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Research Article

Acanthamoeba keratitis - is there another perspective: Extrapolations from the *Acanthamoeba* – fungal keratitis study

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Abstract

Purpose: To describe clinical characteristics of *Acanthamoeba* keratitis from the *Acanthamoeba* –Fungal keratitis study.

Methods: The *Acanthamoeba*-Fungal keratitis study demonstrated that a significant number of co-infections do occur. Forty cases of *Acanthamoeba* were identified in the study; 19 of these did not have a co-infection. The observations regarding demographics, evolution of the disease, clinical presentations, clinical features etc., in this subgroup were catalogued and analysed.

Results: Except for one, all others were non-contact lens users. The clinical presentations, evolution of the various stages of *Acanthamoeba* keratitis, particularly with regard to duration, were noted to be substantially different from what is recorded in the literature. The staged evolution that is characteristically defined and used clinically to suspect *Acanthamoeba* was not observed. Epitheliitis and perineuritis were rarely observed. The most common presentation was stromal disease.

Conclusions: The clinical presentation of *Acanthamoeba* keratitis in non-contact lens wearers varies considerably from the observations made in contact lens related *Acanthamoeba* keratitis. Routine incorporation of non-nutrient agar in all cases of stromal keratitis - irrespective of the clinical presentation - would significantly improve identification of *Acanthamoeba* keratitis in non-contact lens wearers. Identification of more such cases using similar protocols would provide greater clarity in establishing the clinical features.

Keywords: *Acanthamoeba*; *Acanthamoeba*-Fungal keratitis study; Clinical features; Non-contact lens

Identified only in 1974 as an etiological agent of keratitis [1] and occurring primarily in contact lens wearers, *Acanthamoeba* keratitis (AK) occupies a unique niche in microbial keratitis because of its propensity to be misdiagnosed, the paucity of therapeutic options, as well as its recalcitrance to standard medical therapy. Moreover, the tendency of the organism to form cysts under adverse circumstances (that are resistant to amebicides and extremes of temperature) makes eradication of the infection very challenging.

The first case of *Acanthamoeba* keratitis in contact lens wearers was identified in 1985 [2]; subsequent infections were predominantly noted to affect contact lens wearers either as outbreaks or as individual cases [3,4]. Though *Acanthamoeba* keratitis accounts for only 5% of microbial keratitis in contact lens wearers, 80-85% of reported cases of *Acanthamoeba* keratitis are contact lens users [5]. Several preventive strategies, based on the lessons learnt from outbreaks of *Acanthamoeba* keratitis, have failed to stem the rising tide of contact lens related *Acanthamoeba* infections [6,7].

Most of what we know of *Acanthamoeba* keratitis is from the prism of knowledge acquired from dealing with contact lens related *Acanthamoeba* keratitis. The infection is therefore suspected in a symptomatic contact lens user or when one observes the classical 5 stages of *Acanthamoeba* keratitis as described by Elmer Tu, namely epitheliitis, epitheliitis with radial perineuritis, anterior stromal disease, deep stromal disease, and finally the classical ring infiltrate [8].

An understanding of the clinical presentation is critical to diagnosing *Acanthamoeba* keratitis. As described by Dart [5], punctate keratitis, dendritic figures and radial perineuritis are the more common presenting manifestations of AK in patients who have been symptomatic for less than a month. Ulceration, ring infiltrates and uveitis are more common after a period of 2 months. Limbitis can occur at any time in the disease process. Hypopyon, endothelial deposits, corneal melt, perforation, scleritis, glaucoma, and cataract are late manifestations. Radial perineuritis is considered pathognomonic of the condition. As discussed earlier, it is in the presence of these clinical features, the long duration of symptoms and/or a history of contact lens use, that the diagnosis is most often suspected or made.

Acanthamoeba keratitis in non-contact lens wearers does occur, is less frequently reported, and is very often unsuspected and consequently diagnosed late. Risk factors for non-contact lens related *Acanthamoeba* keratitis include trauma, and contact with contaminated water or soil [9,10]. Given the wide-spread distribution of the organism in the environment, the paucity of identified cases of *Acanthamoeba* raises questions – is there another dimension to the clinical presentation(s) of what we conventionally know as *Acanthamoeba* keratitis?

Methods

The *Acanthamoeba* – Fungal keratitis study was based on the premise that *Acanthamoeba* – fungal co-infections are more

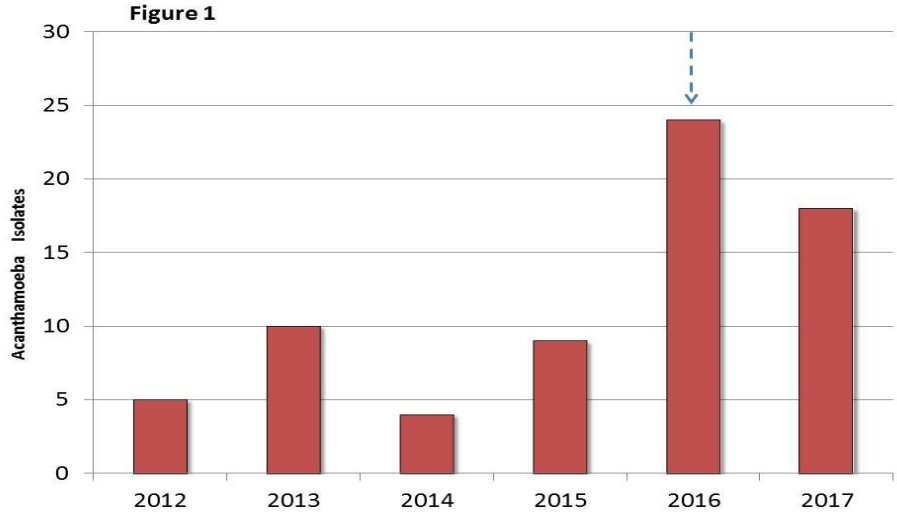

Figure 1: Year-wise number of *Acanthamoeba* isolates (including co-infections). ↓When non-nutrient agar (NNA) was included for all stromal keratitis work-ups.

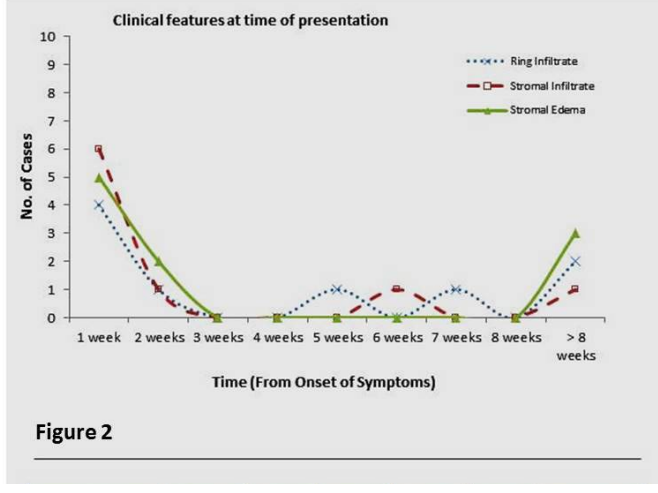

Figure 2: Clinical features at the time of presentation.

common than realised, since the organisms occur ubiquitously in similar environments; and that co-infections are not necessarily confined to contact lens users [11-13]. In this prospective clinico-microbiological diagnostic study, all patients with stromal infiltration irrespective of the provisional clinical diagnosis, were additionally screened for *Acanthamoeba* by the inclusion of non-nutrient agar in the microbiological work-up. The number of cases of *Acanthamoeba* keratitis identified increased significantly (Figure 1). Apart from the co-infections with bacteria or fungi, 19 cases of culture-positive *Acanthamoeba* were identified during the study period from August 2016 to December 2017. However, a substantial number of these cases did not possess the classical features of *Acanthamoeba* keratitis as described in the literature (Figure 2: Table).

The nineteen cases of Acanthamoeba keratitis confirmed via culture positivity after the initiation of the *Acanthamoeba* – Fungal keratitis study (and not on the basis of clinical features) form the substance of this analysis. The demographics, epidemiology, microbiology work-up, and clinical features are presented.

Results

Of the 19 cases, 10 were male and 9 were female. The age group ranged from 13 years to 75 years. Only 12 patients had a clear-cut history of a potentially precipitating event. Ten patients had exposure to organic material (one patient was a contact lens user) and 2 to potentially contaminated water. One patient had a dry eye, another was HIV-positive, while 5 had no history of injury or discernable risk factors.

The time to presentation varied from 1- 60 days, with 14 patients presenting within one month; of which nine presented within a week. Only 4 patients presented after 4 weeks but within 2 months. The duration of symptoms was not known in 1 mentally-challenged patient.

Thirteen patients had prior therapy - of which 12 had antibiotics, antifungals or both. Of the 12, two patients additionally received antivirals and another two, steroids. One patient received only topical steroids.

Clinical features were analysed based on the presenting features, as well as on the presence or absence of features suggestive of *Acanthamoeba* keratitis (Figure 2: Table).

Only 3 of these patients were clinically diagnosed as *Acanthamoeba* keratitis. All others had features suggestive of a bacterial, fungal or viral infection - such as stromal edema, yellowish stromal infiltration, hyphate edges to the lesion etc. Several had features suggestive of both *Acanthamoeba* and bacterial or fungal keratitis, and thus the provisional diagnosis was not clear cut.

An analysis of the clinical features revealed only 2 patients with characteristics suggestive of the early stages of *Acanthamoeba* keratitis. Epitheliitis in the form of an epithelial defect with minimal underlying cellular infiltration was seen in one patient, while the other had perineuritis. Stromal infiltration and ring infiltrates were the most commonly seen features. Stromal edema, though not considered suggestive of *Acanthamoeba* keratitis, was a frequent observation; necessitating the inclusion of viral and/or bacterial keratitis in the provisional diagnosis. The combination of stromal edema with stromal infiltration also led to a consideration of bacterial keratitis, fungal keratitis or both. The classical ring infiltrate was seen in 3 patients, 2 others had hyphate edges, while the remaining ring infiltrates showed patchy anterior to midstromal or deep stromal infiltration.

All patients had smear examinations of corneal scrapings by Gram staining and/ or potassium hydroxide mount, as well as cultures of corneal scrapings on blood agar, non-nutrient agar and potato-dextrose agar. Only 6 cases of *Acanthamoeba* keratitis were identified on smear examinations. Of these, one in addition to the cysts, had hyphae, while another 2 had hyphae only. All were culture positive for *Acanthamoeba* on non-nutrient agar with E.coli overlay.

Discussion

Acanthamoeba keratitis is generally considered to be a gradually evolving infection, with a step wise progression; epithelial involvement is associated with early disease; while ring infiltrates and stromal infiltration are suggestive of late disease. In our cohort, 10 patients had stromal infiltration, either anterior or deep stromal disease, or both. However, with the exception of one case, all presented within 20 days. Ring infiltrates were seen in as little as seven days with the majority presenting well within a month; only 3 cases presented after a month, but within 60 days (Figure 2 and Figure 3).

A plausible explanation for the variation in presenting features between contact lens and non-contact lens users could be that in a contact lens user repeated microtrauma (potentially sustained at the time of insertion and removal of lenses) primarily results in breeching of the epithelial barrier and ingress of *Acanthamoeba*, perhaps in small numbers; thereby manifesting primarily as epithelial disease. With traumatic events as seen in non-contact lens users the organism could be introduced into the deeper layers of the cornea in much larger numbers, resulting in stromal keratitis directly, bypassing what we know as early disease. Figure 3 depicts the predominant clinical presentations in this group of patients, and highlights the lack of correlation between observed features and duration of disease.

The initial therapy of these patients reflected the influence of the clinical findings. Only 6 patients with positive smears received anti-amoebicidal therapy at the first visit. The remaining received antifungal, antibacterial, or antiviral therapy - sometimes in combination. Appropriate therapy was instituted only after cultures were positive for *Acanthamoeba* in the remaining patients.

However, it is evident that *Acanthamoeba* keratitis at least in the tropics, or following trauma, or in non-contact lens users, has a different clinical presentation, appears to progress much more rapidly; perhaps bypassing what we know as early disease in most cases and shares features of fungal, bacterial and/ or viral keratitis; and often presents with a clinical picture suggestive of polymicrobial

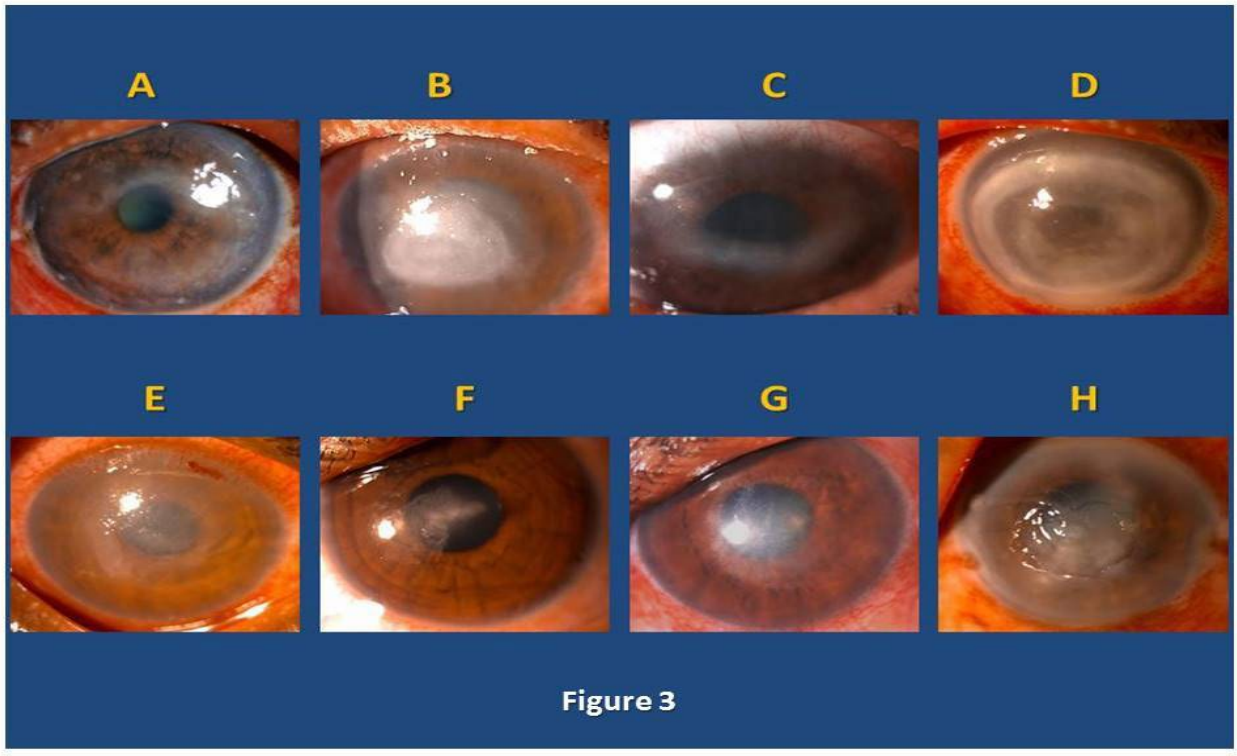

Figure 3: Clinical presentations at first visit (Duration from onset of symptoms). **A.** Anterior stromal Ring infiltrate @ 7 days. **B.** Ring infiltrate w/ Stromal edema @ 30 days. **C.** Stromal infiltration w/ partial ring; in a quiet eye w/ overlying epithelial breakdown; Suggestive of dendritic ulceration @ unknown days. **D.** Ring infiltrate w/ full thickness stromal involvement @ 20 days. **E.** Anterior stromal infiltration w/ stromal edema @ 7 days. **F.** Anterior stromal infiltration @ 3 days. **G.** Stromal edema w/ Descemet's membrane folds and keratic precipitates @ 60 days. **H.** Almost full thickness patchy stromal infiltration w/ Stromal edema @ 10 days.

keratitis. The absence of classical clinical features, the very short duration of symptoms and rapid progression, should not preclude the inclusion of *Acanthamoeba* keratitis in the differential diagnosis.

Garg et al also suggest that non-contact lens related *Acanthamoeba* keratitis varies in some respects from what is observed with contact lens related *Acanthamoeba* keratitis. The authors report that disproportionate pain, radial keratoneuritis and ring infiltrates, were seen only in a small proportion of their cases (less than one third) and that most of their cases presented with diffuse infiltration suggestive of herpes simplex viral keratitis or fungal keratitis [14].

It is also evident that *Acanthamoeba* keratitis is much more frequent than the current perception. Once the study was initiated the number of cases of *Acanthamoeba* identified increased by almost –75%. The low percentage of identified cases in the spectrum of microbial keratitis probably arises from the index of suspicion being restricted to contact lens users, the undue emphasis on the staged, slow progression of the disease, or the presence of conventionally accepted classical features. It is also possible that the classically described features of *Acanthamoeba* keratitis are pathognomonic primarily for contact lens derived infections. The variations we have seen could be attributed not only to the deeper introduction of the organisms but also due to a larger parasitic load at the time of trauma. Given the fact that the establishment of clinical findings that are suggestive of a particular pathogen as fungal or bacterial etc. were laid down in the literature long before *Acanthamoeba* keratitis was known as an entity and that the subsequent cataloguing of clinical signs of *Acanthamoeba* keratitis was primarily from contact lens wearers; it is definitely possible that there is a subset of *Acanthamoeba* keratitis which is unrecognised because of its rapid progression which mimics other forms of keratitis.

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All Authors attest that they meet the current ICMJE criteria for authorship.

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