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Case Report

Case Report - Management of Adenoviral Conjunctivitis with Ganciclovir Gel

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Abstract

Viral conjunctivitis is a clinically common, highly contagious, self-limiting condition commonly of adenoviral etiology. The infection is most contagious from onset to 10-12 days and usually resolves spontaneously within 2-4 weeks. Transmission most often occurs via inoculation of viral particles from the patient's hands, by direct contact with infected surfaces or infected upper respiratory droplets. Treatments vary from lubricating eye drops and isolation to newer medications but still the primary aim being palliative while controlling contagion.

This case describes the presentation, diagnosis and management of a 38-year-old male with adenoviral conjunctivitis and explores the use of biomarker screening diagnostic technology and management with antiviral treatment.

Keywords: *Adenovirus; Biomarkers; Ganciclovir*

Introduction

Viral conjunctivitis is a commonly encountered ocular disease entity often managed in optometry offices. Because of high contagion and viral replication rate, this type of viral infection frequently occurs in epidemics within communities, business offices, families or schools [1].

As a disease category viral conjunctivitis has no gender predilection occurring equally in men and women and equally showing no predilection in age groups. Some viral strains have a shown age infectious predilection patterns with adenoviral etiology usually affects patients in the 20 to 40 age group [1].

Most common patient signs include the presence or absence of a palpable pre-auricular node, presence or absence of infiltrates, and varying degree of bulbar hyperemia. Similarly, most common patient symptoms include ocular generalized ocular discomfort, foreign body sensation, lid swelling, redness and lacrimation [2].

Various viral entities have been noted to be infections to eye tissue and these include Herpes Simplex Virus (HSV) and primary Varicella Zoster Virus (VZV) most often affecting infants and young children. Primary Ocular Herpes Simplex (OHS) infection is common in children with the infections usually caused by HSV type I and commonly associated with follicular conjunctivitis. HSV type II is typically associated with neonates and vaginal delivery [3].

In adults, recurrent infections can be diagnosed and commonly associated with corneal involvement. Infection from Varicella Zoster Virus (VZV) can be caused by direct contact with VZV, zoster skin lesions or as often is the transmission of viruses by inhalation of infec-

tious respiratory secretions. VZV can affect the conjunctiva during primary infection (chickenpox) or secondary infection (zoster). Herpes Zoster Ophthalmicus (HZO) results from reactivation of latent VZV infection and may present in any age group [3].

Case

On January 14, 2014 a 48-year-old adult male patient presented to our clinic with 5-day history of watery, irritated eyes, he noted that the right eye was tearing, not reporting any blurry vision, and starting to get red throughout prior to presentation. The eye gradually became increasingly red and irritated over the ensuing 2 days and the patient noted increased crusting in the mornings. There was a mild "scratchy" sensation noted then. Symptoms did not remit with antibiotic drops prescribed by his PCP 2 days ago and the eye continued to worsen, with early redness and watery sensation in the contralateral eye as well. Six weeks prior to any ocular symptoms, patient reported having upper respiratory discomfort perhaps an infection that lasted about 7 days and had subsided spontaneously.

PMH/FHx/POH: No previous ocular or health problems. No eye surgery, trauma, nor contact lens use. Patient reports using ciprofloxacin ophthalmic drops prescribed by his internal medicine doctor 2 days ago and suing hem compliantly i gtt OU qid.

SMH/ROS: Review of systems was positive for seasonal allergies and otherwise negative. Patient is alert 3x, not taking any systemic medications and reporting not allergic to any medication. Pt is a non-smoker, no alcohol consumption, patient is an avid marathon runner.

EXAM: Uncorrected visual acuity was 20/20 at distance and 20/20 at near OD, and 20/20 at distance, 20/20 at near OS. Best-corrected visual acuity was 20/15-2 OD and 20/15-2 OS, with a manifest refraction of -0.25 -0.50 x 90 OD and -0.25 -0.25 x 090 OS. Pinhole acuity at distance was 20/20 OD, OS.

Color vision testing with pseudo-isochromatic plates (4/4) was normal OD, OS. Pupils were equally round and reactive to light OU; no afferent pupil defect was noted OD or OS. Confrontation fields showed full fields OU. Extra-ocular muscles were unrestricted in all gazes, and cover test demonstrated orthophoria at distance. Intraocular pressure: 16 mm Hg OD and 17 mm Hg OS with Keeler Pulsair tonometer at 2:34 PM.

Anterior segment evaluation by slit lamp examination reveals mild evidence of crusting on lashes and watery discharge, OU. The bulbar conjunctiva is injected OD > OS. A follicular reaction is evident on the palpebral conjunctiva, especially inferiorly, in both eyes. There was grade 2 chemosis and palpebral edema, (Figure 1) and mild inferior conjunctival follicles again R > L. Palpable pre-auricular lymphadenopathy (LAD), R > L. Intact and clear corneas OU; brown irises OU; anterior chamber without cells or flare. The estimate of the anterior chamber angles was 4/4 by VanHerick. Nicox Adenoplus RPS testing done (Figure 2) and showed positive results. Informed consent was obtained for publishable picture and external picture taken with an iPhone 4S.

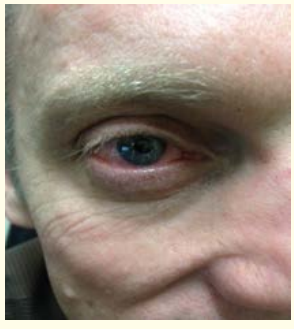

Figure 1: *Grade 2 chemosis and palpebral oedema.*

Figure 2: *Nicox Adenoplus RPS testing.*

The patient was dilated using one drop Tetracaine, one drop 1% Mydriacyl and one drop 2.5% Phenylephrine OU. Once the patient was fully dilated, an evaluation of the posterior segment with slit lamp showed clear lenses OU. Fundus assessment with a 90D lens revealed normal optic nerves with a cup-to-disc ratio of 0.4/0.4 OD & OS. The neuroretinal rims were healthy and intact. There was no evidence of drusen in the optic nerve or defects in the nerve tissue of the optic disc. Retinal vessels appeared normal with an arterial-venous ratio of 2/3 noted OU. Both eyes presented normal macular findings. No retinal pigment epithelial detachment was noted. The peripheral retina was flat and intact with no pathology noted with no holes or tears in the retina.

Working Diagnosis

Adenoviral Conjunctivitis diagnosed by 1. failure of antibiotic therapy and 2. positive disease specific RPS biomarker testing (ruled out bacterial resistance to antibiotic treatment).

Physical Findings

Typical signs of adenoviral conjunctivitis include preauricular adenopathy, epiphora, hyperemia, chemosis, subconjunctival hemorrhage, follicular conjunctival reaction, and occasionally a pseudomembranous or cicatricial conjunctiva reaction. In the more severe infections and with corneal involvement, the cornea can often demonstrate punctate epitheliopathy. The eyelids typically are edematous and ecchymotic. In severe cases, there can be a corneal epithelial defect affecting vision. The initial infection is commonly monocular with progresses to the fellow eye over a few days.

Differential diagnosis of viral conjunctivitis	Differential Diagnoses of other red eye
• Pharyngo-conjunctival fever • Non-granulomatous anterior uveitis • HSV kerato-conjunctivitis • VZV kerato-conjunctivitis • Ocular chlamydial infections • Vernal kerato-conjunctivitis • Foreign body • Epithelial keratitis	• Conjunctivitis, Acute Hemorrhagic • Conjunctivitis, Allergic • Conjunctivitis, Bacterial • Conjunctivitis, Giant Papillary • Conjunctivitis, Neonatal • Contact Lens Complications • Keratoconjunctivitis, Epidemic • Keratoconjunctivitis, Sicca • Superior Limbic Keratoconjunctivitis • Blepharo-conjunctivitis

Table 1: *List of viral and no viral differential diagnosis that could be considered in the case.*

Table 1 shows a list of viral and no viral differential diagnosis that could be considered in this case. Unlike the homogeneous manifestations of the various types of bacterial conjunctivitis, or the more heterogeneous anterior inflammations and contact lens wear related inflammations, viral conjunctivitis shows a more heterogeneous pattern from one disease entity and process to another. It is then that clinical history should focus on eliciting subjective information that will aid in differentiating the various etiologic agents. Direct patient observation that will help differentiate in etiology and office based technology that aids in making accurate clinical decisions are also helpful in aiding the clinician towards a correct diagnosis.

Many authors have noted that it is important to inquire about timing, onset, and duration of both systemic including both respiratory and gastrointestinal in accompanying ocular symptoms; severity and frequency of symptoms; other appropriate risk factors; and personal as well as environmental exposures [4].

Patients with adenoviral conjunctivitis may give a history of recent symptoms of an upper respiratory tract infection or recent exposure to an individual with red eye at home, school, or workplace [5].

Patients may report mild ocular itching, foreign body sensation, tearing, redness, discharge, eyelids sticking often worse in the morning and photophobia when there is corneal involvement. The initial eye infection is often unilateral but can be bilateral. More severe systemic manifestations are rare, except in cases of pharyngo-conjunctival fever [3,5].

Treatment: Topical Ganciclovir gel (Zirgan; Bausch+Lomb) 5x a day for 7 days

Patient Management: With our diagnosis we suggested physical isolation to reduce contagion until remission of infection, hand washing every hour on the hour and no working until the redness had resolved. We instructed the patient to return to office for clinical evaluation in 7 days.

Patient Follow up

Patient returned to office on January 24, 2014 (10 days after initial visit). Uncorrected visual acuity was 20/20 at distance and 20/20 at near OD, and 20/20 at distance, 20/20 at near OS.

Anterior segment evaluation by slit lamp examination reveals no evidence of crusting on lashes or watery discharge, OU. The bulbar conjunctiva was clear and quiet OU with no evident follicular reaction OU. There was no chemosis and palpebral edema has resolved, clear corneas OU; brown irises OU; anterior chamber without cells or flare. Nicox Adenoplus RPS testing was done and showed negative results. At this time the patient was instructed to come back for yearly vision health maintenance and ocular disease screening evaluation. Instructions where given to return sooner in the event of other vision or eye related problems or concerns.

Discussion

Once confirmed, the most common etiology of viral conjunctivitis is adenoviral with particular subtypes being the more common offenders. Because of the highly contagious nature of viral conjunctivitis patients should be advised to avoid touching their eyes, shaking hands, and much public exposure. Transmission often occurs through accidental spreading of viral particles and inoculation from the patient's hands to contaminated surfaces.

VZV is characterized by a generalized vesicular eruption, fever, and constitutional symptoms. Ocular infection usually is unilateral and presents as small, popular lesions that erupt along the lid margin or at the limbus and may be accompanied by a mild follicular conjunctivitis.

Acute hemorrhagic conjunctivitis is often clinically similar to adenoviral conjunctivitis in clinical onset but it is more severe and hemorrhagic in clinical manifestation with similar infections being highly contagious. Acute hemorrhagic conjunctivitis starts unilaterally but rapidly involves the fellow eye within 1 or 2 days. Signs on examination include a swollen, edematous eyelid and pronounced hemorrhage beneath the bulbar conjunctiva. Hemorrhagic conjunctivitis has been reported in epidemics in association with 2 major picornaviruses: enterovirus 70 and Coxsackievirus A24. It mostly affects children and young adults in conditions of lower hygiene. Patient's typical symptomatology includes profuse subconjuctival hemorrhage, epiphora, foreign body sensation, burning, and photophobia most often within 24 hours of exposure [6].

A more chronic entity of viral etiology is Molluscum contagiosum. Molluscum contagiosum produces a chronic follicular conjunctivitis in association with an elevated, hyperemic eyelid lesion. The lesion usually is a small, elevated, pearly, umbilicated nodule near the lid margin. Multiple lesion is often present, in immune-compromised patients and HIV positive [6].

Other viruses are less frequent causes of conjunctivitis. In these cases, conjunctivitis usually occurs in association with a systemic illness and includes infections caused by influenza virus, Epstein-Barr virus, paramyxovirus (measles, mumps, Newcastle), rubella, or HIV [6].

Herpes Zoster Ophthalmicus represents reactivation of latent VZV infection based in the trigeminal ganglion. It is characterized by a systemic prodromal including fever, malaise, nausea, vomiting, and severe tenderness and pain of skin lesions along the ophthalmic division of the trigeminal nerve. In Herpes Zoster Ophthalmicus, look for skin involvement with the appearance of a dermatome pattern of vesicles. These vesicles may become necrotic, resulting in pitted scarring of the skin. Conjunctival involvement includes hyperemia, follicular or papillary conjunctivitis, and a serious or mucopurulent discharge. Preauricular adenopathy is common. Very early in the process, there may be multiple fine, dendritic corneal lesions, which disappear over a few days without treatment [6].

With HSV infection, vesicles may be present on the eyelid or face, the eyelids may be swollen, and an ulcerative blepharitis may be present. Conjunctival involvement includes hyperemia, follicular or papillary conjunctivitis, and a serous discharge. Corneal involvement in HSV manifests as a dendritic keratitis with typical features of linear branching and dendritic figures and corneal hypo aesthesia. Small, papular lesions that erupt along the lid margin or at the limbus are present with varicella conjunctivitis. These lesions may resolve without sequelae, or they may become pustular and form painful, reactive conjunctival ulcers [3-6].

Because of the elimination of smallpox, Vaccine virus has become an extremely rare cause of conjunctivitis, as in most cases of viral entity, the infection occurs through accidental inoculation of viral particles from the patient's hands.

Although less common nowadays, anterior segment findings have been reported in patients with Acquired Immunodeficiency Syndrome (AIDS) with HIV as the etiologic agent [7].

When conjunctivitis occurs in a patient with AIDS, it tends to follow a more prolonged course than in patients without AIDS. Commonly patients with AIDS develop a transient, nonspecific conjunctivitis with the classic viral characteristics of irritation, hyperemia, tearing, symptoms included foreign body sensation, blurred vision, and photophobia. As with most cases, the infection often resolves without antimicrobial therapy [6,7].

In most clinical settings, a diagnosis of viral conjunctivitis is made on the clinical presenting features alone. In our case we had more prominent signs including mild inferior palpebral conjunctival follicles, a tender and palpable preauricular lymph node, watery discharge, red and edematous eyelids and the failure of anti-bacterial agents to act on both signs and symptoms. In our case there were no sub-conjunctival hemorrhages, punctuate keratopathy or membrane/pseudo membrane observed and no intra-epithelial micro cysts, an often observed corneal involvement sign was present [8].

As noted in the follow up visit, our patient did not develop any sub-epithelial corneal infiltrates. Often sub-epithelial corneal infiltrates are part of the sequalea at 1-2 weeks after the onset of the conjunctivitis. This gives rise to more photophobic symptoms and often a concomitant mild reduction in visual acuity. HSV differential can be noted as it often starts with a small corneal involvement and may appear as the better known corneal dendrite [8].

Conventional laboratory test can be useful in determining if the infection is of viral origin but testing and identification can be time consuming. Serum tests are available but require multiple collections which can delay treatment [9].

The clinician should consider cultures, smears and stains should be given in non-improving cases when the inflammation is severe, chronic or recurrent infections, when other atypical conjunctival observations are noted, and with failure to respond to treatment. Conjunctival scrapings and Giemsa staining can be done in office and may aid in characterizing the infectious etiology of the inflammatory response. Under examination, polymorphonuclear (PMN) cells are prevalent in bacterial infections, whereas mononuclear cells and lymphocytes are seen with viruses [9,10].

Viral isolation tests can be helpful in the diagnosis of non-resolving cases, but they are not typically done and often not indicated in chronic conjunctivitis [10].

In this case the Rapid Pathogen Screening test called AdenoPlus was used for in office rapid and accurate differential diagnosis of external red eyes and eye infections. In studies of patients with acute viral conjunctivitis (n = 128), the AdenoPlus test demonstrated 90% sensitivity and 96% specificity as compared with polymerase chain reaction testing and immune-fluorescence assay [11].

The RPS test is based on identifying adenoviral serum biomarkers by using a swab of the lower conjunctival fornix. By using lateral flow assay technology and direct sampling and taking only a few minutes to perform the AdenoPlus biomarker test and is able to detect all known primary serotypes of adenoviral conjunctivitis [12].

The use of the test protocol was essential in identifying a causative organism. In the event the test was negative to adenoviral etiology, another pathological organism would have to be considered.

Classical treatment of adenoviral conjunctivitis is directed at decreasing contagion with isolation and hand washing instructed and supportive with lubricating eye drops and cold compresses as palliative treatment and improved symptomatology.

Some evidence exists suggesting the use of topical anti-virals as a possible treatment. Topical vasoconstrictors and antihistamines have been the preferred and still suggested first line therapy for severe itching yet these medications are minimally helpful and may cause local toxicity and hypersensitivity and might note really reduce contagion time [13,14].

For patients who may be susceptible or immunocompromised, a topical antibiotic may be used to prevent bacterial super infection but once again the risk of surface toxicity and hypersensitivity must be evaluated and monitored.

Topical steroids may be used and are often of great help in the management of pseudo membranes or when sub epithelial infiltrates impair vision. Argument exists as some recent studies have shown that steroids may actually increase the number of days of adenoviral shedding increasing infection and contagion time [14].

It is worth noting that sub epithelial infiltrates may recur even after discontinuing the topical steroids and proper discontinuation dosage management has proven to decrease the recurrence. Also worth noting is that the clinicians must execute extreme caution when using corticosteroids if there is any suspicion of an underlying HSV infection [14].

A more recent animal model study showed that topical steroid when used with dilute povidone-iodine may speed healing and reduce virus load on the ocular surface as it inactivates the extracellular virus load [15].

Povidone-Iodine is an antiseptic known to kill extracellular viruses including those in the tear film and on the ocular surface. It has also been reported as a potential treatment of adenovirus.

In an *in-vitro* study with serotypes adenovirus serotypes 8 and A549, a 1;10 ratio of povidone-iodine was shown to be highly effective against free adenovirus making povidone-iodine 0.8% but failing to be a potential option in managing cases of adenoviral infections as it only reduces viral load.

Similarly, other studies have argued against the use of Povidone-Iodine as an effective treatment for adenoviral infections. Monnerat and coworkers showed that povidone-iodine is ineffective against replicating adenoviruses within conjunctival cells. Isenberg found that 1.25% Povidone-Iodine was infective against viral conjunctivitis but effective against bacterial and chlamydial organisms [14,16,17].

Similar controversies surround anti-virals medications when used against adenoviruses. Studies show that they are either ineffective or too toxic. Acyclovir, valacyclovir, and trifluridine have shown no efficacy against adenoviruses. Cidofovir demonstrated activity against adenoviruses, but controversy surrounds ophthalmic use as it is a safety concern in the etiology of punctal stenosis thus eliminating this agent as a viable treatment option [10].

There are *in-vitro* and animal model studies that suggest Ganciclovir as an effective treatment option against some adenovirus serotypes with demonstrated efficacy against adenoviruses.

Tabbara showed that topical ganciclovir gel shortened the duration of adenovirus kerato-conjunctivitis symptoms by 60% (7.7 days from 18.5 days) while reducing the incidence of sub-epithelial infltrates [18]. Various other authors have shown similar results in reducing duration of symptoms and have advocated for the use of topical ganciclovir in the management of adenoviral infections [19,20].

Patients with conjunctivitis, especially those treated with medications, require follow-up care. Depending on the therapy indicated, patients should be instructed to return at the conclusion of the therapeutic regime, by the time the infection has resolved or sooner if the condition worsens. Our patient was instructed to return in a 10-day period as the course of the disease should have been shorted with the prescribed therapy.

Once an outbreak has been determined, prevention of transmission, especially in health care facilities, is of extremely important. Prevention management strategies must include careful hand washing before and in between every patient, proper cleaning and disinfection of equipment and instruments, and frequent disposing of multiuse topical ophthalmic diagnostic or therapeutic drops for office use. Maintaining an infection control plan within the office and the exam rooms, as well as educating the staff and the patient, is important.

All these strategies have the aim to prevent transmission from patient to patient and patient to doctor. Viral conjunctivitis is an occupational hazard of eye care physicians. Patients should be instructed to take contagion and isolation precautions for at least 2 weeks or as long as their eyes are red and weeping.

In office red eye management protocols should include, proper disinfection of the examination room after seeing any patient with a red eye, not shaking hands with patients with red eye, using cotton applicators to examine lids and lashes, washing the hands immediately after examining the patient.

Conclusion

Adenoviral conjunctivitis is a very common and often misdiagnosed eye infection. Although adenoviral eye infections are frequently a self-limiting clinical entity, the cost of care, public health implications and socioeconomic costs for the affected individual and exposed population is high. Accurate and timely diagnosis by optometrists' will prevent contagion and minimize the impact in the quality of life of the patient and limit viral exposure.

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