

Parasites as a Cause of Keratitis: Need for Increased Awareness

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Introduction

Keratitis is painful inflammation and swelling of the cornea, the transparent domelike portion of the eyeball in front of the iris and the pupil. It can be classified by its location, severity, and cause. If keratitis only involves the surface (epithelial) layer of the cornea, it is called superficial keratitis. If it affects the deeper layers of the cornea (the corneal stroma), it is called stromal keratitis or interstitial keratitis. Often there is inflammation of both the cornea and the conjunctiva, the mucous membrane that lines the inside of the eyelid and covers the sclera. In this case, the condition is called keratoconjunctivitis.

Bacteria, viruses, fungi, and parasitic organisms may infect the cornea, causing infectious or microbial keratitis. The unique structure of the human eye as well as exposure of the eye directly to the environment renders it vulnerable to these microorganisms. These pathogens infect the eye either by direct introduction through trauma or surgery, by extension from infected adjacent tissues, or by hematogenous dissemination to the eye.

The main *parasites* that cause keratitis include: *Acanthamoeba* spp., *Mirosporidia* spp., *Onchocerca volvulus*. Other *parasites* that rarely or uncommonly affect the cornea include; *Leishmania* spp., *Mansonella ozzardi*, *Thelazia* and *Gnathostoma* spp. The symptoms vary, but may include redness, pain, decreased vision, light sensitivity, or a frank opacity within the cornea. It has been almost very difficult to be differentiated between the parasitic keratitis and that caused by other pathogens. Therefore, the timely identification and treatment of the involved microorganisms are paramount.

The aim of this article is to summarize up-to-date information about corneal involvement by some parasitic infections in an attempt helping the ophthalmologist integrate this information into their clinical diagnosis to tailor appropriate therapies

Acanthamoeba Keratitis

Acanthamoeba Keratitis (AK) is a painful sight-threatening ocular infection caused by free living *Acanthamoeba* species [1] which are abundant in the soil, dust, air, natural and treated water, seawater, domestic tap water, hospitals and dialysis units, eyewash stations, and contact lens cases [2, 3]. AK can occur in patients of any age, sex or, race, but mostly manifests in young, healthy adults [4]. Various species have been implicated in human infections including *Acanthamoeba castellanii* (*A. castellanii*), *A. culbertsoni*, *A. polyphaga*, *A. hatchetti*, *A. rhysodes*, *A. lugdunensis*, *A. palestinensis*, *A. griffini*, and *A. quina* [5]. *Acanthamoeba* e have two stages in their life cycle: a vegetative or trophozoite stage that reproduces by binary fission and feeds voraciously on bacteria and detritus present in the

environment, and a non dividing cyst stage with a double cyst wall, providing it with a high resistance to unfavoured and adverse environmental conditions, desiccation and disinfecting compounds [6].

Acanthamoeba keratitis was first recognized in the mid 1970s. Then, a dramatic increase in cases was associated with the increasing use of soft contact lens. The significant association between AK and wearing of contact lenses was confirmed by several investigators who found that wearing of contact lens was associated with 62.5% to 95% of AK cases [7-11]. It is widely believed that manipulation of the contact lenses may result in epithelial breaks that transmit infectious *Acanthamoeba* trophozoites to the eye [8]. Additionally, contact lenses cause chronic hypoxic stress on the corneal epithelium which leads to decreased corneal sensitivity, decreased epithelial mitosis and adhesion, premature desquamation of epithelial cells, increased epithelial fragility, epithelial micro cystic edema and significant thinning of the epithelial cell layer [12, 13].

Corneal abrasion is a leading risk factor for the development of AK that results in the increased expression of mannose glycoproteins on the corneal epithelium [14]. *Acanthamoeba* adhesion to the corneal surface may involve interactions between the mannose-binding protein expressed on the surface of *Acanthamoeba* [15] and mannose glycoproteins of corneal epithelium [16]. This binding leads to secondary events that include the production of several pathogenic proteases that degrade basement membranes and induce cytolysis and apoptosis of the cellular elements of the cornea, culminating in dissolution of the collagenous corneal stroma [17]. The histological changes occurring in AK include epithelial ulceration, loss of keratocytes in all layers and inflammation in two-thirds of the stroma with necrosis. *Acanthamoeba* trophozoites were found in the anterior stroma while the cysts were more prevalent in the deeper stroma with minimal or no inflammatory response [18]. Infiltration of inflammatory cells consisting primarily of polymorpho nuclear leukocytes into the superficial and middle layers of the corneal stroma is commonly seen [19].

Acanthamoeba keratitis is characterized by corneal inflammation, severe ocular pain, photophobia, stromal ring infiltrate and recurrent breakdown of the corneal epithelium. The lesion is typically monolateral and refractory to commonly used antibiotics [3, 20]. The severe pain and involvement of the corneal nerves by trophozoites may be related to their strong chemotactic response to cells of neural crest origin [21]. Stromal infiltration (Figure 1) develops, usually in the central or paracentral cornea. Initially its appearance is not characteristic, involving the anterior stroma as a serpiginous, grey white infiltrate with an overlying epithelial defect [22]. A ring-shaped stromal infiltrate is characteristic of advanced infection and is pathognomonic for AK. It is the result of polymorphonuclear leukocytes infiltration generated by chemotaxis after antigen-antibody precipitation [23]. A more diffuse suppurative stromal process becomes evident in some cases, sometimes leading to erosion of the cornea so the posterior membrane (Descemet's membrane) may bulge forwards leading to descemetocoele formation and perforation. Despite this prolonged stromal inflammation, corneal vascularization is strikingly rare [22]. Also, posterior segment signs are rare, although occasional reports exist of optic nerve edema, optic neuropathy and optic atrophy, retinal detachment, choroidal inflammation, and formation of a macular scar. However, it was not possible to identify amoebas associated with posterior segment inflammation by the histological evaluation [24].

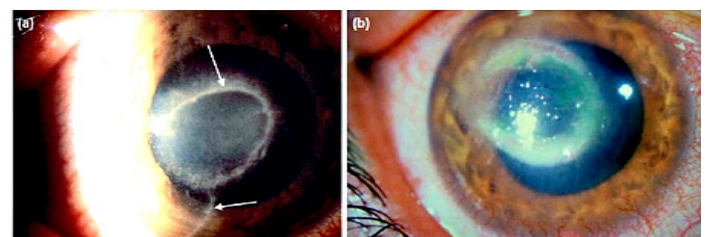


Figure 1: *Acanthamoeba* keratitis (a) *Acanthamoeba* trophozoites cluster around corneal nerves, producing radial keratoneuritis (arrow). (b) Ring-like stromal infiltrate. **From:** Clarke and Niederkorn [17].

Clinically, the features of keratitis associated with *Acanthamoeba* infection resemble those observed with herpes simplex, bacteria or fungi [25]. These similarities often lead to misdiagnosis and inappropriate medical treatment that result in extensive corneal inflammation and profound visual loss. Therefore, accurate and rapid diagnosis of AK is essential for successful treatment and good prognosis [26]. Diagnosis of AK is based on both clinical features and laboratory tests. Definitive diagnosis requires culture, histology, or identification of *Acanthamoeba* deoxyribonucleic acid (DNA) by polymerase Chain Reaction (PCR) [27]. Laboratory diagnosis of AK relies on the demonstration of trophozoite or cyst in corneal scrapings under microscopic observation directly or isolated from the culture. In spite of direct microscopic examination of a corneal smear can provide results in a short span of time, enabling the clinician to start empirical treatment, its low sensitivity highlighted the danger of relying on it for diagnosis of AK infection. Direct smears also can lead to misdiagnosis of *Acanthamoeba* in 60-70% of AK cases [28, 29]. Therefore, several staining techniques were used to enhance the visibility of *Acanthamoeba* cysts including; temporary staining techniques as iodine, eosin, methylene blue, and calcofluor white (CFW) stains and also permanent staining techniques as modified trichrome, Gimenez and Giemsa staining [26].

Several investigators have suggested the most accurate technique for diagnosis of acanthamoebiasis, still requires in vitro cultivation [3,30] due to its low cost and simplicity. Despite of the high specificity of culture based method; it requires a special medium and the results usually need a long incubation time (few days for trophozoites and one to 2 weeks for encystations) and frequent microscopic observations [31]. Long waiting time for the results obtained by cultivation may lead to a delay in proper treatment and, ultimately, worsening of the disease. Therefore, molecular methods amplifying *Acanthamoeba* DNA have been developed to improve AK diagnosis and management [29, 32, 33]. El-Sayed et al. [11] concluded that direct amplification of *Acanthamoeba* DNA by passing nucleic acid extraction using a commercial KAPA PCR kit proved to be a simple and efficient method for detection of

Acanthamoeba even a single cyst did not require high-cost reagents or complicated procedures to extract DNA and offered a much more rapid time. The availability of PCR results within several hours of sample taking allows the clinicians to adapt their treatment very rapidly with a potential positive effect on the final prognosis.

Successful treatments of AK have been reported with the use of a combination of cationic antiseptics (polyhexamethylene biguanide, chlorhexidine) which inhibit the membrane functions, aromatic diamidines (propamidine isethionate, hexamidine, pentamidine) which inhibit DNA synthesis, aminoglycosides (neomycin, paromomycin) which inhibit protein synthesis, and imidazoles (clotrimazole, fluconazole, ketoconazole, miconazole, itraconazole) which destabilize cell walls and polyenes, such as amphotericin B [34]. However, eradication of *Acanthamoeba* from the infection site is difficult because under adverse conditions, the amoebas encyst and medical therapy is often less effective against cysts than trophozoites due to the rigid double-layered wall of the cysts which makes it highly resistant to anti-amoebic drugs. This is problematic as cysts can survive after initial successful chemotherapeutic treatment and cause relapse of the disease [35]. Therefore, the prevention of *Acanthamoeba* infection is always the best approach.

Onchocerca-mediated Keratitis

Onchocerciasis or “river blindness” is a parasitic disease caused by the filarial worm *Onchocerca volvulus* (*O. volvulus*) transmitted by repeated bites of infected black flies (*Simulium* spp.). Human involvement includes both dermatologic and ocular disease. Onchocerciasis is considered the second leading cause of infectious blindness in the world [36]. Onchocercal ocular disease ranges from mild symptoms such as itching, redness, pain, photophobia, diffuse keratitis, and blurred vision, to more severe symptoms such as corneal scarring, night blindness, intraocular inflammation, glaucoma, visual field loss, and, eventually, blindness [37].

In the human body, the adult worms produce microfilariae that migrate from the dermis into the corneal stroma. These microfilariae reach the eye through bulbar conjunctiva, along sheaths of sclera vessels and nerves, or by embolization in choroidal or ciliary capillaries. They can often be seen in the cornea and anterior chamber with slit-lamp biomicroscopy. Major ocular findings in onchocerciasis include corneal changes; there are two types of corneal opacities. Punctate opacities are caused by an acute inflammatory exudates and dying microfilariae in the cornea and give rise to snowflake opacities which usually occur in the peripheral cornea and resolve without sequelae. Sclerosing keratitis (Figure 2) is caused by progress in inflammation of the cornea with fibrovascular pannus causing blindness [38]. The lesion usually starts medially and laterally, then extends and tends to become confluent, and may finally extend to papillary area and may also progress till the entire cornea is opaque and vascularized leading to progressive reduction in vision ending in blindness. Other ocular manifestations include torpid iritis that is characterized by typical pear-shaped deformity of the iris, secondary cataracts, secondary glaucoma, choroidoretinopathy, and optic neuritis [39-40].



Figure 2: Sclerosing keratitis usually begins at the nasal and temporal periphery and slowly progresses centrally. From: <https://www.flickr.com/photos/communityeyehealth/8423594751/>

Most of the ocular changes have been attributed to the presence and/or migration of microfilariae in and through ocular

structures as well as the host's response to their migration [41]. While the *parasites* remain alive, there is no detectable inflammation; however, once the *parasites* die, microfilarial antigens are released and induced a local inflammatory reaction resulting in tissue damage. In heavily infected persons, 100,000 or more microfilariae can die every day [42]. Massive and chronic death of the microfilariae is traditionally associated with sclerosing keratitis. However, death of individual microfilaria within the stroma of the cornea is associated with snowflake opacities [43].

Antigens that are released by dead or dying organisms cause a T-helper cell (Th2) response, which leads to the release of Interleukins (IL), resulting in the influx of neutrophils and eosinophils, and the production of antibodies by plasma cells. These inflammatory responses lead to corneal opacification. The formation of immune complexes seems essential for the development of the keratitis. Specifically, it is thought that the sclerosing keratitis is an effect of modification of intercellular adhesion molecule-1 (ICAM-1) expression and production of IL-4 and IL-14 [44].

Wolbachia and *Wolbachia*-derived molecules are bacterial symbionts of *O. volvulus* that are released upon its death, also cause an immunogenic response. Strains of *O. volvulus* that carry *Wolbachia* DNA are associated with a higher incidence of ocular disease. Experiments using *Wolbachia*-containing extracts of *O. volvulus* in a mouse model of onchocercal keratitis demonstrated that the presence of the bacteria was essential for neutrophil-mediated inflammation, opacity, and corneal haze [45].

Diagnosing onchocerciasis is difficult because it takes about a year and a half for the worms to mature and release enough microfilariae to be detectable. The gold standard for diagnosis is the skin snip microscopy, a biopsy of the skin is taken to microscopically identify larvae after the sample is submerged in saline and incubated. If the results of the initial incubation are not conclusive, PCR may be utilized to amplify the results.

Additionally, eye infections can be determined with a slit lamp examination of the front part of the eye where the larvae or lesions are visible. Serologic testing for antifilarial antibodies to immunoglobulin G (IgG) and IgG4 via enzyme-linked immunosorbent assay (ELISA). A positive IgG result indicates likely exposure. A positive IgG4 results indicates active filarial infection. It has shown that a serum antibody test card using recombinant antigens from a finger-prick blood specimen was successfully used to detect *O. volvulus* specific IgG4 [46]. Antigen detection dipstick assays are also shown to have promising findings [47].

The management of ocular onchocerciasis needs to be evaluated from the level of vector management, management at the community level, and management at the individual level, including medical and surgical management [48]. Ivermectin is a dependable drug used for mass treatment of onchocerciasis. It has been shown to delay the development of optic atrophy, reduce the visual field loss, and decrease the severity of keratitis. Iridocyclitis can result from ivermectin therapy and can be treated with steroids and cycloplegic drops [49]. Doxycycline has been used against *Wolbachia* and has been shown to decrease microfilarial loads [50]. Surgical treatments are usually directed against preventing the loss of vision caused by *O.volvulus* including penetrating keratoplasty for corneal pathology.

Microsporidial Keratitis

microsporidia are obligate intracellular parasites that recognized as human pathogens in AIDS patients, mainly associated with a life-threatening chronic diarrhea and systemic disease [51]. Ocular microsporidiosis was first reported by Ashton et al in 1973 and can be isolated or may present as part of systemic infection. A number of studies were reported on the predisposing factors for microsporidial keratitis in immunocompetent individuals [52-55]. These include contact lens wearing, LASIK surgery, prior use of topical corticosteroids, and soil/mud or dirty water exposure. It was proposed that ocular infection in immunocompromized patients may have

been acquired by reverse passage from a respiratory source through the lacrimal canaliculi and nasolacrimal ducts that drain secretions from the eyes into the nasal sinuses [56]. The normal life cycle of *Microsporidia* includes: once invasion of the spore into the human host cell occurs, the contents are discharged into the cytoplasm. Within the host cell the sporoplast divides by binary fission to form schizont with 2–6 nuclei, which split into unicellular meronts. The meronts then secrete a rigid capsule and the fully formed spore measures about 2.5×1.5 microns. The cell eventually ruptures to continue the cycle and further destruction of the host tissue [57]. There are two clinical presentations of ocular microsporidial infections: superficial punctate keratoconjunctivitis, and corneal stromal keratitis [58, 59]. These two manifestations are directed by the genus involved as well as the immune status of the patient. Deep stromal keratitis, occurring mainly in immunocompetent patients is caused by genus *Nosema* and *Microsporidium*. It shows corneal stromal involvement without epitheliopathy or iritis leads to ulceration and suppurative keratitis. It begins insidiously and mimick a progressive herpes disciform keratitis with recurrent stromal infiltration and uveitis [59]. It has also been described to be presenting as vascularised corneal scar and perforated corneal ulcer with hyphaema, a clinical picture also mimicking herpes simplex virus keratitis. Patients with deep stromal keratitis, suffer from a marked reduction in visual acuity from the infection [60].

Keratoconjunctivitis is usually seen in immunocompromised individuals or in contact lens wearers; mostly by genus *Encephalitozoon* (*E. hellem* and *E. cuniculi*). However, it may also affect immunocompetent individuals [59, 61]. The clinical manifestations of superficial punctate keratopathy include bilateral conjunctival inflammation, foreign body sensation, blurred vision, decreased visual acuity and photophobia. Slit lamp examination revealed conjunctival hyperemia and the cornea reveals bilateral coarse punctate epithelial keratopathy [52].

Accurate identification of *microsporidia* is vital for making a quick diagnosis, and species differentiation of *microsporidia*

may play an important role in treatment assessment and prognosis as well as in understanding the pathogenesis and epidemiology. Diagnosis of ocular microsporidiosis is dependent on the identification of spores in clinical samples which include conjunctival and corneal scraping, swab or biopsy, corneal transplant button and a whole globe from an enucleation. Using staining techniques, either with modified trichrome, potassium hydroxide plus calcofluor white or Gram stain for epithelial keratitis may be useful for the identification of microsporidial spore [52, 53]. The in vivo confocal microscopy appearance of microsporidial keratitis corresponds to the histological features from biopsy material and is a useful technique as it shows up the spores as hyper-reflective dots [62]. The confocal imaging can be used as an aid to monitor the response to the treatment as loss of spores imaged earlier could indicate responsiveness to treatment [58]. Additionally, molecular assays have been used in the research setting to help in identifying species and to monitor response to treatment [63-65].

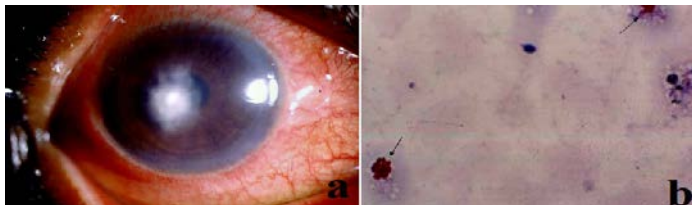


Figure 3: (a) Slit lamp biomicroscopy of cornea showing microsporidial keratitis with central mid to deep stromal infiltrate and surrounding stromal edema. (b) Acid fast stain of corneal scraping showing acid fast positive oval microsporidial spores ($\times 500$). From: Vemuganti et al. [57].

The best treatment for microsporidial keratitis has not been established. Microsporidial infections in HIV-infected individuals may respond to combination of antibiotics and antiparasitic agents, including topical propamidine isethionate, topical fumagillin, topical fluoroquinolones, oral albendazole, and/or oral itraconazole [66]. Whereas, albendazole, a benzimidazole that inhibits microtubule assembly is effective

against several *Microsporidia*, including the *Encephalitozoon* spp. Fumagillin, an antibiotic and antiangiogenic compound produced by *Aspergillus fumigatus*, is more broadly effective against *Encephalitozoon* spp. however, is toxic when administered systemically to mammals [67].

Mansonella ozzardi as a cause of Keratitis

Mansonella ozzardi (*M. ozzardi*) is one of the etiological agents of mansonelliasis, filarial nematode infection for which humans are the definitive host. *M. ozzardi* is transmitted by two types of arthropods that feed on the blood of humans: biting midges (genus *Culicoides*) and blackflies (genus *Simulium*). Infected individuals are usually asymptomatic, but may present ophthalmological and skin lesions. Ocular lesions are due to the presence of the worm in ocular structures, being referred to eye pruritus, conjunctivitis and corneal lesions. The significant association between mansonelliasis and keratitis has been described in Brazil, among Indian and riverine communities living in mansonelliasis foci by several authors [68-71]. It was found that corneal lesions either corneal opacities or keratitis were positively correlated to microfilaremia. In the Amazon, Cohen et al. [70] examined ninety-five mansonelliasis patients whereas punctate keratitis was observed in 12 of them, nummular keratitis in one subject and sclerosing keratitis in another one. Out of 56 patients positive for microfilaremia, 22 patients with nummular keratitis were identified under flash light examination underwent biomicroscopy and corneal confocal microscopy by Vianna et al. [71].

Biomicroscopic investigation and corneal confocal microscopy can identify *M. ozzardi* microfilariae in the cornea. Molecular biology techniques for *M. ozzardi* identification [72, 73] could be helpful to confirm the association between microfilaremia and ocular lesions.

Ivermectin is the treatment of choice for *M. ozzardi* infections. It is a potent macrocyclic lactone that binds to chloride channels, which then open and allow chloride ions to enter the affected cells. These cells hyperpolarize, resulting in muscle paralysis in the *M. ozzardi* microfilariae. This allows host

immune cells to adhere to the microfilariae surface and facilitate their elimination [74].

Thelazia as a cause of Keratitis

Ocular thelaziasis is considered to be an underestimated parasitic disease and mainly limited to clinical case reports. The two important species of *Thelazia* namely *Thelazia callipaeda* and *Thelazia californiensis* are responsible for human infection. *T. callipaeda* is distributed mainly in Asian countries such as China, Japan, Korea, India and Russia while *T. californiensis* is mainly confined to the United States [75, 76]. Transmission of the oriental eyeworm, *T. callipaeda*, occurs via nonbiting diptera that feed on the ocular secretions, tears, and conjunctiva of animals. It usually lives under the nictitating membrane of the eye, where the adult females release first-stage larvae into the lachrymal secretions; these larvae are subsequently ingested by the intermediate arthropod host within which they develop to the infective, third-stage larvae. The latter larvae are then deposited into the eyes of the definitive host [77]. Both adult and larval stages are responsible for eye disease. The lateral serration of the *Thelazia* cuticle (Figure 4) causes mechanical damage to the conjunctival and corneal epithelium. Its presence in the conjunctiva or ocular tissue (Figure 5) can cause excess lacrimation, irritation; and frequent movement across the cornea can cause marked discomfort and corneal scarring.

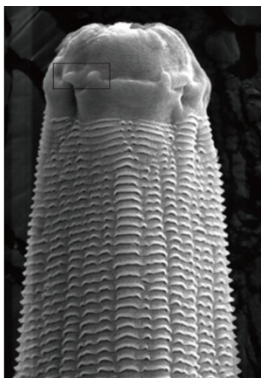


Figure 4: Scanning electron microscopic view of the anterior portion of *T. callipaeda* of adult worm with buccal cavity, 2 cephalic papillae (In box) and cuticular folded striations which are arranged about 375 rows per 1 mm length. From: Sohn et al. [75].

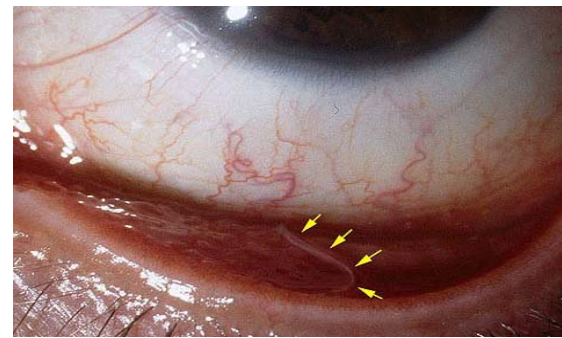


Figure 5: *T. californiensis* in the human eye. From: <http://path.upmc.edu/cases/case279.html>

In human, thelaziasis is characterized by a range of subclinical to clinical signs. Clinical manifestations exhibit epiphora, ocular pruritus, conjunctivitis, excessive lachrymation, corneal oedema, keratitis, corneal opacity and corneal ulceration in severe infection [77, 78]. Four cases of human thelaziasis have been diagnosed in patients from an area of north-western Italy and south-eastern France [79]. Another two cases were described by Sohn et al. [75] in Korea. Infected patients present with exudative conjunctivitis, follicular hypertrophy of the conjunctiva, foreign body sensation, excessive lachrymation, itchiness, congestion, hypersensitivity to light and keratitis, depending on the number of nematodes present in the eye. The adults and larvae of *T. callipaeda* can be removed mechanically by rinsing the conjunctival sac with sterile physiological saline whereas adults can also be isolated with forceps or cotton swabs [77].

Gnathostoma as a cause of Keratitis

Intraocular gnathostomiasis is a rare parasitic infection caused by the third-stage larvae of spiruroid nematode *Gnathostoma* spp. It is a food-borne zoonosis caused by ingestion of raw or undercooked freshwater fish, amphibians, reptiles, birds, and mammals, all of which are known to harbor advanced third-stage larvae of *Gnathostoma* spp. [80]. These larvae have cephalic bulb and tapering body (Figure 6), separated by cervical constriction. Cephalic bulb has a cup shaped mouth with two lips and four circumferential rows of hooklets. Spiny cuticle noticed on the anterior part of the body [81].

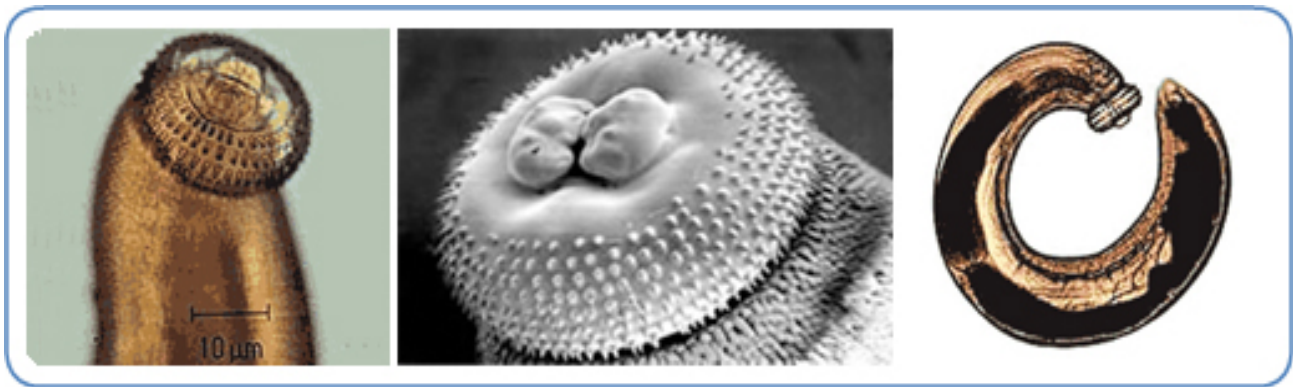


Figure 6: Left/Right: Third-stage larva of *Gnathostoma spinigerum*, head and whole larva respectively. Center: Scanning electron micrograph of a *Gnathostoma spinigerum* worm's head bulb. From: <http://www.cdc.gov/parasites/gnathostoma/>

The larvae preferentially migrate to the skin resulting in mobile cutaneous lesions and migrate into the viscera, eyes and central nervous system causing serious complications [82]. It is thought that the clinical symptoms of gnathostomiasis are due to the inflammatory reaction provoked by the mechanical damage secondary to the larva's migration, the excretions and secretions it produces, and the host's immunological response. The substances released contain various compounds, including one similar to acetylcholine, a “spreading factor” with hyaluronidase, a proteolytic enzyme, and a hemolytic substance. These substances, in addition to the mechanical damage, result in the characteristic hemorrhagic tracks that may be seen in the subcutaneous tissues in patients or in the viscera, or CNS postmortem [83]. In 1937, the first case of intraocular gnathostomiasis was reported by Rhitthibaed and Daengsvang. Since that time, 74 cases have been reported from around 12 countries [80], and the most of them were from South-East Asia [81]. The common manifestation of intraocular gnathostomiasis is anterior uveitis and intraocular parasite, because it mostly localizes itself in the anterior segment of the eye. The other manifestations are edema and hemorrhage of the eyelid, conjunctival chemosis, corneal ulceration, hyphema, retinochoroidal, vitreous hemorrhage, and rarely, central retinal

artery occlusion leading to blindness [82]. The portal of entry into the eye may be posterior retina, because intraocular gnathostomiasis has been associated with macular scarring, rupture of nasal branch of central retinal artery, or retinal tear with choroidal hemorrhage near the optic disc [84].

History of having eaten fresh or blackish-water fish is important suggestive evidence for a diagnosis. Definitive diagnosis was made by detection of *Gnathostoma* larvae either from the anterior chamber or from the vitreous fluid and their identification was confirmed by light microscopy [81]. In cases where the larva was not available, serological detection with specific antibody by ELISA and/or western blotting is helpful [82]. Most of the cases were treated by surgical removal of the parasite. In addition to surgical excision, albendazole and ivermectin have been noted in their ability to eliminate the parasite [85].

Leishmania as a cause of Keratitis

The protozoan *Leishmania*, which is transmitted by the bite of a sand fly, can cause three distinct clinical entities: cutaneous leishmaniasis associated with *Leishmania tropica* in the old world and with subgenera *Leishmania* and *Viannia* in the new world; kala azar associated with *Leishmania donovani* and *L.infantum*; and mucocutaneous leishmaniasis associated with *Leishmania braziliensis*. Although ocular leishmaniasis is a relatively rare disease in the world, it is potentially dangerous and affected patients must be followed up closely, especially immunodeficient ones. All forms of leishmaniasis (cutaneous,

mucocutaneous, and visceral) can involve the eye, but ocular lesions are usually seen in cutaneous form [86,87] particularly, scarring of the lower eyelids, blepharitis, conjunctivitis, cataract, interstitial keratitis, anterior uveitis, glaucoma and finally loss of the eye [86]. Loss of vision may result from exposure keratopathy or hypersensitivity to Leishmanial antigens [88]. A few cases of keratitis associated with cutaneous, mucocutaneous and Post Kala-Azar Dermal Leishmaniasis (PKDL) was reported. In 1979 a reported case of interstitial keratitis from the USA indicated that mucocutaneous leishmaniasis can cause blindness [89].

In 1993 in Iran, during relapse of Kala-Azar, patient had decreased vision of the right eye due to keratitis that was treated with gentamicin and prednisolone. In spite of improvement in her general condition, she lost her vision completely and after 1 year the eye was enucleated. Final pathologic examination revealed total destruction of the eye by leishmaniasis [90]. In 2002 in the USA, a kidney transplant patient was reported who received immunosuppressive drugs and suffered from fever and pain in the legs and thorax. Meanwhile he complained of ocular pain and low vision due to keratitis which was caused by *Leishmania Viania Braziliensis* [91]. The diagnosis of *Leishmania* keratitis is made by direct demonstration of organisms in corneal smears or biopsy in the case of cutaneous or mucocutaneous ocular disease. However, in cases of ocular disease associated with Kala Azar, *Leishmania* organisms identified by culturing on Novy, MacNeal, Nicolle's medium as well as Schneider's *Drosophila* medium supplemented with 30% fetal bovine serum [92]. Treatment with combined stibogluconate and allupurinol in early stages of the disease usually leads to complete healing of the lesions and disappearing of *parasites* from the ocular samples [86].

Conclusion

Increased awareness among the cornea specialists and early recognition of the parasitic infections as a cause of

keratitis is of vital importance, as they will offer hope of successful treatment and reduce the incidence of blindness.

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