Invasive Squamous Cell Carcinoma in Full-thickness Burn Wounds After Treatment with Cultured Epithelial Autografts

Mansher Singh, MD
Kristo Nuutlia, PhD
Anupam Singh Chauhan
Elof Eriksson, MD, PhD

In vitro expansion of cells using cultured epithelial autografts (CEAs) is a useful technique to provide skin coverage in extensive burn injury patients with limited donor site availability.[1,2] However, preparation time of over 2 weeks and lack of a dermal component increase the risk of invasive infection and make the skin susceptible to shearing trauma. Besides, there have been reports of graft site malignancy after treatment of full-thickness burn with CEAs.[3,4] We had earlier described a patient with reports of squamous cell carcinoma (SCC) at multiple full-thickness wound sites treated with CEAs.[3,4] The patient was involved in a gas explosion, which resulted in full-thickness burns to 95% of total body surface area. Given the lack of donor sites, most of his body, including bilateral lower extremities, was grafted with CEAs. The lower extremities had to be grafted up to 3 times because of limited "take" of the CEAs. In our previous communications, we had described the development of SCCs in 6 different locations of the left lower extremity of the patient, which manifested about 14 years after the initial treatment with CEAs.[3,4] We are now reporting 8 additional SCCs in the patient's lower extremities over the past 9 years (October 2005–April 2015).

The patient developed multiple (about 95) exophytic, hyperkeratotic, and ulcerated lesions during this time period. Given the history of multiple SCCs, excisional biopsies were done for all of these lesions. Eight of them were found to be invasive SCC (Table 1). None of these lesions were contiguous to each other. Negative margin was confirmed in all these pathology specimens after the definitive surgery. There was no evidence of metastasis or lymph node involvement. Latest SCC was excised March 2015. Multiple other specimens also demonstrated extensive hyperplasia with cellular atypia but did not reveal carcinoma. The resected area was covered with a split-thickness skin graft from the left forearm since that was the only area with original skin preserved from the burn injury. The patient continues to be closely monitored with regular follow-up clinic visits.

In vitro expansion of keratinocytes into sheets suitable for autografting involves serial subculture in the presence of lethally irradiated 3T3 fibroblasts, epidermal growth factor, and cholera toxin or isoproterenol. Use of mitogenic stimulators, such as Epidermal Growth Factor or cholera toxin, may contribute to malignant transformation of the grafted epithelium. Addition of cholera toxin or isoproterenol to the culture medium causes irreversible activation of adenyl cyclase with increased cellular levels of cyclic adenosine monophosphate.[5] Although this results in markedly increased rate of growth of keratinocytes in vitro, it can also have a mitogenic effect on the regenerated epithelium. We have limited evidence, but based on the reports of multiple SCCs in our patient in the areas grafted with CEAs

Table 1. Description of Multiple Sites of Graft Site Invasive SCCs After Treatment of Full-thickness Burn with CEAs

Site of Lesion	Size of Lesion (cm)	Gross Appearance	Date of Operation
Left lateral thigh	3×3	Exophytic, hyperkeratotic	October 4, 2005
Right lateral thigh	3.5×3	Ulcerated	September 14, 2006
Left proximal lateral thigh	2×2.5	Ulcerated	September 14, 2006
Left medial knee	2.3×2	Exophytic, hyperkeratotic	October 18, 2007
Left lateral lower leg	2.6×2.3	Exophytic, hyperkeratotic	July 24, 2008
Left lateral knee	3.5×3	Exophytic, hyperkeratotic	October 3, 2013
Left popliteal fossa	4×3	Exophytic, hyperkeratotic	May 8, 2014
Left posterior thigh	2.3×2	Exophytic, hyperkeratotic	March 19, 2015

From the Division of Plastic Surgery, Brigham and Women's Hospital, Boston, Mass.
Received for publication May 14, 2015; accepted June 2, 2015.

Plast Reconstr Surg Glob Open 2015;3:e460; doi:10.1097/GOX.0000000000000435; Published online 21 July 2015.

and not outside of these areas, we would recommend close monitoring of such patients and a low threshold for excisional biopsies of any suspicious lesions.

Elof Eriksson
Division of Plastic Surgery
Brigham and Women's Hospital
Harvard Medical School
75 Francis St, Boston, MA 02115
E-mail: eeriksson@partners.org

DISCLOSURE

The authors have no financial interest to declare in relation to the content of this article. The Article Processing Charge was paid by the authors.

REFERENCES

1. Rheinwald JG, Green H. Serial cultivation of strains of human epidermal keratinocytes: the formation of keratinizing colonies from single cells. *Cell* 1975;6:331–343.
2. Green H, Kehinde O, Thomas J. Growth of cultured human epidermal cells into multiple epithelia suitable for grafting. *Proc Natl Acad Sci U S A.* 1979;76:5665–5668.
3. Theopold C, Hoeller D, Velander P, et al. Graft site malignancy following treatment of full-thickness burn with cultured epidermal autograft. *Plast Reconstr Surg.* 2004;114:1215–1219.
4. Green H. Cyclic AMP in relation to proliferation of the epidermal cell: a new view. *Cell* 1978;15:801–811.
5. Theopold C, Eriksson E. The need for aggressive follow-up after cultured epidermal autograft-grafted full-thickness burn. *Plast Reconstr Surg.* 2006;117:708.