Hepresviridae infections of the corneal endothelium

Behnam Rabiee [1,2,3], Chandani Patel [1,2,4], Mansab Jafri [3], Hamad Hussain [3], Michael Gaspari [1,2], Muhamad Festok [1,2], Aaila Chaudhry [1,2], Imtiaz Chaudhry [1,2], Layla Kamoun [1,2], Iftikhar Chaudhry [1,2], & Asim V. Farooq [4,*]

1. Trinity Health Mid-Atlantic, Nazareth Hospital, Department of Ophthalmology, Philadelphia, PA
2. IC Laser Eye Care, Bensalem, PA
3. The University of Chicago, Department of Ophthalmology and Visual Science, Chicago, IL
4. Rowan University School of Osteopathic Medicine, Stratford, NJ

Introduction

The corneal endothelium plays a vital role in maintaining corneal clarity by regulating the amount of fluid in the corneal stroma. Corneal endotheliitis is defined as inflammation of the corneal endothelial layer that leads to corneal edema and haziness, and subsequent loss of vision. Most common causes include cytomegalovirus (CMV), herpes simplex virus (HSV), and varicella zoster virus (VZV). Because corneal endothelial cells cannot regenerate following injury, early diagnosis is essential in proper management and preventing loss of corneal endothelial cells. In the review article we aim to gather the most recent knowledge on viral corneal endotheliitis, focusing on the most common viral causes, to help clinicians with clinical diagnosis, appropriate laboratory tests, and proper management of this potentially debilitating condition.

Methods

A literature analysis was conducted across different databases such as PubMed, Ovid Medline, and Embase. Multiple search terms were used that included corneal endotheliits, HSV endotheliitis, CMV endotheliitis, VZV endotheliitis, keratitis, endotheliitis diagnosis, and treatment.

Results

HSV

HSV endotheliitis is common in individuals who are immunocompromised and thorough history taking may elucidate prior or recurrent herpetic disease (1). Corneal infection with dendritic HSV lesions is most likely a precursor, but it is important to make the distinction that diagnosis cannot be reliant on dendritic HSV as the posterior cornea shows notably different patterns of diseased effect (3,4). Clinical findings include formation of disciform keratic precipitates (KPs), increased intraocular pressure due to trabeculitis and inflammation of the iris. (5-8). One rare clinical presentation of HSV-1 keratitis is herpetic linear endotheliitis, which presents as epithelial and peripheral stromal edema between the limbus and KPs (8, 9). The line of KPs is located at the edge of edema and can be serpiginous, circumferential, and sectorial in appearance

(10). To confirm clinical diagnostic observations, polymerase chain reaction (PCR) analysis of the aqueous humor has proven to be a reliable test, however, negative results do not exclude a viral etiology (82% sensitivity) (11).
Generally, treatment of any viral endotheliitis involves topical steroids to reduce inflammation and concomitant antiviral. Various randomized double-blind trials compared combination of topical betamethasone (0.1% or 0.01%) and topical acyclovir 3% ointment with acyclovir ointment alone (12-15). All these studies concluded that combination treatment of HSV endotheliitis produced a faster response and significantly fewer treatment failures than topical acyclovir alone (12-15). Another study comparing HSV endotheliitis treatment of topical acyclovir 3% five times daily vs oral acyclovir 400mg five times daily found no difference between the two treatment groups (16); However, oral acyclovir showed greater improvement of visual acuity (16). Severe cases of HSV endotheliitis can be managed with surgical intervention. Cases with concurrent anterior stromal scarring may benefit from full-thickness penetrating keratoplasty (PK). However, in eyes with underlying inflammatory status, PK is associated with higher risk of failure or rejection (17). In cases with isolated endotheliitis, descemet membrane endothelial keratoplasty (DMEK) is associated with lower risk of endothelial rejection than descemet stripping automated endothelial keratoplasty (DSEK) (19, 20). Additionally, intense antiviral regime after DMEK has shown to reduce HSV-1 recurrence, graft failure and endothelial immunologic rejection (18).

CMV

CMV-related endotheliitis typically arises in otherwise healthy patients, especially middle aged and older males, with no history of compromised immune systems (1, 2). Of note, many patients diagnosed with CMV-endotheliitis had corneal transplants, encouraging the conjecture that CMV could be responsible for graft failure and/or endothelial dysfunction (21). Clinical findings include pigmented, non-granulomatous keratic precipitates (KPs) and increased intraocular pressure (IOP) (21). Disciform or coin-shaped KPs are the most common pattern, occurring in about 70% of cases (21). Some clinical features of CMV endotheliitis can mimic other diseases; for example, it can present as Posner-Schlossman syndrome, which leads to higher IOP, chronic anterior uveitis, and episodic iritis (2, 24). It can also resemble Fuchs' heterochromic iridocyclitis, which leads to anterior chamber cells and KPs (21-23). Diagnosis is confirmed by PCR analysis of aqueous anterior chamber tap (2, 25). The Goldmann-Witmer coefficient (GWC) can be utilized when the diagnosis is difficult to confirm (2).
Studies have indicated that Ganciclovir and corticosteroids are effective long-term treatments for the preservation of endothelial function in CMV-related endotheliitis (26-28). Potential antiviral regimens are listed below, although the dosing and frequency varies in the literature (1, 26, 28, 30-35). For topical therapy, first line treatment is 0.15% ganciclovir gel 5 times daily (therapeutic dosing) with subsequent taper to prophylactic dosing at TID. Second line treatment is compounded ganciclovir (0.5% - 2%). For systemic antiviral therapy, first line is oral valganciclovir 900 mg BID (therapeutic dose) with subsequent taper to prophylactic dosing at 900 mg QD. Second line is intravenous 5 mg/kg ganciclovir BID. Third line is intravenous foscarnet 60 mg/kg TID or cidofovir are alternatives but can cause significant nephrotoxicity. Today, ganciclovir is under careful review for its tendency to build viral resistance in patients

(29); most cases of CMV-endotheliitis are effectively treated, but ganciclovir can result in recurrent infection after discontinuation of treatment (2). In cases of resistance, alternative drugs may be used such as foscarnet, however, these introduce the risk of corneal toxicity (27, 29).

VZV

VZV corneal endotheliitis manifests primarily in younger patients, like children and adolescents.(1) They generally present within 2 weeks of onset of VZV associated rash with photophobia bilaterally and blurry vision in the affected eye. (36-38). Most common ocular finding is vesicular eruption on the periocular skin and eyelid in the sensory distribution of V1. (39) Patients can also develop prolonged dendritic keratitis like HSV, but VZV usually presents with medusa-like and/or small dendrites without terminal bulbs that stain poorly with fluorescein and rose Bengal. (40) Furthermore, as compared to HSV-associated endotheliitis, VZV usually presents more severe in terms of anterior chamber inflammation and may lead to the development of a hyphema or hypopyon (36-38). VZV is also a major cause of endotheliitis following keratoplasty (41). Unlike HSV and CMV endotheliitis, VZV endotheliitis is not commonly associated with increased IOP, particularly in cases following keratoplasty (39, 42, 43, 41). It is notable that VZV commonly involves the peripheral cornea, so it may spread to the trabecular meshwork which can progress to severe glaucoma that is retractive to glaucoma medications (40). As with any suspected viral endotheliitis, RT-PCR of aqueous humor from the anterior chamber remains the gold standard, although immunoassay via ELISA has also been shown to be effective to a lesser degree (1).

Some studies suggest the necessity of using topical corticosteroids early on to get the inflammation under control and prevent significant irreversible damage to the cornea endothelium, and the possibility of a need for a life-long low dose maintenance (45-48). Oral acyclovir or valacyclovir (43, 44) is used as the main antiviral. The recommended dosage of oral acyclovir is 800 mg five times daily for a total of 4g/day for 7-10 day, or a combination of oral acyclovir 800 mg every five hours, topical betamethasone every 2 hours, oral prednisolone 50 mg daily, and topical cycloplegic until ocular symptoms resolve, followed by taper of the topical betamethasone and oral prednisone (39, 49). Valacyclovir, a prodrug with 3-5 times greater oral bioavailability as compared to acyclovir, can be dosed at 1 gram three times daily, providing the bio-equivalent of the aforementioned dose of acyclovir (39, 49).

Conclusion

Viral corneal endotheliitis is a condition with visually significant and potentially permanent consequences. Given the corneal endothelium’s inability to regenerate after insults, the management of endotheliitis can be a particularly critical task. With prompt recognition and proper treatment, however, the disease burden and need for surgical interventions can be reduced. In this review article, the authors discussed the available literature in hopes to aid clinicians in the management of patients affected by this potentially debilitating condition.

References

1. Moshirfar M, Murri MS, Shah TJ, Skanchy DF, Tuckfield JQ, Ronquillo YC, et al. A review of corneal endotheliitis and endotheliopathy: differential diagnosis, evaluation, and treatment. Ophthalmology and Therapy. 2019;8(2):195-213.
2. Alfawaz A. Cytomegalovirus-related corneal endotheliitis: a review article. Saudi Journal of Ophthalmology. 2013;27(1):47-9.
3. Bronner A. The pathogens of corneal infection: know your enemy. Review of Optometry. 2014;151(4):68-80.
4. Hamrah P, Pavan-Langston D, Dana R. Herpes simplex keratitis and dendritic cells at the crossroads: lessons from the past and a view into the future. International ophthalmology clinics. 2009;49(1):53.
5. Zhu L, Zhu H. Ocular herpes: the pathophysiology, management and treatment of herpetic eye diseases. Virologica Sinica. 2014;29(6):327-42.
6. Carrillo-Arroyo I, Gutierrez-Diaz E, Mencia-Gutierrez E, Gomez-Perez P, Montero-Rodriguez M. Herpetic endotheliitis and trabeculitis with delayed corneal involvement. Archivos de la Sociedad Española de Oftalmología (English Edition). 2012;87(2):47-9.
7. Amano S, Oshika T, Kaji Y, Numaga J, Matsubara M, Araie M. Herpes simplex virus in the trabeculum of an eye with corneal endotheliitis. American journal of ophthalmology. 1999;127(6):721-2.
8. Shen Y-C, Wang C-Y, Chen Y-C, Lee Y-F. Progressive herpetic linear endotheliitis. Cornea. 2007;26(3):365-7.
9. EJ H. Schwartz GS. Classification of herpes simplex virus keratitis. Cornea. 1999;18:144-54.
10. Olsen TW, Hardten DR, Meiusi RS, Holland EJ. Linear endotheliitis. American journal of ophthalmology. 1994;117(4):468-74.
11. Murthy SI, Sangwan VS, Tejwani S, Atmanathan S, Rao GN. Manifestations of Progressive Herpes Simplex Virus Endotheliitis. Asian J Ophthalmol. 2007;9(2):76-81.
12. Collum L, Grant D. A double-blind comparative trial of acyclovir and adenine arabinoside in combination with dilute betamethasone in the management of herpetic disciform keratitis. Current Eye Research. 1987;6(1):221-4.
13. Collum L, Logan P, Ravenscroft T. Acyclovir (Zovirax) in herpetic disciform keratitis. British Journal of Ophthalmology. 1983;67(2):115-8.
14. Collum L, Power W, Collum A. The current management of herpetic eye disease. Documenta ophthalmologica. 1992;80(2):201-5.
15. Power W, Hillery M, Benedict-Smith A, Collum L. Acyclovir ointment plus topical betamethasone or placebo in first episode disciform keratitis. British journal of ophthalmology. 1992;76(12):711-3.
16. Porter S, Patterson A, Kho P. A comparison of local and systemic acyclovir in the management of herpetic disciform keratitis. British journal of ophthalmology. 1990;74(5):283-5.
17. Shtein RM, Garcia DD, Musch DC, Elner VM. HSV keratitis: histopathologic predictors of corneal allograft complications. Transactions of the American Ophthalmological Society. 2008;106:161.
18. Friehmann A, Myerscough J, Giannaccare G, Mazzoni M, Bovone C, Busin M. Successful descemet membrane endothelial keratoplasty in proven herpetic endothelial decompensation requires intensive antiviral therapy. Cornea. 2020;39(2):196-9.
19. Singh A, Zarei-Ghanavati M, Avadhanam V, Liu C. Systematic review and meta-analysis of clinical outcomes of Descemet membrane endothelial keratoplasty versus Descemet stripping endothelial keratoplasty/Descemet stripping automated endothelial keratoplasty. Cornea. 2017;36(11):1437-43.
20. Maier A-K, Gundlach E, Gonnermann J, Klamann M, Bertelmann E, Rieck P, et al. Retrospective contralateral study comparing Descemet membrane endothelial keratoplasty with Descemet stripping automated endothelial keratoplasty. Eye. 2015;29(3):327-32.
21. Koizumi N, Inatomi T, Suzuki T, Shiraishi A, Ohashi Y, Kandori M, et al. Clinical features and management of cytomegalovirus corneal endotheliitis: analysis of 106 cases from the Japan corneal endotheliitis study. British Journal of Ophthalmology. 2015;99(1):54-8.
22. Chee S-P, Bacsal K, Jap A, Se-Thoe S-Y, Cheng CL, Tan BH. Corneal endotheliitis associated with evidence of cytomegalovirus infection. Ophthalmology. 2007;114(4):798-803.
23. Chee S-P, Jap A. Presumed fuchs heterochromic iridocyclitis and Posner-Schlossman syndrome: comparison of cytomegalovirus-positive and negative eyes. American journal of ophthalmology. 2008;146(6):883-9. e1.
24. Jap A, Chee S-P. Cytomegalovirus-associated anterior segment infection. Expert Review of Ophthalmology. 2011;6(5):517-28.
25. Shahrudin NA, Zahidin AZM, Noh UKM, Halim WHWA, Din NM. CMV endotheliitis: a cause for recurrent failed corneal transplant. GMS ophthalmology cases. 2017;7.
26. Fan N-W, Chung Y-C, Liu Y-C, Liu CJ-L, Kuo Y-S, Lin P-Y. Long-term topical ganciclovir and corticosteroids preserve corneal endothelial function in cytomegalovirus corneal endotheliitis. Cornea. 2016;35(5):596-601.
27. Gilbert C, Boivin G. Human cytomegalovirus resistance to antiviral drugs. Antimicrobial Agents and Chemotherapy. 2005;49(3):873-83.

28. Hwang J-H, Ha M, Park Y, Chung S-H. The effect of topical ganciclovir and corticosteroid on cytomegalovirus corneal endotheliitis in Korean patients. Ocular Immunology and Inflammation. 2019;27(2):338-44.
29. Strasfeld L, Lee I, Tatarowicz W, Villano S, Chou S. Virologic characterization of multidrug-resistant cytomegalovirus infection in 2 transplant recipients treated with maribavir. The Journal of infectious diseases. 2010;202(1):104-8.
30. Kumar A, Mehta JS. Diagnosis and Management of CMV Endotheliitis. Current Ophthalmology Reports. 2019;7(2):98-109.
31. Koizumi N, Miyazaki D, Inoue T, Ohtani F, Kandori-Inoue M, Inatomi T, et al. The effect of topical application of 0.15% ganciclovir gel on cytomegalovirus corneal endotheliitis. British Journal of Ophthalmology. 2017;101(2):114-9.
32. Cho A-R, Hong S-U. A case report of alopecia treated by Gagamsunbangpaedok-tang (Jiājiǎnxiānfángbàidú-tāng)-focused on multi-patched alopecia Areata with lymphadenopathy. The Journal of Korean Medicine Ophthalmology and Otolaryngology and Dermatology. 2014;27(1):130-9.
33. Basilious A, Chew HF. Topical ganciclovir for prophylaxis of cytomegalovirus endotheliitis in endothelial keratoplasty. Cornea. 2019;38(1):120-2.
34. Kitazawa K, Jongkhajornpong P, Inatomi T, Koizumi N, Kayukawa K, Wakimasu K, et al. Topical ganciclovir treatment post-Descemet's stripping automated endothelial keratoplasty for patients with bullous keratopathy induced by cytomegalovirus. British Journal of Ophthalmology. 2018;102(9):1293-7.
35. Yu T, Peng R-M, Xiao G-G, Feng L-N, Hong J. Clinical evaluation of intravitreal injection of ganciclovir in refractory corneal endotheliitis. Ocular Immunology and Inflammation. 2020;28(2):270-80.
36. Colin J, Prisant O, Cochener B, Lescale O, Rolland B, Hoang-Xuan T. Comparison of the efficacy and safety of valaciclovir and acyclovir for the treatment of herpes zoster ophthalmicus. Ophthalmology. 2000;107(8):1507-11.
37. Kaufman SC. Anterior segment complications of herpes zoster ophthalmicus. Ophthalmology. 2008;115(2):S24-S32.
38. Liesegang TJ. Herpes zoster ophthalmicus: natural history, risk factors, clinical presentation, and morbidity. Ophthalmology. 2008;115(2):S3-S12.
39. Khodabande A. Varicella endotheliitis: a case report. European journal of ophthalmology. 2009;19(6):1076-8.
40. Li JY. Herpes zoster ophthalmicus: acute keratitis. Current Opinion in Ophthalmology. 2018;29(4):328-33.
41. Morishige N, Morita Y, Yamada N, Sonoda K-H. Differential changes in intraocular pressure and corneal manifestations in individuals with viral endotheliitis after keratoplasty. Cornea. 2016;35(5):602-6.
42. de Castro LEF, Al Sarraf O, Hawthorne KM, Solomon KD, Vroman DT. Ocular manifestations after primary varicella infection. Cornea. 2006;25(7):866-7.
43. Arvin AM, editor Antiviral therapy for varicella and herpes zoster. Seminars in pediatric infectious diseases; 2002: Elsevier.
44. de Freitas D, Sato EH, Kelly LD, Pavan-Langston D. Delayed onset of varicella keratitis. Cornea. 1992;11(5):471-4.
45. Cobo LM. Corneal complications of herpes zoster ophthalmicus. Prevention and treatment. Cornea. 1988;7(1):50-6.
46. Voelker R. Increasing cases of Shingles in the eye raise key questions. JAMA. 2019;322(8):712-4.
47. Borkar DS, Tham VM, Esterberg E, Ray KJ, Vinoya AC, Parker JV, et al. Incidence of herpes zoster ophthalmicus: results from the Pacific Ocular Inflammation Study. Ophthalmology. 2013;120(3):451-6.
48. Tran KD, Falcone MM, Choi DS, Goldhardt R, Karp CL, Davis JL, et al. Epidemiology of herpes zoster ophthalmicus: recurrence and chronicity. Ophthalmology. 2016;123(7):1469-75.
49. Rousseau A, Bourcier T, Colin J, Labetoulle M. Herpes Zoster Ophthalmicus--Diagnosis and Management. US Ophthalmic Review. 2013;6(2).