Squamous Cell Carcinoma Arising in Epidermodysplasia Verruciformis: Case Report and Literature Review

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ABSTRACT

OBJECTIVES: Epidermodysplasia verruciformis (EDV) is a rare autosomal recessive skin condition that predisposes patients to HPV infection and are at high risk for squamous cell carcinoma (SCC). We report a case of forehead SCC in a 24 year old patient with EDV and review the literature regarding the diagnosis, management and outcomes.

STUDY DESIGN: Retrospective chart review and review of the literature via a PUBMED search.

METHODS: The patient's medical record was reviewed and photographs were taken. The PUBMED search was performed using "epidermodysplasia verruciformis."

RESULTS: The patient had a two year history of a right forehead lesion which slowly grew and became ulcerated. Physical exam showed a 5x 7 cm deep ulcerated plaque with a pink base and foci's of necrosis. Frontalis was immobile on the right. There was a history of rash since infancy consisting of hypopigmented macules scattered over the torso, and raised flat warts on the dorsum of the hands and feet. The patient underwent wide local excision, right superficial parotidectomy, selective neck dissection with radial forearm free flap reconstruction. Tumor board discussed post-operative radiation given facial nerve involvement. Literature review suggests avoiding radiation as this increases recurrence and malignant transformation of other lesions.

CONCLUSION: Treatment of cutaneous squamous cell carcinoma is wide local excision with lymph node dissection based upon imaging studies. Radiation is recommended for patients with high risk features which contradicts the most recent literature which does not recommended radiation for patients with EDV.

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INTRODUCTION

Epidermodysplasia verruciformis (EDV) is a rare autosomal recessive skin condition characterized by susceptibility to chronic β-HPV infections, specifically types 3, 5, 8. In immunocompetent hosts, these viruses are non-virulent because they do not possess the E5 protein. In contrast, patient's with EDV, and other immunocompromised patient's, can become infected with these common viruses. Specifically, EDV patient's harbor an inactivating mutation in TMC6 (EVER1) and TMC8 (EVER2), a complex which associates with a zinc transporter. This zinc transporter complex usually blocks infection of β-HPV, but with its inactivity, patients become chronically infected with β-HPV.[1] This infection manifests as pityriasis versicolor-like macules and flat wart-like papules with onset starting between the ages of 1-20 years. Development of non-melanoma skin cancers and other benign skin lesions occurs over time.

In the literature, development of squamous cell carcinoma (SCC) in this patient subset has been described and the treatment has been controversial. The national comprehensive cancer network (NCCN) has defined guidelines for treatment of high risk cutaneous SCC. In these guidelines, radiation therapy is recommended for patients with high risk features. In contrast, radiation therapy in these patients has been associated with aggressive tumor recurrence and the malignant degeneration of current benign lesions.[2]

METHODS AND MATERIALS

A PUBMED literature search was performed using the terms "epidermodysplasia verruciformis", "radiation", "squamous cell carcinoma." The current literature was reviewed regarding the pathogenesis of EDV and squamous cell carcinoma. All cases of patients with EDV and SCC were reviewed. Clinical information such as age, presenting symptoms, progression of disease, all treatment modalities and outcomes were extracted. Our subject's chart was then reviewed for the same information and the case was compared to the literature.

CASE PRESENTATION

A 24-year-old male presented to the emergency department with a lesion on the right forehead that was first noted two years previously and had rapidly increased in size within the past five months. The patient was complaining of headache and decreased peripheral vision from drainage associated with the lesion. Past medical history was notable for a generalized asymptommatic rash that was present since infancy and had increased in distribution over the body during adolescence without periods of resolution. The patient reported a similar rash in his brother and sister. On physical exam of the right forehead, there was a 5 x7 cm deep ulcerated plaque with a pink base with foci of necrosis centrally and along the border. Overlying portions of the ulcer were areas of serous crust. There was no movement of the frontalis on the right. The patient also had inumerable pityrasis versicolor-like lesions and flat verrucae-like lesions on his extensor surfaces and posterior back. The patient was admitted for concern for infection. Biopsy of the right was obtained and was consistent with invasive squamous cell carcinoma with basaloid features arising in a background of squamous cell carcinoma in situ. Biopsy of the acral lesions were consistent verruca plana of epidermodysplasia verruciformis.

Computed tomography (CT) of the brain showed a large ulcerated lesion of the scalp overlying the right frontal bone measuring 5 x 6 x 1 cm and lateral to the right orbit. The underlying bone appeared to be hyperostotic. Magnetic resonance (MR) of the orbits and brain showed periosteal reaction of the right frontal bone with extension into the right eyelid on with increased T2 signal. There was no evidence of invasion of the right levator palpebrae muscle or extraocular muscles. Positron emission tomography (PET) showed multiple subcentimeter right parotid space lymph nodes without any radiotracer uptake.

Laboratory examination including HIV, rapid plasma reagin (RPR), human T-lymphotropic virus I and II (HTLV I/II), quantiferon, and hepatitis B were all negative.

The patient underwent wide local excision, frontal bone drillout, right superficial parotidectomy with facial nerve monitoring, right selective lymph node dissections levels 1 through 3 and reconstruction with left radial forearm free flap and left thigh split thickness skin graft. All final pathological margins were negative except for evidence of cancer along the orbital periosteum. Final tumor size was 6cm x 4cm x 1.5cm. No metastatic squamous cell carcinoma was identified in the 18 lymph nodes that were examined. There was no perineural invasion seen on the specimen. However, given that the right temporal branch of the facial nerve was nonfunctional on physical examination, perineural invasion was presumed. Immunohistochemical staining for P16 was performed on the specimen and revealed positive staining in the invasive cancer cells but was negative in the background epidermis. The final TNM staging of the patient's disease was T4N0M0, Stage IV.

According to the NCCN guidelines, local, high risk squamous cell carcinoma is treated with resection with complete margin assessment followed by adjuvant radiation therapy if there is extensive perineural or large nerve involvement. High risk features that were present in this case were: greater than 2mm in thickness, greater than 2 cm in diameter, reaching subcutaneous tissue and in a high risk anatomic area. Given the presence of the aforementioned high risk features, adjuvant radiation therapy was recommended. The patient received 33 radiation therapy treatments to the right forehead for a total of 60 Grays which was completed in October 2015.

The patient is being followed closely by dermatology for skin cancer surveillance. Several punch and shave biopsies have been performed and are positive for squamous cell carinoma in situ arising in a background of EDV in the right infraorbital area, right cheek, and nose. SCC in situ was also found in the left infraorbital area and right forearm. All of these lesions were present at the time of initial diagnosis of the large right forehead lesion and before radiation therapy. They have not significantly changed from initial observation to biopsy.

Study	Case	Age (years) /Sex	Location of SCC	Size	Pathology	Surgery	Margin	Radiation	Chemo	Outcome
Oliveira (2015)	4	36M	R forehead	NR	poor diff SCC	Wide local excision	NR	yes	no	1yr recurrence: bone, frontal lobe, R parotid, R orbit
		Same	recurrence	NR	NR	craniotomy, parotidectomy, orbital exeneration	NR	NR	NR	20 yrs: recurrence of basaloid SCC in R parietal lobe and death
		36F	forehead	NR	SCC	excision	NR	yes	NR	2 yrs: recurrence on forehead, in parotid, liver mets and death
		55M	forehead	NR	SCC	excision	NR	no	imiquimod	8yrs: met in axilla
		Same	axilla	NR	NR	n/a	NR	yes- to axilla met	yes	1 yr: multiple metastasis then lost to follow up
		22F	R forehead	NR	mod diff SCC	surgery	NR	yes	NR	1 yr: recurrence at site
Emsen et all (2010)	1	14F	L infraorbital	2x2.5cm	SCC	Wide local excision	NR	none	interferon	14 month: no recurrence
Bogdan et all (2007)	2	54M	R frontotemporal	8.5x4cm	well diff SCC	Wide local excision	6mm	none	imiquimod to L	NR
		61M	L supraauricular	5x1.8cm	poor diff SCC	NR	4mm	NR	NR	NR
Gubinelli et all (2003)	1	43F	Mucosal	NR	SCC	Wide local excision	NR	none	PEGylated interferon	no mucosal SCC, regressed flat warts
BU (2015)	1	24M	R forehead	6x4x1.5cm	poor diff SCC	Wide local excision	positive	yes	no	6 months: no evidence of disease

Table 1. Multimodality treatment of squamous cell carcinoma (SCC) in patients with EDV. R= right, L=left, NR= not recorded, n/a= not applicable

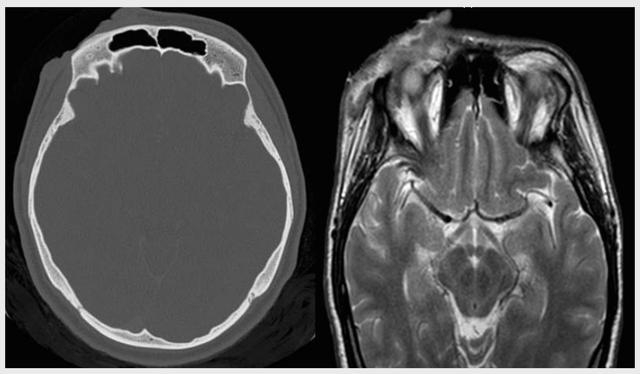

Figure 1. CT (left) showing hyperostosis of right frontal bone. MRI (left) showing extension of lesion into right eyelid.

DISCUSSION

Because EDV is so rare, there have been limited case reports and investigational research. There are two genetic loci that have been identified as EDV-associated genes but the the exact mechanism of pathogensis has not been elucidated.5 Treatment has been based on therapies that have been successfully used on related lesions of differing etiologies. For example, commonplace viral warts not associated with EDV, can be treated with electrodesiccation, cryotherapy, topical retinoids, and contact sensitization. These methods have been shown to be minimally effective when used to erradicate EDV-derived lesions.4 Other therapies have been investigated such systemic interferon-alpha, oral retinoids and zinc with variable efficacy. The mechanism of action for interferon is in its antiviral activity, inhibition of malignant cell growth, and the stimulation of natural killer and T-cells, and has been utilized in patients with nonmalignant EDV lesions with good effect6 . Oral retinoids (such as acitretin) have an antiproliferative effect by controlling epithelial cell differentiation and inciting cytotoxic T-cell responses.6 While therapy of the cutaneous non-malignant EDV lesions to reduce the risk for future skin cancer has been reported, there are no definitive guidelines for the management of squamous cell carcinoma in these patients.

DISCUSSION (CONT'D)

Additionally, the case reports that have been reviewed here are lacking in several points of information that is needed to make more confident treatment generalizations. For example, though wide local exicison was stated to be attempted on all patients described, statements on final pathology margins and presence or lack of local invasion were not mentioned.[1,2,4,6,7] If surgical clearance is not achieved, tumors often recur despite adjuvant radiotherapy.[10] It is Another indicator that worsens prognosis of disease is histologic grade which was not uniformly reported. In a retrospective study by Mullen et all, patients with well differentiated SCC had a cure rate of 88% compared to poorly differentiated histologies with a cure rate of 37% at a median follow up of 2 years.[9] The patients with aggressive recurrence could have been apart of the known natural history of high risk squamous cell carcinoma and not necessarily induced by adjuvant radiation therapy. Lastly, because radiation cycles were not reported, we cannot assume that adjuvant therapy was properly delivered to achieve adequate locoregional control.

In describing the optimal management of EDV, it is important to identify which therapies may accelerate the condition and should thus be avoided. Patients with EDV develop malignant skin lesions in sun exposed areas. Just as in healthy skin, ultraviolet radiation induces malignant transformation of epithelial skin cells. With HPV-associated abberant tumor suppression, this transformation occurs more quickly. Therefore, these patients are highly encouraged to avoid sun and photoprotect (i.e., wear sun screens and sun protective clothing). Similarly, caution is advised with the employment of radiation therapy is patients. In a cohort of patients who had received adjuvant radiation therapy for cutaneous squamous cell carcinomas (3 out of 7 patients), were found to have had 'early promotion of cancer and more destructive lesions'[7]. Another case series described 4 EDV patients with forehead SCCs, of whom 3 underwent wide local excision with subsequent radiation therapy. These 3 patients experienced aggressive local recurrence and distant metastasis between 1 to 2 years after initial treatment. The fourth case had her primary forehead SCC treated with wide local excision alone. Distant metastasis in the axilla was identified and treated with chemotherapy and targeted radiation therapy. The squamous cell carcinoma was reported to progress despite systemic and radiation therapy; and the patient was subsequently lost to follow-up. Three out of the four patients had HPV typing of the malignant lesions which demonstrated type 5, 14 and 14d, all of which are not high-risk HPV types.

CONCLUSIONS

A therapeutic dilemma exists in the management of EDV patients with a high risk squamous cell carcinoma. Per the NCCN guidelines, adjuvant radiation therapy is indicated in the treatment of high risk SCC; however, anecdotal evidence and the known HPV-associated predisposition to malignant transformation, suggests that radiation treatment may induce tumor progression of other EDV lesions in the radiation field.

In our patient, there were positive margins on the orbital periosteum as well as facial nerve involvement. As such, radiation therapy was administered to the patient. He has completed his course and his operative site is well healed. There have been no new lesions observed in the post-radiation period though it is likely too soon to see secondary neoplasms from this radiation. Previously, the reported mean time from completion of therapy to recurrence and metastasis was 1.5 years . [5]

The patient will continue close skin cancer surveillance with dermatology and otolaryngology.

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