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Case Report

Conjunctival squamous carcinoma in an HIV + woman: Association with high-risk human papillomavirus

Jihong Sun [a,b], Mark S. Burke [c], Hui Zhu [a,b], Thom R. Loree [c], Margaret S. Brandwein [a,b,*]

[a] Department of Pathology and Anatomical Sciences, SUNY at the University at Buffalo, Erie County Medical Center, Buffalo, NY, United States
[b] Department of Pathology, Erie County Medical Center, Buffalo, NY, United States
[c] Department of Head & Neck and Plastic & Reconstructive Surgery, Erie County Medical Center, Buffalo, NY, United States

1. Introduction

Human immunodeficiency virus (HIV)-infected patients have an improved life expectancy thanks to highly active antiretroviral therapies (HAART). The incidences of opportunistic infections and AIDS-defining cancers (ADCs) such as Kaposi sarcoma and non-Hodgkin lymphoma, have markedly decreased. However, the incidences of non-AIDS-defining cancers (NADCs) such as Hodgkin lymphoma, anal carcinoma, lung cancer, hepatocellular carcinoma (HCC), and head and neck cancers have been steadily increasing over the past two decades [1–4]. HIV + patients are known to have increased risk for developing NADCs, even when adjusted for known cancer risk factors. In fact, NADCs are a major cause of death of HIV + patients in the HAART era. The overall relative risk for all NADCs is about two fold higher than in the general population, adjusted for age and gender. Risk estimates vary substantially, per cancer type, anatomic sites, study period, and region. Additionally, outcome for HIV + patients with NADCs is much poorer compared to HIV-negative counterparts. The reasons for these findings in HIV-infected patients are not understood and pose challenges on their clinical management. Likely, viral-mediated oncogenesis plays a greater role in HIV + NADCs, compared to the general population and viral causation is well-established with many NADCs. Epstein-Barr virus (EBV) is a known promoter of ADCs (non-Hodgkin lymphoma) and NADCs (Hodgkin lymphoma, nasopharyngeal carcinoma, Burkitt's lymphoma) [5,6]. Human Herpes Virus 8 is associated with Kaposi sarcoma and primary effusion lymphoma [7]. Hepatitis C and B viruses are associated with hepatocellular carcinoma [8]. High-risk Human Papillomavirus is responsible for mediating carcinogenesis of the cervix, anus, and oropharynx [9].

The incidence of conjunctival squamous carcinoma (also referred to as ocular surface carcinomas), another NADC, has dramatically increased in HIV infected patients [10,11]. Conventional conjunctival squamous carcinoma is usually an indolent malignancy of older men [12]. In contrast, HIV + conjunctival squamous carcinomas occur in younger patients, are diagnosed at more advanced stage, and associated with poorer prognoses than the conventional counterparts [13–16]. Emerging publications have established a variable association between HPV and ocular squamous carcinomas both in the general and HIV + populations [17–21]. Here, we report a case of conjunctival squamous carcinoma in HIV + female who experienced rapid tumor progression.

2. Case report

A 46-year-old Caucasian woman tested positive for HIV and hepatitis C virus in July of 2003. She was noncompliant with standard antiretroviral agents. Her initial CD4 cell absolute count was 232 cells/mm [3]. The most recent CD4 absolute count, two months prior to diagnosis, was 80 cells/mm^3. She noted a lesion of the right upper palpebral conjunctiva, which was biopsied and diagnosed as poorly differentiated squamous cell carcinoma.

She underwent resection of the right upper eyelid, with reconstruction involving rotation of the lower lid to replace the upper lid. The carcinoma was 2.5 cm in greatest dimension with a thickness of 7 mm. It involved the entire palpebral conjunctiva extending down to the free eyelid edge, and up to the superior fornix. Microscopically, the poorly differentiated squamous cell carcinoma demonstrated spindle cell (sarcomatoid) features (Fig. 1). Solid and vague papillary architecture was seen. Central necrosis was present in the solid areas. Carcinoma invaded palpebral musculature with a pushing, transitional-like, nonaggressive pattern of invasion. The tumor was nonkeratinizing and basaloid; tumor cells had scant pink cytoplasm, pleomorphic hyperchromatic nuclei and inconspicuous nucleoli. Some areas showed prominent elongated nuclei with spindle cell changes. There were numerous mitoses, up to 23/HPF. No overt keratin production or glandular differentiation were present. No multinucleated tumor giant cells or anaplastic cells were seen. *In-situ* carcinoma extended to the medial conjunctival margin.

Disease recurrence was evident after four months. Clinically, a poorly demarcated, white-pink, retracted mucosal lesion was present close to the medial canthus adjacent to the previous rotated resection site (Fig. 2). Orbital exenteration with reconstruction was performed six months after the first resection, with intention of cure. Microscopic conjunctival carcinoma was present adjacent to prior surgical site with a nonaggressive, pushing pattern of invasion (Fig. 2). The medial canthus, lacrimal sac, and globe were uninvolved. The closest resection margin was 4 mm. Currently, she is disease-free after four months after salvage surgery.

Immunohistochemistry revealed tumor expression of p63 and CK5/6. p16 was overexpressed with a strong, diffuse, nuclear and cytoplasmic pattern (Fig. 3A). HPV *in-situ* hybridization using commercially available probes recognizing HPV genotypes 6/11, 16/18, 31/33 was

* Corresponding author at: Department of Pathology and Anatomical Sciences, SUNY at the University at Buffalo, Chief of Service, Pathology, Erie County Medical Center, Buffalo, NY, United States.
E-mail address: MGensler@Buffalo.edu (M.S. Brandwein).

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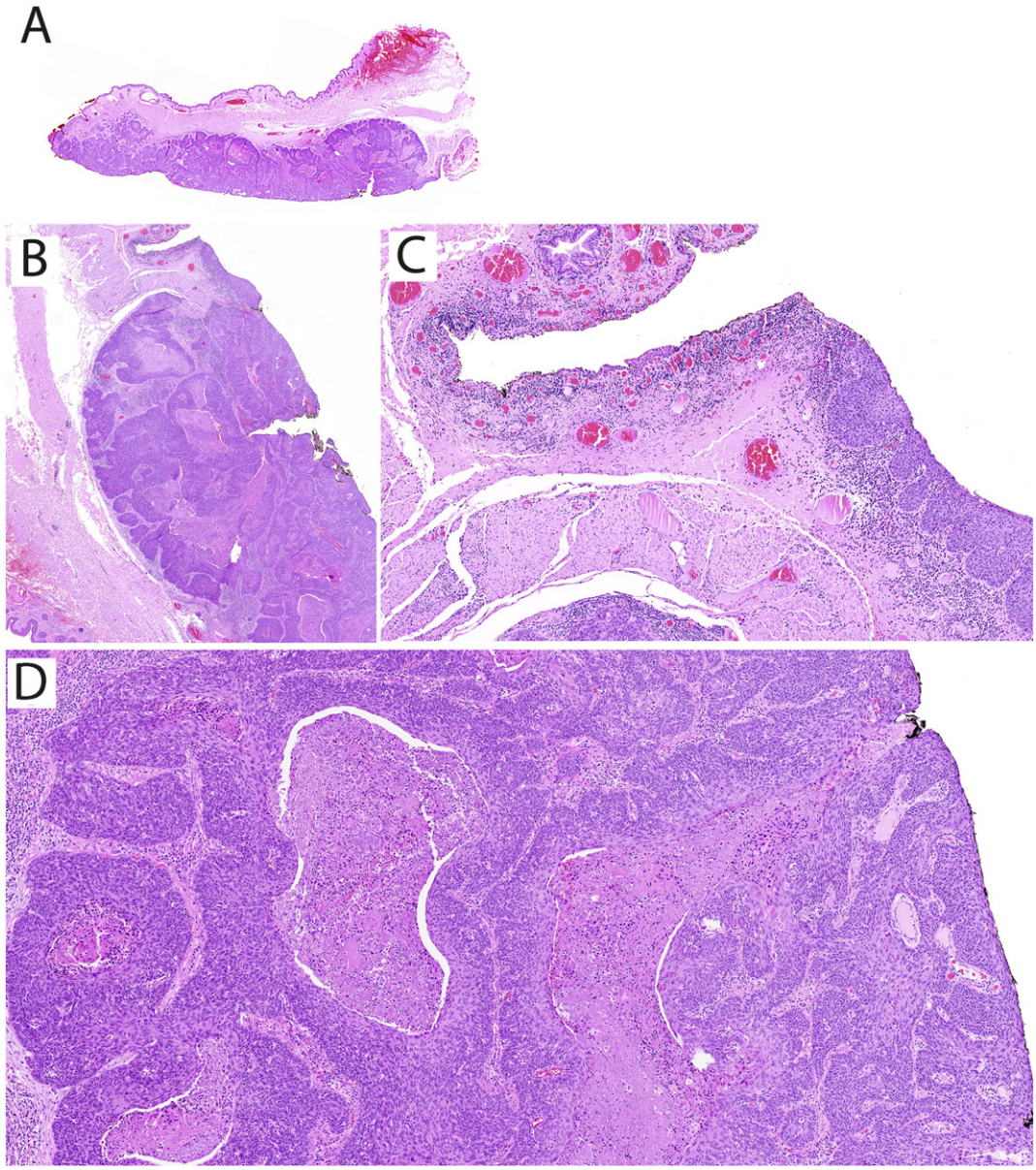

Fig. 1. A, B, C: Low and high-power views of *in-situ* and infiltrating basaloid squamous carcinoma of palpebral conjunctiva. D: Higher power revealing a basaloid squamous carcinoma with palisading and evidence of maturation. No keratin pearls or multinucleated/anaplastic tumor cells were present.

positive for HR-HPV 16/18. (Fig. 3B). No signals were seen for HPV 31/33 or 6/11. EBER *in-situ* hybridization was negative. Immunohistochemistry for HHV-8 was negative.

3. Discussion

Conjunctival squamous carcinoma, also referred to as ocular surface squamous neoplasia, commonly present as a fleshy, gelatinous, papillomatous or sessile lesion in the interpalpebral area of perilimbal conjunctiva. Generally, associated risk factors are HIV, immune suppression from other causes, ultraviolet B radiation exposure, chemicals, ocular injury, and vitamin A deficiency. Two distinct biological and demographic patterns emerge for this cancer. Conventional conjunctival squamous carcinoma is rare, indolent, and seen mostly in middle aged males living in high-latitude regions[12,22,23]. This entity is characterized by slow growth and good outcome. Complete surgical excision with margin clearance is effective; the rates of local recurrence and regional metastases are low [12,22,23].

The second pattern involves younger individuals with no gender predilection who live in equatorial Africa; this group is also likely to be HIV+ [10]. The upsurge of HIV infection and NARCs highlights these changing trends. Overall, conjunctival squamous carcinoma is rare in the United States; the U.S. HIV/AIDS Cancer Match Registry Study (1980 to 2004) contains 15 conjunctival squamous carcinomas, representing a significant increase [13]. Shields et al. report that HIV+ conjunctival carcinomas are clinically more aggressive and require enucleation or exenteration [14]. For example, a 38-year-old Thai HIV+ female sought medical attention 3 months noticing a tumor, which was aggressive enough to cause blindness requiring exenteration [16].

The inherent immunosuppression of HIV infection facilitates the other oncoviruses which initiate or promote carcinogenesis. Coinfections with HPV, EBV and HHV-8, are responsible for the large number of ADCs and NADCs in HIV+ persons. The associations between HIV and HPV infections in general and in the context of cervical neoplasia, are well established [24]. There are only a few studies on head and neck squamous cell carcinoma in the high-risk population of HIV patients [25,26].

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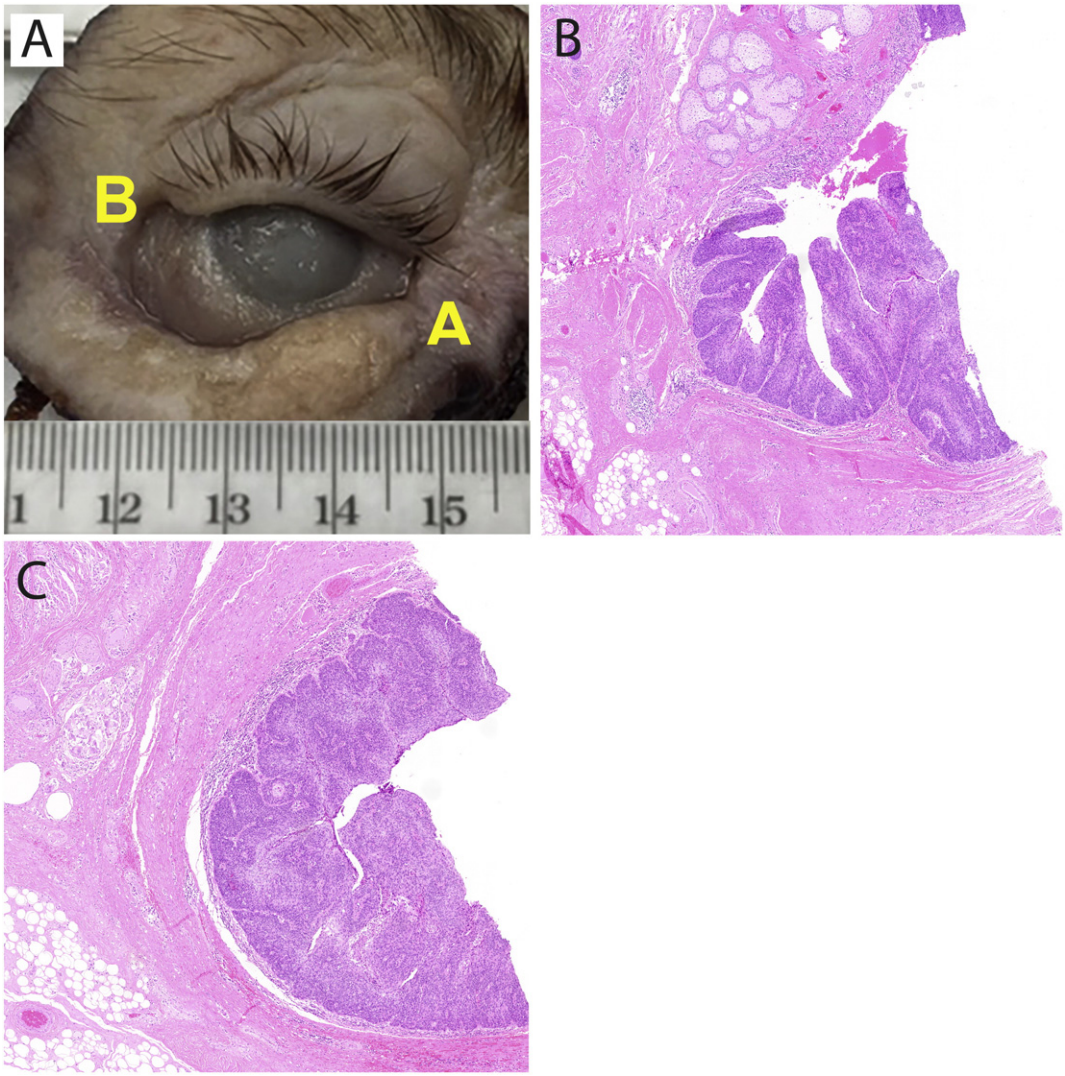

Fig. 2. A. Orbital exenteration: the upper lid had been previously resected and the lower lid was rotated and used to replace the upper lid. Region A (yellow), medial, represents the site of tumor recurrence appearing retracted. The cornea is cloudy due to edema. The red/pink region (B) (yellow) represents exposed, edematous conjunctiva and sclera. B and C represent disease recurrence. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Conjunctival/lacrimal squamous carcinomas have been variably associated with HPV, both in the general population and subset of HIV + patients. Just recently, HPV16 was demonstrated in a high proportion of 52 conjunctival/lacrimal squamous carcinomas and precursors in the US, in a group of predominantly HIV-negative patients [17]. Of interest, the HPV + invasive cancers more likely resembled HPV-mediated

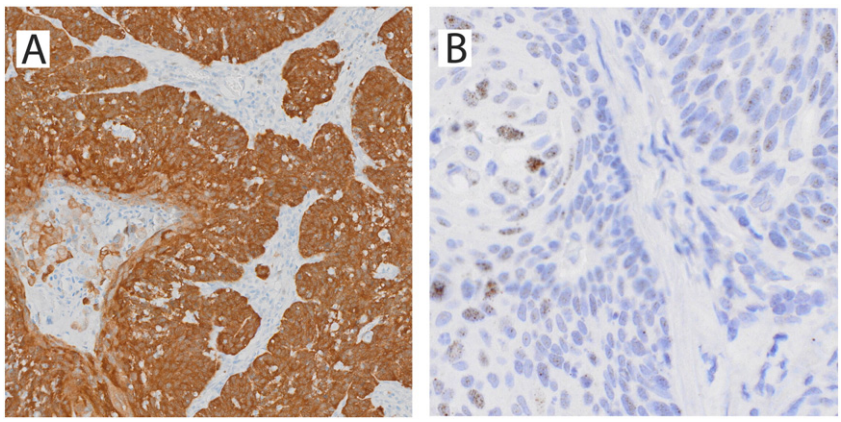

Fig. 3. A: p16 overexpression. B: *In-situ* hybridization for HR-HPV 16/18 reveals nuclear signals (brown) in tumor cells. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

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oropharyngeal cancers (nonkeratinizing, or partially keratinizing), as is illustrated in this case. This finding would then be a rationale for pathologists to test basaloid, nonkeratinizing, or partially keratinizing ocular surface squamous carcinomas, especially in patients under 50 years.

Squamous carcinoma represents the most common form of ocular surface neoplasia [27–31]. Precursors (conjunctival intraepithelial neoplasia) can manifest various appearances and clinically present as leukoplakic, nodular, pigmented, vascular, papillary, or fleshy lesions. Microscopically, the spectrum of precursors are classified as either mild-, moderate-, or severe- dysplasia/carcinoma *in-situ (CIS)*. This represents somewhat of a departure from grading oral dysplasias. In the oral cavity, the tendency is to avoid "moderate dysplasia" as a diagnostic category, thus flattening the classification to low-grade versus high-grade dysplasia/CIS. Ocular surface low-grade dysplasia is characterized by disorganized maturation, binucleated epithelial cells, and some degree of nuclear atypia. Moderate dysplasia is characterized by a greater degree of disorganization and cytologic pleomorphism involving at least the lower half of the thin ocular surface epithelium. Mitotic figures may also be seen. Severe dysplasia/CIS is characterized by yet a greater degree of disorganization and cytologic pleomorphism which spans beyond the lower half of the thin surface epithelium. The basement membrane is intact and no invasion is present.

As mentioned, conventional squamous cell carcinoma (SCC) represents the most common form of ocular surface neoplasia, which can be either nonkeratinizing and basaloid (as this case) or keratinizing. A number of SCC variants may also be seen such as acantholytic or adenoidsquamous variant (producing pseudoglands due to discohesiveness) [32], lymphoepithelial variant, sarcomatoid or spindle cell variant SCC, and mucoepidermoid carcinoma (MEC). The latter is another interesting departure from the upper aerodigestive tract, as here MEC is classified as minor salivary in origin, although it may arise from surface mucosa. Conjunctival mucosa does not contain any submucosal seromucinous glands, rather the mucosa itself has mucinous (goblet cell) differentiation. Ocular surface MEC, and the sarcomatopid and pseudoglandular variants are noteworthy in that they tend towards greater aggressiveness than conventional carcinoma.

A Ugandan study of conjunctival carcinomas (79 HIV+, 15 HIV negative) and precursors (34 HIV+, 5 HIV negative) interrogated both mucosal and cutaneous (β genus) HPV types [18]. Interestingly, cutaneous HPV types (most often HPV5 and HPV8) were significantly more common in cancers and precursors, especially among HIV+ patients; infection with multiple HPV types was common [18]. Not all conjunctival carcinoma studies find evidence of HPV; this might reflect geographic differences, sensitivity of detection methods, or simply the fact that no β genus HPV types were queried [33–35]. Of note, HHV-8 has been detected in 12/48 (25%) HIV+ Ugandans with conjunctival squamous carcinoma by PCR [36].

A recently published meta-analysis based on large study series commencing in the late 1980's confirmed a strong association between HIV and risk of ocular surface squamous neoplasia (RR 8.06, 95% CI: 5.29–12.30) [37]. The increased relative risk associated with mucosal HPV was 3.13 (95% CI: 1.72–5.71). Studies which addressed any association between both cutaneous and mucosal HPV and ocular surface squamous neoplasia demonstrated a stronger relationship with cutaneous HPV (RR 3.52, 95% CI: 1.23–10.08) compared to mucosal HPV (RR 1.08, 95% CI: 0.57–2.05).

It is well-established that outcomes for p16+/HPV mediated oropharyngeal cancers in the general population is improved as compared to p16-/HPV-counterparts [38]. Enhanced adaptive immunity to HPV is one of the factors responsible for this survival benefit [39–43]. On the other hand, NADCs are associated with worse outcomes compared to the general population, likely reflecting decreased immune status. We conclude that the current tumor is mediated by HPV16/18. Future studies of HIV+ conjunctival/lacrimal sac carcinomas should also query and validate the presence of β genus HPV and HHV-8.

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