD

A 19-year-old Indian male presented with decreased vision in both eyes. He reported that the problem began 1 to 1.5 years ago and had worsened gradually while he was being treated on and off with oral corticosteroids. He had no history of systemic illness or any positive findings from prior laboratory tests.

BCVA was hand motion/counting fingers (HM/CF) OD and CF OS. Intraocular pressure was normal, and the anterior segment was quiet OU. His pupils were normal-sized and reactive, and he had full extraocular movements.

Fundus imaging in the right eye showed 2+ media haze and a vascularized retinal fold between the disc and the periphery ***(Figure 9A)****. With indirect ophthalmoscopy, a peripheral lesion was seen in the lower nasal quadrant, with a retinal fold extending between this lesion and the optic disc. This clinical presentation was suspicious for being toxocariasis. Fundus imaging in the left eye showed 2+ media haze and vitritis, disc edema, and inferior* ***(Figure 9B)****; there was no snowbanking.*

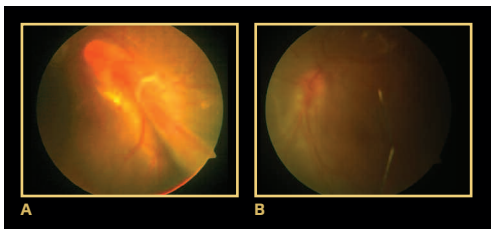

Figure 9. Fundus imaging of right (A) and left (B) eyes

Fluorescein angiography in both eyes showed diffuse leakage from the capillaries, with a fernlike pattern that is classically associated with Behçet disease ***(Figures 10A and 10B)****.*[18] *In the left eye, there was increased leakage in the late phase and retinal neovascularization in the far periphery. There were no areas of ischemia. Late-phase FA showed diffuse leakage, with pooling of the dye.*

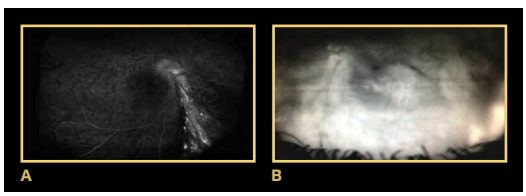

Figure 10. Fluorescein angiography showing fernlike diffuse capillary leakage in the right eye (A) and late-phase leakage in the left eye (B)

*The patient had no history of oral or genital ulcers. Diagnostic evaluations included conventional testing for tuberculosis (PPD, interferon-gamma release assay, and contrast-enhanced chest computed tomography), as well as an abdominal ultrasound and gastric lavage for acid-fast bacilli because he complained of abdominal discomfort. Serology was also done for syphilis (*Treponema pallidum *hemagglutination and venereal disease research laboratory) and human immunodeficiency virus. All the test results were negative.*

Discussion

Behçet disease was ruled out on the basis of the patient's history (absence of oral and genital ulcers), and the diagnostic test results ruled out tuberculosis and syphilis. Idiopathic retinal vasculitis was also ruled out because of the presence of snowballs and other features of intermediate uveitis.

Case Continued

Intermediate uveitis with vasculitis was established as the working diagnosis. The patient was given intravenous methylprednisolone and referred for a rheumatology consult. The rheumatologist initiated subcutaneous adalimumab and mycophenolate mofetil as steroid-sparing therapy. Because of the retinal neovascularization, the left eye was also treated with intravitreal ranibizumab.

Discussion

Initial high-dose systemic corticosteroid treatment was indicated in this case because it can provide rapid control of inflammation, but the dose should be tapered.[17] Adalimumab or infliximab could also be considered. Infliximab, specifically, has a more rapid treatment onset when compared with mycophenolate, other antimetabolites, and T-cell inhibitors.[17,19]

Treatment for the retinal neovascularization was considered necessary in this patient because of his young age and involvement of his better-seeing eye. There was no evidence of ischemia, so the neovascularization was judged to be secondary to inflammation. The decision to inject intravitreal ranibizumab was based on the fact that the neovascularization was not resolving with corticosteroid treatment. Laser treatment would be appropriate to treat neovascularization that is secondary to ischemia, as evidenced by capillary nonperfusion on FA.

A diagnosis of multiple sclerosis (MS) might also be considered in this patient because of his age, even though MS is more common in females than in males. Evaluation for MS would involve magnetic resonance imaging.

Two medications that are used to treat MS, glatiramer acetate and interferon-β, might have a positive effect on ocular inflammation.[20] Tumor necrosis factor alpha inhibitors should not be used to treat uveitis associated with MS because they can exacerbate the neurologic disease.

Case Continued

After 2 months, vision improved from HM/CF to a consistent CF OD and from CF to 20/100 OS. At 6 months, VA was 20/200 OD and 20/40 OS. There was no leakage in the right eye. In the left eye, IOP was elevated and neovascularization and leakage were improved but not resolved ***(Figure 11)****. Current treatment included adalimumab 40 mg every other week, mycophenolate 1.5 g/d, and prednisone 15 mg/d.*

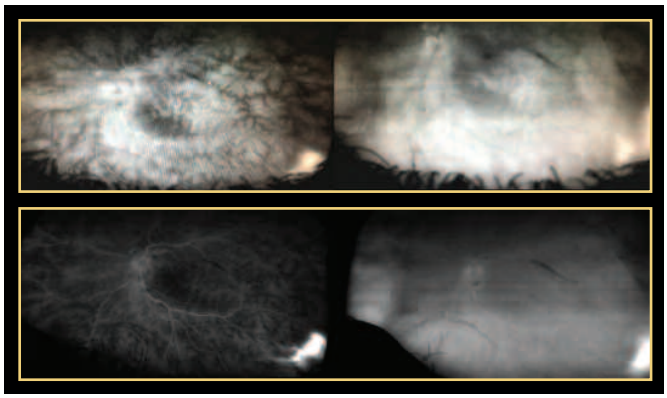

Figure 11. Left eye at baseline showing neovascularization and leakage (top panel). Decreased leakage observed 6 months later, with some improvement in neovascularization (bottom panel).

As a new complaint, the patient reported chest pain and fever. A large subpleural nodule with pleural thickening was seen on the repeat chest computed tomography scan. The patient was diagnosed with fungal pneumonitis and treated with intravenous amphotericin B.

Discussion

The persistent leakage in the left eye indicates a need for additional treatment to control the uveitis. Options include increasing systemic immunosuppression, either by maximizing dosing of existing medications or by using a different agent as a substitute for, or on top of, existing treatment. A need for 3 immunosuppressants to control uveitis, however, might be deemed an indication to reconsider the diagnosis.

As illustrated in this case, systemic immunosuppression is associated with increased susceptibility to infection, and in India, where this patient was seen, there is a heightened risk for fungal infection or reactivation of latent tuberculosis. Because of the infectious complication and because the uveitis is uncontrolled in just 1 eye, local therapy is a good management option for this patient.

Available agents include the fluocinolone acetonide 0.59-mg implant. In a phase 2b/3 trial of patients with noninfectious posterior uveitis, those receiving the fluocinolone acetonide implant had a significantly lower rate of uveitis recurrence at 2 years than controls managed with standard systemic therapy (18.2% vs 63.5%; $P \leq .01$).[21] However, IOP-lowering surgery was needed in 21.2% of implanted eyes.

Efficacy of the dexamethasone intravitreal implant for treating noninfectious intermediate or posterior uveitis was demonstrated in the randomized HURON trial.[22] At 6 months, the proportion of eyes with a vitreous haze score of 0 and with a BCVA gain of 15 or more letters was significantly higher in groups implanted with the 0.35-mg or 0.7-mg dexamethasone implant than in sham-treated controls.

Intraocular pressure elevations in corticosteroid-treated eyes were transient, and no eye required glaucoma surgery, but the trial excluded patients using IOP-lowering medications within the past month and those with an IOP > 21 mm Hg or a history of glaucoma, ocular hypertension, or clinically significant IOP elevation in response to corticosteroid treatment.

A corticosteroid implant would probably not be considered without concomitant glaucoma surgery in this patient because of his elevated IOP. A local corticosteroid injection, either intravitreous or regional, might be given, depending on the IOP level and after informing the patient that glaucoma surgery might be needed if his IOP increases.

Intravitreal treatment with the mammalian target of rapamycin inhibitor sirolimus shows potential as a local therapy for uveitis, with less potential to increase IOP or to cause cataract compared with corticosteroids.[23] Results of the phase 3 SAKURA (Sirolimus Study Assessing Double-Masked Uveitis Treatment) program showed statistically significant differences favoring sirolimus 440 µg over sirolimus 44 µg (control) in the primary end point of percentage of eyes with a vitreous haze score of 0 and in the secondary end point of the percentage of eyes with a vitreous haze score of 0 or 0.5+.[23,24] There was no clinically significant change in mean IOP through 6 months of follow-up in the sirolimus 440 µg group **(Figure 12)**.

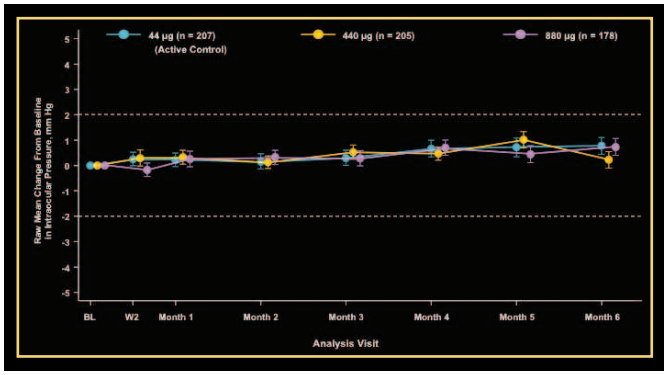

Figure 12. Mean change in intraocular pressure from baseline to 6 months

Abbreviations: BL, baseline; W, week.

Reprinted from *Ophthalmology*, 123, Nguyen QD, Merrill PT, Clark WL, et al, Intravitreal sirolimus for noninfectious uveitis: a phase III Sirolimus study Assessing double-masKed Uveitis tReAtment (SAKURA), 2413-2423, Copyright 2016, with permission from Elsevier.

Take-Home Points

Noninfectious severe posterior uveitis mandates aggressive therapy to prevent ocular morbidity. Systemic therapy, including biologics, is effective, but can cause systemic comorbidities, including infection. Corticosteroid implants should not be administered in patients with elevated IOP without a plan for IOP control and possible concomitant glaucoma surgery. Intravitreal sirolimus is an investigational agent that has demonstrated efficacy in the treatment of noninfectious posterior uveitis, with no clinically significant change in IOP.

CASE 4: MANAGEMENT OF A PATIENT NEEDING CATARACT SURGERY

From the Files of James P. Dunn, MD

A 38-year-old white female with chronic bilateral uveitis was referred for progressive blurred vision in both eyes. She had a history of anterior and intermediate uveitis and Crohn disease that was controlled with adalimumab.

*Uveitis was inactive in the right eye. The patient had 3+ posterior subcapsular cataracts OU. Key clinical findings OS included BCVA HM and extensive posterior synechiae with a pupillary membrane **(Figure 13)**. Assessment for CME was not possible because of an inability to visualize the fundus.*

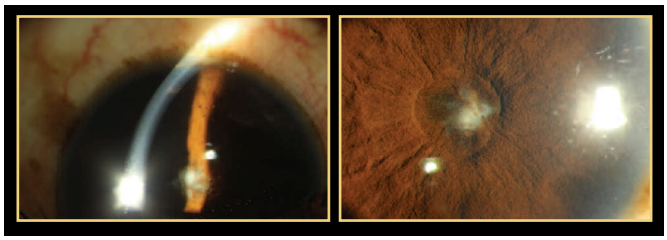

Figure 13. Posterior synechiae with a pupillary membrane observed in the left eye prior to surgery

The patient had undergone peripheral iridectomy at the 11 o'clock position OS prior to her referral because of pupillary block. Intraocular pressure was normal.

Ultrasound was done and showed no mass or retinal detachment. Some fine bridging vessels were seen on gonioscopy, but no iris neovascularization was seen. It was determined that the patient needed cataract surgery.

Discussion

Cataract surgery in uveitic eyes can be challenging, and its safety and success involve special considerations preoperatively, intraoperatively, and postoperatively **(Table)**.

Table. Considerations for Cataract Surgery in Uveitic Eyes

Preoperative (weeks to months)
• Achieve tight control of uveitis and cystoid macular edema
Preoperative (2-7 days)
• Begin "prophylactic" anti-inflammatory regimen
Intraoperative
• Minimize iris trauma and breakdown of blood-aqueous barrier
Postoperative
• Prevent recurrence of uveitis

Preoperative Management

When cataract surgery is indicated in a uveitic eye, the most important preoperative measures are to control the uveitis and resolve existing macular edema. Pharmacologic synechiolysis should be attempted. Corticosteroid and/or immunosuppressive therapy should be used to control the uveitis. However, corticosteroid therapy can worsen the cataract, and patients must understand that temporary worsening of vision might occur before surgery to ensure a better long-term outcome.

The importance of recognizing and controlling uveitic macular edema in eyes needing cataract surgery relates to the fact that of all the uveitis-related structural complications, macular edema carries the worst visual prognosis.[25] Macular thickening has been reported to have a greater adverse effect on VA than macular cysts.[26] According to an analysis of data from the MUST (Multicenter Uveitis Steroid Treatment) trial, a 20% improvement in central foveal thickness predicted a > 10-letter improvement in ETDRS (Early Treatment Diabetic Retinopathy Study) VA.[27] Transient macular edema is most likely to respond to treatment.[28] In the MUST trial, presence of fluorescein leakage was associated with VA improvement in eyes with uveitic macular edema.[29] This information supports the use of both FA and OCT to evaluate macular edema as well as early intervention for macular edema.

Pharmaceutical approaches to prevent or treat uveitic macular edema have been the subject of several prospective, randomized clinical trials that are completed or in progress. The MUST trial randomized patients to receive the fluocinolone acetonide implant or systemic immunosuppression, and results from 7 years of follow-up were published in May 2017.[30] Although visual improvement occurred sooner in the implant group, the visual outcomes at 7 years favored systemic immunosuppression. Compared with patients receiving systemic immunosuppression, those receiving the implant had higher rates of surgery for glaucoma (45% vs 12%) and cataract (90% vs 50%) and a lower rate of antibiotic-treated infections (57.4% vs 72.3%).

The POINT (Periocular and Intravitreal Corticosteroids for Uveitic Macular Edema Trial) study is comparing periocular triamcinolone acetonide, intravitreal triamcinolone acetonide, and the dexamethasone implant in patients with uveitic macular edema.[31] Enrollment in this trial has been completed, with approximately 270 patients entered, and some of the results are expected in 2018.

The MERIT (Macular Edema Ranibizumab v. Intravitreal Anti-inflammatory Therapy Trial) study is enrolling patients who have controlled uveitis but persistent or reoccurring macular edema after an intravitreal corticosteroid injection.[32] The study will randomize eyes to intravitreal methotrexate, the dexamethasone implant, or ranibizumab. Results from some preliminary studies suggested that intravitreal methotrexate might have persistent benefit, perhaps longer than steroid therapy.[33]

Anti–vascular endothelial growth factor (VEGF) agents are not anti-inflammatory, and they tend not to be effective for resolving macular edema in active endogenous uveitis. Anti-VEGF therapy using any of the 3 available agents (ranibizumab, bevacizumab, aflibercept), however, can be very helpful for treating macular edema that persists after uveitis is controlled. There are no controlled trials of anti-VEGF injections in patients with macular edema following uveitic cataract surgery.

The American Academy of Ophthalmology *Preferred Practice Pattern® Clinical Questions* released in 2013 addressed the issue of which perioperative regimen is associated with the best outcomes in patients with uveitic cataract.[34] The panel noted there is widespread consensus among uveitis experts that aggressive perioperative anti-inflammatory therapy should be used in patients with uveitis undergoing cataract surgery and that available data strongly support the importance of sustained control of uveitis and macular edema prior to surgery. In a review of the literature, however, the panel did not find a regimen that had an obvious benefit relative to others.

The idea of rigidly controlling uveitis to achieve a quiescent state for at least 3 months before performing cataract surgery has been popularized by C. Stephen Foster, MD, and other uveitis experts.[35] Bélair and colleagues reported that among uveitic eyes undergoing cataract surgery, the risk of postoperative CME was increased more than 6-fold when active inflammation was present within 3 months prior to surgery.[36] Immunosuppressive therapy using agents from classes that include antimetabolites, T-cell inhibitors, alkylating agents, and biologics might be necessary to achieve this goal.

Once the patient is ready for cataract surgery, perioperative pharmacologic management aims to control surgically induced inflammation and to limit macular edema and uveitis flare postoperatively. Bélair and colleagues also found that CME after cataract surgery was more common in eyes with uveitis than in unaffected eyes (12% vs 4% at 1 month) and was a significant predictor of poorer postoperative vision.[36] Among the uveitic eyes, the rate of CME at 1 month after surgery was significantly lower in eyes that received preoperative oral corticosteroid treatment than in those that did not receive oral corticosteroids (4% vs 27%; $P = .05$).[36]

At 2 to 7 days preoperatively, an aggressive anti-inflammatory regimen should be initiated, which can include oral and topical corticosteroids plus a topical nonsteroidal anti-inflammatory drug (NSAID). Intravitreal injection of a corticosteroid or anti-VEGF agent might also be considered for administration 1 to 2 weeks before surgery, if it can be safely done.

Macular edema from surgery-induced inflammation generally occurs 4 to 6 weeks postoperatively.[37] The dexamethasone implant provides corticosteroid coverage over this period of time. Results of a small prospective study showed no difference in postoperative BCVA, IOP, or central macular thickness among patients with uveitis who received intraoperative placement of an intravitreal dexamethasone implant or oral corticosteroid treatment.[38] An ongoing trial is randomizing patients who have controlled noninfectious posterior uveitis and are undergoing cataract surgery to receive the dexamethasone implant or not, in addition to standard-of-care therapy. In the study, the implant is placed before beginning the cataract surgery because the eye tends to become hypotonous at the conclusion of the case, which could make implant placement more difficult.

Anecdotally, some uveitis specialists are placing the intravitreal dexamethasone implant 7 to 14 days prior to surgery to ensure anti-inflammatory coverage at the time of

surgery. The intraoperative goal when performing cataract surgery in an eye with uveitis is to minimize iris trauma and breakdown of the blood-aqueous barrier.

Case Continued

The patient was continued on adalimumab 40 mg every 2 weeks. Because it was not possible to determine if CME was present because of the dense cataract, she was started on a very aggressive regimen to treat/prevent CME. Two days preoperatively, she was started on prednisone 60 mg/d; topical prednisolone acetate, 1%, every 2 hours; and topical ketorolac, 0.5%, 4 times daily. Intraoperatively, she was given a single dose of intravenous methylprednisolone 125 mg and intravitreal bevacizumab 1.25 mg.

Intraoperatively, taking advantage of the peripheral iridectomy at 11 o'clock, a peripheral scleral incision was created for introducing a viscoelastic cannula behind the iris, and the adhesions were released from the anterior capsule with viscodissection. Pupillary membranectomy was performed through a clear corneal incision. The pupil was stretched with iris hooks, the capsule was stained, and phacoemulsification was completed successfully with IOL implantation in the capsular bag.

Prednisone 60 mg/d was resumed after surgery, with dose tapering over 1 to 2 weeks, and the patient continued on the topical corticosteroid and NSAID with monitoring. At the 1-week follow-up, VA was 20/40.

Discussion

The VA outcome after cataract surgery in an eye with posterior uveitis is typically diminished relative to the general population, probably because visual rehabilitation is limited by pre-existing uveitis-related pathology.[39] Postoperatively, it is important to be vigilant for recurrence of uveitis and CME and to use anti-inflammatory agents, including topical corticosteroids, topical NSAIDs, and oral corticosteroids, to prevent those events. Patients should also be maintained on any existing systemic immunosuppression as necessary, and a topical cycloplegic can be used as needed to prevent recurrence of posterior synechiae.

Cystoid macular edema, if it develops, is treated with corticosteroids that can be administered topically, systemically, with regional injections (periocular or sub-Tenon), by the intravitreal route using preservative-free triamcinolone acetonide, or with the dexamethasone or fluocinolone acetonide implant.

In the event that a patient with uveitis needs posterior segment surgery, scheduling of the operation will depend on the indication. For example, surgery for an epiretinal membrane should be deferred until the uveitis is quiescent, whereas prompt intervention is needed for retinal tear/detachment that develops in the setting of retinitis associated with infectious posterior uveitis. Retinal detachment itself can be proinflammatory and lead to uveitis.[40] In such a situation, surgery to repair the retinal detachment might be the only way to effectively treat the uveitis.

Take-Home Points

Patients with uveitis needing cataract surgery must be involved in their own care and understand that, unlike in routine cataract cases, a long-term approach to treatment is required. Uveitis and macular edema need to be controlled before cataract surgery is performed. Treatment with aggressive corticosteroid therapy might worsen the cataract, so corticosteroid-sparing therapy is important.

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CME POST TEST QUESTIONS

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See detailed instructions at **To Obtain *AMA PRA Category 1 Credit*™** on page 2.

1. Findings of iris transillumination, reduced corneal sensation, and IOP elevation should raise suspicion for:
   A. Acute posterior multifocal placoid pigment epitheliopathy
   B. Ampiginous choroidopathy
   C. Herpetic uveitis
   D. Toxoplasmosis

2. Serpiginous choroiditis in a white patient is suspected to be associated with tuberculosis. A chest x-ray is performed and is normal. The patient reports no history of foreign travel. What test would you order?
   A. Chest magnetic resonance imaging
   B. Interferon-gamma release assay
   C. Repeat the chest x-ray
   D. Vitreous biopsy

3. What treatment is recommended for tuberculous serpiginous-like choroiditis in a patient without active lung disease?
   A. Antitubercular antimicrobial medications
   B. Intraocular corticosteroid injection
   C. Systemic corticosteroids
   D. Treatment is usually not needed for this condition

4. Oral prednisone is initiated to treat a patient with noninfectious posterior uveitis and achieves disease control. Systemic immunomodulatory therapy should be considered if the prednisone dose required to maintain chronic suppression:
   A. Cannot be tapered to discontinuation
   B. Exceeds 1 mg/d
   C. Exceeds 5 mg/d
   D. Exceeds 10 mg/d

5. For the primary end point of the pivotal clinical trials, intravitreal sirolimus 440 µg was effective for improving:
   A. Anterior chamber cell grade
   B. CME
   C. Retinal lesions
   D. Vitreous haze

6. Typical ophthalmic features of VKH syndrome include all the following, EXCEPT:
   A. Outer retina septae
   B. Pinpoint areas of leakage on FA
   C. Placoid retinal lesions
   D. Serous retinal detachment

7. Fundus autofluorescence is helpful for characterizing:
   A. Choroidal neovascularization
   B. Macular edema
   C. RPE health
   D. Retinal vasculitis

8. Which of the following is the most important preoperative consideration in a patient with posterior segment uveitis needing cataract surgery?
   A. Avoid steroids that could worsen the cataract
   B. Lyse posterior synechiae with a pharmacologic agent
   C. Resolve macular edema
   D. Schedule the surgery as soon as possible to improve posterior segment visualization

9. In a patient who has a contraindication to corticosteroid treatment, which of the following systemic agents would you choose to achieve rapid control of uveitic inflammation?
   A. Infliximab
   B. Cyclosporine
   C. Methotrexate
   D. Mycophenolate mofetil

10. In underscoring the importance of aggressive perioperative anti-inflammatory therapy for patients with uveitis undergoing cataract surgery, the American Academy of Ophthalmology *Preferred Practice Pattern®* *Clinical Questions* statement recommends:
    A. Intravitreal anti-VEGF injection 2 to 7 days prior to surgery
    B. Intravitreal injection of a sustained-release corticosteroid implant 2 to 4 weeks prior to surgery
    C. Sub-Tenon injection of triamcinolone acetonide plus intracameral NSAID intraoperatively
    D. No specific regimen was recommended