A Naturally Occurring Ring Seborrheic Keratosis

J.J.		Meffert ^a
K.C.		Deering ^b

Departements of ^aDermatology and ^bDermatopathology, Wilford Hall Medical Center, Lackland AFB, Tex., USA

Key Words

Seborrheic keratosis
Benign neoplasms
Growth factors

Jeffrey J. Meffert, MD, 19626 Encino Knoll, San Antonio, TX 78259 (USA)

Seborrheic keratoses (SKs) are among the most common benign cutaneous neoplasms. Despite this, knowledge of the pathophysiology underlying SKs is incomplete. Much of what is known about the growth and biology of SKs is obtained indirectly while investigating 'more important' tumors, and SKs are studied as 'control neoplasms'. Ho and McLean [1] note that a true understanding of what makes SKs grow the way they do would help explain much about keratinocytes in general and the biology of the skin. We present what may be the first reported case of a naturally occurring ring-shaped SK, an entity which raises provocative questions about the growth factor milieu responsible for SKs.

Case Report

A 35-year-old man presented with an asymptomatic brown ring on his left arm which he had first noticed about 1 year previously (fig. 1). He was unsure if the lesion appeared de novo as a 1 - cm ring or if it had started as a solid papule and spread with central clearing. He denied any prior trauma or treatment such as cryotherapy, curet-tage, intralesional injections or topical wart therapies of any kind. Epi-luminescent biomicroscopy revealed sharp borders to the ring, scattered tiny (< 1 mm) milia, a few small comedo-like openings and the absence of a melanocytic pigment pattern. A punch biopsy revealed acanthosis, papillomatosis and a rare keratin pearl. Although the epidermis was slightly effaced in the center of the ring, there was no fibrosis or other indication of a scar from prior trauma. The patient.

The views expressed in this article are those of the authors and do not reflect the official policy of the Department of Defense or other Departments of the US Government.

Fig. 1. Ring SK (1 cm diameter).

weary of inquiries from friends and family about his 'ringworm', desired treatment and liquid nitrogen cryotherapy to the ring was performed. He presented several months later with a small residual arc-shaped ridge which was successfully treated with a second course of cryotherapy which eliminated the lesion.

Discussion

Many inflammatory conditions (e.g. granuloma annulare, gyrate erythemas, porokeratoses) are characterized by annular growth where the most histopathologically diagnostic areas of the lesion are found at the periphery of the ring rather than the often regressed or histologically nonspecific center. While neoplasms may exhibit centrifugal growth, a perfect ring is a rarity.

Ring SKs, along with ring warts, are usually created when a lesion is incompletely frozen, destroying the center of a papule while not achieving destructive temperatures at the periphery. The SK described above underwent no such therapy and grew in a ring from the onset. The exact mechanism for this growth pattern is unclear, but one may conjecture a balance or 'vector sum' of growth factors which are favorable for SK growth at the periphery but not centrally. Elias et al. [2], in a review of the cytokine network regulating pulmonary inflammation and fibrosis, discuss the concept of a three-dimensional model of cytokine interactions. Depending upon where one looks in the region of inflammation, cytokines and other growth factors interact in different combinations and with a varying gradient of concentrations of those factors. This ultimately leads to different manifestations of the inflammation (fibrosis vs. granuloma vs. abscess) from one area to another [2].

Most of what is known about the biology and growth factors affecting SK growth has come out of studies where the focus was on other neoplasms and SKs were used as controls. The association of eruptive SKs with underlying malignancy (sign of Leser-Trélat) is not considered as meaningful as it once was, but one report describes sheets of SKs and palmar-plantar hyperkeratosis associated with elevated levels of immunoreactive human growth hormone and various underlying malignancies [3]. In another report, linear SKs regressed with removal of malignancies, suggesting that some unidentified epi-

Letters to Dermatology

Dermatology 1996;192:383-384

383

dermal growth factor from the cancers was maintaining SK growth [4].

Regarding growth factor specifics, Yamamura et al. [5] revealed that interleukin 2 and γ -interferon were the dominant SK anti-inflammatory cytokines, different from those seen in basal-cell carcinomas. Other differences between SKs and malignant keratinocytic tumors are the failure of SKs to express bcl-2 protein (over-expressed in basal-cell carcinomas and squamous-cell carcinomas) [6], normal expression of NU-T2 basement membrane zone antigen and type VII collagen (altered in basal-cell carcinomas) [7], and expression of the ras p21 oncogene product similar to normal skin (absent in basal-cell carcinomas) [8]. Studies of SK keratin profiles have shown mixed results. SKs have demonstrated increased expression of cytokeratins 1, 5, 6, 10, 14 and 16 which suggest a 'hyperproliferative' cytokeratin pattern [9]. Other investigators found an increased expression of cytokeratins 8 and 18 which the authors suggested could represent a redifferentiation towards embryonic keratinocytes [10]. Another study found no significant differences from normal skin cytokeratins [11]. The lectin-binding pattern of SKs more closely matches the epidermal basal layer than that of other hyperproliferative states such as psoriasis [12].

We preferred the appellation 'halo SK' to 'ring SK' but found that this term had already been applied to SKs surrounded by rims of depigmentation much in the manner of halo nevi [13]. A halo SK of this type was associated with a localized squamous-cell carcinoma of the colon and showed partial repigmentation with removal of the cancer [14]. Such phenomena, along with the ring SK described above, raise tantalizing questions about factors governing growth of keratinocytic neoplasms and call for further investigations of the 'humble SK'.

References

Ho VCY, McLean DI: Benign epithelial tumors; in Fitzpatrick TB, Eisen AZ, Wolff K, Freedberg IM, Austen KF (eds): *Dermatology in General Medicine*. New York, McGraw-Hill, 1993, pp 855-872.

Elias JA, Freundlich B, Kern JA, Rosenbloom J: Cytokine networks in the regulation of inflammation and fibrosis in the lung. *Chest* 1990; 97:1439-1445.

Millard LG, Gould DJ: Hyperkeratosis of the palms and soles associated with internal malignancy and elevated levels of immunoreactive human growth hormone. *Clin Exp Dermatol* 1976; 1:363-368.

Heng MC, Soo-Hoo K, Levine S, Petressek D: Linear seborrheic keratosis associated with underlying malignancy. *J Am Acad Dermatol* 1988; 18: 1316-1321.

Yamamura M, Modlin RL, Ohmen JD, Moy RL: Local expression of anti-inflammatory cytokines in cancer. *J Clin Invest* 1993;91: 1005-1010.

Nakagawa K, Yamamura K, Maeda S, Ichihashi M: bcl-2 expression in epidermal keratinocytic diseases. *Cancer* 1994;74: 1720-1724.

Yasaka N, Kawabe K, Furue M, Tamaki K, Ishibashi Y: Altered expression of NU-T2-BMZ antigen and type VII collagen in basal cell epithelioma. *J Dermatol Sci* 1994;7: 136-141.

Inohara S, Kitano Y, Sagami S: Immunohistologic localization of ras p21 in normal, hyperplastic, and neoplastic epidermis. *Int J Dermatol* 1993;32: 866-869.

Broekaert D, Leigh IM, Lane EB, Van Muijen GNP, Ramaekers FCS, De Bersaques J, Coucke P: An immunohistochemical and histochemical study of cytokeratin, involucrin and transglutaminase in seborrheic keratosis. *Arch Dermatol Res* 1993;285:482-490.

Nindl M, Nakagawa H, Furue M, Ishibashi Y: Simple epithelial cytokeratin expression in seborrheic keratosis *J Cutan Pathol* 1992; 19: 415-422.

Wollina U, Knopf B, Klinger R, Hipler C, Wetzker R: Seborrhoische Keratosen (SK): Intakte epidermale Differenzierung trotz Morpho-genese-störung. *Z Hautkr* 1990;65: 174-177.

Ming-yang G Xi-ran L, Qi M: Lectin histochemistry in psoriasis, lichen planus and seborrheic keratosis. *Chin Med J* 1992;105: 1020-1025.

Migally M, Migally N: Halo seborrheic keratosis. *Int J Dermatol* 1983;22: 307-309.

Vignale R, Espasandin J, Deneo H, Gonzalez V: Halo seborrheic keratosis associated with colon carcinoma. *Int J Dermatol* 1993;32:846.

Dermatology 1996;192:384-385

Chemotherapy-Associated Supravenous Hyperpigmentation

E. Baselga^a, B.A. Drolet^a, J. Casper¹, N.B. Esterly^a Departments of ^a Dermatology and ^b Pediatric Hematology/Oncology, Medical College of Wisconsin, Milwaukee, Wisc., USA

Key Words

Hyperpigmentation · Chemotherapy · Linear pigmentation

We read with interest the article by Schulte-Hermann et al. [1] reporting supravenous hyperpigmentation in association with CHOP chemotherapy. These authors conclude that although pigmentary changes secondary to chemotherapy are frequent, this particular venous pattern is uncommon, and they attributed it to either cyclo-phosphamide or doxorubicin. We have recently observed 2 patients with similar supravenous hyperpigmentation. The first patient was a 7-year-old black male who underwent a bone marrow transplantation for acute lymphocytic leukemia after a course of polychemotherapy which included methotrexate, Ara-C, L-asparaginase, daunorubicin and 6-mercaptopurine. His pretransplantation conditioning

consisted of total body irradiation, prednisone, cyclosporine, Ara-C and cyclo-phosphamide. All drugs were administered through a central line. One month after bone marrow transplantation, he developed a striking linear hyperpigmentation reproducing the superficial venous plexus of the anterior trunk (fig. 1). There was also banded hyperpigmentation of the nails. The second patient was a 15-year-old black male with stage IIIA nodular sclerosing Hodgkin disease treated with extended mantel radiation and combination chemotherapy with doxorubicin, bleomycin, vinblastine and dacarbazine. Six months after starting the monthly chemotherapeutic regimen he developed linear hyperpigmentation reproducing the venous channels of the right anterior forearm. There was no history of extravasation or phlebitis preceding the hyperpigmentation (fig. 2).

Chemotherapy-induced hyperpigmentation is more frequent and prominent in dark-skinned individuals, and both our patients were African-American. It is difficult to know which drug is responsible for the observed hyperpigmentation. In our first patient, methotrexate, daunorubicin and cyclophosphamide may be implicated as all three are known to induce hyperpigmentation [2, 3]. However, the last doses of methotrexate and daunorubicin were administered more than 1 month before the pigmentary changes developed. In the second patient, the more plausible culprit drugs are bleomycin and doxorubicin. The venous pattern of pigmentation in this patient was distinct from the bleomycin-associated linear, flagellate hyperpigmentation in areas of excoriation and scratching [4].