CASE REPORT

Anterior segment OCT findings and atypical refractive changes secondary to Epstein-Barr virus–associated nummular keratitis

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Introduction: This case study described refractive changes that can occur in the setting of Epstein-Barr virus (EBV)-associated nummular keratitis (NK) and highlighted the role that anterior segment optical coherence tomography can serve in diagnosis and management of this disease.

Patient and Clinical Findings: A 15-year-old girl developed subepithelial and anterior stromal corneal lesions and experienced progressive decline in the corrected distance visual acuity. She also developed a significant myopic shift with increased keratometric and refractive astigmatism.

Diagnosis, Intervention, and Outcomes: Targeted laboratory testing was performed. A diagnosis of chronic EBV-associated NK was made, and the patient was treated with systemic valacyclovir and topical steroids. Clinical appearance of lesions and corrected distance visual acuity improved, although refractive and keratometric changes persisted.

Conclusions: Significant and persistent refractive changes can occur in the setting of EBV-associated NK, similar to those seen after conductive keratoplasty. Anterior segment optical coherence tomography can be a potentially helpful supplementary diagnostic imaging modality to avoid invasive testing in such cases.

Nummular keratitis (NK) is an immune-mediated response to viral antigens characterized by coin-shaped lesions within the corneal stroma, usually associated with viruses such as herpes simplex virus types 1 and 2, varicella zoster virus, or adenovirus. Epstein-Barr virus (EBV) is a well-known causative agent of infectious mononucleosis but has a wide range of anterior segment manifestations, including conjunctivitis, keratitis, and uveitis.

We present a patient with NK associated with EBV that resulted in both classic clinical findings and atypical, unexpected refractive changes. Although corneal pathology improved with treatment, the induced refractive and keratometric changes persisted.

Patient Consent Statement
The patient's legal guardian provided written informed consent for publication. No personally identifiable information is included in the case report.

CASE REPORT
A 15-year-old Native-American girl was referred by her primary eyecare provider for painless, progressive loss of vision in both eyes over the past 6 months. She had moderate myopia and astigmatism previously corrected with spectacles but had no significant ocular history, ocular surgery, medical history, or medication use. Her last known manifest refraction approximately 1 year before presentation was −3.00 +1.00 × 85 in the right eye and −3.75 +1.50 × 90 in the left eye with corrected distance visual acuity (CDVA) 20/20 in both eyes. Family and social histories were unremarkable. Her parents reported an unremarkable birth history with no delay in childhood milestones, and the patient demonstrated appropriate performance in school.

At initial visit, CDVA was 20/40 in the right eye (−5.00 +1.50 × 088) and 20/80 in the left eye (−5.75 +2.50 × 112). Pupils were equally reactive with no relative afferent pupillary defect. Intraocular pressure measured 18 mm Hg in the right eye and 20 mm Hg in the left eye. Ultrasound pachymetry measured 619 μm in the right eye and 625 μm in the left eye. Corneal examination was notable for bilateral, circumferentially scattered subepithelial lesions with admixed haze and 360-degree limbal corneal neovascularization (Figure 1). Notably, there was complete sparing of the central
cornea in both eyes. Anterior chamber was quiet bilaterally. Dilated fundoscopic examination showed normal findings. Topography revealed 5.5 diopters (D) and 7.5 D of with-the-rule corneal astigmatism in the right and left eyes, respectively, which was significantly higher than the refractive astigmatism (Figure 2). Anterior segment optical coherence tomography (AS-OCT) demonstrated subepithelial and anterior stromal lesions that were confined to superficial peripheral corneal layers without involvement of deeper corneal layers and the visual axis (Figure 3).

A working diagnosis of inflammatory vs infectious keratitis was made. The patient underwent laboratory testing, including complete blood count, complete metabolic panel, antineutrophil cytoplasmic antibody titers, antinuclear antibody, human leukocyte antigen-B27, lysozyme, West Nile immunoglobulin (Ig) G/IgM, rapid plasma reagin, fluorescent treponemal antibody absorption, HIV-1/2, interferon gamma release assay, herpes simplex virus types 1 and 2 IgG/IgM, Sjögren syndrome A, Sjögren syndrome B, Lyme IgM, angiotensin-converting enzyme, erythrocyte sedimentation rate, C-reactive protein, and uric acid. All levels were normal besides EBV laboratory values, which revealed an elevated EBV IgG for early antigen (162 U/mL, ref 0.0 to 10.9 U/mL), viral capsid antigen (>750.0 U/mL, ref 0.0 to 21.9 U/mL), and nuclear antigen (423.0 U/mL, ref 0.0 to 21.9 U/mL). Of note, EBV IgM for viral capsid antigen was not detected, suggesting a possible chronic infectious pattern.

Given these results, the patient was started on topical prednisolone acetate 1% 6 times daily and oral valacyclovir 1 g 3 times daily. The patient tolerated this medication regimen well. Over the next 4 months, CDVA declined to 20/200 in both eyes despite improvement on clinical examination. Medications were tapered to once-daily dosing over 9 months. Between 4 and 9 months after initial presentation, CDVA improved, although there was an increase in myopic sphere and refractive cylindrical correction. At 1-year follow-up, CDVA improved to 20/40 in the right eye (−11.25 +2.25 × 94) and 20/50 in the left eye (−10.25 +2.00 × 88). Clinical appearance of lesions improved significantly, and AS-OCT revealed consolidation and demarcation of subepithelial haze and anterior stromal scarring (Figure 4 and Supplemental Figure 1, http://links.lww.com/JC9/A362). Medications were reduced to once in every other day dosing. The patient has maintained this CDVA and refraction at her last visit, approximately 2 years from the time of presentation. Contact lenses have been offered for additional CDVA improvement, but the patient and family have declined pursuing this option now.

**DISCUSSION**

NK can occur as a heterogeneous group of diseases with characteristic corneal changes. EBV-associated NK typically occurs secondary to subclinical and/or prolonged infection. Previous reports have indicated a nearly ubiquitous incidence of infection in both adults and children. EBV-associated keratitis can present in varying categories, broadly summarized as follows: (1) superficial subepithelial infiltrates similar to Thygeson superficial punctate keratitis, (2) bilateral NK with opacities scattered in the mid/anterior stroma in a ring shape, and (3) multifocal keratitis involving all corneal layers with neovascularization. Our patient’s presentation was primarily of the second type, with some elements of the third, given the peripheral neovascularization. Treatment strategies for all types of EBV-associated keratitis involve a combination of topical or systemic steroids, with or without topical or systemic antiviral treatment, as there is no clear consensus regarding preferred practice patterns.

Although polymerase chain reaction testing could have definitively proved the diagnosis of EBV, we chose not to perform this invasive procedure in a pediatric patient, especially given the controversy regarding its value in testing intraocular fluids. Given the aforementioned laboratory testing results, we formulated our management...
based on the positive anti-EBV IgG titers and AS-OCT findings, discussed further in detail.

At present, there is no clear evidence regarding our choice of using systemic valacyclovir and topical steroids. Some authors have advised against using acyclovir (and presumably its prodrug, valacyclovir) for EBV infection as it has no effect on EBV-induced transformation of B lymphocytes or EBV genome replication.9 Trifluorothymidine, which does not require a viral thymidine kinase (vTK) for its activity, may also be a viable treatment option as the lack of a vTK makes EBV relatively resistant to nucleoside analogs that require vTK-linked activation.10

We believe our case is instructive for several reasons. First, to our knowledge, our case is the first to describe significant refractive changes that can occur in the setting of EBV-associated NK. Previous authors have reported refractive changes occurring in the background of varicella disciform stromal keratitis and herpes simplex keratitis.11,12 In both reports, the authors described spontaneous reduction and resolution of myopic refractive error, which was believed to be because of stromal inflammation and thinning causing corneal flattening. In contrast to these hyperopic shifts, our patient had a significant myopic shift with increased keratometric and refractive astigmatism. It is plausible that a significant component of the observed myopic shift can be attributed to age-related progression of myopia, which may include axial myopia along with keratometric steepening. Axial length measurements, such as with optical biometry, were not taken during the course of clinical care to confirm or negate this component. Furthermore, cataractous lens changes were not observed during the 2-year period.

Thus, keratometric changes remain a noteworthy aspect to the presented case. One potential explanation for our patient’s changes is that chronic inflammation induced structural changes in the corneal mid-periphery. This process may be similar to refractive changes observed with conductive keratoplasty, in which heat-induced shrinking of peripheral collagen lamellae causes secondary corneal steepening, inducing a myopic refractive error.13 Thus, chronic EBV infection in the patient may have caused conductive keratoplasty-like biomechanical changes in the periphery that led to central corneal changes. Specifically, we noted corneal steepening of approximately 1.5 D in both eyes over the course of 2 years (Supplemental Figure 2, http://links.lww.com/JC9/A363). In addition, we noted significant inferior corneal thinning, suggestive of stromal compaction in both eyes over the 2-year period, which may indicate development of ectasia and merits close monitoring for progression (Supplemental Figure 3, http://links.lww.com/JC9/A364). More importantly, after prolonged treatment, the progressive changes have stabilized.
over the follow-up period. Although we are unable to definitively prove that EBV-associated changes caused myopic and astigmatic progression, clinicians may consider our findings as they attempt to concurrently treat underlying disease, achieve successful visual rehabilitation, and monitor for future development of corneal ectasia.

Second, we found AS-OCT to be a useful noncontact imaging modality that enabled precise visualization of corneal lesions, for both diagnosis and disease monitoring. We routinely obtain AS-OCT images at our institution when diagnosing atypical corneal disease. Features seen on initial imaging confirmed our suspicions of postviral inflammatory changes and guided our treatment strategy (Figure 3). After therapy, AS-OCT was useful in identifying the extent of peripheral subepithelial scarring with a clear demarcation line between the affected and unaffected corneas. As described by others, although in the context of peripheral inflammatory corneal disease, AS-OCT aided us in monitoring progressive structural changes in the peripheral cornea, such as increased hyperreflectivity of lesions and geographic assessment of corneal thickness. Finally, AS-OCT visualization of the observed lesions bolstered our working diagnosis and obviated the need for an invasive procedure, such as polymerase chain reaction testing and/or corneal biopsy, in a pediatric patient. We recommend that treating providers exercise best clinical judgment regarding what type of testing to ultimately initiate, keeping in mind the favorable results we had in our patient relying on AS-OCT and laboratory testing alone. In recalcitrant and/or worsening cases, clinicians may wish to obtain invasive testing.

In conclusion, clinicians should always consider EBV when encountering NK. A targeted laboratory workup, along with AS-OCT imaging, may help in formulating a customized treatment plan for each patient. Refractive changes may occur, and a myopic astigmatism shift may be seen in some patients. We hope that our findings may help clinicians to better formulate diagnostic strategies and treatment regimens to successfully manage this challenging patient population.

Disclosures: None reported.