An Update on Nonmelanoma Skin Cancer

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ABSTRACT

Estimates from the American Cancer Society suggest that there are more than two million cases of nonmelanoma skin cancer in the United States per year. The following review highlights the topics of actinic keratoses, basal cell carcinoma, squamous cell carcinoma, Kaposi's sarcoma, and Merkel cell carcinoma. This update on the cutting-edge clinical and dermpathologic research will assist the dermatologist in approaching, diagnosing, and managing nonmelanoma skin carcinoma. Immunologic and genetic research into nonmelanoma skin carcinoma has paved the way for novel therapeutic options for patients who were previously without any viable treatment alternatives. While still in preliminary stages, agents, such as ingenol mebutate, vismodegib, and sirolumus, may become integral drugs in the armamentarium of managing cutaneous carcinoma. (*J Clin Aesthet Dermatol.* 2011;4(2):20–27.)

Estimates from the American Cancer Society suggest that there are more than two million cases of nonmelanoma skin cancer (NMSC) in the United States per year.[1] The incidence of NMSC, which has increased over the past 20 years in the United States, may be related to higher levels of outdoor activities and sun exposure, changes in clothing style, and improved skin cancer detection. Analysis of other epidemiological factors, such as geographic variation, age distribution, and ethnicity, has also reinforced the theory that chronic sun exposure acts as a primary causative factor in NMSC.[2]

The following review highlights the topics of actinic keratoses (AKs), basal cell carcinoma (BCC), squamous cell carcinoma (SCC), Kaposi's sarcoma (KS), and Merkel cell carcinoma (MCC). This update on the cutting-edge clinical and dermpathological research will assist the dermatologist in approaching, diagnosing, and managing NMSC.

ACTINIC KERATOSES

AKs are common dysplastic keratinocytic epidermal lesions caused by chronic ultraviolet light (UV) exposure.[3] After acne vulgaris, AK is the most common diagnosis made by dermatologists. The prevalence of AK was reported to have been 11 to 25 percent in 2008 and up to 60 percent in individuals over the age of 40 years old in the northern hemisphere.[4] AKs primarily affect fair-skinned, middle-aged people. Childhood sun exposure, immunosuppression, and age increase risk of developing AK. Historically, AK was classified as a premalignant lesion. In recent years, however, gene expression studies and other evidence is accumulating that asserts that AKs are part of a spectrum of lesions ranging from sun-damaged skin to SCC *in situ* (SCC).[4–7] Furthermore, chromosome analysis has revealed that AK and SCC have an altered p53 gene and altered expression of Bcl-2, an anti-apoptotic gene.[4,7–9]

Although most AKs do not develop into invasive SCCs, the relative risk of developing SCC increases with the number of AK lesions. The relative risk of developing SCC from an existing AK is less than one percent with five or fewer lesions and 20 percent with greater than 20 lesions.[4,10,11] Although it is not possible to predict which AK might progress to SCC, it is accepted that the presence of AK is a biomarker of risk for patients and, therefore, must be treated to avoid possible morbidity and mortality.[4,6,10] Squamous tumors have a metastatic risk of 0.5 to 3.3 percent.[9]

Given the fact that we know that AKs are one part of a continuous spectrum of benign sun damage to SCC, rather than a distinct entity from SCC, it is natural that there is high interobserver variation among experienced dermatologists.[4,10,12,13] As such, a clinical classification for grading AK was developed in 2007 to aid in consistent, reproducible diagnosis. Grade 1 describes slightly palpable AK, Grade 2 describes moderately thick AK, and Grade 3 is very thick, hyperkeratotic, and/or obvious AK.[14] There still remains significant interpretation between Grade 3 AK and

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early invasive SCC. There are no distinct clinical boundaries between AK and invasive SCC, but histologically there is usually a clear differentiation.[4] The potential transformation of AK to NMSC poses the greatest risk of affected individuals, as SCC has a metastatic risk of 0.5 to 3.3 percent.[9]

Given this, AKs are generally treated and there are many options available. Lesion-directed treatment is one option in the setting of single lesions and can include cryotherapy, laser therapy, curettage, and dermabrasion. Although there are no standard guidelines for cryosurgery with liquid nitrogen, it has been effectively used for decades and several studies have assessed efficacy after complete freezing of AKs.[15] Thai et al in 2004 assessed 90 adult patients with 421 eligible AKs. Overall individual complete response rate was greater than 67 percent, a number that increased with freeze duration times from 39 percent for freeze times of less than five seconds up to 83 percent for freeze times greater than 20 seconds.[16] Freeze time was measured as the time from the formation of an ice ball to the commencement of thawing. Cosmetic outcomes were also assessed in this study and deemed to be good to excellent in 94 percent of subjects. Finally, adverse events, such as pain, burning and stinging, and hypopigmentation after healing, were generally rare and the procedure was well tolerated.

Despite the positive numbers associated with the aforementioned study, the choices available for lesion therapy can be painful and result in hypopigmentation and other cosmetically unacceptable outcomes. Furthermore, efficacy is variable depending on technique (e.g., duration of freeze time with cryosurgery). Additionally, it is widely accepted that AK is a field disease that is rarely limited to a single clinically apparent lesion.[5] To this end, field-directed therapy is an alternative option that aims to eliminate not only clinically visible lesions, but also subclinical lesions within the treatment area. Classic approaches include topical diclofenac 3% gel, 5-flourouracil (5-FU), and imiquimod 5%. Photodynamic therapy (PDT) is also being used as a field therapy, alone or in conjunction with other topical therapies.[17] This manuscript reviews only new therapies for AKs.

Topical imiquimod cream, which acts as a toll-like receptor-7 agonist, disrupts tumor proliferation by modifying the immune response and stimulating apoptosis. Initially approved in the 5% form, imiquimod demonstrated 84-percent median lesion reductions of AKs after one 12-week cycle.[18] More recently, a newer 3.75% formulation was approved for the treatment of AKs on the face or balding scalp. Subjects in the Swanson et al[19] trial applied cream daily to the entire face or balding scalp for two two-week treatment cycles, separated by a two-week "rest period" (2 weeks on, 2 weeks off, 2 weeks on). Subjects achieved a median lesion reduction of 82 percent, and more than one-third demonstrated complete clearance.[19] Though imiquimod 3.75% and 5% have not been examined head-to-head, the efficacy data for the 3.75% formulation are similar to imiquimod 5%, with the advantage of improved patient tolerance and a significantly shorter treatment time.

Recently, a new agent derived from the plant *Euphorbia peplus*, ingenol mebutate (PEP005 gel), has been showing promising results in the treatment of both facial and nonfacial AKs. PEP005 gel has a dual therapeutic mechanism of action by not only rapidly inducing primary necrosis, but also instituting a neutrophil-mediated, antibody-dependent, cellular cytotoxicity of residual disease cells.[20–22] This novel therapy, applied topically once daily for three days within a 25cm^2 area, seems to be effective with a favorable safety profile and a short course of treatment.[5] Ingenol mebutate has shown complete clearance rates of 70 percent after just two days of treatment with 0.025% and 0.05% in completed Phase II studies.[5–6] Preliminary Phase III data are available, with PEP005 used on face, scalp, arm, chest, and back of hand, with complete and partial clearance rates of 27.8 to 42 percent and 44.4 to 55.0 percent, respectively. Efficacy rates varied depending on region, with the chest showing an overall clearance rate of 88.9 percent.[23] Therefore, efficacy outcomes of the PEP005 trials demonstrate a high rate of complete and partial clearance of lesions over a short treatment period.[5] Furthermore, common, adverse effects, such as redness, irritation, and burning, resolved generally within 2 to 4 weeks with ingenol mebutate, and adherence rates were high.[6]

Studies examining other agents for the treatment of AK, including nicotinamide (vitamin B_3)[24] or piroxicam 1% gel,[9] did not have as promising results.

BASAL CELL CARCINOMA

BCC is the most common cancer in the United States with an estimated annual incidence of 0.5%.[25] Immunohistochemical studies have defined BCC as a malignant tumor of follicular germinative cells.[26] While mortality rates are low, BCC can grow aggressively causing extensive local tissue damage. More generalized dissemination of BCC is also very low (<0.1%), but cases of metastasis to the lymph nodes, lung, bone, and liver have been described.[27]

The etiology of BCC is secondary to both extrinsic and intrinsic factors, yet UV exposure is thought to cause the majority of cutaneous damage leading to the development of BCC. Even though most BCC cases are cured via surgical excision, significant scarring, tissue loss, and pigmentation changes are commonly associated with these procedures. PDT and imiquimod cream represent alternative topical treatment options often prescribed due to lower comorbidity in conjunction with superior cosmesis.[28] Five-year, long-term follow-up data from a European study have shown impressive sustained histological clearance rates of 90.3 percent in subjects who used 5% imiquimod cream formulation five times a week for six weeks.[29] Similar five-year, follow-up data exists for the use of PDT for superficial BCC. In one study comparing PDT to cryotherapy, there was no difference in five-year recurrence rates with either

treatment (20% with cryotherapy and 22% with PDT, p=0.086). However, more patients had an excellent cosmetic outcome with PDT (60% vs. 16% with cryotherapy, p=0.00078).[30]

Most recently, a novel agent to treat superficial BCC, ingenol mebutate, has been examined in Phase II studies as a promising new therapeutic option for superficial basal tumors in addition to AKs. Comparable to the results garnered from studies of PEP005 gel and AKs,[5] an Australian study showed a favorable safety profile for two applications of PEP005 gel at concentrations of 0.0025%, 0.01%, or 0.05%, given either on consecutive days or dosed one week apart for BCC. The most convincing results were reflected in the histological clearance rate of 63 percent of those randomized to the 0.05% treatment arm as compared to controls. The incidence of adverse events was low. One patient treated with ingenol mebutate gel 0.05% given on consecutive days experienced severe flaking/scaling/ dryness extending beyond the application site. In this same treatment arm, nonsevere, potentially treatment-related events included erythema extending beyond the application site, application-site pain, and headache in two patients each while six patients had one or more severe local skin responses. It should be noted that the sample size of the study was relatively small with only 60 patients; however, favorable preliminary results indicate that PEP005 gel could serve an important role in the topical treatment arena of superficial BCC.[31]

Insight into the pathogenesis of BCC has implicated the hedgehog pathway as the main mutated signaling system responsible for basal tumor formulation. Ordinarily inactive in adults, the hedgehog pathway develops either loss of function[32–33] or, less commonly, a gain of function mutation,[34] which leads to constitutive signaling and the unrestrained proliferation of basal cells of the skin.

A Phase I study investigating the blockage of the hedgehog pathway with the orally active, selective hedgehog inhibitor vismodegib (GDC-0449) has produced successful results in those patients who are no longer amenable to conventional treatment secondary to either locally advanced or metastatic BCC. Of the 33 subjects enrolled, 18 had an objective response to the selective hedgehog inhibitor, two with a complete response and 16 with a partial response. The other 15 patients had stable disease (11 subjects) or progressive disease (four subjects). These findings confirm the role of the hedgehog signaling in the pathogenesis of basal tumors and, most importantly, have implicated vismodegib as an agent that may fill the gap in available treatment options for this patient population.[35]

A trend for smaller biopsies has formed a new challenge for the dermatopathologist when trying to distinguish sclerosing BCCs, desmoplastic trichoepitheliomas, and microcystic adnexal carcinoma.[36] Given the significant difference in surgical approaches required for treatment of these pathologies, a histopathological misdiagnosis can have detrimental clinical consequences.

The monoclonal antibody directed against two glycoproteins (34 and 39 kDA), Ber-EP4, has already proven its diagnostic usefulness in distinguishing basal from cutaneous SCC.[37–39] Recently, Ber-EP4 staining has been shown to reliably differentiate microcystic adnexal carcinoma from both sclerosing BCC and desmoplastic trichoepitheliomas. Ber-EP4 is a positive staining marker for desmoplastic trichoepithelioma, and the absence of staining for this histochemical marker assists with the detection of microcystic adenexal carcinoma.[40]

SQUAMOUS CELL CARCINOMA

Cutaneous SCC is the second most common skin cancer in Caucasians, most frequently occurring on sun-exposed areas of the body. Clinically, SCC often appears as a persistent, red, scaly papule or patch which may bleed spontaneously. Most SCCs are treated surgically, either by excision or Mohs micrographic surgery. Other treatments include curettage and electrodessication or cryosurgery.[41] Additionally, although data on effectiveness and long-term follow up are lacking for topical 5-FU, it is approved for superficial BCC.

The apparent risk of developing SCC depends on the lifetime accumulation of UV radiation damage and the extent of immune suppression. Recipients of solid-organ transplants have a 65 to 250-times increased risk of SCC as compared with the general population and have an increased risk of metastasis.[42]

A large multivariate study helped to establish the key factors associated with the risk of metastasis or local recurrence of SCC by analyzing data taken from a mainly immunocompetant German population. Prospectively analyzing more than 600 patients with a median age of 73 years, Brantsch et al[43] discovered that only four percent of patients developed metastasis. In addition, the first metastasis was found to always affect a regional lymph node. The key independent prognostic factors for metastasis were increased tumor thickness (hazard ratio [HR] 4.79, p>0.0001), immunosuppression (HR 4.32, p=0.035), localization at the ear (HR 3.61, p=0.0040), and horizontal size (>21mm in size, HR 2.22, p=0.0128). The risk of local recurrence depended on increased tumor thickness (HR 6.03, p<0.0001) and desmoplasia (HR 16.11, p<0.0001). The current analysis showed that tumor thickness divides SCC into three main risk categories for metastasis: a tumor thickness of 2.0mm or less had no detectable risk; tumors between 2.1 and 6.0mm in thickness had a low risk; and tumors greater than 6.0mm in thickness showed a high risk of metastasis.[43]

KAPOSI'S SARCOMA

Kaposi's sarcoma (KS) is a multicentric tumor composed of endothelium-lined vascular spaces and spindle-shaped cells. Four clinical variants of KS have been categorized. The classical variant commonly causes symmetric, indurated patches, plaques, or nodules of the lower extremities in elderly men of Eastern European or Mediterranean origin.[44] Endemic KS is indigenous to sub-Saharan Africa where nodules and plaques occur on the

extremities and are commonly accompanied by visceral and lymphatic involvement in young adults.[45–46] Transplantation-associated KS variant is characterized by mucosal, nodal, or visceral involvement, which can commonly occur in the absence of skin lesions.[47] The median time to diagnosis of KS post-transplantation is 30 months.[48] Lastly, acquired immune deficiency syndrome (AIDS)-associated KS, which is considered an AIDS-defining illness by the Centers for Disease Control and Prevention, is the most uncompromising form with lesions often presenting on the skin and on the viscera, especially on the lungs and gastrointestinal tract.[49]

Chang et al[50] first implicated deoxyribonucleic acid (DNA) fragments of a previously unrecognized herpesvirus, now called human herpesvirus 8 (HHV8), to have a causal relationship with KS in 1994. More recently, sequencing of the HHV8 genome has revealed various genes with the molecular potential to induce cellular proliferation and prevent apoptosis. For example, the virus encodes proteins that are homologous to human oncoproteins including a cyclin that inhibits the retinoblastoma protein that controls the G1-to-S phase of cell growth[51] and a Bcl-2-like protein that prevents apoptosis.[52] Sodhi et al[53] demonstrated that a certain protein kinase encoded by HHV8 known as Akt to be highly upregulated in human KS tumor cells implicating this enzyme as a supporting player contributing to Kaposi's sarcomagenesis. Another immunohistochemical investigation has shown AIDS-related KS cell lines to express elevated levels of vascular endothelial growth factor (VEGF) as well as expression of VEGF receptors. This important discovery may explain the principal features of this tumor, namely the abnormal vascularization and proliferation of endothelial cells.[54–55]

Genomic sequencing has shifted clinical research to examine the therapeutic potential of certain drugs, such as sirolimus, an immunosuppressive agent used in kidney transplant recipients, as agents for KS. It has been suggested that the immunosuppressive and antineoplastic effects of sirolimus are due to the inhibition of a target molecule that links protein synthesis and cell-cycle progression. In addition, sirolimus is thought to limit the proliferative response of endothelial cells to VEGF. One trial has shown the clinical efficacy of sirolumus in 15 kidney-transplant subjects who had developed dermal KS while on cyclosporine immunosuppression. After three months of sirolumus monotherapy, all cutaneous KS lesions disappeared in all subjects. Sirolimus also beneficially exerted an antirejection effect on organ allografts. Remission was confirmed histologically in all patients six months after sirolimus therapy had begun.[56]

Topical treatment options available for cutaneous KS has also evolved secondary to the genetic information gleaned from recent virological research of HHV8. For instance, imiquimod, an immune response modifier with antiangiogenic properties, is an agent capable of inducing a variety of cytokines related to cell-mediated immunity, including interferon-alpha (IFN-α).[57] A cytokine with antiprolierative, antiviral, and antiangiogenic activity, IFN-α has been used at high doses to treat AIDS-related KS; however, over time these KS lesions became refractory to topical treatment.[58–59]

A Phase I to Phase II open-label trial of 17 subjects with HIV-negative KS skin lesions aimed to clarify the efficacy of topical imiquimod 5% cream applied under occlusion three times a week for 24 weeks. Antitumor activity was seen in about half of the patients, and overall, imiquimod 5% cream was very well tolerated. The authors note that the dosage regimen utilized in this study was based on the results previously published in nodular BCC and, perhaps, is suboptimal in dosing frequency for the treatment of cutaneous KS.[60]

While there are four variants of KS, all forms share the same pathological features of atypical spindle cells and slit-like vascular spaces. The exact origin of the neoplastic endothelial cells, either vascular or lymphatic, has been readily debated. Traditional thought suggests that KS arises from vascular neoplastic endothelial cells. This hypothesis has been supported by the various endothelial markers found in KS lesions (CD31, CD34, von Willebrand factor).[61–62] However, positive staining with vascular endothelial growth factor receptor-3 and podoplanin support the theory that KS has a lymphatic endothelial origin.[63–64] A report of five cutaneous cases of KS that stained positive with D2-40, a novel monoclonal antibody that is highly sensitive and specific to lymphatic endothelium, suggests at least a partial endothelial differentiation. While the sample size used in this report is small, the report's suggestion of a possible lymphatic origin of KS cells is of significance when researching therapeutic modalities for Kaposi's sacromagenesis.[65]

MERKEL CELL CARCINOMA

MCC is a rare malignancy that originates from the Merkel cell, a neuroendocrine cell in the skin. Highly aggressive in nature, MCC has a mortality of approximately 33 percent in three years, which is more than double that of melanoma.[66] Incidence rates for MCC continue to rise showing a three-fold increase from 0.15 to 0.44 per 200,000 annually from 1986 to 2001. Several factors contribute to the rising trend including the aging population, increase in aggregate sun exposure, and the higher number of immunosuppressed individuals. Additionally, with the advent of cytokeratin-20, recognition of this carcinoma has been greatly aided. Depending on the stage of the MCC at diagnosis, surgical treatment options, such as wide local excision versus sentinel lymph node dissections, are often combined with either radiation and/or chemotherapy.[67]

Prognosis rates of MCC are correlated with the extent of disease at presentation where disease-specific survival for local disease is greater than 90 percent and decreases to 52 percent should there be nodal involvement.[67] Therefore, early detection and clinician recognition of this disease could improve survival rates greatly.

Heath et al[68] sought to identify the characteristics present at diagnosis of MCC to aid the tumor's clinical

recognition. Conducting a cohort study of 195 patients who were diagnosed with MCC, the authors prospectively collected data that showed that 88 percent of MCCs were asymptomatic despite rapid growth in the prior three months and being red or pink. More than half of the MCC lesions were presumed to be benign at biopsy, with cyst/acneiform lesions being the single most common misdiagnosis given (32%). The median delay from lesion appearance to biopsy was three months (range 1–54 months). Comparable to earlier studies, 81 percent of primary MCCs occurred on UV-exposed sites. An additional novel finding was that chronic lymphocytic leukemia was over-represented by more than 30-fold among patients with MCC. Overall, the most significant features of MCC can be summarized in an acronym: AEIOU (asymptomatic/lack of tenderness, expanding rapidly, immune suppression, older than 50 years, and ultraviolet-exposed site on a person with fair skin). In this series, 89 percent of primary MCCs had three or more of these findings. When present in combination, these features may indicate a concerning process that would warrant biopsy.[68]

In 2008, sequences of a previously unknown small double-stranded DNA polyomavirus was detected in 8 of 10 MCC tumors, but only 5 of 59 control tissues. The new virus, coined the Merkel cell polyomavirus (MCPyV), was found to integrate within the tumor genome in a clonal pattern. This discovery of viral integration preceding clonal expansion of the tumor cells suggested that the MCPyV had a causal role in the oncogenesis of MCC.[69]

Utilizing two subjects with MCC, Mertz et al[70] found MCPyV DNA in the subjects' urine, cell-free serum, and in CD14+CD16-inflammatory monocytes, but not in lymphocytes or granulocytes. Elucidating the hematological reservoir to be monocytes has shed some light on how the pathogen is able to shuttle throughout the body and act as a "Trojan horse" transmitting the pathogenic load *in situ*.[70]

The Merkel cell polyomavirus has also been detected in squamous tumors and in the skin surrounds these tumors suggesting a field effect of infection. Interestingly, close to 20 percent of individuals with multiple SCCs have been shown to have more than one SCC test positive for MCPyV, implying a systemic effect of the virus.[71] In addition to MCC and SCC, MCPyV has been detected in KS lesions, which were also HHV8 positive.[72]

This widespread identification of MCPyV in an array of cutaneous carcinomas may be linked to the worldwide distribution of an inadvertently contaminated polio vaccine.[73] The contamination occurred when the vaccine was prepared in primary cultures of kidney cells derived from rhesus monkeys, which are often infected with the Simian virus 40 (SV40). The SV40 subgroup contains all four of the human polyomaviruses including the MCPyV. It has been hypothesized that the infectious SV40 survived vaccine inactivation treatments, and conservative estimates indicate that up to 30 million people in the United States may have been exposed to the live SV40 from 1955 to 1963.[74]

Shortly after its discovery, SV40 was shown to be a potent oncogenic DNA virus in animals. Translational human research has solidified evidence of the same. SV40 is also a human pathogen, and a multivariate analysis has shown that the virus is significantly associated with and may be functionally important in the development of human malignancies including primary brain (OR 3.8, 95% CI 2.6–5.7), malignant mesothelioma (OR 16.8, 95% CI 10.7–25.7), bone cancer (OR 15.1, 95% CI 9.2–25.0), and non-Hodgkin's lymphoma (OR 5.4, 95% CI 3.1–9.3).[75]

CONCLUSION

Immunological and genetic research into NMSC has paved the way for novel therapeutic options for patients who were previously without any viable treatment alternatives. While still in preliminary stages, these agents, such as ingenol mebutate, vismodegib, and sirolumus, may become integral drugs in the armamentarium of managing cutaneous carcinoma.

Additionally, some of the treatment modalities highlighted, such as imiquimod and PEP005 gel, have been successfully utilized for a variety of cutaneous carcinomas, thus signifying a basic connection between these individual entities. Studies involving larger numbers of patients that further examine the efficacy and safety of these therapeutic modalities merit investigation. Additional insight into a questionable infectious etiology of tumorigenesis also reinforces the hypothesis that these varied diagnoses are somehow linked together in a spectrum of nonmelanoma cancer. As our understanding of the genetic foundation of these diseases improves so too will the potential for diagnosing and managing NMSC.

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