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Infectious Uveitis

New Challenges Emerge

Infectious uveitis encompasses an impressive array of potential pathogens and presentations—some familiar and others newly emergent in an increasingly global ophthalmic world. These microorganisms demand the attention of all ophthalmologists, any one of whom may encounter a patient with a puzzling presentation related to an infectious cause.

BY MARIANNE DORAN, CONTRIBUTING WRITER

Keeping tabs on the plethora of organisms that can cause infectious uveitis is becoming more difficult with increasing globalization. “We talk about the increase in travel, but it’s bigger than that,” said Rubens Belfort Jr., MD, at São Paulo Hospital in São Paulo, Brazil. “Hundreds of thousands of people are moving from one country or continent to another, and this is changing the epidemiology of infection in ophthalmology.

“We saw some of this in the United States when so many people immigrated from Asia and Latin America,” Dr. Belfort noted. “In Brazil, we see people from all over Latin America and Haiti. We can no longer say that a disease is specific to one part of the world, and that makes the differential diagnoses of these infections much broader than before.”

And increased commercial air travel is adding to the mix. “It’s definitely a smaller planet because of air travel,” said Johnny Tang, MD, at the Eye Health Vision Center in Dartmouth, Mass. “Whenever I encounter a patient with uveitis, my first thought is, ‘Is this process infectious?’ If the answer is yes, diagnosis and treatment will follow a completely different path from that of non-infectious uveitis. Noninfectious uveitis—we can take care of. But if it’s infectious, and you don’t suspect it, you are in trouble for the duration of the time that you are going to see that patient.”

The initial diagnosis of infectious uveitis is made primarily through pattern recognition of the presenting signs, course, and outcome of the disease. One of the inherent challenges is that the workup must be carefully tailored to the signs, symptoms, and history of each particular patient.

Pattern Recognition Guides High-Stakes Diagnoses

“This must always guide the precise workup,” said Russell N. Van Gelder, MD, PhD, at the University of Washington in Seattle. “That said, certain conditions can present in almost any way in the eye. I think about sarcoidosis, syphilis, and tuberculosis in almost every patient I see. If I lived on the East Coast, I would add Lyme disease to that list.”

While there are a number of potential etiologies for infectious uveitis, this article will focus on the leading culprits and present some clinical clues that can move the diagnostic process forward.

Amod Gupta, MBBS, at the Advanced Eye Centre at the Post-Graduate Institute of Medical Education and Research in Chandigarh, India, said that herpes simplex

Herpes

virus (HSV) is among the more common viruses he sees in his country. “These patients typically have unilateral disease and elevated intraocular pressure [IOP], and they may have pigmented keratic precipitates [KPs] and sectoral iris atrophy. Loss of corneal sensation is a very important clue to the HSV etiology. Because HSV is notoriously recurrent, patients require long-term oral antiviral therapy.”

Viral uveitis is also what Phoebe Lin, MD, PhD, sees the most in her practice at the Casey Eye Institute in Portland, Ore. “I would expect a viral etiology if the patient has an anterior uveitis with corneal anesthesia and transillumination defects in the iris, perhaps associated with elevated IOP. If that is the case, I would suspect one of three viruses in the Herpesviridae family—HSV, varicella-zoster virus [VZV], or cytomegalovirus [CMV]. Those are the things I look for first.”

Dr. Lin added, “The diagnostic test is going to be the key, but what I look for clinically in acute retinal necrosis due to HSV or VZV is a peripheral necrotizing retinitis [Fig. 1], an occlusive arteritis, and varying degrees of vitritis. There is often optic nerve involvement as well.”

The clues to CMV include elevated IOP and the presence of one or two mutton-fat KPs. “We now recognize that cytomegalovirus can cause several forms of uveitis, even among patients who are not immunocompromised,” said Dr. Van Gelder (Fig. 2). “In glaucomatocyclitic crisis—or Posner-Schlossman syndrome—at least a subset of patients has been found to have very high levels of CMV infection in the anterior chamber. This is treatable with valganciclovir but only if the patient has the infection. Biopsying the aqueous humor and testing for CMV by polymerase chain reaction [PCR] can be very useful in these cases.”

Fuchs uveitis is the most commonly misdiagnosed form of anterior uveitis. Diagnostic clues include classic stellate KPs on the back of the entire cornea, dif-

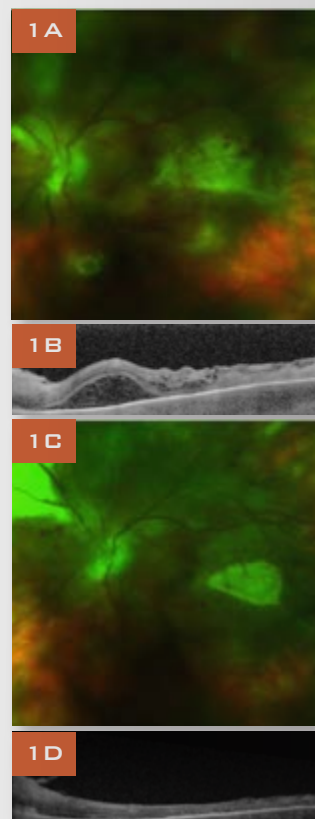
Fuchs Uveitis

fuse iris atrophy with loss of iris crypts, and, possibly, heterochromia. “The patient primarily presents because of decreased vision due to a complicated cataract,” said Dr. Gupta. “Significant vitreous opacities are also common, and patients may have elevated IOP.” Fuchs uveitis is unilateral; in some patients, the color of the irides doesn’t match. The disease has also been linked to the rubella virus and is becoming less common in communities with rubella vaccination programs in place.

A FISHERMAN’S GUIDE TO THE WORKUP

The procedure for evaluating a patient for uveitis is usually straightforward, but people don’t always adhere to it, Dr. Van Gelder said. In one case, an ophthalmologist had conducted a good lab workup but didn’t follow up to ensure that the tests had been completed and the results were in. “Unfortunately, this ophthalmologist proceeded to inject steroids into the eye of the patient, who turned out to have infectious uveitis that became much worse after the steroid was injected.” Dr. Van Gelder said that a case like this offers a number of learning points, which he describes through fishing analogies:

- Bring your fishing rod when you look for uveitis. You really have to fish for the possible causes.
- If you cast your line, you have to reel it in. That is, if you do a lab workup on a patient, you have to follow up on it.
- Don’t fish for things you don’t know how to “cook.” As he noted, “Occasionally, I see ophthalmologists obtain lab tests that they don’t fully understand, such as the antinuclear antibody test. Uveitis cases associated with systemic lupus erythematosus are extremely rare, and when the test comes back positive, the ophthalmologist doesn’t know what to do with it. The patient probably doesn’t have lupus, but now a positive lab test needs to be followed up.”



HERPES. In this case of acute retinal necrosis due to HSV, (1A) the fundus photo on presentation demonstrates vitritis (2+ haze), retinal arteritis, and necrotizing retinitis. (1B) Serous retinal detachment, intraretinal fluid, and retinitis are evident on OCT. (1C) After six days of treatment with intravitreal foscarnet and oral valacyclovir, the fundus photo shows consolidation of areas of retinitis, and (1D) OCT shows resolution of the serous retinal detachment.



CMV. This patient’s cytomegalovirus infection (shown here) resolved after six weeks of treatment with intravenous foscarnet.

Lyme Disease

Lyme disease is typically associated with multisystem abnormalities, the most prominent of which affect the skin, nervous system, musculoskeletal system, and heart. The Lyme disease bacterium, *Borrelia burgdorferi*, is spread through the bite of infected deer ticks in much of the United States, particularly the northeastern, mid-Atlantic, and north central regions. On the West Coast, the culprit is the Western blacklegged tick.

Dr. Tang recalled a 30-year-old patient who was treated for unilateral anterior uveitis with topical steroids for several months by the referring ophthalmologist. Because the patient was from an apparently unaffected area, a detailed history and workup for Lyme disease was overlooked. Upon Dr. Tang's evaluation, the history revealed a camping trip in western Ohio several months before the uveitis began. With the correct diagnosis, the patient was successfully treated with systemic antibiotics.

Early ocular manifestations of Lyme disease may include conjunctivitis and photophobia. But these relatively mild symptoms are often followed by Bell palsy and possibly by Lyme neuroborreliosis, which involves cranial nerve palsy, radiculopathy, and meningitis. During this stage, blurred vision is common and typically results from optic atrophy, papilledema, pseudotumor cerebri, and optic or retrobulbar neuritis. Vitritis, keratitis, pars planitis, and a host of other severe ocular conditions are common in the late stages of Lyme disease (Fig. 3).

Sarcoidosis diagnoses are challenging because the blood tests for angiotensin-converting enzyme or lysozyme levels are neither sensitive nor specific. Dr. Van

Sarcoidosis

Gelder usually begins with a chest x-ray to look for sarcoid and an examination of the conjunctiva to look for granulomas that can be biopsied. If the patient has signs of hilar adenopathy, he orders a chest CT scan; if the scan is positive, he sends the patient to a pulmonologist or thoracic surgeon who can perform either a bronchoscopy or a mediastinoscopy to make the sarcoidosis diagnosis.¹

The recent resurgence of syphilis cases in the United States shows just how easily pathogens can come storming back when public health officials and the target populations let their guards down. According to the Centers for Disease Control and Prevention, syphilis cases have reached their highest level since 1995.² In the United States, the number of cases reported each year nearly doubled from 2005 (8,724 cases) to 2013 (16,663 cases).

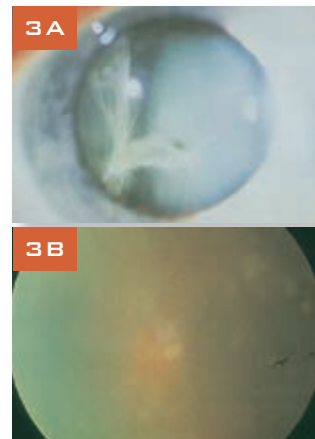
Syphilis

The rapid return of syphilis in less than 10 years is especially concerning because the behaviors associated with syphilis are the same high-risk behaviors linked to HIV infection.

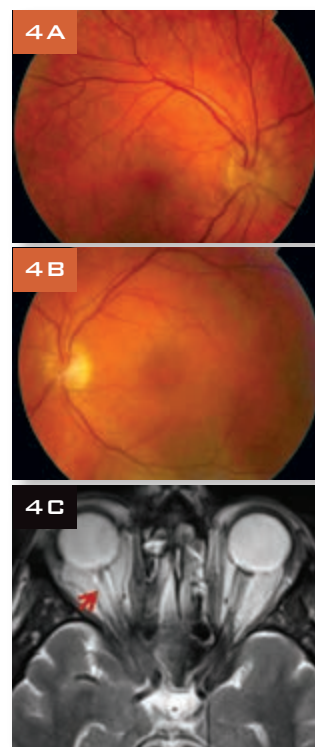
The more typical presentations of syphilis are 1) acute syphilitic posterior placoid retinitis, in which patients present with yellowish placoid outer retinal lesions with varying degrees of anterior chamber and vitreous inflammation, and 2) syphilitic punctate inner retinitis that presents with yellowish dewdrop-like inner retinal precipitates. "If I see either of these two appearances, I think first and foremost [of] syphilis," said Dr. Lin. "Other rare presentations of syphilis include an isolated outer retinal atrophy that can appear clinically similar to an acute zonal occult outer retinopathy [AZOOR]. Occasionally, syphilis can be isolated to an anterior uveitis."

Dr. Tang said ophthalmologists need to remember that syphilis is known as one of the "great masqueraders" for a good reason, as it can present as inflammation in any part of the eye. He cited a case in which a 45-year-old man presented with bilateral uveitis and bilateral optic neuritis (Fig. 4). Prompt recognition of the condition and immediate treatment led to complete resolution of his uveitis.³

Dr. Gupta noted that he tests for syphilis more than any other disease, adding that it is easily curable with intravenous penicillin G at 4 million units every four hours for two weeks.



LYME. (3A) In one patient with Lyme disease, dense anterior vitritis debris caused floaters and blurring. (3B) In another, grade 3 vitreous opacification, as seen by indirect ophthalmoscopy, was reminiscent of severe pars planitis.



SYPHILIS. (4A, 4B) The patient had bilateral optic nerve edema and (4B) vitreous cells and haze in the left eye. (4C) A T2-weighted magnetic resonance imaging sequence revealed increased signal intensity of the optic nerve in the right eye.

Toxoplasmosis

Toxoplasmosis retinitis is a common presentation that is typically identified by the presence of a pigmented chorioretinal scar (Fig. 5A). “If someone has a pigmented scar and either an adjacent or a nonadjacent area of retinitis, the cause is most likely toxoplasmosis,”

Dr. Lin said. This clinical sign is not necessarily specific to toxoplasmosis, she added, and that is why diagnostic tests like PCR are so important.

Other associated signs of toxoplasmosis may include a localized arteritis and varying degrees of vitreous inflammation, from overlying vitreous cells to a diffuse vitreous haze. Anterior chamber inflammation also may be present. According to Dr. Lin, toxoplasmosis can present atypically in immunocompromised patients, who may have more widespread disease with multifocal lesions in the retina.

Dr. Gupta noted that when toxoplasmosis presents as a focal necrotizing retinitis with an intense vitreous haze overlying the retinitis lesion, it creates a distinct “headlight in the fog” appearance (Fig. 5B). These focal retinitis lesions may also occur de novo without a prior scar and are due to acquired toxoplasmosis.

In many countries, the problem with ocular toxoplasmosis is also the damage caused by reactivations, Dr. Belfort said. “A new hypothesis suggests that extraocular organisms trigger these reactivations and may indicate a role for long-term prophylactic treatments.”

As with syphilis, many clinicians are also seeing a resurgence of tuberculosis. Dr. Tang recently examined a 90-year-old man who wasn’t coughing

Tuberculosis

but had experienced eye inflammation for the last three years. “The outside treating physicians were treating him with steroids, and the inflammation would go away and come back, go away and come back,” Dr. Tang said. “When they finally sent the patient to me, he had massive inflammation everywhere. When I see something like this, I always order a panel for Lyme disease, tuberculosis, and syphilis; I also obtain a chest x-ray. I usually look at these entities first because they can mimic everything else.”

The patient did have tuberculosis, and Dr. Tang treated him with a combination of drugs (ethambutol, isoniazid, pyrazinamide, and rifampin). The general recommendation is for the patient to take some combination of these drugs for at least six to nine months.

TB uveitis is often paucibacillary, Dr. Gupta said, and it is believed that most of the inflammation is driven by an immune reaction to the presence of the TB bacilli in the eye. Diagnosis of TB uveitis is often made in the context of suggestive clinical signs, such as the presence of broad posterior synechiae in anterior uveitis, multifocal serpiginous choroiditis, retinal

Diagnostic surgery can be critical to establishing the diagnosis of infectious uveitis

in certain situations, such as the following.

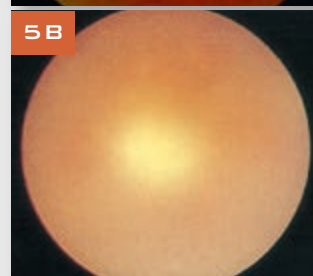
- **Genuine diagnostic dilemma.** Surgery can be helpful in a patient who has a severe condition—usually panuveitis—and the clinical picture isn’t clear. Is it toxoplasmosis? Herpes infection? Endophthalmitis? “In

these cases, taking a vitreous sample, or even an aqueous sample—although vitreous is preferred—and running a molecular test on it can yield a diagnosis in a good number of cases,” said Dr. Van Gelder. PCR is the typical technique for finding pathogens.

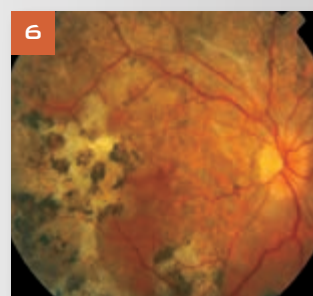
- **No response to treatment.** You treat the patient for what you believe is the correct diagnosis (for example, antiherpes therapy for herpetic retinitis), but she doesn’t respond.

Now you have to reconsider the etiology. Diagnostic procedures may be called for to ensure that the patient receives appropriate treatment.

- **Already in the eye.** If you are going to tap and inject an eye for suspected endophthalmitis, use that opportunity to take a sample while you are in the eye and send the sample off for diagnostic testing. However, any question or concern about a possible ocular malignancy is in a category of its own and requires a biopsy.



TOXOPLASMOSIS. (5A) Retinitis around an old scar, and (5B) the classic “headlight in the fog” appearance of focal, white retinitis with overlying vitreous inflammation.



TUBERCULOSIS. This patient's tuberculous choroiditis masqueraded as recurring atypical serpiginous choroiditis. After anti-TB treatment, vision improved and the vitritis resolved without further recurrences.

INDICATIONS FOR DIAGNOSTIC SURGERY

vasculitis with perivascular active choroiditis lesions or healed choroiditis scars, and choroidal granulomas (with or without exudative subretinal fluid). Significant vitreous inflammation may be present as well (Fig. 6).

Dr. Van Gelder cautioned that tuberculosis can be “overworked up.” This is problematic in that “the risk of a false-positive is fairly high and can lead to patients having to take medicine for six to nine months when they didn’t need it.” He tests for TB if patients are recent immigrants, have spent significant time in an endemic area, have a family member with TB, or have a clinical presentation that raises significant suspicion for the disease. He also tests patients who are starting immunomodulatory drugs.

Dr. Gupta added that viral infections of the retina have emerged in parts of South Asia during epidemics of dengue fever, chikungunya fever, and West Nile virus.⁴ These infections lead to necrotizing retinitis in the posterior pole along with retinal hemorrhages.

More Threats Emerging?

“The presence of necrotizing hemorrhagic lesions in the posterior pole in immunocompetent individuals should raise the possibility of RNA viral infections for which no specific treatment is available,” Dr. Gupta said. “A patient’s travel to endemic areas of epidemic zones may provide vital clues to the diagnosis.”

Despite all the menacing microorganisms and the challenges of trying to stay three steps ahead of the myriad pathogens that can do harm to patients, it’s important for ophthalmologists to know that a lot can be done to prevent and treat infectious uveitis, Dr. Belfort said. “In the future, we will be gathering intraocular specimens from aqueous humor and even the vitreous more and more often for specific analytical tests—not just blood, x-rays, and intraocular workups.” For now, the general ophthalmologist must know how to diagnose infectious uveitis and when to refer the patient to a specialist. “We know that just asking for lab tests or visual tests, such as a fluorescein angiogram or optical coherence tomography, is not good enough,” Dr. Belfort said. “A good history, an intelligent conversation with the patient, and a good bilateral exam are 90 percent of solving the problem.” ■

1 De Niro J et al. *EyeNet Magazine*. 2014;18(6):51-52.

2 Patton ME et al. *MMWR Morb Mort Wkly Rep*. 2014;63(18):402-406.

3 Mustafi D et al. *EyeNet Magazine*. 2011;15(7):47-48.

4 Khairallah M, Kahloun R. *Curr Opin Ophthalmol*. 2013;24(6):574-580.



MORE ONLINE. For a discussion about biologics for noninfectious uveitis, see the Web Extra that accompanies this article at www.eyenet.org. For a slideshow presenting five cases of infectious uveitis, visit the home page at www.eyenet.org.

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