Squamous Cell Carcinoma Arising in Discoid Lupus Erythematosus Lesions of the Ears Infected With Human Papillomavirus

Joanne K. Simpson, MD; Rafael Medina-Flores, MD; Jau-Shyong Deng, MD

We describe a 51-year-old white man with discoid lupus erythematosus (DLE) of the head, neck, trunk, and upper extremities of more than 20 years' duration who developed rapidly progressive squamous cell carcinoma (SCC) of the bilateral ear helices. Human papillomavirus (HPV) was detected from excised specimens from the ears via tissue immunohistochemistry. Human papillomavirus infection of discoid lesions may be responsible for the rapid progression of SCC of this patient's bilateral ear helices.

Cutis. 2010;86:195-198.

Case Report

A 51-year-old white man with discoid lupus erythematosus (DLE) of the head, neck, back, chest, and extremities of more than 20 years' duration presented with development of squamous cell carcinoma (SCC) within his DLE lesions on his ears. He had only been seen at our institution during the last 4 years of his DLE disease course and was noted to have stable erythematous scaly papules and plaques covering his arms, dorsal aspect of the hands, back, and upper chest. Atrophic plaques with hyperkeratotic scale covered his face, and his nose and ears had numerous keratin plugs at the time of presentation. His medical history was remarkable for coronary artery disease, myocardial infarction, anxiety, gastroesophageal reflux disease, and osteoarthritis. His review of systems at that time was positive for decreased visual acuity in both eyes, and negative for arthritis or arthralgia, mouth ulcers, alopecia, and photosensitivity. Results of blood work done at the time of his diagnosis were unavailable; however, laboratory studies conducted when he presented to our clinic revealed an antinuclear antibody titer of 1:40, macrocytic anemia, an erythrocyte sedimentation rate within reference range, and blood urea nitrogen and creatinine levels within reference range. He received treatment with hydroxychloroquine sulfate intermittently and sunscreen within the 4 years he had been in our care and had marked improvement in most of his skin lesions. His ear lesions, however, were refractory to therapy and remained unchanged from his initial presentation.

The patient was lost to follow-up for 1 year due to multiple canceled appointments. At his return visit, he presented with large verrucous nodules on his bilateral ear helices (Figure 1). There was no palpable lymphadenopathy or facial asymmetry on physical examination. His face, trunk, and extremities remained clear of lesions. Routine histologic staining of biopsies from both helices revealed invasive SCC of the skin (Figure 2). Immunohistochemistry using both an anti–human papillomavirus (HPV) protein probe and HPV DNA cocktails as probes showed positive staining as illustrated in Figures 3 and 4, respectively. Computed tomography of his head and neck did not demonstrate lymph node involvement or extension to the facial bones; however, the tumor did extend to the left parotid gland. He was referred to the otolaryngology department at our institution for resection of the carcinoma. The patient underwent

From the Department of Dermatology, Veterans Administration Medical Center, Pittsburgh, Pennsylvania.
The authors report no conflict of interest.
Correspondence: Jau-Shyong Deng, MD, Department of Dermatology, Veterans Administration Medical Center, University Dr C, Pittsburgh, PA 15240 (jaushyong.deng@va.gov).

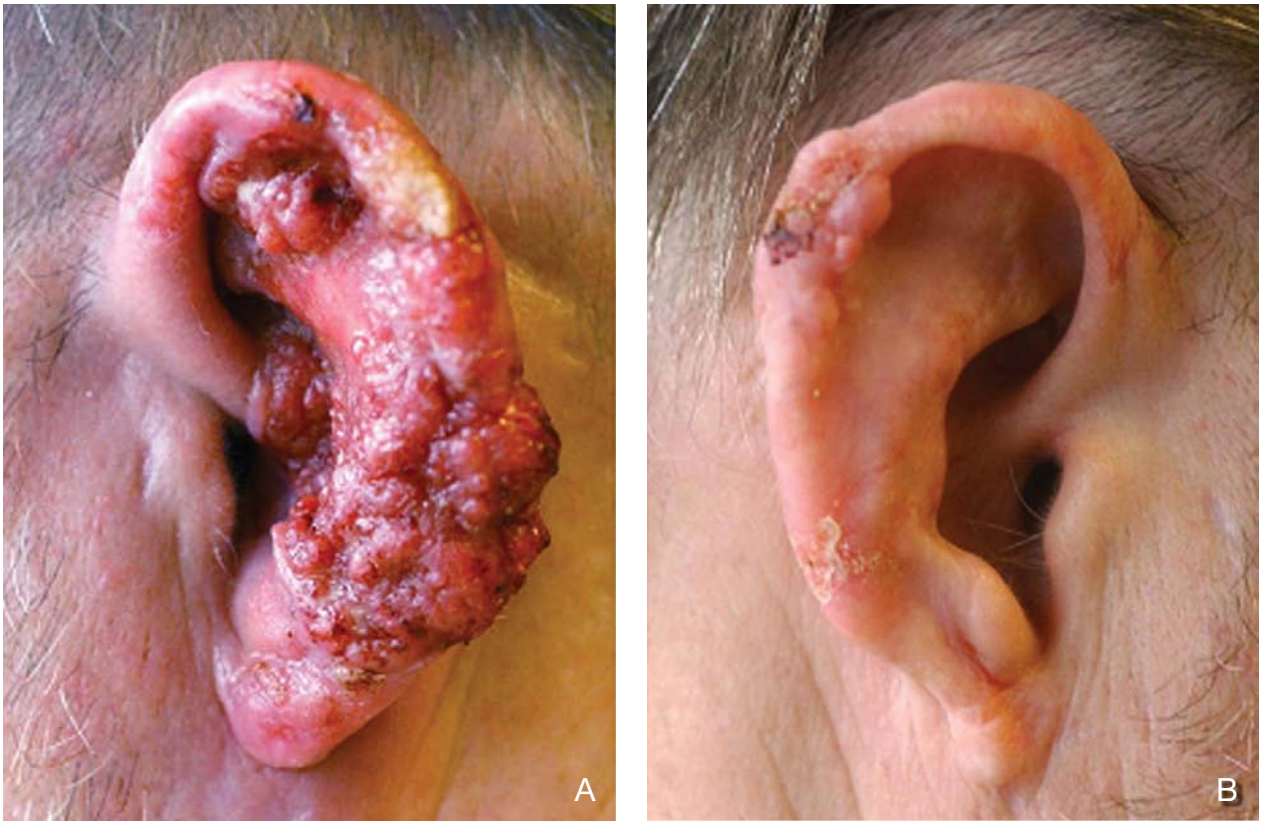

Figure 1. Clinical appearance of lesions on both ears. The entire left ear helix was involved with verrucous growth (A), while only the upper portion of the right helix was affected (B).

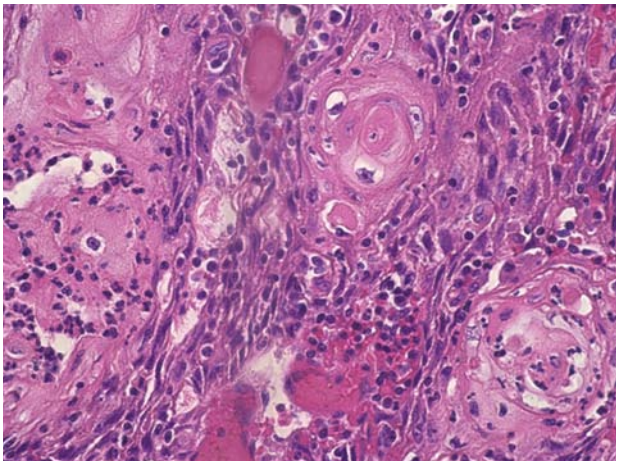

Figure 2. Routine hematoxylin and eosin staining of the biopsy specimen from the left ear showed features of squamous cell carcinoma (original magnification ×400).

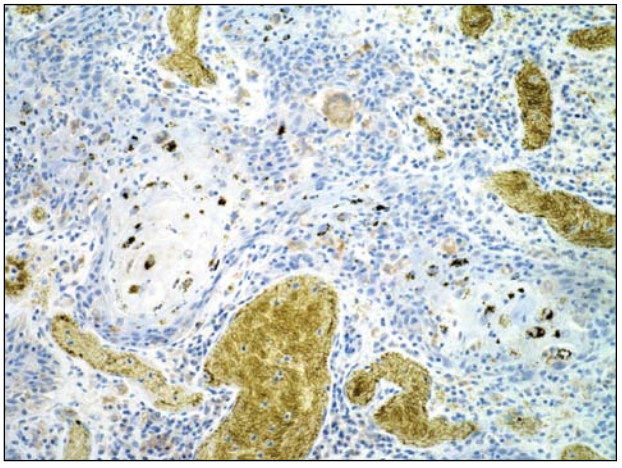

Figure 3. Immunohistochemistry using anti–human papillomavirus (HPV) major capsid protein VP1 as a probe detected the presence of HPV-related protein. Brown staining represented the presence of HPV capsid protein (original magnification ×200).

a total auriculectomy of the left ear with superficial parotidectomy and wedge excision of the right superior helix.

Histopathology—Specimens were obtained from the apparently normal skin adjacent to the tumor lesion and from the center of the tumors on both ears. The specimens were screened for presence of HPV protein by immunohistochemistry staining using an anti-HPV protein probe. The specimens were further verified by in situ hybridization using HPV DNA cocktails as probes (identifying HPV-16, HPV-18, HPV-31, HPV-33, HPV-35, HPV-39,

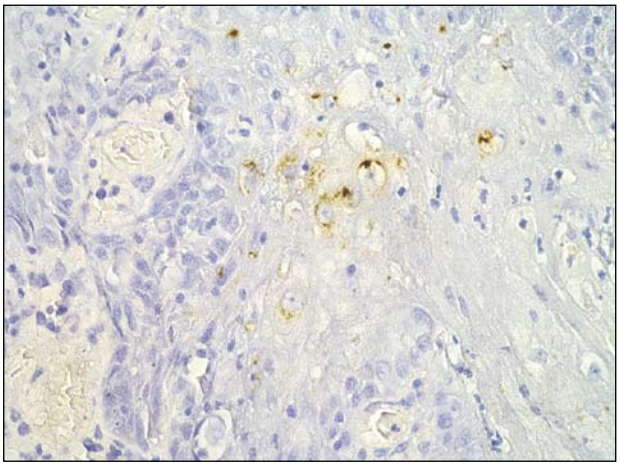

Figure 4. In situ hybridization using human papillomavirus (HPV) DNA cocktails as probes detected the presence of HPV DNA. Brown staining represented the presence of HPV DNA (original magnification ×200).

HPV-45, HPV-51), which was performed by the Molecular Biology Laboratory, Department of Pathology, Veterans Affairs Medical Center, Pittsburgh, Pennsylvania.[1] There was no immunohistochemical evidence of HPV protein or HPV DNA detected from the apparently normal skin adjacent to the SCC tumor lesions (data not shown). However, as shown in Figure 3, HPV protein was detected in SCC tumor cells, suggesting that the SCC in this patient was potentially triggered by HPV. The involvement of HPV in malignant transformation was further confirmed by in situ DNA hybridization, as shown in Figure 4. Both evaluations highlighted the presence of HPV protein and HPV DNA in SCC tumor cells, indicating that HPV infection played a notable role in the development of SCC in this patient.

Comment

There are 2 important findings from this case presentation. The first is that SCC could derive from a cicatricial skin lesion. It is well-known that SCC can arise from lesions, including hypertrophic DLE,[1-5] as in this patient; chronic venous leg ulcers[6]; chronic wounds with osteomyelitis[7-9]; and other chronic infections.[10] The factors contributing to such malignant transformation have been speculated to include chronic UV light exposure,[11] sublethal damage to DNA from phagocyte-derived oxygen metabolites,[12] and HPV infection.[13-16] Human papillomavirus–induced SCC is a well-known mechanism responsible for dysplasia of the genitalia to carcinomas (ie, SCC of the female cervix).[16] Cicatricial skin diseases and chronic wounds have an increased potential to develop SCC. The development of SCC in these lesions usually develops decades after disease onset,[5,17-18] and the mechanism for such transformation is poorly understood but has been speculated to be related to matrix metalloproteinases.[19]

The second important finding is that HPV is found inside the SCC tissue, which indicates that HPV might be related to the malignant transformation that leads to rapid growth of lesions simultaneously. Our patient's rapidly developed SCC, the bilateral distribution of his lesion, and its localization to chronic inflamed skin lesions led us to suspect that HPV infection could be one of the concomitant pathogenic mechanisms responsible for his malignancy. Squamous cell carcinoma of an atypical presentation should alert the clinician to investigate possible etiologies. Viral infection, radiation exposure, and immunodeficiency states are examples of exposures that may accelerate the development of SCC in such diseases.

It has been shown that HPV DNA is highly prevalent among many skin conditions, including actinic keratosis,[20-22] basal cell carcinoma,[20-22] SCC,[20-22] melanoma,[23] and even normal adults.[21] It has been found that HPV DNA is common in superficial layers of lesions but is not necessarily present throughout tumors,[24] indicating that the presence of HPV is not specifically related to the tumor below the skin surface. In this reported case, HPV was found inside the tumor but was not found in the apparently normal skin adjacent to the tumor, which suggests that detecting the presence of HPV DNA inside a tumor may be more appropriate and important. This finding also implies it may be more important to search for the presence of oncogenic strains of HPV DNA inside the tumor tissue.

REFERENCES

1. Jacobson FW, Annamunthodo H. Squamous cell carcinoma arising in discoid lupus erythematosus. *Dermatologica*. 1958;117:455-459.
2. Keith WD, Kelly AD, Sumrall AJ, et al. Squamous cell carcinoma arising in lesions of discoid lupus erythematosus in black persons. *Arch Dermatol*. 1980;116:315-317.
3. Presser SE, Taylor JR. Squamous cell carcinoma in blacks with discoid lupus erythematosus. *J Am Acad Dermatol*. 1981;4:667-669.
4. Garrett AB. Multiple squamous cell carcinomas in lesions of discoid lupus erythematosus. *Cutis*. 1985;36:313-314, 316.
5. Onayemi O, Soyinka F. Squamous cell carcinoma of the scalp following a chemical burn and chronic discoid lupus erythematosus. *Br J Dermatol*. 1996;135:342-343.

6. Baldursson B, Sigurgeirsson B, Lindelöf B. Venous leg ulcers and squamous cell carcinoma: a large-scale epidemiological study. *Br J Dermatol*. 1995;133:571-574.
7. Fitzgerald RH, Brewer NS, Dahlin DC. Squamous-cell carcinoma complicating chronic osteomyelitis. *J Bone Joint Surg*. 1976;58:1146-1148.
8. Sankaran-Kutty M, Corea JR, Ali MS, et al. Squamous cell carcinoma in chronic osteomyelitis. report of a case and review of the literature. *Clin Orthop Relat Res*. 1985;198:264-267.
9. Kirsner RS, Spencer J, Falanga V, et al. Squamous cell carcinoma arising in osteomyelitis and chronic wounds. treatment with Mohs micrographic surgery vs amputation. *Dermatol Surg*. 1996;22:1015-1018.
10. Kampirapap K, Poonpracha T. Squamous cell carcinoma arising in chronic ulcers in leprosy. *J Med Assoc Thai*. 2005;88:58-61.
11. Marks R. Squamous cell carcinoma. *Lancet*. 1996;347: 735-738.
12. Weitberg AB, Weitzman SA, Destrempes M, et al. Stimulated human phagocytes produce cytogenetic changes in cultured mammalian cells. *N Engl J Med*. 1983;308:26-30.
13. Alani RM, Münger K. Human papillomaviruses and associated malignancies. *J Clin Oncol*. 1998;16:330-337.
14. Moy RL, Eliezri YD, Nuovo GJ, et al. Human papillomavirus type 16 DNA in periungual squamous cell carcinomas. *JAMA*. 1989;261:2669-2673.
15. Masini C, Fuchs PG, Gabrielli F, et al. Evidence for the association of human papillomavirus infection and cutaneous squamous cell carcinoma in immunocompetent individuals. *Arch Dermatol*. 2003;139:890-894.
16. Snijders PJ, Steenbergen RD, Heideman DA, et al. HPV-mediated cervical carcinogenesis: concepts and clinical implications. *J Pathol*. 2006;208:152-164.
17. Bowman PH, Hogan DJ. Leg ulcers: a common problem with sometimes uncommon etiologies. *Geriatrics*. 1999; 54:43, 47-48, 50.
18. Grossman D, Leffell DJ. Squamous cell carcinoma. In: Freedberg IM, Eisen EZ, Wolff K, et al. *Fitzpatrick's Dermatology in General Medicine*. 6th ed. McGraw-Hill Medical Publishing Division; 2003:737-747.
19. Impola U, Jeskanen L, Ravanti L, et al. Expression of matrix metalloproteinase (MMP)-7 and MMP-13 and loss of MMP-19 and p16 are associated with malignant progression in chronic wounds. *Br J Dermatol*. 2005;152: 720-726.
20. Weissenborn SJ, Nindl I, Purdie K, et al. Human papillomavirus-DNA loads in actinic keratoses exceed those in non-melanoma skin cancers. *J Invest Dermatol*. 2005;125:93-97.
21. Harwood CA, Spink PJ, Surentheran T, et al. Detection of human papillomavirus DNA in PUVA-associated non-melanoma skin cancers. *J Invest Dermatol*. 1998;111: 123-127.
22. Struijk L, Hall L, van der Meijden E, et al. Markers of cutaneous human papillomavirus infection in individuals with tumor-free skin, actinic keratoses, and squamous cell carcinoma. *Cancer Epidemiol Biomarkers Prev*. 2006;15:529-535.
23. La Placa M, Ambretti S, Bonvicini F, et al. Presence of high-risk mucosal human papillomavirus genotypes in primary melanoma and in acquired dysplastic melanocytic naevi. *Br J Dermatol*. 2005;152:909-914.
24. Forslund O, Lindelöf B, Hradil E, et al. High prevalence of cutaneous human papillomavirus DNA on the top of skin tumors but not in "stripped" biopsies from the same tumors. *J Invest Dermatol*. 2004;123: 388-394.