Ocular Leishmaniasis - A systematic review

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The incidence of leishmaniasis is reported to be up to 1 million per year. To date, there has been no comprehensive review describing the diversity of clinical presentations of ocular leishmaniasis (OL) and its treatment. This systematic review aims to address this knowledge gap and provide a summary of the clinical presentation, natural course, and treatment options for OL. Our study identified a total of 57 published articles as describing cases of OL involving: adnexa (n = 26), orbit (n = 1), retina (n = 7), uvea (n = 18) and cornea (n = 6). Though well described and easily treated, palpebral leishmaniasis is often misdiagnosed and may lead to chronic issues if untreated. The retinal manifestations of Leishmaniasis consist of self-resolving hemorrhages secondary to thrombocytopenia. Two main uveitis etiologies have been identified: uveitis in the context of active Leishmanial infection (associated with immunosuppression) and uveitis occurring as an immune reconstitution syndrome. Corneal involvement in most geographic areas generally follows an aggressive course, most often ending in corneal perforation if left untreated. In the Americas, a chronic indolent interstitial keratitis may also occur. Topical steroids are of little use in keratitis (systemic antileishmanials being the cornerstone of treatment). However, these are essential in cases of uveitis, with or without concomitant systemic antileishmanial therapy. In conclusion, though ocular involvement in Leishmaniasis is rare, severe sight-threatening consequences follow if left untreated. Early diagnosis, enthusiastic follow-up and aggressive treatment are essential for good outcomes.

Key words: Amphotericin-B, cornea, Leishmaniasis, ocular, uveitis

Leishmaniasis is an umbrella term, covering the various clinical presentations of the infection caused by protozoans of the Leishmania genus. Infection is spread by sand-flies of the Lutzomyia genus in the Americas and Phlebotomus genus in other areas of the world.[3] According to the World Health Organization (WHO), up to one million new cases occur each year, leading to approximately 25,000–26,000 deaths worldwide.[4] India is endemic for both cutaneous leishmaniasis (CL) and visceral leishmaniasis (VL), also known as Kala-Azar. Increasing migration to and from endemic regions is likely to lead to an increasingly large pool of healthcare professionals having to manage Leishmaniasis and its complications.[5] Moreover, the emergence of HIV-Leishmania co-infection is already leading to more atypical presentations of the disease.[6]

For descriptive purposes, the term ocular leishmaniasis (OL) is used in this review to describe leishmanial infections affecting the eyelids, orbit, and the structures of the eyeball. The main types of OL are summarized in Table 1. Leishmaniasis, both cutaneous and visceral, is widely distributed in the tropical world, albeit with some geographic variation, with both types often co-existing and occasionally leading to co-infection. Figs. 1 and 2 show the global distribution of both visceral and cutaneous Leishmaniasis.[6,8] In India, CL is particularly prevalent in the North-West of the country, including the states of Punjab and Rajasthan. On the contrary, Kala-Azar is found mainly in a crescent going from the Gulf of Bengal to Uttar Pradesh.[9] Ninety percent of all cases of Leishmaniasis emanate from only six countries, among which India accounts for most of these.[9] Postkala-azar dermal leishmaniasis (PKDL) occurs some time following the treatment of VL with systemic antileishmanial agents. Though its exact pathophysiology remains to be elucidated, it appears to be the result of an immune reconstitution syndrome brought about by the killing of a large number of parasites. This leads the immune system to escape its immuno-tolerant phase and mount an inflammatory response against protozoa remaining in the skin (viscera having been fully cleared owing to pharmacological therapy).[10] PostKala-azar dermal Leishmania (PKDL) presents as a maculopapular or bullous rash over the face, hands, and upper chest.[11] It occurs far more frequently in Africa than in Asia (it complicates up to 60% of cases of VL in Africa against only 5-20% in Asia). It also occurs sooner in Africa (usually within a few months following an episode of VL) than it does in Asia (often several years later).[12] Leishmania and HIV co-infection is an emerging trend, with HIV-induced immunosuppression influencing the clinical presentation and severity of the disease to such an extent that some specialists argue that it should almost be considered as a distinct clinical entity. Such patients can exhibit concurrently signs of VL, CL or PKDL.[13]

A literature review on OL has been published in 2006, however, this paper did not include major contributions to the field published later.[14] To date, there is no systematic review describing the diversity of clinical presentations of OL and its treatment in the published literature. This review

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Table 1: descriptive nomenclature of leishmaniasis\textsuperscript{(1)}

| Cutaneous Leishmaniasis (CL) | Discrete lesions cutaneous |
|------------------------------|----------------------------|
| Simple CL                    |                            |
| Diffuse Cutaneous Leishmaniasis (DCL) | Widespread cutaneous involvement |
| Mucocutaneous Leishmaniasis (MCL or espundia) | Typically involving the mucous membranes of the nasopharynx |
| Visceral (VL or Kala-azar)   | Leishmaniasis with internal organ involvement |
| Post-kala-azar dermal Leishmaniasis (PKDL) | Bullous maculo-papular rash occurring following the treatment of VL with systemic antileishmanials |

Figure 1: Reported cases of VL per 1,000,000 inhabitants/year (2017-2014), WHO data\textsuperscript{(5)}

Figure 2: Reported cases of CL per 100,000 inhabitants/year (2017-2014), WHO data\textsuperscript{(6)}
aims to address this knowledge gap and provide a summary of the clinical presentation, natural course, and treatment options for OL. Though there have been isolated reports of ophthalmological involvement in the context of Leishmaniasis, to our knowledge this is the first review of this entity.

Methods

Search strategy

Ovid MEDLINE (1948–May 2020 week 19), and EMBASE were searched using the key words ‘leishmania*’, ‘eye’ ‘ocular’, ‘kerat*’, ‘uve*’ and ‘retina*’. The relevant keywords were linked using the Boolean operators AND/OR. The Cochrane database was searched for randomized controlled trials (RCT), systematic reviews, and meta-analyses using the same search strategy, as indicated above. Two independent reviewers analyzed the search results and the corresponding full articles. All case reports, retrospective or prospective case series, or randomized control trials reporting ocular manifestations of Leishmaniasis were included. Animal studies, unpublished abstracts/conference proceedings were excluded. The reference lists of included articles were studied to identify additional potentially relevant reports. The data extracted from the papers collected included the immune state of the patient, leishmanial pattern, visual acuity at first presentation, treatments used, number of relapses, ocular manifestations, and visual outcome. The aim of this review was to collate the published literature available on the ocular manifestations of Leishmaniasis. As such, all forms of relevant literature, including case reports and case series, were included in the review. The only exclusion criterion was animal studies.

Results

Literature search

The electronic searches, including reference lists of the retrieved articles, found 998 titles and abstracts. Where relevant, articles were read in full and the decision about the inclusion of an article was not based solely on titles or abstracts. A total of 942 references were not relevant to the scope of the review, because they did not deal with OL or discussed cases in animals only. The remaining 57 references are summarized in Tables 2–5. There are no published RCTs on OL, its diagnosis, pathophysiology or the efficacy and safety of antileishmanial agents in the treatment.

The adnexae and orbit

A total of 26 publications were identified as reporting on adnexal Leishmaniasis. Four of these described conjunctival lesions, four mixed palpebral and conjunctival lesions and 18 purely palpebral lesions. Unlike corneal and uveal pathology, adnexal Leishmaniasis is a well-recognized entity. Large scale studies have estimated that the adnexae are affected in up to 2% of cases of CL.\textsuperscript{[15]} Adnexal involvement has been reported in the context of CL, VL, and PKDL. Though well described, adnexal Leishmaniasis may be a diagnostic challenge, particularly in non-endemic areas or when it is not accompanied by any cutaneous lesions elsewhere on the body.\textsuperscript{[16,17]} Authors have reported a long list of differentials, including chronic blepharitis,\textsuperscript{[38]} terygium,\textsuperscript{[15]} hordeolum,\textsuperscript{[38]} basal cell carcinoma,\textsuperscript{[20]} squamous cell carcinoma,\textsuperscript{[16]} impetigo,\textsuperscript{[21]} histoplasmosis,\textsuperscript{[22]} and an infected infundibular cyst.\textsuperscript{[23]} Leishmaniasis can mimic many conditions and as such, a high index of suspicion is required. Furthermore, palpebral involvement may lead to chronic issues including ectropion and trichiasis, emphasizing the need for a prompt diagnosis and treatment. Nasolacrimal duct function was found to be impaired in a significant proportion of patients having suffered from MCL, secondary to lesions affecting the nasal septum and nasopharynx, leading to epiphoria or a burning sensation.\textsuperscript{[24]} A single case of orbital Leishmaniasis was found. It described the case of an HIV-positive young man presenting with sinusitis, exophthalmos, and unilateral visual impairment.\textsuperscript{[25]}

All papers reported satisfactory outcomes using a wide range of agents and routes of administration. Cure may be obtained using either systemic or intralesional antileishmanials, usually for 3 weeks. Good results have also been reported using paromomycin ointment or systemic allopurinol.\textsuperscript{[16]} It is important to note that recurrence may occur up to several years following surgical excision.\textsuperscript{[20]} Considering the excellent response to pharmacological treatment, we would discourage surgical excision as a first line intervention and encourage the use of biopsies, should there be diagnostic uncertainty.\textsuperscript{[25]}

**Table 2: Summary of the treatment strategies for adnexal and orbital involvement**

| n | Pattern | Treatment |
|---|---|---|
| Yaghoobi et al\textsuperscript{[64]} | 9 | CL | A |
| Mohammadpour et al\textsuperscript{[84]} | 6 | CL | D, C |
| Oliveira-Neto et al\textsuperscript{[64]} | 5 | CL | D |
| Hanafi et al\textsuperscript{[87]} | 1 | CL | A |
| Gaul et al\textsuperscript{[88]} | 1 | CL | A |
| Gupta\textsuperscript{[65]} | 1 | CL | D |
| Doroogdar et al\textsuperscript{[70]} | 1 | CL | D |
| Doroogdar et al\textsuperscript{[71]} | 1 | CL | D |
| Duman et al\textsuperscript{[72]} | 1 | CL | D |
| Khaled et al\textsuperscript{[73]} | 1 | CL | D, H |
| Veraldi et al\textsuperscript{[23]} | 1 | CL | I |
| Jaoueniet al\textsuperscript{[70]} | 1 | CL | C |
| Rahimi et al\textsuperscript{[21]} | 1 | CL | D |
| Vinetz et al\textsuperscript{[74]} | 1 | CL | D |
| Jafari et al\textsuperscript{[79]} | 1 | CL | D |
| Ozdemir et al\textsuperscript{[14]} | 1 | CL | G |
| O’Neill et al\textsuperscript{[76]} | 1 | CL | D |
| Morgan\textsuperscript{[22]} | 1 | CL | D |
| Kifar et al\textsuperscript{[19]} | 1 | DCL | F |
| Chaudhry et al\textsuperscript{[77]} | 1 | CL | H |
| Admassu et al\textsuperscript{[18]} | 1 | VL | D |

**Conjunctival involvement**

| El-Hassan et al\textsuperscript{[80]} | 6 | PKDL | D |
| Razeghinejad et al\textsuperscript{[78]} | 1 | DCL | E |
| Nikandish et al\textsuperscript{[17]} | 1 | CL | I, B |
| Kifar et al\textsuperscript{[19]} | 1 | DCL | F |

**Mixed palpebral and conjunctival involvement**

| Satici et al\textsuperscript{[15]} | 3 | CL | NA |
| Prasad et al\textsuperscript{[26]} | 1 | VL | E |
| Chaudhry et al\textsuperscript{[77]} | 1 | CL | H |
| Admassu et al\textsuperscript{[18]} | 1 | VL | D |

A = Intranasal pentavalent antimonial; B = Intranasal amphotericin B; C = Paromomycin ointment; D = Systemic pentavalent antimonial; E = Systemic Mitefesine; F = Systemic amphotericin B; G = Systemic allopurinol; H = Systemic azole; I= Surgical excision; NA= Not available
Suggested treatment for adnexal involvement

In view of the good outcomes obtained with most agents, treatment should be tailored to patient specific parameters and acceptability. Appropriate options include, but are not restricted to: systemic meglumine antimoniate (20 mg/Kg for a minimum of 3 weeks), intralesional meglumine antimoniate (1 mL/lesion twice a week for 2 weeks, once weekly for a minimum of two months) or paromomycin ointment 20% (one application daily for a minimum of 3 weeks). It must be noted that the cure rate of intralesional meglumine antimoniate may be higher than topical paromomycin.\(^{37}\)

Retinal involvement

Table 3 summarizes articles describing retinal involvement in Leishmaniasis. It is worth noting that retinal involvement has been reported only in VL. All seven publications reported retinal hemorrhages, with two of them describing supplementary changes, including vascular sheathing,\(^{28}\) sub-acute focal retinitis,\(^{29}\) cotton wool spots, whitening and increased vessel tortuosity.\(^{30}\) It is likely that retinal hemorrhages are a direct consequence of the state of thrombocytopenia that accompanies the disease.\(^{31}\) Retinal changes appear to resolve following systemic antileishmanial therapy,\(^{28,30-34}\) or spontaneously,\(^{32}\) with good visual outcomes being the rule.\(^{28,30-34}\) Finally, a case of retinal detachment secondary to leishmanial uveitis has been reported. This was thought to be both tractional and rhegmatogenous in nature.\(^{33}\)

Suggested treatment for retinal involvement

Management should be targeted at treating VL and no specific treatment is necessary to address the retinopathy.

Uveal involvement

Eighteen published reports on uveitis associated with Leishmaniasis are summarized in Table 4. The course of leishmanial uveitis is usually aggressive and punctuated by relapses. At first presentation, visual acuity ranged from light perception to full vision. In many cases, visual loss was significant, with seven patients reporting a best visual acuity in one or both eyes of counting fingers or worse.\(^{36-40}\) The main causes of visual loss included cataracts, corneal edema, pressure mediated damage to the optic nerve, exudative retinal detachments and, catastrophically, phthisis bulbi.\(^{38,40,41}\) Though clinically indistinguishable, uveitis in the context of active Leishmanial infection is to be differentiated etiologically from uveitis occurring soon after treatment with systemic antileishmanials.\(^{36,42-45}\) or Highly Active Antiretroviral Therapy (HAART).\(^{40,46,47}\) In all cases of post-treatment or HAART associated uveitis, ocular symptoms developed between a few days and a few months following the initiation of treatment. The temporal association between systemic treatment for Leishmaniasis and the development of uveitis seems too strong to be purely coincidental. These cases are likely caused by an immune reconstitution syndrome, similar to that underlying PKDL. The fact that resolution could be brought about by topical steroids alone would favor this hypothesis.\(^{34,45}\)

On the contrary, when steroids were used in the absence of any systemic antileishmanial agents to treat uveitis in the context of active infection, the outcome was always bilateral blindness.\(^{41,46}\) It is therefore essential to systematically combine corticosteroids with anti-leishmanials.\(^{38,43}\) The uveitis itself is typically a bilateral anterior uveitis of the granulomatous type, usually associated with ciliary flush, conjunctival hyperemia, anterior-chamber cells, flare and mutton fat keratic precipitates. The intraocular pressure (IOP) is most often raised, with possible optic disc edema, and seclusio pupillae\(^{38}\) have also been reported. Importantly, iris nodules containing leishmania parasites may be visible.\(^{42}\) The rate of visual loss may be gradual\(^{46}\) or extremely rapid,\(^{49}\) requiring prompt diagnosis and referral to an ophthalmology service. Only one article reports the case of a unilateral posterior uveitis with no inflammatory response in the retina, vitreous or anterior chamber. This was diagnosed by fluorescein angiography.\(^{50}\) A single article reports a case of bilateral non-granulomatous uveitis with low IOPs.\(^{51}\)

In endemic areas, cases of post-treatment uveitis were easily identified as such by the authors and treatment initiated without microbiological confirmation of ocular or systemic Leishmanial infection.\(^{36,43}\) On the contrary, in primary cases or cases occurring in countries with a low prevalence of the disease, the range of differential diagnoses was large and attempts were made to objectively determine the cause the uveitis. Such differentials included: Epstein-Barr virus, cytomegalovirus, HIV, toxoplasmosis, toxocarosis, histoplasmosis, herpes simplex virus, varicella zoster virus,
Table 4: Treatment strategies, HIV status and outcomes of Leishmanial uveitis

| Reference               | HIV Status | Visual at first presentation (logMAR) | Treatment | Visual outcome Outcome (logMAR) |
|-------------------------|------------|--------------------------------------|-----------|---------------------------------|
|                         |            |                                      | 1st presentation | 2nd presentation | 3rd presentation |                     |
|                         |            |                                      | 1st presentation | 2nd presentation | 3rd presentation |                     |
| Fox-Lewis *et al.*[46]  | -ve        | NA                                   | B          | -                  | -                | Bilateral blindness |
| Van Os *et al.*[46]     | +ve        | OD: 0.3                              | A          | A, D               | D, H              | OD: 0.7             |
| Perrin-Terrin *et al.*[38] | +ve    | OD: counting fingers                 | A, D       | A, B, D, F         | -                | OD: phthisis        |
| Ramos *et al.*[50]      | +ve        | OS: 0.3                              | F          | -                  | -                | Complete resolution |
| Meenken *et al.*[39]    | +ve        | Light perception                     | A, F, J    | -                  | -                | OD: finger counting |
| Salvanos *et al.*[35]   | NA         | OD: 0                                | A, C       | A, C, E            | -                | OD: 0.52            |
| Perrin-Terrin *et al.*[38] | +ve    | OS: field defect                     | F          | -                  | -                | OS: light perception|
| Meenken *et al.*[39]    | +ve        | OD: full vision                      | F          | -                  | -                | Complete resolution |
| Reinecke *et al.*[41]   | -ve        | NA                                   | A          | NA                 | -                | Bilateral enucleation|
| Ferrari *et al.*[51]    | -ve        | 1 bilaterally                         | A, B, C, E,F | -                | -                | Bilateral enucleation|
| Blanche *et al.*[46]    | +ve        | NA                                   | A          | E                  | -                | OD: enucleation     |
| Davies *et al.*[50]     | +ve        | Full vision bilaterally              | A          | -                  | -                | Resolution          |
| Couture *et al.*[40]    | +ve        | Counting fingers bilaterally         | A, C, G    | -                  | -                | OD: counting fingers|
|                         |            |                                      |            |                    |                  |                      |
| Blanche *et al.*[46]    | +ve        | NA                                   | A          | E                  | -                | OD: enucleation     |
| Davies *et al.*[50]     | +ve        | Full vision bilaterally              | A          | -                  | -                | Resolution          |
| Couture *et al.*[40]    | +ve        | Counting fingers bilaterally         | A, C, G    | -                  | -                | OD: counting fingers|
|                         |            |                                      |            |                    |                  |                      |

| Reference               | HIV Status | Visual at first presentation (logMAR) | Treatment | Visual outcome Outcome (logMAR) |
|-------------------------|------------|--------------------------------------|-----------|---------------------------------|
|                         |            |                                      | 1st presentation | 2nd presentation | 3rd presentation |                     |
|                         |            |                                      | 1st presentation | 2nd presentation | 3rd presentation |                     |
| Dechant *et al.*[37]    | -ve        | 0.3 bilaterally                       | A          | -                  | -                | 0.1 bilaterally     |
| Bouomrani *et al.*[44]  | -ve        | 0.3 bilaterally                       | A          | -                  | -                | 0.1 bilaterally     |
| Khalil *et al.*[43]     | NA         | NA                                   | Nil        | -                  | -                | Bilateral blindness |
|                         |            |                                      | Nil        | -                  | -                | Bilateral blindness |
|                         |            |                                      | Nil        | -                  | -                | Bilateral blindness |
|                         |            |                                      |             |                    |                  | Full resolution     |
|                         |            |                                      |             |                    |                  | Full resolution     |
|                         |            |                                      |             |                    |                  | Full resolution     |
| El-Hassan *et al.*[36]  | NA         | Counting fingers                     | A, F       | -                  | -                | Full resolution     |
|                         |            |                                      | A, F       | -                  | -                | Full resolution     |
|                         |            |                                      | A, F       | -                  | -                | Full resolution     |
|                          |            |                                      | A, F       | -                  | -                | Full resolution     |
| El-Hassan *et al.*[42]  | NA         | 1.08 bilaterally                      | A, F       | -                  | -                | 0.1 bilaterally     |
|                         |            |                                      | A, F       | -                  | -                | 0.1 bilaterally     |
| Sinha *et al.*[45]      | -ve        | Full vision bilaterally              | A          | A                  | A                | Full resolution     |
|                         |            |                                      | A          | A                  | A                | Full resolution     |
|                         |            |                                      | A          | A                  | A                | Full resolution     |

**n**=number of patients; A=topical steroids; B=intra-ocular/sub-conjunctival steroids; C=systemic steroids; D=intra-ocular Amphotericin B; E=systemic amphotericin B; F=systemic antimonial; G=systemic miltefosine; H=pentamidine; J=systemic fluconazole; NA=not available

When attempting to obtain microbiological confirmation of Leishmanial uveitis, it is essential to bear in mind that negative splenic and bone marrow aspirate often co-exist with positive ocular samples. The eye may become infected by rubbing of the eyes with contaminated hands, direct spread from the adnexae or hematogenous spread. In cases of uveitis, due to the absence of adnexal lesions and the temporal association with previous systemic Leishmaniasis, it appears the hematogenous route plays the most important role. When attempting to obtain microbiological confirmation of Leishmanial uveitis, it is essential to bear in mind that negative splenic and bone marrow aspirate often co-exist with positive ocular samples. It is therefore crucial to obtain samples from the eye itself. Successful methods include corneal scrapings, aqueous/vitreous aspirate PCR and Giemsa staining of iris nodule biopsies.
Leishmanial uveitis appears to be mainly a disease of the immunocompromised, with seven papers reporting cases in patients suffering from HIV, one in the context of an inherited immune deficiency, and one in the context of anti-rejection immunotherapy. The choice of antileishmanial and route of administration vary greatly across reported literature. This variability may be explained by the absence of any diagnostic tool or treatment algorithm. The only consistent finding was that all authors but one used topical or intra-ocular corticosteroids. Steroids are of paramount importance in dampening the inflammation associated with infection of ocular tissue and with the killing of a large amount of parasites, when systemic therapy is initiated. This was in the context of a posterior uveitis which responded fully to systemic antileishmanials. Steroids were not used due to the complete absence of inflammatory response in the anterior chamber, vitreous or retina. Reports seem to suggest that a combination of topical corticosteroids, intracameral amphotericin B and a systemic antileishmanial-based agent provides the best results. Subconjunctival steroids may be a useful adjunct to prevent inflammation following intracameral amphotericin B injections. In all cases, steroid monotherapy never brought in preventing the recurrence ofocular symptoms, particularly in the immunocompromised. However, pentamidine showed no effect in terminating or indeed preventing Leishmanial uveitis, when administered prophylactically.

Uveitis as an immune phenomenon post-treatment uveitis and HAART associated uveitis
Outcomes were significantly better for the cases of uveitis occurring in the context of HAART related immune reconstitution or following antileishmanial therapy. Eight out of the 11 patients in this category who received treatment had a full recovery. Post-treatment uveitis has the potential for causing blindness if left untreated. This can arise due to a variety of causes including damage to the optic nerve or phthisis bulbi. If recognized and treated promptly, outcomes have been shown to be excellent. Better visual outcomes are achieved if the uveitis is treated at an early stage.

Research on the etiology of PKDL may provide some insight into the phenomenon of post-treatment uveitis. In PKDL, Leishmania killing allows the immune system to end the immune-tolerant phase, triggering IL2 and IFNγ production which, in turn, stimulate release of macrophage nitric oxide and reactive oxygen intermediates. This results in a transient increase in inflammation, before leading to recovery. Furthermore, recent research has shown that antileishmanial agents possess immunomodulatory properties, directly leading to a reduction in IL-10, an interleukin playing an essential role in the pathogenesis of the pro-inflammatory Th2 response occurring in the skin of those with PKDL. Unfortunately, it is difficult to determine whether parasite killing, or immunomodulation by the antileishmanials is the trigger for post-treatment uveitis. The fact that similar cases of uveitis have been reported in patients receiving HAART, as their CD4 count recovered, adds weight to the immune hypothesis. However, in the context of immunosuppression, reports suggest combining topical steroids with a systemic antileishmanial agent.

Suggested treatment for uveal involvement
Uveitis in the context of active Leishmanial infection is best treated with topical steroids (tapered over two months) along
with meglumine antimoniate (20 mg/day intramuscularly for a minimum of two months), intracameral amphotericin B and subconjunctival steroids (both given at the same time once weekly for a minimum of two months) with/without long term prophylaxis. Miltefosine may be used as an alternative to meglumine. On the contrary, the treatment of post-systemic treatment/HAART related uveitis relies on the use of topical steroids (tapered over two months) along with systemic stibogluconate (20 mg/kg for 2–4 months). In the absence of immunosuppression and under close follow-up, steroid monotherapy may be attempted.

**Corneal involvement**

Primary corneal pathology in the context of Leishmaniasis was reported in only six publications. The manifestations of Leishmanial keratitis varied depending on the form of Leishmaniasis (CL, MCL or PKDL). Findings are summarized in Table 5. Corneal involvement in the context of Leishmaniasis is most often reported as a result of abrasion secondary to trichiasis, palpebral or conjunctival disease. Corneal involvement as a primary process, however, seems to be one of the rarest manifestations of the disease. The fact that up to a third of patients have no palpebral involvement is convincing evidence of the existence of primary Leishmanial keratitis. Furthermore, recently, the presence of the protozoan in the cornea has been proven.

The predominant type of keratitis varies significantly depending on the leishmanial strain involved. Cutaneous Leishmaniasis generally follows an aggressive, but predictable course, most often ending in corneal perforation within a month if untreated. Alternatively, corneal involvement may occur in the form of extensive pannus formation and IK. The natural course of Leishmanial ulcerative keratitis has been first identified and described by Chams, owing to the large number of cases that occurred in the context of the epidemic of 1922–1923 in Iran. During this period, he recorded 18 cases of Leishmanial keratitis. Chams reported that the corneal involvement follows a remarkably predictable course, divided into three successive stages: The Initial phase (first week) consists of symptoms of photophobia, lacrimation and pruritus are accompanied by either a phlyctenular lesion or a corneal ulcer, both followed by extensive interstitial keratitis (IK). The Abscess formation phase follows, occurring during the second–third weeks. Symptoms and pain increase in intensity until the IK has involved the entire stroma, subsiding thereafter, as a large abscess forms. Abscess rupture and resolution (third–fourth week) is the last phase, when the abscess ruptures either outside or inside the anterior chamber leading to a hypopyon. In the Americas, though most cases are of the ulcerative type, a chronic interstitial keratitis may also occur, with symptoms possibly lasting decades.

Only one report of keratitis in the context of PKDL could be found. The patient, a young man from West-Bengal presented with the typical cutaneous manifestations of PKDL along with a limbal nodule spreading superficially to form a pannus, and deeply resulting in IK. Vision was severely impaired, down to counting fingers. Treatment with a prolonged course of urea stibamine allowed for the resolution of his ocular symptoms whilst vision improved significantly (though it never returned to normal). In all cases, it appears that topical steroids have no place in the treatment of Leishmanial keratitis, except in the cases where it is associated with uveitis. On the contrary, systemic antileishmanials are the cornerstone of management and should be continued for some time following resolution.

All authors who reported satisfactory results have adopted this strategy. One can conjecture that the resolution of the keratitis reported by Cairns may be attributed to the systemic uptake of the mepacrine and diffusion in the cornea. Chams has suggested that sooner the treatment is initiated, the better the outcome. 1/4 to 1/20 visual acuity was obtained for patients treated during the first phase and 1/6 to 1/40 for those treated during the second phase. On the contrary, 50% of those treated past the fourth week suffered from a perforation. Resolution of stromal infiltrates has also been reported using intra-stromal amphotericin B (along with intra-camerally amphotericin B). Fig 3 (courtesy of Van Os et al) shows Leishmanial keratitis at baseline [Fig. 3a] and 3 months following intra-stromal and intra-camerally amphotericin B injections. These results would coincide with experimental data showing high corneal concentrations of amphotericin B via intra-stromal injection. Van Os et al. were contacted concerning the long term outcomes of their patient, beyond the publication of their case (it is important to stress this patient was HIV positive and suffered from both keratitis and uveitis).

In addition, miltefosine has been described to cause keratitis in multiple reports from Bangladesh. This keratitis responds very well to topical steroids and cessation of miltefosine therapy.

**Suggested treatment for corneal involvement**

Systemic antileishmanial therapy is required; the choice of agent will depend on patient specific factors and local patterns of resistance. Good results have been reported with intra-stromal amphotericin B. Corticosteroids play a minor role.

**Limitations of this review**

Published evidence on OL consists of only case reports and case series. Unfortunately, no RCT’s have been carried out comparing the efficacy of treatments. Another limitation is that in many cases, the timing of symptoms was difficult to establish precisely, owing to delayed presentation or delayed diagnosis.
Finally, though some reports provide great insight into clinical manifestations and treatment options, the therapeutic agents such as neosalvarsan[20] used are no longer available today.

**Conclusion**

Two distinct types of Leishmanial uveitis have been identified. Uveitis related directly to the presence of the parasite in the globe is difficult to treat, always requiring the use of systemic/intracameral antileishmanial agents. On the contrary, post-treatment uveitis may be controlled using steroids alone, though it is recommended that the concomitant use of a systemic antileishmanial agent is beneficial. Where the cornea is involved, steroids appear to have a very limited therapeutic role. Two patterns of corneal involvement have been found. An aggressive form results in perforation within a month and a chronic indolent interstitial Keratitis. Though ocular involvement in leishmaniasis is rare, severe sight-threatening consequences follow if left untreated. With increasing migration and the rise in immunosuppressant therapies, clinicians will likely have to face some of the rarest forms of leishmaniasis and its ocular manifestations. In this context, early diagnosis and prompt therapy is crucial.

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