Masquerade syndromes in ophthalmology, as originally described, are conditions that simulate inflammatory diseases but are, in fact, neoplastic. The term now has broadened to include non-neoplastic etiologies, as well.

Necrotizing retinitis is a rare and potentially blinding condition that can be challenging to diagnose and to treat. In this installment of Practical Retina, Samuel P. Burke, MS, and Thomas A. Albini, MD, from Bascom Palmer Eye Institute present a case of toxoplasmosis retinitis that masqueraded as acute retinal necrosis and did not respond to initial antiviral therapy.

The authors provide an overview of the appropriate workup of necrotizing retinitis and define both typical and atypical presentations. A treatment algorithm is presented with discussion regarding the strength of the evidence supporting each modality.

Masquerade syndromes often represent uncommon presentations of uncommon diseases and therefore require an astute clinician for a prompt and accurate diagnosis and institution of appropriate therapy.

Toxoplasmosis Retinitis Masquerading as Acute Retinal Necrosis

by Samuel P. Burke, MS, and Thomas A. Albini, MD

A 71-year-old white woman with rheumatoid arthritis treated with abatacept (Orencia; Bristol-Myers Squibb, New York, NY), methotrexate, and low-dose prednisone presents for a second opinion regarding acute retinal necrosis (ARN) in her right eye. Four months prior to presentation, she received the diagnosis of ARN complicated by vitreous hemorrhage and underwent pars plana vitrectomy and endolaser. She was treated with oral valacyclovir (Valtrex; GlaxoSmithKline, Brentfort, United Kingdom) (1,000 mg three times per day) but continued to lose vision.

She presented to our clinic with best-corrected visual acuity (BCVA) of 20/100 in the right eye. Anterior segment examination of the right eye was remarkable for fine inferior keratic precipitates and 2+ anterior chamber cells. Dilated examination of the right eye showed 2+ anterior vitreous cells, a perfused optic nerve head without evidence of edema or pallor, atrophic scars in the macula, an area of preretinal hemorrhage along the inferior vascular arcade, diffuse vascular attenuation, 360° of panretinal photocoagulation, and a peripheral area of retinal whitening with overlying vitreous haze extending from the 9 o’clock meridian to the 12 o’clock meridian (Figure).

The patient underwent anterior chamber paracentesis, intravitreal injection of ganciclovir, and was continued on oral valacyclovir. The anterior chamber fluid was sent for polymerase chain reaction (PCR) analysis for herpes simplex virus (HSV), varicella zoster virus (VZV), cytomegalovirus (CMV), and Toxoplasma gondii genomes; the results were positive only for toxoplasma. Serology was remarkable for a positive

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T. gondii immunoglobulin (Ig) G, an equivocal T. gondii IgM, and a negative HIV. Historic fundus photos obtained by the patient from 5 years earlier demonstrated a large area of extramacular atrophy, consistent with a toxoplasmosis scar. The patient reported a remote mild allergic reaction to sulfa so she received an intravitreal injection of clindamycin. After consultation with an infectious disease specialist, the patient began a regimen of pyrimethamine (Daraprim; Turing Pharmaceuticals, New York, NY) (50 mg daily), folic acid (5 mg three times per week), sulfadiazine (1 mg daily), and prednisone. At 3 months’ follow-up, BCVA in the right eye was 20/60 and examination was significant for 2+ anterior chamber cells, 1+ vitreous cell, and persistent retinitis superotemporally. Optical coherence tomography in the right eye revealed an epiretinal membrane with mild cystoid macular edema. The patient subsequently underwent a sub-Tenon’s triamcinolone acetonide injection. At 6 months’ follow-up, BCVA in the right eye was 20/40, the anterior chamber and vitreous were quiet, and the areas of retinitis had improved with evidence of scar formation.

PATHOGENESIS

During initial T. gondii infection and subsequent flares, the host immune response relies on activated T lymphocytes and proinflammatory molecules, including IFN-γ, TNF-α, IL-1β, IL-6, IL-10, and various chemokines to suppress parasite replication, force conversion to the bradyzoite cyst form, and induce a latent chronic infection.1 In immunosuppressed patients, or for unknown reasons in immunocompetent
patients, *T. gondii* can reactivate with conversion back to the actively dividing tachyzoite form, resulting in cyst rupture and an active disease state. Ocular pathology develops principally as a result of the strong immune response to *T. gondii* and possibly via bystander autoimmune reaction against retinal antigens.  

### TYPICAL AND ATYPICAL PRESENTATIONS

Ocular toxoplamosis (OT) typically presents with characteristic findings of unilateral and focal retinochoroiditis with an adjacent healed retinochoroidal scar and vitreous inflammation. In rare patients, particularly those with immune compromise (eg, HIV infection, iatrogenic immunosuppression, or advanced age), OT presents as aggressive retinochoroiditis; the retinochoroidal lesions present atypically and are bilateral, multifocal and/or extensive. Because of the large size of the lesions and the overlying vitritis, the lesions may be difficult to distinguish from ARN. Historic photos may demonstrate a more typical OT lesion. OT retinochoroiditis lesions often do not follow the vascular spread seen in CMV or the axonal spread seen in VZV and HSV.

### DIAGNOSTIC APPROACH

When OT is incorrectly diagnosed as ARN, PCR may not be performed to confirm the diagnosis due to cost and potential complications. In these cases, PCR is obtained only after presumed ARN fails to respond adequately to standard therapy. Patients with infectious retinitis of uncertain etiology can be successfully diagnosed using real-time PCR for HSV 1/2, VZV, CMV, EBV, and/or toxoplasma with up to 81% sensitivity and 97% specificity. Viral retinitis is especially amenable to PCR identification, with many studies showing greater than 90% sensitivity and 95% specificity. Other advantages of PCR testing include low sampling volume requirement, utility immediately following symptom onset, and decreased influence from immune status. OT, however, has much lower sensitivity using this modality, ranging from only 28% to 75%. There is conflicting evidence as to whether aqueous humor or vitreous sampling is more sensitive for detecting toxoplasma, but vitreous paracentesis is more expensive, more invasive, and more likely to have complications. The lower sensitivity with PCR suggests the need for additional testing when there is high suspicion for OT.

### Antibiotic Regimens for Ocular Toxoplasmosis

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Dosing</th>
<th>Duration</th>
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<tbody>
<tr>
<td><strong>Oral Antibiotics</strong></td>
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<tr>
<td>Triple therapy</td>
<td>Pyrimethamine (25 mg – 50 mg daily), sulfadiazine (500 mg – 1,000 mg once daily), folinic acid (5 mg – 15 mg daily)</td>
<td>4 weeks – 6 weeks</td>
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<tr>
<td>Bactrim monotherapy</td>
<td>Trimethoprim/sulfamethaxazone (800 mg/160 mg twice daily)</td>
<td>6 weeks</td>
</tr>
<tr>
<td>Bactrim + clindamycin</td>
<td>Trimethoprim/sulfamethaxazone (800 mg/160 mg bid), Clindamycin (300 mg once daily)</td>
<td>6 weeks</td>
</tr>
<tr>
<td>Bactrim + azithromycin</td>
<td>Trimethoprim/sulfamethaxazole (800 mg/160 mg bid), azithromycin (500 mg daily)</td>
<td>6 weeks – 8 weeks</td>
</tr>
<tr>
<td>Azithromycin</td>
<td>Azithromycin (250 mg – 500 mg daily)</td>
<td>5 weeks – 10 weeks</td>
</tr>
<tr>
<td>Atovaquone</td>
<td>Atovaquone (1.5 g daily)</td>
<td>6 weeks</td>
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<tr>
<td><strong>Intravitreal Injection</strong></td>
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<tr>
<td>Clindamycin + dexamethasone</td>
<td>Clindamycin (1 mg) + dexamethasone (0.4 mg) per injection. One injection every 2 weeks</td>
<td>Up to three injections</td>
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<tr>
<td><strong>Prophylaxis</strong></td>
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<tr>
<td>Bactrim monotherapy</td>
<td>Trimethoprim/sulfamethaxazole (800 mg/160 mg daily) every 2 days – 3 days</td>
<td>12 months – 20 months</td>
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for OT or work up yields negative results for viral infection.\textsuperscript{7} Assessing for local antibody production by calculating the Goldmann-Witmer coefficient and/or performing immunoblotting in addition to real time PCR is useful in the weeks after symptom onset and raises sensitivity to 73% to 97% with specificity of 93%.\textsuperscript{3,9,14}

TREATMENT STRATEGIES

Typical OT is a self-limiting condition normally resolving within 6 weeks to 8 weeks, and it is not completely established that antibiotics improves short-term disease course or long-term visual outcomes in immunocompetent individuals compared to placebo or observation.\textsuperscript{13} No systemic antibiotic regimen, including 1) classic triple therapy (pyrimethamine, sulfadiazine, and folinic acid), 2) trimethoprim-sulfamethoxazole, 3) azithromycin, 4) clindamycin, or 5) atovaquone (Mepron; GlaxoSmithKline, Brentfort, United Kingdom), has been shown to be more effective, but trimethoprim-sulfamethoxazole and azithromycin have superior safety profiles (Table).\textsuperscript{16} Growing evidence supports the use of intravitreal clindamycin with or without intravitreal dexamethasone as an equally efficacious alternative with fewer systemic side effects.\textsuperscript{17,18} Antitoxoplasma therapy in immunocompromised patients can rapidly inactive toxoplasma retinochoroiditis.\textsuperscript{19,20} Level I evidence supports intermittent treatment every few days with trimethoprim-sulfamethoxazole to significantly decrease the risk of retinochoroiditis recurrence.\textsuperscript{21}

Oral corticosteroids at 0.5 mg/kg are commonly given in conjunction with the above antibiotics to control inflammation despite scarce evidence from randomized clinical trials proving their effectiveness as an adjuvant therapy.\textsuperscript{22} Use of sub-Tenon’s triamcinolone remains controversial, and there is general consensus that intravitreal depot steroids like triamcinolone are best avoided, given the possibility of inducing a fulminant infection despite concurrent antimicrobial therapy.\textsuperscript{23} Monotherapy with corticosteroids is entirely contraindicated due to the high probability of inducing fulminant retinochoroiditis.\textsuperscript{24,25}

CONCLUSION

Atypical toxoplasmosis simulating ARN is rare and difficult to diagnose. The literature documents significant delay in diagnosis even at tertiary medical centers. Often patients are treated for herpetic retinitis and only after there is failure to respond to appropriate treatment is the diagnosis of toxoplasmosis necrotizing retinitis entertained. Disease etiology may be suggested by historic fundus photographs, if available, and can be confirmed with PCR of the anterior chamber or vitreous or by the more cumbersome local antibody tests outlined above. Treatment with systemic or intravitreal antibiotics in combination with steroids is appropriate with little evidence to guide the choice for best treatment. Atypical toxoplasmosis needs to be considered in cases of necrotizing retinitis not responding appropriately to anti-viral treatment along with syphilis, lymphoma, CMV retinitis in non-HIV patients, and Behcet’s disease.

REFERENCES


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