Atypical presentations of ocular toxoplasmosis

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The diagnosis of ocular toxoplasmosis is based most often on the presence of characteristic clinical findings, which include focal retinochoroiditis, an adjacent or nearby retinochoroidal scar, and moderate to severe vitreous inflammation. However, a variety of less common, "atypical" presentations may be unfamiliar to clinicians, delaying both diagnosis and treatment. Patients who are immunocompromised or elderly may, for example, present with large, multiple and/or bilateral lesions. Other unusual manifestations include punctate outer retinal toxoplasmosis, retinal vasculitis, retinal vascular occlusions, rhegmatogenous and serous retinal detachments, a unilateral pigmentary retinopathy mimicking retinitis pigmentosa, neuroretinitis and other forms of optic neuropathy, and scleritis. Although in the past most cases of ocular toxoplasmosis were considered to result from reactivation of a congenital infection, it is now believed that postnatally acquired infection accounts for many cases of this disease. With appropriate use of antiparasitic therapy, the visual prognosis for patients with both typical and atypical forms of ocular toxoplasmosis may be good. Curr Opin Ophthalmol 2002, 13:387–392 © 2002 Lippincott Williams & Wilkins, Inc.

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Ocular toxoplasmosis results from proliferation of the obligate intracellular protozoan *Toxoplasma gondii* within the ocular tissues [3••]. The most common site of ocular involvement by *T. gondii* is the retina, although the underlying choroid is usually inflamed secondarily, producing a retinochoroiditis. Toxoplasmic retinochoroiditis is by far the most common cause of posterior uveitis worldwide [1,2]. The infection may be acquired by ingesting contaminated water or food, or by eating undercooked meat [3••]. In other cases, the fetus is infected transplacentally, resulting in congenital toxoplasmosis.

For most patients the diagnosis of ocular toxoplasmosis is straightforward and is based on the classic appearance of a focal retinochoroiditis with an adjacent or nearby retinochoroidal scar in the setting of a moderate to severe vitreous reaction. So-called "atypical" presentations may also occur, and a high level of clinical suspicion combined with the judicious use of laboratory investigations are required in making the diagnosis. A number of excellent reviews covering the pathogenesis, diagnosis, and management of ocular toxoplasmosis have been published previously [3••,4–7].

Typical presentation of ocular toxoplasmosis

Ocular toxoplasmosis occurs most commonly in otherwise healthy children, teenagers, or young adults. Individual episodes of retinochoroiditis usually result from reactivation of infections acquired either *in utero* or postnatally. Hence, ocular examination generally shows evidence of atrophic, pigmented retinochoroidal scarring (Fig. 1). The area of active inflammation is typically visible as a yellow-white focus with fluffy borders (Figs. 1 and 2). Vitreous inflammation is often present and may be marked, thereby limiting visualization of the posterior pole. There may also be an associated retinal vasculitis, which may be either near to or distant from the focus of active retinochoroiditis. In many cases there is a mild anterior uveitis, with keratic precipitates that may be nongranulomatous, granulomatous, or stellate in appearance. The intraocular pressure is acutely elevated in approximately 10% of patients. Examination of the contralateral eye may reveal additional retinochoroidal scars.

The period of active inflammation lasts on average for 6 weeks, after which time there is regression of the active lesion accompanied by gradual resorption of the vitreous inflammation and debris. The final scar is usually pigmented due to reactive hyperplasia of the retinal pig-

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Figure 1. Typical presentation of toxoplasmic retinochoroiditis with a characteristic adjacent scar and moderate vitreous inflammation
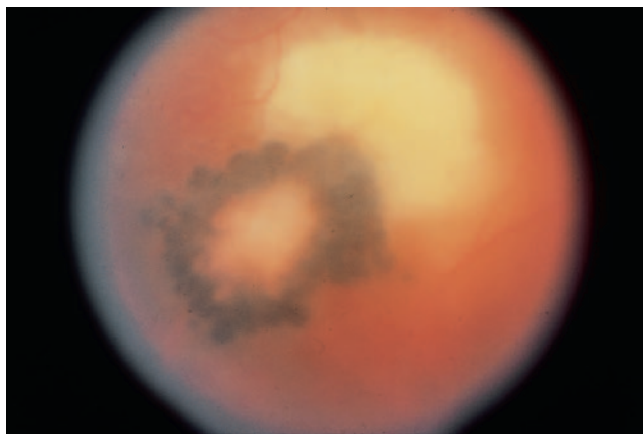
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ment epithelium, but a hypopigmented scar may develop when severe retinochoroiditis destroys the retina and adjacent choroid, exposing the underlying sclera. Multiple reactivations of ocular toxoplasmosis are common. In one large case series conducted in The Netherlands, the estimated mean recurrence rate was 2.8 for a 66-person cohort followed for a minimum of 5 years [8•]. For most patients visual prognosis is good, unless the focus of retinochoroiditis involves the macula, optic disc, or papillomacular bundle.

Spectrum of atypical presentations of ocular toxoplasmosis

A variety of less common presentations of ocular toxoplasmosis have been described, including more aggressive forms of retinochoroiditis characterized by large, multifocal and/or bilateral lesions [9,10•,11–16]. Such presentations may mimic acute retinal necrosis, and the lesions may take months to heal. Certain subgroups of patients appear to be at increased risk of developing this form of disease, including elderly persons [9,10•], patients infected with human immunodeficiency virus (HIV) [11–13], and patients with other forms of systemic immunosuppression [14–16]. Other unusual forms of posterior eye involvement include neuroretinitis [17,18], punctate outer retinal toxoplasmosis [19–21], an occlusive retinal vasculitis [22–24], retinal and subretinal neovascularization [25–27], rhegmatogenous and serous retinal detachment [28–30], a pigmentary retinopathy that may mimic retinitis pigmentosa [31], and various optic nerve pathologies [32–37]. In addition, *T. gondii* may proliferate in other parts of the eye, producing anterior uveitis [38], intermediate uveitis [39], and endophthalmitis [13]. There is a recognized, albeit poorly understood, association between Fuchs heterochromic iridocyclitis and ocular toxoplasmosis [40]. Rarely, scleritis has been reported to be due to *T. gondii* infection [41]. In addition

to the aforementioned "atypical" presentations of ocular toxoplasmosis, there has been a very significant recent change in our understanding of the pathogenesis of ocular toxoplasmosis, which questions the classic description of "typical" disease. Current studies do not support the prior assumption that most cases of ocular toxoplasmosis represent reactivated congenital lesions [42•,43•]. Newly acquired disease is being increasingly recognized in uveitis clinics, and there is good epidemiologic evidence that many cases represent reactivation of disease acquired remotely, but postnatally, rather than *in utero*.

Acquired versus congenital ocular toxoplasmosis

Recently, textbook descriptions of typical ocular toxoplasmosis have been challenged. Previous belief was that the vast majority of cases of toxoplasmic retinochoroiditis represented reactivations of congenital retinochoroidal scars. However, as argued eloquently by Holland [42•] and others [43•], acquired disease is probably not uncommon. In addition, organisms appear to be able to disseminate from previously infected sites in the body remote from the eye, to cause acute ocular toxoplasmosis in later life. Such episodes produce an area of focal retinochoroiditis without the characteristic retinochoroidal scar (Fig. 2), although a scar generally develops during the evolution of the disease [39]. Furthermore, it appears likely that many retinochoroidal scars, which were presumed to be congenital in origin, are postnatally acquired, at least in some countries. For example, a population-based survey undertaken in Brazil revealed a relatively low prevalence of ocular toxoplasmosis in children aged 8 years or less, with a substantially higher rate in children aged over 13 years of age [44]. In fact, ocular disease may occur in as many as 1 in 5 individuals suffering an acute systemic infection [45].

Aggressive retinochoroiditis

While severe disease may occur in any given patient, certain patient groups are at high risk of developing aggressive toxoplasmic retinochoroiditis. These groups include patients with the acquired immunodeficiency syndrome (AIDS) [11–13], persons who are systemically immunosuppressed pharmacologically or as a result of an underlying illness [14–16], and the elderly [9,10•]. Active lesions in such patients may be large, multiple and/or bilateral (Figs. 3 and 4). In some cases, the presentation is difficult to distinguish from that of acute retinal necrosis, due to the extent of the infection and the severity of the vitreous inflammation. Complications are frequent, particularly retinal detachment. Treatment with corticosteroids in the absence of appropriate antiparasitic treatment may also result in severe disease [46].
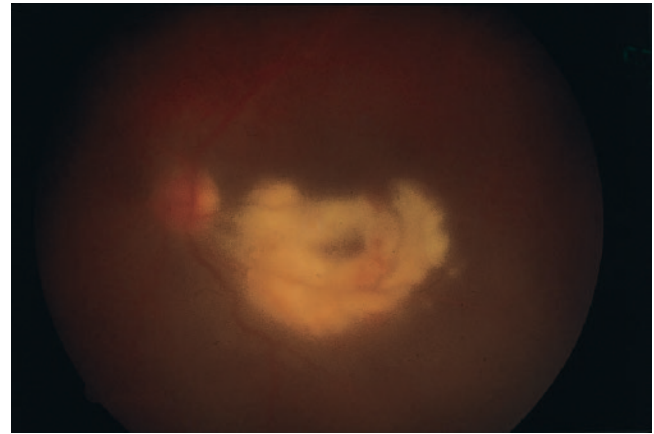
Patients with AIDS are relatively susceptible to toxoplasmosis infections, especially when the CD4-positive T-cell count drops below 100 cells/mL. Retinochoroiditis is

Figure 2. Acquired toxoplasmic retinochoroiditis
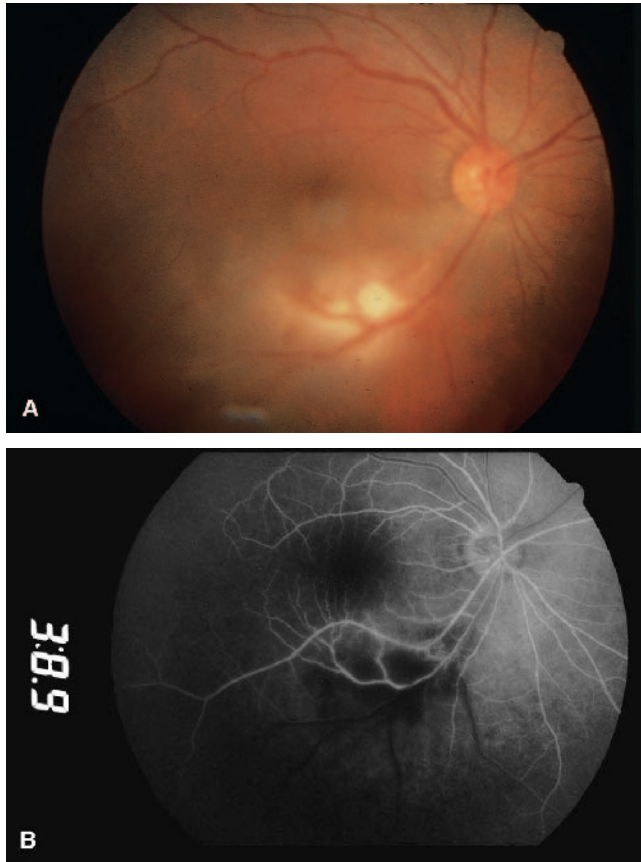
Color **(A)** and fluorescein angiographic **(B)** images of acquired toxoplasmic retinochoroiditis, confirmed by the presence of serum anti-*T. gondii* IgM antibodies. Note the absence of an adjacent or nearby retinochoroidal scar. There is an adjacent nodular arteritis with characteristic Kyrieleis plaques.

Figure 3. Toxoplasmic retinochoroiditis in an HIV-positive patient

There are relatively few satellite lesions at the advancing edge of retinal whitening, as well as moderately severe vitreous inflammation, both of which are observed commonly in patients with retinochoroiditis caused to *T. gondii* infection. In contrast, cytomegalovirus retinitis is often accompanied by satellite lesions at its advancing edge and tends to be associated with mild vitreous inflammation.

most often acquired or spreads from nonocular sites in HIV-positive patients, and, consequently, a scar is frequently absent [11]. In many cases, the retinochoroiditis is aggressive, and it may progress to endophthalmitis and even to orbital cellulitis [13]. So-called miliary toxoplasmic retinitis has also been described in a patient with AIDS [47]. Clues that help distinguish toxoplasmic retinochoroiditis from cytomegalovirus retinitis in HIV-positive patients include a more prominent vitreous inflammation, a smoother edge with few satellite lesions, and a relative lack of intraretinal hemorrhage in toxoplasmosis. Patients with ocular toxoplasmosis who are HIV-positive are also at risk of life-threatening intracranial toxoplasmosis. In one series of HIV-positive patients with clinically diagnosed ocular toxoplasmosis [45], almost one third of patients suffered from cerebral lesions [13].

Ocular toxoplasmosis may occur in individuals with other forms of systemic immunosuppression, including malignancies such as systemic lymphoma, and pharmacologic immunosuppression for rheumatologic disease or to prevent solid organ or bone marrow rejection. A number of case reports and small case series describe aggressive disease and visual loss in these settings [14–16].

Ocular toxoplasmosis has been considered to be rare in the elderly population, although recent data suggest that it may be more common than previously suspected [10•]. Aggressive disease is frequent among older individuals, and it has been postulated that an age-related decline in T-cell–mediated immune responses as well as nutritional deficiencies may at least partly explain this observation [9]. Labalette *et al.* [10•] reported on a cohort of 27 consecutive patients, aged over 50 years, who were diagnosed with ocular toxoplasmosis on clinical and laboratory evidence over an 8-year period [10•]. More than half of the cohort had lesions that were sized at 3 disc areas or

Figure 4. Multifocal retinochoroiditis due to *T. gondii* infection in an HIV-positive patient
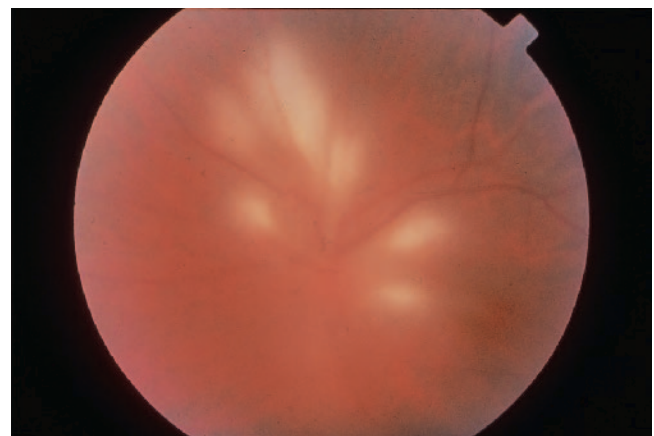
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greater, and most these patients developed complications—including epiretinal membrane, chronic cystoid macular edema, and persistent massive vitreous opacities—that led to loss of best corrected visual acuity in some. Johnson *et al.* [9] described ocular toxoplasmosis in seven elderly patients aged from 69 to 82 years. These patients had fulminant retinochoroiditis that was initially misdiagnosed as acute retinal necrosis in four individuals. Significant visual loss in most eyes was associated with high rate of complications, including retinal detachment, macular scars, and/or epiretinal membrane.

Neuroretinitis

The clinical features of neuroretinitis include optic disc edema accompanied by a complete or partial macular star. A serous peripapillary and/or macular detachment may also be present, and often predates the formation of the macular star by 2 to 4 weeks. Sudden and profound visual loss is typical. While neuroretinitis occurs most commonly in the setting of cat scratch disease, this condition has been described in a small number of patients with serologic evidence of toxoplasmosis (Fig. 5) [17,18]. As is the case for other forms of neuroretinitis, good visual acuity was recovered by most patients, although persistent visual field defects occurred in some individuals. The presence of moderate to severe vitreous inflammation, an adjacent or nearby retinochoroidal scar, and one or more recurrences may be helpful in making the diagnosis [18]. Despite the paucity of relevant published literature, toxoplasmic neuroretinitis is probably best managed by prompt institution of antiparasitic agents.

Punctate outer retinal toxoplasmosis

Although most *T. gondii* infections are severe enough to involve all retinal layers, a more limited "punctate outer retinal toxoplasmosis" has also been described [19–21]. Patients with this condition typically have multifocal

Figure 5. Toxoplasmic neuroretinitis with a partial macular star

Clues that may help differentiate toxoplasmic neuroretinitis from other types of neuroretinitis include the presence of moderate to severe vitreous inflammation and the occurrence of recurrent attacks of inflammation.

gray-white lesions at the level of the outer retina and retinal pigment epithelium. Most lesions have been reported in the macula, but this may be due to the fact that macular lesions are visually the most symptomatic. Vitreous inflammation is usually minimal. Recurrences, when they occur, usually involve the adjacent retina. Appropriate antiparasitic therapy often results in full visual recovery, but resolution may be accompanied by the development of a granular retinochoroidal scar best seen with fluorescein angiography.

Retinal vascular disease

Retinal vasculitis is common in patients with ocular toxoplasmosis and typically occurs in the same quadrant as the retinochoroiditis [24]. This usually takes the form of venular and/or arteriolar sheathing. Less often a nodular arteritis with yellow Kyrieleis plaques may develop (Fig. 2). In rare cases, the vasculitis may be occlusive, resulting in retinal infarction and consequent visual field defects [22–24]. Retinal neovascularization has been described as part of ocular toxoplasmosis, and may predispose patients to vitreous hemorrhage [25]. Subretinal neovascularization may also occur [26], in some cases taking the form of a vasoproliferative retinal tumor producing an overlying exudative retinal detachment, recurrent vitreous hemorrhage, and/or cystoid macular edema [27]. Such lesions have been treated successfully with both cryotherapy and laser photocoagulation [27]. Other rare forms of retinal vascular disease that have been described in association with ocular toxoplasmosis include frosted branch angiitis [48] and Roth spots [49].

Retinal detachment

The majority of retinal detachments observed in individuals with ocular toxoplasmosis are rhegmatogenous or tractional in nature. One study of 150 consecutive patients attending a Dutch ophthalmology department reported a frequency of 6% for retinal detachment and an additional 5% for retinal breaks [28]. There are also a small number of reports in the literature describing exudative retinal detachments in patients with active ocular *T. gondii* infections. In some cases the exudative reaction was severe enough to suggest the diagnosis of Coat disease [29]. In other cases the exudation was limited to the area of the macula [30].

Pigmentary retinopathy

Silveira *et al.* [31] in Brazil described a unilateral pigmentary retinopathy in seven patients with bilateral recurrent ocular toxoplasmosis that was diagnosed on the presence of both typical retinochoroidal lesions and positive serologic tests for *T. gondii*. This form of retinopathy is associated with a nonrecordable electroretinogram mimicking retinitis pigmentosa. However, in contrast to retinitis pigmentosa, the changes are unilateral and in some patients involve only a portion of the fundus.

Optic neuropathies

While optic disc swelling is a common finding in patients with active toxoplasmic retinochoroiditis, reported to have a prevalence of 13% in one recent large series of 154 patients with active lesions [8], other optic nerve abnormalities are less typical. Case reports describe optic nerve pathologies that include an optic nerve head mass, anterior optic neuropathy, and optic neuritis [32–37]. These optic neuropathies generally present as sudden loss of vision, usually in the presence of an afferent pupillary defect and decreased color vision. Visual loss may be permanent, associated with development of optic atrophy, but the prognosis can be excellent with appropriate antimicrobial therapy.

Other forms of uveitis

Although most patients with Fuchs heterochromic iridocyclitis do not have fundus findings consistent with active or prior toxoplasmosis, several studies have documented an increased prevalence of retinochoroidal scars in patients with Fuchs uveitis syndrome [40,50,51]. Lesions may be active or inactive, and can be in the same or contralateral eye. The reason for this association is unknown [52]. In a minority of patients, infection with toxoplasmosis can cause an intermediate or diffuse uveitis in the absence of clinically apparent foci of retinitis or retinochoroiditis [39]. However, retinochoroidal scarring often develops over time, suggesting that foci of retinochoroiditis were previously present, but perhaps too small to be visible clinically. Most of these cases are believed to represent acquired infections, particularly when accompanied by symptoms or signs of systemic toxoplasmosis. Isolated acute anterior uveitis has been described in a patient with AIDS and a *T. gondii* infection of the iris [38].

Scleritis

Scleritis is a rare manifestation of *T. gondii* infection, which may be more common in immunosuppressed individuals [41]. Although scleral inflammation generally results through contiguous spread from a florid focus of retinochoroiditis, it is possible to develop scleritis at a location that is anatomically distant from the active fundus lesion. With prompt recognition and appropriate use of systemic antiparasitic agents, the visual prognosis can be good.

Management of atypical ocular toxoplasmosis

Exceptional visual outcomes have been reported after treatment of atypical ocular toxoplasmosis using standard antimicrobial treatments. On the other hand, the prognosis of these cases can be extremely poor, especially when the diagnosis is delayed and complications such as retinal detachment develop. The key to a successful outcome appears to be early diagnosis, facilitating prompt institution of appropriate therapy. Therefore, when the presentation is atypical, special investigations are often useful. Serologic tests for anti-*T. gondii* IgG antibodies are positive in a large percentage of the population in most countries. In acute disease, however, a positive IgM and/or IgA titer may support the diagnosis. The relative percentage of specific anti-*T. gondii* antibodies in the aqueous humor versus serum, a ratio referred to as the Goldmann-Witmer coefficient, can also be used to make the diagnosis [53], but this test is limited to a small number of centers. More recently, polymerase chain reaction-based assays have been applied to ocular fluid specimens to diagnose ocular toxoplasmosis [54]. A wide variety of anti-parasitic therapies have been used to treat both typical and atypical ocular toxoplasmosis. Currently the most common popular option is the combination of pyrimethamine and sulphadiazine [55••]. Oral folinic acid is prescribed with pyrimethamine, to avoid bone marrow toxicity. Systemically administered corticosteroids may be useful to reduce inflammation or to minimize vision loss associated with peripapillary or macular lesions, but should not be used in the absence of appropriate antimicrobial coverage. Many ophthalmologists consider that periocular corticosteroids injections are contraindicated in the management of toxoplasmic retinochoroiditis. Immunocompromised HIV-positive patients usually require long-term treatment with antiparasitic agents, but drug allergies and/or intolerance often complicate such therapy.

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