

Ocular Manifestations of Toxocariasis in Humans

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A number of parasitic diseases are known to involve ocular and periocular tissues. Filariasis, particularly onchocerciasis, cysticercosis and other *Taenia* infections, echinococcosis, trichinosis, schistosomiasis, toxocariasis, and even ophthalmomyiasis (caused by fly larvae) are recognized conditions. Many of these are extremely uncommon and appear as case reports only in the literature.

Several of the most common ocular parasitic infestations develop from an animal reservoir. Toxocariasis from canines and possibly felines, cysticercosis, and echinococcosis are worldwide problems. *Echinococcus* usually presents as an orbital mass. Cysticercosis may involve the orbit and extraocular muscles but can also be an intraocular infection. In North America, the most common intraocular parasitic infection is toxocariasis.

Intraocular infection by the nematode *Toxocara canis* occurs primarily in children and young adults. The infection is produced by third-stage larvae that gain entrance to the eye. A number of clinical manifestations have been described, the consequences of which can lead to disruption of ocular tissues and/or scarring and ultimately blindness.

T. canis is a member of the ascarid family and is similar to *Ascaris lumbrici-*

oides in humans and the feline roundworm *Toxocara cati*. The human infection is initiated in a fashion similar to that in the dog, namely, by the ingestion of viable eggs or larvae in contaminated soil, oral-fecal transmission, and the ingestion of contaminated food. However, as paratenic hosts, humans cannot support the complete life cycle of the *Toxocara* worm. Third-stage larvae develop in the small intestine and penetrate the bowel wall to enter the portal circulation, subsequently migrating to the liver, lungs, and distant organs. The larvae are believed to enter the eye via the retinal, choroidal, and/or ciliary body vasculature and initiate an inflammatory response.¹

Historical Background

In 1950, Heleanor Campbell Wilder in the Ocular Pathology Branch of the Armed Forces Institute of Pathology (AFIP) reviewed children's eyes enucleated because of endophthalmitis and/or suspected retinoblastoma. In many eyes, a granulomatous inflammation characterized by numerous eosinophils was noted; in 23 of 46 eyes examined, a nematode larva or its capsular remnants were identified, often revealed only after multiple microscopic sections were made and studied.² The type of nematode was not known initially, but shortly thereafter a *Toxocara* species was identified as the etiologic agent of visceral larval migrans (VLM).³ Some of the cases described by Wilder were then reviewed, and *Toxocara* larvae were identified.⁴ Clinical cases in a less advanced state than those reported by the AFIP were soon identified. Clinical presentations of both peripheral^{5,6} and posterior pole⁷ localized inflammatory masses were described and confirmed by histopathology. Subsequently, an unusual inflammation and retinal degeneration, so-called diffuse unilateral subacute retinitis (DUSR), has been described and attributed to *Toxocara* species in some cases.^{8,9}

Sources of Infection

T. canis is commonly found in dogs and other canids such as foxes and wolves. The infection is initiated in adult dogs by the ingestion of eggs or larvae from contaminated soil, feces, and/or infected meat. Within the intestine, the third-stage larva enters the vascular system following infiltration through the bowel wall. The organisms deposit in various tissues, including lung, liver, brain, and eye, and can produce a VLM-like presentation. The organisms encyst

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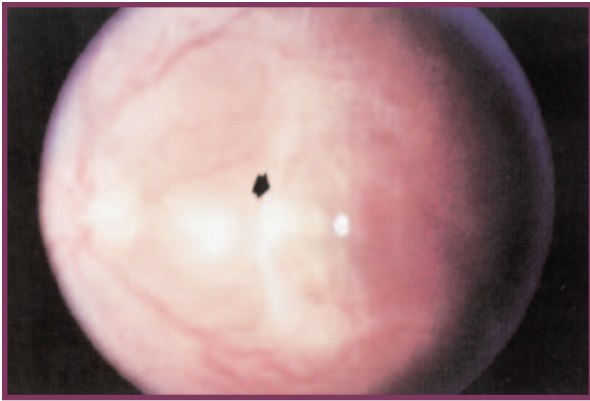


Figure 1—A posterior pole intraretinal lesion with a subretinal granuloma (white arrow), an epiretinal membrane (black arrow), and an exudate adjacent to optic nerve. (From Werner JC, Ross RD, Green WR: Pars plana vitrectomy and subretinal surgery for ocular toxocariasis. *Arch Ophthalmol* 117:532–534, 1999. Copyrighted 2001, American Medical Association.)

in the adult dog and become dormant, maturing only rarely. Most adult dogs are therefore not a source of infection.¹ The primary canine source of infective eggs and larvae is from puppies and lactating bitches.

Encysted larvae become activated in pregnant bitches and can then infect the placenta and breast tissues. Third-stage larvae may develop in puppies in utero, migrate from the intestines to the lungs and trachea, reenter the gastrointestinal tract, and develop into adult worms in the puppy fetus. Beginning about 4 weeks following birth, lactating bitches may also have infective larvae in their milk. The larvae may be swallowed by puppies, and the worms mature in their intestines. In either case the adult worms are the source of eggs in puppy feces beginning about 4 weeks after birth.^{1,10}

T. canis eggs need 1 to 2 weeks of optimal moisture and temperature to become infective, and anything in the puppy environment can be contaminated. *T. canis* eggs can be a ubiquitous finding in soil under the proper conditions of temperature, climate, and the number of dogs/canids in the environment. Most human infections are subclinical and occur in infants and children, primarily from the ingestion of infected soils (pica), fecal-oral contamination, or contaminated foods. The development of seropositivity following ingestion varies greatly, usually ranging between 2% to 10% but can be as high as 80%

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in certain endemic areas.^{11,12} This immunologic evidence of subclinical exposure must be remembered when trying to interpret the significance of an elevated antitoxocara titer in a human with suspected ocular disease.

Although a *T. cati* larva has not been specifically identified in VLM or ocular disease, it is well advised to remember the possibility that this species may be involved in some cases. A case has been made for *T. cati* playing an important role in ocular infections acquired by infants and children from sand in infected litterboxes and play boxes.^{10,13} *T. canis* and *T. cati* larvae share many common antigens. In the future, differentiating between the two may be possible via improved monoclonal antibodies or by DNA polymerase and hybridization techniques. Some cases of eye disease are assumed to be caused by *T. canis* larvae without definite proof and thus the term *nematode endophthalmitis* is sometimes used for ocular infections.

The third-stage *T. canis* larva is typically 400 to 450 μm in length and develops further in canine species. Adult roundworms develop in the intestine, can become 10 cm in length, and can excrete 200,000 eggs each day. The ova becomes infective after a 2- to 3-week period and may remain so for months.¹

Few experimental models exist for the investigation of how the larvae enter the eye, but a new model of systemic larval infection in Mongolian gerbils looks particularly interesting in this regard.^{14,15}

Ocular Manifestations

The most common ocular manifestation attributed to toxocariasis is a dense white mass either in the retinal periphery or in the posterior pole (Figure 1). This inflammatory tissue surrounds the nematode larvae. Although most of these cases are probably due to toxocariasis, larvae of other nematodes have been demonstrated.

Peripheral Retina

In this location, vitreous and retina can be drawn toward the mass and produce a “wadded up” appearance. Membranes in the vitreous may radiate from the mass; most typically, a radial fold of the retina extends from the mass to the optic nerve head. An epiretinal membrane may form and involve the posterior pole and macula. The peripheral

mass itself may not induce symptoms, but secondary changes of retinal scarring can produce profound visual changes, particularly if the macula is involved or if a retinal detachment occurs because of traction.

Posterior Pole

Depending on their location, these lesions may produce no symptoms or profound visual loss. Typically, a white mass is noted next to the optic nerve. The size varies and may be the diameter of the optic disc or encompass the posterior pole, including the macula. Vitreous may not be involved, or a dense vitreal membrane may form. Secondary changes in the retinal pigment epithelium include atrophy and hyperplasia.

Endophthalmitis

A marked inflammation of the vitreous can occur surrounding a larval remnant; it may be accompanied by retinal detachment in which the retinal folds are drawn toward the inflammatory focus, forming a retrolental mass. Cases of this type result in a leukokoria (white pupil) and raise the possibility of a retinoblastoma or endophthalmitis of other cause. Such cases are typical of those originally described by Wilder. In a study of 41 cases by Wilkinson and Welch,¹⁶ peripheral lesions were the most common (43.8%), followed by diffuse vitreous involvement (31.7%) and posterior pole lesions (24.4%). Rarely, an inflammatory mass over the optic disc has been attributed to toxocariasis. Larvae have also been noted in the cornea, anterior chamber, and vitreous in the absence of inflammation, and their movement throughout the eye has been noted.¹⁷⁻¹⁹ Most of these cases were not documented to be *Toxocara*, although an intraocular elevation of *Toxocara* antibody has been demonstrated occasionally.¹⁸ The assumption has been made that the death of the organism initiates the inflammatory response.¹⁹

Diffuse Unilateral Subacute Neuroretinitis Syndrome

Diffuse unilateral subacute neuroretinitis syndrome (DUSN; also called *unilateral wipeout syndrome*) was originally described by Gass and coworkers²⁰ and involves advanced vision loss, vitreous inflammation, and optic disc inflammation associated with typical retinal findings. Multiple focal gray-white lesions develop in the outer retina in clusters and then disappear and recur elsewhere. A localized serous detachment of the retina occurs, the retinal pigment epithelium undergoes changes of color, and eventually focal areas of degeneration develop. A cystoid macular edema may occur.

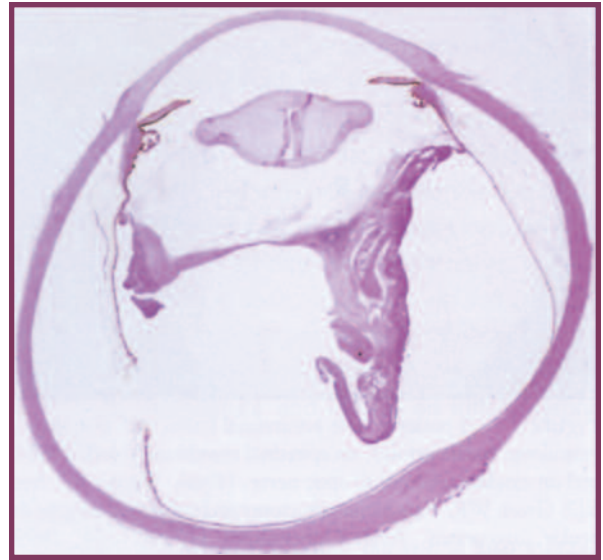


Figure 2—A section of an eye with an intravitreal granuloma and retinal detachment. (H&E; original magnification, $\times 20$; courtesy of University of California San Francisco Eye Pathology Laboratory.)

A subretinal larva is noted in about half the cases, and motility and viability can be documented. The retinal changes have been attributed to toxic metabolic by-products of the worm. Although originally attributed to toxocariasis, the worms vary from 400 μm to 1000 μm in size and the syndrome apparently may result from the larvae of several different nematode species, including *Ancylostoma caninum* and *Baylisascaris procyonis*, an intestinal roundworm of raccoons.²⁰ Cases of DUSN have been associated with contact with raccoons, and an ocular larval migrans caused by this organism has been reported in humans and other animals. Recently, a case of DUSN was documented to be secondary to a nematode larva with the characteristics of *Toxocara*. The intact subretinal nematode, which was removed through a transvitreal surgical approach, could be directly examined and its characteristics determined.⁹

Pathology

The typical histopathologic characteristics originally noted by Wilder are found in all forms in which an inflammatory mass develops (Figure 2). The nonviable organism induces a focal necrotizing granulomatous inflammation characterized by eosinophils in large numbers (Figure 3). Typically, these cells, mononuclear phagocytes ("epithelioid cells"), plasma cells, lymphocytes, and inflammatory giant cells surround a zonal area of necrosis around a larva or remnants thereof (Figure 4). The inflammation is so characteristic that even in the

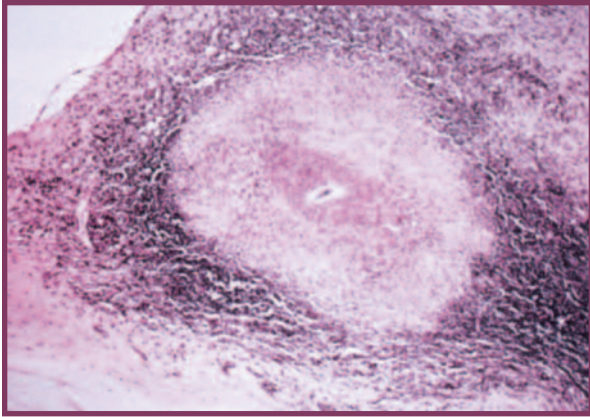
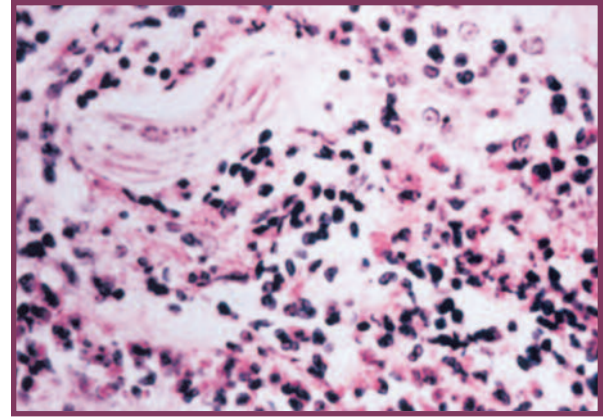


Figure 3—Higher power view of the eye in Figure 2 showing a typical zonal granulomatous response around a degenerating larva. (H&E; original magnification, $\times 100$; courtesy of University of California San Francisco Eye Pathology Laboratory.)



*Figure 4—Degenerating *Toxocara larva* still maintaining a suggestion of a lateral column and central stippled enteric canal. The surrounding inflammatory infiltrate contains numerous eosinophils. (Original magnification, $\times 400$.)*

absence of larvae, the diagnosis is suspected and multiple additional sections are made.

Since the 1970s, few eyes have been removed because of toxocariasis. The clinical presentation is reasonably diagnostic, and treatment can be initiated. Early lesions are also recognized and promptly treated. Surgery has been used to remove inflammatory masses and correct traction effects on the retina. A case of *T. canis* has been identified in a peripheral mass following pars plana vitrectomy. The cellular infiltrate was typical, and the intact nematode was identified as a *T. canis* larva.²¹ The pathology of DUSN has not been elucidated.

Relationship to Visceral Larval Migrants

Ocular toxocariasis rarely occurs at the same time as VLM. Most patients with ocular disease have symptoms and signs relative only to the eye. Patients with ocular findings are generally older (average, 7 to 8 years) than patients with VLM (average, commonly less than 3 years). Antibody titers to the organisms tend to be much higher in VLM than in the ocular form. Why these differences occur is not understood, but most likely a subclinical infection allows larvae to be deposited in ocular tissues. The absence of systemic humoral immunity would actually allow for more ready dissemination of microorganisms.

Diagnosis of Ocular Toxocariasis

The diagnosis is generally based on clinical findings in the eye and supported by imaging or laboratory studies. Ultrasonographic studies may be helpful.²² Recently, ultrasound biomicroscopy has shown a characteristic pseudocystic change in vitreous adjacent to the inflammatory mass.²³

VLM is primarily diagnosed via antibody testing. In contrast, systemic antibody findings may or may not be helpful in diagnosing ocular toxocariasis. The ELISA technique is usually the method of choice, and a larval secretory antigen (TES) is most often the target.¹⁰ Separate values can be determined for IgG, IgM, and IgA antibodies; IgE antibodies may be particularly helpful.¹⁰ In VLM, serum titers greater than 1/32 are found; titers greater than 1/8 are supportive of the ocular form, but occasionally there are no systemic antibodies in documented ocular cases.²⁴ It must also be kept in mind that completely normal children may have serum antibodies to *Toxocara*, the incidence of which varies with the geographic region.¹ Antibodies measured in vitreous and aqueous may indicate an ocular infection, particularly if locally produced antibodies are greater than those in the circulation.^{1,25} The documentation of eosinophils in ocular inflammatory infiltrates can also be helpful in the absence of an increase of circulating eosinophils.

Therapy

The choice of therapy for ocular toxocariasis depends on the clinical presentation and extent of inflammation and scarring. At a stage when the worm is visible and apparently viable and inflammation is minimal, medical therapy with an anthelmintic agent such as thiabendazole (15 mg/kg/day for 5 days) and/or ivermectin (single dose of 9 mg) can be used.²³ Diethylcarbamazine has also been used. Laser photocoagulation has been employed to destroy intraocular nematodes.²¹

If inflammation and/or structural change/scarring is evident, medical therapy with anthelmintic agents may still be warranted; however, the most important therapy

at this stage is to employ systemic or periocular corticosteroids to decrease the inflammatory component and potential for scarring.

Surgical removal of the nematode and inflammatory mass, particularly if it is peripheral, can be successful.²¹ Vitrectomy can also be successful to remove cells and membranes (e.g., epimacular membranes), relieve macular traction, and repair retinal detachments.¹ A recent review of vitreoretinal surgery for macular traction and/or detachment indicates the success of this approach.²⁶

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