GRANULOMATOUS INFLAMMATION IN ACANTHAMOEBA KERATITIS: AN IMMUNOHISTOCHEMICAL STUDY OF FIVE CASES AND REVIEW OF LITERATURE

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Abstract

**Purpose:** Acanthamoeba keratitis usually presents as a necrotizing stromal inflammation. We report a rare presentation of granulomatous inflammation in Acanthamoeba keratitis

**Methods:** Retrospective clinico-pathologic case series.

**Results:** Five corneal tissues (3 corneal buttons, 2-eviscerated contents) from patients suffering from severe Acanthamoeba keratitis not responding to anti-Acanthamoeba treatment, revealed a florid granulomatous inflammation with multinucleated giant cells in the posterior stroma and around Descemet's membrane. Phagocytosed parasites were noted within the giant cells. Vascularization of the corneal stroma was noted in two cases. Immunophenotyping revealed a predominance of T lymphocytes and macrophages. Clinically, four of five cases had shown features of limbal and scleral involvement.

**Conclusion:** Granulomatous inflammation in the posterior corneal stroma, is not an uncommon finding in Acanthamoeba keratitis and could possibly be immune-mediated, contributing to persistence and progression of disease.

**Clinical Relevance:** Presence of granulomatous inflammation in Acanthamoeba keratitis, in most cases is associated with limbal and scleral involvement and therefore could be considered as one of the poor prognostic markers. Further studies are required to ascertain the specific clinical features and appropriate management strategies in these cases.

**Key words:** Acanthamoeba keratitis, Granulomatous inflammation, scleritis, immunophenotyping

Acanthamoeba keratitis is a rare infection of the cornea caused by free-living amoeba.1-3 The infection is characterized by stromal keratitis, ring-shaped stromal infiltrates, severe pain and rarely involvement of episclera.4-5 Medical cure, if diagnosed early, is obtained by the use of one or more drugs which include propamidine isethionate, polyhexamethylene biguanide (PHMB), chlorhexidine, clotrimazole and a judicial use of corticosteroids.6-10 However in severe cases, not responding to adequate medical treatment, surgical intervention in the form of penetrating keratoplasty or evisceration is undertaken.11-12 The histologic changes observed in Acanthamoeba keratitis include, epithelial ulceration, stromal inflammation and necrosis, presence of cysts and trophozoites of Acanthamoeba,13-15 apoptosis of keratocytes16 and rarely granulomatous inflammation of the corneal stroma.17 We herein report clinical, histologic and immunohistochemical features in five cases of Acanthamoeba keratitis with granulomatous inflammation presenting clinically as severe, rapidly progressive disease involving the limbus and the sclera.

**Materials and Methods**

In this retrospective study of cases, the corneal buttons of microbiologically diagnosed cases of Acanthamoeba keratitis submitted to the Ophthalmic Pathology Service and showing features of granulomatous inflammation were reviewed and evaluated further as described below.

**Clinical**

The standard protocol of treatment for microbiologically diagnosed cases of Acanthamoeba keratitis at our Institute is as follows: 0.02% PHMB (Baquasil, ICI, USA) and 0.02% chlorhexidine digluconate (Sigma, C-9394) instilled half hourly for 2-3 days (day and night) and then one hourly for period of 7 days. Subsequently, according to clinical response to treatment, the frequency of biguanides is reduced to 3 to 4 hourly per day and then continued for 2-3 weeks after resolution of inflammatory signs. The patients are observed daily or weekly for few weeks. Decision for surgical intervention is taken if: 1) there is large infiltrate at presentation, 2) progression of the disease despite the initiation of anti-Acanthamoeba treatment for 2 weeks 3) If there is involvement of limbal region, 4) impending perforation. We evaluated medical and microbiology records of these cases, and noted the clinical picture at the time of presentation, medical treatment and its duration and the indication for surgical intervention.

**Microbiology**

Corneal scrapings from all patients had been subjected to smear examination by three methods, viz., potassium hydroxide with calcofluor white, Gram and Giemsa stains and culture on media for bacterial and fungal growth along with
nonnutrient agar with live *Escherichia coli* overlay for growth of *Acanthamoeba*. Corneal buttons, whenever available for microbiologic studies, were processed for bacteria, fungi and *Acanthamoeba* by culture of tissue homogenate on blood agar, chocolate agar, brain heart infusion broth, Sabouraud dextrose agar and nonnutrient agar with *E. coli*.

Paraffin sections of corneal buttons and evisceration materials were used for extraction of DNA by a procedure described earlier and were tested for presence of herpes simplex virus DNA by polymerase chain reaction, using primers specific for glycoprotein D gene of herpes simplex virus. Results of microbiological investigations for all cases is shown in (Table 1).

**Histopathology**

Keratectomy/eviscerated material was fixed in 10% buffered formalin. Multiple sections of 5µ thickness were cut from paraffin embedded tissues. Sections were deparaffinized by placing the slides in the oven at 51°C for 1 hour, followed by immersion in xylene and hydration in decreasing ethanol concentration. Hematoxylin - eosin staining, periodic acid Schiffs and Gomori’s methenamine silver staining were performed on these tissue sections.

**Immunophenotyping**

Immunohistochemistry was performed using monoclonal mouse anti-human antibodies (Dako, Denmark) against, T cell CD 3, Macrophage CD 68 and B cell CD 20 antigen. After deparaffinizing the sections, the endogenous peroxidase activity was neutralized using 100% methanol and 0.4% H₂O₂. Antigenic epitopes of the corneal section were retrieved by incubating the sections with prewarmed citrate buffer for 15 minutes in hot air oven maintained at 100°C. Non-immunologic binding of antibodies was blocked by incubation with bovine serum albumin. Incubation with all the primary antibodies was carried out in a moist chamber at 4°C overnight. On the following day after thorough washing with phosphate buffer saline, secondary biotinylated goat anti-mouse antibody (Dako, Denmark) was added and incubated at room temperature in moist chamber for 30 minutes. This was followed by incubating the sections with avidin-biotin complex wherein the biotin was conjugated with horseradish peroxidase enzyme (Dako, Denmark) for 45 minutes. The peroxidase activity was visualized by incubation with freshly prepared 3’ Diaminobenzidine tetrahydrochloride (DAB) containing 0.0015% H₂O₂. The slides were counterstained with hematoxylin, dehydrated and cleaned in xylene and mounted. Corneal button section, without the incubation with primary antibody was used as negative control, while tonsil section served as positive control. The phenotype of the inflammatory cells was assessed in the region of the granulomatous inflammation, surrounding stroma and limbus.

**Results**

**Clinical profile**

Of the 172 cases of *Acanthamoeba* keratitis diagnosed in our institute from 1995 till May 2003, 18 (10.4%) underwent surgical intervention in the form of penetrating keratoplasty or evisceration. Five of these eighteen keratectomy specimens (27.7%) displayed granulomatous cell reaction. Five patients included 3 males and 2 females and their age at the time of surgery ranged from 20 - 65 years (median 45 years). Two patients underwent evisceration while the other three had penetrating keratoplasty done.

**Case 1**

A 30-year-old male patient presented with complaints of pain, redness, watering and decreased vision of two months.
duration following an injury to the eye while working in the fields. He was diagnosed as a case of ring corneal ulcer and treated with antibiotic eye drops for two months before being referred to our institute. At presentation, he had a vision of hand movements at 2 meters with inaccurate projection of light. The conjunctiva was congested. Cornea showed a ring ulcer (Fig. 1) involving the limbus at the entire periphery. Fundus could not be visualized. B scan revealed choroidal thickening with no gross vitreous opacities. Corneal scrapings revealed 0-4 cysts of *Acanthamoeba* per high power field. Patient was diagnosed as *Acanthamoeba* keratitis and treated with chlorhexidine and PHMB for a period of one month. There was progression of the ulcer, marked thinning and ectasia of cornea with impending perforation. Prognosis of the condition was explained to the patient and was advised for evisceration. The excised contents were subjected to histologic examination.

Case 2

A 65-year-old female who underwent uncomplicated penetrating keratoplasty with extracapsular cataract extraction and posterior chamber lens implantation in her right eye for granular dystrophy presented to her ophthalmologist three months post-operatively complaining of pain, photophobia, and decreased vision. The ophthalmologist diagnosed her condition as graft rejection based on the presence of a raised concentric epithelial line on the donor cornea, diffuse stromal edema and multiple keratic precipitates on the endothelium. She was treated with hourly topical prednisolone acetate. After three days of therapy the epithelial line increased in size and developed areas of epithelial defect. The surgeon suspected recurrent HSV keratitis, therefore reduced the frequency of prednisolone acetate and started topical acyclovir (5%) 5 times a day. When there was no improvement in the patient’s condition, he referred the case to us. At initial examination at our institute her visual acuity was hand movements in the right eye and 20/125 in the left eye. The conjunctiva was injected. Cornea showed two circumferential epithelial defects, about 2 mm inside the graft host junction, associated with granular infiltrate (Fig. 2). Rest of the graft showed diffuse stromal haze associated with multiple keratic precipitates. The host cornea demonstrated minimal superficial vascularization and all interrupted sutures were intact. Anterior chamber was deep and the intraocular pressure appeared normal on digital tonometry. Microscopic examination and culture of the corneal scrapings were positive for *Acanthamoeba*. A review of the patient’s medical and social history revealed she was using pond water for washing face and taking bath. The patient was treated with half hourly topical PHMB 0.02% and chlorhexidine 0.02% and oral itraconazole 100mg twice daily. When the clinical picture did not improve a therapeutic penetrating keratoplasty was done after 2 weeks; the excised corneal button was subjected to histopathology examination. On the first post operative day, there were exudates in the anterior chamber. There was evidence of suture abscess, epithelial defect and endothelial pigments on the 7th post-operative which progressed to scleral abscess at the end of 5 weeks (Fig. 3). The final visual acuity at the end of 6 weeks was perception of light.

Case 3

A 45-year-old man presented with severe pain, redness, watering, pricking sensation and reduced vision of 10 days duration. He gave a history of sand particles falling into his eye while digging pits in the farm. He consulted a local ophthalmologist who diagnosed as hypopyon corneal ulcer (Fig. 4) and referred to our institute for further treatment. On examination, he had edema of lids with pseudoptosis. Conjunctiva was congested and chemosed. Cornea showed an epithelial defect 2 x 2.5mm associated with underlying stromal infiltrates of 8mm. Anterior chamber was deep with 1mm hypopyon. Initial corneal scrapings did not reveal any organisms on microscopic examination of smear while a repeat scraping revealed cysts of *Acanthamoeba*. The patient was treated for five weeks with PHMB and chlorhexidine eye drops along with oral itraconazole. There was no response to the above medication. On the contrary, the ulcer expanded to involve the limbus and the sclera with increase in intraocular

<table>
<thead>
<tr>
<th>Case no.</th>
<th>Epithelium</th>
<th>Bowman’s layer</th>
<th>Stromal inflammation</th>
<th>Vessels</th>
<th>Necrosis</th>
<th>Granuloma</th>
<th>Phenotype</th>
<th>Acanthamoeba load</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>Ulcerated</td>
<td>Absent</td>
<td>Severe (M, P)</td>
<td>Neg</td>
<td>Pos</td>
<td>Pos</td>
<td>T, CD - Pos; B - Neg</td>
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<td>Absent</td>
<td>Diffuse</td>
<td>Pos</td>
<td>Pos</td>
<td>Pos</td>
<td>T, CD - Pos; B - Neg</td>
<td>Cysts 3 +</td>
</tr>
<tr>
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<td>Severe (M, P)</td>
<td>Neg</td>
<td>Neg</td>
<td>Pos</td>
<td>T, CD - Pos; B - Neg</td>
<td>Cysts 3 +</td>
</tr>
<tr>
<td>4</td>
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<td>Absent</td>
<td>Severe (A, M)</td>
<td>Neg</td>
<td>Pos</td>
<td>Pos</td>
<td>T, CD - Pos; B - Neg</td>
<td>Cysts 3+; trophozoites 2+</td>
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<td>Pos</td>
<td>Pos</td>
<td>Pos</td>
<td>T, CD - Pos; B - Neg</td>
<td>Cysts 2 +</td>
</tr>
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M - Mid stroma  A - Anterior stroma  P - Posterior stroma  Neg - Negative  Pos - Positive
**Figure 1:** Slit lamp photograph in diffuse illumination of cornea (case 1) showing a large ring infiltrate with surrounding corneal edema (x 16).

**Figure 2:** Slit lamp photograph of case 2, in diffuse illumination showing ring shaped granular infiltrate involving the graft-host junction (x 16).

**Figure 3:** Slit lamp photograph shows a clear graft and congested sclera showing four abscess of varying sizes, sparing the graft host junction (x 16). These abscess were noted 5 weeks following therapeutic keratoplasty.

**Figure 4:** Slit lamp photograph of cornea with diffuse illumination showing ring shaped infiltrate with surrounding corneal edema. Note the presence of hypopyon.(x16)

**Figure 5:** Picture shows corneal button of *Acanthamoeba* keratitis with epithelial ulceration and inflammatory infiltrates in the anterior one-third of corneal stroma. Note the absence of inflammation in the deeper cornea. (hematoxylin and eosin, x 40)

**Figure 6:** The corneal stroma shows two cysts of *Acanthamoeba* with a double layered wall. (periodic acid Schiff's stain, x 1000)
pressure. In view of advanced disease, not responding to medical treatment, an evisceration was performed after obtaining consent from the patient.

Case 4

A 20-year-old female presented to us with the complaints of pain, redness, watering, photophobia and diminished vision in her left eye of two and half months duration. She gave history of unknown particles falling into her eyes while washing clothes. At the time of presentation, the visual acuity in her affected eye was light perception and accurate projection of rays in all quadrants. Intraocular pressure was normal on digital tonometry. On examination the left eye showed a ring shaped corneal infiltrate 1mm inside the limbus. The corneal stroma within the ring showed a granular infiltrate. Surrounding cornea was edematous with deep vascularization in two quadrants. Anterior chamber was deep. Posterior segment appeared normal on B-scan ultrasonography.

Corneal scrapings revealed *Acanthamoeba* cysts on microscopic examination. The patient was treated with topical 0.02% PHMB and 0.02% chlorhexidine instilled half hourly, atropine sulphate 1% instilled thrice daily and oral ketoconazole 200 mg twice daily. Over the next 10 days the infiltrate increased in density and showed progressive vascularization. We added prednisolone acetate 1% every three hourly. With this therapy the central infiltrated area showed progressive thinning. Therefore, we advised penetrating keratoplasty. The corneal tissue removed during keratoplasty was divided in to two halves; one submitted in saline for microbiology work-up and the other half in formalin for histopathology examination. At the end of 6 weeks, the
A 58-year male patient presented to us with the complaints of pain, redness, watering, and reduced vision in his left eye on 1 month duration. He gave a history of dust/wooden particles falling into his eyes while cutting wood. He was treated with 3-hourly instillation of fluconazole (0.3%), natamycin 5%, ciprofloxacin HCl (0.3%) before presenting to us. At the time of presentation visual acuity was counting fingers close to face in the affected eye. The cornea showed a central 8.1 mm x 5.1 mm epithelial defect with a ring infiltrate measuring 6 x 5 mm and surrounding cellular reaction. The stroma within the ring showed 50% thinning. Anterior chamber was deep with 2 mm hypopyon. B-scan ultrasonography showed an echo-free vitreous cavity with attached retina. Initial corneal scraping did not reveal any organisms on microscopy or on culture. However, the *Acanthamoeba* cysts were seen on microscopic examination and cultured on repeat scrapings. The patient was treated with 0.02% chlorhexidine and PHMB for 11 days. Despite treatment, the infiltrate finally progressed and extended to involve the limbus between 10 to 2 clock hours. Therefore, penetrating keratoplasty was performed. The corneal button was subjected for microbiology and histopathology evaluation. Four weeks post operatively the vision in the left eye was 20/60 with a clear graft.

**Microbiology**

The results of smear and culture of clinical samples from all five cases are shown in (Table 1).

**Histopathology**

The histopathologic features of the five cases are given in table 2. There was epithelial ulceration with destruction of Bowman’s layer in all the cases. The stroma showed inflammatory infiltrates consisting of neutrophils in the anterior two-thirds of stroma (Fig. 5). Vascularization of stroma was noted in mid and deep peripheral stroma in two cases. Viable and degenerated cysts of *Acanthamoeba* were seen in the stroma (Fig. 6). In addition, the deeper stroma and the region around Descemet’s membrane showed a few aggregates of epitheloid cells, lymphocytes and multinucleated giant cells (Fig. 7). Some of the giant cells and occasional keratocytes showed cysts of *Acanthamoeba* in the cytoplasm (Fig. 8), suggesting the phagocytosed parasites. Limbal tissue, when identified in the sections, showed dense lymphoplasmacytic infiltrates admixed with few eosinophils.

**Immunophenotyping**

The inflammatory cells in the corneal stroma were found to be of T cell population. In the granulomatous regions, the cells were positive for T cells (Fig. 9), CD 68 (Fig. 10) and negative for B-cell marker, suggesting a predominance of T lymphocytes with macrophages. The detailed results are depicted in table 2.

**Discussion**

*Acanthamoeba* keratitis is a vision-threatening infection caused by pathogenic species of the genus *Acanthamoeba*. The amoebae are often introduced in the eye by an individual’s use of contaminated contact-lens cleaning solutions, trauma or by swimming in contaminated water. Acanthamoeba keratitis usually results from direct invasion of ocular tissue by the amoeba through minor breaks in the corneal epithelium, caused by trauma, previous episodes of herpes simplex or by abrasion from hard or soft contact lenses. The pathogenesis of *Acanthamoeba* keratitis involves parasite-mediated cytolysis and phagocytosis of corneal epithelial cells, invasion of the extracellular matrix, keratocyte depletion, recruitment of inflammatory infiltrates and dissolution of the corneal stromal matrix.

Histologically, the corneal tissues in *Acanthamoeba* keratitis show evidence of epithelial ulceration, polymorphonuclear infiltrates, stromal necrosis along with the presence of trophozoites and/or cysts in the corneal stroma. Despite the prolonged clinical course of the disease, a few unique observations have been made in *Acanthamoeba* keratitis which include: absence of vascularization, scarcity of lymphocytes, keratocyte loss through apoptosis, and the presence of cysts in the deep stroma, unaccompanied by inflammatory cells. Though acanthamoebic infections of brain usually evoke granulomatous inflammation, this is rarely reported in *Acanthamoeba* keratitis. We herein report five cases of *Acanthamoeba* keratitis presenting with granulomatous inflammation in the posterior corneal stroma, four of which presented with rapidly progressing *Acanthamoeba* keratitis involving limbus and sclera. To understand the significance of these findings we performed the immunophenotyping of the inflammatory cells and attempted a clinicopathological correlation.

Clinically, *Acanthamoeba* keratitis is characterized by severe pain with an early superficial keratitis, followed by radial perineural infiltration, ring infiltration and rarely limbitis and scleritis. Sclerokeratitis in *Acanthamoeba* keratitis is often associated with severe inflammation and is a therapeutic challenge to the ophthalmologist. The limbal and scleral inflammation has been reported to increase on initial intensive topical antiamoebic therapy and this has been related to immune mediated response to dead or dying amoebae within the cornea. Fortunately limbal and scleral extension of *Acanthamoeba* keratitis remains a rare complication. None of the patients in our earlier reported series of 39 patients had developed this complication. Three of five cases reported in this series had a severe clinical course that progressed despite adequate doses of supervised medical treatment, necessitating surgical intervention. One case presented with total corneal ulcer, while the other presented as a graft infiltrate, clinically
mimicking a rejection phenomenon. The median duration of medical treatment was 2 weeks (1–8 weeks). History of trauma was elicited in 4 cases. Though prolonged medical treatment is usually advised for *Acanthamoeba* keratitis, penetrating keratoplasty has been advocated in cases which threaten the integrity of the eye.11 At our institute, 10.4% (18 of 172) of cases underwent surgical intervention in the form of keratoplasty in 72% (13 of 18) and evisceration in 28% (5 of 18).

Histologically, the tissues showed epithelial ulceration and destruction of Bowman’s layer. The stroma showed dense inflammatory infiltrates predominantly consisting of polymorphonuclear infiltrates in all cases, as was reported in most studies.13,15 The deeper stroma showed lymphocytes, macrophages, epitheloid granulomas and giant cells. Though polymorphonuclear cells are believed to be the first line of defense in all infections, including *Acanthamoeba* keratitis, recent evidence however points towards the role of macrophages.24 Van Klink et al performed conjunctival macrophage depletion in Chinese hamsters to determine the importance of macrophages in *Acanthamoeba* keratitis. They selectively eliminated macrophages using macrophagicidal drug dichloromethylene diphosphate. They found profound exacerbation of *Acanthamoeba* keratitis in hamster treated with this drug, strongly suggesting that macrophages play an important role in the corneal infection with *Acanthamoeba*, probably by acting as a first line of defense and eliminating significant numbers of *Acanthamoeba* trophozoites.24

Two of the five cases showed evidence of vascularization in our series. This is different from the observations made by Kremer et al14 who noted the conspicuous absence of vascularization in 10 cases reported by them. In general, it is believed that lymphocytic infiltration in the cornea is closely associated with vascularization.25 When vascularization is present, lymphocytic and plasmaicy infiltrates are usually observed mainly in the immediate vicinity of blood vessels in the corneal stroma or in the vascular pannus. An immune response to chronic inflammation can be expected to further involve macrophages, lymphocytes and macrophage derived epitheloid cells.25

Garner interpreted that absence of lymphoid cell may be due to absence of stromal vascularization and consequent barrier to invasion by relatively immotile cells.13 In all our cases, lymphomononuclear cells were noted in the deep stroma accompanied by macrophages, epitheloid cells and multinucleated giant cells. Though Auran et al in their review article of 35 cases interpreted the presence of granulomatous inflammation in 5 cases,21 best illustration of this finding was reported by Meitz et al in 1997.17 Granulomatous inflammation extending to sclera has been reported by Dougherty et al.26 In the two eviscerated tissues, there was no evidence of granulomatous inflammation in the sclera or other layers.

The frequency of granulomatous inflammation in corneal tissues varies from 2% to 25% depending on the type of tissues included in the study.27,28 It was reported in 2% (6 of 314) of all keratoplasty specimens,27 9% (28/298) in infectious keratitis of all causes,28 and 25% (53 of 215) of keratectomy specimens from patients with a clinical diagnosis of herpes stromal keratitis.29 We reported granulomatous inflammation in 13.8% (23 of 167) of fungal keratitis30 and now report 27.7% (5 of 18) in *Acanthamoeba* keratitis. Though it can be seen in various other infectious and non-infectious corneal diseases, there is enough evidence that it is most commonly associated with disciform herpes simplex keratitis.29 In this study, the DNA isolated from the paraffin sections of the corneal tissue were negative for herpes simples virus DNA, thereby ruling out any associated or pre-existing herpes virus keratitis.

Granulomatous inflammation is a type of chronic inflammation characterized by the collection of modified macrophages, namely the epitheloid cells with or without associated multinucleated giant cells and lymphocytes. Though definite pathogenesis of the granulomatous reaction in general remains unknown, the process may have a non-immune or immune aetiology.27 The non-immune response is the well known foreign body granuloma. There is an influx of macrophages due to chemotaxis and these cells persist in the area if the foreign material is poorly soluble.21 The immune pathway is the result of sensitized T cells releasing lymphokines and causing the accumulation of macrophages.22 The presence of T lymphocytes as found in this study suggests that granulomatous inflammation in cornea appears to be an immune-mediated process. These T cells could either be sensitized to microbial antigens, altered cellular and/or basement membrane structures from the host, or both. Holbach et al28 support the role of viral antigens while Weiner et al suggest a non-viral antigen in the etiopathogenesis of this type of inflammation.27 Though the clinical implications of this type of inflammation is not clearly documented, it has been suggested that granulomatous inflammation around Descemets membrane can be identified clinically and should be considered as an indication for penetrating keratoplasty in herpes stromal keratitis. We speculate that it may be the same for *Acanthamoeba* keratitis. What is important to note is that all four of five cases had a rapid clinical worsening with extension of the inflammation to the limbus, with involvement of sclera in four cases, necessitating an early surgical intervention, suggesting the possibility that it could be a poor prognostic maker. However, whether the granulomatous inflammation is the cause or the effect of the advanced disease cannot be commented upon by these five cases but it is likely that the two are related.

To summarize, granulomatous inflammation, is not an uncommon finding and could be seen in rapidly progressing form of *Acanthamoeba* keratitis, not responding to medical treatment. Further studies are warranted to understand the
References


