ADVANCING THE UNDERSTANDING OF SEBORRHEIC KERATOSIS

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Statement of Need

Seborrheic keratoses are the most common benign tumors found in older patients affecting approximately 83 million Americans. A genetic predisposition to develop a high number of SKs has been identified and the role of epidermal growth factors and their receptors have been the focus of recent study. Variants to the presentation of SK exist; differential diagnosis includes a variety of benign and malignant conditions and inflammatory eruptions. SK treatments include cryosurgery, electrodessication, curettage, shave biopsy, lasers and chemical peels that may result in cosmetic challenges including pigmentary issues, scarring, chance for wound infection and high cost to patient. Dermatology HCPs require expanded clinical skill for understanding the features, benefits and cost of existing surgical and medical interventions offering better cosmetic outcome and patient satisfaction.

Educational Objectives

The educational goal for this series of journal-based continuing education activities is to expand awareness of the growing impact of seborrheic keratosis on the practice of dermatology; provide insights in the current understanding of the pathogenesis and etiology of seborrheic keratosis; distinguish seborrheic keratosis from other benign and secondary tumors and to develop effective SK treatment strategies offering optimal outcomes including patient satisfaction leading to enhanced quality of life.

Upon completion of the CE activity, learners should be able to:

- State clinical features of seborrheic keratosis from other benign tumors presenting in various skin types
- Discuss current evidence-based understanding of the etiology and pathophysiology of SK
- Distinguish SKs from other benign and malignant tumors
- Recognize clinical features of SK from malignant melanoma, actinic keratosis, basal cell carcinoma and squamous cell carcinomas
- Review features and benefits of dermoscopic study in the diagnostic process
- Summarize current therapies indicated for SK treatment
- Utilize current treatment algorithms based on current understanding of the differential diagnosis of SK
- Review new modalities in clinical investigation.

Target Audience

This activity is intended for dermatologists, residents, and fellows in dermatology, and physician assistants and nurses and to provide the dermatology healthcare practitioners with the latest clinical, scientific, and evidence-based information on advances in the understanding of seborrheic keratosis including scope of disease and clinical presentation, issues relating to effective diagnosis and advances in the understanding of the SK pathophysiology, and etiology.

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Advancing the Understanding of Seborrheic Keratosis

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ABSTRACT

The seborrheic keratosis (SK), which is ubiquitous throughout all populations, is a benign tumor of the skin. SKs are among the top 20 dermatologic conditions treated by dermatologists. They have been reported to occur in individuals of all ages including children as young as age 15 years. Familial cases of SKs have been described with an autosomal dominant inheritance pattern. Mutations of the fibroblast growth factor receptor 3 gene (FGFR3) and the gene encoding for phosphoinositide 3-kinase (PIK3CA) have been demonstrated in SKs. In addition to a genetic predisposition, independent risk factors include advancing age and ultraviolet light exposure. It has been proposed that these two risk factors may also contribute to the development of SKs caused by the genetic mutation in FGFR3 gene, which is involved in regulating cell growth, differentiation, migration, and wound healing. The classic description of a SK is a papule or plaque with a soft, friable, hyperkeratotic surface, or a macule with a fine granular appearance. Variants include the stucco seborrheic keratosis and dermatosis papulosa nigra (DPN). Although diagnosed clinically, mimickers of SKs are well known with melanoma being the most concerning. Treatment of SKs is primarily procedural with new treatments in development.

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INTRODUCTION

The seborrheic keratosis (SK), which is ubiquitous throughout all populations, is a benign tumor of the skin. Nomenclature for the SK includes seborrheic wart, seborrheic verruca, basal cell papilloma, pigmented papilloma, verruca senilis, and senile keratosis.[1] Wilmer analyzed data extracted from the National Center for Health Statistics' National Ambulatory Medical Care Survey (NAMCS) from 2001 to 2010.[2] The top 20 dermatologic conditions reported by dermatologists accounted for 85.4% of all diagnoses made by dermatologists and SKs were included in these conditions. Bickers estimated the prevalence of skin diseases in the United States (US) and determined that 83.3 million people in the US had SKs with direct health care cost due to SKs of $179 million, indirect cost of $51 million (from lost productivity) and intangible cost of $6700 million (because of QOL impact).[3]

SKs occur in individuals of all ages including children as young as age 15.[4] Familial cases of SKs have been described in the literature with a report of a German family with at least seven affected members in two generations and the onset of a large number of SKs at a young age.[1] An autosomal dominant inheritance pattern has been identified in some families with familial SKs.[5] The genetic basis of SKs is being elucidated and mutations of the fibroblast growth factor receptor 3 gene (FGFR3) and the gene encoding for phosphoinositide 3-kinase (PIK3CA) have been demonstrated in SKs.[1] In addition to a genetic predisposition, independent risk factors for the development of SKs that have been proposed including advancing age and ultraviolet light exposure.[6,7] These two risk factors may also contribute to the development of SKs caused by the genetic mutation in the FGFR3 gene, which is involved in regulating cell growth differentiation, migration, and wound healing.[8] Although diagnosis is primarily clinical, mimickers of SKs are well known with melanoma being the most concerning. Treatment of the SK is primarily procedural with new treatments in development.

Clinical Presentation

The diagnosis of the SK is primarily clinical. Clinical criteria for SKs include a "stuck on" appearance of papules or plaques with a soft, friable, hyperkeratotic surface, or macules with a fine granular appearance.[6] The color can range from pink or white (nonpigmented) to grey, dark brown, or black. Lesions typically range from 0.5 -1.5 cm with the exception of the clinical variant, dermatosis papulosa nigra (DPN), which are smaller in size. SKs occur commonly on the head, trunk, and extremities. They have not been reported on the palms or soles. However, cases of subungual SKs have been reported and described as longitudinal leucoxanthonychia with filiform/globular haemorrhages and milia-like cysts.[9]

SKs are generally asymptomatic although they may become inflamed or pruritic due to rubbing by external forces, irritation, or infection. In a study by Del Rosso, 19% of subject had symptomatic lesions that were inflamed or irritated.[10] Older patients, ages 60-69 years, were more likely to have a symptomatic SK than patients 40-59 years. Kyriakis studies 787 patients from Greece and found that body mass index did not differ between SK cases and non-SK cases. These authors also reported that skin type was more fair in SK patients.[11]

Clinical variants of SKs include stucco keratosis and DPNs.[12] DNPs seemingly occur more often in individuals with darker

skin types. A prospective study by Niang from Dakar, Senegal, of 30 African patients with an average age of onset of DPNs of 22 years, revealed that the lesions initially appeared on the face and then encompassed all photoexposed areas.[13] DNPs numbered 50-100 (ranging in size from 1-5 mm) in 66.6% of the cases and coalesced to form plaques in 26.6% (reaching a size of 8 mm). There was a family predisposition in 93.3% of the cases of DPNs. The second variant of SKs, the stucco keratoses present as white or white-grey 1-4 mm warty papules on the extremities. The lesions appear to be stuck onto the skin and can be scraped off without bleeding.[14]

SKs may be a feature of paraneoplastic syndrome. The sign of Leser-Trelat has been described as the explosive onset of multiple SKs associated with an underlying malignancy. The three most common malignancies associated with the sign of Leser-Trelat were gastric, colorectal, and breast cancer. [15]

A case of hypoinsulinemic hypoglycemia and the sign of Leser-Trelat associated with a malignant fibrous tumor with insulin-like growth factor-2 (IGF-2), demonstrated improvement in both conditions after tumor excision.[16]This suggests that IGF-2 may play a causative role in SKs. Growth hormone exerts its effects through insulin growth factors. Cells must have receptors for growth factors to act upon. Both growth hormone and insulin like growth factor receptors have been detected in normal keratinocytes. In fact, growth hormone receptors have been reported in benign cutaneous proliferations.[17] Ginarte evaluated the growth hormone receptor (GHR) expression on SKs and found no differences between keratinocytes from normal epidermis and keratinocytes from SKs. This has implications in regard to the etiology of SKs.

The differential diagnosis of SKs includes the benign lesions, common warts, lentigines, melanocytic nevi, as well as the premalignant and malignant lesion, actinic keratosis, Bowen disease, basal cell and squamous cell carcinomas, and melanoma.[13,18]

Quality of Life (QOL)

An observational study by Del Rosso from 10 United States dermatology practices captured how the diagnosis of asymptomatic SKs affected QOL as well as treatment concerns.[10] These authors found that the primary concern for 22% of patients enrolled was related to the appearance of the SKs, 34% were concerned about the health implications, and 45% were equally concerned about appearance and health. 61% of patients, primarily women, attempted to disguise or cover their SKs by avoiding particular types of clothing (12%), wearing clothing designed to hide the SKS (16%), using makeup (28%), or hairstyles (7%) to cover SKs.

In subjects in the Del Rosso study who had previously had SKs removed, the most common reasons included concerns that they represented something serious (57%), not liking the appearance (53%), and not liking how SKs felt when touched (44%). When shown photographs of treatment results, 83% of subjects were at least somewhat interested in having their SKs treated. Del Rosso also evaluated the reasons that the study patients did not remove their SKs. Cosmetic concerns impacted 35% of the subjects who "did not want to risk having a scar" (14%), "didn't want to risk having a white spot" (10%), and "I have too many spots to treat" (10%). As asymptomatic and non-irritated SKs are considered cosmetic in nature, the cost of removal could play a role in the decision not to have a lesion treated. Del Rosso reported that 17% of subjects in their study decided not to have SKs treated because "out of pocket cost of treatment was too high". Thus, the benign asymptomatic SK impacts the QOL of patients in a variety of ways and financial concerns may impact their ability to have SKs treated.

Etiology and Pathogenesis

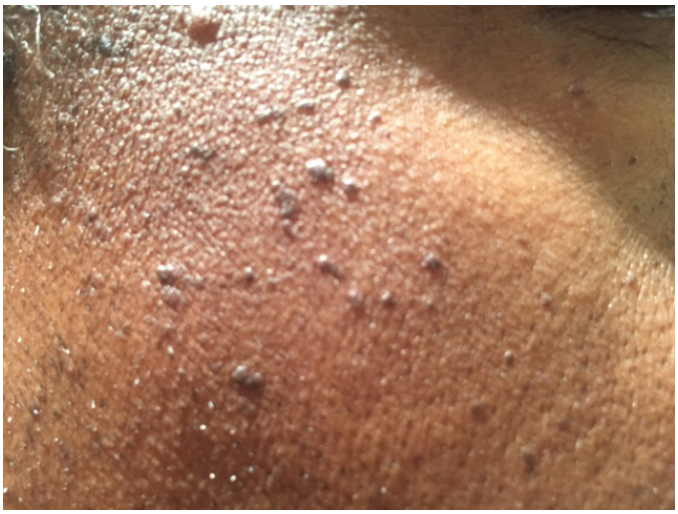
Genetics

Studies in the past decade have identified genomic alterations in benign lesions including SKs. Genomic alterations identified in SKs have included mutations of the FGFR3 and the gene encoding for PIK3CA.[1] Logie first suggested a causative role of somatic FGFR3 mutations after demonstrating a similar mutation in transgenic mice.[8] The mice developed benign epidermal tumors with features of SKs. These investigators went on to find the FGFR3 mutation in 39% of the human SKs that they studied.

Hafner then analyzed 65 acanthotic SKs for FGFR3 mutations.[19] FGFR3 mutations were found in 57% of SKs including flat (or newer) and thick (older) SKs. The mutation was significantly higher in SKs than in normal epidermis and increased age was felt to be a risk factor for the mutation. It was hypothesized that activation of the FGFR3 mutation provided proliferative signals for keratinocytes as well as induction of anti-apoptotic pathways that results in prolonged survival of these keratinocytes. FGFR3 mutations in the Hafner study occurred preferentially in SKs of the head and neck for which the authors suggested a causative role of cumulative ultraviolet exposure. Finally, not all SKs were found to have the FGFR3 mutation, suggesting the involvement of additional genes. In another investigation by Hafner of the stucco and DPN variants of SKs, it was determined that mutations in FGFR3 and PIK3CA also existed.[14] This supports the concept that stucco SKs and DPNs are indeed variants of SK and share a common genetic background with SKs.

Hafner went on to investigate FGFR3 mutations in a German family with 7 affected members in 2 generations with large numbers of SKs at a young age.[1] FGFR3 mutations were present in 3 of 5 SKs analyzed from the family and 1 SK with a FGFR3 mutation was further analyzed and showed a hotspot PIK3CA mutation. However, none of these mutations was

FIGURE 1. Dermatosis Papulosa Nigra. Multiple brown papules on the lateral aspects of the cheeks and on the temples.



present in the germline. Therefore, other mechanisms likely contribute to familial SKs.

It is now known that more than 80% of SKs have at least one oncogene mutation and 45% have more than one mutation, including FGFR3, PIK3CA KRAS, and/or EGFR.[20] Although SKs contain oncogenic mutations that are present in other malignancies, SKs remain benign. Thus, SKs may provide insights for the prevention or treatment of malignancies.

Akt, also known as protein kinase B, plays key roles in cell proliferation, cell cycle progression, survival, metabolism, and apoptosis. Akt overactivation contributes to many pathophysiological conditions, from cancer to SKs. Newer investigations have revealed that both FGFR3 and PIK3CA impinge on Akt kinase. SK cells are characterized by overactive Akt signaling but they are not associated with oncogenesis and remain clinically inert indefinitely according to Neel.[21] High levels of Akt activity underlie the defect in cornification of SKs in which some cells live too long and other undergo inappropriate intraepithelial cornification (pseudocyst formation). Additionally, SKs unlike squamous cell carcinomas, were found to be hypersensitive to inhibition by ATP-competitive Akt inhibitors, A-443654, and GSk690693, which can lead to rapid cell death through apoptosis.

Age

Although SKs are clearly associated with an older population, Yeatman examined 100 Caucasian Australians and identified SKs in 12% of those ages 15-25, 79% in those ages 26 to 50 and 100% of those over the age of 51.[6] Additionally, the number of SKs increased with advancing age with those ages 15-25 having 6 SKs and those older than 75 who had 69 SKs.

An increasing prevalence of SKs with age but the clear occurrence during youth was supported by a larger study by Gill who examined a larger number of Australian Caucasians.[4] In 170 subjects studied, there was a 62% chance of having an SK with each 5 years of advancing age. Additionally, there was an increase in the size of SKs with age. Kwon evaluated 303 Korean males, Fitzpatrick Skin Types 1-V, between the ages of 40 and 70 years and found a prevalence of SKs of 88.1%.[7] Consistent with the Caucasian population, there was an increase in prevalence of SKs with advancing age with 78.9% at 40 years to 93.9% at 50 years. The trend of increasing number of lesions held in this darker skinned population, with 5.5 lesions at 40 years, 9.2 at 50 years, and 13.4 at 60 years. However, the total number of SKs was lower in the Korean population (9.2 lesions at age 50 and 13.4 at age 60) as compared to a Caucasian population (23 lesions at ages 51-75).

Ultraviolet Light

Yeatman reported a higher prevalence of SKs on sun-exposed areas of the body in their 100 Caucasian Australian subjects as compared to non-exposed areas when taking into account surface area.[6] Although absolute numbers of SKs were highest on the trunk (54.7%), when accounting for body surface area, the dorsum of the hands (15.2% of the total), and the head and neck area (11.4% of the total) were over-represented as a proportion of total skin surface area. Additionally, the investigators noted that SKs on exposed areas were more often flat and greater than 3 mm in diameter than those on non-exposed areas. Similar results in regard to sun exposed sites were reported by Gill et al who noted in their 170 subjects, that although the distribution of SKs was predominantly truncal, this location only accounted for 36% of body surface area.[4]

Kwon also reported excessive sun exposure as an independent risk factor for SKs.[7] There was a prevalence of 80.5% on sun-exposed areas (face 32.8% and dorsal hands 17.8%) and 60.4% on partly sun-exposed areas (trunk, arms and inner forearms, and legs) in the study. Lifetime cumulative sunlight exposure of more than 6 hours per day was associated with a 2.28-fold higher risk of SKs than a sun exposure of less than 3 hours per day. These authors reported that sunlight causes multiple smaller SKs and that sunlight is a factor in the development and growth of SKs. In addition, 38.9% of the SKs were classified as dark in color (black, dark brown, and brown) and 61.1% light in color (light brown 94.7% and pink 5.3%). As SKs contain melanocytes, sun-exposure may stimulate pigment production and the transfer of melanin from melanocytes to keratinocytes. This likely explains the fact that all but 5.3% of SKs in the Korean males were pigmented. SKs on exposed skin were darker in color than those on partly exposed skin.

Logie proposed that in addition to ultraviolet exposure being an independent risk factor for the development of SKs, that UV

may also play a causative factor in the mutation of FGFR3, the most common mutation associated with SKs.[8]

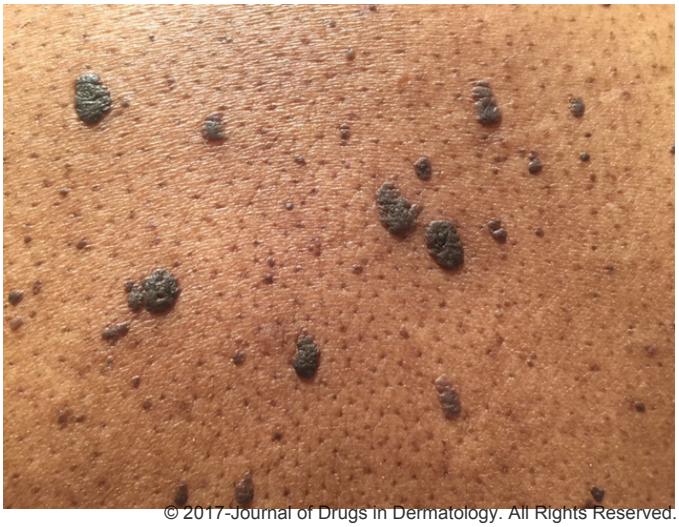
Histology

The three classic histologic features of SKs include hyperkeratosis, acanthosis, and papillomatosis. In 2016, Roh analyzed the clinical and histopathological features of SKs from 271 pathology slides of clinically diagnosed SK as well as 206 cases of biopsy-proven SKs.[12] The major histopathological variants identified in the 206 biopsy-proven SK cases included acanthotic (45.1%), mixed (19.9%), hyperkeratotic (17.0%), melanoacanthoma (9.2%), adenoid (4.4%), clonal (2.4%), and irritated (1.9%) types. The acanthotic type was the most common subtype located on sun-exposed sites, the adenoid type was only observed on sun-exposed areas and the hyperkeratotic type occurred more frequently on nonexposed area.

There were 26 clinicopathological mismatch cases among biopsy-proven SKs. The most common diagnoses mistaken for SK were verruca vulgaris (26.9%), verruca plana (15.4%), basal cell carcinoma (11.5%), squamous cell carcinoma (7.7%), compound nevus (7.7%), actinic keratosis (3.8%), Bowen disease (3.8%), melanoma (3.8%), condyloma acuminatum (3.8%), intradermal nevus (3.8%), and soft fibroma (3.8%). Premalignant and malignant diagnoses represented 23.1% and 7.6% of the mismatch cases.

Of the 271 clinically diagnosed SK cases, 180 were proven to be SK and 91 were found to have alternative diagnoses. The 91 lesions that were most commonly clinically misdiagnosed as SKs were verruca vulgaris (27.5%), actinic keratosis (14.3%), compound nevi (6.6%), intradermal nevi (5.5%), lichenoid dermatitis (5.5%), basal cell carcinoma (2.2%), squamous cell carcinoma (2.2%), Bowen disease (3.3%), and miscellaneous (30.8%). Premalignant and malignant entities represented 17.6% and 6.6% of the mismatch cases, respectively. These mismatches occurred significantly higher for sun-exposed lesions than for non-exposed lesions. It is important to note that a Maize study of nonmelanoma skin cancers in association with SKs reported that all malignant lesions found in their study were associated with SKs on sun-exposed skin and were of the adenoid type.[22] Based upon this data, Roh suggested that SKs on sun-exposed skin be biopsied and analyzed to exclude premalignant or malignant lesions.

FIGURE 2. Multiple seborrheic keratoses on the back.



Izikson studied 9204 consecutive pathology reports containing the diagnosis of SK in the clinical information field, between the years 1992 and 2001, and identified 61 cases (0.66%) of melanoma.[18] All histologic types of melanoma were represented. These authors concluded that melanoma can mimic SKs and they strongly supported submitting all specimens for histological examination.

Effective Diagnosis and Evaluation Criteria

As the diagnosis of SKs is primarily clinical, the ability to accurately identify SKs and rule out a malignant lesion is critically important. SKs may be difficult to distinguish from cutaneous malignacies including pigmented basal cell carcinomas, squamous cell carcinomas, or malignant melanoma.[12] Lin validated a two-step dermoscopy evaluation for 416 clinically suspected SKs with step one consisting of indentifying multiple milia-like cysts; comedo-like openings; fissures/ridges (brain-like appearance); light-brown fingerprint-like structures; and the lack of blue-grey or blue-white color. Step two identifies sharp demarcation, mica-like structure, and yellowish color.[23] The two-step algorithm when optimized, achieved a sensitivity of 95.7% and a specificity of 78.3%. Additionally, they identified a total of 12 dermoscopic patterns for SKs.

Carrera evaluated 134 cases of SKs and determined clues for diagnosing melanomas that resemble SKs.[24] They reported that the most helpful criteria in correctly diagnosing SK-like melanomas were the presence of blue-black sign, blue-white veil, pseudopods or streaks, and pigment network. Multivariate analysis found only the blue-black sign to be significantly associated with a correct diagnosis, and hyperkeratosis, fissures, and ridges were independent risk markers of dermoscopically SK-like melanoma.

Cornice evaluated the role of immunosuppression in squamous cell carcinomas arising in SKs (SCC-SK).[25] SCC have been described to arise from SKs due to malignant transformations of the keratinocytes. However, it is unclear if the SCC actually arises in the SK or represent a collision tumor. The 162 cases of SCC-SK displayed features of SKs but the areas of SCC were characterized histologically by areas of squamous dysplasia, hypogranulosis, squamous eddies, solar elastosis, and brown pigmentation. Furthermore, patients with a history of

immunosuppression had an increased risk for developing SCC-SK particularly when inhibition was transplant associated. The SCC-SK arises most commonly on the head and neck of elderly immunosuppressed men.

Roh determined that the second most common diagnoses mistaken for SK was verruca plana (VP) at 15.4%.[12] VP are benign epithelial proliferation that presents as slightly elevated, flat-topped papules with minimal scale. Kim designed a diagnostic algorithm to distinguish VP and VP-like SKs based on clinical and dermoscope criteria.[26] The algorithm proposed by Kim suggests evaluation of the skin for Koebner's phenomenon (diagnostic of VP), then dermatoscopy (distinguishing VP from VP-like SK). If a diagnosis is not made, the next step is evaluation of the distribution of each lesion (distinguishing VP from VP-like SK). If a diagnosis is not made after these three steps, then a biopsy is recommended.

Treatment

Dermatologists reportedly manage 85% of all episodes of SKs and they managed 89% using low intensity procedures.[27] Dermatologists had the highest diagnostic accuracy for SKs and were more likely than general or plastic surgeons to perform acceptable management procedures.

The therapeutic armamentarium for the treatment of SKs is primarily procedural. Effective low intensity procedures include curettage, electrodessication, cryosurgery, chemical, and laser destruction. Unfortunately, recurrence, scarring, and pigmentation changes are common problems with these techniques particularly in the skin of color population. Topical treatment with cryosurgery, tazarotene 0.1% cream, calcipotriene 0.005% ointment, and imiquimod, have been studied with only cryosurgery demonstrating complete resolution of SKs and twice daily tazarotene 0.1% cream resulting in improvement in 7 of 15 patients.[28]

Gurel compared the efficiency of Er:YAG lasers with cryotherapy in the treatment of SK and reported complete healing in 100% of the lesions treated with Er:YAG lasers compared to 68% for the cryotherapy group.[29] In the Er:YAG laser-treated group, hyperpigmentation was significantly lower but more erythema developed than in the cryotherapy group.

FGFR3 mutations have been implicated in the development of SKs. Dobesilate interferes with the FGF signals and a 5% potassium dobesilate cream daily for 6 months was applied to 2 SKs on the face. Dobesilate achieved complete clearance of the SK lesions with good cosmetic results, and the authors suggested that this compound is a safe and efficient candidate in the treatment of SK.[30]

Additional new compounds being studied for the treatment of SK include aqueous BL-5010 (trichloroacetic acid and formic acid) applied to at least one SK on the face, scalp, trunk, or extremities and A-101 (hydrogen peroxide formulation) 40% Topical Solution applied to four target SKs on the face, trunk, and extremities.[31,32] A phase 1/2 trial of BL-5010 enrolling 60 subjects reported that 90% of subjects had complete remission and 7% partial remission of SKs at trial completion.[31] Adverse events included irritation, itching, and burning at the application site, bleeding, and scale crust formation.

Two phase 3 trials of A-101 enrolling 937 subjects reported that 51.3% of lesions treated with A-101 were clear or near clear at trial completion versus 7.3% of lesions in the placebo group.[32] 65.3% of lesions on the face treated with A-101 were clear or near clear versus 10.5% of lesions in the placebo group. 13.5% and 23.0% of patients in the two trials treated with A-101 achieved clearance of at least three of the four target SK lesions as compared to no placebo subjects. The compound was well tolerated with hypopigmentation, hyperpigmentation, and scarring graded as mild.

SUMMARY

The SKs is a commonly occurring often asymptomatic lesion that is diagnosed and treated by dermatologists. Gaps exist in medical knowledge concerning this benign lesion. The etiology and pathogenesis of the SK is being elucidated with several oncogenic mutations identified. Lesions are diagnosed clinically and the differential diagnosis included both benign and malignant lesions. Melanoma is the most concerning mimicker of the SK. SKs impact the QOL of patients in a variety of ways and financial concerns often impact the ability to have these lesions treated. Treatment of SKs is primarily procedural with new treatments being developed.

DISCLOSURES

Dr. Susan Taylor is an advisory board member and investigator for Aclaris Therapeutics, Inc.

REFERENCES

1. Hafner C, Vogt T, Landthaler M, et.al. Somatic FGFR3 and PIK3CA mutations are present in familial seborrheoeic keratoses. *British J Dermatol.* 2008;159:214-217.
2. Wilmer EN, Gusafaon CJ, Ahn CS, et al. Most common dermatologic conditions encountered by dermatologists and nondermatologists. *Cutis.* 2014;94:285-292.
3. Bickers DR, Lim HW, Margolis D, et.al. The burden of skin diseases: 2004 A joint project of the American Academy of Dermatology Association and the Society for Ivestigative Deramtology. *J Am Acad Dermatol.* 2006;55:490-500.
4. Gill D, Dorevitch A, Marks R. The prevalence of seborrheic keratoses in people aged 15 to 30 years: is the term senile keratosis redundant? *Arch Dermatol.* 2000;136:759-62.
5. Rongioletti F, Corbella L, Rebora A. Multiple familial seborrheic keratoses. *Dermatologica.* 1988;176:43-45.
6. Yeatman JM, Kilkenny M, Marks R. the prevalence of seborrhoeic keratoses in an Australian population: does exposure to sunlight play a part in their frequency? *Br J Dermatol.* 1997:137:411-14.
7. Kwon OS, Hwang EJ, Bae JH, et al. Seborrheic keratosis in the Korean males: causative role of sunlight. *Photodermatol Photoimmunol Photomed.* 2003;19:73-80.

8. Logie A, Dunois-Larde C, Rosty C, et al. Activating mutations of the tyrosine kinase receptor FGFR3 are associated with benign skin tumors in mice and humans. *Hum Mol Genet*. 2005;14(9):1153-1160.
9. Stinco G, Errichetti P, Patrone P. Ungual seborrhoeic keratosis: report of a case and its dermoscopic features. *J Eur Acad Dermatol Venereol*. 2016;30:446-556.
10. Del Rosso J. A closer look at seborrheic keratoses: patient perspectives, clinical relevance, medical necessity, and implications for management. *J Clin Aesthetic Dermatol*. 2017;10:16-25.
11. Kyriakis, KP, Alexoudi I, Askoxylaki K, et al. Epidemiologic aspects of seborrheic keratosis. *Int J Dermatol*. 2012;51:233-237.
12. Roh NK, Hahn HJ, Lee YW, et al. Clinical and histopathological investigation of seborrheic keratosis. *Ann Dermatol*. 2016;28(2):152-8.
13. Niang SO, Kane A, Diall M, et al. Dermatosis papulos nigra in Dakar, Senegal. *Int J Dermatol*. 2007;46:45-47.
14. Hafner C, Landthaler M, Mentzel T, et.al. FGFR3 and PIK3CA mutations in stucco keratosis and dermatosis papulosa nigra. *Br J Dermatol*. 2010;162(3):508-12.
15. Chakradeo K, Narsinghpura K, Ekladious. Sign of Leser-Trelat. BMJ Case Rep 2016 AaPii:bcr2016215316. Doi:10.1136/bcr-2016-215316.
16. Mathez ALG, Moroto D, Dib SA, Roberto de Sa J. Seborrheic keratoses and severe hypoinsulinemic hypoglycemia associated with insulin grow factor 2 secretion by a malignant solitary fibrous tumor. *Diabetol Metab Sundr*. 2016;8:33).
17. Ginarte M, Garcia-Caballero T, Rernandez-Redondo V, et.al. Expression of growth hormone receptor in benign and malignant cutaneous proliferative entities. *J Cutan Pathol*. 2000;27:276-282.
18. Izikson L, Sober AJ, Mihm MC, et.al. Prevalence of melanoma clinically resembling seborrheic keratosis: analysis on 9204 cases. *Arch Dermatol*. 2002;138:1562-6.
19. Hafner C, Hartmann A, vanOers JMM, et.al. FGFR3 mutations in seborrheic keratoses are already present in flat lesions and associated with age and localization. *Modern Pathol*. 2007;20:895-903.
20. Hafner C, Toll A, Fernandez-Casado A, et al. Multiple oncogenic mutations and clonal relationship in spatially distinct benign human epidermal tumors. *Proc Natl Acad Sci USA*. 2010;107:20780-5.
21. Neel VA, Todorova K, Want J, et.al. Sustained Akt activity is required to maintain cell viability in seborheic keratosis, a benign epithelial tumor. *J Invest Dermatol*. 2016;136:696-705.
22. Maize JC, Snider RL. Nonmelanoma skin cancers in association with seborrheic keratoses. Clinicopathologic correlations. *Dermatol Surg*. 1995;21:960-962.
23. Lin J, Han S, Cui L, et.al. Evaluation of dermoscopic algorithm for seborrheic keratosis: a prospective study in 412 patients. *JEADV*. 2014;28:957-962.
24. Carrera C, Sequra S, Aquilera P, et al. Dermoscopic clues for diagnosing melanomas that resemble seborrheic keratosis. *JAMA Dermatol*. 2017; Doi:10.1001/jamadermatol 2017.0129.
25. Conic RX, Napekoski K, Schuetx H, et al. The role of immunosuppression in squamous cell carcinomas arising in seborrheic keratosis. *J Am Acad Dermatol*. 2017 (In press; http://dx.doi.org/10.1016/j.jaad.2016.12.002)
26. Kim W-J, Lee K, Song M, et al. Clinical clues for differential diagnosis between verruca plans and verruca plana-like seborrheic keratosis. *J of Dermatol*. 2015;42:373-377.
27. Duque MI, Jordan JR, Fleischer AB, et al. Frequency of seborrheic keratosis biopsies in the United States: A benchmark of skin lesion care quality and cost effectiveness. *Dermatol Surg*. 2003;29:796-801.
28. Herron MD, Bowen AR, Krueger GG. Seborrheic keratoses: A study comparing the standard cryosurgery with topical calcipotriene, topical tazarotene, and topical imiquimod. *Int J Dermatol*. 2004;43:300-2.
29. Gurel MS, Aral BB. Effectiveness of erbium:YAG laser and cryosurgery in seborrheic keratoses: Randomized, prospective intraindividual comparison study. *J Dermatol Treat*. 2015;26(5):477-80.
30. Cuevas P, Angulo J, Salgüero I, et al. Clearance of seborrhoeic keratoses with topical dobesilate. *BMJ Case Rep*. 2012;2012. pii: bcr0120125628.
31. Levy-Nissenbaum E, Thio HB, Burstein P, et.al. Seborrheic keratosis removal in a multicentre phase I/II clinical trial using a novel topical formulation (BL-5010). *Br J Dermatol*. 2015;173:247-249.
32. Aclaris Therapeutics Announces Positive Top-Line Phase 3 Results for A-101 In Treating Seborrheic Keratosis, a Common Undertreated Skin Condition. https://www.drugs.com/clinical_trials/aclaris-therapeutics-announces-positive-top-line-phase-3-results-101-treating-seborrheic-keratosis-17248.html.

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1. The etiology and pathogenesis of seborrheic keratosis involves:
   a. Genomic alterations of the FGFR3 and PIK3CA genes
   b. Advancing age
   c. Ultraviolet exposure
   d. All of the above

2. Patients with seborrheic keratoses are concerned about the following:
   a. It may represent something serious
   b. The appearance
   c. The feel of the lesion when touched
   d. All of the above

3. Mimickers of seborrheic keratoses include all of the following except:
   a. Melanoma
   b. Verruca plana
   c. Squamous cell carcinoma
   d. Epidermoid cysts

4. Squamous cell carcinomas that arise from seborrheic keratosis occur:
   a. In immunosuppressed patients
   b. Primarily on the head and neck
   c. More frequently in men than in women
   d. All of the above

5. The most helpful dematoscopic clue for distinguishing melanomas from seborrheic keratosis is the presence of:
   a. Milia-like cysts
   b. Blue-white veil
   c. Comedo-like openings
   d. Brain-like appearance

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1 2 3 4 5

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1 2 3 4 5

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