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High-risk human papillomavirus-associated corneal/conjunctival intraepithelial neoplasia in a young patient

Jessica Y. Walia [a,*], George J. Harocopos [a,b], Augustine R. Hong [a]

[a] Department of Ophthalmology and Visual Sciences, Washington University School of Medicine, St. Louis, MO, USA
[b] Department of Pathology and Immunology, Washington University School of Medicine, St. Louis, MO, USA

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ABSTRACT

Purpose: To report a case of high-risk human papillomavirus (HPV)-associated corneal/conjunctival intraepithelial neoplasia (CIN) in a 17-year-old fair-skinned male with no other risk factors.

Observations: A 17-year-old Caucasian male presented with an 18-month history of left eye pain, redness, itchiness, and decreased vision. Examination revealed a leukoplakic nasal limbal/peripheral corneal lesion resistant to topical antibiotic and anti-inflammatory treatments. Excisional biopsy confirmed the diagnosis of CIN, and RNA in situ hybridization testing for high-risk HPV types 16/18 was positive. Subsequent testing of the patient for human immunodeficiency virus (HIV) returned negative.

Conclusions and Importance: The median age of CIN diagnosis in the United States is in the sixth decade of life and is usually associated with a history of ultraviolet (UV) light exposure. There are reports of CIN in young patients with systemic immunodeficiency, immunosuppression, xeroderma pigmentosum, atopic dermatitis, asthma, and vaping. Here we present a case of high-risk HPV-associated CIN in a young, fair-skinned patient with no other identifiable risk factors.

1. Introduction

Ocular surface squamous neoplasia (OSSN) is the most common ocular surface tumor with an incidence of 0.5–6.1 cases per million per year. The average onset of OSSN is 65 years old in the United States.[1,2] The most common risk factor for OSSN is UV irradiation, which induces pyrimidine dimers that distort DNA strands and cause a delay or failure in repair.[3] The incidence of OSSN increases in regions closer to the equator and decreases in temperament climates.[3,4]

Other documented risk factors for OSSN include cigarette smoking; mechanical trauma from contact lens use, dust, or wind; fair skin; and immunocompromising conditions.[3]

OSSN in a young adult is typically associated with HIV, with the mean age of OSSN onset in the third and fourth decade of life in HIV-positive patients.[5] The current literature reports OSSN in patients under 20 years old as an association with xeroderma pigmentosum and Papillon-Lefèvre syndrome; however, HPV testing was not performed in these patients.[6,7]

Here, we report an interesting case of high-risk HPV-associated CIN in a 17-year-old Caucasian patient with no other significant identifiable risk factors.

2. Case report

A 17-year-old Caucasian male presented to our clinic with an 18-month history of left eye pain, itchiness, redness, light sensitivity, and blurred vision. The patient's medical history was unremarkable. His ocular history was remarkable for myopia in both eyes, for which he denied any history of contact lens use. His social history was remarkable for having previously lived in Texas from birth to 9 years old, after which, he moved to Illinois. He denied smoking cigarettes, vaping, alcohol intake, illicit drug use, or history of sexual activity. He was up to date on his vaccinations including two doses of the HPV 9-valent vaccine (GARDASIL®9), designed to protect against HPV types 6, 11, 16, 18, 31, 33, 45, 52, 58.

The patient originally noticed left eye discomfort two years prior but was not evaluated until 15 months after symptom onset. At the time, he was diagnosed with stromal keratitis and started on topical prednisolone acetate 1% every 2 h in his left eye. He was next seen three months later by a different provider and was instructed to stop the topical prednisolone acetate 1%, start oral valacyclovir 1 g three times a day for ten days, and start ganciclovir ophthalmic gel 0.15% five times a day for treatment of suspected herpetic keratitis. One month later, he developed

* Corresponding author. Department of Ophthalmology, Washington University in St. Louis, Campus Box 8096, 660 S. Euclid Ave, St. Louis, MO, 63110, USA.
E-mail address: jessicawalia@wustl.edu (J.Y. Walia).

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worsened pain and redness. Given his worsening clinical examination and symptoms, he was referred to our center for evaluation by a corneal specialist.

On our initial examination, his visual acuity was 20/30 in the right eye and 20/200 in the left eye. The pupil exam and extraocular movements were unremarkable. External examination revealed a pale complexion with diffuse freckling and protective ptosis in the left eye. Slit lamp examination of his left eye revealed 360° of limbal injection with corneal blood vessels growing approximately 1 mm into the peripheral cornea. There was a 1 mm raised leukoplakic superficial lesion on the nasal peripheral cornea with diffusely thickened and hazy epithelium throughout the inferior and nasal aspect (Fig. 1A). There was also a diffusely thickened paracentral corneal lesion in the subepithelial space that herniated through the epithelium and formed a raised 1 mm round nodule that stained with lissamine green (Fig. 1B). The anterior stroma appeared to have a mild haze inferiorly. There were no significant eyelid or palpebral conjunctival findings on eyelid eversion. The slit lamp examination of the right eye was unremarkable.

Anterior segment optical coherence tomography (OCT) of the left eye showed a central subepithelial hyper-reflective lesion that herniated through the variably thickened and thinned, hyper-reflective overlying epithelium (Fig. 2A). Inferior to the central corneal lesion, there was a diffuse subepithelial hyper-reflective sheet with a thickened hyper-reflective epithelium (Fig. 2B). At the temporal edge of the corneal lesion, there was an abrupt transition zone between normal and abnormal epithelium (Fig. 2C). Images through the nasal peripheral/limbal leukoplakic portion demonstrated a thickened hyper-reflective epithelium (image not available). Given the prolonged duration of symptoms and lack of improvement on antibiotic, antiviral, and anti-inflammatory medications, the option of an excisional biopsy was discussed with the patient and his family, and they agreed to proceed.

Two weeks after initial evaluation, an excisional biopsy was performed through careful blunt dissection of the subepithelial and epithelial lesions. The lesion was tightly adherent to the underlying stroma centrally, but loosely adherent elsewhere, and was able to be removed in two pieces and sent to pathology. Pathology confirmed CIN with severe atypia without invasion beneath the basement membrane, with an underlying fibrovascular pannus (Fig. 3A, 3B, 3C). Immunostaining with Ki-67 highlighted over half of the epithelial cells, and in some areas, exhibited full-thickness positivity with proliferative index of about 90% (Fig. 3C). HPV testing of the specimen was performed using RNA in situ hybridization and returned positive for high-risk cocktail, which tests for HPV strains 16, 18, 26, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66, 68, 73, and 82. Additional testing specifically for HPV types 16 and 18 also returned positive (Fig. 3D) (Integrated Oncology, Esoterix Genetic Laboratories, LLC 521 W. 57th Street, 6th Floor, New York, NY 10019). Immunostaining with p53 exhibited mildly increased expression with positive cells scattered through the entire epithelium and not just confined to the basal layer (not shown). Immunostaining for HSV-1 and HSV-2 was negative.

Subsequent bloodwork testing for HIV and syphilis in the patient was negative. One week after surgery, the patient was started on topical interferon alpha-2b (1 million IU/mL) four times a day in his left eye and remained on this course for three months without recurrence. Three months after surgery, his vision in the left eye improved to 20/25.

3. Discussion

There are reported cases of atypical OSSN masquerading as other ocular conditions with resulting misdiagnosis and delayed treatment.[8] Our patient's OSSN was initially misdiagnosed and treated as herpetic disease. This delay can be attributed to the confinement of his lesion to the cornea and limbus, without any obvious involvement of the conjunctiva posterior to the limbus in the form of vascular or squamous features. Furthermore, our young patient falls outside the typical age range for CIN prevalence. The paracentral corneal opacity seen clinically and on OCT imaging was histologically confirmed to be due to a combination of intraepithelial squamous neoplasia and underlying fibrous pannus formation. The underlying fibrous pannus was thicker in the region immediately beneath the corneal nodular opacity and had an overlying one-millimeter epithelial defect. These features associated with the fibrous pannus formation likely contributed to the clinical diagnostic difficulty in this case.

OSSN occurs more frequently in Caucasian males and has an average onset in the sixth decade of life, with only 3% of cases occurring in patients 30 years old or younger.[2]

The current literature suggests an association of OSSN in young patients with HIV infection, immunosuppression, atopic eczema, xeroderma pigmentosum, asthma, and vaping.[3,7,9,10] Upon further questioning and testing, our patient did not have any of these risk factors. His surgical pathology returned positive for high-risk HPV 16/18, which is suspected to be the cause for the unusual occurrence of CIN in such a young patient. A recent study found that 21% of CIN cases were positive for HPV, with HPV type 16 being the most common culprit. High-risk HPV positivity was associated with a significantly greater risk of recurrence. Additionally, at the time of CIN diagnosis, the HPV-positive group was on average 11.5 years younger than the HPV-negative group.[11]

HPV is a non-enveloped double-stranded circular DNA virus that has been associated with OSSN.[12] HPV's role in OSSN formation is still

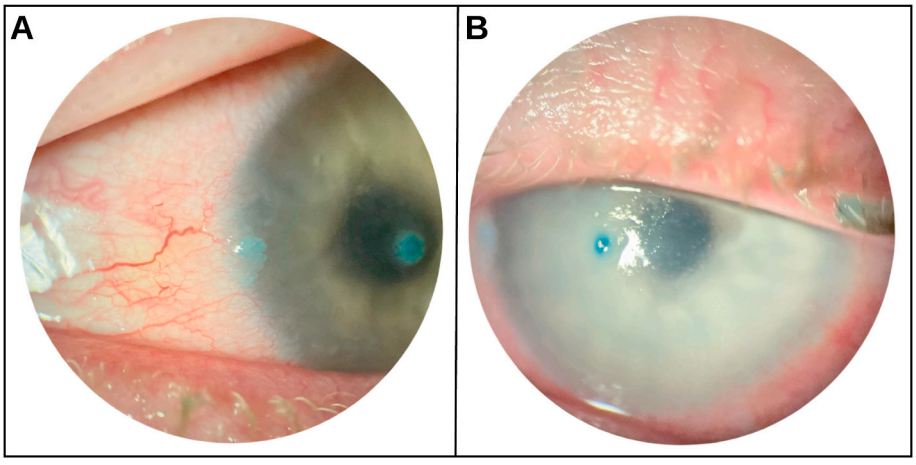

Fig. 1. Photographs of the patient's left eye with lissamine green staining showing (A) a lesion on the nasal limbus and (B) a paracentral nasal focal white lesion on the superficial cornea. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

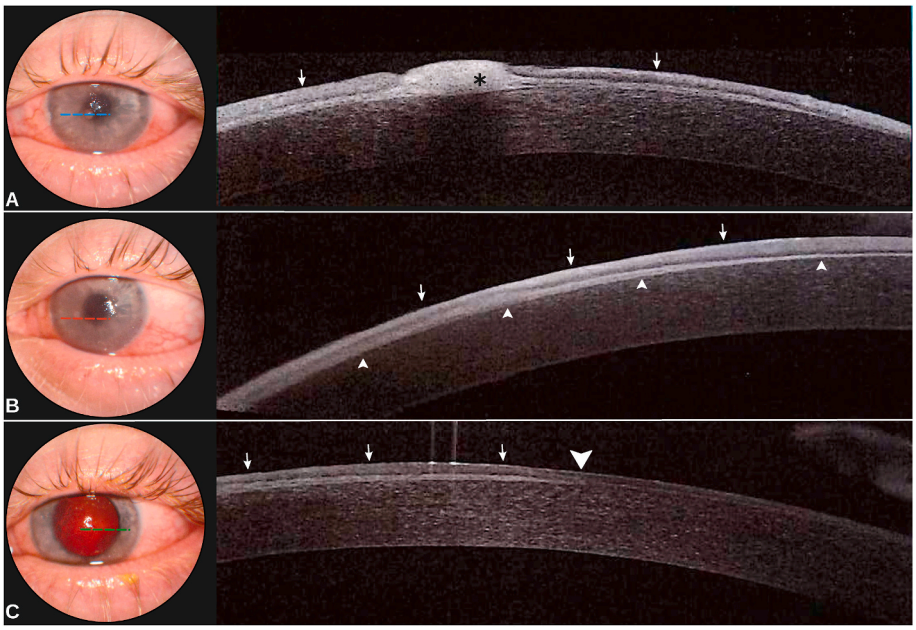

Fig. 2. Anterior segment OCT of the left eye. A) The blue dotted line demonstrates the orientation of the OCT raster over a paracentral corneal lesion. On OCT imaging, there is a corresponding subepithelial hyper-reflective lesion (asterisk) herniating through the variably thickened and thinned, hyper-reflective epithelium (arrows). B) The red dotted line demonstrates the orientation of the OCT raster inferior to the corneal lesion. On OCT imaging, there is a corresponding diffuse subepithelial hyper-reflective sheet (arrowheads) with an overlying thickened hyper-reflective epithelium (arrows). C) The green dotted line demonstrates the orientation of the OCT raster on the temporal region of the corneal opacity. On OCT imaging, there is corresponding thickened hyper-reflective epithelium (arrows) with an abrupt transition zone from normal to abnormal epithelium (arrowhead). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

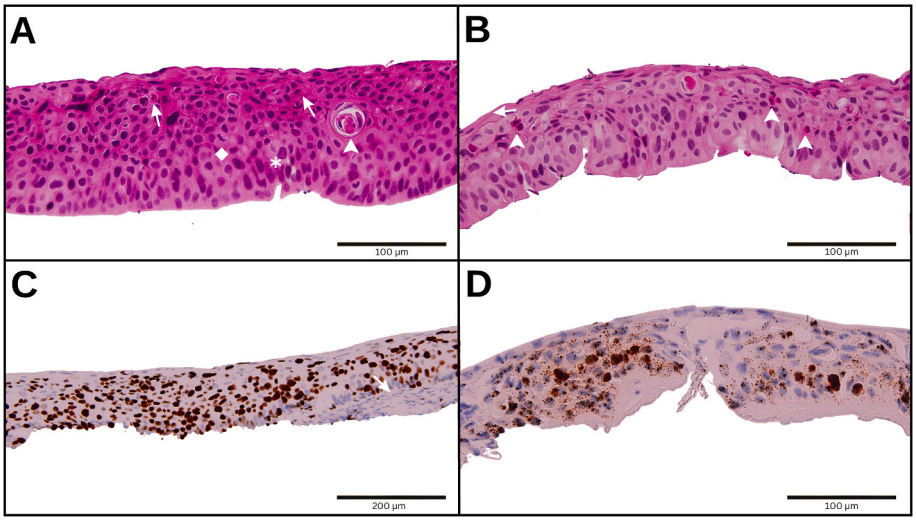

Fig. 3. Histopathology of excised corneal/conjunctival lesion. A) Epithelial hyperplasia with dyskeratosis (arrows), keratin whorl (arrowhead), cellular atypia with pleomorphism (asterisk), and mitotic figures above the basal layer (diamond). The basement membrane is intact. (H&E stain, original magnification: x400) B) Surface keratinization (arrow) and intraepithelial dyskeratosis (arrowheads). (H&E stain, original magnification: x400) C) Ki-67 exhibits an abnormally high proliferative index, approximately 90%. Beneath the basement membrane (arrow), there is a fibrous pannus containing a chronic inflammatory reaction, thereby explaining why there are some Ki-67 positive cells beneath the basement membrane. (Original magnification: x200) D) High-risk HPV (strains 16/18) in situ hybridization demonstrates positive staining. (Original magnification: x400).

controversial and widely debated. Current studies report the average prevalence of HPV in OSSN to be 33.8%; however, with a large range between 0 and 100%.[13] Other reports have found a low frequency of HPV in OSSN in India, Germany, and Taiwan and a high frequency of HPV in OSSN in Miami, Florida.[14,15] Additionally, many reports linking HPV and OSSN do not disclose the patient's HIV status, which can be a confounder.

The currently proposed pathogenesis for how HPV contributes to OSSN formation is through the early (E) region of HPV DNA, which encodes for proteins involved in viral replication. The E6 and E7 proteins have transformative properties and can interact with the host tumor suppressor genes p53 and retinoblastoma family of proteins pRb to alter cell proliferation.[13,16,17]

HPV is also thought to increase conjunctival cell sensitivity to UV-induced mutagenesis and can potentiate UV radiation-related DNA damage, such as the formation of pyrimidine dimers.[18]

Whether or not HPV alone is an independent risk factor for OSSN development or if it increases susceptibility to other known causes of OSSN formation is currently unknown.

In our patient's case of CIN, UV-induced damage from his time spent outdoors in Texas when he was younger may have played a contributing role. It is also reasonable to suspect that HPV potentiated UV-induced damage and contributed to CIN formation at such a young age.

4. Conclusions

We present an unusual case of corneal/limbal CIN in a 17-year-old patient with fair skin, but no other identifiable clinical risk factors. However, high-risk HPV was detected by in situ hybridization on histological examination of the lesion. The diagnosis of CIN was delayed in our patient, likely due to his age and the confined location of the lesion to the cornea and limbus, without any apparent involvement of the conjunctiva posterior to the limbus.

This case is significant because OSSN typically occurs in older patients who have had prolonged exposure to UV light. OSSN presenting in a younger patient is usually associated with immunosuppression or HIV infection and typically occurs in the third or fourth decade of life. OSSN in patients under 20 years of age is rare in the literature, and those cases that have been reported have been associated with systemic risk factors such as xeroderma pigmentosum or Papillon-Lefèvre syndrome. To our knowledge, this is the first case report of HPV being the only identifiable unique risk factor for OSSN in a patient under 20 years of age and without systemic risk factors.

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Authorship

All authors attest that they meet the current ICMJE criteria for authorship.

Patient consent

Consent to publish the case report was not obtained. This report does not contain any personal information that could lead to the identification of the patient.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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