Acanthamoeba

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Contents

Core Messages
- *Acanthamoeba* keratitis has highly variable presentations, usually with ocular pain.
- Intraocular infection or posterior segment inflammation is uncommon.
- Diagnosis may require confocal microscopy, biopsy, or PCR testing.
- Early recognition and treatment greatly improve vision outcomes in *Acanthamoeba*.

127.1 Definition

Acanthamoeba, small, free living protozoans, have been isolated from freshwater, seawater, arctic ice, soil, contact lens cases, and even air [16]. One study based on air sampling estimated that a human inhales, on average, two *Acanthamoeba* organisms per day [15]. *Acanthamoeba* feeds on bacteria, fungi, and other organisms and thrives in biofilms such as on the walls of hot tubs. Human infection is rare and often opportunistic [25].

The earliest reported infections in humans involved the CNS in immunocompromised patients [16, 42], but the first published report of *Acanthamoeba* keratitis was in 1974 [4, 40]. Isolated case reports followed until a relative "epidemic" of cases appeared worldwide, but especially in the USA and Great Britain in the early 1980s, with many of these cases occurring

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in patients wearing contact lenses of all modalities, but most often involving daily-wear soft contact lenses [10, 39]. Often, patients had mixed their own saline solution using large jugs of water and salt tablets or had other non-hygienic lens care habits. *Acanthamoeba* can adhere readily to contact lens surfaces and cases, and adherence is a significant factor in pathogenicity [32]. Most commercially available contact lens disinfectants are ineffective at killing *Acanthamoeba* [11]. Recent epidemic outbreaks have been associated with the use of specific lens disinfectant solutions [22, 28]. Though as many as 85 % of *Acanthamoeba* keratitis occurs in contact lens-wearing patients [38, 39, 79], occurrence in non-contact lens-wearing patients is most often associated with trauma, exposure to contaminated water, or penetrating keratoplasty [13, 38, 48, 56, 64, 67, 78]. Many idiopathic cases have also been reported. The incidence of *Acanthamoeba* keratitis has been estimated between 1.2 and 3.0 cases per million population [60].

127.2 Clinical Manifestations

127.2.1 Systemic Disease

Three distinct clinical syndromes have been observed due to *Acanthamoeba* infection: granulomatous encephalitis; disseminated granulomatous infection of the skin, sinus, or pulmonary tract; and amebic keratitis. Patients with non-ocular disease are usually immunocompromised, whereas those with amebic keratitis are usually immunocompetent. The etiology of systemic infection is thought to involve hematogenous spread from the skin or pulmonary foci of infection. The outcomes of disseminated disease and encephalitis are poor, and treatment strategies are not well defined.

127.2.2 Ocular Disease

127.2.2.1 *Acanthamoeba* Keratitis

Variability in presentation is a hallmark of *Acanthamoeba* keratitis. Bilateral disease has been reported in 7.5 % of cases [60]. Severe pain,

in excess of objective findings, is a common feature, as are symptoms of foreign body sensation, photophobia, and tearing [71]. Clinical signs vary with the stage of presentation, and disease progression is often slow. In early infection, only conjunctival hyperemia with superficial epithelial irregularities (microerosions, pseudodendrites, opacification, microcystic edema, or a diffuse granularity) may be seen [15, 41]. Despite corneal hypesthesia, severe pain thought to be secondary to keratoneuritis is common. In later stages, multifocal, nummular anterior stromal infiltrates develop and may coalesce into annular or crescentic or disciform opacities. A ring infiltrate, initially vague with intact, overlying epithelium, has been reported as pathognomonic of *Acanthamoeba* keratitis [49]. In later stages, the ring often appears more dense and discrete, and the central epithelium sloughs, facilitating stromal necrosis. Several examples of the variable clinical presentation are shown in Fig. 127.1. Anterior chamber reaction is rare. The pathogenesis of the ring infiltrate is uncertain. Residual antigen may cause inflammation in the absence of active trophozoite infection. Cysts have been shown to induce corneal stromal inflammation as long as 31 months following antiamebic therapy [76]. Focal stromal edema with intrastromal inflammatory infiltration is common, and radially oriented perineural infiltration (keratoneuritis) has been described [41]. Over time, presumed release of proteases and collagenases leads to stromal lysis, descemetocele formation, or perforation. Herpetic keratitis is often the most commonly considered differential diagnosis and may delay the diagnosis of *Acanthamoeba* infection [6]. The appearance of satellite lesions in later stages can mimic fungal keratitis. In some studies, the mean delay to diagnosis was 42–48 days [68] and may be longer in non-contact lens-wearing patients [20].

Intraocular inflammation is uncommon, though case reports of intermediate uveitis [60] and chorioretinal lesions [8, 9] have been published. Cases published have described both isolated foci of retinal whitening and also cases with secondary vitreous cells, always associated with a primary keratitis. Less commonly reported findings include secondary immune-mediated scleritis [7], scleritis [18], and anterior uveitis [2].
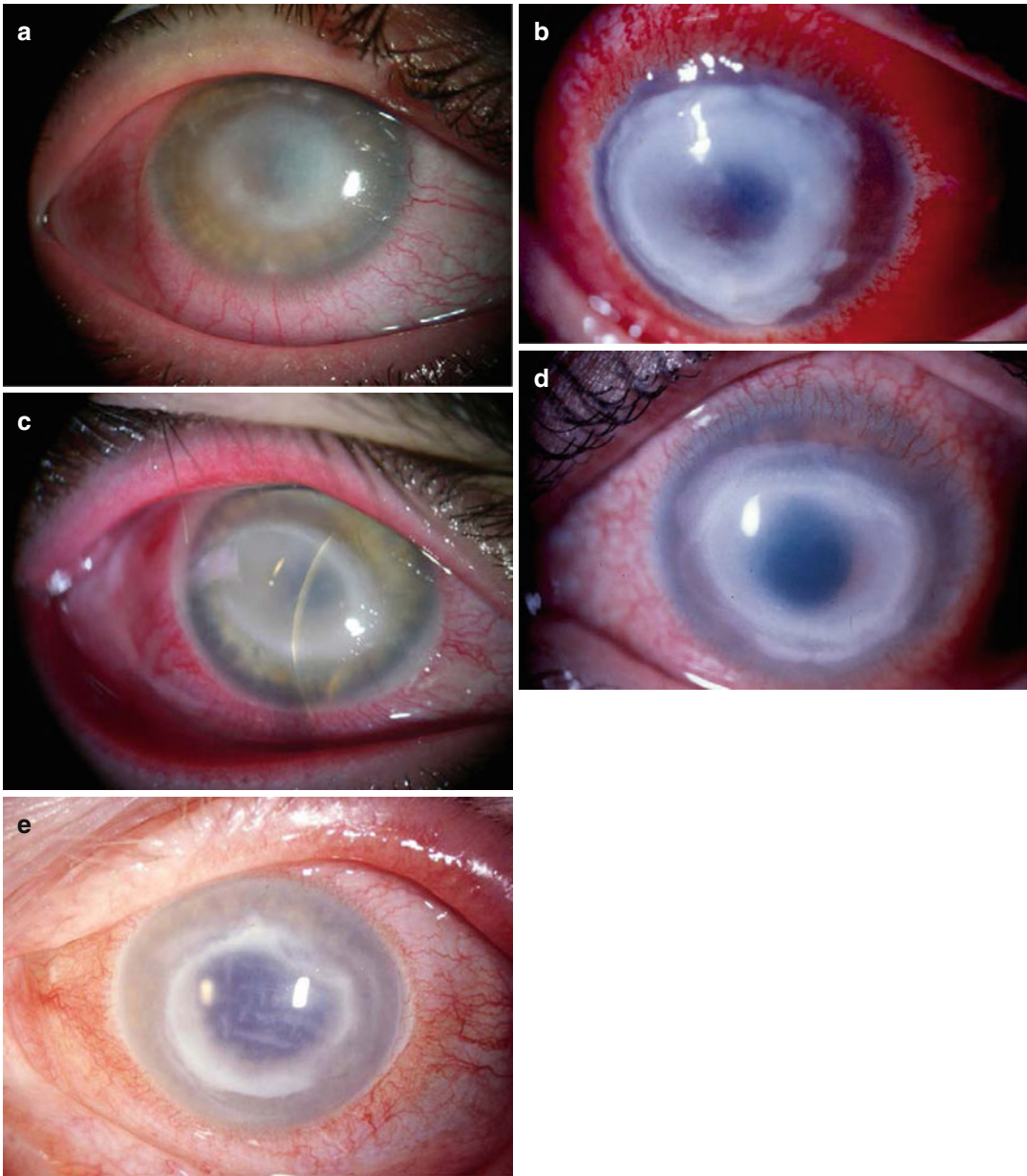
Fig. 127.1 (**a–e**) Ring infiltrates, various clinical presentations

Two cases of chorioretinitis following keratitis [27, 50], and several reports of a culture-positive anterior chamber paracentesis in a patient with keratitis [46] have been reported. More recently, five patients with keratitis have been described having severe posterior segment ischemia of unknown mechanism, all with histologically confirmed *Acanthamoeba* [5].

127.3 Etiology and Pathogenesis

Acanthamoeba exists in two life forms, an active trophozoite and a smaller, double-walled cyst, capable of dormancy for years [15]. Trophozoites are the infectious form and measure from 15 to 45 μm in diameter. Perhaps the major factor accounting for the severity of *Acanthamoeba*

infections is encystment in infected tissues, which occurs as a result of pH changes or adverse changes in oxygen or food supply [12]. Cysts are resistant to wide extremes of temperature, desiccation, and many antimicrobial and disinfectant chemicals, including inorganic chlorine up to 50 ppm, while trophozoites are sensitive at 2 ppm, which is still in excess of levels found in public water supplies (<1 ppm) [1, 32].

Acanthamoeba trophozoites bind to corneal epithelium via lecithin-mediated adhesion facilitated by a mannose-binding glycoprotein [23, 37]. Bacterial coinfection may be involved in amebic pathogenicity [14]. Once bound, trophozoites induce apoptosis and secrete cytolytic proteases, a metalloproteinase (MIP-133), and additional cytolytic factors. Once in stroma, ameba releases collagenolytic enzymes to further dissolve stromal matrix [22, 31]. *Acanthamoeba* does not attract macrophages or neutrophils but is effectively killed by these cells [24]. This may explain the ability of cysts to persist long term in stroma.

127.4 Diagnosis

Ideally, diagnosis of *Acanthamoeba* infection includes microbiologic confirmation and should not be made wholly on clinical grounds. All available sources for culture should be exploited, including contact lens solutions and cases, well water, or hot tub water samples. Diagnosis is most often confirmed by direct inoculation of corneal scrapings, biopsied stromal tissue, or keratoplasty buttons onto appropriate culture media or submission of scrapings from the base of ulcers for histopathologic examination [57, 58]. Recently, confocal microscopy has been reported as a tool to identify cysts or trophozoites in vivo [29, 30, 44, 45, 55], but correlations between confocal images and histopathology remain speculative.

Acanthamoeba organisms grow poorly on media typically used for bacterial keratitis sampling. Early reports recommended culture on non-nutrient agar seeded with an overlay of bacteria, usually Gram-negative, but these are rarely available.

Histopathologic studies have demonstrated both trophozoites and cysts using methenamine silver, PAS, Masson trichrome, and iron-hematoxylin-eosin stains [43, 65]. Fluorescent microscopy can be done using various immunofluorescent stains, and immunoperoxidase staining is available [16, 52, 73, 75]. PCR testing has been reported as the most sensitive method of diagnosis, but uniformity in testing methods has not been achieved [17, 77].

127.5 Differential Diagnosis

As with any keratouveitis, the differential diagnosis must first consider herpetic etiologies, including both herpes simplex and zoster. Fungal keratitis can also mimic this clinical presentation, though often other corneal findings, such as satellite lesions or endothelial precipitates, are helpful in raising suspicion of this class of microbe.

127.6 Treatment

The early years of *Acanthamoeba* keratitis treatment were characterized by failures of medical treatment, recurrence following surgical intervention, and frequent loss of vision. Medical cures were reported using combinations of amebicidal drugs [3, 6, 7, 21, 33, 35, 36, 61, 70], but treatment failures were common and prolonged duration of therapy was required [6, 44, 63, 72]. Better results are achieved when appropriate antiamebic treatment is begun early in the course of disease [6, 26].

Medical therapy has employed aminoglycosides, polymeric biguanides, diamidines, and imidazoles, usually in combinations [3, 41]. Most of these medications are prescribed to be instilled initially every hour and slowly tapered. To date, no report has recommended standardization of the therapeutic regimen [34].

Among the aminoglycosides, neomycin 8 mg/ml solution or fortified up to 20 mg/ml has been demonstrated to have antiamebic efficacy. Paromomycin 10 mg/ml has also been used.

Polymeric biguanides, commercially available as environmental biocides (Baquacil, a swimming pool disinfectant), have been used with success in the treatment of *Acanthamoeba* keratitis [3, 4]. Diluted to a 0.02 % concentration, progressive ocular surface toxicity often forces discontinuation of therapy in patients. The mechanism of action of this agent is believed to be interference with cytoplasmic membrane integrity and inhibition of essential respiratory enzymes [3].

Chlorhexidine 0.02–0.1 % is another cationic antiseptic agent that has shown good efficacy at eradicating *Acanthamoeba* [62, 74]. Because of the lower surface toxicity as compared with PHMB, chlorhexidine has emerged as a favored treatment, whether alone or in combination with other agents [26].

Aromatic diamidines such as Brolene (propamidine isethionate 0.1 % solution), pentamidine isethionate, and dibromopropamidine ointment are available in eyedrop or ointment preparations. Imidazoles [54] have been used as topical preparations and are systemically administered. Systemic itraconazole or ketoconazole may have an important role in adjunctive therapy. Miconazole 1–2 % and clotrimazole 1–2 % have been used successfully, but ocular surface toxicity is common and these drugs are amebastatic rather than amebacidal [59]. There is no "standard of care" in the medical management of *Acanthamoeba* keratitis, either with respect to antimicrobial selection or duration of therapy, but multidrug therapy which includes chlorhexidine is well supported by medical literature.

As is true in other infectious scenarios, the role of topical corticosteroids is controversial, due to risk that inhibition of host defense mechanisms may prolong the course of disease or even worsen outcomes [22, 53]. Steroids have been shown to promote conversion of cysts to trophozoites [47].

Surgical intervention should be delayed until there is clear evidence of control of amebic replication and should not be employed as a strategy to debulk the cornea of amebic load [51]. Sometimes, penetrating keratoplasty is required to maintain the structural integrity of the globe [66], but vigorous attempts should be made to forestall surgical intervention as long as possible [19, 41].

Recurrence of disease following penetrating keratoplasty has been frequently reported [19, 41], often as a crescentic infiltrate near the graft-host junction, and results in reduced likelihood of vision preservation. As in cases of fungal keratitis, postoperative treatment with topical cyclosporine is recommended for prophylaxis against rejection rather than topical steroids. Two cases treated with phototherapeutic keratoplasty and deep lamellar keratoplasty have been reported [69]. Penetrating keratoplasty is best reserved for optical rehabilitation in quiescent, medically cured eyes [19]. In this setting, excellent visual rehabilitation can be achieved. Uveitis in these patients is treated as any other ocular non-ocular surface inflammatory process, with systemic therapy.

127.7 Prognosis

Between 30 and 80 % cases of *Acanthamoeba* keratitis are controlled with medical therapy [34]. Surgical therapy is very effective for vision restoration once infection has been controlled but is not effective in acute infection.

> **Take-Home Pearls**
> - *Acanthamoeba* keratitis affects non-contact lens-wearing patients as well as contact lens wearers.
> - Uveitis mostly is associated with keratitis, but severe posterior ischemia has been described.
> - Multiple drug therapy including chlorhexidine is highly effective in treating *Acanthamoeba* keratitis.

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