Differential Diagnosis of Unusual Infectious and Inflammatory Diseases of the Eye

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Management of infectious and inflammatory diseases of the eye can be a challenge, because even a single diagnosis can have varied presentations. Although laboratory results may aid in the diagnosis, awareness of other potential causes is important. Some of the more unusual diseases "masquerade" as others, often resulting in a delay in diagnosis and appropriate treatment. In this symposium, leading experts in the field presented cases representing some of these masquerades, and described techniques for differentiating potential diagnoses.

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MALIGNANT AND INFECTIOUS MASQUERADES OF UVEITIS

Debra A. Goldstein, MD, Northwestern University, Chicago, Illinois, USA, presented case studies of malignant and infectious conditions presenting as nongranulomatous anterior uveitis. The presentation, diagnostic workup, and diagnoses of the cases are shown in Table 1.

Malignant nongranulomatous anterior uveitis masquerades can be hematologic or solid tumors. In some cases, ocular manifestations are the first signs of disease. A systemic history and review of symptoms are an important part of the diagnostic workup. On examination, large, often refractile cells or iris masses may be observed. There is little flare, and sequelae of inflammation are absent. Such lesions generally respond poorly to steroid therapy.

Herpetic disease is the most frequent infectious masquerade that often is missed in the absence of corneal disease. Patients should be queried about a history of cold sores and herpes zoster. On examination, the intraocular pressure (IOP) typically is high, and iris atrophy is common. Herpetic lesions respond poorly to therapy. Cytomegalovirus (CMV) may cause anterior uveitis in immunocompetent patients. The IOP typically is high, and the condition may mimic Posner-Schlossman syndrome or Fuchs iridocyclitis. The diagnosis can be confirmed by aqueous polymerase chain reaction (PCR).

SCC MASQUERADING AS SCLERITIS, UVEITIS, OR KERATITIS

Carol L. Karp, MD, University of Miami, Miami, Florida, USA, discussed the case of a man aged 66 years with a history of renal transplantation who presented with redness and pain in the right eye. He had a pterygium excised 25 years before, with a 7-month history of "regrowth" of the pterygium associated with progressive decline in vision. At presentation, his visual acuity (VA) was HM OD and 20/25 OS, with afferent pupillary defect, and IOP of 39 OD and 13 OS. He had conjunctival injection, 2+ cells, pigmented keratitic precipitates, midstromal infiltrate with feathery borders, a subepithelial nodule, and iris nodules in the right eye.

The differential diagnosis included infectious or inflammatory scleritis, keratitis, or uveitis, fungal infection, or neoplasia. B-scan ultrasonography showed a thickened conjunctiva, and no scleritis or vitreous membranes. Ultra high-resolution optical coherence tomography demonstrated thickened hyperreflective epithelium, which is characteristic of ocular-surface squamous neoplasia. Cultures were negative, and magnetic resonance imaging (MRI) showed preseptal thickening. An incisional biopsy showed extensive squamous cell carcinoma (SCC) with extension to multiple margins. Anterior chamber (AC) tap was negative.

Because there was a high suspicion of intraocular invasion, enucleation with wide margins and cryotherapy were performed. SCC with mucoepidermoid differentiation was found with invasion into the iris, AC angle, Schlemm's canal, corneal stroma, and ciliary body. A literature search of similar symptomatology found only 42 cases, 27 of which had full details; of these, 55.5% had intraocular invasion, and 59.2% recurred after primary treatment.

Table 1. Case Presentations

Case No.	Case Presentation	Diagnostic Evaluation	Diagnosis/Comments
1	Woman aged 24 y 3-wk history of redness, decreased vision in OS Diagnosis of iritis Referred for nonresponse to topical and injected steroids Visual acuity 20/20 OU; IOP fundus normal OU	Past history: ALL 3 y ago, chemotherapy and radiation Slit lamp examination OD is normal Slit lamp examination OS reveals large iris masses, 4+ large refractile cells, very large refractile cells, 0.5+ flare, and atypical hypopyon AC tap for diagnosis	ALL recurrence History often suggests diagnosis Perform detailed review of systems, history Even without history of cancer, AC tap needed for diagnosis
2	Woman aged 75 y Uveitis OD Nonresponse to steroids Hypertension, COPD 2-pack/d smoker for 60 y Visual acuity 20/25 OU; IOP 23, 19	Slit lamp examination No posterior synechiae or other signs of inflammation Large mass with nodules in iris 4+ large atypical-looking cells Little flare in proportion to cells Gonioscopy showed balls of cells Incisional biopsy and aspiration of nodules Lung CT and biopsy	Metastatic lung cancer
3	Woman aged 42 y 3-y history uveitis OD Subacute onset Visual acuity 20/70, 20/20; IOP 31, 15 Pharmacologic therapy for pressure and inflammation Nonresponse to steroids	Slit lamp examination (2+ AC cells OD, normal OS) Fundus examination (C/D asymmetry, no retinal pathology) Clues suggesting herpes: unilateral disease, subacute onset, high IOP at presentation, subtle corneal scarring, decreased corneal sensation, KP stellate throughout cornea and granulomatous central cornea, dilated pupil in involved eye, iris atrophy (patchy, sectoral, or diffuse), and iris transillumination defects AC tap with PCR confirmed herpes simplex virus	Herpetic uveitis Important to examine fundus Treatment with systemic antivirals, topical corticosteroids, and IOP treatment Long-term therapy often required

AC, anterior chamber; ALL, acute lymphoblastic leukemia; C/D, cup to disc; COPD, chronic obstructive pulmonary disease; CT, computed tomography; IOP, intraocular pressure; KP, keratitic precipitate; OD, right eye; OS, left eye; OU, both eyes; PCR, polymerase chain reaction.

SCC can be misdiagnosed as scleritis, uveitis, or keratitis of unknown cause [Mahmood MA et al. *Ophthalmology.* 2001], and may occur with pterygium. Intraocular inflammation and high IOP may indicate intraocular invasion.

INFILTRATING TUMORS THAT PRESENT AS CHRONIC PANUVEITIS

Arun D. Singh, MD, Cleveland Clinic, Cleveland, Ohio, USA, discussed the presentation and diagnosis of uveal malignancies, which produce infiltrates that can masquerade as uveitis. Both metastatic and primary cancers can result in uveal infiltration. While about 65% of patients with uveal metastasis have a prior history of cancer, 20% are diagnosed subsequent to uveal symptoms. Uveal metastasis may occur with breast, lung, gastrointestinal, prostate, renal, melanoma, and other cancers.

Signs and symptoms of uveal metastasis include the presence of a mass, inflammation, iris neovascularization, and secondary glaucoma. The possibility of malignancy should be considered in patients presenting with scleritis that is nonresponsive to steroids. A patient presenting with scleritis that did not respond to treatment with steroids, for example, was found to have a yellowish infiltrating mass in the iris. Ultrasound biomicroscopy and systemic studies resulted in a diagnosis of metastatic lung cancer.

Once uveal metastasis is diagnosed, treatment can include systemic therapy, enucleation or external-beam radiation therapy, and plaque transpupillary thermotherapy [Singh AD et al. *Clinical Ophthalmic Oncology.* 2007].

Primary uveal tumors typically present as a mass without inflammation, iris neovascularization, or secondary glaucoma. Dr Singh has diagnosed primary melanoma,

Table 2. Differential Diagnosis of Posterior Uveitis

Differential Diagnosis	Duration and Tempo	Intraocular Inflammation	Vitritis Appearance
Toxoplasmic retinitis	Days to weeks	Moderate	Purulent with loose white blood cells; "headlight in the fog"[a]
Fungal endophthalmitis	Days to weeks	Moderate	String-like; "headlight in the fog"[a]
Bacterial endophthalmitis	Rapid worsening within days	Moderate	Purulent with loose white blood cells
Syphilitic retinitis	Weeks to months	Low grade	–
Tuberculosis	Weeks to months	Low grade	–
Acute retinal necrosis	Rapid worsening within days	Moderate	Purulent with loose white blood cells

[a]Suggests a solitary lesion.

sarcoidosis, and lymphomas of the eye. Extranodal marginal zone B-cell lymphoma is a low-grade, slowly progressing lymphoma that can arise in the eye, and can present as human leukocyte antigen (HLA)-A29–negative birdshot retinopathy. Vitreoretinal lymphoma is a diffuse large B-cell lymphoma that can originate in the central nervous system (CNS) or the eye. It can be diagnosed by cerebrospinal fluid cytology, vitrectomy, or CNS biopsy.

Dr Singh concluded that uveal infiltration can indicate infection, inflammation, or cancer. Biopsy is warranted in patients with a past history of cancer, atypical clinical features, discordant laboratory results, or nonresponse to steroids.

SS PRESENTING AS PUK

Esen K. Akpek, MD, Johns Hopkins School of Medicine, Baltimore, Maryland, USA, discussed a case of a man aged 61 years who presented with a 4-day history of decreased vision, dry eye, and other symptoms of peripheral ulcerative keratitis (PUK) that did not respond to previous treatment. On examination, superior corneal epithelium loss and stromal thinning were observed, with thickening and infiltrate around this area. There were 1+ cells and a trace of flare. These features are consistent with PUK, which can be caused by a wide variety of systemic or ocular conditions.

A review of systems revealed that the patient suffered from chronic interstitial nephritis, mononeuropathy multiplex of the ulnar nerves, parotid gland enlargement and xerostomia, chronic interstitial lung disease, monoclonal gammopathy, and hypocomplementemia. The diagnostic workup included autoimmune antibody testing, serology for infectious disease, and corneal culture. The patient tested positive for rheumatoid factor and negative for antinuclear antibodies. Serum protein electrophoresis demonstrated an immunoglobulin G4 spike consistent with monoclonal gammopathy. These findings were suggestive of Sjögren syndrome (SS). A labial salivary-gland biopsy was positive, with a score of 2 focus/4 mm^2, which confirms the diagnosis of SS [Shiboski SC et al. *Arthritis Care Res.* 2012].

In a study of 163 patients with SS, 98% had a history of dry eye for an average of 10.4 years [Akpek E et al. *Ophthalmology.* 2014]. One or more extraglandular ocular manifestations were present in 25% of patients, with vision-threatening findings in 13%, 55% of whom did not have a diagnosis at presentation. Patients with vision-threatening findings were 3.9 times more likely to have systemic involvement (95% CI, 1.4 to 11.0; $P=.010$). Peripheral neuropathy, interstitial nephritis, and vasculitis were more common among patients with vision-threatening ocular findings ($P<.05$). Men with SS were more likely than women to have serious ocular and systemic complications, and were more likely to be seronegative.

Dr Akpek's patient was treated with systemic mycophenolate mofetil, steroids, doxycycline, and topical cyclosporine and medroxyprogesterone. The patient stayed on mycophenolate mofetil for 2 years with no reactivation of ocular disease. Dr Akpek recommended that ophthalmologists should consider evaluating patients with clinically significant dry eye for SS.

DIFFERENTIAL DIAGNOSIS OF POSTERIOR UVEITIS

Lucy H. Young, MD, PhD, Harvard Medical School, Boston, Massachusetts, USA, discussed the differential diagnosis of posterior uveitis. Possible diagnoses

Table 3. Diagnostic Tests and Results for Man Aged 49 Years

Diagnostic Test	Results
Vision	OD, 20/70; OS, 20/40
Intraocular pressure	OU, 14
Slit lamp examination	OD, PCIOL; OS, WNL
Vitreous cells	OD, 1 to 2+ cells; OS, 1+ cell
Vitreous haze	OD, 2+: OS, trace
Fluorescein angiography	Normal
Optical coherence tomography	Normal
Review of systems	Negative; mild lower-back stiffness
HLA-B27	Positive
Rheumatoid evaluation	Negative

HLA, human leukocyte antigen; OD, right eye; OS, left eye; OU, both eyes; PCIOL, posterior chamber intraocular lens; WNL, within normal limits.

include toxoplasmic retinitis, acute retinal necrosis, endophthalmitis, tuberculosis, syphilis, sarcoidosis, autoimmune diseases, intraocular lymphoma, and toxocariasis. Table 2 lists features used to help identify the cause of posterior uveitis.

SYSTEMIC DISEASE IN PRESUMED VITRITIS CASES

Prithvi Mruthyunjaya, MD, Duke Center for Ophthalmic Oncology, Durham, North Carolina, USA, presented the case of a man aged 49 years with vision loss and floaters in both eyes for 1 to 2 months. The patient was diagnosed with idiopathic intermediate uveitis in both eyes 1 year prior. His condition had improved with local injections, but the inflammation continued. After a diagnostic workup (Table 3), the differential diagnosis included sarcoidosis, syphilis, HLA-B27–associated uveitis (ankylosing spondylitis), tuberculosis, inflammatory bowel disease, multiple sclerosis–associated uveitis, and lymphoma.

The patient improved with steroids, but regressed when tapering began. He received multiple injections of triamcinolone, but did not improve. Diagnostic vitrectomy with cytology revealed large-cell lymphoma. The patient was treated with high-dose methotrexate and intravitreal methotrexate. He was tumor free 3 years later, with vision of 20/30 OD and 20/20 OS.

Vitrioretinal lymphoma causes cellular and protein exudation into the vitreous. Intermediate uveitis may be the primary or sole manifestation of disease. Posterior uveitis with vitreous cells can develop as a secondary manifestation. Clinical grading of vitritis is based on the number of vitreous cells and the extent of vitreous haze. The differential diagnosis includes infectious, inflammatory, degenerative, injury-related, and neoplastic causes. Among neoplastic causes are primary vitreoretinal lymphoma, metastatic cancer, and secondary uveal lymphoma.

A systematic approach to diagnosis includes history taking, examination, and directed ancillary testing. Patients who do not respond to vitritis treatment should undergo further testing. Diagnostic vitrectomy is indicated in cases with negative laboratory results, diagnostic uncertainty, atypical therapeutic response, or absence of acute endophthalmitis. Vitreous fluid testing includes culture, cytology, immunopathology, antibody assays, PCR assay, flow cytometry, and cytokine analysis.

A study of 150 eyes in 140 patients undergoing diagnostic and therapeutic vitrectomy reported a diagnostic yield in 42% of the eyes [Scott AW et al. *Graefes Arch Clin Exp Ophthalmol.* 2012].

Vitrectomy guided by the previtrectomy suspected diagnosis provides a high diagnostic yield. Dr Mruthyunjaya

recommended considering a broad range of differential diagnoses in vitritis cases. Targeted laboratory testing is valuable and may need to be repeated.

DEEP SEQUENCING TECHNIQUES OFFER HIGHLY SENSITIVE MICROORGANISM IDENTIFICATION

Russel N. Van Gelder, MD, PhD, University of Washington, Seattle, Washington, USA, delivered the Jones/Smolin Lecture, discussing advances in the diagnosis of ocular infections. Vitritis in an otherwise healthy person presents a diagnostic dilemma, with a range of potential causes including infectious, inflammatory, and neoplastic processes. Although culture has been the gold standard for diagnosis, current PCR technology is highly sensitive. Advances in PCR include multiplex PCR, which can test for multiple pathogens in 1 sample, and real-time quantitative PCR, which can determine the quantity of pathogen genetic material in a sample.

PCR has been used to link specific pathogens to certain diseases, from rubella to Fuchs heterochromic iridocyclitis, CMV to Posner-Schlossman syndrome, and human herpes virus 6 to bilateral panuveitis. In a prospective comparison of microbial culture and PCR for the diagnosis of corneal ulcer, PCR detected microbial DNA in the majority of bacterial and fungal corneal ulcers, and identified pathogenic organisms in 46 of 52 culture-negative samples, including at least 3 novel, previously uncultured microbes [Kim E et al. *Am J Ophthalmol.* 2008].

Sensitive DNA sequencing techniques are limited by amplification of nonpathogenic organisms as well as pathogenic ones. New techniques are being used to characterize the microbiome in healthy and inflamed eyes. Biome representational in silico karyotyping is one technique, which is used for analyzing a defined representation of all DNA in a sample [Muthappan V et al. *Genome Res.* 2011]. A 16S deep sequencing technique was used to identify diverse bacterial populations from healthy human conjunctiva including commensal, environmental, and opportunistic pathogenic bacteria [Dong Q et al. *Invest Ophthalmol Vis Sci.* 2011].

Molecular diagnostics offer superior sensitivity over traditional culture techniques. Deep sequencing technologies are revealing unexpected organisms associated with inflammatory eye disease. The key to the next generation of diagnostics will be an understanding of commensal vs pathogenic ocular microorganisms.