

## Update on pathology of ocular parasitic disease

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Parasites are a group of eukaryotic organisms that may be free-living or form a symbiotic or parasitic relationship with the hosts. Consisting of over 800,000 recognized species, parasites may be unicellular (*Protozoa*) or multicellular (helminths and arthropods). The association of parasites with human population started long before the emergence of civilization. Parasitic zoonotic diseases are prevalent worldwide including India. Appropriate epidemiological data are lacking on existing zoonotic parasitic diseases, and newer diseases are emerging in our scenario. Systemic diseases such as cysticercosis, paragonimiasis, hydatidosis, and toxoplasmosis are fairly common. Acquired *Toxoplasma* infections are rising in immune-deficient individuals. Amongst the ocular parasitic diseases, various protozoas such as Cystoidea, trematodes, tissue flagellates, sporozoas etc. affect humans in general and eyes in particular, in different parts of the world. These zoonoses seem to be a real health related problem globally. Recent intensification of research throughout the world has led to specialization in biological fields, creating a conducive situation for researchers interested in this subject. The basics of parasitology lie in morphology, pathology, and with recent updates in molecular parasitology, the scope has extended further. The current review is to address the recent update in ophthalmic parasites with special reference to pathology and give a glimpse of further research in this field.

**Key words:** Cysticercosis, diffuse unilateral subacute neuroretinitis, hydatidosis, molecular pathology, onchocerciasis, ophthalmomyiasis, parasitology, toxocariasis, toxoplasmosis, zoonoses

Ocular parasitology is the study of parasites that pass on a disease to humans and results in ophthalmic complications.<sup>[1,2]</sup> Parasitology was born as a tropical step-sister of medicine but has become a well-known scientific subject in its own right in these times of global awareness. In the past decade, parasitology has undergone significant transformation.

The causative organisms of parasitic diseases depend on reproduction as a prime function for survival in the definitive host.<sup>[3]</sup> Many progenies are needed to overcome the mortality during transmission of organism to pass on its reproductive character to the next generation.<sup>[2-4]</sup> The host is deprived of vital resources and nutrients which the parasites utilize during their reproductive stages. The consequence of these changes is local or extensive damage to the host tissue, and if these become more severe, there is noticeable deterioration of the host who is then referred to have systemic involvement of parasitism.

A pathological change due to parasitic infections may also cause various faults in the homeostatic regulatory mechanisms that have a primary function to protect the host from infections.<sup>[3,4]</sup> Many species of different parasites have various effects on the host response; hence, pathology, immunology,

and biology are interlinked and disrupt the balance of the host. The importance of the parasite in pathological changes is what we might expect from a progressive arms race, in which its counter-adaptive steps provide the selective environment for the next stride.<sup>[2-4]</sup>

The authors have found a unique method of detecting the live parasites under the compound microscope objectives (Zeiss, Axioskop 40) and documenting them digitally (AxioCam MRc). The entire internal structures including intestine, spine, and striations could be instantly identified under background illumination, and the immediate diagnosis can be communicated to the surgeons. The entire exercise of diagnosis can take 5–10 min from the time of receiving the specimen. Since the management protocol of different worms vary from one another, urgent diagnosis can help overall management of the patient. These were compared with wet-mount preparation of the parasites. Sometimes, opinion of a parasitologist was taken to confirm the diagnosis [Fig. 1].

The relationship between a parasitic organism and its host's immune system is an extremely complex one.<sup>[3,4]</sup> Various pathologies of ophthalmic parasites causing infections in eye and adnexa have been described with newer advancement.

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Manuscript received: 04.01.16; Revision accepted: 18.10.16

## Access this article online

## Website:

www.ijo.in

## DOI:

10.4103/0301-4738.195590

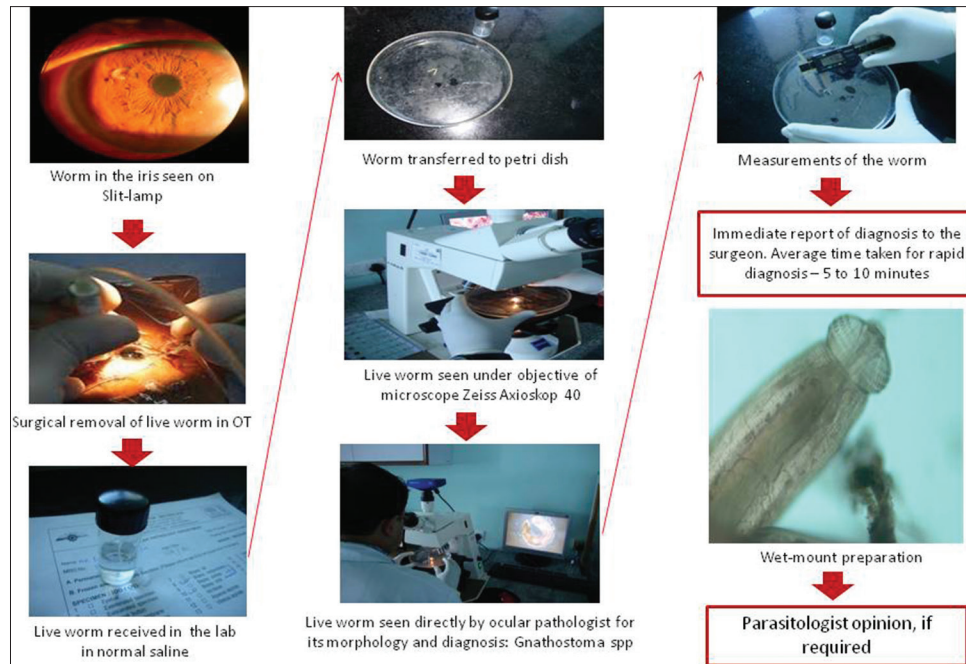
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**Cite this article as:** Das D, Ramachandra V, Islam S, Bhattacharjee H, Biswas J, Koul A, *et al.* Update on pathology of ocular parasitic disease. Indian J Ophthalmol 2016;64:794-802.



**Figure 1:** Algorithm for immediate pathological diagnosis of live worm in the laboratory

## Toxoplasmosis

One of the most common causes of infectious retinitis, ocular toxoplasmosis is also seen to commonly cause posterior uveitis in immune-competent individuals.<sup>[5,6]</sup> It is caused by *Toxoplasma gondii*, an obligate intracellular parasite which exists in three morphological forms, namely, oocyst, tachyzoite, and tissue cyst. The classical clinical presentation in acquired toxoplasmosis in retina is the head light in fog appearance, and pathological feature in this disease entity is a well-demarcated area of coagulative necrosis with adjacent choroiditis, vasculitis, hemorrhage, and vitritis.<sup>[7]</sup> Viable tachyzoites and tissue cysts may be found in superficial layers of the infected retina along with an intense mononuclear inflammatory cell reaction seen in the involved retina as well as adjacent choroid and vitreous.<sup>[8]</sup> The immune status of the host is clearly important as demonstrated by the severe and prolonged disease course in immune-suppressed patients.<sup>[9]</sup> The humoral immune response is the first step toward control of infection but not sufficient to eradicate organism. Cell-mediated immunity is the major mechanism involved in the resolution of active disease.<sup>[10]</sup> Several cytokines have been implicated in controlling the infection, as well as causing a pro-inflammatory state and loss of ocular immune privilege; these include interleukin-2 (IL-2), IL-12, tumor necrosis factor alpha,  $\gamma$ -interferon, and nitric oxide.<sup>[11,12]</sup> An autoimmune mechanism directed against certain retinal antigens is also thought to play a part in the pathogenesis. Histopathologically, *Protozoa* can be seen in free, pseudocyst (a group of *Protozoa* surrounded by retinal cell membranes) or in true cysts form.<sup>[13]</sup> Recent advances show that some tissue cysts can be present in untouched retinal tissue and can produce an inflammatory reaction many years after primary infection.<sup>[14]</sup> *T. gondii* cysts were detected in eyes with necrotizing retinitis that developed secondary to injudicious use of corticosteroids.<sup>[10]</sup> Immunoproteomic technology offers an exceptional tool to help in diagnosis of

toxoplasmosis.<sup>[15]</sup> Bradyzoites, which are viewed as dormant, poorly replicating or nonreplicating entities, were found to be surprisingly active and showed capacity of growth.<sup>[16]</sup> Increased submacular choroidal thickness was seen in active, isolated, and extramacular toxoplasmosis.<sup>[17]</sup> Recurrences in retinochoroiditis are common as satellite lesions, and coexisting choroidal neovascularization is an important presentation of the same.<sup>[18,19]</sup>

## Toxocariasis

Ocular toxocariasis is caused predominantly by *Toxocara canis*, a nematode for which humans serve as intermediate hosts.<sup>[20]</sup> Ocular toxocariasis is usually unilateral and can have several myriad clinical presentations ranging from diffuse endophthalmitis, posterior pole granuloma, peripheral localized granuloma, peripheral or macular disciform retinal detachment to pars planitis, or papillitis.

Tissue damage occurs in this infestation due to mechanical effects of the migrating larvae or secondary to immune reaction. In tissue sections on histopathological examination, circumscribed granulomatous reactions with neutrophil and eosinophil infiltrates are seen sometimes with the larvae located in the center of the reaction. The central area of recent lesions may show fibrinoid necrosis whereas older lesions may reveal fibrous encapsulation. Giant cells, epithelioid cells, macrophages, and lymphocytes are usually present around degenerating larvae. The Splendore-Hoeppli phenomenon denotes eosinophilic precipitate that can be observed around the *Toxocara* larva but is a nonspecific finding.<sup>[21]</sup> Ocular toxocariasis should be considered in the differential diagnosis of unilateral neuroretinitis with subsequent motile retinal lesion.<sup>[22]</sup> Some studies suggest that seroprevalence of antibodies to *Toxocara* is high in patients with ankylosing spondylitis-associated uveitis.<sup>[23]</sup> Ocular toxocariasis can cause cataract with distinctive features which show a granuloma-like

opacity primarily at the posterior subcapsular level.<sup>[24]</sup> It also simulates retinoblastoma (pseudoretinoblastoma) in some cases.<sup>[25]</sup>

## Cysticercosis

It is a tissue infection caused by the larval form of *Taenia solium* (cysticercus cellulosae). Ophthalmic cysticercosis causes features such as loss of vision, periorbital pain, scotoma, and photopsia. Other modes of presentation of the disease may be neurocysticercosis or subcutaneous or muscular cysticercosis.<sup>[26]</sup> The cyst may be localized to the subconjunctival space or orbit or may invade the globe and present in anterior or posterior segment. Retinal involvement causes hemorrhages and edema. Histologically, the necrotic cysticercus is surrounded by a zonal granulomatous inflammatory reaction with an abscess that contains eosinophils.<sup>[27]</sup> The vesicle wall exhibits hyaline degenerations, inflammatory cell infiltration, neuroglial fiber, and glial cell proliferation layers from the inside to outside.<sup>[28]</sup> Death of the larva leads to marked immunological reaction and severe endophthalmitis [Fig. 2], and parasite can be demonstrated in eye and adnexal structures [Fig. 3]. Cases of submacular parasite masquerading as posterior pole granuloma have been reported.<sup>[29]</sup> Rarely, a degenerated cysticercus cyst with chronic inflammation may simulate intravitreal infection.<sup>[30]</sup> It can also present as fibrinous anterior uveitis with secondary glaucoma; the uveitis resolves with removal of the cyst.<sup>[31]</sup>

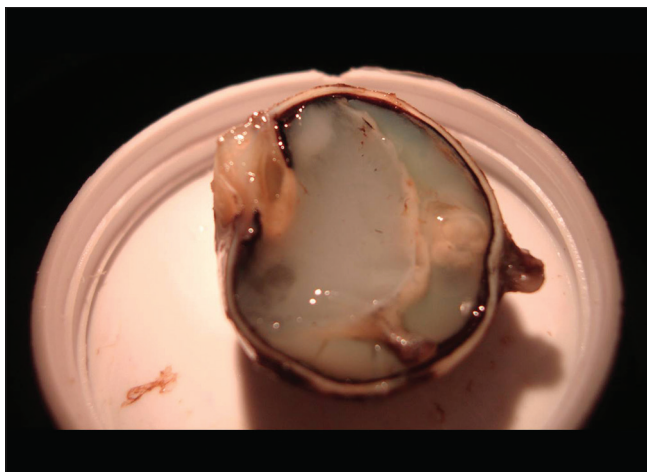
## Onchocerciasis

It is an infectious tropical disease caused by the parasite *Onchocerca volvulus* and transmitted by fly of genus *Simulium*. The exact pathology of the disease involves interplay between the inflammatory response and the host immune response. The larvae migrate in the body for 1 year before they settle in a nodule. The ocular lesions are primarily caused due to living, dying, as well as dead microfilariae. Ocular manifestations of onchocerciasis include punctate keratitis surrounding dead microfilariae, sclerosing keratitis, anterior uveitis with secondary cataract and glaucoma, chorioretinitis, and papillitis with severe constriction of the visual fields. The inflammatory reaction surrounding these microfilariae is also associated

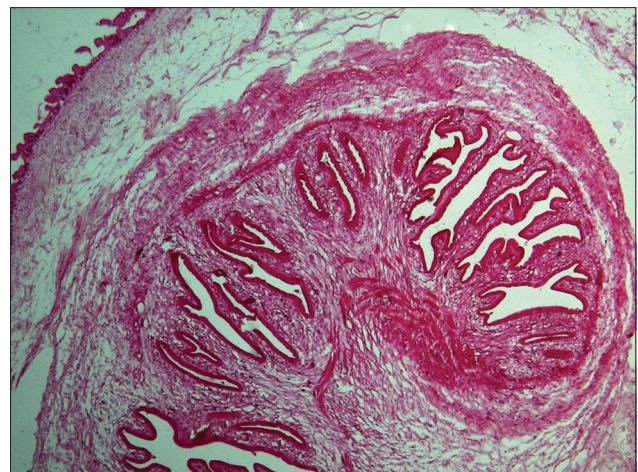
with edema and infiltration by eosinophils.<sup>[32,33]</sup> There is a predominance of CD8<sup>+</sup> suppressor T-cells and increased major histocompatibility complex class II expression along with increased IL-4 and messenger RNA.<sup>[34]</sup> Autoantibodies against retinal S antigen, interphotoreceptor retinoid-binding protein, and inner-retinal and retinal photoreceptors were found in ocular fluids suggesting autoimmunity as a mechanism of the pathogenesis.<sup>[35]</sup> Role of a unique biomarker, N-acetyltyramine-O, beta-glucuronide, a neurotransmitter derived metabolite from the parasite, for diagnosis of the disease has been investigated.<sup>[36]</sup> Although commonly seen in Sub-Saharan Africa and parts of South America, a rare case of onchocerciasis was reported in India where the worm was extracted from the eye.<sup>[37]</sup>

## Hydatid Cyst

The oncospheres of dog tapeworm *Echinococcus granulosus* sometimes form a hydatid cyst that contains larval form of tapeworm. In humans, tapeworm has a predilection for the orbit.<sup>[38]</sup> The tapeworms appear as multiple scoleces provided with hooklets. Histologically, multiple scoleces are seen adjacent to a thick, acellular, amorphous membrane that represents the wall of the cyst. The presence of interferon, tumor necrosis factor-alpha, and IL-6 is observed in cases of human hydatidosis. Surgical removal of the cyst is followed by a rapid decline in cytokine levels.<sup>[39]</sup> Sometimes, the cyst may be primarily located within an extraocular muscle and produce painful eye movements.<sup>[40]</sup> Therefore, it should be considered in differential diagnosis of all solitary cystic enlargements of muscle. Polycystic *Echinococcus* is a variety of the disease thought to be an entirely new entity or an unrecognized form of orbital echinococcosis.<sup>[41]</sup> Pathologically, this condition presents as multiple cysts of various size in a fibrous capsule. The cysts had been observed by the authors, and after doing the differential stain, it was seen that the wall had numerous small pores in the laminated portions. These were thought to be the passage for solutes to pass microfluidics to and fro from the cyst wall maintaining the *in vitro* and *in vivo* pressure within the cysts [Fig. 4]. There was no such finding reported in literature under compound microscopy findings. Some pathologists stain hydatid cyst wall with lectins which brilliantly stain the structures.



**Figure 2:** Gross enucleated eyeball specimen with pus in the vitreous cavity and retinal detachment with subretinal cysticercus lesion



**Figure 3:** Cysticercus lesion in histopathology (H and E, x40). This type of lesion is usually seen in eye and adnexal tissue

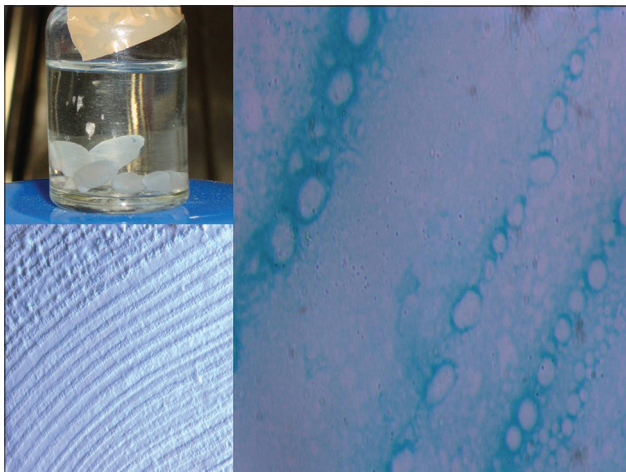


## Diffuse Unilateral Subacute Neuroretinitis

Also called unilateral wipe out syndrome, it is caused by more than one type of motile, subneural retinal, nematode roundworm. It is classically described as a unilateral condition characterized by insidious loss of vision, usually severe in nature. Associated features include vitritis, focal and diffuse pigment epithelial disturbance, retinal vessel narrowing, optic atrophy, and subnormal electroretinogram findings. Diffuse unilateral subacute neuroretinitis (DUSN) is now believed to be caused by small number of different nematode larvae.<sup>[42]</sup> The first pathological change secondary to nematode larva infestation presents as granulomas in the whole globe.<sup>[43]</sup> There have been variable sizes of worms detected and reported with longer worms leaving a tract of coarse clumping of pigment epithelium.<sup>[44]</sup> The shorter worms predispose to leave focal, chorioretinal atrophic scars. Earlier the causative organism was thought to be *T. canis*, but *Baylisascaris procyonis* and the trematode *Alaria* spp. have also been suspected to be involved.<sup>[45]</sup> The focal chorioretinal white spots are an immune response to a secretion or excretion from the worm. Worms, regardless of species, have been observed in the eye for up to 3 years. The role of optical coherence tomography in detecting nerve fiber layer atrophy and edema is under evaluation.<sup>[46]</sup> Studies have also reported anatomical and functional evidence of both inner and outer retinal dysfunction in DUSN, even though the worm is usually located in the subretinal space.<sup>[47]</sup> A macular cyst has also been seen to be an associated finding in DUSN.<sup>[48]</sup>

## Gnathostomiasis

It is a rare parasitic disease caused by third-stage larvae of *Gnathostoma* species which incidentally affects humans after intake of raw meat of any definitive host such as fish, cats, dogs, and wild animals. *Gnathostoma spinigerum* is the most common species that affects the human eye. Clinical features of the disease may be cutaneous and visceral, including ocular involvement. Ocular manifestations of the disease are seen due to migration of the larvae as well as host response to the toxins.<sup>[49]</sup> The most common presenting feature is anterior uveitis.<sup>[50-52]</sup> Other features include lid swelling, iritis, iris atrophy, iris holes,



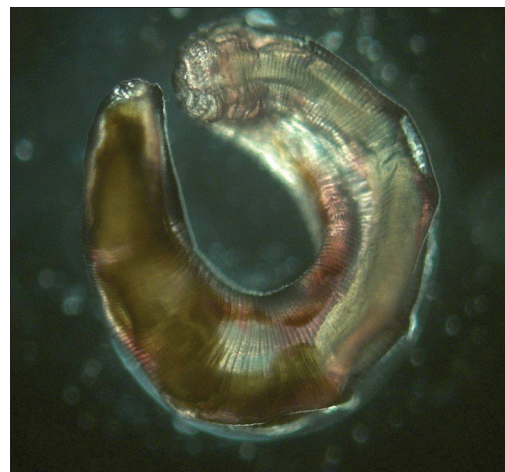
**Figure 4:** *Echinococcus* cysts in Alcian blue stain (x100) with numerous small pores in the laminated portions. These pores are thought to be passage for solutes to pass to and fro from the cyst wall maintaining the *in vitro* and *in vivo* pressure within the cysts

intraocular hemorrhage, retinal scarring, retinal detachment, and rarely glaucoma. Intravitreal gnathostomiasis is a very rare entity. Reports of macular scarring or retinal tear with choroidal hemorrhage near the optic disc point to the posterior retina as a possible route of entry to the eye. The larva of *Gnathostoma* is identified by the number of rows and features of hooklets in the head [Figs. 5 and 6a, b]. The parasite had a head bulb and a tapering body. The head bulb had four circumferential rows or hooklets, each row containing 40–50 hooklets.<sup>[52]</sup> Further, scanning electron microscopy (SEM) and energy dispersive spectroscopy of spine showed carbon, calcium, and silicon deposition which was an interesting observation by the authors [Fig. 6c and d].

SEM improves the ability to distinguish different species as well as helps in staging.<sup>[53,54]</sup>

## Ophthalmomyiasis

It is an insect-mediated ocular disorder caused by botfly larvae (order *Diptera*). Ophthalmomyiasis is characteristically unilateral and the patient complains of tearing, eyelid twitching, ocular irritation, and redness.<sup>[55]</sup> Ophthalmomyiasis can affect external or internal ocular structures and in the latter, mostly subretinal involvement is seen [Fig. 7]. The ocular surface disease is primarily due to mechanical injury caused by the maggots and its oral hooks and intersegmental spine.<sup>[56]</sup> Small conjunctival hemorrhages may occur as a result of tissue damage from oral hooks. Subretinal tracts are representative of mechanical injury to retinal pigment epithelium. Damage to optic nerve, secondary macular hemorrhage, and retinal detachment has been reported. The death of the larva can cause uveitis. The vitreous contains lymphocytes, eosinophils, plasma cells, and epithelioid cells.<sup>[57]</sup> Case reports of rare cases of secondary myiasis of ocular infestation by *Chrysomya bezziana* as well as reports of external ophthalmomyiasis caused by the facultative parasite, *Lucilia sericata*, in a healthy patient are present in literature.<sup>[58,59]</sup> Another case of external ophthalmomyiasis due to *Dermatobia hominis* masquerading as orbital cellulitis was reported.<sup>[60]</sup> Microscopic examination of these cases revealed nonnecrotising granulomatous inflammation surrounding parasitic structures. Dense infiltration by eosinophils seen with distinct areas of Splendore-Hoeppli phenomenon was noted.<sup>[61]</sup>



**Figure 5:** Wet-mount preparation, direct visualization of the parasite (*Gnathostoma spinigerum*) retrieved live from iris and anterior chamber

Cases of external ophthalmomyiasis may present with features of conjunctivitis varying from mild to severe.<sup>[62]</sup>

### *Dirofilaria*

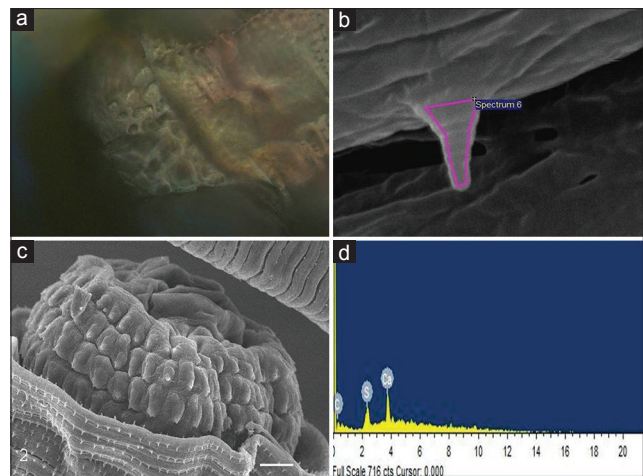
It is a rare disorder caused by *Dirofilaria* spp., a dog tapeworm and transmitted to humans by mosquitoes.<sup>[63]</sup> Ophthalmic involvement may be periorbital, subconjunctival, sub-Tenon with intraocular association. Sometimes, it may be associated with a deep-seated infection such as in the lungs where early and proper diagnosis may prevent major complications.<sup>[64]</sup> Identification of the worm can be done after surgical removal using standard histopathological methods [Fig. 8]. The immature female worm is said to have thick laminated cuticle, broad lateral chords, and female genital system.<sup>[65]</sup> Sometimes, it can mimic a lacrimal sac mucocele, and biopsy is diagnostic in such cases.<sup>[66]</sup> It is also suggested that all patients of multifocal choroiditis in endemic countries should be checked for retinal pigment epithelial tracts to rule out parasitic infestation.<sup>[67]</sup> Intravitreal dirofilariasis is also a rare occurrence.<sup>[68]</sup>

### Ascariasis

Ascariasis is a helminthic infection caused by *Ascaris lumbricoides*, the largest of the human helminths.<sup>[69]</sup> The normal habitat of the adult worm is the jejunum. Infection is acquired by ingestion of embryonated eggs. The larva produces an irritant fluid due to the presence of Ascarase, resulting in allergic manifestation.<sup>[70]</sup> The body fluid of *A. lumbricoides*, when absorbed, is toxic and may damage the tissues. Ocular involvement occurs by migration of the larva via blood circulation and lymphatics. The ocular manifestations include conjunctivitis, xerosis, periphlebitis, papilledema, uveitis, choroiditis, secondary glaucoma, and recurrent vitreous hemorrhage.<sup>[71]</sup> There have also been reports of the parasite in the lacrimal passage.<sup>[72]</sup> Gross and microscopic morphology of typical eggs or adult worm in the feces or vomitus are the primary clues to diagnosis. Diagnosis of intraocular disease requires a high degree of suspicion. Pars plana vitrectomy may be diagnostic.<sup>[69,72]</sup>

### Loiasis

Loiasis is a chronic disease caused by filarial parasite, *Loa loa*. It is endemic in the rain forests of Africa. The infection occurs by the bite of infected mangrove flies, *Chrysops silacea*.<sup>[73]</sup> The disease is characterized by two major forms, calabar swelling which is localized angioedema caused by hyperemic reaction to adult worms, and subconjunctival migration of filarial worm. The presence of the worm in the subconjunctival tissue leads to itching, foreign body sensation, and mild hyperemia.<sup>[74]</sup> A dead worm may induce an acute periorbital angioedema and conjunctival nodule formation. Intracameral migration of the worm is usually well tolerated. After the worm dies, the eye may show signs of extensive iridocyclitis associated with cloudy aqueous, vitreous opacities, and raised intraocular pressure.<sup>[75]</sup> There have been few reports of posterior segment involvement. Extensive hemorrhagic lesions associated with retinal detachment, retinal neovascularization, vitreous hemorrhage, and subretinal exudates are seen. The presence of multiple yellow exudates throughout the retina, and occluded arterioles have also been reported.<sup>[76]</sup> Other systemic manifestations include nephropathy, cardiomyopathy, arthritis, lymphangitis, peripheral neuropathy, and encephalopathy.<sup>[77]</sup> A definitive diagnosis requires the detection of microfilaria in peripheral



**Figure 6:** (a and b) *Gnathostoma spinigerum* head end with hooklets in diffraction microscopy and scanning electron microscopy, respectively. (c) Cuticle in scanning electron microscopy and (d) showing energy dispersive spectroscopy graph depicting carbon, silicon and calcium deposition in the cuticle of *Gnathostoma spinigerum*



**Figure 7:** Subretinal tracts of suspected ophthalmomyiasis interna. The lesion improved after focal laser treatment on the presumed parasite in the retina



**Figure 8:** Different parts of *Dirofilaria* spp. directly visualized by the authors under compound microscope (Axioskop 40, AxioCam MRC Zeiss). The internal structure of different parasites can be identified directly under microscope and can be reported immediately



blood, urine, or other body fluids. The worm is identified by its filiform, cylindrical semi-transparent body with numerous round and smooth protuberances, and a blunt tail. The cuticle is covered with small bosses, which distinguishes *L. loa* from other filarial parasites. Pronounced eosinophilia is seen in association with liberation of microfilaria from the female worm.

## Leishmaniasis

Leishmaniasis is an infection caused by *Protozoa* belonging to the genus *Leishmania*. The disease is transmitted by sandflies: *Phlebotomus* and *Lutzomyia* species.<sup>[78]</sup> The pathogenesis of ocular leishmaniasis remains unclear. It is a sight-threatening condition, which needs to be rapidly recognized and treated to prevent permanent visual loss. Patients with visceral leishmaniasis and HIV coinfection usually have CD4 count <200 cells/ $\mu$ l, and may have involvement of atypical sites, such as eye, and are prone to a relapsing course despite appropriate treatment.<sup>[79,80]</sup>

Cutaneous leishmaniasis may occur on the eyelids where it presents as a swelling, papule, plaque, nodule, or ulcer. The differential diagnosis of eyelid leishmaniasis includes cysts, chalazion, basal cell carcinoma, tuberculosis, syphilis, and sarcoidosis.<sup>[78,81]</sup> Ocular manifestations include ptosis, lagophthalmos, lower eyelid ectropion, lacrimal discharge, ulcerative blepharitis, blepharoconjunctivitis, nodular sclerokeratitis, scleromalacia, ulcerative interstitial keratitis, anterior uveitis, and macular hemorrhage. Biswas *et al.* reported a case of spontaneous resolution of bilateral macular hemorrhage in a patient with kala azar.<sup>[82]</sup> Histopathological examination shows the presence of inflammatory infiltrate consisting mainly of lymphocytes, histiocytes, and plasma cells. Numerous intracellular and extracellular Leishman–Donovan bodies are also seen.

## Pediatric Presumed Trematode Infection

Pediatric presumed trematode infection has been reported in patients from South India who were exposed to pond water.<sup>[2]</sup> The parasite was identified as *Philophthalmus*. Morphologically, these trematodes are a few millimeters to 75 mm in size. The external body surface, referred to as a tegument, is made up of an external plasma membrane and an internal trilaminated plasma membrane.<sup>[83]</sup> The extraocular manifestation includes dermatitis which was self-limiting. The ocular manifestations seen are subconjunctival nodules, anterior chamber nodules, and granulomatous uveitis. Histologically, the nodules show eosinophilic infiltration admixed with chronic inflammatory cells and a specific inflammatory reaction known as Splendore-Hoeppli phenomenon. This phenomenon is characterized by a central deposit of granular, acellular eosinophilic material surrounded by eosinophilic leukocytes, epithelioid cells, histiocytes, and lymphocytes. The acellular eosinophilic material may represent deposits of eosinophil basic protein, immune complexes, or both. These complexes are believed to be complementing products and immunoglobulins directed at antigens derived from parasites. Occasionally, teguments of parasite may also be seen.<sup>[84]</sup>

## Malaria

Malaria is caused by *Plasmodium* species and is transmitted by female anophelid mosquito. The most common forms

of *Plasmodium* species are *Plasmodium vivax* and *Plasmodium falciparum*.<sup>[1]</sup> Ocular complications in patients with malaria have been reported in 10% to 20% of patients.<sup>[85]</sup> The most common complications noted in the acute phase are conjunctival hyperemia and subconjunctival hemorrhage. Yellow pigmentation of the conjunctiva occurs due to breakdown of erythrocytes. Other ocular lesions include retinal hemorrhages, transient ocular nerve palsies, orbital edema, choroiditis, retinal embolism, papilledema, paralysis of the pupillary light reflex, and accommodation. Herpetic keratitis due to immune dysfunction can also develop after malarial infection.<sup>[86]</sup>

*P. falciparum* malaria has the unique feature of being sequestered in the capillary and venule microvasculature and occludes the lumen by cytoadherence and rosette formation. The cytoadherence mechanism is mediated by the development of ligand-associated “knobs” on the surface of infested erythrocyte membranes.<sup>[85,86]</sup> This ultimately leads to thrombosis, occlusion, and hemorrhage.

The malarial pigment is an amorphous, chemically nonstructured component that presents microscopically as black to dark brown granules. Hemozoin is a complex crystalline polymer formed from heme, incidental to hemoglobin digestion within the digestive vacuoles of replicating trophozoites, and schizonts within host erythrocytes. Under polarized microscopy, the hemozoin polymer produces birefringence. This was first reported by Schaudinn in 1903, and is now regarded as diagnostic of malaria.<sup>[85]</sup>

The presence of ocular lesions in malaria indicates poor prognosis, especially in patients with cerebral malaria.<sup>[86,87]</sup> Thus, a patient with unexplained large retinal hemorrhages should be investigated thoroughly for malaria, especially in an endemic country such as India.<sup>[86]</sup>

## Seasonal Hyperacute Panuveitis

An unusual parasitic disease was reported by Malla<sup>[88]</sup> and Upadhyay *et al.* in Nepal.<sup>[89,90]</sup> This was severe panuveitis which does not have a known cause and is usually unilateral. The disease started acutely with red eye and white pupillary reflex with occasional pain. There was fibrinous uveitis in the anterior chamber with hypopyon. Histopathologically, the evidence revealed severe inflammatory reaction with predominance of lymphocytes and plasma cells. The retina was drawn up into a retrolenticular mass. Eosinophils were not observed in the studied section. SEM of the specimens showed Russell bodies and plasma cells. Kathil *et al.*<sup>[90]</sup> found varicella zoster virus in the intraocular fluid of a patient with seasonal hyperacute panuveitis.<sup>[90]</sup>

## Amoebiasis

Ocular infection of amoebae depends on inoculation of a virulent protozoan present in the environment. Amoebae reach ocular surface through contaminated touch, contact lens, or trauma.<sup>[91,92]</sup> IgA and IgA-dependent protective factors often counteract the infective process and are usually sufficient to kill the parasite. Sometimes, cornea remains susceptible to amoebic infection, particularly *Acanthamoeba*. Trophozoites in cornea express the major virulence of trans-membrane protein called mannose-binding protein.<sup>[91,92]</sup> This protein mediates

adhesion of amoebae to the corneal surface. After attachment, the amoebae produce metalloproteases and induced cytopathic effect by killing the host cells.

Another possible factor in the pathogenicity is the presence of bacterial colonization of the ocular surface. Endosymbiosis with bacteria is also observed in *Acanthamoeba*. Histopathology of the affected part shows the presence of neutrophilic presence which is followed by macrophages.<sup>[92]</sup> There is almost complete absence of lymphocytes. Necrosis is seen with the absence of neovascularization. In advanced cases, an immune ring (Wessely ring) results from the deposition of immune complexes.

Amoebae particularly *Acanthamoeba* can cause keratitis, scleritis, and uveitis, and late complications include ocular hypertension and cataract. *In vivo* confocal microscopy can be used to detect the organism. *Acanthamoeba* can be demonstrated in Giemsa, periodic acid-Schiff, and methylene blue, and 0.1% calcofluor white stain can be used with fluorescent microscopy to see the double-walled organism.<sup>[93]</sup> Culture can be done with the help of nonnutrient agar with an overlay of *Escherichia coli*. Polymerase chain reaction for *Acanthamoeba* ribosomal small subunit RNA is a rapid and simple method to detect it in epithelial corneal specimen.<sup>[94]</sup>

## Giardia

Very few investigators have reported the association of *Giardia* with eye infection.<sup>[95]</sup> Ocular manifestations may be secondary to hypersensitivity reaction to *Giardia* antigen because the parasite has never been found in extraintestinal tissue. Anterior uveitis, choroiditis, and retinal pigment changes are thought to be some of the manifestations of *Giardia* infection.<sup>[96]</sup>

## Conclusion

Parasitic worms are responsible for some of the devastating and chronic infectious diseases of human and animal population across the globe.<sup>[1,2,31,41,63]</sup> Ocular damage can be caused directly by the infectious pathogen or indirectly by the toxic products, immune response incited by infection, or ectopic parasitism of preadult or adult stages.<sup>[1,2,31,41,43,92]</sup>

Parasitic diseases are prevalent in various parts of the globe, and specific isolation of these organisms is important for parasitologists, microbiologists, and pathologists. Ocular parasites are important as they cause severe damage to the external and internal structures of the eye. In certain parasitic infestation, removal of the live worm is important because killing of these parasites by antimicrobial agents can incite severe intraocular inflammation and infection such as endophthalmitis.<sup>[1,2,28,30]</sup> The authors have demonstrated a unique method of detecting the live parasites under the compound microscope objectives and documenting them digitally. The entire internal structures can be seen under background illumination by trained ocular pathologists and microbiologists, and immediate diagnosis can be communicated to the surgeons. This method adopted by the authors takes only 5 – 10 minutes to diagnose live ocular parasites.

Proper diagnoses of ophthalmic parasites can save vision and lives. Therefore, appropriate coordination between clinicians, pathologists, and parasitologists needed for better and effective management of ocular parasites.

## Acknowledgment

We would like to acknowledge Sri Kanchi Sankara Health and Educational Foundation.

## Financial support and sponsorship

Nil.

## Conflicts of interest

There are no conflicts of interest.

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