PEER REVIEWED

When a Red Eye is More than Meets the Eye:
a Teaching Case Report on the Public Health Role
of the Eyecare Provider

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Abstract

Cases of "red eye" can be challenging due to the numerous potential etiologies and systemic associations. A systematic evaluation of presenting signs and symptoms with development of an inclusive differential diagnosis is required, but is complicated when unknown concurrent systemic infection is present. Collaboration with the patient's primary care physician and a working knowledge of the epidemiologic contributing factors provide a deeper understanding in this process and add certainty to diagnostic expertise when more rare conditions present. The following case highlights the integral roles of diagnostic ability and understanding of epidemiologic principles in providing optimal patient care.

Key Words: *endotheliitis, mumps (epidemic parotidis), collaborative care, epidemiology, community (herd) immunity, vaccination safety*

Background

Patients presenting for care of "red eye" can be challenging due to the numerous etiologies and potential systemic associations. A systematic evaluation of presenting signs and symptoms with development of an inclusive differential diagnosis is required, but is complicated when unknown concurrent systemic infection is present. Collaboration with the patient's primary care physician (PCP) and a working knowledge of the epidemiologic contributing factors provide a deeper understanding in this process, and add certainty to diagnostic expertise when more rare conditions present. The following clinical case endeavors to teach optometry students two critical aspects of their role as clinicians: the importance of basic knowledge about significant but relatively rare differential diagnoses of a common complaint, and that optimal care and improved outcomes result with application of epidemiologic principles. True proficiency in providing optimal care encompasses more than the understanding of diagnosis and management, and the earlier epidemiological principles are introduced, the better.

This teaching case report is for use with latter second-year optometry students (and beyond) who understand the differential diagnosis and treatment options for conjunctivitis/uveitis and have a basic understanding of epidemiological concepts.

Case Description



Figure 1. Slit lamp image captured at the patient's initial visit.
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A 38-year-old Caucasian male presented to the eye clinic with a chief complaint of an irritated right eye

of two-day duration. The patient complained of burning, tearing, mild photosensitivity and mild foreign body sensation of the right eye. There was no complaint of significant blur, pain, flashes, floaters, diplopia, headache, dryness, recent upper respiratory infection or allergy. The patient had seen his PCP one day prior when symptoms began. The PCP ruled out a corneal abrasion, recommended artificial tears, and referred the patient to the eye clinic for further evaluation if symptoms persisted or worsened.

Initial visit

Mild facial swelling near the jaw observed at the eye clinic visit was due to overnight teeth grinding according to the patient. All other systemic and medical history was negative. Best-corrected visual acuity (BCVA) was 20/25-OD and 20/20 OS. Pupillary reactions and extraocular motilities were normal.

Slit lamp biomicroscopy of the patient's left eye was unremarkable. Slit lamp findings for the right eye **(Figure 1)** were:

- Mild diffuse hyperemia with limbal flush
- Trace anterior chamber reaction (cells and flare) with fine keratic precipitates diffusely
- Moderate, diffuse corneal edema with endothelial folds
- Mild central punctate staining
- Goldmann applanation tonometry: 24 mmHg OD, 14mmHg OS at 11:50 a.m.
- Palpation of preauricular lymph nodes: no discomfort and no significant elevation on the right side relative to the left
- Gonioscopy was inconclusive OD because of poor views due to edema; angles were open 360° OS
- Pachymetry not performed at this visit
- Fundus findings were unremarkable OD, OS and non-contributory

A working diagnosis of anterior uveitis with corneal edema and increased intraocular pressure (IOP) OD without known etiology was determined. **Table 1** lists initial treatment. Initiation of intraocular pressure lowering drops would commence if intraocular pressure remained elevated at follow up visit.

One-day follow-up visit

The next day the patient reported complete adherence to the prescribed topical medication regimen, improved ocular symptoms, and mild worsening with dry mouth and testicular pain. He reported a generalized feeling of being unwell and was to return to his PCP that afternoon. See **Table 1** for treatment changes. Additional findings:

- Continued mild injection OD, improving
- Moderate/severe corneal edema; pachymetry: 760 µm OD, 569 µm OS
- Improving but still elevated IOP (18 mmHg OD, 14 mmHg OS)

Further investigation of the new systemic symptoms, patient physical and ocular presentation revealed a likely diagnosis of mumps-related endotheliitis with associated trabeculitis. The provisional diagnosis of endotheliitis associated with epidemic parotidis was discussed with the PCP by phone. The physician's evaluation of the patient and subsequent immunoglobulin M titers confirmed the diagnosis. Despite vaccination as a child, the patient contracted mumps from an unknown source, which raises the questions "How can this be and how does it influence our future evaluation of vaccinated individuals?"

TABLE 1
Summary of Patient Visits

	Initial	1 day	1 week	2 weeks	1 month	2 months
Best-corrected visual acuity	20/25- OD 20/20 OS	20/30 OD 20/20 OS	20/50-2 OD 20/20 OS	20/25 OD 20/20 OS	20/20+2 OD 20/20+ OS	20/20 OD 20/20 OS
Anterior segment (all findings are OD)	moderate edema with few endothelial folds; trace cells; fine diffuse keratic precipitates; 2+ diffuse injection	moderate to severe edema with many endothelial folds diffusely; no anterior chamber reaction; 1+ injection	severe edema with endothelial folds of central cornea, epithelial edema	mild diffuse edema, few endothelial folds and resolution epithelial edema	few endothelial folds with trace central endothelial opacity	clear, complete resolution of all anterior segment anomalies
Intraocular pressure	24 mmHg OD 14 mmHg OS	18 mmHg OD 14 mmHg OS	16 mmHg OD 13 mmHg OS	11 mmHg OD 12 mmHg OS	13 mmHg OD 14 mmHg OS	13 mmHg OD 14 mmHg OS
Pachymetry		760 µm OD 569 µm OS	646 µm OD	640 µm OD	615 µm OD	580 µm OD 565 µm OS
Treatment (OD)	prednisolone acetate 1% q1h; homatropine 5% qid	prednisolone acetate 1% qid; homatropine 5% qid	prednisolone acetate 1% q2h; discontinue cycloplegic; add Muro 128 5% qid	prednisolone acetate 1% qid; discontinue Muro 128	all drops discontinued by patient; add artificial tears qid	

q1h = once every hour
q2h = once every two hours
qid = 4 times per day

Table 1. Click to enlarge

Education Guidelines

Key concepts

1. Differential diagnosis of endotheliitis systemic etiologies
2. Application of epidemiologic principles and collaborative care practice in providing optimal health care
3. Vaccination against preventable infectious disease

Learning objectives (LO)

Utilization of this case to educate separately on ocular/systemic disease or epidemiological emphasis is possible, but use of this report in its entirety will enhance the student's ability to:

1. Participate collaboratively in the diagnosis of epidemic parotidis with an understanding of the ophthalmic and systemic ramifications
2. Independently diagnose and treat the secondary ocular manifestation of endotheliitis with an understanding of the underlying pathophysiology
3. Utilize and apply the epidemiological concepts determining risk of infection with this and other preventable viral etiologies
4. Gain working knowledge and use of epidemiological resources to aid in the care of patients presenting with infectious disease

Education activities/case discussion

Presenting the case using a grand rounds approach can help students hone their skills as they answer questions in determining additional testing and next steps for care in the evaluation and management of problem-focused exams.

- Poll Everywhere or Turning Point allow for real-time assessment of student participation, or a quiz preceding and after review and discussion of the case can assess understanding of relevant clinical care concepts. The quiz, geared toward the level of learner, can emphasize both epidemiology and ocular/systemic manifestations utilizing content provided in the discussion. (LO 1-4)

Deep learning/critical thinking opportunities exist as students break into smaller groups to independently explore and present back to the larger group or post on the course online learning management system. The discussion section and resources listed provide a starting point for these active learning exercises:

- Develop a problem representation grid (illness script) of the differential diagnosis of conjunctivitis including endotheliitis. Independent development and completion by the students or a grid provided with some data points missing are options. (LO 1, 2)
- Discuss the role of anterior chamber-associated immune deviation (ACAID) in this condition and its effect on management of ocular inflammation. (LO 2)
- Develop a basic protocol for patient medical and visual conditions that require interprofessional collaboration (include examples of which conditions need outreach and why, modes of contacting the PCP and what information should be provided. Knowledge of clinical medicine concepts is helpful or working with the instructor as facilitator are options. (LO 1)
- Access and use the Morbidity and Mortality Weekly Report (MMWR) database to research the prevalence of a viral illness in the United States and its ophthalmic manifestations (herpes zoster, Zika, chikungunya, West Nile, yellow fever, Rift Valley fever, etc.) (LO 3, 4)
- Investigate the autism vaccination controversy and debate it using two peer-reviewed resources on either side. (LO 3, 4)
- Discuss the concepts of herd (community) immunity and long-term seroprevalence/vaccination efficacy for measles, mumps and rubella given recent national outbreaks of measles and mumps. (LO 1, 3, 4)

Assessment of the above learning activities depend on the course type and facilitator goals. While rigorous grading rubrics for the activities for summative evaluations are possible, these activities lend themselves to seminar and adjunctive content and are better assessed in a formative manner for clarity and content. Access to all group activity reports or best examples of each activity posted on the learning management system for student review will maximize learning opportunities to meet all learning objectives.

Literature review

Mumps (epidemic parotidis)

Epidemic parotidis[1] is a contagious acute paramyxovirus infection of the salivary glands presenting as swelling of one or both parotid glands and flu-like symptoms. Hence, this patient's swelling near the jaw was not associated with teeth grinding, and his dry mouth on day two was not due to use of a cycloplegic agent but rather the parotid gland dysfunction. The incubation period of epidemic parotidis is 12-25 days and glandular involvement occurs 16-18 days after exposure. While the parotidis and viral illness are self-limiting and usually resolve within 10 days, significant systemic complications, including pelvic inflammation in males (orchitis) and females (oophoritis), can occur, especially after puberty. The patient's complaint of testicular pain on day two was associated with orchitis, but this presentation rarely results in sterility. Neurosensory hearing loss can occur but usually returns to normal post-infection.

Before the introduction of single-dose vaccination with live attenuated virus in 1967, mumps accounted for a significant percent of cases of aseptic meningitis in the United States. Other serious systemic complications such as pancreatitis were also reported, although death from infection was exceedingly rare. Once the two-dose vaccination regimen came into common use, significant drops were seen in all systemic complications and no deaths were reported.

Endotheliitis typical presentation

The most common ophthalmic manifestation of epidemic parotidis is endotheliitis (sometimes associated with trabeculitis as in this presentation). The condition typically presents as:[2]

- mild to moderate anterior chamber reaction
- unilateral involvement

- fine keratic precipitates that can be confused with endothelial pigment
- sectoral or diffuse corneal edema with endothelial folds
- microcystic edema resulting from aggressive stromal edema
- elevated IOP (if trabeculitis is also present)

Pathology

Corneal endotheliitis is a clinical diagnosis based on specific characteristics **(Table 2)**. The pathology of endotheliitis is endothelial viral proliferation resulting in an inflammatory response.[2] There is subsequent failure of the endothelial cell pump leading to edema and loss of transparency that can lead to long-term endothelial damage.[2] Subsequent inflammation of the trabecular meshwork is possible and leads to reduction in aqueous outflow and increased IOP.

Table 2. Click to enlarge

It was not until 1985 that researchers identified the viral etiology of this presentation by isolating herpes simplex virus (HSV) in the aqueous humor and detecting HSV-1 antigen in the anterior chamber of affected eyes.[3] Some evidence indicates that HSV originates from the trabeculum as patients with endotheliitis have shown HSV on excised trabecular tissue and this is consistent with the peripheral presentation of HSV-related endotheliitis.[4] Later, identification of other contributing viral etiologies, including the rarely encountered epidemic parotidis-related endotheliitis, followed. [5]

The role of ACAID results in a relatively reduced inflammatory response despite the direct infection of ocular tissue due to the suppression of a delayed hypersensitivity reaction.[6] However, the reduced cell-mediated immunity to viral particles shed into the anterior chamber allows for viral proliferation in the corneal endothelium leading to the presentation of endotheliitis.[2] The pathogenesis of mumps-related endotheliitis varies from this and may be associated with the level of viremia, but the rarity of the condition makes further research difficult.[5]

Endotheliitis is not completely benign as endothelial cell loss can occur. As this cell layer does not regenerate, future pathology or necessary procedures such as cataract extraction may result in further corneal decompensation and vision loss. Systemic treatment of recalcitrant HSV-related endotheliitis may be necessary (oral acyclovir or valacyclovir) along with topical corticosteroids. However, cytomegalovirus (CMV)-related endotheliitis often does not respond to topical corticosteroids and requires aggressive systemic management (IV ganciclovir) to protect vision.[8] Consultation with the patient's PCP when confronted with suspicions of systemic herpetic disease is highly recommended for best outcomes. In addition to topical corticosteroids, topical ganciclovir ophthalmic gel 0.15% five times daily supplements treatment of disciform and linear endotheliitis associated with HSV and varicella zoster virus but may show limited effectivity for CMV etiology.[8]

The Centers for Disease Control and Prevention (CDC) is a federal agency under the U.S. Department of Health and Human Services tasked with monitoring and prevention of disease. The agency's mandate is to protect the nation's health, and as part of its mission it "conducts critical science and provides health information that protects our nation against expensive and dangerous health threats, and responds when these arise."[9] Promoting vaccination against preventable infectious disease is a part of this mandate. Current CDC recommendations for infectious childhood diseases include vaccination against varicella, rubella, measles, mumps, polio, and diphtheria. The agency cites studies showing the safety of these recommendations as well as their impact on morbidity and mortality.[1] Patients and their parents may ask healthcare providers for their opinions on vaccination, making a working knowledge of the subject important. Resources for practitioners and the public are available on the CDC website.

Vaccination is the most effective way to prevent the spread of epidemic parotidis. The measles, mumps rubella (MMR) or measles, mumps, rubella, varicella (MMRV) vaccine protocols call for two doses. The first is administered at age 12-15 months; a booster is administered at age 4-6 years.[10]

Other resources such as the CDC publication of the MMWR can provide current, evidence-based public health information as well as recommendations and their impact on public health. The MMWR provides real-time information on outbreaks occurring nationally.[11]

Those most at risk for mumps

Individuals most at risk for contracting epidemic parotidis include:[1]

- those who have not been vaccinated, including infants too young to be vaccinated
- healthcare workers in clinic/hospital settings
- those living in close quarters, such as college students or members of traditional communities
- persons traveling overseas to countries that do not require mumps vaccination
- vaccinated members of a certain U.S. population subset

Outbreaks of mumps have occurred in adult populations and in communities of all ages in the recent past. If healthcare providers are not informed, they may miss important diagnoses and patient education opportunities. The public health impact of optometrists' contributions to care is significant as a solid understanding of epidemiologic principles is critical for evidence-based practice and can inform or guide care protocols and referrals for best patient outcomes. Treatment of a presenting condition such as endotheliitis is only the beginning. A deeper understanding of those at risk for underlying, causative systemic disease will provide for more timely identification and diagnosis with the potential to reduce the spread of infection.

MMR vaccine efficacy

The MMR vaccine is highly successful in providing long-term protection against measles and rubella but is not as effective in maintaining immunity to mumps over time. Mumps seropositivity shows less persistence over time with one dose resulting in 78% immunity (49-92%) and two doses resulting in 88% immunity (66-95%).[1] While herd or community immunity to prevent spread of disease is known to be 92%, the low persistence of mumps seropositivity does not result in pervasive epidemic rates of infection. One study of a small community showed only 74% of residents with measurable immunity 15 years after a second dose of MMR vaccine, yet no members of the community developed epidemic parotidis.[12] This is due to limited rates of exposure to the disease. Therefore, high vaccination rates paired with lack of exposure result in eradication of acute infection, but to be truly effective in this regard, both are required.

Why did this patient get mumps?

A survey of epidemiological resources is helpful in learning why the patient in this case contracted mumps. CDC evaluators used data from the 1999-2004 National Health and Nutrition Examination Survey (NHANES) to assess mumps antibody seroprevalence in the U.S. population.[13] They found 90% of those surveyed were immune (borderline to prevent disease spread). However, some subsets showed lower rates of immunity. Specifically, those born between 1967 and 1976 showed only 85.7% seropositivity. These single-dose recipients were too old to have been exposed naturally as children and too young to have received the more persistent two-dose regimen. Therefore, they were more likely to be at risk of developing infection when exposed.[13] Based on his age, this patient fell into that demographic.

Unfortunately, a reduction in vaccination rates has resulted in outbreaks in the United States in recent

years. In 1998, a paper by Wakefield et al. raised concerns of autism risk in those receiving the MMR vaccine. This led to parental reluctance to immunize children against multiple infectious diseases.[14] Ultimately, significant decreases in vaccination rates resulted in some communities. Although this theory has been debunked through retrospective and prospective research, and the original paper was found to be fraudulent and retracted, the safety concern continues to affect U.S. vaccination rates. Literature review shows that parents opting out of vaccinating their children not only puts the unvaccinated individual at risk for preventable disease but also increases the likelihood of spreading disease throughout the greater community.[15]

Conclusion

A seemingly simple complaint of red eye can signal a significant threat to a patient's health and well-being. The ability to recognize important features that indicate potentially harmful systemic etiology, such as rash, swollen glands, associated symptoms or unique ocular findings, makes optometrists effective contributors to the overall care patients receive. By collaborating with PCPs, optometrists can implement timely and appropriate ocular and systemic treatment. Recognizing a rare presentation such as epidemic parotidis-related endotheliitis is important and may become increasingly so as mumps outbreaks become more prevalent due to a reduction in vaccination rates. Understanding the relevant epidemiologic principles and being familiar with available resources enable a quick response when new infectious diseases are present in local communities and abroad.

References

1. Manual for the surveillance of vaccine-preventable diseases. Centers for Disease Control and Prevention, Atlanta, GA, updated 2017. Clemmons N, Hickman C, Lee A, Marin M, Patel M. Chapter 9: Mumps [accessed 1/10/19]. Available from: https://www.cdc.gov/vaccines/pubs/surv-manual/chpt09-mumps.html
2. Suzuki T, Ohashi Y. Corneal endotheliitis. Semin Ophthalmol. Jul-Aug 2008;23(4):235-40.
3. Robin JB, Steigner JB, Kaufman HE. Progressive herpetic corneal endotheliitis. Am J Ophthalmol. 1985 Aug 15;100(2):336-7.
4. Amano S, Oshika T, Kaji Y, Numaga J, Matsubara M, Araie M. Herpes simplex virus in the trabeculum of an eye with corneal endotheliitis, Am J Ophthalmol. 1999 Jun;127(6):721-2.
5. Singh K, Sodhi PK. Mumps-induced corneal endotheliitis. Cornea. 2004 May;23(4):400-2.
6. Hori J. Mechanisms of immune privilege in the anterior segment of the eye: what we learn from corneal transplantation. J Ocul Biol Dis Infor. 2008 Dec;1(2-4):94-100. doi: 10.1007/s12177-008-9010-6.
7. Krachmer KH, Mannis MJ, Holland EJ, editors. 3rd ed., Vol.1, Cornea. Mosby/Elsevier; 2011. Chapter 79: Herpes Simplex Keratitis; p.967-71.
8. Chee SP, Jap A. Treatment outcome and risk factors for visual loss in cytomegalovirus endotheliitis. Graefes Arch Clin Exp Ophthalmol. 2012 Mar;250(3):383-9.
9. About CDC 24-7, mission, role and pledge. Centers for Disease Control and Prevention, Atlanta, GA, page last reviewed 5/13/19 [accessed 1/10/19]. Available from: https://www.cdc.gov/about/organization/mission.htm
10. Vaccines & immunizations, parents (birth-18 years). Centers for Disease Control and Prevention, Atlanta, GA, updated 10/16/18 [accessed 2/13/19]. Available from: https://www.cdc.gov/vaccines/index.html
11. Morbidity and mortality weekly report. Centers for Disease Control and Prevention, Atlanta, GA [accessed 2/13/19]. Available from: https://www.cdc.gov/mmwr
12. Davidkin I, Jokinen S, Broman M, Leinikki P, Peltola H. Persistence of measles, mumps, and rubella antibodies in an MMR-vaccinated cohort: a 20-year follow-up. J Infect Dis. 2008 Apr 1;197(7):950-6.
13. Kutty PK, Kruszon-Moran DM, Dayan GH, et al. Seroprevalence of antibody to mumps virus in the

US population, 1999-2004. J Infect Dis. 2010 Sep 1;202(5):667-74.
14. Wakefield AJ, Murch SH, Anthony A, et al. RETRACTED: Ileal-lymphoid-nodular hyperplasia, non-specific colitis, and pervasive developmental disorder in children. Lancet. 1998 Feb 28;351(9103):637-41.
15. Omer SB, Salmon DA, Orenstein WA, DeHart MP, Halsey N. Vaccine refusal, mandatory immunization, and the risks of vaccine-preventable diseases. N Engl J Med. 2009 May 7;360(19):1981-8.

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