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Clinical Findings and Management of Epidemic Keratoconjunctivitis

Ting Zhang
4985 Moorhead Ave, Unit 3178, Boulder, CO 80305
720-722-3377

Abstract: Epidemic keratoconjunctivitis (EKC) is a severe, yet self-limiting conjunctival infection and inflammation associated with adenovirus types 8, 19, and 37. This case report follows the clinical course of a pediatric patient with EKC, outlines the importance of history and clinical observations in making the right diagnosis, and discusses treatment and management options for the disease.

Keywords: Acute Viral Conjunctivitis, Adenoviral Conjunctivitis, Epidemic Keratoconjunctivitis, Betadine, povidone-iodine, corticosteroids, off-label treatment

Introduction

Adenovirus is a common cause of clinically diagnosed infectious conjunctivitis.[1] There are over 45 adenoviral serotypes pathogenic to humans.[2] These adenoviral conjunctivitides commonly present as non-specific acute follicular conjunctivitis, pharyngoconjunctival fever (PCF), and in the most severe case, epidemic keratoconjunctivitis (EKC).[3] Patients often complain of burning, scratchy, and watery eyes that start in one eye and subsequently transfer to the other after one to two days. These symptoms are typical but nonspecific to a viral infection; thus, a careful patient history and observation of signs is critical in guiding the clinician to the appropriate diagnosis and treatment plan. Traditionally, treatments for viral conjunctivitis have been largely palliative, including preservative-free artificial tears and cool compresses, because the disease is self-limiting[4] and because an approved and effective anti-adenoviral treatment does not currently exist.[5] Despite this limitation, many eyecare professionals now advocate an off-label treatment with Betadine ophthalmic solution to speed recovery and reduce infectious period for symptomatic patients. [5,6,7,8]

Case Report

A 10-year-old African American female presented to clinic with complaints of red, painful eyes OU that had worsened over the past five days. Her parents were concerned that her tears had begun to show sign of blood. Her father reported the patient had developed a slightly pink and watery right eye on Saturday, December 31, 2016. By Monday, January 2, 2017, the left eye had become pink and watery like the right eye. The father took the patient to an urgent care clinic on Monday, and was prescribed erythromycin ointment to be administered four times daily over seven days in each eye. Symptoms worsened despite compliant treatment. On the morning of January 5, 2017, the patient returned to urgent care clinic, and was switched to Polytrim ophthalmic solution to be instilled every three hours in both eyes for another seven to ten days. Later that afternoon, when the patient noticed blood in her tears, her father brought her to the eye clinic for a second opinion.

At the eye clinic, the patient reported a pain level of 7 out of 10, with worse symptoms in right eye than left. The patient complained of teary, burning, itchy eyes with mucoid discharge and matted lashes in the mornings. She denied recent cold, fever, cough, runny nose and congestion. She also denied photophobia. She did not report any family medical or family ocular history. She confirmed a recent exposure to pink eye from other kids at school.

Her uncorrected vision was 20/20 OD and 20/20-1 OS. Intraocular pressures measured 18mmHg OD and OS at 13:47 with a non-contact tonometer. Extraocular motilities and pupils were normal in both eyes without evidence of any afferent pupillary defect. Slit-lamp exam revealed a 2mm patch of subconjunctival hemorrhage on the temporal, juxta-limbal bulbar conjunctiva in the right eye. In both eyes, 2+ follicles and papillae in the superior and inferior palpebral conjunctiva, chemosis of bulbar conjunctiva, and serous discharge were observed. There was also a 2+bulbar injection 360 in the right eye and a 1+ diffuse bulbar injection 360 in the left eye. The corneas were clear without evidence of any subepithelial infiltrates, and the anterior chambers were deep and quiet in both eyes.

Differential diagnoses considered at this point include:

Non-specific Acute Follicular/Adenoviral Conjunctivitis
Pharyngoconjunctival fever (PCF)
Epidemic Keratoconjunctivitis (EKC)
Acute Hemorrhagic Conjunctivitis (AHC)
Acute Bacterial Conjunctivitis
Allergic Conjunctivitis
Chlamydial Inclusion or Trachomatous Conjunctivitis

- Non-specific acute follicular conjunctivitis typically presents with unilateral teary, burning, diffusely hyperemic eye that could spread to the fellow eye one to two days later. It can be caused by more than 45 different adenoviral serotypes. The palpebral conjunctiva shows prominent follicular reaction. It can present with bulbar conjunctival hemorrhages and ipsilateral preauricular lymphadenopathy.[3]
- Pharyngoconjunctival fever (PCF) is a type of adenoviral conjunctivitis involving serotypes 3, 4, and 7 that affects children predominantly. In addition to the signs and symptoms of an acute follicular conjunctivitis, patients typically present with a mild fever and pharyngitis. Cornea may show superficial punctate keratitis (SPK), and a non-tender node is often present.[3]
- Epidemic keratoconjunctivitis (EKC) is the most severe form of adenoviral conjunctivitis, caused by serotypes 8, 19, and 37. Symptoms typically worsen around day five. Corneal involvement, with subepithelial infiltrates appearing by day 14, is the distinguishing feature of EKC from other adenoviral infections. A tender preauricular node is often palpable. In severe cases, petechial hemorrhages and pseudomembrane can also develop.[3]
- Acute hemorrhagic conjunctivitis (AHC) is a rapid onset, self-limiting episode of painful, teary eye with marked conjunctival hemorrhages lasting one to two weeks. It usually occurs in tropical regions of the world, and is caused by enterovirus and coxsackievirus.[3] It has been linked to late neurologic complications including flaccid motor paralysis and cranial nerve palsies.[2]
- Acute bacterial conjunctivitis is common in children under 12. It typically presents in one eye and spreads to the other after two to three days. Patients typically present with bulbar hyperemia that decreases in intensity towards the limbus, mucopurulent or purulent discharge, velvety papillary reaction on the palpebral conjunctiva, and matting of lashes in the mornings. Petechial hemorrhages on superior bulbar conjunctiva, marginal corneal infiltrates, and pseudomembrane can also develop.[2]
- Allergic conjunctivitis usually presents bilaterally with diffuse hyperemia, mild papillary reaction, positive chemosis, lid edema, and itchy, watery eyes.[3]
- Chlamydial inclusion/trachomatous conjunctivitis often presents with unilateral or bilateral hyperemia with watery and mucopurulent discharge, mixed follicular and papillary response, tender preauricular nodes, bulbar follicles, and superior pannus.[2]

The patient's signs ruled out allergic conjunctivitis, and her history ruled out chlamydial/trachomatous conjunctivitis. Although the presence of both follicles and papillae blurred the classic differentiator between bacterial and viral conjunctivitis, based on history of unresponsiveness to topical antibiotic therapy and findings of watery eyes and lack of mucopurulent or purulent discharge during examination, a viral etiology to the infectious conjunctivitis was ruled in. In addition, due to severity of presentation, a history of recent pink eye exposure at school, worsening of symptoms around day five, epidemic keratoconjunctivitis (EKC) variant of adenoviral conjunctivitis became the prime suspect. The patient and her father were educated on the natural progression of the disease which is the self-limiting, lasting up to 21 days, and worsening around day five. The patient and her father were also educated on the importance of frequent hand washing, especially after touching the eye. The father was also advised to wash all towels and pillowcases, and to take precautions of keeping the patient home from school due to the highly contagious nature of EKC. The father was counseled on the option of supportive care using artificial tears and cool compresses or an off-label treatment using a dilute povidone-iodine solution, which had been shown to decrease infectivity[3] and improve recovery time.[7]

The father and the patient elected to proceed with the off-label Betadine treatment after denying iodine allergy that could result in anaphylactic shock and understanding the potential adverse effects of treatment, including painful, burning, watery eyes, and blurry vision from the solution and saline rinse. For the treatment, two drops of 0.5% Proparacaine hydrochloride ophthalmic solution were instilled in both eyes one minute apart. Then, five drops of 10% povidone iodine topical solution (Betadine Solution) was mixed with five drops of Refresh Plus from a 0.01 fl oz single-use vial in a disposable contact lens case. The diluted Betadine solution is drawn back into the Refresh Plus vial, and five drops were instilled in each eye. The patient was instructed to close her eyes and roll her eyes around for one minute. Each eye was then rinsed with a thimerosal-free Eye Irrigating Solution for a total of three minutes, alternating 10 seconds per eye, until the solution ran clear. Then, one drop of 0.5% Ketorolac tromethamine ophthalmic solution was instilled in each eye followed by one drop of 0.5% Proparacaine hydrochloride ophthalmic solution in each eye one minute later. Then, the corneas were observed with FUL-GLO, 0.6mg fluorescein sodium sterile ophthalmic strip, there were no changes to appearance of the anterior segment, and no evidence of SPK was observed in either eye.

The patient was prescribed 1% Prednisolone (Pred Forte) ophthalmic suspension to be instilled one drop in each eye four times a day for four days. The father was instructed to shake the bottle well prior to instilling the drops. The patient was scheduled to return to the clinic in four days for an anterior segment evaluation and IOP check, and was instructed to return sooner if symptoms worsen.

Follow-up #1

The patient returned on January 9, 2017 with her father for anterior segment evaluation. The patient was evaluated by Dr. Swanson, a colleague at the clinic, while Dr. Zhang was on a temporary duty assignment. The patient had been compliant with Pred Forte drops four times a

day in both eyes. Patient reported her eyes felt much better and denied any pain. Her vision remained stable at 20/20 right eye and left eye, both uncorrected. Her pressures measured 23mmHg, OD and 20mmHg, OS at 08:28 AM via NCT.

The patient's right eyelid showed mild edema in the upper and lower lids, while the left eyelid appeared normal. The right bulbar conjunctiva showed a 1+ bulbar injection with resolving subconjunctival hemorrhage next to the nasal and temporal limbi. There were 1+follicles on the superior and inferior palpebral conjunctiva in the right eye. The left eye appeared white and quiet. The right cornea now had 10 pinpoint spots of SEIs inferiorly. The left cornea remained clear. There were no anterior chamber reactions in either eye.

The patient and her father were instructed to discontinue Pred Forte drops without tapering. The patient was advised to stay out of school for one more day until the right eye looked better. The patient was instructed to return to the clinic in one to two weeks for another anterior segment and IOP check, or sooner if there were any increases in pain, redness or blurred vision.

Follow-up #2

The patient returned to clinic on January 23, 2017 with her father for follow-up, and was seen by Dr. Swanson again while Dr. Zhang was still away. The patient reported her eyes felt and looked much better. The patient reported her mom and brother may have contracted the viral conjunctivitis as well and would be presenting to clinic for treatment. The patient had been off treatment since January 9, 2017. Her vision remained relatively stable, the right eye was 20/20-2 uncorrected and the left eye was 20/20 uncorrected. Her intraocular pressures returned to normal at 12 OD and 13 OS at 12:48 PM. Both conjunctivas were white and quiet without evidence of papillae or follicles. The right cornea had five residual pinpoint scars inferiorly. The left cornea remained clear. The epidemic keratoconjunctivitis OU was deemed resolved at this point, and the patient was advised to return to the clinic when convenient for a complete eye exam.

Discussion

Although it is easy to clinically differentiate an infectious conjunctivitis from a primarily inflammatory process, narrowing down the specific etiology of the infectious agent is often a challenge. Acute infectious conjunctivitis of various etiology share many confounding signs and symptoms. Papillary and follicular reactions on the conjunctiva can be hard to differentiate, especially if they are both present. Mucoid and serous discharge can be present in viral, bacterial and allergic forms of conjunctivitis. Thus, the patient history and time course of symptoms offer invaluable clues for clinicians to make the appropriate diagnosis.

In this case, the absence of mucopurulent discharge and velvety palpebral conjunctiva in both eyes, along with history of unresponsiveness to prior course of antibiotic treatment helped rule out a simple bacterial conjunctivitis. The abundance of watery discharge in the absence of significant itch helps further point convincingly toward a viral etiology. In addition, the history of unilateral onset, worsening of symptoms by day five has been described in many textbooks as a classic natural progression of epidemic keratoconjunctivitis (EKC).[2,4] The report of recent "pink eye" exposure at school also helps corroborate the diagnosis of EKC. At the first follow-

up, the presence of subepithelial infiltrates was the final confirmation needed for the confidence in the presumptive diagnosis.

Epidemic keratoconjunctivitis (EKC) is a severe, yet self-limiting conjunctival infection and inflammation caused by adenovirus types 8, 19, and 37.[3] The virus is transmitted via direct contact with ocular and respiratory secretions or by indirect contact with contaminated surfaces.[5] These adenoviral particles have been shown to maintain its virulence for upwards of one month when deposited on nonporous surfaces, and transmission has been shown to occur via inanimate objects such as door handles.[5] The epidemic nature of EKC is how the condition derived its name. Outbreaks usually occur in crowded locations such as schools and hospitals.[5] Thus, meticulous infection control practices by everyone is essential in limiting the spread of EKC.

Classic textbook discussion of EKC confirms presence of subconjunctival hemorrhages in some cases, but does not mention any findings of hemorrhagic discharge in the tears.[2] The pinkish tears present in this patient is a variation from normal, but could be attributed to red blood cells leaking from the increased vascular permeability as a result of the significant inflammatory response. Similarly, acute hemorrhagic conjunctivitis (AHC) caused by enterovirus and coxsackievirus also presents with severe signs and symptoms including subconjunctival hemorrhages. However, acute hemorrhagic conjunctivitis tends to be rapid in its onset and resolution. Symptoms persist three to five days[9] as opposed to the two- to three-week course of EKC.[3] AHC also occurs more commonly in tropical regions of the world. Ultimately, the time course and location of this case ruled in favor of EKC diagnosis, although treatment and management would not have differed for the two conditions.

The standard of care for management of EKC does not recommend additional work-up for confirmatory diagnosis of viral conjunctivitis unless the condition fails to resolve and becomes chronic.[3,4] The traditional gold standard for diagnosis of EKC involves cell culture with immunofluorescence staining—mononuclear cells are found predominantly in adenoviral infections whereas multinucleated giant cells are more common in herpetic infections.[3] Newer testing using nucleic acid amplification such as PCR has proven to be a more sensitive and specific test compared to the traditional gold standard.[3] Despite their existence, these diagnostic tests are often slow and costly, thereby decreasing their utility in the clinical setting.[10] Recent development of point of care diagnostic testing such as the RPS AdenoPlus offers a solution to these diagnostic challenges by detecting adenoviral antigens directly from the serous discharge.[5] This advancement can help minimize misdiagnoses and ineffective management, however, in the absence of these diagnostic tools, clinicians can still make clinically appropriate treatment decisions based on careful observation of signs and symptoms and a thorough review of the patient history.

Once the presumptive diagnosis for viral conjunctivitis has been ruled in, the clinician faces an additional challenge of limited treatment options. Clinicians often wish to do more to help the suffering patient. The Wills Eye Manual recommends patient education on the infection control practices, preservative-free artificial tears eight times a day for one to three weeks, cool compresses throughout the day, and antihistamine drops for itch relief. If a pseudomembrane should develop, membrane peel is advised along with topical steroids four times a day for one week.[4] Topical corticosteroids suppress inflammation and offer symptomatic relief but at the

expense of prolonging viral replication and delaying viral clearance.[5] Non-steroidal topical therapeutics does not prolong viral clearance, but also does not offer more relief than artificial tears.[5] Studies on cyclosporine therapy showed reduced formation of SEIs, but at the expense of increased viral replication similar to steroid therapy.[5] Research in antiviral therapeutics showed a limited efficacy of Ribavirin against EKC and potential for corneal toxicity with Cidofovir treatment.[5]

Two off-label therapies have shown positive effects in reducing the symptoms and course of adenoviral conjunctivitis. First, topical Ganciclovir 0.15% ophthalmic gel used to treat herpetic keratitis have been shown in a Saudi Arabia study to resolve adenoviral conjunctivitis in 7.7 days compared to 18.5 days with palliative artificial tear therapy.[5] Second, povidone-iodine, a broad-spectrum anti-infective used in pre-and post-operative surgical prophylaxis to kill bacteria, fungi, viruses, has been reported by many clinicians to reduce viral load and improve symptoms in treated patients. [5,7,8]

Due to availability of Betadine solution in clinic, the off-label treatment was offered to patient and her father with the caveat that most anecdotal reports of symptom improvement were in patients who were treated within the first three days of symptom onset. The use of Betadine in children has been reported in literature, although it was a 1.25% concentration used as an ophthalmic drop four times a day as opposed to a 5% one-time treatment.[11] In the setting of severe symptoms, Betadine treatment was recommended because the patient was already symptomatic for the potential stinging that the treatment could cause, and the chance for a faster resolution with treatment further justifies the recommendation.

In the end, the in-office treatment did not result in any significant adverse effects. To further provide relief after the treatment, a topical corticosteroid was prescribed to the patient. In hindsight, a milder topical steroid could have provided the same relief and reduced the risk of spike in intraocular pressure. In addition, the patient could have been treated simply with preservative-free artificial tears with the same relief. Fortunately, due to the short course of the steroid regimen, the intraocular pressure returned to normal after the steroid was discontinued. The final follow-up ensured there were no serious sequelae from the infection, and the patient and her father were made aware that she is a steroid responder, warranting a careful IOP monitoring in the future.

Conclusion

This case highlights the current challenges in diagnosis and treatment of epidemic keratoconjunctivitis. Although there are new diagnostic advances such as the RPS AdenoPlus, traditional clinical analysis based on careful study of disease presentation and history is often the best practice in providing patients with prompt and appropriate care. In addition to palliative treatment options, clinician can also safely offer Betadine treatment to patients with early signs of viral conjunctivitis. Anecdotal cases, including this case report, have shown positive patient relief after in-office treatment with 5% Betadine ophthalmic solution.[5,6,7,8] Although the condition is self-limiting, follow-up until full resolution is recommended. Not only does this practice provide patient with greater reassurance, but it also allows for close monitoring of any adverse reactions to treatment. Further research is needed to establish the efficacy of off-label

treatments beyond anecdotal evidence, but for now, patients suffering from severe adenoviral conjunctivitis can try the 0.5% Betadine therapy in addition to traditional palliative measures.

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