Acta Scientific Ophthalmology (ISSN: 2582-3191)

Volume 6 Issue 12 December 2023

Research Article

Understanding Adenoviral Conjunctivitis

Sameera Irfan*

Envision Squint and Oculoplastics Centre, Johar Town, Lahore, Pakistan

***Corresponding Author:** Sameera Irfan, Envision Squint and Oculoplastics Centre, Johar Town, Lahore, Pakistan.

Received: October 11, 2023

Published: November 27, 2023

Abstract

Acute adenoviral conjunctivitis is a common ocular surface infection that results in epidemics, globally, almost every year. Although it is self-limiting, it is highly infectious with potentially serious visual complications, thus posing considerable public health concerns. It is important to understand the disease process to make a prompt diagnosis, institute proper therapy that limits the infection and associated morbidities. Patients are injudiciously prescribed topical antibiotics and steroids that have no role in managing this condition. The education of healthcare providers and the patients on preventive strategies is necessary to limit the spread of infection.

Keywords: Human Adenovirus; Adenoviral Conjunctivitis; Immunotherapy; Povidone-Iodine; Viral Dissemination; Topical Steroids

Abbreviations

SEI: Sub-epithelial Infiltrates

Introduction

Wallace P. Rowe first discovered Adenovirus in 1953 [1] and up till now, 54 serotypes have been identified [2-4]. It accounts for up to 75% of all conjunctivitis cases that present in ophthalmic clinics [5]. Globally, it is responsible for recurrent epidemics of acute kerato-conjunctivitis every year in the fall and winter. Although mostly children and young adults are affected, no age group is exempt from contracting this infection. This is due to the easy transmission of viruses by direct contact with a patient during the incubation period and the first week of infection. It has become a huge economic burden on the society as it spreads to all family members and people working in a close environment (classrooms, factories, banks, etc.), contributing to the absenteeism of students and employees.

The spectrum of disease varies from mild to severe. In addition to being an economic burden on a family and the society, it can cause chronic ocular complications (corneal sub-epithelial infiltrates) as well as systemic infections like mild gastroenteritis, respiratory disease (pharyngoconjunctival fever), and dissemination in immunocompromised individuals [6]. Since there are many serotypes, a vaccine cannot be prepared due to rapid mutation in the viruses.

The aim of writing this article was to develop an understanding amongst ophthalmologists to diagnose and manage this condition properly. Patients have been wrongly prescribed topical antibiotics +/- steroids that promote viral shedding and disease spread. Simple measures elucidated in this article not only hasten the resolution of symptoms but minimize the complications that may arise from untreated or injudiciously treated adenoviral conjunctivitis. In addition, general public health advice given at the time of issuing a prescription helps reduce the disease's spread.

Viral transmission

The conjunctivitis is highly contagious, usually for 10-12 days from the onset and as long as the eyes are red. The tears, nasal secretions, and stools are loaded with shed viruses. The droplets from eyes, respiratory tract, and from a patient's hands can contaminate any surface they into contact with e.g. furniture, towels, bedding, or a slit-lamp, tonometer, ophthalmoscope in an ophthalmic clinic. The viruses survive for several weeks on fomites at room

temperature [7]. They are also transmitted through contaminated water in swimming pools and drinking water via the feco-oral route.

Prevention of the spread of infection:

According to the guidelines issued by the Centers for Disease Control and Prevention [8]:

- Patients should avoid touching their eyes, shaking hands, and sharing towels, napkins, pillowcases, and other fomites to avoid accidental inoculation of viral particles.
- Eyes and nose should be wiped with disposable tissue paper.
- Patients and children during the epidemic should restrict swimming, going shopping, or socializing.
- Healthcare workers must be educated on the importance of personal hygiene regarding hand-washing before and after patient contact.
- Furniture and equipment in the ophthalmic clinic must be disinfected with 60-80% Ethanol.
- Shared or reusable equipment that has come into contact with a patient's eyes or bodily fluids should be immersed in 3% hydrogen peroxide for a minimum of 10 minutes.
- Useful disinfectants: a bleach-based solution (2000-5000 ppm chlorine) or 10-25 tablespoons bleach per gallon of water is an effective disinfectant. Let the disinfectant dry. Common hand sanitizers are not effective in killing viruses.
- The equipment used for an emergency surgery can be sterilized by autoclaving or heating to 56*C for 30 min, and 60*C for 2 minutes.
- Patients coming to a clinic with red eyes should not be made to sit in the general waiting area but in a separate room. They must be seen and allowed to leave as early as possible.
- Tonometry and other procedures requiring contact with ocular surfaces should be postponed. If necessary, disposable tonometer-tips and single-dose eyedrops should be used in the eye clinic.

Life cycle of adenoviruses [9,10]:

To manage this condition properly, ophthalmologists must understand the life cycle of adenoviruses and the underlying pathogenic mechanism.

- Adenoviruses are DNA viruses made up of a single strand of DNA. They lack a cell wall which is essential for all living organisms to survive and a host's DNA to replicate. They need a host cell to flourish, therefore, they are obligatory intracellular parasites.
- As soon as a load of adenoviruses enters the conjunctival fornix of a host via contaminated fingers or air (as water droplets), the viruses adhere to the conjunctival surface epithelial cells. Next, they shed their DNA inside the host cell nucleus. The viral DNA, now protected by the cell wall of conjunctival epithelial cell, penetrates the nucleus and starts replicating inside it to form tiny strands of DNA called virions. Once they have depleted the energy stores of the host cell, the infected epithelial cell ruptures, and newly formed viruses (virions) are shed into the tears to invade the adjacent epithelial cells as well as spread to other hosts. This constitutes the incubation period of the disease.
- Once a large number of epithelial cells are infected and undergo lysis with the release of virions, this incites an acute Type1 Hypersensitivity reaction to the viral antigens (DNA). The conjunctival mast cells present in the conjunctival stroma are triggered to degranulate and release an abundant amount of histamine and cytokines. This causes ocular irritation, itchy eyes, and vasodilation of conjunctival vessels with outpouring of large amounts of fluid. This is the stage of Acute conjunctivitis. At this stage, the patient develops symptoms of itchy, watery, red eyes, and is highly infective due to viral shedding into the tears. The discharge remains watery which is characteristic of viral infection. The more a patient rubs the eyes, the more histamine is released and increases ocular redness and conjunctival swelling.
- At this stage, the Conjunctival associated lymphoid tissue (CALT) in the conjunctival stroma replicates to limit the infection. The viral antigens initiate the migration and proliferation of B (antibody-producing) and T (killer cells) lymphocytes into the area. This results in the formation of follicles on the tarsal conjunctiva and the lower fornix, characteristic of this condition. The ipsilateral pre-auricular lymph node draining that eye also enlarges due to lymphocytic proliferation and may be tender on palpation.
- Antimicrobial proteins, especially Defensin found in the tear film and expressed by the ocular surface epithelia are innate immune molecules that provide an effective chemical barrier to invading microbes (bacteria and viruses) [11].
- As the viruses replicate and flourish in the conjunctival epithelium, a vicious cycle sets in; rubbing of the eyes releases more histamine and proinflammatory cytokines (TNFα) which induce conjunctival vasodilation and capillary leakage, resulting in conjunctival hyperemia and edema [12]. Petechial hemorrhages may be noticed on the tarsal conjunctiva due to

Adenoviral-induced vasculitis, and even large subconjunctival hemorrhages may appear, with marked eyelid swelling. This is the stage of Florid conjunctivitis. Serum exudes from the engorged conjunctival vessels as yellowish, blood-stained fluid. Fibrin in serum coagulates over the dead conjunctival epithelial cells forming a pseudo-membrane over the tarsal conjunctiva. The replicating viruses hide under it and continue to multiply [13].

- Since the diseased conjunctival epithelium (goblet cells) cannot make the mucus, the protective blanket of the glycocalyx-mucus layer over the corneal surface epithelium is lost [14]. The surface epithelium desiccates and sheds in places. The denuded epithelium exposes sub-epithelial nerve endings and at this time, the patient starts experiencing pain in the eye, especially on blinking as it irritates the nerve endings. If the patient's eye is stained with fluorescein at this stage, tiny epithelial erosions will be visible.
- The flourishing adenoviruses are free to adhere to the space vacated by lost corneal epithelial cells and penetrate the corneal stroma [15]. The B lymphocytes are attracted to the corneal stroma and form antibodies against viral antigens. These antigen-antibody complexes initiate a Type IV hypersensitive reaction which is apparent as uniformly rounded, nummular, sub-epithelial corneal infiltrates (SEI in the corneal stroma beneath the Bowmann's membrane) with the clear cornea in between them during the 3-4th weeks of infection. They may be 2-20 in number. Histopathological examination has shown them to be composed of histiocytes, lymphocytes, and fibroblasts along with a disruption of the collagen fibers of the Bowman layer. Approximately 40%-50% of the patients develop SEI that causes ocular irritation, photophobia, glare, and decreased vision if the infiltrates obscure the optical axis. These infiltrates can persist for months to a year or two.
- Infection often spreads to lacrimal passages and nasolacrimal duct inflammation results in excessive symptomatic tearing in these patients [16].
- The infection usually resolves spontaneously within 1-3 weeks in most cases [17].

Diagnostic lab tests

The clinical symptoms and signs are specific and the diagnosis can be reliably made clinically. Lab tests are available but they are expensive and time consuming.

- Adenovirus PCR testing on a nasal or throat swab or a stool specimen.
- Commercially available adenovirus detection device, AdenoPlus (Rapid Pathogen Screening), can also be done. It is an immunoassay technique with 88% sensitivity and 91% specificity for adenoviral infection.

Management

Currently, there is no specific anti-adenoviral therapy to shorten the course of the infection. The patients developing the adenoviral conjunctivitis are generally healthy children or young adults with a strong immune system. The body's natural defense mechanism takes control of the invading viruses and the whole disease process is over within 7-14 days. But it limits the patient's comfort, daily activities, and almost half of these patients, especially those who had a florid infection, develop visual problems related to the SEIs. Therefore, during this period, the patient needs appropriate therapy with the aim to:

- Reduce the inflammation
- Reduce the natural course of the disease,
- Wash away the shed viruses,
- Minimize the complicationn (corneal seis).

Patient education

Patients should be reassured that it is a self-limiting condition, it may worsen initially for 48 hours and then start improving. They should be advised to rest at home, avoid heat and sunlight, take a good diet to boost their immunity, and avoid social contact (shaking hands, sharing towels with anyone).

Cold compresses

This is the mainstay of therapy. Applying ice packs frequently over the closed eyelids causes vasoconstriction. This reduces conjunctival congestion, eyelid swelling, and further migration of mast cells into the area. Therefore, patients must be advised to use ice-packs as frequently as possible.

Lubricant eyedrops

The inflamed conjunctiva cannot make healthy mucus and the quality of tear-film is also altered. Lack of mucus makes the corneal surface epithelium vulnerable to drying as the protective glycocalyx-mucin blanket is lost. Therefore, the tear-film cannot "wet" the cornea, making it prone to viral adherence and formation of sub-epithelial infiltrates. The longer-acting lubricant eyedrops (carboxymethylcellulose, hyaluronic acid, or polyethylene glycol) should be preferred. Patients that have superficial punctate epitheliopathy, preservative-free lubricants must be used. They

help restore the mucus layer over the cornea and wash away the shed viruses out of the eye, thereby reducing the viral load in the eye. The eyedrops must be kept refrigerated which increases their viscosity and residence time over the cornea. Cold eyedrops add to the vasoconstrictive effect of ice packs.

Lubricant eye ointment

This must be used during the night to keep the cornea lubricated and protected from viral attack. If the patient has developed a painful eye due to punctate corneal erosions, then ointment must be used frequently during the day as it has a longer residence time on the cornea than the eyedrops.

Cycloplegia

The pupil might be dilated with 1% cyclopentolate eyedrops in a painful eye due to punctate erosions. Cycloplegia helps minimize the ocular pain. Dark glasses can be worn outdoors to minimize the photophobia.

Peeling off the pseudo-membrane

In patients with a florid infection, a pale pseudo-membrane forms over the tarsal conjunctiva. It is mostly composed of fibrin and dead conjunctival epithelium beneath which the adenoviruses multiply as they are shielded by it. Peeling it is not painful and no topical aesthetic drops are required. It is gently held with a pair of forceps and it comes off easily. The denuded area needs frequent application of lubricant eye ointment and Tacrolimus ointment or cream, whichever is available. This helps the raw area heal without scarring.

The Role of Disease Modifying Agents, Tacrolimus and Cyclosporine

These are steroid-sparing, anti-inflammatory drugs. In acute conjunctivitis without corneal involvement, they are not required. But once the cornea has developed sub-epithelial infiltrates, or in a patient with pseudo-membrane formation (which predisposes to SEIs) than they become necessary.

Tacrolimus is a macrolide discovered in 1984 from streptomyces bacteria. Its anti-inflammatory effect is mediated by suppressing the activation as well as the proliferation of B and T lymphocytes and the formation of inflammatory mediators like cytokines and interleukin 2. Both Tacrolimus and cyclosporin have the same mechanism of action, Tacrolimus [18,19] is 10-100 times more potent than cyclosporin eye drops. It has the added advantage of causing less ocular stinging and burning as compared to cyclosporin. In the study by S. Irfan., *et al*. [20] the chronic sub-epithelial infiltrates started regressing after 2 weeks of application of Tacrolimus skin cream (Ecczemus 0.03%, Brooke Pharma) in the lower conjunctival fornix once daily. They disappeared after one month of therapy without the need for topical steroids. Both Tacrolimus skin cream and Cyclosporin eyedrops cause slight stinging or burning sensation after installation which is reported to be much less with tacrolimus than cyclosporin [20,21]. This is the only side effect and patients must be made aware of this and instructed to instill lubricant eyedrops 10 minutes after applying Tacrolimus which stops the stinging or burning sensation.

The sub-epithelial infiltrates are notorious for recurrence if this therapy is suddenly stopped. Therefore, Tacrolimus ointment/skin cream along with lubricants must be continued for at least 6 weeks to 2 months after all the infiltrates have cleared up and then stopped gradually. Topical cyclosporine was also reported to reduce the formation of subepithelial infiltrates in other studies [22]. It was also found to be effective in cases who were resistant to steroid tapering or discontinuation [23].

The Role of Povidone Iodine as an antiviral agent

Povidone-iodine is a broad-spectrum antiseptic agent. It is being used in ocular surgeries preoperatively as a prophylaxis against post-operative ocular infections. In a study comparing the effectiveness of multiple antiseptics, only povidone iodine with a concentration higher than 0.5% was shown to inactivate the adenoviruses within 1-minute of exposure, thereby reducing the viral load in adenoviral conjunctivitis [24]. In another study, povidone–iodine 0.1% or 0.5% solution used thrice daily was found to be most effective against adenovirus [25,26]; it maximized free iodine concentration and was found to be less toxic to the already inflamed conjunctiva.

Since it is irritant to the ocular surface, a minimal concentration should be used, twice daily for 2-3 days.

Why topical antibiotics and steroids must be avoided in acute conjunctivitis

Topical antibiotics have no anti-viral activity. They cause toxicity to the already inflamed conjunctiva, alter the tear-film, and promote corneal toxicity. As a result, the corneal micro-erosions promote viral adherence, shedding, and the formation of sub-epithelial infiltrates.

Why the topical steroids must be avoided

Topical corticosteroides are routinely prescribed by general ophthalmologists in acute adenoviral conjunctivitis to reduce inflammation and provide a quick symptomatic relief. This practice has shown to promote viral replication.

It has been highlighted in many studies that patients treated with topical steroids in the stage of acute conjunctivitis show increased viral replication and prolonged viral shedding [27]. Immunosuppressive steroid therapy interferes with the body's innate immune mechanisms and suppress the production of antiviral cytokines that play a major role in inhibiting viral replication [28]. Therefore, they promote the formation of SEIs.

In immunocompromised children (with no prior exposure and immunity to a particular strain of adenovirus) topical steroids induces further immunosuppression; the adenoviruses result in a subclinical infection of tonsillar and adenoid lymphoid tissue and serve as a continuous source of transmitting adenoviruses [29].

Patients with previous adenoviral gastroenteritis continue to pass adenovirus in the stool particularly if their innate immunity has been compromised by using topical steroid therapy.

Topical steroids are potent anti-inflammatory agents but such a therapy is needed for months in a patient with sub-epithelial infiltrates. Their chronic use raises the IOP and may cause secondary glaucoma.

The corneal infiltrates almost always recur after discontinuation of topical steroids.

Conclusion

- Acute adenoviral conjunctivitis is a distressing disease that limits the patient's comfort and daily activities for almost two weeks.
- Almost half of these patients develop sub epithelial infiltrates that results in decreased vision for months.
- The general trend of prescribing steroid and antibiotic eyedrops, alone or in combination needs to be changed.
- The acute stage can easily be managed by lubricants and icepacks.
- In florid infection, diluted povidone-iodine drops for 2-3 days promote the control of infection and prevent the spread of adenovirus in the community.
- SEIs can be avoided by not using steroi-antibiotic eyedrops in the acute stage. They can easily be cleared up by using Tacrolimus skin cream/ointment 0.03% or Cyclosporin eyedrops 0.5%.

Bibliography

1. Rowe WP., *et al*. "Isolation of a cytopathogenic agent from human adenoviroids undergoing spontaneous degeneration in tissue culture". *Proceedings of the Society for Experimental Biology and Medicine* 84.3 (1953): 570-573.

2. Ishiko H., *et al*. "Novel human adenovirus causing nosocomial epidemic keratoconjunctivitis". *Journal of Clinical Microbiology* 46.6 (2008): 2002-2008.

3. Jones MS., *et al*. "New adenovirus species found in a patient presenting with gastroenteritis". *Journal of Virology* 81.11 (2007): 5978-5984.

4. Ishiko H., *et al*. "Novel human adenovirus causing nosocomial epidemic keratoconjunctivitis". *Journal of Clinical Microbiology* 46.6 (2008): 2002-2008.

5. Chintakuntlawar AV and Chodosh J. "Cellular and tissue architecture of conjunctival membranes in epidemic keratoconjunctivitis". *Ocular Immunology and Inflammation* 18.5 (2010): 341-345.

6. Chigbu DI and Labib BA. "Pathogenesis and management of adenoviral keratoconjunctivitis". *Infection and Drug Resistance* 11 (2018): 981-993.

7. Muller MP., *et al*. "Adenovirus-related epidemic keratoconjunctivitis outbreak at a hospital-affiliated ophthalmology clinic". *American Journal of Infection Control* 46.5 (2018): 581-583.

8. Centers for Disease Control and Prevention Guide to infection prevention for outpatient settings: minimum expectations for safe care (2016).

9. Radke JR and Cook JL. "Human adenovirus infections: update and consideration of mechanisms of viral persistence". *Current Opinion in Infectious Diseases* 31.3 (2018): 251-256.

10. Zhang L., *et al*. "Virology and epidemiology analyses of global adenovirus-associated conjunctivitis outbreaks, 1953-2013". *Epidemiology Infection* 144.8 (2016): 1661-1672.

11. Murphy KP and Weaver C. "Janeway's Immunobiology". 9th ed. New York: Garland Science". *Basic Concepts in Immunology* (2017): 1-36.

12. Flint SJ., *et al*. "Principles of Virology". 3rd ed. Vol. 2. Washington, DC: ASM Press. Immune defenses; (2009): 86-132.

13. Chigbu DI and Labib BA. "Pathogenesis and management of adenoviral keratoconjunctivitis". *Infection and Drug Resistance* 11 (2018): 981-993.

14. Yawata N., *et al*. "Dynamic change in natural killer cell type in the human ocular mucosa in situ as means of immune evasion by adenovirus infection". *Mucosal Immunology* 9.1 (2016): 159-170.

15. Kurna SA., *et al*. "Evaluation of the impact of persistent subepithelial corneal infiltrations on the visual performance and corneal optical quality after epidemic keratoconjunctivitis". *Acta Ophthalmology* 93.4 (2015): 377-382.

16. Horton JC and Miller S. "Magnetic resonance imaging in epidemic adenoviral keratoconjunctivitis". *JAMA Ophthalmology* 133.8 (2015): 960-961.

17. Jhanji V., *et al*. "Adenoviral keratoconjunctivitis". *Survey on Ophthalmology* 60.5 (2015): 435-443.

18. Gouider D., *et al*. "Corticosteroids Versus Cyclosporine for Subepithelial Infiltrates Secondary to Epidemic Keratoconjunctivitis: A Prospective Randomized Double-Blind Study". *Cornea* 40.6 (2021): 726-732.

19. Irfan S., *et al*. "To assess the efficacy and safety of Tacrolimus skin cream 0.03% in VKC". *PJO* 31 (2015): 15-21.

20. "Is Post-Adenoviral Keratitis Avoidable/Preventable". *Ophthalmology Update* 14.1 (2016): 42-47.

21. Levinger E., *et al*. "Topical 0.03% tacrolimus for subepithelial infiltrates secondary to adenoviral keratoconjunctivitis". *Graefe's Archive for Clinical and Experimental Ophthalmology* 252.5 (2014): 811-816.

22. Asena L., *et al*. "Comparison of clinical outcome with different treatment regimens in acute adenoviral keratoconjunctivitis". *Eye (Lond)* 31.5 (2017): 781-787.

23. Muftuoglu IK., *et al*. "Effect of 0.05% topical cyclosporine for the treatment of symptomatic subepithelial infiltrates due to adenoviral keratoconjunctivitis". *International Journal of Ophthalmology* 9.4 (2015): 634-635.

24. Monnerat N., *et al*. "Povidone-iodine for treatment of adenoviral conjunctivitis: an in vitro study". *Klin Monbl Augenheilkd* 223.5 (2006): 349-352.

25. Rana Altan-Yaycioglu., *et al*. "Effect of diluted povidone iodine in adenoviral keratoconjunctivitis on the rate of subepithelial corneal infiltrates". *International Journal of Ophthalmology* 12.9 (2019): 1420-1425.

26. Yazar H., *et al*. "The effects of povidone iodine (pH 4.2) on patients with adenoviral conjunctivitis". *Journal of Pakistan Medical Association* 66.8 (2016): 968-970.

27. Kaufman HE. "Adenovirus advances: new diagnostic and therapeutic options". *Current Opinion on Ophthalmology* 22.4 (2011): 290-293.

28. Radke JR and Cook JL. "Human adenovirus infections: update and consideration of mechanisms of viral persistence". *Current Opinion in Infectious Diseases* 31.3 (2018): 251-256.

29. Kosulin K., *et al*. "Persistence and reactivation of human adenoviruses in the gastrointestinal tract". *Clinical Microbiology and Infection* 22.4 (2016): 381 e381-381 e388.