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Acanthamoeba Keratitis in the Absence of Predisposing Risk Factors

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Abstract

Introduction: *Free-living amoebae of the genus Acanthamoeba produce a progressive infection of the cornea termed Acanthamoeba keratitis. Recrudescent disease is rare but has been described as late as five years after initial treatment of the condition. Here we report a case of recrudescent Acanathamoeba keratitis, discuss useful diagnostic techniques and treatments currently available.*

Case presentation: *A forty-four-year-old female contact lens wearer was treated for Acanthamoeba keratitis affecting her right eye with propamidine isothionate or Brolene 0.01% and polyhexamethylbiguanide or PHMB 0.02% for six months. Fifteen months later she re-presented with recurrence of right eye pain and redness. Limbal injection, peripheral stromal haze and radial keratoneuritis were apparent. Resolution of these symptoms and signs occurred after re-treatment with PHMB 0.02%. The patient maintained a visual acuity of 6/7.5.*

Discussion: *One other case of delayed recurrence of Acanthamoeba keratitis in a patient with no obvious risk factors has been described. Despite apparent clinical resolution of an initial infection, viable Acanthamoeba cysts may persist, dormant, in the cornea. Their reactivation causes recurrence and may be due to an alteration in ocular defence mechanisms. Options for the treatment of Acanthamoeba keratitis have expanded.*

Keywords: *Acanthamoeba; Keratitis; Contact lenses; Treatment*

Introduction

Infections of the corneal surface are an important cause of blindness - up to nine million cases of corneal blindness annually [1].

Free-living amoebae of the genus *Acanthamoeba* produce a progressive infection of the cornea termed *Acanthamoeba* keratitis. There are two stages to the life cycle of *Acanthamoeba*; a motile trophozoite and a dormant cyst. The second of these is resistant to many stresses [2].

The main risk factor for *Acanthamoeba* keratitis is contact lens wear[2 - 4]. Its incidence is 1.2 cases per million adults but 18.84 cases per million in contact lens wearers [4]. Both trophozoite and cyst forms can adhere to contact lenses. Worn or spoiled contact lenses bind *Acanthamoeba* more avidly[5, 6]. Failure to dry hands thoroughly after washing them, poor personal and/or contact lens hygiene are also risk factors for *Acanthamoeba* keratitis.

Although more than 95% of the cases of *Acanthamoeba* keratitis occur in contact lens wearers less than one in 10,000 contact lens wearers will develop a corneal *Acanthamoeba* infection[7, 8]. The low incidence of *Acanthamoeba* keratitis is remarkable considering the ubiquity of the organism and the large population of contact lens wearers [3].

It is important to diagnose *Acanthamoeba* keratitis early. Delayed diagnosis allows the amoebae to penetrate deep into the corneal stroma making successful management with available treatments more difficult [8]. Recrudescence can occur and though extremely rare it has been described as late as five years after the successful treatment of previous *Acanthamoeba* keratitis [9].

Here we report a case of late recurrence of *Acanathamoeba* keratitis, discuss those factors that influence recrudescence and the treatments likely to aid in resolution.

Case Presentation

A 44-year-old lady presented to the Ophthalmology department with a six-week history of painful, red, right eye and reduced vision. She wore daily disposable contact lenses twice a week and so did not require a contact lens case. She denied sleeping, showering or swimming in her lenses and gave no history of antecedent ocular trauma.

She had already attended another Ophthalmology department and was treated for suspected herpes simplex keratitis with acyclovir ointment five times daily for two weeks. At a second unit she was commenced on guttate ofloxacin and dexamethasone 0.1%, both four times daily.

At examination in our facility this lady could perceive only hand movements from her right eye. Extensive radial keratoneuritis, a central corneal stromal infiltrate and associated corneal stromal folds were apparent. Keratic precipitates dotted the corneal endothelium centrally. The peripheral cornea was relatively unaffected. No epitheliopathy was evident.

Given the diagnostic clinical features, the absence of an epithelial defect and the risk of development of a non-healing epithelial defect, corneal scrapes were not undertaken. Access to in vivo confocal microscopy was not available.

This lady was commenced on guttate propamidine isothionate 0.1% (Brolene) and polyhexamethylene biguanide 0.02% (PHMB), both every two hours and tapered according to clinical effect.

The patient's condition improved. Four months from diagnosis, the vision from her right eye had improved to 6/60. Mild persistent stromal haze remained. Brolene was discontinued due to intolerance. PHMB was continued at a frequency of three times daily. Guttate prednisolone acetate 0.12% four times daily was commenced. Six months after her initial diagnosis this lady was asymptomatic, the vision from her right eye was 6/7.5 and all topical therapy had been discontinued.

Fifteen months later however, she represented with a two-week history of intermittent sharp pain from her right eye. She had used guttate Brolene four times daily for three days with some symptomatic relief. Her visual acuity was unaffected. There was no evidence of active inflammation or infection. Six weeks later however she continued to experience a dull pain from her right eye and had become photophobic. As figure 1 shows, there was limbal injection temporally, peripheral stromal haze and subtle radial keratoneuritis in the same area.

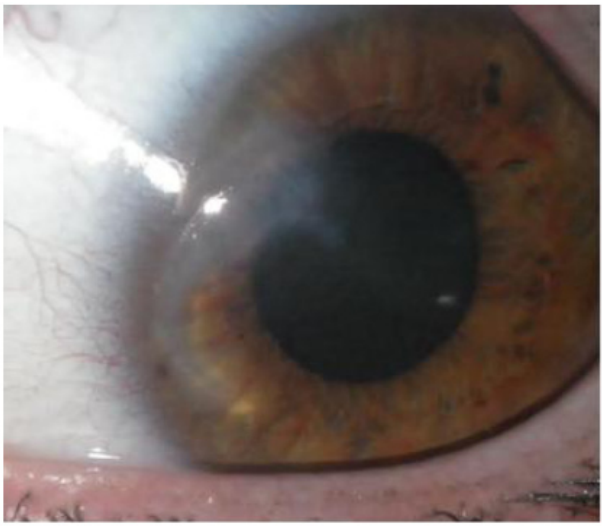

Figure 1. *Case photograph ten weeks post recurrence of her symptoms. Peripheral stromal infiltrates noted supra-temporally.*

Treatment with guttate Brolene two-hourly was commenced but subsequently changed after one week to PHMB, again due to intolerance. After six weeks of treatment, this lady's pain and ocular injection resolved and while she continued to complain of photophobia drop toxicity was thought explanatory. After four months of continued PHMB treatment her symptoms and ocular signs had resolved completely.

Discussion

To our knowledge, there is only one other reported case of delayed recurrence of *Acanthamoeba* keratitis in a patient with no obvious risk factors for the same i.e. repeated contact lens use, administration of topical steroid or corneal trauma, published in the literature [9]. Given the aforementioned low incidence of *Acanthamoeba* keratitis in patients with no identifiable risk factors, it is highly unlikely that the case described here represents a new and unrelated corneal *Acanthamoeba* infection. A more likely scenario is that despite apparent clinical resolution of

the initial infection and six months of treatment with an appropriate combination of anti-*Acanthamoeba* medications, viable *Acanthamoeba* cysts persisted, dormant, in the cornea and were reactivated, although there was no obvious precipitant[1, 8].

Dormant *Acanthamoeba* cysts pose a serious risk for recrudescence in patients that have undergone successful treatment with anti-microbials. These cysts can persist in the corneal stroma for prolonged periods. This may be because they possess weak immunogenic properties and/or because of the' immune privilege' of the cornea[1, 8]. Further, the wall of the *Acanthamoeba* cyst is very resistant to damage. Favourable conditions cause excystment and recurrence of corneal *Acanthamoeba* infection [2].

The greatest risk of recurrence of *Acanthamoeba* keratitis is in patients who have undergone corneal transplantation in an attempt to restore their vision and who must, as a result, use topical steroid for prolonged periods postoperatively[3, 10]. There have also been reports of recurrence in patients who persistently wore contact lenses; one such case was confirmed by confocal microscopy and another by culture of the pathogen[11].

It must be acknowledged that while this patient's initial clinical presentation was typical of *Acanthamoeba* keratitis we cannot be certain of the diagnosis of recrudescent *Acanthamoeba* keratitis. However, a delay in diagnosing is mainly attributed to the lack of a high level of clinical suspicion. It has been shown that up to 85% of patients have corneal changes suggestive of *Acanthamoeba* keratitis[12]. Suspicious clinical findings in this particular case coupled with her favourable response to treatment are consistent with the diagnosis.

Acanthamoeba have been cultured in up to 15% of contact lens cases of patients who have not developed *Acanthamoeba* keratitis[13]. The contact lens care of some contact lens users is poor and yet never develop contact lens related infections. It may be that some human corneas are more susceptible to *Acanthomoeba* infection and indeed re-infection. Individual variations in ocular defence mechanisms may explain this. Patients with lower tear mucosal Anti-*Acanthamoeba* IgA are more susceptible to developing *Acanthamoeba* keratitis[1, 3], while deficiencies in Human B defensin (hBD) and Interleukin 6 levels worsen the prognosis in keratitis patients[14, 15].

Aggressive and prolonged treatment of *Acanthamoeba* keratitis is advocated as therapeutic conditions can produce encystment. Cationic antiseptics i.e. polyhexamethylene biguanide 0.02% also referred to as PHMB or chlorhexidine 0.02% are frequently combined with aromatic diamidines i.e. propamidine isothionate also referred to as Brolene or hexamidine 0.1% also referred to as Desomedine[5, 16].

PHMB and chlorhexidine both contain highly charged positive molecules which result in penetration of the amoeba by the drug which then binds to the phospholipid bilayer of the cell membrane which is negatively charged resulting in membrane damage, cell lysis and death[5, 16].

If misdiagnosis and/or mistreatment allow the protozoa to penetrate deep into the corneal stroma, 'standard' treatments may be less effective. Utilizing PHMB 0.06% or Chlorhexidine 0.2% may be an alternative in these situations[17]. The addition of topical and/or oral voriconazole has also been effective in some persistent infections[18]. In any case, most recommend treatment for between three to nine months. Moreover, when therapy is discontinued, close observation of the patient is necessary in anticipation of recurrent infection.

One possible explanation for the persistence of *Acanthamoeba* in the reported case is organism resistance to the initial chlorhexidine/propamidine treatment. While *in vitro* studies have demonstrated excellent cysticidal performance of chlorhexidine with no demonstrable resistance there may be a poor correlation between the clinical outcomes of individual cases and demonstrated *in vitro* sensitivity[19]. Only 37.5% of patients in one report achieved a medical 'cure' after a prolonged course of treatment[20]. It is possible that therapeutic concentrations are not achieved in the deeper layers of the corneal stroma, that drugs bind to tissue components and are rendered inactive, that agents are inactivated *in vivo* in other ways, that organisms *in vivo* are more resistant than *in vitro*, or that acquired drug resistance may occur during the prolonged treatment period[20].

Newer treatments are on the horizon. Alkylphosphocholines, and in particular hexadecylphosphocholine or miltefosine, which has already been shown to be cytotoxic against Leishmania species, Trypanosoma cruzi and Entamoeba histolytica has, more recently, been

applied in combination with PHMB in *Acanthamoeba* keratitis with treatment effect[15]. Targeting 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase **(**HMGCR), an enzyme that is required to synthesize *Acanthamoeba* cell membrane may also prove a powerful treatment for *Acanthamoeba* keratitis. Statins block this enzyme and early *in vitro* testing with the same has shown promising results [21].

The use of topical steroids prior to starting intensive anti-amoeba therapy is associated with a worse prognosis and may also lead to a delay in its diagnosis[9, 22]. They are however, quite frequently used during treatment. They are useful in alleviating the inflammation and associated pain that accompany *Acanthamoeba* keratitis. On the other hand, corticosteroids exacerbate *Acanthamoeba* infection and promote recrudescence by inducing excystment of dormant cysts and by stimulating proliferation and activation of the emerging trophozoites. *In vitro* treatment with dexamethasone induces up to a six-fold increase in the rate of excystment and a greater than two-fold increase in the proliferation of trophozoites[23]. Corticosteroids also stimulate trophozoites to produce more extensive cytolysis of corneal cells *in vitro*. Treatment with dexamethasone dramatically exacerbated the severity of *Acanthamoeba* keratitis in Chinese hamsters[23]. These effects are compounded by the fact that corticosteroids paralyse the innate immune apparatus that helps to restrict the progression of *Acanthamoeba* keratitis. Depletion of either conjunctival macrophages or neutrophils exacerbates *Acanthamoeba* keratitis[24].

Establishing the most effective treatment regimen for *Acanthamoeba* keratitis will remain challenging for several reasons, not least among which is the relatively rare occurrence of this type of corneal infection, the variable pathogenicity of different strains of the organism, the fluctuating nature of the disease process and the variability in host defence factors already elaborated.

Conclusions

Recrudescent *Acanthamoeba* keratitis is a rare phenomenon and usually occurs post corneal transplant or in those who continue to wear contact lenses. Patients must be warned that after initial resolution of the condition recurrence is possible.

Current combination treatments eradicate trophozoites and cysts *in vitro* but our case demonstrates that cyst forms of the amoeba may persist *in vivo* allowing excystment to occur when the environment becomes more favourable.

There is currently, unfortunately, little published regarding the recurrence rate of *Acanthamoeba* keratitis, the long-term excysting effect of topical corticosteroid in the acute phase, or the effects of their re-introduction years after the acute event.

The number of reported cases of *Acanthamoeba* keratitis is increasing worldwide every year, due to increasing contact lens use for the correction of refractive error and indeed for cosmetic purposes. Currently, the clinical suspicion and early detection of *Acanthamoeba* keratitis are essential to ensure favourable visual outcomes. Confocal corneal microscopy is very helpful in this regard but unfortunately unavailable in Ireland currently.

Although *Acanthamoeba* keratitis is likely to remain a relatively rare corneal disease, the recurrence of dormant infections as described here and the emergence of drug-resistant strains underscore the need for the development of new and effective therapeutic modalities.

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