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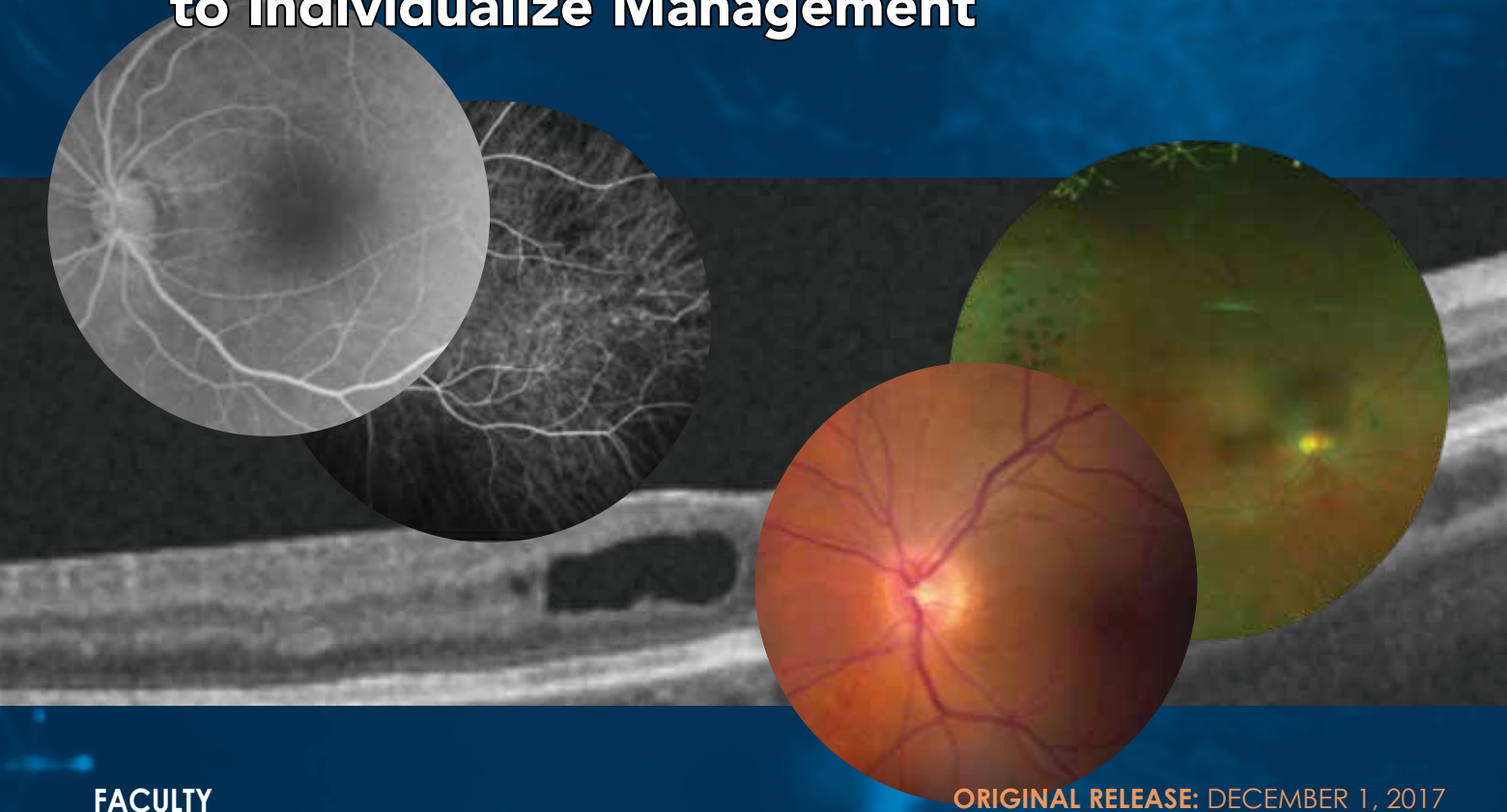
CHRONIC NONINFECTIOUS UVEITIS OF THE POSTERIOR SEGMENT

Current and Future Approaches to Individualize Management



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LEARNING METHOD AND MEDIUM

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CONTENT SOURCE

This continuing medical education (CME) activity captures content from an expert roundtable discussion held on August 11, 2017.

ACTIVITY DESCRIPTION

Uveitis involving the posterior segment is a sight-threatening condition that can be associated with multiple underlying ocular and systemic diseases. Accurate diagnosis is the foundation for selecting treatment that can preserve vision and is guided by the findings of a thorough history, clinical examination, laboratory testing, and imaging. Evaluation and management of posterior uveitis varies globally, however, because of geographic/ethnic variation in its causes, differences in local practices, and varying access to diagnostic modalities and treatments.

This case-based program captures the highlights of a roundtable discussion, in which an international panel of uveitis subspecialists provides their expert perspectives on the diagnosis and management of uveitis involving the posterior segment, including the role of emerging diagnostic techniques and new and emerging therapies. The cases are from the files of Sunil K. Srivastava, MD.

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:

- Discuss the use of diagnostic assessments to differentiate between infectious and noninfectious uveitis of the posterior segment
- Assess which patients with noninfectious uveitis of the posterior segment would be referred to a uveitis specialist
- Demonstrate application of evidence-based treatments for a variety of patients with noninfectious uveitis of the posterior segment
- Describe the mechanism of action and clinical trial outcomes for emerging agents in clinical trials for local therapy for noninfectious uveitis of the posterior segment

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CHRONIC NONINFECTIOUS UVEITIS OF THE POSTERIOR SEGMENT

Current and Future Approaches to Individualize Management

INTRODUCTION

Uveitis involving the posterior segment encompasses a variety of infectious and noninfectious conditions, some of which are associated with systemic diseases. A thorough history, clinical examination, laboratory testing, and imaging are crucial in determining a diagnosis and subsequent treatment plan that can preserve vision. Evaluation and management of posterior uveitis varies globally because of geographic/ethnic variation in its causes, differences in local practices, and varying access to diagnostic modalities and treatments.

This case-based program captures the highlights of a roundtable discussion, in which an international panel of uveitis subspecialists provides expert perspectives on the diagnosis and management of uveitis involving the posterior segment, including the role of emerging diagnostic techniques and new and emerging therapies. The cases are from the files of Sunil K. Srivastava, MD.

Case 1: Differential Diagnosis – Infectious vs Noninfectious Uveitis

A 60-year-old man presents with a 4-day history of seeing a black spot in his central vision and light sparkles when staring at a dark background. He reports getting a shingles vaccine 4 weeks ago and being diagnosed with iritis 1 to 2 weeks thereafter.

The patient is human immunodeficiency virus (HIV) positive and compliant with his antiretroviral therapy. He has hypothyroidism, hypertension, and hyperlipidemia. Results from laboratory tests taken 2 months ago showed a CD4 count of 1032 cells/mm^3 and undetectable viral load. Tests for gonorrhea, chlamydia, syphilis, and tuberculosis (TB) were negative.

Visual acuity (VA) is 20/20 OD, 20/30- OS. The anterior chamber is deep and quiet OU. ***Figure 1*** *shows color fundus images from the right and left eyes.* ***Figure 2*** *shows optical coherence tomography (OCT) images from the left eye.*

Figure 1. Fundus photographs reveal retinitis superior to the arcade in the right eye (A) and involving the fovea in the left eye (B)

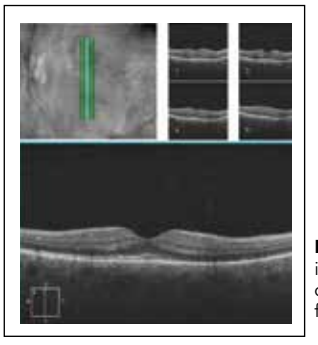

Figure 2. Optical coherence tomography images of the left eye. Superior raster image displays outer retinal loss just superior to the fovea.

Dr Srivastava: Dr Taylor, what imaging do you perform when you see a new patient with posterior uveitis?

Dr Taylor: I get OCT and fluorescein angiography (FA). With FA, I might determine that there is more inflammation than I would have suspected according to the clinical appearance, and I can get a wide-field view.

Dr Srivastava: Dr Banker, what are your thoughts when you look at this patient's FA images **(Figure 3)**?

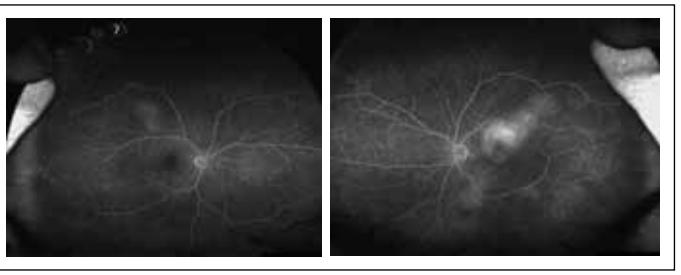

Figure 3. Late frame wide-field fluorescein angiography images reveal staining with mild leakage in both eyes

Dr Banker: The lesion is quite well defined in both eyes, but more so in the left than in the right. There is a lot of staining, but not much leakage or nonperfusion, and there are only a few areas of mild peripheral perivasculitis temporally.

Dr Srivastava: This patient presented with a sudden onset of symptoms, and his condition is bilateral.

Dr Taylor, do the history and imaging findings suggest any particular diagnosis for this patient?

Dr Taylor: Infectious retinitis is first on the list in the differential diagnosis of an HIV-positive patient, and midperipheral retinitis in someone who is HIV positive suggests syphilis, until proven otherwise. An inflammatory etiology or a malignancy is also a possibility.

Dr Srivastava: When the patient was sent to me, the differential diagnosis included central serous retinopathy, but I think this is unlikely, given the retinitis. An infectious process is certainly in the differential diagnosis whenever there is retinitis, and I think about infection first whenever I see uveitis in a patient who is HIV positive. The most common etiologies of infectious uveitis in the United States are syphilis, toxoplasmosis, and viruses. Lymphoma and sarcoidosis would be other diseases to consider as well.

Dr Banker: There is geographic variation in the causes of infectious uveitis in the HIV-positive population.[1] In India, cytomegalovirus retinitis is still the most common infectious ocular manifestation that is seen in these patients, followed by toxoplasmosis.[1,2] We also see other forms of viral retinitis, such as acute retinal necrosis and serpiginous-like choroiditis without vitritis. Ocular TB is being seen more commonly in this era of highly active antiretroviral therapy than it was before.[1]

Dr Srivastava: Although infection is suspected, the patient recently had a laboratory workup that was negative for a variety of infections.

What would you do now?

Dr Sharma: A previous negative workup for infection does not rule out infection, and this is especially true in an HIV-positive patient. I would reorder the laboratory tests.

Case 1, Continued

The laboratory workup was repeated, and the serology came back positive for syphilis (immunoglobulin G [IgG] > 8; rapid plasma reagin [RPR] 1:256).

Dr Sharma: At the Cleveland Clinic's laboratory, the algorithm for syphilis serology testing recommends measuring IgG first, followed by RPR if the IgG test result is positive.[3] The rationale for not doing RPR first is that it can give a false-positive result in a number of situations, including autoimmune disease, acute viral infection, recent immunizations, or drug addiction, and it can give a false-negative result in patients with latent or late syphilis.[3]

Dr Srivastava: At the Cleveland Clinic, this patient would be treated immediately with intravenous penicillin. Would anyone treat the patient differently?

Dr Sharma: Penicillin remains the treatment of choice for syphilis.[4] If the patient reports an allergy to penicillin, doxycycline can be used initially, but the patient should have a skin test for penicillin allergy to determine if the allergy is real. If it is, desensitization for penicillin should be considered.

Dr Srivastava: Let us assume that syphilis was not diagnosed, and the patient was started on systemic corticosteroid therapy for the uveitis. How should the patient be followed?

Dr Banker: You want to make sure that infection was not missed because infectious posterior uveitis can result in rapid vision loss.[5] Infectious uveitis will usually flare quickly after corticosteroid treatment is started, within 1 week. If the etiology of the uveitis is uncertain and infection has not been ruled out, the patient should be seen soon after starting a systemic corticosteroid. I would recommend a return visit in 3 days.

Dr Sharma: It is important to point out that a corticosteroid should never be injected into or around the eye to treat uveitis unless infectious conditions have been ruled out with certainty. Local corticosteroid treatment can be considered after a patient is improving on an oral corticosteroid, but, as a caveat, some infectious uveitis can get better initially with corticosteroids, which help to resolve some of the acute inflammation seen with the infection. The patient, however, will rapidly worsen if the correct treatment is not started immediately.

Dr Taylor: The worst cases of infectious uveitis that I have seen have been undiagnosed toxoplasmosis treated with intravitreal triamcinolone or the intravitreal dexamethasone implant. The problem with intravitreal treatment is that it cannot be easily withdrawn. Oral corticosteroids are less of a problem from this perspective, and in a situation in which there is dense vitritis, the corticosteroid may help to clear the vitreous enough so that it is easier to see evidence of infectious uveitis. If infection has not been ruled out, an oral corticosteroid can be given for a few days, without too much risk so long as the patient is monitored carefully.

Dr Srivastava: If you see a patient with posterior uveitis who is immunocompromised and you suspect infection, but are not certain about the exact etiology, how do you make the diagnosis?

Dr Banker: As a last resort, I would take the patient to the operating room to get a vitreous sample or retinal biopsy, but first, we consult the internist to get a complete systemic evaluation.

Dr Sharma: I am very cautious if I have a concern about an infection and try to get a sample from either the anterior chamber or the vitreous to send for polymerase chain reaction testing to detect viruses or toxoplasmosis. The yield from the anterior chamber sample is pretty good for viruses, including herpes zoster, varicella, and cytomegalovirus, but not as good for toxoplasmosis.[6,7] If I am concerned about viral retinitis, I will start antiviral treatment orally or with an intravitreal injection while waiting for the test results before starting an oral corticosteroid.

Case 1, Continued

The patient was started on intravenous penicillin. After 14 days, there was resolution of the retinitis clinically, but still some hyperfluorescence on the FA ***(Figure 4A)****, raising consideration of persistent inflammation. Optical coherence tomography* ***(Figure 4B)*** *shows improvement in the outer retina, with the ellipsoid zone being visible again.*

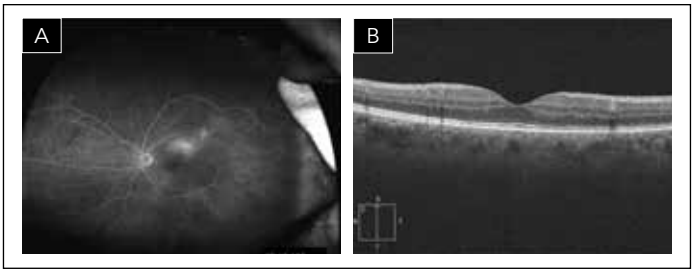

Figure 4. Left eye images from 14 days after starting treatment with intravenous penicillin. Fluorescein angiography displays late hyperfluorescence consistent with staining or leakage (A). Optical coherence tomography (B) reveals recovery of the outer retinal structures (ellipsoid zone and external limiting membrane) superior to the fovea.

Dr Srivastava: In my experience, inflammation can linger for a while in patients with syphilis. Do you see this, and if so, do you treat the inflammation with a topical or an oral corticosteroid?

Dr Taylor: Some patients will have a florid Jarisch-Herxheimer reaction when starting treatment for syphilis, which will require treatment with an oral corticosteroid, but I also see patients who have milder inflammation that I just observe for a while before deciding whether or not to treat.

Dr Sharma: Because of the potential for a Jarisch-Herxheimer reaction when patients with syphilis are started on intravenous penicillin, I will often add an oral corticosteroid to the intravenous penicillin, especially if there is an increase in inflammation on the clinical examination.

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Case 2: Multimodal Imaging for Diagnosis

A 50-year-old Indian male states that he had sudden onset of vision loss in his left eye. He went to the emergency room, was diagnosed with disc edema and elevated blood pressure, and was admitted for blood pressure control. He states he had mild improvement in his vision and was eventually seen by a neuro-ophthalmologist because of the disc edema. He was diagnosed with vasculitis. He presents 7 months after his initial onset of symptoms with persistent blurred vision with distortion.

Testing to date includes QuantiFERON-TB, angiotensin-converting enzyme, fluorescent treponemal antibody absorption, antineutrophil cytoplasmic antibody (ANCA), antinuclear antibody, chest x-ray, magnetic resonance imaging, and lumbar puncture. All results were negative.

Visual acuity is 20/40 OD, 20/60 OS, and there is trace cell in the anterior chamber OU. Fundus examination does not reveal any vitritis, and there are minimal changes on examination. Fluorescein angiography is obtained, and although the images are darker, there appears to be some hypofluorescence dark spots in the left eye along the superior arcade and nasal to the nerve ***(Figure 5A)****. The FA images of the right eye appear normal* ***(Figure 5B)****. Optical coherence tomography imaging reveals normal retinal thickness, although the choroid may be a little thickened* ***(Figures 5C and 5D)****.*

Dr Srivastava: Dr Banker, what are your thoughts on the diagnosis and additional testing?

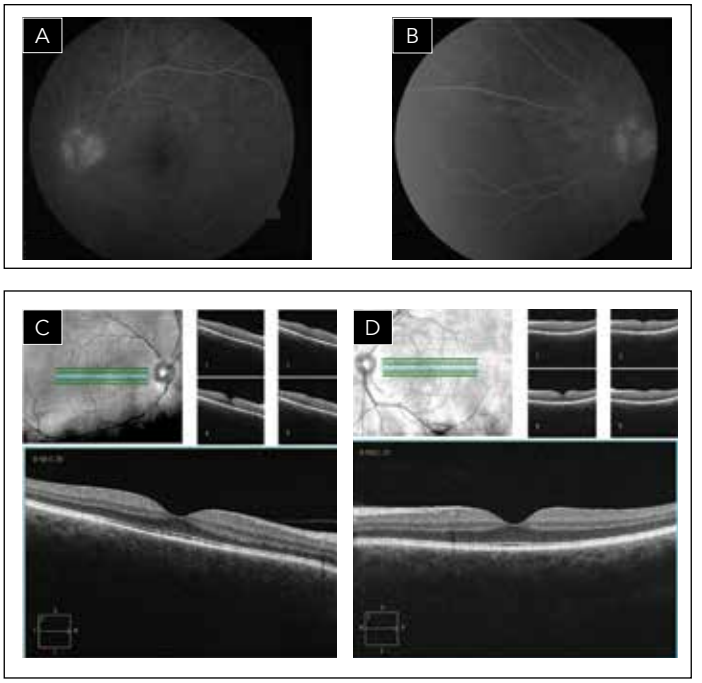

Figure 5. Images from fluorescein angiography (A and B) and from optical coherence tomography (C and D)

Dr Banker: In India, the diagnosis considered for a patient who presents with circumscribed lesions in the outer retina/choroid without overlying vitreous haze would be either TB or sarcoidosis. For a pulmonary evaluation, I would order a high-resolution chest computed tomography (CT), which is preferred over chest x-ray for diagnosing TB and sarcoidosis.[1-3] We also have pulmonologists do bronchoalveolar lavage because analysis of the fluid has been shown to be useful for diagnosing sarcoidosis.[4]

Dr Sharma: Of note, a study from the Cleveland Clinic showed that chest CT was more sensitive than chest x-ray for identifying lesions of sarcoidosis in elderly women with uveitis.[3] When there is suspicion for sarcoid, our pulmonologists prefer getting a high-resolution chest CT without contrast.

Dr Taylor: Ethnicity can be useful in creating the differential diagnosis for uveitis. For an Indian male with this presentation, TB and sarcoidosis would be at the top of the list. To better understand whether the dark patches on the FA represent an abnormality or not, I would order indocyanine green angiography (ICGA), which would enable a better examination of the choroidal circulation. Although ICGA can be difficult to interpret, it can reveal pathology that is not immediately apparent or that is unclear on FA.

Dr Sharma: Although this is not an enhanced depth imaging (EDI) OCT, we cannot see the outer borders of the choroid, and it appears to be thickened in both eyes, which suggests there is something happening deeper to the retina. I order ICGA as part of my initial workup in patients with uveitis only if I think it will be useful according to the findings of my examination, such as if I see deeper lesions or a thickened choroid on OCT, or if there are no changes on the FA that might explain the vision loss. I would get an ICGA in this patient, considering there is some evidence of choroid changes and there are no findings on FA to explain the moderate vision loss.

Dr Srivastava: Multimodal imaging can be valuable in the diagnostic evaluation of patients with uveitis. Because there were just some subtle findings on the OCT and FA, I ordered ICGA, which showed multiple hypocyanescent lesions **(Figure 6)**. The diffuse hypocyanescent lesions provide a clue to the diagnosis.

Would you get any other imaging?

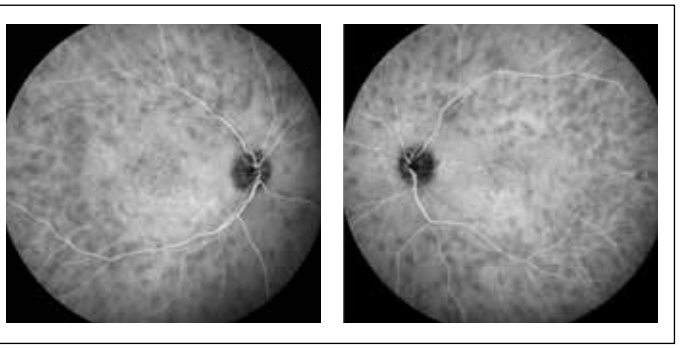

Figure 6. Indocyanine green angiography reveals diffuse hypocyanescent spots throughout the macula in both eyes

Dr Banker: I get EDI OCT almost routinely now. I think it is very helpful in cases with leakage on FA because findings on the EDI OCT allow me to differentiate Vogt-Koyanagi-Harada (VKH) disease from a sarcoid nodule or a tuberculous nodule. With VKH, there is thickening of the larger choroidal vessels, overlying subretinal fluid in acute leakage cases, and loss of the choriocapillaris layer. I do not have OCT angiography (OCTA), but I think some people are using it to study the capillary plexuses at various levels in the retina and are able to see very early changes in VKH.

Dr Srivastava: Dr Sharma, I know you use OCTA. Do you think it would be helpful in this case?

Dr Sharma: I have been doing OCTA because I think we need more experience with it to determine how it can help diagnose patients with uveitis.

Dr Taylor: I think OCTA may have the best utility in follow-up to minimize repeated use of invasive dye-based imaging. In general, I do not repeat the FA very often if a patient is doing well, but I will order it again if the disease is not under control because it gives me something I can follow over time. The same is true for EDI OCT.

Dr Sharma: What do you use as an objective measure for determining activity in a case like this, in which the only abnormal finding was on ICGA? If the patient's vision improved to 20/20, would you conclude that he is doing well and not do any further imaging?

Dr Srivastava: I think Dr Sharma's question makes the important point that sometimes we have to pick an imaging test that we can follow as an end point for treatment. I would not expect in this case that all the spots seen on ICGA will go away, no matter what the cause is. Therefore, in deciding whether or not to repeat the imaging, we need to decide which finding will represent controlled disease.

The differential diagnosis for this case would include TB, lymphoma, sarcoidosis, and birdshot retinochoroidopathy (BSRC). In the United States, BSRC might be at the top of the list if the patient was not an Indian male, and the resident who first saw this patient ordered a human leukocyte antigen A29 (HLA-A29) test that came back positive.

Dr Taylor spoke about ethnicity giving us a clue. Has anyone seen BSRC in an Indian male?

Dr Banker: I have not diagnosed anyone, but I have heard of a few cases.

Dr Sharma: I also have not diagnosed BSRC in an Indian male. It is worthwhile noting that when used as a test for diagnosing BSRC, HLA-A29 has a positive predictive value of less than 50%, meaning it will be wrong more often than it is right.[5] Therefore, in a patient like this who does not have lesions characteristic of BSRC on fundus imaging or FA, a positive HLA-A29 test is not informative.

Dr Srivastava: What we need to think about when ordering testing is Bayes theorem and the probability that the test will be positive.[6]

In Cleveland, many cases of uveitis are BSRC, infectious, or sarcoid related. I tailor my workup with this in mind, so I order a lot of chest CTs. This patient had a chest CT and bronchoscopy, with detection of sarcoid lesions.

Dr Taylor, is there anything else you would do to determine the diagnosis in this case?

Dr Taylor: When sarcoid is suspected, we generally start by measuring serum angiotensin-converting enzyme and getting a chest x-ray. If these tests are negative but suspicion for sarcoid is high, we refer to the chest physicians who would probably order a high-resolution chest CT, and it would be their decision whether to do a biopsy or lavage.

Following these principles, I think a retina specialist could investigate and manage this type of case and would not have to refer the patient to a uveitis specialist. Referral makes sense if the diagnosis is in doubt or if the disease is difficult to control.

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Case 3: Systemic Therapy

A 60-year-old woman presents at the emergency room with severe pain and sudden onset of vision loss in her left eye. Examination of the left eye shows VA of 20/100 and scleritis. The right eye is completely normal.

The fundus image of the left eye shows sheathing along the superior vessel and hemorrhage into the macula and in the nerve fiber layer, along with white-centered hemorrhage and whitish lesions extending out into the periphery ***(Figure 7)****.*

Figure 7. Fundus photograph of the left eye

A late frame of the FA shows staining of the vessels and hyperfluorescence of the disc and a peripheral lesion ***(Figure 8)****. On OCT, there is hyperreflectivity in the middle layer* ***(Figure 9)****.*

Dr Srivastava: What are your thoughts on the diagnosis?

Dr Sharma: The retinitis is worrisome because it suggests infection, which would be important to rule out. The scleritis and other findings, however, raise concern that there may be something else going on.

Dr Taylor: The combination of scleritis and what looks like optic disc vasculitis suggests that this is a very active inflammatory process. Antineutrophil cytoplasmic antibody–associated vasculitis would be at the top of my differential diagnosis. Some evidence suggests that ANCA-associated vasculitis is becoming more common.[1] Because

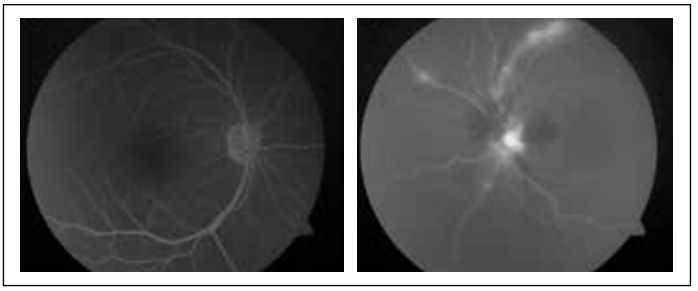

Figure 8. The late fluorescein angiography image from the left eye reveals leakage along the superior arcades and blockage from the hemorrhages

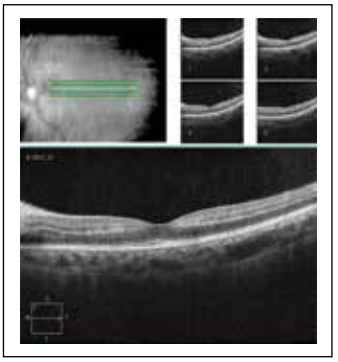

Figure 9. Optical coherence tomography imaging in the left eye reveals some inner and middle retinal hyperreflectance

this patient would probably need to be treated with reasonably heavy immunosuppression to get the vasculitis under control, I would want to make sure that the uveitis is not infectious.

Dr Srivastava: Malignancy is also a possibility. What management advice would you have for a community retina specialist who sees this patient at 5:00 PM on a Friday and is faced with not knowing whether the uveitis is infectious or inflammatory and associated with systemic vasculitis?

Dr Sharma: Both of these situations are associated with a high risk of rapid vision loss, but I would advise covering for infection first. I would recommend doing a tap, if possible, to get a specimen for diagnostic evaluation, injecting an antiviral medication into the eye, and starting oral antiviral treatment or getting the patient into the hospital for intravenous antiviral therapy, along with systemic corticosteroids.

Dr Banker: I would say the patient should be referred to a rheumatologist. Because it will probably take 2 or 3 days to get a complete workup done, I would recommend starting antiviral treatment with a systemic corticosteroid to manage the severe pain, which I expect this patient has, and the potential threat to vision from disc involvement.

Dr Taylor: In a worrisome situation like this, in which the diagnosis has not been made, you need to treat for whichever condition can make the patient go blind in a hurry. I think you cannot go wrong treating for both viral disease and vasculitis by injecting an antiviral agent such as foscarnet, which will cover more than 1 virus, and starting high-dose systemic corticosteroid treatment. It is also useful to do a vitreous tap to help with the diagnosis because otherwise, when the patient begins to improve, you will not know which treatment made a difference and which should be continued.

Dr Srivastava: Foscarnet is a great choice for antiviral treatment, but if it is not available, then high-dose systemic valacyclovir is a good option. The evaluation should also include a good review of systems.

Case 3, Continued

The patient was seen through the emergency room because she also complained of shortness of breath and coughing up blood. She is sent for a chest CT scan, which is abnormal, and she is admitted into the hospital. The patient is given an intravitreal antiviral injection as part of her initial treatment in the hospital. On the floor, her blood oxygen saturation falls and she is transferred to intensive care.

Testing shows a very elevated ANCA level, and a diagnosis of granulomatosis with polyangiitis (formerly Wegener granulomatosis) is made based on evaluation of tissue from a lung biopsy. She was started on intravenous corticosteroids, and her scleritis improved significantly within a few days.

Dr Srivastava: What would be your long-term management of the uveitis in this patient?

Dr Sharma: Granulomatosis with polyangiitis is a sight-threatening disease, and patients tend to do poorly unless they are kept on heavy immunosuppression. If intravenous corticosteroids are given just to quiet the inflammation and then stopped, there is a high risk of recurrence, which can occur with a rapid onset.

I treat these patients aggressively and maintain them on either cyclophosphamide or rituximab. There is evidence showing that both these agents work well, and the choice between them is made in collaboration with the rheumatologist.[2,3]

Dr Srivastava: In some cases of uveitis, we have to decide whether to treat locally or with systemic therapy, but here the decision is easy because the patient has a systemic disease with an ocular complication.

Case 3, Continued

The patient was treated initially with intravenous cyclophosphamide and then transitioned to oral azathioprine. She was lost to follow-up and not seen for 6 months. On examination, her VA was 20/30 and there was some optic nerve cupping ***(Figure 10A)*** *and areas of nonperfusion temporally, with late hyperfluorescence* ***(Figures 10B-10D)****.*

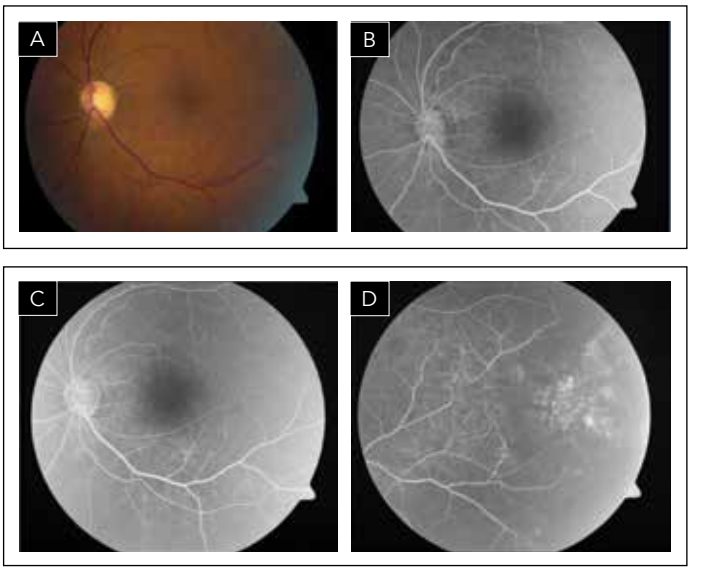

Figure 10. Fundus (A) and fluorescein angiography images (B-D) of the left eye

Subsequently, the patient stopped taking her azathioprine because of side effects. She was found unresponsive in her home, and it was thought that she had experienced a seizure related to cerebral vasculitis. She was started on intravenous rituximab. When next seen in the uveitis clinic 6 years later, her vasculitis was inactive and her VA was 20/20 OD, 20/30 OS.

Dr Srivastava: This patient clearly needed to stay on systemic immunosuppressive therapy and maintain better follow-up. She is an example of a patient who needs a referral to a rheumatologist and/or a uveitis specialist. The complexity of her retinal disease and her systemic illness warrants a team-based approach for management. I often tell colleagues if they have a patient with severe retinal vasculitis with systemic signs, a prompt referral should be made to a uveitis specialist or a rheumatologist. In addition, physicians who are not familiar with immunosuppressive drugs (noncorticosteroids) should refer patients in whom these medications are warranted, per guideline recommendations **(Table 1)**.[4]

What is your first-line choice for a systemic corticosteroid-sparing agent for a patient who has uveitis that is not associated with systemic vasculitis?

Table 1. Indications for Immunosuppressive Therapy in Patients Diagnosed With Uveitis[4]

Management of disease not sufficiently controlled by systemic corticosteroids

- Add an immunosuppressive agent to initial high-dose oral corticosteroid therapy if the disease…
  – Worsens
  – Fails to improve after 2 to 4 weeks
  – Is not completely quiet after 4 weeks

Inability to taper corticosteroid therapy to a safe dose

- Consider an immunosuppressive drug if chronic suppression requires > 10 mg/d prednisone or its equivalent

As first-line therapy for certain types of uveitis, including Behçet disease with posterior segment involvement and mucous membrane pemphigoid with ocular involvement

Patients with certain underlying systemic diseases, including scleritis with systemic necrotizing vasculitis

Dr Taylor: I prefer mycophenolate for adults and methotrexate for children. In my experience, azathioprine is less effective than these agents, and other corticosteroid-sparing immunosuppressive agents are often less well tolerated than mycophenolate and necessitate careful monitoring. Mycophenolate also needs careful monitoring, especially at treatment initiation, but the dosing is often simpler than that of other agents, which require more titration against treatment efficacy and side effects.[4] I do not use cyclosporine at all anymore.

Dr Banker: I also prefer mycophenolate, but after mycophenolate, I use methotrexate and azathioprine about equally. The uveitis types we see in India, including juvenile idiopathic arthritis, sarcoidosis, intermediate uveitis, serpiginous choroiditis, and VKH, respond well to these agents.[4,5]

Dr Sharma: I also prefer mycophenolate for adults, but I find that neither mycophenolate nor methotrexate works that well for scleritis, and I would choose something different, such as rituximab, if there is very severe inflammation.

Dr Srivastava: How long does it take to see benefit after treatment with mycophenolate or methotrexate?

Dr Sharma: Treatment with methotrexate is started at 10 to 15 mg/wk and titrated up by 5 mg every 2 weeks to 20 or 25 mg/wk.[4] A therapeutic response can be seen in 6 to 8 weeks.[4] However, I tell patients it can take 3 months after reaching the full dose to begin to see a benefit. For mycophenolate, I find it takes approximately 2 months after reaching the full dose until we see an onset of effect.

Dr Srivastava: In June 2016, adalimumab, a monoclonal antibody targeting tumor necrosis factor-α, became the first noncorticosteroid agent approved by the US Food and Drug Administration for the treatment of noninfectious intermediate uveitis, posterior uveitis, and panuveitis in adult patients.[6] Its safety and efficacy were demonstrated in patients with active and inactive disease in the VISUAL I **(Figure 11)** and VISUAL II pivotal trials, respectively.[7,8] Both trials analyzed time to treatment failure as the primary end point.

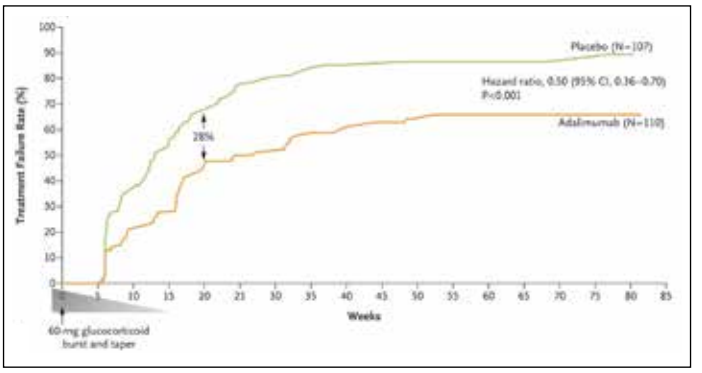

Figure 11. Kaplan-Meier curves of the rate of treatment failure in patients receiving adalimumab vs placebo in the VISUAL I trial

Abbreviation: CI, confidence interval.

From *N Engl J Med*, 375, Jaffe GJ, Dick AD, Brézin AP, et al. Adalimumab in patients with active noninfectious uveitis, 375, 932-943, Copyright© 2016, Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

Adalimumab is given as a subcutaneous injection, with recommended dosing of 80 mg initially, followed by 40 mg every other week.[9] With copays, adalimumab can be less expensive than mycophenolate for patients in the United States. For this reason, adalimumab seems to be emerging as the first-line corticosteroid-sparing systemic agent for noninfectious posterior uveitis. I do not necessarily believe this shift is justified because we have much less experience with adalimumab than with other agents.

How is adalimumab being used at your centers?

Dr Sharma: I, too, am seeing a shift toward increased use of adalimumab now that it is covered by insurance, and patients like it because it involves a self-administered subcutaneous injection that is usually given just every 2 weeks,[9] although I sometimes increase the frequency in very severe cases.

Dr Taylor: In England, adalimumab can only be prescribed as third-line treatment for patients who failed or are intolerant of other corticosteroid-sparing agents.[10]

Dr Banker: In India, we have adalimumab and a biosimilar of adalimumab, but I agree that it is too early to be using adalimumab as a first-line corticosteroid-sparing agent, and rheumatologists seem to think so, too.

One issue that limits the use of adalimumab in India is the high prevalence of TB. Patients are screened for TB before starting adalimumab and monitored for it while being treated. In addition, adalimumab is expensive for patients because there is no insurance reimbursement for it.

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Case 4: Local Therapy

A 35-year-old woman with a history of bilateral intermediate uveitis reports declining vision in her right eye. She failed on methotrexate, refused cyclosporine, and has been on infliximab and methotrexate for many years. She started anti–tumor necrosis factor-α treatment with adalimumab before switching to infliximab 10 mg/kg monthly. She is also getting intravitreal triamcinolone injections occasionally for cystoid macular edema that seem to resolve the edema, but it generally recurs after approximately 2 months.

Visual acuity is 20/80 OD, 20/20 OS. Fundus photographs reveal pigmentary changes peripherally and mild central haze from a cataract in the right eye, whereas the left eye appears normal.

On OCT, there is intraretinal fluid, with irregularly shaped cysts in the foveal area ***(Figure 12)****. The ellipsoid zone and the external limiting membrane appear intact, but there are areas of retinal pigment epithelium loss.*

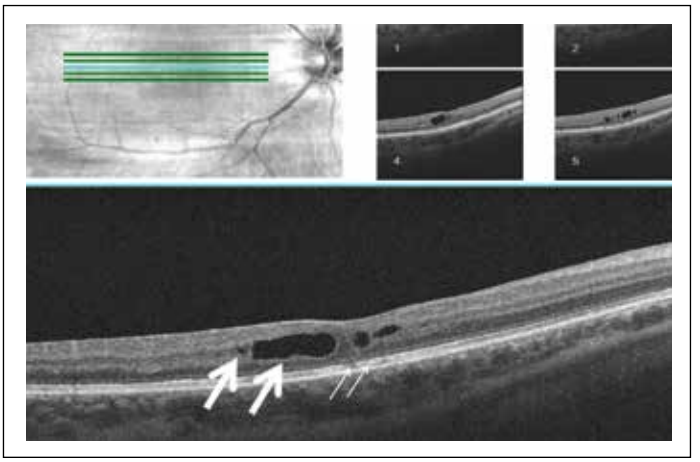

Figure 12. Optical coherence tomography horizontal scan reveals intraretinal edema (large arrows), with some focal retinal pigment epithelium loss (small arrows)

Fluorescein angiography in the right eye shows staining and window defects temporally where the patient has pigmentary changes ***(Figure 13)****. She has significant retinal vascular leakage both in the periphery and in the macula. In the left eye (not shown), she has mild peripheral vascular leakage.*

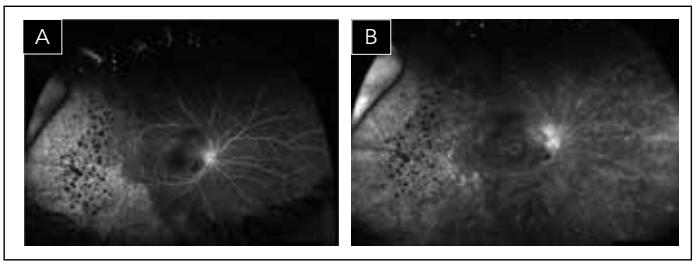

Figure 13. Fluorescein angiogram of the right eye. Early frame (A) reveals normal perfusion. Late frame (B) confirms staining and window defects temporally and retinal vascular leakage both in the periphery and in the macula.

Dr Srivastava: Judging from the irregularity, I believe the cysts have been present for a while. The pigmentary changes on the FA also tell me the inflammation has been smoldering for a long time, which makes me worry about visual potential in this patient. Because her ellipsoid zone and external limiting membrane appear intact, I think there is some potential for visual improvement.

I think we all agree the disease in her right eye is active despite treatment with immunosuppressive medications. Therefore, she is at risk of developing peripheral nonperfusion with complications that can include schisis or detachment. What are your thoughts on treatment?

Dr Banker: I think she is a good candidate for a local therapy that has a sustained duration of action. The dexamethasone implant is the only option available in India, but there is no reimbursement for it. If a patient cannot afford the implant, he or she can continue with intravitreal triamcinolone, and I think even lower doses of 0.5 or 1 mg can be effective while posing a lower risk of intraocular pressure (IOP) elevation and cataract.

Dr Taylor: One could try cyclophosphamide for systemic immunosuppression, but that has quite significant implications for the patient, including an effect on fertility, which could be a particular concern for this 35-year-old woman, as well as the risk of late malignancy.[1] I agree with Dr Banker that local therapy is really preferred for this patient, considering that she has active disease and vision loss in only 1 eye.

Dr Srivastava: In the United States, we have access to the fluocinolone acetonide intravitreal implant, 0.59 mg. I used it in this patient and removed her early cataract at the same time because of the risk of cataract progression with the implant.[2]

Dr Sharma, what would be your end point for determining response to treatment in this patient? Would you look for inactivity on FA or OCT?

Dr Sharma: Fluorescein angiography helps me determine if the disease is active or not, and I order it quite often. Surrogate measures on OCT include changes in cystoid macular edema, thickening of the perivascular area, and nerve fiber layer thickness. With OCT, however, you cannot tell if there is active vasculitis in the periphery.

Case 4, Continued

Follow-up with FA shows an impressive response of the leakage within just a few months after placing a fluocinolone acetonide implant. At the 1-year follow-up, the patient is off infliximab and methotrexate, and VA is 20/40. ***Figure 14*** *is an image from FA done at the 1-year visit. The patient developed elevated IOP that was managed with glaucoma tube surgery approximately 9 months after her fluocinolone implant surgery.*

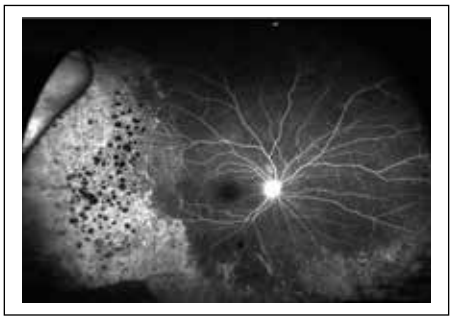

Figure 14. Fluorescein angiogram of the right eye 1 year after placing the fluocinolone acetonide intravitreal implant, 0.59 mg

Dr Srivastava: Intravitreal sirolimus 440 µg is being developed as a local treatment for noninfectious uveitis involving the posterior segment. It is a mammalian target of rapamycin inhibitor that acts to block leukocyte activation and the production of inflammatory cytokines.

The primary and key secondary end points in the 2 phase 3 SAKURA (Sirolimus Study Assessing Double-Masked Uveitis Treatment) studies looked at vitreous haze, and results of an integrated analysis of data from both trials showed statistically significant differences favoring sirolimus 440 µg over sirolimus 44 µg which was the control treatment **(Table 2)**.[3] Other end points, which I consider to have greater clinical relevance, also suggested a benefit with sirolimus. Findings of the integrated analysis suggested sirolimus 440 µg allowed successful tapering of corticosteroid therapy **(Table 2)**.[4]

Table 2. SAKURA Study Results: Data From Month 5 in an Integrated Analysis[3,4]

Intent-to-Treat Population*	Sirolimus 44 µg (n = 208)	Sirolimus 440 µg (n = 208)	*P* Value
Percentage with VH score = 0 (primary end point)	13.5	21.2	.038
Percentage with VH score = 0 or 0.5+ (secondary end point)	40.4	50	.049
Intent-to-Treat Population†	**Sirolimus 44 µg (n = 32)**	**Sirolimus 440 µg (n = 46)**	***P* Value**
Percentage with corticosteroid-tapering success and VH score = 0 or 0.5+	28.1	43.5	.168

Abbreviations: SAKURA, Sirolimus Study Assessing Double-Masked Uveitis Treatment; VH, vitreous haze.

* All enrolled patients had VH score ≥ 1.5+ at baseline.
† Analysis included only patients on overall prednisone-equivalent dose > 5 mg/d at baseline; tapering success was defined as overall prednisone equivalent dose ≤ 5 mg/d.

In addition, published data from SAKURA 1 showed that in the sirolimus 440-µg group, patients with good vision at baseline maintained vision, whereas vision improved in patients with relatively poor vision at enrollment.[5] Best-corrected VA data are not available from SAKURA 2. Importantly, sirolimus also had a favorable safety profile in SAKURA 1, with low rates of cataract and increased IOP.[5]

Dr Taylor, what are your thoughts on the role of sirolimus as local therapy?

Dr Taylor: The downsides of local corticosteroid treatment are the risks of IOP elevation and cataract. Intraocular pressure can usually be controlled and cataract is not a big concern for older presbyopic patients. Nevertheless, any medication that avoids these side effects would be a big step forward, and the hope is that sirolimus will provide efficacy that at least approaches the benefit of corticosteroids, with less risk of cataract and IOP elevation.

Dr Srivastava: It appears that sirolimus may need to be given every 2 months. Do you think patients with uveitis would accept this injection regimen?

Dr Sharma: Assuming that the visit can be reasonably short, I think patients would be happy to return every 2 months for a treatment that is effective and that has a favorable side-effect profile.

Dr Banker: Young patients are tired of being on systemic medications because of the side effects, which also affect their ability to work, so they are excited about the potential of local therapy with sirolimus. I have 42 patients in my investigator-sponsored trial of sirolimus, with follow-up to as long as 4 years (unpublished data). Patients are compliant with their return visits, and I have used sirolimus as primary therapy, with good results, in some patients. Quite a few patients have received 3 or 4 injections and then did not need any treatment for 2 years.

Dr Srivastava: Emerging local therapies make this an exciting time in uveitis. We hope that sirolimus will be approved, and positive results have been reported with the injectable long-acting fluocinolone acetonide intravitreal implant after 2 years of follow-up in a small, investigator-sponsored study.[6] In addition, results of a phase 1/2 study of suprachoroidal triamcinolone acetonide injection were encouraging because they supported the idea that the suprachoroidal route of administration might minimize the side-effect risks of local corticosteroid treatment.[7]

Having more options with new systemic and local therapies will enhance our ability to tailor therapy. A personalized approach will entail more work for the treating ophthalmologist, but with work under way by the Standardization of Uveitis Nomenclature working group to better classify disease phenotypes and by using our imaging technologies, I think we will have better ways to categorize patients, which will help guide treatment decisions.

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TAKE-HOME POINTS

Accurate diagnosis of uveitis depends on a comprehensive assessment that should include a thorough history, ocular examination, review of systems, and laboratory evaluations chosen on the basis of sensitivity, specificity, and pretest probability.

Differentiating infectious uveitis from noninfectious uveitis is critical because infectious uveitis can be rapidly sight threatening.

Multimodal imaging may be needed to fully characterize pathology in patients with posterior uveitis.

Do not inject a corticosteroid into or around the eye for treatment of uveitis until an infectious cause has been ruled out.

Systemic treatment with immunosuppressive agents or biologics is indicated for posterior uveitis when inflammation cannot be controlled by a corticosteroid alone, if the corticosteroid cannot be tapered to a safe dose, and for management of certain underlying systemic diseases.

Do not hesitate to refer patients to a uveitis specialist if the diagnosis is uncertain, if the condition is not responding to the chosen therapy, if the uveitis is associated with a systemic disease, and if systemic immunosuppressive therapy is indicated and the ophthalmologist lacks familiarity with its use.

Subcutaneous adalimumab is the first and only noncorticosteroid medication that is approved by the US Food and Drug Administration for the treatment of noninfectious intermediate uveitis, posterior uveitis, and panuveitis.

Intravitreal sirolimus showed promising efficacy and safety in phase 3 trials as a local therapy for noninfectious uveitis involving the posterior segment.

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1. Prompt identification of an infectious cause for uveitis involving the posterior segment is important because:
   A. All corticosteroids should be avoided until infection is ruled out
   B. Hypotony can occur rapidly with untreated infectious uveitis
   C. The patient requires prompt referral to an ophthalmologist with expertise in managing uveitis
   D. Vision loss can occur rapidly with untreated infectious uveitis

2. Which of the following might be considered in an immunocompromised patient with posterior uveitis when a viral cause is suspected?
   A. Anterior chamber or vitreous tap to check for viruses
   B. Intracameral injection of an antiviral agent
   C. Simultaneous corticosteroid and antiviral intravitreal treatment while awaiting diagnostic confirmation
   D. Observation for progression

3. Multimodal imaging may be needed for a comprehensive diagnostic assessment of pathology in eyes with posterior uveitis, and it might include all the following, EXCEPT:
   A. EDI OCT
   B. ICGA
   C. FA
   D. Wide-field FA

4. Which of the following diagnoses would you consider most likely when seeing midperipheral retinitis in a patient who is HIV positive?
   A. BSRC
   B. Cytomegalovirus retinitis
   C. Lymphoma
   D. Sarcoidosis

5. Oral prednisone is initiated to treat a patient with noninfectious posterior uveitis and achieves disease control. Systemic immunosuppression should be considered if:
   A. The prednisone dose required to maintain chronic suppression exceeds 1 mg/d
   B. The prednisone dose required to maintain chronic suppression exceeds 5 mg/d
   C. The prednisone dose required to maintain chronic suppression exceeds 10 mg/d
   D. Prednisone cannot be discontinued after 1 month

6. The VISUAL I and VISUAL II studies investigated adalimumab as a treatment for noninfectious uveitis involving the posterior segment. In both studies, treatment with adalimumab was given as:
   A. An oral capsule
   B. A subcutaneous injection
   C. An intravitreal injection
   D. An intravenous infusion

7. The anti-inflammatory activity of sirolimus results from:
   A. Binding to lymphocyte function–associated antigen 1 expressed on T cells
   B. Inhibition of leukocyte activation and production of proinflammatory cytokines
   C. Integrin receptor inhibition
   D. Interleukin-17 blockade

8. In an integrated analysis of data from the phase 3 SAKURA studies, statistically significant differences favoring sirolimus 440 µg over control treatment, sirolimus 44 µg, were found for the following end points.
   A. Vitreous haze score = 0 and vitreous haze score ≤ 0.5
   B. Vitreous haze score = 0 and corticosteroid-tapering success with vitreous haze reduction
   C. Vitreous haze score ≤ 0.5 and corticosteroid-tapering success with vitreous haze reduction
   D. Vitreous haze score ≤ 0.5 and time to treatment failure

9. A patient with bilateral panuveitis is started on methotrexate 10 mg once weekly, with upward titration by 5 mg every 2 weeks to the current dose of 20 mg. At 1 month after starting therapy, there is no improvement in vitreous haze, but VA appears to be stable. An appropriate action would be to:
   A. Switch to cyclophosphamide
   B. Continue the methotrexate at the current dose for an additional 1 to 2 months prior to changing therapy
   C. Start the patient on high-dose corticosteroids
   D. Perform a lumbar puncture to rule out lymphoma

10. A male patient with Behçet disease presents with uveitis involving the posterior segment and is started on high-dose prednisone to control the ocular inflammation. At his 2-week visit, the uveitis appears to be worsening. What is your next step?
    A. Treat with intravenous methylprednisolone and raise the prednisone dose
    B. Inject the dexamethasone implant
    C. Refer the patient to a uveitis specialist
    D. Wait 2 more weeks to see if there is improvement

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ACTIVITY EVALUATION/CREDIT REQUEST

CHRONIC NONINFECTIOUS UVEITIS OF THE POSTERIOR SEGMENT: CURRENT AND FUTURE APPROACHES TO INDIVIDUALIZE MANAGEMENT
To receive *AMA PRA Category 1 Credit*™, you must complete this **Evaluation** form and the **Post Test.** Record your answers to the **Post Test** in the Answer Box located below. Scan this completed page and return via e-mail to cme-nyee@nyee.edu or fax it to 212-870-8128. Your comments help us to determine the extent to which this educational activity has met its stated objectives, assess future educational needs, and create timely and pertinent future activities. Please provide all the requested information below. This ensures that your certificate is filled out correctly and is e-mailed to the proper address. It also enables us to contact you about future CME activities. Please print clearly or type. Illegible submissions cannot be processed.

PARTICIPANT INFORMATION *(Please Print)* ☐ Home ☐ Office

Last Name _____ First Name _____

Specialty _____Degree ☐ MD ☐ DO ☐ OD ☐ PharmD ☐ RPh ☐ NP ☐ RN ☐ PA ☐ Other

Institution _____

Street Address _____

City _____State _____ ZIP Code _____Country_____

E-mail _____ Phone_____Fax_____

Please note: We do not sell or share e-mail addresses. They are used strictly for conducting post-activity follow-up surveys to assess the impact of this educational activity on your practice.
Learner Disclosure: To ensure compliance with the US Centers for Medicare and Medicaid Services regarding gifts to physicians, **New York Eye and Ear Infirmary of Mount Sinai** CME requires that you disclose whether or not you have any financial, referral, and/or other relationship with our institution. **CME certificates cannot be awarded unless you answer this question.** For additional information, please e-mail NYEE CME at cme-nyee@nyee.edu. Thank you.
☐ Yes ☐ No I and/or my family member have a financial relationship with **New York Eye and Ear Infirmary of Mount Sinai** and/or refer Medicare/Medicaid patients to it.

☐ **I certify that I have participated in the entire activity and claim 1.5 *AMA PRA Category 1 Credits*™.**

Signature Required _____**Date Completed** _____

OUTCOMES MEASUREMENT

☐ Yes ☐ No **Did you perceive any commercial bias in any part of this activity? IMPORTANT! If you answered "Yes," we urge you to be specific about where the bias occurred so we can address the perceived bias with the contributor and/or in the subject matter in future activities.**

Circle the number that best reflects your opinion on the degree to which the following learning objectives were met:
5 = Strongly Agree 4 = Agree 3 = Neutral 2 = Disagree 1 = Strongly Disagree

Upon completion of this activity, I am better able to:

- Discuss the use of diagnostic assessments to differentiate between infectious and noninfectious uveitis of the posterior segment 5 4 3 2 1
- Assess which patients with noninfectious uveitis of the posterior segment would be referred to a uveitis specialist 5 4 3 2 1
- Demonstrate application of evidence-based treatments for a variety of patients with noninfectious uveitis of the posterior segment 5 4 3 2 1
- Describe the mechanism of action and clinical trial outcomes for emerging agents in clinical trials for local therapy for noninfectious uveitis of the posterior segment 5 4 3 2 1

1. Please list one or more things, if any, you learned from participating in this educational activity that you did not already know.

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2. As a result of the knowledge gained in this educational activity, how likely are you to implement changes in your practice?
4 = definitely will implement changes 3 = likely will implement changes 2 = likely will not implement any changes
1 = definitely will not make any changes 4 3 2 1
Please describe the change(s) you plan to make: _____

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3. Related to what you learned in this activity, what barriers to implementing these changes or achieving better patient outcomes do you face?_____
4. Number of patients with posterior uveitis I see per week
☐ 0 ☐ 1-5 ☐ 6-10 ☐ 11-25 ☐ More than 25
5. Please check the Core Competencies (as defined by the Accreditation Council for Graduate Medical Education) that were enhanced for you through participation in this activity.
☐ Patient Care ☐ Practice-Based Learning and Improvement ☐ Professionalism
☐ Medical Knowledge ☐ Interpersonal and Communication Skills ☐ Systems-Based Practice

6. What other topics would you like to see covered in future CME programs? _____

ADDITIONAL COMMENTS _____

POST TEST ANSWER BOX

1	2	3	4	5	6	7	8	9	10