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Diagnostic vitrectomy for infectious uveitis

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Abstract

The identification of an infectious or noninfectious uveitis syndrome is important to determine the range of therapeutic and prognostic implications of that disease entity. Diagnostic dilemmas arise with atypical history, atypical clinical presentations, inconclusive diagnostic workup, and persistent or worsened inflammation despite appropriate immunosuppression. More invasive intraocular testing is indicated in these situations particularly in infectious uveitis where a delay in treatment may result in worsening of the patient's disease and a poor visual outcome. Laboratory analysis of vitreous fluid via diagnostic pars plana vitrectomy is an important technique in the diagnostic armamentarium, but the most important aspects of sample collection include rapid processing, close coordination with an ophthalmic pathology laboratory, and directed testing on this limited collected sample. Culture and staining has utility in bacterial, fungal, and nocardial infection. Polymerase chain reaction (PCR) analysis has shown promising results for bacterial endophthalmitis and infection with mycobacterium tuberculosis whereas PCR testing for viral retinitides and ocular toxoplasmosis has a more established role. Antibody testing is appropriate for toxoplasmosis and toxocariasis, and may be complementary to PCR for viral retinitis. Masquerade syndromes represent neoplastic conditions that clinically appear as infectious or inflammatory conditions and should be considered as part of the differential diagnosis. Diagnostic vitrectomy and chorioretinal biopsy are thus critical tools for the management of patients in whom an infectious etiology of uveitis is suspected.

Introduction

Identifying the etiology of an infectious or noninfectious uveitis syndrome is important for the clinician and patient because of the range of therapeutic and prognostic implications for each disease entity. For the majority of uveitis syndromes, a diagnosis can be made with a combination of history, clinical examination, laboratory and radiologic testing. Diagnostic dilemmas may arise however, when discrepancies are observed in three specific settings – an atypical history, atypical clinical presentation, or an inconclusive diagnostic workup that has implications from a therapy standpoint. The dilemma is further compounded when intraocular inflammation persists or worsens after seemingly appropriate local or systemic immunosuppression, which may then raise concerns for an infectious or neoplastic etiology. In these situations, diagnostic vitrectomy may greatly assist in the diagnosis and guide alternative management strategies.

Experience in the literature for diagnostic pars plana vitrectomy (PPV) has reported overall yields ranging from 12.4% to 64.3%.[1–12] In analysis of these case series (Table 1), the yield

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for diagnostic vitrectomy resulting in a final diagnosis of infectious uveitis in patients treated clinically for infectious uveitis ranged from 27.9% to 77.1%.[3, 6, 9, 10] Differences in reported yields have been attributed to patient selection with higher diagnostic yields reported when there is higher clinical suspicion for infection or lymphoma (i.e. higher pre-test probability). Irrespective of the variability in reported yields, diagnostic vitrectomy remains a mainstay in the diagnosis and ultimate management of diagnostic dilemmas in patients with intermediate, posterior and panuveitis.

Technique

Initial Evaluation and Indications for Diagnostic Vitrectomy

Approaching a patient with uveitis requires a comprehensive medical and ophthalmic history. The history of present illness, past medical and social history should be directed at identification of key risk factors and pertinent positives and negatives.

Similarly, the ophthalmic examination should focus on key findings such as laterality, location of the uveitic process per the Standardization of Uveitis Nomenclature classification (SUN) classification system,[13] the clinical appearance, and associated ocular and systemic exam findings.

Further systemic evaluation with laboratory testing or imaging should be focused and directed based on the formulated differential diagnosis. In addition, increased pre-test probability of a disease syndrome has been shown to increase the positive predictive value of a disease syndrome when a positive test is identified.[14]

Indications for more invasive ocular testing including diagnostic vitrectomy arise in the setting of diagnostic dilemmas, particularly in diseases with an acute time course where a delay in diagnosis could worsen the patient's visual outcome. One situation commonly encountered arises when a patient fails to respond to conventional local or systemic immunosuppressive treatment. Additional indications include significant vitreous inflammation concerning for infectious endophthalmitis, malignancy, or retained foreign body.[6, 10, 15] The ultimate goal of intraocular testing is to obtain a diagnosis that may guide or change the course of therapy.

Diagnostic Pars Plana Vitrectomy Technique

Various techniques have been reported to obtain vitreous samples including 20-, 23-, and 25-gauge PPV.[1, 5, 6, 8–10, 12] More recently, 27-gauge cutters have been introduced and will likely provide another option for diagnostic PPV. In general, a standard three-port PPV with a wide-angle viewing system allows for adequate visualization to safely harvest a vitreous sample. The phakic or pseudophakic status must be considered prior to surgery, as vitreous debris, hemorrhage, or inflammatory cells may collect on the posterior surface of the lens capsule obscuring the view of posterior segment structures. Poor visualization of the vitreous cavity and retina may ultimately limit the amount of core and peripheral vitrectomy that may be performed and may preclude the identification of iatrogenic retinal breaks. For this reason, it is prudent to harvest the amount of vitreous necessary for laboratory testing, evaluate the retina for any overt pathology and/or iatrogenic injury and instill antibiotics if indicated. Meticulous peripheral vitreous base dissection in the presence of significant media opacity (e.g. corneal edema, lens opacity) is fraught with potential complications and should generally be avoided.

To maximize the diagnostic yield, direct visualization is preferred to ensure that the vitreous cutter remains in the mid-vitreous cavity, avoiding the crystalline lens in phakic patients, and to ensure that the vitreous hand piece is removing vitreous versus infusion fluid.

Specifically, an undiluted vitreous sample is obtained using a 3mL syringe attached to the vitreous cutter. A three-way stopcock closed to the aspiration line can facilitate ease of collection of an undiluted specimen. The use of a three-way stopcock allows the assistant to immediately switch to vacuum aspiration from the machine (vs. manual aspiration). Approximately 1–2 mL of undiluted vitreous specimen may be obtained with this method although careful monitoring of the peripheral retina is needed for choroidal formation, particularly as the intraocular pressure decreases when vitreous is removed.[5, 8–10] During collection, some authors propose maintaining the infusion on air or providing digital pressure to the eye wall to maintain steady intraocular pressure.[12] Turning the infusion to air is less problematic in pseudophakic patients as removal of air bubbles from the peripheral anterior hyaloid risks injury to the crystalline lens in phakic patients.

Vitrector speed does not appear to degrade the quality of the sample obtained.[16, 17] After the undiluted specimen is collected, fluid infusion is initiated and a second syringe is placed on the vitreous cutter to collect 3–10 mL of a diluted vitreous sample.[4, 6, 10] The remaining core vitrectomy, induction of a posterior vitreous detachment, and peripheral vitrectomy may then be performed using a standard approach.[8, 12] The vitrectomy cassette may also be sent for laboratory analysis. If there is significant vitreous debris within the mid-peripheral vitreous, sequential 3-, 5- or 10-cc syringes may be used to collect multiple specimens, which still have a high concentration of material for laboratory analysis (Figure 1).

The undiluted and diluted samples should be sent immediately after collection at room temperature to the ophthalmic pathology laboratory for immediate processing although this may vary based on laboratory preferences.[5, 8, 12] Close coordination and discussion with laboratory services is important to ensure proper specimen handling. Details of sample processing in the laboratory have been previously described.[8] The undiluted vitreous sample is typically sent for cytological analysis with either Papanicolaou or Hematoxylin-eosin staining and immunohistochemical staining.[5, 6, 8–10] The supernatant of the undiluted sample is sent for cytokine analysis and antibody levels.[4, 9] If a quantitative polymerase chain reaction (PCR) test or vitreous proteomic or cytokine evaluation is needed, an undiluted vitreous specimen provides the most accurate method of obtaining a DNA concentration. The diluted vitreous sample is typically used for gram stain, culture, flow cytometry, and PCR testing.[8, 9] Cytologic analysis may also be performed with the diluted specimen after centrifugation by a pathology laboratory.

Chorioretinal Biopsy

Chorioretinal biopsy is a surgical consideration in patients with choroidal or retinal disease, but confers a greater risk of iatrogenic morbidity including subretinal hemorrhage, vitreous hemorrhage, and retinal detachment.[18, 19] A transscleral approach[19–21] was first performed for suspected choroidal malignancy prior to advances in intraocular vitreoretinal surgery, but this technique is used less frequently due to risk of choroidal hemorrhage and extrascleral extension of tumor.[22, 23] Use of a pars plana vitrectomy approach has gained favor due to a lower side effect profile.[19, 24]

Indications for chorioretinal biopsy include a non-revealing workup that may include prior diagnostic PPV, a disease process primarily limited to the choroid and retina with minimal vitreous inflammation, exclusion of malignancy not diagnosed with less invasive means, and progressive macula or vision-threatening process unresponsive to therapy.[19, 22, 24]

To perform a chorioretinal biopsy, 20- or 23-gauge three-port PPV have been described previously; undiluted and diluted vitreous samples are collected first prior to the chorioretinal biopsy.[18, 19, 22–26] Vitreous separation over the biopsy site is performed (with preference for a superotemporal location if possible to assist with post-operative

tamponade[19]) and intraocular diathermy is used to delineate the site of retinal biopsy at the border between the lesion and normal retina.[18, 19, 22–26] During excision of a 1 mm × 1 mm or 2 mm × 2 mm size sample with vertical scissors or a diamond blade, the intraocular pressure is raised to 70 mmHg to 90 mmHg temporarily to prevent bleeding.[18, 24] Intraocular forceps are then used to grasp the tissue and remove it through the sclerotomy site with enlargement as needed. Endolaser is then applied around the biopsy site with long-acting gas or silicone tamponade at the end of the procedure.[18, 19, 23–26]

The specimen should be sent immediately after collection to the ophthalmic pathology laboratory for histology, microbiology, electron microscopy, and directed testing if a neoplasm is suspected. [18, 19] Communication with an ophthalmic pathology laboratory is also needed to determine whether the chorioretinal biopsy should be separated in the operating room for microbiologic evaluation and histology or whether the biopsy should be cut in the laboratory.

Special Considerations Based on Infectious Etiology

Bacterial, Fungal, and Atypical Organisms

Bacterial and Fungal—In cases of bacterial and fungal endophthalmitis (Figure 2A–B), gram stain and culture (aerobic, anaerobic, and fungal) of the dilute vitreous sample is performed to identify the causative organism and obtain susceptibilities. Communication with the microbiology laboratory to hold cultures for at least one month for slower-growing organisms such as *Propionibacterium acnes* and fungi is important to avoid missing a fastidious organism.[6, 9, 10]

The sensitivity of culture after diagnostic vitrectomy for the diagnosis of chronic infectious uveitis has been reported between 16.7 to 96% [3, 9, 10, 27] with higher sensitivity reported in case series were there was a high pre-test probability for chronic endogenous or post-operative endophthalmitis.[9] For acute post-operative endophthalmitis, data from the Endophthalmitis Vitrectomy Study showed a yield of 66% for culture and 41% for gram stain for patients undergoing vitrectomy.[28] Higher yields are obtained with vitreous rather than aqueous samples.[29]

In select culture-negative cases of suspected chronic endophthalmitis, targeted PCR testing of patients with high clinical suspicion has led to the diagnosis of ocular Whipple's disease.[9, 30] Development of bacterial PCR analysis of both aqueous and vitreous fluid has been applied in case series of patients with acute and delayed post-operative endophthalmitis with early promising results. In a case series of 25 patients with unambiguous bacterial endophthalmitis, all aqueous and vitreous samples were positive by PCR with aqueous and vitreous cultures yielding the diagnosis in 33% and 68% respectively.[29] In one series of patients with post-operative endophthalmitis treated with intravitreal antibiotics, eubacterial PCR (targeting the 16S ribosomal DNA common to all bacteria) of vitreous obtained by PPV identified the causative organism in 10 of 16 patients (62%) while culture only identified three (18%).[31] Data from the French Institutional Endophthalmitis Study group showed similar findings with eubacterial PCR of vitreous obtained by PPV identifying the causative organism in 26 of 34 (76.5%) acute postoperative endophthalmitis cases compared with only 2 (5.8%) positive culture results.[32] The low culture results in these studies were postulated to be due to pre-treatment with intravitreal antibiotics prior to vitrectomy, but allowed for identification with PCR despite treatment. In contrast, a series of 64 patients with suspected bacterial endophthalmitis prior to antibiotic treatment reported that PCR of vitreous samples identified a bacterial cause in 66% of patients compared with only 34% by culture.[33] Although PCR yields were not as high as in previous and smaller series [34, 35], the group had a higher proportion of patients outside the immediate postoperative period with

more subtle presentations of intraocular inflammation.[33] PCR for bacterial and fungal endophthalmitis continues to be investigated for the role it will play in the evaluation of infectious uveitis.

Atypical Organisms

Mycobacterium Tuberculosis: Intraocular infection with *Mycobacterium tuberculosis* may have a myriad of presentations including anterior uveitis, posterior uveitis, panuveitis, choroidal granuloma, and retinal vasculitis.[36] Diagnosis is arrived at by combining appropriate clinical history with systemic evaluation including chest radiographic imaging, positive Purified Protein Derivative (PPD) tuberculin skin test, Interferon Gamma Release Assays (IGRA) such as the QuantiFERON-TB GOLD (Qiagen ®, Valencia, California, USA) or T-SPOT.TB test (Oxford Immunotec ®, Marlborough, Massachusetts, USA), or analysis of extraocular sites of potential tuberculosis infection.[36, 37] A dilemma arises in situations where it is unclear that tuberculosis may be related to the patient's ocular presentation such as when tuberculosis is endemic, the patient is immunocompromised, systemic tuberculosis infection is not detected, the patient has received the Bacillus Calmette-Guerin (BCG) vaccine within 10 years of evaluation, or if there is unequivocal response to empiric anti-tubercular treatment.[36–38] Additionally, PPD skin testing and IGRA testing identifies exposure and cannot delineate between active and latent infection. Further evaluation may be warranted especially in sight threatening situations and to guide initiation of anti-tubercular treatment.[36, 37, 39]

Intraocular fluid analysis typically has low yields for Ziehl-Neelsen staining for acid fast bacilli and culture on Lowenstein-Jensen medium may take up to 6 to 8 weeks which limits clinical utility.[36, 37] Although a small case series reported identifying ocular tuberculosis with smear and culture of aqueous and vitreous fluids, these cases had atypical circumstances such as diffuse iris nodules or large subretinal mass with rupture into the vitreous cavity.[38]

Experience with aqueous and vitreous PCR testing of patients with presumed ocular tuberculosis by Gupta et al in India has had a yields ranging from 37.7% (20 of 53) up to 72% (13 of 18) [40–42] with a 5.7% false positive rate in controls with non-tubercular uveitis.[40] With the exclusion of the largest series of 53 patients in which data is unavailable, 77% to 80% of the PCR positive patients in these series were PPD positive.[41, 42] In these series, 90 to 100% of PCR positive patients that pursued anti-tubercular treatment had resolution of inflammation.[40–42] This same group also reported *Mycobacterium tuberculosis* positive PCR from the aqueous and vitreous of 4 patients with presumed tubercular serpiginous-like choroiditis with resolution of disease activity with anti-tubercular treatment.[43] Data from a group in Mexico using PCR testing in 22 patients with a known diagnosis of tuberculosis uveitis showed a yield of 77.2% (17 of 22) with 12 of 17 of PCR positive patients (76.5%) having a positive PPD. All patients improved with anti-tubercular treatment with a false positive rate, derived from testing non-tuberculosis uveitis controls, of 8.8% reported in that series.[44] Limitations for PCR analysis is that clinical diagnosis is treated as the gold standard for comparison since culture for mycobacterium tuberculosis is difficult and may have low yield from the sample obtained.[36, 39, 44]

Nocardiosis: *Nocardia* species are comprised of a group of Gram-positive, filamentous aerobic bacteria that are ubiquitous in soil, dust, and vegetation.[45, 46] *Nocardia* species may cause either exogenous infections (usually keratitis, scleritis, and post-surgical endophthalmitis) in patients with exposure to agriculture [47, 48] or endogenous ocular Nocardiosis (EON) from hematogenous spread in immunocompromised individuals (Figure 3).[49]

EON typically occurs in organ transplant recipients with systemic immunosuppression (steroids or immunomodulatory therapy) but has been reported in patients with underlying connective tissues disease such as systemic lupus erythematosus. Hematogenous spread leads to seeding of the inner choroid producing a subretinal abscess (35 of 46 clinically described eyes in a literature review) which can extend exteriorly leading to anterior segment manifestations (hypopyon, scleritis, proptosis) or internalize leading to serous retinal detachment and vitritis.[49] A dilemma may arise in clinical diagnosis as it may be confused with a neoplastic process in patients with lack of vitritis or confused with fungal infection with *Candida* or *Aspergillus* species as the patient demographic is similar. Although systemic manifestations can be severe including pulmonary, brain, and skin involvement, in 53% of the cases reported in the literature, ocular findings preceded the development of systemic symptoms.[50] With a 25% mortality rate, establishing the diagnosis is important for both ocular morbidity and patient mortality.[50]

The mainstay of diagnosis is histologic staining and culture of ocular or extraocular specimens, which allows for identification of the organism with antibiotic susceptibilities. It is important to request special staining as *Nocardia* is weakly Gram-positive and use of the modified acid-fast Kinyoun stain distinguishes it from other bacteria such as Actinomyces.[50] Culture, the gold standard for diagnosis, may result in 2 days to 3 weeks depending on the size of the inoculum and may be performed on standard culture media such as blood agar, chocolate agar, or Sabouraud medium.[48, 50, 51]

In regards to culture-positive exogenous *Nocardia* endophthalmitis, a retrospective review by a group in south India found Gram stain and modified Kinyoun staining of aqueous and vitreous specimens detected *Nocardia* species in 27.5% of cases highlighting the importance of culture.[48] Another review of 24 culture-proven cases of exogenous *Nocardia* endophthalmitis from India found that aqueous specimens had the highest yield for special staining compared to vitreous specimens (93.75% compared with 4.54% respectively).[47] Similarly, another group exploring exogenous *Nocardia* endophthalmitis found that none of the vitreous samples collected had detectable organisms by microscopy.[51] It is postulated that higher yields from aqueous fluid are due to minimal posterior segment findings in the face of extensive anterior segment manifestations including grossly infected cataract wounds and yellowish-white nodules on the corneal endothelium and iris.[47]

In terms of endogenous ocular Nocardiosis (EON), a variety of intraocular sampling techniques have been used to stain and culture for the organism, yet most often the diagnosis is arrived through analysis of samples from extraocular sites.[50] In 5 cases, 6 vitreous taps were pursued [46, 52–55] of which 4 were non-diagnostic by either microscopic analysis or culture.[46, 52, 54, 55] Pars plana vitrectomy led to identification of *Nocardia* species by staining and/or culture in 8 of 9 cases.[46, 54, 56–61] All cases underwent vitrectomy including retinal biopsy except for two cases [58, 62] of which 1 was non-diagnostic by vitreous fluid analysis.[62] Subretinal fine needle aspiration (FNA) was performed in 5 cases all of which were diagnostic of *Nocardia* species.[55, 63–66] A combination of vitrectomy, retinal biopsy, and subretinal aspiration may also be used to identify multiple intraocular sites of *Nocardia* infiltration, as described in one patient with *Nocardia* infection involving the vitreous, retina, and subretinal space in the context of systemic immunosuppression subsequent to cardiac transplantation.[46]

Although PCR has been described to speciate cultured *Nocardia* from ocular samples,[67] the use of PCR testing has not been described in clinical practice for this organism.

Parasitic

Toxoplasma gondii—A diagnosis of ocular toxoplasmosis typically is made by a characteristic clinical presentation and evidence of serologic exposure. The clinical findings of retinitis adjacent to a chorioretinal with varying level of overlying vitritis may be sufficient for directing the management options. However, atypical presentations of toxoplasmic retinochoroiditis may mimic viral necrotizing retinitis usually in immunocompromised patients and the elderly prompting the initiation of incorrect therapy.[68, 69] Further diagnostic testing for ocular toxoplasmosis is warranted in these instances (Figure 4).

Although a small series described the successful culture of *T. gondii* from the vitreous of 5 patients with HIV and/or AIDS exhibiting severe retinochoroiditis, the limitation of this approach is the long detection time ranging from 2 to 23 days for positive cultures.[70]

The rapid detection of toxoplasmosis DNA using PCR techniques on aqueous fluid has varied in the literature with some reports describing diagnostic yields from 13% to 55% [68, 71–79] with positive PCR results occurring more often in patients with larger chorioretinal lesions,[49, 75] in immunosuppressed patients,[75, 80] and with active anterior segment inflammation.[49]

Antibody levels in the aqueous have been used to supplement results from PCR testing by calculating the Goldmann-Witmer Coefficient (GWC) to determine whether local antibody production is occurring.[49, 73, 75, 81–83] The GWC is calculated as target IgG in the ocular fluid/total ocular fluid IgG divided by target IgG in the serum/total serum IgG. Theoretically, a GWC greater than 1.0 would indicate local antibody production, but most authors designate a coefficient of 3.0 as indicative of local antibody production to take into account passage of antibody through a disrupted blood-retina or blood-aqueous barrier.[81] In one series, calculation of the aqueous GWC for toxoplasmosis antibody prior to and after 3 weeks of clinical manifestation had the highest yield in the delayed sample (57% compared with 70%).[73] In the series by Fardeau of aqueous sampling for toxoplasmosis, of the 34 immunocompetent patients with negative PCR testing for toxoplasmosis, 25 of those 34 patients had a positive GWC detecting ocular toxoplasmosis whereas none of the immunocompromised patients exhibited a positive GWC.[75] In a similar vein, a series by Rothova showed greatest utility of GWC in the diagnosis of ocular toxoplasmosis in immunocompetent patients (93% with final diagnosis of ocular toxoplasmosis) whereas the GWC was of little utility for immunocompromised patients (57% yield).[82] In comparison with PCR, calculation of the GWC had more utility in ocular toxoplasmosis [49, 83, 84] with up to 64% of toxoplasma diagnoses missed had PCR alone been performed [83] and up to 87.5% [49] to 90% [84] of ocular toxoplasmosis diagnoses made with GWC. Despite treatment, it has been observed in a small series that PCR of the aqueous may remain positive.[77]

PCR and GWC analysis has also been performed on vitreous samples during diagnostic and therapeutic vitrectomy albeit in limited numbers with results seeming to indicate similar to improved yields in vitreous samples for toxoplasmosis PCR though not powered sufficiently to make that distinction.[6, 9, 12, 49, 69, 77, 80, 85–87] Yet, the larger amount of undiluted and dilute vitreous collected is thought to allow a larger battery of antibody tests to be performed than on aqueous samples in cases with a large differential diagnosis.

Toxocara canis—Ocular toxocariasis is predominantly a pediatric condition diagnosed in patients with a suggestive history and examination. Detection of acute toxocariasis infection may be difficult but a peripheral granuloma with or without the presence of associated vitreoretinal traction bands is the classical appearance. A posterior pole granuloma may also be observed with ocular toxocariasis. Although a positive serology can assist in evaluation,

the high seroprevalence in certain regions of the world may make it less supportive for diagnosis.[88] In addition, seropositivity declines with time.[89, 90] Furthermore, serum titers have reported to be positive in only 33% to 69% of cases.[89–91] A dilemma may arise when ocular toxocariasis presents as a chronic endophthalmitis or if the presence of the granuloma with or without associated traction mimics retinoblastoma or other infectious uveitides in the setting of negative titers.[90]

Although PPV with biopsy of visible granulomas during retinal detachment repair has led to the identification of the offending helminth in few cases reported in the literature,[92–98] most approaches for identification of toxocariasis involve either aqueous or vitreous Toxocara IgG testing. In these situations, the serum ELISA antibody titers are compared to aqueous or vitreous titers with a qualitatively higher ocular fluid ELISA indicating likely presence of ocular toxocariasis (Figure 5A–B).[90, 91] In a case series from Japan, of 33 intraocular fluid samples collected (12 aqueous and 21 vitreous), 22 of 33 (66.7%) showed higher titers from ELISA testing in the ocular fluids than in the serum indicating a positive result.[91] Case reports and small case series have also shown utility of aqueous and vitreous ELISA testing for Toxocariasis.[90, 99–102] In all these case series, total IgG in the serum and ocular fluids was not measured thus precluding the ability for a more quantitative measurement such as GWC testing. It is thought that GWC testing may prevent false positive results by correcting for passive leakage of antibody in a compromised blood-aqueous barrier during inflammation.[89]

In a series that conducted ELISA antibody titers and GWC determination on serum and ocular fluid samples from 37 adults and 12 children with unknown posterior uveitis, 3 of 12 children had revealing aqueous humor analysis for *Toxocara canis* by ELISA and GWC determination.[89] Aqueous humor analysis enabled the diagnosis in these 3 children who were only considered seropositive by including serum titers below the typical screening dilution cut off for serum Toxocara ELISA testing. It has been suggested that testing serum ELISA to dilutions as low as 1:8[89, 103] or at any detectable dilution [90] may augment Toxocara diagnosis in the appropriate clinical setting.

Although PCR testing for toxocariasis has been attempted, its utility for the diagnosis of this condition is limited.[102, 104] In a recent series of patients with posterior uveitis, none of the 15 patients with typical posterior segment findings and seropositivity for *Toxocara canis* were positive for toxocariasis DNA.[104] One report of vitreous PCR testing for Toxocara was similarly non-diagnostic.[102] PCR may play a limited role in ocular toxocariasis as it may be unlikely for the helminth to shed DNA into the aqueous or vitreous.[88]

Viral

Diagnosing an infectious viral retinitis syndrome due to herpes simplex virus (HSV), varicella zoster virus (VZV), and cytomegalovirus (CMV) can be difficult in situations with significant posterior segment inflammation (Figure 6A–B). Ascertaining this diagnosis may also be problematic in immunocompromised patients who may be at risk for both opportunistic and non-opportunistic infections. Culture is of limited utility because of the amount of time needed for a virus to grow in viral culture media; however, PCR testing of aqueous and vitreous fluid plays a prominent diagnostic role because of high-sensitivity, rapidity of the assay, and low false-positive rate.[105, 106] Early experiences with viral PCR of the aqueous and vitreous were used to test the concordance of PCR results with the clinical diagnosis of CMV Retinitis [105, 107] as well as identify viral etiologies of Acute Retinal Necrosis (ARN) and Progressive Outer Retinal Necrosis (PORN).[107–111]

The diagnostic yield of PCR testing for viral uveitis syndromes varies in the literature, but is the highest when the pre-test probability is high (i.e. patient with more characteristic clinical

features versus atypical findings). In a case series assessing aqueous humor PCR testing for infectious posterior uveitis, PCR testing had a 79% yield for viral infections regardless of patient immune status.[82] A more recent large series of patients described by Harper et al showed that viral PCR had a sensitivity of 80.9% and specificity of 97.4% when considering the final clinical diagnosis as the gold standard.[87] Conversely, in a series by Matos, aqueous PCR testing for viral infections was non-diagnostic while vitreous PCR showed a 53% yield for all causes of viral uveitis including HSV/VZV acute retinal necrosis or CMV retinitis.[85]

The use of quantitative real-time PCR of aqueous fluid is also helpful for monitoring viral DNA levels in response to therapy, and moreover, may be used to detect drug-resistance in patients on chronic valganciclovir therapy for recurrent or recalcitrant CMV retinitis or non-ocular involvement.[112]

To supplement PCR testing, calculation of the GWC for HSV, VZV, and CMV has been undertaken albeit with variable results. In a series by Westeneng of immunocompromised patients with posterior and panuveitis, viral PCR demonstrated superiority to GWC evaluation with viral DNA detected by PCR in 16 of 17 cases (94%) whereas the GWC detected only 3 of those 17 cases (18%).[84] Variations in the performance of GWC for detection of viral retinitides has been shown in other series.[49] In one series, GWC was instrumental in the identification of 92% of HSV and 87.5% of VZV associated infectious uveitis whereas PCR only identified 54% of HSV and 75% of VZV cases.[83] Varying yields of PCR and GWC testing have been postulated to be due in part to timing of ocular fluid analysis – specifically, higher rates of PCR positivity are detected within the first weeks of disease activity while increased GWC positivity later in the disease course may be observed due to a reduction of pathogenic load from increased intraocular IgG production.[83, 87] Another hypothesis is that immunosuppressed patients may not be able to mount a local antibody response, thus explaining the low yield of GWC testing in patients with CMV retinitis.[107]

Although most experience in the literature for viral infectious uveitis involve aqueous humor sampling which can be rapid and easy to perform, diagnostic vitrectomy has a role in situations where the retina cannot be evaluated, vitrectomy can be therapeutic, or malignancy is a diagnostic possibility.[82]

Masquerade Syndromes

Masquerade syndromes are a group of neoplastic disease processes that mimic inflammatory conditions in presentation leading to a diagnostic dilemma.[113, 114] As malignant conditions, they may be life- and vision-threatening. Masquerade syndromes including intraocular lymphoma, melanoma with necrosis, and metastatic disease may mimic infectious uveitis.

Intraocular Lymphoma—Intraocular lymphoma is regarded as the most common masquerade with one tertiary care uveitis service reporting that intraocular lymphoma represented 68% of their 19 patients with masquerade syndromes.[115] Typically, ocular lymphoma presents with vitreous cell and refractory uveitis leading to diagnostic confusion and delay in diagnosis.[5] More advanced cases exhibit characteristic yellow-white subretinal infiltrates.[113, 114] A dilemma may also arise as corticosteroids can lead to an initial improvement clouding the clinical picture.[8, 113, 114] Diagnosis is made definitively by vitreous sampling with pars plana vitrectomy and close coordination with an ophthalmic pathologist. With a high index of suspicion and cautious handling of vitrectomy specimens, a mean of 4 months from symptom onset to diagnosis was achieved in one series compared to a previously reported mean of 21 months to diagnosis.[8] Samples are sent for cytology, flow cytometry, and cytokine analysis to assist with evaluation. Cytology is the gold standard for diagnosis allowing differentiation of malignant cells from inflammation with

several series requiring cytology alone to identifying intraocular lymphoma.[5, 6, 10, 11] Yet, repeat vitreous biopsy and chorioretinal biopsy has been required to establish a diagnosis in intraocular lymphoma [7, 8] which may be due to low yield from the biopsy site, fragility of the cells affected by a delay in immediate sample processing, or cell degradation by steroid treatment.[5, 8, 10]

Although cytology is the gold standard for diagnosis of intraocular lymphoma, flow cytometry has been used to supplement cytology with its primary utility in identifying cell clonality with specific cell surface markers and to signifying the presence of lymphoma instead of inflammation in comparing the CD4:CD8 ratio.[9, 113] Use of flow cytometry in one series identified only 4 of 6 cytology positive cases of intraocular lymphoma demonstrating non-superiority of this modality.[8] Another series, in which cytology and flow cytometry were obtained from the undiluted vitreous sample, concluded flow cytometry was superior,[116] but the results of this study have been disputed due to equivocal appearing flow cytometry results.[8, 113] Other adjunctive tests for intraocular lymphoma have been described including PCR and cytokine analysis but have not replaced cytology in the evaluation of lymphoma.[117]

Uveal Melanoma—Uveal melanoma does not usually pose a diagnostic dilemma due to its characteristic appearance by clinical exam and ultrasonography. Inflammation in the form of scleritis [118–121], anterior uveitis [122–125], posterior uveitis [126], panuveitis [127], and panophthalmitis [128–130] have been described with 22 (4.9%) of eyes in a series of 450 enucleated for uveal melanoma exhibiting some form of inflammation.[113, 131] In a large review of necrotic uveal melanomas from the Armed Forces Institute of Pathology, 75.1% of the 157 totally necrotic uveal melanomas in their registry presented with episcleritis and scleritis.[119] In a similar vein, it was noted in the large pathology series by Font that all patients presenting with panophthalmitis had necrotic uveal melanomas.[131] In these atypical presentations of uveal melanoma, close follow up, serial photography, ultrasonography, and clinical suspicion are primarily employed.[118, 122, 123, 125, 126] In one case of ciliary body melanoma masquerading as chronic uveitis, multiple diagnostic vitrectomies were unrevealing to the diagnosis whereas serial ultrasound of a later identified ciliary body lesion was.[127] Tissue biopsy led to the diagnosis of two patients with uveal melanoma masquerading as scleritis.[120, 121]

Inadvertent vitrectomy for an eye with uveal melanoma may lead to extrascleral extension at the sclerotomy sites.[132] In a case report of an eye with untreated uveal melanoma that had undergone vitrectomy, histologic examination of the enucleated eye showed melanoma cells had diffusely spread to all intraocular surfaces.[133] Fine Needle Aspiration Biopsy (FNAB) with either a 27 gauge needle passed transvitreally for post-equatorial lesions or 30 gauge needle passed transclerally for pre-equatorial lesions has a reported yield of 97% and 75% respectively for chromosome 3 analysis in a case series by Shields et al.[134] Use of a 25-guage sutureless vitrectomy set-up has also been described to obtain a transvitreal retinochoroidal biopsy with the caveat that the vitrector is only used in the substance of the visualized tumor with no further vitrectomy performed once obtained.[135] A recent series by Bagger et al using this method reported a 97.3% yield for chromosome 3 analysis with the authors asserting this method allows for improved sampling of more anteriorly located tumors as biopsy is performed under direct visualization.[135] All biopsies were followed by either enucleation or plaque placement.[134, 135] Although extrascleral extension has not been reported in large case series, a case series of four patients experiencing this complication was reported though it is unclear as to what technique was performed.[136]

Tumor Metastasis—Tumor metastasis is the most common cause of intraocular malignancy in adults.[113] Their typical appearance as well as pre-existing history of cancer

rarely makes them a diagnostic dilemma. Obtaining a careful history is paramount to detection.[114]

Uveal metastasis masquerading as intraocular inflammation has been reported with posterior segment metastasis causing diffuse posterior segment inflammation, anterior segment metastasis causing severe, resistant anterior chamber inflammation,[113, 137–146] and in situations where malignancy presents with a viral retinitis type picture.[147] In the case reports of metastasis masquerading as anterior uveitis, aqueous sampling for cytology has led to the diagnosis in the few reports it was performed [137–142] with the remaining cases diagnosed with suggestive history and imaging. In patients undergoing diagnostic vitrectomy for uveitis of unknown cause, metastasis was rarely identified directly from vitrectomy cytology results [2–4] with only 1 case reported in each of these series despite uveal metastasis being the most common cause of intraocular malignancy in adults. In a case series of 40 patients with uveitis masquerades, only 1 case of metastatic carcinoma was identified [115] likely due to its infrequency as a diagnostic dilemma. In case reports of patients with the extremely rare occurrence of tumor metastatic to the retina and vitreous, these conditions present as intermediate uveitis, vitreous hemorrhage, or retinal vasculitis with vitreous cytologic sampling and retinal biopsy assisting in diagnosis if no primary malignancy is identified.[113, 147, 148]

Biopsy of suspected ocular metastasis plays a role in patients with no known primary tumor and in cases of diagnostic uncertainty as sampling may lead to a significant change in ocular and systemic management.[149] Fine needle aspiration biopsy in a series of 159 cases by Shields et al led to an adequate sample collection in 88% of cases.[150] In a series of 39 patients with uveal metastasis, 25 gauge sutureless vitrectomy had a yield of 100% for cytologic diagnosis.[149]

Summary

Intraocular sampling including diagnostic vitrectomy and chorioretinal biopsy has a major role in uveitic diagnostic dilemmas. Close coordination with an expert ophthalmic pathology laboratory, if available, is paramount prior to and after diagnostic vitrectomy to ensure proper specimen handling and evaluation. The choice of diagnostic testing should be directed to the differential diagnosis of the patient’s presentation for studies that may include cytology, flow cytometry, gram stain, culture, PCR testing, antibody, and cytokine evaluation. Cultures and appropriate special stains have the greatest utility in bacterial, fungal, and nocardial infection. Appropriate communication with the microbiology laboratory is important in infection with fastidious organisms. Bacterial PCR testing of the vitreous has shown promising results even in cases treated with intravitreal antibiotics. PCR is most appropriate for viral infectious disease, but is also very helpful for suspected cases of toxoplasmosis. Antibody testing is appropriate for toxoplasmosis and toxocariasis, and may be complementary to PCR for viral retinitis. Ocular tuberculosis is primarily identified using supporting history, imaging, PPD skin testing, and IGRA testing in the appropriate clinical setting. Intraocular sampling for mycobacterial PCR has been described from series in endemic countries with success. Masquerade syndromes represent neoplastic conditions that clinically appear as infectious or inflammatory conditions and should be considered as part of the differential diagnosis. Cytology from PPV or retinochoroidal biopsy is pursued if the diagnosis is not obvious with less invasive testing.

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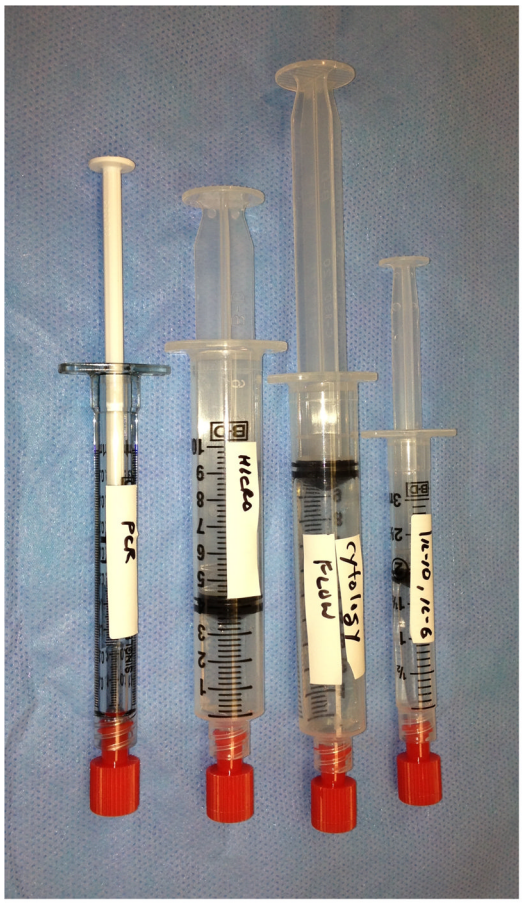


Figure 1.
Diagnostic vitrectomy specimens. Following harvesting a vitreous specimen, diagnostic vitrectomy specimens should be labeled clearly for distribution to molecular diagnostics laboratory (PCR and IL-10/IL-6), microbiology laboratory (MICRO), or ophthalmic pathology laboratory (cytology, flow cytometry). Syringes of varying sizes (1-, 3-, 5- or 10-cc syringes) are used depending on the quantity required from each department conducting the necessary testing.

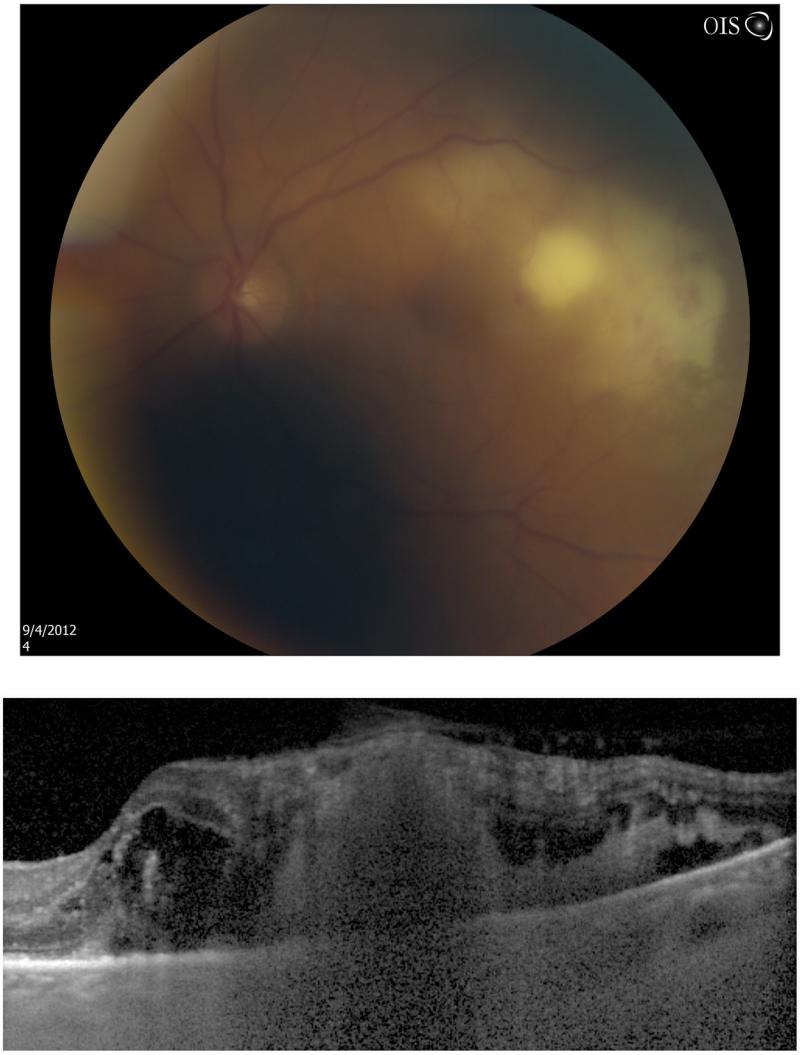


Figure 2.
Fundus photograph (A) and spectral domain optical coherence tomography scan (B) of 73-year-old patient on total parenteral nutrition with endogenous *Candida* endophthalmitis with retinitis. Vitreous cultures and blood cultures were sufficient to diagnosis *Candida albicans* infection.

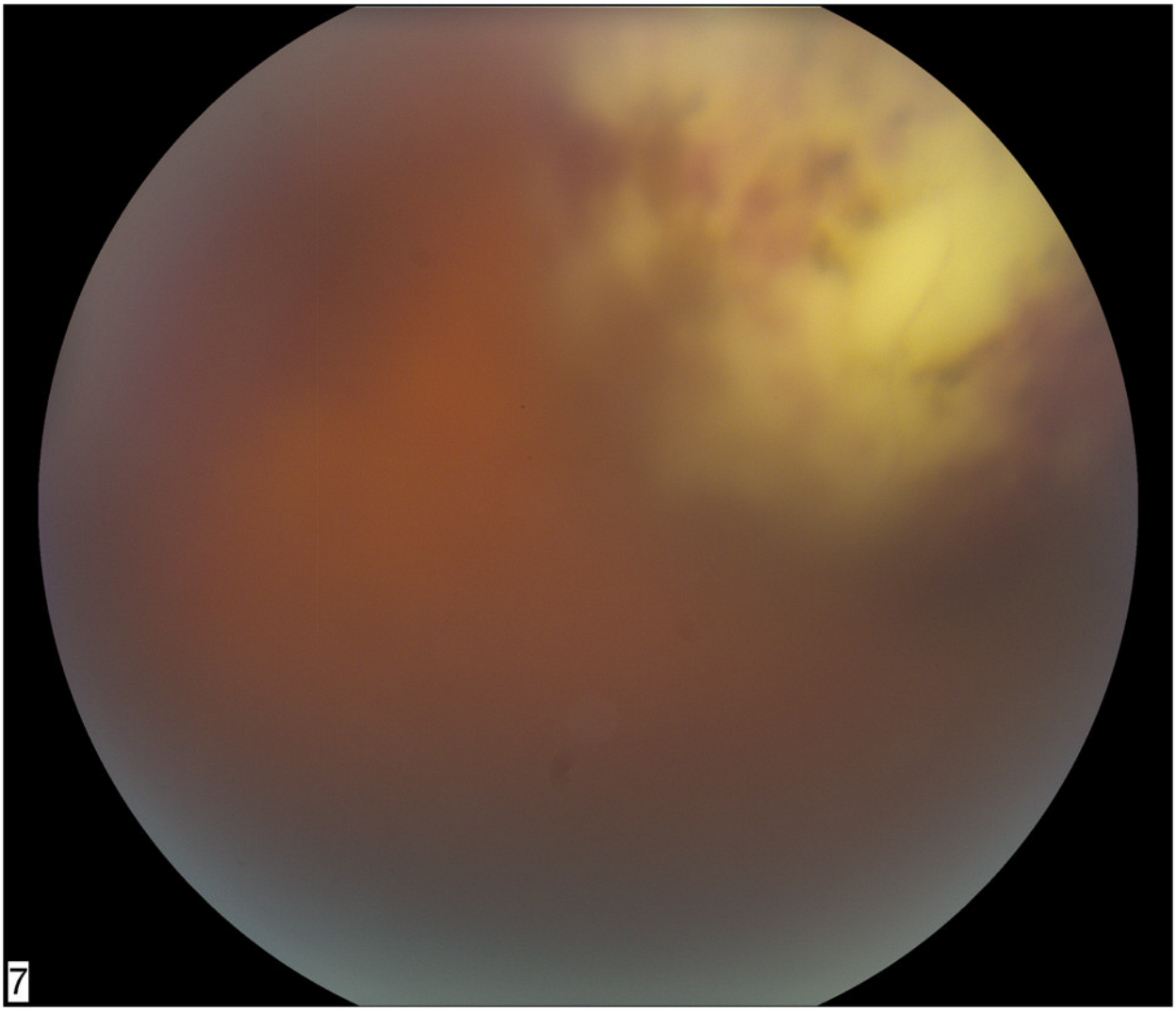


Figure 3.
Fundus photograph of superior/superonasal subretinal lesion in a cardiac transplant patient on mycophenolate mofetil, tacrolimus, and prednisone. Diagnostic vitrectomy and subretinal aspiration biopsy showed Nocardia species.

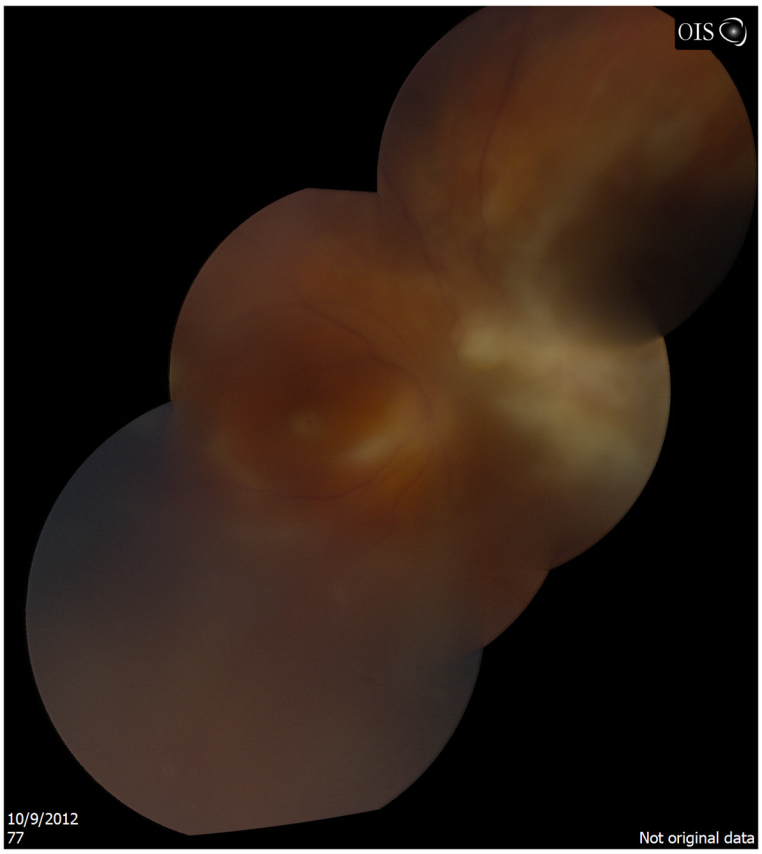
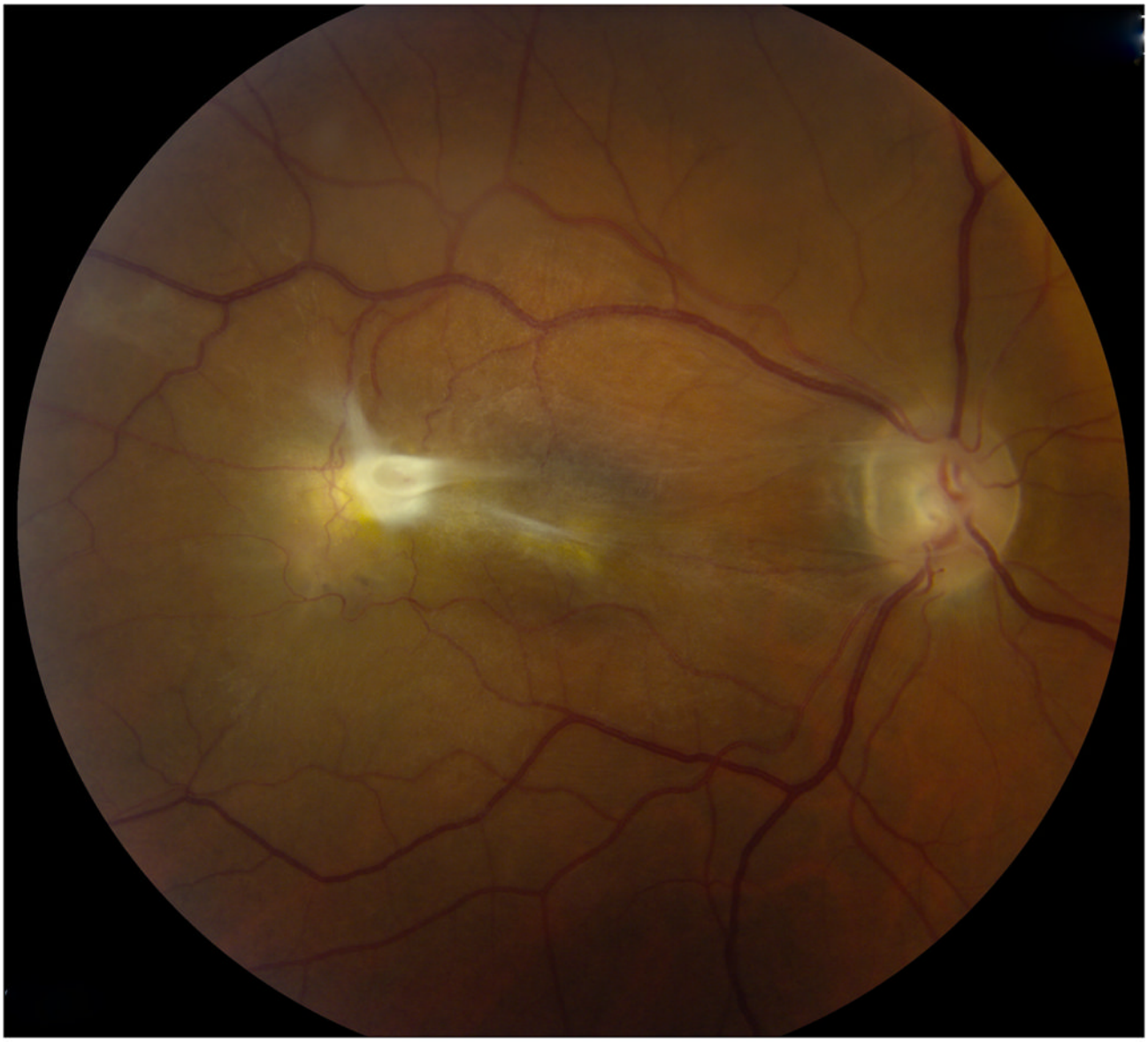


Figure 4.
Fundus photograph montage of patient with dermatomyositis on azathioprine and monthly intravenous immunoglobulin. Anterior chamber paracentesis was positive for toxoplasmosis DNA by PCR testing. The diffuse retinitis mimicked acute retinal necrosis and was atypical for toxoplasmosis, likely secondary to the patient's immunosuppression.



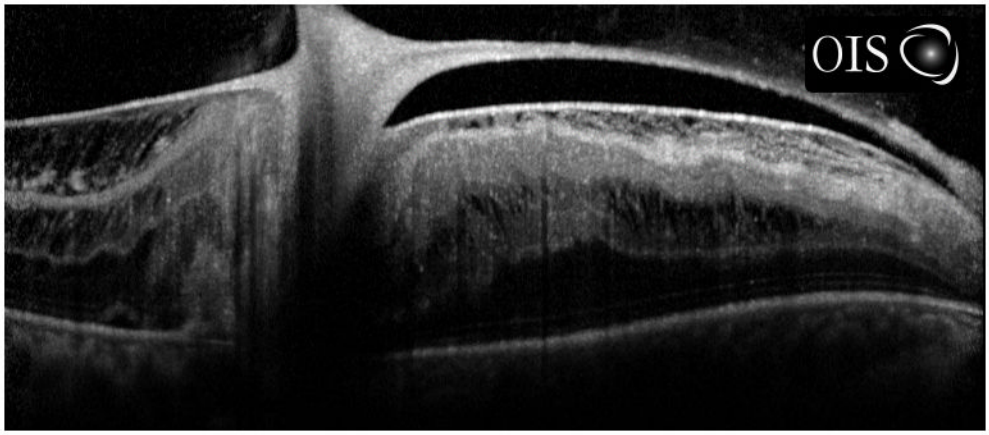
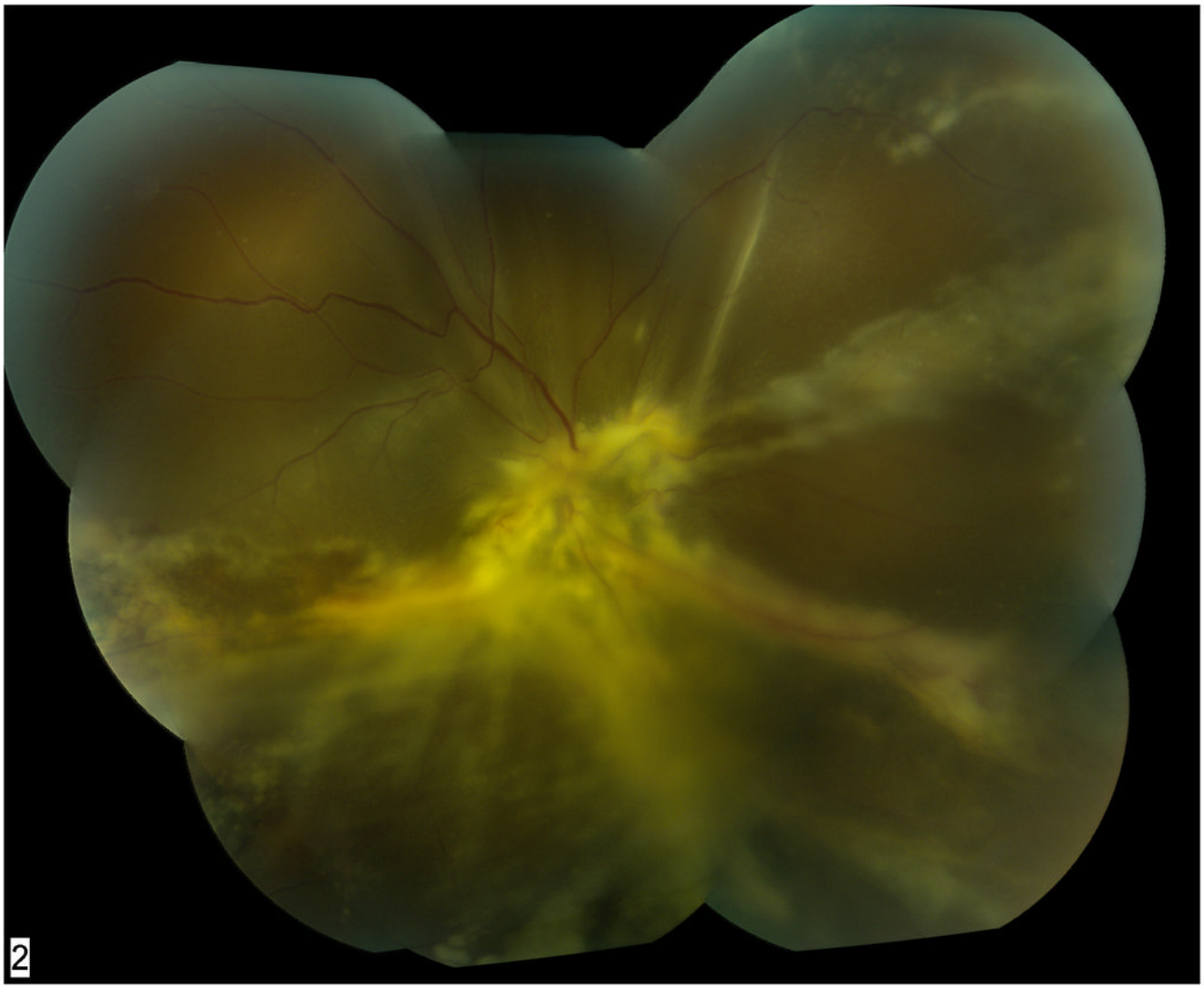


Figure 5.

Fundus photograph of patient with posterior pole granuloma (A) and corresponding spectral domain optical coherence tomography scan (B) suggestive of toxocariasis. Diagnostic vitrectomy showed elevated antibody titer to *Toxocara canis*, establishing the diagnosis of ocular toxocariasis.



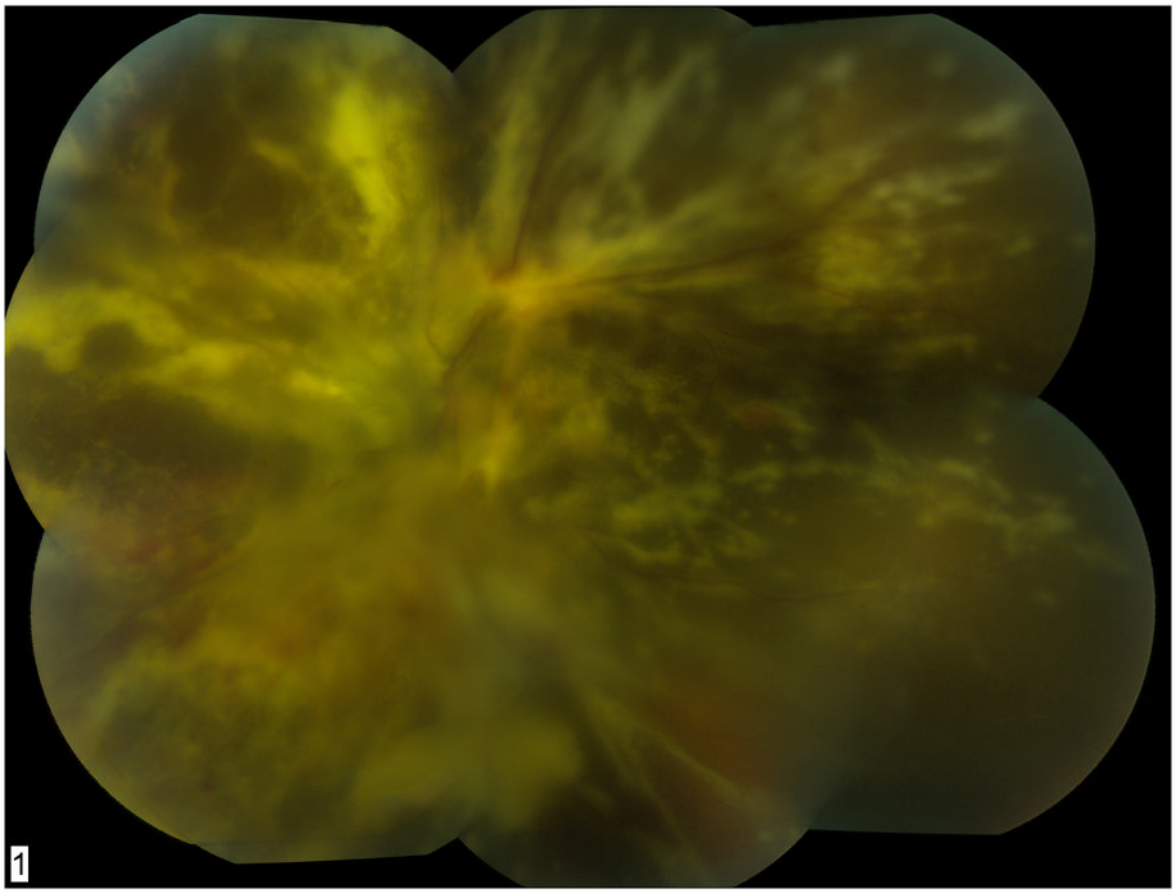


Figure 6.
Fundus photograph of diffuse CMV retinitis with underlying retinal detachment in the right eye (A) and left eye (B). The patient was HIV-positive and not taking recommended anti-retroviral medications. His CD4 count was < 5 cells/mm^3 on presentation. Qualitative PCR testing for CMV DNA was positive. Quantitative real-time PCR from the left eye showed 207,000 copies/mL of CMV DNA.

Table 1

Diagnostic Vitrectomy Yield from Large Series

Author	Reference	Overall Yield		Yield for Infectious Conditions*	
		n	Percentage	n	Percentage
Carroll et al	1	2/8	25	--	--
Priem et al	2	10/34	29.4	--	--
Palexas et al	3	60/215	27.9	60/215	27.9
Verbraeken et al	4	9/28	32.1	--	--
Akpek et al	5	11/34	32.4	--	--
Mruthyunjaya et al	6	35/90	38.9	27/35	77.1
Coupland et al	7	12/84	14.2	--	--
Zaldivar et al	8	9/14	64.3	--	--
Davis et al	9	48/78	61.5	34/50	68
Margolis et al	10	9/45	20	2/6	33.3
Wittenberg et al	11	126/228	55.3	--	--
Oahalou et al	12	18/84	21.4	--	--

*Yield for infectious conditions calculated only in case series reporting final diagnoses of infectious uveitis.