

# Role of Anterior Segment Optical Coherence Tomography in Monitoring Epidemic Keratoconjunctivitis

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## Abstract

**Purpose:** To describe, through anterior segment optical coherence tomography (AS-OCT) images, the different phases of epidemic keratoconjunctivitis (EKC) and show the impact of topical steroid on the course of this disease.

**Methods:** A prospective observational study included 38 eyes (28 patients) with a presumed EKC complicated by subepithelial infiltrates (SEIs) and treated with topical fluorometholone. Slit-lamp examinations and serial AS-OCT were performed on days 7, 14, 30, 90, 180, and 210. The thickness of the whole cornea and thickness of the corneal epithelium were measured with AS-OCT and correlated to the clinical findings on slit-lamp examination in the different EKC phases.

**Results:** In all patients, on day 7, the AS-OCT showed hyperreflective dots that were limited to the epithelial layers of the cornea and slightly rising above the epithelial surface, corresponding to the confluence of the punctuations of punctate epithelial keratitis. On day 14, a hyperreflective line in the Bowman's layer with intact epithelium was noted. On day 30, this hyperreflective band extended rapidly toward the anterior stroma, becoming thicker and more intense, corresponding to the SEI. They gradually decreased in number, intensity, and extent following treatment by topical steroids in 71.4% of the cases. Only two patients had persistent SEI. They were refractory to 3-month treatment by steroids. In these patients, who had persistent SEI, AS-OCT showed that the hyperreflective areas became well-defined, plaque-like lesions with sharp margins associated with disruption of Bowman's layer, localized epithelial thickening, stromal thinning, and a decrease in pachymetry.

**Conclusion:** AS-OCT can be a valuable tool that provides a range of characteristic patterns of EKC and helps in monitoring it.

**Keywords:** Adenovirus, Anterior segment optical coherence tomography, Corticosteroids, Hyperreflective, Subepithelial infiltrates

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## INTRODUCTION

Epidemic keratoconjunctivitis (EKC) represents 65%–90% of viral keratoconjunctivitis.<sup>1</sup> It is the most contagious of all conjunctivitis cases, and it is caused by adenoviruses.<sup>2</sup> It is a widespread cause of urgent care visits and is responsible for significant economic damage.<sup>2</sup> It is characterized by punctate epithelial keratitis associated with preauricular lymphadenopathy in the acute phase.<sup>1</sup> The chronic phase is marked by the appearance of subepithelial infiltrates (SEIs) which are considered a pathognomonic sign of EKC. They are seen in up

to 50% of cases especially with serotype 8.<sup>2,3</sup> Large infiltrates can substantially impair visual acuity and be responsible for intense photophobia.<sup>3</sup> They can disappear spontaneously as they can persist from weeks to years, thus affecting the patient's quality of life.<sup>3</sup> The diagnosis of EKC remains mainly clinical. The laboratory rarely provides rapid help despite the advent of reliable new techniques.<sup>1,4</sup> There is currently no effective antiviral agent for EKC.<sup>2</sup> Several therapeutic alternatives have been proposed to reduce inflammation that persists during the chronic phase. The

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most widely used medications to date are topical corticosteroids and cyclosporine A eye drops.<sup>3,4</sup>

Anterior segment optical coherence tomography (AS-OCT) provides noninvasive and high-resolution *in vivo* cross-sectional images of numerous ocular surface conditions. It visualizes the different corneal layers on an almost histological scale using low-coherence interferometry.<sup>5</sup> Valuable qualitative and quantitative information provided by its images are useful in the diagnosis and management of infectious keratitis from various pathogens.<sup>6-8</sup> Many studies have shown its contribution in fungus, herpes simplex virus, cytomegalovirus, acanthamoeba, and bacteria.<sup>6-8</sup> Assessing their response to treatment has become easier using this technology. However, data on the findings of AS-OCT in EKC are lacking.

Our prospective study aimed to characterize and analyze corneal changes using AS-OCT in eyes with EKC.

## METHODS

The study adhered to the tenets of the Declaration of Helsinki and was approved by the ethics committee of the military hospital. The study included 38 eyes of 28 patients with presumed EKC complicated by central SEI. Informed consent was obtained from all participants. The diagnosis of the acute phase was based on clinical features: Follicular conjunctivitis, punctate keratitis, and preauricular adenopathy, whereas the chronic phase was defined by the SEI appearance. The exclusion criteria were previous anterior or posterior segment morbidity, chronic use of any other topical ocular medication in the last 3 months, contact lens wearers, and patients who could not attend the follow-up period. In the acute phase, patients were treated with preservative-free artificial tears. The patients who had SEI following EKC persisting for 14 days or more were treated with topical fluorometholone Flucon® (Novartis pharmaceuticals Australia) for 6 months. The regimen was the same for all the patients: 4 times a day for 1 month, then 3 times a day for 1 month, and two times a day for 4 months.

Best corrected visual acuity was assessed before and after the regimen. It was converted to a mean logMAR. Slit-lamp photography and serial AS-OCT were performed using the OCT (RTVue-100 applied corneal anterior module; Optovue, Fremont, CA, USA) from the onset of the symptoms up to 7 months of the disease course: On days 7, 14, 30, 90, 180, and 210.

During the observation using AS-OCT, we imaged horizontal and vertical corneal sections. We identified the corneal scars and measured the corneal epithelial and stromal thickness of this portion using the caliper tools that were built into the RTVue 100 system. Corneal pachymetry was measured in all cases.

## RESULTS

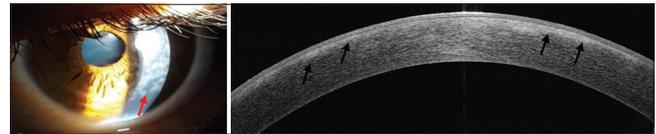
A total of 57 patients were referred to our clinics for EKC. Only 28 patients (38 eyes) were eligible for inclusion in the trial.

The mean age of patients with EKC and developing SEI was  $35.8 \pm 17.5$  (9–70) years. Fifteen cases (54%) were male, and 13 (46%) were female. Bilateral involvement was seen in 64% of the patients. The mean best corrected visual acuity at presentation was 0.28 logMAR.

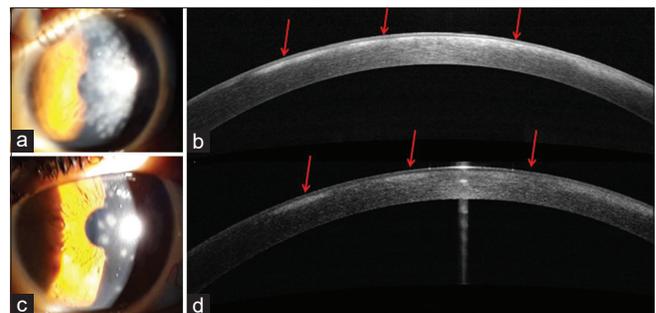
The slit-lamp examination showed diffuse punctate epithelial keratitis in all our patients on day 7. These epithelial punctate erosions became confluent and went deeper toward the anterior stroma on day 14 [Figure 1]. In the following visits over the rest of the regimen, SEIs with an intact epithelial layer were found in all cases [Figure 2]. There were no cells or flare in the anterior chamber. There was no correlation between visual acuity and SEI number. After completion of therapy, 81% of the patients reported a significant improvement in vision quality. Best corrected visual acuity improved significantly compared to baseline, to 0.038 ( $P < 0.0001$ ) and SEI resolved in 75% of the patients [Figure 3]. Only two patients had persistent SEI. No improvement was noticed after 3 months of treatment. A degenerative iron line was noticed on the slit-lamp examination [Figure 4].



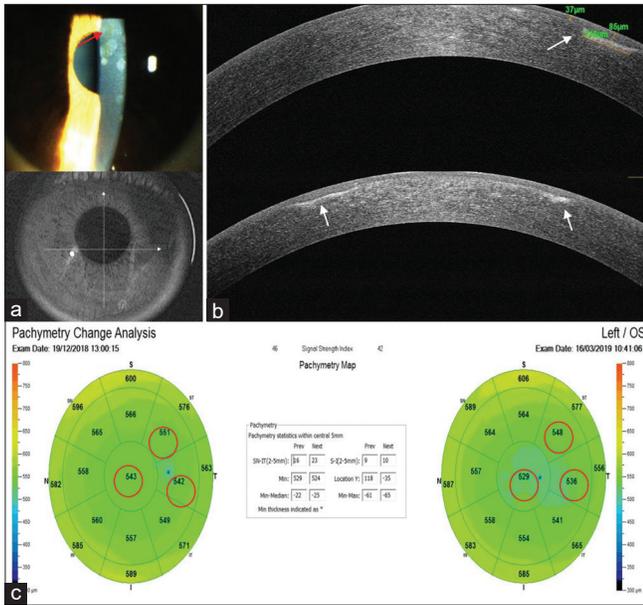
**Figure 1:** Slit-lamp and anterior segment optical coherence tomography of a 10-year-old patient on day 7 of epidemic keratoconjunctivitis showing several keratitic foci that stain brightly with fluorescein (red arrowhead) and hyperreflective dots limited to the epithelial layers of the cornea slightly rising above the epithelial surface (red circle), corresponding to these foci



**Figure 2:** Slit-lamp and anterior segment optical coherence tomography of a 30-year-old patient on day 14 of epidemic keratoconjunctivitis showing diffuse subepithelial infiltrates (red arrowhead) and hyperreflective epithelium and diffuse stromal bands along with the anterior stroma (black arrowhead)



**Figure 3:** Slit-lamp and anterior segment optical coherence tomography images of a 42-year-old patient between day 30 (a and b) and day 90 under topical steroids: We noted a decrease in the number, density, size, and confluence of the subepithelial infiltrates (red arrowhead) (c and d)

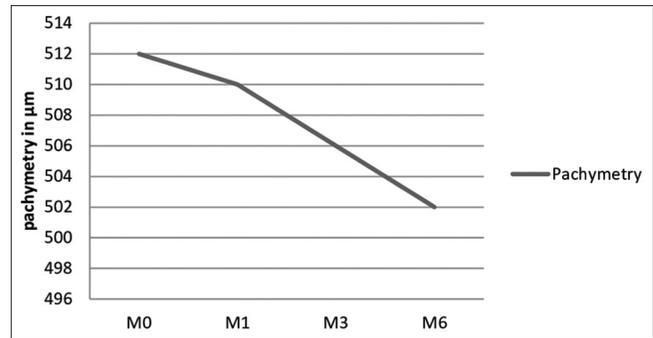


**Figure 4:** The aspect of the scarring phase in a 50-year-old patient after 3 months of treatment by fluorometholone: (a) Photograph of the anterior segment showing the iron degenerative line (red arrowhead); (b) Anterior segment optical coherence tomography showing epithelial thickening (85 μm compared to 37 μm in adjacent normal epithelium), Bowman’s layer disruption, and stromal thinning associated with the scar (white arrowhead). (c) Corneal pachymetry showing localized thinning of the cornea that extended in-depth and in surface (red circles)

One patient developed a recurrence of SEI 1 year after completion of treatment. He reported an acute blurring vision. He did not have the signs of the acute phase of EKC. Slit-lamp examination showed central and dense SEI with negative fluorescein test.

The AS-OCT on day 7 showed hyperreflective dots limited to the epithelial layers of the cornea and slightly arising above the epithelial surface, corresponding to the confluence of the punctuations of punctate epithelial keratitis [Figure 1]. On day 14, a hyperreflective line in the Bowman’s layer with intact epithelium was noted. On day 30, this hyperreflective band extended rapidly toward the anterior stroma, becoming more intense and thicker, corresponding to the SEI [Figure 2]. They gradually decreased in number, intensity, and extent following topical steroids in 71.4% of the cases [Figure 3].

In the two patients (4 eyes), who had persistent SEI after 6 months of treatment, AS-OCT showed that the hyperreflective areas became well-defined, plaque-like lesions with sharp margins associated with disruption of Bowman’s layer, localized epithelial thickening, stromal thinning, and a local decrease in pachymetry [Figure 4]. Areas of stromal thinning had overlying hypertrophic epithelium [Figure 4]. Epithelial thickness in these patients increased significantly by  $15 \pm 6 \mu\text{m}$  from baseline ( $P = 0.005$ ). This was consistent in the scarring phase. Central corneal thickness decreased significantly by  $8 \pm 16 \mu\text{m}$  from baseline ( $P = 0.005$ ) [Figure 5].



**Figure 5:** A curve showing central cornea pachymetry evolution during 6 months of treatment by topical steroids

In the patient, who developed a recurrence, AS-OCT showed bigger and more intense SEI, leading to a treatment switch by topical cyclosporine.

The different slit-lamp and AS-OCT findings are summarized in Table 1.

## DISCUSSION

To the best of our knowledge, the current study is the first observation of AS-OCT findings, describing the different phases of EKC and its response to topical steroids. In this study, AS-OCT allowed an objective assessment of the disease course through serial examinations. Although clinical examination by slit-lamp biomicroscopy is still the gold standard in visualizing SEI, it is nonetheless subjective. Furthermore, it has some limitations in evaluating the lesion dimensions and density, unlike AS-OCT. Pachymetry is also another interesting parameter provided by AS-OCT.<sup>9</sup>

The acute phase of EKC is clinically characterized by diffuse punctate epithelial keratitis, whereas the hallmark of its chronic phase is the appearance of SEI.<sup>3</sup>

Our study shows that focal epithelial keratitis appears approximately a week after the onset of the disease. The small epithelial punctate lesions tend to enlarge, become more confluent, and go deeper toward the anterior stroma, thus forming the focal epithelial keratitis.<sup>3</sup> These focal lesions appear as elevated hyperreflective dots within the corneal epithelium probably corresponding to clusters of dendritic cells, as described in confocal microscopic images.<sup>10</sup> This finding could also be seen in microsporidia keratoconjunctivitis.<sup>6</sup>

The appearance of SEI may be noticed beneath the focal epithelial lesions around the 2<sup>nd</sup> week, marking the transition to the chronic phase of the infection. Our study found that on day 14, hyperreflectivity was located in the anterior stroma. At this phase, dendritic cells migrate to the anterior stroma giving birth to inflammatory foci corresponding to the clinically observed SEI.<sup>10</sup> Pathogenesis most probably includes a persisting viral replication in stromal keratocytes triggering a prolonged immunological reaction. Immune complexes are deposited in the anterior third of the stroma.<sup>3</sup> This hypothesis is supported by

**Table 1: Different phases of epidemic keratoconjunctivitis and its corresponding aspects in slit-lamp examination and anterior segment optical coherence tomography**

	Slit-lamp examination	AS-OCT images
Acute phase (day 7)	Several keratitic foci that stain brightly with fluorescein	Hyperreflective dots limited to the epithelial layers of the cornea slightly raising above the epithelial surface
Chronic phase (after the 14 <sup>th</sup> day)	Diffuse SEI	Hyperreflective epithelium and diffuse stromal bands along with the anterior stroma
Scarring phase	Iron degenerative line	Epithelial thickening, Bowman's layer disruption, and stromal thinning associated with the scar

AST-OCT: Anterior segment optical coherence tomography, SEI: Subepithelial infiltrates

the clinical observation that SEIs usually resolve with topical steroid but recur when treatment has been discontinued.<sup>11</sup>

Infiltrates of infectious keratitis in their acute phase are often seen on AS-OCT as hyperreflective bands in the corneal stroma with increased corneal thickness. When the scar tissue develops, the affected cornea usually becomes thinner than the adjacent healthy tissue.<sup>12</sup> Epithelial hyperplasia is often associated with corneal surface irregularities caused by the infiltrates sequelae.<sup>9</sup>

Unlike other types of stromal keratitis, subepithelial opacities in EKC rarely leave a permanent scar. The SEI irreversible fibrosis manifests clinically as a degenerative iron line and on AS-OCT as plaque-like hyperreflective lesions associated with Bowman's layer disruption, localized stromal thinning and epithelial thickening, and decreased pachymetry.<sup>3,8,13</sup> The histological findings in this phase show the rarefaction of collagen fibers and defects in and along with the Bowman's layer.<sup>14</sup> It is also known that wound healing includes the migration and proliferation of keratocytes and their transdifferentiation into myofibroblasts.<sup>15</sup> These cells interconnect and form a network with other stromal cells, giving birth to hyperreflective stromal plaques on AS-OCT.

Despite their efficiency on SEI, steroids are known for accelerating SEI fibrosis, according to some authors.<sup>3,11,16</sup> Studies on a larger scale are necessary to determine the tomographic effects of steroids during EKC. The presence of fibrosis should indicate the end of steroid therapy because no treatment is effective at this stage.<sup>3</sup> This phenomenon was only documented with steroids. Other treatments such as cyclosporine and tacrolimus did not appear to induce this fibrosis.<sup>11</sup> Comparative studies are needed to prove this fact.

Our study has several limitations including presumptive diagnosis, a relatively limited number of participants, and the lack of a control group, precluding drawing conclusions about the effect of steroids on the disease process. A larger-scale controlled study is needed to better assess the pachymetry changes under steroids and to allow the understanding of the fibrosis phenomenon. AS-OCT cannot replace clinical examination because it only gives information about separate sectional images taken in specific meridians. Thus, the total opacities' number can only be calculated by the slit-lamp examination. However, AS-OCT provides more detailed corneal images, accurately assesses the corneal thickness,

and objectively monitors corneal changes under treatment, particularly in areas of corneal thinning and scarring.<sup>6,12</sup> It also gives a deeper insight into the pathophysiological processes, particularly in the case of EKC.

In summary, AS-OCT provides a range of characteristic patterns that could be helpful for the diagnosis and monitoring of SEI in EKC.

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Nil.

### **Conflicts of interest**

There are no conflicts of interest.

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