Field Cancerization with Multiple Keratoacanthomas Successfully Treated with Topical and Intralesional 5-Fluorouracil

Stephen Hemperly DO
Lehigh Valley Health Network, Stephen.Hemperly@lvhn.org

Sean Branch DO
Lehigh Valley Health Network, Sean.Branch@lvhn.org

Stephen M. Purcell DO
Lehigh Valley Health Network, Stephen.Purcell@lvhn.org

Published In/Presented At

Hemperly, S., Branch, S., & Purcell ,S. (2016, April 26). *Field Cancerization with Multiple Keratoacanthomas Successfully Treated with Topical and Intralesional 5-Fluorouracil.* Poster presented at LVHN Department of Medicine Research Day, Lehigh Valley Health Network, Allentown, PA.

Field Cancerization with Multiple Keratoacanthomas Successfully Treated with Topical and Intralesional 5-Fluorouracil

Stephen Hemperly, DO, Sean Branch, DO, and Stephen M. Purcell, DO
Lehigh Valley Health Network, Allentown, PA

Case Presentation

Patient: 78 year-old Caucasian male.

History of Present Illness: Our patient is a 78 year-old male who initially presented in March 2014 with a papule on his right forearm for 3 months. It was biopsied in March 2014, diagnosed as a well-differentiated invasive squamous cell carcinoma and subsequently excised with clear margins in April 2014. Squamous cell carcinoma formed two additional times at the incision and was excised with clear margins. The fourth squamous cell carcinoma in the area was treated with x-ray therapy. One month after completion, four papules just adjacent to the x-ray therapy treatment field were biopsied and diagnosed as well-differentiated squamous cell carcinoma, keratoacanthoma (KA) type.

Medical History/Surgical History: Squamous cell carcinoma, myocardial infarction, diabetes mellitus II, chronic obstructive pulmonary disease, hypertension, hypercholesterolemia, gout, diverticulosis

Medications: Finasteride, metoprolol tartrate, allopurinol, atorvastatin, furosemide, brimonidine ophthalmic, clopidogrel, travoprost, glimepiride, potassium chloride, losartan, dexlansoprazole, polyethylene glycol ophthalmic, tacrolimus ointment, mometasone cream, hydrocodone/acetaminophen, fluticasone/salmeterol inhaled, aspirin

Physical Examination: Pink patch at radiation site with healing erosion centrally. Several 5-6 mm pink dermal papules at periphery of radiation site.

Studies: A CT with contrast of the chest and right upper extremity did not reveal metastatic disease.

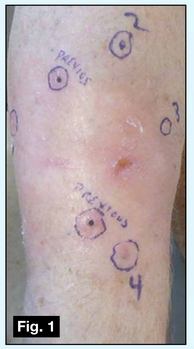
Fig. 1

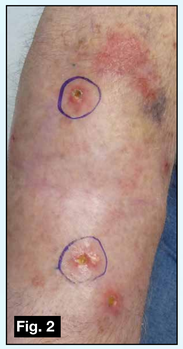
Fig. 2

Figure1: Biopsy proven KAs labeled in an area of prior radiation on the right forearm.

Figure 2: Two firm pink papules adjacent to biopsy proven KAs remain after 4 weeks of treatment with topical 5-FU 5% cream twice daily for 4 weeks, applied to the right arm from the elbow to the wrist and occluded under an elastic bandage.

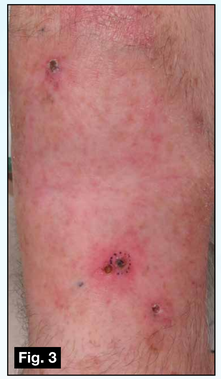
Fig. 3

Figure 3: After three injections with IL 5-FU, both KAs had decreased in size substantially.

Discussion

At this time, the patient had four biopsy proven KAs on the right forearm in the area of prior radiation (figure 1). The patient was treated with topical 5-Fluorouracil (5-FU) 5% cream twice daily for 4 weeks, applied to the right arm from the elbow to the wrist and occluded under an elastic bandage. The patient stated that the biopsy sites became sore and inflamed during the treatment. After 4 weeks of treatment, 2 of the KA biopsy sites had healed without clinical evidence of tumor. The other two biopsy sites had developed adjacent firm pink papules (Figure 2). These 2 lesions were then treated with intralesional (IL) 5-FU injectable 50mg/ml once weekly to resolution at 4 and 5 weeks respectively. The proximal lesion was treated with 7.5mg on week 1 and 5mg on weeks 2, 3, and 4. The larger distal lesion was treated with 12.5mg on week 1 and 5mg on weeks 2, 3, 4, and 5. The volume injected was determined by ability to blanch and indurate the lesion. The volume necessary to achieve this was decreased due to the shrinking size of the tumor. After three injections, both tumors had decreased in size substantially (figure 3). At the end of treatment, both tumors had clinically resolved. These have not recurred, nor has he developed any new tumors at 9 months after his last injection.

The concept of "field cancerization" was first proposed in 1953 by Slaughter et al. while studying oral squamous cell carcinoma in an effort to explain the development of multiple primary tumors and locally recurrent cancer.[1,2] Histopathologically, the authors observed: 1) oral cancer develops in multifocal areas of precancerous change, 2) histologically abnormal hyperplastic tissue surrounds the tumors, 3) oral cancer consists of multiple independent areas that sometimes coalesce, and 4) the persistence of abnormal tissue after surgery may explain local recurrences and the development of new lesions in a previously treated area.1,2 Since its original publication the concept has been applied to several other organ systems including the lung, vulva, cervix, breast, bladder, colon and skin.[2]

In the skin, field cancerization involves clusters and contiguous patches of altered cells present in areas of chronic photodamage.[2] Genetically altered fields form the foundation in which multiple clonally related neoplastic lesions can develop.[2,3] These fields often remain after treatment of the primary tumor and may lead to new cancers that are commonly labeled as a second primary tumor or a local recurrence depending on the exact site and time interval.[3] Brennan et al. found clonal populations of infiltrating tumor cells harboring a p53 gene mutation in more than 50% of histopathologically negative surgical margins of patients with squamous cell carcinoma of the head and neck. Furthermore, 40% of the patients with a margin positive for a p53 gene mutation had local recurrence versus none of the patients with negative margins.[4] These findings are supported by several other studies in which loss of heterozygosity, microsatellite alterations, chromosomal instability or in situ hybridization was used to demonstrate genetically altered fields.[2,4] Histopathologic patterns of epidermolytic hyperkeratosis, focal acantholytic dyskeratosis, and pronounced acantholysis as found in Hailey-Hailey disease may be a consequence of clonal expansion of mutated keratinocytes because of long-term exposure to mutagens such as UV light and HPV.[5]

The development of an expanding neoplastic field appears to play an important role in cutaneous carcinogenesis.[2,3,4] It is necessary to consider the cutaneous field cancerization as a highly photodamaged area that contains clinical and subclinical lesions.[2,3,4] The treatment of cutaneous neoplasms, squamous cell carcinoma in particular, should focus not only on the tumor itself, but also on the surrounding tissue.[4] Adjunctive field-directed therapies should be considered after treatment of the primary tumor.[4]

Our patient continued to develop squamous cell carcinomas on the right forearm after multiple excisions with clear margins. He then developed 4 squamous cell carcinomas, KA type, after radiation therapy to the right forearm. Topical 5-FU is a well-described treatment for field cancerization.[2] In our patient, topical 5-FU 5% cream twice daily under occlusion for 4 weeks led to the involution of 2 out of 4 KAs, and may have prevented the development of new neoplasms for at least 4 months after use. Our patient's 2 remaining KAs resolved with IL 5-FU weekly for 4 and 5 weeks.

IL 5-FU has been described for the treatment of multiple and difficult to treat KAs. 5-FU is an antimetabolite and structural analog of uracil which disrupts DNA and RNA synthesis.[6] It is contraindicated in liver disease, pregnancy or breast feeding and allergy to the medication.[6] IL 5-FU dosing recommendations for KAs include use of a 50mg/ml solution and injecting 0.1mL to 3mL every 1 to 3 weeks.[7] The maximum daily recommended dose is 800mg.6 Recommendations for lab monitoring include a CBC with differential at baseline and weekly.6 Side effects include local pain, erythema, crusting, ulceration and necrosis.[6] Systemic side effects include cytopenias and gastrointestinal upset.[6] IL 5-FU has been used successfully in a single dose of 10mg per lesion in combination with systemic acitretin for the treatment of multiple KAs induced by vemurafenib.[8] It has also been effective in the treatment of multiple recurrent reactive KAs developing in surgical margins.[7] A review article reported that the use of IL 5-FU produced a 98% cure rate in 56 treated KAs.6 Alternative IL agents that may be considered for KAs include methotrexate, bleomycin, and interferon α-2b.[6,7]

Field cancerization may cause the development of multiple clonally related neoplasms within a field of genetically altered cells. These may continue to develop after excision with clear margins or radiation therapy. Given the success of treatment in our patient, we recommend consideration for topical and IL 5-FU in patients who develop squamous cell carcinomas and KAs within an area of field cancerization.

References:

1. Slaughter DP, Southwick HW, Smejkal W. "Field cancerization" in oral stratified squamous epithelium. Clinical implications of multicentric origin. *Cancer* 1953;6:963-8.
2. Torezan LA, Festa-Neto C. Cutaneous field cancerization: clinical, histopathological and therapeutic aspects. *An Bras Dermatol.* 2013;88(5):775-86.
3. Brennan JA, Mao L, Hruban R, et al. Molecular assessment of histopathological staging in squamous-cell carcinoma of the head and neck. *N Eng J Med* 1995;332(7):429-35.
4. Braakhuis, BJ, Tabor MP, Kummer JA, et al. A genetic explanation of Slaughter's concept of field cancerization: evidence and clinical implications. *Cancer Res* 2003;63:1727-30.
5. Carlson AJ, Scott D, Wharton J, Sell S. Incidental histopathologic patterns: possible evidence of "field cancerization" surrounding skin tumors. *Am J Dermatopathol* 2001;23(5):494-6.
6. Kirby J, Miller C. Intralesional Chemotherapy for Nonmelanoma Skin Cancer: A Practical Review. *J Am Acad Dermatol.* 2010;63(4):689-702.
7. Hadley J, Tristani-Firouzi P, Florell S, Bowen G, Hadley M. Case series of multiple recurrent reactive keratoacanthomas developing at surgical margins. *Dermatol Surg.* 2009;35(12):2019-24.
8. LaPresto L, Cranmer L, Morrison L, Erikson C, Curiel-Lewandrowski C. A Novel Therapeutic Combination Approach for Treating Multiple Vemurafenib-Induced Keratoacanthomas Systemic Acitretin and Intralesional Fluorouracil. *JAMA Dermatol.* 2013;149(3):279-281.