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Cutaneous HPV16 and p16 Positive Basaloid Squamous Cell Carcinoma with Brain Metastasis: A Case Report

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Abstract

Basaloid squamous cell carcinoma is an infiltrative and aggressive variant of squamous cell carcinoma with basaloid features. Primary skin-derived basaloid squamous cell carcinoma is rare. Basaloid squamous cell carcinoma is commonly observed in the oropharyngeal and anogenital regions and is associated with high-risk human papillomavirus. We report a case of primary basaloid squamous cell carcinoma overlying the right scapula with metastasis to the regional lymph nodes and brain despite surgical resection and adjuvant chemoradiation. Histopathologic investigations of high-risk cutaneous squamous cell carcinoma do not routinely involve human papillomavirus testing. In contrast, oncogenic human papillomavirus and p16 are screened in head and neck squamous cell carcinoma for prognostication. Since the patient presented with an aggressive variant of squamous cell carcinoma and distal metastasis despite standard therapies, human papillomavirus testing was performed. P16, a surrogate marker for human papillomavirus infection and specifically HPV16 was identified in the tumor. This is a unique report of HPV16 in primary cutaneous basaloid squamous cell carcinoma with distal brain metastasis.

Keywords

Basaloid squamous cell carcinoma, HPV, p16

Introduction

Basaloid squamous cell carcinoma (BSCC) is an aggressive, but rare variant of squamous cell carcinoma (SCC) with atypical basaloid cells.[1,2] BSCC is found in the mucocutaneous and anogenital regions and is not routinely observed as a primary skin cancer.[1] To date, seven cases of primary cutaneous BSCC outside the upper aerodigestive tract and mucosal genital regions have been reported.[2–4] Having BSCC portends a worse prognosis, as up to 75% of patients have advanced nodal or metastatic disease.[3] BSCC can metastasize to any organ, but brain metastasis rarely occurs.[2–4]

Human papillomavirus (HPV) infection upregulates the expression of p16 tumor suppressor in cells.[5,6] Oncogenic HPV16 is strongly associated with BSCC found in oropharyngeal and anogenital areas.[1] There is some evidence for high-risk HPV33 in primary cutaneous BSCC.[2] HPV33 and HPV16 are both in the same phylogenetic species and are implicated in malignant transformation of vulvar, vaginal, cervical, penile, and anorectal cancer.[5,7]

Herein, we report a patient with HPV16 and p16 positive primary cutaneous BSCC with lymph node and brain metastasis originating outside the head and neck and anogenital regions. Whether HPV is a causative agent for malignant transformation of SCC on the skin is currently unknown. Our observations and others suggest that HPV positivity in primary cutaneous BSCC may be a surrogate marker for more aggressive disease with greater metastatic potential.

Case report

In 2006, a 48-year-old male presented to an outpatient dermatology clinic with an enlarging cutaneous lesion on the right scapula. Histologic examination showed invasive BSCC. He underwent wide local excision, with the closest

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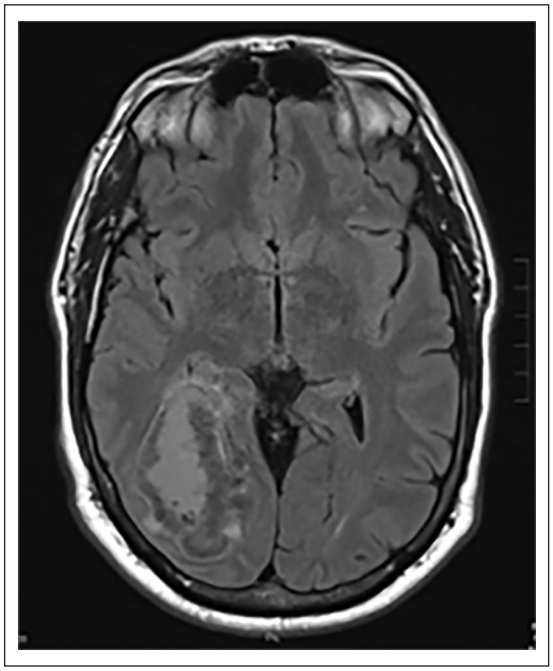

Figure 1. MRI brain with gadolinium demonstrating a 6.3 × 4.5 × 4.2 cm metastatic mass in the right occipital lobe.

peripheral margin reported at 1 mm. He then received adjuvant external beam radiotherapy (45 Gray (Gy) in 15 fractions) due to the narrow margins. Two years later, he developed cutaneous recurrence at the periphery of the radiation field with clinical right axillary lymphadenopathy. A biopsy of the cutaneous lesion and fine needle aspiration of the right axillary lymph node confirmed a locally metastatic BSCC. He subsequently underwent a right axillary complete lymph node dissection with 3/18 positive nodes. He was treated with adjuvant chemoradiotherapy with weekly cisplatin and 54 Gy of external beam radiation in 30 daily fractions to the right axilla and supraclavicular lymph nodes.

He had stable disease without recurrence until 9 years later, when he developed new onset neurological symptoms including headaches and photopsia. A subsequent brain magnetic resonance imaging (MRI) showed a 4.2 cm, large, irregular tumor in the right occipital lobe (Figure 1). He underwent parieto-occipital craniotomy for gross total resection of the tumor, with histological examination demonstrating BSCC. He then received adjuvant fractionated stereotactic radiotherapy (30 Gy in 5 fractions over 1 week). A staging computed tomographic (CT) scan of the chest, abdomen, and pelvis did not show any other evidence of metastasis. Postcraniotomy, his neurologic symptoms returned; however, repeat biopsy revealed necrotic brain tissue without malignancy. He is routinely seen in follow-up and is currently stable, without evidence of relapse. Immunotherapy will be trialed if there is evidence of disease progression.

All the biopsies were retrospectively reviewed. Identical features of BSCC were present in all samples (Figure 2(a)).

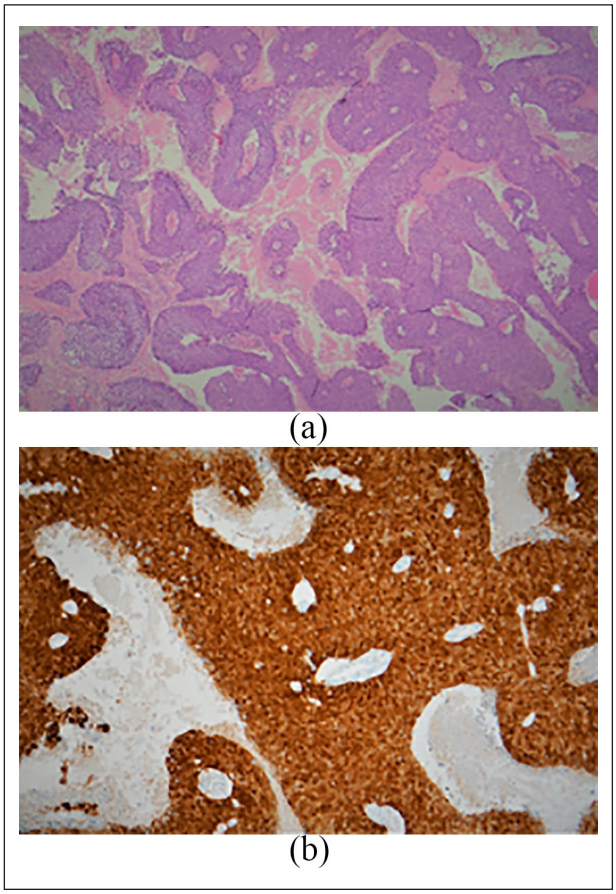

Figure 2. (a) Basaloid squamous cell carcinoma metastasis of the right occipital lobe. (b) Strong nuclear and cytoplasmic positivity with p16 immunohistochemical stain, corresponding with DNA presence of HPV subtype 16.

P16 immunohistochemistry was performed on samples from the brain lesions, which showed strong and diffuse cytoplasmic and nuclear positivity (Figure 2(b)). HPV DNA detection by genotyping demonstrated HPV16 positivity.

Discussion

Primary cutaneous BSCC is a rare clinical entity with seven other cases reported and none of which resulted in brain metastasis.[2–4] BSCC portends a worse prognosis given the high propensity for lymph node and distal metastasis.[1] BSCC shows a strong correlation with oncogenic HPV strains, especially HPV16 in oropharyngeal and anogenital areas.[1] In addition to our case, the literature reports two cases of primary cutaneous BSCC with HPV33.[1,2] Both HPV16 and HPV33 are oncogenic and strongly associated with oropharyngeal and genital cancers.[5] HPV is not routinely tested in skin cancer despite the observation that in aggressive cutaneous SCC, half of the patients showed HPV16 positivity.[8] In our patient, HPV16-induced oncogenesis likely contributed to an aggressive clinical course, including brain metastasis.

HPV infects the stratified squamous epithelia in mucosal and cutaneous sites and upregulates p16 expression.[5,6] The role of HPV in the pathogenesis of primary cutaneous SCC is currently unclear. High-risk HPV causes cancer in subtypes of head and neck squamous cell carcinoma (HNSCC) and testing for HPV and p16 is performed for prognostication.[9] In HNSCC, patients with both HPV and p16 positivity have a better prognosis than patients who test negative for both, and those who have a single HPV or p16 positivity. The presence of p16 suggests HPV-driven HNSCC, whereas HPV infection without p16 upregulation could indicate co-infection without malignant transformation.[9] The improved prognostication for those with both HPV and p16 positivity is related to the different molecular mechanisms underlying HPV tumorigenesis in HNSCC, which makes it more sensitive to chemotherapy and radiation.[6,10] Surgical resection is the standard treatment for cutaneous SCC, which is curative in most cases. The presence of HPV with other high-risk features may suggest that adjuvant radiation or chemoradiation is also warranted. Screening for p16 and HPV in aggressive cutaneous SCC may also facilitate prognostication, but further studies are needed. HPV vaccination may offer the added benefit of also preventing aggressive cutaneous SCC.[6]

Declaration of conflicting interests

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Informed consent

Written, informed consent was obtained from the patient prior to publication.

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